Prolidase Deficiency (PEPD)

Clinical Features:
Prolidase deficiency is a rare autosomal recessive connective tissue disorder with a wide phenotypic spectrum, ranging from asymptomatic to lethal phenotypes.[1-3] Patients typically exhibit recalcitrant chronic skin ulcers, mild to severe intellectual disability, dysmorphic features and recurrent respiratory infections. Skin ulcers are mainly concentrated on the legs and feet, but also have been observed on the arms and face. Other features include splenomegaly, hypotonia, skeletal anomalies, photosensitive rash, telangiectasia, systemic lupus erythematosus, and features of Hyper Ig-E syndrome.[1-5] Inter and intrafamilial variability has been noted.[3]

Genetics:
Prolidase deficiency is an autosomal recessive disorder that is caused by pathogenic variants in the PEPD gene, which encodes the prolidase enzyme. The enzyme is involved in recycling of proline released during the degradation of collagen and dietary proteins. Hyperiminodipeptiduria is a characteristic biochemical abnormality, and reduced prolidase activity in leukocytes, erythrocytes and cultured fibroblasts confirms the diagnosis.

Test Methods:
Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. The DNA is enriched for the complete coding regions and splice site junctions of the requested gene 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 at the exon-level; 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 regions with inadequate sequence or copy number data by NGS. 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, but less for 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 identify most deletions and duplications involving coding exons but are less reliable for

detecting copy number variants of less than 500 base pairs. Assessment of copy number events also depends on the inherent sequence properties of the targeted regions, including shared homology and exon size. Mosaicism detection is limited and balanced chromosome aberrations cannot be identified.

Clinical Sensitivity:

In a number of small studies with a collective total of 50 patients with prolidase deficiency from different families, 47 individuals were found to have two variants in the PEPD gene.[1-3] Copy number variants are rare but have been reported previously in affected individuals.[6-7]

References

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