Panelists

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About Orbis

Orbis is an international NGO that transforms lives through the prevention and treatment of avoidable blindness. www.orbis.org

Training

- Holistic team training for the entire patient care pathway including ophthalmology, optometry, nursing, biomedical engineering and anesthesia

Technology & Innovation

- Simulation solutions
- Telehealth & distance learning
  www.cybersight.org
Orbis Partner Presentation

CYBERSIGHT IS OUR DIGITAL PLATFORM
WWW.CYBERSIGHT.ORG

- 18-year history in telemedicine and online learning
  - Consultation & mentorship from international experts + AI
- Online courses & library
  - Live global lectures & surgical demonstrations
- 20,000+ consultations
- 50,000+ registered users in 200+ countries
- Integrates and pre-populates our existing electronic medical record (EMR) for the FEH & HBTs
Case 1

In Cybersight E-Consult
Case 2
Case 2

Case Location: Thailand

Patient Information

- **Age:** 7 years
- **Gender:** Male
- **Ocular, Family and Medical History:**
  - Blurry vision with current glasses
  - Previous visit at 4-years-old: OD -13.00-1.50x180 OS -12.00-1.50x180
  - This visit at 7-years-old: OD -15.00-1.00x180, 20/70 OS -15.00-2.50x180, 20/100
  - Preterm 30 weeks
  - Birth weight 1,400 g
  - No history of ROP
  - He is Twin B (Twin A – death)
  - No family history of high myopia
  - No nyctalopia, ameralopia

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Case 2: Further Considerations and Pedigree

- Prescribed glasses as cycloplegic refraction, F/U 4-6 months
- Review
  - Preterm with high myopia
  - Preterm with no history of ROP
  - Dragged disc, retinal vessel and macular
  - Vitreous strand
- Considerations
  - ROP?
  - ROPER (FEVR in preterm)?
  - Marfan syndrome?
  - Wagner syndrome?
  - Stickler syndrome?
  - Knobloch syndrome?

![Pedigree Diagram]

High myopia
Findings

Knobloch?
Occipital lesion

Flat malar bone

Sensory neural hearing loss

Stickler?
Cleft palate S/P repair
Case 2: Found optically empty vitreous and vitreous strand
Case 2: R/O Stickler syndrome

- Annual examination by a vitreoretinal specialist.
- Audiologic evaluations every six months through age five years, then annually thereafter.
- Screening for mitral valve prolapse (MVP) on routine physical examination.
- Avoid contact sports that may lead to traumatic retinal detachment.

### Stickler syndrome - PS108300 - 5 Entries

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Knobloch syndrome: high myopia, vitreoretinal degeneration with retinal detachment, and occipital encephalocele.

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<th>Phenotype MIM number</th>
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Case 2: Treatment and Discussion

- Prescribed glasses
- Examination under anesthesia and prophylactic laser around lattice degeneration (Controversy)
- Consult pediatrician for check mitral valve prolapse
- Genetics testing

High myopia patients may have hidden diseases
Case 3
Case Location: Philippines

Patient Information

• **Age:** 19 years

• **Gender:** female

• **Ocular, Family and Medical History:**
  • Congenital cataracts and microcornea
  • S/P cataract surgery both eyes at 4 mos old, given glasses; nystagmus noted before 4 years old
  • At 4 years old seen by another eye doctor, underwent pupilloplasty + anterior vitrectomy due to poorly dilating pupils and inability to examine posterior pole, both eyes. Post op - normal posterior pole with CDR 0.3, both eyes. Corneal diameters were 8mm both eyes
  • At 6 years old noted increasing IOP left eye, with increasing CDR at 0.7, given anti glaucoma meds; increasing IOP prompted Ahmed valve implantation, left eye; corneal diameters at 8.5mm both eyes, Axial length at 21.15mm right eye and 21.45mm left eye
  • Ahmed exchange due to retraction at 8 years old
  • Review of systems unremarkable
  • Maternal uncle (brother of mom) – S/P enucleation (1 eye?) for retinoblastoma at 4 years old
Case 3

- **VA**
  - OD: +13.50 -1.75 x 180 → 20/40
  - OS: +13.00 -1.25 x 135 → 20/70

- **Anterior segment:** (+) nystagmus; corneal diameters: 9mm horizontal and vertical, OU
  - OD: clear cornea, anterior synechia 10-11 o’clock, pupil corectopia, aphakic
  - OS: Ahmed valve tube in place; clear cornea, mid-dilated irregular pupil, aphakic
  - AT: 16mmHg right eye; 13mmHg left (on anti-glaucoma meds, OS)

- **Tonometry**
  - OD: 16mmHg
  - OS: 13mmHg (on anti-glaucoma meds)

- **Posterior segment:**
  - OU: E/N retina with CDR 0.3 right eye and 0.5 left eye

- **Axial length:**
  - OD: 22mm
  - OS: 22.21mm
Case 3

• Summary:
  • 19 year old female
  • Bilateral cataract surgery at 4 months old
  • Glaucoma surgery OS at 6 years old
  • Microcornea, OU
  • Pupillary changes, OU (surgical?)
  • Maternal uncle – retinoblastoma

• Congenital cataract panel – VUS in 4
Clinical summary

A Variant of Uncertain Significance, c.899G>T (p.Ala300Val), was identified in ERCC6.

- The ERCC6 gene is associated with autosomal recessive Cockayne Syndrome II (MIM: 155487) and cerebrohepatorenal syndrome (MIM: 265930).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.1111+44G>C (Intron1), was identified in UNC45B.

- The UNC45B gene is associated with autosomal recessive myopathy, congenital (MIM: 977280). Additionally, there is preliminary evidence supporting a correlation with autosomal dominant cataract (MIM: 603661).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.654G>T (p.Cys218Stop), was identified in YSK2.

- The YSK2 gene is associated with autosomal recessive microphthalmia/anophthalmia/cataract syndrome (MIM: 600548).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.1733C>G (p.Pro578Ala), was identified in XLT1.

- The XLT1 gene is associated with autosomal recessive spondylocostal dysostosis (MIM: 120771).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

Variant details

ERCC6, Exon 5, c.899G>T (p.Ala300Val), heterozygous, Uncertain Significance

- This sequence change replaces alanine, which is neutral and non-polar, with valine, which is neutral and non-polar, at codon 300 of the ERCC6 protein (p.Ala300Val).
- This variant is present in population databases (rs374471374, gnomAD: 0.02%).
- This variant has not been reported in the literature in individuals affected with ERCC6-related conditions.
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious", PolyPhen-2: "Benign", Align-GVGD: "Class C3").
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

UNC45B, Intron 8, c.1111+44G>C (Intron1), heterozygous, Uncertain Significance

- This sequence change falls in intron 8 of the UNC45B gene. It does not directly change the encoded amino acid sequence of the UNC45B protein. It affects a nucleotide within the conserved splice site.
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### Genes analyzed

This table represents a complete list of genes analyzed for this individual, including the relevant gene transcripts. If more than one transcript is listed for a single gene, variants were reported using the first transcript listed unless otherwise indicated in the report. Results are negative unless otherwise indicated in the report. Known and Likely Benign variants are not included in this report but are available upon request. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.
Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50X depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated below. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 10bp of flanking intronic sequence (10bp for BCA1/2), and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed (indicated in the table above). Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read depth and read depth distribution, obtained from a set of clinical samples. Markers across the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Confirmation of the presence and location of reportable variants is performed based on stringent criteria established by Invitae (1400 16th Street, San Francisco, CA 94103). As needed, using one of several validated orthogonal approaches (PubMed ID 30619021). The following analyses are performed if relevant to the requisition. For PM252 exons 12-15, the reference genome has been modified to force all sequence reads derived from PM252 and the PM252c pseudogene to align to PM252, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PM252 and the PM252c pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MURA-seq is run to confirm the variant. If confirmed, both PM252 and PM252c are amplified by long-range PCR, and the identity of the fixed differences between PM252 and PM252c are sequenced by PacBio from the long-range amplicon to abrogate the location of the CNV.

Technical component of confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103), (SSD040778). For C5orf72 repeat expansion testing, hexanucleotide repeat units are detected by repeat-primed PCR (RP-PCR) with fluorescently labeled primers followed by capillary electrophoresis. Interpretation Reference Ranges: Benign (Normal Range): c25-30 repeat units, Pathogenic (RP-MLPA mutation): >31 repeat units. A second round of RP-PCR utilizing a non-overlapping set of primers is used to confirm the initial call in the case of suspected allelic sizes of 12 or more repeats. For RNA analysis of the genes indicated in the Gene Analysis table, complementary DNA is synthesized by reverse transcription from RNA derived from a blood specimen and enriched for specific genomic sequences using capture hybridization. After high-throughput sequencing using Illumina technology, the output reads are aligned to a reference sequence (genomic build GRCh37, custom derivative of the RefSeq transcriptome) to identify the locations of exon junctions through the detection of split reads. The relative usage of exon junctions in a test specimen is assessed quantitatively and compared to the usage seen in control specimens. Abnormal exon junction usage is evaluated as evidence in the Shenkel variant interpretation framework. If an abnormal splicing pattern is predicted based on a DNA variant outside the typical reportable range, as described above the presence of the variant is confirmed by targeted DNA sequencing. RNA sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103), (SSD0204793). Technical component of Fibroblast cell-culturing and cDNA extraction from skin punch biopsy is performed by Invitae Corporation (5 Technology Drive, Irvine CA 92618). (SSD01052993).


An eRS4 is a unique identifier referring to a published single genomic region, and it used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including EvAm (http://pseudobrowser.org), gnomAD (http://gnomad.broadinstitute.org), and dbSNP (http://.ncbi.nlm.nih.gov/SNP/).


Invite uses information from individuals undergoing testing to inform variant interpretation. If “Invite” is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.
Case 4
Case Location: United Kingdom

Patient Information

- **Age:** 20 years
- **Gender:** male

**Ocular, Family and Medical History:**

- Referred from local optician
- Nyctalopia since early teens
- Bumping into people in the streets often ~2 months ago
- Otherwise, healthy. No relevant PMH
- FHx is negative for eye diseases, with the exception of mother with prologed dark adaptation and deceased maternal grandfather with a long-term history of night blindness
Case 4

BcVA: 20/20
Rx: -3.50 esf OD, -4.0 esf OS
IOP: 14/13 mmHg
SL: Tiny central subcapsular opacity OU
Case 4: OCT
Case 4: FAF
Case 4: Other ancillary tests

- VF: Constriction to central 10 degrees
- ffERG: Absent rod and cone-based responses
- mfERG: Extinguished diffusely

- The results of the RP panel came back
- \textit{RPGR}: c.8del (p.Glu3fs)
Case 5
Case 5

Case Location: US

Patient Information

- **Age:** 7 years
- **Gender:** Male
- **Ocular, Family and Medical History:**
  - Decreased visual acuity
  - PMH: born with a solitary, dysplastic kidney currently with stage IV chronic kidney disease
  - Family history non-contributory

**Ocular exam**

- BCVA 20/30 -1 OU
- Normal anterior segment examination
- Dilated eye exam

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<tr>
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<td>Yellow, raised fovea surrounded by hyperpigment; yellow ring with hyperpigmentation</td>
<td>Vitelliform lesion</td>
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<tr>
<td>Vessels</td>
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<tr>
<td>Periphery</td>
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Case 5

OD

OS
Case 5

- Ocular phenotype → Best disease
- In presence of solitary, dysplastic kidney

- Genetic testing
  - Chromosome microarray (more than 1 gene?) – Normal
  - *BEST1* - separate conditions – POSITIVE – c.653G>A (p.Arg218His) heterozygous, classified as pathogenic
**BEST1: Exon 6, c.653G>A (p.Arg218His), heterozygous**

- Small physiochemical difference arg/his (Grantham score 29)
- Conserved across species (GERP score is 4.88)
- CADD 1.458
- Population databases (ExAC 0.009%)
- Observed in individuals with AD Best and AR bestrophinopathy
- ClinVar: 6 submissions - 3 pathogenic, 2 likely pathogenic.
- In Silico = deleterious
- Experimental studies show affect on protein function.
- Other variants at same position = pathogenic
- ACMG classification = pathogenic
Case 6
### Case 6

**Case Location:** US

**Patient Information**
- **Age:** 45 years
- **Gender:** Female
- **Ocular, Family and Medical History:**
  - Presenting for cone-rod dystrophy
  - 15 year history of slow, progressive blurring of vision
  - First noticed trouble driving at night and difficulty seeing letters on road signs

- **Ocular examination**
  - BCVA of 20/150 OD, 20/40 OS
  - Normal pupils, IOP, EOMs, and anterior segment exam
  - Fundus exam

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<tr>
<th></th>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disc</strong></td>
<td>Mild temporal pallor</td>
<td>Mild temporal pallor</td>
</tr>
<tr>
<td><strong>Macula</strong></td>
<td>Geographic atrophy with pigment and surrounding almost radiating subretinal flecks, some scattered larger flecks</td>
<td>Geographic atrophy with pigment and surrounding almost radiating subretinal flecks, some scattered larger flecks</td>
</tr>
<tr>
<td><strong>Vessels</strong></td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Periphery</strong></td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Case 6
Case 6
Likely an *ABCA4*-Stargardt phenotype

Genetic testing $\rightarrow$ *ABCA4* analysis

- *ABCA4*: c.2966T>C (p.Val989Ala), heterozygous; classified as pathogenic
- *ABCA4*: c.4139C>T (p.Pro1380Leu), heterozygous; classified as pathogenic

*Segregation analysis in parents pending*
Case 6

**ABCA4: Exon 20, c.2966T>C (p.Val989Ala)**
- Small physicochemical difference between val/ala (Grantham = 74)
- Other variants observed in ABCA4-related conditions
- GERP score is 5.72
- CADD score 26.1
- Population databases (ExAC 0.3%)
- Observed in individuals with ABCA4-related retinal disease
- ClinVar 7 submissions: 4 pathogenic, 2 likely pathogenic, 1 VUS
- In silico do not agree
- ACMG suggested classification is pathogenic

**ABCA4: Exon 28, c.4139C>T (p.Pro1380Leu)**
- Moderate physicochemical difference pro/leu (Grantham = 98)
- GERP = 5
- CADD score 25.1
- Population databases (ExAC 0.03%)
- Observed in individuals with Stargardt disease
- ClinVar 16 submissions: 13 pathogenic, 3 likely pathogenic
- In silico likely to be disruptive
- Experimental studies show affect on ABCA4 protein function
Cybersight E-Consult Case
Case 1

Case Location: Philippines

Patient Information

- **Age:** 55 years
- **Gender:** male

**Ocular, Family and Medical History:**

- BOV and night vision problems since childhood
- Peripheral vision problems noted at 20+ years
- Diagnosed with retinitis pigmentosa OU in 2005, underwent cataract surgery, left eye in 2005 and right eye in 2007 but had "complications" with minimal improvement in vision, both eyes
- Birth/maternal history unremarkable
- (+) HTN and diabetes controlled with medications; other review of systems unremarkable
- No history or trauma or exposure to chemicals/radiation
- No known family history of night blindness; nephew has "cataract" at 15 years old; no consanguinity
Case 1

- **Visual Acuity:**
  - OD: Hand movement OS: Hand movement (poor ROR)

- **Anterior segment:**
  - E/N except for aphakia both eyes; poorly dilating pupil, left

- **Posterior segment:**
  - Both eyes: Pale discs, attenuated vessels, bony spicules and pigmentary clumping whole retina involving fovea (attached photos)
  - No ERG done
Case 1: 2016
2016

OCT done only in right eye due to poor signal, left eye
Case 1

- Retinal dystrophy, both eyes;
- S/P lens extraction, no IOL, both eyes
- Retinal dystrophy panel - VUS in 7 genes
A Variant of Uncertain Significance, c.359C>T (p.Thr120Met), was identified in AIPL1.

- The AIPL1 gene is associated with autosomal recessive Leber congenital amaurosis (MedGen UID: 344803), cone-rod dystrophy (MedGen UID: 416425), and retinitis pigmentosa (OMIM: 306745).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.3485A>C (p.Gln1162Pro), was identified in CEPI20.

- The CEPI20 gene is associated with autosomal recessive retinal dystrophy (MedGen UID: 1675071). Additionally, the CEPI20 gene has preliminary evidence supporting a correlation with autosomal recessive non-syndromic retinal dystrophy (OMIM: 3098881) and with autosomal recessive retinitis pigmentosa (OMIM: 2271996).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.1376C>A (p.Thr459lys), was identified in NPH4.

- The NPH4 gene is associated with autosomal recessive cerebellar degeneration including nephromegabiosis (MedGen UID: 339627) and Senior-Loken syndrome, type 6 (MedGen UID: 87267).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.5249C>T (p.Pro1750Leu), was identified in PCDH15.

- The PCDH15 gene is associated with autosomal recessive Leber congenital amaurosis (MedGen UID: 359899) and non-syndromic deafness (MedGen UID: 322110). Additionally, the PCDH15 gene has preliminary evidence supporting a correlation with idiopathic Usher syndrome (OMIM: 2451830, 155376).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.2407C>A (p.Ala803Thr), was identified in RB1.

- The RB1 gene is associated with autosomal recessive retinitis pigmentosa (RP) (MedGen UID: 811058).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.2186C>T (p.Pro729Leu), was identified in SEMA4A.

- The SEMA4A gene currently has no well-established disease association; however, there is preliminary evidence supporting a correlation with retinitis pigmentosa (OMIM: 1639551, 2863424) and cone-rod dystrophy (OMIM: 261069).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

A Variant of Uncertain Significance, c.2654T>G (p.Asn878Ily), was identified in TMEM67.

- The TMEM67 gene is associated with autosomal recessive retinal dystrophy and related disorders (ROD) (MedGen UID: 79822).
- Not all variants present in a gene cause disease. The clinical significance of the variant(s) identified in this gene is uncertain. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
- Familial VUS testing is not offered. Testing family members for this variant will not contribute evidence to allow variant reclassification. Details on our VUS Resolution and Family Variant Testing Programs can be found at https://www.invitae.com/family.

**Variant details**

**AIPL1, Exon 3, c.359C>T (p.Thr120Met), heterozygous, Uncertain Significance**

- This sequence change replaces threonine with methionine at codon 120 of the AIPL1 protein (p.Thr120Met). The threonine residue is highly conserved and there is a moderate physicochemical difference between threonine and methionine.
- This variant is present in population databases (rs144579081, ExAC 0.02%).
- This variant has not been reported in the literature in individuals affected with AIPL1-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 324671).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: " Possibly Damaging"; Align-GVGD: "Class C0").
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

**CEP250, Exon 26, c.3485A>C (p.Gln1162Pro), heterozygous, Uncertain Significance**

- This sequence change replaces glutamine, α/β neutral and polar amino acid, with proline, α/β neutral and non-polar amino acid, at codon 1162 of the CEP250 protein (p.Gln1162Pro).
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with CEP250-related conditions.
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Tolerated"; PolyPhen-2: " Possibly Benign"; Align-GVGD: "Class B3").
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.
CEP250, Exon 26, c.3465A>C (p.Gln1162Pro), heterozygous, Uncertain Significance
- This sequence change replaces glutamine, a (n) neutral and polar amino acid, with proline, a (n) neutral and non-polar amino acid, at codon 1 of the CEP250 protein (p.Gln1162Pro).
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with CEP250-related conditions.
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: “Not Available”; PolyPhen-2: “Possibly Damaging”; Align-GVGD: “Not Available”).
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as Variant of Uncertain Significance.

NPHP4, Exon 11, c.1376C>A (p.Thr455Lys), heterozygous, Uncertain Significance
- This sequence change replaces theonine with lysine at codon 459 of the NPHP4 protein (p.Thr455Lys). The theonine residue is moderately conserved and there is a moderate physicochemical difference between theonine and lysine.
- This variant is present in population databases (rs137181983, ExAC 0.05%).
- This variant has not been reported in the literature in individuals affected with NPHP4-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 24096).
- Algorithms developed to predict the effect of missense changes on protein structure and function (SIFT, PolyPhen-2, Align-GVGD) all suggest this variant is likely to be tolerated.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as Variant of Uncertain Significance.

PCDH15, Exon 33, c.5249C>T (p.Pro1750Leu), heterozygous, Uncertain Significance
- This sequence change replaces proline with leucine at codon 1750 of the PCDH15 protein (p.Pro1750Leu). The proline residue is weakly conserved and there is a moderate physicochemical difference between proline and leucine.
- This variant is not present in population databases (ExAC no frequency).
- This variant has not been reported in the literature in individuals affected with PCDH15-related conditions.

RBP3, Exon 1, c.407C>T (p.Ala136Thr), heterozygous, Uncertain Significance
- This sequence change replaces alanine with threonine at codon 136 of the RBP3 protein (p.Ala136Thr). The alanine residue is moderately conserved and there is a small physicochemical difference between alanine and threonine.
- The frequency data for this variant in the population databases is considered unreliable, as metrics indicate poor data quality at this position in the ExAC database.
- This variant has not been reported in the literature in individuals affected with RBP3-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 20996).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: “Tolerated”; PolyPhen-2: “Possibly Damaging”; Align-GVGD: “Class C”).
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

SEMA4A, Exon 15, c.2186C>T (p.Pro729Leu), heterozygous, Uncertain Significance
- This sequence change replaces proline, a (n) neutral and non-polar amino acid, with leucine, a (n) neutral and non-polar amino acid, at codon 729 of the SEMA4A protein (p.Pro729Leu).
- This variant is present in population databases (rs68391865, gnomAD 0.01%).
- This variant has not been reported in the literature in individuals affected with SEMA4A-related conditions.
- Algorithms developed to predict the effect of missense changes on protein structure and function output the following: SIFT: “Tolerated”; PolyPhen-2: “Benign”; Align-GVGD: “Class C”.
- The leucine amino acid residue is found in multiple mammalian species, which suggests that this missense change does not adversely affect protein function.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

TMEM67, Exon 25, c.2634T>C (p.Asn878Lys), heterozygous, Uncertain Significance
- This sequence change replaces asparagine with lysine at codon 878 of the TMEM67 protein (p.Asn878Lys). The asparagine residue is highly conserved and there is a moderate physicochemical difference between asparagine and lysine.
- This variant is present in population databases (rs19288860, ExAC 0.03%).
- This variant has not been reported in the literature in individuals affected with TMEM67-related conditions.
- Advanced modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) performed at Invivo indicates that this missense variant is expected to disrupt TMEM67 protein function.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.
## Case 1: Genes analyzed

| Genes analyzed |

This table represents a complete list of genes analyzed for this individual, including the relevant gene transcript(s). Only those transcripts listed as specific to a single gene are included. The list also includes selected transcripts from other genes. The table includes all relevant genes, even those not identified in the report. Results are ranked from the highest to the lowest.