Title: *CHKB*-Related Muscular Dystrophy *GeneReview* – Skeletal Muscle Biopsy

Authors: Chan S, Nishino I

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Skeletal muscle biopsy. The muscle pathology of all affected patients showed similar characteristic features. In addition to the dystrophic changes with variation in fiber size, interstitial fibrosis, and evidence of necrosis and regeneration in muscle fibers in H&E staining, the most striking finding was the lack of mitochondria in the center of the sarcoplasm and enlarged mitochondria at the periphery of most fibers on the modified Gomori trichrome stain and the oxidative enzyme reactions (NADH-TR and SDH). The same pattern was observed in the cytochrome *c* (COX) and combined COX and succinate dehydrogenase (COX/SDH) stainings. The markedly enlarged mitochondria that look like dabs rather than points are abundant at the periphery of most muscle fibers, leaving the central areas empty [Gutiérrez Ríos et al 2012, Quinlivan et al 2013, Castro-Gago et al 2014]. Electron microscopy confirmed the greatly enlarged mitochondria at the periphery of fibers ("megaconial" appearance) that measured up to 3 or 4 microns in length [Quinlivan et al 2013, Castro-Gago et al 2014] compared to the average mitochondrial length of 0.5-1 micron. The mitochondrial cristae were also densely packed, whorled [Gutiérrez Ríos et al 2012], and disorganized with no paracrystalline inclusions [Castro-Gago et al 2014].

Biochemical evaluation with respiratory chain enzyme analysis on homogenized muscle biopsies of a few patients showed variable results: some were normal [Nishino et al 1998, Mitsuhashi et al 2011, Quinlivan et al 2013, Brady et al 2016, De Fuenmayor-Fernández De La Hoz et al 2016, Vanlander et al 2016], others increased [Quinlivan et al 2013] or decreased [Gutiérrez Ríos et al 2012, Quinlivan et al 2013, Castro-Gago et al 2014, De Fuenmayor-Fernández De La Hoz et al 2016]. Normal findings were reported in a Japanese individual [Nishino et al 1998, Mitsuhashi et al 2011], two British individual (including 1 individual with increased complex IV activities) [Quinlivan et al 2013], a Bulgarian individual [De Fuenmayor-Fernández De La Hoz et al 2016], a Canadian individual [Brady et al 2016], and a Moroccan individual [Vanlander et al 2016], accounting for 60% of all individuals having mitochondrial respiratory chain enzymology study. Four individuals from three different ethnicities had abnormal results. One young African American boy had a low level of complex IV (30%) and complex II (48%) activities with the respiratory chain enzymes corrected for citrate synthase activities [Gutiérrez Ríos et al 2012]. Another British individual confirmed a low level of complex I [Quinlivan et al 2013]. One of the two young Spanish individuals with the same *CHKB* mutation had a combined deficiency of complexes I, III, and IV [Castro-Gago et al 2014]. In contrast, the other had only a single complex one deficiency [10], making interpreting the underlying mitochondrial respiratory chain enzyme defect more complicated.

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