Abstracts of the Second Conference of the Arab Association of Genetic Research (AAGR)

The second Conference of the Arab Association of Genetic Research (AAGR) will be held at the Nile Ritz Carlton Hotel in Cairo, Egypt, over the days of November 24-28th, 2019. The conference theme is "Genetic Research in the Arab World: From the lab to the Clinical Applications", which addresses the importance of the translational nature of Arab genomic research. The conference will tackle various issues and subdisciplines of human genetics and genomics.

Presentations by regional and international renowned speakers as well as by young scientists will address all the scientific and clinical venues of human genetics and genomics. This relatively new field is transforming medicine to a more targeted personalized management approach and predicates a lot of emphasis on medical education and translating the rapidly and highly advanced research outputs into clinical utilizable forms. Thus, the conference will hopefully be a platform for the fruitful interaction of Geneticists, Scientists, Clinicians, other Health Professionals, Sponsors and Exhibitors. Also, the conference program comprises special sessions on rare disorders, with the hope of sowing the seeds for the formation of Arab networks for these understudied diseases. In addition to the two days of 26-27th of the conference, there will be two workshops, a preconference Dental genetics [on November 24-25th] and a bioinformatic course that is sponsored by Pan African Bioinformatics Network for H3-Africa (H3ABionet) on RNA-seq Data Analysis [November 26-28th].

The abstracts of the conference presentations are included underneath, firstly, the talks (T) in their presentation order within the sessions (S), followed by posters (P) according to their topics and numbering. The presenting author name is underlined, if more than one.

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Oral Presentations

Session I: Arab Genomic Research

T1-1: Arab Genome: Catalyst for the genomic medicine revolution

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Decoding the human genome promises to usher in an era of unprecedented precision in medicine. The realization of these benefits depends on how successfully we decode the genomes both at the level of large disease cohorts to gain an understanding of the molecular disease pathogenesis and at the level of individuals to personalize their healthcare. Despite the tremendous progress in recent years, much remains to be done to fully unlock the power of the human genome. One particularly acute need is the interpretation of variants in a medical context. Arab genomes are characterized by a relatively large percentage of autozygosity, a natural phenomenon that has far reaching implications on defining the clinical relevance of variants. In this presentation I will provide an overview of the numerous applications of this phenomenon in genomic medicine that are far beyond the stereotype of novel disease genes discovery. In addition to the global impact of this line of research, I will also emphasize its local impact on individuals and on public health.

T1-2: The gene for the immune system-released activating agent (ISRAA): A novel therapeutic approach to immune mediated disorders

Moiz Bakhiet

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Regulatory interactions between the nervous and the immune systems have become a major focus in immunity. Expression of neuronal genes in splenic B-cells has recently been reported signifying biological similarities between the two systems. In addition, immune cells were demonstrated to produce neurotransmitters and express neurotransmitters receptors. However, till now, there has been no identified single or group of molecules that may function as mediators between the two systems. In our laboratories, a nervous system-inducing agent was discovered to induce immune regulatory activities in immune cells, the immune system-released activating agent (ISRAA). The high concentrations of ISRAA showed positive apoptotic effects while the very low levels resulted in significant proliferative effects on peripheral blood cells. It is the first molecule encoded by a gene sequence that lies within an intron and demonstrates a strong activity on immunosuppressed cells, tumor cell lines, embryonic brain cells and adult peripheral stem cells. Thus, it became a potential candidate for treatment of patients with immunodeficiency by using its stimulatory effects and cancer therapy through its apoptotic effects. Furthermore, ISRAA effects on embryonic and adult stem cells were used to treat neurodegenerative disorders by transplantation of ISRAA-induced peripheral blood stem cells into animal model for neurodegenerative disease to study their therapeutic effects on the clinical course of the disease. Beneficial effects are herein presented.

T1-3: Engaging citizens in genomics research: the first steps for the establishment of a participatory action research in omics in Tunisia and North Africa

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During the last years, Tunisia, as some other countries in the region, is witnessing a great progress not only in genomics research but also in the path of democracy, with more transparency, freedom of speech and the rise of a very active civil society. This raised awareness about the necessity for the research to be more inclusive and to involve Civil Society Organizations (CSO) in the decision-making processes. This also pressed the researchers to be more responsive to the needs of the citizens. For this purpose, “Science Shops” provide an adequate platform to conduct community based participatory research (CBPR).

Health benefits of genomics is becoming evidence, nevertheless, omics research raises several questions related to ethical, social and regulatory issues that could not be answered without the involvement of all the stakeholders.

We will report, in our presentation, on some examples of the recent experience of Institut Pasteur in Tunis and collaborators from national and international institutions for the conduct of participatory action research. We will also present IPT “science shop” entitled “science together” and some of its projects such as Ichara science shop project.

In order to implement effectively omics research in the region, there is a need to set the adequate regulatory framework, to take into consideration ethical aspects, to conduct science education activities, to engage citizens in the research, to make the research results widely accessible and to identify the appropriate governance model. These are the pillars of responsible research and innovation.

T1-4: Genomic services in Egypt

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Genomic medicine in its recent definition revolves around the possibility of unlocking the mysteries of the human genome to understand the molecular pathologies and ultimately personalize healthcare. Egypt is a developing country considered among low-income economies by the World Bank. Economic limitations impose restrictions on the luxury of basic research and research facilities have always been directed towards applied science. This implied that in a trial to use available means to solve pressing needs and problems, genetic services in Egypt have been running in a system which is analogous to that of precision medicine in the omics era.

In the current presentation, we will elaborate on examples of the past and current models within different genetics teams and health providers in Egypt, as well as the current situation and plans for

more omics involvement in health services. More light will be shed on the Division of Human Genetics and Genome Research team at the National Research Centre, the major referral center for Human Genetic disorders in Egypt.

Session 2: Genetics of complex Disorders

T2-1: Four novel mutations in the mitochondrial ND4 gene of complex I in Saudi patients with multiple sclerosis

Ghada Al-Kafaji

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Multiple sclerosis (MS) is an immune-mediated neurological, inflammatory disease of the central nervous system. Recent studies suggest that genetic variants in mitochondrial DNA (mtDNA)-encoded complexes of respiratory chain, particularly, complex I (NADH dehydrogenase) contribute to the pathogenicity of MS among different ethnicities, and targeting mitochondrial function may represent a new approach for MS therapy.

We sequenced ND genes (ND1, ND2, ND3, ND4, ND4L, ND5 and ND6) encoding subunits of complex I in 124 Saudi subjects, 60 patients with relapsing-remitting MS and 64 healthy individuals, to identify potential new mutations in those patients.

We found several variants in ND genes in both patients and controls, and specific variants in MS patients only. While the majority of these variants were synonymous, four variants in ND4 gene were identified as missense mutations in MS patients. Of these, m.11150G>A was observed in one patient, whereas m.11519A>C, m.11523A>C and m.11527C>T were observed in another patient. Functional analysis predicted the mutations m.11519A>C, m.11523A>C and m.11150G>A as deleterious with a direct impact on ND4 protein stability and complex I function, whereas m.11527C>T mutation had no effect on ND4 protein stability. However, the three mutations m.11519A>C, m.11523A>C and m.11527C>T which were observed in the same patient were predicted to cause a cumulative destabilizing effect on ND4 protein and thus could disturb complex I function.

Our study identified four novel mutations in mtDNA-encoded ND4 gene in Saudi patients with MS which could lead to complex I dysfunction, and further confirmed the implication of mtDNA mutations in the pathogenicity of MS. The identified novel mutations in Saudi patients with MS may be ethnic-related and could be important in personalized treatment.

T2-2: Complex trait genomics in Africans: insights and challenges

Michèle Ramsay

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The unique genetic diversity and lower levels of linkage disequilibrium in African populations make them well-suited for novel discovery in genome-wide association studies (GWASs). Diversity in Africa extends across other domains and poses analytical challenges that range from dealing with population sub-structure, unanticipated relatedness, phenotypic diversity and prevalence of infections (HIV and malaria), to cultural and environmental differences. As an example, I will present data from the AWI-Gen population cross-sectional study of adults (40 to 60 years of age) from six study sites across four African countries, that was designed to examine genetic and environmental contributions to cardiometabolic diseases and related traits in Africans. This pan-African GWAS was powered to identify major genetic contributions to lipid level variation in African populations and is the largest continental African study of its kind. In addition to detecting associations with previously associated lead SNVs and novel lead SNVs at known gene loci for lipid traits, we identified a highly associated novel locus with LDL-C. The AWI-Gen study example demonstrated the power for novel discovery for lipid traits, revealing differences in the genetic architecture of complex traits in African populations. There is potential for discovering novel biological insights into the biology of complex traits and to identify new druggable targets. Studies on African populations are essential to assess trans-ethnic transferability and to support the development of appropriate genetic risk prediction algorithms for the continent.

T2-3: A Clinical Approach to Inherited Colorectal and Breast Cancer in the Genomic Era

Mark Rogers

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Using inherited breast and colorectal cancers as paradigms, in this presentation I will describe the practical processes and my experience of very nearly 20 years as a member of the Cancer Genetics Services for Wales (CGSW). And how this service has evolved from single gene molecular genetic testing towards clinical interpretation in the genomic era we are now entering.

I will discuss in brief the Service and relationship to General Clinical Genetics and Oncology, including the referral process, referral criteria and risk calculation. I will outline the type of referral and how these have evolved with changes in service provision with particular emphasis on Inherited Breast Cancers and Inherited Colorectal cancers, but mentioning a general approach to other inherited cancer and tumor susceptibility syndromes and how the spectrum of cases has changed since the service was first established. I will mention the evolution of genetic tests from single gene tests, through site specific panels (including genes of lower penetrance) and now the shift in approach in the era of Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS), including Pan-cancer panels, tumor profiling - somatic vs germline variants. Variants of Uncertain Significance (VUSs) will be also tackled briefly. In the near future, further tests will become available including cell free DNA tests and all of this under the umbrella of personalized medicine.

T2-4: Human-Mycobacterium coevolution and tuberculosis severity

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Genetic studies of both the human host and Mycobacterium tuberculosis (MTB) demonstrate independent association with tuberculosis (TB) risk. However, neither explains a large portion of disease risk or severity. Based on studies in other infectious diseases and animal models of TB, we hypothesized that the genomes of the two interact to modulate risk of developing active TB or increasing the severity of disease, when present. We examined this hypothesis in our TB household contact study in Kampala, Uganda, in which there were 3 MTB lineages of which L4-Ugandan (L4.6) is the most recent. TB severity was modeled as a function of host SNP genotype, MTB lineage, and their interaction, within two independent cohorts of TB cases. No association was found between lineage and severity, but association between multiple polymorphisms in IL12B and severity was replicated in two independent cohorts, supporting previous associations of IL12B with TB susceptibility. We also observed significant interaction between a single nucleotide polymorphism (SNP) in SLC11A1 and the L4-Ugandan lineage in both cohorts. Interestingly, the presence of the derived L4-Uganda lineage in the presence of the ancestral human allele associated with more severe disease. These findings demonstrate that IL12B is associated with severity of TB in addition to susceptibility, and that the association between TB severity and human genetics can be due to an interaction between genes in the two species, providing evidence of host-pathogen coevolution in TB.

T2-5: A missense variant in B4GALT1 reduces low-density lipoprotein and fibrinogen

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Elevated low-density lipoprotein cholesterol (LDL) and fibrinogen are major independent risk factors for Cardiovascular disease (CVD), the leading cause of death worldwide. Isolated founder populations can enable discovery of novel disease-associated genetic variants enriched in these populations but very rare in the cosmopolitan populations and can inform biology relevant to all humans. Using genome-wide association scan, whole-genome sequencing, whole-exome sequencing, direct genotyping and imputation, we identified novel associations between an Amish-enriched missense variant (N352S) in a functional domain of beta-1,4-galactosyltransferase 1 (B4GALT1) and 13.5 mg/dl lower LDL (p=1.6E-15), and 26 mg/dl lower plasma fibrinogen (p= 9.8E-05). To assess the impact of N352S on glycosylation, the carbohydrate deficient transferrin test was performed using serum samples from 28 subjects from the 3 genotype groups and found a strong association with abnormally high levels of carbohydrate deficient transferrin (p=9.12 E-10). N-linked glycan profiling found 352S to be associated (p-values: 1.4E-06 - 1.0E-17) with decreased glycosylation of glycoproteins including: fibrinogen, ApoB100, and immunoglobulin G (IgG). Two complementary in vitro assays found that the mutant (352S) protein had 50% lower galactosyltransferase activity compared to the (352N) wild type. Knockdown of B4GALT1 in zebrafish embryos resulted in significantly lower LDL compared to control, which was fully rescued by co-expression of 352N human B4GALT1 mRNA but only partially rescued by co-expression of 352S human B4GALT1 mRNA. Our findings establish B4GALT1 as a novel gene associated with lower LDL and fibrinogen and suggest that targeted modulation of protein glycosylation may represent a therapeutic approach to decrease CVD risk.

T2-6: A polymorphism in GSTM1 and GSTT1 among Sudanese SLE patients

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Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease. The progression of the disease may be affected by several factors including oxidative stress through reactive oxygen species (ROS). Detoxification of ROS is largely performed by Glutathione S-transferases (GSTs).

Aim: This study aims to determine the effects of GSTM1 and GSTT1 polymorphisms on SLE susceptibility.

Material and methods: Genomic DNA (gDNA) was extracted from blood samples of 47 patients diagnosed with SLE and a matching 47-control group. The polymorphism in GSTM1 and GSTT1 were detected using a restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR).

Results: The GSTM1 null mutation was detected among 44% of the patients and 44% of controls. Furthermore, GSTT1 null mutation presented in 48.9% and 48.9% of the patients; these results were shown to be statistically insignificant (p value > 0.05). Furthermore, the result obtained by this study showed a negative correlation between the presence of the SNPs and the age and gender among the cases and control group.

Conclusion: Our findings suggested that the genetic polymorphisms of GSTM1 and GSTT1 do not influence the risk of SLE, and the deletion of GSTM1, GSTT1 does not influence the clinical manifestation of the disease. However, a large scale study is needed to confirm the results of this pilot study.

Session 3: Genetics of rare diseases I: DSD

T3-1: The European approach to diagnosis and management of rare conditions affecting sex development

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Disorders or differences in sex development (DSD) comprise a heterogeneous group of conditions with an atypical sex development. To expedite progress in the care of people affected by DSD, the European Union has funded a number of scientific networks. Two Actions of the Cooperation of Science and Technology (COST) programs, DSDnet (BM1303) and GnRH network (BM1105), provided the framework for ground-breaking research and allowed the development of position papers on diagnostic procedures and special laboratory analyses, as well as clinical management. This presentation will summarize these position papers.

The development of sex and gender, and the elucidation of variant physiology, are some of the most complex topics in biology and medicine, as well as in society. The clinical assessment of a patient needs to be age-dependent and include an extensive whole-body examination, including the genital status. For DSD, the external masculinization score, which was originally designed to describe genitalia in undervirilized male infants, was modified into a more widely applicable 'external genitalia score' (EGS) to cover the whole spectrum of genital appearances in both male and female infants. In individuals with DSD, the determination of a karyotype is still seen as an initial mandatory step, as numerical or structural chromosomal abnormalities account for a considerable subset of DSD conditions. However, many patients might have an unaffected chromosomal complement, and so detailed studies for molecular genetic conditions are needed. Moreover, accurate interpretation of high-throughput sequencing datasets is challenging in the clinical setting. The challenges arise in part due to emerging evidence that these conditions might be caused by variants in many different genes, and the prevalence of variants in a single gene could be very low. To build robust evidence to support causality, sharing genomic data between research groups and developing informative animal and cellular models are required. Furthermore, clinical benchmarking is necessary to improve patient care in this sensitive area. Needs that can be addressed by the systematic and standardized data collection strategies proposed by the COST Actions include the development of treatment protocols that improve clinical outcomes and quality of life. Furthermore, the collection and analysis of long-term post-surgery data, the effect of living with atypical genitalia, gender well-being and overall health of individuals who have a DSD through the transition phase and at older ages need to be investigated.

Further advancements might be possible through the development of the European Reference Network for Rare Endocrine Conditions

(Endo-ERN), which is a structure without time limits that harbors the clinical participants and stakeholders from the affected community within the political EU. This network will provide the framework for future clinical and translational research, information of patients and caretakers, as well as the benchmarking of health care providers in adhering to the existing guidelines of management.

T3-2: Genetic diagnosis of a cohort of DSD patients*

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Disorders of sex development (DSD) comprise a heterogeneous group of heritable abnormalities of sexual determination and differentiation. In Egypt, the incidence of DSD is 1 in 5 ,000, due to the high rate of consanguinity.

This presentation summarizes our activity during the last 9 years at NRC for proper classification of DSD patients in order to reach a precise diagnosis and consequently better genetic counseling and management. Over eight hundred patients were subjected to detailed clinical evaluation, genital examination and pubertal staging, hormonal profiling, imaging studies and detailed cytogenetic analysis. Laparoscopy with gonadal biopsy taking was performed whenever indicated. Psychological assessment of gender identity was also performed. Sequencing of SRY, androgen receptor, HSD17B3, SRD5A2 and SF1 genes were done 46 XY DSD patients. Next generation sequencing was done for idiopathic cases.

Various numerical and structural chromosomal abnormalities were detected. Molecular analysis revealed reported and novel mutations in genes controlling sexual differentiation. Molecular characterization of 46,XY DSD patients is crucial when sex assignment and therapy outcomes are discussed for proper genetic counseling and diagnosis. It is also essential to provide centers of tertiary pediatric care with a consistent and standardized model of care for patients with DSD.

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T3-3: Dilemma in disorders of sex development management

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Disorders of sex development (DSD), the new term for intersexuality, entail the medical conditions characterized by an atypical chromosomal, gonadal, or phenotypical sex. The DSD patients require comprehensive management to improve quality of life. Early diagnosis is essential for proper clinical management and appropriate gender assignment. In our center most of the genetically proven cases were congenital adrenal hyperplasia, androgen insensitivity syndrome, sex chromosomal DSD and chromosomal DSD, while many others were gonadal dysgenesis with still unresolved diagnosis.

The management of disorders of sex development (DSD) in Indonesia with > 350 tribes and 5 different religions varies widely. The minimal diagnostic facilities and the low education of people living in the villages result in difficulties to fully comprehend the disease states. Emotional problems, rumors, discrimination, isolation and devaluation from friends and community because of their DSD condition put the affected families into struggle in their daily lives.

Parental backgrounds and expectations, family personal relationship, social condition, religion and ethnic or cultural influences should be considered carefully for each case in making gender decision. Diagnosis disclosure, sex assignment and social stigmatization become major dilemma and challenge for managing DSD cases, especially for late identified cases when gender change issue is considered.

T3-4: Clinical and cytogenetic study of sex chromosomal DSD*

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Genetic abnormalities of sexual differentiation are known as disorders of sex development (DSD). Sex chromosome DSD involve conditions associated with either numerical or structural abnormalities of the sex chromosomes. This presentation summarizes the 9-year experience on types and frequencies of sex chromosomal abnormalities among Egyptian DSD patients that were referred to the Endocrinology and DSD clinic, Centre of Scientific Excellence and the Human Cytogenetics department, National Research Centre.

The 803 patients were subjected to chromosomal complement evaluation, using GTG banding and FISH techniques on chromosomes from cultured blood lymphocytes. The X-inactivation study was performed, when required. FISH analysis was also conducted on gonadal tissue for some patients with suspected gonosomal mosaicism. Chromosomal microarray using Genome-Wide Human SNP Array 6.0 (Affymetrix) was conducted for selected patients.

Sex chromosomal abnormalities were found in 37 % of the patients and included an array of numerical and structural anomalies associated with wide phenotypic variability. Gonosomal mosaicism was detected in 5 patients.

The study reports a large number of Egyptian DSD patients and the frequency of different sex chromosome abnormalities in relation to different phenotypes. It also illustrates the importance of comprehensive cytogenetic and molecular cytogenetic analysis for accurate diagnosis of DSD patients, which is crucial for better counseling and long-term management of those patients.

*This study was partially funded by STDF-IRD grant #4632.

Session 4: Fetal Medicine and Prenatal diagnosis

T4-1: From Invasive to NIPT: Egyptian Experience**

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Prenatal genetic testing is now an integral component of routine antenatal care as it provides information for pregnancy and perinatal decision-making and management.

Prenatal screening and diagnosis involve testing for conditions in a fetus before it is born, with the aim of detecting causes of birth defects, abnormalities and genetic conditions. Testing procedures can include non-invasive techniques such as serum screening and ultrasonography, or invasive techniques such as amniocentesis and fetal blood sampling.

Noninvasive prenatal testing (NIPT), where circulating cell free DNA and microRNA are isolated from maternal plasma/serum, have emerged as important tools in prenatal screening and diagnosis.

The presentation gives a brief overview of the three decade-experience of the prenatal diagnosis department at the NRC, passing from invasive to noninvasive prenatal genetic testing.

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T4-2: New Advancements in NIPT for Prenatal Screening of Genetic Diseases

Philippos Patsalis

NIPD Genetics

Unlike Noninvasive prenatal testing (NIPT) for aneuploidy screening, limited clinical utilization of the detection for single gene diseases has been reported. We hereby present the development and validation of single comprehensive NIPT of major aneuploidies, microdeletions and more than 100 monogenic diseases. All monogenic diseases under investigation are associated with moderate or severe phenotype, including hematological, ophthalmological, neurological, and inherited metabolic diseases. We employed proprietary targeted capture enrichment technology combined with multi-engine bioinformatics analysis on thousands of cfDNA samples referred for NIPT and paternal genomic DNA. The parental carrier status was investigated for more than 2000 mutations. An enriched sequencing library was prepared using custom Target Capture Sequences (TACS). TACS were designed based on genomic locations of known causative mutations for more than 100 autosomal recessive and x-linked monogenic diseases, in addition to select regions on chromosomes 13, 18, 21, X, Y and critical regions of 22.q11, 1p36, Wolf-Hirschhorn and Smith-Magenis microdeletion syndromes. Enriched products were sequenced using NGS and the data was processed using a custom bioinformatics pipeline. All aneuploidies, microdeletions and single gene diseases were correctly classified with 100% specificity and sensitivity. This is the first time that such a comprehensive NIPT is available for a high number of single gene diseases together with aneuploidies and microdeletions.

T4-3: Association of miRNA-27a and Leptin Polymorphisms with recurrent pregnancy loss

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Leptin is an important hormone during implantation processes and plays a pivotal role in regulating the development of placenta and endometrial receptivity. MicroRNAs (miRNA) are associated with endometrial diseases and preeclampsia, alluding to their potential role in the function of normal reproductive system.

The aim of this study was to investigate the role of miRNA-27a and leptin polymorphisms in the development of idiopathic recurrent pregnancy loss (RPL) among Egyptian women. Methods: This is a case-control study involving 99 women with at least two consecutive recurrent pregnancy losses and 100 females as a control group. The rs7799039 G/A variant in leptin gene (LEP) and miR-27a rs895819 were genotyped by polymerase chain reaction-restriction fragment length polymorphism assay.

Results: Statistical analysis showed that rs7799039 G/A was associated with an increased risk of RPL GA+AA (0.006); 0.379 (0.190-0.758). There was a strong association of the of A allele with RPL A vs G (<0.001); 0.416 (0.278-0.621). For rs895819A/G AA vs. GA: (0.05); 0.492 (0.242-1), there was an associated increased risk of RPL after adjustment for multiple tests using the FDR correction, the P value was significant (0.003). There was a strong association of the of G allele with RPL G vs. A (<0.001); 0.425 (0.281-0.643).

Conclusion: Our results showed that the rs7799039 G/A in LEP and miR-27a polymorphisms are associated with an increased susceptibility to RPL in the Egyptian Women.

Session 5: Bilingual session (French & English presentations): Biobanking and populations genetics

T5-1: Biological Resources Center (BRC) issues, objectives, duties, and requirements in the service of science

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Biological Resource Centers (BRCs or biobanks) collect, store, process and distribute human biological materials for research purposes. In a few years, the BRCs have become indispensable tools for scientific research, especially biomedical, in epidemiology, biology, and health as well as for research in genetics, in genomics and the development of biotechnologies.

However, the biobanks and their evolutions present ethical, legal and social issues that must not be ignored.

T5-2: The value of biobanking and cohort studies for medical research

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For decades, biobanks and cohort studies have been carried out with the goal of accurately assessing the relationships between risk factors and health outcomes. More recently, these studies are incorporating molecular data providing opportunities to study complex diseases and for discovery and interpretation of the downstream molecular effects of genetic variants at different omics data levels. However, implementation of cohort studies in Africa and the Arab world faces many challenges and requires engagement of study participants, health care providers and researchers among others. Here I will share our experience setting up two cohort studies including the UAE Healthy Future Study designed to study and identify associations between genetic and environmental risk factors of complex diseases such as obesity, diabetes, and cardiovascular disease among Emiratis.

T5-3: Discovering genetic variants under natural selection in genes associated with respiratory disease in worldwide populations

Michael C. Campbell
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Pathogens are arguably among the strongest selective pressures to influence levels and patterns of variation in modern human populations. Thus, natural selection has played a pivotal role in the evolution of our species, and the genetic signatures of this microevolutionary force continue to linger in the genome. To investigate patterns of selection in humans, we analyzed sequence variation in several known immunity-related genes, namely IL4, TLR2, CCL2, and SLC11A1—associated with respiratory diseases, including tuberculosis—in 2,039 individuals from the 1000 Genomes Project originating from 21 globally diverse populations. Here, we identified 18 polymorphisms that were inferred to be targets of positive selection mainly in non-African populations. Furthermore, a subset of these variants were predicted to alter transcription factor binding site affinity, implying they influence gene expression. In addition, we detected a strong bias against missense substitutions in the coding sequences of all of the genes under study. Intriguingly, this bias was consistently observed between species comparisons spanning ~65 million years of evolution. Lastly, we identified several polymorphisms in our genes that were also present in Neandertal and Denisovan hominins and argue that these alleles were likely inherited from the last ancestor that modern humans shared with these archaic species >500,000 years ago. Overall, our study identified candidate alleles that likely contribute to phenotypic variation and offers new insight into the microevolutionary forces that have shaped patterns of diversity at medically relevant genes in human populations.

T5-4: A Partnership Framework to Support Population Genomics (PopGen) at Scale

Paul Jones
Population Genomics, EMEA, Illumina

Population Genomics (PopGen) is an enabler of a precision medicine, personalized and preventative healthcare future. The emphasis is on using genomics at scale to deliver clinical utility, i.e. making use of what we know today about the genome, whilst at the same time engaging

the research community to help unlock future value for patients. This is what is described as a 'learning health system', with a never-ending cycle that accelerates the translation of research insights into clinical care and back into research. Data is at its core. Success will require the simultaneous engagement of clinical, research, industry and government/economic development agendas with change embedded throughout to ensure the system is ready to accept current and future innovation.

Session 6: Genetics of rare diseases II: Hereditary Blood diseases

T6-1: The double life of Fanconi anemia proteins: from safeguarding replication to the maintenance of bone marrow homeostasis

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Fanconi anemia (FA) is the most frequent and genetically heterogeneous inherited bone marrow failure (BMF) disorder. Beyond BMF, FA is associated with developmental abnormalities, predisposition to cancer and chromosomal instability.

The key function of the molecular pathway defined by FA proteins (FANC) is to rescue stalled or delayed replication forks and to repair DNA interstrand crosslinks (ICLs), which can arise from endogenous aldehyde metabolism or following exposure to chemicals, as mitomycin C, or Cisplatin. Even if the loss-of-function of one among more than 20 genes is recognized as involved in FA, FANCA bi-allelic inactivating mutations account for more than 70% of FA cases worldwide. Beyond the DNA repair/DNA damage response, the FANC pathway has been associated with several other cellular and systemic biological activities, including pro-inflammatory cytokine production and responses, transcription, mRNA splicing and reactive oxygen species metabolism.

However, how the cellular, biochemical and molecular alterations reported in FA converge to lead to the observed attrition of the hematopoietic stem cells (HSCs) pool (the key element underlying progressive BMF in patients) remains poorly understood.

After reviewing our contribution to the role of the FANC pathway in replication and chromosomal stability maintenance, we will present still unpublished data on the involvement of FANCA in nucleolar activity and ribosome biogenesis as well as on the impact of its loss-of-function on HSC and bone marrow homeostasis.

T6-2: TET2 Deficiency promotes B-cell Lymphomagenesis

Said Aoufouchi
CNRS UMR8200, équipe labelisée Ligue Nationale Contre le Cancer, Gustave Roussy, Université Paris-Saclay, Villejuif, France

TET2 somatic mutations occur in about 10% of diffuse large B-cell lymphomas (DLBCL) but are of unknown significance. In the presentation I will show that TET2 is required for the humoral immune response and is a DLBCL tumor suppressor. TET2 loss of function disrupts transit of B cells through germinal centers (GC), causing GC hyperplasia, impaired class switch recombination, blockade of plasma cell differentiation, and a preneoplastic phenotype. TET2 loss was linked to focal loss of enhancer hydroxymethylation and transcriptional repression of genes that mediate GC exit, such as PRDM1. Notably, these enhancers and genes are also repressed in CREBBP-mutant DLBCLs. Accordingly, TET2 mutation in patients yields a CREBBP-mutant gene-expression signature. CREBBP and TET2 mutations are generally mutually exclusive, and hydroxymethylation loss caused by TET2 deficiency impairs enhancer H3K27 acetylation. Hence, TET2 plays a critical role in the GC reaction, and its loss of function results in lymphomagenesis through failure to activate genes linked to GC exit signals.

T6-3: Molecular studies among adult Egyptian patients with myeloproliferative neoplasms: Kasr Aleini Adult Clinical Hematology Unit experience

Mervat Matar
Faculty of Medicine, Cairo University, Cairo, Egypt

Myeloproliferative neoplasms are rare disorders comprising polycythemia rubra vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) with different risks of blood count abnormalities, splenomegaly, constitutional symptoms and thrombosis. They are associated with driver gene mutations including JAK2, CALR and MPL, along with other non-driver mutations including ASXL2, DNMT3 and others. Egyptian patients demonstrate special features including lower age incidence and different male to female ratios.

We studied the molecular characteristics of 100 Egyptian patients including clinical features, constitutional symptom score (MPN10) and correlation between JAK2 mutation and both the incidence of pulmonary hypertension and the incidence of systemic venous thrombosis. Their data will be summarized.

T6-4: Genetics of hereditary blood disorders in Egypt**

Hereditary Blood Disorders Research Team (Khalda Amr)
Division of Human Genetics and Genome Research, National Research Centre

Hereditary blood disorders (HBD) are chronic genetic disorders where the affected suffers ill health all throughout his life, imposing emotional and socioeconomic burdens on the family as well as the society. Genetic diagnoses of HBD have profound implications on the choice of management allowing prevention and implementation of new therapeutic measures in the current genomic era.

During the past years, we established multidisciplinary approaches through a complementary team to tackle the HBD group. About 1000 patients were clinically classified into cases of hemoglobinopathies, Inherited bone marrow failure syndromes (IBMFS), bleeding disorders, coagulopathies, some metabolic disorders and pregnant females with previous sibling suffering from HBD, or recurrent abortion.

The laboratory workup included analytical tests for cytogenetics (G-banding, DEB, MND, Telomeric length), biochemical genetics (MSMS), immunogenetics, prenatal diagnosis and molecular genetics (Sanger sequencing, MLPA and NGS).

Up to 27 different beta thalassemia mutations could be characterized with no intra-familial heterogeneity helping genetic & prenatal counseling. Sixteen percent of IBMF cases were diagnosed by DEB as FA and assessed for disease prognosis through micronuclear damage and telomeric length assessment, in addition to molecular characterization. Molecular diagnosis for some bleeding disorders such as Hemophilia-A and B, Von Willebrand disease and Glanzmann thrombasthenia were initiated. Also, successful linkage studies for some hemophilia-A patients allowed prenatal diagnosis and genetic counseling within informative families.

In conclusion, identification of different genetic alterations underlying HBD positively impacted patients' counseling and management and predicated research challenges for adopting more advanced technologies like gene editing for better disease treatment and prevention.

**This study was partially funded by STDF grant #5253.

T6-5: Challenges in HSCT for Thalassemia: Tanta University Experience

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Hematopoietic stem cell transplantation (HSCT) is now a well-established treatment for patients with transfusion-dependent thalassemia. Although transfusion therapy and iron chelation have

been serving those patients well till now, the patients and their families are always looking forward to a cure, rather than a life-long therapy. Tanta Bone Marrow Transplantation Unit was established three years ago, and since then thalassemia formed the majority of cases that underwent allogenic HSCT. We provided care for a variety of age groups and different risk classes, using different conditioning protocols. In addition, we faced many challenges not only related to the process of HSCT, but more specifically related to the special nature of patients with thalassemia. Some of these challenges will be addressed with emphasis on certain individual case presentations.

Session 7: Regenerative and precision medicine

T7-1: Combined cell and gene therapy for Epidermolysis Bullosa

Michele De Luca

Centre for Regenerative Medicine "Stefano Ferrari", University of Modena and Reggio Emilia, Modena, Italy

LAMB3-dependent generalized Junctional Epidermolysis Bullosa (JEB) was targeted by transplantation of epidermal cultures originated from transgenic epidermal stem cells. We report life-saving regeneration of the entire epidermis on a seven-year-old JEB child suffering from a devastating form of JEB. The regenerated transgenic epidermis remained stable throughout the entire follow-up period and did not form blisters, even upon shear force. The proviral integration pattern was maintained in vivo and epidermal renewal did not cause any clonal selection. Clonal tracing showed that the human epidermis is sustained by a limited number of long-lived stem cells, detected as holoclones, that can extensively self-renew and produce short-lived progenitors that replenish terminally differentiated keratinocytes.

In studying the different behaviour of JEB and COL7A1-dependent generalized Dystrophic EB (RDEB) cultures, we discovered a pivotal role of YAP in sustaining human epidermal stem cells, which explains the progressive stem cell loss observed in JEB. Epidermal stem cell depletion of primary JEB keratinocytes is due to perturbation of the YAP/TAZ pathway. YAP/TAZ expression is significantly decreased in JEB keratinocytes, which do not contain nuclear YAP but only phosphorylated, inactive YAP. The JEB phenotype is recapitulated by Laminin 5 ablation and consequent YAP/TAZ down-regulation in normal cells. Restoration of adhesion properties by Laminin 5-gene therapy rescues normal nuclear levels of YAP/TAZ and clonogenic potential. Enforced YAP recapitulates Laminin 5-gene therapy in JEB cells, thus uncoupling adhesion from proliferation in epidermal stem cells. This work has important clinical implication for an efficient ex vivo gene therapy of JEB.

T7-2: Revealing new intestinal stem cell genetic programs using the fruit fly (Drosophila melanogaster)

Dani Osman

Azm Research Center and Faculty of Science, Lebanese University, Lebanon

The fruit fly Drosophila melanogaster has been extensively used as a powerful genetic model organism to decipher basic cellular and molecular mechanisms of many biological processes. In the first part of my talk, I will present recent studies that have been carried out on the fly gut leading to considerable advances in our understanding of intestinal homeostasis and pathology. Then I will present unpublished data revealing a previously unknown role of the conserved Svb/OvoL transcription factor in the intestine, where Svb/OvoL acts as a common effector of signaling pathways that is essential for adult intestinal stem cell survival and self-renewal. Moreover, Svb/OvoL is required in intestinal stem cell progenies, the enterocytes, to maintain their differentiation. I will give insights on how the same factor, Svb/OvoL, can control both stem cell renewal and differentiation.

T7-3: Metagenomics for Disease Diagnosis

Ahmed Moustafa

American University in Cairo, Egypt

Recent advances in genome sequencing and analytics have transformed our understanding of the human genome and microbiome. High-throughput genomics and metagenomics have proven to be a valuable approach for characterizing the personalized genetics and the structure of the microbial communities inhabiting the human body and for determining the association between the human microbiome and the health and disease states. We are presenting results of our recent studies on the microbiomes of different body parts and the potential clinical diagnosis and therapeutics.

T7-4: Crosstalk between gasotransmitters and non-coding RNAs in Breast Cancer

Rana Ahmed Youness, Mohamed Zakaria Gad

German University in Cairo, Egypt

Recently, myriad studies have straightened out the versatile ability of gasotransmitters and their synthesizing enzymes to play a "Maestro" role in orchestrating several oncological circuits and thus nominating them as possible therapeutic targets. Although a significant amount of work has been conducted on the role of nitric oxide (NO) and carbon monoxide (CO) and their interrelationship in the field of oncology, yet research about hydrogen sulphide (H2S) remains in its infancy. The main objective of this study was to unravel the role of exogenous and endogenous H2S in Breast cancer (BC) and to further investigate any possible crosstalk between H2S and non-coding RNAs (ncRNAs) in BC cell lines. Upon examining the role of exogenous H2S on BC progression, a dose- and time-dependent bell-shaped effect of exogenous H2S on BC hallmarks was repeatedly observed in the aggressive TNBC cell line, MDA-MB-231 and not in MCF-7 cells. We further aimed at investigating the impact of exogenous H2S on endogenous NO production within BC cells, where a similar bi-modal effect was observed on NOS3-mediated NO production in MDA-MB-231 cells. To unveil the potential link between exogenous H2S and NOS3/NO machinery in MDA-MB-231, sONE, a novel lncRNA validated to directly target NOS3, was found to be significantly altered in TNBC cells post-NaHS treatment, thus supporting a possible role of sONE in conveying the signals between the exogenous H2S and the endogenous NO in TNBC cells.

T7-5: Towards Defining the Genetic Architecture of Cardiomyopathy in Egypt

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Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease with regards to phenotype, genotype and mode of inheritance. To date, the genetic determinants of HCM in Egypt have not been studied, particularly in relation to the healthy local population.

Aim: To analyze the genetic architecture of HCM in the Egyptian population in comparison to Caucasians as well as global and local healthy controls.

Methods: A clinical cohort of 500 HCM patients and 400 Egyptian healthy volunteers (EHVols) underwent cardiovascular Magnetic Resonance imaging at Aswan Heart Centre. Samples from both cohorts were sequenced using a targeted panel of 174 genes with reported roles in inherited cardiac conditions. Rare genetic variation was compared between the Egyptian HCM patients and ethnically matched controls as well as the Caucasian HCM cohort. Results and Conclusion: Our analysis revealed that the proportion

of Egyptian patients with double mutations (8.7%), was significantly higher compared to Caucasians (4.2%) ($p<0.0028$ after Bonferroni correction). 33.3% of Egyptian patients with double mutations carried homozygous variants compared to 3.4% of Caucasians, owing to the high rate of consanguinity. Additionally, 22.5% of Egyptian patients presented with unique, ethnic-specific variants as opposed to 3.9% of Caucasians. A greater subset of Egyptian patients (% 33.1) presented with variants of uncertain significance compared to Caucasians (14.2%), which limits their actionability in the clinical setting. Defining the genetic architecture of HCM in our population, including the effect of homozygosity on the disease phenotype, will improve the diagnosis, disease management as well as aid in developing targeted therapy.

Session 8: Genetics of rare diseases III: Neurogenetics

T8-1: Malformations of Cortical Development (MCD) among Egyptian Patients: Phenotype-Genotype correlations**

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Malformations of cortical development (MCD) constitute major causes of seizures, cognitive deficit and motor disabilities in children. They represent a group of disorders that results from alterations of neurogenesis, migration to the cortical plate and cortical organization.

In this work, we present 143 patients derived from 130 families with MCD. Patients were classified according to their neuroimaging for targeted gene sequencing or whole exome sequencing.

There was abnormal neurogenesis in 48 families, microcephaly in 43 and megalencephaly in 5. Lissencephaly was the most common migration defects in our series (55 families) and cobblestones complex representing about 50 % of them was linked to GPR56, POMGNT1, LAMB1 and B3GLANT2 genes. Classical lissencephaly was in 14 families including LIS1, DCX, DYNC1H1, TUBA1A genes and lissencephaly cerebellar hypoplasia (LCH) was linked to RELN, CDK5 and VLDLR genes in 6, 1 and 8 families, respectively. Periventricular nodular heterotopia type 2 were in 2 families. Rest of our families were polymicrogyria and calcification allied to OCLN gene in 5 families, other polymicrogyria in 6 families, microlissencephaly in 4 families, schizencephaly in 6 families, parasagittal heterotopia in 3 families and cortical dysplasia in 4 families.

In this work, we highlight different categories of MCD and their incidence among our Egyptian patients. We elucidate that the cobblestones complex and LCH conveyed major groups of migration disorders in our series owing to their autosomal recessive inheritance in our inbred population. Also, this work emphasizes the importance of accurate phenotyping of cases with MCD.

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T8-2: Development of RT001 to treat infantile neuroaxonal dystrophy (INAD)-Use of an open-label treatment protocol with a concurrent natural history registry

Paldeep Atwal, Jayshree Krishnaswami, Frederic Heerinckx, Peter Milner, Mark Midei

Retrotope

Introduction: Drug development for ultra-rare disorders is challenged by the paucity of subjects eligible to participate, the wide geographic dispersion of subjects, and parental reluctance to enroll their children in a long-term, placebo-controlled trial. Infantile neuroaxonal dystrophy (INAD) is an autosomal recessive, ultra-rare neurodegenerative disease caused by pathogenic variants in PLA2G6. In order to test the effectiveness of RT001 in INAD, we conducted a treatment protocol along with a concurrent natural history registry to serve as an external control.

Prior Expanded Access Use: RT001 has been used in 2 subjects (1 for 10 months, 1 for 30 months) with INAD prior to the current treatment protocol. These protocols served as the basis for dosing, treatment duration, and a customized INAD efficacy scale.

Trial Design: Nineteen subjects with genetic and clinical evidence of INAD underwent baseline scoring with a structured pediatric neurological development examination customized for INAD (see below) at 2 US sites. In addition, other pediatric neurodevelopmental scales including the Modified Ashworth spasticity, Hammersmith, and CHOP-INTEND scales were also utilized. Global clinical impression, severity assessment, and visual analogue scales were also scored by parents. Subjects were placed on RT001 1.92 g BID for 1 month and are currently on RT001 0.96 g TID for the remainder of the 11-month treatment period. The neurodevelopmental scales are measured at 6-month and 12-month visits. The parental scales were reported monthly by parents.

Simultaneously, up to 50 subjects are being enrolled in a natural history registry of subjects with genetic and clinical evidence of INAD at sites in Tunisia, Cairo, Riyadh, Mumbai, and Beijing. Inclusion/exclusion criteria, and neurodevelopmental scale assessments are identical to the treatment protocol. The duration of observation is indefinite.

INAD Scale: This scale, customized for INAD patients, includes 5 broad categories of neurodevelopmental skills including: 1) Gross motor, 2) Fine motor, 3) Bulbar, 4) Ocular, and 5) Fronto-temporal. A total of 40 component elements are individually scored 0-2, according to pre-defined characteristics for a maximum score of 80.

Analysis: The primary efficacy analysis will be change from baseline in the customized INAD neurodevelopmental scale in the subjects treated with RT001 compared to the natural history subjects at 1 year. The various sub-components of the scale, the other scales, and the parental assessments will also be compared between groups as secondary endpoints.

Conclusion: Comparison of open-label treatment groups with a comparable group of external controls from a natural history registry is a practical alternative to a randomized, double-blind, controlled trial for an ultra-rare disease.

T8-3: A randomized, double-blind, controlled, study of RT001 in subjects with Friedreich's ataxia

Frederic Heerinckx, Jayshree Krishnaswami, Paldeep Atwal, Peter Milner, Mark Midei.

Retrotope

Background: Friedreich's ataxia (FA) is an autosomal recessive, neurodegenerative disease (ND) caused by GAA repeat expansion or loss-of-function variants in FXN. Downstream frataxin activity level <30% leads to mitochondrial dysfunction and lipid peroxidation (LPO). RT001 is a di-deuterated linoleic acid that reinforces cell membranes leading to decreased LPO and decelerates toxic cellular cascades.

Prior Study: In a placebo-controlled study of RT001 in FA (RT001-002), subjects receiving RT001 had increased cardiac workload capability after one month.

Trial Design: This trial is a randomized, double-blind, placebo-controlled phase 2/3 study of RT001 to assess the efficacy, safety, and tolerability of RT001 in subjects with FA over an 11-month exposure period. Sixty ambulatory subjects with genetic and clinical evidence of FA will undergo baseline cardiopulmonary exercise testing (CPET). They will also undergo multiple tests of function and neurological status including mFARS, a timed 1-minute walk test, FARS-ADL, fatigue scale, Clinical Global Impression, and Visual Analogue scale.

They will then be randomized in equal proportions to receive either RT001 or an inactive comparator for 11 months. Subjects randomized to RT001 will receive 2.88 g TID for 1 month followed by 2.88 g BID for the remaining 10 months of treatment. CPET and the other functional tests will be repeated at 4, 8, and 11 months after study initiation. Patient reported outcomes will be collected monthly. After the randomized period, an open-label study extension may be offered to any eligible patients in either arm of the study.

Analysis: The primary efficacy analysis will be maximum workload performed during CPET. If a significant improvement in CPET is demonstrated in the RT001 group vs placebo, the other functional tests will be used to confirm the clinical significance of the CPET findings.

Conclusion: The prior pilot study (CLN-RT001-002) demonstrating improvement in cardiac workload in FA subjects treated with RT001 was used to design the current randomized, double-blind, placebo-controlled study of 60 subjects over an 11-month exposure period.

T8-4: Microcephaly: An Overview

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Microcephaly is a major congenital anomaly that inevitably needs exhaustive genetic work-up before reaching an ultimate diagnosis. The prognostic value of this sign depends mainly on the etiology. Obviously, a sector of microcephaly presentations has a genetic background and is termed primary, while the other is caused by environmental factors and coined as secondary. When delineated at birth, it is known as congenital (most probably due to abnormal neuronal proliferation during development) but when developed after the first 6 months, it is called acquired and postnatal (due to decreased dendritic connection/activity with a normal number of neurons). Morphologically, it is isolated when not associated with any congenital anomalies but syndromic if associated with other congenital abnormalities. Microcephaly is clinically and genetically heterogeneous. The nosology in syndromic cases involves many known and many more as yet unknown forms. Progress in cytogenetics and molecular genetics has led to the identification of copy number variants and an emerging number of genes. In this report, we provide a selected retrospective overview of the important clinical cytogenetics and molecular features of microcephaly. In general, the recognizable imaging patterns usually predict the most likely causative etiology. Our data reflect our clinical experience in the evaluation of microcephaly. Thus, this will help in genetic counseling and prenatal diagnosis and recognize unrelated signs that would require further investigations and management.

T8-5: Genetic studies of primary microcephaly reveal novel pathways regulating brain development and pathogenic mechanisms

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Microcephaly is defined as head circumference at birth falling below –2 SD for the gestational age. Although between -2 SD and -2.5 SD microcephaly is defined as “mild”, most sources refer to primary microcephaly as that presenting with an occipital-frontal circumference below – 2.5 SD. Before the era of next generation sequencing, linkage analysis studies identified about 25 loci related to autosomal recessive primary microcephaly (MCPH), which in time were filled with genes in the loci causally involved with biallelic pathogenic variants. A diagnostic radiological mainstay of primary microcephaly is the presence of simplified gyral pattern at brain MRI, indicating an insufficient development of gyri and hence decreased proliferation of neuroglial progenitors or increased apoptosis. Most of the MCPH related disorders are characterized by a relatively stable disease course, variable intellectual disability and impairment mostly of speech and cognitive skills with a relatively normal motor development.

In parallel, several studies have described genetic disorders that were characterized by primary microcephaly followed by rapid neurodegeneration, often evolving into early demise in infancy. This type of microcephaly is often referred to as “secondary” microcephaly, i.e. with normal head circumference at birth. However, many patients with secondary microcephaly are already microcephalic at birth. Therefore, the distinction between primary and secondary as predictor of the disease course can be blurred at birth.

Thanks to the application of next generation sequencing technologies, including whole exome sequencing, whole genome sequencing, RNAseq and proteomics analysis, our group has succeeded in identifying the cause of new syndromes characterized by primary microcephaly and severe neurodegeneration, i.e. syndromes which at birth cannot be distinguished as primary or secondary. The first example is linked to autosomal recessive mutations in the gene SMPD4 coding for the neutral sphingomyelinase 3, an integral membrane protein of the ER, which we demonstrated to localize at the outer nuclear envelope. Patients present with microcephaly, simplified gyral pattern, hypomyelination, congenital arthrogryposis and central hypoventilation. Although disease pathogenesis still needs to be clarified, patient cells reveal abnormalities of mitosis, of the nuclear envelope, and are more susceptible to apoptosis. The second disorder is caused by autosomal recessive mutations in the gene TMX2, coding for the thioredoxin-related transmembrane-2 protein, a member of the protein disulfide isomerase family. Patients often present, besides congenital microcephaly, diffuse polymicrogyria of the cortex, whereas brain pathology shows severe dyslamination and massive overmigration of neurons in the subarachnoid space. We demonstrate that TMX2 is essential for regulation of the redox state signaling pathway, functioning as an oxidoreductase responsive to oxidative stimuli. This work uncovers novel pathways that are involved in the pathogenesis of primary microcephaly with early neurodegeneration.

T8-6: Cytogenomic Techniques as a Diagnostic Tool for Intellectual Disability and Multiple Congenital Anomalies**

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This study included 5,443 patients with Intellectual disability (ID)/ multiple congenital anomalies (MCA) through projects funded by the National Research Centre and Centre of Excellence for Human Genetics, STDF. The patients were referred from 2010-2019 to the Human Cytogenetics Department from outpatient clinics of Clinical Genetics Department (NRC). Our aims were to reveal genetic causes of ID/MCA and raising the percentage of diagnosed patients through the application of cytogenomic methods. Clinical examination, pedigree analysis and karyotype analysis were performed for all patients. According to the clinical presentations, some patients were subjected to analyses of Fluorescence in situ hybridization (FISH), multiple ligation probe amplification (MLPA), X-chromosome inactivation, Array CGH, and whole genome gene expression. Down syndrome was reported in 21% and chromosomal abnormalities in 6%. FISH analysis was applied on 11.6% of ID patients. Microdeletion was detected in 26% of clinical microdeletions.

MLPA analysis detected copy number variation in 17% of investigated patients, (127 patients). Array CGH was done for 70 patients and could explain the cause of ID in 50% of the analyzed patients. Skewed X-inactivation in X-autosome translocation could explain the escape of inactivation to rescue autosomal genes.

Karyotype and FISH could explain the genetic causes of ID in 30% of patients. The application of MLPA and array CGH on ID/MCA patients increased the % of identified genetic causes of ID. Gene expression may delineate the role of up or down regulation of certain genes as a cause of ID in patients with numerical X-chromosome anomalies.

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T8-7: Infantile Neuroaxonal Dystrophy: Genetic and Clinical spectrum of Egyptian Patients

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Infantile Neuroaxonal dystrophy (INAD) is a rare autosomal recessive genetic disorder due to bi-allelic mutations in phospholipase A2, group VI (PLA2G6) gene, which catalyzes the hydrolysis of the ester bond in phospholipids. The disease is characterized by early infantile neurodegeneration with loss of previously acquired milestones between the age of 12-24 months.

Herein we report 21 Egyptian patients with INAD. The patients were 14 males (66.7%) and 7 females (33.3%) and were all born to consanguineous couples. Optic atrophy and nystagmus were present in all cases (100%) with variable degrees and severity. In addition, hypotonia and hyporeflexia were noted in all cases (100%). All patients showed variable severity of loss of gross and fine motor skills. EMG studies showed chronic denervation potentials at the level of the anterior horn cells. Moreover, brain MRI showed progressive cerebellar atrophy in all patients. Molecular diagnosis by either whole exome sequencing or Sanger sequencing revealed pathogenic PLA2G6 mutations in all patients. Sixteen different mutations were identified including 10 novel ones. Of them, an inframe deletion of 1 amino acid was recurrent in 5 unrelated patients strongly suggesting a founder mutation in our population. Our data expands the mutational spectrum of INAD and highlight the importance of neurological and brain imaging findings as a key for the diagnosis of this neurodegenerative disorder.

Session 9: Genetic testing and biomarkers I

T9-1: The control of dolichol linked oligosaccharide (DLO) biosynthesis in Type I Congenital Disorders of Glycosylation: potential roles of DLO diphosphatases

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Protein N-glycosylation occurs by the transfer of an oligosaccharide from a lipid linked precursor ($Glc_3Man_9GlcNAc_2$-PP-dolichol, DLO) onto newly synthesized proteins in the lumen of the endoplasmic reticulum (ER). This process is essential for life and mutations in genes required for biosynthesis of DLO, or the transfer of its oligosaccharide onto protein, underlie several of the rare Type I Congenital Disorders of Glycosylation (CDG-I). Although genetic lesions in the DLO biosynthetic pathway cause glycoprotein hypoglycosylation and accumulation of truncated DLO intermediates, for most of these multisystemic, often severe, diseases the link between genotype and phenotype is poorly understood. For the majority of CDG-I, there are no etiological treatments, in part, because the regulation of DLO biosynthesis in normal and disease situations is poorly understood. DLO diphosphatases (DLODPs), orphan enzymes whose genes have not been identified, cleave DLO intermediates seen in certain pathophysiological situations like CDG-I to generate oligosaccharyl phosphates (OSP), but the roles of these activities in normal and disease cells remain to be determined.

We hypothesise that DLODPs destroy toxic truncated DLO intermediates, which are generated under pathological/stress conditions like CDG-I, that would otherwise cause cell pathology. We have identified two OSP generating systems in mammalian cells. One OSP-generating process is associated with a Co^{2+}-stimulated DLODP activity that co-localises with markers of the Golgi apparatus during subcellular fractionation and becomes apparent when cells are treated with brefeldin A, which causes elements of the Golgi apparatus to fuse with the ER. Under these conditions a population of OSP are generated from mature DLO ($Glc_3Man_9GlcNAc_2$-PP-dolichol) within the ER/Golgi fusion compartment. In the second process, OSP are generated on the cytoplasmic face of the ER from truncated DLO intermediates by an as yet uncharacterised enzyme activity. This second process occurs in cells from CDG patients and is not affected by brefeldin A. Presently, we are identifying DLODP genes so that we can understand the roles of these enzymes in protein N-glycosylation. If the N-glycosylation pathway is to be understood in such a way that its behaviour can be predicted in the face of pharmacological or genetic perturbation, then the molecular identity, partners, regulation and biochemical characteristics of all the players must be described. Therefore, identification of DLDOP proteins and genes will lead to both fundamental insights into DLO and protein N-glycosylation homeostasis and the potential development of CDG-I treatment strategies.

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T9-2: Twenty-Five Years of biochemical diagnosis of Gaucher Disease: The Egyptian Experience

Ekram Fateen

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Gaucher disease is a rare multi-systemic metabolic disorder resulting from the deficiency in acid β-glucosidase activity, with consequent accumulation of glucocerebroside. Less than 15% of the mean normal activity of leukocytic acid β-glucosidase is the gold standard for the diagnosis of Gaucher disease, which is supplemented by a massive elevation in chitotriosidase enzyme activity. We report here our experience in the biochemical diagnosis of Gaucher disease by showing the heterogeneity of the activity of enzymes over 25 years from 1993-2017, through the analysis of 5128 clinically suspected Gaucher disease cases referred to Biochemical Genetics Department, National Research Centre, as the main reference lab in Egypt for the diagnosis of inherited metabolic disorders.

Methods: β-glucosidase and chitotriosidase enzymes activity were measured to all referred cases. Sphinogmylinase activity was estimated for all cases with normal activity of β-glucosidase and moderate elevation of chitotriosidase.

Results: Out of the 5128 suspected cases, 882 (17%) showed deficiency in acid β- glucosidase activity, accompanied with high chitotriosidase activity levels, [range: 213-66700 umol/l/h and mean: 7254.8 umol/l/h]. Zero chitotriosidase activity was found in 9 patients (1%) with low β-glucosidase. 451 cases were diagnosed as Acid Sphingomyelinase deficiency patients (8.8%).

Conclusion: Other biochemical markers are needed in addition to chitotriosidase enzyme for disease diagnosis and follow up. Molecular testing was done to a relatively small number and need to be done to all diagnosed patients as many mutations are known to predict the course of the disease.

T9-3: Application of various genetic techniques in clinical practice

Dmitri Ossipov
CeGaT GmbH, Germany

Among other advantages for patients and healthcare system, genetic diagnostics helps to give or confirm a correct diagnosis. The talk covers all process steps of medical genetic tests like PCR, MLPA, Sanger, NGS and Array-CGH and explains how to select a proper method of testing exemplified by real clinical cases.

T9-4: WGS to Identify Disease-causing mutations in twins with OI III

Susan Alicia Fernol, Alan Christoffels, Manogari Chetty
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Osteogenesis imperfecta type III (OI III) is a rare well-defined entity that is characterized by autosomal recessive (AR) inheritance and severe physical deformity. In South Africa and Zimbabwe, OI III was found to be fairly common in the indigenous Black African population. FKBP10 is one of the newer members of an expanding list of AR OI genes and was described in OI III.

The current study aimed to identify the disease-causing mutation that segregates with the affected individuals, twins, in a South African family of mixed ancestry using whole genome sequencing.

Whole genome sequence analysis identified variants that were unique to each of the affected twins and not their parents. These variants have not been previously reported within the 14 genes known to play a role in the recessive form of OI III. These variants have been documented in a recently established repository for dental genetics phenotypes and genotypes based at the Faculty of Dentistry, University of the Western Cape. Genes not previously associated with OI have been identified. Clinical observation of phenotype in a collection of South African families of mixed ancestry is unique. Different genes may be contributing to the different phenotypes that we see.

Future studies of this disease will benefit from larger sample sizes, greater participant diversity in terms of age and development stage, genetics and clinical phenotypes. This information may be useful for diagnostic screening of future patients with similar phenotypes.

T9-5: Interplay between genes and DNA damage, hormones and/or the immune system in breast and liver cancers

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Extensive research for new biomarkers is considered pivotal not only to optimize disease diagnosis and patient monitoring, but also to understand cancer mechanism(s). Although breast and liver cancers have not been traditionally considered as immunogenic tumors, recent data suggest that immunity and its interaction with tumor cells and tumor microenvironment, might play an important role in these malignancies. Therefore, the interest in studying immune aspects in the tumor subtypes has become appealing. Nevertheless, some scattered evidence indicates that immunity and inflammation may be implicated in cancer biology. Breast cancer associated-susceptibility risk factors in obese, insulin resistant, or pre-diabetic patients need to be assessed. Cancer is a considered a heterogeneous disease with many different outcomes, however, the effect of protooncogenes and transcription factors are to be considered in the mechanistic studies.

T9-6: FOXP2 gene Involvement in Speech and Language Disorders

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One important language gene is FOXP2, a mutation of which affects language and speech mainly in relatively rare and severe forms. However, other genes likely related to FOXP2 gene, and certain genetic markers adjacent to it may be highly suspected to be involved in more common forms of language impairment. FOXP2 gene is a transcription factor, that regulates the expression of other genes. Identification of the structure of FOXP2 gene, its mutations, and the pathways related to it in acquisition of speech and language may yield new insights into the causes of different speech and language disorders, along with improved diagnosis, and treatment.

This presentation will address the importance of FOXP2 gene as a speech and language gene, highlighting its structure, function and outcome of its breakdown in different speech and language disorders.

Session 10: Genetic testing and biomarkers II

T10-1: Cloning and expression of human insulin gene in Pichia pastoris

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The main goal of the current study was cloning and expression of the human insulin gene in Pichia pastoris expression system, using genetic engineering techniques. Total RNA was purified from fresh normal human pancreatic tissue. RNA of good quality was chosen to obtain a first single strand cDNA. Human preproinsulin gene was amplified from cDNA strand, by using two sets of specific primers contain EcoR1 and NotI restriction sites. The amplified preproinsulin gene fragment was double digested with EcoRI and Not 1 restriction enzymes, then inserted into pPIC9K expression vector. The new pPIC9K-hpi constructive expression vector was transformed by the heat-shock method into the E. coli DH5α competent cells. pPic9k –hpi, which was propagated in the positive transformant E. coli cells, was isolated from cells, linearized by restriction enzyme SalI, and then transformed into Pichia pastoris GS115 using electroporation method. Genomic DNA of His+ transformants cell was extracted and used as a template for PCR analysis. The results showed, that the pPic9k – hpi was successfully integrated into the P. pastoris genome, for selected His+ transformants clones on the anticipated band at 330 bp, which corresponded to the theoretical molecular size of the human insulin gene. To follow the insulin expression in transformants, Tricine–SDS gel electrophoresis and Western blot analysis were conducted. The results showed a successful expression of recombinant protein as detected by the presence of a single major band of about 5.8 Kda on the gel. This band corresponded well with the size of human insulin with the theoretical molecular weight of 5.8 Kda.

T10-2: Diagnosis and prognosis of Egyptian SMA patients and carriers

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease that is characterized by degeneration of the anterior horn cells in the spinal cord and caused by decreased levels of survival motor neuron protein (SMN) due to mutations in SMN1 gene. The carrier frequency of SMA shows very high frequency in the general population (1:35). Most SMA patients have homozygous absence of SMN 1 due to lack of the gene or SMN 1 – SMN 2 conversion.

The NRC is a major referral center for SMA patients from different parts of Egypt. We applied a rapid, conventional, low cost and high throughput test for accurate diagnosis of SMA patients and carriers, and also prediction of the severity of the disease. Additionally, we have determined carrier frequency in an Egyptian cohort.

SALSA multiplex ligation-dependent probe amplification (MLPA) KIT P021-A2 SMA was used to determine SMN1, SMN2, NAIP and GTF2H2 genes copy numbers in 91 SMA patients, and 57 healthy individuals. The results showed that 69.2% of SMA patients had homozygous deletion of exon 7 of SMN1 gene. Variations in SMN2, NAIP, GTF2H2 genes were calculated to be correlated to the severity of the disease. In addition, the healthy Egyptians showed that the carrier frequency was 31.6% of the studied group.

MPLA assay is a relatively rapid technique to determine variations in 4 genes with accurate and reproducible approach and help in providing proper genetic counseling to reduce the burden of giving birth of an affected child with this lethal disease.

T10-3: First Egyptian Carpenter syndrome patient diagnosed using whole exome sequencing

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Carpenter syndrome is a rare genetic developmental syndrome known by the cardinal features of acrocephaly with variable craniosynostosis, peculiar facies, polysyndactyly of the hands and feet, congenital heart defects, and mental retardation. In this study, we report the first Egyptian Carpenter patient from a consanguineous family that was diagnosed using whole exome sequencing (WES) analysis. Full clinical examination of the patient was performed and showed atypical skeletal features with signs of autism. Family history and pedigree were documented with informed consent from parents. This work was done in collaboration with the Baylor-Hopkins Center for Mendelian Genomics at Johns Hopkins University for WES analysis. VCF files were analyzed in PhenoDB. Approximately one hundred homozygous variants were identified and filtered according to allele frequency, gene function, and the variant's effect on the protein function and tolerance of the gene.

A homozygous variant in RAB23 gene (NM_001278668: c.416 T<C:p.Leu139Pro) was detected with coverage of 60X. This variant is rare and not present in large public allele frequency databases such as gnomAD and dbSNP. It is predicted to be pathogenic using seven computational prediction algorithms. Varsome engine predicts the variant to be likely pathogenic using ACMG criteria for variants classification. The RAB23 variant was confirmed by Sanger sequencing in the proband and segregated in both parents in heterozygous form. Our patient's phenotype correlates well with the clinical features of Carpenter syndrome. With the identification of this variant in RAB23, we report the first Egyptian patient with Carpenter syndrome diagnosed by WES.

T10-4: Delineating the phenotypic and mutational spectrum of AMPD2-related pontocerebellar hypoplasia

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Pontocerebellar hypoplasia (PCH) is a clinically and genetically heterogeneous group of progressive neurodegenerative disorders with 12 different types (PCH1-12) and 18 identified causative genes till now. PCH type 9 is characterized by severe microcephaly, severe psychomotor delay, spasticity and intractable seizures. The brain MRI usually shows hypogenesis of the corpus callosum, cerebellar hypoplasia, ventral pontine degeneration and variable degrees of cortical atrophy. This unique type of PCH is caused by biallelic mutations in the adenosine monophosphate deaminase 2 (AMPD2) gene. To date, only 24 patients from 14 families have been reported in the literature. Herein we describe 16 new patients from 15 unrelated families with PCH9. They were 9 males and 7 females, aged from 3 months to 2 6/12y and parental consanguinity was evident in 100% of cases. All patients had progressive microcephaly, severe global developmental delay, spasticity with intractable generalized and myoclonic seizures and the unique neuroimaging findings as small cerebellum, hypoplasia of brain stem, hypogenesis of corpus callosum and cortical atrophic changes. Twelve different mutations in the AMPD2 gene were identified including many novel ones. Our results expand the mutational spectrum and reinforce the clinical and brain imaging characteristics of the disorder.

T10-5: Role of Genetic Polymorphism in diabetic patients using Anti-vascular endothelial

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Introduction: Patients with diabetes mellitus may have an ocular complication in the form of diabetic retinopathy (DR). This occurs secondarily to high blood sugar levels that cause damage to retinal blood vessels. These blood vessels can swell and leak or get clogged, stopping blood from passing through. Sometimes, aberrant new blood vessels grow within the retina.

Aim: To assess the probable association of 2549 insertion/deletion (I/D) polymorphism of vascular endothelial growth factor (VEGF) with DR in Egyptian diabetic patients.

Subjects and methods: A cross-sectional study enrolled 176 unrelated diabetic subjects. PCR–RFLP analysis of this polymorphism was carried out.

Results: There was a statistically significant difference in genotypic and allelic distributions of the 2549 insertion/ deletion polymorphism of vascular endothelial growth factor (VEGF) in diabetic patients with retinopathy versus those in diabetics without retinopathy.

Conclusion: The present study suggested the association between the development of DR and the (I/D) polymorphism of VEGF.

T10-6: Regulation of breast cancer stem cells associated genes by miRNAs

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Introduction: Complexity of microRNAs (miRNAs) interaction network is attributed, but not limited, to ability of individual miRNAs to target several mRNAs and the involvement of transcription factors (TFs) as a second layer of miRNA-mediated gene regulation.

Aim: Our work investigated the involvement of miR-150 and miR-203 in regulating genes related to cancer stem cells phenotype. The method included transfecting cancer cells with miRNA mimic or inhibitor, then performing downstream analysis.

Results and conclusion: Restoring miR-203 and inhibiting miR-150 expression led to decreased breast cancer stem cells subpopulation in MDA-MB-231. Targeting DNMT3B and DNMT3A resulted in regulation of expression of genes related to cancer stem cell properties. However, knocking-down DNMT3B resulted in inconsistent results in breast cancer stem cells. Additionally, restoring miR-203 inhibit breast cancer cell migration by inhibiting PKC theta as a direct target which mediate change in chromatin accessibility of cancer stem cells related genes. A positive feedback loop was found between miR-203 and its target DNMT3B and a negative feedback loop between miR-203 and PRKCQ. MiR-141 and miR-200c expression was increased in response to restoring miR-203 which suggests that “microRNA-mediated microRNA regulation” is involved in breast cancer cells.

Poster Presentations

P1-Genetics of rare diseases

P1-1: Thalassemia Syndromes in Egypt: National Research Centre Experience**

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Introduction: Thalassemia syndromes are the most common single-gene disorder worldwide. The treatment of affected individuals presents a substantial global disease burden. Alpha, β, and δβ thalassemia are the main types with clinical importance.

Aim: To investigate the spectrum of globin gene mutations among Egyptians to provide appropriate premarital and prenatal counseling.

Material & Method: This study was done in accordance to the Medical Research Ethics Committee (MREC) at NRC on 500 β-thalassemia and 20 α- thalassemia patients attending the Hereditary Blood Disorder clinic, NRC. After signing an informed consent, blood samples were analyzed for globin gene mutations by StripAssay kit and sequencing analysis.

Results & Conclusion: The most common mutations in β-thalassemia were IVS I-6[T>C] 26.33%, IVS I-110[G>A] 20%, IVS I-1[G>A] 18.7% followed by IVS II-745[C>G] 7.1%, Cd 6[A>T; Hbs] 5.3%, IVS II-848[C>A] 4.5%, Cd27[G>T] 4.3%, Cd39[C> T] 3.7%, Cd5[-CT] 2.6%, -87[C>G] 2%, while IVS II-1[G>A] 1.4%, Cd 44[-C] 1.35%, IVS I.5[G>C] 1.1%, Cd 6[G>A: Hbc] 0.5%, -29[G>A] 0.25%, -101[C>T] 0.12%, Cd8/9[+G] 0.12% and Codon 37[G>A] 0.12% were the rarest. Many polymorphic sites in β-globin gene were also detected including IVS II-16 (G>C), IVS II-74 (T>G), IVS II-81(C> T), IVS II-666(C>T) and -31(C>T). Molecular characterization of α-thalassemia revealed that the most common mutation was −α3.7 (single gene deletion), α2 polyA-1 [AATAAA > AATAAG] and α2 IVS1 (5bp deletion). However, the structural chain variant; Hb-lepore was detected in only one case. This study recalls the necessity of establishment of thalassemia mutation database and awareness raising programs for proper preventive strategy of the disease in Egypt.

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P1-2: Identification of large intragenic deletion mutations in Egyptian Fanconi anemia**

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Fanconi anemia (FA), the most common inherited bone marrow failure (BMF) syndrome, is characterized by hypersensitivity to clastogenic agents & cancer predisposition. Progressive BMF is the main cause of mortality. To date, 22 FANC genes have been identified, including 18 well-known bona fide FA genes. FANCA gene is the most commonly mutated gene among FA patients with percentage of 85%. Large intragenic deletions in the FANCA gene are more common due to Alu-mediated recombination.

The current study aimed at screening for deletion mutations within the FANCA gene among Egyptian FA patients using multiplex ligation-dependent probe amplification (MLPA) method for the delineation of the spectrum of underlying molecular pathology.

Subjects and Methods: The study included 55 FA patients, who were referred to the Hereditary Blood Disorders Clinic, NRC, Egypt. Their age range was from 4 months to 17 years and they were descending from unrelated consanguineous families. Patients' diagnosis was confirmed by DEB chromosomal breakage

Results: Out of 55 patients, 14 had five different intragenic homozygous deletions in FANCA gene, ranging from a single exon loss to large exons deletion. Deletions detected in FA-A patients correlated with clinical characteristics and cytogenetic results. Reviewing the literature, all different deletion patterns detected in this study were novel.

Conclusion: Molecular analysis using recent technologies could detect causal mutations, help genetic counseling and prenatal diagnosis. Investigating the physical and hematologic manifestations associated with specific FANC gene mutations among the Egyptian FA patient sample might enhance the understanding of the influence of the distinct FA genotypes on the clinical course of this disease.

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P1-3: Epigenetic effects towards new insights as potential therapy in B-thalassemia**

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Fetal hemoglobin (HbF) induction has shown promise for the treatment of patients with β-hemoglobinopathies. HbF induction in β-thalassemia patients could overcome ineffective hematopoiesis and thus terminate transfusion dependency for formerly transfusion-dependent patients. Through implementing this approach, it will be used as a novel therapeutic goal for thalassemia and sickle cell disease (SCD) cases as well. Several miRNAs have been found to reactivate □-globin gene expression and increase HbF.

In this study, we aimed to investigate the expression of 4 miRNAs (miR-15a, miR-16-1, miR-96 and miR-486-3p) in high HbF thalassemia patients and correlate their levels with the patients' HbF levels. The differential expression was measured by Real time PCR for 40 patients with high HbF and compared to 20 healthy controls. Bioinformatic study was conducted involving functional annotation and pathway enrichment analyses. The results of the studied microRNAs were significantly deregulated in thalassemia patients in correlation with the patients' HbF levels. Bioinformatic analysis for functional annotation and pathway enrichment analyses revealed a major role of miR-486-3p and miR-15a in HbF induction.

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P1-5: Genetic aspects of Turner syndrome and its variants in patients with primary amenorrhea

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Introduction: Turner syndrome and its variants are structural and numerical chromosomal anomalies. Female with the syndrome present with primary amenorrhea (PA) as a common complaint. The observation of PA with short stature, webbed neck and ovarian failure are an indication for cytogenetic testing.

Aim of study: This study aims to determine the cytogenetic profiles indicating Turner syndrome or its variants among patients firstly presenting with primary amenorrhea.

Methods: This is a retrospective descriptive study of 79 PA patients, who were referred to Cytogenetic and Molecular unit, Center for Biomedical Research (CEBIOR), Faculty of Medicine, Diponegoro University from 2004 to 2016, for karyotype analysis.

Results: The cytogenetic results revealed that 8 out of 79 patients (10.1%) had monosomy X, 3 (3.8%) with 45,X/46,XX; 3 (3.8%) with

Isochromosome 45 X/46,XX, 2 (2.5%) with 45,X/46,XY; 1 (1.3%) with marker chromosome 45,X/46,X+mar and 1 (1.3%) with chromosome 1 and X translocation 46,XX,t(1;X)(p34;q25).

Conclusion: Turner syndrome is one of the most common causes of primary amenorrhea, which attests the importance of cytogenetic analysis for clinical diagnosis in primary amenorrhea patients.

P1-6: Aromatase deficiency in an Egyptian girl with ambiguous genitalia

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Introduction: Aromatase deficiency is a rare autosomal recessive disorder that is caused by an impairment of androgen conversion to estrogens. Affected 46, XX individuals generally present with Virilization of external genitalia at birth and have mutations in CYP19A1 gene. There were reports of subjects with aromatase deficiency who may manifest during fetal life with maternal virilization due to low aromatase activity in the steroid metabolizing fetal–placental unit and the high levels of androgens. During infancy, girls often have ovarian cysts and thereafter fail to enter puberty showing signs of variable degree of androgen excess. Moreover, impact on growth, skeletal maturation and other metabolic parameters is seen in both sexes.

Case report: The current study describes the clinical features, investigations and the biochemical diagnosis of a case of ambiguous genitalia in a 46, XX baby born at term to consanguineous parents. The mother had signs of virilization during pregnancy. The investigations comprised karyotype analysis, hormonal assays [including DHEA, testosterone, dihydrotestosterone, 17 alpha-hydroxyprogesterone, cortisol am & pm, ACTH am & pm, estradiol, FSH and LH] and Ultrasonography on the internal genital organs.

The levels of androgens and FSH were high, of 17 alpha-hydroxyprogesterone and estradiol low and of cortisol and ACTH within normal. The patient had bilateral ovarian cysts.

In conclusion, aromatase deficiency was diagnosed in a 46, XX girl presenting with ambiguous genitalia and had maternal virilization during pregnancy. Maternal virilization should prompt consideration of aromatase deficiency, preventing unnecessary interventions in pregnancy.

P1-7: The Natural history of infantile neuroaxonal dystrophy

Fadie Altuame, Fowzan Alkuraya, Gretchen Foskett, Paldeep Atwal, Frederic Heerinckx, Peter Milner, Sarah Endemann, Robert Molinari, Harry Saal, Mark Midei

The design of clinical studies in rare diseases requires a thorough understanding of the natural history (NH) of patients treated with standard care. Infantile neuroaxonal dystrophy (INAD) is an autosomal recessive, ultra-rare neurodegenerative disease caused by pathogenic variants in PLA2G6. In the current study, we sought to define the NH of INAD and to identify markers of disease status and progression.

This study was conducted in compliance with the Declaration of Helsinki principles and the IRBs at the respective study sites. Twenty-eight subjects were enrolled at multiple international sites. Delayed development was noted in 19 subjects (68%) prior to developmental regression. The others had normal development prior to disease onset. Speech (84%) and walking (88%) impairments were the most common among subjects with developmental delays. All subjects experienced developmental regression once symptoms developed and a diagnosis was confirmed. Speech and gross motor regression predominate early, with later deterioration in fine motor and bulbar function. Temporo-frontal signs were among the last milestones to be lost. Mean age of death was 9.7 years (range 6-14) with respiratory causes predominating.

In conclusion, INAD is an ultra-rare neurodegenerative disorder that presents in early childhood. It is relentlessly progressive with speech and gross motor impairment as the earliest signs. Fine motor and bulbar dysfunction develop gradually after the other symptoms develop, followed by temporo-frontal dysfunction in the later stages of the disease. Knowledge of the natural history of INAD may facilitate the design of clinical trials to treat this disease.

P1-8: Assessment of diagnostic value of MLPA in patients with Williams-Beuren-syndrome

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Introduction: Williams-Beuren syndrome (WBS) is considered a rare multisystem genetic syndrome resulting from the hemizygous deletion of approximately 26-28 genes on chromosome 7q11.23. Fluorescence in situ hybridization (FISH) is considered the gold standard for diagnosis of WBS. However, FISH does not allow the detection of the exact size of the deletion.

Aim: This study aimed to compare the efficiency and validity of multiplex ligation-dependent probe amplification (MLPA) and Fluorescence in situ hybridization (FISH) techniques in diagnosing and confirming clinically diagnosed WBS patients.

Materials and Methods: An informed consent was obtained for each studied case. The used MLPA kit (SALSA P029) contained probes for eight genes in the WBS critical region: FKBP6, TBL2, STX1A, FZD9, LIMK1, ELN, RFC2, and CYLN2.

Results: nineteen patients out of 23 studied cases (82.6%) showed positive deletion of the WBS chromosome region (WBSCR) by both FISH and MLPA techniques. One patient (4.3 %) showed negative result by FISH while a duplication of the WBSCR was detected by MLPA. Three patients (13.1 %) were negative for both FISH and MLPA.

Conclusion: MLPA analysis has an advantage over FISH as it is less time consuming and detects smaller, atypical deletions and duplications in the WBSCR.

P1-9: Clinical and genetic studies of different categories of DSD*

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Disorders of sex development (DSD) are congenital conditions with atypical development of chromosomal, gonadal or anatomical sex. They are not uncommon in Egypt. A previous study reported an incidence of 1/5000 with ambiguous genitalia in a 20,000 newborn/infant sample. DSD are categorized into 46,XY DSD, 46,XX DSD and Sex chromosome DSD.

The objective of the current work was to study Clinical, cytogenetic and molecular characteristics of DSD and determine the frequency of each type. Two hundred and twenty-three patients were referred to the genetic endocrinology clinic, NRC between 2017 and 2019 with different DSD presenting features. All cases were subjected to clinical and genital examination, cytogenetic studies, pelvic sonar, hormonal assays of testosterone, its precursors and DHT. Molecular study of androgen receptor, SRD5A2, NR5A1 and 17 BHSD genes were done when indicated. Exome sequencing was done for undiagnosed cases.

Sex chromosome abnormalities were detected in 109 patients including both numerical and structural abnormalities in 3 subcategories; Turner syndrome, 58 patients, Klinefelter syndrome, 36 patients and other sex chromosome DSD, 15 patients. The commonest presenting complaints were primary amenorrhea, 33 patients, hypogonadism/ azoospermia, 28 patients, short stature, 27 patients and ambiguous genitalia, 9 patients.

46,XY DSD were detected in 76 patients in 3 subcategories; disorders of androgen synthesis or action, 45 patients, disorders of gonadal development, 16 patients and other XY DSD, 15 patients. The commonest presenting complaints were ambiguous genitalia, 44 patients, primary amenorrhea, 18 patients and undescended testes, 10 patients.

46,XX DSD were detected in 38 patients in 3 subcategories including disorders of androgen excess, 25 patients, disorders of gonadal development, 11 patients and other XX DSD, 2 patients. In conclusions, this study enlarges the scope of genotypic and phenotypic presentations of DSD and emphasizes application of exome sequencing for more accurate diagnosis and better genetic counseling for patients.

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P1-10: Clinical and genetic finding in patients with white matter disease**

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Introduction: Leukodystrophies are genetically determined leukoencephalopathies, which can occur at all ages, be progressive or static, be genetic or acquired. Generally, it presents early in life, but age at onset of symptoms has a wide range from childhood throughout adolescence. It is classified into four categories: hypomyelinating, demyelinating , dysmyelinating and myelinolytic diseases .They are group of disorders that are characterized by: (a) a genetic basis; (b) a progressive course; (c) involvement of the CNS white matter (d) a primary disease of myelin and myelin generating cells.

Aims:1-To study patients with white matter diseases and identify their molecular background in order to create a new algorithm of white matter diseases based on clinical, radiological and biochemical presentations. 2-Determine the genetic etiology of different types of white matter diseases which is important to serve a proper genetic counseling and future prenatal diagnosis.

Material and methods: One hundred and fifteen patients with inclusion criteria suggestive of white matter changes were referred to the Neurogenetics clinics. Age range was from few months to 12 years old, putting in consideration the correlation of white matter development with age during the first 2 years of life.

Results: Among 115 patients, 68 patients (59.1%) were with neurodegenerative brain disease (Demyelination), 6 with brain malformation (5.2%), 6 with congenital muscular dystrophy (5.2%) , 30 with hypomyelination (26.2%) and only 5 cases with unclassified white matter disease (4.3%). Canavan disease was the most common neurodegenerative disorder Conclusion: White matter disorders entail a wide spectrum of neurological disorders.

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P1-11: Mutational screening of GBA gene in Egyptian Gaucher patients**

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Introduction: Gaucher disease (GD, MIM#230800, 230900, 231000) is an autosomal recessive lysosomal storage disorder resulting from deficiency in the acid β-glucocerebrosidase enzyme (GBA). This causes an accumulation of glucocerbroside in the cells' lysosomes leading to multisystem abnormalities. Three major clinical types are delineated by the absence (type I) or presence (types II and III) of primary central nervous system involvement.

Aim: Identifying mutations of the coding region of GBA gene among 15 Egyptian patients with Gaucher disease.

Patients and methods: Written informed consent was obtained in each case. Patients were from 15 unrelated families, age ranged from 10 months to 10 years with parental consanguinity in 12 families out of 15 (80%). All patients were subjected to all necessary clinical, radiological and biochemical assessments. Molecular analysis was carried out using Sanger sequencing technique for the 11 coding exons of the GBA gene for the 15 studied patients.

Results: Three mutations were detected among the studied patients in this study. The disease-causing mutations were revealed in 11 patients. Seven patients were homozygous for p. L483P mutation (46.6%). Two patients were homozygous for p.N409S mutation (13.3%). One patient revealed compound heterozygous for p. N409S/ L483P mutation (6.6%) while one patient revealed homozygous p.R87W mutation (6.6%).

Conclusion: The most common mutations in the studied cohort are p.L483P (50%) followed by p.N409S mutation (16.6%), and p.R87W mutation (6.6%) and exons 9 and 10 carry most of the identified mutations.

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P1-12: Mild phenotype Molybdenum cofactor deficiency type B diagnosed by WES**

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Molybdenum Cofactor Synthesis 2 (MOCS2) gene mutation is a rare type of MoCD, where its prevalence is estimated to be 1: 100000 to 200000 newborns world-wide. Only 30 cases of molybdenum cofactor (MoCo) type B have been recognized.

Case I: A female patient aged 3 8/12 years was referred to the genetics clinic at the National Research Centre, presenting with progressive loss of acquired developmental milestones and convulsions, starting at 3 years of age. The parents were 1st degree cousins and the pregnancy and delivery were uneventful. There was history of two other affected siblings. The patient's head circumference was below normal (<-2D) with a tendency to microcephaly. The patient was not dysmorphic, hypertonic with brisk reflexes more on the left side. EEG showed epileptogenic dysfunction. MRI brain showed right frontal subdural hygroma with frontal lobe atrophy and cerebellar atrophy. Convulsions responded to antiepileptic therapy.

Case II A female patient aged 1 6/12 years had progressive loss of acquired milestones at age of 1 year, convulsions and CHD. She was the first child of a consanguineous marriage. She was not dysmorphic and with normal anthropometric measurements. She had opithotonus with dystonia and brisk reflexes. Uric acid was low. MRI revealed bilateral abnormal signals in the globus pallidus with bilateral basal ganglia calcification and cerebellar atrophy. The patient died at 2 8/12 years.

Whole exome sequencing (WES) analysis for the two patients was performed at the sequencing core facility at the Imagine Institute. WES. MoCD type B diagnosis was proved by WES analysis. In

conclusion, MOCS2 is a rare AR type of MoCD and could present at a late onset.

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P1-13: Biochemical Diagnosis of Wolman disease among clinically suspected patients

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Wolman disease is a rare autosomal recessive disorder, caused by a mutation in LIPA gene responsible for producing the lysosmal acid lipase (LAL) enzyme. The enzyme is responsible for breaking down certain lipids inside the cell and its deficiency results in massive accumulation of cholesterol and triglycerides inside the liver cells causing hepatomegaly.

This study aimed at diagnosing Wolman disease by a new Fluorometric method using dried blood spot. Eighty-four patients and controls were recruited for this study, 30 healthy normal controls, 31 clinically suspected patients and 23 positive patients of Gaucher and Niemann Pick diseases. The method entailed measuring lysosomal acid lipase (LAL) enzyme, in the presence of a specific inhibitor called Lalistat. The activity of LAL was measured by using 4-methylambelliferylpalmitate as a substrate, to assess the total lipase activity. Second, measuring lipases in presence of a definite inhibitor called Lalistat 2, which inhibits specifically LAL, then the difference between the two concentrations is the real activity of LAL.

Two Wolman patients were diagnosed from the 31 suspected patients. Both were 3 and 4 months old, with hepatosplenomegaly, anemia, adrenal calcifications and failure to thrive. In both patients, the activity measured for LAL were almost zero activity. A mutation in the LAL gene was found to be a homozygous mutation resulting in no production of the enzyme at all in one of the two patients confirming the diagnosis of Wolman disease.

P1-14: First reported Egyptian sibs with the rare Laron syndrome

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Laron's syndrome, or Laron-type dwarfism, is an autosomal recessive disorder characterized by insensitivity to growth hormone. There are exceptionally low levels of insulin-like growth factor (IGF-1) caused by homozygous or compound heterozygous mutation in the growth hormone receptor gene. It causes severe short stature and can be treated with injections of recombinant IGF-1. Laron syndrome is a rare disorder; about 350 people have been diagnosed with the condition worldwide. The majority of reported cases of Laron syndrome have been in people with Semitic origin. Here, we are presenting the first reported Egyptian sibs affected with this rare disorder, 2 boys born to first cousins, nine- and seven-years old presenting with abnormally severe short stature (dwarfism), prominent forehead, depressed nasal bridge, underdevelopment of mandible and micropenis. Development and mentality were normal. Several studies are now investigating the role of Cyproheptadine HCl (CyproH) as a treatment for this disorder. CyproH is an appetite-stimulating drug and while it was prescribed for a patient with growth hormone insensitivity syndrome (GHIS) for increasing appetite, his height growth was surprisingly increased. Our patients are now on CyproH treatment; 0.25 mg/kg/24 hours as an alternative to recombinant IGF-1 which is very expensive, and interestingly, a marked increase in height is noticed.

P1-15: Genetic evaluation of 46,XY DSD using MLPA technique

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Knowledge of the molecular basis of disorders of sex development (DSD) strongly influences case diagnosis and management. Mutations in sex-determination genes; SRY, SOX9, WNT4, DAX1, and NR5A1 and others account for 50% of 46,XY DSD. Screening for CNVs are often missed and not detected by conventional karyotype. MLPA technique is a useful tool for accurate identification of CNVs in syndromic or non-syndromic 46,XY DSD. This study aims to detect genomic abnormalities in 46,XY DSD.

We report on forty patients with ambiguous genitalia, hypospadias, or a female phenotype with primary amenorrhea or short stature. Patients were subjected to full history taking, general and genital examination, hormonal analysis, imaging studies, histopathology, cytogenetic studies and FISH technique. DNA extraction and MLPA were done using two kits: Intersex probe kit and gonadal dysgenesis kit.

Patients showed 46,XY karyotype, among them 2.5% were 46,inv(Y) and 5% were mosaic 46,XY/46,XYY and 46,XY/45,X. SRY gene-FISH analysis was done for selected cases (5% positive). MLPA analysis showed duplication of DAX1 in 12.5%, deletion of DMRT1 in 12.5%, duplication of DMRT1 in 5%, deletion of SRY in 5%, deletion of SOX9 in 5%, duplication of CYP17A41 in 5%, duplication of SRD5A in 2.5% and duplication of HSD17B3 in 2.5%. Our study demonstrates that introduction of MLPA in the diagnostic workup helps the diagnostic yield in 46,XY DSD cases. It will also contribute to improve patient care and will have positive outcome in treatment strategies and family counselling.

P1-16: Oculodentodigital dysplasia: a report of an Egyptian case

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Introduction: Oculodentodigital Dysplasia (ODDD) is a rare genetic disorder, characterized by facial, ocular, dental, limb and neurological abnormalities. ODDD is caused by mutations in GJA1 gene, that encodes the protein connexin-43. This condition is inherited in an autosomal dominant pattern with a high penetrance and variable expression and less commonly, it can be inherited in an autosomal recessive manner. The exact incidence of ODDD is unknown. It has been diagnosed in fewer than 1,000 people worldwide.

Case report: This report describes an Egyptian case with the characteristic features of ODDD. An informed consent was obtained, according to the ethical guidelines of the Medical Research Institute, Alexandria University. This work was compliant with the Declaration of Helsinki of the World Medical Association guiding principles for experimental procedures on human subjects. A 2-year-old male, born to non-consanguineous Egyptian parents, presented with microphthalmia, microcornea, thin nose with hypoplastic alae nasi, prominent columella, abnormal teeth, complete syndactyly of 4th and 5th fingers with camptodactyly, and partial syndactyly involving the 2nd to 4th toes.

In conclusion, the presenting case had the clinical features that were concordant with the clinical diagnosis of ODDD. ODDD is a complex disorder which needs a multidisciplinary team for management. Early accurate diagnosis allows adequate monitoring and treatment of the wide variety of clinical manifestations and complications.

P1-17: Genetic and clinical characterization of Mowat-Wilson syndrome by array CGH**

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Mowat-Wilson syndrome is a rare autosomal dominant developmental disorder with prevalence estimated to be 1 per 50,000-70,000 live births. It presents with a wide spectrum of clinically heterogeneous features including microcephaly, facial features, moderate-to-severe mental retardation, epilepsy and variable congenital malformations that may include Hirschsprung disease (HSCR), genital anomalies (particularly hypospadias in males). congenital heart disease (CHD) and agenesis of corpus callosum (ACC). Mowat-Wilson syndrome (MOWS) is mainly caused by de novo heterozygous mutation in the ZEB2 gene on chromosome 2q22.

The present study describes a case presenting with CHD, delayed milestones, microcephaly, elongated face, deep set eyes and other dysmorphic features, that matched the reported features of Mowat-Wilson syndrome. Conventional cytogenetic analysis revealed normal karyotype. Multiplex Ligation-dependent Probe Amplification (MLPA) analysis was done using commercial kits (SALSA MLPA P245 microdeletion and MLPA subtelomere kits) as a screening test for cases presenting with congenital heart disease associated with extracardiac manifestations and showed normal results. The case was further investigated using Chromosomal Micro Array analysis [Affymetrix Genome-Copy Number Variation/Wide Human SNP Array 6.0, Thermo- Fisher Scientific, UK]. The patient had an interstitial 0.6-Mb deletion at chromosome 2q22 including the entire ZEB2 gene.

In conclusion, the study highlights the significance of Chromosomal Micro Array in detection of microdeletion/microduplication syndromes and its importance as a diagnostic test in cases presenting with CHD and extracardiac manifestations.

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P1-18: Clinical, Biochemical and molecular characterization of PKU and HPA patients

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Introduction: Phenylketonuria (PKU) is one of the preventable causes of intellectual disability. It is the most prevalent disorder of amino acid metabolism in Caucasians.

Aims: 1-Assessment and correlation of clinical and biochemical progress of patients. 2- Assessment of the effect of age at diagnosis on the clinical outcome. 3-Follow-up of dietary compliance of patients. 4-PAH gene sequencing for selected cases to investigate genotype-phenotype correlation.

Materials & Methods: This study investigated 104 PKU patients including 79 early diagnosed patients, 22 late diagnosed patients and 3 untreated patients regarding clinical characteristics and phenylalanine (Phe) metabolic control. This included thorough history taking, clinical and neurological assessment, follow up of dietary compliance with monthly assessment of blood Phe levels. Four patients were selected for PAH gene sequencing as a pilot study.

Results: Regarding early-diagnosed patients, 3.8% had ADHD and 12.7% showed delayed language development and/or phonological disorder. For the late diagnosed patients, 68.2% showed abnormal behavior with an IQ range of 38–90. Hyperactivity was detected in 33.3%% of the untreated group, and the IQ ranged from 45–67. Parental consanguinity was found in 67.3% of cases. On average, 72 % of patients had well- controlled blood phenylalanine levels. The genotyped cases in this study showed positive correlation with the phenotype.

Conclusion: There is a wide range of clinical heterogeneity among PKU patients. Several factors determine the clinical outcome including age at diagnosis, blood phenylalanine levels, degree of compliance to dietary therapy, interventional therapies as well as blood- brain barrier selectivity.

P1-19: Agonadia in Male Patient with Balanced Robertsonian Translocation (13;22)

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Introduction: Robertsonian translocations have an estimated incidence of 1/1000 births, making this type of rearrangement the most common structural chromosomal abnormality seen in the general population. The t(13;22) Robertsonian translocation constitutes a rare form of rearrangement between acrocentric human chromosome. Carriers of Robertsonian translocations may have normal phenotype but can have infertility problems associated with severe oligospermia in adult males and miscarriage in adult females. However, reports on phenotype of this karyotype in children are very rare.

Case report: We report a case of agonadia in male patient with balanced Robertsonian translocation (13;22). A male patient aged 5.5 months presented with bilateral undescended testicles to our genetic clinic at Human Genetics Department, MRI, AU. An informed written consent was obtained from parents. Clinical examination revealed prominent metopic ridge , sloping narrow forehead, rounded full cheeks, small penis, hypoplastic scrotal sac, unfelt testes bilaterally and no history of inguinal hernia. No testicular tissue could be detected by ultrasonography or MRI of the abdomen and pelvis.

Karyotype analysis for the patient and his parents was done using an imaging system for GTG-banded metaphases at 400-550 band level resolution (Auto image analysis software for FISH and karyotype LIKIA). The abnormalities were designated following ISCN 2016. The proband had 45,XY,rob(13;22)(p12;p12). The father showed normal karyotype while the mother showed unexpected karyotype of mos 46,XX (98%)/46,XX,rob(13;22)(p12;p12)+13 (2%). In conclusion, Robertsonian Translocation (13;22) should be considered in the differential diagnosis of gonadal dysgenesis.

P1-20: A GALNT3 gene mutation in two sibs with CRMO**

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Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is an uncommon inflammatory disease mostly affecting the metaphyses of long bones. It can be distinguished from osteomyelitis by multifocality and recurrence. Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare genetic disorder characterized by increased re-absorption of phosphate through the renal proximal tubule leading to increased phosphate concentration and deposition of calcified deposits in cutaneous and subcutaneous tissues, as well as some visceral organs. HFTC is inherited in an autosomal recessive manner and is caused by mutations in three different genes, FGF23, GALNT3 and KLOTHO. The current study aims to report the clinical, radiological and molecular findings of two sibs with CRMO associated with HFTC. Case report: Two siblings were the product of a consanguineous marriage. There were no similarly affected family members, and they had a non-affected sibling. They presented with spontaneous bony pains not responding to NSAID and later on developed tender hard masses. Laboratory testing revealed normal results for blood cultures and sensitivities, serum calcium and 25(OH) vitamin D, renal functions, albumin, alkaline phosphatase and parathormone hormone. Both siblings had mildly elevated ESR and hyperphosphatemia. Initial x-rays revealed lytic lesions with a sclerotic margin. Follow up x-rays showed healing with sclerosis and hyperostosis. After developing the hard masses, x-rays showed calcified masses. Mutational analyses of the FGF23, GALNT3 and KLOTHO genes was carried out by Sanger sequencing of the entire coding region of each gene. A GALNT3 gene mutation was detected in the two sibs In conclusion, this is the first

Egyptian family to be clinically diagnosed with CRMO associated with HFTC and confirmed by molecular studies.

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P1-21: Increased S100A12 and resolvin D1 pro-inflammatory biomarkers in familial Mediterranean fever

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Introduction: Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease and is characterized by recurrent attacks of fever and polyserositis. The damaged molecular pattern (DAMP) of S100A12 protein has proven to be a sensitive marker for disease activity and inflammation. Resolvin switches inflammation to the resolution phase by inhibition of endothelial migration and infiltration of leukocytes. It promotes the clearance of apoptotic polymorphonuclear leukocytes.

Aim: This work aimed to study the role of S100A12 and resolvin D1 in the silent period for better estimation of the degree of inflammation and help to adjust the doses of colchicine to ameliorate the symptoms of the disease.

Material and methods: Thirty-nine FMF patients in the silent state and 30 healthy age and sex matched individuals were studied. S100A12 and Resolvin D1 were quantitatively measured using enzyme-linked immunosorbent assay. Levels of c-reactive protein, erythrocytic sedimentation rate and hemoglobin were determined.

Results: The mean levels of S100A12 and Resolvin D1 were 847.4 and 793.3, respectively which were highly significantly increased (p= 0.001) compared to the controls (324.3 and 235.1 respectively). The ROC Curve test showed that S100A12 had a sensitivity of 97.4% and specificity 80% with cut off 529.5, while Resolvin D1 showed sensitivity 100% and specificity 50% with cut off 231.2.

Conclusion: This study delineated that, S100A12 and Resolvin are good sensitive biomarkers to detect the degree of inflammation in the FMF patients and consequently adjust the colchicine dose to ameliorate the symptoms of the disease and improve the quality of life of patients.

P1-22: WNT10A gene mutational analysis in ten Egyptian ectodermal dysplasia patients**

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Introduction: Ectodermal dysplasia (ED) is a heterogeneous group of disorders characterized by a constellation of findings involving primary defect in ectodermal structures including the skin, teeth and appendageal structures such as hair, nail and exocrine and sebaceous glands. It can be inherited in X-linked, autosomal dominant (AD) or autosomal recessive (AR) modes. WNT10A gene mutations have been implicated for various manifestations ranging from isolated tooth agenesis to different forms of ED and were found to be the most frequent cause of AD and AR ED.

Aim: The aim of this study was to investigate WNT10A gene mutation among a group of Egyptian patients suffering from autosomal dominant and recessive ED.

Patients and Methods: Ten patients from nine families with oligodontia associated with other ectodermal abnormalities were included in this study. The Patients underwent thorough clinical examination and mutational analysis of WNT10A gene was done.

Results: Molecular analysis revealed no pathogenic mutations in WNT10A gene.

Conclusion: Unlike other studies, WNT10A gene mutation does not seem to be a common finding among Egyptian autosomal ED cases.

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Genetics of common complex disorders

P2-1: Combined Markers for Preclinical Identification of Alzheimer's Disease

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Alzheimer's disease (AD) is the most widely recognized type of dementia. It is associated with cell cycle abnormalities including genomic instability and increase formation of micronuclei (MNi) with subsequent chromothripsis. These changes usually evolve many years before the appearance of the clinical manifestations. Digital electroencephalogram (EEG) has a role in perceiving brain changes in dementia and in early detection of cognitive decline. This study aimed to assess the competency of using combined markers (genetic and neuroimaging markers), as a step towards early as well as preclinical diagnosis of AD. The study was conducted on 15 patients diagnosed as sporadic AD and a group of 12 age and sex matched controls. All subjects were subjected to Mini-Mental State Examination (MMSE), conventional EEG, digital EEG and Cytokinesis-block micronucleus assay (CBMN) in peripheral blood lymphocytes.

Conventional EEG showed a normal background activity in both the controls' and the patients' groups and there were no detected abnormal epileptogenic discharges. Digital EEG showed high statistically significant reduction of the absolute power of alpha waves for AD patients as compared to the control group. Score of MNi showed significant statistical difference between the two groups. Combination of both genetic and neuroimaging markers can be expressive for early detection of cognitive decline and may lead to preclinical identification of individuals at increased risk for AD, where at this stage treatment could be constructive.

P2-2: Effect of nanoparticles/laser on the treatment of atherosclerotic rat model

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Cardiovascular diseases are the leading cause of death worldwide. Atherosclerosis (AS) is a complex disease caused by lipid build up and inflammation in the arteries, so hyperlipidemia is the major reason for AS. Nanoparticles offer a variety of modalities for biomedical application. The use of gold nanoparticles (GNPs) in cardiology is promising to develop fundamentally new methods of diagnosis and treatment due to their unique biological properties. The present study evaluates the effect of intraperitoneal administration of GNPs and laser on the treatment of atherosclerosis, the histological alterations of the heart and aortic tissues and DNA damage in rats.

A total of 80 male albino rats weighing 180-220 gm were divided into eight groups (10 rats for each group) as control (Group1), laser (650nm) (Group2), GNPs (20 nm spheres) (Group3), laser + GNPs (20 nm spheres) (Group4), high fat diet (HFD) (Group5), HFD+ laser (Group6), HFD+GNPs (20 nm spheres) (Group7) and HFD+ laser+ GNPs (20 nm spheres)(Group8).

Data showed a significant increase in levels of total cholesterol, triglycerides and LDL cholesterol in Group5 compared to Group1, while there was a significant increase in DNA damage in groups 2-7 when compared to Group1. The current study elucidated the role of GNPs or/and laser in the treatment of atherosclerosis and showed that GNPs potentiates oxidative stress, thus providing further proof of their oxidant effect.

P2-3: CNVs profiling for non-syndromic short stature Egyptian children using MLPA

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Short Stature is defined as a body height below the third percentile for chronological age or -2 SD. Deficiencies of several genes have been associated with the etiology of short stature. SHOX gene is one of the important candidate genes, as its haploinsufficiency underlies syndromic and non-syndromic short stature. Furthermore, partial and complete SHOX duplications had been reported in patients with short stature. Growth Hormone (GH) and insulin-like growth factor 1 (IGF-1) have been recognized as the main regulators of longitudinal growth. Defects in GH1 gene, deletions or point mutations, were recognized as a cause of isolated GH deficiency (IGHD). IGF1R haploinsufficiency is associated with impaired growth. Moreover, IGF1R copy number variants can cause pre- and postnatal growth restriction or overgrowth. Proper genetic diagnosis of these children leads to an appropriate therapeutic approach. GH treatment may induce a considerable height improvement in IGHD and IGF1R or SHOX haploinsufficient subjects. Since results of large genome-wide association studies have emphasized copy number variation (CNVs) as a possible mechanism to explain interhuman variability and pathogenic disease, MLPA technique should be used as an initial screening technique.

The aim of our study was to carry out CNVs profiling for Egyptian children with non-syndromic short stature using MLPA technique. Fifty cases were studied using different MLPA probemixes such as P018-G1 SHOX probemix and P217-B2 IGF1R probemix. Different CNVs were detected. This is one of the first studies on Egyptian children with short stature in whom CNVs in different stature related regions were investigated.

P2-4: MicroRNA as a potential diagnostic marker and promising therapeutic target in T2DM

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MicroRNAs (miRs) are short, noncoding RNA molecules, which regulate mRNA stability and translation by binding to their target mRNAs. miR-146a- is a nuclear factor-kappa B (NF-kB) responsive miRNA and acts as an inhibitor of NF-kB-activated inflammation. NF-KB, a nuclear transcription factor, regulates multiple gene pathways involved in inflammation and apoptosis, and has been implicated in the development of type 2 diabetes mellitus (T2DM) and its complications.

This study aimed to investigate whether the single nucleotide polymorphism (SNP) of miR 146 rs2910164 G/C is associated with T2DM and to correlate the genotype results with serum levels of miR-146 and NFKB.

The study was conducted on ninety patients having T2DM and sixty matched healthy individuals. The amplification-refractory mutation system-PCR was performed to detect single nucleotide polymorphism of miR 146 rs2910164 G/C gene.

Serum miRNA 146 was down regulated in T2DM group compared to control group while serum NF-kB level was significantly elevated in diabetic patients compared to controls. The rs2910164 G/C polymorphism in the miR 146 gene showed significant higher frequencies of the GC/CC genotype and C allele in the diabetic group compared to those in the control group. The miR 146 rs2910164 G/C polymorphism was associated with susceptibility of T2DM accompanied with reduced mi-RNA146 and elevated serum NF-kB levels. This suggested that this polymorphism may decrease the miR-146 expression, upregulate NF-kB expression and have functional consequences in T2DM.

In conclusion, miR146 and its signaling pathway may be considered novel potential biomarkers for T2DM and its modulation provides a promising new approach for management of T2DM.

P2-5: Association of mir-34 with markers of dyslipidemia in T1DM

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Introduction: The prevalence of dyslipidemia in children with type 1 diabetes mellitus (T1DM) varies between 29% and 66% in studies from different countries. Dyslipidemia is considered a preventable risk factor for CVD. Dyslipidemia is a multifactorial disease, which can be influenced by both genetic and environmental factors. Limited data is available on the factors affecting the presence of dyslipidemia in children and adolescents with T1DM.

Aim: We aimed at assessing the influences of exosomal miR-34a on lipid profiles and the prevalence of dyslipidemia in children and adolescents with T1DM.

Subjects and Methods: The study included 100 T1DM patients and 100 healthy controls. Assessment of exosomal miR-34a expression was done using quantitative reverse transcriptase PCR.

Results: The relative expression of exosomal miR-34a showed a significant increase in patients compared to controls (p=0.001). Serum levels of total cholesterol, triglycerides, LDL and oxidized LDL were significantly elevated in T1DM compared to controls. Inverse moderate correlation was detected between exosomal miR-34a and total cholesterol and LDL. Conclusions: Our findings demonstrate for the first time that exosomal miR-34a is associated with T1DM and increased expression of miR-34a may play a role in the pathogenesis of T1DM and associated dyslipidemia in children and adolescent patients. This may open a new window for understanding the pathogenesis of T1DM and associated dyslipidemia and finding a new plan for therapies. Further studies performed on larger sample sizes and another independent Egyptian sample, are recommended to validate and confirm our findings.

P2-6: Language and speech disorders in a cohort of Egyptian children with cerebellar malformations

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The cerebellum was thought to be exclusively involved in motor skills, visual-motor coordination and balance. Recently, evidence of a linguistic role of the cerebellum have been emerged.

In the present study, the language and IQ of 15 patients (8 males and 7 females) between 3-10 years with different cerebellar malformations were assessed using the Modified Preschool Language Scale (PLS-4)-Arabic edition and the Stanford Binet Intelligence Scale “5th Arabic version” respectively, in order to investigate the impact of cerebellar malformations on the proper development of the language skills. The speech was also assessed using specially designed analysis sheet and the severity of cerebellar dysarthria was evaluated using Modified Scale for the Assessment and Rating of Ataxia. According to their brain MRI, the patients were divided into three groups:

group 1 with cerebellovermis hypoplasia (4 patients), group 2 with cerebellar hypoplasia affecting vermis mainly (7 patients) and group 3 with pontocerebellar hypoplasia (4 patients). All patients included in this study showed linguistic deficit, regardless to their cognitive development.

Patients in group 3 showed the worst score in cognitive and language development followed by group 1 then group 2, except for expressive language that showed equal delay in group 1 and 2. Syntax was much more affected than semantics in all patients in both language domains. Cerebellar dysarthria was a feature in all children included in this study and was most severe in group 1, followed by group 2 then group 3.

Our results highlight the importance of both cerebellar hemispheres and the vermis for normal cognitive and language development as well as for normal speech.

P2-7: Transcriptome unraveling and molecular profiling underlying adipogenesis

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For years, adipose tissue (AT) has long been characterized as a lipid storage depository as well as hormone secreting organ with relevant biological significance. However, when in a dysfunctional state, AT contributes to the development of various chronic diseases (i.e. diabetes, cardiovascular diseases, arthritis). This is mainly due to irregularities towards cell morphology that contribute to hyperplasia (increase in cell number) and hypertrophy (increase in cell size). These changes in cell structure can prompt alternative gene programming mechanisms. Due to this, throughout the years, efforts have been implemented in understanding the molecular and cellular signatures of adipocyte differentiation focusing mainly on mature preadipocyte cellular models (i.e. 3T3-L1, mouse embryonic fibroblasts) to adipocyte transformation. However, little is known about the molecular events (i.e. key transcriptional and epigenomic regulators) at earlier phases of preadipocyte and its lineage commitment. As such, we implement the use of various embryonic models in addressing several topics using molecular and cell biology tools as well as next generation sequencing methodologies to unravel adipogenesis and in vitro adipocyte differentiation.

P2-8: Comparison between Intensive and Conventional Phototherapy Effect on Oxidative Stress

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Introduction: Jaundice is a common condition that occurs in more than 60 % of all neonates. Phototherapy has been used since 1958 for the treatment of neonatal hyperbilirubinemia. However, it might have a negative impact on the oxidant/antioxidant defense system.

Aim: The study aim was to compare intensive and conventional phototherapy effects on oxidant/antioxidant status.

Patients and Methods: In this randomized controlled non-blinded clinical trial, 80 neonates ≥35weeks gestational age with unconjugated hyperbilirubinemia reaching phototherapy level were enrolled. This study was approved by the ethical committee of Ain Shams University. Informed consents were obtained from the parents of each participant before enrollment. Neonates were assigned to two groups; 40 neonates received conventional phototherapy and 40 received intensive phototherapy. Complete blood count (CBC), total serum bilirubin (TSB), total antioxidant capacity (TAC), malondialdehyde (MDA), nitric oxide (NO), copper (Cu), zinc (Zn), and iron (Fe) levels were measured before and 24 hours after phototherapy.

Results: TSB and TAC decreased post-phototherapy in both groups ($P<0.05$ for both). MDA, NO, Fe, Zn and Cu increased post-phototherapy ($p<0.05$ for both), with significant increase in intensive phototherapy group in comparison to conventional phototherapy group ($P<0.05$). Positive correlation was found between post-phototherapy TSB with TAC, Zn and Cu ($P<0.05$) and negative correlations with MDA, NO and Fe ($P<0.05$).

Conclusion: Both phototherapy devices are effective in decreasing TSB. Both types have an impact on oxidant/antioxidant status and cause significant increase in oxidative stress markers. However, intensive phototherapy devices have higher effect on oxidative stress as manifested by significant increase in MDA and NO.

Fetal medicine

P3-1: Oxidative stress, neutrophil elastase and vascular endothelial growth factor levels in obese pregnant women with pre-eclampsia

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Introduction: Oxidative stress, inflammation, vascular endothelial proliferation and obesity are risk factors associated with pre-eclampsia (PE).

Aim: The present study aims to investigate the levels of malondialdehyde (MDA) as a putative circulatory marker of oxidative stress, of neutrophil elastase (NE) as an inflammatory marker and of vascular endothelial growth factor (VEGF) as a marker for vascular permeability in obese women with pre-eclampsia (PE) and to compare the results to those of normotensive non pre-eclamptic pregnant women with average normal body mass index (BMI).

Subjects and Methods: The study was carried out on 50 pregnant obese women with PE and 50 normal pregnant women. The pre-eclampsia women showed characteristics of high blood pressure (160/110 mmHg) and proteinuria. The gestational age ranged from ≥ 32 weeks to < 37 weeks. Pre pregnancy weight was recorded. Body mass index (BMI) was calculated at delivery. Serum MDA, NE and VEGF were estimated by ELISA.

Results: Significantly higher levels of serum MAD, NE and VEGF were observed in obese PE patients.

P3-2: Importance of genetic counselling in recurrent hydatidiform mole: case presentation

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Introduction: accurate diagnosis is an essential part of genetic counselling. Recurrent hydatidiform mole (RHM), which refers to at least two molar pregnancies in the same patient, is a very rare condition, with sequalae of malignancy and high risk of maternal morbidity and mortality. Molecular testing for cases of RHM is highly recommended as NLPR7 mutations are found with high rate in patients with RHM and KHDC3L as the second responsible gene. Affected women are predisposed to molar pregnancies of diploid, biparental origin rather than androgenetic origin. Proper counselling in such cases depends on clinical history, previous investigations performed, as well as documentation of pedigree and family information.

Aim: the study aimed to highlight the importance of molecular testing and genetic counseling in patients with familial RHM.

Patients and methods: Two sisters presented with RHM in previous pregnancies. The elder has a history of three consecutive molar pregnancies while the younger sister has a history of two. Whole exome sequencing was performed for both patients at Centogene labs.

Results: A homozygous likely pathogenic variant was identified in the NLRP7 gene in both sisters. This result is consistent with a genetic diagnosis of autosomal recessive recurrent hydatidiform mole type 1. Recurrence risk for RHM is high, and this was communicated to the sisters and their physicians. Genetic counseling was given to each of the two sisters concerning their future reproduction.

Conclusion: Physicians should be aware of the genetic molecular testing and counselling in pregnancy-induced complications, for better counselling regarding the prognosis of future pregnancies.

P3-3: Biomarkers of vitamin B12 status and the risk of NTDs**

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The aim of this study was to evaluate the association between vitamin B12 and its biomarkers and the risk of neural tube defects. Methods: A total of 120 pregnant Egyptian women were included in the study. They were classified into two groups. Group A consisted of 50 women with neural tube defects in current pregnancy or with a history in previous pregnancies, and Group B consisted of 70 women with no history of neural tube defects in previous or current pregnancies. All women were subjected to ultrasound anomaly scan and serum analysis of vitamin B12, homocysteine (Hcy), methyl malonic acid (MMA) and active vitamin B12 concentrations. Receiver operating characteristic curve analysis was used to determine the best cut-off values of vitamin B12.

Serum levels of vitamin B12 were decreased in Neural tube defects (NTDs) cases compared to controls (2.736 vs 3.091 ng/mL; P = 0.0015), while Hcy and MMA concentrations were elevated (18.39 vs 13.95 µmol/L; P = 0.0008 and 263 vs 229.7 µmol/L; P = 0.003, respectively). Active vitamin B12 reduction was not statistically significant (96.8 vs 99.36 pmol/L; P = 0.8013). The optimal cut-off value of vitamin B12, 2.9 ng/mL, is the best threshold to expect neural tube defects, with a sensitivity of 60% and specificity of 74.29%.

In conclusion, low vitamin B12 is a risk factor for having a fetus with neural tube defects. The monitoring of MMA and Hcy levels might be important in understanding and following cases with neural tube defects.

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Dental genetics

P4-1: KBG syndrome: Radiological, dental and craniofacial observations

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Introduction: KBG syndrome (KGBS) is characterized by macrodontia of the upper central incisors, distinctive craniofacial findings, short stature, skeletal anomalies, and neurologic involvement that includes global developmental delay, seizures and intellectual disability KBGS is caused by a heterozygous mutation in the ANKRD11 gene on chromosome 16q24. Case Report: A 15-year-old female patient of mixed ancestry heritage, with a confirmed diagnosis of KBG Syndrome was referred to the Faculty of Dentistry for clinical management. A CBCT was performed in order to develop a comprehensive treatment plan. Radiological Observations, that were previously reported, included macrodontia of the upper and lower incisors with a mild depression of the supraorbital ridge and an increased height distance to the inferior orbital rim, in addition to bilateral aplasia of the frontal sinuses. Moreover, the patient had other radiological findings that were, to the best of our knowledge, not previously reported. These included osteopenia of the middle and posterior segments of the maxilla and mandible, platybasia of the base of skull, macrodontia of the upper lateral and lower incisors and delayed root closure of the lower premolar. A triangular face was not observed in this patient. Conclusion: The dental practitioner, probably the first to diagnose hereditary dental anomalies, will remain responsible for the detection of any additional defects in order to provide the best treatment and should always keep in mind that some of those dental anomalies can coexist with certain syndromes.

P4-2: Genetics in the oral health curriculum

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Genetic and genomic research has improved the understanding of the origins of growth, development and disease. Dentists may encounter genetic disorders or oral manifestations of a genetic-based systemic disease and need to have a sound understanding of genetics if accurate information is to be given to patients. This study evaluated the attitudes, perceptions and knowledge of undergraduate and postgraduate dental students towards genetics in the curriculum at a tertiary oral health facility in Cape Town, South Africa.

P4-3: Inflammatory Mediators Associated with Periodontitis in Pre-eclampsia

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Periodontitis is reported to be associated with preterm low birth weight and preeclampsia in developing countries such as India, Brazil, India and South America. Contradictory to reports from developing countries, periodontitis was not associated with preeclampsia in Canadian pregnant women. To the best of our knowledge, there are no published reports documenting the association between periodontitis and pre-eclampsia (PE) in South Africa.

Our role as dental personnel is to increase the awareness of the possible association between periodontitis and PE among pregnant women. A case- control study was initiated to determine whether there is a significant association between periodontitis and the associated release of pro-inflammatory cytokines and pre-eclampsia in the Western Cape, South Africa. The study included 200 pregnant women who were periodontally assessed and had their blood sampled; 100 with a confirmed diagnosis of pre-eclampsia and 100 normotensive pregnant women. This project is currently in the data analysis stage and we envisage that the outcome of this study will highlight the importance of dental referrals of women during the pregnancy& improving the dental management.

Bioinformatics:

P5-1: SNPs of c-MYC gene in Burkitt's lymphoma

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Introduction: Burkitt's lymphoma (BL) is an aggressive form of non-Hodgkin lymphoma and originates from germinal center B cells. The MYC gene (MIM ID 190080) is an important proto-oncogene transcriptional factor encoding a nuclear phosphoprotein for central cellular processes. Dysregulated expression or function of c-MYC is one of the most common abnormalities in BL.

Aim: This study focused on the investigation of the single nucleotide polymorphisms (SNPs) in MYC gene in association with BL.

Materials and methods: MYC SNPs were obtained from NCBI database. SNPs in the coding region that are nonsynonymous (nsSNPs) were analyzed by multiple programs such as SIFT, Polyphen2, SNPs&GO, PHD-SNP and I-mutant.

Results: A total of 286 Homo sapiens SNPs were found. Roughly, forty-eight of them were deleterious and were furtherly investigated. According to the used programs, 8 SNPs were considered disease causing [rs4645959 (N26S), rs4645959 (N25S), rs141095253 (P396L), rs141095253 (P397L), rs150308400 (C233Y), rs150308400 (C147Y), rs150308400 (C147Y), rs150308400 (C148Y)]. Two of which have not been reported previously [rs4645959 (N25S), rs141095253 (P396L)].

Conclusion: SNPs analysis may be of help as a disease marker and of significance in the management plans. Bioinformatic analysis is a useful step that may guide further experimental validation of the results.

P5-2: Gene synthesis and molecular cloning of chromogranin-A N-46 anticancer peptide

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Introduction: The percentage of people suffering from cancer and multi resistant infections has increased worldwide. Lately, a novel class of peptides turned out to be promising to combat these major health problems. Anticancer peptides (ACPs) are endogenously created polypeptides by multicellular organisms to protect the host from pathogenic microbes. ACPs can be obtained either by isolation from diverse biological sources or by chemical synthesis. Gene cloning and expression might be an efficient way for producing ACPs. Chromogranin A N-46 (CGA-N46) is an ACP consisting of partial N terminus of human chromogranin A. Recently, free online bioinformatics tools are used for designing of oligonucleotides for in vitro gene synthesis.

Aim To use Gene2Oligo software to create synthetic DNA of CGA-N46 gene by PCR assembly of a set of short oligonucleotides.

Materials & Methods The coding sequence of CGA-N46 gene was obtained by three steps: 1st PCR to generate short DNA fragments using specific oligonucleotides, 2nd step was overlap extension PCR (OE-PCR) to overlap the short DNA fragments and the final PCR was the assembly of the whole gene. The obtained CGA-N46 gene was cloned into pCR II TOPO TA cloning vector to create a DNA library. Transformation of recombinant vector into chemically competent E. coli TOP10 bacteria was performed. Results PCR results revealed that the CGA-N46 gene was successfully synthesized and cloned into TOPO TA cloning vector. Conclusion In this study, an improved method for a simple low-cost error free gene synthesis that uses overlap extension PCR was presented.

P5-3: SMN1-RBFOX2 interaction model; A new interpretation to SMN-dependent SMA sensitivity

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Introduction: The survival motor neuron (SMN) protein is a phylogenetically conserved molecular chaperone for RNA biogenesis. Reduction of SMN level causes selective deleterious effects to motor neurons resulting in the neurodegenerative disease spinal muscular atrophy (SMA). Therefore, a fundamental question is how reduced levels of the ubiquitously expressed SMN protein selectively target motor neuron dysfunction.

Aim: The current study aimed to postulate actionable hypothesis to the aforementioned fundamental question through the characterization of the structural stoichiometry determinants of SMN binding proteins.

Methods: The current structural stoichiometry study approach entailed (i) use of protein-protein interaction prediction tools and databases, (ii) building dataset of motor neuron-enriched alternatively spliced exons, (iii) motif analysis and methylation prediction tool, (vi) defining the RGG/RG Motifs in RBFOX2 splicing factor, and (iv) protein modeling (SWISS-MODEL).

Results: Computational analysis found that (1) both the Tudor domain of smn1 and RBFOX2 exhibit common hydrophobic patch of the aromatic residues, and different conserved overall charge surface, (2) there was significant affinity interaction model between RBFOX2 and Tudor domain of SMN1 protein supported by three strong hydrogen bonds (3) there was spatial coexistence of RNA binding motifs for RBFOX2 and SMN1, respectively on most of motor neuron pre mRNA.

Conclusion: Selective deleterious effect of reduced SMA levels on motor neuron cells may be due to the putatively intrinsic binding of RBFOX2 and SMN1. So, it is envisaged that spatial coexistence of binding motifs of RBFOX2 and SMN1 increases specificity and regulation of neuronal RBFOX2 RNA-binding protein. Although the current study gives a putative mechanism for SMA pathogenesis, further experimental studies are needed for confirmation of this hypothesis.

Genetic testing

P6-1: Methylation PCR diagnosis of Fragile X syndrome in Egyptian patients

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Introduction: Fragile X syndrome (FXS) is the most common form of inherited intellectual disability especially in males, affecting 1:5000–7000 men and 1:4000–8000 women. It is caused by an alteration in FMR1 gene. More than 99% of FXS patients have a CGG expansion (>200 triplets) in the 5 UTR of the gene that leads to hypermethylation and inactive transcription of the gene, and <1% of them have point mutations and duplication/deletion. FXS patients suffer complex mixture of physical, cognitive and behavioral features. Childhood Autism Rating scale (CARS) was done to all patients to assess the degree of severity of autistic features. Early molecular diagnosis would make prenatal diagnosis available for future pregnancies in these families and improve quality of treatment.

Aim: The aim of this study was to detect expected FMR1 gene alleles using DNA-PCR followed by methylation-sensitive PCR among male Egyptian cases.

Subjects and Methods: This study included 50 Egyptian males (group 1) with provisional diagnosis of fragile X syndrome and 50 healthy age matched volunteers (group 2). A written informed consent was obtained for each studied subject. All suspected fragile X males were subjected to full history taking, clinical and neurological examination. Molecular analysis included DNA-PCR and Methylation sensitive PCR techniques of the FMR1 gene.

Results: Normal FMR1 gene alleles were detected in the whole control group (group 2) with (100%) and in 36 males of group1 (72%). Affected alleles were detected in 14 patients (28%) of group 1; 12 patients with full mutation and two patients were permutation carrier.

P6-2: Design and production of FISH probes to detect chromosomal abnormalities**

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Fluorescence in situ hybridization (FISH) is a technique used to detect and confirm chromosomal abnormalities using fluorescently labeled probe.

Aim: This study focused on the design and production of FISH probes to covers our research requirements, mapping the breakpoints of the chromosome rearrangements and confirming the results of other techniques.

Material and methods: The probes were produced through the determination of the targeted sequence then the selection of the DNA source either genomic DNA or BAC clones. This was followed by amplification and direct labeling of the selected DNA by Nick translation, PCR or DOP-PCR. The produced PCR product was precipitated and dissolved to produce the probe. Then, the quality of the probe was tested by applying the FISH technique on normal slides. Finally, the produced probe for FISH technique was applied for mapping the break points of chromosomal rearrangements on patients who had chromosomal abnormalities.

Results and conclusion: FISH probes for centromere X and Xp21 were generated and we could localize the break point in a patient with X chromosome rearrangement. Also, BAC clones for five different regions on chromosome 9p and one on 9q were used to diagnose the break points in a patient with 9p deletion. Moreover, probes for centromere 1, 7, 17 and 18 were produced. Currently, we are working to produce FISH for subtelomeres, 1p36 and 16p13.3 loci. In conclusion, FISH technique is an important tool in the confirmation of the exact break points and other cytogenomic results.

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P6-3: Molecular Cytogenetics Description of a Female Patient With add 18q**

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Introduction: Genetic causes of global developmental delay (GDD)/ intellectual disability (ID) are heterogeneous. The recorded rate of ID/ GDD prevalence is 1-3% depending on the population, criteria and methods applied. Chromosomal imbalance has been recognized as the most frequent cause of intellectual disability for 50 years.

Case report: The presented case was a female patient with history of failure to thrive, global developmental delay and dysmorphic features. The underlying cytogenetic cause of intellectual disability was assessed using various molecular cytogenetics techniques: 1-conventional cytogenetics analysis on peripheral blood lymphocytes using GTG banding technique for the patient and her parents; 2-MLPA analysis using the MLPA® probe mix P070 for subtelomeric screening; and 3-Array comparative genomic hybridization (aCGH) to confirm the breakpoints.

Conventional karyotype revealed that the patient had 46,XX,add(18)(q). Parental karyotypes were normal indicating a de-novo chromosomal aberration in their offspring. Subtelomeric screening by MLPA revealed subtelomeric deletion of q arm of chromosome 18 but didn't reveal the added material origin denoting it was interstitial. Array CGH was done and the origin of the added material and the breakpoints was confirmed.

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P6-4: Clinical And genetic analysis of 46,X,add(X)(p22.3) infertile male

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Introduction: XX male syndrome is part of the disorders of sex development (DSD). The patients generally have normal external genitalia and discover their pathology in adulthood because of infertility.

Case report: The study adhered to the tenets of the Declaration of Helsinki and the regulations of the ethical committee of the Medical Research Institute, Alexandria University. An informed consent was obtained from the patient.

The reported patient had a normal body height. Hair distribution including pubic hair was normal, and there was no gynecomastia. Genital examination revealed that the testes were small in volume, soft in texture but with normal penis. Erectile dysfunction was reported. Semen analyses showed azoospermia. The patient was diagnosed to have hypergonadotropic hypogonadism. Karyotype analysis showed additive material on the short arm of X chromosome: 46,X,add(X)(p22.3), and FISH analysis showed that SRY gene were positive and translocated to Xp. Molecular analysis revealed that the SRY gene were present, with deletion of one of AZF regions.

P6-5: Presence of oncogenic viruses: Clinical relevance among breast cancer women

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Introduction: Onocogenic viruses including Mouse Mammary Tumor Virus (MMTV), Adenovirus (ADV), Polyomavirus (PoV), Human-Papillomavirus (HPV), and Epstein–Barr virus (EBV) are one of main causes of breast cancer (BC) worldwide. In Egypt, BC is accounting for 32% of all female cancers. The study aimed to evaluate the presence of these viruses among Egyptian familial and non-familial BC patients and their impact on the clinical course of the disease.

Patients & Methods: This study was conducted at NCI on 20 cases of BC patients (Fresh frozen tissue and blood) and 10 apparently healthy women (blood) as a control. All samples were subjected to qualitative and quantitative PCR assays to detect viral DNA and load for all tested viruses. The results were correlated with the clinicopathological parameters. Informed written consent was obtained from all individuals.

Results: MMTV, ADV, PoV, HPV and EBV DNAs were detected in 11 (55%), 13 (65%), 8 (40%), 0 (0%) and 0 (0%), respectively of 20 blood BC patients using qualitative PCR. Screening of 13 fresh frozen tissues, MMTV, ADV, PoV, HPV and EBV DNAs were present in 12 (92%), 12 (92%), 2 (15.3%), 11 (84.6%), and 11 (84.6%), respectively of the BC patients using quantitative PCR. ADV and HPV DNAs were the most replicative viruses. None was detected in controls. Presence of viral DNAs were not associated with any clinicopathological parameters except for the larger tumor size in patients with positive MMTV results. Conclusion: MMTV and ADVDNAs were the most common viruses present in both blood and tissues of BC patients but their impact on the clinical course and outcome of the disease will be evaluated on a larger sample size.

Regenerative medicine

P7-1: Differentiation of adipose tissue stem cells into insulin-producing cells

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Diabetes mellitus is a chronic metabolic disorder affecting nearly 350 million people worldwide. Mesenchymal stem cells (MSCs) are adult

stem cells known for their ability to differentiate into mesodermal lineages such as adipocytes and osteocytes, etc. MSCs would be an interesting cell-based therapy for diabetes.

In this study, MSCs were isolated from human adipose tissue and propagated for three passages. The expressions of cell surface antigens were detected morphologically and by flow cytometry. Adipose tissue derived mesenchymal stem cells (ADSCs) were induced to differentiate into osteocytes and adipocytes, and after induction in an adipogenic medium or an osteogenic medium, the cells were observed by Oil Red O staining and alkaline phosphatase staining. ADSCs were differentiated into functional insulin-producing cells in vitro by chemical induction using several inducing factors for differentiation into islet β-like cells. The expression of the genes related to islet β-cells was detected by RT-PCR analysis. Insulin secretion were assayed by ELISA.

Cancer genetics

P8-1: Gene Expression Profiles of Hodgkin and Anaplastic Large Cell Lymphomas

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Introduction: Hodgkin's lymphoma (HL) and Anaplastic large cell lymphoma (ALCL) are subtypes of human malignant lymphomas. The borderline is not well characterized in the context of morphologic, immunophenotypic, and clinical characteristics between the two diseases, as well as they both express CD30. The use of gene expression microarray in diseases is a genomic technology that improves and provides more accurate diagnosis.

Aims and Methods: Here TM4 suits software was used to analyze gene expression microarray data for four hematopoietic cell lines, namely KMH2 and L428 of human HL-derived cell lines and DEL and SR786 of ALCL-derived ones.

Results: An overall of hundred and twenty-one genes were showed to have significant differential expression patterns in all cell lines, among which five of them were considered to be a diagnostic biomarker candidate. Furthermore, the candidate differentially expressed genes were subjected to pathway and protein-protein interactions analysis. The study showed that three of them were found to be involved in different 83 pathways and the majority were shown to have interactions with many other proteins.

Conclusion: Significant findings have showed a resemblance to other analogous studies in the literature. In contrast, some genes have exhibited different levels of expression from those in previous reports. On the other hand, part of the findings has not been previously reported in lymphoma literature, but it has been involved in other types of cancer. Further downstream analysis with tissue microarray and protein array is needed for the validation and confirmation of these results.

P8-2: The Effect of Some Herbal Extracts on Liver Cell Line

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Usnic acid (UA), a natural botanical product, is a constituent of some dietary supplements used for weight loss. It has been associated with clinical hepatotoxicity leading to liver failure in humans. The present study was undertaken to evaluate metabolism and toxicity of (+)-UA enantiomer on cultured HepG2 cell line.

The cells were treated with a vehicle control and (+)-UA at concentrations of 0–100 μM for 24 h at 37°C in 5% CO_2 incubator. Following the treatment period, the cells were evaluated by biochemical and toxicogenomic endpoints of toxicity that included MTT activity and LDH release. Exposure to (+)-UA resulted in increased cytotoxicity and mitochondrial dysfunction in HepG2 cells. Compared to controls, low non-toxic concentrations of UA separately showed no effect on the cells as determined by the biochemical endpoints, contrary to higher concentrations ($P<0.001$). In conclusion, the study findings demonstrated the toxicity of the (+) (UA) to human hepatoblastoma HepG2 cells, suggesting an oxidative mechanism of action.

Pharmacogenomics

P9-1: Pharmacogenetic Variations and voriconazole levels in pediatric cancer patients

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Introduction: Voriconazole is a second-generation triazole antifungal with broad-spectrum activity against Aspergillosis and is metabolized mainly by CYP2C19 in the liver. Despite the use of weight-based dosing, plasma voriconazole blood levels show inter-individual variability, which is attributed to many factors such as weight, age, food, drug interactions, and CYP2C19 polymorphism. Voriconazole metabolism in pediatrics has been reported to be profoundly impacted by CYP2C19 genotypes.

Aim: To evaluate the frequencies of CYP2C19 variant alleles (*2, *3, and *17), genotypes, and phenotypes in Egyptian pediatric cancer patients and to investigate the correlation between CYP2C19 genetic variability and other factors with voriconazole plasma levels.

Methods: This study was conducted on 100 pediatric cancer patients with probable fungal infection treated with voriconazole. DNA was extracted from blood samples and analyzed by the TaqMan SNP genotyping assay. Identified genotypes were classified accordingly into various predicted phenotypes.

Results: Voriconazole plasma levels widely varied, with only 49.5% reaching therapeutic levels. Frequencies of CYP2C19*2 and *17 allelic variants were 10.6 and 18.3%, respectively, while allele *3 was not detected in the study population. A significant correlation was found between plasma levels and CYP2C19 phenotypes: ultra-rapid metabolizers had statistically significantly lower plasma levels ($P=0.003$) relative to the extensive metabolizer genotype. Conclusion: Determination of the CYP2C19 genotype at the initiation of therapy, followed by drug monitoring, would serve as a valuable tool for the optimization of voriconazole therapy for pediatric cancer patients. It would also be an essential step in the advancement of precision medicine to optimize therapeutic efficacy and minimize toxicity.

Ethical aspects of genetics

P10-1: Ethical and political dimensions: Biobanks and Genomic sovereignty

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Scientific biobanks with human biological samples store the biological capital of the population and have the status of national biodiversity resources. They constitute an essential part of the infrastructure of global bio-techno-science where the territorial boundaries of the states are diluted. The concept of genomic sovereignty presents controversies for its use in research. The evolution of the term from biopolitics includes the biological sample as a natural resource that is redefined and controlled from a

molecular laboratory, where it is identified, isolated, mobilized and recombined through intervention practices that build their own rules. Their new meaning rethinks governance on access, control, results and benefits of studies in the context of a globalized world where its same logic crosses all scenarios. The research with human biological samples requires the informed consent to protect each person and is fundamental for the science. From the principle of respect to autonomy, the individual rights are protected in the industrialized countries, but are not protected by collective rights of the population including future generations. The Biobanks as national resources require mechanisms that respect the genomic sovereignty in each population.

The current work aims to analyze and reflect on the concept of genomic sovereignty using qualitative research of exploratory character as well as qualitative techniques [participant observation and study of cases]. In conclusion, consideration should be given to think about the genomic resources where sovereignty of people requires thinking from ethical and political perspectives to protect the collective rights and respect the interests and cultures of current and future populations.