Mutations in *DHDPSL* Are Responsible For Primary Hyperoxaluria Type III

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Primary hyperoxaluria (PH) is an autosomal-recessive disorder of endogenous oxalate synthesis characterized by accumulation of calcium oxalate primarily in the kidney. Deficiencies of alanine-glyoxylate aminotransferase (AGT) or glyoxylate reductase (GRHPR) are the two known causes of the disease (PH I and II, respectively). To determine the etiology of an as yet uncharacterized type of PH, we selected a cohort of 15 non-PH I/PH II patients from eight unrelated families with calcium oxalate nephrolithiasis for high-density SNP microarray analysis. We determined that mutations in an uncharacterized gene, *DHDPSL*, on chromosome 10 cause a third type of PH (PH III). To overcome the difficulties in data analysis attributed to a state of compound heterozygosity, we developed a strategy of "heterozygosity mapping"—a search for long heterozygous patterns unique to all patients in a given family and overlapping between families, followed by reconstruction of haplotypes. This approach enabled us to determine an allelic fragment shared by all patients of Ashkenazi Jewish descent and bearing a 3 bp deletion in *DHDPSL*. Overall, six mutations were detected: four missense mutations, one in-frame deletion, and one splice-site mutation. Our assumption is that *DHDPSL* is the gene encoding 4-hydroxy-2-oxoglutarate aldolase, catalyzing the final step in the metabolic pathway of hydroxyproline.

Primary hyperoxaluria (PH) type I and type II are relatively rare autosomal-recessive disorders of endogenous oxalate synthesis. Overproduction of oxalate by the liver results in marked hyperoxaluria. The calcium salt of oxalate is highly insoluble; therefore, hyperoxaluria leads to renal stone formation and nephrocalcinosis in childhood, followed by progressive renal damage, renal failure, and reduced life expectancy. Type I PH (MIM 259900) is caused by absent, deficient, or mistargeted activity of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT; MIM 604285).[1] PH II (MIM 260000) is caused by deficiency of the enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR; MIM 604296).[2]

A third group of patients has been described with an autosomal-recessive disorder having a phenotype similar to that of PH I and PH II but not due to hepatic AGT or GRHPR deficiency. These patients are referred to as non-PH I/PH II patients.[3] To date, non-PH I/PH II forms of inherited PH account for approximately 5% of all cases.[3] The specific etiology of the disease in these patients is unknown. Possible pathogenetic mechanisms may include alterations in pathways of oxalate synthesis in the liver and/or kidney or in tubular oxalate handling. The underlying cause remains elusive despite several attempts to define additional genetic loci that could affect urinary oxalate excretion resulting in stone formation. The possibilities that alterations in the gene encoding glycolate oxidase[4] or in *SLC26A6* (MIM 610068)[5] are responsible for this type of PH have been refuted.

High-density SNP microarray analysis is a promising approach for identifying disease susceptibility genes. We implemented this technique in trying to identify the gene that in its mutated form causes non-type I/II PH.

The cohort consisted of 16 patients from nine unrelated families: five of Ashkenazi Jewish descent and four of European American origin. The impetus to launch this project was the presentation of two sisters from family 1 (II-9 and II-10) at 22 and 36 months of age with kidney stones composed of calcium oxalate associated with persistent elevation of urine oxalate and normal hepatic AGT and GRHPR enzymatic activity (family 1, Figure 1A). A second, unrelated Ashkenazi Jewish family (family 2) with two children affected with non-type I/II PH, one of whom (II-1) developed nephrolithiasis in infancy, was enrolled (family 2, Figure 1A). After completion of this study, we diagnosed non-type I/II PH in another child of Ashkenazi Jewish descent who presented with nephrolithiasis in infancy (family 3). Eight additional children with non-type I/II PH from six unrelated families treated at the Mayo Clinic Hyperoxaluria Center (Rochester, MN, USA) were also included (Table 1). Of note, two of these families were of Ashkenazi Jewish descent (families 11 and 12).

Family 1 is a nonconsanguineous Ashkenazi Jewish family with five affected and five unaffected children

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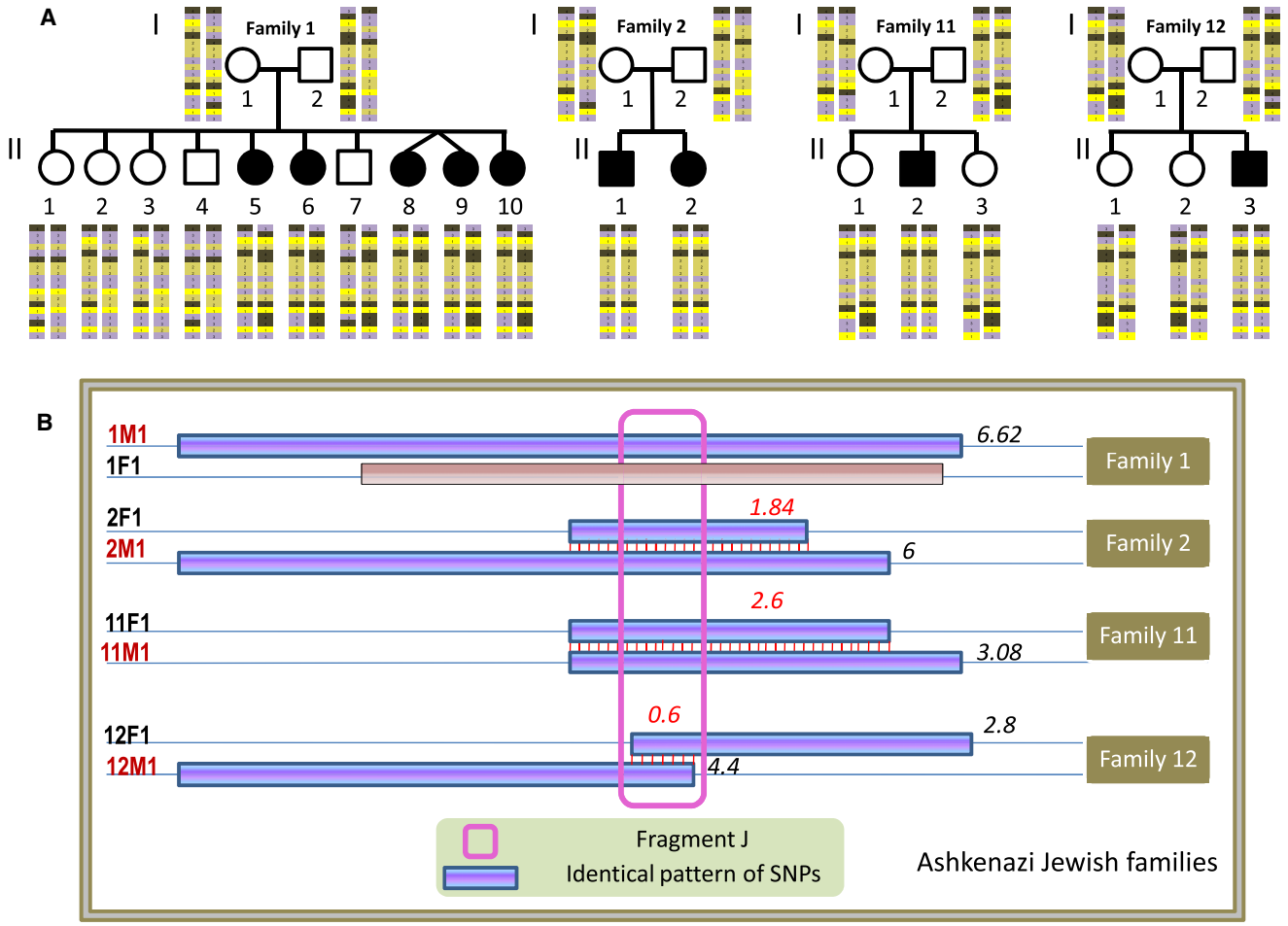

Figure 1. Alleles of Ashkenazi Jewish Families
(A) Pedigrees of families 1, 2, 11, and 12, which enabled us to identify *DHDPSL* and the pattern of adjacent SNPs.
(B) Distribution of the shared allele among Ashkenazi Jewish families. Black numbers indicate the length of the shared fragment, red numbers indicate the length of the homozygous fragment, and the pink frame indicates the common fragment J. The lengths of the fragments are presented in megabase pairs.

(Figure 1A). Both parents were healthy, and the family history was negative for nephrolithiasis in previous generations. Biochemical workup of the probands revealed a persistent increase in urinary oxalate excretion (1.20 ± 0.49 mmol/1.73 m^2/d [range 0.54–2.24; normal values < 0.49]) with milder degree of glycolic aciduria (125.2 ± 60.6 μmol/mmol creatinine [normal values = 6–90]). There was normal urinary excretion of phosphate, citrate, glycerate, and amino acids. The sisters II-9 and II-10 had normal growth and development, without any signs of gastrointestinal illness that might point to secondary or enteric hyperoxaluria.

The clinical characteristics of the entire cohort of 16 patients with non-type I/II PH from nine unrelated families are displayed in Table 1. The proband in each family presented with calcium oxalate renal stone disease in early childhood (mean age 2.0 ± 1.6 years). The clinical manifestations were hematuria, pain, and/or urinary tract infection. Biochemical analysis demonstrated persistent hyperoxaluria in all children, with mildly increased urinary glycolic aciduria in approximately half of them. In a number of cases, there was hypercalciuria and/or hyperuricosuria, but those were unrelated to the incidence of nephrolithiasis. The clinical characteristics of a subgroup of children were previously described.[4] The proband in each family underwent liver biopsy, and the measurements of AGT and of GRHPR enzymatic activity were within normal range. None had any signs or symptoms consistent with enteric hyperoxaluria. The six children in Monico's report were confirmed to have normal enteric oxalate absorption by [^{13}C]oxalate testing.[4] Taken together, they were diagnosed as having a new recessive form of hyperoxaluria: non-type I/II primary hyperoxaluria. Five individuals never formed stones. Increased fluid intake was recommended for all. No specific therapy was provided in patients from families 1–3. Children from families 11–16 received neutral phosphate therapy, and some were also treated with citrate medication or thiazides. They all had well-preserved renal function at most recent follow-up clinic visit (Table 1). In all patients of Ashkenazi Jewish

Table 1. Clinical Characteristics of Patients with Non-Type I/II Primary Hyperoxaluria

Family	Patient	Sex	Age First Stone (Years)	Age Last Stone (Years)	Age Last Follow-up	Serum Creatinine Last Follow-up (mg/dl)	Ethnicity
1	A	F	1.8	1.8	11.8	0.8	AJ
	B	F	3	3	14.2	0.9	AJ
	C	F	never	–	14.2	0.8	AJ
	D	F	never	–	19.2	NA	AJ
	E	F	never	–	21.2	NA	AJ
2	A	M	0.38	0.38	11.5	0.6	AJ
	B	F	never	–	14	NA	AJ
3	A	M	1.5	3.83	4.2	0.5	AJ
11	A	M	2	5	14	0.8	AJ
12	A	M	0.33	6	14	0.5	AJ
13	A	M	0.75	23	23	1.1	EA
	B	M	2	2.25	20	0.9	EA
14	A	M	5.4	13	15	0.7	EA
15	A	F	0.83	19	24	0.8	EA
16	A	M	4	12	12	0.9	EA
	B	M	never	–	–	NA	EA

The following abbreviations are used: NA, not available; AJ, Ashkenazi Jewish; EA, European American.

descent, there was no recurrence of stone formation beyond 6 years of age despite the fact that the degree of hyperoxaluria remained constant.

High-density SNP microarray analysis of 39 individuals from eight unrelated nonconsanguineous families including 15 affected individuals and all of their siblings and parents was performed on an Affymetrix GeneChip Human Mapping 250K Nsp Array (Centre National de Genotypage, Evry, France). Family 3 was recruited later and was not included in this analysis. All experiments involving DNA from patients and their relatives were performed after obtaining informed consent and were approved by the Shaare Zedek Medical Center Ethics Committee (number 1/09) and the National Committee for Genetic Studies of the Israeli Ministry of Health (number 019-2009) or the Mayo Clinic Rochester Institutional Review Board. Genomic DNA was extracted from lymphocytes via standard molecular biology techniques. Linkage analyses under a recessive model with penetrance = 1 were performed with MERLIN software for a combined set of all families and for individual families. The analyses failed to detect loci with high LOD score. The maximal LOD score of approximately 2.2 was contributed exclusively by family 1: a flat LOD score over several Mbp on chromosomes 4 and 10. The relatively low LOD score excluded the possibility that the affected children from family 1 share disease alleles identical by descent (inherited from a common ancestor). Indeed, no large homozygous fragments shared only by the affected individuals were identified.

In order to overcome these obstacles, an analytic strategy (heterozygosity mapping) was adopted that enabled us to detect and refine the fragment of interest. Analysis of the SNP pattern in the relevant regions on chromosomes 4 and 10 revealed identical heterozygous patterns in all patients of family 1 that were distinct from their healthy parents and siblings. These fragments were of 19.6 and 42.4 Mbp, respectively. This fits the compound heterozygous origin of the disease in family 1. In family 2, we identified a heterozygous fragment of 35 Mbp on chromosome 10 unique to both affected children. This region partly intersects with the corresponding fragment of family 1, yielding a locus of 27.6 Mbp in length. The fact that both families are of Ashkenazi Jewish origin led us to consider that they might represent one clinical entity with possible sharing of a founder mutation at least in one allele on chromosome 10. A recent publication showed that identity by descent between Ashkenazi Jewish individuals exhibits high frequencies of shared segments similar to those shared by fourth or fifth cousins in a completely outbred population, although typically with shorter segments.[6] We implemented the approach of homozygosity haplotype (HH), a haplotype defined only by the homozygous SNPs obtained following omission of the heterozygous SNPs.[7,8] We searched for a fragment in which HHs of both families were identical. Such a fragment would suggest that within this region, the two families share at least one common disease allele. This approach enabled us to narrow the genomic region of interest to 6.1 Mbp.

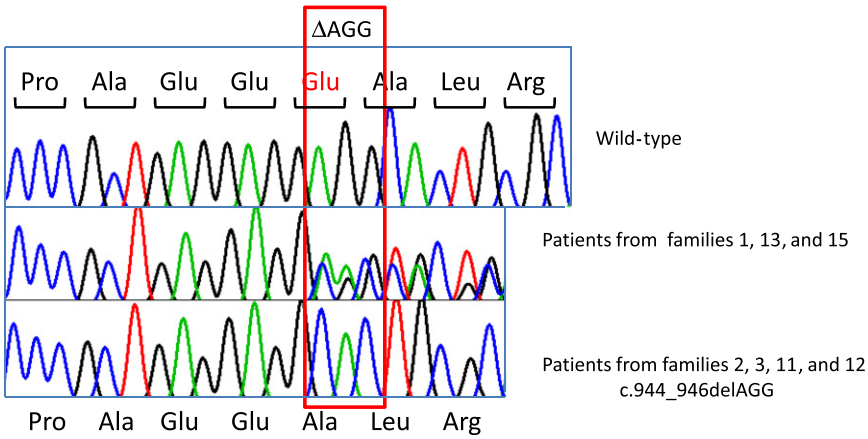

Figure 2. DNA Sequencing of an Amplicon of Exon 7 of *DHDPSL* Demonstrating the Deletion Mutation c.944_946delAGG Found in All Ashkenazi Jewish Patients and Two Additional Families
The red box marks the deletion. (Note: SNP rs1124116 upstream of exon 7 should be avoided in designing primers.)

We subsequently reconstructed individual haplotypes in the 6.1 Mbp locus of interest of the mother and father of family 1 by using the microarray data derived from the genetic analysis of the parents and the siblings. Comparison of each haplotype of the affected individuals of family 1 with those of family 2 demonstrated that the SNP pattern of the maternal allele (1M1) completely matched the haplotype of both patients of family 2.

Families 11 and 12 (Figure 1A) were also of Ashkenazi Jewish descent, so we used data from them to refine the region of interest. All Ashkenazi Jewish patients were found to share the pattern of the maternal allele (1M1); however, the exact position of the homologous fragment was different in each case. The intersection of all shared regions resulted in a very small fragment (J) of 0.6 Mbp in length (Figure 1B).

This locus contained altogether 19 characterized or uncharacterized genes. A priority list for sequencing was generated, taking into account the known or presumed protein function, the expression in liver and/or kidney, and, when available, the phenotype associated with a given mutated gene. *DHDPSL* (SwissProt accession number Q86XE5) was selected as the preferred candidate gene based on its unique expression pattern mostly in liver and kidney and its presumed involvement in metabolic processes. PCR primers were designed for amplification of the entire coding region and the adjacent intron/exon boundaries of *DHDPSL* by using NCBI Primer-BLAST (see Table S1 available online). Genomic DNA samples were subjected to PCR amplification and direct sequencing. All patients of families 2, 11, and 12 were found to be homozygous for a deletion c.944_946delAGG leading to the loss of one glutamic acid residue (Figure 2). As we had speculated, all affected individuals in family 1 were compound heterozygotes: they were heterozygous for this mutation inherited from their mother, whereas their paternal mutation was c.860G>T (p.Gly287Val). Mutation screening of *DHDPSL* in the Ashkenazi Jewish patient from family 3 confirmed that he was also homozygous for the deletion allele. The c.944_946delAGG deletion was also detected in two non-Jewish families (family 13 and family 15) in a heterozygous fashion (Figure 2; Table 2.) The second mutation in family 13 was c.289C>T, and the second mutation in family 15 was c.701+4G>T. Mutations were also found in family 14 (compound heterozygous

Table 2. Distribution of Mutations in *DHDPSL* among Children with Primary Hyperoxaluria Type III

	Maternal Allele			Paternal Allele		
	Mutation	**Length[a]**	**Protein**	**Mutation**	**Length[a]**	**Protein**
Ashkenazi Jewish						
Family 1	c.944_946delAGG	6.6 Mbp	p.Glu315del	c.860G>T	–	p.Gly287Val
Family 2	c.944_946delAGG	6 Mbp	p.Glu315del	c.944_946delAGG	1.8 Mbp	p.Glu315del
Family 3	c.944_946delAGG	ND	p.Glu315del	c.944_946delAGG	ND	p.Glu315del
Family 11	c.944_946delAGG	3.1 Mbp	p.Glu315del	c.944_946delAGG	2.6 Mbp	p.Glu315del
Family 12	c.944_946delAGG	4.4 Mbp	p.Glu315del	c.944_946delAGG	2.8 Mbp	p.Glu315del
European American						
Family 13	c.289C>T	–	p.Arg97Cys	c.944_946delAGG	<0.5 Mbp	p.Glu315del
Family 14	c.209G>C	–	p.Arg70Pro	c.701+4G>T	<0.5 Mbp	in-frame splice site
Family 15	c.701+4G>T	<0.5 Mbp	in-frame splice site	c.944_946delAGG	1 Mbp	p.Glu315del
Family 16 (A)	c.769T>G	8 Mbp	p.Cys257Gly	c.769T>G	8 Mbp	p.Cys257Gly
Family 16 (B)	–	–	–	–		–

ND, not determined.
[a] Maximal length of fragment shared with the corresponding allele.

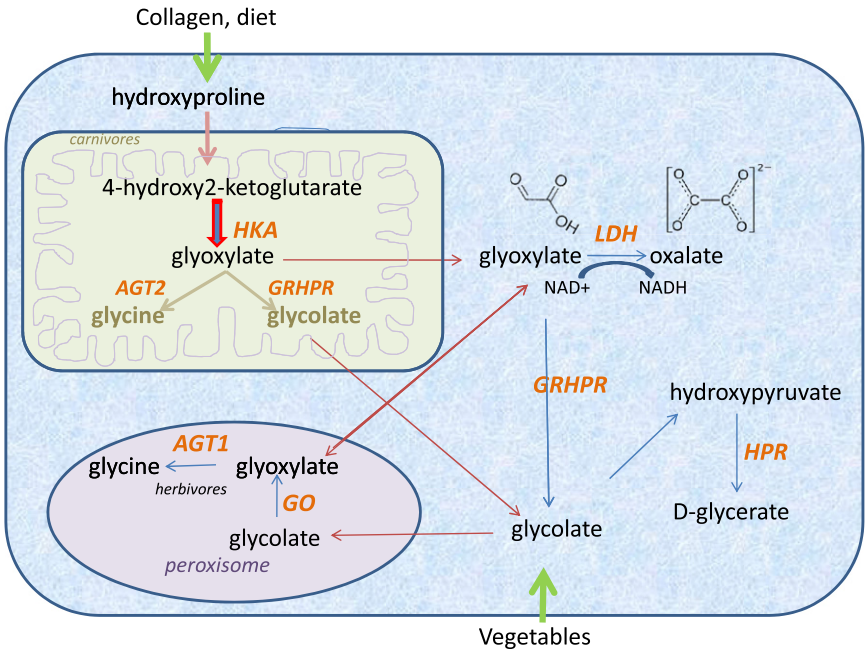

Figure 3. The Metabolic Pathways of Oxalate Production in Humans

c.209G>C and c.701+4G>T) and in patient A from family 16 (homozygous c.769T>G). Out of 16 patients, we found either homozygous or compound heterozygous mutations in this gene in 15 cases. In every patient, it was confirmed that mutations were found on separate alleles inherited from their respective parents (Table 2). Only one patient (16B) was found not to carry mutations in this gene. His affected brother (patient 16A) was homozygous for a missense mutation (c.769T>G). This phenomenon could be attributable to erroneous diagnosis of non-type I/II PH in patient 16B. In fact, review of the clinical data demonstrated that this patient had had only transient hyperoxaluria and had never formed a kidney stone, which represents a phenotypic misclassification. In all, six different mutations were detected: deletion of three base pairs, four missense mutations, and a presumed splice-site mutation. Whether the missense mutations are expected to bear pathogenic consequences was assessed by the PolyPhen predictor. Three mutations were described as probably (c.860G>T and c.769T>G) or possibly (c.209G>C) damaging and one (c.289C>T) as benign (damaging in this context represents a nonneutral change and may also refer to gain of function). The deletion mutation skips one amino acid. The splice-site mutation switches to another donor splice site 51 nucleotides downstream (predicted by the NetGene2 server) and results in in-frame insertion of 17 amino acid residues. Unfortunately, the splicing effect could not be confirmed, because both patients carrying this mutation were lost to follow-up and their RNA samples were unavailable to us. None of the mutations introduces a premature stop codon. This leaves the two modes of functional effect, namely loss of function and activation, to still be potentially applicable. We searched for the two mutations detected in families 1, 2, 3, 11, and 12 in 216 chromosomes of anonymous DNA samples derived from healthy unrelated Ashkenazi Jewish individuals. None were found to carry either of these mutations. Screening by direct sequencing of exonic and flanking intronic regions of *DHDPSL* in 226 chromosomes of European American control samples from Mayo Clinic Rochester also confirmed absence of any of the pathogenic variants in this population. These findings exclude the possibility that the genetic variants are merely polymorphisms. Analysis of haplotypes of shared mutations confirmed in most instances a founder effect as displayed in Table 2. In three cases, the shared haplotype was less than 0.5 Mbp (10 SNPs) in length, which leaves the option of a recurrent mutation valid.

The automatic annotation of *DHDPSL* describes it as a mitochondrial dihydrodipicolinate synthase-like enzyme. However, the homology between the protein encoded by *DHDPSL* and the original enzyme DHDPS (SwissProt accession number P0A6L2) is rather poor (28% identities, 47% positives), and, even more importantly, there is little homology in the vicinity of the putative substrate-binding region, residues 77 and 78 of *DHDPSL*. Neither lysine biosynthesis nor sialic acid metabolism (for which DHDPS is responsible) takes place in vertebrate mitochondria. Taking these data together, we conclude that only general annotation of the enzymatic function can be suggested: a mitochondrial enzyme that belongs to the lyase family and catalyzes a lyase reaction with pyruvate as one of the products. We assumed that *DHDPSL* encodes a metabolic rather than a regulatory or a transport protein and that it is involved in glyoxylate synthesis. Oxalate is a product of oxidation of glyoxylate by cytosolic lactate dehydrogenase. Thus, the increased production and excretion of oxalate would be a direct result of glyoxylate overproduction.

Glyoxylate is produced in organisms via two pathways: the oxidation of glycolate contributed by vegetable matter, and catabolism of hydroxyproline supplied by turnover of collagen and protein from animal products (Figure 3). We assume that the enzyme encoded by *DHDPSL* is involved in the hydroxyproline pathway, which takes place solely in mitochondria. This pathway includes four steps (Figure 4); the last one is catalyzed by a pyruvate lyase enzyme, 4-hydroxy-2-oxoglutarate aldolase. We speculated that the putative function of the protein encoded by *DHDPSL* best matches the pyruvate lyase reaction catalyzed by 4-hydroxy-2-oxoglutarate aldolase

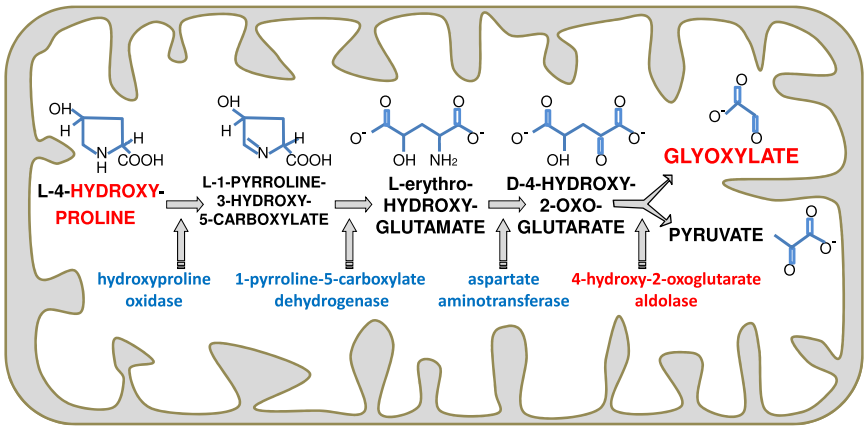

Figure 4. The Metabolic Pathway of Hydroxyproline Degradation in Humans

(4-hydroxy-2-oxoglutarate glyoxylate-lyase) (IUBMB enzyme nomenclature EC 4.1.3.16). This assumption was based on similarities drawn between the *DHDPSL* product and 4-hydroxy-2-oxoglutarate aldolase with regard to the following parameters:

- Both enzymes are involved in glyoxylate metabolism.
- Both catalyze the pyruvate lyase reaction and contain lysine in the active site necessary for the formation of a Schiff base intermediate.
- Both are localized in the mitochondria.
- Both are strongly expressed in kidney and liver.
- Their corresponding molecular masses are 35 kDa and 36 kDa, respectively.

The mammalian gene encoding 4-hydroxy-2-oxoglutarate aldolase was unknown until now. However, the protein has been extensively investigated, purified, and characterized (see KEGG and references [9–12]). Our assumption that *DHDPSL* is the gene encoding 4-hydroxy-2-oxoglutarate aldolase, or KHGA, was supported by the comparison of the amino acid composition of the protein encoded by bovine *DHDPSL*, short of the mitochondrial signal, with the protein purified from the bovine kidney.[12] Indeed, there is almost complete identity between the putative *DHDPSL* product and 4-hydroxy-2-oxoglutarate aldolase as shown in Figure 5. These findings are in contrast to the marked differences detected in the amino acid content between the bovine KHGA protein and the same protein from various eukaryotic species. Similar differences have been demonstrated between the bovine KHGA and a number of other lyases.

Prokaryotic organisms are divided into two superkingdoms: eubacteria and archaebacteria. The enzyme from eubacteria *E. coli* that catalyzes this reaction, kgdA, shares no similarity with DHDPSL and belongs to the ED aldolase family. In archaebacteria, the kgdA enzymes are not similar to the eubacterial enzymes and belong to the DHDPS/N-acetylneuraminate pyruvate lyase family.[13,14] The archaebacteria are closer to eukaryotic mitochondria, and in fact, the archaebacteria *Halobacterium salinarum* kgdA enzyme does show homology with DHDPSL (33% identities, 47% positives; NCBI Blast), in particular in the region encompassing the substrate-binding site.

Taking these data together, we speculate that the putative function of the protein encoded by *DHDPSL* best matches 4-hydroxy-2-oxoglutarate aldolase and suggest that in patients with non-type I/II PH, this enzyme bears activating mutations leading to oxalate overproduction. The relatively large number (six) of different activating mutations could be explained, at least in part, by the homotetramer structure of the enzyme and the interactions between its subunits. Alternatively, in compound heterozygous conditions, one mutation may inactivate a portion of the product, for instance by altering tetramer formation. This would result in an enzyme that is completely encoded by the second allele bearing the activating mutation.[15]

Human His-DHDPSL was expressed in *E. coli* and affinity purified (Figure S1). We failed, however, to determine the presumed 4-hydroxy-2-oxoglutarate aldolase activity of the recombinant protein. We speculate that the inability to demonstrate the predicted activity may be the result of misfolding of the recombinant protein in the bacterial system, presumably as a result of the high hydrophobicity of the molecule (grand average of hydropathicity index > 0) and the tetrameric composition. Studies aimed at assessing the function of the *DHDPSL* wild-type and mutated gene products expressed in different systems are underway.

We propose to name the form of PH caused by mutations in *DHDPSL* primary hyperoxaluria type III (PH III). The role of dietary hydroxyproline as a contributor to hyperoxaluria in patients with type III PH warrants investigation. Inhibitors of 4-hydroxy-2-oxoglutarate aldolase encoded by this gene should be the optimal treatment for children with this form of PH.

Supplemental Data

Supplemental Data include one table and one figure and can be found with this article online at http://www.cell.com/AJHG.

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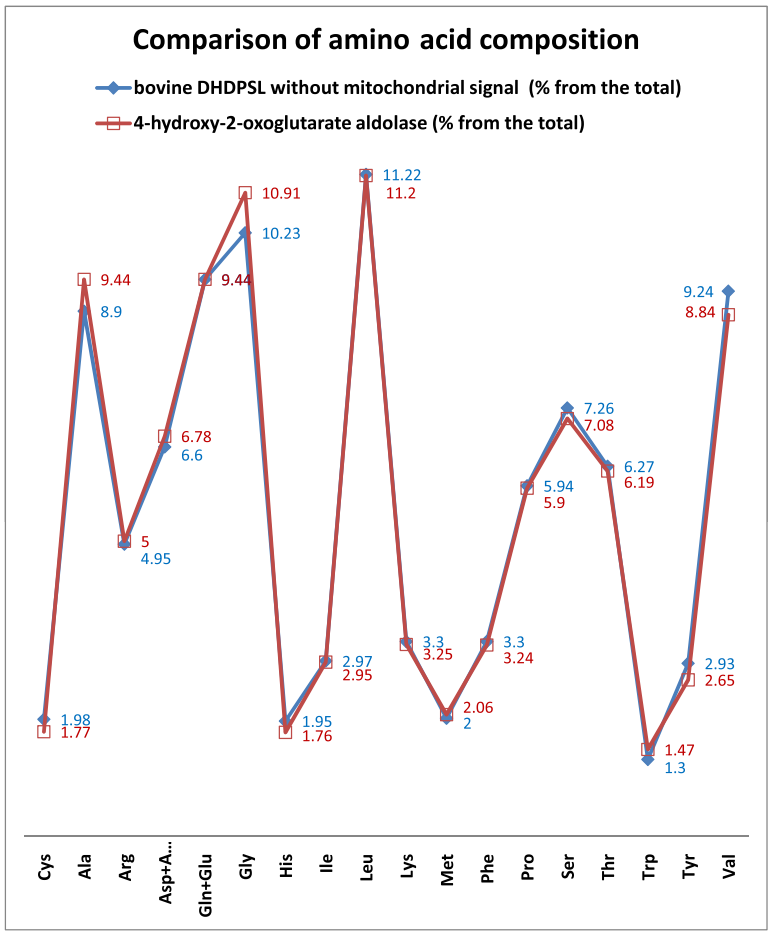

Figure 5. Comparison of Amino Acid Composition of DHDPSL and 4-Hydroxy-2-Oxoglutarate Aldolase
Blue, protein encoded by the bovine *DHDPSL* (0P515) lacking the mitochondrial localization signal; red, 4-hydroxy-2-oxoglutarate aldolase.[12]

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Web Resources

The URLs for data presented herein are as follows:

KEGG, http://www.genome.jp/kegg/kegg2.html
MERLIN, http://www.sph.umich.edu/csg/abecasis/Merlin/
NetGene2, http://www.cbs.dtu.dk/services/NetGene2/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/
PolyPhen, http://genetics.bwh.harvard.edu/pph/
SWISS-MODEL server, http://swissmodel.expasy.org/

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