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ORIGINAL ARTICLE

Phenotypic and molecular spectrum of Korean patients with Lesch-Nyhan syndrome and attenuated clinical variants

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Abstract

Lesch-Nyhan syndrome (LNS) is an X-linked recessive disorder caused by mutations in the *HPRT1* gene. The clinical features and mutation spectrum of 26 Korean LNS patients from 23 unrelated families were retrospectively reviewed. The *HPRT1* gene was analyzed by direct sequencing of genomic DNA. The median age at diagnosis was 2.3 years (range, 4 months–22.6 years) and the initial presenting features included developmental delay, orange colored urine, and self-injurious behaviors. Most patients were wheelchair-bound and suffered from urinary complications and neurologic problems such as self-mutilation and developmental delay. Twenty different mutations in *HPRT1* were identified among 23 independent pedigrees, including six novel mutations. The most common mutation type was truncating mutations including nonsense and frameshift mutations (45%). Large deletions in the *HPRT1* gene were identified in exon 1, exons 5–6, exons 1–9, and at chr X:134,459,540–134,467,241 (7702 bp) including the 5′-untranslated region, exon 1, and a portion of intron 1. In conclusion, this study describes the phenotypic spectrum of LNS and has identified 20 mutations from 23 Korean families, including six novel mutations in Korean patients with LNS.

Keywords *HPRT1* · Hypoxanthine guanine phosphoribosyltransferase · Hyperuricemia · Lesch-Nyhan syndrome

Introduction

Lesch-Nyhan syndrome (LNS, OMIM #300322) is a rare X-linked recessive disorder caused by a deficiency in hypoxanthine-guanine phosphoribosyl transferase (HPRT) (Lesch and Nyhan 1964). HPRT plays a crucial role in the purine salvage system by catalyzing the conversion of hypoxanthine and guanine to their respective 5′-mononucleotides, inosine monophosphate (inosinic acid, IMP), and guanine monophosphate (guanylic acid, GMP) (Jinnah et al. 2010; Nguyen et al. 2012). The prevalence of LNS is estimated to be 1 in 380,000 live births in Canada (Crawhall et al. 1972), and 1 in 235,000 live births in Spain (Torres and Puig 2007).

A HPRT deficiency is characterized by hyperuricemia with hyperuricosuria and a variable spectrum of neurological manifestations that accord with the extent of the enzyme deficiency (Fu et al. 2014a; Jinnah et al. 2010; Nguyen et al. 2012). A complete HPRT deficiency results in an excessive uric acid synthesis and neurological disorders such as motor dysfunctions, cognitive impairment, and behavioral disturbances. In contrast, there are attenuated clinical variants of LNS with a partial HPRT deficiency (Jinnah et al. 2010; Nguyen et al. 2012). The mildest variant, HPRT-related hyperuricemia (HRH), is characterized by an isolated overproduction of uric acid but no overt neurological or behavioral abnormalities. HPRT-related neurological dysfunction (HND) has an intermediate level of severity between LNS and HRH, and is manifested by an overproduction of uric acid along with some neurological symptoms or behavioral problems, but not self-injurious behaviors (Fu et al. 2014a; Zennaro et al. 2017).

The *HPRT1* gene is located on chromosome Xq26–27.2 and produces a 1.6-kb mRNA transcript encoding a 218

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amino acid protein (Patel et al. 1986). Affected individuals are predominantly hemizygous males, whilst heterozygous females are asymptomatic carriers. Molecular analysis of *HPRT1* is required for a confirmatory diagnosis of LNS in males, the determination of a carrier status in females, and for the prenatal diagnosis of the fetuses at risk.

To date, 615 different *HPRT1* mutations have been identified worldwide (http://www.lesch-nyhan.org/), including 242 missense mutations (39.3%), 158 deletions (25.7%), 90 splice site mutations (14.6%), 49 nonsense mutations (8.0%), 40 duplications (6.5%), and 36 other mutations (5.9%). There have been several previous case reports on Korean patients with LNS (Kim et al. 1997; Oh et al. 2011) and some studies on clinical outcomes and genotype-phenotype correlations in patients with LNS (Fu et al. 2014a, b). Our present study was performed to further investigate the clinical characteristics and mutation spectrum of *HPRT1* in Korean patients with LNS.

Subjects and methods

Subjects

This study included 26 LNS patients from 23 unrelated families who were diagnosed between March 1994 and December 2018 at the Department of Pediatrics, Asan Medical Center Children's Hospital, Seoul, Korea. The diagnosis of LNS was based on their clinical characteristics and on mutation analysis of *HPRT1*. Clinical features such as neurologic symptoms, hip dislocation, serum uric acid levels, and renal ultrasonography findings were retrospectively reviewed from the medical records. This study was approved by the Institutional Review Board at Asan Medical Center. Blood samples were collected from the 26 LNS patients and their families after obtaining written informed consent.

Analysis of hypoxanthine guanine phosphoribosyl transferase (HPRT) enzyme activity and molecular analysis of the *HPRT1* gene

The enzyme activity of HPRT was assayed in hemolysates using a previously described radiochemical technique (Kelley et al. 1967). Genomic DNA was extracted from peripheral blood leukocytes using a Puregene DNA isolation kit (Qiagen, Hilden, Germany). Nine exons of the *HPRT1* gene was amplified by polymerase chain reaction (PCR) using specific oligonucleotide primers. PCR products were directly sequenced using an ABI3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

To identify the region of the large deletion in the case involving a deletion of the 5′-untranslated region of *HPRT1*, small-sized primers were designed to amplify this predicted putative DNA region. The following primers were used for PCR: 5'-TTTTCAGATTCAATATAAGAACTTGTGTGG-3′ as the forward and 5'-AATCTACTTGGTGGCCTATA ATCTTATTAG-3′ as the reverse primer. This was followed by direct sequencing. In addition, the mRNA expression level was analyzed from cultured skin fibroblasts and quantitative real-time PCR. The mRNA was extracted from skin fibroblasts using the RNAeasy Mini kit (Qiagen Inc., Valencia, CA, MD, USA) in accordance with the manufacturer's protocol. cDNA was subsequently synthesized using 1–2 μg of total RNA after treatment with DNase in a reverse transcriptase reaction mixture using random primers (PrimeScript II 1st Strand cDNA Synthesis kit, TAKARA, Tokyo, Japan). Aliquots of 7 μL of cDNA were then used in the PCR reactions or stored at −20 °C. The primer sequences used for amplification were 5'-TGCTCGAGATGTGATGAAGG-3′ as the forward and 5'-TCCCCTGTTGACTGGTCATT-3′ as the reverse primer. The PCR amplification conditions were 30 cycles of denaturation at 95 °C for 10 s, annealing at 60 °C for 10 s, and extension at 72 °C for 20 s.

Results

Clinical characteristics and outcomes of in Korean patients with Lesch-Nyhan syndrome

The clinical characteristics of the Korean LNS patients in our current study cohort are summarized in Table 1. Clinical data were not available for 3 patients from 3 different families. The median age at diagnosis was 2.3 years (range, 4 months–22.6 years). All of the 23 patients for whom data were available showed neurological manifestations such as dystonia with a baseline hypotonia, spasticity, or motor developmental delay. Self-injurious behavior occurred in 21 of these subjects (91.3%) and only Subjects 1 and 24 did not demonstrate this condition. Partial seizures were observed in only one patient (Subject 7), who required antiepileptic drug medications. His brain magnetic resonance image (MRI) findings were normal but electroencephalography revealed occasional sharp wave discharges from the left or right centro-temporal area and intermittent theta slowing at the right occipital area. Brain MRI was performed in four patients (Subjects 1, 7, 8, and 21), and revealed nonspecific changes of atrophy in one case (Subject 8), but no abnormalities in the other three patients.

Twenty one of the 23 LNS patients with available data (91.3%) showed renal manifestations such as hyperuricemia, nephrocalcinosis, or urinary stones (Table 1). The mean serum uric acid level at diagnosis was to 9.4 ± 2.2 mg/dL in the 21 cases. Two patients (Subjects 10 and 17) showed normal serum uric acid levels at first visit in our institute at the age of 7.5 and 8.1 years, respectively. However, they were diagnosed by referral doctors at the age of 6.5 and 6.0 years, respectively and had been treated with allopurinol.

Table 1 Clinical characteristics of 26 Korean patients from 23 unrelated families with Lesch-Nyhan syndrome (LNS)

Family No.	Subject No.	Age at diagnosis, yrs	Neurological disease	Self-injurious behavior	Seizure	Renal ultrasonography	Joint disease
1	1	1.9	DD	–	–	No nephrocalcinosis	–
2	2	0.6	DD	+	–	Nephrocalcinosis	–
3	3	11.2	DD	+	–	Nephrocalcinosis	–
4	4	22.6	NA	NA	NA	NA	NA
5	5	9.2	DD	+	–	Not done	–
6	6	2.5	NA	NA	NA	NA	NA
7	7	1.8	DD	+	+	Nephrocalcinosis	–
8	8	1.4	DD	+	–	Not done	–
9	9	0.4	DD	+	–	Nephrocalcinosis	–
10	10	6.5	DD	+	–	Nephrocalcinosis	Hip dislocation
10	11	0.4	DD	+	–	No nephrocalcinosis	–
11	12	14.5	DD	+	–	Nephrocalcinosis	–
11	13	11.2	DD	+	–	Nephrocalcinosis	–
12	14	10.3	DD	NA	NA	NA	NA
13	15	0.9	DD	+	–	Nephrocalcinosis	–
13	16	5.9	DD	+	–	Nephrocalcinosis	Hip dislocation
14	17	6.0	DD	+	–	Nephrocalcinosis	–
15	18	3.6	DD	+	–	Nephrocalcinosis	–
16	19	8	DD	+	–	Nephrocalcinosis	–
17	20	16.6	DD	+	–	Nephrocalcinosis	Hip dislocation
18	21	0.6	DD	+	–	Nephrocalcinosis	–
19	22	1.2	DD	+	–	Nephrocalcinosis	–
20	23	1.7	DD	+	–	No nephrocalcinosis	Hip dislocation
21	24	0.4	DD	–	–	No nephrocalcinosis	Hip dislocation
22	25	1.3	DD	+	–	Not done	–
23	26	2.0	DD	+	–	Nephrocalcinosis	–

DD developmental delay, *NA* not available

Unfortunately, the information on initial uric acid levels were not available. Renal ultrasonography was performed in 20 patients. Among them, nephrocalcinosis were detected in 16 of 20 study patients (80%) by renal ultrasonography. Renal ultrasonography was not done yet in 3 patients, and the information was not available in the remaining 3 patients. Seven cases (30.4%) had a urinary stone, and three of these patients (Subjects 10, 13, and 26) underwent surgical management at a median age of 21.5 years (range, 11.2–25.4 years). Stone analysis revealed 100% of xanthine calculi. One patient (Subject 26) manifested chronic kidney disease with a serum creatinine level of 2.76 mg/dL at the age of 17 years. Hip dislocations were noted in five of the 23 patients (21.7%) via an X-ray of the hip joint (Table 1).

All of the LNS patients in our current series were treated with allopurinol to reduce the high blood uric acid levels and sodium bicarbonate to alkalinize the urine pH. Baclofen ($n = 20$), diazepam ($n = 6$), clobazam ($n = 1$), or clonazepam ($n = 1$) were administrated to relieve spasticity and dystonia. The median age of our patients at the last follow-up was 16.6 years (range, 1–28 years). All patients were wheelchair-bound or bed-ridden. Two patients (Subjects 11 and 19) died while sleeping at home at the age of 21 and 19 years, respectively.

HPRT enzyme assay

The HPRT enzyme analysis was performed in 5 of the 26 patients in the total cohort, with no activity detected in any of these cases (Table 2).

Mutation spectrum of the *HPRT1* gene

Twenty different mutations in *HPRT1* were identified from 23 independent pedigrees (Table 2 and Fig. 1). Most mutations were distributed equally throughout the gene, i.e., there were no evident mutational hotspots. Truncating mutations including nonsense and frameshift mutations were the most common (9/20, 45%), followed by missense mutations (4/20, 20%), large deletions (4/20, 20%), and splice site mutations (3/20, 15%).

Table 2 Molecular analysis of the *HPRT1* gene in 26 Korean patients from 23 unrelated families with LNS

Family No.	Subject No.	Mutation type	Amino acid change	Nucleotide change	HPRT activity (nmol/min/mgHb)
1	1	Large deletion	Exons 5–6 deletion	c.385-222_485 + 1024del	ND
2	2	Large deletion	Exon 1 deletion	c.1-?_27 +?del	ND
3	3	Large deletion	Exons 1–9 deletion	c.1-?_657 +?del	ND
4	4	Missense	p.F74 L	c.222C > G	ND
5	5	Missense	p.F74 L	c.222C > G	ND
6	6	Missense	p.F74 L	c.222C > A	ND
7	7	Missense	p.L68F	c.202C > T	0
8	8	Missense	p.A64P	c.190G > C	ND
9	9	Missense	**p.I42S**	**c.125 T > G**	ND
10	10	Nonsense	p.K215*	c.643A > T	ND
10	11	Nonsense	p.K215*	c.643A > T	ND
11	12	Nonsense	p.R51*	c.151C > T	ND
11	13	Nonsense	p.R51*	c.151C > T	ND
12	14	Nonsense	p.R51*	c.151C > T	ND
13	15	Nonsense	p.Q109*	c.325C > T	ND
13	16	Nonsense	p.Q109*	c.325C > T	ND
14	17	Small deletion	p.T211Lfs*40	c.631del	ND
15	18	Small deletion	p.V97Rfs*10	c.288_289del	ND
16	19	Small deletion	p.S148Lfs*6	c.441_442del	0
17	20	Small deletion	**p.A218Pfs*33**	**c.651del**	ND
18	21	Small insertion	**p.G112Rfs*10**	**c.333_334ins(A)**	0
19	22	Small insertion	**p.S209 fs*1**	**c.623_624ins(A)**	ND
20	23	Splice site	**IVS7(−2)A > C**	**c.533-2A > C**	ND
21	24	Splice site	IVS7(−9)T > A	c.533-9 T > A	0
22	25	Splice site	IVS7(+5)G > A	c.532 + 5G > A	ND
23	26	Large deletion	**5'-UTR, exon 1, and part of intron 1 deletion**	**c.-614_1 + 6904del**	ND

HPRT hypoxanthine-guanine phosphoribosyl transferase, *ND* not done; **bold, novel mutation**

A total of six novel sequence variants were identified (Fig. 1) that were not found in normative population databases including Exome Aggregation Consortium database (http://exac.boradinstitute.org/) and genome aggregation database (http://gnomad.broadinstitute.org/). The missense variant, c.125T > G (p.I42S) was predicted to be deleterious by in silico prediction programs including PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT (http://sift.jcvi.org/). The other novel variants included three frameshift mutations (p.A218Pfs*33, p.G112Rfs*10, and p.S209 fs*1), one splice site variant (c.533-2A > C), and a large deletion including the 5′-untranslated region (UTR), exon 1, and a part of intron 1, leading to an absent expression of mRNA levels from skin fibroblasts by quantitative real time PCR. Direct sequencing using small-sized primers indicated that chromosome X:134,459,540–134,467,241 (7702 bp) had been deleted (c.-614_1 + 6904del).

Family screening was performed in 11 (45.8%) of 24 unrelated families in our current series. The mutation was inherited from the mother in 9 of these 11 families (81.8%). De novo mutations had occurred in 2 of 11 probands (18.2%). All heterozygous females were clinically normal. Prenatal diagnoses were conducted in 10 fetuses from 6 at-risk families using chorionic villi sampling. Six normal males, three female carriers, and one male patients with a c.631del mutation were identified.

Discussion

We have investigated the clinical characteristics and molecular spectra of 26 Korean patients with LNS from 23 unrelated families. Most patients of the cases in our current cohort were classified as a classical LNS phenotype involving self-injurious behavior. However, as the emergence of self-injurious behavior is age-dependent, the wide age range at evaluation and the current age could lead to a misclassification of the LNS phenotype (Fu et al. 2014a). Two patients in our present series (Subjects 1 and 24) were categorized as HND without self-mutilation but were 4.5 and 10 years old children,

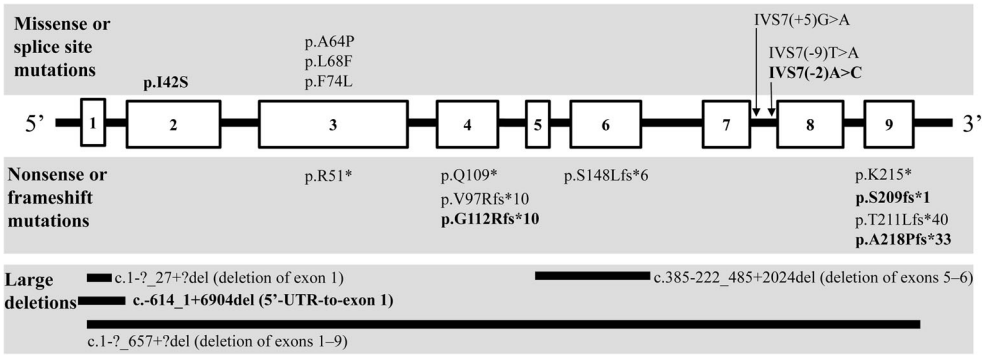

Fig. 1 Mutation spectrum of the *HPRT1* gene in 23 unrelated Korean families with Lesch-Nyhan syndrome (**bold**, novel mutations). Most were private mutations. However, p.F74 L and p.R51* were identified in three and two families, respectively

Bold, novel mutations

respectively. These patients will need to be followed up as several reported cases initially classified as HND were reclassified as LNS upon the later emergence of a self-mutilation phenotype (Fujimori et al. 1994). Moreover, the most common mutations in our present study series were nonsense (15%), frameshift (30%), and large deletion mutations (20%), all leading to a classical LNS phenotype.

The overproduction of uric acid can not only cause hyperuricemia but can also increase the urinary excretion of uric acid, resulting in nephrolithiasis, urinary obstruction, and renal failure. Nephrolithiasis usually occurs in the second or third decades in LNS patients (Jinnah et al. 2010), consistent with our present observations. Urinary tract stones are composed primarily of uric acid in patients with LNS. However, allopurinol treatment increases urinary excretion of hypoxanthine and xanthine about 5- and 10-fold, respectively. As a result, the risk of xanthine calculi increases with allopurinol therapy (Fu et al. 2014b; Torres and Puig 2007). LNS patients usually survive into their second or third decades of life, and the causes of death include pneumonia and other infectious diseases (Torres and Puig 2007). In some cases sudden and unexpected death has been reported, which appears to have a respiratory rather than a cardiogenic origin (Neychev and Jinnah 2006).

Most of the *HPRT1* mutations we detected in our current study were private mutations. However, two recurrent mutations in exon 3 were also identified: p.F74 L and p.R51*. The p.R51* mutation is at a known hot spot and involves the methylation of a CpG motif (Fu et al. 2014a). The amino acid substitutions p.F74 V, p.F74C, and p.F74 L have been reported previously in patients with classical LNS (Jinnah et al. 2000; Jurecka et al. 2008), suggestive of another mutational hotspot. In the present study, small indels ($n = 6$) and large deletion ($n = 4$) mutations accounted for 50% of the variants. Among these mutations, a gross deletion of a 7.7 kb region incorporating the 5'-UTR, exon 1, and part of intron 1 was confirmed, resulting in a null mRNA level. Deletions at the 5′ end of the *HPRT1* gene, including the gross deletion of exons 1–3, have been previously described and cause severe disruption (Wehnert and Herrmann 1990). Splicing mutations located on IVS7(−1) or IVS7(−2) result in the skipping of exon 8, leading to an out-of-frame transcript with a chain termination at a new codon 187 (de Gemmis et al. 2010; O'Neill et al. 1998). These splice site mutations, which are located within the highly conserved polypyrimidine tract, may disrupt lariat formation during the splicing process, resulting in aberrant splicing. The IVS7(−9)T > A variant also generates an exon 8-skipped *HPRT1* mRNA, and the predicted size of the translated protein is 182 amino acids consisting of 177 normal and 5 different amino acids (Kim et al. 1997).

The effect of *HPRT1* gene mutations on residual HPRT enzyme activity is the most significant contributor to the LNS phenotype (Fu et al. 2014b). There is a reported relationship between residual HPRT activity and the severity of disease in LNS and its variants (Fu et al. 2015), but no consistent relationship has been found between the type of mutation or the location of the mutation and the phenotypic severity in LNS. However, more severe mutations of the *HPRT1* gene such as gross deletions and nonsense and frameshift mutations are found in patients with the classical LNS phenotype. Missense mutations are more commonly observed in patients with milder LNS variants, likely because a single amino acid substitution is more likely to permit some residual enzyme function (Fu et al. 2014a). In addition, missense mutations in regions that encode the active site of the enzyme are closely associated with the clinical phenotype of LNS (Ceballos-Picot et al. 2013; Rebai et al. 2014). However, *HPRT1* mutations with very different clinical manifestations often overlap, and the same mutation can be associated with more than one clinical variant of LNS (Hladnik et al. 2008; Jinnah et al. 2004).

This present study had several limitations. As the clinical features of LNS in our patient series were analyzed retrospectively, there were missing data in some cases. In addition, the severity of the self-injurious behavior was not systematically analyzed using the Behavior Problems Inventory (BPI-01) (Rojahn et al. 2001). In addition, HPRT activity was measured in only five patients.

In conclusion, we have here described our clinical and molecular genetic findings in a cohort of Korean LNS patients and summarized 20 different pathogenic *HPRT1* variants from

the 23 different families of these cases. Most of the *HPRT1* mutations were presumed to be functionally detrimental due to high prevalence of small indels, large deletions, and nonsense mutations. Males with a developmental delay, and with neurologic and behavioral problems that are typical of LNS, should be suspected to have this disorder, particularly in cases of hyperuricemia.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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