
Copyright:

© The Author (2014). Published by Oxford University Press on behalf of the Guarantors of Brain. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

DOI link to article:

http://dx.doi.org/10.1093/brain/awu034

Date deposited:

06/07/2015

This work is licensed under a Creative Commons Attribution 3.0 Unported License
LETTER TO THE EDITOR

Reply: Hereditary myopathy with early respiratory failure is caused by mutations in the titin FN3 119 domain

Gerald Pfeffer and Patrick F. Chinnery

Institute of Genetic Medicine, Newcastle University; and Department of Neurology, Royal Victoria Infirmary, Newcastle, NE1 3BZ, UK

Correspondence to: Prof Patrick F. Chinnery,
E-mail: patrick.chinnery@ncl.ac.uk

Sir, The response by Lange et al. (2014) provides important confirmatory information. The coincidence of the FN 119 domain mutation (p.P30091L) with the kinase domain variant (p.R2450W or R279W) in all patients previously reported by Lange et al. (2005) confirms speculation (Hedberg et al., 2013; Pfeffer et al., 2013) that the HMERF in the original family was primarily a result of the p.P30091L FN 119 mutation, and not to the kinase domain variant (p.R2450W or R279W). The kinase domain variant (p.R2450W or R279W) was originally reported to be the cause of HMERF by Lange et al. (2005), but has subsequently been reported in healthy control subjects. On the other hand, the p.P30091L FN 119 mutation has been reported repeatedly and exclusively in HMERF families.

Lange et al. (2014) suggest that we contradict ourselves regarding the pathogenicity of the p.P30091L variant, citing out of context (and out of chronological order) our report in which we considered p.P30091L as a possible neutral variant (Pfeffer et al., 2014). However, we had also written that the variant may be pathogenic with variable penetrance and/or expressivity. At that time, it was the first published report of HMERF with this mutation, so we could not reach a final conclusion with confidence. Since then, another study confirmed the association of the p.P30091L mutation with HMERF (Palmio et al., 2013), and in retrospect, a patient with this mutation and ‘myopathy with cytoplasmic aggregates’ (Vasli et al., 2012) could also have HMERF. Lange et al. (2014) now report that their HMERF patients originally reported in 2005 have the same mutation. Although we had previously been uncertain regarding the pathogenicity of the p.P30091L variant, current evidence repeatedly links this mutation with HMERF (Vasli et al., 2012; Hedberg et al., 2013; Palmio et al., 2013; Pfeffer et al., 2014; Lange et al., 2014).

The very interesting question is the reason for the more severe disease expressivity and complete penetrance in the patients reported (Edstrom et al., 1990; Lange et al., 2005), compared with other patients who have the p.P30091L mutation (Palmio et al., 2013; Pfeffer et al., 2014). Lange et al. (2014) hypothesize that the kinase domain variant is the cause of the more severe phenotype in their patients. For the time being, there is no additional evidence to support this hypothesis. As indirect evidence, Lange et al. (2014) cite the importance of recessive kinase domain mutations in a recent publication (Chauveau et al., 2013), although the principal clinical finding in most of these patients was cardiomyopathy, which does not occur in HMERF patients, and the patients have a different mode of inheritance (HMERF is autosomal dominant).

We attempted to find evidence for a modifier effect for kinase variants by screening a HMERF population of 33 patients, but our findings did not support this hypothesis (Pfeffer et al., 2013). At present we can only reach the following conclusions with any confidence: (i) HMERF is caused by mutations in the FN119 domain of TTN (Ohlsson et al., 2012; Pfeffer et al., 2012, 2013a; Vasli et al., 2012; Hedberg et al., 2013; Izumi et al., 2013; Palmio et al., 2013; Toro et al., 2013; Lange et al., 2014); (ii) one particular mutation in the FN119 domain, p.P30091L, has variable expressivity and penetrance (Palmio et al., 2013; Pfeffer et al., 2014; Lange et al., 2014), and the inheritance pattern may be dominant (Lange et al., 2005; Pfeffer et al., 2014) or may be recessive (Palmio et al., 2013); (iii) in two screening studies of patients with undiagnosed myofibrillar myopathy, sequencing of 172 families identified nine patients with FN119 domain mutations, but none with kinase domain mutations (Pfeffer et al., 2014; Toro et al., 2013); (iv) the kinase variant of interest (R32450W/R279W) is reported in controls (it is listed in dbSNP as rs140319117 with an allele frequency of 0.2%, and we have also recently reported a healthy control with this variant) (Pfeffer et al., 2013). This kinase variant does not appear to be capable of causing HMERF; and (v) R32450W/R279W has only been associated with HMERF in the original report by Lange et al.
In this family, a common haplotype contains both a FN119 domain mutation and the kinase domain variant (Lange et al., 2014). Given the more severe phenotype in these patients, it is possible (but not proven) that the kinase domain mutation may be a modifier of the condition caused by the mutation in the FN119 domain. Other possible explanations include a different monogenic factor on the same haplotype, complex genetic factors, environmental factors, or a combination of these. Further evidence is required to substantiate the hypothesis proposed by Lange et al. (2014), that R32450W/R279W modifies the phenotype of HMERF.

References


