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ORIGINAL ARTICLE

Novel *HEXA* variants in Korean children with Tay–Sachs disease with regression of neurodevelopment from infancy

Ji Hong Park[1] | **Jung Min Ko**[1,2] | **Min Sun Kim**[1] | **Man Jin Kim**[2,3] | **Moon-Woo Seong**[2,3] | **Taekyeong Yoo**[4] | **Byung Chan Lim**[1,2] | **Jong-Hee Chae**[1,2]

[1]Department of Pediatrics, Seoul National University College of Medicine, Seoul National University Children's Hospital, Seoul, Korea

[2]Rare Disease Center, Seoul National University Hospital, Seoul, Korea

[3]Department of Laboratory Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea

[4]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea

Correspondence
Jung Min Ko, Department of Pediatrics, Seoul National University College of Medicine, Seoul National University Children's Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: jmko@snu.ac.kr

Abstract

Background: Tay–Sachs disease (TSD) is a lysosomal storage disease caused by mutations in the *HEXA* gene that encodes the HexosaminidaseA (HEXA) enzyme. As HEXA normally functions to degrade the protein GM2-ganglioside in lysosomes, decreased levels of HEXAcauses an accumulation of the protein and leads to neurological toxicity. Typical clinical manifestations of TSD include neurodevelopmental regression, muscle weakness, hypotonia, hyperreflexia, ataxia, seizures, and other neurological symptoms. It is quite rare in Asian populations, wherein only two cases have been reported in Korea to date.

Methods: Clinical records, radiological assessments, and laboratory findings, such as plasma hexosaminidase assay and *HEXA* analysis, were extracted from the medical records of three (1 male and 2 female) independent Korean children with infantile form of Tay–Sachs disease.

Results: All three children presented with neurodevelopmental regression and strabismus at around 8 months of age. Presence of cherry-red spots in the macula led to conduction of biochemical and genetic studies for TSD confirmation. The plasma hexosaminidase assay revealed decreased HEXA activity and low to normal total hexosaminidase activity. Similarly, genetic analysis revealed 4 variants from 6 alleles, including 2 previously reported and 2 novel variants, in the *HEXA* gene.

Conclusion: We presented three Korean children, who were recently diagnosed with infantile-type TSDvia enzyme assay and genetic analysis. Furthermore, results showed that fundus examination can be helpful for early diagnosis of children with neurodevelopmental regression.

KEYWORDS

cherry-red spot, GM2-gangliosidosis, hexosaminidase A deficiency, neurodevelopmental regression, Tay–Sachs disease

1 | INTRODUCTION

Tay–Sachs disease (TSD, OMIM#272800) is an autosomal recessive lysosomal storage disorder caused by mutations of *HEXA* gene on chromosome 15q23, which encodes the α-subunit of the enzyme Hexosaminidase A (HEXA) (Lew et al., 2015). HEXA is an enzyme that degrades GM2-gangliosides in the lysosomes of neuronal cells. Accumulation of GM2-gangliosides causes fatal neurological toxicity and function decline (Lew et al., 2015). TSD, the acute infantile form, is one of three clinical subtypes of HEXA deficiency disorders. These three subtypes (i.e., TSD, juvenile HEXA deficiency, and late-onset HEXA deficiency) differ in the levels of HEXA residual enzymatic activity. Patients with TSD usually have no or extremely low levels of HEXA activity, while those with juvenile or late-onset forms have higher residual levels of HEXA activity (Kaback & Desnick, 2011; Solovyeva et al., 2018). TSD is a progressive neurodegenerative disorder characterized by loss of motor skills, progressive muscle weakness, increased startle responses, and seizures (Kaback & Desnick, 2011). Typical physical examination findings include hypotonia, spasticity, hyperreflexia, and cherry-red spots on the retina (Kaback & Desnick, 2011). Regression of neurodevelopment begins in early infancy between 3 and 6 months of age, and most patients do not survive beyond 4 years of age (Solovyeva et al., 2018).

The worldwide prevalence of TSD is one in 100,000 births, with a carrier frequency of one in 250 births (Solovyeva et al., 2018). In certain populations, such as the Ashkenazi Jews and French Canadians, the prevalence is higher, with an incidence of one in 3,900 births in unscreened Jewish populations (Lew et al., 2015). However, the disease is relatively rare among Asians, which has an estimated prevalence of one in 360,000 births (Jin et al., 2004). Specifically, there have been only two reported TSD cases in Korea to date (Choi et al., 1999; Jin et al., 2004).

We present three independent Korean children with typical clinical manifestations and neurodevelopmental regression at around 8 months of age, who were biochemically and molecularly confirmed as an infantile form of TSD.

2 | CLINICAL REPORTS

The Institutional Review Board of Seoul National University Hospital approved this study (H-1904-054-1027). The study was performed in accordance with the Declaration of Helsinki and written informed consent for molecular study and publication was obtained from the parents. Clinical and molecular characteristics of three patients are summarized in Tables 1 and 2.

2.1 | Patient 1

A Korean male was born at a gestational age of 41 weeks, with a birth weight of 3.06 kg (3–10th percentile), without prenatal and perinatal problems. The result of newborn screening for inherited diseases was normal. He was the first child of healthy parents with no family history of inherited metabolic or neurologic diseases. At 3 months of age, he could control his head incompletely; however, at 7 months of age, he could not roll over. When he visited a local hospital due to excessive vomiting at 8 months of age, delays on motor development were observed, which prompted rehabilitation therapy.

At 12 months of age, he visited our hospital due to developmental regression without improvement from the previous therapy. His height, weight, and head circumference were 77 cm (25–50th percentile), 10.2 kg (50–75th percentile), and 47.5 cm (75–90th percentile), respectively. In addition, he could only control his head incompletely and was not able to roll over, crawl, or speak any meaningful words. Neurologic examination revealed truncal hypotonia, intermittent spasticity, hyperreflexia of the lower extremity, and a positive Babinski sign on both feet. He also showed hypersensitivity to sound and startle responses. He could not make eye contact, and thick eyebrows and exotropia were observed. Chromosome analysis and metabolic screening results, including serum amino acid, urine organic acid, lactate, pyruvate, ammonia, and carnitine profiles, were normal. Brain MRI performed at 8 months of age showed bilateral subtle T2 hyperintensities in the putamen/caudate and relatively low signal intensity in the bilateral thalamus (Figure 1a). Ophthalmologic examination revealed bilateral cherry-red spots in the macula (Figure 2a).

Plasma hexosaminidase assay was examined due to suspicion for HEXA deficiency. Results showed a moderately decreased level of HEXA (41.0%, ref. 55–72%) and a normal total hexosaminidase level. Aspartate aminotransferase level was elevated (183 IU/L, ref 1–40 IU/L); however, abdominal ultrasonography findings were normal. *HEXA* gene analysis was performed, and two reported pathogenic variants, NM_000520.6:c.[571-1G>T];[1168C>T], were found. He was diagnosed as TSD and both parents were found to be carriers of the variants (Figure 3a).

He started taking anti-epileptic drugs (AEDs) due to recurrent seizures at 14 months of age. He underwent fundoplication and percutaneous gastrostomy operation due to excessive gastric reflux and recurrent aspiration events at 17 months of age. He is currently in a bed-ridden state at 42 months of age.

2.2 | Patient 2

A Korean female was born at a gestational age of 39 + 2 weeks, with a birth weight of 3.2 kg (10–50th percentile). She was

TABLE 1 Clinical manifestations, enzyme activities, and causative *HEXA* variants of three Korean children with infantile form TSD

Patient	1	2	3
Sex	Male	Female	Female
Onset of developmental regression	8 months	8 months	8 months
Age at diagnosis	18 months	16 months	14 months
Current age	42 months	32 months	28 months
Head and neck			
Cherry red spot	+	+	+
Blindness	+	+	−
Respiratory			
Aspiration tendency	+	+	+
Gastrostomy	+	+	+
Tracheostomy	+	+	+
Neurologic			
Increased startle response	+	+	+
Hypotonia	+	+	+
Late hypertonia	+	+	+
Increased deep tendon reflex	+	+	−
Poor head control	+	+	+
Seizures	+	+	+
Spasticity	+	+	+
Results of biochemical and genetic studies			
Hexosaminidase A (HEXA) activity (%, ref. 55–72)	41	44.6	29
Total hexosaminidase activity (nmol/hr/mg protein, ref. 620–1000)	677.1ss	442.8	503.2
HEXA variants	c.1168C>T (p.Gln390*) c.571-1G>T	c.488A>G (p.Asp163Gly) c.571-1G>T	c.965A>G (p.Asp322Gly) c.965A>G (p.Asp322Gly)

the first child of healthy parents, and the result of newborn screening was unremarkable. She was able to control her head at 3 months of age, roll over at 5 months of age, and creep backwards at 6 months of age. However, developmental regression was observed after 8 months of age, and she could not crawl or roll over upon reaching 12 months of age. At a local hospital, she underwent several laboratory and imaging studies, such as brain MRI. Results showed an increased level of aspartate transaminase (189 IU/L, ref. 1–40 IU/L) and increased signal intensities in the bilateral basal ganglia and thalamus (Figure 1b). A target next generation sequencing (NGS) panel study for neurodevelopmental disorders was performed; however, results were inconclusive.

At 14 months of age, she visited our hospital for a second opinion. Her height, weight, and head circumference were 77.5 cm (10–25th percentile), 10.2 kg (50–75th percentile), and 48.9 cm (>97th percentile), respectively. Likewise, coarse facial features, thick eyebrows, macrocephaly, and exotropia were observed. Neurologic examination revealed spasticity, hypersensitivity to sound, hyperreflexia, and a positive ankle clonus and Babinski sign. Ophthalmological examination showed bilateral cherry-red spots in the retina. Under the suspicion of metabolic storage disorders, such as GM1 and GM2 gangliosidoses, we performed a plasma hexosaminidase assay and reviewed the raw data of the target NGS panel study previously performed. Along with decreased HEXA activity (44.6%, ref. 55%–72%), we identified two heterozygous variants, NM_000520.6:c.[488A>G];[571-1G>T], in *HEXA*. NM_000520.6:c.571-1G>T was a previously reported pathogenic variant; meanwhile, NM_000520.6:c.488A>G (p.Asp163Gly) was a novel and could be classified as a likely pathogenic variant (PM1 + PM2 + PM3 + PP3 + PP4). Hence, TSD was confirmed with both parents harboring each of the two mutations (Figure 3b).

She was started on AEDs at 19 months of age for hypotonic seizures and underwent percutaneous gastrostomy at

TABLE 2 Information for pathogenicity assessment of two novel variants identified in Patient 2 and 3

Novel variant	NM_000520.6:c.488A>G (p.Asp163Gly)	NM_000520.6:c.965A>G (p.Asp322Gly)
Patient	2	3
In silico prediction tool (score)		
SIFT	D (0)	D (0)
Polyphen2_HDIV	D (0.998)	D (1)
Polyphen2_HVAR	D (0.989)	D (1)
LRT	D (0)	D (0)
MutationTaster	D (0.81)	D (0.81)
FATHMM	D (−7.96)	D (−6.9)
PROVEAN	D (−6.75)	D (−6.83)
CADD_phred	29.2	31
GERP++	5.44	5.46
Population database		
ExAC_ALL	.	.
ExAC_EAS	.	.
1000G_ALL	.	.
1000G_EAS	.	.
gnomAD_ALL	.	.
gnomAD_EAS	.	.
Allele depth from NGS		
Alteration/total read count variant allele frequency (%)	170/354 (48.0)	
ACMG classification	Likely pathogenic (PM1 + PM2 + PP3 + PM3 + PP4)	Likely pathogenic (PM1 + PM2 + PP3 + PP4)

Abbreviations: D, deleterious, EAS, eastAsianpopulation

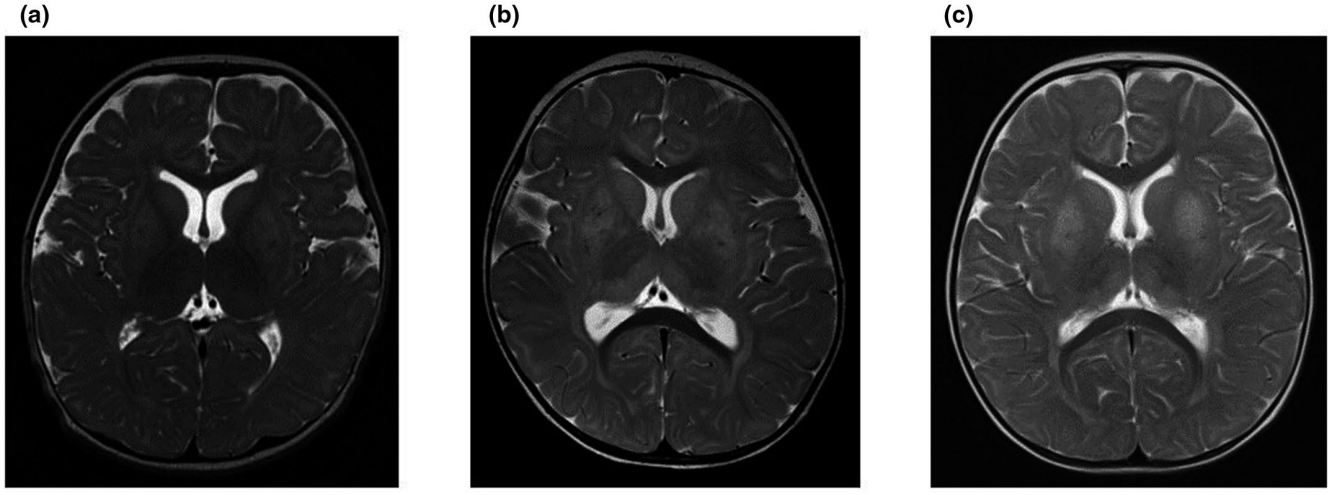

FIGURE 1 Brain MRI of the three patients showed high T2 signal intensities in the putamen and caudate and low signal intensity in the bilateral thalamus in Patient 1 (a), increased signal intensities in the bilateral basal ganglia and thalamus in Patient 2 (b), and high T2 signal intensities in the putamen and bilateral caudate head with decreased signal intensity in the bilateral ventral thalamus in Patient 3 (c)

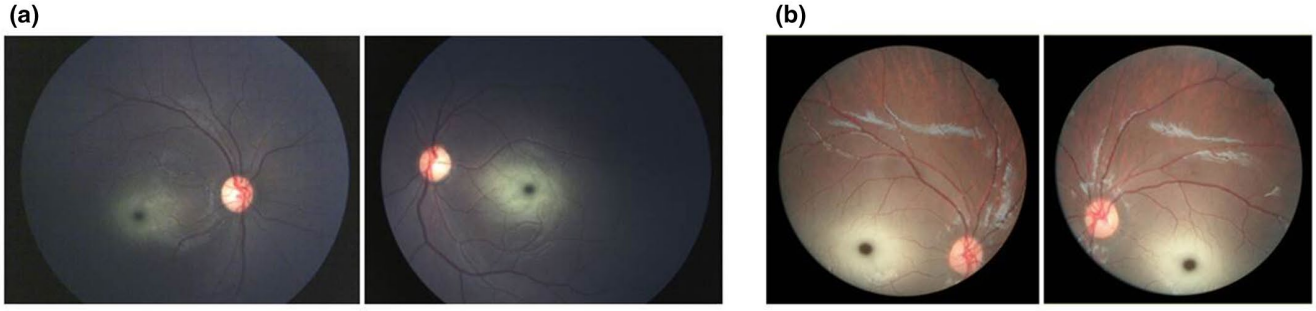

FIGURE 2 Fundus photographs of patient 1 (a) and 3 (b) show the characteristic bilateral cherry-red spots in the macula

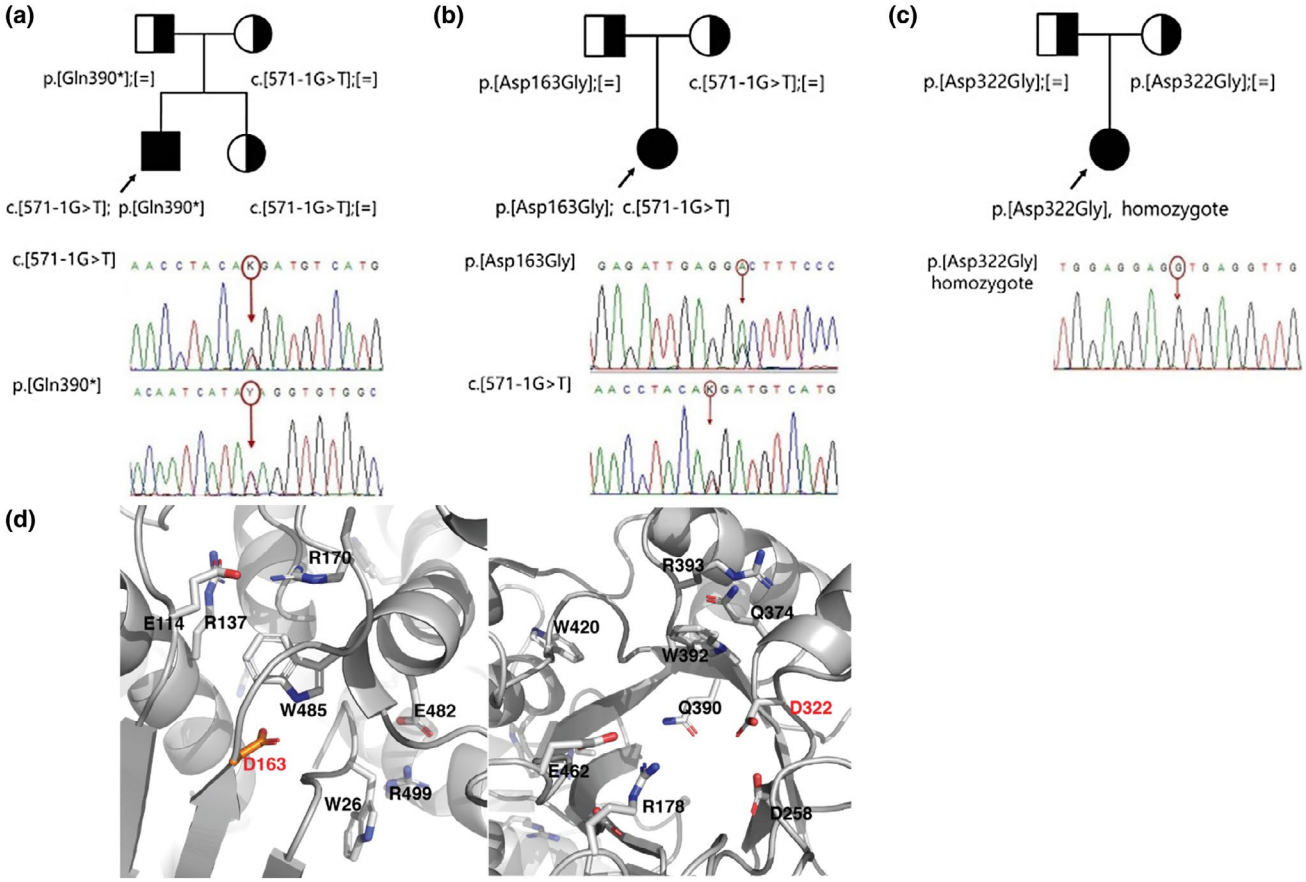

FIGURE 3 Family pedigrees of the patients with infantile form of Tay–Sachs disease, carrying recessively inherited *HEXA* variants. Affected and unaffected individuals are indicated by closed and open symbols, respectively. *HEXA* alleles are represented by '[=]' (wild-type), 'p.Gln390* (c.1168C>T)' and 'c.571-1G>T' found in Patient 1 (a), 'p.Asp163Gly (c.488A>G)' and 'c.571-1G>T' in Patient 2 (b), and homozygous 'p.Asp322Gly (c.965A>G)' in Patient 3 (c). (d) Location of the two novel missense variants (p.Asp163 and p.Asp322) identified in this study were estimated to be adjacent to the location of the pathogenic variants on ClinVar database (marked in black, https://www.ncbi.nlm.nih.gov/clinvar), respectively. Molecular figures were generated using Pymol (http://www.pymol.org)

20 months of age for feeding intolerance. At 32 months of age, the patient is currently in a bed-ridden state.

2.3 | Patient 3

A Korean female was born at a gestational age of 38 + 1 weeks via vaginal delivery, with a birth weight of 3.03 kg (10–50th percentile). She was the first child of healthy parents, and the result of newborn screening for inherited metabolic diseases was normal. She was able to roll over at 4 months of age and showed normal developmental milestones until 6 months of age. However, developmental regression was observed upon reaching 8 months of age. She visited our hospital's ophthalmologist due to infantile esotropia at 12 months of age, and subsequent fundus examination revealed bilateral cherry-red

spots in the macula (Figure 2b). She was then referred to the pediatric department for further evaluation.

Her height, weight, and head circumference were 73.6 cm (25–50th percentile), 8.8 kg (25–50th percentile), and 46.2 cm (75–90th percentile), respectively. Neurological examination revealed hypotonia, increased startle responses, and a normal deep tendon reflex. Brain MRI presented with T2 hyperintensities in the bilateral caudate head and putamen and decreased signal intensity in the bilateral ventral thalamus (Figure 1c). Laboratory studies showed an increase of aspartate transaminase level (239 IU/L, ref. 1–40 IU/L), while abdominal ultrasonography was normal. We performed a plasma hexosaminidase assay, and results showed a decrease of HEXA level (29.0%, ref. 55%–72%) and a slight decrease of total hexosaminidase activity (503.2 nmol/hr/mg protein, ref. 620–1000 nmol/hr/mg protein). *HEXA* gene sequencing was performed and revealed a novel homozygous and likely pathogenic variant (PM1 + PM2 + PM5 + PP3 + PP4), NM_000520.6:c.[965A>G];[965A>G], diagnosingher as TSD (Figure 3c). Both parents were also found to be carriers of the variant.

She is currently 28 months of age and has started taking muscle relaxants and AEDs for the past 8 months due to spasticity and seizures. Due to feeding intolerance and gastroesophageal reflux, she also underwent gastrostomy and fundoplication at 23 and 27 months of age, respectively.

3 | DISCUSSION

GM2-gangliosidosis is a group of diseases caused by a deficiency of the hexosaminidase enzyme, which is responsible for degrading GM2-gangliosides. Two isoenzymes of hexosaminidase are known: HEXA, which consists of one α-subunit and one β-subunit, and HEXB, which consists two β-subunits (Ferreira & Gahl, 2017). These α-subunit and a β-subunit are encoded by *HEXA* and *HEXB*, respectively (Dersh et al., 2016; Mark et al., 2003). Mutations in *HEXB* lead to Sandhoff disease (OMIM#268800), which is another type of GM2-gangliosides. Compared to TSD patients, those who are diagnosed with Sandhoff disease have deficiencies of both HEXA and HEXB. They may be clinically indistinguishable from TSD patients because their onset and type of neurological symptoms are very similar. However, some non-neurological characteristics, including hepatosplenomegaly and skeletal abnormalities, are more common in Sandhoff disease (Kaback & Desnick, 2011).

Characteristic cherry-red spots in the macula are seen due to GM2-ganglioside accumulation in the ganglion cells of the retina for all TSD patients. The swollen ganglion cells located on the edge of the macula of the retina become pale, thus emphasizing the cherry-red color of the choroid (Ferreira & Gahl, 2017). In our report, ophthalmologic examinations revealed cherry-red spots in the retina in all three patients. However, this finding is not pathognomonic for GM2-gangliosidosis, as it can be found in other lysosomal storage diseases, such as GM1-gangliosidosis, Gaucher disease, and Niemann-Pick disease (Ferreira & Gahl, 2017; Kaback & Desnick, 2011).

Currently, more than 130 mutations in the *HEXA* gene associated with TSD have been identified worldwide (Mistri et al., 2012). Among these, six mutations were most commonly found. This includes the following: three null alleles (NM_000520.6:c.1073+1G>A, c.1421+1G>C, c.1274_1277dupTATC) that causes infantile form TSD, one allele associated with the adult onset form, NM_000520.6:c.805G>A (p.Gly269Ser), and two pseudodeficiency alleles,NM_000520.6:c.739C>T (p.Arg247Trp), c.745C>T (p.Arg249Trp), that are not associated with HEXA deficiency itself, but with falsely lowered levels of HEXA activity during enzyme activity assay using synthetic substrate (Kaback & Desnick, 2011). The type and frequency of mutations vary greatly across different ethnic groups. In Ashkenazi Jew populations, the most common mutations of *HEXA* are NM_000520.6:c.1421+1G>C, c.1274_1277dupTATC (p.Tyr427Ilefs*5), c.805G>A (p.Gly269Ser), where the first two are null alleles and the third being associated with the later-onset form (Kaback & Desnick, 2011). On the other hand, the most common variant in French Canadians is a 7.6 kb deletion, including exon 1 and the promoter of *HEXA* gene, and in about 80% of Japanese TSD patients, the NM_000520.6:c.571-1G>T variant has been found (Tanaka et al., 1993).

Two out of three from our independent TSD patients also had NM_000520.6:c.571-1G>T, which could be a frequent allele among Far East Asian populations. Another mutation found in patient 1, NM_000520.6:c.1168C>T (p.Gln390*), is a previously documented pathogenic mutation (Akerman et al., 1997). Additionally, we found two novel and likely pathogenic variants in this study: NM_000520.6:c.488A>G (p.Asp163Gly) and c.965A>G (p.Asp322Gly). NM_000520.6:c.488A>G (p.Asp-163Gly) found in patient 2 is located in the chitobiase/beta-hexosaminidase domain 2-like region; meanwhile, NM_000520.6:c.965A>G (p.Asp322Gly) found in patient 3is located in the glycoside hydrolase family 20 catalytic domain. Both are well-established functional domains (PM1), and there have been previous reports from India of a pathogenic variant at the same codon, p.Asp322 Tyr (Mistri et al., 2012) (PM5 for patient 3). Also, these novel variants could not be found in well-known population databases such as ExAC, 1000G, and gnomAD (PM2). All identified variants were in trans from the parents' analyses (PM3 for patient 2). From in silico analysis using Pymolsoftware (http://www.pymol.org), p.Asp163 and p.Asp322 were estimated to be adjacent to the location of the reported pathogenic variants on ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar) (Figure 3d).

Interestingly, the residual HEXA activity was only mildly decreased (29.0%–44.6%) for all three patients, as opposed to other studies where infantile form TSD patients have markedly low levels of HEXA activity. However, the phenotypes of our patients were suggestive of infantile TSD. In Korea, TSD is extremely rare. Only a couple of centers could measure HEXA activity, and the internal data of positive controls might be limited. Hence, reassessment of the reference range is required by including our three patients as positive controls. A previous article from Japan also reported that the HEXA activity that were determined by heat inactivating procedure was generally much higher compared to the Jewish infantile form TSD patients (Tanaka et al., 1993). The article presented 24 infantile TSD patients and 23 patients were revealed to have the c.571-1G>T mutation, either heterozygously or homozygously. Average HEXA activity of the 23 patients was approximately 10.5%. The c.571-1G>T mutation, which is found in 80% of Japanese patients, generated a mutant mRNA with skipping of exon 6. The authors also suggested that a frame shift did not occur because exon 6 only consisted of 102 base pairs; therefore, it generates a rather stable mutant mRNA and creates a stable α-subunit of HEXA (Tanaka et al., 1993). In our report, patient 1 and patient 2, who have the heterozygous c.571-1G>T mutation, have residual HEXA levels over 40%, which is higher compared to that of patient 3, who does not have the c.571-1G>T mutation. Additionally, a previous report presented a patient with HEXA activity of 0% and genetic analysis revealed the c.1168C>T mutation, which was also found patient 1 of our report (Jin et al., 2004). This suggests that quality control and standardization of inter-laboratory and inter-method difference is necessary using more positive and negative control samples.

Currently, there is no known curative therapy for TSD. Thus, majority of treatments are based on relieving neurological symptoms. However, there have been several attempts to manage the disease itself which have been mostly used in preclinical research. This includes enzyme replacement therapy, substrate reduction therapy, bone marrow transplantation, and gene therapy (Solovyeva et al., 2018). Enzyme replacement therapy has already been known to be effective for several lysosomal storage diseases. Animal studies, performed using mice with Sandhoff disease, have shown some probability, and the use of recombinant HEXA increased motor function and survival rate (Tsuji et al., 2011). In addition, intraventricular administration of chimeric HEXB has shown to restore HEXA activity and reduce GM2-gangliosides in mice (Matsuoka et al., 2011). Substrate reduction therapy has been introduced to prevent the accumulation of certain substances by the suppression of a proximal enzyme involved in the synthesis of these substances. N-butyldeoxynojirimycin, a drug used for type 1 Gaucher disease, has been shown to prevent GM2-ganglioside accumulation in TSD mice (Bembi et al., 2006). However, the neurological symptoms and signs did not improve in human TSD cases (Bembi et al., 2006).

Although bone marrow transplantation along with N-butyldeoxynojirimycin intake showed an increase in HEXA activity in the plasma and leukocytes for a child with TSD, it was unable to prevent the progression of neurological dysfunction (Jacobs et al., 2005). Gene therapy, which uses viral vectors to deliver DNA encoding α-subunit and β-subunit of *HEXA*, is being developed and tested in mice. However, these studies have not yet been applied to humans, and effective delivery across the blood-brain barrier and adequate function in the brain remains a challenge (Solovyeva et al., 2018).

4 | CONCLUSION

GM2-gangliosidosis including TSD should be considered in children presented with neurodevelopmental delay, regression, and upper motor neuron signs. Similarly, a retinal examination could also be helpful for timely diagnosis. Advancements in genetic testing have led to the discovery of many variants associated with TSD and their relation to ethnicity. However, further studies can be performed to understand the origin of specific mutations in certain populations and to explain the relatively high levels of HEXA activity in Far East Asian TSD patients.

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ETHICAL COMPLIANCE

The Institutional Review Board of Seoul National University Hospital approved this study (H-1904-054-1027). The study was performed in accordance with the Declaration of Helsinki and written informed consent for molecular study and publication was obtained from the parents.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Ji Hong Park: data assembly and manuscript preparation; Man Jin Kim, Taekyeong Yoo, Min Sun Kim and Byung Chan Lim: data assembly and clinical analysis; Moon-Woo Seong, Jong-Hee Chae and Jung Min Ko: molecular genetic analysis; Jung Min Ko: design of this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Jung Min Ko https://orcid.org/0000-0002-0407-7828
Moon-Woo Seong https://orcid.org/0000-0003-2954-3677

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