پنجمین سمینار یک روزه ژنتیک پزشکی تشخیصی- تحقیقی

Medical Genetics

پنجمین سمینار یکروزه

ژنتیک پزشکی
تشخیصی-تحقیقی

Medical Genetics

WWW.Medical-Genetics-Seminar.ir

Email: Medical.Genetics.Seminar@gmail.com

تاریخ برگزاری
جمعه ۵ بهمن ماه ۱۳۹۷
Friday, January 25, 2019
(ساعت برگزاری سمینار: ۸ صبح الی ۱۹ عصر)

محل برگزاری
تهران، انتهای فاز ۳ شهرک اکباتان
بیمارستان فوق تخصصی صارم
(دسترسی از طریق خط ۴ مترو/ ایستگاه اکباتان)

هدف سمینار:
تبادل علمی و انتقال تجربیات عملی و کاربردی در حوزه تشخیصی ژنتیک پزشکی در ۴ حیطه، ۱- سیتوژنومیک ۲- ژنتیک مولکولی (کلاسیک و NGS) ۳-ژنتیک بالینی ۴- ویرایش‌ژنی و مداخلات ژنتیکی (CRISPR)، در قالب معرفی موردی و مطالعات و تجربیات گسترده‌تر

گروههای هدف:
۱- مسئولین فنی آزمایشگاه‌های تشخیصی ژنتیک پزشکی و اعضای هیئت علمی ژنتیک پزشکی
۲- پزشکان متخصص ژنتیک، کودکان، نورولوژیست‌ها، زنان و زایمان، پرینالوژیست‌ها، داخلی و غیره.
۳- دانشجویان / فارغ التحصیلان دکتری ژنتیک پزشکی و کارشناسان آزمایشگاه های ژنتیک پزشکی
۴- دانشجویان/ فارغ التحصیلان کارشناسی ارشد ژنتیک انسانی
۵- اعضای هیات علمی ژنتیک مولکولی وزارت علوم
۶- دانشجویان/ فارغ التحصیلان دکتری ژنتیک مولکولی وزارت علوم

ثبت نام آنلاین
از طریق وب‌سایت

مهلت ارسال خلاصه مقالات: ۲۰ دیماه ۱۳۹۷

هزینه ثبت نام: ۵۰هزار تومان
(با احتساب هزینه ناهار و پذیرایی)

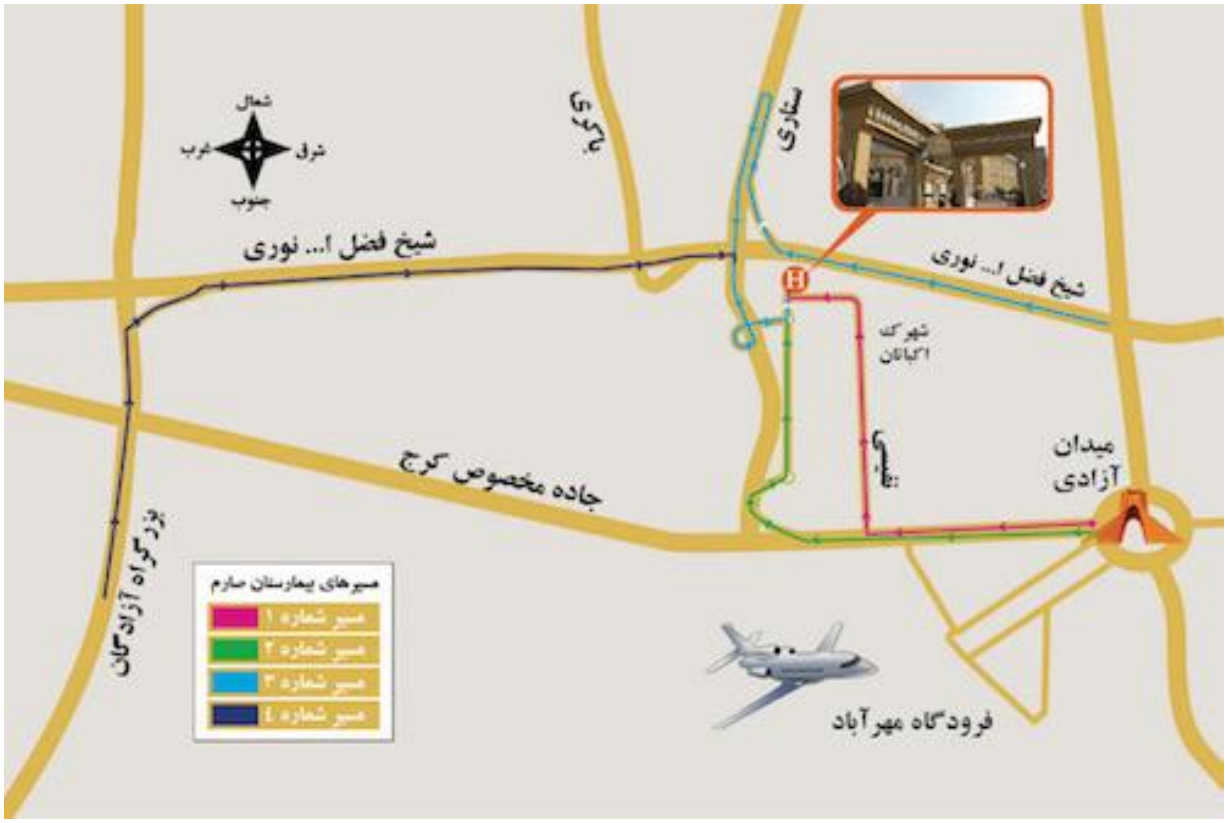
تلفن دبیرخانه:
۰۲۱-۴۷۰۲
داخلی ۲۴۸۵

برگزارکنندگان:
مرکز تحقیقات باروری و ناباروری صارم با همکاری
پژوهشکده سلولی-مولکولی و سلولهای بنیادی صارم و بیمارستان فوق تخصصی صارم

راههای دسترسی به محل برگزاری سمینار:

1 -اتومبیل شخصی: چهار مسیر با رنگ های مختلف روی نقشه نشان داده شده است.

2 – مترو: استفاده از ۴ متروی تهران به سمت ارم سبز و خارج شدن از مترو در ایستگاه اکباتان



سازمان سمینار

رئیس سمینار: دکتر ابوطالب صارمی
دبیران علمی سمینار: دکتر فرخنده بهجتی، دکتر جواد کریم زاد حق
دبیران اجرایی سمینار: دکتر آرش پولادی، دکتر محمد سلیمی اصل

اعضای کمیته علمی

دکتر فرخنده بهجتی
دکتر جواد کریم زاد حق
دکتر آرش پولادی
دکتر محمد سلیمی

اعضای کمیته اجرایی

دکتر سعید دهخدایی	اقای یوسف شریف زاده
دکتر فرخنده بهجتی	فهیمه موسوی
دکتر جواد کرم زاد حق	رضا موسوی
دکتر آرش پولادی	میترا انصاری دزفولی
دکتر محمد سلیمی	دکتر حمیدرضا خدادادی
دکتر حمید قائدی	دکتر بهزاد داورنیا
رسول علیزاده	رویا باصر
مهناز تاجیک	مهسا رضایی
زهرا بهمن پور	ابوالحسن پادروند
کتایون فروزان فر	معصومه سلیمانی
مهشید فتاحی	کلثوم احمدی
سعید فرج زاده ولیلو	دکتر مجید خیراللهی
پریسا معینیان	نگار چگنی نژاد
سید خلیل رشیدی	نیما کاظمی
ساناز جمشیدی	نوشین دلفان
مصطفی کریمیان	لیلا امراهی
عاطفه دخانچي	

پنجمین سمینار یک روزه ژنتیک پزشکی تشخیصی- تحقیقی

برنامه پنجمین سمینار یک روزه ژنتیک پزشکی تشخیصی – تحقیقی

زمان: جمعه ۵ بهمن ۱۳۹۷/ مکان: بیمارستان فوق تخصصی صارم/ شهرک اکباتان/ تهران

تکمیل ثبت نام ها، پذیرایی چای و شیرینی و بازدید از انجمن ها	۷:۰۰ الي ۸:۰۰
افتتاح سمینار با تلاوت قرآن و پخش سرود جمهوری اسلامی ایران	۸:۰۰ الی ۸:۱۵
خوش آمد گویی دبیر علمی و اجرایی سمینار	۸:۱۵ الی ۸:۳۰

پنل سیتوژنومیك

دکتر فرخنده بهجتی، دکتر رکسانا کریمی نژاد، دکتر داود زارع عبداللهی، دکتر عباس شکوری و دکتر جواد کریم زاده حق

ردیف	سخنران		عنوان سخنرانی	زمان سخنرانی (با احتساب ۵ دقیقه بحث)	زمان بندی ارائه پنل
۱	فهیمه موسوی- دکتر فرخنده بهجتي	کارشناسی ارشد ژنتیک انسانی، مرکز تحقیقات باروري، ناباروري و سلولهای بنیادی بیمارستان فوق تخصصی صارم	A fetus with abnormal maternal serum screening test, increased nuchal translucency, and a mosaic isoXq/45, X karyotype	۱۰ دقیقه + ۵ دقیقه بحث	۸:۳۰ الی ۱۰:۴۵
۲	اکرم عبدی- دکتر فرخنده بهجتي	کارشناسی ارشد ژنتیک انسانی، مرکز تحقیقات باروري، ناباروري و سلولهای بنیادی بیمارستان فوق تخصصی صارم	Clinical and Cytogenetic characterization of two patients with Premature Ovarian Failure	۱۵ دقیقه + ۵ دقیقه بحث	
۳	دکتر رکسانا کریمی نژاد	PhD ژنتیک پزشکی، آزمایشگاه پاتولوژی و ژنتیک کریمی نژاد	Chromosomal microarray in prenatal diagnosis: Indications, clinical findings, and case reports	۲۰ دقیقه + ۵ دقیقه بحث	
٤	دکتر داود زارع-عبداللهی	PhD ژنتیک پزشکی، استادیار دانشگاه علوم بهزیستی و توانبخشی	Report of a Nager Acrofacial Dysostosis with a de novo Multi-exonic New Copy Number Variant	۲۰ دقیقه + ۵ دقیقه بحث	
۵	دکتر جواد کریم زاد حق	PhD ژنتیک پزشکی، مرکز تحقیقات باروري، ناباروري و سلولهای بنیادی بیمارستان فوق تخصصی صارم و آزمایشگاه پاتوبیولوژی و ژنتیک پارسه	Detection of X-Ring Chromosome in a prenatal case: A comprehensive Study from QF PCR to NGS	۱۵ دقیقه + ۵ دقیقه بحث	

٦	طرلان نایب باقر	مرکز تحقیقات هماتولوژی، انکولوژی و پیوند سلول های بنیادی	Common Chromosomal Abnormalities in Gastric Cancer Cell lines and Ascetic Fluids of metastatic gastric cancer patients	۱۰ دقیقه + ۵ دقیقه بحث	
۷	دکتر سحر مقبلی نژاد	دپارتمان ژنتیك پزشكي دانشگاه علوم پزشكي قزوين	A case report of fetus with 46, X, del X (p11.2) karyotype	۱۰ دقیقه + ۵ دقیقه بحث	
		پذیرایی چای و شیرینی و بازدید از انجمن ها			۱۰:۴۵ الی۱۱:۱۵

پنل ژنتیک بالینی

دکتر آسیه جعفری، دکتر شهلا فرشیدی، دکتر سوسن اکبر اوغلی، دکتر میر مجید مصلائی و دکتر آرش پولادی

ردیف	سخنران		عنوان سخنرانی	زمان سخنرانی (با احتساب ۵ دقیقه بحث)	زمان بندی ارائه پنل
۱	دکتر سوسن اکبر اوغلی	بیمارستان کودکان مفید، دانشگاه علوم پزشكي شهيد بهشتی	Presentation of cases with developmental delay and dysmorphic features	۱۵ دقیقه + ۵ دقیقه بحث	۱۱:۱۵ الی ۱۳:۳۰
۲	دکتر اکبر محمدزاده	MD، ژنتيك PhD دانشجوي پزشكي، دانشگاه علوم بهزيستی و توانبخشی و مرکز تحقیقات باروری و ناباروري بيمارستان فوق تخصصي صارم	Investigation of Genomic Imbalance in some Iranian Patients with Multiple Congenital Anomalies by Karyotyping and MLPA	۱۵ دقیقه + ۵ دقیقه بحث	
۳	دکتر آرش پولادی	MD، PhD ژنتيك پزشكي مرکز تحقیقات باروري، ناباروري و سلولهای بنیادی بیمارستان فوق تخصصی صارم	How clinical signs and symptoms provide an effective final diagnosis: Lessons from two NGS-cases	۱۵ دقیقه + ۵ دقیقه بحث	
۴	دکتر آفاق علوی	PhD بیولوژی سلولي- مولكولي، استادیار مرکز تحقیقات ژنتیك دانشگاه علوم بهزیستی و توانبخشی	Genetics heterogeneity of Hereditary Spastic Paraplegia (HSP) is more than it appears	۱۵ دقیقه + ۵ دقیقه بحث	

۵	دکتر آسیه جعفری	متخصص پزشکی قانونی	پرسش و پاسخ	۳۰ دقیقه	
٦	دکتر عطا بوشهری	MD، دانشجوی PhD ژنتیک پزشکی، دانشگاه علوم بهزیستی و توانبخشی	Molecular Genetics to Revolutionize Inherited Disorders Diagnosis and Prognosis.	۱۵ دقیقه + ۵ دقیقه بحث	
نماز + ناهار + بازدید از انجمن ها				۱۳:۳۰ الی ۱۴:۳۰	
پنل ژنتیک مولکولی + NGS					
دکتر محمد کرامتی پور، دکتر حمید قائدی، دکتر محمد صابری و دکتر محمد سلیمی					
ردیف	سخنران		عنوان سخنرانی	زمان سخنرانی (با احتساب ۵ دقیقه بحث)	زمان بندی ارائه پنل
۱	دکتر محمد کرامتی پور	MD، PHD ژنتیك پزشكي، دانشیار، دانشگاه علوم پزشكي تهران	Lessons learned from implementing NGS in clinical genetic practice in Iran	۲۰ دقیقه + ۱۰ دقیقه بحث	۱۴:۳۰ الی ۱۷:۰۰
۲	دکتر محمد سلیمی	PhD ژنتیك پزشكي مركز تحقيقات باروري، ناباروري و سلولهای بنیادی بیمارستان فوق تخصصی صارم	WES detect a new heterozygous mutation in GUCY2C causing meconium ileus	۱۵ دقیقه + ۵ دقیقه بحث	
۳	دکتر محمد امین طباطبائی فر	PHD ژنتیك پزشكي، دانشیار، دانشگاه علوم پزشكي اصفهان	Next-generation sequencing in Deafness Diagnosis: A Multi-Center Experience	۱۵ دقیقه + ۵ دقیقه بحث	
٤	دکتر محمد صابری	دانشگاه علوم پزشکی تهران، دانشکده پزشکی، گروه ژنتیک پزشکی	Whole exome sequencing، راهکارهای افزایش بازدهی تشخیصی و چالش های پیش رو در آنالیز	۱۵ دقیقه + ۵ دقیقه بحث	

۵	دکتر احمدرضا صالحی	دپارتمان ژنتیک پزشکی، دانشکده پزشکی، دانشگاه تربیت مدرس	A Possible Novel Pathogenesis Scenario in CRD-6 Disease	۱۵ دقیقه + ۵ دقیقه بحث	
پذیرایی (چای و شیرینی) + بازدید از انجمن ها				۱۷:۰۰ الي ۱۷:۳۰	
تریبون انجمن ها					
۱	انجمن سندرم رت		۱۰ دقیقه	۱۷:۳۰ الی ۱۸:۰۰	
۲	انجمن ناشنوایی		۱۰ دقیقه		
۳	انجمن اوتیسم		۱۰ دقیقه		
بحث های صنفی و مشکلات جامعه ژنتیک پزشکی کشور					

A fetus with abnormal maternal serum screening test, increased nuchal translucency, and a mosaic isoXq/45,X karyotype

Fahime Mousavi[1], Iman Bagherizadeh[1], Dr Javad Karim Zad Hagh[1], Dr. Yousef Shafeghati[1,2], Dr. Farkhondeh Behjati[2,1]

1- Department of Medical Genetics and Sarem Cell Reaserch Center (SCRC), Sarem Womens'Hospital,Tehran, Iran
2- Genetics Research Center, University of Social Welfare and Rehabilitation Sciences,Tehran, Iran

Corresspondent: Dr. Farkhondeh Behjati, Department of Medical Genetics and Sarem Cell Reaserch Center (SCRC), Sarem Womens'Hospital,Tehran, Iran & Genetics Research Center, University of Social Welfare and Rehabilitation Sciences,Tehran, Iran.
E-Mail address: fbehjati@gmail.com & f_behjati@uswr.ac.ir

Background: Turner syndrome (TS) is characterized by short stature, gonadal dysgenesis, and anatomic malformations, including pterygium colli, congenital heart disease, renal anomalies, and cubitus valgus. Finding of different mosaic cell lines of Turner Syndromes in amniotic fluid culture has been rarely described. One of these mosaic cell line is Isochromosome X with the presence of a structurally abnormal X chromosome consisting of two long arms and 45, X cell line.

Objective: This report presents a fetus with abnormal maternal serum screening test and high Nuchal translucency referred for QF-PCR and karyotyping tests.

Material and methods: A 36 – year –old pregnant woman was referred for genetic counseling. Her gestational age was 15 weeks and 5 days and maternal biochemical serum screening test indicated high risk for Down Syndrome and presented high Nuchal translucency indication; 2.3 mm. She underwent amniocentesis for QF-PCR and chromosomal study using standard high resolution GTG banding technique.

Results: Karyotype result was 46,X,i(X)(q10)[93]/45,X[7] and QF-PCR result was Normal.

Discussion and Conclusion: Turner syndrome with 45,X karyotype has been observed in 1-2% of human conceptions, 10% of first trimester pregnancy losses and 1% of stillbirths. More than 99% of 45,X fetuses end with abortion, typically by the 28th week of gestation, which suggests that living 45,X individuals must have mosaicism for another cell line. This study indicates the role of chromosomal investigation in detecting structural abnormalities and mosaicism cell lines.

.

Keywords: Prenatal diagnosis, Tuner Syndrome, Isochromosome X, QF-PCR

Clinical and Cytogenetic characterization of two patients with Premature Ovarian Failure

Akram Abdi[1],Iman Bagherizadeh[1] ,Fatemeh Hadipour[1] ,Zahra.Hadipour[1],Yusef Shafaghati[1,2], Farkhondeh Behjati[1,2]

1-Sarem Cell Research Center & Department of Medical Genetics, Sarem Women's Hospital, Tehran, Iran

2- Genetics Research Center, University of Social Welfare and Rehabilitation Seiences, Tehran, Iran Correspondent: Dr. Farkhondeh Behjati: Genetics Research Center, University of Social Welfare and Rehabilitation Seiences, Tehran, Iran**.** Email Address : f_behjati@uswr.ac.ir & fbehjati@gmail.com

Background: Premature ovarian failure (POF) is identified as a heterogeneous disorder. It is defined by the association of amenorrhea, sex steroid deficiency and elevated (menopausal) levels of serum gonadotropins before the age of 40 years. Its incidence is estimated to be 1 in 100 by the age of 40, and 1 in 1000 by the age of 20 years. Chromosome abnormalities presented in 5-10% of POF patient. The abnormalities, in particular involving chromosome X with structural anomalies such as translocations with autosomes, isochromosomes and aneuploidies have been reported in patients with POF.

In addition to the genetic anomalies and chromatin structure of specific genome environment, autoimmune factors and toxins are reported as other important causes of the disease. The exact reason for POF development still remains unknown in many cases. In this study we report chromosomal abnormalities in two patients with Premature Ovarian Failure, referred to Sarem Women's hospital in Tehran in 2015-2016.

Patient and Methods: Chromosomal analysis was carried out on peripheral blood using standard Cytogenetics techniques. A minimum of 50 metaphase spreads were examined under the light microscope using high resolution GTG banding technique.

Results and Discussion: In this study chromosome structural anomalies were detected in a 16 year old female with 46,X,der(X**)** and a 26 year old female with 45,X,dic(X;22)(q22;p12) karyotypes, both associated with premature ovarian failure.

Conclusion: Cytogenetics investigation in patients with POF are of great value. Phenotype-genotype studies in these two patients is warranted.

Key words: Premature ovarian failure (POF), Chromosome abnormality,Chromosome X

A case report of fetus with 46, X, del X (p11.2) karyotype

[1,2]Moghbelinejad S, [1]Ansari J, [1]Momeni AM, [1]Khairkhah MR, [1]Ghobadi A

1. Khatam Pathobiology & Genetic lab.
2. Department of Medical Genetic, school of Medical science, Qazvin university of Medical Science.

Turner syndrome is a well-defined sex chromosomal disorder characterized by short stature, gonadal dysgenesis, and somatic stigmata, the majority of patients show monosomy of chromosome X (45, X), while a small number of patients present (45, X/47, XXX) karyotype. The present abstract report a rare case of Turner syndrome with a special karyotype of 46, X, del (X) (p11.2). A amnion sample of 18 week pregnant women with NIPT result 45,XO was referred to our lab for doing of confirmation tests. We did QF-PCR, FISH and Karyotype for detection of chromosome X monosomy. The QF-PCR result showed two X chromosome. We saw two green signal for X chromosome in FISH technique. But result of karyotype and chromosomes analysis showed 46, X, del X (p11.2). Given that the mentioned deletion includes SHOX gene, deletion of this gene involves in turner syndrome and other disease. On the other hand for the reason of limitation of QF-PCR, FISH for the detection of X (p11.2) deletion, in this cases we recommended doing of urgent array-CGH method.

Chromosomal microarray in prenatal diagnosis: Indications, clinical findings, and case reports

Roxana Kariminejad, Phd, Kariminejad Najmabadi pathology and genetics center, Tehran Iran

Traditionally chromosomal study of amniotic fluid cells and chorionic villi biopsy has been the method of choice for prenatal diagnosis of Cytogenomic aberration. In the past years, chromosomal microarray has and is replacing routine karyotyping. Prenatal diagnosis using this technique has its challenges, advantages and disadvantages. At present, there are still different approaches to dealing with chromosomal microarray in prenatal diagnosis. There are many who believe that all karyotypes should be replaced by chromosomal microarray. And still others who believe that the advantages of karyotyping cannot be overlooked and chromosomal microarray should not be used in all cases.

We will discuss the present guidelines and our experience. To elucidate the clinical significance of the technique we will present some case reports.

Report of a Nager Acrofacial Dysostosis with a *de novo* Multi-exonic New Copy Number Variant

Davood Zare-Abdollahi[1,2], Mir Majid Mossalaeie[2], Seyed Behrooz Mohseni Moghadam[2], Javad Karimzad Hagh[2]

1- Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.

2- Parseh Pathobiology and Genetics Laboratory

Background: Here we report on a pregnancy delivered preterm with craniofacial anomalies. At birth, severe micrognathia, submucous cleft palate and bilateral ear anomalies were observed. The baby died immediately after delivery, because of acute respiratory failure and with the clinical diagnosis of a type of acrofacial dysostoses.

Method and Results: After genetic counseling, given the genetic heterogeneity of acrofacial dysostoses, the large size of the known genes, whole exome sequencing (WES) was offered to the family but no pathogenic Single Nucleotide Variant (SNV) have been detected in 24 genes associated with syndromes characterized by mandibulo-facial anomalies. The next step of our envisaged strategy consisted of coverage assessment looking for Copy Number Variants (CNVs) for known genes. When compiling the corresponding data, we noticed low coverage sequence reads for exons 2 to 5 of SF3B4. We targeted the critical exons by PCR and Sanger sequencing and final decision was a heterozygous multi-exon deletion in SF3B4 as underlying cause of the disease, Nager syndrome (MIM 154400), according to ISCN 2016 designated as:

seq[GRCh37] rsa 1q21.2(SF3B4exons2-6)×1

chr1:g.(149926133_149927401)del

Conclusion: Nager syndrome is the prototype for a group of disorders collectively referred to as the acrofacial dysostoses, which are characterized by malformations of the craniofacial skeleton and the limbs. The major facial features of Nager syndrome include downslanted palpebral fissures, midface retrusion, and micrognathia.

The versatility of WES for large and rare CNV detection suggests its future usage as a potential comprehensive mutation detection assay in clinical and research labs, although detection of rare and intragenic CNVs from WES data is a challenge and need to be addressed. The present report expands SF3B4 pathogenic mutation repertoire in patients suffering from acrofacial dysostosis. We demonstrated that identification of rare heterozygote deletions in already known genes, are likely to be missed by routine WES approach, and should be taken into consideration in the context of families in which clinical presentation within the family was rather uniform and fully compatible with a clinical diagnosis.

Key words: Acrofacial dysostosis; Nager syndrome; SF3B4; Copy number variation; CNV; ISCN

Detection of X-Ring Chromosome in a prenatal case: A comprehensive Study from QF PCR to NGS

Javad Karimzad Hagh [1,2], Arash Poladi[1,6], Mohammad Salimi Asl[1,10], Sima Giti [1], Pasha Mosaed[1], Iman Bagerzadeh[1], Mohammad keramatipour[1,5], Eren Akdeniz [9], Dirk Biskup[8], Gamza Serim[9], Kai-J. Lüthgens[7], Hamed Abdi[1], Akram Abdi[1], Samira Rezai[1], Ensieh Ghadami[1], Mahbube Rojhannajad[1], Sanaz Samadpour[1], Sepideh Shohani[1,10], Saeed Farajzadeh Valilou[1], Farkhondeh Behjati[1,3]

1. Sarem Fertility & Infertility Research center (SAFIR) & Cell Research Center (SCRC), Sarem Women's Hospital, Tehran, Iran.
2. Parseh Pathobiology and Genetic Laboratory, Tehran-Iran.
3. Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.
4. Tehran-Lab Pathobiology and Medical Genetics Laboratory, Tehran, Iran.
5. Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
6. Department of Medical Genetics and Molecular Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran.
7. Labor Prof. Enders und Kollegen, MVZ, Rosenbergstr Stuttgart, Germany.
8. Cenata GmbH, Tübingen, Germany.
9. Genoks Genetics Diagnostic Center, Ankara, Turkey.
10. Tehran-Lab Pathobiology and Medical Genetics Laboratory, Tehran, Iran.

Background: X-ring chromosome arise following breakage and rejoining in both chromosome arms. Precise genotype-phenotype correlations for ring chromosomes may not be possible as influencing factors vary depending on the extent of deletion in ring formation, ring instability and the level of mosaicism. Turner Syndrome (TS) is the consequence of complete or partial absence of one X chromosome in a phenotypic female usually accompanied by short stature and gonadal dysgenesis. A constitutional karyotype of 45,X accounts for nearly 50% of TS patients, while X-mosaicism and other X-chromosomal structural abnormalities, including deletions, duplications, ring, isodicentric chromosomes, inversions and translocation, have been reported in *Turner syndrome variants*. Although ring chromosomes usually arise as *de novo* events, familial transmission of rings from carrier to offspring has been described and prenatal diagnosis for any pregnancies should always be considered.

The structural X-chromosome abnormalities are generally well tolerated because of the preferential inactivation of the abnormal X. This beneficial effect of X inactivation results in a mild phenotype in most patients with structural abnormalities of the X, similar to that found in TS patients with a 45,X karyotype.

Case report

We report a prenatal case which was referred because of an abnormal increased NT-value (NT=3,5mm). She, as a so-called "*surrogate Mother",* was a 28-year-old woman with an IVF-pregnancy. The donner embryo originated from an apparently normal biological mother (43yr) and father (45yr) with history of 9 unsuccessful IVF procedures. QF PCR results from amniotic cells indicated a structurally abnormal ring X-chromosome suspected to be a paternal-UPD. The karyotyping of cultured amniotic cells revealed a mosaicism with three cell line including a ring chromosome 46,r[28]/47,X,rx2[14]/45,X[8]. FISH analysis confirmed origination of the X-chromosome, which was a reconfirmation of the previously abnormal finding in QF-PCR results. Also FISH analysis revealed other very low mosaicism with less than 2% in interphase cells. The karyotyping of peripheral blood of biological mother shows a normal female constellation of 46,XX, indicating a *de novo* event. Later, according to cytogenetic results, the maternal uniparental disomy of X-chromosome (UPDXmat) could not be confirmed. Fetal anomaly scan at 18 weeks shows several anomalies including oligohydramnios, dolichocephaly, abnormal kidneys, pericardial effusion and mild alignment. Contrary to our expectations, the result of echocardiography was normal. Non-invasive prenatal testing was performed using two well-known brands of the market, Harmony (Cenata GmbH/Roche) and NIFTY (BGI) both reported Turner syndrome. However, the NGS-based fetal cell free DNA analysis with two fundamentally different methods (Harmony and BGI Companies) could not detect the existence of the X-ring chromosome. The both results identified a monosomy X-chromosome (XO) with different percentage of fetal fraction DNA. The induced termination was done. The Post-mortem exams showed a few additionally abnormalities in fetus such as hypoplastic nose, low-set ears, long philtrum, hypertelorism, micrognathia and narrow lips which missed in fetal anomaly scan. For more characterization of breakpoints in X-ring chromosome Array-CGH is highly recommend.

Key Words: Turner Syndrome Variants, X-Ring Chromosome, NT, IVF, Mosaicism, NIPT, NGS, NIFTY, Fetal Anomaly Scan, Echocardiography, Array CGH.

Common Chromosomal Abnormalities in Gastric Cancer Cell lines and Ascetic Fluids of metastatic gastric cancer patients

T Nayebbagher, M Yaghmaie, H Pashaiefar, K Alimoghaddam, M Jalili, M Esfandbood, M Saberian, H Behroozi, M Izadifard, A Ghavamzade

Hematology, oncology and stem cell transplantation research center, Tehran university of medical sciences, Tehran, Iran

Cell therapy and hematopoietic stem cell transplantation research center, Tehran university of medical sciences, Tehran, Iran

Hematologic management research center, Tehran university of medical sciences, Tehran, Iran

Background: Gastric cancer (GC) is one of the most prevalent cancers worldwide that is associated with poor survival rates and accounts for a considerable amount of cancer-related morbidity. Detection of specific and recurrent chromosomal abnormalities in GC not only is useful to identify specific genes involved in tumor progression but also these outcomes of GC patients. However, to date, no specific patterns of chromosomal abnormalities has been established in GC patients.

Methods: In order to identify chromosomal abnormalities specific to GC, we performed a conventional karyotyping on two established cell lines (AGS and MKN-45) as well as cancerous ascetic fluid of 9 gastric cancer patients. All numerical and structural chromosomal abnormalities were confirmed by fluorescence in situ hybridization (FISH) technique.

Results: Structural and numerical abnormalities were detected in all of 9 patients and GC cell lines. A total of 26 different types of numerical and structural chromosomal abnormalities in five main clusters, were identified in GC patients. The most frequent structural chromosomal rearrangements were: der(8)t(1;8)(q12;p23), add (17)(q25), del(2)(p16), der(7)t(6;7)(p?;q?)trp(7)(q31), del (17)(p13) and der(12)t(7;12)(q32;q15).Cytogenetic alterations clustering provided evidence for the presence of distinct cytogenetic subgroups. In contrast to structural abnormalities, gain or loss of a whole chromosome was infrequent, except for the loss of chromosome 18, which was detected in 6 patients and AGS cell line. Chromosomal abnormalities, are linked to the histological type, survival and further clinicopathological parameters of GC patients.

Conclusion: The non-random chromosomal abnormalities detected in GC patients and related cell lines, may serve as landmarks for the cloning of GC-causing genes and may suggest these cytogenetic abnormalities as a new diagnostic and prognostic markers.

Key words: Chromosome abnormality, Ascetic fluids, Gastric cancer, Cell lines, Malignant neoplasm of stomach Stage IV.

Presentation of cases with developmental delay and dysmorphic features

Susan Akbaroghli
Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences,Tehran, Iran.

Genetic counseling for dysmorphic patients has an important role in a tertiary referral pediatric hospital.

In Mofid Children's Hospital as one of major tertiary referral pediatric hospitals in Tehran, any day there are many dysmorphic patients with different problems admitting in different subspecialty wards and also there are many patients as the clients of the outpatient clinics who are dysmorphic and they need and seek genetic counseling. At recent years, there has been a clinical genetics clinic in Mofid Hospital.

The Clinical geneticist is asked to see children for the following reasons:

To give a diagnostic opinion, to help understand the etiology, to discuss the genetic aspects of the condition, to advise about the prognosis and suggest various therapeutic options, to discuss the risk of recurrence in another pregnancy, to discuss if prenatal testing is available.

The Consultation starts with a referral or a request for a ward or out- patient visit: use of the given information, asking for hospital notes & X-rays, contact with the patient's family, taking child's history & family history, observation, family photographs, physical examination.

The structure of the consultation includes: introduction, observation, history, physical Examination, further investigations, conclusions (e.g. genetic risk), correspondence and follow up.

Central to the practice of clinical genetics is making an accurate diagnosis.

In this article there are some dysmorphic patients with accurate clinical diagnoses approved by genetic testing:

1. A one year old girl with developmental delay, Growth delay and dysmorphic features especially abnormal ears.
2. A five years old girl with developmental delay, weakness, generalized edema, special facies and other dysmorphic features.
3. A ten years old boy with mental retardation, recent convulsion and Prader-Willi Phenotype.
4. A six months old girl with developmental delay and multiple anomaly and special facies compatible with a genetic syndrome.
5. A 5.5 years old boy with developmental delay and abnormal facies compatible with Chromosomal abnormalities.
6. A five months old boy with overgrowth Syndrome
7. A 7 years old boy with convulsion and developmental delay

Investigation of Genomic Imbalance in some Iranian Patients with Multiple Congenital Anomalies by Karyotyping and MLPA

Akbar Mohammadzadeh, M.D.[1], Susan Akbaroghli, M.D.[2, 3], Ehsan Aghaei-Moghadam, M.D.[4], Nejat Mahdieh, Ph.D.[5], Reza Shervin Badv, M.D.[4], Payman Jamali, M.D.[6], Roxana Kariminejad, Ph.D.[7], Zahra Chavoshzadeh, M.D.[8, 9], Saghar Ghasemi Firouzabadi, Ph.D.[1], Roxana Mansour Ghanaie, M.D.[9], Ahoura Nozari, Ph.D.[1], Sussan Banihashemi, B.Sc.[1], Fatemeh Hadipour, M.D.[10, 11], Zahra Hadipour, M.D.[10, 11], Ariana Kariminejad, M.D.[7], Hossein Najmabadi, Ph.D.[1, 7], Yousef Shafeghati, M.D. [10, 11,1], Farkhondeh Behjati, Ph.D.[1, 10, 11*]

1. Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
2. Pediatric Neurology Research Center, Mofid Children's Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Clinical Genetics Division, Mofid Children's Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran
5. Cardiogenetic Research Laboratory, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
6. Genetic Counseling Center, Shahroud Welfare Organization, Shahroud, Iran
7. Kariminejad-Najmabadi Pathology and Genetics Center, Tehran, Iran
8. Department of Immunology and Allergy, Mofid Children's Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
9. Pediatric Infections Research Center, Research Institute for Children's Health, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
10. Sarem Fertility and Infertility Research Center (SAFIR), Sarem Women's Hospital, Tehran, Iran
11. Sarem Cell Research Center (SCRC), Sarem Women's Hospital, Tehran, Iran

*__Corresponding Address__: P.O.Box: 1985713871, Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Daneshjoo Blvd, Koodakyar St, Evin, Tehran, Iran

Email: f_behjati@uswr.ac.ir

The incidence of multiple congenital abnormalities is reported one percent. Patients with multiple congenital abnormalities are associated with high mortality rate, creating great concerns for their parents and societies. Genetic factors account for 20 percent of cases and Chromosomal abnormalities and copy number variations are responsible for 15 percent of cases. There is no obvious etiology for about 80% of cases. For this reason we used Karyotyping, MLPA to detect chromosomal imbalances, microdeletions, and microduplications in the patients. Clinical evaluation was carried out for fifty patients with multiple congenital anomalies. A conventional cytogenetic investigation using GTG high-resolution banding technique was performed using standard procedures. Multiple ligation probe amplification (MLPA) technique was utilized for patients suspected of having microdeletion or microduplication syndromes using P245 Microdeletion Syndromes-1 and P311 congenital heart diseases kits. Three out of 50 patients showed chromosomal imbalances as follows:

1. 46,XY, der(18)[12]/46,XY, der(18), +mar[18] dn
2. 46,XY,der(4)t(4;12)(q33;q15) mat
3. 46,XY, del(3)(3p26.3p25.3)

Four out of 20 patients suspected of having microdeletion or microduplication syndromes had microdeletions of 22q11(DiGeorge syndrome), 16p13.3(Rubinstein-Taybi syndrome), 5q35.3(Sotos syndrome), and 7q11(Williams syndrome).The detection rate of chromosome abnormalities and microdeletions was 14 percent. Genotype-phenotype correlation in abnormal patients will be presented.

This study reiterates the importance of karyotyping and micredeletion/duplication investigations in patients with MCA.

Key words: Multiple Congenital Anomalies, Karyotyping, Chromosomal Abnormalities, Microdeletions, Microduplications, MLPA

How clinical signs and symptoms provide an effective final diagnosis: Lessons from two NGS-cases

Arash Pooladi, Mohammad Salimi Asl, Javad Karimzad Hagh, Yousef Shafeghati, Mahboobeh Rojhan Nejad, Hamed Abdi, Samira Rezaie, Sanaz Samadpour, Saeed Farajzadeh Valilou

Sarem Fertility & Infertility Research Center (SAFIR), and Sarem Cell Research Center (SCRC), Department of Medical Genetics, Sarem Women's Hospital, Tehran, Iran.

Background: Nowadays, genetic diagnosis of the rare and complex diseases are conducted using whole exome sequencing (WES) technique. Data analysis based on phenotype-genotype correlation is one of the most important steps in reaching a successful clinical diagnosis. Candidate pathogenic variants were found in about 40 to 60 percent of all candidate patients, whom WES was performed in the medical genetic centers.

Case Presentations: Herein, we present two complex cases that were remained unknown and undiagnosed for several years.

I. The first one was a 5 years old boy from a consanguineous marriage (first cousins parents) that referred for skin rash, poor-feeding and alopecia from the first 6 months of the life. One of the important conditions was the relative response to the Biotin supplement (that reduced the signs and symptoms of the patient). The Holocarboxylase synthetase deficiency was considered as a primary clinical diagnosis. Afterward, WES was performed. Nonetheless, the initial data analysis was unsuccessful in finding a candidate pathogenic variant. Further clinical investigation for new signs and symptoms revealed some changes in the patient's clinical presentations including xerodermia, photosensitivity and photophobia with reduced sweating (ectodermal specific involvement manifestations). The complementary clinical data led to the identification of two candidate variants in separate genes *PKP1* and *LAMC2*. Co-segregation analysis confirmed the pathogenic variant c.269G>A in *PKP1* gene that is known as causative for *ectodermal dysplasia/skin fragility syndrome* with an autosomal recessive pattern of inheritance.

II. The other case is a 3 years old boy that was referred for the neurodevelopmental delay (NDD), general hypotonia and strabismus. He was from a consanguineous marriage. The initial investigation of metabolic syndromes was normal. The first next generation sequencing (NGS) data analysis was failed to find candidate variants.

Later, further intensive clinical examination and follow-up study provided additional clinical features including stereotypic movements, lack of eye contact, teeth grinding and poor language in the patient, that guided us for the re-analysis of the NGS data. It is worth mentioning that primary brain MRI reported as a normal condition and in detailed brain MRI analysis, the mild atrophy and white matter enhancement was detected. Finally, the cooperation of a clinician, a radiologist and a medical geneticist led to the identification of a nonsynonymous VUS variant c.532G>A in ST3GAL5 gene that was present in the homozygous state and causative for *Rett Syndrome-Like Phenotypes* with an autosomal recessive pattern of inheritance. Co-segregation analysis was confirmed our findings.

Keywords: NGS, WES, phenotype-genotype correlation, ectodermal dysplasia/skin fragility syndrome, Rett Syndrome-Like Phenotype

Genetics heterogeneity of Hereditary Spastic Paraplegia (HSP) is more than it appears

Afagh Alavi[1], Mohammad Masoud Rahimi Bidgoli[1], Mohammad Rohani[2], Leila Javan Parast[1], Mahdieh Pashaei[1], Farzad Fatehi[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, Tehran University of Medical Sciences, Tehran, Iran.

E-mail: afaghalavi@gmail.com

Background: Hereditary spastic paraplegia (HSPs) is a group of inherited neurodegenerative disorders characterized by progressive spasticity and weakness in lower limbs. The mode of inheritance in HSP can be autosomal-dominant, autosomal-recessive, X-linked, or mitochondrial. There is significant genetic heterogeneity in HSP, with at least 65 genes and 80 loci identified thus far. Whole exome sequencing (WES) has been used for gene discovery in HSP since 2011, resulting in a marked increase in the rate of novel disease-causing genes being identified. Despite the use of WES, genetic analysis has failed in finding of causative genes in 45%-60% in the autosomal dominant-HSP (AD-HSP) and 71%-80% in the autosomal recessive-HSP (AR-HSP) groups, indicating that, the majority of HSP-genes especially AR-HSPs have remained unknown.

Materials and Methods: DNAs were isolated from peripheral blood leukocytes of 12 unrelated Iranian families affected to AR-HSP. Exome sequencing was done on probands. Preliminary filtering of sequence variations was done to identify all (nonsynonymous, stopgain, stoploss, deletion, insertion, and splice sites) homozygous changes present in the probands. Subsequently, variations with a MAF>0.01 in public databases (1000Genomes, ExAc, ESP, GnomAD, Iranome, HEX, SISu and GME-Variome) were removed to find the disease-causing variations. Candidate variants were PCR amplified and sequenced by Sanger method subsequently checked in family members in order to co-segregation analysis.

Results: This approach led us to identify the mutations in seven known disease-causing genes including *SPG7* (two cases), *CAPN1*, *CYP7B1*, *ENTPD1*, *GJC2*, *ERLIN2*, and *SPG11* (two cases) and three novel candidate HSP genes. Functional analyses to evaluate of the biological implication of the novel genes and the GAL4-UAS method for targeted gene expression in Drosophila are ongoing.

Discussion: Here, we could find nine variations in the known HSP-causing genes in 12 cases (75%) and three novel HSP genes in the remaining ones using WES method. The research presented the powers of exome sequencing for facilitating gene discovery, and identification of causative genes for diseases such as spastic paraplegia, wherein extensive genetic heterogeneity are observed.

Conclusions: The precise mechanisms underlying the HSPs are unknown and the rapid and affordable methods like next generation sequencing methods are useful for rapid acceleration of new genes discovery. Identification of novel genes and novel molecular pathways will greatly enhance our understanding of the cellular pathways that are critical for axonal health and our knowledge about pathogenesis of the disease.

Keywords: Hereditary spastic paraplegia, HSP, Whole exome sequencing, WES, Novel genes

Molecular Genetics to Revolutionize Inherited Disorders Diagnosis and Prognosis

Dr. Ata Bushehri[1,2], Davood Zare-Abdollahi[1,2], Mir Majid Mossalaeie[2], Seyed Behrooz Mohseni Moghadam[2], Javad Karimzad Hagh[2]

1- Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran.
2- Parseh Pathobiology and Genetics Laboratory

Medicine is fascinatingly changing. Innovatively, molecular genetics has fundamentally revised the concept of disease etiology and classification, and promisingly proposes novel therapeutic interventions.

Today, gene mutational analysis are giving much clearer answers on the etiology than clinical classification, in which genotype may specify or reverse previous diagnosis or assumed mode of inheritance. Advances in discovering effective disease managements are highly dependent on the identification of the genes and mutations involved, which must include both gene discovery and mutation screening in affected individuals and families.

Next Generation Sequencing with the application of targeted sequencing demonstrated to be effective in genotype detection in Europe and North America. However, different studies in Iran using disease panels were hardly successful. Apparently, Whole Exome Sequencing (WES) approach seems to be much more promising, due to the different ethnic background and probably to the involvement of novel genes.

The rapidity of the genetics revolution has left many physicians behind; even for those who might have been aware of molecular genetics and its possible impact, the field was often viewed as highly specialist and not necessarily relevant to everyday clinical practice.

Here, we present a 15 year old intellectually disabled patient with early severe vision loss, sluggish pupillary response and roving nystagmus accompanying motor and speech apraxia in favor of Leber congenital amaurosis (LCA), mistakenly labeled as prenatally teratogenized at the first place. After implementing extensive clinical examination with the diagnosis of retinal dystrophy (RD), mutational analysis was the reliable answer on specifying the disease. Due to the consanguinity of the parents and the history of congenital blindness in the extended family, suggesting recessive pattern of inheritance, also with regard to the tremendous genetic heterogeneity of RD, the family was approached through WES.

Having filtered the WES data against genes expressed in retina, a homozygous deleterious variant was identified in *RPGRIP1* which was a LCA associated gene. Clinical reassessment supported the diagnosis of LCA. Co-segregation analysis, furthermore, validated the variant as the causative mutation.

This study is intended to discuss the impact of molecular genetics on précising the diagnosis. In addition, WES is the most favorable and preferred method once approaching single gene disorders in Iranian families because of the distinctness of our genetic background in comparison to western countries, as well as the low yield of genetic testing of known pathogenic variants.

Lessons learned from implementing NGS in clinical genetic practice in Iran

Mohammad Keramaipour, MD, PhD
Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. Email: keramatipour@sina.tums.ac.ir

Next generation sequencing revolutionized genomic approaches in clinical practice. This was resulted by the possibility of sequencing large fraction or even entire human genome in a short time. Having such ability, makes NGS the choice technology to tackle many of issues related to human health. Therefore, we witness a sharp increase in using NGS in screening, diagnosis or even therapy of human diseases. This trend created lots of opportunities as well as many challenges to be addressed. In addition to general issues, implementing NGS in clinical practice in Iran, has its own benefits and concerns.

Over the last several years we performed several thousands of NGS experiments for clinical purposes. In addition to serving patients and families, this experience brought us many lessons that should be investigated, educated and even added to the routine code of practices for our health professionals.

One major issue that NGS revealed is the limitations or even errors of traditional techniques such as PCR-Sanger sequencing in detecting genomic variations. Without NGS probably we would never realize the extend of false results we obtained from traditional techniques.

Another valuable effect of NGS is the way it changed the connection between genetic laboratories, physicians and families, as well as the way pre-test and post-test counseling should be offered. Proper crosstalk in this triangle creates many opportunities for the benefit of patients and families, while mis-practicing may cause real damages.

Applying NGS for expanded carrier screening in several hundreds of individuals gave us huge data regarding the carrier frequencies of common hereditary diseases in our population. This knowledge is very important considering the high rate of inbreeding in our society.

Ethical, cultural, legal and educational issues surrounding implementing NGS in our clinical practice, are also among the important lessons that should be acknowledged properly.

In this talk, I intend to review some of these lessons by presenting challenging cases and pedigrees.

WES detect a new heterozygous mutation in GUCY2C Causing meconium ileus

Sepideh Shohani[1,2], Arash Pouladi[1,2], Seyed Maziyar Mortazavi[1,2], Samira Rezaei[1,2], Hamed Abdi[1,2], Mahbubeh Rojhannezhad [1,2], Mohammad Salimi Asl[1,2], Sanaz Samadpour[1,2], Javad Karimzad Hagh[1,2]

1- Department of Medical Genetics and Sarem Cell Research Center (SCRC), Sarem Women Hospital, Tehran, Iran

2- Sarem Fertility and Infertility Reaserch Center (SAFIR), Sarem Women Hospital, Tehran, Iran. E-Mail address: smgeneticslab@yahoo.com

Intestinal obstruction in the newborn due to guanylate cyclase 2C deficiency is an extremely rare, autosomal recessive, gastroenterological disorder reported in three families so far that is characterized by meconium ileus without any further stigmata of cystic fibrosis including pulmonary or pancreatic manifestations. Two of the reported patients developed chronic diarrhea in infancy. Homozygous mutations in the *GUCY2C* gene (12p12) leading to marked reduction or absence of enzymatic activity of guanylate cyclase 2C were found in the affected patients. The disease was reported to show partial penetrance. In contrast to MI, an autosomal dominant familial diarrhea syndrome has been reported in a Norwegian family due to a change in the GUCY2C gene. It started in infancy and was fairly constant over the years, but improved by middle age in some. To our knowledge only six pathogenic changes in the GUCY2C gene have been reported to date, including this current family. The 3140-g infant boy was born after high-risk pregnancy (Polyhydramnios), amnioreduction in 35w and cesarean delivery. At the age of 5 hours, he developed clinical signs of intestinal obstruction, with transabdominal sonographic findings consistent with Mel. The obstruction was treated successfully by surgery fallowed by gastrografin enema. The chronic diarrhea occurred after discharge. Fecal pancreatic elastase-1 and all sweat tests were normal and ruled out cystic fibrosis. WES detected one new heterozygous mutation in GUCY2C gene as a VUS genotype based on ACMG guideline. We are currently undergoing segregation analysis to confirm its pathogenesis, but absence of the other affected person in the family, confront interpretation with difficulty. This study is the first report of autosomal dominant meconium ileus cause by GUCY2C gene mutations.

Keywords: WES, meconium ileus, GUCY2C, diarrhea.

Next-generation sequencing in Deafness Diagnosis: A Multi-Center Experience

Mohammad Amin Tabatabaiefar[1,2], Mohammad Reza Pourreza[1], Mahboubeh Kouhiyan[1,3], Hamidreza Abtahi[4], Morteza Hashemzadeh-Chaleshtori[3,5]

1. Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2. Department of Genetics, Erythron Pathobiology and Genetics Lab, Isfahan, Iran
3. Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
4. Department of Otolaryngology, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
5. Department of Genetics, Milad Pathobiology Lab, Isfahan, Iran

Background: Hearing loss (HL) is the most common sensory-neural defect and the most heterogeneous trait in humans with the involvement of over 130 genes, which make molecular diagnosis problematic. Whole Exome Sequencing (WES) and Next-generation sequencing (NGS) panels are a new strategy that could overcome this problem.

Subjects and Methods: A comprehensive family history, clinical evaluations and pedigree analysis were performed in a series of families with multiple HL individuals referred to our centers. As first tier, *GJB2* was sequenced to rule out the most common cause of the disease. WES, NGS panels and complementary molecular genetic studies were used to unravel the molecular etiology of the disease in the probands. Pre-implantation genetic diagnosis (PGD) was accomplished via linkage analysis and direct sequencing of the pathogenic variants in a couple of families.

Results: Several known and novel homozygous pathogenic variants were determined in the studies families. Careful phenotypic examinations, proper filtration and co-segregation analysis before and after NGS could help illuminate the status of the identified variants.

In one family, for example, two homozygous variants, c.367G>A (p.Gly123Ser) and c.1392+1G>A, were identified in cis status. c.367G>A (p.Gly123Ser) met the criteria for being pathogenic, according to the ACMG variant interpretation guideline. PGD was successfully performed to prevent the recurrence of the disease in the related family.

Conclusion: We report several novel mutations and help get insight into the molecular profile of HL. We have shown the effectiveness of the combined application of phenotyping, NGS and PGD in diagnosis and prevention of hereditary HL.

Keywords: hearing loss, Iran, next-generation sequencing, preimplantation genetic diagnosis

Whole Exome Sequencing، راهکارهای افزایش بازدهی تشخیصی و چالش‌های پیش رو در آنالیز

محمد صابری[۱]، آرزو کرم زاده[۱]، یگانه اسحاق‌خانی[۱]، زهرا گلچهره[۱]، مصطفی اسدالهی[۱]، مریم شرفی[۲]، ریحانه بهداد[۳]، سعید طالبی[۴]، محمد کرامتی‌پور[۱]

۱- دانشگاه علوم پزشکی تهران، دانشکده پزشکی، گروه ژنتیک پزشکی

۲- دانشگاه آزاد اسلامی واحد پزشکی تهران

۳- دانشگاه آزاد اسلامی واحد پیشوا، ورامین

۴- دانشگاه علوم پزشکی ایران، دانشکده پزشکی، گروه ژنتیک پزشکی

هتروژنی لوکوسی موجود در بسیاری از بیماری‌های ژنتیکی به عنوان یک چالش بزرگ در تشخیص ژنتیکی مبتنی بر فنوتیپ می باشد. با این وجود نقش Whole Exome Sequencing (WES) به عنوان ابزاری قدرتمند برای تشخیص جهش‌های عامل بیماری و شناسایی ژن‌های جدید در چنین بیماری‌هایی به اثبات رسیده است. با این حال، وجود برخی مشکلات از قبیل عدم پوشش دهی مناسب، خوانش با عمق پایین، ژن های با همولوژی بالا و سودوژن‌ها و جهش‌های بزرگ، بازدهی این ابزار را تحت تاثیر قرار می‌دهند. این مطالعه سعی در ارائه راهکارهایی جهت مقابله با این چالش‌ها دارد. ضمناً سه مورد که در آنالیز دیتای WES با چالش های متعددی همراه بوده‌اند، ارائه می گردند. مورد اول دختری ۲ ساله و از والدین منسوب با علائم هپاتواسپلنومگالی، multiple congenital anomalies می باشد. واریانت عامل ایجاد فنوتیپ این بیمار در نواحی یافت گردید که به دلیل mapping quality پایین در فایل VCF گزارش نشده بود. مورد دوم، نمونه نوزادی فوت شده با multiple congenital anomalies و از والدین منسوب و با سابقه دو فرزند قبلی فوت شده با علائمی مشابه، مورد WES قرار گرفت. در این بررسی به دلیل وجود سودوژنی با همولوژی بالا واریانتی هموزیگوت به اشتباه هتروزیگوت گزارش گردید. مورد سوم مربوط به بیماری با تشخیص دیستروفی عضلانی می باشد که یک حذف هموزیگوت اگزونی در آنالیز مربوط به Copy Number Variations (CNV) برای ایشان یافت گردید. این حذف در چندین بیمار دیگر با علائمی مشابه نیز تکرار شده است. لذا مشخص می گردد این حذف از فراوانی نسبتا بالایی در جمعیت ایرانی برخوردار می باشد.

هدف از ارائه این موارد، تاکید بر اهمیت بازبینی دیتای خام و تغییر برخی متغیرها، تائید واریانت های یافت شده با روش های دیگر از جمله PCR-Sanger Sequencing و Quantitative PCR و قرار دادن CNV-Analysis در پروتوکل استاندارد آنالیز دیتای Next Generation Sequencing (NGS) می باشد. با بکار گیری این نکات می توان بازدهی تشخیصی (Diagnostic Yield) بر اساس WES را تا حد زیادی افزایش داد.

A Possible Novel Pathogenesis Scenario in CRD-6 Disease

Ahmad Reza Salehi Chaleshtori[1], Shermineh Heydari[1], Ali Salehi[2]

[1]Department of Medical Genetics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[2]Department of Ophthalmology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Cone-Rod Dystrophy (CRD) is a childhood retinal dystrophy represents extensive clinical and genetic heterogeneity. Molecular characterization of new CRD mutations mightily results in more accurate genetic counseling, preventive options, and hope for a possible successful gene therapy in the near future. Here we described a male sibling of early onset retinal dystrophy who born in a consanguineous population as part of a cohort with visual impairment in central Iran. To establish clinical diagnosis, we performed fundoscopy, slit lamp examination, ERG, and OCT scanning. Quad exome sequencing recruited to identify possible genetic defects and variants were validated by Sanger sequencing. Patient's fundus persists on CRD clinical diagnosis and we identified a novel deletion mutation in GUCY2D and a novel missense VUS BEST1 gene. Segregation studies revealed co-segregation of these variants in a double heterozygosity manner. In addition, the missense VUS of the BEST1 gene recognized in some healthy controls as same as these patients. These results confirmed that BEST1 variant might be a benign heterozygote variant while accumulation of clinical and molecular findings may suggest a possible GUCY2D-BEST1 double heterozygosity mechanism for pathogenesis of CRD-6 disease in this family. This scenario is a possibility and examination of this hypothesis with more sophisticated methods is highly recommended.

Keywords: Cone-Rod Dystrophy, GUCY2D, BEST1, Double Heterozygosity, Iran