Bethlem myopathy: long-term follow-up identifies COL6 mutations predicting severe clinical evolution.


Abstract

OBJECTIVE: Mutations in one of the 3 genes encoding collagen VI (COLVI) are responsible for a group of heterogeneous phenotypes of which Bethlem myopathy (BM) represents the milder end of the spectrum. Genotype-phenotype correlations and long-term follow-up description in BM remain scarce.

METHODS: We retrospectively evaluated the long-term clinical evolution, and genotype-phenotype correlations in 35 genetically identified BM patients (23 index cases).

RESULTS: Nineteen patients showed a typical clinical picture with contractures, proximal weakness and slow disease progression while 11 presented a more severe evolution. Five patients showed an atypical presentation, namely a limb girdle muscle weakness in 2 and a congenital myopathy pattern with either no contractures, or only limited to ankles, in 3 of them. Pathogenic COL6A1-3 mutations were mostly missense or in frame exon-skipping resulting in substitutions or deletions. Twenty one different mutations were identified including 12 novel ones. The mode of inheritance was, autosomal dominant in 83% of the index patients (including 17% (N=4) with a de novo mutation), recessive in 13%, and undetermined in one patient. Skipping of exon 14 of COL6A1 was found in 35% of index cases and was mostly associated with a severe clinical evolution. Missense mutations were detected in 39% of index cases and associated with milder forms of the disease.

CONCLUSIONS: Long-term follow-up identified important phenotypic variability in this cohort of 35 BM patients. However, worsening of the functional disability appeared typically after the age of 40 in 47% of our patients, and was frequently associated with COL6A1 exon 14 skipping.
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**KEYWORDS:** COLLAGEN; GENETICS; MYOPATHY; NEUROMUSCULAR

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[Index for MEDLINE]