RESEARCH REPORT

An ancestral variant causing type I xanthinuria in Turkmen and Arab families is predicted to prevail in the Afro-Asian stone-forming belt

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Abstract

Classical xanthinuria is a rare autosomal recessive metabolic disorder characterized by lack of xanthine dehydrogenase activity that often manifests as xanthine urolithiasis and risk of drug toxicity. Variants in the *XDH* or *HMCS* gene underlie classical xanthinuria type I and type II, respectively. Here we present two Israeli Arab families affected by type I xanthinuria in whom a c.2164A>T (Lys722Ter) variant in the *XDH* gene, previously reported in a Turkish family of Turkmen origin, was identified. Analysis of polymorphic markers surrounding the variant site revealed common haplotypes spanning 0.6 Mbp shared by all three, and 1.7 Mbp shared by two of the studied families. By applying Bayesian methods to a simple model of crossover events through generations in the chromosomes carrying the variant, the most recent common ancestor of these families was found to be 179 (95% credible limit 70) generations old. The estimated antiquity of the variant, the historical genealogy of the affected families and the history and present day dispersion of their people strongly suggest prevalence of this variant in the Afro-Asian stone-forming belt. As far as we are aware, this is a first report of an ancient variant causing xanthinuria with potential wide geographical dispersion.

KEYWORDS

Afro-Asian stone-forming belt, ancestral mutation, Arabs, genealogical history, time to most recent common ancestor, Turkmens, xanthinuria, *XDH* gene

1 | INTRODUCTION

Classical xanthinuria is a rare autosomal recessive metabolic disorder due to impaired xanthine dehydrogenase (XDH) activity resulting in lack of uric acid (UA) formation and accumulation of its precursors xanthine and hypoxanthine. Type I xanthinuria (MIM 278300) is caused by variants in the *XDH* gene[1] and results in isolated XDH deficiency. In type II xanthinuria (MIM 603592) variants in the human molybdenum cofactor sulfurase gene (*HMCS*) cause combined XDH and aldehyde oxidase (AO) deficiency.[2] The clinical manifestations of the two types of xanthinuria are indistinguishable, the most prominent being formation of xanthine calculi in the urinary tract in about 40% of the affected individuals.[3] Both XDH and AO are drug-metabolizing enzymes[4] and their absence may lead to drug induced toxicity. Interestingly, more than 2/3 of the xanthinuria cases have been reported from Mediterranean and Middle Eastern countries,[3] a region that belongs to the Afro-Asian stone-forming belt.[5] In Israel we encountered five Jewish and eight Arab families affected by classical xanthinuria (Peretz et al., unpublished data).[6,7] Among them, in two apparently unrelated Arab families we identified a c.2164A>T (Lys722Ter) variant in the *XDH* gene that was previously reported in a Turkish family.[8] The aim of the present work was to find out whether this variant might be an ancient variant that is widely dispersed in Afro-Asian regions prone to urolithiasis.

2 | METHODS

2.1 | Patients and control subjects

Three families with six affected individuals were studied (pedigrees depicted in Figure 1A). Eleven DNA samples of members of these families and 28 control DNA samples from four apparently unrelated Israeli Arab families were analyzed.

2.2 | DNA analyses

DNA was manually extracted from peripheral blood samples.[6] The c.2164A>T variant (**m**) and three single nucleotide polymorphisms (SNPs) designated m1, m2 and m3 were analyzed by PCR amplification followed by Sanger sequencing (Hylabs, Rechovot, Israel) (Table S1, Figure 1B). Microsatellite polymorphic markers designated M1-M10, within and in the vicinity of the *XDH* gene were analyzed by PCR (Table S1) and validated by Sanger sequencing. For fragment length evaluation PCR was performed using 5′-6FAM labeled forward primers followed by separation of PCR products on a 3130xl Genetic Analyzer (Applied Biosystems) according to manufacturer's instructions (Figure S1A). The

SYNOPSIS

This work presents evidence for an ancient founder variant causing type 1 classical xanthinuria in apparently unrelated Turkmen and Arab families; it raises the awareness to its potential presence in regions of the Afro-Asian stone-forming belt and may help identification of new cases and prevention of significant adverse clinical and pharmacological implications.

apparent allele sizes slightly differed from the actual number of bp obtained by Sanger sequencing yet the observed alleles were consistent with Mendelian segregation in the studied families (Figure S1B) and thus haplotypes associated with variant and control chromosomes were derived accordingly.

2.3 | Estimation of the time to the most recent common ancestor

For estimation of the time to the most recent common ancestor (MRCA) Bayesian methods were applied to a simple model of crossover events through generations in the chromosomes carrying the inherited variant. The model relates the length U (in Morgans) of the intact interval (on one side of the variant site) to the number T of generations between the common ancestor and the recently selected carriers (detailed description of the method is presented in Supporting Information).

2.4 | Genealogical history of the affected families

The method of "networking" between families was employed[9] using several sources of information. On the study of Arab families extensive literature consisting of files containing thousands of family trees, divided into "Qays" and "Yaman" or "the northern tribes" and "the southern tribes" and other subdivisions was consulted.[10] Information on the migration routes of the families and tribes throughout the entire Arab region and marriage ties with other families as well as how new branches were formed with new names was extracted from records of the Muslim Shari'a court and the Ottoman land registry authorities in Jenin and Nablus. Documents belonging to the families, as well as memoirs and biographies of prominent members of these families and studies on various social aspects served as additional source for studying the families' "networking."[11-13]
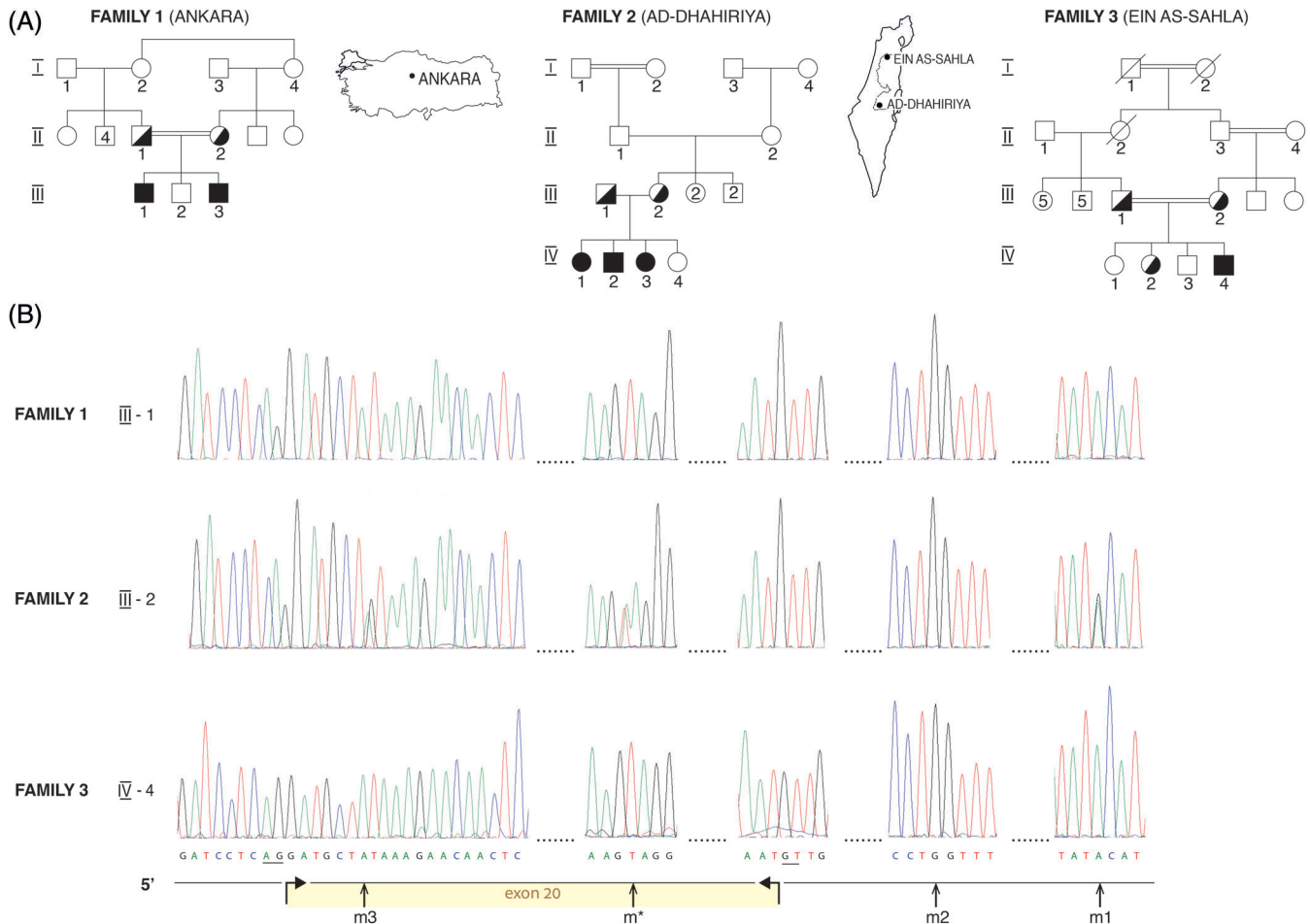
(A)

(B)

FIGURE 1 Geographic origin, pedigrees (A) and sequence chromatograms showing the c.2164A>T variant and three associated SNPs in the *XDH* gene in members of the affected families. A, In families 1 and 3 the current residence is shown, whereas in family 2, the mother's native origin is indicated. The geographic maps were adapted from https://commons.wikimedia.org/w/index.php?curid=6064736. Conventional genetic symbols are used to depict family pedigrees. B, Below the chromatograms the horizontal arrows demarcate the 5′ (c.2101) and 3′ (c.2197) ends of exon 20 of the *XDH* gene. The acceptor AG and donor GT intronic splice sites are underlined. The vertical arrows point to the mutation and SNPs sites. Note that the patients in families 1 and 3 are homozygous TT for the c.2164A>T variant and homozygous AA, GG and AA for the m3 (c.2107A/G), m2 (c.2197+42G/C) and m1 (c.2197+68G/A) polymorphisms, whereas the carrier mother in family 2 is heterozygous AT for the variant and heterozygous AG, homozygous GG and heterozygous AG, for the respective polymorphisms

3 | RESULTS

3.1 | Demographic, clinical, and molecular findings

Six affected individuals were identified in three families.

Family 1, residing in Ankara, Turkey is of Turkmen origin and was previously described in detail.[8] Two symptomatic brothers of consanguineous parents (Figure 1A) presented with renal calculi and were homozygous for the c.2164A>T (Lys722Ter) variant in the *XDH* gene.

Family 2 is part of an extended Bedouin-Arab pedigree (not shown) residing in the Negev in Southern Israel. Three affected children were identified in this family. The mother was born in ad-Dhahiriya south-west to Hebron in the West Bank of the Jordan River (Figure 1A). The index case

(IV-1), a young girl, was followed for a neurogenic bladder and was asymptomatically found to have undetectable levels of UA in serum and urine. Consequently, two older asymptomatic siblings were also found to have zero levels of serum and urinary UA. Renal ultrasound did not reveal any stones in the three patients. An additional sibling had normal levels of UA. The mother is carrier of the c.2164A>T (Lys722Ter) variant (Figure 1B), the father is carrier of another variant in the *XDH* gene (Peretz et al., unpublished data) and the affected children are compound heterozygotes (Figure S1B).

Family 3 is an Arab family living in the 'Ayn al-Sahala village, located in the Wadi 'ara area in Northern Israel. The parents of the affected child are cousins (Figure 1A). He first presented at the age of 5.5 years with abdominal pain and

ultrasound scanning of the abdomen revealed a small sized kidney without hydronephrosis. At the age of 7 years the boy had an episode of urinary retention and an obstructing stone was identified in the urethral meatus. The stone was extracted. Four years later a dimercaptosuccinic acid (DMSA) scan showed a hypoplastic left kidney and a compensatory hypertrophy of the right kidney. Since the left kidney contributed only 7% to the total kidney function and because of the past history of urolithiasis, left nephrectomy was performed. Classical xanthinuria was suspected based on undetectable UA levels in blood and 0.2 mg/dl UA in urine. No additional episodes of urolithiasis were reported. Recent levels of serum creatinine (10/2017) were within normal limits (0.8 mg/dl), microalbuminuria (90 µg/mg creatinine, normal <30) was present. The affected child is homozygous for the c.2164A>T (Lys722Ter) variant in the *XDH* gene whereas the parents and one of the unaffected siblings are carriers (Figure 1).

3.2 | Identification of progenitor haplotypes

Segregation analysis of 13 polymorphic markers in the affected families revealed conserved alleles of six markers linked to the c.2164A>T variant that construct a putative progenitor haplotype spanning 0.6 Mbp. An extended shared haplotype of eight markers spanning 1.7 Mbp was identified in families 1 and 2 (Figure 2B). The distribution and frequencies of the polymorphic alleles in control chromosomes is shown in Table S2. In 28 independent control chromosomes 27 different haplotypes were discerned, none of which were the putative progenitor haplotype (not shown).

3.3 | Time to the MRCA

The intervals in Morgan units between the variant and the polymorphic markers used in the computation of the MRCAs are given in Table S3. Based on this data, the estimated distance between all three families is 179 generations
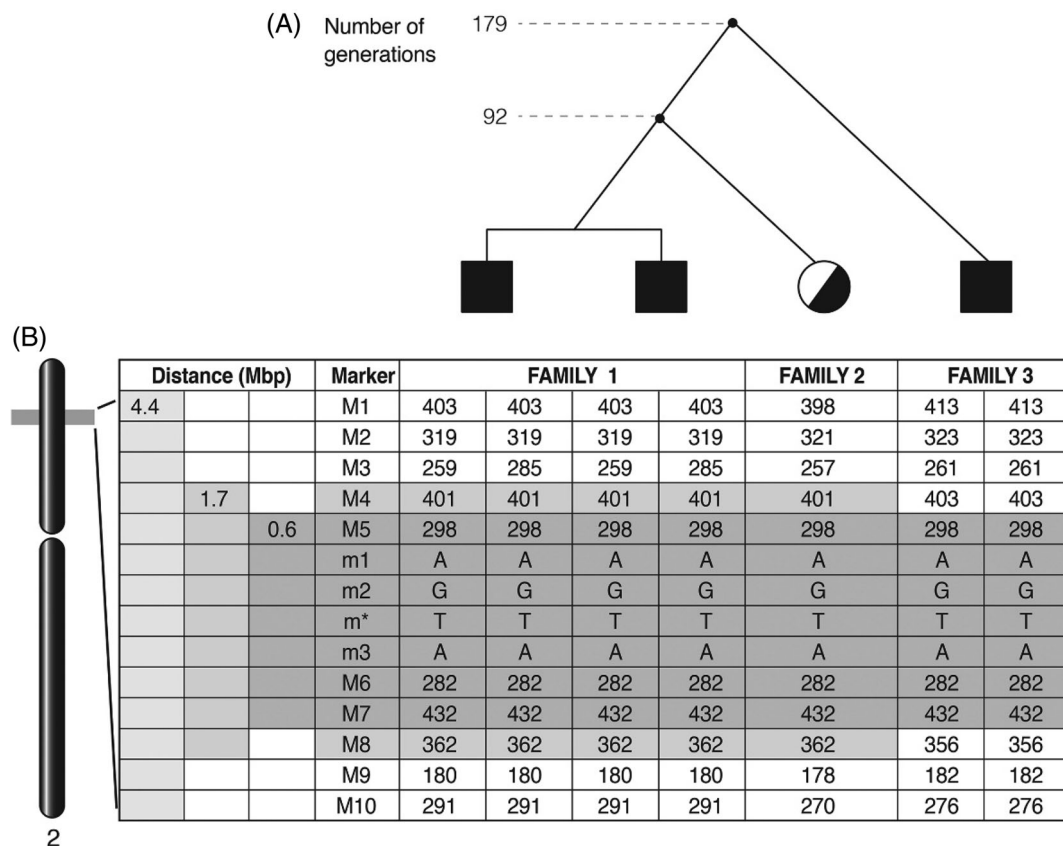

Distance (Mbp)			Marker	FAMILY 1				FAMILY 2	FAMILY 3	
4.4			M1	403	403	403	403	398	413	413
			M2	319	319	319	319	321	323	323
			M3	259	285	259	285	257	261	261
	1.7		M4	401	401	401	401	401	403	403
		0.6	M5	298	298	298	298	298	298	298
			m1	A	A	A	A	A	A	A
			m2	G	G	G	G	G	G	G
			m*	T	T	T	T	T	T	T
			m3	A	A	A	A	A	A	A
			M6	282	282	282	282	282	282	282
			M7	432	432	432	432	432	432	432
			M8	362	362	362	362	362	356	356
			M9	180	180	180	180	178	182	182
			M10	291	291	291	291	270	276	276

FIGURE 2   Proposed genealogical tree and estimated times to MRCAs (A) based on shared haplotypes linked to the *XDH* gene c.2164A>T variant (B) in families 1, 2, and 3. A, The proposed genealogical tree with two knots linking the three families and the estimated number of generations to the MRCAs. B, The variant (**m***) and the haplotypes of 13 polymorphic markers surrounding the mutation, encompassing a distance of 4.4 Mbp on the short arm of chromosome 2 (2p22-23) in members of the three affected families is shown. Putative progenitor haplotypes defined by the conserved alleles at distances of 1.7 and 0.6 Mbp, respectively, are highlighted. Note that both affected children in family 1 are heterozygous for marker M3, yet homozygous for the more distant markers M2 and M1 suggesting a de novo variant in marker M3 in a former generation rather than a recombination event

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(95% credible limit 70 generations); and the estimated distance between families 1 and 2 is 92 generations (95% credible limit 37 generations). The credible limits are quite robust with respect to the upper limit of the prior distribution.

3.4 | Genealogic history of the affected families

Family 1 is of Turkmen origin and belongs to the Kaya (Qayi) tribe. According to the family tree (Figure 1A) the grandmother sisters are the most probable source of the variant in this family and we assume that they also originate from the Qayi tribe or from a historically closely related tribe. The Qayi tribe belongs to the "Ughuz" coalition that affiliates itself with the Seljuks, the origin of the Ottoman dynasty. Branches of this coalition settled in Palestine (particularly in the western margins of the Jezreel Valley, the region of Karkur-Caesarea and in the Hebron/Al Khalil region) starting from the 12th century under the Ayyubid (UNESCO document[14]), Mameluke and Ottoman rules. Some of their members occupied senior military and administrative positions and became well known, such as the al-Askari, al-Jundi, and Churbaji families. The large majority underwent a process of Arabization and even married into the local population, and their tribes were called "Arab al-Turkeman" (http://www.alnssabon.com/t11489.html).

In family 2 the origin of the mother's variant could be either paternal or maternal (Figure 1A). Her paternal grandparents are related and belong to the Battat clan from the town of ad-Dhahiriya in the southern Hebron hills. Some of its members settled from the 12th century in the city of Hebron as well. The Battat families see themselves as originating from the tribe of Quraysh and the house of Prophet Muhamad. These families have branches in both Egypt and Iraq (http://alsadaalalawenthiqar.rigala.net). The mother's maternal grandparents belong to the Rabba and Hawarin clans that maintain long lasting coalition with the Battat families and frequently intermarry with them.

In family 3, which is one of numerous Kabha families living in the region, the family tree (Figure 1A) suggests that the variant comes from the maternal side belonging to the Milhim clan. Because the Kabha and Milhim families are historically interrelated by multiple family ties we choose to investigate both of them. The Kabha families' origins are from the city of Ta'if located in the province of Hejaz, presently Saudi Arabia. It is recognized as originally affiliated with the Thaqif coalition comprised of the northern tribes in the Arabian Peninsula, also known as the "Qays" tribes. They arrived to Palestine in the seventh century as part of the Muslim conquests and settled in the Hebron hills, in the villages Yatta, Dura, ad-Dhahiriya, and Bayt Jibrin. In the 16th century, once Ottoman rule of the land had been initiated, some of its members moved to the northern slopes of the Nablus hills and resided in the town of Ya'abad, from where they embarked westwards and founded seven small villages that in time became full villages. These are Tura, Bart'ah, Um al-Qataf, Baydus, Wad 'Ara, 'Ayn al-Sahala, and Khur Saqer,[15] interview with 'Abad al-Rahaman Dawoud Kabha, May 8, 2009). The Kabha families have marriage ties with all the other families in the region. Among others with the Turkmen tribes who settled in the area of Karkur, the Milhim families and with members of the Kabha families in the eastern suburbs of 'Ar'ara. The Milhim family that lived in the neighborhood of Wadi al-Qasab is one of the founding families of 'Ar'ara in the 18th century. They came to 'Ar'ara from the town of Halhul in the Hebron hills, where one of the major families still carries the name Milhim. They are recognized as originally affiliated with the coalition of Yemenite (Southern) tribes which since the third century migrated and settled in the area of Wadi Sarhan and associated with the tribe of Sirhan (Sarahin) in the northern Arabian Peninsula.[16]

4 | DISCUSSION

In this report we demonstrate that the c.2164A>T (Lys722Ter) variant of the *XDH* gene identified in a Turkmen family from Turkey[8] and two Israeli Arab families is a common ancestral mutation. As far as we are aware this is the first description of an ancestral mutation causing classical xanhinuria. Among 21 distinct variants causing hereditary xanthinuria reported so far (Table 1) several were identified in more than one family (highlighted in Table 1). Yet all, except the c.2567delC and c.2164A>T variants in the *XDH* gene, occurred at mutational hot spots, for example, C<T transitions at CpG sites and deletions/insertions in mononucleotide tracks. Thus, these are most probably recurrent variants as was demonstrated by analysis of nearby polymorphisms in two cases[2,7] while in another case genetic tests failed to prove relatedness of the affected families.[23] In our study of two Arab and a Turkmen family the c.2164A>T *XDH* gene variant was linked to an extended haplotype of polymorphic markers that was absent in 25 control chromosomes, demonstrating its common origin (Figure 2). We found that the MRCA of the three families is 179 (95% credible limit 70) generations old. Interestingly, the Turkmen family 1 and the Arab family 2 are more closely related than the Arab families 1 and 3 (Figure 2). The genealogical history of these families revealed their lengthy settlement in the Hebron hills and an extended geographical network of their family branches. Taken together with the general history of the region and the present day dispersion of the Turkmens and Arabs (see details in Supporting Information) these findings strongly suggest a wide dispersion of the *XDH* gene c.2164A>T variant in a region prone to urolithiasis, the Afro-Asian stone-forming belt.[5]

TABLE 1 Variants reported in patients with classical xanthinuria

	Variant	Patients' origin	Reference
	XDH gene		
1	**c.682C>T**[a]	Japan	1
	p.Arg228Ter	Japan	
2	**c.2567delC**	Japan	1
	p.(Thr856fs)	Japan	17
		Japan	18
3	c.1658insC p.(Ala556fs)	Israel (Iranian-Jewish)	6
4	c.445C>T p.Arg149Cys	Japan	19
5	**c.2164 A>T**	Turkey (Turkmen)	8
	p.Lys722Ter	Israel (Arab)	Peretz et al. (this report)
6	**c.2729C>T** **p.Thr910Met**	Armenia	20
		Poland	21
		Afghanistan	22
7	**c.641delC** **p.(Pro214fs)**	Poland	21
		Czech Republic	23
		Czech Republic	
		Germany	24
8	**c.141insG** **p.(Cys48fs)**	Afghanistan	22
		UK-Indian Subcontinent	25
9	c.2473C>T p.Arg825Ter	Czech Republic	23
10	c.2641C>T Arg 881Ter	Czech Republic	23
11	exon2-4 del (~11 kbp)	Germany	26
12	c.3536T>C p.Ile1179Thr	France	27
13	c.651+1G>T	France	27
14	c.3129-3132del TCAT p.(His1044fs)	France	27
15	c.3847C>T p.Arg1283Ter	Japan	28
16	c.305A<G p.Gln102Arg	Japan	18
	MOCOS gene		
1	**c.1255C>T**	Japan	2

(Continues)

TABLE 1   (Continued)

	Variant	Patients' origin	Reference
	p.Arg419Ter	Japan	
		China	29
2	c.169G>C p.Ala57Pro	Japan	30
3	c.881C>T p.Thr294Ile	Germany	31
4	**c.2326C<T**	Israel (Bedouin Arab)	7
	p.Arg776Cys	Israel (Italian Jewish)	
5	c.1034insA p.(Ser344fs)	Israel (Italian Jewish)	7

[a]Same variants identified in apparently unrelated patients are highlighted by bold letters.

Our finding contributes to the view that hereditary xanthinuria might be not such a rare disease.[3,32,33]

The biochemical hallmark of classical xanthinuria is very low to undetectable levels of UA and elevated levels of Xanthine and Hypoxanthine in blood and urine. A review of more than 150 cases of classical xanthinuria reported from 22 countries[3,33] shows that the disorder is partially penetrant regarding its clinical symptoms. Around 40% of the patients presented with symptoms that could be attributed to the defect: irritability, hematuria, urinary tract infection, renal colic, crystallurias, urolihiasis and acute renal failure. The rest were totally asymptomatic sibs (20%) or detected during population studies or during routine laboratory tests for presumably unrelated disorders. Symptoms may appear as early as the neonatal period[34] or not appear at all until advanced age.[6,7] The clinical features of the six patients, bearing the c.2164 A>T *XDH* variant described in this investigation are consistent with this statistics. Three affected children in family 2 were asymptomatic and came to the attention of the treating physicians during the follow up of the index case for a neurogenic bladder. In family 1 both affected siblings were symptomatic. One presented at the age of 8 months with failure to thrive, vomiting, and discomfort during urination, gross hematuria and passage of stones. The older brother had bladder and kidney stones that were removed surgically at the age of 5 years.[8] A very similar case of early onset (9 months) of severe symptoms of the disorder was reported from Turkey quite recently.[35] The most severe presentation was in family 3 were the disorder progressed to a non-functioning left kidney necessitating nephrectomy at the

age of 11 years. An even more rapid progression of the disorder leading to nephrectomy in a 3 years old boy was recently reported from Tunisia.[36] Another important health aspect of classical xanthinuria, irrespective of its clinical manifestation is the risk of drug toxicity/inefficiency due to the fact that both XDH and AO are drug-metabolizing enzymes.[4] Two cases of severe thiopurine-induced toxicity in xanthinuria patients were recently reported.[37,38]

We believe that our work will increase the awareness to classical xanthinuria among the Arab and Turkmen populations, will lead to identification of more cases allowing for further investigation of its dispersion and prevention of its potential severe, in some instances life threatening clinical and toxicological complications.

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CONFLICT OF INTEREST

H.P., M.K., D.M.S., M.K., S.U., I.K., H.S., D.La., and D. Le. declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

H.P. conceived, initiated, designed the experiments, analyzed the data, and wrote the initial version of the manuscript. M.K. and D.M.S. designed, performed, and wrote the text for estimation of MRCAs. M.K. researched and wrote the historical genealogy of the studied families. S.U. planned and performed the laboratory experiments. I.K., H.S., D.La, and D.Le. provided and wrote the text for demographic, family tree, and clinical data.

All coauthors read and approved the final version of the article.

COMPLIANCE WITH ETHICAL STANDARDS

All procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study and the study was approved by the Institutional Helsinki Committee of the Tel Aviv Sourasky Medical Center, approval number 0367-08-TLV.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Table S1. Published physical and recombination map positions of polymorphic markers on chromosome 2p22-23 and primers' sequences used for the PCRs

Table S2. Range and frequency of polymorphic alleles identified on control chromosomes

Table S3. Published and calculated genetic map positions and calculated distances to the site of the mutation of the polymorphic markers used in computation of the MRCAs

Figure S1. Genotyping of microsatellite markers (A) and segregation analysis of alleles (B) in family 2