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Mutational Analysis and Genotype Investigation of Less Known Gaucher Mutations through Haplotype Analysis in Iranian Gaucher Patients

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ABSTRACT

Gaucher's disease (GD) is the most frequent lysosomal storage disorder resulting from a deficiency of the enzyme glucocerebrosidase (GBA) which causes the accumulation of glucocerebroside. More than 500 mutations have been reported on the GBA gene so far. In this study, we aimed to investigate more on the genotype of less known mutations through haplotype analysis to explain their disease-causing inheritance. Eight patients and three carriers from nine different families were enrolled in the study. DNA sequencing of all GBA gene's exons was performed and pathogenicity of the mutations was investigated. Using GBA gene-linked STR markers, allele segregations were determined in some families. A total of six different mutations were determined. Five and three patients were identified to carry mutations in homozygous and compound heterozygote patterns respectively, three participants also were identified as carriers. The most prevalent mutations were c.1448 T>C and RecNcil, however, three less common mutations were identified (i.e., c.1223 C>T, c.1315 A>G, and c.1214 G>C). In conclusion, we evaluated six different mutations in Iranian patients and elucidated the inheritance of the three less-known mutations by linkage analysis.

Keywords: Gaucher disease, beta-glucocerebrosidase, lysosomal storage disorder, haplotype analysis, Iran

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Introduction

Gaucher disease (GD) is the most prevalent lysosomal storage disorder, caused by an inherited deficiency of a lysosomal enzyme responsible for cleaving the glycolipid glucosylceramide. The gradual enzyme deficiency leads to the deposition of its substrate, glucosylceramide, within the lysosomes of macrophages. This accumulation can result in the buildup of macrophages in various tissues such as the brain, spleen, liver, and lungs. (1).

GD is an autosomal inherited disorder categorized into three types based on the absence or presence of neurological symptoms (2). Type I of the GD presents clinical symptoms such as anemia, splenomegaly, hepatomegaly, bone involvement, and thrombocytopenia (3). This type of disease is characterized by the lack of neurological involvement. Type II, the rarest type of disease, is associated with severe neurologic deterioration and proves lethal in early childhood. Prolonged apnea and massive aspiration are other symptoms of type II GD which can lead to death (4). Neurological symptoms in Type III manifest later, resulting in the chronic neuropathic form of the disease (5, 6). Enzyme replacement therapy and substrate reduction therapy are the current effective treatments to minimize the symptoms of the disease, although there are no treatments for brain damage caused by type II and III of the disease (7, 8).

The gene encoding glucocerebrosidase enzyme, GBA beta, is located on chromosome 1q21 and comprises 11 exons, totaling 7.6 kb (NM_000157.3). Downstream of the gene lies a pseudogene at a distance of 16 kb (9, 10). This pseudogene in DNA sequence and its proximity to the GBA gene increases the chance of homologous recombination between the two genes (11). Furthermore, more than 300 mutations including point mutation, deletion, insertion, splice junctions and rearrangements have been reported to date (12, 13).

The mutational spectrum of the GBA gene varies across different ethnicities. The c.1226A < G is the most frequently observed mutation among the Ashkenazi Jewish population, however this mutation is rare within the Japanese and Chinese population (9).

Previously, GD mutational spectrum of Iranian patients has been reported across various ethnic groups (14). In the current study, our objective is to investigate the mutation pattern of this disease within Iran utilizing DNA sequencing. Specifically, we will explore the genetic inheritance of less known mutations through haplotype analysis to clarify disease-causing genotypes in GD patients of Iran.

Materials and methods

Nine unrelated families, having eight affected individuals and three carriers, were enrolled in this study. All patients were diagnosed with Gaucher disease based on clinical findings and biochemical beta-glucosylceramides activity assay. They were referred to the Medical Genetics Laboratory of Dr. Zeinali at the Kawsar Human Genetics Research Center for mutation confirmation and/or prenatal diagnosis. Genetic counseling was provided to all families, during which their consanguinity, ethnicity, and clinical data were collected. Informed consent was obtained from all patients or their guardians. In addition, 50 healthy volunteers as a control group were enrolled in this study. These volunteers consisted of individuals from various Iranian ethnic backgrounds. The selection of these individuals was based on the aim of representing the same geographical regions as the patients under investigation. The control group participants were drawn from families seeking beta-thalassemia carrier screening or prenatal diagnosis.

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For the molecular study, 10 ml of peripheral blood was collected. Genomic DNA was extracted using either salting-out or proteinase K methods (15). Only GBA gene exons (excluding the pseudogene) were amplified using primers designed by UCSC In-Silico PCR (http://genome.ucsc.edu/) (16). Primer sequences are provided at Table 1. Subsequently, PCR products were subjected to Sanger sequencing using BigDye Terminator kit (Thermo Fisher Scientific, USA, TF) at KBC facility (Kawsar Biotech Co., Tehran, Iran, KBC).

Table 1. The primer sequences of GBA gene's exons.

names	Forward Primers	Tm	%GC	Length	Reverse Primers	Tm	%GC	length	Length of PCR Product
GBAE1,2	TCACTTCCT GTGTCATGT AACG	62.4	45.5	22	CCAAAGTT GGTCTCAGT CACTC	62.9	50	22	820
GBAE3	GAAACCGT GTTCAGTCT CTCC	62.6	52.4	21	ACTTCTGTT CTGGCTGC AGG	64.1	55	20	435
GBAE4	CCATCCAG GCTAATCA CACG	65.1	55	20	TGAGGCAG GAGAATCA CTATAGC	65.4	47.8	23	481
GBAE5	CTTTGGACC CTGACTTCT GC	63.5	55	20	AGGTCTGG TGGTAGAT GTATCC	61.7	50	22	775
GBAE6	AGAAACTG TAGGGTAG GTCTGCT	63.6	47.8	23	GAGTGGGC AAGATTGA GAGG	63.3	55	20	496
GBAE7	TTCCTGTTC TCTCGGTCT GG	63.6	55	20	CCTAGAAA GGTTTCAA GCGA	61.9	45	20	792
GBAE8	TCACCCAA CTCCAGGA TTCC	65.7	55	20	AGGGAAGA TAGGGAAT CATGG	64.3	47.6	21	464
GBAE9	GCAAAGCA GACCTCAG ACCTC	65.5	57.1	21	TCACTTCCT GCCTCCATG GT	66.3	55	20	699
GBAE10,11	AGGCAGGA AGTGACTA GGTAGC	64.4	54.5	22	TTACGTCGC TGTAAGCTC ACA	63.8	47.8	21	661

The results were analyzed using Gene Runner v 5 (http://www.generunner.net/)). Additionally, the sequenced results were aligned with the RefSeq sequence of the GBA gene in NCBI database, with the accession number of NM_001005742.3. The pathogenicity of the identified mismatches was analyzed using databases such as HGMD (http://www.hgmd.cf.ac.uk/), online software Hope Project (https:// svn.cmbi.ru.nl/ hope/), Fathmm (http://fathmm.biocompute.org.uk), and Polyphen-2 (http:// genetics. bwh. harvard. edu/ pph2).

Haplotype analysis

For further investigation, haplotype analysis was conducted on five families. The aim was to employ linkage and segregation analysis to validate the mutation pattern and determine whether unaffected

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individuals within the families share a common pattern. Additionally, the analysis aimed to identify compound heterozygote patterns among individuals harboring compound heterozygous mutations.

To extract DNA directly from diluted blood samples, GT Blood Lysis Buffer (Genetek Biopharma, Berlin, Germany, GT) was utilized. The GT HapScreen GBA kit (Genetek Biopharma, Berlin, Germany, GT) was used to amplify STR markers flanking the GBA gene. Fragment analyses of the PCR products used for haplotyping were conducted at KBC using 3130/xL Genetic Analyzer from TF. The haplotyping process and result analysis were executed based on the kit user manual (GT).

Results

Eight patients and three Carriers for GD were enrolled in this study. Five out of eleven individuals were female and six of them were male. All eight patients were the result of consanguineous marriages, however five of them exhibited homozygosity for their mutations, while three of them showed compound heterozygosity for the mutations. Their ethnicities included seven from Fars province in the South of Iran, one from Sistan and Baluchestan in the southeast, and three from Lorestan in the West. Furthermore, the mutations of the three carrier participants have been indicated in Table 2 as the case 3, 4, and 10. No mutations

Table 2. Detected mutations of eleven GBA cases, genotype, ethnicity and haplotypes homozygosity.

Case number	Patient/ Carrier	Sex	Genotype	Amino Acid change	Consanguinity of the parent	Ethnicity	Haplotype homozygosity
1	P	M	[c.1448T > C; c.1483G > C; c.1497G > C] / c.1448 T>C	RecNcil/ p.L483P	+	Fars	NI
2	P	M	c.1226 A>C / c.1226 A>C	p.N409S/ p.N409S	+	Fars	NI
3	C[1]	M	c.1223 C>T	p.T408M /	NI	Fars	-
4	C	F	[c.1448T> C; c.1483G > C; c.1497G > C] ? c.1223 C>T [2]	RecNcil? pT408M	NI	Fars	-
5	P	F	c.1448 T>C / c.1448 T>C	p.L483P/ p.L483P	+	Lor	+
6	P	M	c.1315 A>G /c.1315 A>G	p.S439G/ p.S439G	+	Lor	+
7	P	F	c.1226 A>C /c.1226 A>C	p.N409S/ p.N409S	+	Lor	NI
8	P	M	[c.1448T> C;c.1483G > C;c.1497G> C]/ c.1448 T>C	RecNcil/ p.L483P	+	Fars	+
9	P[3]	M	[c.1448T>C;c.1483G > C; c.1497G > C; c.1214 G>C] /c.1214 G>C	RecNcil+ p.S405T/ p.S405T	+	Fars	
10	C	F	[c.1448T > C; c.1483G > C; c.1497G > C]	RecNcil / -	-	Fars	-
11	P	F	c.1448 T>C / c.1448 T>C	p.L483P/ p.L483P	+	Baluch	NI

Abbrevation: F, female. M, male. NI, Not investigated

Case 3 &4 are cousins; Case 9 & 10 are relative. Trans or cis relation of the mutations has not been determined.

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were detected in 50 healthy individuals as the control group.

DNA Sequencing of the exons of the GBA gene revealed a total of six mutations. These mutations were located in exons 8,9,10 (two mutations each) and all were single nucleotide missense substitutions. However, the linkage of c.1448 T>C, c.1483 G>C and c.1497 G>C mutations indicated the presence of a recombinant complex allele named RecNcil. The most common mutation was c.1448 T>C which substitutes leucine 483 to proline.

In total, five genotypes were identified, with the most common being RecNcil/p.L483P, p.L483P/ p.L483P, and p.N409S/ p.N409S (Table 3).

Table 3. Mutation analysis of the patients.

Nucleotide change	Amino acid change	HGMD	Fathmm	Poly-phen	Mutation taster	Hope project
			Missense			
c.1448T > C	p.Leu483Pro	Disease causing	Disease causing	Disease causing	Disease causing	Disease causing
c.1226 A>C	p.Asn409Ser	Disease causing	Disease causing	Disease causing	Disease causing	Disease causing
c.1223 C>T	p.Thr408Met	Not ascertain	Probably damaging	Non-disease causing	Non-disease causing	Non-disease causing
c.1315 A>G	p.Ser439Gly	Disease causing	Probably damaging	Probably damaging	------	------
c.1214 G>C	p.Ser405Thr	Disease causing	Disease causing	Probably damaging	Non-disease causing	Non-disease causing
			Complex allele			
c.1448T > C; c.1483G > C; c.1497G > C]	p.Leu483Pro; p.Ala495Pro ; p.Val499Val	Disease causing	Disease causing	Disease causing	Disease causing	Disease causing

Three non-common mutations c.1223 C>T (p.T408M), c.1214 A>G (p.S405T) and c.1315 A>G (p.S483G) were detected in three cases. The disease-causing nature of the c.1223 C>T mutation remains unclear according to the HGMD database. However, Mutation Taster, Hope Project, and Polyphen-2 all predicted this mutation to be non-disease-causing. Conversely, Fathmm indicated a high probability of damage for the c.1223 C>T mutation.

The mutation c.1214 A>G was predicted to cause disease in HGMD and Fathmm databases. Additionally, Polyphen-2 suggested a significant likelihood of this mutation causing damage. The mutation c.1315 A>G was also predicted to be potentially damaging by polyphen-2 and Fathmm servers. HGMD database predicted this mutation as disease-causing.

Haplotype analysis information is shown in pedigrees for seven cases in five families. Figure 1 demonstrates homozygosity for the markers flanking the GBA gene in case 5,6 and 8 which are the result of consanguinity marriage and homozygous for their disease- causing mutations. Case 9 also indicates different haplotypes and compound heterozygosity for the mutations, although his parents are relative. (Figure 2)

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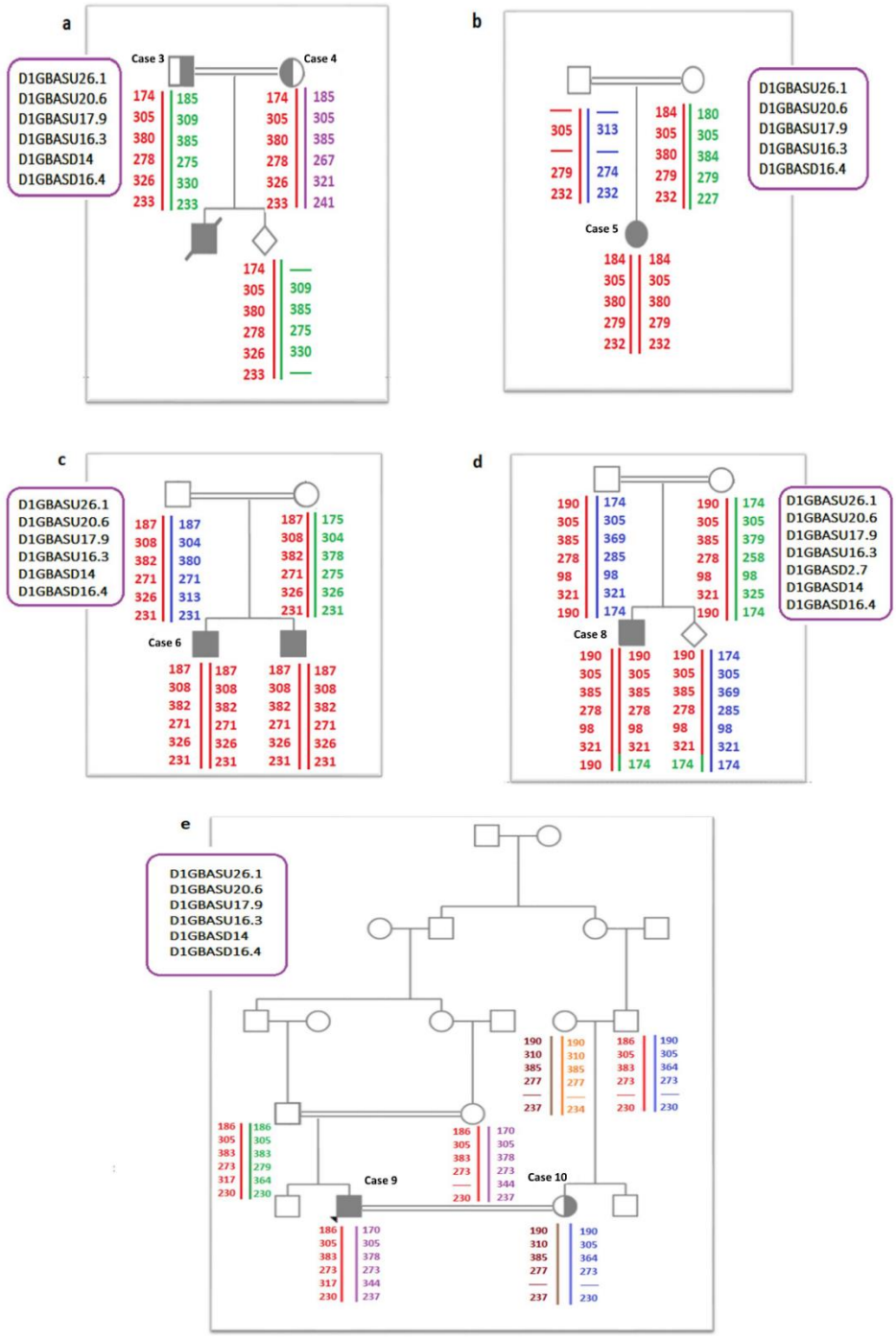

Fig.1. The figure 1(a-e) shows haplotype analysis of families for cases (3 and 4), 5,6,8, (9 and 10) respectively. All patients were the result of a consanguineous marriage, however only cases 5,6 and 8 indicate homozygosity for STR markers. 5 to 7 STR markers flanking GBA gene have been used in this study which were shown in the figure. The numbers in STR marker's name demonstrate markers distance to GBA gene location. Upstream and downstream markers have been indicated by U and D respectively.

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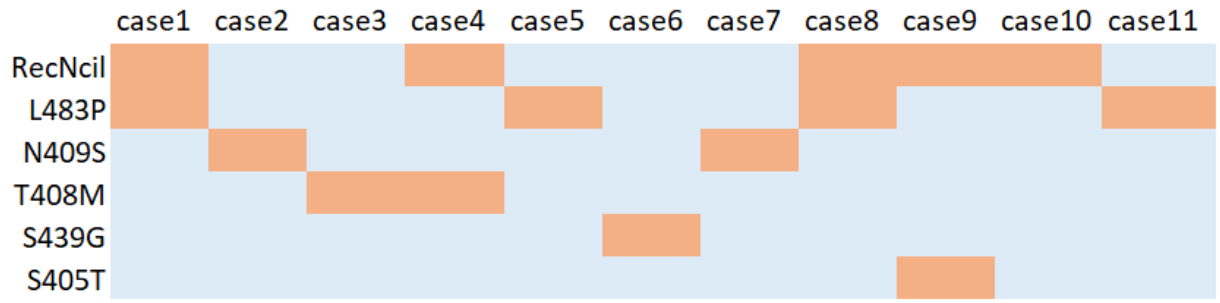

Fig.2. Heat map analysis of mutational profile for 11 participants in the study.

Discussion

In Iran, due to the high rate of consanguineous marriage, autosomal recessive disorders are more frequent than in other parts of the world. Prenatal diagnostics are routinely performed for families suspected of having any genetic disease. This diagnostic process is extended by conducting DNA sequencing on obtained amniotic samples from pregnant individuals to identify the disease-causing mutations already found in either the affected sibling or parents. Moreover, as a definitive confirmation or to address any uncertainties, haplotype analysis can be undertaken to assess the inheritance of the disease-causing haplotype using STR linkage analysis techniques.

Haplotype analysis in cases of consanguineous marriages can serve as a suitable approach for identifying and analyzing genetic causes of the disease. It may help to confirm detected mutations and trace their inheritance pattern. Sometimes, the disease-causing nature of an identified mutation may be invalidated when segregation analysis contradicts mutation inheritance pattern. To further investigate some cases, including three cases with less known mutations, we have used both sequencing and haplotype analysis, using STR markers linked to the GBA beta causative mutations.

Within this study, c.1315 A>G (p.S439G) mutation was observed in exon 9 of the GBA gene in one patient as homozygous mutation. Furthermore, Autozygosity mapping of the patient in Figure 1c revealed the presence of homozygote haplotypes. In a previous study, this mutation had been detected in 2 out of 26 patients within the Kurd population of Iran. Both patients exhibited GD type I with moderate to mild symptoms. The Structure prediction of S483G mutated GBA determined H-bond disruption between D438 and S439 in loop 2 of the protein (14).

The c.1214 A>G (p.S405T) mutation was detected in exon 8 of the GBA gene in a single case displaying a compound heterozygous genotype p.S405T/ p.S405T+RecNcil. Although he was the result of consanguinity marriage, autozygosity mapping indicated haplotype heterozygosity associated with the disease, possibly due to the absence of identical haplotype between parents (Figure 1e). Earlier, this novel mutation had been identified in a Type I GD Turkish patient as a compound heterozygous with p.N409S allele. Clinical investigations unveiled glucocerebrosidase activity level of 0.3 nmol/h/mg protein, despite the absence of neurological. In this study, the 3D modeling of the mutated glucocerebrosidase revealed the

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placement of the of p.Ser405Thr mutation within the glycosyl hydrolase domain of the enzyme, potentially leading to alterations in the enzyme's interaction with its substrates (17).

Two cases related to one family were found to be carriers of the p.T408M mutation. The phenotypic implications of this mutation have remained contentious thus far. It has been shown that mutations in this gene are associated with some diseases other than Gaucher such as Parkinson's disease (PD), rapid eye movements (REM) and sleep behavior disorders (RBDs)(18-20) In the study conducted by Greuel et al ,it was asserted that glucocerebrosidase mutation p.T408M, appears to be a polymorphism. This assertion was supported by its discovery in the control group at a frequency of 1.5%, in contrast to the patient group where it appeared at a frequency of 0.4% (21). However, another study focused on Czech and Slovak Gaucher patients presented a different perspective. This study identified the genotype p.N448S/p.D409H + p.T408M in a GD patient with splenectomy, mild hepatomegaly, and severe cardiopulmonary amyloidosis (22).

The c.1448 T>C (p.L483P) mutation has been observed as one of the most common mutations in the Gaucher-affected patients across various populations around the world. Frequency of this mutation has been shown to be more than half of the mutated alleles in Syrian, Egypt and Indian populations (23, 24).

Gaucher mutation analysis of Iranian patients in the study by Mozafari, *et al* revealed the frequency of 32.7% for the p.L483P mutation, making it the most common mutation among the patients (14). In the current study, two patients were identified as compound heterozygotes for the p.L483P mutation, which both were co-allele with RecNcil. Additionally, two cases were found to be homozygous for this mutation, as the result of consanguinity marriage.

Phenotype-genotype analysis in different studies have consistently shown that p.L483P mutation can be associated with all three types of Gaucher disease (25-27).

In this study, two patients were identified as homozygous for p.N409S mutation. The homozygosity of the alleles resulted from consanguinity marriage in both cases. According to multiple studies, this mutation is not correlated with development of neurological involvement and is predominantly observed in patients with Gaucher disease type 1. (17, 28, 29).

Earlier studies have demonstrated that homozygosity for the p.N409S alleles was associated with milder manifestation of the phenotype in GD patients. However, when these alleles were in compound heterozygosity with p.L444P, it resulted in more severe symptoms of the disease (30).

In the study by Mozafari, et al, four patients with p.N409S/ p.N409S genotype, one patient with p.L483P/ p.N409S genotype, and another patient with p.N409S/ p.W420X genotype were identified among Azari, Gilaki and Fars ethnicities of Iran. All of these cases were associated with type 1 of the disease. Overall, the p.N409S mutation was determined to be the second most common mutation in Iranian GD patients, occurring with a frequency of 19.2% (14). However, this mutation is more prevalent in other populations.

The frequency of the p.N409S mutation in the Turkish population reached up to~70% of mutant alleles (18). In Italian, German, Spanish and Portuguese GD patients, this mutation was noted at rates of 36.5%, 40.48%, 50.2%, and 62.5%, respectively (12, 31-33). Additionally, in other populations such as American, Venezuelan and Brazilian, the p.N409S mutation emerged as the most common mutation (28,34,35). Structural and functional analysis of the p.N409S mutant GBA protein revealed a reduced Vmax and an increased Km for the substrate p-nitrophenyl-β-D-glucopyranoside (36).

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The RecNcil is a gene-pseudogene recombinant allele formed through the incorporation of GBA gene and highly homologous adjacent GBAP1 pseudogene via crossing over. The recombinant allele encompasses p.A495P, p.L483P and p.V499V mutations in exon 10 and 11 which is obtained from cross-overed part of GBAP1 pseudogene. If the co-occurrence of p.L483P with p.A495P and p.V499V is not investigated, the misclassification of the p.L483P mutation as a point mutation rather than a recombinant allele could be anticipated.

In this study, two patients were identified with genotype RecNcil/ p.L483P, and one patient with genotype RecNcil/ p.S405T. Although case 1 and 9 were the result of consanguineous marriage, homozygosity was not observed in their genotypes, and they are identified as compound heterozygous. Additionally, case 8 is the result of consanguineous marriage, and as indicated in Figure 1d, he exhibits haplotype homozygosity, however his mutations are not homozygous. De novo mutation or de novo gene-pseudogene recombinant in his parents could be an explanation which needs to be further investigated.

In case 9, co-allelic of p.S405T and recombinant allele RecNcil was detected in cis relation. Homozygosity for p.S405T mutation, alongside heterozygosity of RecNcil recombinant allele resulted in compound heterozygosity with the genotype p.S405T + RecNcil/ p.S405T, which is corroborated by the haplotype analysis in Figure 1e.

According to Figure 1a, cousin cases share the same haplotype and carry p.T408M mutation. As the case 4 also carries RecNcil allele and she is not patient, trans relation of the mutations could not be justified The possibility of the cis relation is also uncertain, given that her cousin, sharing the same haplotype, does not have RecNcil in cis relation with p.T408M. Therefore, her genotype RecNcil / p.T408M or RecNcil +T408M /- remains undetermined.

Another possible explanation could classify the p.T408M as the non-pathogenic mutation within compound heterozygous individuals. Under this consideration, genotype RecNcil / p.T408M can be assumed for case 4, designating her as a carrier.

The prevalence of RecNcil allele varies among different populations. While it is rare among Ashkenazi Jewish patients, it ranks as the second most frequent GD mutation in the study on 31 GD Argentinian patients (37, 38). Notably, a high prevalence of the RecNcil allele in this population was attributed to a founder effect, as revealed by Southern blot pattern analysis (38). In other populations, the frequency of the RecNcil allele stands at 14.7% in Egypt and 7.2% in Australia (39, 40).

The primary objective of this study was to investigate disease-causing mutations in Iranian patients with Gaucher disease. However, certain participants were included in the study due to undergoing prenatal diagnosis. As a result, haplotype analysis was conducted to confirm the inheritance of the haplotype carrying disease-causing mutations to the fetus, particularly in cases of consanguineous marriages involving affected children as it was assumed that both parents could carry the disease-causing haplotype.

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