Blueprint Genetics

Family Member Testing

REFERRING HEALTHCARE PROFESSIONAL

NAME

HOSPITAL

PATIENT

NAME

DOB

AGE
53

GENDER
Female

ORDER ID

PRIMARY SAMPLE TYPE
Blood

SAMPLE COLLECTION DATE

CUSTOMER SAMPLE ID

FMT TEST INFO

FAMILY MEMBER TEST
1 mutation

INDEX ORDER ID

TEST RESULT

A heterozygous *RPGR* c.2601_2602del, p.(Glu868Glyfs*210) variant was identified in this individual. Genetic counseling is recommended.

STATEMENT

DESCRIPTION

This individual is a 53-year-old female. She reports mild difficulties seeing at night, no formal evaluation has been performed. Blueprint Genetics (BpG) Retinal Dystrophy Panel analysis done for the index patient identified a hemizygous 2-bp deletion c.2601_2602del, p.(Glu868Glyfs*210) in exon ORF15 of *RPGR*. The variant is classified as pathogenic. Targeted testing of the variant was requested.

There are no individuals with *RPGR* c.2601_2602del, p.(Glu868Glyfs*210) in the Genome Aggregation Database (gnomAD, n>120,000 exomes and >15,000 genomes). The variant results in a frameshift transcript with a premature stop codon at the new position 1077 instead of codon 1153 as in the wild-type transcript. Such changes are predicted to cause loss of normal protein function through protein truncation. The variant was initially reported by Bader et al. who identified it in one family in a *RP2* and *RPGR* mutation screening of 58 index patients from families with X-linked retinitis pigmentosa (described as g.ORF15 848_849delGG in the publication PMID: 12657579). Subsequently the variant has been reported in additional male patient with X-linked RP (PMID: 28322733). In addition, we have detected the variant in two patients with X-linked retinitis pigmentosa (BpG unpublished observations).

RPGR (MIM*312610) encodes a protein with a series of six RCC1-like domains (RLDs), characteristic of the highly conserved guanine nucleotide exchange factors. This protein localizes to the outer segment of rod photoreceptors and is essential for their viability. Mutations in *RPGR* are mainly associated with X-linked retinitis pigmentosa (XLRP, MIM#300029), however few mutations have also been described in patients with other retinal dystrophies including cone rod dystrophy, atrophic macular degeneration and syndromal retinal dystrophy with ciliary dyskinesia and hearing loss. XLRP accounts for 10-20% of families with RP and it is the most severe form of RP. Typically retinal disease in females with XLRP is less severe than that seen in males. In XLRP, the affected males are symptomatic from early childhood and most patients are blind by the end of the third decade. Female carriers show a broad spectrum of fundus appearances, ranging from normal to extensive retinal degeneration. In a study by Rozet et al, age at disease onset in affected females was delayed compared to affected males with similar truncating variants (20-40 years vs. 10-20 years; PMID: 11950860). Mutations in *RPGR* account for over 70% of the patients with XLRP. Exon ORF15, encoding 567 amino acids, with a repetitive domain with high glutamic acid and glycine content has been identified as a mutation hotspot (PMID: 10932196, 12657579). The RPGR isoform including ORF15 is encoded by exons 1-15 and part of intron 15 (1152 amino acids, transcript id NM_001034853). The other major isoform has 815 amino acids and is encoded by exons 1-19 (NM_000328). Both isoforms share exons 1–15 (residues 1–635). Mutations are either identified in exons 1-15 or in the ORF15, and no disease-causing mutations are reported in exons 16-19 (PMID: 17195164). Currently, HGMD lists 203 different *RPGR* mutations in NM_000328.2 and 231 in NM_001034853.1 (ORF15) (HGMD Professional 2018.1). Majority of the mutations are nonsense and frameshift variants leading to loss of function. There is notable inter- and intrafamilial phenotypic variability in XLRP caused by *RPGR* mutations. In particular, patients with mutations in exons 1–14 have been shown to demonstrate smaller visual fields than patients with mutations in ORF15 (PMID: 14564670). Truncating variants in the c-terminal part of ORF15 have been associated with XL cone rod dystrophy (i.e c.2965G>T, p.Glu989*, c.3197_3198delAG, c.3300_3301delTA) (HGMD; PMID: 23150612). Only two individuals in ExAC reference population (60,000 individuals) carry truncating *RPGR* variant affecting major transcripts, much less than expected (21) by gene size. Both carriers are females, indicating rarity of such alteration in population cohort and suggestive that the change is not tolerated.

Mutation nomenclature is based on GenBank accession NM_001034853.1 (*RPGR*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

This targeted variant testing was performed with Sanger sequencing. The test does not exclude other possible variants in these genes.

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STEP	DATE
Order date	Aug 14, 2018
Sample received	Aug 14, 2018
Reported	Aug 30, 2018

On Aug 30, 2018 the statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results:

Kati Kämpjärvi, Ph.D.

Geneticist

Juha Koskenvuo, MD, Ph.D.

Lab Director, Chief Medical Officer