



HAL
open science

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

Virginie Kergourlay, Gaëlle Blandin, Veronique Blanck, Nicolas Lévy, Marc Bartoli, Martin Krahn

► To cite this version:

Virginie Kergourlay, Gaëlle Blandin, Veronique Blanck, Nicolas Lévy, Marc Bartoli, et al.. Comment on: A novel dysferlin-mutant pseudoexon bypassed with antisense oligonucleotides. *Annals of Clinical and Translational Neurology*, 2015, 2 (7), pp.783-784. 10.1002/acn3.216 . hal-01610015

HAL Id: hal-01610015

<https://hal.science/hal-01610015>

Submitted on 18 Apr 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

LETTER

Comment on: A novel dysferlin-mutant pseudoexon bypassed with antisense oligonucleotidesVirginie Kergourlay^{1,2}, Gaëlle Blandin^{1,2}, Véronique Blanck³, Nicolas Lévy^{1,2,3}, Marc Bartoli^{1,2,3,a} & Martin Krahn^{1,2,3,*}¹Aix Marseille Université, GMGF, 13385 Marseille, France²Inserm, UMR_S 910, 13385 Marseille, France³AP-HM, Département de Génétique Médicale et de Biologie Cellulaire, Hôpital d'Enfants de la Timone, 13385 Marseille, France***Correspondence**

Tel: ++33 491 32 49 40; Fax: ++33 491 80 43 19; E-mail: martin.krahn@univ-amu.fr

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' tgctgtttgagatgagctt 3' and reverse 5' gagatggggaacaggcatg3'.

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-2⁵ 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 descent. 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.

^aAuthors at equal contribution.

References

1. Dominov JA, Uyan Ö, Sapp PC, et al. A novel dysferlin mutant pseudoexon bypassed with antisense oligonucleotides. *Ann Clin Transl Neurol* 2014;1:703–720.
2. Blandin G, Beroud C, Labelle V, et al. UMD-DYSF, a novel locus specific database for the compilation and interactive analysis of mutations in the dysferlin gene. *Hum Mutat* 2012;33:E2317–E2331.
3. Krahn M, Borges A, Navarro C, et al. Identification of different genomic deletions and one duplication in the dysferlin gene using multiplex ligation-dependent probe amplification and genomic quantitative PCR. *Genet Test Mol Biomarkers* 2009;13:439–442.
4. Kergourlay V, Raï G, Blandin G, et al. Identification of splicing defects caused by mutations in the dysferlin gene. *Hum Mutat* 2014;35:1532–1541.
5. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nat Methods* 2010;7:248–249.