Lesch-Nyhan Variant Syndrome
Variable Presentation in 3 Affected Family Members

Kyriakie Sarafoglou, MD; Krista Grosse-Redlinger, CGC; Christopher J. Boys, PhD; Laurence Charnas, MD; Noelle Otten, MS; Robyn Broock, PhD; William L. Nyhan, MD, PhD

Background: Lesch-Nyhan disease is an inborn error of purine metabolism that results from deficiency of the activity of hypoxanthine phosphoribosyltransferase (HPRT). The heterogeneity of clinical phenotypes seen in HPRT deficiency corresponds to an inverse relationship between HPRT enzyme activity and clinical severity. With rare exception, each mutation produces a stereotypical pattern of clinical disease; onset of neurologic symptoms occurs during infancy and is thought to be non-progressive.

Objective: To document a family in which a single HPRT gene mutation has led to 3 different clinical and enzymatic phenotypes.

Design: Case report.

Settings: A university-based outpatient metabolic clinic and a biochemical genetics laboratory.

Patients: Three males (2 infants and their grandfather) from the same family with Lesch-Nyhan variant, including one of the oldest patients with Lesch-Nyhan variant at diagnosis (65 years).

Main Outcome Measures: Clinical and biochemical observations.

Results: Sequencing of 5 family members revealed a novel mutation c.550G>T in exon 7 of the HPRT gene. The considerably variable clinical phenotype corresponded with the variable enzymatic activity in the 3 males, with the grandfather being the most severely affected.

Conclusions: The different phenotypes encountered in the enzymatic analysis of cultured fibroblasts from a single mutation in the same family is unprecedented. The significant decrease in the grandfather’s HPRT enzymatic activity compared with that of his grandchildren could be a function of the Hayflick Limit Theory of cell senescence.

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Lesch-Nyhan disease, first reported in 2 brothers with hyperuricemia, mental retardation, involuntary movements, and self-destructive behavior, results from decreased activity of the hypoxanthine-guanine phosphoribosyltransferase (HPRT1) enzyme resulting from mutations of the HPRT1 gene. Heterogeneity of clinical phenotypes is seen in hypoxanthine phosphoribosyltransferase (HPRT) deficiency, and there is an approximately inverse relationship between HPRT enzyme activity measured in intact cells and clinical severity. Affected patients with classic Lesch-Nyhan disease, the most severe and frequent form, have the lowest HPRT enzyme activity (<1.5% of normal) in intact cultured fibroblasts, and they display the full spectrum of clinical abnormalities. Patients with partial HPRT deficiency, designated as Lesch-Nyhan variants (LNVs), have HPRT enzyme activity ranging from 1.5% to 8.0%. Individuals with the intermediate form of LNV (also known as neurologic variants) have a variable clinical phenotype and, in most cases, are neurologically indistinguishable from patients with Lesch-Nyhan disease. However, they do not have self-injurious behaviors, and their intelligence is normal or near normal. The least-affected patients with LNV have residual HPRT enzyme activity exceeding 8%, and their only manifestations have been attributed to hyperuricemia and include gout, hematuria, and nephrolithiasis. There is another LNV, HPRT Salamanca, that is characterized by spastic gait, mental retardation, and skeletal abnormalities.

We describe a family with 3 affected individuals with LNV. Diagnosis of the pro-
neuropsychological assessment at 15 and 32 months revealed cognitive function to be average (as measured by the Bayley Scales of Infant and Toddler Development, Third Edition). His cognitive composite score was 95 (average range, 85-115), and his overall language composite score was 79. Fine motor ability was at the 15-month age equivalency, but gross motor skills were within the 10-month age equivalency, which was below the average range. At 39 months, his full-scale IQ was 87, nonverbal IQ was 88, and verbal IQ was 76.

Repeated measurement revealed that the uric acid level was elevated at 7.5 mg/dL, and allopurinol therapy (100 and 150 mg on alternate days) was started at 15 months. At 2 years, the patient was walking, but he struggled in transitioning from a fast walk to running. Magnetic resonance imaging of his brain showed no abnormalities.

**CASE 2**

Patient 2 (III-2), grandfather of the proband, was evaluated at 65 years and was found to have an elevated uric acid level in plasma of 6.8 mg/dL. He was the 2.7-kg product of a 20-year-old woman who arrived in labor at a military hospital when no physician was present; a nurse advised the mother to inhibit labor, allegedly leading to asphyxia, to which was attributed his cerebral palsy diagnosed at approximately 3 to 4 years when he displayed an abnormal gait and poor speech. At 17 years, he had his first kidney stone; knee and ankle swelling were diagnosed as gout. After that, he had progressive renal dysfunction, at report approximating 40% of normal glomerular filtration. He had not had active podagra or symptomatic nephrolithiasis since age 40 years. He had been treated with allopurinol since age 17 years.

Results of a recent neuropsychological examination revealed reading and spelling skills at a kindergarten level, mathematic skills at a first grade level, severe dyslexia, and borderline intellectual functioning (his estimated Wechsler Adult Intelligence Scale, Third Edition, full-scale IQ was 73). There was little variation in his performance across the 9 Wechsler Adult Intelligence Scale, Third Edition, subtests administered, with all scores falling in the borderline to below average range.

On physical examination, he was edentulous. His right hand was remarkable for flexion contractures of the fingers. He had mild limitation of motion at the left elbow and tenderness and limited range of motion in the right shoulder that he attributed to work-related trauma. Muscle tone was mildly increased in the lower extremities. His gait showed mild in-toeing and a rolling alternating hip motion. He was unable to walk on his heels, and he could not stand on his right foot for more than 7 seconds. He had brisk reflexes at the knees.

**CASE 3**

After identification of the proband, uric acid levels in patient 3 (V-3), the proband’s cousin, were found to be elevated on 2 occasions—8.1 and 7.5 mg/dL. At diagnosis he was 26 months old and had had an unremarkable medical history. Findings from physical and neurologic examinations were normal except for mild generalized hypotonia. He had walked at 15 months and was running but tripping frequently. He had bilateral focal dystonia of his lower extremities, resulting in toe walking. He spoke 10 to 12 clear words but rarely used 2-word phrases. Allopurinol therapy was started. Renal ultrasonography was normal.

Neuropsychological assessment was made at 24 and 39 months. His cognitive composite score was 85, but it
declined slightly to a full-scale IQ of 81 on the second test. His motor composite score was 79, which was below average. Nonverbal IQ was 88, but verbal IQ was 76.

**FAMILY HISTORY**

All female relatives carrying the mutation have been asymptomatic. A male (I-3) died at 90 years with a history of gout; a male (II-3) had an unclassified muscular dystrophy; and a male (III-4) had severe mental retardation, blindness, and a history of seizures (Figure 1).

**METHODS**

Activity of HPRT in erythrocyte lysates was determined at the Baylor Biochemical Genetics Laboratory. The HPRT activity in intact cultured fibroblasts was determined as previously described. Sequencing of the HPRT (OMIM 308000) gene was performed at Baylor Biochemical Genetics Laboratory. Amplification of exons 1 to 9 of genomic DNA and direct sequence analysis of polymerase chain reaction products were performed in the forward and reverse directions.

**RESULTS**

The HPRT enzymatic activity levels in the red blood cells of the proband and V-3 were 0 nmol/min/g of hemoglobin, and that of III-2 was 16 nmol/min/g of hemoglobin. Sequencing showed that the proband, his cousin (V-3), his grandfather (III-2), his grandfather’s sister, and 1 of her 2 daughters had a novel mutation c.550G>T in exon 7 of the HPRT gene. This change predicts an amino acid substitution of arginine to methionine at residue 167 (p.R167M) of the hypoxanthine-guanine phosphoribosyltransferase enzyme. The proband’s mother and her sister (mother of V-3) were found to be heterozygous for the mutation.

The intact cell activities of HPRT were low in the proband but very different from zero. The level of HPRT was 369 pmol/110 nmol UV (control, 1160-5228 pmol/110 nmol UV), guanine phosphoribosyltransferase (GPRT) was 455 pmol/110 nmol UV (1597-6041 pmol/110 nmol UV), and adenine phosphoribosyltransferase (APRT) was 10 045 pmol/110 nmol UV (6880-13 044 pmol/110 nmol UV). The HPRT activity of the cousin (V-3) was 125 pmol/110 nmol UV; GPRT, 185 pmol/110 nmol UV; and APRT, 10 340 pmol/110 nmol UV. Intact cell HPRT activity of the grandfather (III-2) was 27 pmol/100 µmol UV; GPR, 27 pmol/100 µmol UV; and APRT, 9880 pmol/100 µmol UV. Cells from the grandfather grew more slowly than did those from the children; the grandfather’s cells seemed less robust, had more cytoplasm, and did not fit together as tightly.

**COMMENT**

We described a clinically noteworthy family in which diagnosis of the 14-month-old proband led to diagnosis of his older cousin (26 months) and his grandfather (65 years). All 3 patients, and several female carriers, were found to carry the c.550G>T nucleotide change in exon 7 of the HPRT gene. This nucleotide change predicts a change from arginine to methionine and, to our knowledge, has not been previously identified as a disease-causing mutation. It is of interest that nondisease polymorphisms in the HPRT gene have not been described. Arginine 167 in the HPRT1 gene is highly conserved across mammalian species, and the pR167M change replaces a positively charged amino acid with a nonpolar amino acid. This change does not seem particularly conservative, but, clearly, it permitted residual HPRT enzyme activity in the intact cell preparation.

There was considerable variation in phenotype and severity among the 3 affected members. The grandfather was most affected; both grandchildren had mild delays of gross motor and speech development. Results of formal psychometric testing revealed that both children performed at the low average range of overall cognitive abilities. The grandfather’s cognitive abilities were well below the average range, and his difficulties with academic achievement were consistent with severe dyslexia. He also had neurologic abnormalities that interfered with motor functioning.

The grandfather was one of the oldest patients with LNV at diagnosis. Although he had dysarthria, mild spasticity, and cognitive impairment all his life and gouty arthritis and nephrolithiasis at age 17 years, his treating physicians had attributed all his neurologic abnormalities to cerebral palsy. All 3 patients were less severely impaired than are patients with the neurologic phenotype because they all walked. In this sense, they more aptly fit the HPRT Salamanca phenotype, type 3 in the classification of Puig and Torres and colleagues. There is also the issue of the differences in age. It has long been con-
sidered that the neurologic features of HPRT deficiency were nonprogressive, but that view reflects that few adults had been studied. It is clear that there may well be worsening of neurologic function with age,11 but certainly not enough to account for the differences between these infants and their grandfather.

The different phenotypes encountered in the enzymatic analysis of cultured fibroblasts is, in our experience, unprecedented. It seems to be consistent with clinical phenotypes. It could be a function of the Hayflick Limit Theory of cell senescence.12 The very late diagnosis of the grandfather points out the importance of considering HPRT deficiency in patients with hyperuricemia and any neurologic abnormalities. It also highlights the importance of examining for increased uric acid excretion in hyperuricemic patients and considering HPRT deficiency in the evaluation for hyperuricemia and its consequences, such as nephrolithiasis and hyperechoic renal pyramids.13 Measurement of plasma and urinary uric acid levels is not part of routine diagnostic panels in infancy and childhood. Commonly, HPRT deficiency is considered only in patients with self-injurious behavior. Nephrolithiasis and gout may be late findings, and waiting for them may delay diagnosis. An apparent diagnosis of cerebral palsy with no history of perinatal problems in a hyperuricemic patient should trigger an HPRT assay, which can readily be performed on dried blood spots on filter paper.9

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Correspondence: Kyriakie Sarafoglou, MD, Department of Pediatrics, University of Minnesota, MMC 8404, 13-124 PWB, 516 Delaware St SE, Minneapolis, MN 55455 (saraf010@umn.edu).

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sarafoglou, Grosse-Redlinger, and Nyhan. Acquisition of data: Sarafoglou, Boys, Charnas, Otten, Broock, and Nyhan. Analysis and interpretation of data: Sarafoglou and Nyhan. Drafting of the manuscript: Sarafoglou, Grosse-Redlinger, Boys, Otten, and Nyhan. Critical revision of the manuscript for important intellectual content: Sarafoglou, Charnas, and Broock. Administrative, technical, and material support: Grosse-Redlinger.

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