Peroxisomal Disorders Panel

PANEL GENE LIST

ABCD1, ACOX1, AGPS, AMACR, DNM1L, FAR1, GNPAT, HSD17B4, PEX1, PEX2, PEX3, PEX5, PEX6, PEX7, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26, PHYH, SCP2, TRIM37

PEROXISOMAL DISORDERS OVERVIEW

Peroxisomal disorders comprise two heterogeneous subgroups of conditions: peroxisomal biogenesis disorders (PBD) which are characterized by defects in peroxisome synthesis, assembly and biochemical functions, and disorders of single peroxisomal enzymes and beta-oxidation deficiencies which are involved in ether lipid biosynthesis, phytanic, pristanic, and pipecolic acid catabolism, fatty acid beta-oxidation and other functions localized to peroxisomes.

CLINICAL FEATURES OF PEROXISOMAL BIOGENESIS DISORDERS

Peroxisomal biogenesis disorders consist of i) Zellweger spectrum disorders, including Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum syndrome, and ii) rhizomelic chondrodysplasia punctata. Zellweger spectrum disorder involves a range of symptoms such as hypotonia, liver dysfunction, hearing loss, retinal dystrophy, optic nerve abnormalities, seizures, leukodystrophy, chondrodysplasia punctata, and characteristic facial features. While children with Zellweger syndrome are typically diagnosed in the neonatal period, individuals with neonatal adrenoleukodystrophy and Refusm syndrome may present with less severe symptoms and may be diagnosed later in childhood. Rhizomelic chondrodysplasia punctata is characterized by rhizomelia, epiphyseal and metaphyseal abnormalities, intellectual disability, seizures, cataracts, coronal clefts, contractures, characteristic facial features, and pulmonary hypoplasia.[1,2]

CLINICAL FEATURES OF PEROXISOMAL ENZYMES AND BETA-OXIDATION DEFICIENCIES

Disorders of peroxisomal single enzyme deficiencies include adult Refsum syndrome, X-linked adrenoleukodystrophy, rhizomelic chondrodysplasia punctata type 2 and type 3, acyl-CoA oxidase deficiency, D-bifunctional enzyme deficiency, alpha-methylacyl-CoA racemase deficiency, DNM1L-related leukoencephalopathy, and mulibrey nanism. The clinical features of peroxisomal enzyme deficiencies vary depending on the specific disorder, however many patients may present with neurological deficits and symptoms similar to Zellweger spectrum disorder. A diagnosis of peroxisomal disorders is based on clinical features, biochemical studies that include analysis of very long chain fatty acids, phytanic acid, pipecolic acid, pristanic acid, plasmalogens and bile acids, and complementation analysis in fibroblasts.[3]

UTILITY OF MOLECULAR TESTING

The diagnosis of peroxisomal disorders is challenging; many PBDs have overlapping clinical and biochemical features which, in the absence of complementation analysis in fibroblasts, may make it difficult to identify the underlying molecular etiology. In addition, biochemical analysis may not always reveal evidence for abnormal peroxisome function.[1,4,5] Due to the biochemical complexity, genetic heterogeneity, and the need for a fibroblast biopsy for complementation studies, many clinicians are using peroxisomal-targeted Next generation sequencing panels in the diagnosis of patients. In addition, clarification of the underlying genotype may have prognostic value, and is essential for genetic counseling and subsequent family studies.

GENETICS

With the exception of X-linked adrenoleukodystrophy and DNM1L-associated leukoencephalopathy, peroxisomal disorders are inherited in an autosomal recessive manner. X-linked adrenoleukodystrophy is caused by pathogenic variants in the ABCD1 gene, while DNM1L-associated leukoencephalopathy has been reported with both autosomal dominant and autosomal recessive inheritance.

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Concurrently, multiplex ligation-dependent probe amplification (MLPA) was performed to evaluate for an exon-level deletion or duplication of the ABCD1 gene. 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.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. This test does not include deletion/duplication testing of exon 9 of ABCD1.

CLINICAL TEST SENSITIVITY

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype. For example, sequence analysis of 14 peroxin genes associated with PBDs is estimated to detect ~96% of affected individuals; ~70% of cases are caused by pathogenic variants in PEX1, while ~26% of cases are due to pathogenic variants in PEX6, PEX10, PEX12, or PEX26. [1,2,3] In a large study of patients with a clinical diagnosis of X-ALD, sequencing analysis of ABCD1 detected pathogenic variants in 95% of individuals.6 Deletions have been detected in approximately 3% of individuals with X-ALD.[7]

Class of Disorders	Gene Name	Associated Disorder(s)	OMIM #
Peroxisomal biogenesis disorders	PEX1	Zellweger spectrum disorder Heimler syndrome 1	602136
	PEX2	Zellweger spectrum disorder	614866
	PEX3	Zellweger spectrum disorder	617370
	PEX5	Zellweger spectrum disorder Rhizomelic chondrodysplasia punctata type 5	600414
	PEX6	Zellweger spectrum disorder Heimler syndrome 2	601498
	PEX7	Rhizomelic chondrodysplasia punctata type 1/ Refusm syndrome	614879
	PEX10	Zellweger spectrum disorder	614870
	PEX11B	Zellweger spectrum disorder	614920
	PEX12	Zellweger spectrum disorder	614859
	PEX13	Zellweger spectrum disorder	614883
	PEX14	Zellweger spectrum disorder	614887
	PEX16	Zellweger spectrum disorder	614876
	PEX19	Zellweger spectrum disorder	614886
	PEX26	Zellweger spectrum disorder	614872

Disorders of single peroxisomal enzymes and beta-oxidation deficiencies	ABCD1	X-linked adrenoleukodystrophy	300100
	ACOX1	Peroxisomal acyl-CoA oxidase deficiency	264470
	AGPS	Rhizomelic chondrodysplasia punctata type 3	600121
	AMACR	Alpha-methylacyl-CoA racemase deficiency	614307
	DNM1L	DNM1L-associated leukoencephalopathy	614388
	FAR1	Peroxisomal fatty acyl-CoA reductase 1 disorder	616154
	GNPAT	Rhizomelic chondrodysplasia punctata type 2	222765
	HSD17B4	D-bifunctional protein deficiency Perrault syndrome 1	601860
	PHYH	Adult Refsum syndrome	266500
	SCP2	Sterol carrier protein deficiency	604105
	TRIM37	Mulibrey nanism	253250

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