

**1- Renal function can be impaired in children with primary hyperoxaluria type 3.**

Lise Allard, Pierre Cochat, Anne-Laure Leclerc, François Cachat, Christine Fichtner, Vandr ea Carla De Souza, Clotilde Druck Garcia, Marie-Christine Camoin-Schweitzer, Marie-Alice Macher, C ecile Acquaviva-Bourdain, Justine Bacchetta.

**Pediatr Nephrol (2015) 30:1807–1813**

**Background:** Primary hyperoxaluria type 3 (PH3) is characterized by mutations in the 4-hydroxy-2-oxoglutarate aldolase (*HOGA1*) gene. PH3 patients are believed to present with a less severe phenotype than those with PH1 and PH2, but the clinical characteristics of PH3 patients have yet to be defined in sufficient detail. The aim of this study was to report our experience with PH3.

**Methods:** Genetic analysis of *HOGA1* was performed in patients with a high clinical suspicion of PH after the presence of mutations in the alanine–glyoxylate aminotransferase gene had been ruled out. Clinical, biochemical and genetic data of the seven patients identified with *HOGA1* mutations were subsequently retrospectively reviewed.

**Results:** Among the seven patients identified with *HOGA1* mutations the median onset of clinical symptoms was 1.8 (range 0.4–9.8) years. Five patients initially presented with urolithiasis, and two other patients presented with urinary tract infection. All patients experienced persistent hyperoxaluria. Seven mutations were found in *HOGA1*, including two previously unreported ones, c.834 + 1G > T and c.3G > A. At last follow-up, two patients had impaired renal function based on estimated glomerular filtration rates (GFRs) of 77 and 83 mL/min per 1.73 m<sup>2</sup>, respectively.

**Conclusions:** We found that the GFR was significantly impaired in two of our seven patients with PH3 diagnosed during childhood. This finding is in contrast to the early-impaired renal function in PH1 and PH2 and appears to refute preliminary reassuring data on renal function in PH3.

**2 – Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria.**

Katharina Hopp, Andrea G. Cogal, Eric J. Bergstralh, Barbara M. Seide, Julie B. Olson, Alicia M. Meek, John C. Lieske, Dawn S. Milliner, Peter C. Harris, on behalf of the Rare Kidney Stone Consortium

**J Am Soc Nephrol 26: 2559–2570, 2015.**

**ABSTRACT**

Primary hyperoxaluria (PH) is a rare autosomal recessive disease characterized by oxalate accumulation in the kidneys and other organs. Three loci have been identified: AGXT (PH1), GRHPR (PH2), and HOGA1 (PH3). Here, we compared genotype to phenotype in 355 patients in the Rare Kidney Stone Consortium PH registry and calculated prevalence using publicly available whole-exome data. PH1 (68.4% of families) was the most severe PH type, whereas

PH3 (11.0% of families) showed the slowest decline in renal function but the earliest symptoms.

A group of patients with disease progression similar to that of PH3, but for whom no mutation was detected (11.3% of families), suggested further genetic heterogeneity. We confirmed that the AGXT p.G170R mistargeting allele resulted in a milder PH1 phenotype; however, other potential AGXT mistargeting alleles caused more severe (fully penetrant) disease. We identified the first PH3 patient with ESRD; a homozygote for two linked, novel missense mutations. Population analysis suggested that PH is an order of magnitude more common than determined from clinical cohorts (prevalence, approximately 1:58,000; carrier frequency, approximately 1:70). We estimated PH to be approximately three times less prevalent among African Americans than among European Americans because of a limited number of common European origin alleles. PH3 was predicted to be as prevalent as PH1 and twice as common as PH2, indicating that PH3 (and PH2) cases are underdiagnosed and/or incompletely penetrant. These results highlight a role for molecular analyses in PH diagnostics and prognostics and suggest that wider analysis of the idiopathic stone-forming population may be beneficial.

**Comments:**

Two papers regarding the primary hyperoxalurias (PHs), rare autosomal recessive inborn errors of hepatic glyoxylate metabolism characterized by oxalate overproduction and elevated excretion.

The papers demonstrate that the difference between the expected and observed prevalence, for PH3 and to a lesser extent for PH2, is likely due to underdiagnosis of these diseases, which have overall milder phenotypes and are much less likely than PH1 to result in ESRD. In addition, relatively mild disease in a subset of PH1 patients (especially p.G170R homozygotes) and a wide variability in age at first symptom, may account for the 2-fold underdiagnosis of PH1. They highlight the need of PH genotype analysis of idiopathic stone disease populations and other patients with PH phenocopies but no known mutations. Also the need of the long term follow-up especially for PH3 which is mainly regarded as a benign condition but might be also associated with impaired renal function.