

Primary Hyperoxaluria Type III Gene *HOGA1* (Formerly *DHDSL*) as a Possible Risk Factor for Idiopathic Calcium Oxalate Urolithiasis

Carla G. Monico,* Sandro Rossetti,* Ruth Belostotsky,[†] Andrea G. Cogal,* Regina M. Herges,* Barbara M. Seide,* Julie B. Olson,* Eric J. Bergstrahl,* Hugh J. Williams,[‡] William E. Haley,[‡] Yaacov Frishberg,[†] and Dawn S. Milliner*

Summary

Background and objectives Primary hyperoxaluria types I and II (PHI and PHII) are rare monogenic causes of hyperoxaluria and calcium oxalate urolithiasis. Recently, we described type III, due to mutations in *HOGA1* (formerly *DHDSL*), hypothesized to cause a gain of mitochondrial 4-hydroxy-2-oxoglutarate aldolase activity, resulting in excess oxalate.

Design, setting, participants, & measurements To further explore the pathophysiology of *HOGA1*, we screened additional non-PHI-PHII patients and performed reverse transcription PCR analysis. Postulating that *HOGA1* may influence urine oxalate, we also screened 100 idiopathic calcium oxalate stone formers.

Results Of 28 unrelated hyperoxaluric patients with marked hyperoxaluria not due to PHI, PHII, or any identifiable secondary cause, we identified 10 (36%) with two *HOGA1* mutations (four novel, including a nonsense variant). Reverse transcription PCR of the stop codon and two common mutations showed stable expression. From the new and our previously described PHIII cohort, 25 patients were identified for study. Urine oxalate was lower and urine calcium and uric acid were higher when compared with PHI and PHII. After 7.2 years median follow-up, mean eGFR was 116 ml/min per 1.73 m². *HOGA1* heterozygosity was found in two patients with mild hyperoxaluria and in three of 100 idiopathic calcium oxalate stone formers. No *HOGA1* variants were detected in 166 controls.

Conclusions These findings, in the context of autosomal recessive inheritance for PHIII, support a loss-of-function mechanism for *HOGA1*, with potential for a dominant-negative effect. Detection of *HOGA1* variants in idiopathic calcium oxalate urolithiasis also suggests *HOGA1* may be a predisposing factor for this condition.

Clin J Am Soc Nephrol 6: 2289–2295, 2011. doi: 10.2215/CJN.02760311

Introduction

The amount of oxalate excreted in the urine (normal <0.46 mmol/1.73 m² per 24 h) is a major risk factor for calcium oxalate–stone formation (1,2). Marked hyperoxaluria (>0.8 mmol/1.73 m² per 24 h) can arise from gene defects of hepatic glyoxylate metabolism: primary hyperoxaluria type I (PHI), caused by deficiency or mistargeting of alanine:glyoxylate aminotransferase (AGT) activity (EC 2.6.1.44) (3), or primary hyperoxaluria type II (PHII), caused by glyoxylate reductase/hydroxypyruvate reductase (GRHPR) (EC 1.1.1.79) deficiency (4).

Marked hyperoxaluria not caused by PHI or PHII was first described in 1996 (5). Careful study and phenotypic characterization of a subsequent cohort of affected children excluded gastrointestinal hyperabsorption and other secondary causes of hyperoxaluria (6). These observations, along with findings of an affected sibship in one pedigree, suggested an inher-

ited disorder of primary or metabolic cause, referred to as non-PHI-PHII primary hyperoxaluria. However, screening of two promising candidate genes relevant to oxalate metabolism, glycolate oxidase, and SLC26A6 yielded negative results (6,7).

Recently, we identified mutations in a novel gene *HOGA1* as one cause of non-PHI-PHII primary hyperoxaluria, hypothesizing a gain of hepatic or renal mitochondrial 4-hydroxy-2-oxoglutarate aldolase (*HOGA1*) activity as the underlying metabolic source of excess oxalate (8). Hyperoxaluria caused by mutations in *HOGA1* is now referred to as primary hyperoxaluria type III (PHIII).

At present, our understanding of the pathways (and subcellular compartments) that contribute to and metabolize glyoxylate in human liver (and kidney), including that of hydroxyproline, which is implicated in PHIII, is incomplete (9–11). It is noteworthy, however, that clinical experience to date suggests that

*Mayo Clinic Hyperoxaluria Center, Divisions of Nephrology and Hypertension, and Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; [†]Division of Pediatric Nephrology, Shaare Zedek Medical Center, and the Hadassah-Hebrew University School of Medicine, Jerusalem, Israel; and [‡]Mayo Clinic, Divisions of Nephrology & Hypertension and Diagnostic Radiology, Jacksonville, Florida

Correspondence:

Dr. Carla G. Monico, Mayo Clinic, Division of Nephrology, 200 First Street, SW, Rochester, MN 55905. Phone: 507-266-1045 Fax: (507) 266-7891; E-mail: monico.carla@mayo.edu

PHIII is an autosomal recessive trait (6,8), an observation that is incongruent with a gain of function mechanism for HOGA1 (8).

To explore alternative mechanistic explanations and reach more definitive conclusions about the pathogenic mechanism of HOGA1, we set out to study the effect of the two most common HOGA1 mutations, an in-frame deletion (c.944_946 del AGG, p.Glu315del) and a splice site variant (IVS700 + 5 G>T), at the RNA level. Using a variety of *in silico* tools, we also developed a scoring system of pathogenicity for HOGA1 missense variants.

In an effort to establish the frequency of PHIII, we performed HOGA1 screening in additional probands meeting criteria of non-PHI-PHII primary hyperoxaluria, ascertaining 10 new unrelated families. Their genotype data are presented here, along with phenotypic characterization of the 25 PHIII cases described so far, including comparative analyses with PHI and PHII, using data from the International Primary Hyperoxaluria Registry (IPHR).

Postulating that genetic variants in HOGA1 may influence urine oxalate and hence the risk of idiopathic calcium oxalate-stone formation, we screened 100 unrelated idiopathic calcium oxalate stone formers and found three HOGA1 variants: two novel and one previously described (in PHIII). None were detected in negative controls. The findings lend support to HOGA1 as a susceptibility gene for idiopathic calcium oxalate urolithiasis.

Materials and Methods

Patient Recruitment

From routine inquiries and referrals to the Mayo Clinic Hyperoxaluria Center, we first selected for HOGA1 screening patients who met clinical criteria for primary hyperoxaluria (urine oxalate, >0.8 mmol/1.73 m² per 24 h in the absence of gastrointestinal disease or other identifiable secondary causes) who were also AGXT and GRHPR mutation negative and/or proven to have normal hepatic AGT and GRHPR activities by hepatic enzyme analysis. Patients with milder degrees of hyperoxaluria (0.46 to 0.8 mmol/1.73 m² per 24 h) and negative AGXT, GRHPR, and SLC26A6 mutation screening were also subsequently included in the analysis.

In collaboration with Mayo Clinic Jacksonville, we also recruited for testing a population of idiopathic calcium oxalate stone formers and controls. The patients were identified from routine referrals to the Division of Nephrology, and controls were chosen from patients undergoing computed tomography imaging in the Department of Radiology at Mayo Clinic Jacksonville. Controls were defined as patients with radiographic confirmation of absence of urolithiasis and a negative personal history of symptomatic urolithiasis.

Phenotype Analyses

Phenotype data were obtained from studies in our laboratory or extracted from patients' outside medical records. All patients and first degree relatives provided informed consent to DNA testing and record review under research protocols approved by the Mayo Clinic Institutional Review Board. Comparative phenotypic data in PHI and PHII was obtained from the IPHR.

Molecular Screening of Human HOGA1

Genomic DNA was extracted from peripheral blood leukocytes using standard methods. Mutation screening was accomplished by direct sequencing of the seven exonic and flanking intronic regions of HOGA1. PCR conditions are as listed in the Supplemental Methods section. Sequencing was performed in both directions using an ABI PRISM 3730 DNA Analyzer (Applied Biosystems), and sequencing chromatograms were analyzed using version 3.24 of Mutation Surveyor software.

The significance of novel missense variants was assessed using PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph/>), SIFT (<http://blocks.fhcrc.org/sift/SIFT.html>), Align GVGD (http://agvgd.iarc.fr/agvgd_input.php), and PhD-SNP (<http://gpcr2.biocomp.unibo.it/~emidio/PhD-SNP/PhD-SN.htm>). Scores derived from the single tools were added into an overall score as "highly likely pathogenic" (when four to five of five tools predicted pathogenicity), as "likely pathogenic" (when three of five tools predicted pathogenicity), as "indeterminate" (when two of five tools predicted pathogenicity), and "neutral" (when 0 to one of five tools predicted pathogenicity).

The effect of a common in-frame deletion mutation (c.944_946 del AGG) and a splice site variant (IVS700 + 5 G>T) was assessed by reverse transcription (RT)-PCR using HOGA1-specific exonic primer pairs on exons 5 (forward) and 7 (reverse). RT-PCR primer pairs and conditions are as listed in the Supplemental Methods section. RNA was isolated from Epstein Barr Virus-transformed lymphoblast cell lines using TRizol (Invitrogen, Carlsbad, CA) or from peripheral blood lymphocytes isolated in a PAXgene blood RNA tube from Qiagen, and cDNA was generated using the Superscript III cDNA synthesis kit from Invitrogen.

Statistical Analyses

Comparisons between PHI, PHII, and PHIII were done using the chi-squared test (nominal factors) or Kruskal-Wallis ANOVA (continuous or ordinal factors). All of the tests were two-sided using an α level of 0.05.

Results

First, we sequenced the entire HOGA1 coding region in a panel of 28 unrelated hyperoxaluric patients meeting criteria of marked hyperoxaluria not caused by PHI, PHII, or any identifiable secondary cause. From this group of patients, we identified 10 patients (36%) with two HOGA1 mutations. HOGA1 mutation data, hepatic enzyme analysis, and metabolite data are shown in Table 1. Clinical features and the corresponding laboratory parameters at presentation are listed in Supplemental Table 1.

The two most common HOGA1 mutations identified so far are c.944_946 del AGG (p.Glu315del) and IVS700 + 5 G>T, with calculated allelic frequencies of 46% and 24%, respectively, and an apparent founder effect for c.944_946 del AGG in Jewish-Ashkenazi individuals (8). RT-PCR data for IVS700 + 5 G>T are shown in Figure 1. This variant appears to weaken the wild-type donor splice site allowing a downstream GT cryptic donor site at position + 52 to become active, resulting in an in-frame insertion of 51

Table 1. HOGA1 screening, hepatic enzyme analysis, and metabolic profile

| Pt | HOGA1 Mutation 1 | HOGA1 Mutation 2 | AGT Activity (Normal 19.1 to 47.9 μmol/hr/ mg protein) | GRHPR Activity (Normal 23 to 207 nmol/min/ mg protein) | Urine Glyoxylate (Normal <3) (μg/mg creat) | Urine Glycolate (Normal <79 μg/mg creat) | Urine Glycerate (Normal <19 (μg/mg creat) | Plasma Oxalate (Normal <1.8) (μmol/L) | Screat (mg/dl) @ Pox | Enteric Oxalate Absorption (Normal <15%) (%) ^a |
|----|-----------------------------|------------------------------|---|---|--|---|---|---|----------------------------|--|
| 1 | IVS700 + 5G>T | c.944_946 het_delAGG | 47.8 | 58 | NA | 19 | 1 | NA | NA | NA |
| 2 | c.907C>T, p.R303C | c.944_946 het_delAGG | 29.7 | 49 | 0 | 6 | 0 | 3.3 | 1.6 | 3.1 |
| 3 | c.944_946 het_delAGG | c.944_946 het_delAGG | AGXT mutation negative | GRHPR mutation negative | NA | NA | NA | NA | NA | NA |
| 4 | IVS700 + 5G>T | c.944_946 het_delAGG | AGXT mutation negative | GRHPR mutation negative | 1.6 | 16 | 4 | NA | NA | NA |
| 5 | IVS700 + 5G>T | c.860G>T, p.G287V | AGXT mutation negative | GRHPR mutation negative | NA | NA | NA | NA | NA | NA |
| 6 | IVS700 + 5G>T | IVS700 + 5G>T | 45 | 74 | 1.0 | 17 | 2 | 3.3 | 0.6 | 2.3 |
| 7 | IVS700 + 5G>T | c.569C>T, p.P190L | 40.4 | 43 | 0.7 | 10 | 0 | 6.6 | 1.2 | NA |
| 8 | IVS700 + 5G>T | c.763C>T, p.R255X | AGXT mutation negative | GRHPR mutation negative | 0 | 16 | 40 | NA | NA | NA |
| 9 | IVS700 + 5G>T | IVS700 + 5G>T | 32 | 53 | 0 | 58 | 10 | NA | NA | NA |
| 10 | IVS700 + 5G>T | c.839 C>T, p.T280I | AGXT mutation negative | GRHPR mutation negative | 0.7 | 8 | 0 | 2.4 | NA | NA |

Novel variants are depicted in bold type. Measurement of enteric oxalate absorption whenever available. Pt, patient; Screat (mg/dl) @ Pox, serum creatinine at time of plasma oxalate measurement; AGT (alanine:glyoxylate aminotransferase); GRHPR (glyoxylate/hydroxypyruvate reductase); NA, not available.

^aLiterature-derived normal.

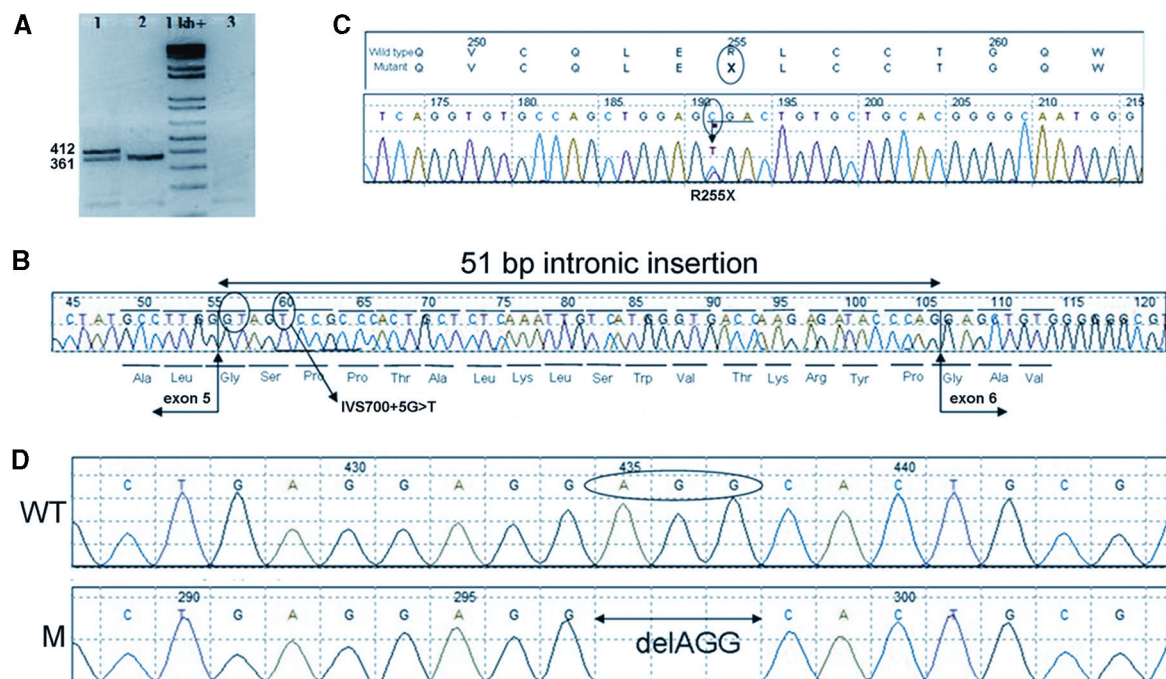


Figure 1. | Reverse transcription (RT)–PCR results for the IVS700 + 5G>T, c.944_946 del AGG (p.Glu315del), and c.763 C>T (p.R255X) *HOGA1* mutations. (A) Gel electrophoresis. Analysis by RT-PCR of wild-type and mutant cDNA from patient 7 (heterozygous for the IVS700 + 5G>T variant) is shown. The presence of a larger product derived from the insertion of 51 bp (412 bp in lane 1 versus 361 bp in the normal control in lane 2) is apparent. (B) Sequencing results for the mutant cDNA (excised band) in patient 7. The G>T change in the + 5 position (3' circle) weakens the wild-type donor site (5' circle), allowing a downstream GT cryptic donor site at position + 52 to become active and leading to the in-frame insertion of 51 nucleotides (17 codons), including the actual wild-type donor site. (C) Sequencing results. Analysis by RT-PCR of mutation c.763 C>T (p.R255X) in patient 8 is shown. The mutant T nucleotide that generates a termination codon is as equally represented as the wild-type C nucleotide. This suggests that the truncating, mutant allele is stably expressed and is not subject to nonsense-mediated decay. (D) Sequencing results for the mutant cDNA generated from patient 3 (homozygous for the c.944_946 del AGG variant) demonstrating in-frame deletion of AGG (p.Glu315del). Mutant cDNAs were derived from Epstein Barr Virus-transformed lymphoblast cell lines in all three patients.

nucleotides (17 codons), including the wild-type donor site.

RT-PCR analysis of mutant cDNA from patient 8, who harbors a novel stop codon (c.763 C>T, p.R255X), is also shown in Figure 1. The mutant T nucleotide that creates the STOP is equally represented, suggesting that this truncating allele is stably expressed and is not subject to nonsense-mediated decay. RT-PCR analysis of mutant cDNA from patient 3 (c.944_946 del AGG homozygous) is also shown in Figure 1.

Scoring of *HOGA1* missense variants for likely pathogenicity is provided in Supplemental Table 2, and a multi-sequence alignment of *HOGA1* and six orthologues (*Pan troglodytes*, *Sus scrofa*, *Bos taurus*, *Mus musculus*, *Rattus norvegicus*, and *Xenopus laevis*) showing the affected substitutions is shown in Supplemental Figure 1. Our *in silico* analysis was predictive of moderate to severe pathogenicity for all variants.

To further characterize the PHIII phenotype, we pooled our clinical experience, assembling a total of 25 cases from 19 unrelated families, some of which have been published previously in part (6–8,12), and compared the findings with PHI and PHII, using data from the IPHR. Urine oxalate, calcium, and uric acid at diagnosis are shown in Figure 2. Urine oxalate was lower ($P = 0.02$), whereas urine calcium ($P < 0.0001$) and urine uric acid ($P = 0.0006$) were

higher in PHIII when compared with PHI and PHII. PHIII was also characterized by symptomatic calcium oxalate stone disease early in life, with 50% of the patients presenting with stones before 5 years of age. At diagnosis, estimated GFR was 98 ± 32 ml/min per 1.73 m² (mean \pm SD), and at last follow-up (median 7.2 years from diagnosis), estimated GFR was 116 ± 28 ml/min per 1.73 m². To date, none of the patients have progressed to ESRD.

From our referral base of hyperoxaluric patients, we also identified two with a milder degree or a more variable pattern of hyperoxaluria who were heterozygous for *HOGA1* mutations (and negative for *AGXT*, *GRHPR*, and *SLC26A6* variants), both of whom developed symptom onset in adulthood (Table 2). One patient (patient 1a) was the brother of a PHIII proband (patient 2). The second patient (patient 2a) was unrelated to the families. The sequencing findings were confirmed in duplicate. Urine oxalate was normal in other obligate heterozygous parents and siblings when available (*data not shown*). These observations prompted us to study a cohort of 100 idiopathic calcium oxalate stone formers in whom we also detected three *HOGA1* heterozygous patients (Table 2). One of these variants (c.860 G>T, p.G287V) was also detected in PHIII (patient 5 in this report and in Belostotsky et al) (8).

None of the six novel *HOGA1* variants documented in the patients (PHIII, mildly hyperoxaluric or idiopathic cal-

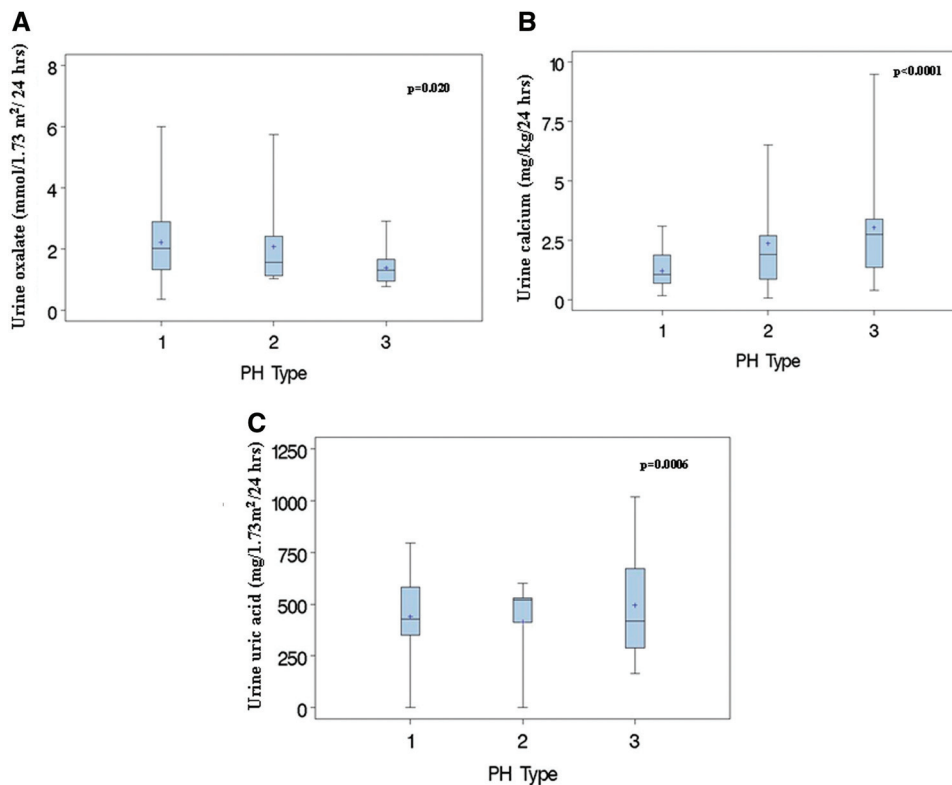


Figure 2. | Box plots of PH type versus urine oxalate (mmol/1.73 m² per 24 h [A]), urine calcium (mg/kg/24 h [B]), and urine uric acid (mg/1.73 m² per 24 h [C]). The box plots display the 25th and 75th percentiles (bottoms and tops of boxes), the median (inside lines), the means (+), and the minimum and maximum values (bottoms and tops of vertical lines).

cium oxalate stone formers) were detected in 100 negative controls from Mayo Clinic Jacksonville (this report) or in 66 controls from Mayo Clinic Rochester (8). The possibility that variant c.714 C>T (p.G238G) (patient 5a) simply represents a silent polymorphism still exists.

Discussion

Here, we provide further evidence for the genetic basis of PHIII, describing four novel *HOGA1* variants (three missense and one nonsense) in 10 newly identified families. Detection of a novel stop codon (c.763 C>T, p.R255X) favors a loss-of-function mechanism for *HOGA1*, in keeping with the autosomal recessive pattern of inheritance observed in PHIII families to date (6,8). Our observation of *HOGA1* heterozygosity for some variants (c.944_946 del AGG and c.907 C>T, p.R303C) in association with milder phenotypes (mild or variable hyperoxaluria), however, suggests that these hypomorphs may behave in a dominant-negative fashion, a mechanism supported by the tetrameric structure of *HOGA1* and our demonstration of stably-expressed transcripts for the two most common *HOGA1* mutations (c.944_946 del AGG and IVS700 + 5 G>T). Given that a phenotype was not consistently detected in heterozygous individuals, it is probable that other susceptibility factors, genetic or environmental, are involved. Detection of a variant (c.860 G>T, p.G287V) common to both PHIII and idiopathic stone formers also suggests that some alleles may be partially penetrant, predisposing to idiopathic calcium oxalate urolithiasis.

One possibility as to how the loss of *HOGA1* enzymatic activity causes a phenotype of hyperoxaluria in PHIII is through a rerouting of its substrate, 4-hydroxy-2-oxoglutarate and/or any of its precursors (4-hydroxy-L-proline, or 4-hydroxy-2-ketoglutarate) to glyoxylate and/or oxalate. We propose that under normal conditions glyoxylate is strictly prevented from contact with the cytosol, remaining distributed in peroxisomes and mitochondria. The flux across these subcellular compartments is facilitated by its conversion to glycolate (Supplemental Figure 2).

When *HOGA1* is absent, a build-up of KHG (4-hydroxy-2-oxoglutarate and/or its metabolites) in mitochondria may leak into the cytosol, where it can be converted to glyoxylate. Such a reaction would be catalyzed by a cytosolic pyruvate aldolase. Aldolases are known to be fairly nonspecific and to tolerate a wide range of aldehydes as acceptor compounds (13). A possible candidate aldolase that may provide cytosolic formation of glyoxylate from hydroxyoxoglutarate is NPL (N-acetylneuraminase pyruvate-lyase) (NPL human, Q9BXD5). It has rather high homology to *HOGA1* but is lacking a mitochondrial signal and is localized in the cytosol (Supplemental Figure 2). Once excess cytosolic glyoxylate is formed, it would be rapidly oxidized to oxalate by lactate dehydrogenase, ensuing in hyperoxaluria.

Because in humans 4-hydroxy-L-proline is derived from collagen (from bones and connective tissue) as well as from dietary sources (animal protein and gelatin) and some of these sources are also known to influence urine calcium and uric acid (14), it is possible that a defect in *HOGA1* also

Table 2. HOGA1 variants in patients with mild hyperoxaluria and/or calcium oxalate urolithiasis

| Pt | HOGA1 | | Urine Oxalate (Normal <0.46) (mmol/24 h) | Urine Calcium (Normal <300) (mg/24 h) | Urine Uric Acid (Normal <750) (mg/24 h) | Urine Citrate (Normal >150) (mg/24 h) | Urine Glyoxylate (Normal <3) (μg/mg creat) | Urine Glycolate (Normal <79) (μg/mg creat) | Urine Glycerate (Normal <19) (μg/mg creat) | Plasma Oxalate (Normal <1.8) (μmol/L) |
|--|------------------------------|---------------|--|---------------------------------------|---|---------------------------------------|--|--|--|---------------------------------------|
| | Mutation 1 | Mutation 2 | | | | | | | | |
| Patients with mild hyperoxaluria | | | | | | | | | | |
| 1a | c.907 C>T, p.R303C | None detected | 0.58 | 426 | 710 | 813 | NA | NA | NA | NA |
| 2a | c.944_946 het del AGG | None detected | 0.18 to 1.48 | 11 to 24 | 417 to 541 | <50 to 531 | NA | 2 to 11 | 0 to 27 | <1 to 14.3 |
| Idiopathic calcium oxalate stone formers | | | | | | | | | | |
| 3a | c.745 C>G p.Q249E | None detected | 0.38 | 143 | 756 | 697 | NA | NA | NA | NA |
| 4a | c.860 G>T, p.G287V | None detected | 0.45 (1) 0.52 (2) 0.45 (3) | 248 (1) 152 (2) 261 (3) 166 | 560 (1) 553 (2) 851 (3) 501 | 734 (1) 637 (2) 490 (3) 737 | NA | NA | NA | NA |
| 5a | c.714 C>T, p.G238G | None detected | 0.36 | 166 | 501 | 737 | NA | NA | NA | NA |

Novel variants are depicted in bold type. Patient 1a is a brother of patient 2. There were three available 24-hour urine collections for patient 4a. Normal adult reference values apply: urine oxalate (<0.46 mol/24 h), urine calcium (<300 mg/24 h), and urine uric acid (<750 mg/24 h). Pt, patient; creat, creatinine; NA, not available.

gives rise to these phenotypes under certain circumstances. Urine oxalate, calcium, and uric acid measurements in PHIII and idiopathic stone formers harboring HOGA1 variants on diets carefully controlled for animal protein and other dietary factors are needed. Metabolic studies and further functional characterization of HOGA1 are also needed to definitively confirm its role and pathophysiology in PHIII. Given that we were able to isolate RNA and generate mutant cDNA from affected patient lymphocytes, further examination of the expression and function of HOGA1 in lymphocytes is warranted.

Acknowledgments

This work was made possible by National Institutes of Health (Grants DK73354 and U54KD083908 to the Rare Kidney Stone Consortium) and P50DK83007 to the Mayo Clinic O'Brien Center) and by funding from the Oxalosis and Hyperoxaluria Foundation. The Rare Kidney Stone Consortium is a part of the National Institutes of Health Rare Diseases Clinical Research Network. Funding and/or programmatic support for this project has also been provided by the National Institutes of Health Office of Rare Diseases Research.

We are grateful to our patients and their families for their gracious participation and to their referring physicians for kindly providing clinical information regarding PHIII patients: M. Aigbe (Las Vegas, NV), Manju Chandra (Manhasset, NY), L. Espinosa Roman (Madrid, Spain), Eduardo Garin (Gainesville, FL), David Goldfarb (New York, NY), D. Grapey (Greensboro, NC), L. Greenbaum (Atlanta, GA), A. Herndon (Birmingham, AL), John Lieske (Rochester, MN), J. Lingenman (Indianapolis, IN), Corina Nailescu (Indianapolis, IN), M. Rocklin (Denver, CO), Christine Sethna (New Hyde Park, NY), A. Shamsuddin (London, UK), and M. Sheehan (Denver, CO). We are also indebted to Dr. Peter C. Harris for his insightful review of the manuscript and Ms. Katharina Hopp for technical assistance. Finally, we sincerely appreciate the contributions of the following physicians to the IPHR: D. Adey (San Francisco, CA), S. Ahmed, S. Alexander, M. Anders (Buenos Aires, Argentina), N. Amin (Los Angeles, CA), J.R. Asplin (Chicago, IL), N. Azam (Houston, TX), N. Balakrishnan (Coimbatore Tamilnadu, India), S. Bhandare (St. Louis, MO), M. Baum (Boston, MA), David Beckman (Faribault, MN), Beiken (New York, NY), S. Belani (Petaluma, CA), A. Bellucci (Lake Success, NY), R. Berkseth (Minneapolis, MN), P. Berry (Austin, TX), N. Bhakta (Los Angeles, CA), A. Bhat (Roseville, CA), S. Bhupalam (East Lansing, MI), M. Bia (New Haven, CT), T. Blydt-Hansen (Winnipeg, Canada), R. Bousquet (Whitehorse, Canada), M. Braun (Houston, TX), E. Brewer (Houston, TX), C. Brueggmeyer (Jacksonville, FL), T. Bunchman (Grand Rapids, MI), L. Butani (Sacramento, CA), M. Cadnapaphornchai (Aurora, CO), E. Castillo-Velarde (Lima, Peru), M. Chandra (Mineola, NY), M.J. Choi (Baltimore, MD), F. Chybowski (Appleton, WI), F. Ciuitarese (Carnegie, PA), L. Copelovitch (Philadelphia, PA), F. Corbin (Quebec, Canada), H. Corey (Morristown, NJ), D. Creemers (the Netherlands), R. Cunningham (Cleveland, OH), K. Dalinghaus (Whitehorse, Canada), I. Davis (Cleveland, OH), C. de Souza (Uruguay), M. DeBeukelaer (Toledo, OH), V. Delaney (Hawthorne, NY), P. Devarajan (Cincinnati, OH), Z. Dolezel (Czech Republic), H.A. Doll (Tallahassee, FL), P. Douville (Quebec, Canada), S. Ecklund (Sioux Falls, SD), K. Eidman (Minneapolis, MN), M. Emmett (Alvarado, TX), D. Ford (Aurora, CO), J. Foreman (Durham, NC), C. Fritsche (Milwaukee, WI), S. Garcia (Barcelona, Spain), E. Garin (Gainesville, FL), D. Geary (Toronto, Canada), D. Gipson (Chapel Hill, NC), B. Greco (Springfield, MA), W. Haley (Jacksonville, FL), P. Hall (Cleveland, OH), M. Hames (Greenville, NC), C.D. Hanevold

(Seattle, WA), F. Harris (Metairie, LA), G. Hart (Charlotte, NC), E. Harvey (Toronto, Canada), R.L. Heilman (Scottsdale, AZ), R. Helman (Duluth, MN), J. Herrin (Boston, MA), M. Hertl (Boston, MA), G. Hidalgo (Chicago, IL), S. Hmiel (St. Louis, MO), B. Hoppe (Cologne, Germany), H. Hotchkiss (New Brunswick, NJ), T. Hunley (Nashville, TN), J. Johnston (Pittsburgh, PA), B. Kaiser (Wilmington, DE), U. Kannapadi (Pittsburgh, PA), C. Kashani (Minneapolis, MN), F. Kaskel (Bronx, NY), E. Kendrick (Seattle, WA), O. Khan (Chicago, IL), S. Knohl (Syracuse, NY), R. Kossman (Santa Fe, NM), A. Krambeck (Indianapolis, IN), C. Langman (Chicago, IL), L. Larch (Clarksville, IN), J. Leiser (Indianapolis, IN), S. Lerman (Los Angeles, CA), D.L. Levy (Bangor, ME), D.S. Lirenman (Vancouver, Canada), N. Maalouf (Chattanooga, TN), M. Maddy (Duluth, MN), M.A. Mansell (London, UK), M. Martin (Worcester, MA), R. Mathias (San Francisco, CA), M. Mauer (Minneapolis, MN), M. May (Jacksonville, FL), M. McHugh (Columbus, OH), P. Metcalfe (Edmonton, Canada), B. Morgenstern (Phoenix, AZ), G. Murphy (Greenville, NC), C. Nailescu (Indianapolis, IN), M. Narkewicz (Denver, CO), M. Navarro (Madrid, Spain), H.G. Pohl (Washington, DC), H. Powell (Parkville, Australia), I. Randeree (Umhlanga Rocks, South Africa), V. Rao (Omaha, NE), D. Raskin (Phoenix, AZ), R. Ravichandran (Chennai, India), L. Restall (Dallas, TX), C. Richardson (Tacoma, WA), P. Sacks (Phoenix, AZ), M. Sanderson (Saint Paul, MN), J.D. Scandling (Palo Alto, CA), C. Sethna (New Hyde Park, NY), J. Sharma (Bangalore, India), K. Sievers (Rolla, MO), E. Simon (Boston, MA), R. Sirota (Willow Grove, PA), C. Smith (Minneapolis, MN), M. Sobel (Westerville, OH), Somasundaram (Indianapolis, IN), T. Starzl (Pittsburgh, PA), J. Steinke (Minneapolis, MN), M. Suarez (Houston, TX), J.M. Symons (Seattle, WA), I.Y.S. Tang (Chicago, IL), J. Tariq (Karachi, Pakistan), M. Teruel (Fort Collins, CO), A. Tolaymat (Jacksonville, FL), M.M. Tomsho (Summersville, WV), A. Torres (La Laguna, Spain), S. Tuchman (Washington, DC), M.A. Turman (Oklahoma City, OK), R. Unwin (London, UK), R. Venick (Los Angeles, CA), S. Venkatesh (Nashville, TN), A. Vera (Bogota, Columbia), H. Viko (Oslo, Norway), R. Villa (Lubbock, TX), J. Wang (Minneapolis, MN), B. Warady (Kansas City, KS), B. Warshaw (Atlanta, GA), C. Weimer (Thibodaux, LA), J. Weinstein (Dallas, TX), R.A. Weiss (Valhalla, NY), P. Wertsch (Madison, WI), J. Wesson (Milwaukee, WI), C. Wong (Albuquerque, NM), W. Wong (Boston, MA), E. Worcester (Chicago, IL), O. Yadin (Los Angeles, CA), and V. Yiu (Edmonton, Canada).

Disclosures

None.

References

- Robertson WG, Peacock M: The cause of idiopathic calcium stone disease: Hypercalciuria or hyperoxaluria? *Nephron* 26: 105–110, 1980
- Robertson WG, Hughes H: Importance of mild hyperoxaluria in the pathogenesis of urolithiasis: New evidence from studies in the Arabian peninsula. *Scanning Microsc* 7: 391–401, 1993
- Danpure CJ, Jennings PR: Peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type I. *FEBS Lett* 201: 20–24, 1986
- Giafi CF, Rumsby G: Kinetic analysis and tissue distribution of human D-glycerate dehydrogenase/glyoxylate reductase and its relevance to the diagnosis of primary hyperoxaluria type 2. *Ann Clin Biochem* 35: 104–109, 1998
- Van Acker KJ, Eyskens FJ, Espeel MF, Wanders RJA, Dekker C, Kerckaert IO, Roelset F: Hyperoxaluria with hyperglycoluria not due to alanine:glyoxylate aminotransferase defect: A novel type of primary hyperoxaluria. *Kidney Int* 50: 1747–1752, 1996
- Monico CG, Persson M, Ford GC, Rumsby G, Milliner DS: Potential mechanisms of marked hyperoxaluria not due to primary hyperoxaluria I or II. *Kidney Int* 62: 392–400, 2002
- Monico CG, Weinstein A, Jiang Z, Rohlinger AJ, Cogal AG, Bjornson BB, Olson JB, Bergstralh EJ, Milliner DS, Aronson PS: Phenotypic and functional analysis of human SLC26A6 variants in patients with familial hyperoxaluria and calcium oxalate nephrolithiasis. *Am J Kidney Dis* 52: 1096–1103, 2008
- Belostotsky R, Seboun E, Idelson GH, Milliner DS, Becker-Cohen R, Rinat C, Monico CG, Feinstein S, Ben-Shalom E, Magen D, Weissman I, Charon C, Frishberg Y: Mutations in DHAPSL are responsible for primary hyperoxaluria type III. *Am J Hum Genet* 87: 392–399, 2010
- Lowry M, Hall DE, Brosnan JT: Hydroxyproline metabolism by the rat kidney: distribution of renal enzymes of hydroxyproline catabolism and renal conversion of hydroxyproline to glycine and serine. *Metabolism* 34: 955–961, 1985
- Holmes RP, Assimos DG: Glyoxylate synthesis, and its modulation and influence on oxalate synthesis. *J Urol* 160: 1617–1624, 1998
- Knight J, Jiang J, Assimos DG, Holmes RP: Hydroxyproline ingestion and urinary oxalate and glycolate excretion. *Kidney Int* 70: 1929–1934, 2006
- Monico CG, Milliner DS: Hyperoxaluria and urolithiasis in young children: An atypical presentation. *J Endourol* 13: 633–636, 1999
- Samland AK, Sprenger GA: Microbial aldolases as C-C bonding enzymes: Unknown treasures and new developments. *Appl Microbiol Biotechnol* 71: 253–264, 2006
- Breslau NA, Brinkley L, Hill KD, Pak CY: Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. *J Clin Endocrinol Metab* 66: 140–146, 1988

Received: March 23, 2011 **Accepted:** June 12, 2011

Published online ahead of print. Publication date available at www.cjasn.org.

Supplemental information for this article is available online at www.cjasn.org