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Lesch-Nyhan disease in two families from Chiloé Island with mutations in the *HPRT1* gene

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ABSTRACT

Lesch-Nyhan disease (LND) is a rare X-linked inherited neuro-genetic disorder of purine metabolism in which the enzyme, hypoxanthine-guanine phosphoribosyltransferase (HGprt) is defective. The authors report two independent point mutations leading to splicing errors: IVS 2 +1G>A, c.134 +1G>A, and IVS 3 +1G>A, c.318 +1G>A in the hypoxanthine-phosphoribosyltransferase1 (*HPRT1*) gene which result in exclusion of exon 2 and exon 3 respectively, in the HGprt enzyme protein from different members of two Chiloé Island families. Molecular analysis has revealed the heterogeneity of genetic mutation of the *HPRT1* gene responsible for the HGprt deficiency. It allows fast, accurate carrier detection and genetic counseling.

Introduction

Lesch-Nyhan disease (LND) is a rare X-linked inherited neurogenetic disorder of purine metabolism caused by deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGprt, EC. 2.4.2.8; MIM 300800).[1,2] Complete or severe deficiency of HGprt activity leads to LND (MIM 300322).[1] Classical features of LND include hyperuricemia and its sequelae (gout, nephrolithiasis, and tophi), motor disability (dystonia, chorea, and spasticity), intellectual impairment, and self-injurious behavior. Partial deficiency of HGprt enzyme activity (MIM 300323) is characterized by consequences of overproduction of uric acid and variable spectrum of neurological manifestations, without the manifestations of self-injurious behavior: Lesch-Nyhan variants, LNVs.[3,4] The mildest variants have isolated overproduction of uric acid. These patients do not have clinically overt neurological

or behavioral abnormalities, and most often are described as having HGprt-related hyperuricemia (HRH). In between the two extreme phenotypes of LND and HRH is a spectrum of phenotypes with varying degrees of neurological and behavioral abnormalities, designated HGprt-related neurological dysfunction (HND). Patients with HND suffer from overproduction of uric acid along with some neurological or behavioral difficulties, but they do not exhibit the self-injurious behaviors seen in classic LND. The etiology involves a mutation of the hypoxanthine phosphoribosyltransferase 1 (*HPRT1*) gene, which is on the long arm of the X chromosome (Xq26.1), which contains nine exons and eight introns.[3] The *HPRT1* gene is on the X-chromosome, so males are affected and females in families at risk may be carriers of the mutation. To date, more than 600 heterogeneous mutations in the *HPRT1* gene have been reported.[4] In this study, we report two independent point mutations leading to splicing errors: IVS 2 +1G>A, c.134 +1G>A, and IVS 3 +1G>A, c.318 +1G>A in the *HPRT1* gene which result in exclusion of exon 2 and exon 3, respectively, in the HGprt enzyme protein from members of two Chiloé Island families.

Materials and methods

Patients

Chiloé Island is the largest island in the archipelago off coast of Chile (GPS coordinates: 42°40′36″S 73°59′36″W). Both families described in this report derive from the indigenous peoples known anthropologically as the "huilliches," or "people of the south," to distinguish them from the more distantly related to the "mapuche" people of continental south-central Chile and southwestern Argentina.

This study includes members of two Chiloé Island families # 1 and # 2.

Family # 1: This family consists of three members: Mother, 41 years old (**1**) and two affected male patients of 19 years old (**2**) and 15 years old (**3**). Both of them had complete deficiency of HGprt activity in erythrocytes, but intellectual disability was mild to moderate and there was no self-injurious behavior. Both affected brothers also had pyramidal and extrapyramidal symptoms, with moderate difficult in speech, and of the hands use. They were wheelchair bound and classified as HND (Table 1).

Family # 2: This family consists of three members: Mother, 38 years old (**4**), one daughter, 20 years old (**5**), and one affected male patient of 13 years old (**6**). This male patient (**6**) had complete deficiency of HGprt activity. He had a history of an orange-colored urine during the first year of life, high serum concentration of uric acid, severe intellectual disability, and self-injurious behavior. He also had pyramidal and extrapyramidal symptoms, with severe difficult in speech, and of the hands use. He was wheelchair bound and classified as LND (Table 1).

Dried blood spots of whole peripheral blood were obtained from all members (**1–6**) of these two families.

Table 1. Point mutations leading to splicing errors in the HPRT1 gene.

Patient[a]	Age	Genotype	Results	HGprt activity[b]	APRT activity[c]	Clinical phenotype	Clinical symptoms
1	41	IVS2+1G>A E2	Excluded	14.76	1.00	Normal	Carrier (Het-erozygous)
2	19	IVS2+1G>A E2	Excluded	− 0.16	5.45	−Mild to moderate intellectual disability -without self-injurious behavior	HND
3	15	IVS2+1G>A E2	Excluded	− 0.13	6.51	−Mild to moderate intellectual disability -without self-injurious behavior	HND
4	38	Normal	Normal	15.14	2.98	Normal	Normal
5	20	Normal	Normal	12.11	3.27	Normal	Normal
6	13	IVS3+1G>A E3	Excluded	− 0.23	5.57	−Severe intellectual disability -with self-injurious behavior	LND

[a]Patients # 1-3 and # 4-6 are the different members of the families # 1 and # 2, respectively.
[b]HGprt activity is the mean of the three determinations and is expressed in nmol/hour/blood spot. The normal range values are between 5.27 and 14.87 mmol/h/blood spot.
[c]APRT activity is the mean of the three determinations and is expressed in nmol/h/blood spot. The normal range values are between 1.32 and 3.22 nmol/h/blood spot.

Enzyme assay, isolation of genomic DNA, and amplification

Assay of the HGprt enzyme and isolation of genomic DNA from dried blood spots of whole peripheral blood following amplification by PCR using specific primers were performed as previously described.[5]

Results

Sequencing analysis of the nine exons and flanking intronic sequences of the human *HPRT1* gene from the DNA genomic was performed on members of families # 1 and # 2. This revealed a G → A substitution at the exon-2/intron-2 junction: IVS2 +1G>A, c.134 +1G>A from the two affected male patients (**2**) and (**3**) of family # 1 (Figure 1b). This IVS2 +1G>A splice site mutation could presumably result in abnormal splicing of HPRT1-mRNA and lead to a complete deletion of exon 2 responsible for HGprt deficiency. This splice site mutation leading to HND was previously identified.[6] The mother (**1**) was heterozygous for the IVS2 +1G>A splice site mutation (Figure 1c). The affected male patient (**6**) of the family # 2, had a G>A substitution at the exon-3/intron-3 junction: IVS3 +1G>A, c.318 +1G>A (Figure 1e). This IVS3 +1G>A splice site mutation could presumably result in abnormal splicing of HPRT1-mRNA and lead to a complete deletion of exon 3, responsible for HGprt deficiency. This splice site mutation is a new one. The mother (**4**) and the sister (**5**) of this family # 2 were not affected by this mutation (Figure 1f). They are not carriers. This IVS3 + 1G>A splice site mutation of family # 2 appears to be a new genetic mutation. However, we cannot rule out the possibility of germline
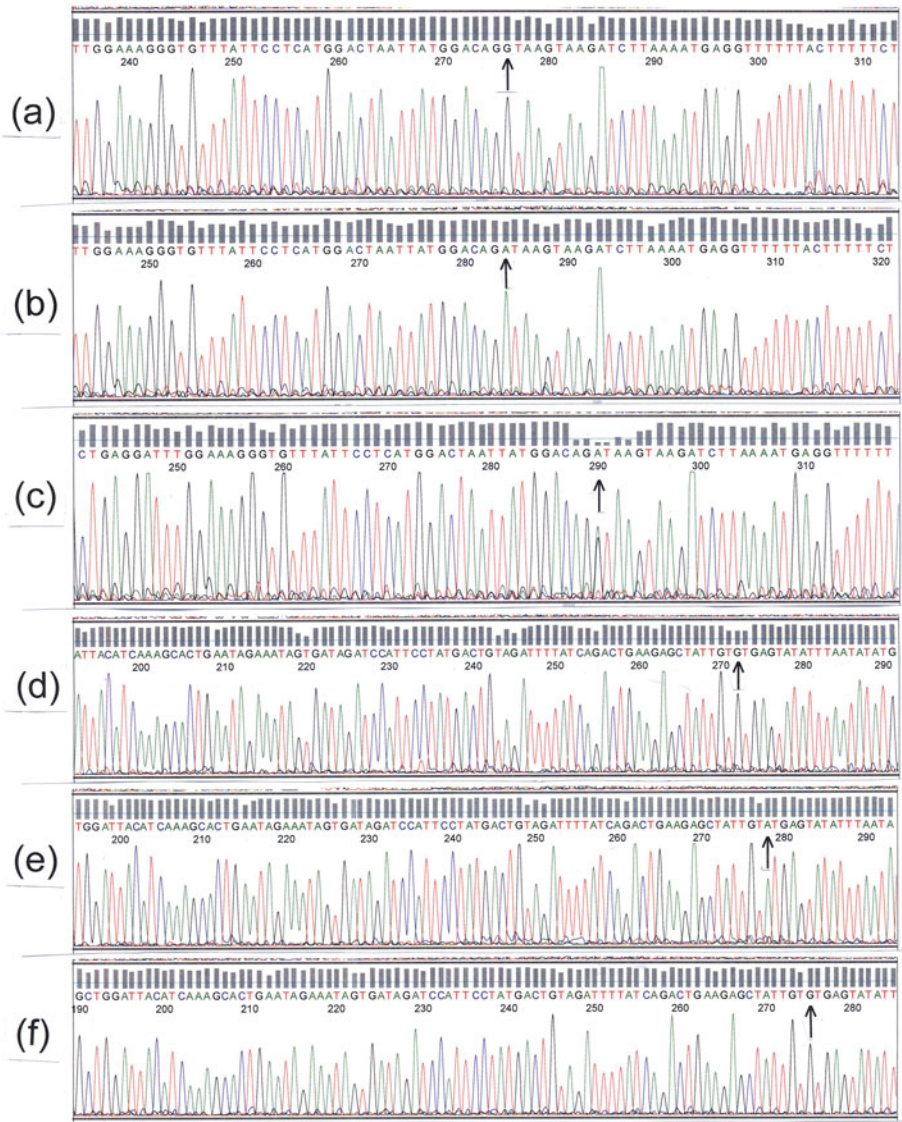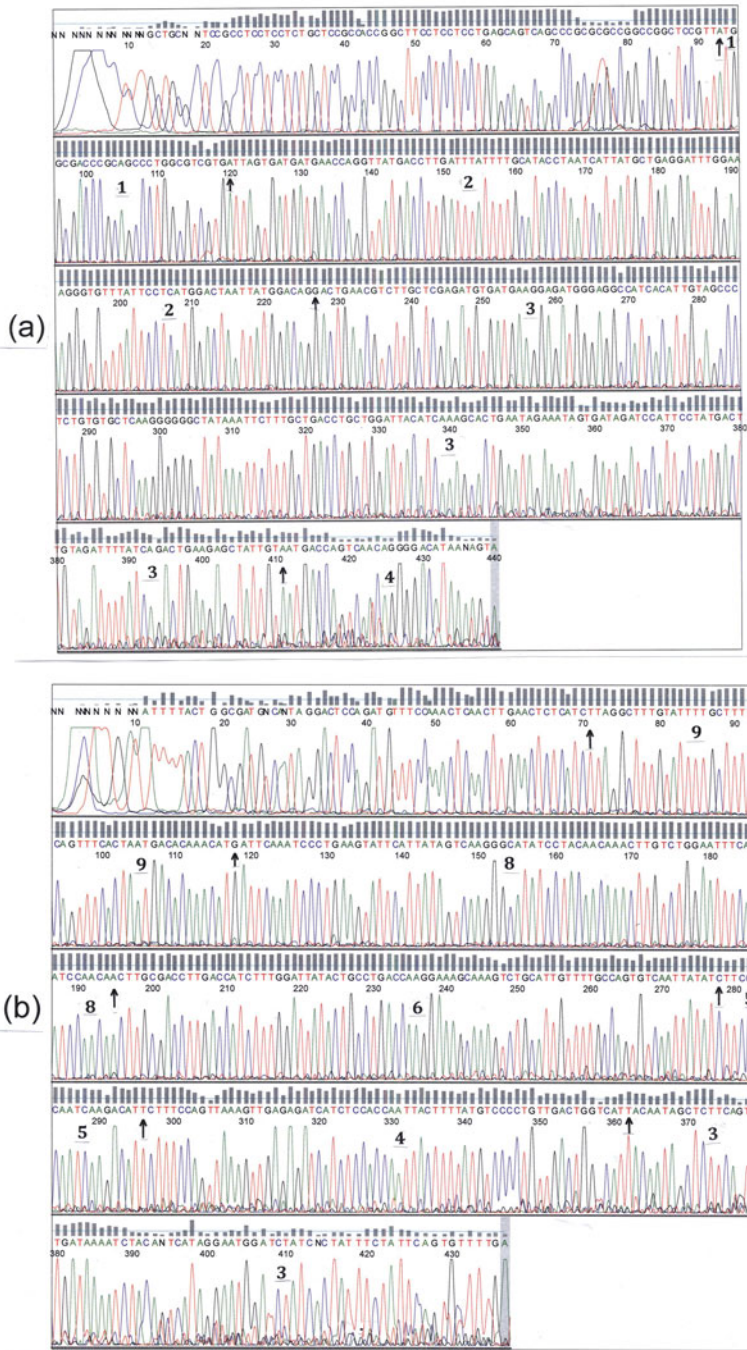
Figure 1. Automated direct DNA sequence analysis of PCR-amplified HPRT1 genomic exon/intron fragments of exons 2 (381 bp) and exon 3 (558 bp) from the normal subject (control), and different members of the two Chiloé Island families # 1 and # 2, respectively. Based on GenBank M26434, the DNA sequence read from left to right (5→3′) showed: Family # 1, the presence of the nucleotide G at bp 276: G_{276} at the exon-2/intron-2 of the chromatogram (↑) obtained from the normal subject, control (a); an A_{284} to G substitution at the exon-2/intron-2 junction of the chromatogram (↑) obtained from the affected male patients (**2**) and (**3**) (b); and a heterozygous A_{290} to G substitution at the exon-2/intron-2 junction of the chromatogram (↑) obtained from the mother (**1**) (c). This corresponds to an IVS 2 + 1G>A, c.134 +1G>A splice mutation; Family # 2, the presence of the nucleotide G at bp 272: G_{272} at the exon-3/intron-3 of the chromatogram (↑) from the normal subject, control (d); an A_{278} to G substitution at the exon-3/intron-3 junction of the chromatogram (↑) obtained from the affected male patient (**6**) (e). This corresponds to an IVS 3 +1G>A, c.318 +1G>A splice site mutation. The mother (**4**) and the sister (**5**) of this family # 2 were not affected by this IVS 3 +1G>A, c.318 + 1G>A splice site mutation: see G_{275} of the chromatogram (↑).

mosaic inheritance from the mother (**4**). By using the PCR coupled with direct sequencing, we also verified that theses mutations were not present in chromosomes from 100 control subjects. Consequently, these mutant alleles found from these patients were not polymorphic variants. The predicted consequence of the defective splicing of HPRT1-mRNA with a complete deletion of exon 2 and exon 3 resulted from the IVS2 +1G>A and IVS3 +1G>A splice site mutations respectively could not be verified since RNA for transcript analysis was not available. However, as an example, a chromatogram showing the complete deletion of exon 7 in HPRT1-mRNA, responsible for HGprt deficiency from the cultured fibroblasts of a LND affected male patient resulting from an IVS7 +1G>A, c.532 +1G>A splice site mutation[6,7] is presented in Figure 2b. The mutations found from these two families are summarized in Table 1.

Discussion

In this study, we report two independent point mutations leading to splicing errors: IVS 2 + 1G>A, c.134 +1G>A, and IVS 3 +1G>A, c.318 +1G>A in the *HPRT1* gene which result in exclusion of exon 2 and exon 3, respectively, in the HGprt enzyme protein from different members of two Chiloé Island families. The wild type of HGprt enzyme protein has 218 amino acid residues with four side chains A, B, C, and D. This enzyme exists as a dimer or tetramer in solution, depending on the ionic strength and pH, although the enzyme seems to form tetramer to exert its catalytic function.[8,9] The monomer of HGprt enzyme is composed of ten β-strands and six α-helices. The monomer is folded into a single-domain structure, which can be divided into subdomains, a core, and a small hood. The core region of the monomer consists of a parallel β-street of five β-strands between four α-helices. In the tetramer structure, the HGprt monomers are in contact with each other through three separate dimer interfaces. All three interfaces consist primarily of neutral hydrogen bonds with hydrophobic van der Walls interactions. The residues involved in dimer interactions may be important for the stability and enzymatic function of the protein. The largest dimer interface A-B involves regions around residues 23-28, 70-101, and 198-204; the A-C dimmer interface involves regions around residues 7-23 and 38-51; and finally the smallest interface, A-D, involves residues 84-90. An interesting observation is that 35% of the A-B interface residues are hydrophobic and 28% are charged (Glu, Asp, Arg, and Lys). The corresponding numbers for the A-C interface are 36 and 35%. The protein-protein interfaces are unusually hydrophilic, suggesting that each monomer may exist independently, although the enzyme seems to form tetramer to exert its catalytic function. For most of the substitutions, we could explain the resulting phenotype by possible structural changes in the dimer interactions, ligand-binding site, or protein hydrophobic core. In the present study, the splice site mutations: IVS2 +1G>A, c.134 +1G>A, and IVS3 +1G>A, c.318 +1G>A in the *HPRT1* gene which result in exclusion of exon 2 (35 amino acids, residues 10-44) and exon 3 (62 amino acids, residues 45-106), respectively, in the HGprt enzyme protein. As a result, the HGprt

Figure 2. Automated direct of the entire coding sequence (CDS) analysis of the HPRT1-mRNA obtained by RT-PCR coupled with direct sequencing from the cultured fibroblasts of complete HGprt deficiency of a LND affected male patient resulting from an IVS7 +1G>A, c.532 +1G>A splice site mutation.[6,7] The RT and PCR primers used to amplify the CDS sequence are available under request. Based on GenBank NM_000194, the CDS sequence read from left to right (5→3') (a) and right to left (5→3') (b), in which the numbers # 1-9 starting at A_{93} (↑) of initiation codon ATG for exon 1 (a) and ending at T_{71} (↑) of TTA, that is, Ochre termination codon TAA for exon 9 (b) are the 9 exons (↑) of the CDS sequence of HPRT1-mRNA, showed a complete deletion of exon 7 (b).

monomers produced by the patients (**2**), (**3**), and (**6**) had only 183 amino acids (exclusion of exon 2) and 156 amino acids (exclusion of exon 3), respectively, of the normal chain of 218 amino acids (data not shown). The A-B, A-C, and A-D dimer interfaces could not therefore be done efficiently from these truncated HGprt monomers and such a tetramer structure of the HGprt enzyme protein could not function.

LND historically has served as a model for exploring genotype-phenotype correlations.[4] The differences between LND and LNVs suggest that mutations resulting in null enzyme function are more likely to cause the more severe LND phenotype, while mutations that may permit some residual enzyme function more frequently underlie the milder LNVs phenotypes. Thus, deletions, insertions, and duplications are uncommon in LNVs because they most often result in a structurally abnormal protein with no functional activity. Nonsense mutations are similarly uncommon in LNVs because they result in premature termination of translation and absent enzyme activity. The missense mutations may be over-represented in LNVs because a single amino acid substitution is more likely to permit some residual enzyme function. Nevertheless, there are several exceptions where LNVs were associated with mutations predicted to cause complete loss of enzyme activity.[4] Although uncommon, these exceptions are important, because they could provide evidence against the concept that residual HGprt enzyme activity is the primary determinant of clinical severity. One explanation for exceptions is that erythrocyte activity of zero may be observed in patients in whom intact cell enzyme assays on cultured fibroblasts reveal appreciable activity.[10] In addition, p.R48H has repeatedly been associated with relatively mild clinical phenotypes with 20–39% residual activity in live fibroblast assays. The same mutation was reported to cause nondetectable residual activity in erythrocyte-based assays.[4] The live cell assays appear to yield results that are closer to those occurring in vivo. It is interesting to note herein that the IVS3 +1G>T, c.318 +1G>T and IVS3 +1G>C, c.318 +1G>C splice site mutations resulted in exclusion of exon 3 leading to LND were previously identified.[4,5] Furthermore, an IVS2 +1G>C, c.134 +1G>C splice site mutation resulted in exclusion of exon 2 leading to LND was also reported.[11,12]

In any case, a major unsolved question is how the loss of HGprt enzyme function affects the brain to cause the neurobehavioral syndrome in LND/LNVs. Histopathological studies of autopsy tissues from LND patients revealed no signs suggestive of a degenerative process in any brain region,[4,13] and found a larger reduction in white matter (26% reduction) than in grey matter (17% reduction) volumes.[14-16] However, neurochemical studies of LND brains collected at autopsy have revealed 60–80% loss of dopamine, a critically important neurotransmitter in the basal ganglia. Profound dysfunction of dopamine neurons also has been documented in imaging studies of patients with LND.[4] The reasons for the relatively prominent disruption of dopamine neurons remain unknown. Also, an implication of hypoxanthine excess in LND leads, directly or indirectly, though its action in adenosine transport, to aberrations in neuronal development has been proposed.[17] Nevertheless, none of these studies showed the pathogenic mechanism whereby HGprt deficiency affects

the neuronal development, and the mechanism by which features of LND/LNVs result from impaired purine metabolism is still not well understood. However, it was also documented that (a) adhesion of HGprt-deficient neuroblastoma as well as fibroblasts from patients with LND/LNVs exhibited dramatically enhanced adhesion compared to control cells,[18] and could have consequences for the maturation of the central nervous system, as seen in the smaller brain size of LND/LNVs children[14-16]; (b) Alzheimer's disease (AD) shares gene expression aberrations with purinergic dysregulation of HGprt deficiency[19]; (c) role for the amyloid precursor protein (*APP*) is a key developmental gene related to cell-cell or cell-substrate adhesion, generation of neurons, their differentiation and migration, neurite outgrowth, regulation of synaptic function, and is important for brain morphology and highly coordinated brain function such as memory and learning has been suggested.[20,21] Hence, the APP pathway is possibly implicated in the development of LND/LNVs. Recently, expression of the amyloid precursor protein (*APP*) gene, for the first time, was shown to be under epigenetic regulation caused by genetic and environmental factors as well as life events and aging,[22-24] and a link between LND/LNVs and the expression of *APP* gene was reported.[7] The results indicated an epistasis (gene–gene interactions) between mutated *HPRT1* and *APP* genes.[7] A gene does not function by itself, but rather acts with other genes (epistasis) in a network, to influence complex traits.[25] Multiple variations of APP-mRNA isoforms encoding divers APP protein isoforms ranging from 120 to 770 amino acids such as APP_{120}, APP_{168}, APP_{175}, APP_{193}, APP_{216}, APP_{207}, APP_{334}, APP_{751}, and APP_{770} (with or without mutations and/or deletions) were found from normal subjects as well as LND/LNVs patients.[22-24] As a result, the different isoforms of APP-mRNA can exist and the most abundant one quantitatively may decisive for the normal status or disease risk: APP-mRNA isoform of 624 bp, with a deletion starting after 49 bp of the 5′end of exon 3 followed by a complete deletion of exons 4-15, mutations in exon 1: c.22C>T, p.L8F, and exon 3: c.269A>G, p.Q90R encoding APP_{207} isoform, was the most abundant one in most of the LND patients and would be responsible for the neurobehavioral syndrome in these patients.[7] The type of mutation and its location in the *HPRT1* gene is therefore an important factor for provoking disease (LND or LNVs), not only through its effect on residual HGprt enzyme activity but also through its effect on interactions between mutated *HPRT1* and *APP* genes. The degrees of the neurological and behavioral abnormalities will depend on the functional compensation by the amount of the normal APP-mRNA isoforms and this amount, under epigenetic regulation of alternative APP pre-mRNA splicing as a result of environmental factors as well as life events and aging may vary among individuals carrying the same mutation. A large or low amount of the normal APP-mRNA isoforms may be responsible for the functional compensation. This could explain the manifestation of different clinical phenotypes from different patients such as the IVS2 +1G>C, c.134 +1G>C splice site mutation resulted in exclusion of exon 2 leading to LND as mentioned above[11,12] and the one in this study including the other,[6] and also from different affected family members[4,7, 26,27] as well as the evolution of the severity of the disease from HND reported at a very young

age to LND when self-injury emerged later.[4] This could explain the cases of HND with mutations predicted to cause complete loss of HGprt enzyme activity[4] and also the cases of LND that involve non-coding mutations and that have an effect on the HGprt enzyme activity or do not have an effect on the HGprt enzyme activity but they have an effect on interactions between mutated *HPRT1* and *APP* genes.[4] A quantitative kinetic measurement of APP-mRNA isoforms[7] from these patients would be useful for clarifying the discrepancies in genotype-phenotype correlations.

In conclusion, APP, a housekeeping gene[28] and an endogenous ligand (http://www.genenames.org/genefamilies/ENDOLIG), is an important molecular hub at the center of interacting pathways and acts as a permissive factor for various neurodevelopmental and neural circuit processes,[29] altered APP processing may affect brain function through a host of altered cellular and molecular events. Although LND often is considered a relatively "simple" disorder because it is monogenic and inherited in an X-linked recessive manner permitting evaluation of single allelic defects, the unexpected and sometimes unusual mechanisms that influence genotype-phenotype relationships provide useful principles for other more complex disorders. In this study, by using the PCR technique coupled with direct sequencing, we report two independent point mutations leading to splicing errors. These two mutations found add to the growing list of *HPRT1* gene mutations that result in clinical disease. Molecular analysis allows fast, accurate carrier detection and genetic counseling.

Acknowledgments

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