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Correspondence

Correspondence to: "Heterozygous mutation in the X chromosomal NDUFA1 gene in a girl with complex I deficiency" and "A novel NDUFA1 mutation leads to progressive mitochondrial complex I- specific neurodegenerative disease"

Dear editor:

A specific variant in *NDUFA1* (c.94G > C, p.Gly32Arg) has been reported pathogenic in two separate papers; we have re-evaluated the variant and suggest that it should presently not be considered a disease-causing variant.

Pathogenic variants in *NDUFA1* were first reported in 2007 in two unrelated male patients with an isolated complex I deficiency and developmental delay, hypotonia, ataxia, nystagmus, choreoathetosis, bilateral cerebral MRI lesions compatible with Leigh syndrome, and psychomotor delay, hypotonia, epilepsy, respectively [1].

In 2011, Mayr et al. reported a girl with mild muscular hypotonia and lactic acidosis, where a muscle biopsy showed an isolated complex I deficiency. Sequencing of DNA from blood and fibroblasts revealed a heterozygous variant, c.94G > C, p.Gly32Arg in the X-chromosomal gene *NDUFA1* [2] that was evaluated causative. In addition, in 2009 Potluri et al. reported two male patients with complex I deficiency, both hemizygous for the variant, which was not found in 150 ethnically matched controls. They were first cousins (their mothers were sisters). One of the male patients developed a neurodegenerative disorder with psychomotor retardation, epilepsy, ataxia and retinitis pigmentosa, whereas his cousin developed epilepsy, hearing loss, ataxia and hypotonia. The entire mtDNA, as well as 40 nuclear genes encoding mainly structural subunits of complex I, were sequenced in both patients [3].

In a search for nuclear genetic factor involved in Leber Hereditary Optic Neuropathy (LHON) we have identified the c.94 G > C, p.Gly32Arg variant in *NDUFA1* in one individual. The variant is reported in GnomAD (http://gnomad.broadinstitute.org/) with an overall allele frequency of 1 in 171. In Europeans (non-Finnish), the allele frequency is 1 in 104, including four homozygotes and 309 hemizygotes reported.

Using various in silico prediction tools, the effect of the variant is predicted tolerated via SIFT (http://sift.jcvi.org/www/SIFT_enst_submit.html); possibly damaging with a score of 0.767 via Polyphen2 (http://genetics.bwh.harvard.edu/pph2/) and a polymorphism via MutationTaster (http://www.mutationtaster.org/).

In summary, based on the frequency of the p.Gly32Arg variant in *NDUFA1* and in silico predictions of pathogenicity, we believe that it is unlikely that the variant in itself causes complex I deficiency in the three patients reported. Our revised interpretation will help avoid potential misdiagnosis or other associated actions, such as reproductive decisions, given that published variants are often automatically considered pathogenic because of their annotation in public variant databases. These findings underscore the importance of continued re-interpretation of variants in a time of constantly improving technology, expanding variant databases and changing annotation.

References

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