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RESEARCH REPORT

Prevalence and Novel Mutations of Lysosomal Storage Disorders in United Arab Emirates

LSD in UAE

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Abstract Lysosomal storage disorders (LSD) are rare entities of recessive inheritance. The presence of a "founder" mutation in isolated communities with a high degree of consanguinity (e.g., tribes in the Middle East North Africa, MENA, region) is expected to lead to unusually high disease prevalence. The primary aim of this study was to estimate the prevalence of LSD and report their mutation spectrum in UAE. Between 1995 and 2010, 119 patients were diagnosed with LSD (65 Emiratis and 54 non-Emiratis). Genotyping was performed in 59 (50 %) patients (39 Emirati from 17 families and 20 non-Emiratis from 17 families). The prevalence of LSD in Emiratis was 26.9/100,000 live births. Sphingolipidoses were relatively common (9.8/100,000), with GM1-gangliosidosis being the most prevalent (4.7/100,000). Of the Mucopolysaccharidoses VI, IVA and IIIB were the predominant subtypes (5.5/100,000). Compared to Western countries, the prevalence of fucosidosis, Batten disease, and α-mannosidosis was 40-, sevenfold, and fourfold higher in UAE, respectively. The prevalence of Pompe disease (2.7/100,000) was similar to The Netherlands, but only the infantile subtype was found in UAE. Sixteen distinct LSD mutations were identified in 39 Emirati patients. Eight (50 %) mutations were reported only in Emirati, of which three were novel [c.1694G>T in the *NAGLU* gene, c.1336 C>T in the *GLB1* gene, and homozygous deletions in the *CLN3* gene]. Twenty-seven (42 %) patients were clustered in five of the 70 Emirati tribes. These findings highlight the need for tribal-based premarital testing and genetic counseling.

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Introduction

Lysosomal storage disorders (LSD) are rare inherited entities with more than 50 distinct types. Individually, these diseases are rare, but collectively they are relatively common with a prevalence ranging from 12 to 25 per 100,000 live births (Pinto et al. 2004). Their prevalence in the Middle East North Africa (MENA) region, however, is unknown. These disorders are inherited as autosomal recessive (except for Fabry disease, Danon, and MPS II, which are X-linked recessive) and are more common in the MENA region when a "founder" mutation is present in the tribe (al-Gazali et al. 1997)." Thus, there is a need for accurate data about LSD prevalence and mutation spectrum in UAE and other Arab populations in order to design and implement preventative programs, such as premarital testing and neonatal screening. Such data are also required to assess the impact of treating these disorders on the public health care system.

UAE citizens (Emiratis) are ethnically diverse, with ancestries from Arabian Peninsula, Persia, Baluchistan, and

East Africa. The local society however remains tribal in nature and consists of at least 70 distinct tribes. Despite this ethnic diversity, inter-tribal marriages are less common than intra-tribal ones. Thus, the culture enforces appearance of rare recessive conditions. About 80 % of the current eight million UAE inhabitants are expatriates; in whom related marriages are also common (e.g., Palestinians and Pakistanis). In this report, all UAE citizens (including tribal living citizens) are termed Emiratis and all expatriates are termed non-Emiratis.

This study estimates the birth prevalence of LSD among Emiratis (in comparison to Western populations) since data from the MENA region are unavailable. It also describes the mutation spectrum in UAE citizens and expatriates.

Materials and Methods

Patients

All patients were diagnosed and followed in the only two metabolic referral centers in UAE, Latifa Hospital in Dubai and Tawam Hospital in Abu Dhabi. The LSD diagnostic center at Latifa Hospital was established in 1995 and at Tawam Hospital in 1992.

Between 1995 and 2010, 119 patients were diagnosed with LSD (65 Emiratis and 54 non-Emiratis). The entities spanned 26 distinct subtypes of LSD and the diagnosis was made by clinical presentation and biochemical analysis. Genotyping was performed in 59 (50 %) patients (39 Emiratis from 17 families and 20 non-Emiratis from 17 families).

Birth Prevalence

"Disease birth prevalence" in Emiratis, expressed as number of patients per 100,000 live births, was calculated using the method reported by Poorthuis et al. (1999). Briefly, the prevalence was set as the total number of Emirati patients with the specific disease divided by the total number of Emirati live births during the "birth period". The birth period was defined as the time interval between year of birth of the oldest patient and year of birth of the youngest patient. Live births per year were obtained from the National Bureau of Statistics (http://www.uaestatistics.gov.ae). Affected siblings and fetuses with GM1-gangliosidosis and α-mannosidosis were also included in calculating the disease birth prevalence.

The method of Pinto et al. (2004) was used to estimate disease birth prevalence when only a single patient was diagnosed with the disease, using the number of live births between 1995 and 2010 (Pinto et al. 2004). The overall prevalence was calculated by adding the prevalence of each phenotype.

Mutation Analysis

Direct genomic sequencing of the most known genes responsible for LSD was performed on samples from affected individuals by accredited genetic diagnostic laboratories. All novel variants were tested by damage-prediction assessment, using the softwares SIFT, PolyPhen-2, and Mutation Taster. For the *CLN3* gene, deletion/duplication studies were performed, using multiplex ligation-dependent probe amplification (MLPA).

Results

Table 1 shows the prevalence of LSD in UAE and compares it with five other countries. The prevalence of LSD among Emiratis was 26.9 per 100,000 live births. This rate was similar to Portugal, but twice that in The Netherlands, Czech Republic, or Australia. Sphingolipidoses were most common (9.8 per 100,000), with GM1-gangliosidosis being the most frequent (4.7 per 100,000, ~7.6-fold higher than Portugal). The remaining sphingolipidoses were comparable to other countries, with the exception of Gaucher disease which was ~6-fold lower in Emiratis. The single case of Gaucher disease in Emirati patient was the lethal type 2. By contrast, Gaucher disease type 1 is the most common one found worldwide.

In Emiratis, MPS IIIB, IVA, and VI are most common types were the most common subtypes of mucopolysaccharidoses, with a sum birth prevalence of 5.5 per 100,000. This value was ~2.9-fold higher than other countries. By contrast, MPS I and II are the most common ones worldwide. The only oligosaccharidoses noted in Emiratis were fucosidosis and α-mannosidosis, occurring ~40-fold and fourfold higher than the Western countries, respectively. Lipid storage disorders and mucolipidoses, on the other hand, were comparable to the other populations. The prevalence of Pompe disease was similar to that in The Netherlands, but only the infantile type was found in this study. Batten disease was ~7-fold higher than Portugal (Table 1).

Thirty-five distinct mutations were identified in UAE, 16 in Emiratis (Table 2) and 19 in non-Emiratis (Table 3). Eight mutations were documented only in Emiratis. Eleven mutations (three in Emiratis and eight in non-Emiratis) were novel, including eight missense, two frame-shift, and one large deletions. Most mutations resulted in severe infantile disease, except for c.499dupC in the *GNPTG* gene, which resulted in mild mucolipidosis type III.

Table 1 Prevalence of lysosomal storage disorders in UAE and other countries

UAE								
		Emiratis		Other countries				
Disorders	Total No. of patients	No. of patients	Prevalence (per 100,000)	NL[1] Prevalence (per 100,000)	Portugal[2]	Czech[3]	Australia[4]	Turkey[5]
Mucopolysaccharidoses (MPS)								
MPS I	4	1	0.25	1.19	1.33	0.72	1.14	–
MPS II	2	0	–	0.67	1.09	0.43	0.74	–
MPS IIIB	6	5	1.05	0.42	0.72	0.02	0.47	–
MPS IIIC	1	1	0.25	0.21	0.12	0.42	0.07	
MPS IVA	4	2	1.41	0.22	0.60	0.71	0.59	–
MPS VI	13	2	2.51	0.15	0.42	0.05	0.43	–
Oligosaccharidoses								
α-Mannosidosis	6	5	1.51	0.09	0.12	0.38	0.1	–
β-Mannosidosis	0	0	–	0.13	0.12	0.16	0	–
Fucosidosis	3	2	2.02	0.05	0	0	0	–
α-*N*-acetyl-galactosaminidase defic.	0	0	–	0.2	0	0	0	–
Aspartylglucosaminuria	0	0	–	0.13	1.72	0	0.05	–
Sialidosis	0	0	–	–	–	–	–	–
Galactosialidosis	0	0	–	–	–	–	–	–
Sphingolipidoses								
GM1 gangliosidosis	20	14	4.66	0.41	0.62	0.26	0.26	0.54
Tay-Sachs	7	3	0.74	0.41	3.13	0.30	0.5	0.23
Sandhoff	10	4	1.21	0.34	1.49	0.19	0.26	0.95
Galactosialidosis	0	0	–	0.04	0.77	0	0	–
Metachromatic leukodystrophy	3	2	1.50	1.42	1.85	0.69	1.09	1.43
Niemann-Pick A	0	0	–	–	–	0.18	–	–
Niemann-Pick B	1	1	0.25	–	–	0.15	–	–
Gaucher (all types)	5	1[a]	0.25	1.16	1.35	1.13	1.75	0.45
Fabry	1	1	0.25	0.21	0.12	0.52	0.86	0.015
Krabbe	2	0	0	1.35	1.21	0.4	0.71	1
Farber	2	2	0.96	–	–	–	–	–
MSD	1	0	0	0.05	0.48	0.26	0.07	–
Lipid storage disorders								
Niemann-Pick C	3	1	0.25	0.35	2.2	0.91	0.47	–
Wolman	1	0	–	0.19	–	0.27	–	–

(continued)

Table 1 (continued)

UAE								
		Emiratis		Other countries				
Disorders	Total No. of patients	No. of patients	Prevalence (per 100,000)	NL[1] Prevalence (per 100,000)	Portugal[2]	Czech[3]	Australia[4]	Turkey[5]
Mucolipidoses								
Mucolipidosis I	0	0	–	0.05	0	0.07	0.02	
Mucolipidosis II/III	11	7	1.35	0.24	0.81	0.22	0.31	–
Mucolipidosis IV	0	0	–	–	–	0.02	–	–
Other disorders								
Cystinosis	1	1	0.25	–	–	–	–	–
ISSD	0	0	–	0.07	0	0.02	0.19	–
Pompe disease	10	8	2.66[b]	2.0	0.17	0.37	0.69	–
Batten disease	2	2	3.54	–	0.48	0.27	–	–
Total	**119**	**65**	**26.87**	**11.75**	**20.92**	**9.12**	**10.77**	

Note: The diagnosis was based on enzyme analysis and not all patients had genotyping.

NL The Netherlands, *MPS* mucopolysaccharidoses, *MSD* multiple sulfatase deficiency, *ISSD* infantile sialic acid storage disease

[a] Gaucher type 2

[b] All cases are the infantile type

[1] Poorthuis et al. 1999

[2] Pinto et al. 2004

[3] Poupetova et al. 2010

[4] Meikle et al. 1999

[5] Ozkara and Topcu 2004

Table 2 Genotypes and phenotypes of LSD in Emiratis

Disorders	Phenotype	Gene	Nucleotide change	Amino acid change
Mucopolysaccharidoses (MPS)				
MPSIIIB(MIM 252920)	HSM, coarse face, hyperactivity, aggressive behavior, MR	*NAGLU*	c.1694G>T[a,b]	p.R565L
MPS IVA(MIM 253000)	Early-onset obstructive sleep apnea, HSM, atlantoaxial dislocation	*GALNS*	c.319G>A	p.A107T
MPS VI(MIM 253200)	Delayed diagnosis, on ERT, growth retardation, ventilator-dependent	*ARSB*	c.979C>T[1]	p.R327Stop
Oligosaccharidoses				
α–Mannosidosis(MIM 248500)	Severe MR, hearing loss	*MAN2B1*	c.2368C>T[a,2]	p.Q790X
	Early diagnosis, BMT, mild MR		c.2119C>T[a,2]	p.Q707X
Sphingolipidoses				
GM1-gangliosidosis(MIM 230500)	Infantile onset	*GLB1*	**c.1336 C>T**[a,b]	p.K446F
			c.1768C>T	p.R590C
Niemann-Pick type B(MIM 257220)	Obstructive sleep apnea, HSM	*SMPD1*	c.1244C>T[2]	p.A415V
Farber Lipogranulomatosis(MIM 228000)	Infantile onset, failure-to-thrive, cherry-red spot, painful joints, hoarseness, no subcutaneous nodules	*ASAH1*	**c.533T>C**[a,3] **/ c.1144A>C**[a,3]	P.W185R[a,]/ P.K382P[a]
Fabry disease(MIM 301500)	Isolated renal phenotype, end-stage renal disease	*GLA*	c.1277_1278delAA[4]	p.K426RfsStop24
Mucolipidoses				
I-Cell Disease(MIM 252500)	Infantile onset	*GNPTAB*	c.3503_3504delTC[5]	p.L1168fs
Mucolipidosis type III(MIM 252600)	Normal development, mild skeletal involvement	*GNPTG*	c.499dupC[6]	P.L167PfsStop32
Other disorders				
Batten Disease(MIM 204200)	Juvenile onset	*CLN3*	Homozygous deletions[a,b,c]	
CystinosisMIM 219800	Infantile onsetTreated early, normal growth, learning difficulties	*CTNS*	681G>A[a,7]	Splice
Pompe Disease(MIM 232300)	Infantile cardiomyopathy	*GAA*	c.1327-2A>G[8]	Splice

MR mental retardation, *HSM* hepatosplenomegaly, *ERT* enzyme replacement therapy, *BMT* bone marrow transplantation

[a] Reported only in Emiratis

[b] Novel mutation

[c] Homozygous deletions of exon 3, introns 6 and 8, and exons 11, 14, and 15 in the *CLN3* gene

[1] Karageorgos et al. 2004

[2] Lan et al. 2009

[3] Al-Jasmi 2012

[4] Eng and Desnick 1994

[5] Kudo et al. 2006

[6] Raas-Rothschild et al. 2000

[7] Ben-Rebeh et al.

[8] Kroos et al. 2008

With respect to MPS IIIB, five blood-related patients had the homozygous (novel) variant c.1694G>T in exon 6 of the *NAGLU* gene. The amino acid substitution (p.R565L) involved a highly conserved residue, Table 2. Other mutations affecting the same amino acid were previously shown to cause MPS IIIB (Beesley et al. 1998; Bunge et al. 1999; Weber et al. 1999). The two siblings with Batten disease had homozygous (novel) deletions involving exon 3, introns 6 and 8, and exons 11, 14, and 15 of the CLN3 gene (Table 2).

MPS I and II were mainly noted in Palestinians and Pakistanis. They had severe phenotype with central nervous system involvement. They had two (novel) premature stop codons [c.784delC (p.H262TfsX55) in the *IDUA* gene and

Table 3 Genotypes and phenotypes of LSD in non-Emiratis

Disorder	Gene	Phenotype	Nucleotide change	Amino acid change	Ethnic origin
Mucopolysaccharidoses (MPS)					
MPS I MIM 607015	*IDUA*	Severe disease with CNS involvement	c.784delC[a]	p.H262TfsX55	Pakistan
			c.192C>A[1]	p.Y64Stop	Palestine
MPS II MIM 309900	*IDS*	Severe disease with CNS involvement	c.1418delC[a]	p.P473Lfsx10	Palestine
MPS VI MIM 253200	*ARSB*	Diagnosed early, on ERT, mild limitation of joint movements	c.944G>A	p.R315Q	Sudan
Sphingolipidoses					
GM1-Gangliosidosis MIM 230500	*GLB1*	Infantile onset	c.914+4A>G[2]	Splice	Palestine
			c.1465-1466del AT[3]	p.I489fs	India
Sandhoff GM2-Gangliosidosis MIM 268800	*HEXB*	Infantile onset	16 kb deletion[4]		Iran
			c.850C>T	p.R284X	Pakistan
			c.884 C>G[a] / c.1507 T>C[a]	p.T295R / p.W503R	Lebanon
Tay-Sachs disease (MIM 272800)	*HEXA*	Infantile onset	c.2T>C[5]	p.Met1?	Iran
Multiple sulfatase deficiency MIM 272200	*SUMF1*	Tetralogy of fallot, hypoplastic lungs, hydrops fetalis, short limbs, inguinal hernia	c.603-2A>G[6]	Splice	Iran
Gaucher disease MIM 230900	*GBA*	Normal growth, development, and neurological exam, icthyosis, hoarsness, splenomegaly	c.854 T>C[a]	p.F285S[a]	Palestine
Gaucher disease type II MIM 230800	*GBA*	Progressive neurological impairment, died at 1 year of age	c.160G>A[7]	p.V54M	Palestine
Mucolipidosis					
Mucolipidosis type III MIM 252600	*GNPTG*	Mild skeletal involvement, normal development	c.499insC[a]	p.V167fs[a]	Pakistan
Lipid storage					
Niemann-Pick C disease MIM 257220	*NPC 1*	Juvenile onset	c.1408 G>C / c.1408 G>C[a] c.2509A>G/ c.2509A>G[a]	p.A470P[a] p.I837V[a]	India
			c.2974 G>T	p.G992W	Palestine
Other disorders					
Pompe Disease (MIM 232300)	*GAA*	Infantile cardiomyopathy	c.340_341insT[3]	p.K114*fs*	Palestine

[a] Novel mutation

[1] Bach et al. 1993

[2] Georgiou et al. 2004

[3] Ali et al. 2011

[4] Zhang et al. 1994

[5] Harmon et al. 1993

[6] Ben-Rebeh et al.

[7] Alfonso et al. 2004

c.1418delC (p.P473Lfsx10) in the *IDS* gene], causing truncated protein or mRNA degradation by the nonsense-mediated decay mechanism (Table 3).

The patient with Gaucher disease had a novel variant (c.854 T>C), Table 3. He presented in infancy with severe thrombocytopenia, splenomegaly, icthyosis, and hoarseness. Patient improved significantly on high dose of enzyme replacement therapy. At 7 years of age, he still has icthyosis and hoarseness but his growth, development, and neurological examination are all normal.

The patient with juvenile Niemann-Pick C disease had two distinct (novel) inherited homozygous missense var-

Table 4 Distribution of LSD in 26 Emirati tribes

Disorders	No. of patients	Tribes																										
		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	Others*
MPS I	1												1															
MPS IIIB	5	1[a]	3[a]											1	1													
MPS IIIC	1															1												
MPS IVA	2								2																			
MPS VI	2						2																					
α-Mannosidosis	5					3[b]				2[b]																		
Fucosidosis	2																1										1	
GM1-gangliosidosis	14	10[c]																1	1							2		
Tay-Sachs	3																											3
Sandhoff	4																			1	1							2
Metachromatic leukodystrophy	2										2																	
Niemann-Pick B	1																								1			
Gaucher	1																											1
Fabry	1				1																							
Farber	2				2																							
Niemann-Pick C	1																					1						
Mucolipidosis II/III	7			5[d]																			1					1
Cystinosis	1																							1				
Pompe disease	8		2[e]									1[e]																5
Batten disease	2							2																				
Total	**65**	**11**	**5**	**5**	**3**	**3**	**2**	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**			**12**

Values are number of patients

*Belong to unidentified tribes

[a] The same mutation

[b] Two distinct mutations

[c] Two families with two distinct mutations

[d] One family with the same mutation

[e] Two families with the same mutation

Table 5 Distribution of LSD mutations in 13 Emirati tribes

Tribe	LSD	Gene	Mutation	No of patients
A	MPS IIIB	*NAGLU*	c.1694G>T	1
	GM1-gangliosidosis	*GLB1*	c.1336 C>T	3
			c.1768C>T	7
B	MPS IIIB	*NAGLU*	c.1694G>T	3
	Pompe	*GAA*	c.1327-2A>G	2
C	Mucolipidosis III	*GNPTG*	c.499dupC	5
D	Fabry	*GLA*	c.1277_1278delAA	1
	Farber	*ASAH1*	c.533T>C c.1144A>C	2
E	α-Mannosidosis	*MAN2B1*	c.2119C>T	3
F	MPS VI	*ARSB*	c.979C>T	2
G	Batten	*CLN3*	Homozygous deletions	2
H	MPS IVA	*GALNS*	c.319G>A	2
I	α-Mannosidosis	*MAN2B1*	c.2368C>T	2
K	Pompe	*GAA*	c.1327-2A>G	1
V	Mucolipidosis II	*GNPTAB*	c.3503_3504delTC	1
W	Cystinosis	*CTNS*	681G>A	1
X	Niemann-Pick B	*SMPD1*	c.1244C>T	1

iants in the *NPC1* gene. Both were predicted to be damaging, with the c.1408 G>C variant being more so than the c.2509A>G variant (Table 3). The parents were carriers and a healthy sibling had normal alleles.

Table 4 shows distribution of the 20 distinct LSD in Emirati tribes. Among the 65 patients with LSD, 53 (82 %) were linked to 26 UAE tribes based on the last name. Twenty-seven (44 %) patients were clustered in five tribes (labeled A–E). Three tribes (A, B, and D) had two distinct LSD. MPS IIIB was found in four tribes, GM1-gangliosidosis in four tribes, α-mannosidosis in two tribes, Sandhoff in two tribes, and Pompe in two tribes. This tribal information is important for genetic counseling and disease prevention.

Table 5 shows distribution of the 16 distinct LSD mutations in Emirati tribes. The identified mutations were clustered in 13 tribes. The two distinct mutations of *GLB1* gene were found only in tribe A, affecting 10 patients with GM1-gangliosidosis from two families. For MPS IIIB, the founder mutation c.1694G>T in *NAGLU* was found only in tribes A and B, in whom cross tribal marriages were common. For Farber disease, two distinct mutations of *ASAH1* gene were identified in tribe D. For Pompe disease, the c.1327-2A>G mutation of *GAA* was present in tribes B and K. The remaining tribes had one mutation per disease.

The 10 patients with GM1-gangliosidosis in tribe A belong to two families; one family had the c.1336 C>T mutation and the other had c.1768C>T. The remaining patients with specific LSD disease within the tribe are siblings (Table 5).

Discussion

The overall prevalence of LSD in Emiratis is 1 in 3,717 live births (26.9 per 100,000 live birth), which is similar to that in Portugal (25 per 100,000) (Pinto et al. 2004). The prevalences of LSD in The Netherlands, Czech Republic, and Italy, on the other hand, are ~50 % less than UAE (14, 12, and 12 per 100,000, respectively), Table 1 (Poorthuis et al. 1999; Dionisi-Vici et al. 2002; Poupetova et al. 2010). Consistently, 37 of the 39 (95 %) Emiratis who had genotyping were homozygous and other 2 were compound heterozygous (Table 2). This finding reflects the high rate of consanguinity in UAE.

In Emiratis, GM1-gangliosidosis is the most common LSD (14 of 65 patients, or ~21 %), with a prevalence of ~1 in 21,000 live births. GM1-gangliosidosis is also the most common sphingolipidoses (14 of 28 patients, or ~50 %). GM2 Tay-Sachs, on the other hand, is the most prevalent sphingolipidoses in Portugal (Pinto et al. 2004), while Gaucher type 1 is the most prevalent sphingolipidoses worldwide(Poupetova et al. 2010). The treatable Gaucher type 1 and adult form of Pompe were not found in Emiratis (Table 1). The lethal Gaucher type 2 was found in one Emirati family.

In this series, most of the recognized cases of LSD are of the severe infantile form, while the treatable adult forms are less frequent. The severe forms of LSD are easily recognized by their striking features, while the milder forms are easily missed. Therefore, it is likely that the milder forms of LSD are under diagnosed in UAE. Since

data on disease prevalence were mainly based on clinical diagnosis, the reported prevalences should be considered as minimum estimates. A high risk group screening or newborn screening may thus reveal higher prevalences, especially in entities with a wide clinical spectrum such as late-onset Pompe disease.

In this study, mutation analyses were performed in 59 patients with LSD (39 Emiratis and 20 non-Emiratis). Thirty-five different mutations are described, 16 in Emiratis and 19 in non-Emiratis. Eleven mutations are novel and 24 are reported in the literature (Tables 2–3). Identification of these mutations will certainly aid the diagnosis and prevention of LSD.

The national inhabitants of UAE are ethnically diverse, with ancestries from north and south of Arabian Peninsula, Persia, Baluchistan, and East Africa. The majority of the current eight million inhabitants in UAE are expatriates. In spite of this mixed population, intermarriages are rare and consanguineous marriages within local tribes are the norm. Consanguinity leads to a higher birth prevalence of autosomal recessive diseases if a "founder" mutation is present in the tribe. Otherwise, it actually protects against the occurrence of recessive diseases. As shown in Tables 4–5, diseases with low birth prevalence (e.g., MPS VI and fucosidosis, with mutations are present in homozygous form) have an unusually high prevalence in our tribes with high degree of consanguinity. Other more frequently encountered diseases (e.g., MPS IIIA) are absent in the community.

Most of the families had more than one affected child (Tables 4–5), highlighting the need for genetic counseling, pre-implantation genetic diagnosis, and prenatal diagnosis. The data also strongly point to the importance of premarital testing and counseling, which could be tribal based. Early detection and treatment of LSD (with enzyme replacement or stem cell transplantation) prevents irreversible organ damages. Nevertheless, disease prevention through tribal-based premarital testing is the ultimate goal.

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