



Clinical and Molecular Findings of Nine Cases with Tay-Sachs Disease From Türkiye

Tay-Sachs Hastalığı Olan Türkiye’den Dokuz Olgunun Klinik ve Moleküler Bulguları

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ABSTRACT

Objective: Tay-Sachs disease is a fatal inherited lysosomal storage disease that mostly has an early infantile onset. We presented a case series of Tay-Sachs disease, describe the clinical and molecular findings, and compare the genetic spectrum with previously reported mutations from Türkiye.

Methods: Patients with Tay-Sachs disease who were referred to the İstanbul University, İstanbul Faculty of Medicine, Department of Medical Genetics between January 2016 and December 2021 were included in this study. The diagnosis was confirmed by determining the level of serum β -hexosaminidase activity and the detection of a biallelic related variant upon Sanger sequencing of the *HEXA* gene. The clinical and molecular findings of nine cases were re-evaluated.

Results: Three disease-causing variants in the *HEXA* gene including c.78G>A (p.(Trp26Ter)) in three cases, c.1177C>T (p.(Arg393Ter)) in two cases, and c.1100_1111del (p.(Gly367_Tyr370del)) in three cases were determined. Moreover, a novel c.786C>G (p.(His262Gln)) variant was detected in one case. All of the stated variants were identified in the homozygous state.

Conclusion: Our study both reassessed and expanded the known mutation spectrum of Tay-Sachs disease in Türkiye. Given the expanding horizon of newborn screening and population carrier testing, understanding the spectrum of population-specific disease-causing variants will facilitate early diagnosis of patients and carriers.

Keywords: *HEXA* gene, Tay-Sachs disease, neurometabolic diseases

ÖZ

Amaç: Tay-Sachs hastalığı, çoğunlukla erken infantil başlangıçlı, ölümcül kalıtsal bir lizozomal depo hastalığıdır. Tay-Sachs hastalığı olan bir olgu serisini sunmayı, klinik ve moleküler bulguları tanımlamayı ve Türkiye’den daha önce bildirilen mutasyonlarla genetik spektrumunu karşılaştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya Ocak 2016-Aralık 2021 tarihleri arasında İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Tıbbi Genetik Anabilim Dalı’na refere edilen Tay-Sachs hastalığı olan olgular dahil edildi. Tanı, serum β -heksozaminidaz enzim aktivitesi ve *HEXA* geni Sanger dizisi analizinde biallelik hastalıkla ilişkili varyant saptanması ile doğrulandı. Tay-Sachs hastalığı olan dokuz olgunun klinik ve moleküler bulguları yeniden değerlendirildi.

Bulgular: *HEXA* geninde üç olguda c.78G>A (p.(Trp26Ter)), iki olguda c.1177C>T c.1177C>T (p.(Arg393Ter)) ve üç olguda c.1100_1111del (p.(Gly367_Tyr370del)) varyantları tespit edildi. Ayrıca bir olguda daha önce literatürde bildirilmeyen novel c.786C>G (p.(His262Gln)) değişimi saptandı. Tüm varyantlar olgularda homozigot olarak bulunmaktaydı.

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Cite as: Aslanger AD, Güleç Ç, Kalaycı T, Şengencer E, Avcı Ş, Altunoğlu U, Karaman V, Toksoy G, Karaca M, İşcan A, Gökçay G, Yeşil G, Uyguner O. Clinical and Molecular Findings of Nine Cases with Tay-Sachs Disease From Türkiye. Med J Bakirkoy 2023;19:222-228

Received: 26.10.2022
Accepted: 08.06.2023

Sonuç: Çalışmamız, Türkiye’de Tay-Sachs hastalığının bilinen mutasyon spektrumunu hem gözden geçirmiş hem de genişletmiştir. Yenidoğan taraması ve popülasyon taşıyıcılık testinin genişleyen ufku göz önüne alındığında, popülasyona özgü hastalığa neden olan mutasyonların anlaşılması hastaların ve taşıyıcıların erken tespitini kolaylaştıracaktır.

Anahtar Kelimeler: *HEXA* geni, Tay-Sachs hastalığı, nörometabolik hastalıklar

INTRODUCTION

Tay-Sachs disease (TSD), a type of GM2-gangliosidosis, is an autosomal recessive, progressive neurodegenerative disease caused by β -hexosaminidase A (HEXA) deficiency. This lysosomal enzyme, necessary for degradation of gangliosides, is a heterodimer comprising α and β subunits encoded by the *HEXA* and *HEXB* genes, respectively. Biallelic mutations in the *HEXA* gene located at 15q23 are responsible for TSD disease in which only the β -hexosaminidase A isoenzyme becomes deficient. TSD is characterized by abnormal accumulation of gangliosides in neurons and retinal ganglion cells. Neuronal accumulation of GM2 gangliosides causes progressive loss of function in the central nervous system, whereas accumulation of GM2 in retinal ganglion cells leads to blindness (1).

The spectrum of TSD is classified into lethal infantile, juvenile, and adult forms based on the clinical presentation age (2). The most common form, generally known as the classic or acute-infantile form, results from a complete absence or extremely low level of enzyme activity and is characterized by onset before 6 months and rapidly progressive neurodegenerative clinical findings. Affected children show progressive weakness, loss of motor skills, hypotonia, increased or exaggerated startle response to loud sounds or other sudden stimuli, and myoclonic jerks between 3 and 6 months. Between 8 and 10 months, neuromotor regression, hypotonia with pyramidal findings, apathy, and decreased attentiveness is observed. Seizures and progressive macrocephaly occur in children after one year of age. The cases died in the first 4-5 years of their lives due of respiratory complications. Juvenile (subacute) and adult (late onset) forms are very rare with slower progression on a clinical course. The juvenile form is characterized by ataxia, dysarthria, and loss of independent ambulation starting after two years of age, following normal development. Tremor, psychiatric symptoms, or progressive neurogenic weakness are more common in the late-onset form, beginning in older teens or young adults.

The appearance of fundus -cherry red spot-refers to a reddish area of macula is characteristic for infantile form (3). Cranial magnetic resonance imaging (MRI) of infantile

TSD shows symmetrical T2-weighted (T2W) hypointense and T1W hyperintense signals in the thalami, diffuse-progressive T2W hyperintensity in the cerebral white matter suggestive of demyelinating disorder, and cerebral atrophy in the later phase of disease (4,5).

The diagnosis of TSD is established with low HEXA activity on enzyme testing in serum or leukocytes (6). This can be confirmed by molecular genetic testing for mutations in the *HEXA* gene. The *HEXA* gene consists of 14 exons. To date, 182 mutations in the *HEXA* gene have been reported in the Human Genome Mutation Database (HGMD Professional 2021.2). In this study, the clinical, biochemical, and molecular results of nine patients were evaluated. Furthermore, the mutation spectrum profile of previously reported cases from Türkiye will be discussed.

METHODS

Cases with a definite diagnosis of TSD who were referred to the İstanbul University, İstanbul Faculty of Medicine, Department of Medical Genetics clinic between 2016 and 2021 were included in the study. The study was reviewed and approved by the İstanbul University, İstanbul Faculty of Medicine, Clinical Research Ethics Committee (decision no: 18, date: 07.10.2022) and written informed consent was obtained from all parents of the patients included in the study (no: 07.10.2022/1316113). Clinical, biochemical, and molecular findings of the patients were retrospectively reviewed. Low beta-hexosaminidase A activity was demonstrated in all cases. DNA isolation (DNA Isolation Kit for Mammalian Blood, Roche Diagnostics/Elips-İstanbul) was performed from EDTA blood samples taken from nine cases and their parents. All encoded exons and exon-intron regions of the *HEXA* gene were Sanger sequenced (ABI 3500). Variants were cross-checked with ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) and HGMD (<http://www.hgmd.cf.ac.uk/ac/>) databases. The novel variant was assessed using dbSNP, gnomAD (<https://gnomad.broadinstitute.org/>), and Turkish Variome (TRV) (7). *In silico* prediction software, Mutation Taster (<https://www.mutationtaster.org/>), Sorting Intolerant From Tolerant (SIFT, <https://sift.bii.a-star.edu.sg/>), and PolyPhen-2 HumVar (<http://genetics.bwh.harvard.edu/pph2/>) were used to predict

the pathogenicity. The American College of Medical Genetics and Genomics (ACMG 2015) classification was used for evaluation (8). The low activity of the HEXA enzyme in patients' plasma was consistent with TSD. Enzyme activity was determined as nmol/mL/h in cases 1 and 6 (Istanbul University, İstanbul Faculty of Medicine, Department of Medical Biochemistry) and as $\mu\text{mol/L/h}$ in the remaining cases (Duzen Laboratory Group, Ankara, Türkiye). Diagnoses were determined by reduced HEXA activity characteristic clinical and molecular findings. We did not perform statistical analysis because we only had nine patients.

RESULTS

Clinical Findings

A total of nine patients (6 females and 3 males) from unrelated families diagnosed with infantile form-TSD were included in this study. There was a history of consanguineous marriage between the parents in eight cases. The remaining one family came from the same village. Also, a positive family history (affected siblings and/or cousins) was found in seven cases. All the families came from Türkiye the following cities; Tokat, Siirt, Nevşehir, Adana, Hakkari, Urfa and Sivas. The mean age of symptom onset was 7 months (range 3-9 months). Neuromotor regression was noted in seven of the nine cases (mean age of neuromotor regression is 8 months) and startle in the remaining 2 cases at 3 and 4 months. The age of definitive diagnosis, determined by low enzyme levels, ranged between 6 months and 20 months (mean age: 12.7 months). The delay between the first presentation signs and definitive diagnosis ranged from 1 month to 16 months in this case series (mean age: 5.7 months). While eight of nine patients had macrocephaly, head circumference was normal in the remaining one patient. All the cases except case 3 had cherry-red eye findings. All cases suffered from epilepsy as the disease progressed. Available cranial MRI from four cases (case 3-6) revealed T2 thalamic hypointensity, hyperintense signal changes in the basal ganglia and periventricular white matter (Figure 1). The patient demographics and clinical and molecular findings are summarized in Table 1.

Molecular Findings

Molecular genetic findings are presented in Table 1. Sequencing of the HEXA gene revealed three formerly known variants, including c.78G>A, c.1177C>T, and c.1100_1111del, in eight patients. In case 9, previously unreported c.786C>G variant was detected in homozygous form (Figure 2). The same variant was found to be homozygous in his similarly affected brother and heterozygous in his parents. According

to ACMG criteria, variants received scores for PM2, PP2 and PP3 and were determined as Variants of Uncertain Significance. The functional effect was predicted to be disease causing by MutationTaster with a score of 0.9999, deleterious by SIFT with a score of 0.00 (<0.05 is predicted to be deleterious), and harmful by PolyPhen-2 HumVar with a score of 1 (1.0 is predicted to be deleterious).

DISCUSSION

In this study, we evaluated the clinical and molecular characteristics of nine cases of infantile TSD. The estimated incidence of TSD in Ashkenazi Jews was 1 in 3,600 compared to 1 in 360,000 in other populations, with carrier frequencies of 1 in 30 in Ashkenazi Jews and 1 in 300 in non-Jews, respectively (9). For our country, the incidence of TSD was calculated as 0.23 per 100,000 (10). The families in this case series come from the Black Sea, Mediterranean, Central Anatolia, and Southeastern Anatolia regions of our country. The absence of any cases in the Marmara, Aegean, and Eastern Anatolian regions can be explained by the distribution of consanguineous marriages in our country, rather than the low carrier rate of this disease in these regions. As in all autosomal recessive diseases, the incidence of this disease increases in places where consanguineous marriage is common. According to recent studies, the prevalence of consanguineous marriages in Türkiye is highest in the Southern Anatolian Region (44.8%) and least in the West Marmara Region (6.4%) (11), which follows the regional distribution in our case series.

All cases in our study had a history of consanguineous marriage between their parents, except one whose parents were from the same village. A positive family history (affected siblings and/or cousins) was also found in seven cases. Considering the families with a family history of TSD, the total number of confirmed cases of TSD in nine families was 12 (Figure 1). According to this finding, it can be predicted that the number of affected cases will decrease if appropriate genetic counseling and carrier screening are performed when TSD is diagnosed for the first time in the family. While evaluating the family pedigree in our case series, we encountered that the number of affected cases in nine families was so high -in total 21 cases-, including index cases. Because this disease has a fatal prognosis, it is essential to recognize it in countries like Türkiye with a high rate of consanguineous marriages. Although the diagnosis is made by the enzyme level, carriers of childbearing age can be detected only in the family by clarifying the molecular pathogenesis. In this case series, although four families had children with TSD before, they did not prefer prenatal

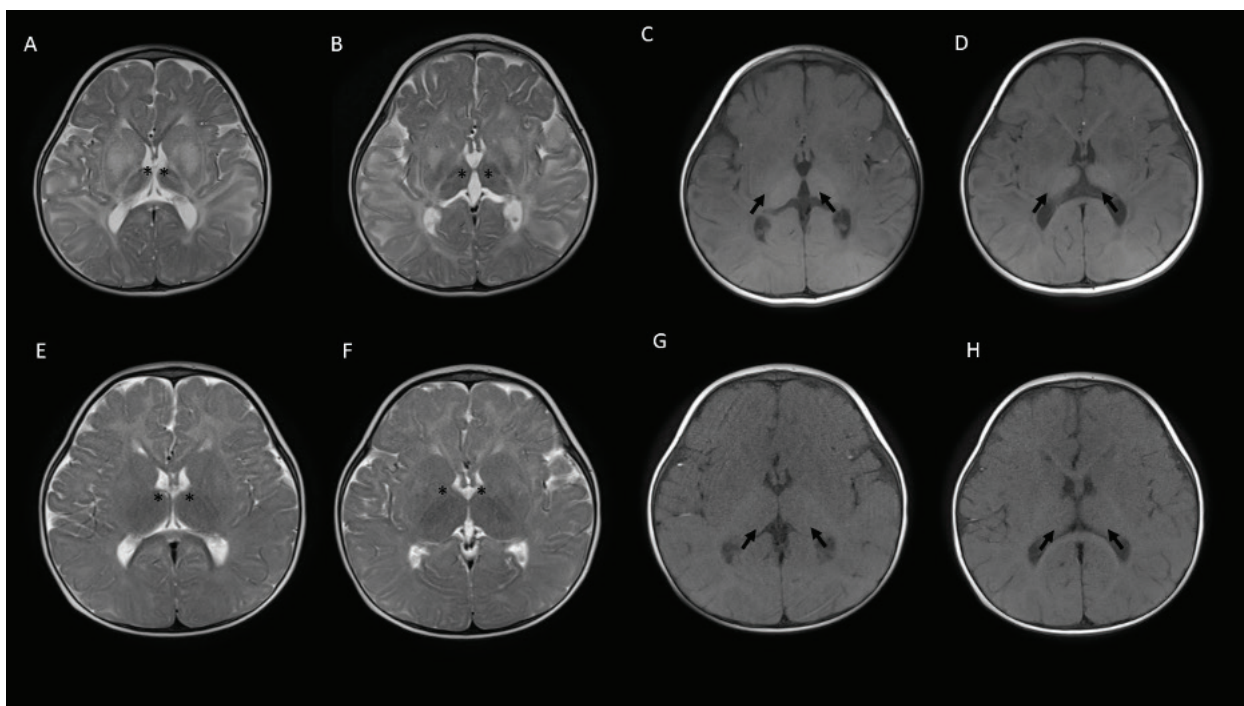


Figure 1. Cranial MRI findings in case 5 with TSD. At the age of 13 months (A-D), sagittal T2-weighted (T2W) images showed hyperintense signal changes in thalami in **A,B** (black asterisk) and sagittal T1W images showed hypointense signal changes in thalami in **C,D** (black arrow). At the age of 8 months (E-H), sagittal T2W images showed minimal hyperintense signal changes in thalami in **E,F** (black asterisk) and sagittal T1W images showed minimal hypointense signal changes in thalami in **G,H** (black arrow)

MRI: Magnetic resonance imaging, TSD: Tay-Sachs disease

diagnosis or preimplantation diagnosis. Even though there was a positive family history in seven cases, none of the cases were diagnosed before the symptoms.

The infantile form of TSD begins to manifest before six months of age, with neuromotor regression, hypotonia, and increased startle response (12). Smith et al. (13) reported that the mean age of first symptoms in 33 individuals with infantile TSD was 6.2 months (range 3-11), while according to a case series from Türkiye, the first symptoms began at 8.6 months of age (range 4-14 months for 8 cases) (14). As in the literature, the mean age at the first symptoms was 7 months (range 3-9 months) in our study. Neuromotor regression as the first symptom was observed in 7 of our 9 cases. The mean age of neuromotor regression was 15 and 12.3 months in cases from Iran and Türkiye, respectively (15,14). In this case series, the mean age of developmental regression was eight months, which is earlier than the literature.

TSD, like other sphingolipidoses, presents with neurodegenerative findings. While some clues or initial hallmarks may help in early diagnosis, ignoring these important symptoms may delay the diagnosis. Hypersensitivity to auditory stimuli and an exaggerated startle response are considered initial hallmarks for diagnosis. Positive family history can also increase the

awareness of startle, which is an important helpful sign in the early diagnosis of cases. In the two cases (case 3 and case 4), the initial symptom was startle, noticed by the family, which started at four and three months, respectively. The earliest diagnosed case had a history of an affected brother, and the family had noticed the startle sign when he was three months old, and his diagnosed age five months. Another helpful clue is the doll face, which appears in six of our case series. This sign, typical for type 1 glycogen storage, can also be seen in Sandhoff disease (SD), another GM2 gangliosidosis associated with deficiencies in both HEXA and HEXB enzyme activity caused by mutations in the HEXB gene with neurodegenerative manifestations. Although SD is indistinguishable from TSD in terms of clinical course and ocular findings, hepatosplenomegaly seen in SD is typically absent in TSD (12). Because the cherry-red spot is found in lysosomal storage diseases, including TSD, SD, GM1 gangliosidosis, Niemann-Pick disease, Farber disease, metachromatic leukodystrophy, and sialidosis, all children with neuromotor regression require eye examination by an experienced ophthalmologist (16).

It has been reported in the literature that less than 10% of the cases does not have cherry red spots, as in this case series. This may be caused by poor technique or the loss of cherry-red appearance because of the wear of retinal ganglion

Table 1. Clinical, radiological, and molecular findings of our TSD cases

Case	Demographic findings consanguinity family history region	Presentation history age of onset presentation symptoms	Clinical findings	Cherry red sign	Diagnosis determined by biochemical results Age of diagnosis HEXA enzyme level	Mutation results
Case 1 [♀]	1.5° cousin one affected brother Tokat	7 months neuromotor regression	Hypotonia spasticity macrocephaly doll-like face	+	11 months 46.6 nmol/mL/h (n=163-527)	Homozygous c.78G>A (p. Trp26Ter)
Case 2 [♂]	2° cousin two affected siblings Siirt	9 months neuromotor regression	Hypotonia spasticity macrocephaly doll-like face	+	10 months 21.5 µmol/L/h (n=140-250)	Homozygous c.1177C>T (p.(Arg393Ter))
Case 3 [♂]	1.5° cousin no family history Nevşehir	4 months startle	Hypotonia macrocephaly doll-like face	-	20 months 10.9 µmol/L/h (n=140-250)	Homozygous c.78G>A (p.(Trp26Ter))
Case 4 [♀]	1° cousin one affected brother two affected cousins Adana	3 months startle	Hypotonia normocephaly doll-like face	+	6 months 2.3 µmol/L/h (n=140-250)	Homozygous c.1100_1111del12 (p.(Gly367_Tyr370del))
Case 5 [♀]	The same village one affected cousin Tokat	8 months neuromotor regression	Hypotonia spasticity macrocephaly doll-like face	+	14 months 6.10 µmol/L/h (n=140-250)	Homozygous c.78G>A (p.(Trp26Ter))
Case 6 [♀]	1.5° cousin two affected cousins Hakkari	7 months neuromotor regression	Hypotonia spasticity macrocephaly doll-like face	+	13 months 67 nmol/mL/h (n=140-250)	Homozygous c.1177C>T (p.(Arg393Ter))
Case 7 [♀]	1° cousin no family history Urfa	8 months neuromotor regression startle	Hypotonia macrocephaly spasticity	+	18 months 2.4 µmol/L/h (n=140-250)	Homozygous c. c.1100_1111del12 (p. Gly367_Tyr370del)
Case 8 [♀]	1° cousin two affected cousins Tokat	9 months neuromotor regression	Hypotonia macrocephaly spasticity	+	14 months 2.4 µmol/L/h (n=140-250)	Homozygous c. c.1100_1111del12 (p.(Gly367_Tyr370del))
Case 9 [♂]	1.5° cousin one affected brother Sivas	8 months neuromotor regression	Hypotonia macrocephaly	+	9 months 2.4 µmol/L/h (n=50-250)	Homozygous c.786C>G (p. (His262Gly))

cells in the advanced stage of the disease. Although almost all children with the infantile disease have a characteristic cherry-red macula, the last diagnosed case (case 3) had a normal 12-month-old eye examination. In case 3, the absence of cherry-red sign in eye examination at 12 months of age and the delay of the cranial MRI examination for up to 22 months due to the necessity of anesthesia led to a diagnostic delay for this case. His diagnosis was made by lysosomal scanning, with cranial MRI detecting symmetrical T2W hypointense and T1W hyperintense signals in the thalamus, diffuse progressive T2W hyperintensity suggesting demyelinating disorder in cerebral white matter (13). As in this case, cranial MRI findings are helpful in making the diagnosis. Although cranial imaging findings in TSD may vary during the clinical course of the disease process,

especially in the early period of the disease, thalami may be hypointense on T2W images and hyperintense on T1W images due to the deposition of calcium. The combination of hyperdensity on T2W and hypointense signal involving bilateral thalami suggests TSD.

The definitive diagnosis of TSD in a clinically affected individual is established by demonstrating low HEXA activity and/or biallelic HEXA gene mutations. Gort et al. (12) reported that the age at diagnosis for 34 TSD cases was between 7 and 36 months. Similarly, in the case series reported from Türkiye, the mean age at diagnosis was 13.4 months (range 2-23) for nine TSD cases and 14.5 months for eight TSD cases (range 8-36) (14,17). The age of definitive diagnosis, determined by low enzyme levels, ranged

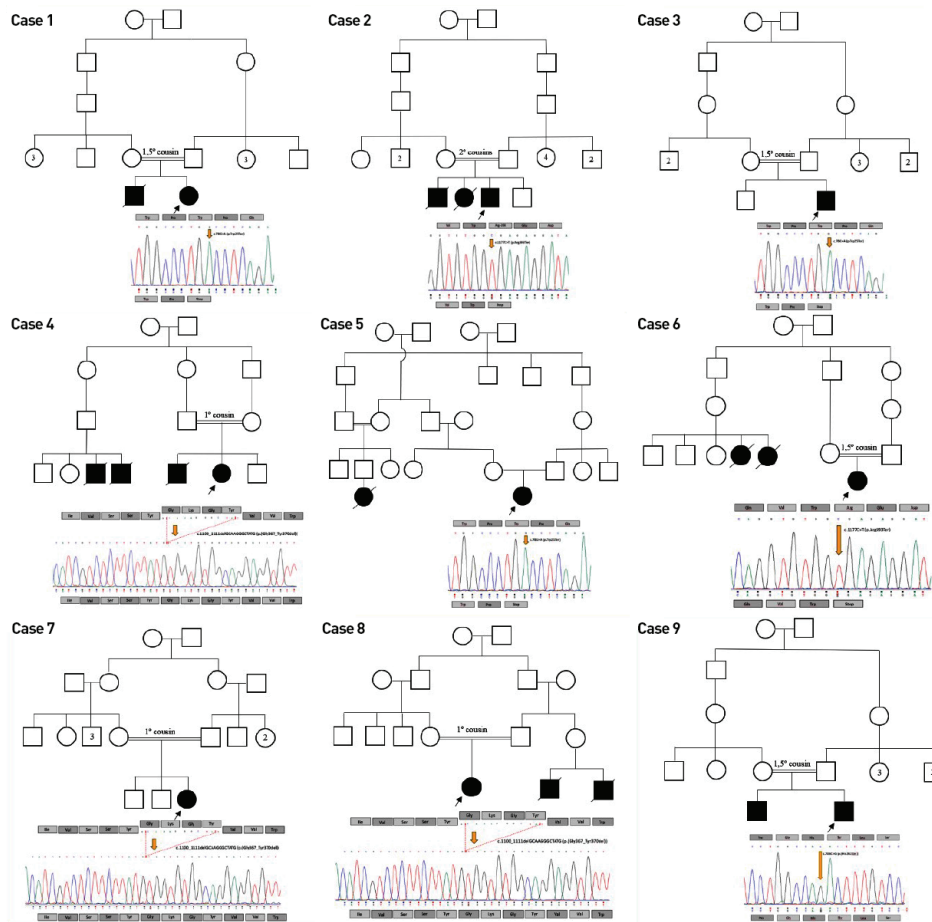


Figure 2. Pedigree analysis and molecular results of our cases

between 6 months and 20 months (mean age: 12.7 months) in our study compatible with the literature.

Since Ozkara et al. (18) described a homozygous mutation at the donor junction of intron 5 c.570+1G>A in the first Turkish patient with TSD in 1995, the following mutations have been reported, c.409C>T (p.(Arg137Term)), c.1177C>T (p.(Arg393Ter)), c.1100_1111del (p.(Gly367_Tyr370del)), c.1361G>A (p.(Gly454Asp)), c.412+1G>T (p.(*)), c.1510C>T (p. Arg504Cys), c.78G>A (p.(Trp26Ter)), c.798G>C (p. Trp266Cys), c.902T>G (p.(Met301Arg)) (14,17,19-24).

In our study, we identified three known variants, c.78G>A, c.1177C>T, and c.1100_1111del, and one novel variant, c.786C>G predicted pathogenic. According to the literature of cases from Türkiye, the most common associated variant in patients from Türkiye was found to be c.1100_1111del (p.(Gly367_Tyr370del)), a 12-bp deletion in exon 10 predicted to result in an in-frame deletion of four residues. This variant has been reported as c.1133_1144del or c.1096_1107del in previous publications. This variant has been corrected from publications to conform to the Human Genome Structural Variation nomenclature. The novel variant c.786C>G in case

9 was found to be compatible with the inheritance model, and clinical findings with in silico predictions supported that the c.786C>G variant is a novel disease-causing variant.

CONCLUSION

Because TSD is a well-known disease, cases with low beta-hexosaminidase A activity are often referred to genetic diagnosis centers for molecular genetic tests, and the diagnosis is confirmed by determining the mutation status. After the diagnosis of the case, families may not be able to receive genetic counseling because they deal with the medical needs of their children with severe disease.

In addition, parents of cases with homozygous mutations are not usually tested for carrier conditions. However, it is very important to prove that they are carriers in order to better explain to parents that the disease is hereditary. For this reason, it is important to provide genetic counseling to the family of each diagnosed case. For national premarital screening programs, it may be recommended that consanguineous parents seek genetic counseling before having children. It is also very useful to draw a family

tree by the genetic counselor to explain the autosomal recessive inheritance pattern of a family receiving genetic counseling and to give information that fertile siblings and cousins of the parents may also carry the disease. Giving the prenatal diagnosis/preimplantation option by giving genetic counseling to the family will prevent the emergence of new cases of this disease in the family. In neurometabolic diseases diagnosed with enzymes such as TSD, knowing the mutation that causes the disease in the family allows the carriers to be screened and the families to be given accurate genetic counseling.

ETHICS

Ethics Committee Approval: The study was reviewed and approved by the İstanbul University, İstanbul Faculty of Medicine, Clinical Research Ethics Committee (decision no: 18, date: 07.10.2022).

Informed Consent: Written informed consent was obtained from all parents of the patients included in the study.

Authorship Contributions

Surgical and Medical Practices: A.D.A., Ç.G., T.K., E.Ş., Ş.A., U.A., V.K., G.T., M.K., A.İ., G.G., G.Y., O.U., Concept: A.D.A., Ç.G., T.K., E.Ş., Ş.A., U.A., V.K., G.T., M.K., A.İ., G.G., G.Y., O.U., Design: A.D.A., Ç.G., V.K., M.K., G.Y., O.U., Data Collection or Processing: A.D.A., Ç.G., T.K., E.Ş., Ş.A., U.A., V.K., G.T., M.K., G.Y., Analysis or Interpretation: A.D.A., Ç.G., U.A., V.K., G.T., G.G., G.Y., O.U., Literature Search: A.D.A., Ç.G., U.A., V.K., G.T., G.G., G.Y., O.U., Writing: A.D.A., Ç.G., A.İ., G.G., G.Y., O.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

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