My Journey in Genetics the last 50 years

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Johann Friedrich Miescher
Gregor Johann Mendel
Archibald Garrod
Victor A. McKusick
Dr. Jerome LeJeune 1959
Methymalonic Acidemia
Dysmorphology is a word coined by Dr. David W. Smith in 1966 to describe the study of human congenital defects.
Francis Collins
Dr. Pinar Ozand
Huntington Chorea
The Protein called Huntingtin
DNA segment CAG normal 10-35
CAG 40 or more develop the disease
Neurofibromatosis  Type 1
NFI- Protein Neurofibromin 17Q11.2
T2 FIESTA sequence shows symmetric masses in bilateral CP angle widening the adjacent porus acusticus and extending down the infundibulum of internal auditory canals.
Coronal & axial T1 pre-contrast shows soft tissue extending into infundibulum of internal auditory canals bilaterally
Coronal & axial T1 post gadolinium sequences show avid homogenous enhancement of lesions bilaterally.
Vestibular schwannoma
MOLECULAR GENETICS REPORT:
Neurofibromatosis Type 2 Testing via NF2 Gene Sequencing

SUMMARY OF RESULTS: POSITIVE

METHODS: Using this patient's genomic DNA, we amplified and sequenced all coding exons of the NF2 gene as well as ~20 bases of flanking non-coding sequences. We then aligned and compared the patient's sequences with the reference sequences. ALL differences from the reference sequences are reported.

RESULTS AND INTERPRETATIONS: This patient is heterozygous in the NF2 gene for a sequence variant defined as c.431dupA, and predicted to result in premature protein termination p.Tyr144Stop. This variant was reported to be causative for neurofibromatosis type 2 (Kluwe et al. Hum Mol Genet 7:2051-5, 1998). This result is consistent with a diagnosis of Neurofibromatosis type 2.

<table>
<thead>
<tr>
<th>Exon</th>
<th>DNA Sequence Variation</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>c.431dupA, Heterozygous duplication</td>
<td>p.Tyr144Stop; Documented causative</td>
<td>Kluwe; 1998</td>
</tr>
</tbody>
</table>

We found no other sequence variants. ALL genetic tests have limitations. Please see limitations and other notes for this particular test on pages 2 - 3.
Neurofibromatosis Type 2
Chromosome 22q12.2
Mutation in Merlin Protein
Polydactyly – Syndactyly Syndrome

with Triple phalangeal thumbs

Eaton- McKusick Syndrome
Carpenter Syndrome
Acrocephalosyndactyly Type II
Sakati-Nyhan-Tisdale Syndrome
Acrocephalo Polysyndactyly Type III
Dec 4, 2011

Developmental Genetics Research Result

Through research-based testing in the Alkuraya lab, the following genetic alteration of apparent medical significance has been identified in the above noted individual:

Disease: Retinitis Pigmentosa
Gene: TULP1
Mutation: NM_003322.3 :c.901C>T; p.(Gln301*)

This result indicates that [redacted] carries two pathogenic copies of TULP1 that causes his disease.

We'd like to emphasize that the above results were generated in a research lab. Genetic counseling is highly recommended for this family.

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Department of Genetics
Consanguinity
Bardet-Biedl Syndrome
Meckel Gruber Syndrome
Sanjad-Sakati Syndrome
Hypoparathyroidism
Intellectual Disability
Dysmorphism
Mutation in the TBCE Gene
Homozygous for 12bp deletion
155 – 166 Del on chromosome 1Q42
Ulna and Fibula absence with Severe Limb deficiency

Al-Awadi-RAAS-Rothschild Syndrome

Schinzel Phocomelia
Homozygous Mutation in WNT7A gene on chromosome 3P25
Woodhouse Sakati Syndrome

Hypogonadism, Alopecia, Diabetes Mellitus, Mental retardation, Deafness and Extrapyramidal syndrome caused by Homozygous Mutation in the C2ORF37 genes DCAF17 on chromosome 2q31
Larsen Syndrome
Dislocation of large joints
Heterozygous FLNB mutation
Autosomal dominant

Homozygous mutation in CHST3
Autosomal recessive
Skeletal Dysplasia with large joint dislocation
Autosomal Recessive Form of Larsen syndrome
Large joint dislocation
Severe myopia
Homozygous mutation
GZF1 gene (Dr. Fawzan AlKhurayya)
Geroderma osteodysplasticum caused by Homozygous Mutation in GORAB gene on chromosome 1q24
MOLECULAR GENETICS REPORT: Geroderma Osteodysplasticum (GO) Testing via GORAB Gene Sequencing

SUMMARY OF RESULTS: POSITIVE

RESULTS AND INTERPRETATIONS: This patient is apparently homozygous in the GORAB gene for a sequence variant defined as c.306dupA, which is predicted to result in premature protein termination (p.Pro103Thrfs*20). This variant was reported to be pathogenic for Geroderma Osteodysplasticum in three affected consanguineous families from the central province in Saudi Arabia (Al-Dosari et al. Am J Med Genet A 149A: 2093, 2009; reported as c.226_227insA, p.Q76QfsX20).

These results should be interpreted in context of clinical findings, family history and other laboratory data. All genetic tests have limitations. Please see limitations and other information for this test on pages 3 - 4.

RECOMMENDATIONS: Genetic counseling is recommended. Parental testing for the c.306dupA variant is recommended to rule out the possibility that only one of this patient’s GORAB alleles was amplified and sequenced. Targeted testing of other biological relatives can also be performed to determine their carrier status.
Gillespie Syndrome
Aniridia and Cerebellar Ataxia and Intellectual Disability
Caused by ITPR1 Gene on chromosome 3P26
TARGET MUTATION DNA ANALYSIS FOR GILLESPIE SYNDROME (ITPR1 GENE)

Gillespie syndrome (GLSP) is an autosomal recessive disorder that can be caused by mutations in ITPR1 gene. Testing for the c.6862C>T (p.Arg2288*) mutation previously reported in the family was performed.

**Methodology:** Amplification of the region of the gene (ITPR1: NM_002222.5) surrounding the reported mutation using polymerase chain reaction (PCR) followed by sequencing both sense and anti-sense strands of the amplicon. In addition, Human Identifier multiplexed microsatellite marker set was used to test for maternal cell contamination of the sample.

**Sensitivity:** Excluding genetic variants that may interfere with PCR amplification, the detection of target mutations by sequencing is highly sensitive.

**RESULTS**

<table>
<thead>
<tr>
<th>Target Sequence Variant</th>
<th>Genotype</th>
<th>Amino Acid Change</th>
<th>Zygosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.6862C&gt;T</td>
<td>T / T</td>
<td>p.Arg2288*</td>
<td>HOMOZYGOUS</td>
</tr>
</tbody>
</table>

**INTERPRETATION**

The sequence variant c.6862C>T previously reported in the family was detected in both copies of the ITPR1 gene. The fetus is most likely AFFECTED (HOMOZYGOUS) with the disease. Microsatellite genotyping ruled out maternal cell contamination of the sample. It is recommended that this result is reconfirmed using a postnatal sample. Genetic counseling is recommended.
Pax6 Gene 11P Aniridia
Lesch-Nyhan Syndrome
Duchenne Muscular Dystrophy, Adrenal Hypoplasia and Glycerol Kinase Deficiency due to deletion of short arm of the X chromosome from XP21.1 to XP22.11.
Madelung Deformity
Dyschondroosteosis
Mutation of shox gene
Located on XP 22.3
The pseudoautosomal region of the X-chromosome which escapes inactivation
Dyschondroosteosis

Gene map locus
YPter-P11.2
XPter- P22.32

Is caused by mutations in the Pseudoautosomal genes SHOX or SHOXY

The gene is deleted or site of point mutation.
Homozygous shox gene Mutation results in Langer Mesomelic dysplasia
Give a child with Down Syndrome the gift of education

Your support will help us transform the lives of children with Down syndrome in Saudi Arabia. For as little as 12 riyals a month, you can make an impact!

Donate Now
Down syndrome
William Syndrome
Microdeletion Syndrome 7Q11.3
Osteogenesis Imperfecta Type 1
COL 1A1 gene
Or
COL 1A2
Type VII
CRTAP Autosomal Recessive
Clinically relevant variants with significant phenotype overlapping with your patient

<table>
<thead>
<tr>
<th>Gene (transcript)</th>
<th>Nucleotide (protein)</th>
<th>Zygosity</th>
<th>Described by</th>
<th>In silico parameters*</th>
<th>MAF**</th>
<th>Variant classification***</th>
<th>Disorder (OMIM#, inheritance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRTAP (NM_006371.4)</td>
<td>c.160_167del (p.Lys54Argfs*104)</td>
<td>Hom</td>
<td>Het</td>
<td>Not reported</td>
<td>Frameshift Premature stop codon</td>
<td>Not reported</td>
<td>Class 2 Likely pathogenic</td>
</tr>
</tbody>
</table>

*: number of applied in silico prediction programs that are pathogenic, benign, or not applicable/not conclusive (NA/NC) as well as if the position is conserved (both GERP++ and PhyloP have positive values) or not. **: minor allele frequency (MAF) of Exome Aggregation Consortium database (ExAC), Exome Sequencing Project (ESP), or 1000Genome project (1000G)). ***: variant classification based on CentoMD® and ACMG recommendations (see additional information below for details on the classification). Further information can be found in the interpretation, disclaimer and methods section.

The result of WES analysis and clinical information provided for the fetus is very likely consistent with the genetic diagnosis of osteogenesis imperfecta type VII.

Given the results, retrospective clinical evaluation of the prenatal findings will help in determining the compatibility of the phenotype with the identified variant and thus further support the variant’s pathogenicity and its causation for the fetal symptoms. Genetic counselling is recommended to explain the implications of this result and address any concerns.

Interpretation
By whole exome sequencing we detected the following variant which has also been confirmed by Sanger sequencing:
- a homozygous likely pathogenic variant in exon 1 of the CRTAP gene, c.160_167del (p.Lys54Argfs*104). This deletion creates a frame shift starting at codon Lys54. The new reading frame ends in a STOP codon 103 positions downstream. To date, this variant is not described in the Exome Aggregation Consortium, Exome Sequencing Project or the 1000 Genomes Browser. This is the first time we detect this variant based on Centogene’s mutation/variation database (CentoMD®). It is classified in class 2 according to the recommendations of Centogene and ACMG (please, see additional information below for details on the
Ataxia - telangietasia

- Gene map locus 11Q22.3
- Caused by mutation in AT mutated gene (ATM)
Thank you.