

Primary Hyperoxaluria Panel

Panel Gene List: *AGXT*, *GRHPR*, *HOGA1*

Clinical Features:

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.¹⁻⁴

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.² 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.⁵ Clinical features include failure to thrive, hematuria, anemia, abdominal pain, urinary tract infections, nephrocalcinosis, recurrent nephrolithiasis, metabolic acidosis, ESRD, and systemic oxalosis.^{4,5} 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.⁵

Primary hyperoxaluria type 2 (PH2) is caused by pathogenic variants in the *GRHPR* gene, which encodes the enzyme glyoxylate reductase/hydroxypyruvate reductase. Age of onset is typically childhood and clinical symptoms include recurrent nephrolithiasis, nephrocalcinosis, ESRD, and systemic oxalosis.³ 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.^{6,7}

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.⁸⁻⁹ 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. Although systemic oxalosis is well-recognized in PH1 and PH2, it has not been reported to date in PH3.⁴

Inheritance Pattern:

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

Genetics:

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.¹⁰

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.⁴

Test Methods:

Using genomic DNA from the submitted specimen, analysis of the *AGXT*, *GRHPR*, and *HOGA1* genes is performed using bi-directional sequence analysis of the coding exons and the corresponding intron/exon boundaries. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of these genes. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Clinical Sensitivity:

In individuals affected with primary hyperoxaluria, approximately 70% have PH1, 10% have PH2, and 10% have PH3. About 10% of individuals with a PH-like phenotype are not found to have pathogenic variants in *AGXT*, *GRHPR*, or *HOGA1*.^{6,11}

References:

1. <https://ghr.nlm.nih.gov/condition/primary-hyperoxaluria>
2. Milliner DS, Harris PC, Cogal AG, et al. Primary Hyperoxaluria Type 1. 2002 Jun 19 [Updated 2017 Nov 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1283/>
3. Rumsby G, Hulton SA. Primary Hyperoxaluria Type 2. 2008 Dec 2 [Updated 2017 Dec 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK2692/>
4. Milliner DS, Harris PC, Lieske JC. Primary Hyperoxaluria Type 3. 2015 Sep 24. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK316514/>
5. Al Riyami et al. (2015) Int J Nephrol 2015 :634175 (PMID: 25918646)
6. Hopp et al. (2015) J. Am. Soc. Nephrol. 26 (10):2559-70 (PMID: 25644115)
7. Webster et al. (2000) Human genetics 107 (2):176-85 (PMID: 11030416)
8. Belostotsky et al. (2010) Am J Hum Genet. 87(3):392-9 (PMID: 20797690)
9. Williams et al. (2012) Nephrol Dial Transplant 27:3191-3195 (PMID: 22391140)
10. Stenson et al. (2014) Human genetics 133 (1):1-9 (PMID: 24077912)
11. Cochat P and Rumsby G (2013) N. Engl. J. Med. 369 (7):649-58 (PMID: 23944302)

Gene Name	Associated Disorder(s)	OMIM #
<i>AGXT</i>	Hyperoxaluria, primary, type 1	259900 (AR)
<i>GRHPR</i>	Hyperoxaluria, primary, type II	260000 (AR)
<i>HOGA1</i>	Hyperoxaluria, primary, type III	613616 (AR)