KLHL41, a BTB-Kelch protein, is critical for skeletal muscle function

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Nemaline myopathy (NEM) is a rare congenital muscle disease that in severe cases results in neonatal death due to respiratory insufficiency. NEM is characterized clinically by skeletal muscle dysfunction (most frequently hypotonia and weakness) and the presence of electron-dense nemaline bodies (rods) on muscle biopsy (Romero *et al.*, 2013). Mutations in eight known genes have previously been found to cause NEM, with six of these encoding thin filament or thin filament-associated proteins (skeletal muscle α-actin, cofilin-2, nebulin, α- and β-tropomyosins, and troponin T1) (Romero *et al.*, 2013). Most recently, causative mutations in genes encoding BTB-Kelch proteins have been identified in myopathies associated with nemaline bodies (*KBTBD13* in autosomal dominant core-rod disease (Sambuughin *et al.*, 2010) and *KLHL40* in autosomal recessive NEM (Ravenscroft *et al.*, 2013). We performed whole exome sequencing of genetically unresolved severe NEM patients and identified recessive small deletions and missense changes in a third gene encoding a skeletal muscle specific BTB-Kelch protein (Kelch-like family member 41; *KLHL41*) in four individuals from unrelated NEM families. Subsequent Sanger sequencing identified compound heterozygous changes in *KLHL41* in a fifth NEM family. Functional studies in zebrafish showed that loss of klhl41 results in diminished motor function and myofibrillar disorganisation. KLHL40 (also known as sarcosin, Krp1 and KBTBD10) has previously been implicated in myofibril assembly (Greenberg *et al.*, 2008; Paxton *et al.*, 2011; du Puy *et al.*, 2012). Studies of BTB-Kelch proteins, have indicated that members of this protein family (there are over 50 in humans) act as substrate adaptors for E3 ubiquitin ligases (Prag & Adams, 2003; Sambuughin *et al.*, 2012). Despite these studies, the roles of BTB-Kelch proteins in skeletal muscle remain largely unknown. In conclusion, these studies expand the genetic heterogeneity of NEM, and further implicate a critical role of BTB-Kelch family members in maintenance of sarcomeric integrity.

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