AGXT, GRHPR, and HOGA1 Gene Analysis in Disorders of Primary Hyperoxaluria

CLINICAL FEATURES AND GENETICS

The primary hyperoxalurias are inborn errors of glyoxylate metabolism that result in the excess production of oxalate, a compound filtered through the kidneys and excreted in urine. Excess oxalate combines with calcium to form calcium oxalate deposits, which can damage the kidneys and other organs, resulting in clinical manifestations such as kidney and bladder stones, hematuria, urinary tract infections, kidney damage, end stage renal disease (ESRD), and systemic oxalosis. There are three types of primary hyperoxaluria.[1-3]

Primary hyperoxaluria type 1 (PH1) is due to pathogenic variants in the AGXT gene. This gene encodes the liver peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), which converts glyoxylate to glycine.[1] When AGXT is defective, glyoxylate is converted to oxalate. PH1 is a clinically heterogeneous disorder with median onset between 4 and 6 years of age, but with a range of onset from the early neonatal period to the 6th decade of life.[4] Clinical features include failure to thrive, hematuria, anemia, abdominal pain, urinary tract infections, nephrocalcinosis, recurrent nephrolithiasis, metabolic acidosis, ESRD, and systemic oxalosis.[3, 4] Individuals may remain asymptomatic into late adulthood. The diagnosis of PH1 is suspected in an individual with an elevated oxalate to creatinine ratio in urine and an elevated plasma oxalate concentration.[4]

Primary hyperoxaluria type 2 (PH2) is caused by pathogenic variants in the GRHPR gene, which encodes the enzyme glyoxylate reductase/hydroxypyruvate reductase. Onset is typically in childhood and clinical symptoms include recurrent nephrolithiasis, nephrocalcinosis, ESRD, and systemic oxalosis.[2] Variable expression has been reported, even among related individuals who are homozygous for pathogenic variants.[6] PH2 is characterized by excessive urinary excretion of oxalate and L-glycerate.[5,6]

Primary hyperoxaluria type 3 (PH3) is caused by pathogenic variants in the HOGA1 gene. The HOGA1 gene is expressed primarily in liver and kidney and encodes 4-hydroxy-2-oxoglutarate aldolase (HOGA), which catalyzes the final step in the processing of hydroxyproline in the mitochondria.[7,8] Phenotypic features of PH3 overlap with PH1 and PH2, and include nephrolithiasis, nephrocalcinosis, and end stage renal disease with a history of renal stones or calcinosis and onset is typically in childhood or adolescence.[3] Although systemic oxalosis is well-recognized in PH1 and PH2, it has not been reported to date in PH3.[3]

INHERITANCE PATTERN

Variants in the AGXT, GRHPR, and HOGA1 genes are inherited in an autosomal recessive manner.

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the AGXT, GRHPR, and HOGA1 genes 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 the reference sequence 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. 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.

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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.

VARIANT SPECTRUM

Many types of variants have been reported in the AGXT, GRHPR, and HOGA1 genes, with missense variants and small deletions being the most common. Exon-level deletions or duplications have not been reported in GRHPR or HOGA1 to our knowledge.[9]

Four AGXT variants [p.Gly170Arg, p.Phe152Ile, p.Ile244Thr, and c.33dupC (p.Lys12GlnfsTer156)] account for >65% of PH1 disease-causing alleles. The p.Gly170Arg, p.Phe152Ile, and p.Ile244Thr variants occur on the minor AGXT allele haplotype; this haplotype includes the p.Pro11Leu variant which creates a cryptic mitochondrial targeting sequence. The c.33dupC variant occurs on the major allele haplotype, defined by the transcript variant NM_000030.2.2 The c.944_946delAGG (p.Glu315del) and c.700+5G>T variants on the HOGA1 gene account for approximately 75% of PH3 disease-causing alleles. The c.944_946delAGG variant is common in the Ashkenazi Jewish population.[3]

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Gene Name	Associated Disorder(s)	OMIM #
AGXT	Hyperoxaluria, primary, type I	259900 (AR)
GRHPR	Hyperoxaluria, primary, type II	260000 (AR)
HOGA1	Hyperoxaluria, primary, type III	613616 (AR)

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