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ABSTRACTS

1st Congress of Tunisian Society of Human Genomics, October 17-19, 2024, Sousse, Tunisia

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Conferences Session

001

History of Human Genetics in Tunisia: From Phenotypic Markers to Genomics

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The history of human genetics in Tunisia has followed the stages of technological development of this discipline. It began in the late 1970s with the introduction of genetic counselling and cytogenetics. In the 1980s, access to serological and biochemical analysis techniques made it possible to understand genetic diversity through protein and cellular markers. Initiated with the description of Tunisian myopathy and the discovery of the mutations responsible for thalassemia, deafness and myopathies, the study of other rare genetic diseases such as genodermatosis, metabolic diseases, mitochondrial diseases, hemostasis deficits, congenital disabilities with monogenic determinism, mental retardation, immune deficiencies, sterility, hereditary cancers, abnormalities of sexual differentiation, etc. has been the subject of several researches.
The high prevalence of these hereditary diseases as well as the genetic heterogeneity observed within the population is the result of a complex history of settlement accompanied by an ancestral practice of endogamy and inbreeding favoring the emergence of recessive diseases. This has implications for the investigation of multifactorial diseases that are typically undertaken on the basis of case-control studies. Many pathologies with hereditary and environmental components have been the subject of several studies showing the additive effects between several risk factors. These diseases include diabetes, obesity, asthma and different types of cancers. In these cases, the search for genetic and epigenetic alterations at the somatic level not only makes it possible to explain the carcinogenesis process but also to adapt the treatment.
The time has now come to move towards pharmacogenomics and precision medicine, benefiting from the high-throughput sequencing technologies and development of technological platforms, which are essential for medical genomics implementation. The first International Congress organized by the Tunisian Society of Human Genomics will be an opportunity to take stock of the subject.

002

Human Genetic Diversity and the Problem of Population: Lessons for Sustainable Health Care

Aouatef Amade M'charek
Department of Anthropology, University of Amsterdam

In this talk I draw on research that has centered the tension between the individual and the population in genetic diversity research. While problematizing the concept of population I will argue that holding on to the tension between the individual and the population is crucial in health care research and beyond.
As an anthropologist of science, I have worked in different sites where population genetics and genomics came to play crucial roles, advancing knowledge in fields such as human diversity, forensics, archeology and medicine. Despite pre- and post-Human Genome Project contributions of population-oriented research, "population" has also constituted a problem. Not only because any definition thereof is arbitrary, but especially because the population always risks fixing biological differences. It thus risks introducing race as a biological fact, racializing groups of people, and contributing to biological racism. Personalized and precision medicine, which focuses on the individual patient, seems to provide a way out as the goal thereof is to move beyond population. In this talk I will address both the problem of population and the promises of personalized medicine. While the examples and debates that I draw on are mostly situated in Europe and the United States, I hope that they will contribute to a productive conversation on a sustainable health care and the future of genomics in Tunisia.

003

Small RNAs in Epigenetic Inheritance

Germano Cecere
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Heritable traits have traditionally been attributed to mutations in DNA. However, emerging research reveals the pivotal role of epigenetic mechanisms, including DNA methylation, histone modifications, and

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small RNAs in transmitting non-genetic information across generations. In our laboratory, we explore the role of small RNAs in epigenetic inheritance using the model organism Caenorhabditis elegans. I will present results from our work illustrating how small RNAs can act as epigenetic molecules capable of transmitting traits across generations. I will provide an example of heritable small RNAs, which gradually reduce worms' fertility across multiple generations, and discuss the players and mechanisms underlying the transmission of small RNAs from one generation to another. Finally, I will show how the germline can acquire small RNAs from the soma to provide environmentally acquired heritable information to facilitate the inheritance of stress resilience.

004

The Human Genome Project (HGP): From the realization to the application: The contribution of a Tunisian laboratory

Hammadi Ayadi
Faculty of Medicine in Sfax since

The launch of the HGP in 1986 pushed several laboratories around the world to adapt their research projects with the objectives of this project and to use the first results emanating from research within the framework of this project. Two approaches were used by the researchers involving i) the first one was based on physical and genetic maps with the construction of giant clones in the bins and the alignment of genetic markers on the chromosomes. Thanks to this approach, it was possible to order the sequences in a juxtaposed manner by the overlapping giant clones ii) the second approach used the "shot gun" technique which is much easier to manipulate and sequence but difficult to align. Interestingly, the first approach was the most effective. Thus, family data with high prevalence of hereditary diseases were beneficial for positioning certain genetic markers and localizing some pathogenic genes. At the same time as the realization of the HGP advances, several techniques of cloning, sequencing, diagnosis, robotics, statistical analysis and bioinformatics were developed.
Several genetics laboratories have contributed to this dynamic and have benefited from the publication of the first results of physical and genetic maps as well as the sequencing of the first chromosomes, particularly in the identification of genes responsible for hereditary diseases.
In this context, the laboratory of Human Molecular Genetics was pioneer in unraveling genetic component in both hereditary neurosensory and autoimmune disorders based on large consanguineous Tunisian families.

005

Beyond the Genome: Metabolomics Pioneering a New Era in Precision Medicine

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The field of precision medicine is undergoing a paradigm shift, driven by the integration of metabolomics—a cutting-edge approach that examines the complete set of small molecules within cells, tissues, and biofluids. Metabolomics provides an unparalleled window into the biochemical activities that define health and disease, offering insights that go beyond the static information of the genome to capture the dynamic interactions within the body.
This conference will highlight how metabolomics is redefining the landscape of precision medicine. By profiling the metabolome, researchers and clinicians can identify subtle metabolic changes that precede or accompany disease, leading to earlier diagnoses, more accurate prognoses, and the development of targeted therapies tailored to an individual's metabolic profile. This approach not only deepens our understanding of complex diseases but also accelerates the discovery of novel biomarkers and therapeutic targets. We will explore the potential of metabolomics to uncover hidden disease pathways and its integration with other omics data to create a holistic view of patient health. Furthermore, we will address the practical challenges of translating metabolomic research into clinical practice, including issues of standardization, validation, and ethical considerations.
As we advance beyond the genome, metabolomics is at the forefront of precision medicine, offering transformative potential in diagnosing, treating, and preventing disease. This conference will explore how the metabolome is shaping the future of healthcare, paving the way for highly personalized medical strategies that promise improved patient outcomes and a new era of medicine.

006

Establishing molecular diagnostics and genetic counselling services in Low- and Middle-Income Countries (LMICs) – A case study of Tanzania

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The integration of molecular diagnostics and genetic counseling services is crucial for advancing healthcare in Low- and Middle-Income Countries (LMICs), where genetic diseases are often underdiagnosed and undertreated due to limited resources. This study examines the efforts to establish these services in Tanzania, highlighting the collaborative initiatives by local geneticists and the formation of the Tanzania Human Genetics Organization (THGO). Key strategies include capacity building for molecular diagnostics, developing genetic counseling frameworks, and fostering collaborations with international partners. A case study approach showcases how these efforts address pressing issues such as sickle cell disease, ethical considerations in genomics, and the challenges of bioinformatics training and biobanking. The findings suggest that a multidisciplinary approach and international partnerships are essential for overcoming the limitations in genetic healthcare services in LMICs, paving the way for more equitable global health outcomes.

007

Facing the picture of the development sexual disorder dilemma: a genomic approach

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Disorders of sex determination/differentiation (DSD) comprise a heterogeneous group of congenital conditions in which chromosomal, gonadal, anatomical sex and psychological aspects could be discordant. Recently, a huge number of candidate genes have been identified to be associated with DSD facing an outstanding dilemma in the of the diagnosis yield.
A global genomic approach in a large Tunisian cohort (143 patients) has enlarged the previously reported genes network field. Chromosomal rearrangements, including sex chromosome abnormalities could

explain more than the half of these disorders. New and known pathogenetic gene variants could explain the third of the picture enlarging the whole DSD phenotypic and genotypic spectrum. Moreover, a pleiotropic and very conservative evolutionary genes as WNT and SOX network has been identified to act in this field.
These data emphasize the usefulness of global genetic approach to make an accurate genetic diagnosis for genetic counseling and knowledge-based management of DSD patients. This could underline a multidisciplinary action in order to face the exiting dilemmas in the DSD field.

008

Pharmacogenetic of cardiovascular drugs

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Acute Coronary Syndromes (ACS) are a global public health issue and a leading cause of mortality in our country. Cardiology societies recommend secondary prevention that begins in the hospital and continues for life. This prevention is based on the acronym BASIC: Beta-blockers, Antiplatelet agents, Statins, ACE Inhibitors, and Control of cardiovascular risk factors. The effectiveness of this prevention significantly impacts the patient's prognosis. However, considerable interindividual variability exists, explained by both genetic and non-genetic factors. Therefore, a genotypic approach should allow for the personalization of treatment and lifestyle measures to enhance their efficacy and safety. This introduces the concepts of pharmacogenetics, nutrigenetics, and kinesio-genetics. Pharmacogenetics enables the prediction of an individual's response to a given treatment based on genetic polymorphisms affecting key pharmacokinetic and pharmacodynamic factors, facilitating the selection of the appropriate drug and dosage. Nutrigenetics aims to identify the impact of genetic variations on nutrient responses, allowing for tailored nutritional advice for specific individuals. Kinesio-genetics studies the heterogeneity of responses to physical exercise interventions, which can help design more effective and personalized exercise programs. Integrating these three aspects with artificial intelligence techniques, such as Machine Learning, enhances and facilitates the development of dosing algorithms and decision trees for choosing the most appropriate drugs, dietary measures, or physical exercise interventions. These algorithms can be validated in multicenter studies with the expertise of Tunisian scientific societies, paving the way for personalized medicine. This intervention will summarize our main pharmacogenetic findings related to cardiovascular drugs.

009

Phenotype-genotype spectrum of Retinal Dystrophies in a large Tunisian cohort

Yousra Falfoul
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Inherited retinal dystrophies represent a set of rare diseases characterized by progressive degeneration of the photoreceptors. We report the largest Tunisian cohort with inherited retinal dystrophies (IRD) to identify disease-causing pathogenic variants and describe genotype–phenotype correlations
Descriptive retrospective clinical and genetic study including patients with inherited retinal dystrophies who consulted the oculo-genetics laboratory, LR14SP01, at Hédi Rais Institute of ophthalmology.
We examined 470 individuals from 294 families (247 affected, 223 unaffected).
Non-syndromic retinitis pigmentosa (RP) was the most common disorder, 65.7% of patients.
Several non-syndromic RP phenotypes were identified according to the age of symptoms onset; Leber's congenital amaurosis (15.6%), early onset retinal dystrophy (EORD) (11.9%), classical RP had the highest rate (60.5%) and the late RP was quite rare (0.8%).
Hereditary macular dystrophies represented 16.8% of the consultants and Stargardt disease was predominant (87.1%).
The genetic study was contributive in 68 patients and identified 32 different genes responsible for these diseases. Many phenotype-genotype correlations were established.
Inherited retinal dystrophies are rare clinic, genetic and molecular heterogeneous affections. Multimodal analysis had largely facilitated their diagnosis.
Although, identification of phenotype-genotype correlations has been an aid in diagnosis and genetic counseling, genetic identification of the causal mutations, which is indispensable for future therapy, remains partly defined.

010

Socio-Genomics Risk Determinants of Prostate Cancer Among Black Men

Solomon Rotimi
Directorate of Research and Innovation, National Institute for Cancer Research and Treatment, Nigeria

Prostate cancer (PCa) poses a significant health challenge in Africa, marked by disparities in incidence and outcomes. Emerging evidence suggests that an interplay between social and biological determinants of health contributes considerably to the risk and aggressiveness of PCa among African men. This presentation will explore the intersection of genetic predisposition and social determinants of health in the context of PCa in African populations. This talk will delve into the socio-genomic landscape, highlighting how genetic variants associated with African ancestry correlate with increased risk and disease severity. The role of sociobiological factors, such as stress and allostatic load, will also be examined to understand their impact on the prevalence and prognosis of PCa in African men. Specifically, this presentation will discuss our study that analyzed whole exome sequence data from Nigerian men with advanced-stage, treatment-naïve primary PCa and benign prostate hyperplasia. This study identified a pattern of germline variants in genes such as BRCA1, BRCA2, and PMS2, which are crucial for DNA repair mechanisms and may influence PCa risk and treatment responses. This talk aims to shed light on the multifaceted risk determinants of PCa in Africa and outline a path toward integrating genomics into a broader public health framework that addresses biological and social determinants of health.

011

Molecular diagnostics and targeted therapies of lung cancer

Ayda Ayadi
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Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases and remains a leading cause of cancer-related mortality globally. Recent advancements in molecular diagnostics have revolutionized the management of NSCLC, enabling the identification of specific genetic alterations that drive tumor growth. Notable molecular targets, including EGFR mutations, ALK rearrangements, ROS1

fusions, and BRAF mutations, have been identified in distinct subsets of NSCLC patients. These discoveries have led to the development of targeted therapies, such as tyrosine kinase inhibitors (TKIs) like erlotinib, crizotinib, and dabrafenib, which have significantly improved progression-free survival and overall survival compared to traditional chemotherapy.

Molecular testing has become indispensable in NSCLC management, guiding the selection of targeted therapies and facilitating a personalized treatment approach. However, challenges such as the emergence of resistance mutations and the need for continuous molecular profiling persist. To address these issues, emerging strategies like combination therapies and next-generation inhibitors are under investigation to overcome resistance and enhance therapeutic efficacy. Additionally, liquid biopsies are gaining prominence as a minimally invasive technique for detecting actionable mutations and monitoring treatment response.

In conclusion, the integration of molecular testing and targeted therapies has profoundly reshaped the treatment landscape of NSCLC, offering renewed hope for improved patient outcomes in a disease once deemed uniformly fatal. Ongoing research and innovation in this field are crucial for optimizing patient care and further extending survival rates in NSCLC.

012

Cytogenetic markers in Hematologic malignancies

Ahlem Amouri
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Conventional cytogenetics provided the first chromosomal marker for malignancy in 1960, known as the so-called Philadelphia chromosome and was the first identification in human hematopoietic malignancies. Since this discovery, cytogenetic studies have been instrumental in detecting clonal, acquired somatic chromosome abnormalities (CAs) by chromosome banding.

Types of hematologic malignancies include myeloid and lymphoid neoplasms with myeloproliferative neoplasms (MPN), Leukemias (Lymphoblastic/Myeloblastic), Myelomas, and Melodysplasic neoplasms (MDS). Each hematological neoplasm is defined by a spectrum of genetic aberrations of diagnostic and/or prognostic significance.

In patients with hematological malignancies, routine cytogenetic abnormalities is the first step in the diagnosis of chromosomal abnormalities, one of the most substantial findings remains the karyotype of bone marrow cells at the time of diagnosis and the detection of clonal chromosome aberrations which are either primary, detected in all cytogenetically abnormal cells, or secondary, being present in one or multiple subclones, indicating clonal evolution. Chromosome banding analysis (CBA) during the disease course also allows monitoring of the treatment success.

Besides clinical and hematological criteria, cytogenetic, molecular genetic alterations highly impact treatment stratification. In routine diagnostics, combination of cytogenetic and molecular methods is used to decipher different types of genetic variants.

We will present the role of conventional and molecular cytogenetics in hematological malignancies. The main advantages are that they provides whole-genome analysis detecting both numerical and structural abnormalities and permits the identification of clonal evolution as well the presence of multiple independent clones that are essential for precise disease classification and choice of suitable therapy.

We want to focus on the main relevant CA detected by chromosome banding analysis, completed by Fluorescent In Situ Hybridization (FISH), Chromosomal Microarray (CMA) and recently, optical genome mapping (OGM), highlighting the continued clinical utility of these techniques, the subtleties and complexities that are relevant to treating physicians and the strengths of cytogenetics that cannot yet be paralleled by the current high-throughput molecular technologies.

In conclusion, despite the large development of new sequencing technologies and the discovery of many acquired gene mutations, cytogenetic analysis supplemented by the molecular cytogenetic methods still remains a very important part of diagnostics of hematological malignancies.

013

Genetic biomarkers and their clinical implications in Leukemia

Samia Mnif
Pasteur Institute of Tunis, Tunisia

Leukemia is a heterogeneous group of hematologic malignancies characterized by abnormal proliferation of hematopoietic cells driven by somatic gene mutations.

The era of genomic medicine has allowed leukemia researchers to improve disease characterization, optimize risk-stratification systems and develop new treatments.

Improvements in genomic analysis achieved thanks to New technologies and the implementation of next-generation sequencing (NGS) allowed an increased understanding of the biology and molecular basis of leukemia. These genetic abnormalities are used as diagnostic, prognostic and predictive biomarkers that play an important role in earlier disease detection and more accurate risk stratification.

Deeper characterization of leukemic cell genetic abnormalities has discovered new subtypes of leukemia, and identified many genomic alterations that have therapeutic implications.

Genomic characterization has opened the door to Precision medicine and personalized therapy for specific leukemia patient populations with promising results.

Several targeted therapies have been approved or are being tested for specific mutations , obtaining improvements in clinical outcomes and less toxicity as compared with intensive treatment, allowing potential combination therapy.

Genome-wide analyses have also unraveled the role of inherited cancer predisposing genes and small nucleotide polymorphisms of several genes in the development of childhood leukemia further improvement in the treatment outcome and quality of life of patients will require better understanding of the mechanisms of drug resistance, and optimizing treatment based on host pharmacodynamics and pharmacogenomics.

014

Egypt Genome: Towards an African new genomic era

Khaled Amer
Military Medical Academy and International Medical Center, Egypt

Studying the human genome is crucial to embrace precision medicine through tailoring treatment and prevention strategies to the unique genetic makeup and molecular information of individuals. After human genome project (1990–2003) generated the first full sequence of a human genome, there have been concerns towards Northern bias due to underrepresentation of other populations. Multiple countries have now established national genome projects aiming at the genomic knowledge that can be harnessed from their populations, which in turn can serve as a basis for their health care policies in the near future.

The intention is to introduce the recently established Egypt Genome (EG) to delineate the genomics and genetics of both the modern and Ancient Egyptian populations. Leveraging genomic medicine to improve precision medicine strategies while building a solid foundation for large-scale genomic research capacity is the fundamental focus of EG.

Key scientific concepts: EG generated genomic knowledge is predicted to enrich the existing human genome and to expand its diversity by studying the underrepresented African/Middle Eastern populations. The insightful impact of EG goes beyond Egypt and Africa as it fills the knowledge gaps in health and disease genomics towards improved and sustainable genomic-driven healthcare systems for better outcomes. Promoting the integration of genomics into clinical practice and spearheading the implementation of genomic-driven healthcare and precision medicine is therefore a key focus of EG. Mining into the wealth of Ancient Egyptian Genomics to delineate the genetic bridge between the contemporary and Ancient Egyptian populations is another excitingly unique area of EG to realize the global vision of human genome.

015

Insights into North African human populations through genome analysis

David Comas
UPF Doctoral School, Spain

The population history of North African groups exhibits unique demographic characteristics compared to the rest of the African continent. This region has been inhabited since Paleolithic times, though subsequent contacts and extensive gene flow from neighboring areas have shaped the current North African gene pool. There is considerable debate about the continuity between the earliest inhabitants and the current populations of North Africa. The genetic makeup of present-day North Africans is a blend of West Eurasian and sub-Saharan components, along with an autochthonous component unique to North Africa Ancient genetic data and complete genomes offer new insights into the population history of the region, suggesting genetic evidence of continuity in North African populations despite significant genetic changes during the Neolithic period and the impact of historical events such as Arabization. There is no direct correlation between major linguistic groups (Arab and Amazigh) and genetics in North Africa. However, recent estimates indicate that these populations have different temporal origins, with an early split of Amazigh groups occurring in Epipaleolithic times.
One limitation in reconstructing the population history of North Africans is the relative scarcity of genetic data compared to other geographical areas. This scarcity poses challenges for biomedical studies and their applications.

016

The AGenDA Network: bridging major gaps in the coverage of African genomic diversity

Ananyo Choudhury
Sydney Brenner Institute for Molecular Bioscience, University of Witwatersrand, South Africa

The African genomic diversity is strongly stratified along the dimensions of geography and ethnolinguistic affiliations. This stratification originating in the deep history of African populations is outlined by layers of population splits and migrations resulting in recurring periods of contact and isolation. Most of the population genetics work conducted on African populations so far has been driven by the ability to access samples and has consequently left several huge gaps in covering both geographic and ethnolinguistic spread.
The Assessing Genomic Diversity in Africa (AGenDA) is an initiative to bridge some of the major gaps and generate a more continuous and high-resolution map of African diversity. In the first phase of this study, we have sequenced ~1200 high-depth whole genomes with a particular focus on unrepresented/under-represented populations and geographies. This African led initiative was implemented by a network of African researcher from 9 different countries.
The first part of the presentation will provide a brief introduction to African history, the major ethnolinguistic divisions and their distribution on the Africa map. Based on data from recent genomic studies, we will see how this genomic diversity is intricately linked with history as well as key demographic events. In the second part we will revisit the conception of the AGenDA study, the establishment of the network, the collaborative framework, ethics and regulatory compliance, capacity development and mechanism of data sharing. In the final part of the presentation, we will discuss where we are with the project and the way forward.

017

Harnessing Collaboration: H3Africa and DS-I Africa – Updates & Opportunities for African Scientists

Michelle Skelton
H3Africa and DS-I Africa Coordinating Centre, University of Cape Town, South Africa

This keynote will delve into the transformative impact of H3Africa and DS-I Africa in reshaping the scientific landscape of Africa. Specifically, this presentation will focus on the significant contributions of the H3Africa and DS-I Africa initiatives in fostering scientific collaboration and capacity building within the African continent. I will provide updates on recent developments and achievements, including the African Genomics Data Hub, Open Data Science Platform and Coordinating Centre. Furthermore, this presentation highlights the collaborative efforts between researchers, public and private institutions, and governments. Additionally, the talk will explore the vast opportunities that these initiatives present for African scientists, including access to cutting-edge technologies, policies, data-sharing platforms, and international partnerships. By leveraging the strengths of both H3Africa and DS-I Africa, this presentation aims to inspire and empower African researchers to address pressing health challenges, drive innovation, and contribute to global scientific advancements.

018

The Genome Tunisia Project: Paving the Way for Precision Medicine in Tunisia

Yosr Hamdi
Pasteur Institute of Tunis, Tunisia

Several discoveries in the field of human genetics have led to the foundation of modern molecular and personalized medicine. Here, we are presenting the Genome Tunisia Project that aims to determine the reference sequence of the Tunisian Genome in order to, ultimately, implement precision medicine in Tunisia.
The main goal of this initiative is to develop a healthcare system capable of incorporating Omics data for use in routine medical practice, enabling medical doctors to better treat, prevent and diagnose patients. Therefore, a multidisciplinary partnership involving Tunisian experts from different regions has come to discerning all requirements that would be of high priority to fulfill the project goals. One of the most urgent priorities is to determine the reference sequence of the Tunisian Genome.
To achieve these goals, hundreds of Tunisian Genomes have been already sequenced and data analysis is in progress. In addition, extensive situation analysis of the education programs, community

awareness, training, appropriate infrastructure as well as the ethical and regulatory framework have been undertaken towards building sufficient capacity to integrate genomic medicine in the Tunisian healthcare system.
The Genome Tunisia initiative seeks to demonstrate the major impact that can be achieved by implementing National Human Genome Projects in LMICs to improve disease management and treatment outcome. Additional efforts are now made for the advancement of patient care by accelerating research and innovation and supporting necessary changes in policy and regulation.

019

Streamlining the ethical-legal governance of data sharing

Pamela Andanda
University of Witwatersrand, Johannesburg

Sharing data from diverse sources is essential for addressing grand challenges in global health. The Covid-19 pandemic, which affected the world at a global scale, demonstrated the benefits of data sharing but also revealed challenges that stakeholders face such as lack of data interoperability, accessibility, and lack of guiding principles for ensuring responsible sharing of data that are distributed across multiple organizations, institutions, and ecosystems. This paper reviews current literature on clinical research that focus on tuberculosis, malaria, HIV/AIDS, and COVID-19 in South Africa, Nigeria, Rwanda, and Kenya, as case study countries, to highlight key governance concerns and gaps in regulatory frameworks relating to privacy, data sharing, data protection and consent processes. It then suggests how ethical-legal governance can be streamlined to ensure responsible data sharing in the health data ecosystems.

020

Data and sample stewardship in the African context: underlying benefit sharing

Collet Dandara
Africa Academy of Sciences (AAS) and the South African Academy of Sciences (ASSAf)

Genomics research and data generated is on an upward trajectory among Africans in Africa but remains scarce compared to other global populations. Even in its scarcity, genomic data from Africans remains extremely valuable due to the abundance of diverse genetic variants often absent in populations across the world. Humans originated in Africa, and African genomes retain more genetic diversity affording opportunities to improve human genome reference sequences through fine-mapping resolution. The history of research among Africans has not been a rosy one, often associated with "helicopter" research that did not meaningfully including African investigators and tended not focussed on Africans "questions" or "problems". Thus, with the rising interest in the genomes of Africans, it is important that proper Stewardship is exercised on the access to both biological samples and data that is generated from these samples. In this lecture I will comment on the experiences of exercising such stewardship as part of an African Data and Biospecimens Access Committee (DBAC). Through DBAC we have catalysed connections through access to African data, which are contributing to capacity and expertise development. Requests seeking to answer questions that contribute to African populations have been "favoured" while those which appear to have a greater risk of stigmatising African populations, not supported. The experience has been an evolving one, with lessons learnt. Ultimately, stewardship of African data is rests on the need to ensure responsible of data and biospecimens emanating from Africans and African researchers.

021

Clinical Registries: A transitional bridge to personalized Medicine

Rabii Razgallah
Department of Community Medicine of Sousse

For several years, Tunisian Scientific Societies have rushed to manage clinical registries with the aim of satisfying a hunger for data and exploring the profile of the targeted populations, in cardiovascular prevention, oncology, primary care conditions and several other interests of the health sector. This data collection dynamic has resulted in a rich and up-to-date scientific publications as well as the development of clinical practice guidance.
In this way, a clinical registry is a very useful reflection of the targeted population, which makes it possible to describe its current state, the challenges encountered in its routine care, but also to guide in a more targeted manner the accurate research questions to be explored. A clinical registry is positioned as a data warehouse, designed in specific methodological references and aiming to get as close as possible to the dynamics of the disease in its individual and populational environments. Yet, with the advent of artificial intelligence, real-life data of clinical registries take on deeper dimension.
In 2019, the Tunisian Association for the Study and Research on Atherosclerosis (ATERA) conducted a national survey of 13,610 subjects aged over 25. The ATERA survey, led by Pr Amani Kallel and Pr Riadh Jemaa, found a very high prevalence of cardiovascular diseases, with 22% diabetes and 44% high blood pressure. Another clinical registry, NATURE-HTN (National Tunisian Registry on Hypertension), conducted by the Tunisian Society of Cardiology and Cardiovascular Surgery, with 25,890 hypertensive patients, showed that less than 20% of treated patients had well-controlled blood pressure figures. In 2023 and 2024, two national surveys conducted by Pr Jannet Labidi, nephrologist, under the aegis of the Tunisian Society of Nephrology, Dialysis and Renal Transplantation, among more than 21,000 diabetic and/or hypertensive patients, showed a very high level of chronic kidney disease. In total, nearly twenty large-scale clinical registries were conducted in Tunisia, using digitalized data capture systems, in accordance with regulatory requirements and specifications for the security of personal data and health data. These research projects have generated a very active dynamic in structuring the medical data and have enabled the development of intelligent systems for therapeutic counselling and drug development. In this direction, Pr Amel Ben Ammar El Gaïed and Dr Nejla Stambouli with the support of a scientific team were able to identify a biological marker (sCXCL16) involved in predicting the mortality of patients with COVID-19. Involving bioinformatics modeling, this marker paves the way for precision medicine, through the development of new treatments based on vaccines or immunotherapy, as well as the design of screening reagents for lethal forms of the disease. Another experiment coordinated by Pr Jannet Labidi, as part of the surveys carried out by the Tunisian Society of Nephrology, Dialysis and Renal Transplantation, paved the way for the digitalization of care pathways for the improvement and personalization of the management of chronic diseases, based on harmonized processes and the development of intelligent algorithms.
On a more global scale, clinical registries are striding the path of decentralized clinical trials and "Real World Data" projects, to become a tool for evaluating pharmaceutical products (example: FDA guide in 2023 "Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products"). And thus several questions arise about the real interest of the data captured by the clinical registries, and the impact they have on the personalization of health care, on the ethics of the reallocation and reuse of real-world data, on good data management practices and on upcoming perspectives in the development of increasingly "intelligent" health products.

022

Bioinformatics: With great power comes great responsibility

Houcemeddine Othman
Department of Genetics at Farhat Hached University Hospital, Sousse, Tunisia and University of the Witwatersrand in South Africa

The paradigm in biomedical research has significantly shifted towards OMICS approaches, which involve analyzing massive and complex datasets. This shift necessitates a greater involvement of bioinformatics to manage and interpret the vast amounts of data generated, ultimately advancing our understanding of biological systems and disease mechanisms. For decades, bioinformatics has been a cornerstone of the biomedical research landscape in Tunisia, continuously evolving to meet new challenges namely to handle the influx of data generated by OMICS studies. However, the current implementation of bioinformatics research in both academia and clinical settings has faced several challenges, leading to suboptimal utilization. These challenges include limited resources, issues with reliability and reproducibility, and underappreciated capacities. With the rapid pace of advancements enabling greater democratization of sequencing, the need to address these issues becomes an urgency.

023

The Impact of AI and Language Models in Genomics Research for Industry

Marie Lopez
Instadeep

Artificial intelligence (AI) and advanced language models are transforming genomics research, providing new tools for industries like biotechnology, agriculture, and healthcare. Two key innovations, the Nucleotide Transformer and Agro Nucleotide Transformer, apply AI to DNA analysis, enabling high-precision predictions at the single-nucleotide level. This technology allows businesses to better understand genetic data, improve product development, and optimize processes in areas such as drug discovery and crop improvement.
SegmentNT, another AI model, is designed for pinpointing specific elements within DNA sequences, providing even more accurate insights into genetic structures. These AI-driven models outperform traditional methods, thanks to their ability to process large and diverse datasets from human and plant genomes. The Agro Nucleotide Transformer, for example, is specialized for crop species and offers state-of-the-art results in predicting gene expression, a key area for improving agricultural productivity.
The release of these open-source models means that companies and research institutions can now use the technology to drive innovation. With simple integration into existing systems, businesses can apply these models to a wide range of tasks, from improving crop yields to accelerating genomics-based healthcare solutions.
The advanced features of these models, such as improved accuracy and the ability to handle larger data, make them a powerful tool for companies looking to leverage genomics for competitive advantage. As industries continue to integrate AI into genomics, these breakthroughs will shape the future of precision medicine and agriculture.

024

Tunisia's Positioning in Precision Medicine within the Framework of International Cooperation
Helmi Merdessi

Helmi Merdessi
Tunisian Ministry of Higher Education and Scientific Research

Oral Communications Session

025

Oral communication 1: Next generation sequencing reveals novel congenital disorders of glycosylation variants in SRD5A3, PIGN and PIGT variants in North African families

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Introduction: Congenital disorders of glycosylation (CDGs) are a large group of inborn metabolic disorders leading to multi-systemic diseases with significant clinical and genetic heterogeneity. In Africa, CDGs are under-diagnosed, partly due to limited access to advanced genetic testing. Methods: In this work, we report 8 patients from 4 unrelated North African families (F1-F2-F3-F4) referred for neurodevelopmental disorders (NDDs). Four patients underwent clinical exome sequencing. To better understand the impact of each variant, we performed 3D modelling for F1 and functional analysis using Knockout HEK293 cells transfected with the mutant for F2.
Results: We identified three (likely) pathogenic variants. A homozygous missense variant in the SRD5A3 gene (p.Ser154Pro) in F1. Two Tunisian sisters were referred for syndromic intellectual disability associated . Analysis of molecular dynamics simulations using 3D modelling showed that (p.Ser154Pro) variant is located in a high potential active site of the SRD5A3 protein and is able to reduce its catalytic efficiency. A homozygous missense variant in the PIGT gene (p.Arg507Trp) in F2. the Libyan boy was referred for severe psychomotor retardation and epilepsy. functional analysis demonstrated that the p.Arg507Trp variant leads to mildly reduced activity of the protein. A homozygous missense variant in the PIGN gene (p.Arg565Leu) segregated in three affected siblings in F3 and two affected brothers in F4, all referred for epileptic and developmental encephalopathy.
Conclusion: Our work highlights the involvement of CDGs as a metabolic cause of NDDs and the contribution of next generation sequencing to the diagnosis of this entity

Key words: Next generation sequencing, Neurodevelopmental Disorders, Congenital disorders of glycosylation, SRD5A3, PIGN, PIGT

026

Oral communication 2: **Molecular Investigation of Rare Ichthyosis Disorders in Tunisian Patients: Enhancing Diagnosis and Understanding of the Genetic Landscape by Uncovering Novel Variants through Exome Sequencing**

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Introduction: Ichthyoses are a diverse group of rare disorders characterized by abnormal skin scaling and generalized hyperkeratosis, with varying clinical presentations. The genetic diversity and overlapping phenotypes raise challenges in diagnosing ichthyoses in many Tunisian patients. This study aimed to assess the effectiveness of Exome Sequencing (ES) in identifying genetic variations in Tunisian patients with different subtypes of ichthyosis to improve molecular diagnosis.
Methods: ES was performed on 46 patients suspected of having various forms of ichthyoses.
Results: Variants were detected in 38 (83%) patients. Two patients had compound heterozygous variants in the TGM1 gene. In a subgroup of 23 patients with autosomal recessive congenital ichthyosis (ARCI), 7 variants were found in CYP4F22, 7 in NIPAL4, 2 in CERS3, 1 in ALOXE3, 1 in ALOX12B, and 5 in TGM1. A new variant in the KRT1 gene was discovered in a patient with epidermolytic hyperkeratosis. In contrast, another patient with the same phenotype had a heterozygous pathogenic variant in the KRT10 gene. Twelve patients carry LORICRIN, ABHD5, SLC27A4, RAG1, FLG and STS gene variants, corresponding respectively to Vohwinkel syndrome with ichthyosis, Chanarin-Dorfman syndrome, premature ichthyosis syndrome, Omenn syndrome, ichthyosis vulgaris and X-linked ichthyosis, whereas they were clinically suspected of having the ARCI phenotype. Overall, ES revealed 32 pathogenic and likely pathogenic variants, and 8 variants of unknown significance (VUS), of which 13 were novel.
Conclusion: The high detection rate of pathogenic variants (83%) highlights the utility of ES in improving molecular diagnosis and guiding personalized management of these complex disorders. Additionally, discovering new variants enhances the understanding of the genetic landscape of ichthyoses, aiding in better diagnostic accuracy and the potential development of targeted therapies.

Key word: Ichthyoses, Exome Sequencing (ES), Genetic variations, Rare diseases, Genetic landscape

027

Oral communication 3: Comparative genomics reveals an unpreceded number of genome rearrangements in addition to the expected nucleotide changes

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Introduction: Human disease vectors, like mosquitoes, play a key role in the transmission of serious diseases, posing a major public health challenge. Bacillus thuringiensis israelensis is commonly used as a biopesticide due to its invertebrate specific toxins. However, the accumulation of spores in the environment can cause ecological problems. This study aims to reduce sporulation and to increase toxin production through random mutagenesis.
Methods: Nitrous acid mutagenesis was applied on strain BUPM98. The genomes of the wild-type strain and its mutants were sequenced using Nanopore technology. Genome assembly was performed with Flye-2.9.3, identification of structural variants using MUMmer-3.23. Bakta-1.9.2 was used for genomic annotation. Biopesticidal genes were detected using IDops and InterProScan. Mobile genetic elements were identified using Phastest and ISEScan-1.7.2.3. COGclassifier was used to categorize functional affected genes.
Results: BUPM98 mutagenesis was employed to generate oligosporogenic and hyperproducer strains. A rigorous selection process identified mutant strains with improved toxin yield and decreased sporulation. Comparative genomics revealed responsible genomic modifications. This comparative genomics approach revealed extensive activation of mobile genetic elements, including an activation of phage replication
Conclusion: Some of the observed phenotypic changes in the mutant strain correlate with mobile genetic elements. A final prove of the connection between mobilome and the phenotypes impacting Cry-toxin production and sporulation remains to be done. These findings suggest that random mutagenesis induces genome plasticity in addition to the expect point mutations and thereby explain the multiple observed phenotypes

Key words: Bacillus thuringiensis israelensis, Human disease vectors, Mutagenesis, Genome Sequencing (NGS), Nanopore technology, Mobile genetic elements

028

Oral communication 4: Genetic and Clinical Features of Inflammatory Breast Cancer in Tunisia: Insights from a 50-Patient Cohort

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Introduction: Inflammatory Breast Cancer (IBC) is a rare and aggressive subtype of breast cancer characterized by distinct clinical and pathological features. This study investigates the epidemiological and genetic characteristics of IBC in the Tunisian population. Methods: A cohort of 50 patients have been studied. A genetic investigation in 24 patients using sanger and /or Next generation sequencing have been conducted. Bioinformatics tools were employed to interpret the functional significance of the identified genetic variants
Results: The average age at diagnosis was 49.1 years, with 22% of patients diagnosed at a young age (≤35 years), including two cases of diagnosed during pregnancy. A family history of breast cancer was reported in 40.8% of cases. The predominant molecular subtype was Luminal B (57.5%), while 20% of tumors were either triple-negative or HER2-enriched. Nearly 50% of tumors were classified as grade III, and over 97% of patients exhibited a high Ki67 index (>14%). Nearly 30% of the patients developed distant metastases. Our genetic analysis revealed BRCA mutations in four patients, three of which were located within the BRCA2 gene, including a large deletion spanning exons 1–16. Additionally, relevant variants were detected in the STK11 (c.836G>T), CHEK2 (c.710C>T), and MUTYH (c.419A>G) genes, along with a novel mutation in the RAD54L gene. Copy number variations (CNVs) were also observed in the ABRAXAS1, XRCC2, and FANC genes
Conclusion: Young age at diagnosis, a high proportion of familial breast cancer cases, and aggressive tumor profiles were key features of the IBC cases in this study. These findings offer valuable insights into the molecular mechanisms underlying IBC, providing a deeper understanding of the disease in Tunisia and highlighting its relevance to other North African populations with similar epidemiological and genetic profiles.

Key words: Inflammatory Breast Cancer, Next generation Sequencing, Epidemiological features, Genetic characteristics

029

Oral communication 5: Challenge of secondary findings in Whole Exome Sequencing: About a Tunisian family

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Introduction: Secondary findings (SFs) are genetic variants identified in the context of genomic testing for a specific clinical indication but unrelated to that condition. While clinicians generally support returning SFs from a curated list of actionable genes, it remains controversial in pediatric participants. Key concerns include the unpredictability of the condition due to incomplete penetrance, variable expressivity, uncertain age of onset, and unknown severity of the condition.
Methods: Report of a patient referred to our department for a severe intrauterine growth retardation, microcephaly and developmental delay. After DNA sampling and consent signing, a WES was performed. Results: The patient is a consanguinous12-year-old boy with a history of a congenital cataract operated at the age of 5 years. He has a 5-year-old sister with a similar clinical presentation. Clinical examination revealed facial dysmorphia, micropenis, genu valgum, ligament hyperlaxity, pectus excavatum, loose skin and microcephaly. Brain MRI showed cortical atrophy. WES revealed two variants: a pathogenic homozygous missense variant in the ALDH18A1 gene confirming a Cutis Laxa syndrome and a heterozygous likely pathogenic variant in the LDLR gene, associated with familial hypercholesterolemia. This gene is considered as one of 81 medically actionable genes list established by the ACMG. As consent was signed, familial segregation of the two variants was realized to establish an adequate management of patients and their parents
Conclusion: Our observation highlights the paramount importance of reporting secondary findings for early intervention and management of conditions that might otherwise go undetected until later in life.

Key words: Secondary findings, Cutis Laxa, Familial hypercholesterolemia,WES

030

Oral communication 6: Comparative Transcriptomic Analysis of U87 Glioblastoma Cells Treated with Various Therapeutic Agents

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Introduction: Glioblastoma multiforme is an aggressive brain cancer with limited treatment options. This study aimed to assess the transcriptomic response of U87 glioblastoma cells to various therapeutic agents, including Belinostat, long-term AsiDNA, A34, A41, A80, and A98, using RNA-seq data. Methods: U87 cells were treated with the drugs, and RNA-seq data were obtained from the SRA database. Reads were processed and aligned to the human genome using HISAT2. Differential expression was analyzed with EdgeR, and DAVID was used for functional enrichment analysis to identify pathways affected by each treatment
Results: The analysis revealed distinct molecular responses in U87 glioblastoma cells for each drug. Belinostat upregulated DNA damage response and apoptosis genes, promoting cancer cell death. AsiDNA downregulated DNA repair genes, increasing apoptosis susceptibility. A34 enhanced cytokine production, possibly stimulating immune responses, while A41 affected extracellular matrix-related genes, inhibiting cell adhesion and migration. A80 and A98 downregulated ribosomal proteins, impairing protein synthesis and reducing cell proliferation. A98 also disrupted cytoskeletal integrity, impacting cell division and tumor growth. These distinct mechanisms suggest that each treatment targets key cancer-related pathways, highlighting the potential for combination therapies to improve outcomes.
Conclusion: RNA-seq analysis revealed that the treatments impact critical processes such as DNA repair, immune modulation, and protein synthesis. These findings suggest potential strategies for combination therapies to enhance glioblastoma treatment efficacy.

Key words: Glioblastoma, U87 cells, RNA-seq, Differential expression, Cancer treatment.

031

Oral communication 7: A Machine Learning Approach for Predicting Major Cardiovascular Events in Coronary Patients Receiving Clopidogrel: A Clinical and Pharmacogenetic Perspective

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Introduction: Cardiovascular diseases are the leading cause of mortality in Tunisia (26%) involving both genetic and environmental factors. Although therapeutic management of these diseases has increased survival, long-term cardiovascular morbidity and mortality remain high. In this perspective, prediction systems using artificial intelligence appear as a source of hope to improve patient care and life quality. The objective of this study is to develop and validate machine-learning models that predict the risk of major cardiovascular events (MACE) using clinical, biological and pharmacogenetic data of 202 patients from the CHU Hédi Chaker department, Sfax for one-year follow-up under clopidogrel therapy.
Methods: Through the clinical and biological data, the genotyping results of 47 SNPs located at the genes coding for enzymes involved in intestinal absorption (ABCB1) and hepatic metabolism (Cytochrome CYP450 and Paraoxonase-1(PON-1)) of clopidogrel were recorded and analyzed by the Sequenom MassARRAY platform. The following 6 models (logistic regression, Decision trees, SVM, XGBOOST and random forests) were developed and then evaluated on the test set using several performance metrics.
Results: The Lasso logistic regression was found to be the best global model because of its optimal balance between accuracy (0.78), recall (0.78), F1-score (0.76) and AUC (0.82), for an optimal CUTOFF value of 0.18. The significant factors were: age, administration of beta blockers, hypertension, coronary status and 21 SNPs located within CYP2B6, CYP1A2, CYP3A5, ABCB1 and PON1 genes.
Conclusion: A prognostic model based on the genotyping of pharmacogenes and cardiovascular risk factors has been developed and validated, which can be utilized to predict (MACE) in coronary patients in Tunisia.

Key words: Cytochrome P450, Coronary Artery Disease, MACE, Clopidogrel, pharmacogenes, Machine Learning, Prognostic Model

032

Oral communication 8: Characteristics of H3K27M-mutant diffuse gliomas with a non-midline location

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Introduction: Diffuse midline gliomas (DMG) with H3K27 alterations (H3K27M-DMG) are a highly aggressive form of brain cancer. In rare cases, H3K27 mutations have been observed in diffuse non-midline gliomas (DNMG). It is currently unclear how these tumors should be classified. Herein, we analyze the characteristics of DNMG with H3K27M mutations.
Methods: We reviewed the clinical, radiological and histological characteristics of all patients with an H3K27M mutated diffuse glioma diagnosed in our institution, between 2016 and 2023. We then performed a molecular characterization (DNA methylation profiling, whole genome and transcriptome sequencing or targeted sequencing) of patients with an H3K27M-mutant DNMG and reviewed previously reported cases.
Results: Among 51 patients (18 children and 33 adults) diagnosed with an H3K27M diffuse glioma, we identified two patients (4%) who had a non-midline location. Including our two patients, 39 patients were reported in the literature with an H3K27M-mutant DNMG. Tumors were most frequently located in the temporal lobe (48%), affected adolescents and adults, and were associated with a poor outcome. Median age at diagnosis was 19.1 years. In DNA methylation analysis, H3K27M-mutant DNMG clustered within or close to the reference group of H3K27M-mutant DMG. Compared to their midline counterpart, non-midline gliomas with H3K27M mutations seemed more frequently associated with PDGFRA alterations.
Conclusion: DNMG with H3K27M mutations share many similarities with their midline counterpart, suggesting that they correspond to a rare anatomical presentation of these tumors. This is of paramount importance, as they may benefit from new therapeutic approaches such as ONC201.

Key words: Pediatric glioma, H3K27M, Methylation, Non-midline, Diffuse midline glioma H3 K27-altered, Diffuse intrinsic pontine glioma, H3K28M

033

Oral communication 9: Genetic and Phenotypic Spectrum Of Inherited Retinal Dystrophies In A Series Of Tunisian Patients

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Introduction: Inherited retinal dystrophies cluster a wide group of congenital retinal degenerative diseases caused by alteration in genes with critical roles for retinal function and support. These entities are characterized by various inheritance patterns and wide phenotypic and genetic heterogeneity, making genetic diagnosis a challenging task. We report the clinical and genetic findings in a cohort of Tunisian patients molecularly investigated for IRD by next-generation sequencing (NGS).
Methods: The study included all the patients referred to our genetic department for molecular investigation of IRD over 12 years (2013–2024). NGS was performed on genomic DNA using either whole exome sequencing (WES) or multigene panel analysis (MGP). In familial cases, sanger sequencing was used in the affected siblings after identification of the genetic variation in the proband by NGS.
Results: Sixteen patients were enrolled in the study (12 isolated cases and four familial cases). The ocular manifestation was isolated in nine cases, whereas it was part of a syndromic presentation in seven patients. MGP, performed in five patients, revealed a clinically relevant result in four cases. WES, carried out in ten patients, identified a pathogenic/likely pathogenic variant in nine cases. In syndromic cases of IRD, four genetic syndromes were confirmed: Cohen syndrome, Refsum disease, Joubert syndrome and Mental retardation autosomal dominant 54. In the isolated cases of IRD, the main retained diagnosis was Leber congenital amaurosis with various affected genes (CRB1, RP65, AIPL1).
Conclusion: NGS allowed a considerable etiologic yield in our cohort. The impact of the molecular confirmation was crucial for optimizing the clinical management of the patients and the genetic counseling in the families

Key words: Inherited retinal dystrophies, Leber congenital amaurosis, Next-generation sequencing

Posters' Session

034

Poster 1: Optimazing Genetic Testing Strategies for Congenital Malformations Diagnosis

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Introduction: Congenital malformations CMs are developmental anomalies affecting approximately 3% of live births and 20% of stillbirths. Genetic causes are responsible for up to 25% of cases. Given recent technological advances in genetics, what strategy should be adopted to explore the genetic causes of CMs?
Methods: In our study, we examined a cohort of 30 patients presenting with CMs at the Genetics Department of Farhat Hached University-Hospital Sousse, between January 2019 and June 2021. All patients initially underwent karyotyping, followed by array-based comparative genomic hybridization aCGH. Fluorescence in-situ hybridization FISH was performed on certain patients and whole exome sequencing WES was conducted on five patients.

Results: ACGH identified four anomalies previously detected by karyotyping in four patients. Among the 26 patients with normal karyotypes, aCGH revealed three additional chromosomal anomalies. Thus, positive results could be obtained in 23.3% of cases if aCGH was performed as a first-line test, compared to 13.3% when karyotyping is performed as the first-line test. WES investigations were further pursued for five patients: four patients whose aCGH results were negative and one patient carrying a copy number variant CNV of uncertain significance identified by aCGH. WES was positive for two patients.
Conclusion: Based on our findings, we propose performing aCGH as a first-line test in the exploration of CMs. In case aCGH results are positive, we suggest conducting FISH and karyotyping to elucidate the chromosomal mechanism underlying the CNV and to refine genetic counseling. For cases with negative aCGH findings, we recommend proceeding with WES and potentially whole genome sequencing.

Key words: Congenital malformations, Array-CGH, NGS, WES

035

Poster 2: ALFI Syndrome and Structural Chromosome Rearrangement: Clinical and Cytogenetic Particularities

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Introduction: Alfi syndrome is a rare chromosomal disorder resulting from a 9p monosomy. It is characterized by psychomotor delay(PD), trigonocephaly, facial dysmorphism(FD), genital anomalies, and other congenital malformations. The chromosomal aberration underlying this syndrome is variable and may influence the phenotypic expression of the syndrome.
Methods: We report the cases of two patients, P1 and P2, respectively aged 1 month and 2 years and 3 months who presented to the genetics department of Farhat Hached Hospital Sousse. P1 was referred for suspected trisomy 21, while P2 underwent molecular cytogenetic analysis for a mosaic ring chromosome 9.
Results: Karyotyping and Fluorescence In-Situ Hybridization (FISH) in P1 demonstrated a derivative chromosome 9 resulting from an apparently balanced reciprocal translocation between paternal chromosomes 2 and 9. Cytogenetic explorations of P2 confirmed the presence of a de novo mosaic ring chromosome9 in karyotyping; Array comparative genomic hybridization (aCGH) showed an isolated 18Mb deletion at 9p24.3-p22.1 encompassing 48OMIM genes, and FISH confirmed the 9p subtelomeric deletion and the integrity of the 9q subtelomeric region. P1 and P2 presented some common features as trigonocephaly and FD. The differences in clinical features may be explained by the variation of the size of the 9p deletion, and the presence of 2q duplication in P1. A characterization of the chromosomal anomalies in P1 by aCGH is necessary to establish a precise genotype-phenotype correlation.
Conclusion: Regardless of the underlying chromosomal anomaly, 9p deletion exhibits common clinical manifestations. The study of multiple cases could help better refine phenotype featuresassociated with this syndrome.

Key words: Structural chromosome rearrangement, Congenital malformations, Array-CGH

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Poster 3: From The Gene to The Molecule: A Case Report Of Leukodystrophy Type 18 And Targeted Therapy

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Introduction: Leukodystrophies are hereditary disorders that disrupt the axon-glia unit, primarily affecting the white matter of the central nervous system. The DEGS1 gene, associated with autosomal recessive leukodystrophy type 18 (HLD18), encodes a dihydroceramide desaturase that catalyzes a critical step in sphingolipid biosynthesis pathway. Sphingolipids are essential for myelin genesis and maintenance. Currently, there is no cure for leukodystrophies, and treatment primarily focuses on symptom management and supportive care.
Methods: In this case report, we describe a comprehensive clinical and genetic evaluation and management of a patient diagnosed with HLD18 using exome sequencing (ES).
Results: A 1-year-old female proband, was referred to the department of Genetics at Mongi Slim Hospital for global developmental delay and early-onset epilepsy. Despite well-maintained antiepileptic drug treatment, her seizure frequency progressively worsened. Physical examination showed dysmorphic features, generalized hypotonia, and abolished deep-tendon reflexes. The patient's cerebral MRI was normal, and laboratory tests revealed hypocholesterolaemia. ES identified a biallelic missense variant in the DEGS1 gene: NM_003676.4:c.764A>G (p. Asn255Ser), classified as pathogenic according to ACMG criteria. Following clinical and genetic assessment, the diagnosis of HLD18 was confirmed. Based on the underlying genetic anomaly, Fingolimod, a medication typically used in the treatment of multiple sclerosis, was proposed as a potential treatment option for this patient. ES not only facilitated an accurate diagnosis but also helped explore novel treatment options.
Conclusion: This case illustrates the significance of ES in diagnosing and managing rare diseases and highlights the necessity of pursuing tailored made treatments based on the underlying genetic causes.

Key words: Leukodystrophy Type 18, Exome Sequencing, DEGS1, Fingolimod, Precision Medicine

037

Poster 4: Diagnosis and Management of invdupdel(8p) Syndrome in a Tunisian Patient characterized by chromosomal microarray analysis

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Introduction: Inverted duplication associated with terminal deletion of the short arm of chromosome 8p (invdupdel(8p)) is a chromosomal rearrangement occurring in 1 in 10,000 to 30,000 newborns. It is clinically characterized by distinctive dysmorphic features, neurodevelopmental delay, behavioral issues, congenital heart defects, and frequent brain malformations. Clinical severity varies depending

on the rearrangement's size and the expression and dosage effect of the genes involved.
Methods: We report the observation of a patient referred for global developmental delay and dysmorphic features. Cytogenetic investigation included standard R-banded Karyotype, followed by chromosomal microarray analysis (CMA) with 8×60K microarray format. Results: The 2-year-old girl proband was a the first-born child of healthy unrelated parents. She suffred from severe psychomotor delays. Physical examination showed microcephaly and dysmorphic traits along with axial hypotonia and peripheral hypertonia. Transfontanellar ultrasound showed agenesis of the corpus callosum. Karyotype analysis showed the formula 46,XX,add(8)(p23). Parental karyotypes were normal. CMA revealed a 6.69 Mb terminal deletion at 8p23.3p23.1, in addition to a 30.7 Mb duplication at 8p23.1p11.1. Our patient's clinical presentation was in line with that from literature patients with invdupdel(8p), particularly the specific dysmorphic features and the corpus collosum agenesis. The neurodevelopmental phenotype could be explained by the additional effect of terminal 8p deletion and the interstitial 8p duplication. In the light of the cytogenetic findings, an appropriate clinical management was planned for our patient, including cardiac ultrasound, ophthalmic investigation and specialized behavioral management.
Conclusion: Besides characterizing the chromosomal findings on karyotype, CMA was crucial for optimizing the clinical management for the patient and the genetic counselling for the family.

Key words: Chromosomal microarray analysis, Invdupdel(8p) Syndrome, Dysmorphic features, Neurodevelopmental delay

038

Poster 5: The Role Of Epigenetic Factor Macroh2a1.1 On DNA-Damaging Response

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Introduction: The main goal for any cells is to pass integrated genetic material to the next generation. To achieve this target an appropriate DNA damage repair system must be chosen by cell. Several mechanisms are involved in detecting DNA damage and repair. However, the factors that mediate these processes are not fully understood. Several studies have confirmed that macroH2A1.1 is involved in cell proliferation and suppression of gene transcription. MacroH2A1- depleted Mice (Knock out, KO) seem to be more vulnerable to irradiation-induced death in vivo (data not published). Here we wanted to investigate the potential role of an epigenetic protein macroH2A1 in DNA damage response.
Methods: In the current study we investigated the sensitivity of mouse embryonic fibroblast cells (MEFs) treated with the anticancer drug doxorubicin. We analysed both the growth inhibition by doxorubicin and doxorubicin-induced cell death in the macroH2A1.1 KO and WT MEFs.
Results: The patient initially responded well to pembrolizumab, maintaining disease control for several years. She tolerated the 31 doses of treatment with minimal side effects. However, over time, imaging revealed the development of a new mass in her left lung. A biopsy confirmed that this mass was metastatic squamous cell carcinoma, originating from the nasopharyngeal carcinoma. Despite the tumor continuing to express PD-L1, the appearance of lung metastasis indicated that resistance to pembrolizumab had developed. While genetic profiling was explored, no definitive mutations responsible for the resistance were identified. This case emphasizes the challenges of treating recurrent NPC, especially with prolonged immunotherapy, and suggests that combination treatments may offer a way to overcome treatment resistance and improve patient outcomes.The study showed that there was no significant change observed in the responses of these cells to doxorubicin. Notably, proliferation rate of macroH2A1.1 KO cells was less than (Wild Type, WT), and interestingly, only at higher dose of doxorubicin the proliferation rate of macroH2A1.1 KO MEFs was increased.
Conclusion: Since macroH2A1.1 significantly recruited to the sites of DNA damage by irradiation, these findings illustrated the importance of genotoxic insults in determining the ability of macroH2A1.1 to influence the DNA damage response.

Key words: Epigenetics, DNA damage, Histone H2A, Cell proliferation.

041

Poster 6: Feedback and challenges of Next Generation Sequencing in Tunisia: Experience of Targeted Panels

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Introduction: Next-Generation Sequencing (NGS) in Tunisia is limited by high costs and infrastructure challenges, resulting in many patients remaining undiagnosed. Since 2016, our laboratory has integrated NGS to investigate multigenic disorders, including deafness and neurodevelopmental disorders using Miseq Illumina platform. This research was funded through both national and international projects.
Methods: Custom Targeted NGS testing panels were applied to over 180 patients using Sure Design (Agilent) and Design Studio (Illumina). This approach was adapted to explore 30 patients with non-GJB2-related hearing impairment (HI) (30-gene panel), 60 with a specific dysmorphic syndromes (DS) (90-gene panel), and 88 with developmental and epileptic encephalopathies (DEE) (116-gene panel). Clinical exome sequencing usingTruSight One Illumina panel was performed for 30 patients with intellectual disability without clinical orientation.
Results: The NGS allowed us to confirm the genetic diagnosis for 35% of DEE and ID patients, and 50% of HI and DS patients, identifying 75 pathogenic or likely pathogenic variants, 50% of which were newly described. Additionally, over 20 variants of unknown significance were identified as candidate variants. Four variants of DI/DEE were identified as recurrent in the Tunisian population, as they were found in other families from the same region. Diagnostic confirmation led to enhanced patient care and identified potential targets for precision medicine in specific DEE syndromes. It also facilitated the provision of appropriate genetic counseling for families, including the option of prenatal diagnosis, which was carried out for ten families.
Conclusion: Our work over the past six years has allowed us to gain expertise in the field of NGS, from library preparation to data analysis, and to better understand the genetic architecture of these pathologies in Tunisia using targeted panels that reduce the cost of NGS testing. Expanded access to NGS would provide essential public health benefits by improving diagnostic capabilities for genetic disorders.

Key words: Next-Generation Sequencing, Targeted Panel, Hearing Impairment, Intellectual disability, Developmental and epileptic encephalopathies, Precision medicine, Genetic counseling

042

Poster 7: Kabuki Syndrome: A Report on Two Cases

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Introduction: Kabuki syndrome is a rare genetic disorder with a prevalence of 1 in 32,000. It is caused by mutations in the KMT2D or KDM6A genes.
Methods: We report the clinical presentation of Kabuki syndrome in two patients.
Results: We present observations of two patients with Kabuki syndrome. The first case is a 9-year-old boy from a non-consanguineous marriage. He was admitted at the age of 3 for a convulsive state, global developmental delay, and characteristic facial features: arched eyebrows, long eyelashes, and lower eyelid eversion. The electroencephalogram showed a normal background rhythm with paroxysmal anomalies. Magnetic resonance imaging, karyotype (46XY), and testing for fragile X syndrome were normal. The second case describes a 10-year-old girl from a consanguineous marriage, with a history of cleft palate. She presents with mixed hearing loss, dental anomalies, growth retardation, intellectual disability, and language disorders. She consulted for thrombocytopenic purpura. On examination, she had arched eyebrows, bilateral ptosis, elongated eyes, and a flattened nasal tip. The diagnosis of Kabuki syndrome in both cases was suggested and confirmed by the KMT2D gene mutation. They are currently being followed up in our clinic, a genetic disease service, by an ENT specialist, a child psychiatrist, and a speech therapist.
Conclusion: These two cases highlight the importance of a multidisciplinary approach in the management of Kabuki syndrome, with early clinical assessment and personalized follow-up.

Key words: Kabuki, Hearing loss, Intellectual disability, Autism

043

Poster 8: Genetic investigation of non- syndromic intellectual disability in a Tunisian population cohort

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Introduction: Non-syndromic intellectual disability (NSID) is a rare hereditary cognitive disorder characterised by early-onset cognitive impairment as a sole disability. NSID may be associated with autism, spectrum, pharmacoresponsive epilepsy, corpus callosum agenesis and neuromuscular deficits. The NSID's high heterogeneity complicates the identification of its aetiology. Research on NSID in the Tunisian population is limited, and its prevalence and genetic factors remain unknown. This study aimed to explore the genetic profiles of 24 Tunisian patients with NSID, referred to the Genetics Department at Farhat HACHED University Hospital, Sousse, between January and September 2024.
Methods: A karyotype was performed on all patients. Fragile X syndrome was then tested in all males and in some females with a personal or familial history suggestive of this syndrome. Based on the phenotypic profile, various microdeletion syndromes and subtelomeric gene microrearrangements were investigated. Clinical exome sequencing was performed for all patients with negative results from previous tests. Results: The cohort, with a mean age of 11 and a sex ratio of 15:8, exhibited low IQ scores, developmental, psychomotor, and speech delays. Karyotyping showed a normal chromosomal formula. Fragile X syndrome was absent in males, with no suggestive signs in females. Microdeletion tests and clinical exome sequencing are ongoing.
Conclusion: Preliminary results have not identified specific genetic causes. Therefore, we plan to establish a genetic basis for NS-ID by developing a specialized NS-ID gene panel to enhance genetic and prenatal counselling, particularly in consanguineous cases.

Key words: NS-ID, Tunisian population, Karyotype, Fragile X syndrome, Microdeletion syndromes, Clinical exome, NS-ID gene panel

044

Poster 9: In vitro functional characterization of androgen receptor gene mutations localized within the ligand binding domain.

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Introduction: Androgens are critical for male sex differentiation. Their actions are mediated by the androgen receptor (AR). Mutations disrupting AR function result in the androgen insensitivity syndrome (AIS) which is a rare X-linked disorder in which 46,XY individuals have complete or partial impairment of androgen action. Clinically, AIS is characterized by a wide spectrum of genital phenotypes. It ranges from complete AIS (CAIS) over different forms of partial AIS (PAIS) to mild forms (minimal AIS, MAIS). In this study, we identified a novel AR mutation p.R856L in a CAIS female patient who was complaining of inguinal hernia.
Methods: To investigate the functional properties of p.R856L, we performed functional studies of this novel mutation in comparison to the already described mutations p.R856C and p.R856H in different assays. For this purpose, we recreated AR p.R856L, p.R856H and p.R856C mutations by site directed mutagenesis. Then, we studied their impact on both transactivation ability of full-length AR constructs using two structurally different promoters fused separately to a reporter gene and expressed in two different cell lines as well as the effects on AR N/C interaction. Results: Our results demonstrated that all mutations were able to transactivate the (ARE)2-TATA promoter expressed in CHO cells more highly. Moreover, we confirmed the pathogenicity of the p.R856L and p.R856C mutations, and their associations with complete AIS. In contrast, the p.R856H mutation, which is associated with a spectrum of AIS phenotypes, showed less severe transcriptional constraints.
Conclusion: Altogether, our studies allowed us to better characterize arginine residue at p.R856 position.

Key words: Androgen insensitivity syndrome, Androgen receptor (AR), Disorders of sexual development, XY DSD

045

Poster 10: The potential of hTERT gene as a diagnostic and prognostic marker in hematologic malignancies

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Introduction: The hTERT gene encodes the catalytic subunit of telomerase reverse transcriptase, responsible for maintaining the length of telomeres. Thus, this enzyme is strongly involved in the process of tumor cell transformation, its activity is absent in most normal somatic tissues. Besides, it has been demonstrated that the level of hTERT expression is correlated with telomerase activity, itself correlated with the evolution of tumor burden in many solid cancers. However, little is known in haematological malignancies. This research aims to explore the potential of hTERT gene as a diagnostic and prognostic marker in hematologic malignancies and to elucidate the principal mechanisms involved in hTERT reactivation
Methods: 42 Tunisian patients with hematologic malignancies are included in this study. Among them patients with myelodysplastic syndromes, acute and chronic myeloid leukemia, and acute and chronic lymphoblastic leukemia. For all individuals, DNA and RNA is extracted from peripheral blood. RNA is used to quantify the hTERT gene transcript, by using quantitative PCR, during the different stages of malignant hematological diseases. Sanger sequencing is performed on DNA, to investigate the mutations that could affect the hTERT gene promoter and lead to telomerase reactivation. Results: This study aims to demonstrate that hTERT mRNA quantification is correlated with tumour burden and could be used as a genomic biomarker of diagnostic and prognostic, principally in patients without specific cytogenetic or molecular genomic biomarker
Conclusion: Besides, the identification of gene mutations and the elucidation of the mechanisms responsible for hTERT reactivation, will lead to the better understanding of the pathophysiology of hematological diseases and to consider new personalized therapeutic strategies geared towards precision medicine

Key words: Hematologic malignancies, hTERT gene, Telomerase reactivation, Promoter mutations, mRNA quantification

046

Poster 11: Contribution of genetic analysis in a rare immune deficiency: Familial hemophagoctic lymphohistiocytosis

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Introduction: Familial hemophagoctic lymphohistiocytosis (FHL) is an immune deficiency characterized by overactivation and excessive proliferation of T lymphocytes and macrophages, leading to infiltration and damage of organs such as bone marrow, liver, spleen and brain. The diagnosis of FHL is established in a subject with suggestive findings by the identification of pathogenic biallelic variants in one of the four genes (PRF1, STX11, STXBP2 or UNC13D) or a heterozygous gain-of-function variant in STXBP2. Methods: to analyse the role of genetic analysis in the diagnosis of rare immune deficiencies syndromes
Results: A 13-month-old female from a non-consanguineous marriage, eutrophic for age and showing good psychomotor development. Admitted to investigate a prolonged fever. Hepato-splenomegaly and biology showed signs of macrophagic activation syndrome (anemia, thrombocytopenia, hyponatremia, hepatic cytolysis and hyperferritinemia). A broad etiological investigation failed to reveal an exact etiology (autoimmune and immune work-up without abnormalities, viral and leishmaniasis serologies negative, myelogram showing hemophagocytes). The patient subsequently developed convulsive seizures in a febrile setting, with the diagnosis of acute demyelinating encephalomyelitis confirmed by imaging, which led to her being put on venoglobulin. The persistent clinical and biological signs of activation syndrome prompted a liver biopsy, which revealed lyosomal overload disease and chronic hepatitis lesions of minimal activity. However, faced with a diagnostic and therapeutic problem, a genetic investigation was initiated, showing a perforin deficiency. The genetic study showed the presence of two heterozygous variants in the PRF1 gene encoding perforin (c.200T>C or p. (Leu67Pro)) and (c.1183T>C or p. (Cys395Arg). Combined with the decreased expression of perforin in the patient's NK cells, these findings may be compatible with an autosomal recessive perforin deficiency. Following her hospitalization, she developed respiratory distress requiring mechanical ventilation with corticosteroids and chemotherapy based on cyclosporine and VP 16. However, while awaiting a bone marrow transplant, the patient died of refractory septic shock.
Conclusion: FHL usually presents as an acute illness with prolonged high fever, cytopenias and hepatosplenomegaly. It is inherited in an autosomal recessive fashion. Genetic analysis is an important tool to contribute in the diagnosis confirmation for patient and to assist parents in prenatal diagnosis for future pregnancies

Key words: Rare immune deficiencies, familial hemophagoctic lymphohistiocytosis, genetics

047

Poster 12: Molecular Characterization of inv dup del(8p)

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Introduction: Inverted duplication deletion of 8p is a rare and complex chromosome 8 rearrangement. This anomaly is associated with a variety of clinical manifestations depending on the formation mechanism, the size of the rearrangement and the encompassed genes . In this work, we present the cytogenetic characterization results of two inv dup del (8p) patients. Methods: A conventional R-band karyotype was performed for Patient 1 (P1) and patient 2 (P2). In a second stage, comparative genomic hybridization(CGH-array) and Fluorescent in-situ hybridization(FISH) was performed to characterize these rearrangements and parental origins
Results: For P1, conventional cytogenetics revealed (13;14) Robertsonian translocation and CGH-array showed a 18,2Mb duplication at 8p21.2 and a 7,1 Mb deletion at 8p23.2. For P2, conventional cytogenetics didn't show anomalies, however array CGH showed a 18,9Mb duplication at 8p22 and 6,4Mb a deletion at 8p23.1.In both cases, disomic sequence (spacer) of approximatively the same size (5,3Mb and 5,7Mb for P1and P2 respectively) between the terminal deletion and the inverted duplication was seen. The spacer existence indicates that the mechanism of formation is non-allelic homologous recombination which is facilitated by a parental inversion in 8p23

seen in both patients' mothers. This demonstrates the OR gene clusters impact in meiotic recombination events due to the presence of an inversion heterozygosity at 8p23.1
Conclusion: Understanding the genesis of these processes has been made possible by chromosomal microarray research.This enabled us to provide another line of evidence for the causal relationship between inv dup del(8p), maternal inv(8)(p23) and genetic counselling

Key words: 8p inv dup del, CGH-array, spacer

048

Poster 13: Implication of Mir27a, and Mir146a polymorphisms in acute coronary syndrome in the Tunisian population.

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Introduction: Acute Coronary Syndrome (ACS) is one of the highest mortality causes in the world. As a complex condition, enviromental factors such as smoking, and numerous genetic susceptibility genes have been associated with this disease. MicroRNAs (miRNAs), small noncoding RNA, have been identified as critical regulators of molecular mechanisms underlying ACS. Notably, miR-146a modulates inflammatory pathways, while miR-27a is involved in dyslipidemia, endothelial function and atherosclerosis. Given these roles, investigating miRNAs in ACS is particularly relevant. Single nucleotide polymorphisms (SNPs) affecting these miRNAs, such as miR-146a rs2910164 and miR-27a rs895819, may affect susceptibility to ACS by disrupting their regulatory functions. The aim of our study was to investigate the association of the SNPs Mir146a rs2910164, and Mir27a rs895819 with ACS in Tunisian population
Methods: SNPs genotyping were performed by mutagenically separated polymerase chain reaction (MS-PCR) in 238 patients and 245 age- and gender-matched controls. Results: In our cohort, association analysis showed that miR146a rs2910164 was not significantly associated with ACS (p=0.38; OR=1.12 [0.87–1.46]). Similarly, miR27a rs895819 was also not associated with ACS (p=0.22; OR=1.19 [0.9–1.57]). However, among smoking patients, the C allele of miR-146a rs2910164 was identified as a protective factor against ACS (p=0.005; OR=0.47 [0.28–0.8])
Conclusion: Our study revealed that Mir27a rs895819 polymorphism is probably not a susceptibility factor to ACS in the Tunisian population. However, the Mir146a rs2910164 C allele is associated with a decreased risk of ACS in smoking patients. Further investigations are needed to elucidate the role of these gene polymorphisms

Key words: Acute Coronary Syndrome, Genetic susceptibility, Mir146a, Mir27a- PCR

049

Poster 14: Clinical and genetic characterization in a large cohort of patients with corpus callosum malformations in the Tunisian population

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Introduction: Corpus Callosum malformations (CCM) are the most common neurological anomalies, with a prevalence of approximately 1 in 4000 births. This study analyzes a cohort of 100 patients referred for genetic evaluation between 2010and 2024. CCMs present with varying manifestations: total agenesis in66% of cases, partial agenesis in12.2%, and hypoplasia in36.6%. In this cohort, CCMs were isolated in4.44% of cases, while 95.56% were associated with other cerebral or extracerebral malformations and neurological developmental disorders
Methods: Patients underwent extensive genetic assessments using cytogenetic and molecular techniques, including karyotyping, FISH, MLPA, CGH array, and exome sequencing based on clinical indications.
Results: The analysis identified 17 chromosomal abnormalities, comprising 17% of all diagnosed cases. These included deletions on chromosomes 14q12, 4p, 1q43q44, 1p32, 5p14.3, 5q35, 16q, 18p, and 9p21, along with duplications on 4q, 18p(isochromosome), 15q13.1, and 15q11.2. Additionally, 4 small CNV-type duplications were detected: 3VUS in 1q31.1, 20q11.22, and 12q12, and one pathogenic CNV in 2p23.2. Four genetic variants were also identified: a composite heterozygous missense variant in WLS(linked to Zaki syndrome) and a homozygous variant in ERCC8(associated with Cockayne syndrome) in the same patient with a 1q31.1 CNV. A homozygous ERCC8 variant was also found in another family. Additionally, a homozygous missense variant in the VPS39 gene was identified in two siblings. Conclusion: Genotype-phenotype correlations identified both known genes(ZNF238, HNRNPU, FOXG1, NFIA...) and novel candidates(BRINP3, PLD5, FMN2, ERCC8, WLS, VPS39…). Validating these gene functions is essential for highlighting the complexity of CCM, and the need for comprehensive genetic evaluations in clinical management and genetic counseling.

Key words: Corpus callosum malformations, genetic anomalies, NGS, Brain malformations, CNV,

050

Poster 15: Unraveling the Genetic Basis of Corpus Callosum Malformations: Insights from Exome Sequencing and CGH Array in a Case with Multiple Genetic Variants

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Introduction: Malformations of the corpus callosum (MCC) are among the most common congenital brain anomalies, affecting approximately 1 in 4,000 births. These anomalies range from complete agenesis to structural abnormalities like hypoplasia and dysplasia.
Methods: We report here the case of a 7-year-old patient presenting with facial dysmorphia, psychomotor and language delay, microcephaly, paraplegia, and corpus callosum hypoplasia. Results: The karyotype analysis showed no abnormalities. However, the CGH array detected a 180 Kb duplication in the 1q31.1 region, encompassing the BRINP3 gene, which is linked to autism spectrum disorders. Exome sequencing identified two missense variants: a homozygous variant in ERCC8 (5q12.1), associated with Cockayne syndrome type A, which involves central nervous system abnormalities such as intellectual disability, white matter demyelination, cerebral atrophy, and seizures; and a compound heterozygous variant in WLS (1p31.3), associated with Zaki syndrome, characterized by developmental delays, brain malformations, including hypoplasia of the corpus callosum, cerebellar vermis, and enlargement of the fourth ventricle. Parental segregation analysis is planned to investigate the inheritance pattern.
Conclusion: The co-occurrence of these genetic variants suggests possible gene-gene interactions during embryogenesis, although current databases classify them as independent. Given that MCC is linked to the WLS variant, functional studies are necessary to elucidate their roles in MCC pathogenesis. This case underscores the importance of a comprehensive genetic strategy to improve genotype-phenotype correlations and enhance diagnostic precision. The advancement of diagnostic tools will contribute to better understanding, management, and genetic counseling for MCC.

Key words: Corpus callosum malformations, NGS, genetic variants, syndromes, CNV, brain abnormalities

051

Poster 16: Genetic Causes Underlying Sertoli Cell-Only Syndrome: Case Series and Review of Current Insights

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Introduction: Sertoli Cell Only Syndrome (SCOS) is one of the most common causes of azoospermia, characterized by absence of germ cells in seminiferous tubules. We report in this study SCOS cases and investigate the underlying genetic causes.

Methods: Four patients with SCOS at Farhat Hached University Hospital were assessed through clinical and biological evaluations, biopsy with histology, karyotyping, and Y chromosome microdeletion analysis. Results: All patients presented secretory azoospermia, with one patient being professionally exposed to heat and another one having a history of testicular trauma. Testicular biopsies confirmed the absence of spermatozoa, diagnosing three patients with complete SCOS and one with focal SCOS. Complete SCOS results from improper gonocyte migration and lack of germ cells in all seminiferous tubules, while focal SCOS has residual normal spermatogenesis in a few tubules. Karyotyping and Y chromosome microdeletions analysis were without abnormalities, excluding the incrimination of Klinefelter syndrome (47,XXY), 45,X/46,XY mosaicism, and AZF regions deletions. With the emergence of high-throughput Sequencing, other genetic causes have been reported in genes implicated in spermatogenesis and Sertoli cells' function (FANCM, ETV5, PLK4, AR, FGF9, etc.). Epigenetic dysregulations have also been suggested. In fact, highly acetylated histone H4 was found intesticular sections with SCO pathologic pattern. In addition, some SCOS patients had a large number of deregulated miRNAs, moderating cell proliferation and survival.
Conclusion: Further investigations into the genetic and epigenetic underlying causes of SCOS are crucial for improved patient management and genetic counseling.

Key words: Sertoli Cell Only Syndrome, Azoospermia, Infertility, Genetics

052

Poster 17: Genomic Literacy, Prescription Practices, and Perceptions of Genomic Medicine Among Cancer Care Physicians in Tunisia: Insights from a Middle-Income Country

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Introduction: To effectively implement genomic medicine in cancer care, it is crucial to understand the current capabilities, gaps, and needs of healthcare providers. A needs assessment serves as a systematic process to identify and address discrepancies between existing conditions and desired outcomes. Methods: We conducted such an assessment by inviting medical doctors treating cancer patients in Tunisia to participate in a national survey distributed between June and November 2023. The key objectives were to: 1) evaluate the knowledge of genetics and genomics among physicians managing cancer patients in Tunisia and identify their educational needs; 2) assess the current use of genomic testing in cancer care, including barriers preventing its prescription; and 3) explore physicians' perceptions of precision medicine (PM) and its feasibility in Tunisia. Genomic testing in this survey refers to high-throughput sequencing (HTS) methods, including targeted panel sequencing, whole exome sequencing (WES), and whole genome sequencing (WGS).
Results: Seventy-six medical practitioners, representing various specialties involved in cancer care (e.g., oncologists, hematologists, pulmonologists), responded to the survey. The average genomic

literacy score among respondents was 38.36 (SD: 18.88). Of the respondents, 27.6% reported prescribing genomic tests using HTS techniques on a regular basis in their clinical practice, while 31.6% had occasionally prescribed these tests, and 40.8% had never done so. Notably, most prescribed tests were patient-funded, with 64.3% of prescribing physicians indicating that patients bore the entire cost. Despite the relatively small cohort, our study identified significant trends, such as the greater likelihood of private-sector physicians prescribing genomic tests and perceiving PM as essential compared to their public-sector counterparts.
Conclusion: This study provides a snapshot of the current landscape of cancer care providers' knowledge and practice in genomics in a middle-income country, offering critical insights to guide the strategic implementation of oncology precision medicine at the national level.

Key words: National survey, Needs assessment, Cancer care physicians, Genomics, Precision medicine

053

Poster 18: Sequencing and Analysis of Draft Genomes of Five Tunisian Macrofungal Species with Potential Benefits for Human Health

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Introduction: Mushroom cultivation is expanding worldwide. Asian communities extensively consume mushrooms for their immune-boosting effects and benefits for gut health due to bioactive molecules like glutathione and ergothioneine. Despite Tunisian's rich Fungal biodiversity, most macrofungal species remain undescribed. The NGS-4-ECOPROD project, funded by the European Union, has enabled us to begin generating, to our knowledge, the first genomic dataset for Tunisian macrofungal species using Illumina and Nanopore technologies.
Methods: Using an optimized DNeasy Plant Pro Kit Protocol for genomic DNA extraction and Illumina DNA Prep and Rapid Barcoding Kit for library preparation, sequencing on NextSeq550 or PromethION 2 Solo was performed on five cultivated pure mycelia of Northwest Tunisian mushroom species. Draft assemblies were analyzed using a local Galaxy server. Raw data reads were trimmed with Trimmomatic v.0.39 or Porechop v.0.2.4, assembled with SPAdes v.3.15.4 or Flye Assembler v2.9.1 for Illumina or Nanopore reads respectively, and evaluated using QUAST v.5.2.0. Results: Based on QUAST metrics, the GC content of the five assembled draft genomes ranged from 48% to 57%. Nanopore metrics improved the assembly compared to Illumina, with total length ranged from 33,151 Mbp to 63,566 Mbp, largest scaffolds from 653,474 kbp to 3,510 Mbp and contigs number from 9 to 220, respectively.
Conclusion: Primary assembly metrics from Illumina or Nanopore draft genomes statistically support the optimized genomic DNA extraction protocol. Complete annotation is crucial for discovering new bioactive compounds like ergothioneine, with significant application in applied sciences. A hybrid assembly is recommended to improve the quality of sequenced, assembled and annotated mushroom genomes.

Key words: Genomic Assembly, Mushroom, Illumina, NextSeq550, Nanopore, PromethION 2 Solo, Local Galaxy Server

054

Poster 19: Cardio-Facio-Cutaneous Syndrome Resulting from a Novel Germline MAP2K1 Mutation: A Complex Disorder with Cerebral Abnormalities and Staturoponderal Retardation

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Introduction: Cardio-Facio-Cutaneous (CFC) syndrome is a RASopathy caused by gain-of-function mutations in genes involved in the RAS/MAPK signaling pathway, including BRAF, MAP2K1, MAP2K2, and KRAS. Clinically, CFC syndrome presents with features similar to other RASopathies, such as Noonan syndrome and Costello syndrome. It is characterized by craniofacial dysmorphism, congenital cardiac defects, dermatological anomalies, and psychomotor delays often with intellectual disabilities.
Methods: We report the case of a 3-year-old child from a non-consanguineous marriage who was referred to the Medical Genetics Department of Ibn Rochd University Hospital due to global developmental delay. Her medical history includes intrauterine growth restriction, persistent crying. Clinical examination revealed psychomotor and growth retardation (height <−2.5 SD), thoracic deformity, and facial dysmorphism. Biochemical tests showed hypercalcemia (116.43 mg/L, normal range: 90.00–110.00), an elevated corrected calcium level of 2.95 mmol/L (normal range: 2.24–2.61), and a calcium-to-creatinine ratio of 17.57 mg/mg (normal: G; p.Tyr130Cys) in the MAP2K1 gene, confirming CFC syndrome type 3 diagnosis (OMIM: 615279). Recombinant growth hormone (rGH) therapy was initiated.
Conclusion: Genetic research is crucial for accurate diagnosis of CFC syndrome and RASopathies genotype-phenotype variability understanding. Given the multifaceted nature of CFC syndrome, increasef awareness among pediatricians is essential to avoid diagnostic delays.

Key words: Cardio-Facio-Cutaneous syndrome, MAP2K1 gene, rasopathy, growth hormone

055

Poster 20: Homozygous Pathogenic Mutation in the TNNI3 Gene Causing Severe Early-Onset Dilated Cardiomyopathy in a Moroccan Family

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Introduction: Dilated cardiomyopathy (DCM) is a rare condition characterized by heart failure due to cardiac muscle dysfunction, specifically marked by left ventricular dilation and impaired systolic function. Genetic screening facilitates early diagnosis and prognostic evaluation in patients with suspected hereditary cardiomyopathy.
Methods: Here, we present a Moroccan family referred to the medical genetics department of Ibn Rochd University Hospital for genetic assessment. The family history revealed a first-degree consanguinity and neonatal deaths with a complex clinical presentation. Indeed, two children have previously died at 4 years and 14 months, respectively, both presented symptoms consistent with neonatal DCM. Clinical and

paraclinical examination of the third living child, born on July 27, 2023, showed no anomalies or particularities.
Results: The whole exome sequencing (WES) of the surviving child identified a pathogenic heterozygous variant in the TNNI3 gene(NM_000363.5 :c.204del (p.Arg69AlafsTer8)), associated with DCM 2A (OMIM: 611880). This variant is inherited in an autosomal recessive pattern and confirms familial neonatal DCM diagnosis. Allelic contribution from both parents was confirmed by segregation analysis.
Conclusion: The TNNI3 gene encodes the cardiac isoform of troponin I, a critical component of the myocardial sarcomere structure. This mutation in TNNI3 represents a novel pathogenic mechanism for neonatal DCM. Therefore, systematic use of diagnostic tools, advanced risk models, and a deeper understanding of the underlying mechanisms are crucial to reducing morbidity and mortality associated with this condition.

Key words: Dilated cardiomyopathy, autosomal recessive, TNN13, whole exome sequencing, morocco

056

Poster 21: MicroRNA regulation of human Telomerase Reverse Transcriptase (hTERT) during digestive cancer progression

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Introduction: Telomerase, an enzyme promoting the extension of "telomeres", has an important role in tumor proliferation. In our previous study we proved that telomere length in digestive cancers fluctuates according to stage, stages 2 and 4 displaying higher length than stages 1 and 3. Our aim is to explain this fluctuation, by investigating the mutation status and the epigenetic regulation of hTERT gene, encoding the catalytic subunit of telomerase, in the digestive tumor stages.
Methods: The somatic mutations, 250C>T and 228C>T, in the hTERT gene promoter, involved in the telomerase reactivation were searched by Sanger sequencing, in 50 tumors at different stages and adjacent tissues. Furthermore, we identified the microRNAs which can target telomerase mRNA and analyzed through the TCGA database their expression evaluated by RNAseq during digestive cancer progression.
Results: We showed the absence of the mutations of interest in tumoral and adjacent tissues, confirming that they are not involved in the telomerase activation in digestive cancers. Secondary, we identified a set of microRNAs which significantly decreased their expression from stage 1 to stage 2 and from stage 3 to stage 4. Furthermore, a set of microRNAs increased their expression from stage 2 to stage 3 in accordance with the opposite variation of telomere length between stages.
Conclusion: Hence telomerase reactivation in digestive cancer does not depend on 250C>T and 228C>T mutations but rather on fluctuation of microRNAs expression according to tumor stages. This epigenetic regulation may explain tumor progression with the prospect of identifying new prognostic biomarkers and therapeutic targets stage dependent.

Key words: Digestive cancer, Tumor stage, Telomerase reactivation; hTERT promoter mutation; microRNA

057

Poster 22: Prognostic significance of additional chromosomal abnormalities at the time of diagnosis in patients with chronic myeloid leukemia: Experience of our Medical Genetics department

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Introduction: The introduction of tyrosine kinase inhibitors (TKIs) has changed the evolution of chronic myeloid leukemia (CML), leading to an improvement of the outcome of CML patients. However, the minority of patients who fail treatment still have poor prognosis. Additional cytogenetic abnormalities (ACA) are considered a high risk feature in CML. However, its prognostic significance at the time of diagnosis in the setting of new tyrosine kinase inhibitors (TKIs) is less well understood.
Methods: Routine karyotype with G- Banding was performed in seven patients with CML in chronic phase in our Medical Genetics department from January to May 2024. These patients came from clinical hematology department of Hedi Chaker Hospital of Sfax and Saddek Mkadem regional Hospital of Djerba. Results: Among 7 patients treated, 3 had ACA. These patients included 2 treated with imatinib 400 mg and one with dasatinib 140 mg. Abnormalities identified included trisomy 8, 6 and 9 ; der(20)t(1;20) ; der(22)t(9;22) ; del(1) and t(4 ;15). One patient presented failure response with 20% of Bcr-Abl at 6 months. Patients without ACA presented complete cytogenetic response (CCyR) at 6 months.
Conclusion: Our results demontrated that 2 out of patients with ACA presented adverse prognostic. Compared with literature data, the prognostic relevance of ACAs in CML-ACA patients has been controversial. This variability may be related to the type of ACA present. Current ELN recommendations suggest that patients at diagnosis with high-risk ACAs (+8, (+Ph), i(17q), +19, 7/7q-, 3q26.2 or 11q23 aberrations and complex karyotypes) should be accordingly treated as high-risk patients.

Key words: Chronic myeloid leukemia, Additional cytogenetic abnormalities, prognosis

058

Poster 23: Exploring differential abundance approaches in gut microbiota analysis of coronary artery disease patients

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Introduction: Accumulating evidence has linked gut microbes to coronary artery disease (CAD) by modulating immune responses and inducing systemic inflammation. Several studies have analyzed the gut microbiota in CAD highlighting a divergence in CAD-specific microbiota signatures.
Methods: On five available datasets, results of ten alpha diversity measures were combined by random-effect meta-analysis. Then, various differential abundance (DA) approaches were used to identify CAD-specific alterations across cohorts. For single and combined datasets, three DA methods (WMW, Deseq2, ANCOM) and three compositional DA methods (Selbal, clr-lasso, coda-lasso) were applied. Distance-based redundancy analyses (dbRDA) was also performed on combined datasets. These analyses were complemented by a random-effect meta-analysis.

Results: The analysis of the alpha-diversity suggests that the gut microbiota of CAD patients is less diverse than controls. For DA analysis, the pairwise concordance between DA methods applied to single datasets ranged from 20% to 66.66%, indicating the significant influence of individual study characteristics on the results. On combined datasets, 13/45 (28.88%) differentially abundant taxa were detected by at least two approaches. Overall, enrichment of the genera Lactobacillus and Akkermansia, and depletion of the genera Bacteroides and Lactoclostridium, were the most consistent CAD gut microbiome alterations.
Conclusion: Our study confirms the alteration of gut microbiota composition in CAD patients with an imbalance between trimethylamine-producing bacteria and short chain fatty acides (SCFAs) producing bacteria. Our study also confirms the lack of an optimal model for microbiome data analysis, yet demonstrates the potential for combining multiple methods to comprehensively determine gut microbiota alterations.

Key words: Gut microbiota, Coronary artery disease, Differential abundance, Metagenomics

059

Poster 24: Development of a Health Literacy Tool for Hemoglobinopathies and Genetic Self-Counseling Prospects for Tunisian Youth

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Introduction: Health literacy (HL) pertains to an individual's capacity to comprehend and apply health-related information in order to make informed decisions about their health. In Tunisia, the primary prevention of hemoglobinopathies relies on behavioral changes related to screening and genetic counseling. The progression in cognitive and functional literacy in human genetics serves as a crucial aspect of this transformation. The objective of this research was to create a comprehensive scale called Hemoglobinopathies Health Literacy (HLS-HB) and assess its psychometric properties within among Tunisians youth.
Methods: A questionnaire covering Nutbeam's framework, namely functional and interactive HL (FHL and IHL), and critical HL (CHL) within three subdomains: critical appraisal of information, understanding of social determinants of health, and actions to address social determinants of health, was developed based on previous literature review. Reliability, validity, and cultural equivalence were studied using data from expert consultations, cognitive interviews, and two pilot studies. Cognitive interviews were performed to examine all items' face validity in terms of three aspects: comprehensiveness, clarity, and acceptability.
Results: Twenty high school students interviewed participated in the cognitive interviews in September 2021. Based on the comments of the respondents, elements were reformulated. A total of 356 students responded to the questionnaire survey between January 2021 and May 2022. After excluding one item with low inter-item correlations, the scale's internal consistency reliability was acceptable. Conceptual, item, and semantic equivalences were all respected, with good to excellent Cronbach's alpha (0.8–0.9). Exploratory factor analysis produced a five-factor model, as shown in the original theoretical framework. Confirmatory factor analysis confirmed that the fit indices for this model were acceptable. The scale is also significantly correlated with theoretically selected variables, including education.
Conclusion: The HLS-HG is a valid and reliable tool for evaluating HL. This scale extended the operationalization of FHL, IHL, and CHL and fully operationalized the CHL via three subdomains. It can be used to understand the difficulties and barriers that youth may encounter when they use hemoglobinopathies-related information and screening services.

Key words: Hemoglobinopathies, health literacy, genetic self-counseling, primary prevention, Tunisian youth

060

Poster 25: The contribution of High-throughput sequencing in hereditary predispositions to cancers: first experience of the genetics department of the Charles Nicolle hospital in Tunis

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Introduction: Hereditary predispositions to cancer constitute a significant proportion of cancer cases. They are caused by genetic variants that increase the risk of neoplasia for affected individuals and their relatives. Next-generation sequencing (NGS) has emerged as an essential tool for the rapid and comprehensive analysis of multiple genes related to these predispositions. Thanks to its high sensitivity and ability to detect rare variants, NGS offers a more efficient alternative to traditional sequencing methods. This work explores the impact of NGS in the detection of hereditary variations, its clinical benefits, as well as the challenges associated with its integration into routine practices.
Methods: This study involved 92 Tunisian patients, recruited according to well-defined anamnestic and clinical criteria. Consultants were sent to our department over a period of 8 years (2016 to 2024). A high-throughput sequencing of a panel of cancer genes on genomic DNA has been carried out.
Results: 18 pathogenic variations spread over 14 genes were identified in 17 patients. For breast cancer patients (11/17), the most frequently affected genes were BRCA1 (36%), ATM (27%), BRCA2 (18%), CHEK2 (9%) and RAD51D (9%). For patients with digestive cancer (5/17), the most frequently mutated genes were MLH1 (30%), MSH2 (30%),MUTYH (20%), PMS2 (20%). Genetic advice was given and a pre-symptomatic test was proposed for related relatives.
Conclusion: The NGS has transformed the management of hereditary predispositions to cancer by offering a precise, large-scale approach for simultaneous analysis of multiple genes, Contributing to better risk stratification and personalization of patient monitoring and treatment strategies.

Key words: Hereditary predisposition, cancer, NGS, Panel

061

Poster 26: Cryptic 9pter deletion in patient with de novo apparently balanced translocation and pathological phenotype

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Introduction: Carriers of apparently balanced translocations (ABT) are usually phenotypically normal. However, 6% of de novo cases present a pathological phenotype. Previous studies had estimated that 40% of de novo ABT with pathological phenotype were associated with cryptic deletions. Methods: A 5 months-old female was referred to the genetics department of Farhat Hachad university Hospital with a down-like phenotype: facial dymorphism, hypotonia and developmental delay. Cytogenetic analysis, including karyotyping and fluorescence in situ hybridization (FISH), was performed. Parental karyotypes were also examined.
Results: Karyotyping revealed an apparently balanced reciprocal translocation between the short arms of chromosome 1 and chromosome 9. FISH analysis confirmed the presence of a cryptic terminal deletion on the short arm of chromosome 9. Parental karyotypes were normal. Genetic advice was given and a pre-symptomatic test was proposed for related relatives.
Conclusion: This case illustrates the association of cryptic deletions with apparently balanced translocations in individuals with abnormal phenotypes. High-resolution techniques like FISH are crucial. We also highlight the importance of genome wide exploration. We will complement our findings with Comparative Genomic Hybridization arrays data.

Key words: Apparently balanced reciprocal translocation, Pathological phenotype, Cytogenetic analysis, 9pter deletion

062

Poster 27: Improving Porokeratosis Diagnosis: The Impact of Genetic Analysis on Clinical Outcomes

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Introduction: Porokeratosis (PK) is a rare keratinization disorder resulting from abnormal clonal expansion of keratinocytes. Its clinical presentation can overlap with other dermatological conditions, such as lupus and psoriasis, complicating the diagnostic process. Accurate diagnosis can be challenging due to overlapping features with other dermatological conditions. This study aimed to investigate the genetic basis of PK in a cohort of patients and their relatives.
Methods: We analyzed a cohort of 9 patients and 10 healthy relatives from 3 unrelated Tunisian families for PK. All patients presented with heterogeneous hyperkeratinization lesions. Sanger sequencing targeting mutational hot spots in mevalonate pathway genes was performed for all PK cohort patients. Exome sequencing (ES) was subsequently conducted for one patient, P9, who exhibited 3 painful nasal lesions since adolescence, followed by the development of plaques on the neck and abdomen. Results: Sanger sequencing revealed a heterozygous PMVK variant in 8 patients, but no pathogenic variants associated with PK were identified in patient P9. ES identified a heterozygous insertion/deletion (indel) variant in the HLA-C gene: c.357_358insGG; p.Gln120fs*32 in P9. This variant, associated with lupus, involves the insertion of 2 guanines at positions 357_358, leading to a frameshift and a premature stop codon after 32 amino acids. This alteration is predicted to cause mutant mRNA degradation and produce a truncated HLA-C protein.
Conclusion: This study underscores the critical role of genetic analysis in refining clinical diagnoses, especially in cases with overlapping phenotypic features. The integration of high-throughput sequencing technologies into clinical practice enhances diagnostic accuracy and improves patient management for complex cases of genodermatoses.

Key words: Porokeratosis, Lupus, HLA-C variant, Exome sequencing, Genetic diagnosis.

063

Poster 28: Enhancing Diagnostic Precision in Hereditary Epidermolysis Bullosa: The Impact of Exome Sequencing in a Tunisian Cohort

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Introduction: Hereditary epidermolysis bullosa (EB) is a heterogeneous group of genodermatoses characterized by skin fragility and blister formation. The clinical presentation of EB often overlaps between subtypes, and incomplete clinical data can obscure accurate classification, complicating patient management and prognosis.
Methods: This study analyzed 9 Tunisian patients with clinically diagnosed EB, including several with incomplete clinical data and unclassified subtypes. Exome sequencing (ES) was performed on all patients to identify pathogenic variants in EB-associated genes. Bioinformatic analyses were used to predict the pathogenicity of novel variants and prioritize candidates for further functional study.
Results: We identified 11 pathogenic variants in 4 genes (COL7A1, LAMA3, DST, and FERMT1), including 3 novel variants in 3 patients with initially unclassified subtypes, which confirmed diagnoses of recessive dystrophic EB and junctional EB. For patients with incomplete data, ES enabled reclassification by correlating genetic findings with clinical phenotypes, thereby enhancing diagnostic precision. Bioinformatic analyses provided critical validation by predicting variant pathogenicity, facilating the identification of clinically relevant mutations and minimizing the need for extensive functional studies. The integration of ES with bioinformatic tools also streamlined the diagnostic process, significantly reducing time, cost, and effort compared to traditional diagnostic workflows reliant on serial testing.
Conclusion: ES is crucial for overcoming diagnostic challenges in EB, especially in cases with incomplete or unclear clinical data. Combining ES with bioinformatics enhances diagnostic accuracy and aligns molecular diagnoses with clinical phenotypes. This study underscores the importance of integrating genetic analysis into clinical diagnostics for genodermatoses, improving patient management through early, accurate, and cost-effective diagnosis.
Key words: Epidermolysis bullosa, Exome sequencing, Genetic diagnosis, Bioinformatics, Genodermatose

064

Poster 29: In Silico Modelling of Novel Variants of Unknown Significance (VUS) in Autosomal Recessive Congenital Ichthyosis Genes in Tunisian Patients: Structural Insights

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Introduction: Understanding how single-point variations affect protein stability is a crucial step toward understanding the relationship between protein structure and function. This study employed in-silico modelling to investigate novel variants of unknown significance (VUS) identified in Tunisian patients with suspected autosomal recessive congenital ichthyosis (ARCI), a genetic skin disorder characterized by abnormal keratinization.
Methods: We focused on Tunisian patients harbouring VUS in genes associated with ARCI. Using computational approaches, we generated three-dimensional structural models of the proteins encoded by these genes to predict the effects of the VUS on protein stability. Various computational tools were employed to assess alterations in protein conformation, stability, and potential functional implications. Results: The in silico analysis revealed several VUS that may affect protein stability, disrupt functional domains, or alter critical interactions within the protein structure. These changes could potentially contribute to the pathogenesis of ARCI. Our findings provide valuable insights into how specific VUS may affect protein function, enhancing understanding of their role in ARCI. This highlights the importance of integrating in silico modelling with experimental data to better understand the genetic basis of complex diseases.
Conclusion: This study demonstrates the utility of computational modelling in predicting the functional consequences of VUS in ARCI-associated genes. By combining in silico and experimental approaches, we can achieve a more comprehensive understanding of the genetic variants involved in complex disorders, thereby improving diagnostic accuracy and guiding therapeutic strategies.

Key word: In silico modelling, Variant of Unknown Significance (VUS), ARCI, 3D structure.

065

Poster 30: Genetic Insights into MODY: A Multicentric Study Using Saliva Samples in Tunisian patients

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Introduction: Maturity-Onset Diabetes of the Young (MODY) is the most common type of monogenic diabetes, with at least 14 known mutations identified to date. However, this condition remains underdiagnosed. The aim of this study was to investigate MODY in patients with atypical diabetes and to perform phenotype-genotype correlation.
Methods: A multicenter cross-sectional study was carried out across various centers in northeastern and central-eastern Tunisia, including three reference centers for diabetes care. Included patients exhibited characteristics suggestive of MODY. Molecular analysis was performed on saliva samples using next-generation sequencing (NGS) techniques. Results: Twenty-seven (62.9% females) participated in the study with a mean age at diagnosis of 24.3 ± 9.6 years. Diabetes transmission over three generations was observed in 17 cases (62.9%). The probability score for having MODY exceeded 25% in 17 patients (62.9%). Molecular analysis identified 5 mutations in 5 (18.5%) participants, including one pathogenic mutation in the HNF4A gene (p.Gln255*) in one individual and a mutation in the HNF1A gene (p.Arg159Gln) in two cases. The others were missense mutations of unknown significance in the HNF4A, ABCC8, and KLF11 genes. Patients with MODY had no diabetic complications and were younger, thinner, had lower HbA1c, cholesterol and triglycerides levels, and higher HDL-cholesterol than the other patients.
Conclusion: Few studies investigated MODY in Tunisia due to technical and economic constraints, and no predominance of any specific subtype were noted compared to other countries. Further investigations are required in countries with a high prevalence of diabetes to enhance the selection of patients requiring molecular analysis.
Key word: Diabetes mellitus, MODY, HNF1A, HNF4A, Next Generation Sequencing

066

Poster 31: Lessons learned from a nationwide genome sequencing project for rare disease patients

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Introduction: As part of a government-funded collaborative initiative launched in South Korea to equip genetic clinics with a comprehensive diagnostic tool to expedite the diagnosis of patients with rare diseases, particularly those living outside major urban areas where diagnostic resources are limited, a total of 400 patients highly suspected of having a rare genetic disorder underwent whole genome sequencing (WGS) test. Methods: WGS was performed at a centralized reference laboratory. Variants including structural variants were analyzed using a highly automated and accurate AI-based analytical system adopting the ACMG guideline. Each patient data was manually curated by medical geneticists and the results were reviewed by the physicians. Pathogenic, likely pathogenic, and highly suspected variants of uncertain significance were reported for both primary and secondary findings.
Results: The overall diagnostic yield was 36.3% with 11.0% of the diagnosed patients being detected with variants that could not have been identified by chromosomal microarray or exome sequencing. The turn-around-time (TAT) of <=35 days was met. Segregation analysis by Sanger sequencing played a crucial role in confirming or reclassifying variant pathogenicity by elucidating inheritance patterns.
Conclusion: Successful implementation of the program was demonstrated by patients not having to travel far to have access to the test, practical workflow monitored within a secure online portal managed by the government, comprehensive testing, diagnostic yield comparable to

previous reports, and reasonable TAT. The study also confirmed that WGS is a preferred first-line diagnostic tool for rare disease patients, providing a high diagnostic yield while being fast and accessible.

Key words: Diagnosis, Rare Diseases, Whole Genome Sequencing, AI-based analysis

068

Poster 32: Comprehensive Clinical and Genetic Characterization of Pancreatic Cancer in Tunisia

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Introduction: Pancreatic cancer (PC) represents a critical public health challenge due to its high mortality rate. According to the GLOBOCAN database, 513 new cases were diagnosed in Tunisia in 2022, ranking it as the tenth most common cancer, with 503 related deaths. This study aims to deliver a comprehensive clinical and genetic profile of PC in the Tunisian population using advanced genomic analyses and computational biology.
Methods: A total cohort of 200 pancreatic cancer patients, diagnosed between January 2019 and July 2024, was included in the study at the Gastroenterology Department of Taher Maamouri Regional Hospital, Nabeul. Genetic analysis was performed on a subset of 20 selected patients, chosen based on clinical indicators of hereditary predisposition or familial cancer history. Whole exome sequencing (WES) and next-generation sequencing (NGS) were employed for these selected cases. Computational biology was used to analyze and interpret both the clinical and genetic data from these 20 patients.
Results: Among the 200 patients (male-to-female ratio of 1.73, mean age: 61.70 ± 14.21 years), several significant genetic findings were uncovered. Whole exome sequencing in a patient with a strong family history of cancer identified three variants of unknown significance (VUS) in the FANCF, MSH3, and NBN genes. Furthermore, NGS was performed on 20 patients with suspected hereditary predisposition, including 17 previously sequenced cases and 3 newly screened for BRCA1/2 mutations. No pathogenic mutations in BRCA1 or BRCA2 were detected, indicating the absence of recurrent mutations in this cohort.
Conclusion: The genetic landscape of pancreatic cancer in Tunisia is characterized by the absence of common BRCA1/2 mutations. Ongoing studies aim to expand the gene panels and explore genotype-phenotype correlations to deepen the understanding of hereditary pancreatic cancer in this population. These findings could lead to the development of personalized treatment strategies and improve the clinical management of pancreatic cancer patients in Tunisia.

Key words: Pancreatic Cancer, Clinical Genetics, Computational Biology, Next-Generation Sequencing, BRCA1/2

069

Poster 33: Pancreatic Cancer in Tunisia: An Integrated Analysis of Clinical, Epidemiological, and Genetic Profiles

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Introduction: The high mortality rate makes pancreatic cancer (PC) a major public health concern. According to estimates from the GLOBOCAN database for the year 2022, 513 new cases of PC were diagnosed in Tunisia, making it the tenth most common cancer subtype, with 503 deaths reported in the same year. This study aims to provide a comprehensive epidemiological and genetic profile of PC among the Tunisian population, using advanced analytical techniques.
Methods: We conducted a retrospective epidemic-clinical study involving 200 pancreatic cancer cases at the Department of Gastroenterology, Taher Maamouri Nabeul Regional Hospital, from January 2019 to July 2024. Advanced computational biology algorithms were utilized to process and interpret clinical and genetic data. This approach enabled us to discover correlations between various variables, giving us a deeper understanding of pancreatic cancer in the Tunisian population. Results: The study included 200 patients with a male-to-female ratio of 1.73 and a mean age of 61.70 ± 14.21 years. Smoking was reported in 40.95% of the patients, while 25.77% were alcohol consumers. Additionally, 28.31% had diabetes, 8.8% had a family history of chronic pancreatitis, and 40% had a family history of cancer. The most common symptoms at presentation were jaundice (66.66%) and abdominal pain (30%). Tumors were predominantly located in the pancreatic head (78.05%). At the time of diagnosis, 35% of patients had metastatic disease, with the liver being the most frequent site of metastasis. In terms of genetic analysis, following a molecular investigation through whole exome sequencing in a patient with pancreatic cancer and a strong family history of cancer, we identified three variants of unknown significance (VUS) in the FANCF, MSH3, and NBN genes. Conventional sequencing of 17 patients revealed no recurrent BRCA1 or BRCA2 mutations.
Conclusion: The epidemiological characteristics of pancreatic cancer in Tunisia align with broader North African trends, though distinct particularities were observed in our cohort, such as the high prevalence of a family history of cancer and specific genetic variants. These findings contribute to a deeper understanding of pancreatic cancer within the Tunisian population. Ongoing genomic studies aim to investigate the genetic factors underlying these particularities and perform Genotype-Phenotype correlations, which may ultimately enhance the clinical management of pancreatic cancer patients.

Key words: Pancreatic Cancer, Clinical Genetics, Computational Biology, High-Throughput Sequencing

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Poster 34: Relation of rs846910, rs4844880 11β-hydroxysteroid dehydrogenase type 1 (HSD11B1) polymorphisms with the risk of preeclampsia: A case-control study

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Introduction: The 11β-hydroxysteroid-dehydrogenase 1 (11β-HSD1) enzyme catalyzes the interconversion of cortisone and cortisol, with mainly oxoreductive activity in intact cells due to co-expression with hexose-6-phosphate dehydrogenase (H6PD). The uterine localization of 11β-HSD1 and its reduced placental expression in women with preeclampsia (PE) suggest a role for 11β-HSD1 in PE pathogenesis. We investigated the association of rs4844880 and rs846910 variants in the HSD11B1 gene with PE in Tunisian women.

Methods: The study cases comprised 334 women who presented with PE and 314 age-matched normotensive women who served as controls. The rs4844880 and rs846910 HSD11B1 gene variants were genotyped by realtime PCR.
Results: The rs4844880 T > A and rs846910 G > A minor allele frequencies were not different between PE cases and control women, which persisted after adjusting for age, BMI, gestational age, premature delivery, and baby weight. An association was noted for rs4844880 A/A genotype with a heightened risk of PE, which persisted after controlling key covariates. The (minor) A allele of rs4844880 was linked with elevated serum ALT and higher serum AST. In contrast, carriage of the rs846910 minor (A) allele was connected with higher baby weight on delivery and serum AST levels. Setting the major allele homozygotes (T-G) as a reference, a higher prevalence of double minor allele (A-A) haplotype was seen in PE cases than in corresponding controls, which persisted after controlling for age and BMI. Controlling for gestational age and baby weight identified the T-A haplotype and confirmed the association of the A-A haplotype with a heightened risk of PE.
Conclusion: Our results support an association between HSD11B1 polymorphisms and increased risk of PE and PE-associated clinical features.

Key words: 11β-hydroxysteroid-dehydrogenase 1, Cortisol; Haplotypes, Hypertension, Preeclampsia, Pregnancy

071

Poster 35: Mir27a and PPARG Polymorphisms in Type 2 Diabetes Onset and Complications in the Tunisian population

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Introduction: Type 2 diabetes (T2D) is a prevalent complex metabolic disorder influenced by both environmental and genetic factors. PPARG gene has been implicated in T2D as a transcription factor that regulates insulin sensitivity and lipid metabolism. Variants in PPARG gene can lead to insulin resistance, a hallmark of T2D. The expression of PPARG gene is regulated by Mir27a which was associated with T2D susceptibility. Our study aims to investigate the association of miR27a rs895819 and PPARG rs1801282 with T2D and its complications in the Tunisian population.
Methods: Our retrospective study included 134 patients diagnosed with T2D according to the criteria established by the World Health Organization in 1999 and the American Diabetes Association in 1997, along with 227 age- and sex-matched controls. Genotyping of SNPs was performed using mutagenically separated polymerase chain reaction (MS-PCR).
Results: Association analysis revealed no significant association between Mir27a rs895819 and T2D (p=0.81, OR=0.95 [0.67–1.35]) .Similarly, PPARG rs1801282 was not significantly associated with T2D (p=0.23, OR=1.77 [0.69–4.57]). Furthermore, no significant association was identified between these SNPs and the disease complications nor the delay of their onset . Conclusion: Our study revealed that Mir27a and PPARG polymorphisms are probably not susceptibility factors to T2D in the Tunisian population. To improve the statistical power of our findings, we plan to expand the sample size. Further investigations are needed to elucidate the role of these gene polymorphisms.

Key words: Single nucleotide polymorphism, Diabetes type 2, Mutagenically separated polymerase chain reaction, Mir27a - PPARG

072

Poster 36: Genetic anthropology of Algerian population. Investigation of maternal lineages diversity in Chaouia and Kabyle autochthons

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Introduction: Algeria is a key region for understanding human settlement in North Africa, it is characterized by a complex demographic history that shaped its gene pool, nevertheless, the whole landscape regarding its maternal genetic history still largely ambiguous. Methods: We have analyzed the HVS1 mitochondrial DNA region of 192 carefully collected samples from two autochthonous Berbers communities; Chaouia (Batna, Khenchela and Tebessa) and Kabyle (Bejaia) from the North East of Algeria. Our aim is to investigate the Algerian population's genetic diversity in order to further characterize its genetic structure and to contribute to the understanding of the past and recent North African population demography.
Results: The genetic parameters as well as the mitochondrial lineages showed a typical North-west African profile composed of North African, Eurasian and sub-Saharan lineages. The Fst matrix and the NMDS analysis clustered our studied populations with the North Africans, with a particular affinity between Khenchela and the Middle East populations. The phylogenetic analysis of the U5b and L1b haplogroups provided answers regarding their introduction into the Northeast of Algeria. The L1b dated back around 6,767 ± 2,036 y, coinciding with the end of the Neolithic. The U5b revealed an earlier date (22,300 ± 13,800 y) which dates back to the LGM.
Conclusion: The genetic makeup of the Algerian population perfectly reflects its geographical position. This mosaic structure results from different episodes of population migrations and invasions occurring at different historic and prehistoric periods.

Key words: Algeria, ADNmt, HVSI, L1b, U5b

073

Poster 37: Resolving diagnostic challenges and enabling targeted therapy in rare hereditary hemolytic anemia through exome-based genomic analysis

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Introduction: Hereditary hemolytic anemia (HHA) encompasses a group of disorders characterized by phenotypic and genetic variability, making accurate diagnosis difficult. Traditional diagnostic methods have limitations, leading to underdiagnosis or misdiagnosis. Factors like donor blood contamination and elevated reticulocytes due to compensatory erythropoiesis from hemolysis further complicate these analyses. This underscores the need for molecular diagnostics. However direct sequencing is time-consuming and inadequate for addressing multiple gene targets. Next-Generation Sequencing (NGS) has revolutionized the diagnostic process for diseases by providing faster and more accurate analyses. In our laboratory, we are frequently consulted for molecular diagnosis in cases where conventional tests yield inconclusive results.

Methods: Mutational analysis were performed in 4 patients with HHA using WES on the Illumina platform and confirmed by direct sequencing.
Results: The identification of deleterious mutations allowed us to set up a diagnosis for all the patients. These cases included 2 patients with pyruvate kinase deficiency, confirming the suspected diagnosis; one previously undiagnosed patient with ATR-X syndrome; and one patient with hexokinase I deficiency, initially misdiagnosed as pyruvate kinase deficiency. Molecular diagnosis was essential in both providing a definitive diagnosis and correcting a misdiagnosis, both critical for guiding appropriate therapeutic strategies.
Conclusion: WES efficiently identifies pathogenic variants, accelerating diagnosis and reducing delays in patients care for rare hematological conditions. Moreover, NGS has expanded our understanding of the genetic diversity in the Tunisian population, revealing novel variants. These insights are crucial for improving genotype-phenotype correlations, which are essential for accurate prognosis and personalized treatment strategies.

Key words: Rare hereditary hemolytic anemia, WES, Diagnosis, Specific treatment

074

Poster 38: Implication of the RS4532 (A-48G) polymorphism of the Dopamine Receptor Gene (DRD1) in the Onset of Schizophrenia

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Introduction: Schizophrenia is a chronic psychotic disorder that affects emotional, cognitive, and social functioning. Studies have shown an association between several genetic alterations in the dopamine D1 receptor gene (DRD1) and neuropsychiatric disorders. Our study aims to determine the association between the rs4532 (A-48G) polymorphism located in the 5'-untranslated region of the DRD1 gene and schizophrenia In our laboratory, we are frequently consulted for molecular diagnosis in cases where conventional tests yield inconclusive results.
Methods: This is a case-control study conducted on 60 patients suffering from schizophrenia and 60 controls. After DNA extraction, we performed DNA amplification using the Polymerase Chain Reaction (PCR) technique followed by enzymatic digestion using the Restriction Fragment Length Polymorphism (RFLP) technique. We then calculated and compared the distribution of genotypic and allelic frequencies. Odds Ratio and Chi-square tests were performed using the Epi Info software. Results: Our results show that the healthy homozygous AA genotype is the most frequent in both groups, with a prevalence of 58.33% among patients vs. 71.66% among controls. The heterozygous AG genotype is more frequent in patients (35%) than in controls (25%). The mutated homozygous GG genotype is the least frequent in both groups, with a prevalence of 6.66% among patients vs. 3.33% among controls. Furthermore, the healthy A allele predominates in both groups, with 75.83% in schizophrenic patients and 84.16% in controls. Statistical tests showed that the results are not statistically significant between the two groups (p-value > 0.05 and a $\chi 2$ value < 3.84).
Conclusion: Our results suggest that the rs4532 (A-48G) polymorphism of the DRD1 gene is not a risk factor for schizophrenia in our study population.

Key words: Schizophrenia, rs4532 (A-48G), DRD1 gene, Risk factor

075

Poster 39: Implication of the STin2 VNTR polymorphism of the serotonin transporter gene SLC6A4 in the occurrence of migraine Dopamine Receptor Gene (DRD1) in the Onset of Schizophrenia

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Introduction: Migraine is a very common primary headache. Studies have shown that genetics plays a crucial role in the susceptibility and manifestation of migraine, particularly through alterations affecting the serotonergic system. Our study aims to investigate a possible correlation between the STin2 VNTR polymorphism of the serotonin transporter gene SLC6A4 and migraine.
Methods: This is a case-control study involving 60 migraine patients and 60 controls. Genomic DNA was extracted, amplified by PCR, and analyzed by agarose gel electrophoresis. Genotypic and allelic frequencies were compared, and statistical analysis was performed using Epi Info software with Odds Ratio and Chi-square tests. Results: Genotypic frequency analysis showed that the homozygous genotype STin2.10/STin2.10 is rare in both groups (20% in the patient group and 10% in the control group). The homozygous genotype STin2.12/STin2.12 is the most common among patients (50%) and also frequent in the control group (42%). In contrast, the heterozygous genotype STin2.10/STin2.12 is more common in the control group (48%) than in migraine patients (30%). Allelic frequency analysis revealed that the allele STin2.10 is moderately present in both populations (35% in patients and 34% in controls). However, the allele STin2.12 is predominant in both groups (65% in patients and 66% in controls). Statistical tests indicated no significant association between the STin2 VNTR polymorphism and migraine (p-value > 0.05, $\chi 2 < 3.84$).
Conclusion: The molecular study of the serotonin transporter gene SLC6A4 did not reveal a statistically significant correlation for the STin2 VNTR polymorphism, indicating that it does not represent a risk factor for migraine.

Key words: Migraine, Serotonin transporter, SLC6A4, STin2 VNTR polymorphism

076

Poster 40: Investigating Marfan Syndrome in Tunisia: Insights and Advances in Genetic Diagnosis

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Introduction: Genetic diseases pose a significant public health challenge as they are a leading cause of chronic morbidity and premature death. In Tunisia, there are 589 reported genetic disorders, with 23% being autosomal dominant. Among them, Marfan syndrome (MS) is a connective tissue disorder that primarily affects the cardiovascular, ocular, and skeletal systems profoundly affecting patients and their families' quality of life. The molecular aetiology of MS is unknown in the Tunisian population.
Methods: We conducted multicentric recruitment of Tunisian patients in collaboration with referring clinicians. In order to elucidate the

molecular aetiology of MS, Sanger sequencing was initially performed for targeted FBN1 mutations. If results were inconclusive, whole exome sequencing (WES) will be carried followed by bioinformatic analysis. Results: To date, 11 families have been recruited, comprising 13 Tunisian patients, 6 of whom were born to consanguineous unions originating from different regions of Tunisia. Clinical investigation revealed a heterogeneity. Sanger sequencing identified one FBN1 mutation in one family.
Conclusion: Our pilot study highlights that conventional Sanger screening for targeted mutations is not always efficient for diagnosing genetic disorders. By using WES, we aim to identify the MS mutation spectrum in order to provide an efficient molecular diagnostic tool, establish genotype-phenotype correlations, and provide valuable insights to clinicians for developing tailored management programs. Newly identified mutations are being integrated into a developing genetic disease database in Tunisia, PREMEDIT, a platform expected to revolutionize healthcare decision-making and contribute to innovation across the scientific community, including clinicians, pharmaceutical companies, researchers, patients, and families.

Key words: Marfan syndrome, Genetic diseases, Molecular diagnosis, Tunisian population, WES

077

Poster 41: Association of breast cancer and neurofibromatosis type 1

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Introduction: Neurofibromatosis type 1 (NF1) is a genetic disease predisposing to tumors. The association NF1 and breast cancer has been reported in the literature, women with NF1 had five times the risk of developing breast cancer compared to the general population before the age of 50. Our work aimed to describe patients presenting this association.
Methods: We conducted a descriptive, retrospective, and multicenter study involving 52 patients.
Results: In our study, two families had this association. In the first one, cancer in the right breast was diagnosed in a 42 years old woman with NF1, for which she had undergone a total mastectomy and chemotherapy. She had a cousin with breast cancer who had perhaps café-au-lait macules and a nephew who developed neuroblastoma at the age of 18 months. In the second family, the mother of a girl with NF1 had developed breast cancer at the age of 36 for which she had a lumpectomy with chemotherapy. She had no clinical signs of NF1.
Conclusion: The diagnosis of breast cancer in patients with NF1 is most often made at an advanced stage, hence the importance of establishing systematic screening in these women by performing a mammogram every year from the age of 30 years and by a breast MRI between 30 and 50 years.

Key words: Neurofibromatosis type 1, Breast sein, Clinical features

078

Poster 42: Clinical phenotype of Oculo-Dento-Digital Dysplasia

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Introduction: Oculo-dento-digital dysplasia (ODDD) is characterized by characteristic craniofacial abnormalities, ocular, dental, digital and neurological abnormalities. The aim of our work was to describe the phenotypic characteristics of DODD.
Methods: We report the clinical presentation of this syndrome through a sporadic case and two familial cases. Results: Three patients (two girls and one boy) were referred for genetics consultation in the orthopedic-pediatric department for exploration of extremity abnormalities with bilateral syndactyly of the 4th and 5th finger in association with facial dysmorphism. All patients presented with thin nose, hypoplasia of the nasal alae, small anteverted nostrils and a prominent columella. They also had rarefied hair. The 2nd case presented microphthalmia, microcornea and neurological abnormalities with urinary and fecal incontinence, spastic paraparesis and camptodactyly of the 4th and 5th fingers. The rest of his family had the same clinical features. His mother had also scoliosis. The 3rd case was a sporadic case; he had cataract, microcornea and glaucoma with anterior segment dysgenesis. Currently he is 21 months' old; he presented blindness, dental enamel abnormality, oligodentia and strictly normal psychomotor development.
Conclusion: The variability of the clinical presentation reported in the DODD was verified in our study. It is necessary to discuss this diagnosis early in order to establish care and monitoring to prevent a disability as in our third patient.

Key words: Oculo-dento-digital Dysplasia, Syndactyly, Cataract, Glaucoma, Dysmorphy

079

Poster 43: Genetic analysis of sporadic Tunisian patients with idiopathic dilated cardiomyopathy using next generation sequencing

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Introduction: Dilated cardiomyopathy (DCM) is one of the most common cause of heart failure. Clinically, DCM is defined by ventricular dilatation associated with impaired contractile function. Currently, despite several conditions have been reported as aetiologies of the disease, a large number of cases remain classified as idiopathic. Dilated cardiomyopathy (DCM) is characterized by notable genetic heterogeneity. Although over 50 genes have been associated with DCM, these collectively explain 35% of idiopathic DCM cases. The objective of this study was to identify genetic variants for Tunisian DCM idioppathic cases.
Methods: 8 patients diagnosed with idiopathic DCM without a family history and 8 controls were included in the present study. Whole-exome sequencing (WES) was performed, using the clinical Exome TruSight One Sequencing Panel, followed by assessment of genetic variants in previously reported cardiovascular disease genes.
Results: We identified 5 variants of clinical interest, 2 were classified as pathogenic or likely pathogenic (P/LP) and 3 of unknown clinical significance for idiopathic DCM patients. Of P/LP variants, one was found in TTN (Titin) and one in LDR (Low density lipoprotein receptor).
Conclusion: Our results highlight the potential of NGS in the genetic characterization of DCM. Mutations in TTN and LDR remained the most common genetic causes of inherited DCM in this cohort of sporadic Tunisian DCM cases

Key words: dilated cardiomyopathy (DCM), Idiopathic, Variant detection, Whole-exome sequencing (WES), Heart failure

080

Poster 44: Screening of BRCA1 variants in Libyan breast cancer patients

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Introduction: Hereditary breast cancer is often linked to mutations in the BRCA1 and BRCA2 genes. This study aimed to investigate the prevalence of mutations in BRCA1 exons 2, 5, 8, 9, 11, 13, 18, and 20 among Libyan breast cancer.
Methods: Two cohorts of Libyan breast cancer patients, totaling 72 individuals, were recruited from Tripoli Central Hospital and Tripoli Medical Center. Participants were selected based on family history of cancer and early-onset breast cancer (<40 years). Genetic analysis was performed using Sanger sequencing.
Results: Six variants were identified in the BRCA1 gene, distributed across exons 2, 5, 8, 9, 10, and 18. Of these, one was a coding sequence variant in exon 2, while the remaining five were intronic. One variant was classified as benign, and the others were of uncertain significance.
Conclusion: This study revealed a spectrum of genetic variants in the BRCA1 gene among Libyan breast cancer patients with a family history of the disease. While some variants were benign, several remained unclassified, highlighting the need for further research to elucidate their clinical implications and potential role in breast cancer development.

Key words: Genetic variants, Breast cancer, Unclassified variants, Libyan

081

Poster 45: Strategy for Exploring the Genetic Landscape of Autism Spectrum Disorder in the Era of Genomics medicine: From Karyotyping to CGHarray and Beyond to Next-Generation Sequencing

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Introduction: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition. Although the etiology of ASD remains enigmatic, genetic factors play an important role. This study aimed to explore the genetic landscape of ASD by evaluating the relevance of Comparative Genomic hybridization using DNA microarrays in identifying genetic anomalies, while highlighting the potential offered by Next-Generation-Sequencing (NGS).
Methods: This study involved 404 autistic patients. A conventional R-banded karyotype was performed for all patients. Some patients with syndromic ASD were selected for array CGH and WES. Results: The karyotype identified chromosomal abnormalities in only 1% of cases while array CGH detected or characterize copy number variations(CNVs) in 9 patients. These CNVs were de novo in all cases: gain in 4 cases (X trisomy in two cases, a derivative of an extrachromosome 9, a supernumerary-marker chromosome) and 5 deletions (at 7q11.23, 10q26ter, 1p32.2, 1p34.2 and 18q22). Our results, along with those from the literature, show the significant contribution of rare variants to the genetic etiology of ASD. However, despite its advantages, array CGH has limitations, particularly in detecting subtle genetic variants. Interestingly, the patient harboring the 1p32 deletion underwent a WES but it was inconclusive. Nevertheless, advances in NGS offer promising prospects; a revolutionary tool in genetic exploration of ASD.
Conclusion: As NGS technology continues to evolve and costs decrease, a new exploration strategy "first-line Whole-Exome-Sequencing (WES)" that explores non-syndromic ASD for a more in-depth genome focus. A finer resolution and a better understand the pathophysiological mechanisms will be approved in order to play a more significant role in the ASD diagnosis and treatment.

Key words: Autism spectrum disorder, Comparative Genomic Hybridization, Sequence Analysis

081

Poster 46: In silico prospection of microorganisms producing biodegradable plastic from hypersaline

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Introduction: Plastic pollution presents critical environmental challenges and increasingly severe risks to human health. Conventional petroleum-based plastics are non-biodegradable, leading to the persistent accumulation of plastics in diverse ecosystems. Given the health risks posed by plastic pollution, including potential toxicity, cancer concerns, and disruptions to human biological systems, the need for sustainable and biodegradable alternatives has become urgent. such as polyhydroxyalkanoates (PHAs), which offer both biocompatibility and environmental degradability. This study aims to characterize hypersaline metagenome for discovering novel metabolic pathways involved in PHA production.
Methods: Next-generation sequencing (NGS) technologies specifically Oxford Nanopore long-read sequencing and Illumina short-read sequencing were used to generate metagenome from different hypersaline ecosystems. Hidden Markov Model (HMM) screening and bioinformatics tools were applied to identify key PHA biosynthetic genes and their associated pathways across hypersaline metagenome.
Results: HMM screening identified multiple gene clusters associated with PHA biosynthesis within the archaeal domain, revealing previously unknown pathways for PHA production. Genetic engineering techniques will be employed to validate their role in the production process.
Conclusion: Through the implementation of HMMs, a cluster of genes involved in PHA metabolism was identified, with a largely conserved structure of phaC which was found in a large array of halophilic micro-organism.

Key words: Plastic Pollution, Polyhydroxyalkanoates, Hypersaline Ecosystems, Next-Generation Sequencing, Hidden Markov Model

082

Poster 47: Allele Frequency and Implications for Benzodiazepine Metabolism in the Tunisian Population

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Introduction: Benzodiazepines are commonly prescribed for their sedative and anxiolytic effects. Their clearance from the body relies on glucuronidation, a process mediated by the UGT2B15 enzyme in the liver. Genetic variations in the UGT2B15 gene, such as the UGT2B15*2 (rs1902023, G>T) polymorphism, can affect drug metabolism and alter therapeutic outcomes. This study aimed to identify UGT2B15 polymorphisms and their prevalence in the Tunisian population.
Methods: This study was carried out on the Pharmacogenetic Platform of the National Center of Pharmacovigilance of Tunisia (CNPV). It involved 54 unrelated Tunisian volunteers. DNA was isolated from whole blood using the Blood gDNA MiniPrep System Extraction Kit (PROMEGA, ReliaPREP™ USA). The purity and concentration of extracted DNA were quantified using the Thermo Scientific™ NanDrop™ One Spectrophotometer, and the samples were genotyped for UGT2B15 polymorphisms using an Illumina Sequencing Kit on the iSeq 100 Sequencer. Results: Among the 54 sequenced samples, the most common mutation in the study population was UGT2B15*2 (rs1902023), with a frequency of 87%. Within this group, 40.4% of individuals were identified as having the homozygous mutant genotype (T/T), while 59.5% were heterozygous (G/T), demonstrating the presence of both alleles.
Conclusion: The UGT2B15*2 variant is highly prevalent in this population, with frequencies similar to those found in Caucasians (about 50%) and somewhat higher than in Hispanic, African-American, Chinese, Japanese, and Korean populations (36–49%) [2]. This polymorphism is linked to reduced clearance of drugs like oxazepam and lorazepam. Since oxazepam is an active metabolite of benzodiazepines such as diazepam and temazepam, its reduced metabolism may impact the clearance of these drugs as well [2,3]. Further studies are needed to understand how these genetic variations affect treatment outcomes by integrating genetic and clinical data.

Key words: Benzodiazepine metabolism, Genetic polymorphisms, Pharmacogenetics

083

Poster 48: Contribution of pharmacogenetics in the cardiovascular field, the example of statins: prevalence of genetic polymorphism in the Tunisian population

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Introduction: Statins are crucial for cardiovascular disease (CVD) prevention, but their effectiveness and tolerance can vary due to genetic factors. Key among these are polymorphisms in the organic anion transporting polypeptide 1B1 (OATP1B1; SLCO1B1) gene, which influence statin metabolism and risk of myotoxicity. The SLCO1B15 (rs4149056; 521T>C) and SLCO1B11B (rs2306283; 388A>G) polymorphisms are particularly notable, with SLCO1B1*5 being specifically recommended for genotyping to manage statin-associated muscle symptoms (SAMS) [1,2]. This study aimed to assess the prevalence of these SLCO1B1 polymorphisms in the Tunisian population.
Methods: This study, conducted at the pharmacogenetics department of the National Pharmacovigilance Center of Tunisia (CNPV), involved 54 Tunisian volunteers. DNA was isolated from whole blood using the Blood gDNA MiniPrep System Extraction Kit (PROMEGA) and quantified with the Thermo Scientific NanDrop One Spectrophotometer. SLCO1B1 polymorphisms were genotyped using the Illumina Sequencing Kit and iSeq 100 sequencer.
Results: Three SLCO1B1 polymorphisms were identified: SLCO1B11B (rs2306283; 388A>G) was present in 63% of individuals, with 44.1% homozygous (G/G) and 55.9% heterozygous (A/G). SLCO1B15 (rs4149056; 521T>C) was found in 29.6% of cases, with 12.5% homozygous (C/C) and 93.5% heterozygous (T/C). The SLCO1B1*15 mutation (rs2306283+rs4149056) was observed in 25.9% of participants. Conclusion: SLCO1B1 variant frequencies vary by ethnicity, with 5 found in 20% of Caucasians, 6–19% of Asians, and 4% of African Americans, and SLCO1B115 in 10% of Japanese, indicating higher myopathy risk [3]. Our findings align with Caucasian frequencies. SLCO1B1*5 genotyping is recommended to manage myotoxicity risks before starting statin therapy or if SAMS or rhabdomyolysis occurs [4]. Personalized treatment regimens based on these genetic insights could enhance clinical outcomes.

Key words: SLCO1B1 Polymorphisms, Statin-Associated Muscle Symptoms (SAMS), Pharmacogenetics

083

Poster 49: A Comparative Analysis of Circulating Microparticle Profiles in Sickle Cell Disease Patients and Healthy Subjects

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Introduction: Sickle cell disease (SCD) is one of the most common hereditary hemoglobin disorders worldwide. It results from a single nucleotide substitution in the gene encoding β-globin, leading to the production of abnormal hemoglobin, known as sickle hemoglobin. This mutation causes the formation of sickle-shaped erythrocytes, leading to abnormal interactions with other blood cells, including white blood cells, platelets, and endothelial cells. These interactions trigger the release of Circulating Blood Cell Microparticles (MPs) which range in size from 0.1 to 1.0 µm. MPs are released in response to oxidative stress, cellular activation, injury, or apoptosis. They possess pro-coagulant and pro-inflammatory properties and have garnered considerable attention for their potential role in modulating biological functions. Existing research suggests that MPs may be involved in the pathophysiology and subsequent manifestations of SCD. Therefore, this study aimed to determine the profiles of MPs in SCD patients and compare them with those of healthy subjects.

Methods: We recruited healthy volunteers and patients with homozygous SCD from the National Bone Marrow Transplant Center to participate in hematological and cellular tests. Blood samples were collected from all participants and analyzed for circulating MPs using flow cytometry. To identify the cellular origin of these MPs, we used multiple labeling with specific antibodies and dyes.
Results: The analysis revealed a clear increase in MPs derived from endothelial cells, platelets, and red blood cells in patients with sickle cell disease compared to healthy individuals. Conclusion: Our results suggest that MPs may contribute to the increased risk of thrombosis, chronic hemolytic anemia, and vaso-occlusive crises in patients with sickle cell disease.

Key words: Sickle cell disease, Microparticles, Flow Cytometry

084

Poster 50: Expanding DSD phenotypes associated with novel genomic variants, in Tunisian patients with 46,XY DSD

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Introduction: Disorders of Sexual Development (DSD) represent a major clinical concern that most often present in the newborn or the adolescent. Our study aims to determine the genetic etiology in a cohort of 46,XY DSD Tunisian patients and discuss genes that have been recently recognized to cause GD as well as new insights into the mechanisms by which well-established genes cause DSD.
Methods: A prospective analysis was conducted on a cohort of 25 XY female patients who consulted for unexplained amenorrhea from January 2018 to December 2021. All of them are from Tunisian ancestry and presented XY karyotype. The Patients underwent a complete clinical examination including genitalia examination, Imaging examination and hormonal evaluation. Whole exome sequencing (WES) was performed, and all pathogenic variants were validated by Sanger sequencing.
Results: WES revealed a likely pathogenic cause in 80% of cases with a various mutational spectrum. This includes rare and novel pathogenic variants in key players of testis-determination and new genes that are recently described to be related to XY DSD (SOX8, ZNRF3 and HHAT). Our study provides new insights about the molecular diagnosis of 46,XY DSD and highpoints the contribution of SOX8 and ZNRF3 proteins in male sex development Conclusion: This study shows the power of WES in detecting very rare genetic causes of DSD in genes such as ZNRF3, SOX8 or HHAT that would otherwise have been difficult to determine using other approaches. Reaching a specific genetic diagnosis at the appropriate time can help clinicians to establish the risk of malignant germ cell tumors since this last reached up to 30% in patients with 46,XY DSD. As genomic data continues to be generated from DSD cohorts, we propose several recommendations to help interpret the data and establish causality.

Key words: Disorders of sexual development (DSD), 46,XY DSD, Genetic diagnosis, Whole exome sequencing (WES)

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Poster 51: Triple Negative Breast Cancer in Tunisia: A Comprehensive Exploration Of The Epidimiological Features, Clinical Patterns And Genetic Profiles

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Introduction: Triple Negative Breast Cancer (TNBC) is a challenging subtype of breast cancer lacking estrogen, progesterone, and HER2 receptors. This study investigates the epidemiological and genetic characteristics of TNBC patients in Tunisia.
Methods: In our cohort of 172 TNBC patients, clinical data encompassed demographics, tumor characteristics, and lifestyle factors. Genetic analysis was conducted on 117 patients using gene panel sequencing, whole exome, and Sanger sequencing. Results: Clinical observations revealed that 45.28% were diagnosed at age 40 or younger, with 91.57% having invasive ductal carcinoma. A significant 66.67% exhibited Grade SBR III tumors, 89.86% had a Ki67 index over 20%, and 80.58% reported a family cancer history. 34.85% developed metastases, primarily in the brain and lungs. Genetic testing identified 16 patients with BRCA1 mutations. Notably, the BRCA1: c.211dupA mutation was found in four individuals from the northeastern region, while the BRCA1: c.5266dupC mutation was detected in two from the western region, along with other recurrent BRCA1 mutations in additional patients. Genetic analysis also revealed three variants of unknown significance (VUS) in three patients: two VUS on the BRCA2 gene and one VUS on the MSH6 gene.
Conclusion: The clinical profile, marked by early onset and high-grade tumor presentations, highlight the aggressive nature of TNBC in Tunisia. The identification of BRCA1: c.211dupA and c.5266dupC carriers in both the northeastern and western regions highlights complex local genetic predispositions. These findings are crucial for genetic counseling and personalized treatment, supporting tailored therapies such as PARP inhibitors for TNBC patients with BRCA1/2 germline mutations.

Key words: Triple Negative Breast Cancer, Precision oncology, Genetic testing, Tunisian population

086

Poster 52: Multiple Sulfatase Deficiency: a case report

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Introduction: Multiple sulfatase deficiency (MSD) is a rare autosomal recessive inborn error of lysosomal metabolism. The clinical phenotypic spectrum encompasses overlapping features of variable severity and suggests individual single sulfatase deficiencies (i.e., metachromatic leukodystrophy, mucopolysaccharidosis, and X-linked ichthyosis).
Methods: We describe a 7-year-old girl with hypotonia, developmental regression, progressive neurodegeneration, coarse facial features, and ichthyosis. Results: She has had generalized tonic seizures since she was 6 years old. The electroencephalogram showed a fast diffuse rhythm. The magnetic resonance imaging demonstrated a supra and sub tentorial cortico-subcortical atrophy associated with enlargement of the ventricular system and hypersignal involving the periventricular white matter. The identification of a homozygous pathogenic variant in the SUMF1 gene: c.836 C>T (p.A279V), by exome sequencing, confirmed the diagnosis of MSD.
Conclusion: Given the clinical heterogeneity of MSD, high-throughput sequencing is essential for confirming the diagnosis.

Key words: Multiple sulfatase deficiency, Clinic, Molecular diagnosis, Exome sequencing

087

Poster 53: Exome Sequencing Is an Efficient Tool for Neuronal Ceroid Lipofuscinosis Molecular Diagnosis

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Introduction: Neuronal ceroid lipofuscinosis (NCL) is a rare progressive neurodegenerative disorder. To date, 13 forms of NCL have been described and their clinical diagnosis remains difficult due to the similarity of clinical presentations. This study aimed to examine the clinical and genetic characteristics of NCL among Tunisian patients.
Methods: A Retrospective study of 17 patients, followed in the Pediatric Neurology and Medical Genetics departments at Hédi Chaker Sfax Hospital, for suspicion of NCL. The molecular study consisted of performing a targeted search for the 2 hot spot mutations in exon 6 of the TPP1 gene for 12 patients, and/or whole exome sequencing (WES) for 6 patients. Results: The average age of onset of symptoms was 2 years and 9 months. Epileptic seizures, noted in all our patients, were the main reason for consultation, and the most common type was myoclonus (17/17). Visual impairment was observed in 3 patients. Neurological examination revealed cerebellar ataxia in 11/17 patients and abnormal movements in 5/17. Brain MRI was performed in 15 patients, showing cortical and/or cerebellar atrophy (12/15) and periventricular white matter abnormalities (4/15). Targeted genetic analysis of the 2 mutations of the TPP1 gene was negative in all 12 patients. WES confirmed the diagnosis of NCL2 in 4 patients and NCL6 in 2 patients.
Conclusion: High-throughput sequencing is crucial for early diagnosis of NCL, enabling timely implementation of targeted therapies such as CLN2 enzyme replacement and providing families with appropriate genetic counseling.

Key words: Neuronal Ceroid Lipofuscinosis, Clinic, Molecular diagnosis, High-throughput sequencing

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Poster 54: The Response To Imatinib In Tunisian Patients With Fip1l1-Pdgfrαlpha Fusion: A Report Of 5 Patients With A Follow–Up Of 18 Months To 14 Years.

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Introduction: The FIP1L1-PDGFRA fusion gene (F/P) is an important oncogenic driver of chronic eosinophilic leukemia. The resulting F/P protein is a constitutive active tyrosine kinase that is highly sensitive to the Tyrosine Kinase Inhibitor (TKI) imatinib, and treatment with this drug results in rapid complete remission.
Methods: A retrospective descriptive study between January 2018 to January 2024, including patients presenting the F/P rearrangement in diagnosis, referred to the hematology laboratory of Pasteur Institute of Tunis to assess residual disease using nested RT-PCR on peripheral blood collected on EDTA. Results: The F/P was found in 12 patients, 11 male and one female. The mean age of positive patients was 46.7 [22–77]. F/P + patients were treated with imatinib 100mg/day. Complete hematologic response (CHR) was obtained in all patients. Only 5 patients benefited from molecular follow-up with a mean of 6 years [18 months-14 years]. For 3 patients the imatinib dose was tapered with a maintenance dose of 100 mg/d, allowing sustained CHR and CMR. Imatinib was stopped in 2 patients; 1 of them relapsed, but the other remained in persistent CHR or CMR for 5 years and then relapsed. 1 patient has beneficed from treatment free remission after 5 years and only 1 one patient was resistant to Imatinib and retained F/P + after 18 months. Conclusion: With this series of patients we can notice that the response to imatinib therapy is durable but depends on continuous therapy. At the least, we need to complete a large series to confirm these findings.

Key words: FIP1L1-PDGFRA, Eosinophilia, Imatinib

089

Poster 55: Impact of Blood Transfusions on Plasmatic Microparticle Levels in Beta-Thalassemia Major Patients

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Introduction: Microparticles (MPs) are submicrometric fragments released during the plasma membrane remodeling of cells undergoing apoptosis or activation. They prominently exhibit phosphatidylserine (PS) on their outer surface, along with additional surface markers characteristic of their cellular origin. Initially overlooked and dismissed as circulating platelet "dust" in plasma, MPs have recently garnered increased attention due to their implicated roles in various diseases, notably beta thalassemia. It is an hereditary blood disorder arising from diminished or absent synthesis of β-globin chains in hemoglobin, leading to an imbalance between alpha and non-alpha globin chains. Consequently, this disrupts membrane phospholipids in erythrocyes, promoting membrane blebbing and the release of pro-coagulant MPs.

Consequently, patients are at heightened risk of thrombotic complications. Individuals with beta thalassemia major, the most severe form of the disease, require regular blood transfusions to manage chronic hemolytic anemia effectively. Our aim is to compare the plasmatic microparticles levels among pediatric and adult beta-thalassemia major patients, before and after transfusion, to assess the impact of transfusions on MPs and to evaluate their potential use as cellular biomarkers for thrombotic risks.
Methods: We obtained informed consent from participants, including healthy donors and clinically diagnosed pediatric and adult polytransfused beta-thalassemia major patients from the National Bone Marrow Transplant Center in Tunis and the Rabta Hospital. We used flow cytometry to quantify apoptotic MPs originating from erythrocytes, platelets, and endothelial cells. Results: Our findings revealed significantly higher microparticle (MPs) levels in pediatric patients compared to adults, with a decrease post-transfusion. We also observed increased apoptotic MPs, particularly those derived from endothelial cells and erythrocytes, in comparison to healthy donors.
Conclusion: These results suggest that transfusions play a role in managing MPs concentration, in addition to treating chronic anemia. The elevated apoptotic MPs indicate excessive apoptosis and suggest a potential contribution of MPs to thrombotic risk. This underscores the potential of MPs as cellular biomarkers for thrombotic complications in beta-thalassemia.

Key words: Beta-thalassemia, Blood transfusion, Microparticles, Biomarkers

090

Poster 56: MMP-2 and MMP-9 Polymorphisms and Preeclampsia Risk in Tunisian Arabs: A Case-Control Study

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Introduction: The abnormal production of matrix metalloproteinases (MMPs), especially MMP-9 and MMP-2, plays a pivotal role in hypertensive disorders of pregnancy, and as such, can influence the development of preeclampsia. These alterations may result from functional genetic polymorphisms in the promoter region of MMP-9 and MMP-2 genes, which modify MMP-9 and MMP-2 expression.
Methods: We investigated the association of MMP-9 polymorphism rs3918242 (−1562 C>T) and MMP-2 polymorphism rs2285053 (−735 C>T) with the risk of preeclampsia. Results: An increased frequency of heterozygousMMP-9 −1562 C/T genotype carriers was observed in women with preeclampsia compared to healthy controls ($p = 0.03$). In contrast, the MMP-2 −735 C>T polymorphism was not significantly different regarding frequency distribution of the allele and genotype between healthy pregnant women and women with preeclampsia.
Conclusion: Our study suggests that the MMP-9 −1562 C/T variant, associated with high MMP-9 production, could be a genetic risk factor for preeclampsia in Tunisian women.

Key words: Genotyping, Preeclampsia, MMP-9, MMP-2, SNPs

091

Poster 57: Comprehensive Genetic Profiling of Triple-Negative Breast Cancer In Moroccan Patients: Insights From Whole-Exome Sequencing

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Introduction: Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer characterized by the absence of hormone receptors and HER2, resulting in limited treatment options and poorer prognoses. This study investigates the genetic landscape of TNBC in Moroccan patients through high-throughput whole-exome sequencing (WES) to identify genetic alterations that could enhance diagnostic accuracy and inform targeted therapies.
Methods: The study involved 10 unrelated Moroccan patients, with blood samples collected under ethical approval. Exome sequencing was performed using the Twist Human Core Exome kit on the Illumina NovaSeq 6000 platform, followed by variant detection using GATK. An in-house pipeline filtered for rare, protein-altering variants with a minor allele frequency (MAF) < 0.01.
Results: Analysis revealed 688,007 single nucleotide variants (SNVs) and 136,487 insertions/deletions (Indels). Key variants were identified in CTBP2, LRRK2, and ZNF334 genes, including a pathogenic variant in LRRK2 implicated in breast cancer pathogenesis, and a novel nonsynonymous variant in CTBP2. A variant of uncertain significance in ZNF334, was also identified, suggesting its role in tumor progression. Further analysis revealed that the genetic interaction between ZNF334 and CTBP2 underscores a complex regulatory network potentially affecting MYC activity, a key oncogene involved in cell proliferation and survival. Pathway analysis and gene-disease association studies, along with gene interaction assessments underscore the significance of these genetic alterations and their complex interplay in TNBC, suggesting that targeting these molecular interactions may offer novel therapeutic strategies for this challenging cancer subtype.
Conclusion: This research provides valuable insights into the genetic factors of TNBC in Moroccan patients, highlighting potential biomarkers and therapeutic targets for improved management of this challenging cancer subtype.

Key words: Triple-Negative Breast Cancer (TNBC), Whole-Exome Sequencing, Genetic Profiling, Moroccan Population, Pathogenic Variants

092

Poster 58: A rare supernumerary chromosome 15 following 3:1 segregation of a maternal t(11;15) balanced reciprocal translocation

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Introduction: Reciprocal translocation is a balanced structural chromosomal exchange. Patients with reciprocal translocations may have offspring with a variety of phenotypes as a result of the formation of unbalanced gametes.
Methods: The 9-month-old patient was referred for genetic investigations for facial dysmorphia, growth retardation and deafness. Lymphocytes R-band karyotypes were performed for the patient and her parents completed with FISH.
Results: The patient's karyotype showed a marker chromosome. The father's karyotype was normal, 46,XY; however, the mother's showed a reciprocal translocation, 46, XX, t(11;15)(q24;q15). FISH analysis showed that the marker was a derivative chromosome 15 resulting from the maternal reciprocal translocation. In the case of a reciprocal translocation, there are three possibilities of segregation. In order of type 2:2, type 3:1 type 4:0 segregations. We report the case of an infant with a derivative chromosome 15 supernumerated by a type 3:1 segregation of a maternal t(11;15)(q24;q15) reciprocal translocation. The reciprocal translocation in our case involved an acrocentric chromosome and a terminal breakpoint, explaining 3:1 segregation during gamete formation. Very few cases of t(11;15) reciprocal translocations have been published in the literature. Chromosome 15 is subject to genetic imprinting diseases. Abnormalities in the 15q11-q13 region are responsible for Prader-Willi syndrome and Angelman syndrome. The 3:1 segregation could lead to the loss of one copy of chromosome 15 and be the cause of Prader-Willi syndrome or Angelman syndrome, depending on whether the carrier of the translocation is the father or the mother respectively.
Conclusion: The discovery of this translocation implies a family investigation and genetic counseling.

Key words: t(11;15) balanced reciprocal translocation, Supernumerary chromosome 15, 3:1 segregation

093

Poster 59: Prenatal diagnosis of a mosaic X ring chromosome with omphalocele: a curious association

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Introduction: Ring chromosome is a rare structural abnormality in which the two ends of a chromosome fuse together to form a circular, ring-like structure. It can be associated with terminal breaks or It may be formed with telomere fusion without deletion. It can affect any human chromosome. Associate phenotype depends.
Methods: A 19-year-old, primigravida, nulliparous woman was referred to the Cytogenetics Department for antenatal diagnosis because of an omphalocele. Fluorescence in-situ hybridization (FISH) and R-banding amniotic fluid karyotype were performed. Results: Interphasic amniocytes FISH showed a chromosomal mosaic X monosomy. The karyotype confirmed the mosaicism and revealed a mosaic X-ring chromosome and monosomic X cells : 45,X[5]/46,X,r(X)[7]. Metaphasic FISH showed the deletion of the XIST gene on X-ring chromosome. X-ring chromosome is a rare entity and is mostly associated with Turner syndrome. The X ring chromosome can have various effects, depending on whether it is inactive or active. XIST gene (X inactive specific transcript) is responsible for the inactivation of the second X chromosome in women, ensuring the balance of X chromosome genes between the two sexes. X rings chromosome without the XIST gene cannot be inactivated and frequently associated with severe phenotypes including intellect deficiency, facial dysmorphia and congenital anomalies. This may be related to the functional disomy of the genes present in the ring.
Conclusion: Our case presents an unusual association between omphalocele and Turner syndrome with X-ring chromosome. Molecular analysis of the ring and the search for other genetic factors with a genotype-phenotype correlation is necessary to explain this association.

Key words: Prenatal diagnosis, X-ring chromosome, Omphalocele, Turner syndrome

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Poster 60: Mps1 knockdown in glioblastoma induces DNA damage and up regulation of histone methyltransferase SETD2

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Introduction: The diagnosis and treatment of glioblastoma is a real challenge due to the fast growing nature of the tumour. Finding new hallmarks of the disease is important for better patient care.
Methods: Kaplan-Meier curve analysis. To analyze a Kaplan-Meier survival curve, in function of Mps1 expression, we used the R2-Genomics analysis and visualisation platform (https://r2platform.com), developed within the Department of Oncogenomics the Academic Medical Center (AMC) in Amsterdam, the Netherlands. Gene ontology analysis Network analysis and Gene Ontology analysis associated with Mps1 silencing in U251 cells were obtained with the Cytoscape software and related plugin (GeneMANIA and ClueGO).
Results: In our study, we found that overexpression of the cell cycle checkpoint kinase Mps1 was associated with poor overall patient outcome. We then took advantage of available online data of transcriptomic and proteomic data after Mps1 knockdown in U251 glioblastoma cells and performed gene ontology enrichment analysis. We found that cell cycle transition and the intrinsic apoptosis pathway in response to DNA damage were the top pathways activated after Mps1 knockdown. 3 genes and proteins emerged as common targets, BCL2L1 (encoding the protein Bcl-xL) was found to be downregulated, and CDKN1A (encoding p21) and the SETD2 gene (encoding the histone methyltransferase SETD2) were found to be upregulated.
Conclusion: Our analysis is the first to report the association of Mps1 inhibition with SETD2 overexpression and suggests a new perspective for glioblastoma therapeutics.

Key words: Mps1, Glioblastoma, Gene Ontology, Transcriptomic, Proteomic, SETD2

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Poster 61: Genetic Comorbidity: When One Anomaly Can Hide Another One

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Introduction: The co-occurrence of genetic anomalies refers to the presence of two or more distinct genetic alterations in the same individual. The consequences of this co-occurrence on the phenotype can vary considerably, as the effects of the different anomalies can add up, cancel each other out or interact in unpredictable ways.
Methods: We report the observation of a patient referred for a polymalformative syndrome. A standard karyotype was performed, followed by fluorescent in situ hybridisation (FISH) for the 22q11 locus. Chromosomal microarray analysis (CMA) was then used on lymphocytic DNA. A multi-gene panel for anterior pituitary deficiencies was finally applied.
Results: The patient was referred at birth for polymalformative syndrome, including complex cardiac malformation and facial dysmorphia. Standard karyotype and 22q11-locus FISH were normal. On clinical follow-up, growth retardation and global developmental delay were noticed. The patient suffred also from recurrent hypoglycaemia episodes. Hormonal evaluation retained the diagnosis of anterior pituitary dysfunction and MRI scan revealed the absence of the pituitary stalk. CMA revealed a heterozygous interstitial deletion at 10q22.3q23.2 of approximately 7.4 Mb. This deletion was classified as pathogenic according to the American College of Medical Genetics (ACMG), as it could explain the congenital malformations and the developmental delay. Multi-gene panel analysis identified a heterozygous probably pathogenic nonsense variant in the *GLI2* gene, responsible for the hormonal dysfunction.
Conclusion: Our case highlights the need for a meticulous diagnostic methodology to accurately identify the genetic mechanisms underlying multiple congenital anomalies. Thus, improving the patient's management, and the family genetic counselling in a tailored approach.

Key words: Polymalformative syndrome, Co-occurrence, Chromosomal microarray analysis, Multi-gene panel analysis, Genetic conseling

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Poster 62: Molecular defects identified by whole exome sequencing in a child with Fanconi anemia

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Introduction: Fanconi Anemia (FA) is a rare genetic disease, characterized by genomic instability. congenital abnormalities, bone marrow failure, and a high cancer risk. FA is genetically heterogeneous and caused is by germline pathogenic variants in any of the 22 genes encoding for a group of proteins that cooperate in a unique FA/BRCA DNA repair pathway, Transmission is autosomal recessive except for the very rare X-linked or autosomal dominant forms. In Tunisia, previous reports showed that FANCA is the most frequent gene (94%) associated with FA and the deletion of exon 15 in the FANCA gene is a founder mutation present at a frequency of 54% among FA-A Tunisian patients.
Methods: We report here a young Tunisian patient referred for suspicion of FA. The chromosome breakage test has been performed using mitomycin C (MMC) while molecular analysis was realised by PCR and Sanger sequencing of exon 15 FANCA. In addition, whole exome sequencing was used to identify the affected gene(s).
Results: In this patient and in MMC treated cells, 21 % of metaphases showed chromosomal breakage with an average of 1 break/cell and no radial figures. As positive test is considered when at least 30% of metaphases with chromosomal breakage are found, a diagnosis of somatic mosaicism was strongly suspected. We found no deletion of exon 15. But we detected a novel mutation in the FANCE gene. Conclusion: In the current study, whole exome sequencing was used to identify the affected gene(s) in a boy with Fanconi anemia. It has allowed, for the first time in Tunisia, to describe a mutation in another gene than FANC A. Genetic testing in FA patients often requires a multi-method approach, not only to confirm the clinical diagnosis of FA in affected individuals, but also to enable identification of carriers of FA gene(s) alterations, as it has implications for diagnostic and genetic counselling process.

Key words: Fanconi anemia, Bone marrow failure, Chromosome breakage test, Mosaicism, Sequence analysis

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Poster 63: Molecular investigation of mutations in the hTERT gene responsible of telomerase reactivation in hematologic malignancies

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Introduction: Replication capacity is one of the most critical characteristics of cancer cells, which is achieved by telomere maintenance. Telomerase, a specialized DNA polymerase, is responsible for maintaining telomeres in the majority of human cancers, but its activity is absent in most normal somatic tissues. This differential role makes telomerase and its regulatory mechanisms cancer biomarkers with relevant implications in clinical practice Several studies have identified that hTERT reactivation in cancers, mainly in solid cancers, can be achieved via diverse mechanisms that involve amplification of the hTERT gene itself, activation or overexpression of cancer cell-specific oncogenic transcription factors, chromosomal rearrangements, and cancer-specific promoter mutations. Information on reactivation mechanisms in hematologic malignancies is not well characterized.

In this context, this study aims to establish the mutational profile in the promoter region of the hTERT gene in Tunisian patients with hematologic malignancies.
Methods: Sanger sequencing was performed on DNA extracted from peripheral blood of 42 Tunisian patients with hematologic malignancies, there are 7 patients with myelodysplastic syndrome, 11 patients with acute lymphoblastic leukemia and 8 patients with acute myeloid leukemia, 5 patients with chronic lymphoblastic leukemia, 8 patients with chronic myeloid leukemia and 6 patients with newly diagnosed acute leukemia.
Results: The identification of mutations in the TERT promoter and evaluation of the mechanisms responsible for the upregulation of TERT offers important information that can be used for diagnosis, prognosis, and treatment follow-up in hematologic malignancies.
Conclusion: A better understanding of these mechanisms could promote their translation into effective targeted therapies against cancer.

Key words: Ematologic malignancies, hTERT gene, Telomerase reactivation, Mutations in the hTERT gene

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Poster 64: PREMEDIT: A centralized platform dedicated to genetic diseases and medications in Tunisia

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Introduction: Genetic diseases pose a significant public health challenge as they are a leading cause of chronic morbidity and premature death. In Tunisia, there are 589 reported genetic disorders, with more than 60% being autosomal recessive. In 40 % of them, the molecular aetiology is unknown. This highlights the urgent need for advanced genetic research and diagnostic tools. Addressing this gap is crucial for improving patient outcomes and guiding effective therapeutic interventions.
Methods: A text mining using manual curation and AI is performed to collect complex genetic data on genetic diseases in Tunisia. Python and R scripts are used for data validation and biological database queries. Bioinformatic approaches are being used for in silico drug discovery and repurposing. Cutting-edge technologies are employed for data integration and development of the PREMEDIT platform. Results: To date, more than 600 genetic diseases have been identified in Tunisian patients with approximately 1000 mutations representing the most comprehensive mutatome of the Tunisian population. The genetic, epidemiological and pharmaceutical data have been integrated in a centralized platform called PREMEDIT.
Conclusion: By consolidating comprehensive data on genetic mutations and their correlation with specific treatments, PREMEDIT aims to enhance diagnosis and tailor therapeutic strategies for the Tunisian population. This platform serves as a crucial resource for healthcare professionals and researchers helping to bridge the gap between genetic research and clinical practice in Tunisia, contributing to innovation across the scientific and medical communities, pharmaceutical companies for a better patient quality of life.

Key words: PREMEDIT, Genetic diseases, Data integration, Tunisian population, Precision Medicine

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Poster 65: Genomic and Bioinformatics Advances in Cutis Laxa

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Introduction: Genetic diseases (GD) represent a significant public health in Tunisia, with over 60% of 589 identified diseases being autosomal recessive. Comorbidities, where two GD coexist, are increasingly recognized complicating diagnosis. In Tunisia, 40% of GD lack a defined molecular etiology, particularly in connective tissue diseases like cutis laxa (CL).
Methods: Six CL Tunisian families comprising seven patients were recruited. Whole exome sequencing (WES) was used among two families from southern Tunisia. For other families, Sanger sequencing was performed for mutations already identified by WES. In case of inconclusive results, WES will be conducted among them.
Results: Remarkably, broad clinical heterogeneity was observed among these families, even within the same family, making diagnosis more challenging. Bioinformatic WES data analysis identified a rare ATP6V0A2 gene mutation in both families, suggesting a founder effect. Additionally, a COL5A1 duplication was detected in one patient, indicating comorbidity with another ultra-rare disease. ATP6V0A2 gene mutation was also detected in two other families through targeted Sanger sequencing. WES will be performed in undiagnosed families for more reliable results. These findings facilitated the development of routine molecular diagnosis protocols for CL at Charles Nicolle Hospital and prenatal diagnosis for one family for improved genetic counselling and family support.
Conclusion: Post-genomic tools are expanding the mutational spectrum in Tunisia, significantly impacting disease diagnosis and management. Newly identified mutations are being incorporated into the PREMEDIT genetic disease database, which is set to revolutionize healthcare decision-making and drive innovative advancements across the scientific community, including clinicians, pharmaceutical companies, researchers and patients.

Key words: Cutis laxa, Genetic diseases, Molecular diagnosis, WES, Consanguinity, Founder mutation, Tunisia

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Poster 66: Investigating the Role of Hereditary Thyroid Cancer Predisposition in a Familial Cluster from Central Tunisia

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Introduction: Thyroid cancer is the most common endocrine malignancy, with its incidence increasing by 300% over the past three decades. Notably, it appears disproportionately common among individuals sharing a specific family name and originating from a particular region in central Tunisia, suggesting a potential thyroid cancer hereditary predisposition linked to endogamous practices in the area.

Methods: In this context, whole exome sequencing (WES) was performed on germline DNA from seven young patients with papillary thyroid cancer, all originating from this region and sharing the surname in question. Sanger sequencing of the TERTp, KRAS, HRAS, and BRAF genes was conducted on tumor DNA in three of these patients.
Results: WES revealed no germline variants indicative of a hereditary predisposition to thyroid cancer. This could be attributed either to the limitations of the technique, which cannot detect intronic or intergenic variants, or to the genuine lack of a hereditary predisposing factor. The high incidence of thyroid cancer in this family may result from a shared carcinogenic environment among the seven patients. The latter hypothesis is supported by the results of somatic analysis, which identified in three patients BRAF: p.Val600Glu mutation, commonly associated with sporadic cases of papillary thyroid cancer.
Conclusion: Our study supports the hypothesis that environmental factors may play a pivotal role in the elevated incidence of thyroid cancer within this family. Further investigation into shared environmental influences is warranted.

Key words: Familial Thyroid Cancer, Hereditary Predisposition, Environmental Carcinogenic Factors, Central Tunisia

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Poster 67: Effect of NGF and NTRK1 single nucleotide polymorphisms on acute coronary syndrome in the Tunisian population

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Introduction: Acute coronary syndrome (ACS) is a predominant cause of mortality. It arises from a multifactorial process that implicates environmental and genetic factors. Previous studies suggested the contribution of signaling pathways involving NTRK1 and NGF in ACS. We hypothesize that Single Nucleotide Polymorphisms (SNPs) in these genes might influence these pathways. Our study aims to elucidate the association between SNPs: NTRK1 rs6334(G/A), NGF rs6330 (G/A) and the risk of ACS.
Methods: A cohort of 238 patients diagnosed with ACS and 246 age and gender matched controls was assembled. Assessment on environmental exposures and medical history was conducted. Genotyping of the two SNPs was performed by Mutagenically separated polymerase chain reaction (MS-PCR). Results: The results of the MS-PCR showed no significant difference between the coronary patients and the controls for both NGF (G/A) and NTRK1 (G/A): p=0.874 and p=0.564, respectively. However, in smokers, individuals who were homozygous AA for the NGF gene showed a significant predisposition to ACS, with p= 0.013. In contrast, no association was found between this polymorphism and ACS in individuals with diabetes, dyslipidemia, or obesity.
Conclusion: Our findings suggest that the NGF (G/A) and NTRK1 (G/A) polymorphisms are not associated with an increased risk of ACS in our cohort. However,the homozygous AA genotype in NGF may confer a heightened susceptibility to ACS among smokers.

Key words: Acute coronary syndrome, NGF, NTRK1, SNPs, Association study

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Poster 68: EGFR mutations in Libyan lung cancer patients

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Introduction: Epidermal growth factor receptor (EGFR) gene mutations are frequently seen in non-small cell lung cancer (NSCLC), especially in the histology of adenocarcinoma. Ethnic groups differ in the prevalence of EGFR mutations; Asian people have been revealed to have a larger proportion of these mutations than Caucasian ones. Libyan data on these mutations are limited.
Methods: Between 2022 and 2023, tumor tissues from Libyan patients diagnosed with non-small cell lung cancer (NSCLC) were obtained from the pathology department of the National Cancer Institute-Misurata in order to determine the frequency and types of EGFR mutations. The Idylla-Biocartis System was used to assess tumors, and exons 18, 19, 20, and 21 were sequenced.
Results: Of the 71 patients that were enrolled, 59 (83.1%) were men and 12 (16.9%) were women. Thirteen cases (18.30%) out of the 71 lung cancer samples were positive for EGFR mutations. The exon 19 deletion (61.50%) was the site of the majority of mutations, followed by exon 21 L858 (30.80%) and exon 20 S768I (7.70%). The identification of an EGFR mutation was independently correlated with sex in individuals with advanced non-small cell lung cancer (50% female vs. 11.86% male).

Conclusion: Our findings confirmed the incidence of EGFR mutations and the genetic changes observed among NSCLC Libyan patients. Key words: Non-Small Cell Lung cancer(NSCLC), EGFR, Mutation.

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Poster 69: Unravelling the molecular etiology of Inherited Ichthyosis in Tunisian patients: A comprehensive In silico computational analysis of novel genetic variants.

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Introduction: Inherited ichthyosis (ICH) is a clinically and etiologically heterogeneous group of rare keratinization disorders, characterized by abnormal skin scaling and hyperkeratosis. The defective formation of intracellular lipid layers in the epidermal barrier is the main pathophysiological mechanism. So far, over 60 causative genes have been identified that affect skin barrier function. An insufficient correlation between disease-causing mutations and specific ICH phenotypes has been observed, and no curative therapy exists
Aims: This study aims to assess the impact of ICH-causative mutations on protein structure and function, enhancing our understanding of molecular mechanisms underlying skin barrier formation and identifying potential therapeutic targets.
Methods: Eight patients with different ICH phenotypes were enrolled. Whole-exome sequencing (WES) was used to determine the molecular etiology, while molecular docking studies evaluated the impact of mutations on protein structure, function, and the interaction between mutated proteins and potential ligands. Results: The previously frequent nonsense TGM1 (p.W263X) mutation was

identified in three patients. Moreover, three missense variants were identified: one in CYP4F22, documented in the literature, and two novel variants in PNPLA1 and KRT10, described as ICH-involved genes in the Tunisian population. Computational analysis predicted the loss of functional domains in the TGase-1 enzyme, resulting in the absence of catalytic function, contributing to severe phenotypes. The CYP4F22, p.D304E variant disrupts electrostatic interactions, blocking substrate access to the catalytic site. The effects of PNPLA1 and KRT10 variants on helical structures and calcium-binding sites were also assessed.
Conclusion: This study advances understanding of genotype/phenotype correlations in ICH and opens avenues for targeted therapies.

Key words: Bioinformatic analysis, Consanguinity, Inherited Ichthyosis, Molecular docking, Whole exome sequencing

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Poster 70: High-Throughput Sequencing: A Game Changer in Diagnosing Hereditary Colorectal Cancer

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Introduction: Colorectal cancer (CRC) can arise, in 2% to 5% of cases, in the setting of well defined inherited syndromes including Lynch syndrome (LS), familial adenomatous polyposis, MUTYH-associated polyposis, and certain hamartomatous polyposis conditions. We aimed to present our department's experience in diagnosing and managing hereditary CRC syndromes.
Methods: Our retrospective descriptive study included 10 patients referred to our oncogenetic consultation for suspected CRC predisposition. They underwent genetic investigation, clinical assessment, and molecular analysis by gene panel sequencing. Results: All patients came from unrelated families and three had consanguinous parents. Seven patients were referred for CRC (7/10), one patient for endometrial cancer (1/10), and one for cervical cancer (1/10). All patients had a significant family history of cancers. Molecular study identified pathogenic variants in several genes: in a heterozygous state in MLH1 (3/10), MSH2 (3/10) and APC (1/10) and in a homozygous state in MLH1 (1/10) and MUTYH (2/10). This confirmed LS in six patients (6/10), CMMRD in one patient (1/10) and MUTYH-associated polyposis in two patients (2/10). Genetic counseling was provided, and cascade screening was proposed for their relatives. This screening in the CMMRD patient enabled us to identify the same variant in a heterozygous state in his father, his mother, his brother, and unrelated sister-in-law. These individuals were therefore predisposed to developing cancers associated with LS, and appropriate management was initiated.
Conclusion: High-throughput sequencing has revolusionized CRC management. It facilitates, in addition to rapid diagnosis, personalized risk assessment, guiding preventative measures and tailored treatments for patients and their families.

Key words: Colo-rectal Cancer, NGS, MMR, APC, MUTYH

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Poster 71: Should the ATM gene still be overlooked in hereditary breast cancer in the Tunisian population?

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Introduction: The ATM gene plays key roles in DNA damage response and suppression of cancer. Recently, ATM germline pathogenic variants have been found to be associated with several types of cancers. Our objective was to highlight the role of the ATM gene in the diagnosis of hereditary breast cancer in the Tunisian population.
Methods: Our study involved three patients (P1, P2 and P3) referred for clinical suspicion of a cancer predisposition syndrome. Following a family investigation genomic DNA was extracted. Molecular study was conducted using the TruSight Hereditary Cancer Panel on an Illumina NextSeq 550. Variants were confirmed by Sanger sequencing.
Results: Our patients were three unrelated women aged 40, 47 and 64 years old. P1 was from Gabes, P2 from Monastir and P3 from Sfax. P1 and P2 were referred for BC and P3 for rectal cancer. All had a strong family (F) history of cancers mainly BC : six cases in F1, nine cases in F2 and eight cases in F3. Molecular study identified two variants in a heterozygous state in the ATM gene. The (NM_000051) c.6115G>A p.(Glu2039Lys) was found in P2 and P3. This likely pathogenic variant has already been reported in Tunisia. The (NM_000051) c.5716C>T (p.Gln1906Ter) pathogenic variant was found P1.
Conclusion: With the rise of precision medicine, integrating ATM genetic testing into routine breast cancer risk assessments, especially in families with a high prevalence of breast cancer, can lead to more tailored treatment and preventive approaches.

Key words: ATM, Hereditary breast cancer, NGS, Cancer predisposition

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Poster 72: Further evidence of the contribution of Structural Variation in Hearing Impairment etiology: First report of STRC-related Copy Number Variations in Tunisia

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Introduction: Hearing impairment (HI) is a common neurosensory disorder worldwide, affecting 1–2/1000 newborns and over 5% of the global population. About 50% of HI cases are genetic, with CNVs contributing to 18.7%. Tunisia, like other MENA countries, has high consanguinity, increasing autosomal recessive HI cases. Screening for the c.35delG variant in the GJB2 gene (35% of recessive HI cases) is recommended. However, the CNVs screening remains underexplored due to limited technology access. This study aims to

investigate the contribution of CNVs in the molecular etiology of HI in GJB2-negative Tunisian individuals, with a focus on the STRC gene (DFNB16-locus) which is the second most common cause of moderate HI after GJB2.
Methods: WES was performed in six cases with HI ranging from moderate to severe. Firstly, WES data analysis was conducted to explore potential single nucleotide variants (SNVs) in a list of 298 prioritized genes. For CNVs, an in-house R pipeline was optimized. Secondly, experimental validation of the identified CNVs was carried out using Touchdown-PCR and Sanger sequencing.
Results: Two large deletions, encompassing the STRC gene, were identified in two cases exhibiting moderate and severe HI. One of these deletions includes the CATSPER2 gene associated with Deafness-Infertility-Syndrome. Experimental validation further confirmed the identified deletions. Conclusion: To our knowledge, this study highlights for the first time the contribution of CNVs in the molecular etiology of HI in Tunisia. Therefore, it is recommended to integrate CNVs analysis into genetic diagnostic approaches and include DFNB16-locus screening in the genetic diagnostic workflow for GJB2-negative cases.

Key words: Bioinformatics analysis, Copy Number Variants (CNVs), Hearing impairment (HI), STRC gene, Whole Exome Sequencing (WES)

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Poster 73: Exploring The Variation of TAS2R38 In North Africa

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Introduction: The present study focuses on the SNP variation of the TAS2R38 (TASTE 2 Receptor member 38) locus in Northern Africa a part of the world that is relatively understudied. This locus codes for taste receptors implied in the perception of bitter taste. Our study analyses the diversity in North Africa of the functional SNPs rs713598 and rs1726866 in the context of the locus global diversity.
Methods: Two of the three functional SNPs at the TAS2R38 gene (rs713598 and rs1726866) were previously genotyped with Taqman in 375 unrelated subjects (305 Tunisians from seven sites: Mahdia, Sousse, Kesra, Nebeur, Kairouan, Smar and Kerkennah plus 70 Libyans). Using ARLEQUIN (ver 3.5.2.2) software, we computed the allele frequencies, the expected heterozygosity and performed the Hardy-Weinberg Equilibrium test as well as the Exact Test of Differentiation. Then we used Phase.2.1.1 to reconstruct the genotypes. The haplotypes and genotypes were then compared to data from global populations.
Results: Our main result is represented by the frequencies for each of the four possible haplotypes. Considering rs713598 and rs1726866 respectively, the nucleotide haplotype (C-A) leading to the amino acid haplotype PV is extremely rare almost everywhere, but is relatively frequent (between 6% and 10%) in North Africa where it coexists with the globally common haplotypes (PA, AA, and AV).
Conclusion: Given its higher frequency in North Africa, the haplotype (C-A) may be used as a biogeographic marker.

Key words: TAS2R38, Bitter taste, Autosomal SNP, Diversity, North Africa

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Poster 74: Investigating HTERT Gene Promoter Methylation in Various Forms of Leukemia: Insights from the Tunisian Population

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Introduction: The HTERT gene (Human Telomerase Reverse Transcriptase) encodes the catalytic subunit of the telomerase enzyme, which is crucial for preserving the length of telomeres and maintaining the replicative potential of cells while preventing cellular senescence. Studies have revealed that overexpression of the HTERT gene is a hallmark of most human cancers, as it allows cells to divide indefinitely and become resistant to apoptosis. This overexpression is primarily attributed to aberrant epigenetic regulation, particularly DNA methylation at promoter regions. In this study, we aim to investigate the methylation status of the promoter region of the HTERT gene as a hallmark of several forms of leukemia in the Tunisian population.
Methods: We conducted an MS-PCR assay using peripheral blood DNA from consenting patients admitted to the Clinical Hematology Department at CHU Farhat Hached Sousse, who were diagnosed with various forms of leukemia. We selected primers specifically to assess the methylation status of the targeted promoter regions of the HTERT gene.
Results: We successfully designed primers to amplify both methylated and unmethylated regions of the HTERT promoter. We assessed the methylation status of the HTERT gene in several forms of leukemia, and specific promoter regions showed varying degrees of methylation.
Conclusion: The detected methylation alterations could potentially serve as biomarkers for diagnosis or prognosis and might offer new targets for therapeutic intervention. Further investigation into how these changes impact disease progression and treatment responses is warranted.

Key words: HTERT, Epigenetics, DNA methylation, Leukemia, Tunisian population, Biomarkers

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Poster 75: Genetic Exploration Of Childhood Epilepsy: Advances And Implications For Personolized Medicine

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Introduction: Childhood epilepsy, a complex neurological disorder affecting around 4,000 children under the age of 10 each year, presents a major diagnostic challenge, with 20–30% of cases resistant to

standard treatments necessitating advanced genetic analysis to uncover underlying causes. Genetic factors, implicated in 70% of cases, underline the importance of genomic analysis in understanding and managing this disease.
Methods: In this study, We analyzed 38 pediatric patients referred to the Genetics Department of Farhat HACHED Hospital for genetic evaluation of epilepsy. All patients underwent standard karyotyping, as well as additional analyses such as CGH array FISH and exome sequencing.
Results: One patient was diagnosed with Klinefelter's syndrome and another with X chromosome inversion. CGH array analysis was performed on eleven patients, and exome sequencing on seven, revealing two pathogenic mutations: a heterozygous variant in the SLC35A2 gene and a substitution in the GOLGA2 gene. Confirmation of these mutations by Sanger sequencing is in progress.
Conclusion: This study highlights the importance of incorporating a range of genetic testing techniques, from cytogenetics to nmportant than the literature datas ,where exome sequencing yields a diagnostic rate of 20–25%, this difference may be due to the small size of thecohort.
These results support the potential of personalized medicine in epilepsy, where treatments are increasingly tailored to the genetic profile of each patient, leading to more effective and better-tolerated therapies.ext-generation sequencing, in the diagnosis of childhood epilepsy. While traditional cytogenetic approaches detect abnormalities in less than 4% of cases, CGH array can identify pathogenic CNVs in 10–15% of pediatric epilepsy cases. The exome sequencing in this study identified two pathogenic mutations, which account for 7% of the identified genetic abnormalities.

Key words: Epilepsy, Cytogenetics, CGH-array, Exome sequencing

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Poster 76: Correlation of epigenetic markers with Glioblastoma patients' survival and molecular subtypes

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Introduction: Glioblastoma (GB) is a heterogeneous group of tumors with poor patient's outcome. The epigenetic markers could influence patient's outcome and add more precision in GB sub-typing.
Methods: Our study objective was to determine a correlation between the methylation status of 65 genes and the overall survival (OS) in 50 GB Tunisian patients using Methylation Specific-MLPA technique.
Results: OS was significantly longer for patients with tumors harboring unmethylated tumor suppressor genes ATM, BRCA1, BRCA2, TP53 and TP73 and the DNA repairing gene MSH6. Furthermore, simultaneous unmethylation of ATM, BRCA2, CD44 and VHL genes was associated with GB presenting normal EGFR status. Depicting, thus, a better prognosis GB group (OS=15 months, p=0.005). Our results showed also that, combined methylation of TP73, THBS1, GSTP1 and ESR1 genes in amplified EGFR GB subtype resulted in a poor prognosis group (OS=3 months, p=0.041).
Simultaneous methylation of HLTF and SFRP5 genes was associated with wild-type IDH1 GB defining therefore a very poor prognosis group (OS=1 month, p=0.026). Besides, BRCA1 methylation in wild-type IDH1 group was significantly associated with poor prognosis (OS= 6 months, p=0.002). Interestingly, RBM14 and PCCA genes were co-methylated in 80% of prolonged survival GB cases (GB+). In absence of EGFR amplification and with unmethylation of BRCA1, BRCA2, ATM, VHL, CD44, HLTF and SFRP5 genes, GB+ tumors seem to respond better to treatment, avoid the relapse and confer prolonged survival (> 36 months).
Conclusion: Combining epigenetic biomarkers with molecular subtypes will help in improving GB prognosis evaluation as well as patients' outcome.

Key words: Glioblastoma, Prognosis, Tumor suppressor genes, Methylation, Epigenetic markers

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Poster 77: Advances in Diagnostic Strategies for Intellectual Disability: Insights from Clinical and Genetic Characterization of a Patient Cohort

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Introduction: Intellectual disability (ID) is a clinically and genetically heterogeneous condition that affects 1–3% of the world's population. Recent studies estimate that a genetic origin could be found in 60% of affected patients, in the form of a multitude of rare causes, some of which have yet to be identified. Because of this extreme genetic heterogeneity, diagnostic strategies are complex. Recent technological advances in cytogenetics and next-generation sequencing (NGS) have revolutionized the diagnostic management of intellectual disability.
Methods: A total of 27 patients with intellectual disability (ID) were included in the study, with ID assessed through neuropsychological evaluations and developmental data (schooling, autonomy…). All patients underwent standard karyotyping, with 9 referred for targeted FISH analysis due to clinical signs indicative of specific syndromes. Additionally, 11 patients had chromosomal analysis using DNA microarrays (CGH array), and exome sequencing was performed on 9 patients.
Results: The study achieved an 11% positive diagnosis rate, identifying structural chromosomal abnormalities in 3.7% of casesby conventional and molecular cytogenetic: a supernumerary chromosomal marker and a 1p36 microdeletion. A likely pathogenic variant in the POU3F3 gene, classified according to ACMG guidelines, was identified through exome sequencing. Recent research shows that while chromosomal anomalies are a major cause of intellectual disability (ID), newer techniques like CGH-array and next-generation sequencing (NGS) have boosted diagnostic rates to up to 70%.
Conclusion: This study highlights the significant genetic heterogeneity of intellectual disability (ID) and underscores the importance of combining conventional, molecular cytogenetic, and high-throughput sequencing techniques in diagnosis, with whole-genome sequencing (WGS) increasingly used in research, and debates around the use of WES and WGS in individual or trio testing.

Key words: Intellectual disability, Cytogenetic, Karyotype, FISH, WES

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Poster 78: hTERT gene expression as a monitoring biomarker in malignant hemopathies

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Introduction: Telomerase expression alterations have been reported in various kinds of hematological malignancies and some of them appear to have prognostic significance. High telomerase activity is reported in most patients with acute leukemia and is associated with poor prognosis in both acute lymphocytic leukemia and acute myeloid leukemia.
This study aims to quantify the hTERT transcript in Tunisian patients with malignant hemopathies, to investigate whether levels of hTERT mRNA expression reflect the tumour burden and are associated with prognosis and clinical course in these patients.
Methods: 42 peripheral blood-specimens from 42 patients diagnosed with malignant hemopathies were included in our study: 14 patients with acute lymphoblastic leukemia, 8 patients with actue myeloid leukemia, 8 patients with chronic myeloid leukemia, 4 patients with chronic lymphocytic leukemia, and 8 patients with myelodysplastic syndromes. The mean age of the patients was 54 years, ranging from 3 to 87 years.
We measured expression levels of hTERT mRNA by quantitative real-time RT-PCR (RocheLC480).
Results: Quantification of the hTERT gene is performed in patients in different stages of haematological malignancies. These quantifications were compared between two groups: those at the initial diagnosis and those in ongoing follow-up. Statistical software is employed to perform these comparisons rigorously. Variations in HTERT gene levels are correlated with disease progression, making this data highly valuable.
Conclusion: By quantifying hTERT levels, we can enhance patient management, particularly for those who lack available cytogenetic or molecular markers for disease monitoring. Our data indicate that hTERT expression in malignant hemopathies may serve as a molecular prognostic marker.

Key words: Malignant hemopathy, hTERT gene transcript, Quantitative PCR, Diagnostic and prognostic biomarker

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Poster 79: Whole-Genome Shotghun Sequencing of Streptomyces Cyaneofuscatus Ctm50504 Expands Understandings of Extremozymes

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Introduction: Selected genomics-based studies have shown that microorganisms living in extreme environments restructure their genomes using various approaches such as insertion or reduction of genome size; gene reshuffling through displacements and gene reorganization; GC Chargaff skewness in the genome; horizontal gene transfer; change in polyploidy level; and a preference for specific codon usage in genes whose products are required during adaptations to ecological inhospitable biotopes.
Methods: Next-generation sequencing (NGS) methods quantify the functionality and dynamics of microorganisms in their biotopes. Enormous volume of data NGS produces necessitates understanding structural and functional genomics through omics techniques. Streptomyces cyaneofuscatus strain CTM50504 is a potential extracellular hydrolase producer, isolated from a terrestrial hot spring in Korbous (Nabeul, Tunisia). This polyextremophilic Actinomycetota strain can grow at 50 °C and a pH range of 6–9. It requires the presence of NaCl for growth and secretes lipases, phospholipases, proteases, amylases, and chitinases. The whole-genome shotgun sequence (WGS) analysis was performed on strain CTM50504 to identify protein-encoding genes, including hydrolases.
Results: The genome sequence was assembled into 1,252 contigs with an average G+C content of 71% and a total length of 8,591,922 bp. Genome annotation revealed 770 protein-coding enzymes with 323 open reading frames (ORF) encoding for hydrolases, including 10 phospholipases, 20 lipases, 179 proteases, 5 amylases, and 5 chitinases. The assembly of WGS was deposited in the DDBJ/ENA/GenBank databases under the sequence read archive accession number PRJNA1065629.
Conclusion: This study is the first to target the hydrolase repertoire of a Streptomyces cyaneofuscatus strain, providing insight into the tremendous biotechnological potential of the enzymes identified.

Key words: Extremophiles, Hydrolases, Whole-Genome Sequence, Illumina, Assembly, Annotation

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Poster 80: Genetic Analysis Of Acute Myeloid Leukemia

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Introduction: Understanding the molecular abnormalities in acute myeloid leukemia (AML) has indeed revolutionized our comprehension of its biology and prognosis. Two recurrent mutations, NPM1 and FLT3-ITD, have emerged as crucial markers in AML.
NPM1 mutations are often linked with a favorable prognosis in AML cases. NPM1 (nucleophosmin 1) is a gene that encodes a nucleolar phosphoprotein involved in various cellular processes, including ribosome biogenesis and regulation of cell growth. Mutations in NPM1 typically involve the insertion of nucleotides in exon 12 of the gene, leading to the abnormal cytoplasmic localization of the protein. These mutations are associated with a specific subtype of AML and are often seen in cases with a normal karyotype. Patients with NPM1 mutations typically respond well to standard chemotherapy and have a higher likelihood of achieving complete remission, resulting in a favorable prognosis.
On the other hand, FLT3-ITD mutations represent an independent poor prognostic factor in AML. FLT3 (Fms-like tyrosine kinase 3) is a receptor tyrosine kinase involved in regulating cell survival and proliferation. Internal tandem duplications (ITDs) in the FLT3 gene result in constitutive activation of the receptor, leading to uncontrolled cell growth and proliferation. FLT3-ITD mutations are associated with a more aggressive disease course, higher rates of relapse, and poorer overall survival compared to AML cases without FLT3 mutations.

However, targeted therapies against FLT3 mutations, such as FLT3 inhibitors, have shown promise in improving outcomes for patients with FLT3-ITD-positive AML.
Methods: An NPM1 and FLT3-ITD multiplex polymerase chain reaction assay was optimized to screen AML patients for the respective mutations and were confirmed using Sanger sequencing.
Results: The identification of NPM1 and FLT3-ITD mutations has not only improved the understanding of AML's molecular underpinnings but has also enhanced risk stratification, allowing for personalized treatment approaches.
Conclusion: This progress in understanding AML's molecular abnormalities marks a significant step toward more personalized and effective treatment strategies in oncology.

Key words: Acute myeloid leukaemia (AML), NPM1, FLT3-ITD

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Poster 81: Genetic analysis of ataxia-telangiectasia in Tunisian children

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Introduction: Ataxia-telangiectasia is a rare autosomal recessive disorder due to a DNA repair defect characterized by progressive neurological impairment with cerebellar syndrome, oculocutaneous telangiectasias, defects in B- and T-cell-mediated immunity, and increased susceptibility to malignancies. High sensitivity to ionizing radiation limits patient treatment. A-T is caused by loss of function of the ATM gene (11q22.3), which encodes a protein kinase involved in double-strand break DNA repair. Few clinical studies on A-T disease have been conducted in Tunisia. Our aim is to determine the clinical and genetic spectrum of Tunisian A-T patients and to explore the potential underlying mechanism of variant pathogenicity.
Methods: High-throughput sequencing was performed on patients with clinical A-T. All pathogenic and probably pathogenic variants were confirmed by a second appropriate technique in all patients and their parents.
Results: We enrolled 3 children with a mean age at diagnosis of 3 years. We performed exome sequencing in one child and a panel of 31 genes in 2 children. We found pathogenic or probably pathogenic variants in all cases, in the ATM gene, in homozygous (2 cases) or compound heterozygous state (1 case). All parents are heterozygous. These 4 variants are in exons 5, 26 and introns 38 and 60. Among them there is one nonsense variant, one nucleotide duplication and two variants affecting the canonical splice sites. Two variants were reported in Tunisian children.
Conclusion: Our study characterizes the mutational landscape of A-T in Tunisian patients, which will allow to set up genetic counseling, prenatal diagnosis, and cancer predisposition research for families.

Key words: Ataxia-telangiectasia-ATM-Sequencing

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Poster 82: Genetic landscape in North Africa, Middle East and South Europe based on pharmacogenomic variants

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Introduction: This study is focused on the genetic variation of 157 variants located in 36 pharmacogenes. A total of 242 healthy samples from 8 different populations: Tunisia, Libya, Spain, Italy, Saudi Arabia, Kuwait, Bahrain and Turkey were analyzed.
Methods: Markers were genotyped using Sequenom's high-throughput matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) with the iPLEX® ADME PGx Pro Panel and the iPLEX ADME CYP2D6 Panel. The results were visualized with the MassARRAY® Analyzer 4 System (Agena Bioscience).
Statistical analyses were elaborated using the packages of R. Minor allele frequencies (MAF) of SNPs were calculated and used together with data from GnomAD database to generate a Principal Component Analysis (PCA). Then the genetic distance matrix calculated based on MAFs has served to establish a Multidimensional Scaling (MDS). Haplotypic data coded into classes were applied to perform binary logistic regressions leading to the prediction of each population's specific model based on significant genes. The 8 obtained models have been used to establish the genetic profile of each population through Classification and Regression Trees (CART).
Results: Only 18 genes were retained in 8 distinct models characterizing each population separately. The pharmacogenes NAT1, GSTM1, CYP1A2, CYP2E1, VKORC1, ABCB1 and ABCG2 were observed in more than 5 models. The CART algorithm based on the established models has led to a specific haplotypic profile for each population, significantly different from the others (Chi-squared tests) with high levels of accuracy and sensitivity.
Conclusion: Each geographic region is characterized by its specific profile based on genetic variants of the pharmacogenes.

Key words: Pharmacogenetics, Variants, MAF, Populations, Model, PCA, MDS

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Poster 83: Diagnostic Efficiency of Whole Exome Sequencing for Hereditary Cancer Predisposition in the Tunisian Population

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Introduction: Genetic counseling plays a crucial role in identifying hereditary cancer predisposition, allowing for personalized

management plans that can significantly enhance patient outcomes. With advancements in genetic testing, the focus is shifting from analyzing individual genes or syndromes to broader, more comprehensive studies using Next-Generation Sequencing (NGS). Although this approach is becoming increasingly available, its diagnostic value among Tunisian patients remains underexplored. We report our clinical laboratory's experience with whole exome sequencing (WES) as a diagnostic strategy in this specific context.
Methods: The present study was carried out on a cohort of patients referred to the genetic department of the Farhat Hached University Hospital (Sousse, Tunisia) for genetic counseling related to hereditary cancer predisposition. All selected patients underwent WES.
Results: Our cohort included 63 patients with an average age of 39.5 years. Among them, 60.3% had a family history of cancer in either the first or second degree. WES yielded positive results in 14.3% of our patients, identifying 10 pathogenic and likely pathogenic variants. Additionally, 11% of cases revealed variants of uncertain significance (VUS). Notably, five of these variants were not previously documented in literature. These novel variants were classified as follows: 1 pathogenic, 1 probably pathogenic, 2 hot VUS and 1 warm VUS. In addition, two patients (1.5%) had incidental findings.
Conclusion: WES is a valuable alternative for diagnosing hereditary cancer predisposition. However, it is important to acknowledge the limitations of this approach, as demonstrated by the high percentage of negative results.

Key words: Hereditary Cancer Predisposition, Whole Exome Sequencing, Tunisian Population

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Poster 84: Sex chromosome 45,X/46,XY mosaicism in infertile men

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Introduction: Mosaicism 45,X/46,XY is a rare gonosomal abnormality characterized by a broad phenotypic spectrum, ranging from women with or without Turner syndrome stigmata, to men apparently normal, passing by the ambiguous phenotypes.
Methods: A patient was referred to the Genetics Department of Farhat-Hached Hospital (Sousse, Tunisia) due to primary infertility of 2 years duration related to azoospermia. He underwent semen analysis, constitutional karyotype analysis using the R-banding technique, Fluorescence In Situ Hybridization (FISH) analysis and Y chromosome microdeletion screening using the Multiplex-Ligation-dependent Probe Amplification (MLPA) technique.
Results: The patient exhibited an adult male phenotype, with notable physical anomalies including short stature, a low posterior hairline, webbed neck, and low-set ears. He had a history of unilateral cryptorchidism corrected during childhood. Testicular ultrasound revealed a hypotrophic right testicle and a normal left one. Biochemical and semen analysis showed secretory azoospermia. Karyotype analysis revealed 45,X(77%)/46,X,der(Y)(23%) mosaicism. FISH performed on cells from the buccal mucosa showed that 30% had an X signal, while 70% were 46,XY. The SRY-specific FISH results were normal in the 46,X,der(Y) cells. MLPA analysis revealed the presence of several cell clones, some lacking the Y chromosome and others with variable levels of deletions, involving the AZF regions.
Conclusion: Although early theories emphasized the ratio between X0 and XY cells, it has been suggested that these proportions may shift after testicular differentiation. In cases with a higher percentage of 46,XY cells and no SRY deletion, micro-TESE is recommended as a potential option for assisted reproductive technology.

Key words: Infertility, Gonosomal Mosaicism, AZF deletion

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Poster 85: Machine learning prediction of human allergy to plant-derived protein

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Introduction: Despite the advancements in healthcare, food allergies remain a significant public health challenge due to the severity of their effects and the unpredictability of their onset. One of the key applications of ML is the modelling of protein functions. This study aims to investigate the ability of ML algorithms to predict allergenicity of plant proteins using sequence-based features.
Methods: Different sequence-based features were extracted from protein sequences and used as input for seven classifiers: RF, SVM, LR, KNN, XGBoost, LightGBM, and MLP. The models were trained on each feature group and evaluated using a separate validation set, with performance assessed by Accuracy, Precision, Recall, F1 score, and MCC.
Results: The evaluation of trained classifiers revealed that the best-performing combination was LightGBM with RF-selected features, achieving an accuracy of 93.94%, an MCC of 0.8763, and an F1-score of 0.9470. However, it was surpassed in Precision (0.9626) and Recall (0.9773) by a KNN trained on physicochemical and sequence features respectively. The RF-selected features (585) outperformed the full set of features (2415). Among others, 56 n-grams, 72 Distribution and 145 Conformation features were selected as important, strengthening the biological notion that specific motifs trigger allergic responses.
Conclusion: Understanding allergenic proteins is crucial for improving human health outcomes, particularly in individuals genetically predisposed to allergies. Although traditional ML classifiers are effective in predicting allergenicity, their efficacy is mostly reliant on the training dataset and features. DL models offer a promising alternative, as they excel with high-dimensional embeddings and can capture effectively the complex features of a protein.

Key words: Machine Learning, Food Allergy, Prediction, Feature Extraction

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Poster 86: Evaluating a Variant of Uncertain Significance (VUS) in Familial Hematological Disorders: A Bioinformatics Perspective

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Introduction: Variants of uncertain significance (VUS) identified in hematological malignancies pose a significant challenge in clinical practice. Bioinformatics tools can aid in predicting the pathogenicity of these variants, providing valuable insights into their potential role in disease development.
we aim trough this study to explore the potential pathogenicity of a specific VUS identified in the context of familial hematological malignancies through a comprehensive bioinformatics analysis.
Methods: The variant's impact on protein structure and function was assessed using various bioinformatics tools. These included tools for protein sequence alignment (BLAST), protein structure prediction (AlphaFold), and pathogenicity prediction (PolyPhen-2, SIFT). Additionally, the variant's frequency in control populations was evaluated using public databases (e.g., gnomAD). Additionally, we utilized structural modeling with SWISS-MODEL and assessed evolutionary conservation through multiple sequence alignments to understand the variant's impact on protein function.
Results: The bioinformatics analysis revealed that some identified VUS was located critical conserved region of the protein, suggesting a potential functional impact. However, despite these indicators of potential pathogenicity, clinical data from familial cases did not fully confirm the variant's role in the disease. Some variant's frequency in control populations was found to be low wich may supporting its potential association with hematological malignancies.
Conclusion: Bioinformatics tools provided valuable insights into the potential pathogenicity of the identified VUS in familial hematological malignancies. While the results were inconclusive, the low frequency of the variant in control populations and its predicted impact on protein structure and function suggest that it may be a contributing factor to disease development. Further functional and clinical studies are warranted to definitively determine the variant's significance and its role in the pathogenesis of hematological malignancies.

Key words: Variant of Uncertain Significance (VUS), Bioinformatics, Familial hematological malignancies, Computational prediction, Genetic variant analysis

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Poster 87: Identification by Whole Exome Sequencing of an ancestral deletion in CFAP251 in Tunisian infertile men with Multiple Morphological Abnormalities of the Sperm Flagellum

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Introduction: Multiple Morphological Abnormalities of sperm Flagellum (MMAF) is a specific type of astheno-teratozoospermia leading to infertility and features a combination of absent, short, coiled, bent and irregular flagella. Previous studies have identified several MMAF-associated genes (like DNAH1 and CFAP members family), highlighting the condition's genetic heterogeneity. However, known MMAF-associated genes explained only 50% of MMAF cases. In this study, we identify the genetic factor of MMAF syndrome in Tunisian infertile men using whole exome sequencing in a familial case.
Methods: Our cohort includes 15 infertile patients with MMAF. After informed consent, genomic DNA was extracted from blood lymphocytes. Semen analysis was conducted in the source laboratory during routine biological examination of the individuals according to the World Health Organization (WHO) guidelines 2010. The whole sequencing was performed on Illumina NovaSeq 6000. Pathogenic variant is confirmed by Sanger sequencing.
Results: The median age of the cohort of 15 patients, was 41.25 years. Semen analysis showed a reduced total motility and teratospermia with mostly short and coiled flagella. Two patients are brothers. WES was performed for one of them and identified a homozygous deletion of exon 20–21/22 of CFAP251 gene which was confirmed in his brother. This deletion was absent in 13 other MMAF patients.
Conclusion: We confirm here that the deletion in CFAP251 is a common genetic cause of male infertility in Tunisian men presenting MMAF and we underlie the importance of undertaking WES in a large cohort to investigate this heterogeneous phenotype in our population.

Key words: Male infertility, Teratozoospermia, MMAF, Whole exome sequencing, CFAP251

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Poster 88: MEDNIK Syndrome: The Contribution of NGS in Syndromic Ichthyoses

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Introduction: MEDNIK syndrome is a recently described copper metabolism disorder characterized by intellectual disability, ichthyosis, hearing loss, peripheral neuropathy, and enteropathy. It is caused by variants in the AP1S1 gene and follows an autosomal recessive inheritance pattern.
Methods: We report the case of a Tunisian female patient, for whom a clinical exome sequencing was performed using TruSight One Expanded Panel from Illumina on the NextSeq550 system at the genetics department of Charles Nicolle Hospital, Tunis.
Results: Our patient, an only child born to consanguineous parents, was referred for psychomotor delay and congenital bilateral deafness. The patient also developed epilepsy at the age of 1.
Clinical examination revealed distinct facial dysmorphisms, including a prominent forehead, convergent strabismus, bulbous nose, and a pronounced philtrum, as well as microcephaly, axial hypotonia, and ichthyosis on the extremities and skin folds. In the absence of a clear diagnostic hypothesis, clinical exome sequencing was performed.
Bioinformatic analysis revealed a homozygous frameshift variant in the AP1S1 gene (NM_001283.4): c.364dupG, classified as likely pathogenic based on ACMG criteria. This result confirmed the diagnosis of MEDNIK syndrome in the patient, enabling appropriate genetic counseling for the family.

Conclusion: To our knowledge, this is the first reported case of MEDNIK syndrome in Tunisia. This case highlights the crucial role of next-generation sequencing in diagnosing rare diseases and underscores its importance in guiding family support and genetic counseling.

Key words: MEDNIK, Intellectual disability, Ichthyosis, Hearing loss, NGS

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Poster 89: Nephrocalcinosis: the Genetic Spectrum of Tunisian patients

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Introduction: Nephrocalcinosis is a condition marked by diffuse deposition of calcium crystals in the renal parenchyma, leading to impaired kidney function. It can result from hereditary tubulopathies, particularly distal renal tubular acidosis, metabolic abnormalities such as primary hyperoxaluria, and primary familial hypomagnesemia with hypercalciuria.
Methods: We conducted a retrospective study analyzing the mutational spectrum in 186 families referred for nephrocalcinosis. Sanger sequencing was performed for the AGXT, ATP6V1B, ATP6V0A4, and CLDN16 genes at the genetics department of Charles Nicolle Hospital.
Results: Sequencing of the AGXT gene was carried out for 133 families with nephrocalcinosis associated with primary hyperoxaluria. This identified 10 homozygous mutations across 46 families. The most frequent mutations were c.731 T>C (p.1224T), found in 33 families, and c.568 G>A (p.G190R), present in 5 families.
For 45 families with nephrocalcinosis linked to distal renal tubular acidosis, sequencing of the ATP6V1B gene revealed 4 mutations. The most common variant was c.1155 dup (p.Ile386fs), identified in a homozygous state in 11 families. Additionally, ATP6V0A4 gene analysis in 3 families detected the variant c.16C>T (p.Arg6Ter).
Primary hyperoxaluria/familial hypomagnesemia with hypercalciuria was investigated in 8 families by analyzing the CLDN16 gene. Three homozygous variations were found, with c.211C>G (p.His71Asp) being the most frequent.
Conclusion: Our study highlights a broad mutational spectrum and lack of genotype-phenotype correlation in genetic nephrocalcinosis. Identifying familial mutations is crucial for effective therapeutic management and providing accurate genetic counseling.

Key words: Kidney, Nephrocalcinosis, AGXT, Sanger, Genetic counseling

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Poster 90: Molecular cytogenetic characterization of complex X structural abnormalities in a patient with growth retardation

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Introduction: Various deletions and microdeletions delineating a contiguous gene syndrome on Xp22.3 have been reported in recent years in female patients with short stature and some somatic traits typical of Turner syndrome. Duplications of variable size on Xq have been mainly reported in male patients. Complex chromosome X rearrangements involving Xq duplication and Xp terminal deletion have been rarely reported.
Methods: We report the observation of a patient who was referred for short stature and developmental delay. A karyotype analysis was initially performed, followed by chromosomal microarray analysis (CMA) (8 x 60K microarray from Agilent Technologies).
Results: Our patient was a 2-year-old girl born to healthy related parents. She had a medical history of intra-uterine growth restriction and developmental delay. Physical examination revealed short stature (−3,6 SD), bilateral clinodactyly of the 5th finger, hand lymphedema and widely spaced nipples. Brain MRI revealed an enlargement of the subarachnoid spaces.
karyotype revealed a de novo additional material on both arms of chromosome X (46,X,der(X),t(X;?)(p22;?)). CMA detected a 19Mb terminal deletion on Xp22.13-p22.33, along with a 38 Mb duplication on Xp11.21-p22.12 and a 93 Mb duplication on Xq11.1-q28. The Xp terminal deletion has encompassed 91 protein coding genes including SHOX, associated with short stature, and CLCN4, FRMPD4, MSL3 implicated in developmental delay. The haploinsufficiency of these genes escaping X-inactivation in the terminal deleted region could explain the proband's phenotype. Nonetheless, the mild clinical presentation seems to be in contrast with the large size of the chromosomal duplicated segments. That could suggest that the X-inactivation skewed towards the abnormal X chromosome.
Conclusion: This report underlines the critical role of molecular cytogenetic techniques in characterizing structural chromosomal abnormalities. Further analysis of the X-inactivation is needed to elucidate the mechanism and consequences of this complex rearrangement.

Key words: X-Structural abnormalities, Xp deletion, Xq duplication, SHOX, Short stature, Developmental delay

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Poster 91: Clinical and molecular analysis of seven patients with suspected inherited kidney disease

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Introduction: The advent of next-generation sequencing technologies has significantly improved the diagnostic yield of inherited kidney disease (IKD). To date, more than 450 identified genes have explained approximately 30% of cases of chronic kidney disease.
Methods: A genetic study using a panel of genes involved in IKD was conducted on seven patients divided into two groups based on their clinical presentation: Group 1 for renal ciliopathies (autosomal dominant or recessive polycystic kidney disease, nephronophthisis) and Group 2 for inherited tubulopathies.
Results: In group 1, the main reason for consultation was polycystic kidney disease (5/6). Renal impairment appeared in the prenatal period (1/6), in childhood (2/6), or in adulthood (3/6). Extra-renal

manifestations were noted in four patients and progression to end-stage renal disease was reported in two patients. A genetic cause was identified in four patients, in three different genes: TTC21B (2/4), PKHD1 (1/4), and PKD1 (1/4).
In group 2, a 36-day-old patient was referred for a suspicion of Bartter syndrome. He presented an hyponatremic dehydration episodes with hypokalemic hypochloremic metabolic alkalosis. The clinical course was marked by rapid progression to end-stage renal disease and subsequent death. Molecular analysis revealed a pathogenic homozygous variant in BSND.
Conclusion: Gene panel sequencing allowed us to identify pathogenic variants in five families with suspected IKD. Thus, presymptomatic and prenatal diagnosis were performed in two different families.

Key words: Inherited kidney disease, Gene panel sequencing, Polycystic kidney disease, Nephronophthisis, Bartter syndrome

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Poster 92: A novel intragenic NLRP7 duplication causing a recurrent biparental hydatidiform mole

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Introduction: Hydatidiform mole is a rare gestational disorder marked by abnormal placental growth, leading to excessive proliferation of vesicular trophoblasts and impaired fetal development. This disorder includes sporadic moles, which can be complete or partial, and less frequently, recurrent biparental moles. Complete moles have only paternal genetic material, while partial moles possess a diandric triploid genome with a predominant paternal contribution. Recurrent hydatidiform moles, despite sharing features with complete and partial moles, have a normal diploid biparental contribution and are often caused by epigenetic abnormalities affecting genomic imprinting, typically involving NLRP7 and KHDC3L gene variations.
Methods: We report a 33-year-old woman with recurrent hydatidiform moles who underwent exome sequencing.
Results: Our patient was born to consanguineous parents and had nine pregnancies, including an undocumented first miscarriage and eight confirmed molar pregnancies. Complete and partial mole differentiation was not performed, and the couple's karyotype was normal. Exome sequencing identified a 4.2 kb duplication in the 19q13.42 region, duplicating exons 4, 5, and 6 of the NLRP7 gene, with an estimated copy number of five. Intragenic breakpoints likely caused a frameshift mutation, leading to nonsense-mediated mRNA decay (NMD). The clinical presentation was consistent with NLRP7-related pathology. This variant, classified as "likely pathogenic" per ACMG/CLINGEN 2020 guidelines. The estimated copy number of five (three extra copies) and the autosomal recessive inheritance pattern of the affection suggest that the patient doesen't have a normal allele and inherited one duplication from each parent. This duplication was confirmed by conventional PCR and targeted sequencing. Quantitative PCR for exact copy number is ongoing.
Conclusion: Exome sequencing identified the genetic cause of the patient's recurrent molar pregnancies, allowing for the recommendation of effective contraception due to high recurrence risk and potential choriocarcinoma. The diagnosis guided the patient towards adoption.

Key words: Hydatidiform mole, NLRP7, Biparental mole, genomic imprinting

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Poster 93: SETD2 variant at codon 1740 in a Case with Polymalformative Syndrome

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Introduction: Polymalformative syndromes, characterized by the combination of various congenital malformations, are often genetically driven. They can arise from genetic mutations or chromosomal abnormalities like aneuploidies, deletions, or duplications (copy number variations, CNVs). Traditional diagnosis methods, including karyotyping, FISH, and targeted sequencing, may not fully detect these abnormalities. Next-generation sequencing, especially exome sequencing, has greatly improved diagnosis precision by enabling detailed identification of genetic mutations and genomic imbalances.
Methods: We describe a 11-year-old child with a polymalformative syndrome followed since the age of one. Extensive genetic testing, including trio exome sequencing, was performed.
Results: The child, born to non-consanguineous parents with a family history of cleft palates, exhibited intrauterine growth restriction. At birth, she was diagnosed with growth retardation, microcephaly, facial dysmorphism, cleft palate, congenital heart disease, renal cysts, extremity anomalies, and axial hypotonia. She also had hearing loss, language delay and intellect disability. Brain MRI showed cerebral and vermian atrophy. Karyotyping and array CGH results were normal. Trio exome sequencing identified a de novo heterozygous variant in the SETD2 gene (NM_014159.6): c.5218C>T (p.Arg1740Trp). This variant is pathogenic, associated with a distinct phenotype, concordant with the patient's manifestations: intrauterine growth retardation, facial dysmorphism, severe congenital malformations, and neurological issues. This contrasts with mutations in other SETD2 codons, which are linked to stature advancement, obesity, macrocephaly, and milder neurological symptoms.
Conclusion: Exome sequencing identified the p.Arg1740Trp variant as the cause of the child's symptoms, concluding a long diagnosis process. As a de novo variant, it provided reassuring genetic counseling for the parents and facilitated the planning of future family decisions.

Key words: Exome sequencing, SETD2, Polymalformative syndrome, Congenital malformations