LETTER TO THE EDITOR

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

Carola Hedberg,1 Atle Melberg,2 Kathe Dahlbom3 and Anders Oldfors1

1 Department of Pathology, University of Gothenburg, Gothenburg, Sweden
2 Department of Neuroscience, Neurology, Uppsala University, Uppsala, Sweden
3 Department of Neurology and Clinical Neurophysiology, Örebro University Hospital, Örebro, Sweden

Correspondence to: Carola Hedberg,
Department of Pathology,
Sahlgrenska University Hospital,
Gula Stråket 8,
413 45 Gothenburg, Sweden
E-mail: carola.hedberg@gu.se

Sir, Hereditary myopathy with early respiratory failure (HMERF) is a neuromuscular disease associated with aggregation of various proteins in muscle fibres and muscle degeneration (Fig. 1) and was described in detail in several families by Edström et al. (1990). Linkage analyses indicated that the disease locus was in the distal part of the long arm of chromosome 2 (Nicolao et al., 1999). Titin was a candidate gene and a missense variant that segregated with the disease in two of the families and in a sporadic case was later identified (Lange et al., 2005). This variant p.R32450W (R279W Lange et al. (2005)) was localized to a part of the giant titin protein that exhibits kinase properties. We identified a missense mutation in the fibronectin-like FN3 119 domain of A-band titin in several Swedish families with HMERF (Ohlsson et al., 2012). Eight different missense mutations in this FN3 domain have to date been identified (Ohlsson et al., 2012; Pfeffer et al., 2012, 2013; Vasli et al., 2012; Izumi et al., 2013; Palmio et al., 2013; Toro et al., 2013). These findings made us hypothesize that HMERF is always associated with missense mutations in this particular domain. We have now analysed Swedish HMERF patients including relatives of the families described by Lange et al. (2005) and found that patients with the titin kinase variant in fact also carry a missense mutation in the FN3 119 domain. This FN3 119 domain mutation (p.P30091L) has been identified as the cause of HMERF in other families, without any concomitant titin kinase variant (Vasli et al., 2012; Palmio et al., 2013; Pfeffer et al., 2013). The titin kinase variant p.R32450W (R279W Lange et al. (2005)) is a polymorphism (rs140319117) with a frequency of 0.0018 among European Americans.

These data strongly suggest that the titin kinase variant p.R32450W described by Lange et al. (2005) does not cause HMERF by itself. However, with reference to the article by Lange et al. (2005) this titin kinase variant is continuously reported in the literature to cause HMERF. The knowledge that the titin kinase variant p.R32450W by itself does not cause HMERF is crucial for correct genetic counselling.

Figure 1 Muscle biopsy from a patient with HMERF demonstrating muscle fibre protein aggregates (arrow) stained purple by Gomori trichrome.
References


