# Identification and Phenotyping of a Healthy Human with Mutations in *HAO1* Supports Glycolate Oxidase Knockdown as a Potential Approach to Therapy for Primary Hyperoxaluria Type 1

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## *Background and Objective:*

### Primary Hyperoxaluria Type 1 (PH1):

**Disease Background:**

- Prevalence of PH1: 1-3/1,000,000 in Europe[1] and ~ 32/1,000,000 in Middle East[2]
- Phenotype varies significantly in patients; may present at any age, typically in childhood
- Wide spectrum of clinical manifestations and unpredictable progression rate lead to a delay in diagnosis and thus increase disease burden

**Pathophysiology[1]**

- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Overproduction of oxalate results in insoluble calcium oxalate crystals leading to urolithiasis, nephrocalcinosis, and kidney failure
- Disease course ultimately leads to multi-organ damage from systemic oxalosis

**No therapies are approved for treatment of PH1**

- A therapeutic specifically designed to reduce the substrate needed for oxalate production could potentially halt or prevent disease progression

### Glycolate Oxidase (GO)[4]:

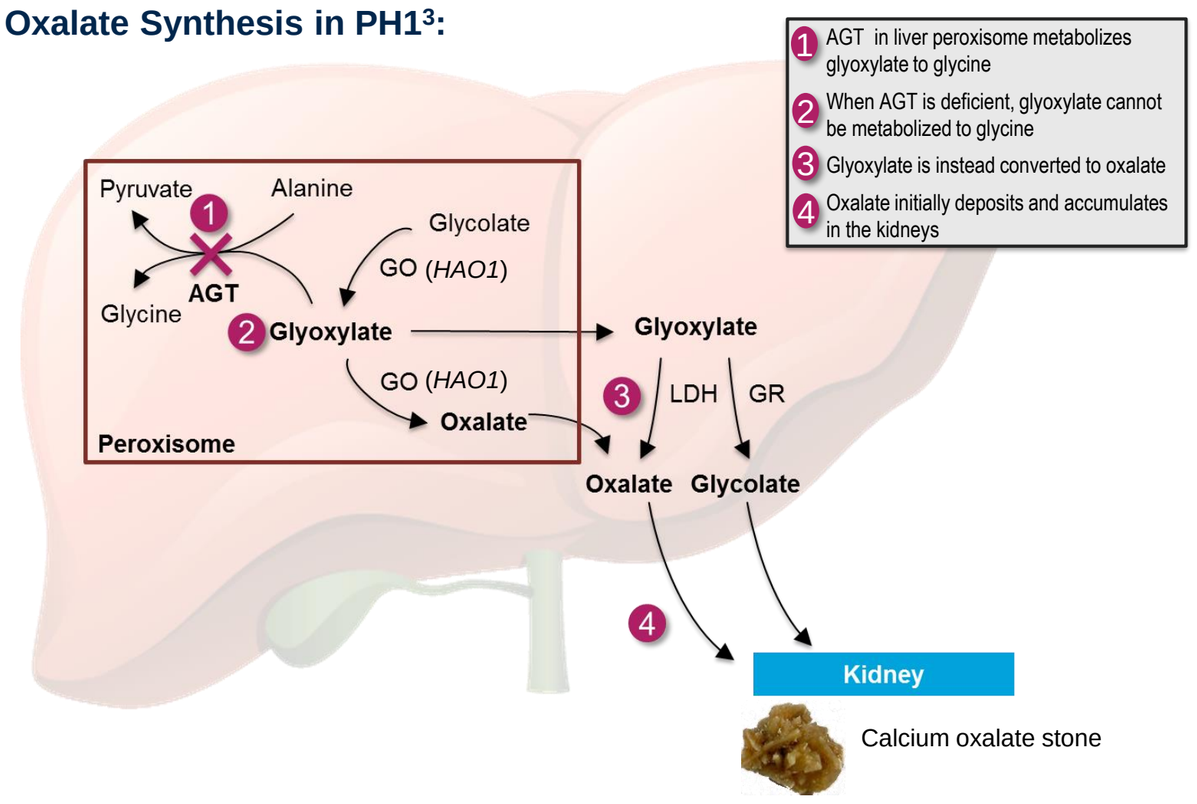
**A liver-specific enzyme encoded by *HAO1***

- GO has the sole purpose of converting glycolate to glyoxylate, a major substrate required for oxalate production
- Reducing GO could reduce the production of oxalate

### Objective:

**Further understand potential consequences of chronic GO reduction in humans for drug target validation**

### Oxalate Synthesis in PH1[3]:




## *Methods*

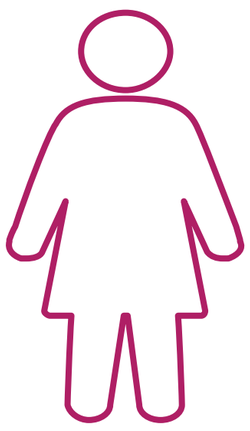
### Large population sequencing and health records program[5]

**Adult with homozygous mutations in *HAO1* Identified**

- Medical history, detailed phenotyping and biochemical investigation was completed for this individual

## *Results*

### Medical History of Identified Individual



- Healthy female in fifth decade of life
- Mother of 3 healthy children
- Overweight (BMI: 30-35 kg/m$^2$)
- No unexpected medical history other than common non-serious short term illnesses and symptoms associated with pregnancy
- Liver function, transaminases, renal function, and renal ultrasound were normal
- Clinical chemistries repeatedly normal at recall and over the previous decade

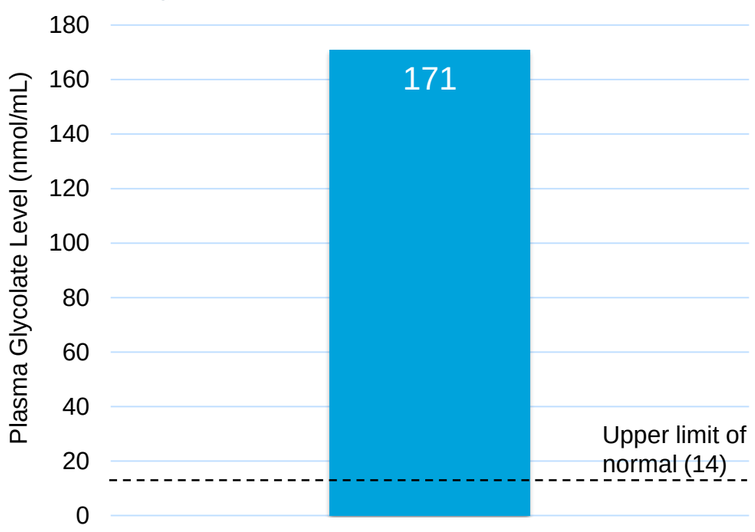
### Detailed Genotyping

**DNA sequencing confirmed homozygous *HAO1* genotype**

- Exome analysis showed the individual was 7.4% autozygous at the DNA level due to known parental consanguinity
- *HAO1* genotype was within an autozygous genomic region
- Standard Sanger dideoxy sequencing in a further saliva DNA sample additionally confirmed the genotype
- Individual was not homozygous for any other rare (minor allele frequency <1%) nonsense mutations

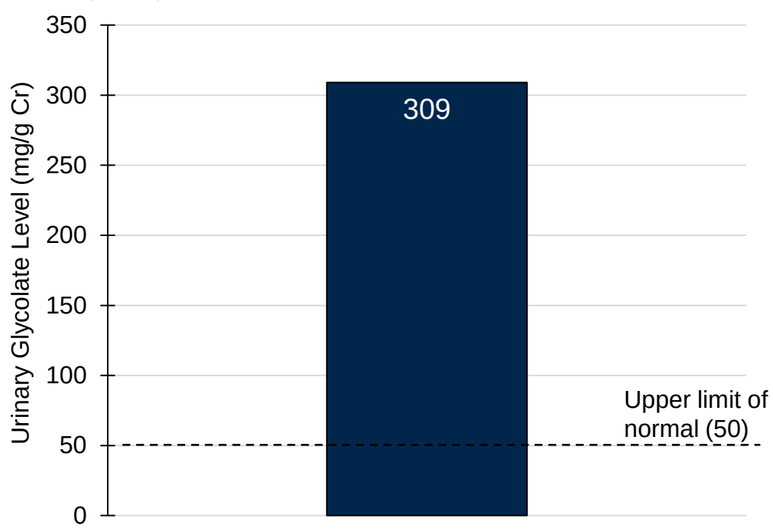
### Biochemical Investigation of Glycolate

**Plasma Glycolate**




**12x**
Upper limit of normal

**Urinary Glycolate**




**6x**
Upper limit of normal

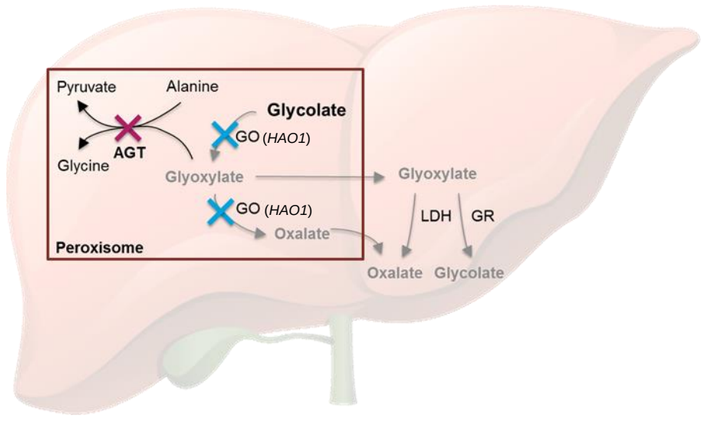
- Notably elevated plasma and urinary glycolate levels provide support for confirmation of the loss-of-function phenotype and are consistent with <2% remaining GO activity in this individual
- Plasma and urine oxalate levels were normal

## *Discussion*

**This case report of a healthy mother of three provides further support for the hypothesis that very low or absent levels of glycolate oxidase function is well tolerated with no apparent clinical consequences over the course of decades[6-8]**

**Lumasiran is an investigational RNAi therapeutic which harnesses the body's natural process to cleave *HAO1* mRNA, thereby knocking down production of glycolate oxidase[4]**

- Lumasiran is in development for the treatment of PH1 in adults and children




## *Conclusion:*

**These data support the approach of *HAO1* silencing, which is the mechanism of lumasiran, an investigational RNA interference therapeutic in development for the treatment of PH1 in adults and children**

References: 1. Cochat P, et al. *New Engl J Med.* 2013. 2. Abumwais JQ, et al. *Saudi J Kid Dis Transpl.* 2012. 3. Cochat P. *Kidney Int*. 1999. 4. Liebow A, et al. *J Am Soc Nephrol.* 2017. 5. Narasimhan, V. M. *Science*. 2016. 6. Frishberg Y, et al. *Journal of Medical Genetics*. 2014; 7. Craigen WJ. *J Inherit Metab Dis*. 1996; 8. Clifford-Mobley O, et al. *Pediatr Nephrol*. 2017.

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