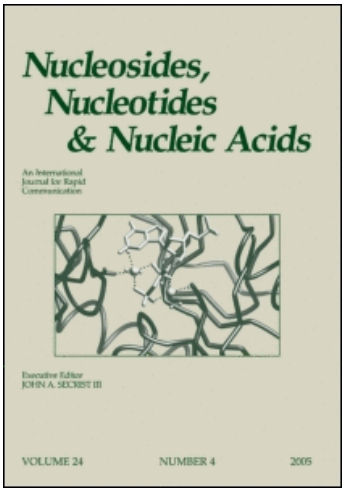

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Mutations in the Hypoxanthine Guanine Phosphoribosyltransferase Gene (*HPRT1*) in Asian HPRT Deficient Families

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Mutations in the Hypoxanthine Guanine Phosphoribosyltransferase Gene (*HPRT1*) in Asian HPRT Deficient Families

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ABSTRACT

Inherited mutation of hypoxanthine guanine phosphoribosyltransferase, (HPRT) gives rise to Lesch-Nyhan syndrome or HPRT-related gout. We have identified 34 mutations in 28 Japanese, 7 Korean, and 1 Indian families with the patients manifesting different clinical phenotypes, including two rare cases in female subjects, by the analysis of all nine exons of HPRT from the genomic DNA and reverse transcribed mRNA using PCR technique coupled with direct sequencing.

Key Words: HPRT; Deficiency; Mutations; Lesch-Nyhan syndrome; Kelley-Seegmillar syndrome.

INTRODUCTION

Inherited mutation of a purine salvage enzyme, hypoxanthine guanine phosphoribosyltransferase (HPRT, MIM308000), gives rise to Lesch-Nyhan syndrome (MIM 300322) or HPRT-related gout (MIM300323). The HPRT gene (*HPRT1*) is located in Xq26.1, composed of nine exons and transcribed into a 1.6-kb mRNA, which encodes

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218 amino acids. We have identified a number of such HPRT mutations in the patients manifesting different clinical phenotypes. In this paper, we represent all the mutations and their phenotypes detected from Asian HPRT deficient families.

MATERIALS AND METHODS

All the methods for *HPRT1* analysis, identification of the genomic mutation and the altered mRNA, were described previously.[1,2] DNA sequences were determined according to the simplified direct sequencing method as described previously.[1]

RESULTS AND DISCUSSION

All the mutations identified and their phenotypes are summarized in Table 1. In the three partial HPRT deficient patients with hyperuricemia and gout, three missense mutations in the exon 8 of *HPRT1* were identified. Three independent missense mutations were detected from the patient manifested with hyperuricemia and mild neurological symptoms, such as ataxia and spasticity. In a severe form of partial HPRT deficiency referred as Lesch-Nyan syndrome without self-mutilation, a single nucleotide substitution (532 + 2T>C) resulted in splicing error and markedly decreased expression of normal mRNA. By the analysis of *HPRT1* from classical Lesch-Nyhan patients, we have defined lots of mutations, which include 2 nonsense mutations, 4 missense mutations, 6 single base substitutions causing splicing error, 3 insertions, 9 deletions, a translocation, and an abnormal methylation. Some mutations resulted in two or three types of abnormal mRNAs. Recently, we have identified a large genomic deletion (~15 kb) including the promoter region and the whole exon 1 of *HPRT1*, by the Southern analysis and PCR methods referring the sequences from human genome database. Four mutations, 575C>T, 403-2A>G, 330insA, and 15-kb deletion are new to the *HPRT1* mutation database.

The marked heterogeneity of HPRT deficiency is well known, as reported many mutations at the HPRT gene locus (deletion, insertions, duplications, abnormal splicing and point mutations at different sites of the coding region from exons 1 to 9).[3] The similar observations are obtained in our studies, whereas three missense mutations resulting in partial deficiencies without neurological symptoms are located in exon 8. We reported two unusual cases of female Lesch-Nyhan patients.[4–6] The molecular mechanisms of the first female patient are 1) a total matenal *HPRT1* deletion and 2) a gene inactivation due to the abnormal methylation at the first intron of the paternal *HPRT1*.[5] In the second case, a nonsense mutation R51X was detected in the *HPRT1* on one of alleles, and the decreased normal mRNA expression from the other allele were observed.[6] Including other two cases,[7,8] the genotypes of the female patients were heterozygous for the mutations similar to the carriers with no symptoms. Nonrandom X-inactivation seems to cause female Lesch Nyhan patients. Moreover, prenatal gene diagnoses were carried out in 12 fetuses in 9 families by PCR-RFLP and direct sequencing using both mRNA and genomic DNA from chorionic villi or amniotic fluid cells.

Table 1. *HPRT1* mutations in Asian HPRT deficient families.

Mutation	Location	mRNA	Amino acid	Phenotype
563T>C	Exon 8	563T>C	V188A	A
575C>T	Exon 8	575C>T	**A192V**	A
584A>G	Exon 8	584A>G	Y195C	A
215A>G	Exon 3	215A>G	Y72C	B
440T>C	Exon 6	440T>C	L147P	B
475A>G	Exon 6	475A>G	K159E	B
532+2T>C	Ex 7-int 7	< 1/1000	Normal	C
		ins 4-bp	178fs183X	
		Skip exon 7	163fs166X	
151C>T	Exon 3	151C>T	R51X	D
190G>C	Exon 3	190G>C	A64P	D
194T>C	Exon 3	194T>C	L65P	D
209G>A	Exon 3	209G>A	G70E	D
233T>A	Exon 3	233T>A	L78Q	D
325C>T	Exon 4	325C>T	Q109X	D
		Skip exon 4	107del22aa	
27+1G>T	ex 1-int 1	ins 49-bp	10fs27X	D
28-1G>C	int 1-ex 2	Skip exon 2	10fs12X	D
318-1G>T	int 3-ex 4	del 9-bp	107del3aa	D
		Skip exon 4	107del22aa	
403-2A>G	int 5-ex 6	ins G	**135fs138X**	D
533-9T>A	int 7-ex 8	Skip exon 8	178fs183X	D
610-1G>A	int 8-ex 9	del 17-bp	H204X	D
212insG	Exon 3	212insG	72fs73X	D
330insA	Exon 4	330insA	**111fs121X**	D
435insTTTG	Exon 6	insTTTG	127fs135X	D
50delA	Exon 2	50delA	17fs41X	D
632delA	Exon 9	632delA	211fs250X	D
289delGT	Exon 3	289delGT	96fs106X	D
		Skip exons 2,3	10del97aa	
316delGT	ex 3-int 3	316delGT	C106X	D
		Skip exons 2,3	10del97aa	
318delAATG	int 3-ex 4	del 4-bp	107fs113X	D
		del 9-bp	107del3aa	
		Skip exon 4	107del22aa	
609+1delGT	ex 8-int 8	Skip exon 8	178fs183X	D
610-16del74	int 8-ex 9	del 58, ins 26-bp	204fs233X	D
1-368del353	~ exon 1	No mRNA		D
del ~15 kb	~ intron 1	No mRNA		D
Total deletion		No mRNA		D

Novel mutations reported first in this paper are indicated with **boldface**. Phenotypes: A, partial deficiency without neurological symptom; B, partial deficiency with mild neurological symptom; C, partial deficiency with severe neurological symptom (Lesch-Nyhan syndrome without self-mutilation); D, classical Lesch-Nyhan syndrome.

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REFERENCES

1. Yamada, Y.; Goto, H.; Suzumori, K.; Adachi, R.; Ogasawara, N. Molecular analysis of five independent Japanese mutant genes responsible for HPRT deficiency. Hum. Genet. **1992**, *90*, 379–384.
2. Yamada, Y.; Nomura, N.; Kitoh, H.; Wakamatsu, N.; Ogasawara, N. Novel genetic mutations responsible for the HPRT deficiency and the clinical phenotypes in Japanease. Adv. Exp. Med. Biol. **2001**, *486*, 29–33.
3. Sculley, D.G.; Dawson, P.A.; Emmerson, B.T.; Gordon, R.B. A review of the molecular basis of hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. Hum. Genet. **1992**, *90*, 195–207.
4. Ogasawara, N.; Stout, J.T.; Goto, H.; Sonta, S.; Matsumoto, A.; Caskey, C.T. Molecular analysis of a female Lesch-Nyhan patient. J. Clin. Invest. **1989**, *84*, 1024–1027.
5. Ogasawara, N.; Yamada, Y.; Goto, H. HPRT gene mutations of a female Lesch-Nyhan patient. Adv. Exp. Med. Biol. **1992**, *309B*, 109–112.
6. Yamada, Y.; Goto, H.; Yukawa, T.; Akazawa, H.; Ogasawara, N. Molecular mechanisms of the second female Lesch-Nyhan patient. Adv. Exp. Med. Biol. **1995**, *370*, 337–340.
7. Aral, B.; Basile, G.S.; Al-Grawi, S.; Kamoun, P.; Ceballos-Picot, I. Novel nonsense mutation in the hypoxanthine guanine phosphoribosyltransferase gene and nonrandom X-inactivation causing Lesch-Nyhan syndrome in a female patient. Human Mutat. **1996**, *7*, 52–58.
8. DeGregorio, L.; Nyhan, W.L.; Serafin, E.; Chamoles, N.A. An unexpected affected female patient in a classical Lesch-Nyhan family. Mol. Genet. Metab. **2000**, *69*, 263–268.