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NLM Citation: Rumsby G, Hulton SA. Primary Hyperoxaluria Type 2. 2008 Dec 2 [Updated 2017 Dec 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Primary Hyperoxaluria Type 2

Synonym: Glyoxylate Reductase/Hydroxypyruvate Reductase Deficiency

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Created: December 2, 2008; Updated: December 21, 2017.

Summary

Clinical characteristics

Primary hyperoxaluria type 2 (PH2), caused by deficiency of the enzyme glyoxylate reductase/hydroxypyruvate reductase (GR/HPR), is characterized by recurrent nephrolithiasis (deposition of calcium oxalate in the renal pelvis/urinary tract), nephrocalcinosis (deposition of calcium oxalate in the renal parenchyma), and end-stage renal disease (ESRD). After ESRD, oxalosis (widespread tissue deposition of calcium oxalate) usually develops. Symptom onset is typically in childhood.

Diagnosis/testing

The diagnosis of PH2 is established in a proband by identification of biallelic pathogenic variants in *GRHPR* by molecular genetic testing. If no pathogenic variants or only one pathogenic variant is identified by molecular genetic testing, identification of reduced glyoxylate reductase enzyme activity on liver biopsy can establish the diagnosis of PH2.

Management

Treatment of manifestations: Reduction of urinary calcium oxalate supersaturation through adequate daily fluid intake and treatment with inhibitors of calcium oxalate crystallization (orthophosphate, potassium citrate, and magnesium); temporary intensive dialysis for ESRD, followed by transplantation.

Surveillance: Biannual assessment of renal function, urinalysis with measurements of urine oxalate excretion (using 24-hour collection if easy to facilitate or spot urine oxalate to creatinine ratio), and calcium oxalate saturation if available, blood pressure, and full blood count including hematocrit; assessment of renal stone burden every six to 12 months by urinary tract imaging (renal ultrasound or CT); assessment of cardiac, skin, bone, joint, eye, thyroid, and hematologic involvement annually after progression to ESRD.

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Agents/circumstances to avoid: Dehydration. Ascorbate (vitamin C) ingestion and foods rich in oxalate (chocolate, rhubarb, and star fruit) may cause additional minimal increase in urinary oxalate levels in select individuals; excess should be discouraged; high salt (sodium) diet should be discouraged; excessive stone interventions with extracorporal shock wave lithotripsy.

Evaluation of relatives at risk: For asymptomatic at-risk relatives offer urine analysis and, if indicated by the results of urine analysis, molecular genetic testing (if the pathogenic variants in the family are known) so that early diagnosis can inform treatment.

Genetic counseling

PH2 is inherited in an autosomal recessive manner. Each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Primary hyperoxaluria type 2 (PH2) **should be suspected** in individuals with the following clinical and laboratory features.

Clinical features

- Symptoms of nephrolithiasis (e.g., hematuria, renal colic, obstruction of the urinary tract)
- Frequent recurrent nephrolithiasis
- Nephrocalcinosis
- End-stage renal disease with a history of nephrolithiasis

Laboratory features

- **Kidney stone analysis.** Kidney stones containing predominantly calcium oxalate
- **Increased urinary oxalate,** typically greater than 0.7 mmol/1.73 m^2/24h (normal <0.46 mmol/1.73 m^2/24h). A 24-hour collection in acid is preferable to a random sample.
- **Increased urinary L-glycerate.** This analyte may be detected on an organic acid screen, but there is considerable variability between methods and a specific method for glycerate is preferable.
- **Increased plasma oxalate.** After the onset of renal failure, measurement of plasma oxalate concentration may be helpful. In contrast to the elevated plasma oxalate concentrations in persons with renal failure from other causes, plasma oxalate concentrations in individuals with primary hyperoxaluria with glomerular filtration rate lower than 20 mL/min/1.73 m^2 often exceed 50 µmol/L.

Establishing the Diagnosis

The diagnosis of PH2 **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *GRHPR* by molecular genetic testing (see Table 1). If no pathogenic variants or only one pathogenic variant is identified by molecular genetic testing, identification of reduced glyoxylate reductase enzyme activity on a liver biopsy can establish the diagnosis of PH2.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *GRHPR* variants of

uncertain significance (or of one known *GRHPR* pathogenic variant and one *GRHPR* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *GRHPR* is performed first and may be followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *GRHPR* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Primary Hyperoxaluria Type 2

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
GRHPR	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Author, personal communication
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Assay of glyoxylate reductase enzyme activity

- The enzyme is primarily expressed in the liver [Cregeen et al 2003] and can be analyzed in liver tissue using the method described by Giafi and Rumsby [1998]. A needle biopsy (~20 mg of tissue) is required and the sample must be frozen immediately and shipped frozen to the laboratory.
- Note: The enzyme has also been shown to be expressed in leukocytes [Knight et al 2006]; however, because of questions about the expression of the gene in leukocytes [Bhat et al 2005] and the low activity, measurement of enzyme activity in liver biopsy rather than leukocytes is recommended for diagnosis [Author, personal observation].

Clinical Characteristics

Clinical Description

The age of onset of primary hyperoxaluria type 2 (PH2) is typically in childhood [Milliner et al 2001, Johnson et al 2002], with those diagnosed in later life often relating symptoms from childhood [Rumsby et al 2001, Takayama et al 2007]. As in PH1, diagnosis is often delayed, sometimes even for years.

Presenting symptoms are typically those associated with the presence of renal stones including hematuria, renal colic, or obstruction of the urinary tract [Johnson et al 2002]. Affected individuals may also present with nephrocalcinosis or end-stage renal disease (ESRD).

The majority of individuals have renal stones composed of calcium oxalate [Milliner et al 2001, Johnson et al 2002].

Nephrocalcinosis, observed on ultrasound examination, abdominal x-ray, or CT examination, is a much less common finding in PH2 than in PH1.

The disease can progress to ESRD although this outcome appears to be later in PH2 than in PH1, in which 50% of affected individuals have ESRD by age 25 years [Leumann & Hoppe 2001]. In a recent review of data collected through the OxalEurope Registry, of 83 individuals with PH2, 20% developed ESRD at follow up [S Hulton, personal communication].

Oxalosis. Once ESRD occurs, deposition of oxalate can occur in organs other than kidney, including bone, bone marrow, joints, retina, and myocardium [Wichmann et al 2003, Wachter et al 2006] along with calcified nodules on the fingers [Yamanouchi et al 2016].

Oxalate deposition in bone results in x-ray findings of transverse translucent symmetric bands with fixed sclerotic margins at the end of long bones followed by cystic rarefaction of the bones. Osteodystrophy causes bone pain and multiple pathologic fractures occur in advanced disease. Involvement of the bone marrow can result in anemia refractory to erythropoietin-stimulating agents.

Additional clinical manifestations of oxalosis may include visual disturbance due to retinopathy and/or maculopathy, cardiac conduction disturbances such as heart block, cardiomyopathy, and synovitis secondary to oxalate deposition in the joints. Vascular involvement can lead to ischemia, most often manifest as non-healing cutaneous ulcers. Dental complications include periodontal disease. Hypothyroidism is also reported.

Genotype-Phenotype Correlations

The low prevalence of PH2 does not allow genotype-phenotype correlations at the present time.

Nomenclature

Primary hyperoxaluria type 2 was originally described as:

- L-glyceric aciduria, referring to the excessive production of urinary L-glycerate;
- D-glycerate dehydrogenase deficiency, referring to the non-physiologic action of the enzyme in catalyzing the dehydrogenation of D-glycerate.

As the more important enzyme reaction appears to be that of glyoxylate reduction, the name glyoxylate reductase is now favored.

Prevalence

No data regarding the prevalence of PH2 exist. It is thought to be less common than primary hyperoxaluria type 1, which has a prevalence of approximately 1:1,000,000. However, there may be ascertainment bias in that individuals with early signs of PH2 may be misclassified clinically as having PH1 on the grounds of severity of symptoms, and the correct diagnosis recognized only with appropriate testing.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with pathogenic variants in *GRHPR*.

Differential Diagnosis

Primary hyperoxaluria type 1 (PH1) is the most common form of inherited hyperoxaluria, accounting for approximately 80% of cases. It is caused by a deficiency of the liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT), which catalyzes the conversion of glyoxylate to glycine. When AGT activity is absent, glyoxylate is converted to oxalate, which forms insoluble calcium salts that accumulate in the kidney and other organs. Individuals with PH1 are at risk for recurrent nephrolithiasis (deposition of calcium oxalate in the renal pelvis/urinary tract), nephrocalcinosis (deposition of calcium oxalate in the renal parenchyma), or ESRD with a history of renal stones or oxalosis. Although the hyperoxaluria is present from birth and most individuals present in childhood or adolescence, age at symptom onset ranges from infancy to adulthood. Approximately 15% of affected individuals present before age four to six months with severe disease including nephrocalcinosis; 55% present in childhood or early adolescence with symptomatic nephrolithiasis; and the remainder present in adulthood with recurrent renal stones. Untreated PH1 often progresses to nephrolithiasis/nephrocalcinosis, decline in renal function, systemic oxalosis (widespread tissue deposition of calcium oxalate), and death from ESRD. Diagnosis relies on: (1) either (a) detection of increased urinary oxalate excretion (or elevated oxalate:creatinine ratio) or (b) in the setting of moderate to advanced renal failure, increased plasma oxalate concentration; and (2) deficiency of AGT catalytic activity from liver biopsy or molecular genetic testing of *AGXT*, the only gene known to be associated with PH1. Inheritance is autosomal recessive.

Primary hyperoxaluria type 3 (PH3) has a phenotype similar to that of PH1 and PH2 and accounts for approximately 10% of cases of primary hyperoxaluria [Cochat & Rumsby 2013]. A provisional biochemical diagnosis can be made by the finding of elevated 4-hydroxy-2-oxoglutarate and dihydroxyglutarate in urine followed by confirmation with sequence analysis of *HOGA1*. Pathogenic variants in *HOGA1* result in deficiency of mitochondrial 4-hydroxy-2-oxoglutarate aldolase, an enzyme that catalyzes one of the steps in the metabolism of hydroxyproline. The hyperoxaluria in individuals with PH3 arises from breakdown of the substrate for the enzyme rather than excessive production of glyoxylate. Inheritance is autosomal recessive.

Other hereditable causes of kidney stones. Other heritable disorders that present with early stone formation include Dent disease, renal tubular acidosis, cystinuria (OMIM 220100), xanthinuria (OMIM 278300, 603592), and adenine phosphoribosyltransferase deficiency. In individuals presenting with symptoms related to renal stone disease it is essential to analyze the stone if possible as this can help to direct the clinician to a particular line of investigation. Urine should be analyzed for a stone risk profile that typically includes assessment of urine volume, oxalate, calcium, magnesium, citrate, phosphate, sodium, and urate.

End-stage renal disease (ESRD). For persons presenting in ESRD, reliable measurement of urine oxalate excretion is not possible. Plasma oxalate elevations ranging up to 40 µmol/L may be detected with any form of ESRD; plasma oxalate concentrations exceeding 50 µmol/L are suggestive of primary hyperoxaluria. While PH1 and PH2 are a rare cause of ESRD in adults, PH can account for 0.7%-1.6% of ESRD in children. In a native kidney or renal allograft biopsy, PH should be considered if birefringent crystals are seen under polarized light. Although the measurement of plasma L-glycerate can identify individuals with PH2 who are in ESRD, such

testing is not routinely available. Definitive diagnosis requires molecular genetic testing or analysis of relevant enzymes in a liver biopsy.

Enteric hyperoxaluria. Disorders of the gastrointestinal tract leading to malabsorption (e.g., celiac disease, Crohn disease, pancreatitis, short bowel syndrome) have the potential to increase oxalate absorption and lead to hyperoxaluria; they can usually be excluded based on history. Gastric bypass procedures have been associated with increased oxalate absorption, high levels of hyperoxaluria, and increased risk of kidney stone formation [Asplin & Coe 2007, Kleinman 2007, Duffey et al 2008, Lieske et al 2008]. Urinary risk factors for stones such as hyperoxaluria occur more commonly in individuals with Roux-en-Y gastric bypass than gastric banding [Semins et al 2010, Kumar et al 2011, Tasca 2011].

Dietary hyperoxaluria. Excess intake of foods high in oxalate including chocolate, cocoa, leafy greens (especially rhubarb and spinach), black tea, nuts, peanut butter, or starfruit may increase urinary concentration of oxalate. Between 24% and 53% of urinary oxalate is attributable to oxalate from the diet [Holmes & Assimos 2004]. Therapy consists of dietary oxalate restriction and use of calcium carbonate or calcium citrate at meal times to bind dietary oxalate [Penniston & Nakada 2009].

Megadoses of vitamin C (4 g/day) have led to hyperoxaluria [Nasr et al 2006], as has (deliberate or accidental) ingestion of ethylene glycol.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with primary hyperoxaluria type 2 (PH2), the following evaluations, originally outlined for PH1, are recommended if they have not already been completed [Cochat et al 2012]:

- Assessment of renal function
- If moderate to advanced ESRD is present, assessment of systemic oxalate deposition in tissue and bone:
  - Bone x-rays to look for radiodense metaphyseal bands followed by cystic rarefaction of bones
  - Ophthalmic examination of the retina to look for oxalate crystals
  - Evaluation of cardiac function by echocardiography and EKG
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Management follows general guidance for that of renal stones: to relieve obstruction, and to manage symptoms of renal impairment as they arise.

Reduction of Calcium Oxalate Supersaturation

As with PH1, conservative therapy is applied with the aim of minimizing oxalate-related renal injury and preserving renal function. Treatment of persons with preserved renal function, reviewed by Cochat et al [2012], essentially aims to improve oxalate solubility as follows:

- Adequate fluid intake (>2.5 L/m^2 surface area/day)
- Urinary inhibitors of calcium oxalate crystallization:
  - Orthophosphate treatment (20-30 mg/kg body weight/day)
  - Potassium citrate (0.1-0.15 g/kg body weight/day)

Dialysis

Because the plasma oxalate concentration begins to rise when the renal clearance is less than 40 mL/min/1.73 m^2, early initiation of dialysis or preemptive kidney-only transplantation is preferred.

Oxalate clearance on hemodialysis is greater than on peritoneal dialysis (120 mL/min on hemodialysis vs 7 mL/min on peritoneal dialysis): standard hemodialysis programs will result in clearance of oxalate of 6-9 mmol/ 1.73 m^2/week, which is equivalent to two to three days of endogenous production of oxalate. Thus a combination of modalities, with intermittent daily hemodialysis together with overnight peritoneal dialysis, or intense home hemodialysis, enhances the overall clearance of oxalate and attempts to reduce the rebound that occurs after hemodialysis. These combination therapies, with the use of high flux dialyzers or long episodes of hemofiltration, have all been advocated to improve oxalate removal [Hoppe et al 1996, Illies et al 2006].

For individuals in ESRD, intensive (daily) dialysis is required to maximize oxalate removal. As in PH1, the longer the individual with PH2 is on dialysis the more likely systemic oxalate deposition will occur.

Organ Transplantation

Kidney transplantation alone has been used in PH2 with varying success. Careful management in the postoperative period, with attention to brisk urine output and use of calcium oxalate urinary inhibitors, minimizes the risk of allograft loss as a result of oxalate deposition. As it is not unusual for such transplants to fail in individuals with PH2 and as there is more enzyme present in the liver than in other tissues [Cregeen et al 2003], combined liver-kidney transplant may have some merit.

To date, there is just one published report of a successful liver-kidney transplantation in an individual with PH2 with a previously failed renal allograft [Dhondup et al 2018]. Urine glycerate and oxalate and plasma oxalate all normalized within one month post transplant and remained normal for the 13-month follow up.

Other

Pharmacologic doses of pyridoxine are used as a treatment in individuals with PH1 because of its role as a cofactor for the defective enzyme. There is no supportive evidence for the use of pyridoxine in individuals with PH2.

Prevention of Primary Manifestations

The main preventive treatment is to maintain adequate hydration status and to enhance calcium oxalate solubility with exogenous citrate and neutral phosphates as described in Treatment of Manifestations.

Surveillance

Frequency of recommended screening can vary; however, as a guide, the following are recommended.

Individuals with preserved renal function (i.e., measured or estimated GFR ≥60 mL/min/1.73 m^2) require the following to evaluate/ensure treatment efficacy:

- **Biannually.** Assessment of renal function, urinalysis with measurements of urine oxalate excretion using 24-hour collection if easy to facilitate; or spot urine oxalate-to-creatinine ratio, and calcium oxalate saturation if available, blood pressure, and full blood count including hematocrit. The presence of blood in the urine may indicate stones, but protein in an early morning sample necessitates review of renal function as it may herald a decline in GRF.
- **Biannually to annually.** Renal imaging (ultrasound or CT examination) to assess renal stone burden as appropriate. Note: Annual scans are appropriate if no stones or nephrocalcinosis are visualized.

Individuals with a GFR <60 mL/min/1.73 m^2 should have the above evaluations performed quarterly, as well as the following testing **annually** to evaluate for involvement of other organ systems apart from the renal tract.

- **Bone.** X-ray examination to evaluate for the development of transverse translucent symmetric bands with fixed sclerotic margins at the end of long bones, cystic rarefaction of bones, and pathologic fractures. DXA (dual-energy x-ray absorptiometry) scanning may be considered every five years. MRI or CT scanning of bones may provide further information but are not routinely recommended at present.
- **Hematology.** Full blood count with hematocrit for anemia; a bone marrow aspirate may rarely be required to determine if oxalate crystals in the bone marrow are contributing to an erythropoietin resistant anemia.
- **Eye.** Ophthalmology examination with fundoscopy to evaluate for retinopathy and maculopathy
- **Cardiac.** Electrocardiogram for cardiac conduction defects and echocardiogram to evaluate contractility if appropriate
- **Skin.** Clinical examination for subungual deposits of oxalate and cutaneous ulcers as evidence of vasculopathy
- **Joints.** Clinical examination for evidence of synovitis; arthroscopy may be considered on an individual basis.
- **Teeth.** Dental examination for periodontal disease
- **Thyroid.** Thyroid function tests including TSH and free T4 for hypothyroidism
- **Plasma oxalate.** Measure every four to six months until GFR falls below 15 mL/min/1.73 m^2 when levels will be noted to rise in keeping with renal impairment and may become more difficult to interpret. While on dialysis, measure plasma oxalate monthly to inform changes in dialysis prescription.

Agents/Circumstances to Avoid

The following should be avoided:

- Dehydration
- Excessive ascorbate (i.e. vitamin C; >1000 mg/day)
- Foods rich in oxalate (chocolate, rhubarb, spinach, and star fruit in particular)
- High salt (sodium) diet should be discouraged.
- Excessive stone interventions with extracorporal shock wave lithotripsy

Evaluation of Relatives at Risk

In order to delay disease onset in asymptomatic relatives, it is prudent to evaluate at-risk family members before symptoms occur. Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Measurement of urinary oxalate excretion if the pathogenic variants in the family are not known.

Molecular genetic testing tends to be more reliable as urine oxalate output can be variable in childhood.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

For pregnant women with PH2, close monitoring by both an obstetrician and nephrologist is indicated because of the increased risk of decline in renal function together with developing nephrolithiasis during pregnancy or after delivery.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Oxalobacter formigenes treatment did not demonstrate significant effect in reducing oxalate via gut excretion in individuals with PH1 but continues to undergo clinical trials in individuals with hyperoxaluria and impaired renal function [Hoppe et al 2017].

Other proposed trials include the use of inhibitors of glycolate oxidase (ALN-GO1) to reduce the amount of glyoxylate produced, although this treatment would be mainly relevant to treatment of individuals with PH1.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary hyperoxaluria type 2 (PH2) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of *GRHPR* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with PH2 are obligate heterozygotes (carriers) for a pathogenic variant in *GRHPR*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *GRHPR* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *GRHPR* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *GRPHR* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful. Complications relating to renal and/or liver transplantation and scarcity of suitable organs for transplantation may be a consideration for parents who already have one affected child.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Primary hyperoxaluria
- **Oxalosis & Hyperoxaluria Foundation**
  Phone: 212-777-0470
  Email: info@ohf.org
  ohf.org
- **Kidney Health Initiative Patient and Family Partnership Council (KHI PFPC)**
  Engaging the Patient Voice
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **OxalEurope Registry (OER)**
  oxaleurope.org/registry
- **Rare Kidney Stone Consortium Registry**
  Phone: 800-270-4637 (toll-free)
  Email: hyperoxaluriacenter@mayo.edu
  Rare Kidney Stone Consortium Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Primary Hyperoxaluria Type 2: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GRHPR	9p13.2	Glyoxylate reductase/ hydroxypyruvate reductase	GRHPR database	GRHPR	GRHPR

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Primary Hyperoxaluria Type 2 (View All in OMIM)

260000	HYPEROXALURIA, PRIMARY, TYPE II; HP2
604296	GLYOXYLATE REDUCTASE/HYDROXYPYRUVATE REDUCTASE; GRHPR

Gene structure. *GRHPR* (previously known as *GLXR*) is composed of nine exons spanning approximately 9 kb. The transcript NM_012203.1 encodes a protein of 328 amino acids (NP_036335.1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Information on specific pathogenic variants is available in the HGMD, ClinVar, and locus-specific databases in Table A.

Table 2. Selected *GRHPR* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.103delG	p.Asp35ThrfsTer11	NM_012203.1 NP_036335.1
c.403_404+2delAAGT	Missplicing	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The normal protein is a homodimer. The protein has a large coenzyme-binding domain (residues 107-298) and a smaller substrate-binding domain (5-106 and 299-328) [Booth et al 2006]. A prominent extended helical and loop region wraps around the other subunit (dimerization loop, residues 123-149). The apex of this loop contains a tryptophan residue at position 141 and the residue from one subunit is projected into the active site of the other subunit and contributes to substrate specificity [Booth et al 2006]. The protein is found primarily in the cytosol although some immunoreactivity has been found within the mitochondria of cells [Knight & Holmes 2005, Behnam et al 2006]. The significance of this finding in vivo is unknown.

Abnormal gene product. All the pathogenic missense variants described to date result in proteins with no catalytic activity [Webster et al 2000, Cregeen et al 2003]. Other variants that affect splicing or create frameshifts or nonsense variants would also fail to yield a functional product. All pathogenic variants are, therefore, essentially null alleles.

Chapter Notes

Revision History

- 21 December 2017 (sw) Comprehensive update posted live
- 5 May 2011 (me) Comprehensive update posed live
- 2 December 2008 (me) Review posted live
- 9 September 2008 (gr) Original submission

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