

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 obtained from the submitted biological material, the entire coding region and splice junctions of RLBP1 (exons 3-9) are PCR amplified. Bi-directional sequence is obtained and analyzed to evaluate for variants in this gene. In Bothnia retinal dystrophy and NFRCD, variants-specific testing is available for members of the respective populations. Targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene. Any variant found in the first person of a family to be tested is confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

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/RDS¹¹ and RHO¹² 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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