Nonpenetrance of the Most Frequent Autosomal Recessive Leber Congenital Amaurosis Mutation in NMNAT1

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IMPORTANTThe NMNAT1 gene was recently found to be mutated in a subset of patients with Leber congenital amaurosis and macular atrophy. The most prevalent NMNAT1 variant was p.Glu257Lys, which was observed in 38 of 106 alleles (35.8%). On the basis of functional assays, it was deemed a severe variant.

OBSERVATIONS The p.Glu257Lys variant was 80-fold less frequent in a homozygous state in patients with Leber congenital amaurosis than predicted based on its heterozygosity frequency in the European American population. Moreover, we identified this variant in a homozygous state in a patient with no ocular abnormalities.

CONCLUSIONS AND RELEVANCE On the basis of these results, the p.Glu257Lys variant is considered not fully penetrant. Homozygotes of the p.Glu257Lys variant in most persons are therefore not associated with ocular disease. Consequently, genetic counselors should exercise great caution in the interpretation of this variant.

Published online May 15, 2014.

The activity of NMNAT1 was measured in erythrocytes in the 1 homozygous patient and was significantly lower than in his heterozygous mother. This variant was also tested in a gene construct in HeLa cells and was suggested to be the most severe allele of 4 NMNAT1 variants.

In the Department of Human Genetics, Radboudumc, Nijmegen, exome database, the p.Glu257Lys variant was found in 10 of 850 persons. One of these individuals (patient II-4), who had intellectual disability, was carrying this substitution in a homozygous state (Figure). Interestingly, an unaffected sibling (individual II-1) was also homozygous for p.Glu257Lys. After clinical and ophthalmologic examination, individuals II-1 and II-4 did not have any ocular abnormalities.

On the basis of these findings, we assume that in persons of European descent there is a much larger group of healthy individuals who carry the p.Glu257Lys variant in a homozygous state than there are patients with LCA who carry this variant on both alleles. In patients with LCA carrying one p.Glu257Lys variant, the other NMNAT1 allele would then be predicted to be more severe. Additional evidence for this assumption was obtained using haplotype analysis. The patient with LCA who was previously homozygous for the p.Glu257Lys mutation was analyzed for single-nucleotide polymorphisms in NMNAT1 and proven to harbor this variant on 2 different haplotypes. In our patients, one of these haplotypes was present in every person with the p.Glu257Lys variant, including the healthy individual (patient II-1) (data not shown). Consequently, we hypothesize that there may be differential expression of the 2 alleles harboring the p.Glu257Lys mutation due to trans- or cis-acting elements. This would ren-
Reduced penetrance is frequently observed in both dominant and recessive disorders. The relevant variants can be hypomorphic for several reasons. Besides environmental factors (such as in the case of breast cancer in BRCA1/2 [OMIM 113705/600185] mutation carriers), incomplete penetrance may be due to trans- or cis-acting elements, which would influence its expression, rendering the variant mild and benign. An example of a trans-acting modifier was provided for the PRPF31 gene implicated in autosomal-dominant retinitis pigmentosa with reduced penetrance.10 A haploinsufficiency model was proposed for PRPF31-associated retinitis pigmentosa. CNOT3 (OMIM 604910) was found to act as a transcriptional repressor of PRPF31, thereby influencing the expression level of the wild-type PRPF31 gene.11,12 The identification of this kind of transcriptional regulators is possible if the target gene of interest and its regulators are expressed highly enough in accessible patient cells. The identification of this kind of modifiers through high-throughput sequencing is challenging in view of the enormous genetic variation observed in the human population.

Taken together, we propose that the NMNAT1 p.Glu257Lys variant is a hypomorphic variant that almost without exception causes LCA in combination with more severe NMNAT1 variants. Other variants in NMNAT1 are far less frequent and therefore have not been observed in a homozygous state. However, it may be speculated that they also represent combinations of mild and severe mutations or 2 alterations exerting a moderate effect, which cumulatively result in disease. In a homozygous state, the mild variants would generally not cause LCA, unless one or both gene copies show reduced transcription, possibly due to trans- or cis-acting modifier elements. This conclusion should be taken into consideration when families carrying this variant are genetically counseled, especially when the retinal phenotype lacks the macular atrophy and does not occur early in life. In those cases, the causal variants are most likely situated in other genes.


