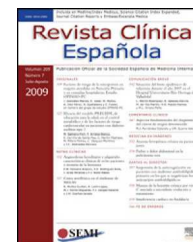


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EDITORIAL

Lesch–Nyhan disease with no HPRT1 gene mutation?



¿Síndrome de Lesch-Nyhan sin mutación genética HPRT1?

Lesch–Nyhan disease is a classical inherited metabolic disorder that was among the first genetic diseases to have its gene identified and cloned. This gene is designated *HPRT1*, and it is among the most intensively studied of all genes in the human genome, with more than 400 clinically relevant mutations documented.³ There is a very strong relationship between mutations in the *HPRT1* gene and clinical disease. Every known change in the human *HPRT1* gene has been associated with disease; there are no reports of benign sequence variants, and all mutations are fully penetrant.

If this relationship is so strong, how is it possible for the gene to have no discoverable mutation in a patient with Lesch–Nyhan disease? In this issue, Trigueros-Genao and Torres describe a patient for whom no mutation could be detected in the coding region of the *HPRT1* gene.⁵ Others also have described similar cases, although they appear to be quite rare.³ One possible explanation is that there is a second gene that may cause clinical features closely resembling Lesch–Nyhan disease. This possibility is unlikely because the clinical phenotype of Lesch–Nyhan disease has never been associated with any other gene. Another possibility is that there are non-coding changes in the *HPRT1* gene that block the production of the associated protein, HGPRT. This possibility has been verified in some of the recently described cases by demonstrating a normal coding region of the gene together with low or absent HGPRT enzyme function.

How is it possible for an apparently normal gene to fail to produce mRNA and associated protein? Here again, there are two possibilities. One of them involves hidden mutations in non-coding regions of the gene that control its transcription. Most gene tests examine only exons, the regions of a gene that code protein, because these regions are most likely to disrupt the protein function. Genetic tests often omit the non-coding regions, such as introns and promoter regions, because of the low probability of documenting a pathological change, and the high costs associated with sequencing these very large stretches of DNA. However, it

is known that mutations in introns or promoter regions can block the transcription of normal mRNA. If production of mRNA is impaired, there will be reduced production enzyme function, even with an entirely normal coding region for the gene. For example, there are reports for three cases with Lesch–Nyhan disease who had deletions in the promoter region up to 33 kb from the transcriptional starting site, blocking mRNA transcription.^{8,9} Two other cases had single base substitutions in introns, creating a false splice site and a grossly abnormal mRNA to be transcribed.^{1,7}

Another possible reason that an apparently normal gene may fail to produce mRNA and associated protein involves epigenetic mechanisms, as summarized nicely by Trigueros-Genao and Torres.⁵ Here there are no mutations in coding regions, introns, or promoter regions. Instead, methylation of specific bases in the DNA is a potential mechanism that can block transcription. Methylation is part of a normal mechanism designed to silence unwanted genes at different stages of development and in specific types of cells. However, abnormal patterns of methylation can also cause abnormal gene silencing leading to disease. Another mechanism involves abnormal function of microRNAs. These microRNAs do not code for protein, but serve as regulatory molecules and alter transcription from other mRNAs. Theoretically, and an abnormal microRNA that targets the *HPRT1* transcript could block transcription and cause reduced enzyme function. So far, there are no proven examples of epigenetic abnormalities involving abnormal methylation or microRNAs for Lesch–Nyhan disease. However, these mechanisms could explain the case of Triguero-Genao and Torres, as well as several other patients who had normal *HPRT1* coding regions.^{2,4,6}

Although Lesch–Nyhan disease is quite rare, it has led the way in understanding the complex mechanisms underlying genotype-phenotype correlations in human disease.³ Because the relationship between the disease and the gene is so strong, any apparent exceptions deserve further scrutiny, because they are likely to lead to novel mechanisms that apply also to other genetic diseases.

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