TRPV4 neuropathy-causing mutations localize to the convex face of the ankyrin repeat domain

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Re: "Phenotypic spectrum and incidence of *TRPV4* mutations in patients with inherited axonal neuropathy" Echaniz-Laguna, et al., 82:1919-1926.

We read with interest the report by Echaniz-Laguna et al. on *TRPV4* mutations in inherited neuropathy [1] and appreciate the excellent clinical descriptions. Nonetheless, we have a couple of concerns we felt were important to convey. We note that the authors refer to the Arg186Gln mutation as "not being previously reported" [1]. In fact, we reported this mutation in *Neurology* [2] along with descriptions of its location in the TRPV4 ankyrin repeat domain (ARD) and its functional effects in cell-based studies. Another concern regards the localization of the mutated residues. The authors state, "the side chain of Arg186 is directed toward the concave part of the domain, as is the case for Arg232, Arg269, Arg315, and Arg316." Despite being based on our published crystal structures of the TRPV4-ARD (although without appropriate citation) [3, 4], these conclusions appear to be in contradiction to our findings indicating that the mutated arginine residues reside on the convex face of the ARD [2-5]. Given that the location of the mutations has very significant implications regarding their pathogenicity, we do not believe this is a minor point and feel it is important that the authors either correct or make a complete case for their conclusions.

1. Echaniz-Laguna A, Dubourg O, Carlier P, et al. Phenotypic spectrum and incidence of *TRPV4* mutations in patients with inherited axonal neuropathy. Neurology 2014;82:1919-1926.

2. Landouré G, Sullivan JM, Johnson JO, et al. Exome sequencing identifies a novel TRPV4 mutation in a CMT2C family. Neurology 2012;79:192-194.

3. Landouré G, Zdebik AA, Martinez T, et al. Mutations in *TRPV4* cause Charcot-Marie-Tooth disease type 2C. Nature Genetics 2010;42:170-174.

4. Inada H, Procko E, Sotomayor M, Gaudet R. Structural and biochemical consequences of disease-causing mutations in the ankyrin repeat domain of the human TRPV4 channel. Biochemistry 2012;6195-6206.

5. Zimoń M, Baets J, Auer-Grumbach M, et al. Dominant mutations in the cation channel gene *transient receptor potential vanilloid 4* cause an unusual spectrum of neuropathies. Brain 2010;133:1798-1809.