هفتمین سمینار ملی و اولین سمینار/وبینار بین المللی ژنتیک پزشکی (تشخیصی–تحقیقی)

ایران- سنندج- ۱۹ الی ۲۰ فروردین ماه ۱۴۰۰

7th National & 1st International Seminar/Webinar in Medical Genetics: Diagnostics & Research

Iran/ Sanandaj/ 8-9 April 2021

دانشکده پزشکی

دانشگاه علوم پزشکی و خدمات بهداشتی درمانی کردستان

Kurdistan University of Medical Sciences

نشانی : سنندج، خ پاسداران، دانشگاه علوم پزشکی کردستان
www.muk.ac.ir

وبینار سراسری / بین المللی

۷مین سمینار

ژنتیک پزشکی

تشخیصی - تحقیقی

Medical Genetics

زمان برگزاری

۱۹ و ۲۰ فروردین ماه ۱۴۰۰

پنجشنبه ۱۹ فروردین ماه از ساعت ۱۳ الی ۱۷

جمعه ۲۰ فروردین ماه از ساعت ۱۰ الی ۱۴

برگزار کننده دانشگاه علوم پزشکی کردستان

برگزاری از طریق نرم افزار Adobe Connect

vc3.muk.ac.ir/genetics

سایت سمینار: www.medical-genetics-seminar.ir

پخش زنده @maadgenetic

اهداف سمینار:

تبادل علمی و انتقال تجربیات علمی و کاربردی در حوزه تشخیصی ژنتیک پزشکی در ۴ حیطه:

۱- سیتوژنومیک

۲- ژنتیک مولکولی (کلاسیک و NGS)

۳- ژنتیک بالینی

۴- ویرایش ژنی و مداخلات ژنتیکی (CRISPR) در قالب معرفی موردی و مطالعات و تجربیات گسترده تر

گروه های هدف:

۱- مسئولین فنی آزمایشگاه های تشخیصی ژنتیک پزشکی

۲- اعضای هیئت علمی و دانشجویان ژنتیک پزشکی

۳- پزشکان متخصص ژنتیک، کودکان، نورولوژی، زنان و زایمان، پریناتولوژی، داخلی و غیره.

۴- دانشجویان/فارغ التحصیلان کارشناسی ارشد ژنتیک انسانی

۵- دانشجویان / فارغ التحصیلان و اعضای هیئت علمی دکتری ژنتیک مولکولی وزات علوم

دارای امتیاز باز آموزی

برای ثبت نام و ارسال خلاصه مقالات به ایمیل زیر مشخصات خود را ارسال فرمایید

7th.medicalgenetics.seminar@gmail.com

آخرین مهلت ارسال خلاصه مقالات

۳۰ اسفند ۱۳۹۹

ثبت نام و شرکت در سمینار رایگان می باشد

برگزار کننده:

دانشکده پزشکی

دانشگاه علوم پزشکی و خدمات بهداشتی درمانی کردستان

Kurdistan University of Medical Sciences

www.muk.ac.ir

پلی‌کلینیک و آزمایشگاه ژنتیک ماد

MAAD Genetics Polyclinic & Lab

www.maadgenetic.com

MaadGene® Co. Ltd

شرکت مادژن

Medical Genetics

رییس سمینار / وبینار

دکتر فرزین رضاعی، ریاست دانشگاه علوم پزشکی کردستان

اعضای کمیته علمی سمینار / وبینار

دکتر فرخنده بهجتی، استاد تمام و متخصص ژنتیک پزشکی

دکتر جواد کریمزاد حق، متخصص ژنتیک پزشکی

دکتر آرش پولادی، متخصص ژنتیک پزشکی

اعضای کمیته اجرایی (کارگروه تخصصی ژنتیک پزشکی) سمینار / وبینار

۱. دکتر فریدون عبدالملکی، متخصص ژنتیک پزشکی
۲. دکتر اسعد آذرنژاد، متخصص ژنتیک پزشکی
۳. دکتر مریم شهرابی فراهانی، متخصص ژنتیک پزشکی
۴. دکتر امید ایروانی، متخصص ژنتیک پزشکی
۵. دکتر احمدرضاصالحی، متخصص ژنتیک پزشکی
۶. دکتر فهیمه پیریائی، متخصص ژنتیک پزشکی
۷. دکتر آهورا نوذری، متخصص ژنتیک پزشکی
۸. دکتر الیکا اسماعیل زاده، متخصص ژنتیک پزشکی
۹. دکتر فاطمه بحرینی، متخصص ژنتیک پزشکی
۱۰. دکتر بهار نقوی، متخصص ژنتیک مولکولی
۱۱. ژیلا قادری، کارشناس ارشد ژنتیک انسانی
۱۲. معصومه سلیمانی، کارشناس ارشد ژنتیک انسانی

اعضای کمیته پشتیبانی و فنی سمینار / وبینار

۱. دکتر فرزین رضاعی	۱۶. مهندس حمیدرضا عبدالملکی
۲. دکتر بهرام نیکخو	۱۷. مهندس جلیل آدابی
۳. دکتر ابراهیم قادری	۱۸. مهندس مجتبی ساعد پناه
۴. دکتر خالد رحمانی	۱۹. فاطمه ملایی
۵. دکتر محمد فتحی	۲۰. دکتر اسماعیل رحیمی
۶. دکتر آرزو فلاحی	۲۱. دکتر نیکو درویشی
۷. دکتر آرش پولادی	۲۲. شب بو خدایاری
۸. دکتر اسعد آذرنژاد	۲۳. سارا خالدی
۹. دکتر فریدون عبدالملکی	۲۴. یدالله فاتحی
۱۰. مهندس سالار شادمان	۲۵. محمد فرح یار
۱۱. مهندس کمال زیباسرشت	۲۶. ابراهیم عبدالعظیمی
۱۲. مهندس اقبال خاطری	۲۷. ژیلا قادری
۱۳. ماجد آریاپور	۲۸. معصومه سلیمانی
۱۴. دکتر شهرام شریفی	۲۹. مهندس شهرام صادقی
۱۵. مهندس میلاد رستمی	۳۰. امیر ساعدی

برنامه سخنرانی‌ها در وبینار دو روزه

پنجشنبه و جمعه

۱۹ و ۲۰ فروردین ۱۴۰۰

روز اول: از ساعت ۱۲:۳۰ الی ۱۷:۳۰

روز دوم: از ساعت ۱۰ الی ۱۵:۳۰

آدرس لینک ورود:

Webinar Link:

VC3.muk.ac.ir/genetics

روز اول: پنج شنبه ۱۴۰۰/۰۱/۱۹ – First Day: 8 April 2021

جلسه افتتاحیه	
تلاوت قرآن کریم و سرود جمهوری اسلامی ایران	12:30-12:35
خوشامدگویی و افتتاحیه (رئیس وبینار)- دکتر فرزین رضاعی، رئیس دانشگاه علوم پزشکی کردستان	12:35-13:00
گزارش دبیر وبینار- دکتر آرش پولادی	

بخش اول: سیتوژنومیک (Cytogenomics)

اعضای پانل: دکتر فرخنده بهجتی، دکتر جواد کریم زاد حق، دکتر مرجان یغمایی، دکتر احمد رضا صالحی، دکتر اسعد آذرنژاد

گرداننده: دکتر اسعد آذرنژاد

Affiliation/انتساب	Lecturer/سخنران	Title/موضوع	Time/زمان
Professor of Medical Genetics, Genetics Research Centre, University of Social Welfare and Rehabilitation Sciences, Tehran, **Iran** مسئول فنی آزمایشگاه ژنتیک پزشکی بیمارستان فوق تخصصی صارم	Prof. Farkhondeh Behjati, PhD, Dip R C Path (**UK**) پروفسور فرخنده بهجتی	ISCN 2020: A Change in the Way we look at Chromosomes	13:00-13:25 (13:15-13:20 Discussion)
Associate Professor of Medical Genetics, Research Institute for Oncology, Hematology and Cell Therapy, Tehran, **Iran** مسئول فنی بخش ژنتیک بیمارستان شریعتی تهران	Marjan Yaghmaie, PhD دکتر مرجان یغمایی	Importance of Genetic Evaluation and Measurable Residual Disease in AML Patients	13:30-13:55 (13:55-14:00 Discussion)
IVF centrum Heinsberger Höfe, Heinsberg, **Germany**/ ArtinZist Company, **Tehran** متخصص ژنتیک پزشکی از دانشگاه دوسلدورف آلمان، مرکز نازایی شهر هایسنبرگ آلمان/ شرکت آرتین زیست تهران	Javad Karimzad Hagh, PhD دکتر جواد کریم زاد حق	Prenatal diagnosis of a de novo 264kb microduplication in 18p11.22 by array-CGH in a fetus with abnormal sonography: Genetic counseling challenges in CNVs-VUS detection	14:00-14:15 (14:15-14:20 Discussion)
Sarem Fertility & Infertility Research Center (SAFIR) & Sarem Cell Research Center (SCRC), Sarem Women's Hospital, **Iran**	Fahimeh Mousavi, MSc فهیمه موسوی	Report and Evaluation of Array-CGH utility in a Genetics Diagnostic Centre in Tehran	14:20-14:35 (14:35-14:40 Discussion)

بخش دوم: ژنتیک بالینی (Clinical Genetics)

اعضای پانل: دکتر سعید طالبی، دکتر احسان غیور کریمیانی، دکتر امید ایروانی، دکتر عطا بوشهری، دکتر فایزه مجاهدی، دکتر فریدون عبدالملکی

گرداننده: دکتر فریدون عبدالملکی

Affiliation/انتساب	Lecturer/سخنران	Title/موضوع	Time/زمان
Professor of Human Genetics Department of Genetics and Genome Biology, University of Leicester, Leicester, **United Kingdom**	Prof. Raymond W.M. Dalgleish, PhD پروفسور ریموند دالگلیش	Interpreting NGS variants in the context of all gene transcripts and the importance of standardised reporting	14:40-15:10 (15:10-15:20 Discussion)
Professor and Chief, Division of Medical Genetics, East Tennessee State University, Quillen College of Medicine, **USA**	Prof. Mohammad Javad Hajianpour, MD, PhD پروفسور محمدجواد حاجیان پور	Clinical Genetics in Practice	15:20-15:50 (15:50-16:00 Discussion)
Medical Geneticist, Director of Education and Research, Isfahan Legal Medicine Center, **Iran.** متخصص ژنتیک پزشکی، آزمایشگاه ژنتیک ملل و پلی کلینیک ژنتیک نوژن اصفهان	Omid Iravani, MD, PhD دکتر امید ایروانی	Preventive ways to medical malpractice & medical errors راههای پیشگیری از تخلفات و قصور پزشکی	16:00-16:30 (16:30-16:40 Discussion)
Assistant Professor, Department of Medical Genetic & Molecular Medicine, Faculty of Medicine, Kurdistan University of Medical Sciences Sanandaj, **Iran** متخصص ژنتیک پزشکی، پلی کلینیک و آزمایشگاه ژنتیک ماد، سنندج	Arash Pooladi, MD, PhD دکتر آرش پولادی	A Rare Case of Muscular Dystrophy: Advantage of Target NGS Panel for Diagnosis & Chromosome Walking-Jumping for Confirmation	16:40-16:55 (16:55-17:00 Discussion)
Assistant Professor, School of Medicine, Ilam University of Medical Sciences ,Ilam, **Iran** متخصص ژنتیک پزشکی، دانشگاه علوم پزشکی ایلام	Ata Bushehri, MD, PhD دکتر عطا بوشهری	Early Onset Non Syndromic Retinitis Pigmentosa due to a variant in INPP5E: phenotypic expansion of the ciliopathy gene previously associated with Joubert syndrome	17:00-17:15 (17:15-17:20 Discussion)
جمع بندی و خاتمه روز اول			17:20-17:30

روز دوم: جمعه ۱۴۰۰/۰۱/۲۰ – Second Day: 9 April 2021

(http://VC3.muk.ac.ir/genetics)

آغاز برنامه روز دوم	
تلاوت قرآن کریم و سرود جمهوری اسلامی ایران	9:50-10:00

بخش سوم: بیوانفورماتیک، ژنتیک مولکولی و NGS
(Bioinformatic, Molecular Genetics & NGS)

اعضای پانل: دکتر مسعود گرشاسبی، دکتر مجید مجرد، دکتر محمد امین طباطبایی، دکتر محمد سلیمی اصل، دکتر امین اردشیر دوانی، دکتر آفاق علوی، دکتر آرش پولادی

گرداننده: دکتر آرش پولادی

Affiliation/انتساب	Lecturer/سخنران	Title/موضوع	Time/زمان
Amedes Genetics, Georgstrasse. 50, 30159 Hannover, **Germany** پروفسور ژنتیک پزشکی، از بنیانگذاران انگشت نگاری DNA آلمان	Prof. Dr. med. Jörg Thomas Epplen پروفسور یورگ توماس اپلن	Amedes geneticsDB – a new database for human genetic DNA diagnostics	10:00-10:30 (10:30-10:40 Discussion)
Belgium university Cimorgh Medical IT Solutions, Tehran, **Iran** متخصص بیوانفورماتیک از بلژیک	Amin Ardeshirdavani, PhD دکتر امین اردشیردوانی	An important role of bioinformatic data analysis in clinical grade diagnosis	10:40-10:55 (10:55-11:00 Discussion)
Laboratory of Complex Biological Systems and Bioinformatics (CBB), Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, **Iran**	Fahimeh Palizban, PhD Candidate دکتر فهمیه پالیزبان	Genomine: Cloud-based platform for NGS data analysis	11:00-11:15 (11:15-11:20 Discussion)
Research Assistant Professor, Genetic Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, **Iran**	Afagh Alavi, PhD دکتر آفاق علوی	Autosomal dominant hereditary spastic paraplegic (AD-HSP): Evidences of anticipation in families with *SPAS* gene mutation	11:20-11:35 (11:35-11:40 Discussion)

Genetics Research Center University of Social Welfare and Rehabilitation Sciences, Tehran, **Iran** مرکز تحقیقات ژنتیک، دانشگاه علوم بهزیستی و توانبخشی	Zohreh Elahi, MSc زهره الهی	Benefits and yeilds of Whole Exome Sequencing data reanalysis in Iranian undiagnosed neuromuscular patients: a Pilot Study	11:40-11:55 (11:55-12:00 Discussion)
Medical Geneticist, Rouzbeh Genetic Lab. Tehran, **Iran** متخصص ژنتیک پزشکی، مسئول دپارتمان و آزمایشگاه ژنتیک روزبه	Fatemeh Alizadeh, PhD دکتر فاطمه علیزاده	Psychiatric Onset Alexander Disease: An Important Challenge in Neuropsychiatric Diagnosis	12:00-12:15 (12:15-12:20 Discussion)
Assistant Professor, Department of Medical Genetic & Molecular Medicine, Faculty of Medicine, Kurdistan University of Medical Sciences Sanandaj, **Iran** متخصص ژنتیک پزشکی، پلی کلینیک و آزمایشگاه ژنتیک ماد، سنندج	Fereydoon Abdolmaleki, MD, PhD دکتر فریدون عبدالملکی	A rare case of a first cousin couple carrier for both beta thalassemia and SMA	12:20-12:35 (12:35-12:40 Discussion)
Department of Molecular Medical Genetics, Tehran Genetics Laboratory, Tehran, **Iran** متخصص ژنتیک پزشکی، مسئول فنی آزمایشگاه ژنتیک پزشکی تهران	Elika Esmaeilzadeh-Gharehdaghi, PhD دکتر الیکا اسماعیل زاده - قره داغی	Presentation of a complicated case of α/β thalassemia Combined with Homozygous Form of Hemoglobin-D in an Iranian couple	12:40-12:55 (12:55-13:00 Discussion)
Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, **Iran** متخصص ژنتیک پزشکی، مسئول فنی آزمایشگاه ژنتیک پزشکی تهران	Ahmad Reza Salehi Chaleshtori, PhD دکتر احمدرضا صالحی چالشتری	Identification of two pathogenic variants in a family with mild and severe forms of developmental delay	13:00-13:15 (13:15-13:20 Discussion)
Break time (Prayer & Lunch) - نماز و ناهار			13:20-13:40

Medical Genetics laboratory, Shahrekord University of Medical Sciences, Shahrekord, **Iran** متخصص ژنتیک پزشکی، مسئول فنی آزمایشگاه ژنتیک پزشکی صدرا، شهرکرد	Ahoura Nozari, PhD دکتر آهورا نوذری	Clinical and molecular genetic characterization of a female patient with fragile X syndrome: A novel case with two expanded alleles	13:40-13:55 (13:55-14:00 Discussion)
Human Genetics Research Center, Baqiyatallah University of Medical Sciences, Tehran, **Iran**	Shirin Ghadami, PhD دکتر شیرین قدمی	Molecular genetic characterizations of 130 patients with neurofibromatosis type 1	14:00-14:15 (14:15-14:20 Discussion)
Watson Genetic Laboratory, North Kargar Street, Tehran, **Iran**	Mahdieh Taghizadeh, PhD دکتر مهدیه تقی زاده	Identification of Two Novel *UBE3A* Mutations Causing Angelman Syndrome	14:20-14:35 (14:35-14:40 Discussion)
Assistant Professor Department of Biochemistry and Genetics, School of Medicine, Arak University of Medical Sciences, Arak, **Iran**	Milad Gholami, PhD دکتر میلاد غلامی	The novel bi-allelic p.Asn197_Ser201del mutation causing profound biotinidase deficiency in an Iranian consanguineous family	14:40-14:55 (14:55-15:00 Discussion)
Assistant Professor Department of Medical Genetics, Ahvaz Jundishapur Univercity of Medical Sciences, **Iran**	Eskandar Taghizadeh, PhD دکتر اسکندر تقی زاده	A novel variant in *C5ORF42* gene is associated with Joubert syndrome	15:00-15:15 (15:15-15:20 Discussion)
اختتامیه وبینار با قرائت «**بیانیه وبینار**» دو روزه			15:20-15:30

چکیده سخنرانی‌ها

Oral Presentations

Abstracts

OP:01

ISCN 2020: A change in the way we look at chromosomes

Farkhondeh Behjati, PhD, Professor of Medical Genetics, Genetics Research Centre, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran. Email: fbehjati@gmail.com

ISCN, An International System for Human Cytogenomic Nomenclature, is a compile of recommendations of the international standing committee on Human Cytogenomic Nomenclature developed in close collaboration with the Human Genomic Variation Society (HGVS) sequence variant description working group.

The history of modern Cytogenetics goes back to 1956, when Tjio and Levan reported the correct human chromosome number from 48 to 46. By 1960, several laboratories were engaged in the study of human chromosomes and a variety of classifications and nomenclature systems for human chromosomes had been proposed. For these reasons, for the first time in 1960, in Denver conference the foundation of a standard system of nomenclature of human mitotic chromosomes was set up.

The ISCN has been reviewed and updated every few years in order to cover the new Genetics techniques. In recognition of the increasing use of DNA sequencing technologies and the need for the description of sequence-based changes, the Cytogenomics community in collaboration with members of the Human Genome Variation Society (HGVS) sequence variant description working group developed a new nomenclature covering both the Molecular Genetics and Cytogenetics communities. As a result of these

changes Cytogenetics was replaced with Cytogenomics in ISCN 2016.

However, in ISCN 2020, due to increased use of technologies such as microarray and sequencing which orientate chromosomes by nucleotide number from the end of chromosomes, pter to qter, the Cytogenomics committee decided to standardize this approach across all techniques, including banded chromosomes.

For the description of chromosome abnormalities, sex chromosome abnormalities are presented before those affecting autosomes for all techniques (Banded chromosomes, FISH, Microarray, and sequencing).

A new section to nomenclature for inherited chromosome abnormalities was introduced. This system clarifies whether an inherited rearrangement is intact or partially a derivative.

A specific nomenclature for the analysis of polar bodies is introduced.

An improvement of the 2016 ISCN nomenclature based on sequencing technology has been implemented. There is an optional use of comma for any abnormality showing nucleotide number, making it easier to read.

All changes made in ISCN 2016, are marked in the margin of the new edition to assist the reader.

Reference: ISCN 2020; An International System for Human Cytogenomic Nomenclature (2020)

Editors: Jean McGowan-Jordan, Ros J. Hastings, Sarah Moore. Karger Publication.

OP:02

The importance of genetic evaluation and measurable residual disease in AML patients

Marjan Yaghmaie, PhD, Associate Professor of Medical Genetics, Research Institute for Oncology, Hematology and Cell Therapy.
Email: m-yaghmaie@sina.tums.ac.ir

In patients with AML, treatment decisions are mostly based on pre therapeutic risk assessment according to the European LeukemiaNet (ELN) cytogenetic and molecular classification. Knowledge of the pre-treatment mutation status of various genes and cytogenetic abnormalities has improved our ability to assign initial treatment. Besides, knowledge of whether patients in remission have measurable residual disease (MRD), which can influence their subsequent management, is of particular importance. Genetics encompassing both classical cytogenetics and the mutational status of various genes is also the most important predictor of resistance to therapy. MRD evaluation is an important tool to assess early response to therapy and to monitor longer follow-up to detect the relapse earlier and guide potential preemptive therapy. MRD has emerged as one of the strong independent predictors for relapse and survival after HLA-matched transplants, regardless of the methodology used. Several studies have also shown that post-HCT MRD, detected by polymerase chain reaction (PCR), multiparameter flow cytometry (MFC), or levels of mixed chimerisms (as a surrogate), can identify patients at high risk of relapse and poor outcome. Using NGS for MRD detection is also appealing because its flexibility allows using almost every mutated gene as an MRD marker.

OP:03

Prenatal diagnosis of a *de novo* 264kb microduplication in 18p11.22 by array-CGH in a male fetus with abnormal sonography: Genetic counseling challenges in CNVs-VUS detection

Karimzad Hagh, Javad, PhD, IVF centrum Heinsberger Höfe, Heinsberg, Germany
Email: JK@cuypers-cuypers.com

Background and Objectives: Array-CGH is a high resolution genomic test to assess deletion or duplication of whole genome in pre- and postnatal diagnosis. Array-CGH should be considered for the replacing of conventional chromosome karyotyping because of its increased diagnostic yield. Utilizing array comparative genome hybridization (aCGH) in prenatal genetic diagnosis – whether on its own or in combination with karyotyping – can lead to challenges and controversy. We report a *de novo* 264kb microduplication in 18p11.22 in a male fetus by aCGH with abnormal sonography.

Material and methods: Array-CGH was performed directly on an amniocentesis sample due to increased fetal nuchal translucency (NT Value= 3,2mm) in the routine first trimester screening at 12 weeks and 2 days of gestation. The routine rapid tests and karyotyping of amnion cells were not conducted. For a *de novo* study, we also have performed a-CGH on the peripheral blood of the parents of the fetus using same resolution of Agilent 8×60k microarrays. The results were analyzed using CytoGenomics software.

Results: The array-CGH analysis revealed a 18p11.22 microduplication (264kb) by fetus:
arr[GRCh37] 18p11.22(10520416_10784606)x3,(X,Y)x1

Array-CGH results of fetus' parents were normal.

Discussion & Conclusion: The use of aCGH could shed further light on the correlation between the genes identified in the chromosomal region of interest and the patient's phenotype. The application of aCGH in this field has been increasing dramatically and some professional bodies strongly recommend it as the first-tier prenatal genetic test in cases of fetal ultrasound abnormalities. Despite of aCGH greater resolution, the detection of CNVs-VUS can cause a lot of complication in respect to interpretation of the findings and genetic counselling.

264kb gained CNV in this case is classified, according the ACMG guidelines, as a CNV-VUS and overlaps two OMIM genes: PIEZO2 and NAPG. The heterozygous mutations in PIEZO2 are associated with OMIM diseases and link Gordon syndrome (distal arthrogryposis type3), Marden-Walker syndrome and Arthrogryposis (Distal Arthrogryposis Type 5). The heterozygous mutations in the NAPG are associated with various kinds of cancers. Similar reported CNV-duplications that cover complete or part of this 264kb region are classified from benign and VUS to pathogenic types associated with autism and ID, according to the DECIPHER database. A fetal anomaly scan and echocardiography of the fetus during the prenatal period, including a physician examination after delivery, is advisable. In cases of CNVs-VUS, the decision-making concerning termination of the fetus must solely be left to the parents.

Keywords: Array Comparative Genomic Hybridization (aCGH), Miroduplication, CNVs-VUS, CNV Classification, ACMG,

Intellectual Disability (ID), prenatal diagnosis, Genetic Counseling, OMIM-Genes

OP:04

Report and evaluation of array-CGH utility in a genetics diagnostic centre in Tehran

Fahimeh Mousavi[1*], Fatemeh Vand-Rajabpour[1], Iman Bagherizadeh[1], Roxana Kariminejad[2], Kamran Bahadori[3], Sima Giti[3], Mozhgan Karamnia[3], Farkhondeh Behjati* [1,4]

1. Sarem Fertility & Infertility Research Center (SAFIR) & Sarem Cell Research Center (SCRC), Sarem Women's Hospital, Iran University of Medical Science (IUMS), Tehran, Iran.
2. Karimi-Nejad Najmabadi Genetics & Pathology Center, Tehran, Iran.
3. Sarem Fertility and Infertility Research Center (SAFIR), Sarem Women's Hospital, Iran University of Medical Science (IUMS), Tehran, Iran.
4. Genetics Research Centre, University of Social Welfare and Rehabilitation Centre, Tehran, Iran

*Correspondent: fbehjati@gmail.com & f_behjati@uswr.ac.ir

Background and Objectives: Array comparative genomic hybridization (aCGH), as a known molecular cytogenetic technique, has been widely used in diagnostic laboratories for the evaluation of individuals with intellectual disability/developmental delay, autism spectrum disorders and/or multiple congenital anomalies/dysmorphic features. It is also being increasingly used in the prenatal diagnosis and products of conception. Clinically available whole-genome aCGH can detect unbalanced chromosomal rearrangements (deletions and/or duplications) with coverage of about one probe per 6 kb to one probe per 70 kb, however, the traditional Giemsa-stained metaphase chromosome karyotyping identifies both balanced and unbalanced chromosomal abnormalities with more than ~4 Mb resolution.

Material and Methods: We report the aCGH results of 142 samples which were referred to the Sarem Cytogenetic laboratory for cytogenetic analysis from 1396 to 1399. The 142 studied

samples comprised 52 products of abortion, 60 prenatal amniotic fluid samples, and 30 post-natal peripheral bloods samples.

Results: Four out of fifty-two (7.7%) aborted fetuses had pathogenic aCGH results including two male fetuses with gain of whole chromosome 21 (compatible with trisomy 21), one male fetus with gain of whole chromosome 9 (compatible with trisomy 9), and one female fetus with pathogenic gain of 78.2 Mb on 13q13.3q34 and loss of 612 Kb on 20p13p13 which overlap with 175 OMIM genes (2 OMIM disease), and 7 OMIM genes (3 OMIM disease), respectively. The aborted fetus's karyotype result shows 46,XX,der(20)t(13;20)(q13;p13) which is inherited from the father. Also, five out of sixty (8.33%) amniotic fluid samples exhibited some pathogenic chromosomal abnormalities. Ten out of thirty (33%) postnatal peripheral blood samples showed abnormal chromosomal aCGH results.

Discussion & Conclusion: These findings help us to overview the utility of aCGH at different stages in the routine genetic diagnosis of Iranian patients. In line with other findings, this report shows that aCGH contributes to find the chromosomal deletions and duplications in more detail, so it complements the karyotype findings. Likewise, in some cases aCGH could find the abnormalities with less than 4 Mb that is not detectable by karyotype. For unsolved cases additional high throughput genetic testing need to be performed. The findings of this report emphasizes use of array CGH technique in patients with Intellectual disabilities/ Multiple congenital abnormalities and Autism as well as in fetuses showing major structural abnormalities with sonography. In

particular when a non-syndromic situation arises, use of array CGH, with its genomic coverage can reveal a deletion or duplication of a gene, which can lead to the introduction of a new syndrome.

Keywords: Array comparative genomic hybridization (aCGH), Intellectual disabilities, Multiple congenital abnormalities, Autism, Balanced and unbalanced chromosomal abnormalities

OP:05

Interpreting NGS variants in the context of all gene transcripts and the importance of standardised reporting

Professor Raymond Dalgleish, Department of Genetics & Genome Biology, University of Leicester, Leicester, United Kingdom.
Email: ray@le.ac.uk

The Human Genome Variation Society (HGVS) variant nomenclature is widely used to describe sequence variants in scientific publications, clinical reports, and databases. However, the nomenclature is complex and inaccurate variant descriptions are often reported, especially in the scientific literature. VariantValidator (https://variantvalidator.org/) is a web-based tool assists users who wish to accurately describe and report HGVS-compliant sequence-level variations. VariantValidator was designed to ensure that users are guided through the intricacies of the HGVS nomenclature, *e.g.*, if the user makes a mistake, VariantValidator automatically corrects the mistake if it can, or provides helpful guidance if it cannot.

In addition, VariantValidator can interconvert genomic variant descriptions in HGVS and Variant Call Format (VCF). The conversion of VCF calls to HGVS descriptions is performed comprehensively in the context of all overlapping gene transcripts. Furthermore, VariantValidator correctly handles base mismatches between reference transcripts and human genome builds GRCh37 and GRCh38.

The importance of correct use of HGVS variant nomenclature and of the projection of genomic DNA variants onto all relevant gene transcripts will be illustrated using examples drawn from the histone 3.3 *H3-3A* gene and the type V collagen *COL5A1* gene.

OP:06

Clinical Genetics in Practice

Prof. MJ. Hajianpour, MD, PhD, Professor and Chief, Division of Medical Genetics, East Tennessee State University, Quillen College of Medicine, USA
Email: mj@hajianpour.com

This presentation is focused on the basis of clinical medical genetics and understanding the interaction between genes, health and disease.

The causes of birth defects and congenital anomalies are chromosomal disorders (6-10%), single gene disorders (7.5%), multifactorial (20%), infection (TORCH, etc.) (2-3%), maternal diabetes / metabolic disorders (1.5%), maternal medication (1-2%) and unknown (~50%), 20-35% of which can now probably be identified by CMA (additional 6%), and about 20-25% can be revealed by gene sequencing/ del/dup analysis, gene panel (NGS) and WES/WGS.

Genetic Syndromes are recurring pattern of clinical findings and are identified by the combination of findings based on structural anomalies and functional abnormalities.

In this lecture some useful genetic websites are introduced, and a few patients with clinical dysmorphology are presented. Branchio-Oto-Renal Syndrome (BOR Syndrome), Noonan syndrome, Phenylketonuria (PKU), MPS1, MPS4, Fabry disease, Smith-Lemli-Opitz syndrome, Costtelo syndrome and congenital disorders of Glycosylation are some of the examples.

OP:07

Ways to avoid medical errors and malpractice

Omid Iravani, MD, PhD; Clinical and Molecular Geneticist, Isfahan Legal Medicine Center.
Email: om_iravani@yahoo.com

Today, along with significant advances in medical knowledge, the influence of the media and cyberspace, willingly or unwillingly, exposes the general public to the onslaught of information. Correct information has raised the level of public awareness and their greater mastery of their civil rights and citizenship, so that in recent years in the judiciary we have seen an increasing number of public complaints to demand their rights. One of the types of lawsuits that has almost doubled in the last five years has been complaints against health care workers. In this situation, a significant part of the time and income of health care personnel is spent on responding to trade union and judicial lawsuits, while these people have little information about legal issues related to their field. Therefore, it is necessary for the health care staff to be aware of their rights in order to act, if necessary and in due time, not to infringe on the rights of others but to defend their legitimate rights, because ignorance of the law does not relieve individuals of their responsibility. In fact, the most important way to prevent complaints is to familiarize people with laws and regulations, the non-observance of which simply leads to disciplinary (union), civil or criminal punishments. Awareness of laws, regulations and punishments is not only effective in preventing crimes and offenses but also blocks the way for abusers to misuse the law. Medical malpractice and disciplinary offenses are two major categories of

offenses that enforce different penalties for law enforcement. In the field of laboratory sciences, actions that lead to non-diagnosis, delay in diagnosis or misdiagnosis have different levels and consequences and depending on its type and severity in causing or not causing physical injury or causing financial damage will result in various consequences and punishments. In general, professional behavior, honesty, observance of common rules and regulations, observance of scientific and technical standards, documentation, correct registration and archiving of documents, obtaining informed consent, clear reporting, confidentiality, non-issuance of false certificates, reporting scientific and technical restrictions and uncertainty in measurement of lab tests are key items that minimize the complaint and, in the case of a complaint, create a relatively safe margin for joint response. On the other hand, although the liability insurance coverage is strongly recommended to the health and medical staff, this insurance does not provide coverage for criminal liability.

Keywords: rules and regulations, crimes, errors, medical malpractice, punishment

OP:08

A rare case of muscular dystrophy: Advantage of target NGS panel for diagnosis & use of chromosome walking-jumping for the confirmation

Arash Pooladi, MD, PhD [1,2,*], Fereydoon Abdolmaleki, MD, PhD [1,2], Esmail Rahimi, PhD [2], Nikou Darvishi, PhD [2], Shabbou Khodayari, BSc [2], Sara Khaledi, BSc [2]

1. Department of Medical Genetic & Molecular Medicine, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran.
2. MAAD Genetics Polyclinic & Lab., Sanandaj, Kurdistan, Iran

*Correspondent: Arash.pooladi@gmail.com

Background and Objectives: Muscular dystrophy (MD) is a group of inherited diseases that damage and weaken muscles over time, due to the lack of some proteins which are necessary for normal muscle function. Muscular dystrophy can occur at any age, but most diagnoses occur in childhood. Some of MDs are rare and uncommon like Merosine-deficient congenital muscular dystrophy type 1A (MDC1A) that is caused by homozygous or compound heterozygous mutation in the laminin alpha-2 gene (LAMA2; 156225) on chromosome 6q22. Merosin is a protein specifically found in the basement membranes of striated muscle and Schwann cells. Twenty percent of mutations of this gene are large deletions and are detected by target analysis.

Material and methods: A 7-year-old female due to consanguineous marriage with a history of NVD, hypotonia in birth and granting and motor development delay came to our clinic. The family history is positive for hypotonia and quadriplegia in third degree family member. She has been evaluated for neuromuscular diseases. She has quadriplegia (especially in proximal muscles), atrophic muscles, raise in serum CPK, neck weakness, areflexia in

tendons stimuli, contracture in Hip and Knee joints, stiffness of back and waist vertebrae with mild scoliosis, and triangular face with narrow mandible. She has normal IQ, normal Babinski sign and no seizure. In NCV-EMG study, generalized myopathy is mentioned. Pedigree is compatible with autosomal recessive pattern of inheritance.

Results: In the first step of genetic study the MLPA-SMA was tested and we obtained a normal result (SMN1=2 copy/SMN2=1 copy). In the next step the target NGS panel was chosen for this patient with CNV analysis. The result is *LAMA2*; EX2-4DEL (hom.) for LAMA2-MD disease (AR) which is compatible with the patient phenotype and pedigree. For the confirmation of the finding, due to unavailability of the MLPA kit and inadequate coverage of the array-CGH, we chose the Chromosome walking/Jumping technique. It was used for clarifying two end deletion points (in about 5 to 6 steps by the middle backward/forward primers technique) and detected a deletion of over 110 kb. The triple PCR fragment analysis for parents also segregated the above finding. As a result, using linkage analysis, this family is now a candidate for PND in the next pregnancy.

Discussion & Conclusion: Because of the prevalence of large rearrangements in most of the genes responsible for Muscular dystrophies, targeted NGS Panels seem to be a better choice for their genetic diagnosis. The gene coverage and CNV analysis are the important and unavoidable step in the analysis of this category of disease. Due to large depth of the reading fragments in the target NGS panels, the CNV analysis is preferred. MLPA technique is the

best choice for its confirmation, but the conventional PCR techniques by a planned strategy can also be performed in the event of rare findings.

Keywords: Muscular Dystrophy, *LAMA2*, Large Deletion, Targeted NGS-Panel, Chromosome Walking-jumping

OP:09

Early onset non syndromic Retinitis Pigmentosa due to a variant in INPP5E: Phenotypic expansion of the ciliopathy gene previously associated with Joubert syndrome

Mona Lotfikar[1], Mahshid Fattahi[2], Yunes nourizadeh[3], Ata Bushehri[1*]

1. Mana Genetic Lab, Ilam, Iran
2. Departments of Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3. Welfare organization, Ilam, Iran

*Correspondent: Ata.bush.gen@gmail.com

Background and Objective: Retinitis Pigmentosa are a group of genetically and phenotypically heterogeneous inherited degenerative retinal diseases primarily affecting retinal photoreceptors. INPP5E loss-of-function variants cause Joubert syndrome, a systemic disorder characterized by the retinal degeneration among other clinical features such as the absence or underdevelopment of the cerebellar vermis and a malformed brain stem.

Materials and methods: Detailed clinical examination and genomic DNA extraction were collected from an Iranian family presenting with autosomal recessive rod-cone dystrophy. The impact of candidate disease-causing variant was modeled on a tertiary INPP5E protein structure and analyzed for the deleteriousness and phenotypic correlation.

Results: A novel likely pathogenic variant is INPP5E gene was identified in a homozygous state which was confirmed by Sanger sequencing and co-segregated with disease status, as well as by protein structure analysis.

Discussion and Conclusions: The study expands the phenotypic spectrum of disorders due to the pathogenic variant in INPP5E and describes a new disease association with previously under diagnosed forms of non-syndromic retinitis pigmentosa.

Keywords: JSRD; INPP5E; retinitis pigmentosa; Joubert syndrome; non-syndromic retinal dystrophy.

OP:10

Amedes geneticsDB – a new database for human genetic DNA diagnostics

Jörg T. Epplen, Ralf Glaubitz; amedes genetics, Georgstr. 50, 30159 Hannover, Germany.
Email: joerg.t.epplen@rub.de

Recent advancements in next-generation sequencing (NGS) have provided the foundation for extended modern DNA diagnostics. Multigene panel testing is expanding so rapidly that medical practice is racing to keep pace. We strive to find middle ground in assembling the genes in panels, returning both clinically relevant and most compelling DNA sequence findings, but minimizing the risk to encounter unwanted information and especially also variants of unknown significance. Hence the amedes geneticsDB has been newly established comprising nearly 1.000 DNA diagnostic panels for all medical disciplines and more than 6.600 genes. In addition to the panels` curation (according to panelapp, genereviews, OMIM, ORPHANET and the most recent literature etc) the human genetic information is compiled in easily and efficiently usable format. The panels are elaborated and explained for the clinician, and the molecular genetic yield for the (groups of) diseases are explicitly stated. The DNA panels in geneticsDB are updated constantly and shall be accredited by to the German *Akkreditierungsstelle* (DAkkS) before fall 2021.

OP:11

An important role of bioinformatic data analysis in clinical grade diagnosis

Amirhossein Mehrtash [1], Sanaz Ajami [2], Amin Ardeshirdavani [1*]

1. Cimorgh Medical IT Solutions, Tehran, Iran.
2. Omid Genetic Laboratory, Tehran, Iran.

*Correspondent: davani@cimorgh.ir

Background and Objectives: Geneticists and physicians will increasingly refer patients suffering from inherited and acquired human genetic disorders for genome sequencing if their condition warrants it. In multiple situations, genome sequence information can significantly improve the diagnostic process and help guide therapeutic decisions. In clinical use of NGS, lab technicians will then prepare the samples and run the test. As soon as the raw data becomes available, bioinformaticians can start to analyze the data, create an appropriate report, and send the results back to the clinic for diagnosis and follow-up. Next-generation sequencing (NGS) is a disruptive technology. The enormous throughput of NGS instruments has mandated the development of a new generation of algorithms and data formats capable of storing, processing, and analyzing massive amounts of sequence data. NGS has led to an increase by several orders of magnitude in biological data available for genomics and transcriptomics. Therefore, extensive bioinformatics frameworks have to be developed to ensure a correct biological interpretation of this data.

Material and methods: Here, we would like to present three clinical cases which we re-analyzed and interpreted by using GenAP: Cimorgh Medical Genetics Genomics Analysis Platform:

1- An intragenic disease-causing deletion in the *SGBC* gene
2- Novel Missense *COL11A1* Mutation Resulting in an 18-week Male Aborted Fetus with Fibrochondrogenesis 1
3- Lichen Planus OR Neurofibromatosis, how much data do we need to have an accurate result.

Initial clinical results did not support the phenotype or medical status of the patients therefore these cases were tagged as unsolved or uncertain results.

Discussion & Conclusion: Clinical labs seek the advice of bioinformaticians regarding what kind of software and data sources to use. The usual standard answer is to use the current best of genomics software. Unfortunately, it is often found that these tools are not even always capable of doing the clinical application job, for example detecting specific mutation types. So, clinicians usually face two problems: i) Buy an expensive hardware and non-transparent, and more often than not, very computer time-consuming commercial software from the platform vendor, or ii) seek advice from trained bioinformaticians who may point them to academic tools developed for genome analysis, but not necessarily suitable for amplicon sequencing. The solution is not easy. Platform vendors cannot be blamed for proposing a technically sound solution which, for the moment, has no chances to follow the exponential growth of clinical analysis needs. So, it is the task of future bioinformatics projects to develop accurate and flexible solutions for clinical applications As we did in Cimorgh Medical IT solutions by developing GenAP.

Keywords: NGS, WES, Clinical Data Analysis, Bioinformatics, GenAP.

Genomine: Cloud-based platform for NGS data analysis

OP:12

Fahimeh Palizban, Laboratory of Complex Biological Systems and Bioinformatics (CBB), Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran. Email: fahimehpalizban@ut.ac.ir & https://mineomix.com

Background and Objectives: Next-generation sequencing has made major progress in the area of precision medicine and accordingly the number of studies based on large sequencing data sets is growing. Deeply investigation of these data requires researchers to use large-scale computational resources. In this regard, cloud computing can be a suitable method for genomics research whereby users can rent computers and storage from their data analysis. By developing an automated genomic data analysis pipeline on the cloud computing platforms, studying genomics data from a huge amount of samples will lead to a more accurate understanding of normal and disease diversity. By applying this method combining different data types, global accessibility and availability, the security of the data, and high-performance data processing will no longer be a major issue. However, this approach requires technical knowledge and ever-growing compute and storage resources. Accordingly, Our well- established product, "Genomine" is developed to achieve this objective.

Material and methods: In Genomine, raw NGS data particularly genomic data can be processed through automated well-defined workflows consisting series of steps as part of a pipeline that can be modified by users to transform into a form that is ready for analysis. In order to fulfill this objective , previously validated bioinformatic tools and pipelines such7 th Seminar/Webinar on Medical Genetics

(Diagnostic & Research) as GATK have been implemented on the cloud-based services which facilitate the process of NGS data analysis by users.

Results: Validating the performance of the proposed platform, "Genomine" was done on WES data related to a female patient with a risk of Dyskeratosis congenita-3 and Revesz syndrome. By analyzing the raw genomic data in Genomine, the annotated VCF file of the mentioned patient was generated including the pathogenic variant in the TINF2 gene which was identified in concordance with genetic expert reports.

Discussion & Conclusion: As we know, the NGS market is highly competitive and growing with high speed, so having highly efficient and accurate platforms like Genomine that allows for fast adoption of new methods and technologies is critical in this area.

Keywords: NGS data analysis, Cloud computing, Genomics, Genomine, Variant annotation

OP:13

Autosomal dominant hereditary spastic paraplegia (AD-HSP): Evidence for anticipation in families with *SPAST* mutations

Afagh Alavi[1], Reza Hajati[1], Atefeh Davarzani[1], Seyyed Saleh Hashemi[1], Mohammad Rohani[2], Shahriar Nafissi[3]

1. Genetics research center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
2. Department of Neurology, Iran University of Medical Sciences, Hazrat Rasool Hospital, Tehran, Iran
3. Department of Neurology, Neuromuscular research center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

*Correspondent: afaghalavi@gmail.com & af.alavi@uswr.ac.ir

Background and Objectives: Hereditary spastic paraplegia (HSP) is a heterogeneous neurodegenerative disorder that is characterized by lower-limbs spasticity and weakness. HSP has several modes of inheritance, including autosomal dominant (AD-HSP), autosomal recessive (AR-HSP), X-linked, and mitochondrial. AD-HSP patients usually present a pure form of the disease, while AR-HSP cases often show a complex form. The most frequent mutated gene among all patients and specially AD-HSP ones is the *SPAST* gene (SPG4). It comprises approximately 60% of AD-HSPs, a third of all HSP-affected patients, and 15% of sporadic cases. SPG4 patients usually present pure-HSP with variable age-at-onset (AAO). The decreased AAO and/or increased severity of the symptoms during subsequent generations, which is called anticipation, have been reported in SPG4. However, the presence of anticipation in SPG4 cases is still doubtful. This phenomenon might occur more than expected, but due to inadequate knowledge and the small size of families, it is often overlooked or underestimated in clinical

practice. So, further studies of large pedigrees with *SPAST* mutations are needed to confirm whether anticipation exists in SPG4 families.

Material and methods: DNA samples of 14 unrelated Iranian AD-HSP probands were whole-exome sequenced (WES). Data were analyzed and candidate variants were validated by Sanger sequencing. Multiplex ligation-dependent probe amplification (MLPA) using the SALSA® MLPA® Probemix P165-C3 HSP mix-1 (16 probes for the *ATL1* gene and 20 probes for the *SPAST* gene) was done for seven WES-undiagnosed families including a family who presented anticipation. To assess probable anticipation, clinical presentations were recorded and evaluated in the families.

Results: WES identified the disease-causing variants in seven probands (7/14; 50%); three with variants in the *KIF5A*, *ATL1*, and *MFN2* genes, and four with *SPAST* mutations. MLPA identified a large deletion of exon 17 in *SPAST*, only in one proband, who presented anticipation as was expected. In the current study, SPG4 was the common subtype of HSP. Altogether, there were five multi-generational SPG4 families, and we focused on 39 affected patients. The average AAO in different generations showed a progressive decline in later generations of all SPG4 pedigrees but not in other subtypes of HSP. In the family who carried deletion of exon 17, the mean of AAO declined from ~60 to 2.5 years during four successive generations. The decrease of AAO in other SPG4 families was 47 to 23 years, comprising ~60 to 27 ,~50 to 3, and 68 to 6.8 years (p-value<0.05).

Discussion & Conclusion: It seems *SPAST* will be the first candidate gene in families presenting a pure form of AD-HSP which manifests anticipation. Therefore, it may be a powerful situation of genotype-phenotype correlation. Anticipation has been typically attributed to dynamic mutations, rarely static mutations such as *SPAST* mutations, highlighting the role of other genetic, epigenetic, and environmental factors. Among the genetic factors intronic microsatellites may affect gene expression, hence variable AAO of the disease. There are two microsatellites in *the SPAST* gene, and anticipation may occur when these repeats expand beyond a threshold length.

Keywords: Autosomal dominant-hereditary spastic paraplegia (AD-HSP), *SPAST* mutations, anticipation

OP:14

Benefits and yields of whole exome sequencing data reanalysis in Iranian undiagnosed neuromuscular patients: A pilot study

Zohreh Elahi[1*], Mojgan Babanejad[1], Kimia Kahrizi[1], Hossein Najmabadi[1, 2], Zohreh Fattahi[1, 2]

1. Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
2. Kariminejad-Najmabadi Pathology & Genetics Center, Tehran, Iran
Email: zohreh.elahi@yahoo.com

Background and Objectives: Molecular diagnosis of neuromuscular disorders (NMDs), which is confined by their heterogeneous genetic nature is nowadays enhanced by implementation of whole exome sequencing (WES) in diagnostic laboratories. However, the diagnostic yield has been still limited to less than 50% in different studies. Besides, hereditary types of NMDs are common in populations with high rate of consanguinity such as Iran, displaying higher diagnostic rates up to 73% in some cohorts. However, there are still lots of undiagnosed patients despite having supportive clinical and pathological evidence. Over recent years, reanalysis of exome data with simultaneous WES-based detection of CNVs has allowed genetic diagnosis in patients who have not received positive results from the initial evaluation and has increased the clinical diagnosis in 10-15% of patients. To the best of our knowledge, no specific study is performed to evaluate the added value of WES-reanalysis in molecular diagnosis of NMDs, which is imperative as an average of 28 genes are being introduced annually.

Material and methods: To address this issue, the current study is designed as a pilot phase to assess the effect of WES-reanalysis in improving the diagnostic yield of NMDs, especially in populations with consanguineous background. Therefore, twenty undiagnosed Iranian patients suffering from neuromuscular disorders, who have received a negative result from the initial WES analysis, were selected. WES reanalysis was performed applying the most updated versions of GATK and other algorithms to increase variant detection and annotation. The variants in newly identified NMD genes were reassessed, and WES-based CNV analysis using the GATK GermlineCNVCaller was applied.

Results: Thus far, our initial analysis has shown 20% increase in diagnostic yield based on the identification of pathogenic variants in the following genes: *MICU1*, *MTM1*, *RYR1* and an intragenic deletion in *SGCB*.

Discussion & Conclusion: These causal variants were not detected in initial WES analysis; the *MICU1* was not a known gene at the time of analysis, the *MTM1* gene was not selected for investigation in panel analysis, the *RYR1* variant was reclassified from VUS to likely pathogenic, and CNV analysis was not part of the initial WES evaluation to identify the intragenic deletion of exon 2 in *SGCB* gene. The identification of this intragenic deletion in such a small cohort is in line with recent studies presenting LGMD2E as the most common type of sarcoglycanopathies in Iranian patients, while this deletion is considered as one of the most frequent mutations in this gene, proposing the possibility of being a founder mutation in Iran. In conclusion, the current study shows the

importance of careful re-evaluation of NGS data in line with multidisciplinary approach to detect different mutation types and achieves significant increase in diagnostic yields of NMDs compared to other Mendelian disorders

Keywords: Neuromuscular disorders, WES-reanalysis, WES-based CNV analysis, Iran.

OP:15

Psychiatric Onset Alexander Disease: An Important Challenge in Neuropsychiatric Diagnosis

Fatemeh Alizadeh[1], Fatemeh Mohammadian[2]*

1. Department of Genomic Psychiatry and Behavioral Genomics, Roozbeh Hospital, Tehran University of medical Sciences, Tehran, Iran
2. Department of Psychiatry, Roozbeh Hospital, Tehran University of medical Sciences, Tehran, Iran

*Correspondent: fmohammadianr@sina.tums.ac.ir

Background and Objectives: Alexander disease is a heterogenous group of diseases with various manifestations based on age of disease onset. This rare leukodystrophy syndrome with mutations in GFAP Gene could present with developmental delay and seizure in infantile form to ataxia and bulbar palsy in adulthood. However psychiatric symptoms are not well-defined and usually evaluate after disease diagnosis not before disease investigations.

Material and methods: Our patient is a fifty-two-year-old Iranian woman with history of depression from about 17 years ago, suicidal attempt two years ago and ingestion a large amount of opium with the intention of suicide 2 months ago who was presented with disorientation and probably delirious state in the last interview.

Results: Eventually in comprehensive investigations, white matter hyperintensity and leukodystrophy was diagnosed and ultimately to determine the cause of these changes with gene study, whole Exon deletion of GFAP Gene and Late Onset Alexander disease was determined.

Discussion & Conclusion: Neurological-onset manifestation of Alexander disease specifically late onset form is the most common clinical picture of disease and was seen in about 90% of patients but

psychiatric symptoms are not well-known and psychiatric- onset disease was not described yet.

On the other hand, various Gene Mutation were described in Late Onset Alexander Disease, however large whole Exon deletion which was revealed in our patient is a novel mutation and significantly need to be declared. Here authors describe a late onset Alexander disease with psychiatric onset symptoms and novel large Exon deletion in GFAP Gene.

Keywords: Alexander disease, Late-onset, GFAP mutation, Psychiatric symptoms, Leukodystrophy

OP:16

A rare case of a first cousin couple carrier for Beta thalassemia and SMA

Fereydoon Abdolmaleki, MD, PhD [1,2, *], Arash Pooladi, MD, PhD [1,2], Esmail Rahimi, PhD [2], Nikou Darvishi, PhD [2], Shabbou Khodayari, BSc [2], Sara Khaledi, BSc [2]

1. Medical Genetics Department , Kurdistan University of Medical Sciences, Sanandaj, Iran.
2. MAAD Genetics Polyclinic & Lab., Sanandaj, Iran.

*Correspondent: f.abdolmaleki@gmail.com

Background and Objectives: Beta thalassemia is one of the most common inherited diseases in the world that is transmitted to children through carrier parents. Onset of the disease symptoms is from 6 months with pale, sleep disorders, weakness and lethargy, followed by complications such as changes in the patient's face, hepatosplenomegaly, growth disorders. These patients need regular blood transfusions.

Spinal muscular atrophy refers to a group of clinically and genetically heterogeneous disease that are one of the most common causes of death in childhood , transmitted to children through carrier parents. An important feature of the disease is the involvement and destruction of the cells of the anterior horn of the spinal cord, which causes progressive muscle weakness and eventually death. Based on the severity and age of the disease onset, it is divided into three types: type1, the most common and severe, type 2 and type 3.

Material and methods: A woman was referred to a genetic polyclinic at 10 weeks of pregnancy following the death of two of her offsprings, due to thalassemia major and paralysis, and one case of spontaneous abortion at 8th week.

The marriage is consanguineous (first degree cousin) and no similar family history was observed in the pedigree. Fatigue and weakness in both couple was seen and on examination, the woman suffered from paleness and palpitations. The CBC test of the couple showed decreased Hct, Hb, MCV, and MCH and increased HbA2. Based on the above medical evidence, peripheral blood samples were taken from the couple and DNA was extracted. For the genetic investigation, Beta thalassemia was assessed by direct sequencing and SMA was tested by MLPA.

Results: The results showed that both partners were carriers for beta-thalassemia and SMA diseases, each having a wild-type allele and a mutant allele.

Discussion & Conclusion: Studies show that this is the first reported case in the world. Due to the fact that both partners are autosomal recessive carriers for two diseases, in each pregnancy the probability of affected beta thalassemia major is 18.75%, the probability of affected SMA is 18.75% and the probability of developing both conditions is 6.25% and a total of 43.75%. The best way to prevent the occurrence of the above disorders is extensive social education in reducing consanguineous marriages as well as screening carrier parents and performing prenatal diagnosis before birth. With this risk, PGD is recommended. Studies show that this is the first case reported in the world. Given that couples are autosomal recessive carriers for two disorders, in each pregnancy the probability of beta thalassemia major is 18.75%, the probability of having SMA is 18.75% and the probability of both

conditions is 6.25% and in total 43.75% compared to 25% in ordinary autosomal recessive disorders.

The best way to prevent the occurrence of genetic disorders is widespread social education in the field of reducing consanguineous marriages, as well as screening of carrier parents and prenatal diagnosis before birth. In this case, especially in view of the very high risk for the genetic disorders, PGD is recommended. Also, relatives' screening tests are emphasized.

Keywords: Beta thalassemia, Spinal muscular atrophy, Consanguineous Marriage

OP:17

Presentation of a complicated case of α/β thalassemia Combined with Homozygous Form of Hemoglobin-D in an Iranian couple

Elika Esmaeilzadeh-Gharehdaghi[1,*], Leila Motaghi[1], Esmat Ghalkhani[1], Mohammad Taghi Akbari[1]

1. Department of Molecular Genetics, Tehran Medical Genetics Laboratory, Tehran, Iran
*Correspondent: elika. esmaeilzadeh@gmail.com

Background and Objectives: Beta thalassemia is caused by reduction or absence of β-globin chain synthesis due to several different mutations in *HBB* gene. HbD-Punjab and HbD-Los Angeles are identical hemoglobins in which glutamine replaces glutamic acid at position 121 in the β chain ($\alpha_2\beta_2^{121Glu\rightarrow Gln}$). Homozygous HbD can be confused with the compound heterozygous state for HbD and β^0-thalassemia. The two disorders can be differentiated based on the MCV, levels of HbA_2, and family studies. HbD-β^0-thal produces a low MCV and an elevated HbA_2, whereas both values are usually normal in HbDD disease. Numerous publications have shown co-inheritance of HbD and β-globin chain mutations in individuals who were not required to blood transfusion; Therefore according to the Iran national protocol of the prevention of the beta thalassemia, prenatal diagnosis is not required for combination of HbD and β-globin chain mutations except of HbD/HbS. Here we want to introduce a complicated couple from a consanguineous marriage with HbDD in the wife with elevated amount of HbA2 (4.5).

Material and methods: This couple was referred to the Tehran Medical Genetics Laboratory, Tehran, Iran. After genetic

counseling and drawing the pedigree blood sampling was done from the couple, two brothers and mother of the wife. Diagnosis of beta thalassemia variants and molecular study for common alpha deletions were performed by *HBB* gene sequencing and Gap-PCR respectively. SALSA MLPA (Multiplex ligation-dependent probe amplification) probmix p102-C1 was utilized to investigate deletion/duplication in *HBB* gene. Study for indirect segregation analysis was performed by using RFLP sites (Gγ/HindIII, 5'ψβ/HincII, 3'ψβ/HincII, β/HinfI, β/RSaI) in β-globin gene cluster.

Results: The β-globin gene variants for the wife and her husband were identified as being c.364G>C (HbD) in homozygous form and IVS-I-5(c.92+5G>C) in heterozygous form respectively. No deletion/duplication was found using MLPA test for the wife. Furthermore Gap-PCR revealed $-\alpha^{3.7}$ mutation in homozygous and heterozygous state for the wife and her husband respectively.

Discussion &Conclusion: In this family the expected specific β-globin gene mutation (β^0 or β^+) according to the hematological indices (augment of HbA2) was not identified for the wife. Indirect segregation analysis was not informative; therefore finally our observations conclude that prenatal diagnosis is required for the future fetuses of this couple according to the hematological indices. We suggested after performing an informative genetic counseling the future fetuses of this couple be examined for the paternal mutation.

Keywords: Homozygous form of HbD; augment of HbA2; α/β thalassemia

OP:18

Identification of two pathogenic variants in a family with mild and severe forms of developmental delay

Noriko Miyake[1], Shermineh Heydari[2], Masoud Garshasbi[2], Shinji Saitoh[3], Jafar Nasiri[4], Kohei Hamanaka[1], Atsushi Takata[1], Naomichi Matsumoto[1], Farnaz Hosseini Beheshti[4], Ahmad Reza Salehi Chaleshtori[2],*

1. Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan
2. Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, P.O. Box, 14115-331 Tehran, Iran
3. Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, Nagoya 467-8601, Japan
4. Department of Pediatric Neurology, Child Growth and Development Research Center & Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

*Correspondent: Arsalehch@gmail.com

Background and Objectives: Intellectual disability (ID) accounts for 1% of the general population, and it is caused by the interplay between the genetic and/or environmental factors. The genetic components responsible for the development of ID are highly heterogeneous, and the phenotype and severity of the disease vary in patients even if they have an identical pathological variant and/or belong to the same family. Herein, we report two male siblings with ID in an Iranian family.

Material and methods: First, we performed clinical examination of all patients and then employed methylation specific PCR to study methylation pattern and possible deletion mutation in the SNRPN locus. Subsequently, we recruited quad exome sequencing to unravel the possible genetic defects in the family. We also used Sanger sequencing and in-silico analysis to validate identified variants and evaluation of pathogenicity. Besides, the copy number variation (CNV) analysis was performed in both affected

individuals by the data obtained from whole-exome sequencing using XHMM. We also confirmed the variants of UBA3A and KCNQ3 genes based on the proportion of identity-by-descent (PI_HAT values) that occurred de novo.

Results: By means of the whole-exome sequencing method, elder brother affected by a moderate form of ID exhibited a de novo missense variant in the KCNQ3 gene, while another sibling afflicted with a severe form of the disease exhibited a de novo in-frame deletion in the UBE3A gene. Both variants have been previously ascribed to similar clinical phenotypes and validated through Sanger sequencing. Through CNV analysis, we did not characterize any pathogenic CNVs in both affected subjects. We also confirmed the variants of UBA3A and KCNQ3 genes based on the proportion of identity-by-descent (PI_HAT values) that occurred de novo. Through calculating PI-HAT we understand that patiant's parents are not cousins.

Discussion & Conclusion: We identified two distinct genetic causes in affected siblings in an Iranian family. The variants we identified can explain the clinical features in these patients. To the best of our knowledge, this is the first report of familial transmission of FBN2 due to the KCNQ3 mutations in the world. Our familial case with a KCNQ3 variant might develop the clinical spectrum of KCNQ3-related DD as its milder phenotype could be inherited. This study strengthens the fact that precise clinical and genetic evaluations in each family should be recommended to achieve reasonable conclusions. We also keep in mind that, in a culture like Iran, the paternity is an issue, which should be treated

with caution. The current report highlights the significance of the clinical evaluation and non-biased assessment of the genetic analysis.

Keywords: *KCNQ3, UBE3A,* Familial Benign Neonatal Seizure, Mutation, Iran

OP:19

Clinical and molecular genetic characterization of a Female patient with fragile X syndrome: A novel case with two expanded alleles

Nozari Ahoura[1*], Habibi Mahvash[2], Banitalebi Setareh[3], Karimzad Hagh Javad [4]

3. Medical Genetics laboratory, Shahrekord University of Medical Sciences, Shahrekord, Iran.
4. Sadra Medical Genetics Lab, Shahrekord, Iran.
5. Sadra Medical Genetics Lab, Shahrekord, Iran.
6. IVF centrum Heinsberger Höfe, Heinsberg, Germany.

*Correspondent: nozari.a@skums.ac.ir

Background and Objectives: Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment. Usually, males are more severely affected by this disorder than females. Most males and about half of females with fragile X syndrome have characteristic physical features that become more apparent with age. These features include a long and narrow face, large ears, a prominent jaw and forehead, unusually flexible fingers, flat feet. In males, although fertile, they have enlarged testicles (macroorchidism) after puberty, and carrier females are expected to show primary ovarian failure (POF).

Material and methods: A consanguineous family referred to medical genetics lab because of their family history of high incidence of mental retardation in their small village population. Their pedigree shows multiple affected in each generation with male to female ratio of 3:1. Considering their clinical evalution including physical features and almost all women with primary ovarian insufficiency, Fragile-X syndrome was suspected. Given that we don’t expect a female patient; it was requested to perform

the test for a mild mental retarded 65-year-old woman with narrow face, POF, and tremor ataxia symptoms. DNA extraction was performed from her peripheral blood, followed by *FMR1* gene CGG repeat-number expansion evaluation, using FRAXA Kit (**ArtinZist Company**) and analyzed by Gene Marker software.

Results: It was established that the patient has two expanded alleles; one full-mutated allele and one permutated allele with accurate size of 74-CGG repeat expansion.

Discussion & Conclusion: As so far as we know this is the first reported case worldwide, with two expanded alleles in *FMR1* gene in a female patient. In comparison with women harboring one expanded allele ,full mutation/or permutation, the physical characteristic of the woman with 155 height, a narrow face, POF, mild mental retardation, and apparent tremor ataxia. In this woman, similar to other male and female patients, fertility was not affected; so she has two daughters with apparent normal features, except with POF. In the next generation five grandchildren were born; two of them affected with Fragile-X syndrome (one girl and one boy). Considering the recent identification of this case in the family, it is necessary to examine the size of the expanded allele in different generations. In this small population, consanguineous marriage of Fragile-X affected/permutated male and female carriers is common. Therefore, the necessity to examine and screen their relatives is warranted.

Keywords: Fragile X syndrome, *FMR1* gene, Mental Retardation, Consanguineous marriage, Dynamic Mutation

OP:20

Molecular Characterizations of 130 patients with Neurofibromatosis type 1

Sepideh Behpouri[1] (M.Sc), Helia Ghasemi[2] (M.Sc), Tina Hoa Nguyen[3] (M.Sc), Shaghayegh Zarei[1] (M.Sc), Ebrahim Kiani[4] (M.Sc), Zohreh Sharifi[1](M.Sc), Mahdi Khodaverdi Nezhad[4] (M.Sc), Iman Samiei Mosleh[5], Fahimeh Baghbani-arani[6] (Ph.D.), Somayeh Kamali [7](M.Sc), Zahra Soleimani[8] (MD), Mahmood Tavallaie[4] (Ph.D.), Shirin Ghadami [4] (Ph.D.)*

1. Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
2. Department of Biology, Friedrich Alexander University of Erlangen-Nürnberg, Germany.
3. Department of Biochemistry and Molecular Biology, School of Medicine, LSU Health Sciences Center, New Orleans, LA, USA.
4. Human Genetics Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.
5. Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran
6. Department of Genetics & Biotechnology, School of Biological Science, Varamin-Pishva Branch, Islamic Azad University, Varamin, Iran.
7. Department of Cellular and Molecular Biology, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
8. Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.

*Correspondent: Sghadami2020@gmail.com

Background and Objectives: One of the common hereditary disorders characterized by multiple café au lait spots and neurofibromatosis masses is called Neurofibromatosis type 1. To date, various mutations have been reported in the NF1 gene which corresponds to Neurofibromatosis type 1. This study aims to gain a better insight into the most frequent types of NF1 gene mutations in the Iranian population.

Materials and Methods: In this cohort, the NF1 gene mutations were analyzed in 130 Iranian patients using Sanger sequencing, and MLPA techniques.

Results: We report 26 different mutations, including 9 novel point mutations and 2 large deletions. However, despite the same mutational pattern in unrelated cases, they were different in their clinical presentation.

Conclusion: Our study provides a common genetic profile to facilitate the pre-implantation genetic diagnosis (PGD) as yet the most valuable prophylactic method to prevent the birth of children with neurofibromatosis.

Keywords: Neurofibromatosis; NF1 gene, novel mutation, genotype-phenotype correlation, Neurofibromin structure

OP:21

Identification of two novel *UBE3A* mutations causing Angelman syndrome

M. Taghizadeh[1], S.R. Taheri[1], Y. Eshaghkhani[3], Z. Golchehre[3], P. Nourmohammadi[1], N. Noorpour[2], M. Sharafi[1], M. Jamshidifar[2], A. Keramatipour[2], M. Keramatipour[1,2,3*]

1. Watson Genetic Laboratory, North Kargar Street, Tehran, Iran
2. NGS Department, Pishgam Biotech Company, North Kargar Street, Tehran, Iran
3. Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

*Correspondent: keramatipour@sina.tums.ac.ir

Background and Objectives: The Angelman syndrome (AS) is neurodevelopmental disease associated with maternal disruption of the *UBE3A* gene and is mainly characterized by global developmental delay, sever mental retardation with absence of speech, seizures, dysmorphic facial features, and distinct behavioal profile.

Material and methods: In this study two pedigrees with two affected members with neurodevelopmental disease were investigated by Whole Exome Sequencing (WES). DNA was extracted from whole blood and library was prepared using Agilent V6 capturing system. WES was performed on Illumina HiSeq 4000 platform. GATK was used for variant calling. Classification of selected variants was done based on ACMG guideline for variant interpretation 2015.

Results: WES revealed that the probands have previously unreported heterozygous nonsense variant (c.2459T>G) and stop loss variant (c.2616_*6delGTAAAACAAA) in *UBE3A* gene, confirming the diagnosis of Angelman syndrome.

Discussion & Conclusion: This study emphasis the role of WES in the early diagnosis and better management for AS patient. Although rare, *UBE3A* mutation, represent a small fraction of AS patients without a genetic diagnosis. Testing for *UBE3A* mutations should be performed in those AS patients with a normal methylation pattern and no deletion in the *UBE3A* gene.

Keywords: Angelman syndrome, Whole Exome Sequencing, *UBE3A* Mutation

OP:22

The novel bi-allelic p.Asn197_Ser201del mutation causing profound biotinidase deficiency in an Iranian consanguineous family

Milad Gholami[1*], Shahram Torkamandi[2] and Reza Mirfakhraie[3]

1. Department of Biochemistry and Genetics, School of Medicine, Arak University of Medical Sciences, Arak, Iran.
2. Department of Medical Genetics and Immunology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran.
3. Department of Medical Genetics, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[*]Correspondent: mtu.q220@gmail.com

Background and Objectives: Biotinidase deficiency (BD) is an autosomal recessive inherited inborn error of biotin metabolism. Biotin is an essential water-soluble vitamin that acts as a coenzyme for several human carboxylases including pyruvate carboxylase, 3-methylcrotonyl-COA carboxylase, propionyl-COA carboxylase, and acetyl-COA carboxylase. Biotinidase deficiency is clinically heterogeneous and based on enzymatic activity, patients are divided into two categories, profound and partial form. The profound enzyme deficiency if left untreated can lead to a multisystem disorder manifesting ataxia, sensorineural hearing loss, developmental delay, vision problems, seizure, skin rash, alopecia, and candidiasis. BD is caused by pathogenic variants in the *BTD* gene.

Materials and Methods: One affected patient diagnosed with BD from the outpatient clinic and three unaffected subjects from a consanguineous Iranian family were registered in this study. The diagnosis was verified by assessing the enzyme activity in the serum. The PCR reaction was performed for the coding exons (exon

1-4) and the exon-intron boundaries of the *BTD* gene. The PCR products for genotyping were subjected to direct Sanger sequencing on an automated ABI PRISM 3130XL). The segregation analysis of the *BTD* mutation was performed in the family.

Results: The patient at the age of 7 months was diagnosed with biotinidase deficiency through biochemical studies (Lactate: 41.0, PCO2:37.0, PO2:30.7, BE: -1.4, biotinidase activity <10 percent). At the age of 8 years, the patient was referred with seizures, feeding difficulty, hearing loss, speaking problems, weak muscle tone (hypotonic), gaits, walking on toes, Gower sign, skin rash, mental retardation and a history of closure of Patent ductus arteriosus (PDA). A novel pathogenic variant in the *BTD* gene (in exon-4), c.528_542del15 (p.Asn197_Ser201del) was detected. The parents were heterozygote carriers for the deletion and did not manifest any symptom of the disease. This variant was computationally predicted to be located in the intolerant region by MetaDome, and be deleterious and, disease causing by Mutation Taster, PROVEAN, and CADD.

Discussion & Conclusion: We report a novel homozygous deletion mutation in the *BTD* gene in a patient with symptoms of profound BD. The pathogenicity of the identified mutation was confirmed by all family members' segregation analysis, computational modeling, and assessment of the conservation among different species. Moreover, due to the high rate of consanguineous marriages in Iran and probably the great prevalence of BD, we recommend molecular testing should be considered in the newborn metabolic screening to

identify neonates soon after birth to avoid serious permanent symptoms.

Keywords: Biotinidase deficiency, mutation, *BTD* gene, Iran.

OP:23

A novel variant in *C5ORF42* gene is associated with Joubert syndrome

Eskandar Taghizadeh[1*], Daryoush Rostami[2], Gordon A Ferns[3], Majid Ghayour-Mobarhan[4]

1. Department of Medical Genetics, Faculty of Medicine, Ahvaz University of Medical Sciences, Ahvaz, Iran
2. Department of Anesthesia, school of Paramedical Sciences, Zabol University of Medical Sciences, Zabol, Iran
3. Department of Medical Education, Brighton and Sussex Medical School, Falmer, Brighton, UK.
4. Metabolic Syndrome Research Centre, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

*Correspondent: taghizadeh941@mums.ac.ir

Background and Objectives: Joubert syndrome (JS) disease is a clinically and genetically heterogeneous disorder with mutations in more than 35 genes involved in its pathogenicity. Molecular genetic methods including next generation sequencing (NGS) and Sanger sequencing are effective techniques used for identifying rare genetic variants that have a strong effect on disease pathogenesis.

Material and methods: In this study, we tested a large pedigree with a history of several affected members with JS. At first the proband was sequenced by NGS technique then, confirmed by sanger sequencing method. After this, all available members of the pedigree were subjected to molecular analysis by sanger sequencing technique

Results: The results of this study showed a novel variant in the C5ORF42 gene c.3080A>T: p. D1027V leading to a substitution of a valine for aspartic acid (D1027V) and may be associated with JS. This variant was present in proband compatible with autosomal

recessive pattern. Also this variant was present in all parents (both father and mother) of affected individuals in a heterozygous state

Discussion & Conclusion: It seems that mutations in C5ORF42 gene are associated with JS. Approximately more than 40 variants in the C5ORF42 gene have been confirmed which are associated with JS features. The encoded protein by C5ORF42 gene is a transmembrane protein and expressed in several tissues such as brain which interacts with small ubiquitin-like modifier 1 (SUMO1) and p21-activating kinase 1 (PAK1). Therefore, it is an important protein for cell functions and it is likely that mutations in the C5ORF42 gene can disrupt the function of their encoded protein and leads to defective ciliogenesis and human ciliopathies However, the substantial mechanism requires further investigation

Keywords: Joubert syndrome, *C5ORF42* gene, whole exome sequencing

چکیده

پوسترها

Posters

Abstracts

P:01

Breast cancer-related lncRNAs SNHG12 and HAGLR might serve as subtype-specific non-invasive diagnostic biomarkers

Rasoul Abdollahzadeh[1], Abdollah Gravand[2], Yaser Mansoori[3], Sahereh Paknahad[1], Javad Tavakkoly- Bazzaz[1], Asaad Azarnezhad[4*], Keivan Majidzadeh-A[5*]

1. Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Genetics, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran
3. Department of Medical Genetics, Fasa University of Medical Sciences, Fasa, Iran
4. Liver and Digestive Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran
5. Genetics Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran

*Corrspondent: asad.azarnezhad@muk.ac.ir & azarnezhad@gmail.com

Background and Objectives: To improve breast cancer (BC) molecular classification, prognosis, and diagnosis, the expression status of SNHG12 and HAGLR lncRNAs in BC subtypes and their role as potential biomarkers were assessed.

Material and methods: The expression levels of selected lncRNAs were measured by qRT- PCR in 150 breast tumors and compared to corresponding tumor-adjacent normal (TAN), truly normal (TN) tissues, and plasma of participants.

Results: Significant upregulation of SNHG12 and HAGLR lncRNAs in tumor tissues compared to TAN and TN, as well as in TAN compared to TN was observed in all BC subtypes. Increased levels of SNHG12 were observed in TNBC patients with larger tumor sizes and positive status of lymph node metastasis (LNM+), while elevated expressions of HAGLR were associated with LNM+, advanced grades, and advanced stages in luminal B and A

subtypes. The negative associations were found for SNHG12 levels in TNBC and luminal A, as well as for HAGLR in HER2-enriched, luminal B, and A cases with the 3-year survival rates. Furthermore, we found noticeable subtype-dependent associations with reproductive factors. Interestingly, the receiver operating characteristic curve analysis highlighted the diagnostic importance of SNHG12 in TNBC subtype, and HAGLR as specific diagnostic biomarker in luminal A and B subtypes.

Discussion & Conclusion: Our results suggest a BC subtype-specific expression profile of SNHG12 and HAGLR, indicating the potential of these lncRNAs as useful diagnostic and prognostic biomarkers for breast cancer.

Keywords: Breast Cancer, Biomarker, Gene Expression, Molecular Subtype, SNHG12, HAGLR

P:02

Transcriptome mining revealed new association between diabetes and pancreatic cancer

Monireh Rezaei[1], Zinat Shams[2], Bahareh Sadat Rasouli[3], Katayoun Dadeh Amirfard[4], mohadeseh Soleymani sadrabadi[5], Salar bakhtiyari[6*]

1. Department of Medical Genetics, Faculty of Medical Science, Tarbiat Modares University, Tehran, Iran.
2. Department of Biological Science, Kharazmi University, Tehran, Iran.
3. Department of Medical Biotechnology, School of Allied Medicine, Iran University of Medical Science, Tehran, Iran.
4. Department of Microbiology, North Tehran Branch, Islamic Azad University, Tehran, Iran.
5. Department of Biology, Faculty of Science, Shahid Bahonar University of Kerman.
6. Department of Biochemistry, Faculty of Medical Sciences, Ilam University

*Correspondent: bakhtiyaribio@gmail.com

Background and Objectives: Diabetes is a global issue which has impressed the life of many people all over the world. This disorder which also called mother of all disease, possess high pathogenicity and results in emergence of many disorders. One of the known correlated diseases is pancreatic cancer which can be accompanied by diabetes.

Material and methods: In this study, in order to survey this relationship, we analyze in common genes of these disorders by bioinformatics tools. For this purpose, we screened 17 shared genes from microarray data downloaded from Gene Expression Omnibus (GEO) database. In addition, relationship between identified genes were constructed by STRING and DAVID tools.

Results: In this study, 17 in common genes were screened which has not been considered in diabetes and pancreatic cancer which can get more attention in clinical approaches and in vitro studies.

Discussion & Conclusion: Diabetes is background of several disorders which cancer can be one of them. There are not clear answers to detect this correlation but hyperinsulinemia, hyperglycemia, inflammation and increased oxidative stresses can be involved in this relationship. In order to identify the correlation mechanisms between pancreatic cancer and diabetes, we screened 17 in common genes via bioinformatics tools in this study. As a conclusion, in this study we have shed light into in common genes of diabetes and pancreatic cancer. Obviously we have reported some in common genes which has not been researched in vitro studies. In worth mentioning that every single gene can be nominated as a potential clinical target in clinical approaches.

Keywords: Diabetes, pancreatic cancer, bioinformatics

P:03

LncRNAs; New Potential Treatment Modulators in Cancers

Kambiz Banihashemi, MD, Ministry of Science Research and Technology, Allameh Tabataba'i University
Email: kambiz.banihashemi@atu.ac.ir

Background and Objectives: Long non-coding RNAs (LncRNAs) are a class of RNA molecules with the ability to regulate gene expression process and make a delicate controlled pathway for stem cells differentiation and maintenance. Inherently these molecules show the capacity to interact at genomics, transcriptomics and proteomics level to interfere with cell-type specific gene expression patterns and phenotypic characterizations and appear as effective modulators of cell fate determination.

Material and methods: It has been recognized that some lncRNAs indicate a direct implication in the pathogenesis of some important congenital or adult disorders like cancers. To get a conceptual framework on this, the literatures on LncRNAs network have been evaluated.

Results: Considering all these facts eventually annotate the presence of vast critical and complicated networks of molecular interactions through which cellular maintenance and homeostasis may happen and also could provide us an excellent opportunity to distinguish the exact mechanisms of cell repair the damage which may lead to new treatment options

Discussion & Conclusion: This paper explains some of the critical waypoints in cell differentiation in cancer, respecting to LncRNAs interfering and probable genetic interventions in future.

Keywords: Genetic Disease, LncRNAs, Cell Differentiation, Cancer

P:04

The importance of NIPT as a screening test: A case report

Afsaneh Bazgir, Department of Genetics, Fardis central laboratory, Alborz, Iran. Email: bazigar.afsaneh@gmail.com

Background and Objectives: A 43 year-old woman with an intermediate risk for first trimester screening, normal ultrasound, and normar nuchal translucency (NT) was referred to our center for further investigation.

Material and methods: At first, Non Invasive Prenatal Testing (NIPT) was done. The NIPT showed an extra region on chromosome 18. Therefore, for the exact diagnosis amniocentesis and (Comparative Genomic Hybridization) CGH array were done.

Results: The diagnostic amniocentesis test was performed for precise and definitive diagnosis, Examination of cultured fetal cells showed that chromosome markers were present in 40% of embryonic cells. So in the next step, CGH array was done which confirmed NIPT and partial trisomy 18 was diagnosed.

Discussion & Conclusion: In our study NIPT could help us in precise diagnosis, and the birth of an abnormal child was prevented. NIPT has received significant attention for the purposes of prenatal genetic testing in the past decade, NIPT is one of the screening tests with very high sensitivity and specificity during pregnancy and our result indicated that NIPT is an excellent screening method for intermadiate and high risk pregnancy, so nowdays, more attention has been paid to this test.

Keywords: Non-Invasive Prenatal Testing, CGH array, Karyotype

P:05

The impact of *Foxp3* expression and epigenetic alteration in pathogenesis of endometriosis

Samaneh Chegeni[1*], Maryam Shahhoseini[1], Fariba Ramezanali[2], Elham Amirchaghmaghi[3]

1. Department of Genetics, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran. Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran.
2. Department of Regenerative Biomedicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR,Tehran,Iran

*Corresponent: Samaneh.chegeni@yahoo.com

Background and Objectives: Endometriosis is a common disease in women of childbearing age that is characterized by the growth of endometrial tissue outside the uterine cavity. This disease is also an important cause of infertility. The pathogenesis of endometriosis has not been completely determined. However several studies suggest that the immune system alterations contribute in both initiation and progression of the endometriosis. Regulatory T cell (Treg), as a subtype of T lymphocytes, plays an important role in controlling and directing the immune system, as well as creating and maintaining immunological tolerance. Several studies showed that the number and function of regulatory T cells has changed in endometriosis and Treg is likely to be involved in the tolerance of ectopic endometrial tissues outside the uterine cavity. *FOXP3* (Forkhead Box P3), as a master transcription factor of regulatory T cells, is a protein involved in immune system responses. In this study, we aimed to know whether there is any change in gene expression and epigenetic profiles of *FOXP3* in endometriosis tissues of patient with endometriosis.

Materials and methods: In this case-control study, ectopic and eutopic endometrial samples were obtained through laparoscopic procedure from 20 women with endometriosis. As control group, endometrial tissue biopsies were collected by pipelle from 20 women without endometriosis. Six samples from each group were selected for epigenetic alteration study.

The relative mRNA expression of *FOXP3* was studied by use of quantitative-PCR technique. Chromatin Immunoprecipitation (ChIP) coupled with real-time PCR was used to monitor histone modifications (methylation/acetylation) on lysine 9 of histone 3 (H3K9me/ ac) and presence of MeCP2 in the promoter of *FOXP3* gene.

Results: The results indicated a significant decrease in the expression level of *FOXP3* gene in the ectopic and eutopic tissues of women with endometriosis compared to the control ones ($P<0.05$). In eutopic and ectopic tissues of endometriosis patients, a significant H3K9 hypo acetylation was detected in regulatory region of *FOXP3* gene compared to controls ($p<0.05$). In addition, a significant H3K9 hyper methylation was detected in promoter of *FOXP3* gene in eutopic tissues of endometriosis patients compared to control groups ($p < 0.05$). These epigenetic changes were aligned with *FOXP3* gene expression profile. In the eutopic and ectopic tissues of women with endometriosis, MeCP2 had a significant decrease compared to the control ones ($p < 0.05$) whose epigenetic alteration was not aligned with *FOXP3* expression changes.

Discussion & Conclusion: Our findings suggest that alteration in expression level of *FOXP3* gene may be involved in pathogenesis

of endometriosis beyond its role in Treg responses. In addition, it seems epigenetic alteration in lysine 9 of histone 3(H3K9me/ ac) in promoter of *FOXP*3 (but not MeCP2) can affect the expression of this gene.

Keywords: Endometriosis, *FOXP3*, Epigenetic

P:06

Evaluation of five novel STR markers linking to *PAH* gene applicable in phenylketonuria homozygosity mapping

Iman Samiei Mosleh[1], Shaghayegh Zarei[2], Mahmood Tavallaie[3], Shirin Ghadami[3*]

1. Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran
2. Department Of Cellular and Molecular Biology, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
3. Human Genetics Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.

*Correspondent: Sghadami2020@gmail.com

Background and Objectives: Defects in phenylalanine hydroxylase enzyme is the most common hereditary aberration of amino acid metabolism worldwide which is known as Phenylketonuria (PKU). Without early diagnosis and treatment, this disease might lead to severe intellectual disability. Therefore, extensive and up-to-date research is underway for easier and more accurate identification and treatment of this disease. Besides Sanger sequencing which is a common method for phenylalanine hydroxylase (*PAH*) mutation diagnosis, homozygous mapping can be considered as an accurate, fast, and cost-effective alternative method. This method is performed on appropriate STR markers inside or on the side of the target gene. In this study, we aimed to find a novel Multiplex-STR-based panel for homozygosity mapping, which might be applicable for PKU indirect diagnosis.

Materials and Methods: 100 unrelated healthy individuals were selected for haplotype analysis. Blood samples were collected. Five novel STR markers were selected using the UCSC genome browser (https://genome.ucsc.edu/) web site and SERV sequence software

(http://www.igs.cnrs-mrs.fr/SERV/). Then Genotyping was determined by the multiplex PCR method. Also, multiplex PCR data were evaluated using Gene Marker software V2.7.0. Finally, allele frequencies and observed heterozygosity rates were calculated using PowerStatV12.

Results: In total, 80 alleles were detected. Based on the results, all selected five STR markers in PAH loci showed a high percentage of heterozygosity, ranging from 56 % to 71 %, and met Hardy-Weinberg equilibrium in the Iranian population. The observed range of allele frequencies was from 0.5% to 58.5% for PAH-selected STR loci.

Discussion & Conclusion: Ultimately, the most important achievement of this study was to find 5 novel *PAH* flanking STR markers with high heterozygosity in the Iranian population. Accordingly, they can be considered as efficient markers to be used in indirect PKU diagnosis or homozygosity mapping, and also they might be applicable in PND and PGD methods.

P:07

Effects of Alantolactone on stemness genes expression in the breast cancer cell line (MDA-MB-231)

Shiva Gholizadeh-Ghaleh Aziz[1*], Mojgan kadkhodazadeh[2],

1. Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
2. Dr. Seyedhassani medical genetic center,Yazd. Iran.

[*]Correspondent: gholizadeh.sh@umsu.ac.ir & doctorgholizadeh@gmail.com

Background and Objectives: Breast cancer is the most common cancer and the second leading cause of death among women. 10 to 20 percent of breast cancer samples have a triple negative phenotype (such as the MDA-MB123 cell line). One of the most important signaling pathways in cancer cells is the STAT3 pathway, for unlimited expansion (Stemness), located upstream of all pathways associated with tumor proliferation. To reduce the side effects of conventional chemotherapy drugs, new herbal remedies such as alantolactone are used, which in this study, we evaluated the association between Stemness and EMT process in triple negative breast cancer cells treated with alantolactone whose target gene is STAT3.

Material and methods: In this study, MDA-MB-231 cell line was used as one of the negative triple breast cancer cell lines. MTT assay was used to evaluate cell viability and drug dose at three time points of 24, 48, and 72 hours and three doses of 1, 0.1, and 0.01 mM alantolactone were used to evaluate cellular behavior in proliferative. Then, real-time PCR was used to evaluate the expression of regular genes by cancerous cell proliferation, STAT3 NANOG and SOX-2. All tests were repeated three times and the results were analyzed with Prism 7 software.

Results: In this study, increasing the dose of alantolactone increased the rate of cell killing. Therefore, the three doses selected for cell culture research did not differ significantly from the control group in order to evaluate cellular behavior at desired times without significant lethality. Expression of SOX-2, STAT3 NANOG and Gene in the treated cells decreased with increasing dose of drug.

Discussion & Conclusion: Alantolactone through the STAT3 signaling pathway affects the expression of NANOG, and SOX2 genes, inhibiting the Stemness, and may potentially be used for therapeutic use in the improvement of cancer patients.

Keywords: Breast cancer, Stemness, alantolactone.

P:08

Investigation of cystic fibrosis corresponding mutations among Iranian population

Shirin Ghadami[1] (Ph.D)[1*], Shaghayegh Zarei[2] (MSc), Iman Samiei Mosleh[4] (MSc), Zahra Soleimani[3] (MD), Zahra Motezaker[5] (MSc), Mahdi Khodaverdi Nezhad[1] (MSc), Atoosa Amooshahi[2] (MSc), Zahra Ghamarchehreh[4] (MSc), Mahmood Tavallaie[1] (Ph.D), Soheila Khalilzade[6] (MD, Ph.D)

1. Human Genetics Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.
2. Department Of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
3. Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.
4. Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran
5. Department of Molecular and Cellular Biology, Faculty of Basic Sciences and Advanced Technologies in Biology, University of Science and Culture, Tehran, Iran
6. Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Disease, (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Correspondent: Sghadami2020@gmail.com

Background and Objectives: Cystic Fibrosis (CF) is one of the most life-threatening diseases during infancy which is caused by molecular defects in the *CFTR* gene. The *CFTR* gene is comprised of 27 large exons, and to date, various pathogenic mutations have been reported in this gene. This project aims to have a better insight into the frequency of CF causing mutations in the Iranian population comprising different ethnicities

Materials and Methods: 38 patients whose Sweat chloride test result was above 60 mmol/L and clinical symptoms were relevant to CF were included in this study. After collection of peripheral blood samples and DNA extraction, the corresponding mutations of

the *CFTR* gene were investigated using Sanger sequencing and MLPA methods.

Results: The highest frequency was observed for c.1521_1523delCTT, c.2988+1G>A, c.2051_2052delAAinsG mutations. No statistically significant correlation between mutations and clinical symptoms was observed and for the first time frequency of Deletion of exon 2 of the *CFTR* gene was reported to be 6.4% and the fourth top frequent mutation in the Iranian population.

Discussion & Conclusion: Our findings demonstrated a variety of mutations causing CF in the Iranian population. Some of the mutations, such as exon 2 deletion of the *CFTR* gene, were found to be among the top five frequent ones and were not included in the CF diagnosis panel previously used in Iranian genetic laboratories. Therefore, it is recommended to use Sanger sequencing and MLPA methods for the identification of *CFTR* mutations instead of just looking for the so-called CF common mutations in the Iranian population.

Keywords: Cystic Fibrosis, *CFTR*, Mutation,

P:09

Association of abortion and infertility with a balanced transmission of t (15; 1)(p11.2; p36.1) in an infertile man: A case study

Mohadeseh Khoshandam[1*], Naser kallhor[2], Leila naserpoor[3]

1. Qom, Department of Reproductive Biology, Academic Center for Education, Culture, and Research (ACECR),Qom branch, Iran,
2. Qom, Department of Mesenchymal Stem Cells, theAcademic Centre for Education, Culture and Research, Qom Branch, Qom, Iran, ,
3. Qom, Department of Reproductive Biology, Academic Center for Education, Culture, and Research (ACECR), Qom branch, Iran.

*Corresponent: mohi_khosh70@yahoo.com

Background and Objectives: Infertility affects about 15 per cent of couples are, almost 20-30% of male factorinfertility have been found. However, many aspects of male infertility are not well understood,and many cases of idiopathic male infertility are diagnosed. Cytogenetic analysis has becomeincreasingly important to describe a number of causes of infertility. Male infertility has beenreported to be associated with chromosomal aberrations, which usually include sex andautosomal chromosomes.

Materials and Methods: We report a 36-year-old man with 5 years of primary infertility and4 miscarriages at 8 weeks. Peripheral blood lymphocytes were obtained for karyotype and 39metaphases were studied by the standard trypsin GTG method. His wife is also normal in termsof karyotype testing.

Results: A seemingly unique reciprocal displacement t (15: 1) (p11.2; p36.1) was found tobe one of the causes of miscarriage. In this study, we reported a shift between chromosomes 1and 15 in an infertile man with 4 miscarriages in the first trimester.

Conclusion: Physical contact of unpaired autosomal material with sex chromosomes,leading to the spermatogenic arrest, may be a factor in infertility in men with autosomalabnormalities. therefore supports the link between chromosomal aberrations and maleinfertility and abortion. Genetic changes in infertile men should be performed before anyassisted reproductive procedure

Keywords: Infertility, Cytogenetic analysis, Balanced translocation

P:10

A case report of Whole Exome Sequencing with homozygous mutation c.140 G> T *ADA2* gene associated with VAIHS syndrome in an individual with a healthy phenotype

Mohadeseh Khoshandam (MSc)[1*], Naser kallhor (MSc)[2], Leila naserpoor (MSc)[3]

1. Department of Reproductive Biology, Academic Center for Education, Culture, and Research (ACECR), Qom branch, Iran.
2. Department of Mesenchymal Stem Cells, the Academic Centre for Education, Culture and Research, Qom Branch, Qom, Iran
3. Department of Reproductive Biology, Academic Center for Education, Culture, and Research (ACECR), Qom branch, Iran.

*Correspondent: mohi_khosh70@yahoo.com

Background and Objectives: Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome (VAIHS) is an autosomal recessive multisystem disorder with onset in childhood. The phenotype is highly variable, but most patients have features of a systemic vascular inflammatory disorder with skin ulceration and recurrent strokes affecting the small vessels of the brain resulting in neurologic dysfunction. Other features may include recurrent fever, elevated acute-phase proteins, and myalgias, lesions resembling polyarteritis nodosa, and/or lived racemose or reticularis with an inflammatory vasculitis on biopsy. Some patients may have renal and/or gastrointestinal involvement, hypertension, aneurysms, or ischemic necrosis of the digits. Some patients present with clinical immunodeficiency. The clinical features are highly pleiotropic, and patients can present with only some of these main features. The hematologic manifestations of the disorder may sometimes resemble Diamond-Blackfan anemia.

Material and methods: We performed Whole Exome Sequencing (WES) for a 24-year-old woman with 6 years of infertility. She was phenotypically healthy and had only a history of anemia, the couple had a normal karyotype. But his nephew suffered a stroke as a child. Symptoms of VAIHS syndrome can be recurrent bleeding strokes. Moreover, the three-generation pedigree exhibits several cases of infertility in both men and women. For recognizing the mutated gene, variants were analyzed by the autosomal recessive inheritance model.

Results: Eventually, by several filtering processes, a site mutation in *ADA*2 (NM_001282225) on chromosome 22q11. The c.140G> T mutation is identified as the most likely type of susceptibility to the disease, which is also identified in the WES nephew.

Discussion & Conclusion: *ADA*2 (Adenosine deaminase 2) this gene encodes a member of a subfamily of the adenosine deaminase protein family. The encoded protein is one of two adenosine deaminases found in humans, which regulate levels of the signaling molecule, adenosine. The encoded protein is secreted from monocytes undergoing differentiation and may regulate cell proliferation and differentiation. This gene may be responsible for some of the phenotypic features associated with the cat-eye syndrome. Mutations in this gene have been implicated in VAIHS Syndrome and Sneddon syndrome.

Keywords: VAIHS syndrome, WES, autosomal recessive

P:11

Genotype-phenotype correlation and description of two novel mutations in Iranian patients with Glycogen storage disease 1b (GSD1b)

Maryam Eghbali[1], Maryam Abiri[2], Saeed Talebi[2], Zahra Noroozi[3], Marjan Shakiba[4], Parastoo Rostami[5], Hosein Alimadadi[6], Mehri Najafi[6], Fatemeh Yazarlou[1], Ali Rabbani[5], Mohammad Hossein Modarressi[1*].

1. Department of Medical Genetics, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
2. Department of Medical Genetics and Molecular Biology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
3. Department of Molecular Medicine, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran.
4. Department of Pediatric Endocrinology and Metabolism, Mofid Children's Hospital, Shahid Beheshti University of medical sciences, Tehran, Iran.
5. Growth and Development Research Center, Department of Endocrinology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.
6. Department of Gastroenterology, Children's Medical Center, Tehran University of Medical Science, Tehran, Iran.

*Correspondent: Modaresi@tums.ac.ir

Background and Objectives: Glycogen storage disease (GSD) is a rare inborn error of the synthesis or degradation of glycogen metabolism. GSD1, the most common type of GSD, is categorized into GSD1a and GSD1b which are caused by the deficiency of glucose-6-phosphatase (*G6PC*) and glucose-6-phosphate transporter (*SLC37A4*), respectively. The high rates of consanguineous marriages in Iran provide a desirable context to facilitate the finding of homozygous pathogenic mutations. This study is designated to evaluate the clinical and genetic characteristics of patients with GSD1b to assess the possible genotype-phenotype correlation.

Material and Methods: Autozygosity mapping was performed on nineteen GSD suspected families to find the causative loci. The

mapping was done using two panels of short tandem repeat (STR) markers linked to the corresponding genes. The patients with autozygous haplotype block for the markers flanking the genes were selected for direct sequencing.

Results: Six patients showed autozygosity in the candidate markers for SLC37A4. Three causative variants were detected. The recurrent mutation of c.1042_1043delCT (p.Leu348Valfs*53) and a novel missense mutation of c.365G>A (p.G122E) in the homozygous state were identified in the *SLC37A4*. In silico analysis was performed to predict the pathogenicity of the variants. A novel whole *SLC37A4* gene deletion using long-range PCR and sequencing was confirmed as well. Severe and moderate neutropenia was observed in patients with frameshift and missense variants, respectively. The sibling with the whole gene deletion has shown both severe neutropenia and leukopenia.

Discussion and Conclusions: The results showed that the hematological findings may have an appropriate correlation with the genotype findings. However, for a definite genotype-phenotype correlation, specifically for the clinical and biochemical phenotype, further studies with larger sample size are needed.

Keywords: GSD1b, Autozygosity mapping, Novel variants, Genotype-phenotype correlation.

P:12

Investigation of the human transcriptional response to SARS-COV2 and A type Influenza using bioinformatics tools

Mozhgan Mondeali, Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Email: Mondealitums74@gmail.com

Background and Objectives: Coronavirus disease (COVID-19) caused by the new coronavirus, SARS-COV2, has now spread to the entire world as a highly contagious pandemic. This study aims to identify the shared and unique transcriptional signatures of samples infected with SARS-CoV-2 and A type Influenza samples by comparing the different expression profiles in these samples.

Material and Methods: Initially, The RNAseq data were downloaded from Gene Expression Omnibus dataset (GSE152418, GSE97672), including 17 SARS-CoV2 infected and 17 control samples and 32 A type Influenza infected and 32 mock samples Respectively . Differential Expressed Genes (DEGs) were analyzed by galaxy Tool software. Then, gene ontology (GO) analysis was performed using the online Database for Annotation, Visualization and Integration Discovery (DAVID) software. Finally, significant pathway analyses were implemented based on the information derived from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Results: a total of 8 common DEGs were identified between A type Influenza and SARS-CoV2 infected samples, including 3 up-regulated and 5 down-regulated genes. The GO analysis results of DEGs revealed that response to external stimulus, anatomical structure formation involved in morphogenesis, leukocyte

migration, cell motility and localization of cell were the most effective terms.

Discussion & Conclusion: Our data provide a perspective for understanding the Pathogenesis of SARS-COV2 and A type Influenza.

Keywords: SARS-CoV-2, A type Influenza, Gene expression

P:13

Expression analysis of *ALDH1A1* and *ALDH1A3* genes in oral squamous cell carcinoma patients

Fatemeh Karami [1⅄], Omid Ghasemi [2⅄], I. Salahshourifar [1], M. R. Noori Daloii[3*]

1. Department of Medical Genetics, Applied Biophotonics Research Center, Science and Research Branch, Islamic Azad University, Tehran, Islamic Republic of Iran
2. Department of Biology, School of Basic Science, Science and Research Branch, Islamic Azad University, Tehran, Islamic Republic of Iran
3. Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran

*Correspondent: Nooridaloii@sina.tums.ac.ir

⅄These authors contibuted equally in this work.

Background and Objectives: Oral squamous cell carcinoma (OSCC) is still one of the leading cancer related death, worldwide. Owing to the critical role of ALDH1 isoforms in the pathogenesis of cancers and controversies in previous reports, the present study was conducted to determine the expression of two challenging *ALDH1* isoforms in OSCC tissue samples.

Material and Methods: RNA was isolated from 30 OSCC and normal fresh tissues margins and then was converted to cDNA using Thermo Scientific™ Fermentas cDNA synthesis kit. Reverse Transcription Real time polymerase chain reaction (RT-Real time PCR) was performed on synthesized cDNA using primer pairs specific to *ALDH1A1* and *ALDH1A3* genes.

Results: The *ALDH1A1* mRNA expression was significantly higher in OSCC samples compared to normal margins (P-value= 0.001). *ALDH1A1* and *ALDH1A3* expression was significantly associated with alcohol drinking (P-value= 0.01) and smoking (P-value=0.008), respectively. There was no correlation among ALDH1A1 and *ALDH1A3* expressions and clinicopathological

features (p-value>0.05). Confirmation of the over-expression of *ALDH1A1* isoform in OSCC samples may indicate that it plays a critical role in the pathogenesis of OSCC. However, owing to the discrepant findings on the association of *ALDH1A1* expression with clinicopathological features, further studies are required to identify its role as driver or passenger carcinogenic alteration and its exact association with smoking.

Keywords: *ALDH1A1*, *ALDH1A3*, Gene expression, Oral squamous cell carcinoma

P:14

A Novel Pathogenic frameshift Mutation in *BLOC1S6* Gene Responsible for the fifth reported case of extremly rare autosomal reccesive Hermansky-pudlak syndrome 9

Ahoura Nozari[1*], Roya Choupani Dastegerdi[2], Anahita Farahzad Broujeni[3], Ghobad Mashayekhi[4] , Mahvash Habibi[5], Setareh Banitalebi[6]

1. Medical Genetics laboratory, Shahrekord University of Medical Sciences, Shahrekord, Iran.
2. Department of Pediatrics, Shahrekord University of Medical Sciences, Shahrekord, Iran.
3. Shahrekord Neuroscience Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran.
4. Shahrekord University of Medical Sciences, Shahrekord, Iran.
5. Sadra Medical Genetics Lab, Shahrekord, Iran.
6. Sadra Medical Genetics Lab, Shahrekord, Iran.

*Correspondent: nozari.a@skums.ac.ir

Background and Objectives: Hermansky-Pudlak syndrome (HSP) is a multi-system disorder characterized by oculocutaneous albinism, bleeding diathesis and, in some cases, neutropenia, pulmonary fibrosis, or granulomatous colitis. HPS comprises nine known disorders (HPS-1 to HPS-9), the majority of which present with the same clinical phenotype to varying degrees of severity. Hermansky- Pudlak syndrome 9 (HPS- 9) is a recessive disorder caused by mutations in *BLOC1S6* gene. There are only four variants identified from four HPS- 9 patients so far.

Material and methods: An infant admitted to the NICU of Hajar Hospital in Shahrekord city due to refractory infections and moderatly elevated liver enzymes. Pediatrician considering the consanguineous marriage of the baby's parents, and also positive history of their expired previous infant, requested to perform Whole exome sequencing on her blood sample. Whole exome Sequencing

was performed using NovaSeq6000 platform, library type: Sure Select V-7Post, and Coverage:100X.

Results: Several steps were taken to prioritize the entire set of high-quality variants in recessive manner. A pathogenic novel variant in *BLOC1S6* (NM_012388.4:c.491dupT:p.Leu164PhefsTer33) gene was identified. After clinical evaluations and genotype-phenotype correlations by her medical team, we confirmed and segregated the variant in parents and the patient.

Discussion & Conclusion: According to OMIM database *BLOC1S6* is responsible for Hermansky-pudlak syndrome 9 (#614171). It is an extremely rare multisystem disorder characterized by tyrosinase-positive oculocutaneous albinism; a bleeding diathesis resulting from a platelet storage pool deficiency; and, in some cases, pulmonary fibrosis, granulomatous colitis, or immunodeficiency. Our patient shows oculocutaneous albinism (with optic atrophy), immunodeficiency, and general hypotonia. It is the first identified case of Hermansky-pudlak syndrome 9 in Iran, and given the identification of a less than five patients worldwide due to mutations in this gene, it is necessary to provide accurate clinical information for these patients.

Keywords: Hermansky- Pudlak syndrome 9, *BLOC1S6* gene, immunodeficiency, oculocutaneous albinism, Whole Exome Sequencing

P:15

A novel pathogenic missense mutation in *FBN1* gene responsible for autosomal dominant Weill-Marchesani syndrome with complete penetrance and large interfamilial clinical expressivity

Ahoura Nozari[1*], Anahita Farahzad Broujeni[2] , Mahvash Habibi[3], Setareh Banitalebi[4]

1. Medical Genetics laboratory, Shahrekord University of Medical Sciences, Shahrekord, Iran.
2. Shahrekord Neuroscience Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran.
3. Sadra Medical Genetics Lab, Shahrekord, Iran.
4. Sadra Medical Genetics Lab, Shahrekord, Iran.

*Correspondent: nozari.a@skums.ac.ir

Background and Objectives: Weill-Marchesani syndrome (WMS) is an autosomal dominant rare condition with variable expressivity characterized by short stature, brachydactyly, joint stiffness, congenital heart defects, and characteristic eye abnormalities including microspherophakia, ectopia of the lens, severe myopia, and glaucoma.

Material and methods: A consanguineous family referred to medical genetics lab because of their 6 years old girl affected with mild intellectual disability. They also complained of bilateral deformities of hands and feet fingers expected to be dominantly inherited in at least 8 affected cases in their family. After accurate medical examination by her physician and normal karyotype result for the girl, Whole exome Sequencing was performed for her using NovaSeq6000 platform, library type: Sure Select V-7Post, and Coverage: 100X.

Results: Several steps were taken to prioritize the entire set of high-quality variants in both recessive and dominant situations. Although we couldn't find a pathogenic, likely pathogenic or VUS variant relevant to our medical records in homozygote variants, a likely pathogenic novel variant in *FBN1* (NM_000138:c.2066A>G:p.Glu689Gly) gene in *TGF*-β-binding protein-like domain was identified. We segregated the variant in the family (affected ones and obviously unaffected ones).

Discussion & Conclusion: According to OMIM database *FBN1* is responsible for 8 different kinds of autosomal dominant genetic conditions. The last one is Weill-Marchesani Syndrome (#608328), an extremely rare systemic connective tissue disorder with large interfamilial clinical expressivity. Medical specialist team assessed the family members and it was confirmed that the variant could explain mild Intellectual deficit in the girl. According to the literature Intellectual deficit has been reported in 13% of cases and is always mild. It is important to note that when evaluating the clinical symptoms of patients with mental retardation, all members of the family should have a thorough clinical examination.

Keywords: Weill-Marchesani syndrome, *FBN1* gene, Mild intellectual disability, Whole exome sequencing

P:16

Investigating the effect of transient silencing of the *WDR*81 gene on the exosomal level of the human Glioblastoma cell line, U-373 MG

Amin Tadayoni nia[1,2], Zahra Bazi[1,3], Ayyoob Khosravi[1,4], Morteza Oladnabi[1,2,5,6]*

1. Stem Cell Research Center, Golestan University of Medical Sciences, Gorgan, Iran
2. Department of Medical Genetics, Faculty of Advanced Medical Technologies, Golestan University of Medical Sciences, Gorgan, Iran
3. Department of Medical Biotechnology, Faculty of Advanced Medical Technologies, Golestan University of Medical Sciences, Gorgan, Iran
4. Department of Molecular Medicine, Faculty of Advanced Medical Technologies, Golestan University of Medical Sciences, Gorgan, Iran
5. Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran.
6. Gorgan Congenital Malformations Research Center, Golestan University of Medical Sciences, Gorgan, Iran

*Correspondent: Oladnabidozin@yahoo.com

Background and Objectives: Glioblastoma is the most common and invasive brain tumor that affects 15 out of every 100,000 people over the age of seventy. Its common treatment protocol includes surgery and radiotherapy, with an average survival of only 2.5 months increases. Glioblastoma has a poor prognosis and leads to death 14 months after initial diagnosis. Recent functional studies have shown that the *WDR*81 gene (a protein containing WD40 repetitive domains) is expressed in most cancerous tissues. Especially glioma goes up. It is mainly involved in the transport of vesicles and inhibition of autophagy. Studies show that decreased autophagy is associated with increased production of exosomes, which is a major factor in the pathogenesis of glioma cancer. The *WDR*81 gene appears to play an important role in increasing the production of exosomes through the inhibition of BECN1 (Beclin

1), which is a key component of autophagy in glioma cancer. In this study, we tried to inhibit the *WDR*81 gene by siRNA Specific to this gene, to evaluate the effect of gene silencing on the release of exosomes in the U373-MG cell line.

Material and methods: We first cultured the U373-MG cell line. In order to investigate the entry of siRNA into the cell, FITC-conjugated control siRNA was used. The expression of *WDR*81 gene expression in cells was then silenced with specific siRNA. Total RNA was extracted and after cDNA synthesis, the expression level of *WDR*81 gene was measured by Real Time qRT-PCR in two groups of control and treatment (transfected). Cell survival was assessed by MTT assay. Exosomes were extracted from control and treatment cells using exosome extraction kit and then the accuracy of the exosomes was confirmed by DLS. Then, in order to measure the total amount of exosomes, exosome's Total RNA and protein of both control and the treatment groups were extracted and the proteins were compared using BCA method.

Results: Results of qRT-Real Time PCR showed that the specific siRNA of *WDR*81 gene reduces the expression of the gene in a time and dose dependent manner and 24 hours after transfection, the *WDR*81 gene was inactivated by 82%. Also, cell transfection with control siRNA conjugated to FITC had no effect on gene expression compared to the control group.

Discussion & Conclusion: Our findings suggest that the *WDR*81 gene may play a role in inhibiting autophagy through PI3KinaseIII.

Keywords: *WDR*81, U373-MG, Exosome

P:17

Genetic knowledge: First priority of healthcare offices staffs

Binaafar S.[1], Rashidi-Nezhad A.[2*], Mahdieh N.[1*]

1. Cardiogenetic Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.
2. Maternal, Fetal and Neonatal Research Center, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

*Correspondent: arashidinezhad@sina.tums.ac.ir & nmahdieh@gmail.com

Background and Objectives: Attempts to advances in the molecular genetic technology, created wisdom profits. Also, it had been continued to the growing demand for genetic diagnosis and/ or predicting services. This powerful era was accompanied with Genetic Counseling (GC.) Services development. Fortunately, these services are provided in our country, Iran.

Material and methods: Today, we encounter with many healthcare offices establishment to support GC. Services, with growing interest in employing Social Assistants and Midwifes to support their clients. At the first view, it seems as a helpful supporting arm for GC. Clinical and Practical team, particularly in special cases. Please wait, there is a big challenge. Knowledge.

Results: Knowledge is a cornerstone of this critical plan and effective GC. Services provider, sufficient and updated knowledge is required for accurate information transfer and on-time taking up genomic testing services (screening/ diagnostic), particularly in unexpected cases such as Down Syndrome screening during pregnancy for young couples. “No need to screen young couples for Down Syndrome just because they are young “, this is a simple sample of incorrect and misleading tips that we encountered

in our clients, a young healthy couple with a Down Syndrome affected infant, whom did not get screened during pregnancy on the advice of their midwife. This is so harmful.

Genetic counseling (GC.) is a complex, sophisticated, deeply precise Clinical and Practical (C.P.) service. The GC. Service is a collection of different issues, concerns and needs. This complex nature, particularly in complicated condition, requires professional members in different majors, in better word, GC. Services needs a Genetic Counseling, Clinical and Practical (GC. C.P.) team with professional informed members that is the first step of effective medical intervention in precision health. It seems that improving the knowledge of occupational groups such as midwives and social workers, who active in this field of health services should be one of our priorities.

Discussion & Conclusion: Genetic counseling (GC.) is a complex, sophisticated, deeply precise Clinical and Practical (C.P.) service. The GC. Service is a collection of different issues, concerns and needs. This complex nature, particularly in complicated condition, requires professional members in different majors, in better word, GC. Services needs a Genetic Counseling, Clinical and Practical (GC. C.P.) team with professional informed members that is the first step of effective medical intervention in precision health. It seems that improving the knowledge of occupational groups such as midwives and social workers, who active in this field of health services should be one of our priorities.

Keywords: Genetic Counseling, Clinical service, Practical service

P:18

Study of *DOK4, LTF, ELF5* genes expression and promoter methylation in sporadic breast cancer

Azar Heidarizadi (Ph.D)[1,2], Mahdieh Salimi (Ph.D.)[3*], Hossein Mozdarani (Ph.D.)[4]

1. Department of Genetics, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran
2. Department of Genetics, Fars Science and Research Branch, Islamic Azad University, Marvdasht, Iran
3. Department of Medical Genetics, Institute of Medical Biotechnology, National Institute of Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran.
4. Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

*Correspondent: Salimi@nigeb.ac.ir

Background and Objectives: Breast cancer is a complex disease due to several genetic and epigenetic changes. The *ELF5* gene plays a key role in breast cancer malignancy, especially in basal-like and resistant forms of endocrine disruption. *DOK4*, as an inhibitor of tyrosine kinase, promotes cell proliferation and differentiation. The *LTF* gene is involved in the migration and resistant forms of breast cancer. In the present study, the *ELF5*, *DOK4*, and *LTF* genes were examined from two aspects of promoter methylation status and expression in tissue and plasma.

Materials and Methods: To evaluate promoter methylation, 67 tumor tissues, 67 adjacent tumor tissues, 67 tumor plasmids, 30 normal plasma and 10 normal tissues were analyzed using MS - PCR. To evaluate the gene expression of 67 tumor tissues, 67 adjacent tumor tissues and 30 normal tissues were analyzed by Real-Time PCR. Finally, *ELF5*, *DOK4*, and *LTF* were measured with ROC curve.

Discussion & Conclusion: The results showed that *ELF5*, *DOK4*, and *LTF* genes had a significant decrease in expression (P <0.05). The promoter methylation status of the studied genes was strongly methylated in the tissues and plasma of patients whereas in the plasma and tissues of the healthy subjects no methylation was observed. Also, there was a statistical significance with clinical characteristics of patients (P <0.05). The results of this study showed that methylation and expression of *ELF5*, *DOK4*, and *LTF* genes have the ability to differentiate and detect early breast cancer between normal and cancer groups. The sensitivity and specificity of these genes were obtained with P <0.05 and could potentially be suggested as biomarker candidates.

Keywords: *ELF5*, *DOK4*, *LTF*, Methylation, Breast cancer, Biomarker, ROC curve