ARTÍCULO DE REVISIÓN

A NEW MUTATION AT EXON 2 OF HPRT1 LOCUS CAUSING LESCH-NYHAN SYNDROME

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ABSTRACT

Introduction: Lesch-Nyhan syndrome (LNS) is an X-linked recessive inborn error of metabolism, due to deficiency of the enzyme Hypoxanthine-guanine-phosphoribosyl transferase (HGPRT; EC.2.4.2.8) resulting in hyperuricemia, neurological and behavioural disturbances. In the present work, we report the results of the study of a Colombian family, where LNS was previously clinically and biochemically diagnosed.

Material and Methods: The full HPRT gene, including 9 exons and 8 introns, was amplified on eight separate DNA fragments. Both strands, forward and reverse, of the amplified DNA fragments were analyzed and the obtained sequences were compared with those deposited at National Center for Biotechnology Information.

Results and conclusions: Sequence analysis allowed the detection of new LNS causing mutation, an adenine deletion in exon 2 of HPRT1 gene resulting in a frameshift which determines a premature stop codon. This study, besides adding a new mutation to the already large spectrum of disease causing variation at HPRT, allows therefore providing genetic counseling for the family as well as prenatal diagnosis.

Keywords: Lesch-Nyhan, HGPRT deficiency, genetic counseling, X-linked recessive, mutation

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Lesch-Nyhan syndrome (LNS) is an X-linked recessive inborn error of metabolism, due to deficiency of the enzyme Hypoxanthine-guanine-phosphoribosyltransferase (HGPRT; EC.2.4.2.8) resulting in hyperuricemia, neurological and behavioural disturbances. In the present work, we report the results of the study of a Colombian family, where LNS was previously clinically and biochemically diagnosed. Sequence analysis allowed the detection of new LNS causing mutation, an adenine deletion in exon 2 of HPRT1 gene resulting in a frame shift which determines a premature stop codon.

The Lesch-Nyhan syndrome (LNS) is an inborn error of purine metabolism caused by a virtually complete deficiency (less than 1.5% of the normal level) of the enzyme Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) causing hyperuricemia and profound neurological disturbances (OMIM#300322). LNS is characterized by an overproduction of uric acid, neurological dysfunction, varying degrees of learning disability, and some behavioral abnormalities including self-mutilation. Three main phenotypic subgroups are recognized. The most severe subgroup is Lesch-Nyhan disease (LND), in which full classical syndrome occurs. Least affected subgroup is HGPRT-related hyperuricemia (HRH), where patients exhibit overproduction of uric acid and show a residual enzyme activity of 8%. In HRH the neurobehavioral features are absent or sufficiently mild with no clinical significance. An intermediate subgroup is HGPRT-related neurological dysfunction (HND), where patients exhibit overproduction of uric acid along with varying degrees of neurological impairments and display 1.5–8% of residual enzyme activity.

The mutations are dispersed all over the gene, both in exons and intronic regions, and are very heterogeneous both in type and effects on HPRT activity. However, recent studies have revealed multiple unrelated patients with similar mutations, providing an opportunity to examine genotype–phenotype correlations. The full HPRT gene, including 9 exons and 8 introns, was amplified on eight separate DNA fragments following a previous described protocol. Both strands, forward and reverse, of the amplified DNA fragments were sequenced employing Big Dye Terminator Cycle Sequencing Kit (Applied Biosystems) in an ABI PRISM 377 DNA sequencer (Applied Biosystems). Obtained sequences were compared with those deposited at NCBI.

Complete sequencing of the 9 exons and 8 introns of HPRT gene of both affected individuals, has revealed an adenine deletion at position 52 of exon 2. No other variation previously associated with the disease was found. The sequencing results of the affected male and a normal homozygote female are shown in Fig 2 and Fig 3 respectively.
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