Genetic and epigenetic studies of the FSHD-associated D4Z4 repeat

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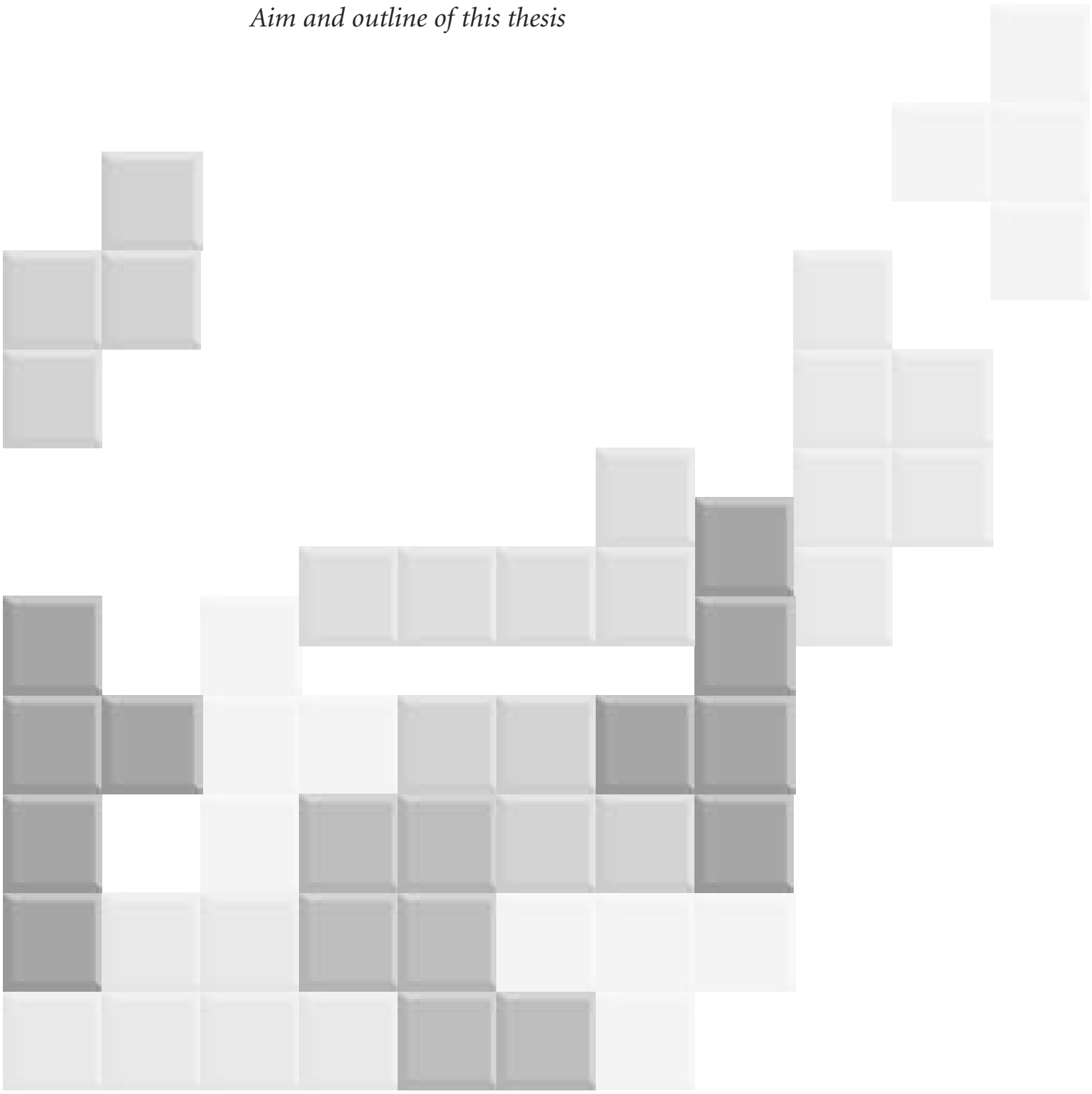
Preface

Aim and outline of this thesis



Facioscapulohumeral muscular dystrophy (FSHD) is a myopathy with an autosomal dominant pattern of inheritance. After Duchenne muscular dystrophy and myotonic dystrophy, this disease is the third most common hereditary muscular dystrophy with a prevalence of approximately 1 in 20000 worldwide. FSHD is characterised by progressive muscle weakness of the facial and shoulder girdle muscles, which may then progress to pelvic girdle weakness or foot-extensor weakness with highly variable expression. The muscle weakness is often asymmetrical. Also the rate and extent of disease progression may differ greatly per patient. In most cases FSHD is associated with a contraction of an *Eco*RI fragment that contains a repeat array, D4Z4, consisting of 3.3 kb repeat units, located within the subtelomeric region 4q35 on the long arm of chromosome 4. The majority of affected individuals has a parent with clinical characteristics and a contraction of this repeat array on 4q35 and are thus described as familial FSHD patients. Approximately 10-30% of individuals will develop FSHD as a result of a new mutation and are therefore called *de novo* or sporadic patients. A small percentage of patients (5%; so-called phenotypic FSHD patients) has a phenotype characteristic for FSHD, but lack the 4q35 contraction.

Since the linkage of FSHD to chromosome 4 in 1990, important observations have been made with respect to the molecular characteristics and pathogenesis of the disease. Unfortunately, no true candidate gene or genes responsible for the development and progression of FSHD have thus far been identified. Unravelling the molecular structure of the 4q35 region and gaining more knowledge of the behaviour of the D4Z4 repeat are therefore important to elucidate the disease mechanism, as both features can give more insight in complex genetic events and possible molecular mechanisms triggering or modifying FSHD pathology. The aim of this thesis was therefore to focus on the structure and behaviour of D4Z4, which would add to our understanding of the molecular mechanism underlying the disease. The research described here focuses on three topics: (1) interactions of the subtelomeric region 4q35, in which D4Z4 resides, with other regions in the genome; (2) the consequences of mosaicism for FSHD pathology; and (3) epigenetic modifications of the 4q35 region, including DNA methylation and histone acetylation.

A literature overview on the FSHD phenotype and molecular characteristics of the chromosomal region 4q35 associated with FSHD is provided in ***Chapter 1***. Furthermore, this chapter contains a broad overview on repeat characteristics, subtelomeric regions, the possible consequences of mosaicism, and the diverse functions of DNA methylation and histone modifications in the human genome in general. The observed interactions of the subtelomeric region 4q35 with chromosomal region 10q26 and the size distributions of chromosomes 4 and 10 are described in

Chapters 2 and ***3***. The studies on mosaicism for the FSHD-associated region presented in ***Chapters 3*** and ***4*** mainly concentrate on the occurrence of mosaicism and the determination of frequency and possible consequences for FSHD. The epigenetic modifications of the 4q35 region, D4Z4 and the proximal sequences, and their possible effects on chromatin conformation are addressed in ***Chapters 5***, ***6*** and ***7***. ***Chapters 5*** and ***6*** pertain to DNA methylation of D4Z4, with special attention to phenotypic FSHD patients and the effect of repeat array length on DNA methylation, whereas ***Chapter 7*** outlines observations on histone acetylation. ***Chapter 8*** summarises the results described in this thesis and discusses the consequences of structure and behaviour of D4Z4 for FSHD pathology and perspectives for future research.