Kidney and Blood Pressure Research

Research Article

Kidney Blood Press Res 2025;50:189–197
DOI: 10.1159/000544093

Received: May 4, 2024
Accepted: February 5, 2025
Published online: February 11, 2025

Genetic Diagnosis of Hyperoxaluria Type 3 Patients Using Haplotype Analysis

Sadegh Tavakoli Ataabadi[a] Leila Behi[a] Marzieh Mojbafan[a, b]
Nakysa Hooman[c]

[a]Department of Medical Genetics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; [b]Department of Medical Genetics, Ali-Asghar Children's Hospital, Tehran, Iran; [c]Department of Pediatrics, School of Medicine, Ali-Asghar Children's Hospital, Tehran, Iran

Keywords
Hyperoxaluria · Next-generation sequencing · Iranian · Sanger sequencing

Abstract
Introduction: An autosomal recessive hereditary disorder of the glyoxylate metabolism, primary hyperoxaluria (PH), causes an excess of oxalate to be formed in the body. Three genes have so far been found to cause the three forms of PH (I, II, and III). Overall, 10% of PH patients are type III and are caused by a mutation in the *HOGA1* gene. Pathogenic variants responsible for the disease have been identified in several populations. In the present study, we are going to genetically analyze 14 Iranian patients who are suspicious of being affected with PH III. ***Methods:*** We studied 14 patients from 11 unrelated Iranian families with a clinical diagnosis of hyperoxaluria disease. The kidney stone was detected in all patients. All of them had high levels of creatinine and oxalate in their urine. Sanger sequencing of the *HOGA1* gene was performed in all 14 patients. Next-generation sequencing has also been performed on 1 patient who did not have any causative variants in the *HOGA1* gene. ***Results:*** We identified one homozygous likely pathogenic missense variant in the *HOGA1* (c.266G>A). ***Conclusion:*** This is the first report of analyzing the *HOGA1* gene in Iranian patients suspicious of being affected with hyperoxaluria type III, which can expand our knowledge about this gene and its mutations.

Introduction

Primary hyperoxaluria (PH) is an autosomal recessive genetic disease of the metabolism of glyoxylate, which results in excessive oxalate formation [1–3]. PH has 3 types and the most prevalent form is PH type I, which results from a mutation in the *AGXT* gene (AGT) [4–6]. Primary hyperoxaluria type 2 (PH II), caused by deficiency of the enzyme glyoxylate reductase/hydroxypyruvate reductase (*GRHPR*), and PH III result from mutations in the *HOGA1* gene. Numbers of research indicated that PH III is more common than PH II [7]. PH patients usually reveal polyurea, dysuria; and rising urine oxalate levels may appear in childhood and adulthood [1, 8–11].

HOGA1 gene, which is located on the 10q24.2, contains 7 exons and is translated into the mitochondrial protein of 4-hydroxy-2-oxoglutarate aldolase (*HOGA1*), which is also known as dihydrodipicolinate synthase like (DHDPSL). This protein consists of 327 amino acids, 17

karger@karger.com
www.karger.com/kbr

Correspondence to:
Marzieh Mojbafan, marziyeh_mojbafan@yahoo.com

Table 1. Patients' clinical information

Patient	F1	F2	F3A	F3B	F3C	F3D	F4	F5	F6	F7	F8	F9	F10	F11
ESRD	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Reduced kidney function	No	No	*	*	*	*	**	No	No	No	**	No	No	NA
Kidney stone	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sex	M	M	F	F	M	F	M	F	F	M	F	F	F	F
Age of onset	7 Ms	6 Ms	2 Ys	1.5 Ys	6 Ms	6 Ms	6 Ms	2 Ys	6 Ms	3 Ys	2.5 Ys	11 Ms	1 Y	6 Ms
Age at diagnosis	7 Ms	1 Y	2 Ys	1.5 Ys	8 Ms	8 Ms	11 Ms	2 Ys	1 Y	3 Ys	2.5 Ys	1 Y	1.5 Ys	10 Ms
Family history	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Creatinine	18.2	20	24.5	18.5	6.63	6.8	13.5	71.1	9.8	15	54	NA	22	16
U. oxalate, mmol/24 h	9.3	7.1	12.2	14.5	3.3	3.5	1.4	29	5.3	NA	21.5	NA	24	8
U. oxalate/creatinine, mmol/mg	510.9	355	498	783	497.7	514	933.3	321	540	NA	398.1	NA	1,010	500
Oxalate precipitation in kidney	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA

Ms, months; Ys, years; NA, not available; *, low; **, high.

helices, 8 B strands, and 3 turns and it also has 2 dimers; it produces a tetrameric structure [12].

There are numerous techniques to map the mutation location such as haplotype analysis [13]. Haplotype analysis uses the fact that patients who are born to consanguineous marriages or from a small geographical area probably inherit two recessive copies of a mutant allele from a common ancestor. In this study, Sanger sequencing was done followed by haplotype analysis utilizing SNP markers on individuals suspected of being affected by PH III.

Methods

Patients

Fourteen patients from 11 unrelated families who were determined to have PH III were referred to the Ali Asghar Children's Hospital. Consent forms were obtained from all participants before sampling. This study was approved by the Iran University of Medical Sciences (IUMS) research committee (IR.IUMS.FMD.REC.1401.149). PH I was ruled out in all studied patients using Sanger sequencing of the *AGXT* gene. Patients' clinical information is summarized in Table 1.

Molecular Analysis

DNA was extracted from whole blood samples by salting-out approach [14]. Haplotype analysis was performed using SNPs. Four different SNPs surrounding the *HOGA1* gene were selected including rs2275090, rs1124116, rs3750614, and rs2296438. ARMS-PCR primers were designed for each of our selected SNPs to genotype them. Primers for all coding exons and exon-intron boundaries of the *HOGA1* gene were designed. Sanger sequencing of this gene was performed on those affected individuals who showed the homozygous haplotypes.

In silico Analysis

Different in silico tools such as Combined Annotation Dependent Depletion (CADD) [15], MutationTaster [16], Mutation Surveyor [17], Have Our Protein Explained (HOPE), Protein Variation Effect Analyzer (PROVEN) [18], Sorts Intolerant From Tolerant (SIFT) [19], Polymorphism Phenotyping (PolyPhen) [20], and Genomic Evolutionary Rate Profiling (GERP) [21] were applied for variant analysis and finally they were interpreted according to American College of Medical Genetics and Genomics (ACMG) guideline [22].

Next-Generation Sequencing

One of our studied patients (F3) had a large inbred family with lots of members affected with stone kidney. Sanger sequencing of the *AGXT* gene did not reveal any causative variant in the family's proband. The haplotype analysis for the *HOGA1* gene did not show homozygous haplotypes. This patient was selected to be tested by NGS. Whole exome enrichment was performed using an Agilent sure select V7 target enrichment kit and the library was sequenced on the

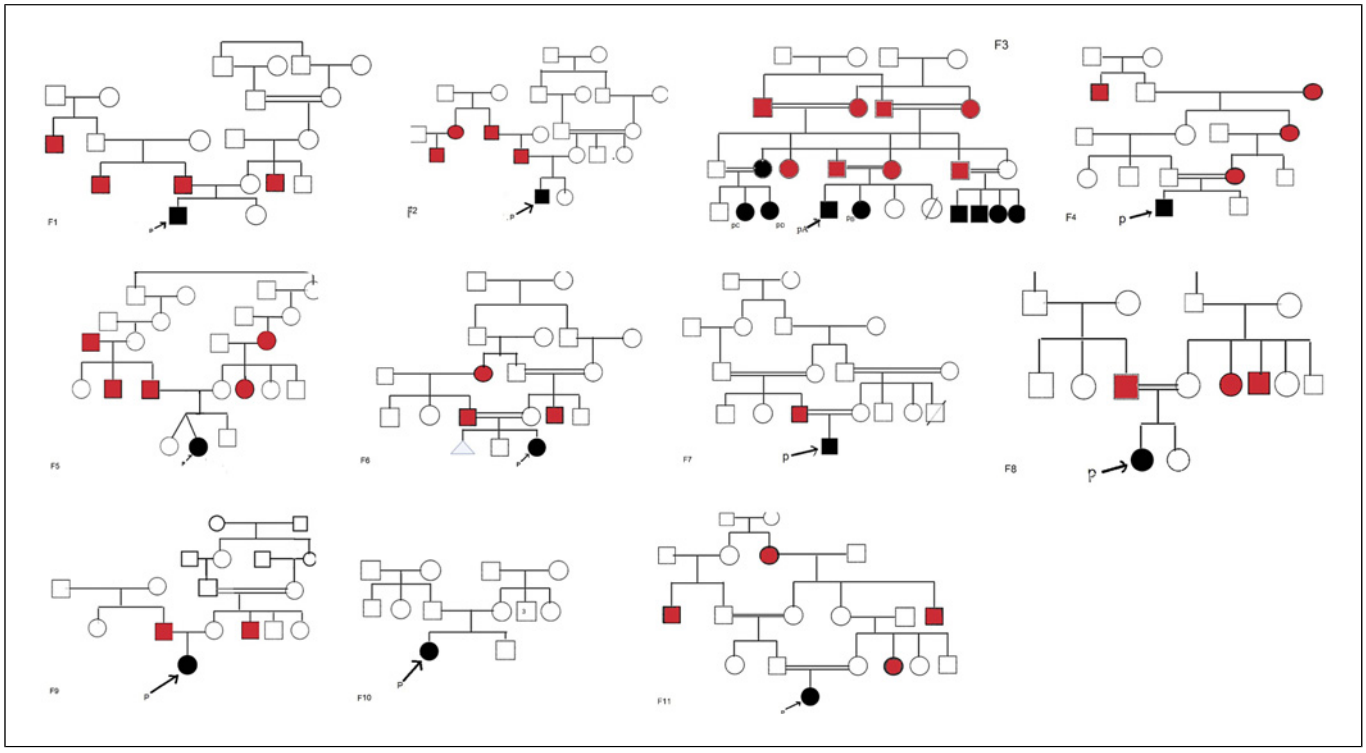

Fig. 1. Pedigrees of affected people participated in this study. White color indicates healthy people, black color means persons who are suspicious of being affected by PH III, and red color shows those who have nephrolithiasis.

Illumina HiSeq 6000 platform with an average depth of 100X for target regions. Nearly, all exons and flanking 10 bp were covered. Paired-end reads are aligned to the NCBI reference sequence (GRCh37). Bioinformatics analysis of the sequencing results was performed using international databases and standard bioinformatics software. The analysis was performed with emphasis on the variants within more than 3,500 genes with the phenotype-causing mutation in the "Online Mendelian Inheritance in Man" (OMIM; 2024-09-01) catalog.

Results

Patients

Our study was performed on 14 unrelated patients who were suspicious of being affected with PH III from different regions of Iran. All of the patients were aged from 1 to 5 years. Overall, 64.2% of them are from consanguineous marriages, and the remaining are from the same ethnicity. The median age at onset of clinical symptoms was 2.93 (range: 1.5–5.5) years. Figure 1 shows the pedigrees of our studied patients.

Prior to genetic analyses like ruling out of PH1, haplotype analysis for the *HOGA1*, and Sanger sequencing of this gene, clinical and paraclinical evidence of the patient F11 was highly consistent with PH III: kidneys were normal in size and parenchymal echogenicity. They had a few scattered stones, but no hydronephrosis was seen. The ratio of oxalate to creatinine was high in this patient [23, 24].

Molecular Analysis

The result of the haplotype analysis of 14 affected individuals along with their parents showed that only 2 patients (F4 and F11) had the homozygous haplotypes (Fig. 2). Sanger sequencing was done in the patients of both families. A homozygous mutation of c.266G>A (p.Arg89His) has been detected in F11, which was found in exon 2 of the *HOGA1* gene. As shown in Figure 3, her parents were heterozygous for this variant. The result of ARMS-PCR of 4 SNPs in this family along with controls is shown in Figure 4.

Sanger Sequencing in the F4 Family Did Not Show Any Causative Variant

Next-Generation Sequencing

We performed NGS on the proband of the family of F3. No pathogenic or likely pathogenic variant related to the patients' phenotype was found after analysis.

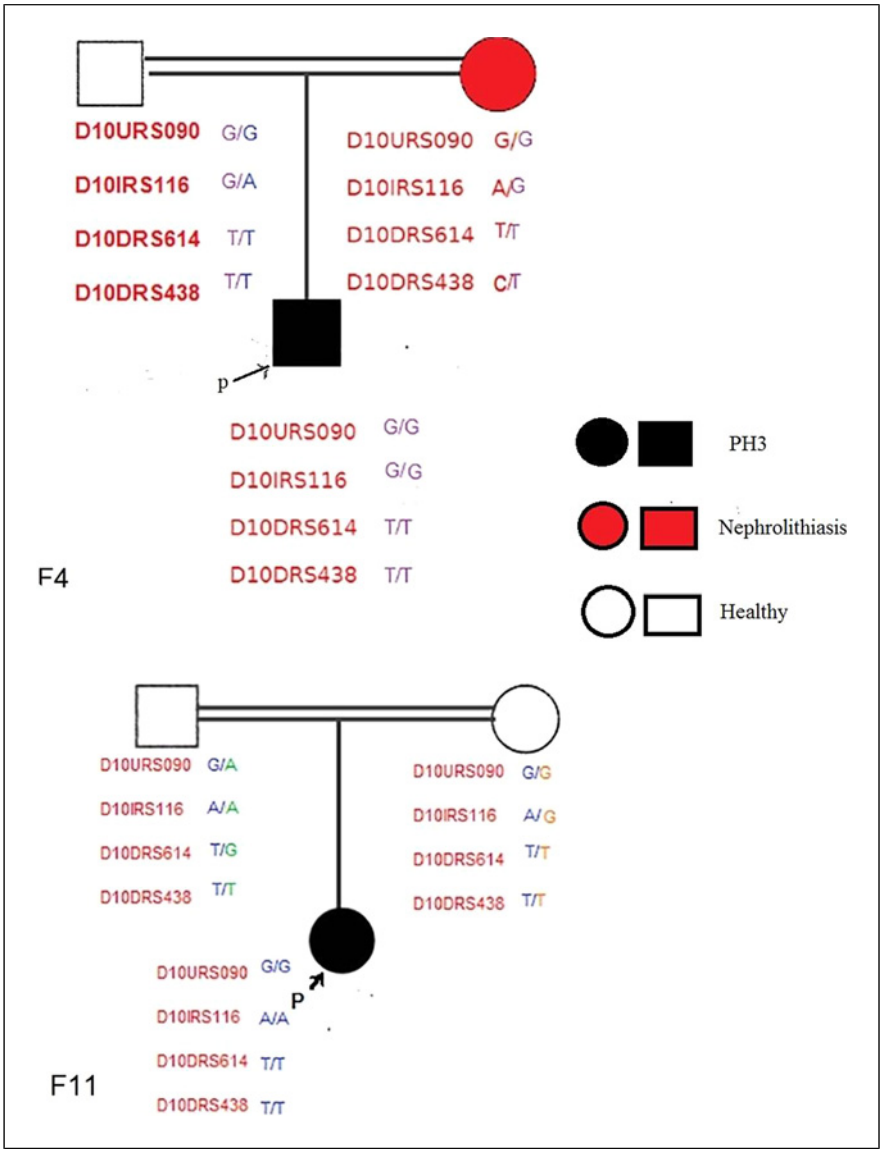

Fig. 2. Haplotype analysis of the F4 and F11 families.

More analysis showed some (run of homozygosity) ROH regions in the affected individual, which are shown in Table 2. The genes whose mutations potentially cause kidney stones are also revealed in Table 2.

In silico Tools

DANN score is a pathogenicity scoring methodology and it ranges from 0 to 1 and score 1 is predicted to be the most damaging. CADD score is a tool for scoring the deleteriousness of variants in which a score of greater than or equal to 20 is demonstrated to be the 1% most deleterious (Table 3). According to the ACMG guideline, this variant is a likely pathogenic one.

Discussion

PH III is the less severe form of PH with a milder phenotype and good prognosis in most patients [25]. The frequency of each type of mutation based on the HGMD database in this gene is 77% missense/nonsense and splice site/deletions are 16% and the rest are indels [26].

The identified variant (c.266G>A[p.Arg89His]) in the present study is a missense one in the *HOGA1* gene, which is the first report in the Iranian population (Fig. 5). According to the ACMG guideline, this variant is likely pathogenic because (1) it was not found in the gnomeAD and ExAC database (PM2), (2) several in silico tools such as BayesDel addAF, MetaRNN, DANN, DEOGEN2, FATHMM-XF,

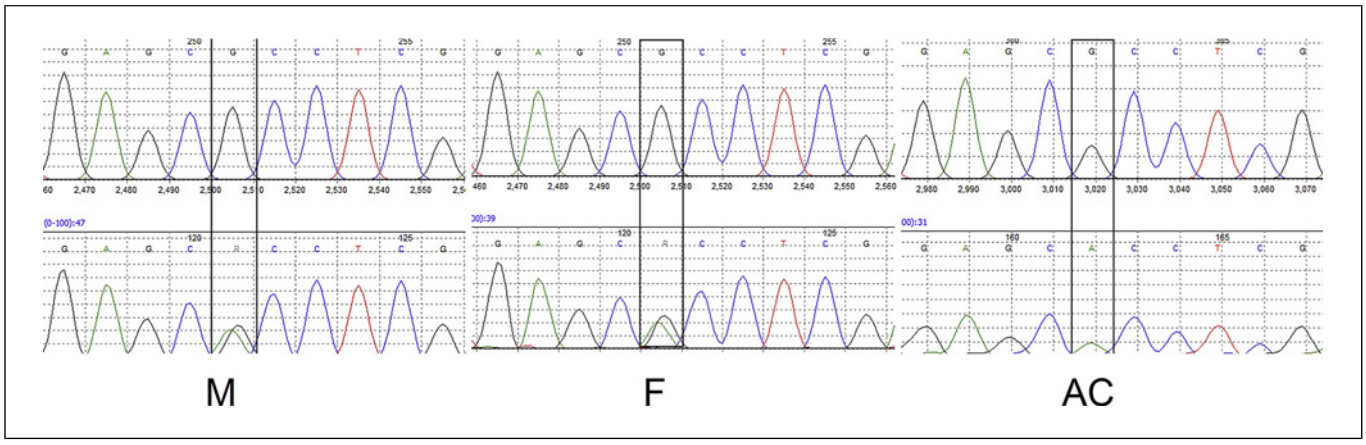

Fig. 3. Result of Sanger sequencing analysis in the F11 family. The affected child (AC) had a homozygous mutation c.266G>A (p.Arg89His) and his parents were heterozygous. F, father; M, mother.

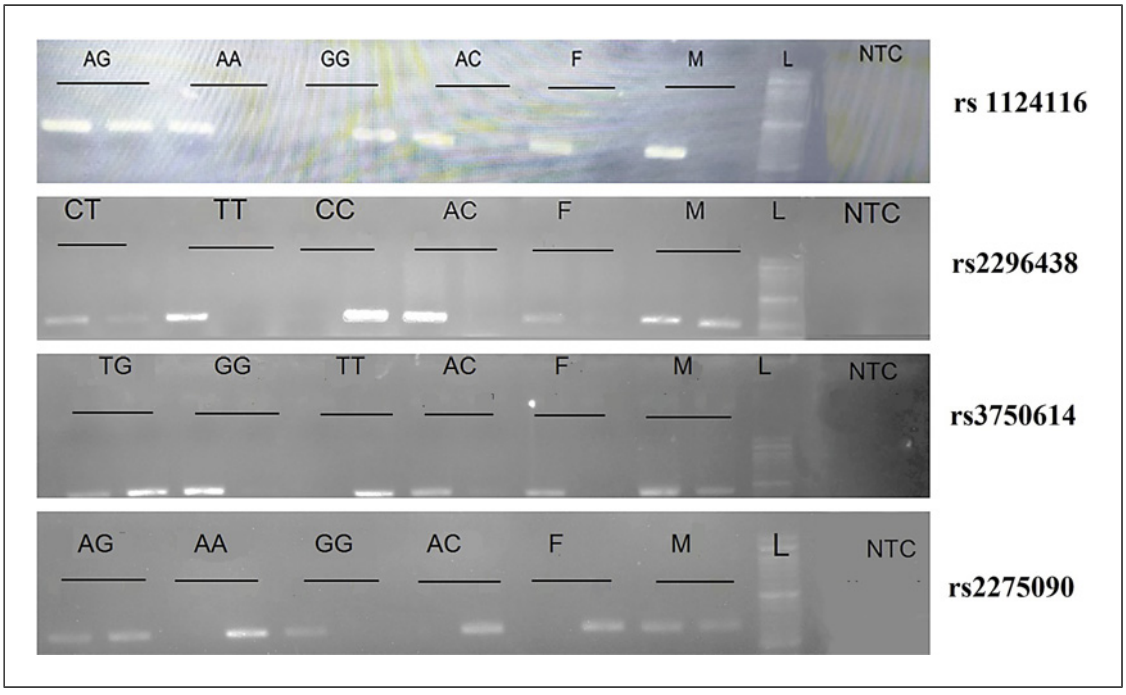

Fig. 4. ARMS-PCR for all 4 SNPs in the family of F11. Two nonidentical letters indicate heterozygous genotype of that SNP (AG-CT-TG-AG) and two identical letters indicate homozygous genotype of that SNP (AA-GG-TT-CC-TT-GG-AA-GG). AC, affected child; F, father; M, mother.

M-CAP, and MetaRNN revealed it could be a disease-causing variant (Table 3). Based on the HOPE [27], the mutant residue is smaller than the wild-type residue and the size difference between them puts the new residue in the incorrect position to make the hydrogen bond as the original wild-type residue did. Moreover the wild-type residue charge was positive whereas the mutant residue charge is neutral (PP3). (3) This variant is found in a homozygous state (PM3). (4) This non-synonymous variant is located in a mutational hot spot and critically well-established functional domain (PM1). (5) Missense variant is a common mechanism of this disorder and the *HOGA1* gene has a low rate of benign missense variants (PP2) after all functional study is suggested for confirming the pathogenicity of this variant.

Kidney Blood Press Res 2025;50:189–197
DOI: 10.1159/000544093

Table 2. The genes whose mutations potentially cause kidney stones are shown in the found ROH region of the WES data from the patient of F3 family

Chromosome	Start	End	Length	Number of variants	Number of homozygotes	Percentage of homozygotes, %	Number of heterozygotes	Percentage of heterozygotes, %	Gene
chr1	0	3,809,423	3,809	199	199	100.00	0	0.00	
chr2	42,275,725	47,388,766	5,113	70	70	100.00	0	0.00	MTA3
chr2	209,035,657	228,883,721	19,848	348	332	95.40	16	4.60	
chr3	3,170,791	5,241,223	2070	22	22	100.00	0	0.00	
chr3	14,526,537	53,882,903	39,356	562	562	100.00	0	0.00	
chr3	168,840,570	186,370,333	17,529	106	106	100.00	0	0.00	
chr4	36,069,804	126,373,789	90,303	735	734	99.86	1	0.14	
chr5	112,256,813	150,704,724	38,447	485	480	98.97	5	1.03	PCDH12
chr5	157,285,727	160,097,632	2811	21	21	100.00	0	0.00	
chr6	33,255,102	47,847,683	14,592	402	395	98.26	7	1.74	ITPR3
chr7	4,946,876	27,702,390	22,755	272	270	99.26	2	0.74	
chr7	91,503,227	120,740,103	29,236	395	395	100.00	0	0.00	MUC3A
chr8	0	7,718,187	7,718	99	99	100.00	0	0.00	
chr8	133,918,768	146,364,022	12,445	412	412	100.00	0	0.00	WDR97
chr9	36,674,841	39,103,743	2428	22	22	100.00	0	0.00	GRHPR
chr9	71,002,553	78,601,268	7,598	58	58	100.00	0	0.00	PIP5K1B
chr11	47,440,282	50,246,956	2806	57	56	98.25	1	1.75	
chr11	82,641,363	135,006,516	52,365	667	667	100.00	0	0.00	
chr12	6,128,442	9,311,265	3,182	164	156	95.12	8	4.88	
chr14	34,243,476	38,679,473	4,435	31	31	100.00	0	0.00	
chr14	53,529,668	56,085,812	2556	26	25	96.15	1	3.85	
chr14	95,918,465	107,349,540	11,431	326	321	98.47	5	1.53	
chr16	8,728,952	13,002,359	4,273	132	132	100.00	0	0.00	
chr16	80,577,097	86,585,905	6,008	194	194	100.00	0	0.00	
chr21	45,170,284	48,129,895	2,959	188	186	98.94	2	1.06	

Table 3. The in silico tools' scores are shown for c.266G>A mutation

DANN	0.9995	Pathogenic supporting
DEOGEN2	0.8052	Pathogenic supporting
FATHMM-XF	Coding score 0.9021	Pathogenic supporting
LRT	0	Pathogenic supporting
M-CAP	0.4739	Pathogenic supporting
MutPred	0.615	Pathogenic supporting
Mutation assessor	1.81	Benign supporting
BLOSUM	−1	Uncertain
EIGEN	Raw coding 0.4689	Uncertain
EIGEN PC	PC raw coding score 0.4426	Uncertain
FATHMM	−3.61	Uncertain
FATHMM-MKL	Coding score 0.9687	Uncertain
LIST-S2	0.9521	Uncertain
MutationTaster	1, 0.9999, 1	Disease causing
MVP	0.8357	Uncertain
PROVEAN	−3.92	Uncertain
SIFT	0.007	Uncertain
SIFT4G	0.003	Uncertain
PHRED	27.2	Damaging
CADD	26.8	Damaging

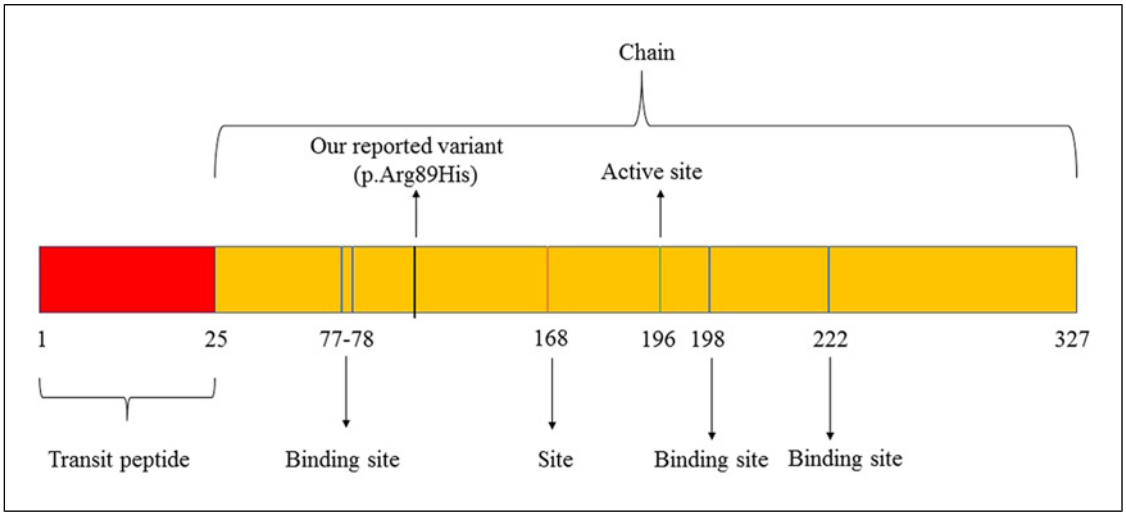

Fig. 5. The position of the reported mutation in the present study is mapped on the 2D structure of HOGA1 protein.

No causative variant was detected in the F4 family's proband. This might be due to that the variant may locate in the regulatory elements/promoter regions, which were not covered by Sanger sequencing, or other genes except for *HOGA1* may be responsible for the disease. It is suggested to perform whole genome sequencing to find out the causative mutation in this family.

NGS Analysis

After NGS analysis and checking the relevant genes in the different databases such as GeneCard, MalaCard, and OMIM, no gene related to the phenotypic disorder of the affected person was found. It is suggested that the mutation may be located in the non-exonic regions such as promoter or regulatory elements. Since the patient (F3) was born into a consanguineous marriage, we tried to find an ROH region to guide us to the possible causative locus in the patient. Different genes were found in these regions as shown in Table 2; the only gene that was related to this disease was the *GRHPR* gene. As no pathogenic/likely pathogenic variant was detected in all coding regions of this gene, we assume that the causative variant may be in the non-exonic region of the *GRHPR* gene; therefore, performing a whole genome sequencing for this case is suggested. To the best of our knowledge, this is the first genetic study on hyperoxaluria patients in Iran and it can provide a good context for future research.

Conclusion

Out of 14 patients taking part in this study, a likely pathogenic variant (*HOGA1*: exon 2:c266G>A) in one of them was detected. NGS analysis could be a good approach for those who did not show homozygous haplotypes.

Acknowledgment

The authors would like to thank Ali Asghar Clinical Research Development Center for search assistance.

Statement of Ethics

This study protocol was reviewed and approved by the Iran University of Medical Sciences (IUMS) research committee (Approval No. IR.IUMS.FMD.REC.1401.149). For this study, written informed consent was obtained from participants' parents. Written informed consent was obtained from their parents for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

This research was funded by IUMS. Author Marzieh Mojbafan has received research support from IUMS.

Author Contributions

Sadegh Tavakoli Ataabadi performed the experiment and collected data and analyzed and interpreted data and drafted the manuscript. Leila Behi cooperated in the project. Marzieh Mojbafan designed and supervised the study and critically revised the manuscript. Nakysa Hooman contributed to sample collection and clinical and paraclinical examination of patients.

Data Availability Statement

All date generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Wang X, Zhao X, Wang X, Yao J, Zhang F, Lang Y, et al. Two novel HOGA1 splicing mutations Identified in a Chinese Patient with primary hyperoxaluria type 3. Am J Nephrol. 2015;42(1):78–84. https://doi.org/10.1159/000439232

2 Lorenzo V, Torres A, Salido E. Primary hyperoxaluria. Nefrologia. 2014;34(3):398–412. https://doi.org/10.3265/Nefrologia.pre2014.Jan.12335

3 Belostotsky R, Seboun E, Idelson GH, Milliner DS, Becker-Cohen R, Rinat C, et al. Mutations in DHDPSL are responsible for primary hyperoxaluria type III. Am J Hum Genet. 2010;87(3):392–9. https://doi.org/10.1016/j.ajhg.2010.07.023

4 Fargue S, Acquaviva Bourdain C. Primary hyperoxaluria type 1: pathophysiology and genetics. Clin Kidney J. 2022;15(Suppl 1):i4–i8. https://doi.org/10.1093/ckj/sfab217

5 Buchalski B, Wood KD, Challa A, Fargue S, Holmes RP, Lowther WT, et al. The effects of the inactivation of Hydroxyproline dehydrogenase on urinary oxalate and glycolate excretion in mouse models of primary hyperoxaluria. Biochim Biophys Acta, Mol Basis Dis. 2020;1866(3):165633. https://doi.org/10.1016/j.bbadis.2019.165633

6 Hoppe B. The enzyme 4-hydroxy-2-oxoglutarate aldolase is deficient in primary hyperoxaluria type III. Nephrol Dial Transpl. 2012;27(8):3024–6. https://doi.org/10.1093/ndt/gfs308

7 Sikora P, Zaniew M, Grenda R, Jobs K, Rubik J, Zawadzki J, et al. Still diagnosed too late and under-recognized? The first comprehensive report on primary hyperoxaluria in Poland. Pol Arch Intern Med. 2020;130(12):1053–63. https://doi.org/10.20452/pamw.15698

8 Cazzolla A, Zhurakivska K, Ciavarella D, Lacaita MG, Favia G, Testa NF, et al. Primary hyperoxaluria: orthodontic management in a pediatric patient: a case report. Spec Care Dentist. 2018;38(4):259–65. https://doi.org/10.1111/scd.12302

9 Milliner DS, McGregor TL, Thompson A, Dehmel B, Knight J, Rosskamp R, et al. End points for clinical trials in primary hyperoxaluria. Clin J Am Soc Nephrol. 2020;15(7):1056–65. https://doi.org/10.2215/CJN.13821119

10 Fang X, He L, Xu G, Lin H, Xu M, Geng H. Nine novel HOGA1 gene mutations identified in primary hyperoxaluria type 3 and distinct clinical and biochemical characteristics in Chinese children. Pediatr Nephrol. 2019;34(10):1785–90. https://doi.org/10.1007/s00467-019-04279-7

11 Monico CG, Rossetti S, Belostotsky R, Cogal AG, Herges RM, Seide BM, et al. Primary hyperoxaluria type III gene HOGA1 (formerly DHDPSL) as a possible risk factor for idiopathic calcium oxalate urolithiasis. Clin J Am Soc Nephrol. 2011;6(9):2289–95. https://doi.org/10.2215/CJN.02760311
12 Riedel TJ, Johnson LC, Knight J, Hantgan RR, Holmes RP, Lowther WT. Structural and biochemical studies of human 4-hydroxy-2-oxoglutarate aldolase: implications for hydroxyproline metabolism in primary hyperoxaluria. PLoS One. 2011;6(10):e26021. https://doi.org/10.1371/journal.pone.0026021
13 Mojbafan M, Bahmani R, Bagheri SD, Sharifi Z, Zeinali S. Mutational spectrum of autosomal recessive limb-girdle muscular dystrophies in a cohort of 112 Iranian patients and reporting of a possible founder effect. Orphanet J Rare Dis. 2020;15:14–0. https://doi.org/10.1186/s13023-020-1296-x
14 Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988;16(3):1215. https://doi.org/10.1093/nar/16.3.1215
15 Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M. CADD: predicting the deleteriousness of variants throughout the human genome. Nucleic Acids Res. 2019;47(D1):D886–94. https://doi.org/10.1093/nar/gky1016
16 Schwarz JM, Cooper DN, Schuelke M, Seelow D. MutationTaster2: mutation prediction for the deep-sequencing age. Nat Methods. 2014;11(4):361–2. https://doi.org/10.1038/nmeth.2890
17 Minton JA, Flanagan SE, Ellard S. Mutation surveyor: software for DNA sequence analysis. Methods Mol Biol. 2011;688:143–53. https://doi.org/10.1007/978-1-60761-947-5_10
18 Venables AJ. Using natural resources for development: why has it proven so difficult? J Econ Perspect. 2016;30(1):161–84. https://doi.org/10.1257/jep.30.1.161
19 Ng PC, Henikoff S. SIFT: predicting amino acid changes that affect protein function. Nucleic Acids Res. 2003;31(13):3812–4. https://doi.org/10.1093/nar/gkg509
20 Adzhubei I, Jordan DM, Sunyaev SR. Predicting functional effect of human missense mutations using PolyPhen-2. Curr Protoc Hum Genet. 2013;Chapter 7(1):Unit 7.20–41. https://doi.org/10.1002/0471142905.hg0720s76
21 Huber CD, Kim BY, Lohmueller KE. Population genetic models of GERP scores suggest pervasive turnover of constrained sites across mammalian evolution. Plos Genet. 2020;16(5):e1008827. https://doi.org/10.1371/journal.pgen.1008827
22 Amendola LM, Jarvik GP, Leo MC, McLaughlin HM, Akkari Y, Amaral MD, et al. Performance of ACMG-AMP variant-interpretation guidelines among nine laboratories in the clinical sequencing exploratory research consortium. Am J Hum Genet. 2016;98(6):1067–76. https://doi.org/10.1016/j.ajhg.2016.03.024
23 Singh P, Viehman JK, Mehta RA, Cogal AG, Hasadsri L, Oglesbee D, et al. Clinical characterization of primary hyperoxaluria type 3 in comparison with types 1 and 2. Nephrol Dial Transpl. 2022;37(5):869–75. https://doi.org/10.1093/ndt/gfab027
24 Wang W, Liu Y, Kang L, He R, Song J, Li Y, et al. Mutation hot spot region in the HOGA1 gene associated with primary hyperoxaluria type 3 in the Chinese population. Kidney Blood Press Res. 2019;44(4):743–53. https://doi.org/10.1159/000501458
25 Fang X, He L, Xu G, Lin H, Xu M, Geng H. Nine novel HOGA1 gene mutations identified in primary hyperoxaluria type 3 and distinct clinical and biochemical characteristics in Chinese children. Pediatr Nephrol. 2019;34(10):1785–90. https://doi.org/10.1007/s00467-019-04279-7
26 Abid A, Raza A, Khan AR, Firasat S, Shahid S, Hashmi S, et al. Primary hyperoxaluria: comprehensive mutation screening of the disease causing genes and spectrum of disease-associated pathogenic variants. Clin Genet. 2023;103(1):53–66. https://doi.org/10.1111/cge.14240
27 Venselaar H, te Beek TA, Kuipers RK, Hekkelman ML, Vriend G. Protein structure analysis of mutations causing inheritable diseases. An e-Science approach with life scientist friendly interfaces. BMC bioinformatics. 2010;11:548–10. https://doi.org/10.1186/1471-2105-11-548