Collagen VI mutations in Bethlem myopathy

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Summary

Bethlem myopathy is an autosomal dominant myopathy with contractures. Its clinical features consist of slow progression of generalized weakness with limb-girdle preponderance from early childhood onward with periods of arrest for some decades and contractures of several joints, especially the fingers, elbows and ankles. The contractures are not due to joint abnormalities but to relative shortening of muscles compared to their antagonists. There is no cardiac involvement and life expectancy is unaffected. Chapter 1, a review of the literature, contains a discussion on the clinical characteristics, including attention to differences among Bethlem myopathy kindreds and delineation from other nosological entities. Most patients are reported to become symptomatic in their early childhood albeit that detailed observation provides evidence for a congenital nature of the disorder (Chapter 3). During adolescence most patients display little or no weakness but from middle age onward weakness slowly worsens. Insidious progression eventually leads to more impairment than evident from the epitaph "benign" which is usually assigned to this disorder. More than two-thirds of patients aged 50 years and over experience sufficient weakness to necessitate a wheelchair (Chapter 3).

The key objective of the study was molecular characterization of Bethlem myopathy. In the absence of a biochemical clue a genome-wide linkage investigation was undertaken in six kindreds (Chapter 2.1). After exclusion of roughly one-third of the genome, cosegregation of genetic markers with the Bethlem myopathy trait eventually lead to identification of the first locus, the \textit{COL6A1-COL6A2} cluster in the telomeric region of chromosome 21q. The highest two-point lod score obtained within one family exceeded 3 and genetic homogeneity seemed more likely than heterogeneity, for the six families studied. Genetic linkage to the \textit{COL6A1-COL6A2} locus in three additional families affirmed genetic homogeneity (Chapter 2.2). Equivocal clinical features of two individuals and conflicting orientations of the \textit{COL6A1-COL6A2} gene cluster on genetic maps hampered interpretation of the genetic data, which possibly even ruled out \textit{COL6A1} and \textit{COL6A2} as candidate genes.

In collaboration with Speer et al., exclusion of the \textit{COL6A1-COL6A2} locus in a
Summary

French-Canadian kindred ultimately established collagen VI as the protein at stake, as this family displayed genetic linkage to COL6A3 markers on chromosome 2q. Subsequently, sequencing of the entire coding sequence of COL6A1 and COL6A2 in four families revealed a mutation in either gene in three families (Chapter 2.3). Collagen VI mutations had not been described before. The COL6A1 and COL6A2 mutations consisted of a nucleotide substitution that gave rise to a putative disruption of a conserved amino acid sequence, the Gly-X-Y motif. Analogous to mutations in other collagen disorders with a similar disruption of the Gly-X-Y motif, these nucleotide substitutions were thought to be pathogenic instead of linked polymorphisms.

A collagen VI molecule consists of three peptides, α1(VI), α2(VI) and α3(VI), encoded by the COL6A1, COL6A2 and COL6A3 genes. Mutations in all three genes have now been identified in Bethlem myopathy. Collagen VI, a widespread extracellular matrix protein, is thought to be involved with anchorage of cells to the surrounding matrix. Several myopathies are caused by perturbation of cell anchoring structures like dystrophinopathies and congenital muscular dystrophies. Chapter 1 addresses the possible pathophysiology with particular attention to the dominant effect of the mutations and candidate matrix and transmembrane structures that interact with collagen VI.