RS1 Gene Analysis in X-Linked Juvenile Retinoschisis

Clinical Features:
X-linked retinoschisis is the most common cause of juvenile retinal degeneration in males usually presenting between age 5 and 10 years, and resulting in decreased visual acuity during childhood and adolescence. Vision after that period generally stabilizes at 20/60-20/120, although progressive visual deterioration often occurs later in life. The disorder is characterized by splitting of the nerve fiber layer in the retina. Eye findings include macular schisis, often in a spoke-like pattern; peripheral (usually inferotemporal) schisis in about 50% of subjects; “vitreous veils”; and a decreased b-wave with an intact a-wave on electroretinogram (ERG). The prevalence is estimated to be between 1/5,000 and 1/25,000 males. Although distinct from retinal detachment, retinoschisis may eventually lead to detachment of the retina or retinal atrophy resulting in blindness.

Inheritance Pattern/Genetics:
X-linked recessive

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. If present, apparently homozygous sequence variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:
Several studies have shown the sensitivity of full gene sequencing in affected males to be 90-95%. Deletions spanning one or more exons, which have been shown to occur in approximately 5% of cases, are detected in females by ExonArrayDx.

Variants include missense, nonsense and splice site alterations. Small deletions and insertions have also been observed, as have intragenic rearrangements and deletions spanning one or more exons. Variants are found throughout the gene, with some clustering of variant in the 5' end of the coding sequence.

References:

1. The Retinoschisis Consortium, Functional implications of the spectrum of mutations found in 234 cases with X-linked juvenile retinoschisis, Human Molecular Genetics 7:1185-1192 (1998)
2. Hiriyanna, K.T. et al., Novel mutations in XLRS1 causing retinoschisis, including first evidence of putative leader sequence change, Human Mutation 14:423-427 (1999)
3. Sieving PA et al., Juvenile Retinoschisis: A Model For Molecular Diagnostic Testing of X-Linked Ophthalmic Disease, Am Ophth Soc Vol XCV11 (1999)