Journal of Inborn Errors
of Metabolism & Screening
2021, Volume 9: e20200027
DOI: https://doi.org/10.1590/2326-4594-JIEMS-2020-0027

Lesch–Nyhan Disease and Its Variants: Phenotypic and Mutation Spectrum of Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency in Argentine Patients

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Abstract

Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is a disorder of purine metabolism responsible for Lesch-Nyhan Disease (LND) and its variants, HPRT-related hyperuricemia with neurologic dysfunction (HND) and HPRT-related hyperuricemia (HRH). The objective of this study was to characterize a cohort of Argentine patients with HPRT deficiency diagnosed in a single center. Results: Twenty nine patients were studied, including 12 LND,15 HND and 2 HRH. The average onset age was 0.64 years for LND with motor delay as the main manifestation, 8.84 years for HND and 2.5 years for HRH; nephrological manifestations predominated as presenting features in these variants. The average diagnosis age was 3.58 years for LND, 17.21 years for HND and 2.5 years for HRH. Clinical heterogeneity was more evident in HND, even in members of the same family. All patients presented hyperuricemia and no detectable HPRT activity in erythrocyte lysate. The molecular study allowed to identify 9 different mutations in *HPRT1* gene from 24 patients (11 independent pedigrees) and to establish genotype-phenotype correlation. In conclusion, this study describes the genotypic/phenotypic spectrum of HPRT deficiency in Argentine patients and highlights the need to increase awareness about the suspicion of these diseases, especially the LND variants with high clinical heterogeneity.

Keywords

Hypoxanthine-guanine phosphoribosyltransferase deficiency, hyperuricemia, Lesch-Nyhan disease, Lesch-Nyhan variant, HPRT1 mutation.

Introduction

Hypoxanthine-guanine phosphoribosyltransferase (HPRT; EC 2.4.2.8) deficiency (MIM 308000) is an X-linked genetic defect of the purine salvage pathway whereby purine bases are recycled into nucleotides[1,2]. The HPRT enzyme catalyzes the transfer of the 5-phosphoribosyl group from 5-phosphoribosyl-1-pyrophosphate (PRPP) to a purine base hypoxanthine or guanine to form IMP or GMP, respectively. The metabolic consequence of HPRT deficiency is an increase of de novo purines synthesis, which leads to increased production of uric acid, causing a variety of renal and joint symptoms. HPRT deficiency causes also an increased in the concentration of hypoxanthine, which is not reused, and contributes to uric acid increases[2,3].

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Received November 30, 2020, and in revised form February 02, 2021. Accepted for publication February 09, 2021.

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HPRT deficiency involves a large spectrum of neurological and behavioural abnormalities. Depending on the degree of the enzyme deficiency three main clinical phenotypes have been described: fully developed Lesch-Nyhan disease (LND) presenting severe neurologic dysfunction (self-injury, motor disability, gout, and renal problems); the intermediate phenotype designed HPRT-related hyperuricemia with neurologic dysfunction (HND); and HPRT-related hyperuricemia (HRH), associated with marked overproduction of uric acid, with resultant hyperuricemia, nephrolithiasis, and gout[2]. Affected individuals with the classical or variant forms show excessive production of uric acid that increases the risk for renal stones, renal failure, gouty arthritis, and tophi. Since the disease is inherited in an X-linked recessive manner, the most cases are males; however, several manifesting females have been reported[4].

The HPRT enzyme is encoded by a single gene (*HPRT1*) that has nine exons spanning approximately 45 kb at Xq26–27[5]. More than 600 different disease-causing gene variants have been reported for the *HPRT1* gene (www.lesch-nyhan.org). Spread through nearly the whole gene are missense variants, nonsense variants, splicing variants, small and large coding and non-coding deletions or insertions, partial duplications, non-coding regulatory variants, and more complex changes[4].

The mechanism of neurological and behavioural features of the disease is not clear, although the role of basal ganglia circuits and dopaminergic system have been demonstrated to be impaired[6–8].

Treatment of HPRT deficiency comprises pharmacological therapy of hyperuricemia with administration of allopurinol for renal failure prevention. In addition, the treatment for LNS includes comprehensive medical management, dental management, physical therapy, behavioural, and psychiatric interventions. Behaviour and psychiatry management targets self-injury through the use of restraints, behavioural management, psychopharmacologic management, and deep brain stimulation[9].

There are a few population studies that allow the prevalence of LND to be estimated:[3,10–16] which is approximately 1:380,000[17]. Furthermore, due to the clinical heterogeneity of the patients (especially in the LND variants), the number of affected individuals is not well studied and may be underestimated. Patients with the classical phenotype (LND) rarely survive beyond the third decade; however, lifespan may be normal for Lesch–Nyhan variants without severe renal involvement[9].

The present study describes a cohort of 29 Argentine patients with HPRT deficiency, including both LND and its attenuated variants, diagnosed in a single referral center (CEMECO, Children's Hospital of Córdoba, Argentina).

Patients and Methods

We performed a retrospective, descriptive and comparative study in a cohort of Argentine patients with HPRT deficiency in CEMECO, Children's Hospital of the Santísima Trinidad de Córdoba, between 1996-2020. Informed consent was obtained from parents and, when possible, from patients.

This study included 29 Argentine male patients from 15 unrelated families who were diagnosed between 1996-2020. HPRT deficiency in probands was diagnosed on the basis of: a) suggestive clinical symptoms and signs; b) laboratory findings indicative of purine overproduction (serum uric acid levels and urine oxypurines; c) markedly reduced HPRT activity in haemolysates with simultaneously increased of adenine phosphoribosyltransferase (APRT) activity; and d) confirmed by *HPRT1* gene mutation.

The patients were classified according to previously established subgroups: LND, HND and HRD and based on the presence or absence of different signs/symptoms[2]. Some cases have been described in previous studies (detailed in Results and Discussion). The data were obtained retrospectively from medical records of consultations with paediatric specialists in hereditary metabolic diseases or by referring physicians.

Blood and urine samples were collected from patients with clinical suspicion of HPRT deficiency to perform a metabolite study, enzyme activity and investigation of the genetic defect. The determination of purine metabolites (urine) and HPRT enzymatic assay (erythrocyte lysates) were performed by HPLC methods according to Simmonds et al, 1991[18]. The molecular analysis of the HPRT gene mutations included amplification of the entire coding region of the HPRT mRNA by rt-PCR[19] and genomic multiplex PCR, followed by direct sequencing of PCR products[20,21].

The t-test for independent samples from the Infostat program was used for comparison of onset age and diagnosis age between the groups.

Results and Discussion

This study represents the serial recognition of HPRT deficiency with classical phenotype of LND and its variants in Argentina. A total of 29 male patients from 15 unrelated families were identified. Demographic data is showed in Table 1. The phenotypic distribution was 41.4% (12/29) patients with LND, 51.7% (15/29) with HND the intermediate phenotype, and 6.9% (2/29) with HRH variant. The phenotypic distribution in this study is influenced by several members coming from the same family. There is the possibility that a large family with 10 patients results in bias of distribution.

Disease onset, age at diagnosis and first/main manifestations

The average age of onset of symptoms (Table 1) was 0.64 years (range 0.33-1 year) for LND patients, whose main manifestation was motor delay, while the onset of self-injury was present in 100% of the cases at the average age of 4.22 years (range 2-8 years), the most frequent self-injurious behaviours were biting fingers, tongue or lips. Other early symptoms present in the LND patients were the appearance in 9/12 cases of involuntary movements (dystonia and other abnormal movements) and abnormalities resembling cerebral palsy in 5/12. LND patients who had nephrological manifestations such as kidney stones and uric acid crystals were those diagnosed after three years of age. The degree of cognitive impairment was not evaluated in this group of patients.

In patients classified as variants (LNV), the age of onset of symptoms was 8.84 years (range 0.1-28 years) for HND and 2.5 years (range 1-4 years) for HRH. Nephrological manifestations predominated as presenting symptoms in 60% (9/15) and 100% (2/2) in HND and HRH, respectively; followed by joint disease 33% (5/15) and motor retardation 26.7% (4/15) in HND and without these types of manifestations in HRH. Regarding the clinical outcome and the appearance of new symptoms, 93.3 % (14/15) HND patients presented different degrees of cognitive impairment (even in the same family), one patient was a newborn without data about cognitive abnormalities; 66.6% (10/15) HND and 50% (1/2) HRH had nephrological manifestations; joint disease was present in 66.6% (10/15) cases HND, all older than 13 years and with a delay in diagnosis. Comparing the groups of patients, there was a significant difference ($p < 0.005$) in the age of onset between LND and HND.

The average age of diagnosis in the groups was 3.58 years (range 0.5-10 years) for LND, 17.21 years (range 0.1-56 years) for HND and 2.5 years (range 1-4 years) for HRH. The diagnostic delay was significantly lower in LND than patients affected by HND ($p < 0.005$), according to previous reports;[3,23] this could be because the diagnosis of the classic form is more oriented due to self-injury symptoms.

Regarding family 13, it should be noted that these cases (n=10) have a different degree of kinship relationship with a common ancestor 5 generations ago (Figure 1). Some of them came to our center for consultation due to the appearance of different symptoms (Table 1) and only 2 did so prior to the appearance of clinical manifestations due to family history regarding the disease. The clinical heterogeneity observed in those affected in the family is very high, although all are classified as HND; the outcome and complications were strongly related to the age of diagnosis. The broad spectrum of clinical features in HND variant reported by Jinnah et al (2010)[22] indicates, in addition to the overproduction of uric acid, different degrees of varying degrees of motor, cognitive, or behavioural abnormalities.

Metabolites, enzymatic activity and genotype

All patients had hyperuricemia (Table 1) with a mean value of 11.86 mg/dl (range 7.7-17); the urine purine study performed in 21/29 patients (pooled data) showed an increase of uric acid (range 1400-2300 µmol/mmol creatinine; normal values> 1300), hypoxanthine (range 55-778 µmol /mmol creatinine; normal values> 45) and xanthine (range 23-200 µmol/mmol creatinine; normal values> 43); these metabolites are indicative of HPRT deficiency[18].

The HPRT enzyme assay in erythrocyte lysate was performed in all the entire cohort of patients, with no activity detected in any of these cases (Table 1); these results were not correlated with the different phenotypes in which the patients were grouped. These differences could be observed using tests on intact red

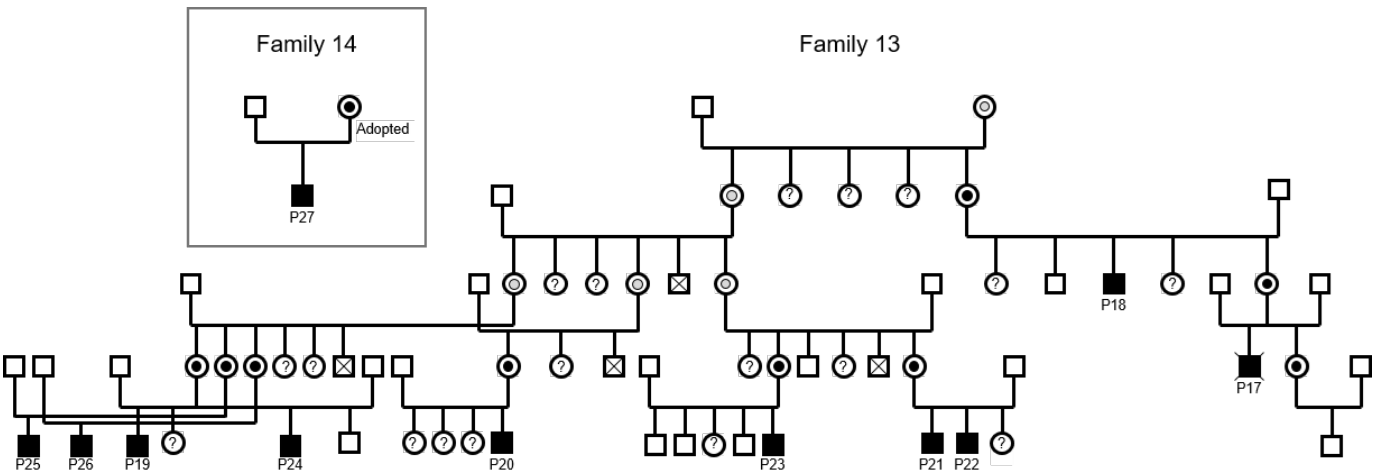

Figure 1. Genealogy of families 13 and 14 with HPRT deficiency, carriers of same HPRT1 mutation: c.584A>C (p.Y195S).

■, affected male; □, unaffected male; ⊙, carrier female; ◎, obligate carrier female; ?, status unknown; X, deceased subject. The code names are shown for the patients analysed in this study.

Table 1. HPRT deficiency in Argentine patients: age of onset / diagnosis, uric acid in blood, enzymatic activity, main features and treatment.

Case	Family	Age (diagnosis)	Blood UA[1] (diagnosis)	HPRT Activity[2]	Self-injury (onset)	Neurological dysfunction	Nephrological manifestations	Joint disease	Treatment
Lesch-Nyhan disease									
1	1	5 years	11.0 mg/dl	<1	x (5 years)	**Motor delay (6 months)** Dystonia superimposed on hypotonia	Recurrent renal stones	–	Allopurinol Risperidone Folate SAM
2	2	10 years	8.1 mg/dl	<1	x (6 years)	**Motor delay (8 months)** Dystonic and ballismic movements at 1 year Epilepsy	Recurrent renal stones	–	Allopurinol Carbamazepine Clonazepam Folate
3	3	9 years	9.2 mg/dl	<1	x (8 years)	**Motor delay (8 months)** Dystonia Generalized hypotonia with hyperreflexia	Uric acid crystals	–	Allopurinol Clonazepam
4	4	11 months	9.8 mg/dl	<1	-	**Spastic quadriplegia (10 months) Dystonia Axial hypotonia**	-	–	Allopurinol
5	5	4 years	7.7 mg/dl	<1	x (8 years)	**Motor delay (4 months)** Dystonia Choreoathetosis	Kidney stones	–	Allopurinol Risperidone
6	5	3 years	8.2 mg/dl	<1	x (3 years)	**Motor delay (7 months)** Dystonia Choreoathetosis Generalized hypotonia with hyperreflexia	Kidney stones	–	Allopurinol Clonazepam
7	6	nd	nd	<1	x	**Motor delay** Dystonia Choreoathetosis	Nd	nd	nd
8	7	1 year	8.0 mg/dl	<1	x	**Dystonic cerebral palsy**	–	–	nd
9	8	2 years	12.5 mg/dl	<1	x (2 years)	**Motor delay (5 months)** Spastic-dystonic tetraparesis Microcephaly	–	–	nd
10	9	2 years	nd	<1	x (2 years)	**Spastic quadriplegia**	–	–	nd
11	9	2 years	nd	<1	x (2 years)	**Spastic quadriplegia**	–	–	nd
12	10	6 months	8 mg/dl	<1	-	**Motor delay (5 months)**	–	–	nd

Table 1. Cont.

Case	Family	Age (diagnosis)	Blood UA[1] (diagnosis)	HPRT Activity[2]	Self-injury (onset)	Neurological dysfunction	Nephrological manifestations	Joint disease	Treatment
HPRT-related hyperuricemia with neurologic dysfunction									
13	11	9 years	9.0 mg/dl	<1	–	**Motor delay (<1 year)** Slightly slow gait Speech delay, slightly slow and indistinct Hypomimia Brisk leg reflexes, ankle clonus Significant cognitive impairment	–	–	Allopurinol
14	11	56 years	with allopurinol treatment	<1	–	Moderate dystonic dysarthria Slightly slow gait Brisk leg reflexes, peripheral neuropathy Mild cognitive impairment	Nephrolitiasis Renal insufficiency	**Tophus on knee (28 years)**	Allopurinol Glibencamide
15	11	37 years	with allopurinol treatment	<1	–	**Motor delay (1.5 year)** Slightly slow gait Moderate dystonic dysarthria Slow/clumsy hand movements; brisk arm and leg reflexes, neuropathy Mild cognitive impairment	Gout Nephrolithiasis	Recurrent tophi Joint deformities of the hands and feet	Allopurinol
16	12	20 years	11.5 mg/dl	<1	–	**Psychomotor development retardation (<1 year)** Slightly indistinct speech Normal gait but can´t edge-walking Slow/clumsy hand movements Brisk arm and leg reflexes, ankle clonus Severe cognitive impairment	Bilateral renal lithiasis	Asymmetric polyarthritis of hands, both knees, ankles and feet	Allopurinol
17	13	14 years	16.0 mg/dl	<1	–	**Motor delay (2 years)** Hypophonic speech Normal gait Slightly slowed hand movements Marked cognitive impairment	Renal insufficiency Nephrolitiasis	Tophi Joint deformities of the hands, feet, elbows	Allopurinol Enapril
18	13	19 years	14.6 mg/dl	<1	–	Normal speech and gait Minor overflow posturing of one hand Mild cognitive impairment	**Gout (19 years)**	Tophi	Allopurinol
19	13	15 years	13.8 mg/dl	<1	–	Mild cognitive impairment Speech and gait: nd	Renal insufficiency Nephrolitiasis	**Uric acid crystal in finger (14 years)** Tophi	Allopurinol
20	13	13 years	**9.6 mg/dl**	<1	–	**Moderate cognitive impairment** Speech and gait: nd	–	Tophi	Allopurinol

Table 1. Cont.

Case	Family	Age (diagnosis)	Blood UA[1] (diagnosis)	HPRT Activity[2]	Self-injury (onset)	Neurological dysfunction	Nephrological manifestations	Joint disease	Treatment
21	13	3 years	14.4 mg/dl	<1	–	Mild cognitive impairment Speech and gait: nd	**Recurrent urinary infections (3 months)** **Nephrocalcinosis (10 months)**	–	Allopurinol Iron supplement Folic acid Sodium bicarbonate
22	13	2 months[3]	**8.5 mg/dl**	<1	–	Mild cognitive impairment Speech and gait: nd	–	–	Allopurinol
23	13	7 days[3]	**17.0 mg/dl**	<1	–	nd	–	–	Allopurinol
24	13	21 years	19.0 mg/dl	<1	–	Moderate mental retardation Speech and gait: nd	**Polycystic kidney disease (1 year)** Chronic renal failure Kidney transplant	Tophi	Allopurinol
25	13	20 years	13.0 mg/dl	<1	–	Moderate mental retardation Speech and gait: nd	**Kidney stones**	**Inflammation of the toe**	Allopurinol Colchicine
26	13	24 years	14.0 mg/dl	<1	–	Moderate mental retardation Speech and gait: nd	nd	**Tophus on ear** **Knee inflammation**	Colchicine
27	14	9 years	17.3 mg/dl	<1	–	Mild cognitive impairment Speech and gait: nd	**Acute renal failure (9 years)**	–	Allopurinol
HPRT-related hyperuricemia									
28	15	4 years	15.6 mg/dl	<1	–	–	**Acute renal failure (4 years)**	–	Allopurinol
29	15	1 year[3]	**9.0 mg/dl**	<1	–	–	–	–	Allopurinol

[1]Blood uric acid, normal range 3.4–7 mg/dl; [2]HPRT activity in erythrocyte lysate, normal range 80–130 nmol/h/mg Hb; [3]Diagnosis prior to the appearance of clinical manifestations due to family history. In bold letters, the presenting problem and age of onset; nd, no data. Neurological features, in special speech, gait and other motor abnormalities were evaluated in six HND patients.

blood cells that detect a significant residual activity due to the fact that the cell structure remains intact, which does not occur in lysed cells[2,3]. Parallel to the HPRT activity, APRT enzyme assay was also performed, which was found to be elevated in all the cases (data not shown) as a compensatory mechanism in the increased purine nucleotide synthesis via the salvage pathway and increased availability of PRPP[24].

Nine different genetic variants in *HPRT1* gene were identified from 24 patients with 11 independent pedigrees, all these changes were descripted previously (Table 2). Molecular analyses of 5 patients have not been performed. Variants were distributed throughout the gene, and included missense variants (44.4%, 4/9), splice site variants (33.3%, 3/9), a large deletion (11.1%, 1/9), and a duplication (11.1%, 1/9).

The molecular study was carried out on patients, their mothers and other female relatives (data not shown); molecular diagnosis in HPRT-deficient patients allows characterize the genetic variants and perform the detection of carrier women. Only patient 2 had a de novo variant (c.209G>A, G70E), that has been reported in several cases; therefore, this variant qualifies as a hotspot and is clearly a de novo germinal event[25]. It should be noted that patient 16 (family 12) had the same variant (c.143G>A p.R48H) as that identified in family 11 with a similar phenotype[25,26], without knowing any relationship between them; and the case 27 (family 14) had the same variant (c.584A>C, p.Y195S) as members of family 13 (Figure 1), no relationship could be established since the genealogical data of family 14 are not known.

In this family, with a large number of identified cases and the same genetic variant, there is great clinical heterogeneity as shown in Table 1. Yamada et al (2014) also reported phenotypic variability in 3 cases of affected siblings with the same *HPRT1* mutation[28].

A comparison of local genetic variants findings with a review article by Fu and colleagues[4] and the web site http://lesch-nyhan.org/en/research/mutations-database, reveals that the majority of recurrent variants produced a similar phenotype even in unrelated patients. However, there were a few exceptions where the same variant caused discordant phenotypes. Respect to our data, the missense mutation c.143G>A has 12 reports associated with LNV, HND and HRH; c.209G>A with 8 reports in LND; and c.584A>C has only been described in our series of HND patients and it is the most frequent variant in our report (11/29). The only variant with discordant clinical phenotype was c.203T> C, described in 2 LND and 1 HND. The splicing variant c.485+5G>A was reported twice in LNV, c.532+1G>A with 4 reports in LND and c.609+6T>G described in 2 reports of LND. The splicing variants that result in exon exclusions are mostly associated with LND, however c.485+5G>A with exon 6 exclusion showed a mild phenotype. The exons 4–6 deletion with 3 reports was associated like all large deletions with a severe phenotype (LND). The 212dupG duplication was considered a hot spot for variants, it has arisen multiple times in unrelated patients (n= 15) with LND; this variant produces a frame shift and premature stop.

Another analysis is focused on the missense variants and their location in the *HPRT1* gene, in which conserved regions associated with the active site of the enzyme were recognized[4]; the four variants identified in our patients occurred in 3 of the 5 recognized "hot clusters". Furthermore, the c.203T> C (p.L68P) and c.209G> A (p.G70E) mutations identified in patients with LND are located in highly conserved amino acids of the HGprt protein with importance for the active site[4].

Treatment and other remarks

Although this work is not focused on the treatment and outcomes of patients, it is important to remark that allopurinol is widely used to treat renal and joint disease, this medication is also used by our patients for this purpose (Table 1). The management or treatment of neurological involvement and behavioural abnormalities varies. However, some therapies were associated to an improvement of at least some manifestations of the disease. The therapies include benzodiazepines, anxiolytics/hypnotics, antidepressants, antipsychotics and muscle relaxants[3]. One of the cohort used S-adenosylmethionine without showing noticeable changes in mood and behaviour improvement. There are no data on the evolution of most of the patients, according to records of those who are followed up in our hospital, 3 have died (2 LND, 1 HND), 2 HND are on dialysis and 1 was HND had a kidney transplant.

Conclusions

This report describes the main clinical features, and biochemical and molecular genetic findings in a cohort of 29 Argentine patients with HPRT deficiency diagnosed in a single center. According to the clinical presentation the patients were classified as LND, HND and HRH. The result of HPRT enzyme activity in erythrocyte lysates could not be correlated with the different phenotypes. However, the identification of mutations allowed genotype-phenotype correlation in most patients and the detection of carrier women.

The main limitation of this study was the data collection method; the clinical characteristics of the patient series were retrospectively analysed with missing data in some cases and based on evaluations made by different physicians. The clinical data are of great importance for the classification and its follow-up, it is necessary to carry out a complete clinical evaluation including renal and joint manifestations, neurological dysfunction and behavioural disorders.

It is important to raise awareness about this disease in the classic form of LND and its variants. Males with developmental delay, neurological and behavioural problems, and hyperuricemia could be affected by HPRT deficiency with severe phenotype; the association of juvenile gout, hyperuricemia and elevated urinary uric acid excretion with or without neurological

Table 2. *HPRT1* gene mutations with corresponding protein level alterations/consequences, phenotypic classification of the 24 patients whose genotypic characterization was available and previous descriptions.

Case	Family	Phenotype	Mutation	Result	Remark	Prior reports
13	11	HND	c.143G>A	p.R48H		Laróvere et al., 2007 [25] Jinnah et al., 2010 [22]
14	11	HND	c.143G>A	p.R48H		Laróvere et al., 2007 [25]
15	11	HND	c.143G>A	p.R48H		Laróvere et al., 2007 [25]
16	12	HND	c.143G>A	p.R48H		Sapag et al., 2012 [26]
1	1	LND	c.203T>C	p.L68P		Jinnah et al., 2006 [27] Laróvere el al., 2007 [25]
2	2	LND	c.209G>A	p.G70E	*de novo*	Jinnah et al., 2006 [27] Laróvere et al., 2007 [25]
3	3	LND	212dupG	Frame shift in E3		Fu et al., 2014 [4]
28	15	HRH	c.485+5G>A	Exon 6 excluded		Fu et al., 2014 [4]
29	15	HRH	c.485+5G>A	Exon 6 excluded		Fu et al., 2014 [4]
4	4	LND	c.532+1G>A	Exon 7 excluded		Fu et al., 2014 [4]
17	13	HND	c.584A>C	p.Y195S		Laróvere et al., 2004 [19] Laróvere et al., 2007 [25] Jinnah et al., 2010 [22]
18	13	HND	c.584A>C	p.Y195S		Laróvere et al., 2004 [19] Laróvere et al., 2007 [25] Jinnah et al., 2010 [22]
19	13	HND	c.584A>C	p.Y195S		Laróvere et al., 2004 [19] Laróvere et al., 2007 [25] Jinnah et al., 2010 [22]
20	13	HND	c.584A>C	p.Y195S		Fu et al., 2014 [4]
21	13	HND	c.584A>C	p.Y195S		Fu et al., 2014 [4]
22	13	HND	c.584A>C	p.Y195S	New case	
23	13	HND	c.584A>C	p.Y195S	New case	
24	13	HND	c.584A>C	p.Y195S	New case	
25	13	HND	c.584A>C	p.Y195S	New case	
26	13	HND	c.584A>C	p.Y195S	New case	
27	14	HND	c.584A>C	p.Y195S	No knowledge of family history (from mother)	Fu et al., 2014 [4]
5	5	LND	c.609+6T>G	E8 excluded		Fu et al., 2014 [4]
6	5	LND	c.609+6T>G	E8 excluded		Fu et al., 2014 [4]
7	6	LND	Exons 4–6 deleted	3 exons deleted		Fu et al., 2014 [4]

compromise suggests an attenuated variant. An early diagnosis allows establishing treatment with allopurinol, thus avoiding the development of gouty manifestations and renal failure.

Acknowledgements

The authors gratefully acknowledge Dr. Patrick O'Neill for verifying the mutations in some patients. They also thank colleagues who referred cases.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by grants from Secretaría de Ciencia y Tecnología, Universidad Nacional de Córdoba and Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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