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Genotypic and Phenotypic Spectrum in Attenuated Variants of Lesch-Nyhan Disease

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Abstract

Lesch-Nyhan disease and its attenuated variants are caused by deficiency of the purine salvage enzyme, hypoxanthine-guanine phosphoribosyltransferase (HGprt). All patients exhibit excessive production of uric acid, which increases the risk for nephrolithiasis, renal failure, gouty arthritis and tophi. The mildest phenotypes include only problems related to overproduction of uric acid. The most severe clinical phenotype includes prominent neurological abnormalities and the universal feature is self-injurious behavior. In between the mildest and most severe syndromes is a broad spectrum of phenotypes with varying degrees of neurological, neurocognitive and behavioral abnormalities. The effect of *HPRT1* gene mutations on residual HGprt enzyme activity is the most relevant factor contributing to disease phenotype. Attenuated clinical phenotypes are associated with residual enzyme function, whereas the most severe phenotype is usually associated with null activity. In cases of gouty arthritis with urate overproduction, a careful evaluation for motor impairments or neurocognitive abnormalities may help to identify attenuated variants of Lesch-Nyhan disease for better management.

Keywords

Lesch-Nyhan disease; Lesch-Nyhan variant; genotype; phenotype

Introduction

Mutations of the *HPRT1* gene cause Lesch-Nyhan disease (LND) and its attenuated variants. The disorder is inherited in an X-linked recessive manner so patients are virtually always males. The gene encodes an enzyme, hypoxanthine-guanine phosphoribosyltransferase (HGprt), which plays a key role in the salvage of purine nucleotides. Patients with severe

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deficiency of HGprt have a characteristic clinical phenotype that includes excessive production of uric acid, neurological involvement, and neurocognitive and behavioral abnormalities. Patients with partial deficiency of the enzyme have attenuated phenotypes in which the neurobehavioral abnormalities may be clinically insignificant or absent. All HGprt-deficient patients exhibit excessive production of uric acid, which increased the risks for nephrolithiasis, renal failure, gouty arthritis, and tophi. The pathogenic processes leading to the clinical manifestations due to over-production of uric acid are well-understood. On the other hand, the mechanisms leading to the neurological, neurocognitive and behavioral abnormalities have yet to be clarified.

Several prior reports have focused on the more severe phenotype of LND, and particularly on the neurobehavioral manifestations and their biological basis. Fewer articles have more specifically addressed the variants, or the metabolic problems related to overproduction of uric acid. The current review therefore focuses on the milder clinical variants and clinical difficulties associated with uric acid.

Spectrum of clinical phenotypes

The classical clinical phenotype of LND has several clinical manifestations, including uric acid overproduction, motor dysfunction, neurocognitive disability, and the hallmark behavioral problem of recurrent self-injury. Self-injurious behavior usually emerges before 4 years of age, but may be delayed until the second decade of life. The neurobehavioral phenotype also includes severe motor disability that resembles dystonic cerebral palsy [18,48]. Most patients also have mild or moderate neurocognitive abnormalities with intellectual disability and IQ scores in the 55–75 range, but severe mental retardation is uncommon [1,24,37,41].

However, there also are attenuated clinical variants in which some of the clinical features in classic LND are clinically insignificant or even absent [9,16,33,45]. The mildest clinical phenotype includes only overproduction of uric acid and its associated problems. In principle, these patients do not have clinically overt neurological or behavioral abnormalities. The minor motor clumsiness or neurocognitive impairments of these patients are sometimes barely detectable and revealed only with appropriate neurological or psychometric testing. These patients are described as having HGprt-related hyperuricemia (HRH). In between the severe phenotype of LND and the mildest phenotype of HRH is a continuous spectrum of neurological, neurocognitive and behavioral abnormalities, designated HGprt-related neurological dysfunction (HND). HND patients 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. Additionally, their motor and cognitive impairments tend to be less severe than those seen in LND. Collectively, patients with HRH and HND phenotypes are designed as LND variants. Although the patients are classified into three subgroups, the clinical spectrum exhibits continuous grades of severity.

Historically, the eponym Kelley-Seegmiller syndrome was used to describe the mild LND variants in recognition of the identification of the biochemical basis of 18 patients with

partial HGprt enzyme deficiency [21]. However, the term has never been clearly defined and three applications have been used in prior articles. Some authors consider Kelley-Seegmiller syndrome to reflect uric acid overproduction and no significant neurological involvement, corresponding to HRH. However, others use the term for a much broader spectrum in both HRH and HND which includes hyperuricemia along with variable neurological manifestations but no self-injurious behavior. Others apply the eponym only to patients with mild or absent neurological symptoms, but not for more severe manifestations. These disparities have created confusion especially now that the phenotype of LND and its variants are recognized as a continuous spectrum of severity. In view of these issues, the eponym “Kelley-Seegmiller syndrome” probably should be discarded, because it implies a distinct and readily definable clinical sub-phenotype.

Recently, 615 cases with *HPRT1* mutations have been summarized [10]. The mildest phenotype with only overproduction of uric acid alone is quite rare. Only 52 (8.5%) cases had the mildest clinical phenotype of HRH (Table 1). Most cases (461, 75%) had the LND phenotype and 76 cases (12.4%) had the intermediate phenotype. In our experience, most patients referred with the HRH phenotype have some minor neurological or behavioral abnormalities, suggesting that the diagnosis of this phenotype depends on the extent of neurobehavioral testing. If this is the case then this phenotype is even more uncommon than currently appreciated.

In HRH patients, the behavioral and neurological manifestations are absent or very mild, so the patients usually come to medical attention as a result of overproduction of uric acid, including gout, hyperuricemia, crystalluria, hematuria and other problems involving the kidney and urogenital tract. Furthermore, the overt clinical consequences of uric acid overproduction often take time to develop; HRH patients presented with a wide range of ages, from birth to the late 60s. Gout is rarely observed in patients younger than 15 years old, but is much more common in patients after 20 years of age (Figure 2). When patients with the HRH phenotype present very early in life, the initial problem often is acute renal failure. This presentation may reflect the fact that renal clearance of uric acid is higher at younger ages, increasing the burden of uric acid accumulating in the kidneys and urogenital systems. In contrast, most LND patients usually develop the full characteristic features before 4 years of age [16].

Genotype-Phenotype Correlations and Discrepancies

More than 600 unrelated cases have been reported with various *HPRT1* gene defects [10]. The mutations are spread through the whole gene, and include missense mutations, nonsense mutations, splicing mutations, small and large coding and non-coding deletions or insertions, partial duplications, non-coding regulatory mutations, and more complex changes [17]. The severity of the clinical phenotype correlates with the enzyme activity. Missense mutations are more commonly observed in the LND variants, because a single amino acid substitution is more likely to permit some residual enzyme function. On the other hand, deletions, insertions, and duplications are uncommon in the milder variants because they most often result in a structurally abnormal protein with no functional activity. Nonsense

mutations are similarly uncommon in LND variants because they result in premature termination of translation and absent enzyme activity.

Forty-seven cases (90%) of HRH with *HPRT1* gene defects had missense mutations. Only 2 cases had splicing errors [11,40], 2 cases had deletion mutations [15,40], and 1 had an unknown regulatory defect [8] (Table 1). However, all cases with mutations predicting null HGprt enzyme activity were found to have unusual mechanisms permitting some residual enzyme function. In the case of the splicing errors, molecular analysis revealed the presence of multiple transcripts resulting from variations in the fidelity of the splicing mechanism, including small amounts of one normal transcript encoding the normal enzyme. Aberrant mRNA splicing was also reported in one case with a deletion, where a small portion of normal transcripts was again detected [40]. In another case, a deletion occurred at the extreme C-terminus, with loss of only 2 amino acids and allowed residual enzyme function [15]. There is one case with a normal coding region and presumed mutation of the non-coding region resulting in reduced mRNA [8].

Virtually all mutations causing HRH retain some residual enzyme activity. However, there are several exceptions reported to have a very mild clinical phenotype and no apparent residual HGprt enzyme activity [7,13,19,32]. In most of these cases, the biochemical assays used did not reproduce normal physiological conditions in vivo. Commonly, lysed cells from either erythrocytes or fibroblasts are used for in vitro assay of the enzyme. At least three weaknesses of this assay should be acknowledged. First, HGprt mutants with unstable structure are vulnerable outside of the normal cellular environment, a problem that could lead to artificially low enzyme activity in the in vitro environment. Second, mutations resulting in a change in the kinetic properties of the enzyme, such as increased K_m for either purine substrate or PRPP, will be associated with inaccurate results unless the substrates provided in vitro resemble the situation in vivo. Third, some mutations with splicing errors might have multiple transcripts depending on the splicing fidelity machinery. A small amount of normal transcripts may account for the residual enzyme activity, which will vary among samples tested in vitro based on the source of the sample from the patient.

Biological Basis of Uric Acid Overproduction in HGprt Deficiency

The biochemical mechanisms responsible for overproduction of uric acid in HGprt deficiency have been well established [4]. Uric acid is an end product of the metabolic breakdown of purines in humans. Purine metabolism consists of purine synthesis and purine degradation. Purines can be produced in two distinct pathways, de novo purine synthesis and the purine salvage. De novo synthesis begins with ribose-5-phosphate, which reacts with ATP to form 5-phosphoribosyl-1-pyrophosphate (PRPP), and then goes through multiple enzymatic steps that consume considerable energy. The end nucleotide product, inosine monophosphate (IMP) requires six molecules of ATP, two molecules of glutamine, one molecule of glycine, one molecule of CO₂, one molecule of aspartate and two molecules of formate. PRPP-amidotransferase is the committed and rate-limiting step of de novo synthesis, which replaces the pyrophosphate of PRPP with the amide group of glutamine. This enzyme is regulated by its substrate, PRPP, which is also a co-substrate of several other enzymes involving in purine and pyrimidine nucleotide metabolism. Usually, the

intracellular concentration of PRPP is below the K_m of PRPP-amidotransferase, so increases in the concentration of PRPP will activate the enzyme [49]. This enzyme is also under tight allosteric control and is inhibited by its nucleotide end products, IMP, adenosine monophosphate (AMP) or guanosine monophosphate (GMP).

The alternative pathway of purine production is the salvage pathway. In humans, approximately 90% of free purines generated in intracellular metabolism are recycled [25,39]. Two enzymes play key roles in the purine salvage pathway, HGprt and adenine-phosphoribosyltransferase (Apt). HGprt recycles hypoxanthine and guanine, while Apt recycles adenine. These enzymes recycle purine bases from not only intracellular metabolism but also from extracellular sources such as the diet. Nucleic acids from dietary vegetables and animal products can be digested in the intestinal tract and degraded to nucleosides or free purine bases, which can be recycled through the circulation and incorporated into the cellular purine pool via the salvage pathways.

Purine nucleotide degradation is initiated by dephosphorylation of nucleotide 5'-monophosphate. Specific 5'-nucleotidases and non-specific phosphatases hydrolyze AMP, IMP and GMP to adenosine, inosine and guanosine. Inosine and guanosine are converted to hypoxanthine and guanine by purine nucleoside phosphorylase. Adenosine is deaminated to inosine by adenosine deaminase. Hypoxanthine and xanthine are oxidized to uric acid by xanthine oxidase, while guanine is deaminated to xanthine by guanine deaminase. In general, these reactions are regulated by substrate availability. A tightly regulated balance between new purine production and degradation provides a homeostatic mechanism for the maintenance of the nucleotide pool. Unlike most other mammals, humans produce uric acid as the final product of purine degradation as a result of lacking the enzyme uricase.

HGprt deficiency was the first inborn error recognized to cause gout due to overproduction of uric acid [23,26]. The defect of HGprt leading to overproduction of uric acid results from failure of recycling of hypoxanthine and guanine (Figure 1). These purine bases cannot be recycled so they are oxidized to uric acid, which results in increased uric acid levels. On the other hand, decreased purine salvage leads to a sparing of PRPP, which is a substrate for PRPP-amidotransferase. The increased intracellular PRPP causes increased synthesis of purines by the de novo pathway. Both decreased salvage of the purine bases and elevated purine de novo synthesis result in overproduction of uric acid in HGprt deficiency [6,35,42]. It has been estimated that HGprt-deficient patients produce uric acid at rates approximately 5–10 times that of healthy individuals [2,20,43]. The overproduction of uric acid results in elevated uric acid levels in serum and/or urine [45]. Due to the very low solubility of uric acid in the body, even small increases in the uric acid level increase the risk for the aggregation of the monosodium urate crystals in the vulnerable body regions. For example, precipitation in the urogenital system, where uric acid is concentrated by the rapid excretion by the kidney, results in nephrolithiasis and associated problems such as urinary obstruction and renal failure. Precipitation in the subcutaneous tissues due to temperature gradients leads to solid masses known as tophi. Precipitation in the joints of the hands and feet followed by phagocytosis of the crystals by polymorphonuclear cells leads to inflammation in the joints and gouty arthritis.

Biological Basis for Neurobehavioral Abnormalities

The biological basis for the neurological and neurocognitive abnormalities in classic LND have been the focus of several prior reports [18,47], so they will not be reviewed extensively here. Briefly, these problems do not result from overproduction of uric acid, but are thought to be due to a direct effect of HGprt deficiency on the developing brain. Within the brain, basal ganglia dopamine systems appear to be most vulnerable [3,18,47]. However, other regions of the brain such as the cerebral cortex also appear to be affected [36]. The mechanisms by which HGprt deficiency affects the developing brain are not understood.

The neurological and neurocognitive abnormalities in the LND variants have received less attention [37,38]. Patients with HRH often are described as having no neurological or neurocognitive defects. However, our experience with many referrals is that careful clinical assessments almost always reveal some abnormalities [16]. The neurological exam often reveals clumsiness, cognitive testing may reveal a normal IQ but serious difficulties with sustained attention, and behavioral assessments sometimes reveal oppositional or other difficult behavior patterns. These problems are even more apparent in patients with HND. Presumably partial loss of HGprt activity in these clinically milder cases has less severe, but still measurable impact on the brain. This concept is consistent with recent quantitative MRI studies, which show reduced brain volumes in HRH and HND that are less severe than those seen in LND [36].

Diagnosis

The diagnosis of LND and its attenuated variants is based on both clinical and laboratory evidence. The full clinical phenotype with neurological, neurocognitive and behavioral problems, and especially self-injurious behavior, is highly characteristic and usually leads to appropriate diagnostic testing quickly. However, the neurological features unfold over the first few years of life, and self-injury may be delayed for several years, resulting in an apparently incomplete syndrome and a challenging clinical diagnosis.

The clinical diagnosis is even more challenging when self-injury is absent, or when the neurological difficulties are particularly mild, as in the LND variants. In these cases, hyperuricemia or one of its consequences such as nephrolithiasis or gout provides an important clue for the diagnosis. Although hyperuricemia and its consequences are common in older adults, they are very uncommon in children and young adults. The occurrence of these problems before age 30 should raise suspicion for an attenuated variant, especially if they are combined with any evidence for poor motor skills or neurocognitive function.

High uric acid levels shown in blood and urine test might prompt an enzymatic diagnosis, which is carried out by measurement of HGprt enzyme activity in blood or live fibroblasts grown from a skin biopsy. Living cells provide a more faithful result because they provide assay conditions much closer to the natural environment. Both intact erythrocytes and live fibroblasts have been employed for this assay. Both of them provide good correlations between residual enzyme function and clinical severity [10,30,31]. A pulse of radiolabeled purine base is given in the culture medium, and the apparent activity is estimated by measuring the formation of radiolabeled nucleotides under physiological conditions where

the cell produces normal endogenous amounts of PRPP. However, some limitations still exist. First, the erythrocyte assay is still vulnerable to artificially low activities for HGprt mutants that are structurally unstable. The reason is erythrocytes lack a nucleus for mRNA production, which is required for synthesizing new protein. Thus in blood samples residual HGprt activity is influenced by the structural stability of the enzyme. Also, live erythrocytes are vulnerable to rapid deterioration of function after collection and must be studied within 2 days of collection. In contrast, fibroblasts are nucleated. With this assay, patients with the most severe phenotype of LND typically have less than 1.5% of normal enzyme activity, while the mildest phenotype of HRH is generally associated with more than 10% of activity. Patients with intermediate phenotypes of HND have activity that normally falls in between. However, this assay is technically challenging because it requires establishing cultures from skin biopsies and the assay requires the time-consuming and expensive task of growing cells. This makes it difficult to use for routine clinical diagnostic testing.

Identification of a molecular genetic mutation in the *HPRT1* gene confirms the diagnosis. About 30% of the patients carry de novo mutations but about 70% of the mothers are somatic carriers [27]. Genetic diagnosis permits carrier detection and prenatal screening of at-risk pregnancies.

Treatments

Allopurinol is an isomer of hypoxanthine and acts as xanthine oxidase inhibitor, which blocks the conversion of xanthine and hypoxanthine into uric acid. Although the treatment does not improve the neurological outcome, it is still the most widely used medication to control uric acid in HGprt deficiency [22,44]. It is usually started to reduce complications such as nephrolithiasis and gout as soon as the enzyme deficiency is diagnosed. In adults, or when there are substantial tissue urate deposits, colchicine prophylaxis or non-steroidal anti-inflammatory drugs can be given. However, excessive use of these drugs must be avoided because they can contribute to renal injury. Uricosuric drugs are also not recommended since they can contribute to kidney stones. The initial dosage of allopurinol is 5 to 10 mg/kg/day, with final total doses ranging from 50–600 mg/day. Treatment with allopurinol results in a mean reduction of about 50% in serum urate and a 74% reduction in urinary uric acid to creatinine ratio [46]. Allopurinol resistance appears to be uncommon, and patients who seem to respond poorly should raise concerns regarding medication noncompliance. However, allopurinol may cause severe cutaneous adverse reactions, which include the drug hypersensitivity syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis. These problems may be life-threatening. A case-control association study revealed the HLA-B*5801 allele was present in all 51 patients studied with hypersensitivity reactions, but only in 20 (15%) of 135 tolerant patients in Taiwan [odds ratio 580.3]. As HLA-B*5801 allele is probably an important genetic risk factor, testing for HLA-B*5801 may be considered before starting therapy [14]. Overall however, these hypersensitivity reactions are rare, occurring in only 0.4% of treated patients. To our knowledge, no such hypersensitivity reaction has been reported for LND or its variants.

Generally, urinary tract calculi are composed primarily of uric acid in LND and its variants. However, the risk of xanthine calculi increases when on allopurinol therapy. In healthy

individuals, hypoxanthine and xanthine are only a small percentage of total urinary purines. In HGPrt deficiency patients, hypoxanthine and xanthine are markedly increased, and allopurinol treatment increases them about 5- and 10-fold, respectively [2,43]. As a result, the concentration of xanthine may increase to a level exceeding its solubility, leading to xanthine stones. In this situation, increasing the allopurinol dose will aggravate stone formation, and the better strategy would be to lower allopurinol doses. When unexpected stones form during therapy, they should be collected and chemically examined. Therapy can be adjusted according to the composition of the stones. Many physicians do not perform studies to search for stones routinely, and they wait for clinically-relevant problems to arise. When stones are detected, they can be addressed via lithotripsy. However, enormous stones may develop without symptoms, when they then create a management problem requiring surgical removal. As a result, some have suggested routine imaging surveillance for stones, although the practice is not universal.

In LND and its variants, urine alkalization and hydration have been advocated to minimize the formation of uric acid stones. Human urine can have pH ranging from about 4 to about 8. Uric acid is a weak acid with a pKa of 5.75. At pH of 7.4 under a physiological environment, 98% of uric acid is in the ionized form as a monosodium urate salt [28,29]. When urine pH drops below 5.75, uric acid becomes much more insoluble with a predominant non-ionized form. Sodium urate is 18 times more soluble than uric acid in aqueous solutions. This solubility difference provides the therapeutic rationale for alkalization of the urine. Consistently low pH in the urine is a risk factor for uric acid stones. Achieving a urine pH above 6.0 is desirable. On the other hand, xanthine calculi are less responsive to urinary alkalization. The pKa of xanthine is 7.4. Therefore, pH changes have only a minor influence on xanthine stone solubility. Since xanthine stones are far more difficult to dissolve than uric acid stones, allopurinol doses should be titrated to maintain serum uric acid levels in the high-normal range. Allopurinol and urinary alkalization should be accompanied by a regular program to maintain generous hydration at all times, so that all purine metabolites can be flushed rapidly from the body.

Febuxostat, a novel structurally unrelated nonpurine selective xanthine oxidase inhibitor, is a potential alternative to allopurinol for patients with hyperuricemia and gout [5]. Febuxostat works on both oxidized and reduced form of xanthine oxidase since it inhibits the enzyme activity by non-competitively blocking the enzyme active site center. Differing from allopurinol, febuxostat does not inhibit enzymes involved in purine or pyrimidine metabolism, such as HGPrt or orotate phosphoribosyltransferase, purine nucleoside phosphorylase and orotidine-5-monophosphate decarboxylase. As a result of the structural and selectivity differences, febuxostat tends to have higher potency and long-lasting action. Febuxostat is not routinely used in HGPrt-deficient patients but can be used for patients who are intolerant of allopurinol.

The majority of mammals have very low serum urate levels because of the presence of the hepatic enzyme, urate oxidase, which converts uric acid to a very soluble excretion product, allantoin. In humans, due to the mutations of the uricase gene during evolution, urate oxidase is non-functional and uric acid is the end product of purine metabolism. Rasburicase was formulated to control high levels of uric acid in the blood and tumor lysis syndrome.

Rasburicase is a recombinant version of urate oxidase purified from *Aspergillus flavus*. It is administered intravenously at doses of 0.20 mg/kg/day during a short period of 5 to 7 days. Theoretically, uricase treatment can also be employed to HGprt-deficient patients with xanthine lithiasis.

Recently, rasburicase treatment has been reported in one LND patient, who presented with renal failure in the first month of life [34]. After receiving rasburicase at established doses, followed by allopurinol treatment, renal function improved. However, no long-term data are available regarding the safety of rasburicase. Because it is a foreign protein that is known to induce an antibody reaction and potential allergic anaphylaxis, its use must be carefully considered. Its short half-life (18 h) and its intravenous means of administration render it inconvenient for chronic therapy. However, rasburicase may be effective in cases with acute kidney injury.

Dietary manipulation has been recommended for management of hyperuricemia in HGprt deficiency too. However, there has no conclusive evidence suggesting the effect of purine-free diets on serum uric acid [12]. On the other hand, many HGprt-deficient patients have difficulty swallowing and are chronically malnourished, so dietary restriction may not be wise. Most patients should follow a balanced, high-calorie diet until more information regarding the value of a low-purine diet is available.

Conclusions

Deficiency of the purine salvage enzyme, HGprt causes LND and its attenuated variants. All of these patients have a marked overproduction of uric acid and its consequences, including gouty arthritis. Patients with the classic phenotype present with a characteristic clinical syndrome including neurological abnormalities and self-injurious behavior, while patients with attenuated phenotypes may present without obvious neurobehavioral problems. However, in cases of gouty arthritis with urate overproduction, a careful assessment for motor dysfunction or neurocognitive disability may help to identify the LND variants. Allopurinol combined with generous hydration provides a safe and effective approach to treat uric acid overproduction and dramatically reduces the risk of nephrolithiasis and gout.

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References

1. Anderson LT, Ernst M, Davis SV. Cognitive abilities of patients with Lesch-Nyhan disease. *J Autism Dev Disord.* 1992; 22:189–203. [PubMed: 1624404]
2. Balis ME, Krakoff IH, Berman PH, Dancis J. Urinary metabolites in congenital hyperuricosuria. *Science.* 1967; 156:1122–1123. [PubMed: 6024192]
3. Baumeister AA, Frye GD. The biochemical basis of the behavioral disorder in the Lesch-Nyhan syndrome. *Neurosci Biobehav Rev.* 1985; 9:169–178. [PubMed: 3925393]
4. Becker, MA. Hyperuricemia and gout. In: Scriver, CR.; Beaudet, AL.; Sly, WS.; Valle, D.; Childs, B.; Kinzler, KW.; Vogelstein, B., editors. *The metabolic and molecular basis of inherited disease.* New York: McGraw-Hill Book Company; 2001. p. 2513-2535.

5. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, Streit J, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005; 353:2450–2461. [PubMed: 16339094]
6. Brosh S, Boer P, Kupfer B, De Vries A, Sperling O. De novo synthesis of purine nucleotides in human peripheral blood leukocytes. *J Clin Invest*. 1976; 58:289–297. [PubMed: 956368]
7. Cossu A, Micheli V, Jacomelli G, Carcassi A. Kelley-Seegmiller syndrome in a patient with complete hypoxanthine-guanine phosphoribosyltransferase deficiency. *Clin Exp Rheumatol*. 2002; 19:851–853.
8. Dawson PA, Gordon RB, Keough DT, Emmerson BT. Normal HPRT coding region in a male with gout due to HPRT deficiency. *Mol Genet Metab*. 2005; 85:78–80. [PubMed: 15862284]
9. Emmerson BT, Thompson L. The spectrum of hypoxanthine-guanine phosphoribosyltransferase deficiency. *Quart J Med*. 1973; 166:423–440. [PubMed: 4785440]
10. Fu R, Ceballos-Picot I, Torres RJ, Larovere LE, Yamada Y, Nguyen KV, Hegde M, Visser JE, Schretlen DJ, Nyhan WL, et al. Genotype-phenotype correlations in neurogenetics: Lesch-Nyhan disease as a model disorder. *Brain: a journal of neurology*. 2014; 137:1282–1303. [PubMed: 23975452]
11. Gaigl Z, Shin YS, Gathof BS. Novel splice mutation in a patient with partial hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. *J Inherit Metab Dis*. 2001; 24(Suppl 1):142.
12. Hayman S, Marcason W. Gout: is a purine-restricted diet still recommended? *Journal of the American Dietetic Association*. 2009; 109:1652. [PubMed: 19699845]
13. Hersh JH, Page T, Hand ME, Seegmiller JE, Nyhan WL, Weisskopf B. Clinical correlations in partial hypoxanthine guanine phosphoribosyltransferase deficiency. *Pediatr Neurol*. 1986; 2:302–304. [PubMed: 3508703]
14. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, Lan JL, Yang LC, Hong HS, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102:4134–4139. [PubMed: 15743917]
15. Igarishi T, Minami M, Nishida Y. Molecular analysis of hypoxanthine-guanine phosphoribosyltransferase mutation in five unrelated Japanese patients. *Acta Paediatr Jpn*. 1989; 31:303–313. [PubMed: 2572141]
16. Jinnah HA, Ceballos-Picot I, Torres RJ, Visser JE, Schretlen D, Verdu A, Larovere LE, Chen CJ, Cossu A, Wu CH, et al. Attenuated variants of Lesch-Nyhan disease. *Brain: a journal of neurology*. 2010; 133:671–689. [PubMed: 20176575]
17. Jinnah HA, DeGregorio L, Harris JC, Nyhan WL, O'Neill JP. 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. [PubMed: 11018746]
18. Jinnah HA, Visser JE, Harris JC, Verdu A, Larovere L, Ceballos-Picot I, Neychev V, Torres RJ, Dulac O, Desguerre I, et al. Delineation of the motor disorder of Lesch-Nyhan disease. *Brain: a journal of neurology*. 2006; 129:1201–1217. [PubMed: 16549399]
19. Jurecka A, Popowska E, Tytki-Szymanska A, Kubalska J, Ciara E, Krumina Z, Sykut-Cegielska J, Pronicka E. Hypoxanthine-guanine phosphoribosyltransferase deficiency-The spectrum of Polish mutations. *J Inherit Metab Dis*. 2008; 136
20. Kaufman JM, Greene ML, Seegmiller JE. Urine uric acid to creatinine ratio--a screening test for inherited disorders of purine metabolism. *J Pediatr*. 1968; 73:583–592. [PubMed: 5678000]
21. Kelley WN, Greene ML, Rosenbloom FM, Henderson JF, Seegmiller JE. Hypoxanthine-guanine phosphoribosyltransferase deficiency in gout. *Ann Int Med*. 1969; 70:155–206. [PubMed: 4884382]
22. Klinenberg JR, Goldfinger SE, Seegmiller JE. The Effectiveness of the Xanthine Oxidase Inhibitor Allopurinol in the Treatment of Gout. *Ann Intern Med*. 1965; 62:639–647. [PubMed: 14274828]
23. Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. *Am J Med*. 1964; 36:561–570. [PubMed: 14142409]
24. Matthews WS, Solan A, Barabas G. Cognitive functioning in Lesch-Nyhan syndrome. *Dev Med Child Neurol*. 1995; 37:715–722. [PubMed: 7672468]

25. Murray AW. The biological significance of purine salvage. *Ann Rev Biochem.* 1971; 40:811–826. [PubMed: 4330582]
26. Nyhan WL, Oliver WJ, Lesch M. A familial disorder of uric acid metabolism and central nervous system function II. *J Pediatr.* 1965; 67:257–263.
27. O'Neill JP. Mutation carrier testing in Lesch-Nyhan syndrome families: HPRT mutant frequency and mutation analysis with peripheral blood T lymphocytes. *Genet Testing.* 2004; 8:51–64.
28. Oh MM, Ham BK, Kang SH, Bae JH, Kim JJ, Yoo KH, Yoon DK, Moon du G. Urine alkalization may be enough for the treatment of bilateral renal pelvis stones associated with Lesch-Nyhan syndrome. *Urol Res.* 2011; 39:417–419. [PubMed: 21331772]
29. Oka T, Utsunomiya M, Ichikawa Y, Koide T, Takaha M, Mimaki T, Sonoda T. Xanthine calculi in the patient with the Lesch-Nyhan syndrome associated with urinary tract infection. *Urol Int.* 1985; 40:138–140. [PubMed: 3925607]
30. Page T, Bakay B, Nissinen E, Nyhan WL. Hypoxanthine-guanine phosphoribosyltransferase variants: correlation of clinical phenotype with enzyme activity. *J Inher Metab Dis.* 1981; 4:203–206. [PubMed: 6796771]
31. Page T, Nyhan WL. The spectrum of HPRT deficiency: an update. *Adv Exp Med Biol.* 1989; 253A:129–133. [PubMed: 2624181]
32. Popowska E, Sulek A, Kubalska J, Pronicka E, Jezewska MM, Trembacz H, Goryluk-Kozakiewicz B, Krajewska-Walasek M. Different mutations in Polish patients with HPRT deficiency - the Lesch-Nyhan and Kelley-Seegmiller syndromes. *J Appl Genet.* 1998; 39:103–111.
33. Puig JG, Torres RJ, Mateos FA, Ramos TH, Arcas JM, Buno AS, O'Neill P. The spectrum of hypoxanthine-guanine phosphoribosyltransferase deficiency: Clinical experience based on 22 patients from 18 Spanish families. *Medicine.* 2001; 80:102–112. [PubMed: 11307586]
34. Roche A, Perez-Duenas B, Camacho JA, Torres RJ, Puig JG, Garcia-Cazorla A, Artuch R. Efficacy of rasburicase in hyperuricemia secondary to Lesch-Nyhan syndrome. *Am J Kidney Dis.* 2009; 53:677–680. [PubMed: 18992978]
35. Rosenbloom FM, Henderson JF, Caldwell IC, Kelley WN, Seegmiller JE. Biochemical bases of accelerated purine biosynthesis de novo in human fibroblasts lacking hypoxanthine-guanine phosphoribosyltransferase. *J Biol Chem.* 1968; 243:1166–1173. [PubMed: 5650894]
36. Schretlen DJ, Varvaris M, Ho TE, Vannorsdall TD, Gordon B, Harris JC, Jinnah HA. Regional brain volume abnormalities in Lesch-Nyhan disease and its variants: a cross-sectional study. *Lancet neurology.* 2013; 12:1151–1158. [PubMed: 24383089]
37. Schretlen DS, Harris JC, Park KS, Jinnah HA, Ojeda del Pozo N. Neurocognitive functioning in Lesch-Nyhan disease and partial hypoxanthine-guanine phosphoribosyltransferase deficiency. *J Int Neuropsychol Soc.* 2001; 7:805–812. [PubMed: 11771623]
38. Schretlen DS, Ward J, Meyer SM, Yun J, Puig JG, Nyhan WL, Jinnah HA, Harris JC. Behavioral aspects of Lesch-Nyhan disease and its variants. *Dev Med Child Neurol.* 2005; 47:673–677. [PubMed: 16174310]
39. Seegmiller JE. Contributions of Lesch-Nyhan syndrome to the understanding of purine metabolism. *J Inher Metab Dis.* 1989; 12:184–196. [PubMed: 2502677]
40. Sege-Peterson K, Chambers J, Page T, Jones OW, Nyhan WL. Characterization of mutations in phenotypic variants of hypoxanthine phosphoribosyltransferase deficiency. *Hum Mol Genet.* 1992; 1:427–432. [PubMed: 1301916]
41. Solan A, Matthews W, Barabas G, Robey K. Cognition in LND: a two-year follow-up study. *Dev Med Child Neurol.* 1997; 39:492–493. [PubMed: 9285444]
42. Sorensen LB. Mechanism of excessive purine biosynthesis in hypoxanthine-guanine phosphoribosyltransferase deficiency. *J Clin Invest.* 1970; 49:968–978. [PubMed: 5441549]
43. Sweetman L, Nyhan WL. Excretion of hypoxanthine and xanthine in a genetic disease of purine metabolism. *Nature.* 1967; 215:859–860. [PubMed: 6049739]
44. Torres RJ, Prior C, Puig JG. Efficacy and safety of allopurinol in patients with hypoxanthine-guanine phosphoribosyltransferase deficiency. *Metabolism.* 2007; 56:1179–1186. [PubMed: 17697859]
45. Torres RJ, Puig JG, Jinnah HA. Update on the phenotypic spectrum of Lesch-Nyhan disease and its attenuated variants. *Current rheumatology reports.* 2011; 14:189–194. [PubMed: 22198833]

46. Torres RJ, Puig JG, Jinnah HA. Update on the phenotypic spectrum of Lesch-Nyhan disease and its attenuated variants. *Current rheumatology reports*. 2012; 14:189–194. [PubMed: 22198833]
47. Visser JE, Baer PR, Jinnah HA. Lesch-Nyhan syndrome and the basal ganglia. *Brain Res Rev*. 2000; 32:449–475. [PubMed: 10760551]
48. Watts RWE, Spellacy E, Gibbs DA, Allsop J, McKeran RO, Slavin GE. Clinical, post-mortem, biochemical and therapeutic observations on the Lesch-Nyhan syndrome with particular reference to the neurological manifestations. *Quart J Med*. 1982; 201:43–78. [PubMed: 7111674]
49. Wood AW, Becker MA, Seegmiller JE. Purine nucleotide synthesis in lymphoblasts cultured from normal subjects and a patient with Lesch-Nyhan syndrome. *Biochem Genet*. 1973; 9:261–273. [PubMed: 4354564]

Highlights

- *HPRT1* gene mutations cause a spectrum of clinical phenotypes, including LND and its attenuated variants.
- Residual HGprt enzyme activity is the most relevant factor contributing to the severity of the clinical phenotype.
- A careful evaluation for motor impairments or neurocognitive abnormalities may help to identify attenuated variants of Lesch-Nyhan disease.
- Allopurinol combined with generous hydration provides a safe and effective approach to treat uric acid overproduction.

Figure 1.

Purine metabolism pathway. Abbreviations used are: ADP, adenosine diphosphate; AMP, adenosine monophosphate; AS, adenylosuccinate; asp, aspartic acid; ATP, adenosine triphosphate; GDP, guanosine diphosphate; gln, glutamine; gly, glycine; GMP, guanosine monophosphate; Gprt, guanine phosphoribosyltransferase; GTP, guanosine triphosphate; Hprt, hypoxanthine phosphoribosyltransferase; IMP, inosine monophosphate; PRPP, phosphoribosylpyrophosphate; XMP, xanthine monophosphate. In this diagram, **HGprt** is shown separately at its two distinct functional sites (**Hprt** and **Gprt**).

Figure 2.

The presenting age according to initial problems in previously reported 71 HRH cases. Individuals are overlaid with a box-whisker plot, where the middle horizontal line in each box shows the median. The upper and lower limits of the box define the 25th and 75th quartiles. Whiskers span the entire data range excepting outliers, defined as values that fell outside the upper or lower quartile plus 1.5 times the inter-quartile distance. Patients presenting first with gout had a mean age of 33.7 ± 9.9 and a median age of 32 years ($n = 29$). Patients with presenting first with renal failure had a mean age of 5.9 ± 11.8 and a median age of 1 year for 11 cases. The remaining 31 cases first presented with other problems, such as nephrolithiasis, hyperuricemia, colic, hematuria, crystalluria and dysuria, had a mean age of 16.9 ± 15.5 and a median age of 13 years.

Table 1Summary of previously reported *HPRT1* mutations

Mutation	LND	HND	HRH	NA
single base substitution	255	61	47	18
missense	131	50	45	16
nonsense	47	1	0	1
splice error	77	10	2	1
deletion	146	3	2	7
duplication	37	3	0	0
others	15	9	1	1
translocation	1	0	0	0
regulatory	2	3	1	0
double mutation	0	2	0	0
insertion	3	1	0	0
complex deletion	9	3	0	1
females	8	0	2	0
% of total	75.0	12.4	8.5	4.2
Total	461	76	52	26

This data came from Fu et al, 2014 [10]. A complete list of mutations is available at www.lesch-nyhan.org. Abbreviations: NA, clinical phenotype not available; LND, Lesch-Nyhan disease, HRH, HGprt-related hyperuricemia, HND, HGprt-related neurological disorder.