Genetic testing of the *RLBP1* gene in Retinitis Punctata Albescens, Fundus Albipunctatus, Newfoundland Rod-Cone Dystrophy and Bothnia Retinal Dystrophy

Clinical Features:

Retinitis punctata albescens (RPA): RPA is a disease characterized by night blindness from infancy, decreased visual acuity, presence of tiny white deposits and patches of atrophy in peripheral retina, progressive attenuation of retinal arterioles, abnormal fundus pigmentation, progressive restriction of visual fields, and non-detectable or severely reduced electroretinogram amplitudes.[5]

Fundus albipunctatus (FA) is a distinct form of stationary night blindness. Patients with fundus albipunctatus complain of night blindness or of delays in dark adaptation after exposure to bright light. Their fundi have numerous small, white or pale-yellow dots scattered in the retina. All of the dots can fade in patients during the fourth to fifth decade. The electroretinogram rod and cone amplitudes are substantially reduced.[1] Phenotypic similarities exist between patients with RPA and fundus albipunctatus, but most patients with fundus albipunctatus have a non-progressive disease.

Bothnia retinal dystrophy (BRD): BRD is an atypical variant of retinitis pigmentosa diagnosed in individuals who reside in northern Sweden, north of the Gulf of Bothnia, and is historically known as Bothnia Occidentalis. BRD is characterized by severe night blindness in early childhood, retinitis punctata albescens, macular degeneration, and a predilection to develop an atrophic-appearing macular lesion in older age.[2,3]

Newfoundland rod-cone dystrophy is characterized by night blindness that is present in infancy, along with a progressive loss of peripheral, central and color vision beginning in childhood. The end result is severe vision loss by the second to fourth decade of life. The optic nerve is either normal or minimally pale until a late stage of disease. The macula is normal or may exhibit a “beaten-bronze” atrophy. Young patients also exhibit a perimacular ring of white stippling and a scallop-bordered lacunar atrophy of the mid-peripheral retinal pigment epithelium, which is similar in appearance to early gyrate atrophy or choroideremia (Eichers et al., 2002).

Retinitis pigmentosa (RP): For more information please refer to the GeneDx arRP information sheet (http://www.genedx.com/services/dis_arrp.php)

Inheritance Pattern/Genetics:
RLBP1-related disorders are inherited in an autosomal recessive manner. Small deletions, gross deletions, missense, and splice site variants have all been reported as pathogenic variants in the RLBP1 gene. Large partial gene deletion of the RLBP1 has been reported in a patient with RPA.[10]

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:
Retinitis punctata albescens (RPA): Morimura et al, 1999 identified homozygous and compound heterozygous variants in the RLBP1 gene in 11% (3 out of 28) of the patients diagnosed with RPA. Variants in the PRPH2/RDS[11] and RHO[12] genes have also been found in patients with RPA. Genetic testing for both genes is available at GeneDx; please refer to their gene-specific information sheet for further information.

Fundus albipunctatus: Only one missense variant in the RLBP1 gene was reported in only one family from Saudi Arabia, with Fundus albipunctatus.[6] RDH5 is the other main known gene associated with fundus albipunctatus. Genetic testing for the RDH5 gene is available at GeneDx; please refer to its gene-specific information sheet for further information.

Bothnia retinal dystrophy: All patients with this disorder were found to be homozygous for the R234W variant.[2,3]

Newfoundland rod-cone dystrophy: All patients with this disorder were found to harbor either the IVS4+2 T>C variant reported as IVS3+2 T>C by Eichers, 2002 or the c.141 G>A (p.Lys47Lys) variant reported as c.324 G>A by Eichers, 2002.[4]

Autosomal recessive retinitis pigmentosa (arRP): A homozygous variant in the RLBP1 gene has been identified in 1 out of 19 (5%) of families of Indian origin diagnosed with non-syndromic arRP.[9] In another study, no variant in the RLBP1 gene was identified in 189 arRP patients.[8]

References:

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