Collagen VI mutations in Bethlem myopathy

Jöbsis, G.J.

Citation for published version (APA):
General introduction and outline of this thesis
The findings presented here are part of a genetic investigation that started in 1992. The development of novel, highly informative genetic markers had given impetus to genetic linkage studies. These markers, short sequence repeats like dinucleotide repeats (also known as CA-repeats), were relatively suitable to be employed on a large scale. Thus it became feasible to undertake genome wide searches. The work was carried out at the Neurology laboratory of the Academic Medical Center. Unlike this thesis, the study was not limited to Bethlem myopathy. In addition, familial amyotrophic lateral sclerosis, paramyotonia congenita, Kennedy's disease, autosomal dominant cerebellar ataxia type II, and distal spinal muscular atrophy were investigated. The publications listed at the end of this booklet give an indication of the findings in the other disorders studied.

Bethlem myopathy is an autosomal dominant, relatively benign myopathy with contractures. Previously, patients from six families had been characterized at the "Spierziekten" clinic of the Academic Medical Center by Bethlem, van Wijngaarden, Arts, de Visser, and Boers. At the start of the study, these families were contacted. Thirty-four patients and 34 unaffected sibs donated a blood sample for DNA isolation. Contacting the families for obtaining blood samples yielded follow-up data that disclosed novel aspects on the course of the myopathy. After the identification of the first Bethlem myopathy locus, three additional kindreds participated, two from Italy and one from Finland.

Chapter 1 gives a review of the literature on Bethlem myopathy. Chapter 2 deals with the genetic investigations. Firstly, the identification of genetic linkage to markers in the $\text{COL6A1-COL6A2}$ locus on chromosome 21q in six Dutch pedigrees. Secondly, the confirmation of linkage to the same locus for the three additional families. And thirdly, the sequence analysis of the $\text{COL6A1}$ and $\text{COL6A2}$ gene in four families, establishing a mutation in three. Chapter 3 provides a further delineation of the clinical features of the disorder, with particular attention to the mode of onset in children and the progression of weakness in adults.
Figure 1. Participating sibships of six Bethlem myopathy kindreds. Individuals genotyped are indicated with a dot below the pedigree symbol. Gray pedigree symbol refers to an individual with equivocal clinical findings.
The findings presented here are based on a population of 1,000 individuals. The development of genetic markers associated with specific traits is crucial in genetic linkage analysis. These markers can help in identifying regions of the genome that are associated with a particular trait. It is essential to ensure that the markers are informative and reliable for accurate analysis.