ANNALS of Clinical and Translational Neurology
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LETTER

Comment on: A novel dysferlin-mutant pseudoexon bypassed with antisense oligonucleotides

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doi: 10.1002/acn3.216

Dear Editor,

We read with great interest the publication of Dominov et al.[1] demonstrating for the first time the implication of a deep intronic sequence variant (NM_003494.3: Intron 44: c.4886+1249G>T) as a disease-causing mutation for the dysferlin gene (*DYSF*). As referenced by the authors in their article, we previously underlined that for an important proportion of patients (19.5% of patients, based on the analysis of a large cohort of dysferlinopathy patients)[2] affected with dysferlinopathy, no second expected disease-causing mutation of *DYSF* could be identified using sequence analysis of all coding exons and flanking intronic boundaries.[2] This situation is most probably related to the difficulty of systematically identifying "atypical" mutations using Sanger sequencing, which includes exonic deletions and/or duplications,[3] and deep intronic mutations causing in particular splicing defects.[1,4]

In their article, Dominov et al. detected this mutation in three out of seven analyzed index patients, for whom only one disease-causing *DYSF* mutation had previously been identified using sequence analysis of all coding exons and flanking intronic boundaries.

To further evaluate the frequency of this deep intronic mutation, we screened 33 index patients initially included for *DYSF* mutational analysis based on reduced or absent dysferlin protein evidenced on muscle tissue or monocyte samples, and for whom sequence analysis of all coding exons and flanking intronic boundaries previously identified only one (15 patients), or no (18 patients) disease-causing mutation. Direct sequencing of the genomic sequence encompassing c.4886+1249G>T in intron 44 was done with the following primers: forward 5′ tgctgtttggatgtgagctt 3′ and reverse 5′gagatggggaaacaggcatg3′.

The c.4886+1249G>T mutation was retrieved in only one case out of the 33 studied, in a patient with complete absence of dysferlin evidenced using immunoblot testing, and at a compound heterozygous state with a c.1168G>A (p.Asp390Asn) variant, for which currently available data orientate toward a possibly deleterious effect, but are not concluding (not referenced in the data compiled by the Exome Aggregation Consortium (ExAC), Cambridge, MA, http://exac.broadinstitute.org; and bioinformatics predictive pathogenicity score using UMD-Predictor®[2] of 41, classified nonpathogenic; and PolyPhen-2[5] score of 0.983, classified as probably damaging).

Our results therefore underline that the c.4886+1249G>T mutation does not constitute a prevalent recurrent mutational event, at least in a heterogeneous population as the one we studied, including patients of mainly European and African descend. Noteworthy, as in the report by Dominov et al.[1] this patient is of Northern European descent, underlining the interest of further investigations regarding a possible founder effect.

Acknowledgments

We thank Véronique Blanck, Eugénie Dionnet, and Mathieu Cerino for their technical help, and Laura Rufibach for helpful discussions. This work was supported by INSERM, Aix Marseille University, grants from the AFM-Téléthon (Strategic pole MNH Decrypt) and the Jain Foundation.

Conflict of Interest

None declared.

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