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Letter to the Editor

Linkage between HPRTB STR alleles and Lesch–Nyhan syndrome inside a family: Implications in forensic casework

Dear Editor,

The use of neutral markers in the forensic field has been recommended in order to avoid ethical concerns. Therefore, genetic markers that disclose diseases or genetic risks should not be considered in forensic investigations and, for this reason, in 2005, Szibor and co-authors discarded the use of HumARA [1]. The HPRTB is a polymorphic tetranucleotide repeat located in the intron 3 of the HPRT gene, which was first reported in 1991 [2] with alleles presenting 9–17 TCTA repeat units. Together with HumARA, HPRTB was one of the first X chromosome specific STRs used in forensic genetics and it is still widely used because of its inclusion in a commercial kit *Investigator Argus X-12 Kit* (Qiagen) (e.g. [3–7]).

Although no association between HPRTB alleles or genotypes and the risk for diseases was until now reported, some mutations on HPRT gene are known to be responsible for the Lesch–Nyhan syndrome (LNS). The LNS is a recessive innate error of the purines metabolism caused by a deficiency in the enzyme Hypoxanthine-guanine Phosphoribosyl Transferase (HPRT; OMIM 300322). The partial deficiency of HGPRT is characterized by hyperuricemia and neurological disorders (OMIM 300323). In LNS patients HPRT activity is reduced to less than 1.5% of the normal level. The LNS is characterized by an overproduction of uric acid synthesis, neurological dysfunction, varying degrees of learning disability, and some behavioral abnormalities including self-injurious with mutilation [8]. HPRT coding gene is located on X chromosome, at Xq26–q27 region, and consists of nine exons and eight introns in a total length sequence of 45 kb [9].

In this letter we report the segregation of HPRTB STR alleles inside a Colombian family, where LNS was previously clinically and biochemically diagnosed [10,11] (Fig. 1). Trying to establish the carrier status of the women in this family, the HPRTB was typed in a PCR multiplex reaction as previously described [5,6]. This multiplex also includes DXS8378, DXS9898, DXS8377, GATA172D05, DXS7423, DXS6809, DXS7132, DXS101 and

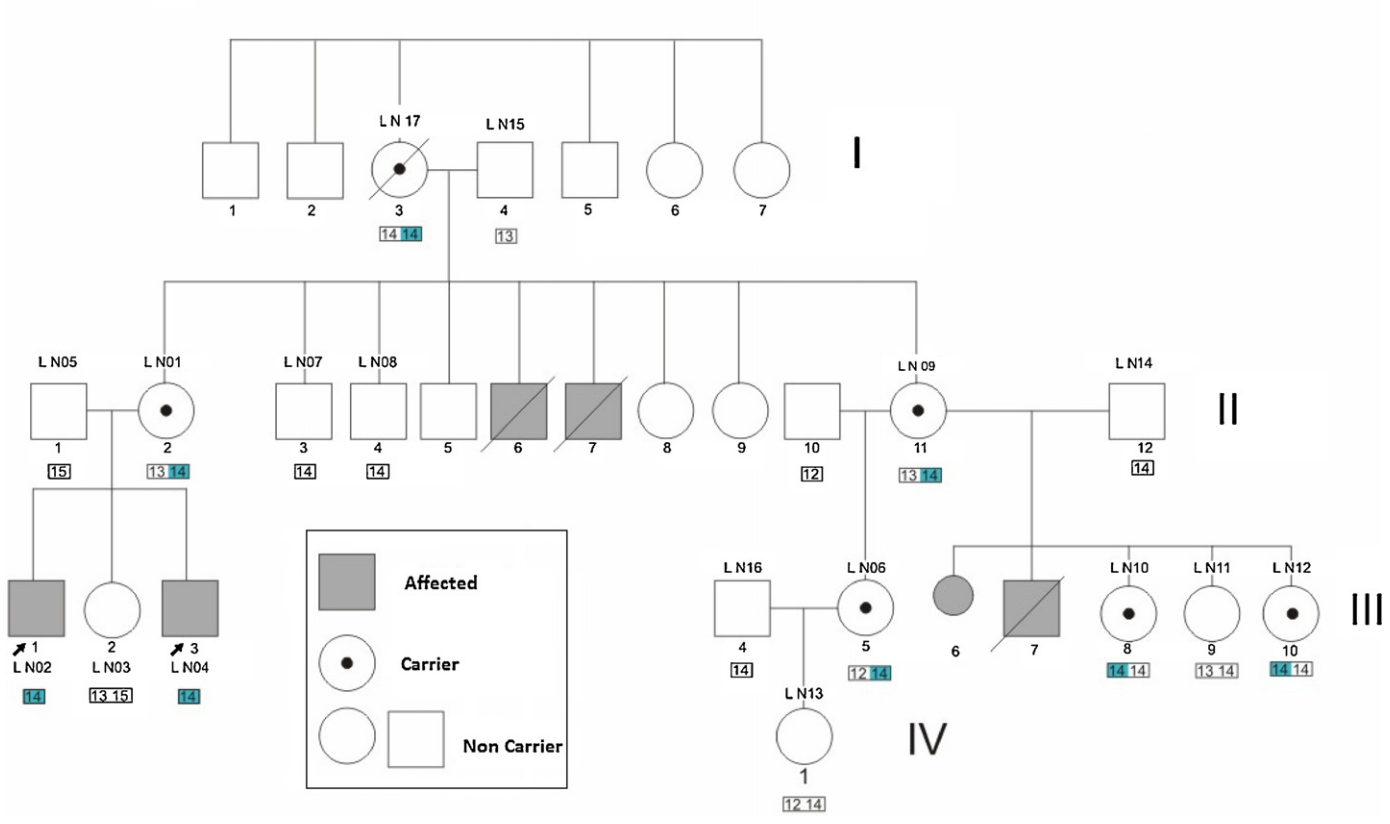

Fig. 1. Pedigree representing the studied family and the observed HPRTB genotypes in the 17 individuals accessible to the present study, which are represented by the codes LN01–LN17.

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Table 1
Carrier status of all women in the third and fourth generations of Fig. 1, based on their HPRTB genotypes, and corresponding risk of having an affected son.

Code	Status	Genotypes	Maternal allele	Paternal allele	Risk of transmission
LN01	Carrier	13/14	14	13	50%
LN09	Carrier	13/14	14	13	50%
LN03	Non-carrier	13/15	13	15	0%
LN06	Carrier	12/14	14	12	50%
LN10	Carrier	14/14	14	14	50%
LN11	Non-carrier	13/14	13	14	0%
LN12	Carrier	14/14	14	14	50%
LN13	Non-carrier	12/14	12	14	0%

DXS6789 markers that were used to confirm kinships among the subjects. The results obtained are presented in Fig. 1. Based on genotypes from LN15 (represented in the first generation) and their descendents (second generation), it was possible to establish that allele 14 co-segregates with the mutation causing LNS, after inferring HPRTB genotype of the individual LN17 (see Fig. 1). The genotype of the subjects from generation II shows that LN07 and LN08 inherited an allele 14 from the mother that was not linked to the LNS causing mutation. On the contrary, LN01 and LN09 have inherited another allele 14 from the mother that co-segregates with the disease, which is confirmed by their affected offspring. Finally, the HPRTB genotype of the two affected males in this family (LN02 and LN04) allowed confirming the co-segregation of the maternal allele 14 and LNS. Therefore, based on HPRTB genotypes, it was possible to establish the carrier status of all women in the third and fourth generations (the results are presented in Table 1).

This study demonstrates that, as expected from the localization of HPRTB in intron 3 of the gene, and the high diversity of this STR in most human populations (e.g. [3,6]), this marker can be a useful tool to detect LNS carrier females inside affected families. Nevertheless, until now, no association could be established between STR alleles or genotypes and LNS phenotype at a population level. In the current family, the disease causing mutation was linked to the STR allele 14, which is the most frequent allele detected in the Santander population (from where this family originates), with a frequency of 34% [6]. Allele 14 is also one of the most frequent alleles in Africans, Europeans and Asians [4,5]. Moreover, the mutations that have been so far detected in HPRT1 gene are very heterogeneous, and up to 400 different mutations have been reported in LNS affected families worldwide (www.lesch-nyhan.org). Therefore, unless a strong founder effect occurring in a small endogamous population, it is not expected that HPRTB genotype information will be able to disclose HPRT1 associated diseases or genetic risk in the absence of a family history [12].

In summary, although located inside a coding gene, HPRTB seems to be safely usable for forensic purposes without revealing any health risks of the subjects. In the few cases with a known familiar history of LNS or other HPRT1 associated mutations or diseases, in the same way as for other forensic markers that are physically linked to disease-causing mutations, the use of HPRTB for identification purposes should be avoided, or the possibility of inferring genetic risk should be communicated.

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