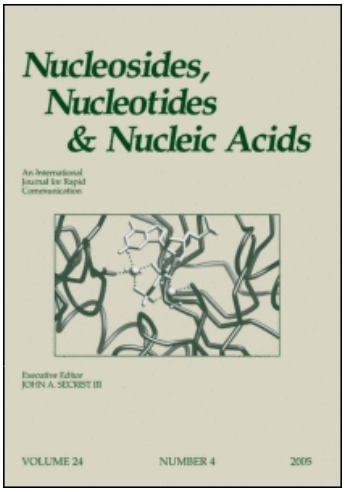

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Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency: Biochemical and Molecular Findings in Six Argentine Patients

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HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE DEFICIENCY: BIOCHEMICAL AND MOLECULAR FINDINGS IN SIX ARGENTINE PATIENTS

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□ *Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is an inborn error of purine metabolism responsible for Lesch-Nyhan Disease (LND) and its partial phenotypes, HPRT-related hyperuricemia with neurologic dysfunction (HRND) and hyperuricemia alone. We report here the recognition of six Argentine patients, two with LND and four with HRND. All patients presented elevated excretion of uric acid, hypoxanthine, and xanthine and decreased HPRT enzyme activities <1 nmol/h/mg Hb. The molecular analysis demonstrated in the two LND patients a novel inherited transition mutation, c.203T $>$ C (L68P), in one subject and a germline transition mutation, c.209G $>$ A (G70E), in the other. In the HRND patients a novel transversion mutation, c.584 A $>$ C (Y195S), was found in three related patients and an inherited transition mutation, c.143G $>$ A (R48H), in the fourth subject.*

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Keywords HPRT; hypoxanthine-guanine phosphoribosyltransferase deficiency; Lesch-Nyhan disease; Lesch-Nyhan variant; *HPRT* mutation

INTRODUCTION

Hypoxanthine-guanine phosphoribosyltransferase (HPRT; EC 2.4.2.8) deficiency (MIM 308000) is an X-linked genetic defect of purine metabolism associated with three main clinical phenotypes: fully developed Lesch-Nyhan disease (LND) presenting severe neurologic dysfunction (compulsive self-injury biting, motor disability, gout, and renal symptoms); the intermediate phenotype designed HPRT-related hyperuricemia with neurologic dysfunction (HRND); and hyperuricemia alone, associated with marked overproduction of uric acid, with resultant hyperuricemia, nephrolithiasis, and gout.[1]

The HPRT enzyme is encoded by a single gene that has nine exons spanning approximately 45 kb at Xq26–27.[1] Currently, more than 300 different mutations throughout the *HPRT* gene have been reported,[2] with some sites appearing to represent relative mutational hot spots.[3]

Here, we report biochemical and enzymatic findings, and mutation analysis of six Argentine patients with HPRT deficiency.

PATIENTS AND METHODS

The cases were grouped into two of the three categories described above: LND (n = 2) and HRND (n = 4). The clinical evaluation in the LND group (patients 1 and 2) revealed generalized dystonia superimposed on hypotonia, ballism, self-injury behavior, and dysarthria. The neurological involvement in 2 patients (4 and 5) of HRND group included minor cognitive and motor anomalies, and the other cases (3 and 6) showed significant cognitive impairment, minor motor clumsiness and mildly dysarthria.

The determination of purine metabolites (urine, plasma) and HPRT enzymatic assay (erythrocyte lysates) were performed by HPLC methods according to Simmonds et al.[4] The molecular analysis of the *HPRT* gene mutations included amplification of the entire coding region of the *HPRT* mRNA by rt-PCR,[5] and genomic multiplex PCR, followed by direct sequencing of PCR products.[6]

RESULTS AND DISCUSSION

This study represents the first serial recognition of HPRT deficiency with classical and neurological phenotypes in Argentina.

TABLE 1 Urinary purine metabolites and erythrocyte HPRT activities in Argentine subjects with HPRT deficiency

Patient	Phenotype	Plasma UA (mg/dl)	Urine Metabolites (μmol/mmol creatinine)			HPRT activity (nmol/h/mg Hb)
			UA	Hyp	Xan	
1	LND	11.0	2300	480	200	<1
2	LND	6.1	1900	405	160	<1
3	HRND	11.0	1700	530	190	<1
4	HRND	14.6	NE	NE	NE	<1
5	HRND	13.8	1800	380	150	<1
6	HRND	9.0	NE	NE	NE	<1
Controls		3.4–7	<1300	<45	<43	83–150

UA, uric acid; Hyp, hypoxanthine; Xan, xanthine. NE, not evaluated before allopurinol treatment.

The diagnosis of HPRT deficiency in the six patients were established with the determination of purine metabolites and HPRT enzyme activity (Table 1). All the patients experienced severe HPRT deficiency in the lysate assay employed. It is known that the enzyme activity assayed in erythrocyte lysates does not correlate with the clinical phenotype; although the enzymatic HPRT assays in live cells might detect significant residual activity with a good clinical correlation.[1]

Four different mutations were identified in the patients, two of these were associated with LND phenotype and two with HRND phenotype; all of them were missense mutations (Table 2).

With respect to the mutational analysis of *HPRT* gene in LND group, patient 1 presents a novel transition mutation: c.203T>C (L68P). The patient's mother is a carrier with both the wild type T and mutant C at nucleotide 203. The position of this change is the same as a previously reported transversion mutation c.203T>G (L68R) that also was associated with the LND phenotype.[3] Patient 2 displays a missense transition mutation c.209G>A (G70E) that has been reported in three other families.[3] His mother shows only the wild type G at nucleotide 209. Therefore, this mutation qualifies as a hotspot and is clearly a de novo germinal event. With regard to HRND group, patients 3, 4, and 5 show the same novel

TABLE 2 *HPRT* mutations identified in Argentine patients

Patient	Family	Mutation	Exon	Codon	Result
1	1	c.203T>C	3	68	leu>pro
2	2	c.209G>A	3	70	gly>glu
3	3	c.584A>C	8	195	tyr>ser
4	3	c.584A>C	8	195	tyr>ser
5	3	c.584A>C	8	195	tyr>ser
6	4	c.143G>A	3	48	arg>his

transversion mutation in *HPRT* c.584A>C (Y195S).[5] Patients 3 and 4 are relatives. We could prove the suspected connection between this family and patient 5. The position of this mutation is the same as previously reported transition mutation c.584A>G (Y195C) associated with the less severe phenotype of HPRT deficiency.[7] Patient 6 presents a transition mutation, c.143G>A(R48H), that has been reported in several other "variant" cases.[3]

Although mutation analysis does not provide precise information for predicting disease severity, it offers a valuable tool for diagnostic confirmation and for the identification of female carriers and new cases in an affected family.

REFERENCES

1. Jinnah, H.A.; Friedman, T. Lesch-Nyhan disease and its variants. In *The Metabolic and Molecular Bases of Inherited Disease,* 8th ed.; Scriver, C.R., Beaudet, A.L., Sly, W.S., Valle, D., eds. McGraw-Hill, New York, 2001. pp. 2537–2570.
2. Jinnah, H.A.; Harris, J.C.; Nyhan, W.L.; O'Neill, J.P. The spectrum of mutations causing HPRT deficiency: An update. *Nucleosides, Nucleotides Nucleic Acids* **2004**, 23, 153–1160.
3. Jinnah, H.A.; De Gregorio, L.; Harris, J.C.; Nyhan, W.L.; O'Neill, J.P. The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases. *Mutat. Res.* **2000**, 463, 309–326.
4. Simmonds, H.A.; Duley, J.A.; Davies, P.M. Analysis of purines and pyrimidines in blood, urine, and other physiological fluids. In *Techniques in Diagnostic Human Biochemical Genetics: A Laboratory Manual*; ED. Hommes, F.A., Wiley-Liss, New York, 1991, 397–424.
5. Laróvere, L.E.; Romero, N.; Fairbanks, L.D.; Conde, C.; Guelbert, N.; Rosa, A.L.; Dodelson de Kremer, R. A novel missense mutation, 584A>C (S195Y), in two unrelated Argentine patients with hypoxanthine-guanine phosphoribosyltransferase deficiency, neurological variant. *Mol. Genet. Metab.* **2004**, 81(4), 352–354.
6. Gibbs, R.A.; Nguyen, P.N.; Edwards, A.; Civitello, A.B.; Caskey, C.T. Multiplex DNA deletion detection and exon sequencing of the hypoxanthine phosphoribosyltransferase gene in Lesch-Nyhan families. *Genomics* **1990**, 7, 235–244.
7. 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(3), 195–120.