Hum Mol Genet. 2014 May 1;23(9):2353-63. doi: 10.1093/hmg/ddt637. Epub 2013 Dec 13.

Mutations in the collagen XII gene define a new form of extracellular matrix-related myopathy.

Hicks D[1], Farsani GT, Laval S, Collins J, Sarkozy A, Martoni E, Shah A, Zou Y, Koch M, Bönnemann CG, Roberts M, Lochmüller H, Bushby K, Straub V.

Author information

Abstract

Bethlem **myopathy** (BM) [MIM 158810] is a slowly progressive muscle disease characterized by contractures and proximal weakness, which can be caused by **mutations** in one of the **collagen** VI genes (COL6A1, COL6A2 and COL6A3). However, there may be additional causal genes to identify as in ~50% of BM cases no **mutations** in the COL6 genes are identified. In a cohort of -24 patients with a BM-like phenotype, we first sequenced 12 candidate genes based on their function, including genes for known binding partners of **collagen** VI, and those enzymes involved in its correct post-translational modification, assembly and secretion. Proceeding to whole-exome sequencing (WES), we identified **mutations** in the COL12A1 **gene**, a member of the FACIT collagens (fibril-associated collagens with interrupted triple helices) in five individuals from two families. Both families showed dominant inheritance with a clinical phenotype resembling classical BM. Family 1 had a single-base substitution that led to the replacement of one glycine residue in the triple-helical domain, breaking the Gly-X-Y repeating pattern, and Family 2 had a missense mutation, which created a mutant protein with an unpaired cysteine residue. Abnormality at the protein level was confirmed in both families by the intracellular retention of **collagen XII** in patient dermal fibroblasts. The mutation in Family 2 leads to the up-regulation of genes associated with the unfolded protein response (UPR) pathway and swollen, dysmorphic rough-ER. We conclude that the spectrum of causative genes in **extracellular** matrix (ECM)-related myopathies be extended to include COL12A1.

PMID: 24334769 DOI: 10.1093/hmg/ddt637

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances, Grant support

LinkOut - more resources

PubMed Commons

PubMed Commons home

0 comments

How to join PubMed Commons