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Compound heterozygosity in a South African patient with Facioscapulohumeral muscular dystrophy

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Abstract

Facioscapulohumeral muscular dystrophy (FSHD) is characterised by weakness and atrophy of the facial and shoulder girdle muscles. The FSHD phenotype segregates as an autosomal dominant trait and is caused by a deletion of an integral number of 3.3 kilobase pair (kb) repeat units on chromosome 4q35. Haplotype and Southern blot analyses of chromosome 4 resulted in the detection of two BlnI resistant deletion fragments, of 24 kb and 34 kb respectively, in a single individual from a South African FSHD family. The patient had moderate facial weakness and marked winging and high-riding of the scapulae with prominent pectoral and proximal arm muscle atrophy and weakness. Quadriceps and anterior tibial muscles were weak and the patient had bilateral foot drop. Although none of his children were symptomatic yet and only two showed very mild clinical signs, one had inherited the 24 kb deletion fragment, while the other two had the 34 kb deletion fragment. Molecular analysis conclusively identified the first compound heterozygous case in the South African FSHD population. However, in accordance with other studies of compound heterozygotes and clinical findings, no direct correlation between the clinical severity of this patient and the number of deletion fragments was observed.

Keywords: Facioscapulohumeral muscular dystrophy; FSHD; Compound heterozygote; Muscular dystrophy; Genotype–phenotype correlation

1. Introduction

FSHD (OMIM 158900) is part of a group of inherited muscle disorders characterised by progressive involvement of the facial and shoulder girdle muscles predominantly. However, the degree of muscle involvement varies considerably on the clinical level, from almost asymptomatic eye closure weakness to marked disability with weakness of the shoulder and pelvic girdle as well as bilateral drop feet. This forms the basis of the extremely heterogeneous nature of the FSHD phenotype in patients [1].

The majority of FSHD cases are associated with a deletion of an integral number of 3.3 kb tandem repeats localised to the D4Z4 locus on chromosome 4q35 [2]. Unaffected individuals are observed to harbour 10 to 100 repeat units, while affected individuals have 1 to 10 residual repeat units [2]. Detection of this DNA rearrangement using probe p13E-11 allows for the molecular diagnosis of FSHD [3]. This probe p13E-11, however, was observed to cross-hybridise to regions on chromosome 10q26 as well

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as the Y-chromosome [4]. Restriction mapping of chromosome 10q26 indicated that this region contains similar 3.3 kb repeat units to that on chromosome 4q35. Comparison between sequences of chromosome 4q35 and 10q26 fragments indicated the presence of a unique chromosome 10-specific BlnI site, allowing for discrimination between chromosome 4 and 10 alleles [5]. BlnI digests the 10q-derived fragments into ca. 2 kb fragments, while the 4q-derived fragments remain intact, but are decreased in size by ca. 3 kb.

In 2002, the presence of two different 4q telomeric alleles, namely 4qA and 4qB, was reported [6]. The most prominent difference between the 4qA and 4qB alleles is the presence of a 6.2 kb beta-satellite and a 260 bp pLAM sequence in the 4qA allele [6]. Although the alleles are present with almost equal frequencies in the general population, only individuals with a deletion fragment localised on a chromosome harbouring the 4qA allele are symptomatic of FSHD [7]. Lemmers et al. (2007) demonstrated the presence of a simple sequence length polymorphism (SSLP) positioned 3.5 kb proximal to the D4Z4 locus. A 161 bp fragment was observed to segregate with the 4qA allele in FSHD individuals [8].

FSHD is therefore associated with a specific configuration, consisting of a deletion at the D4Z4 locus, the SSLP, the 4qA variant as well as the single nucleotide polymorphism (SNP) ATTAAA in the pLAM region. This configuration was indicated by Lemmers et al. (2010) to be predisposing for the development of FSHD, as the SNP creates a polyadenylation signal within the DUX4 gene, which encodes for a double homeobox protein [9]. This results in the synthesis of mRNA from the distal copy of DUX4. It is hypothesised that FSHD is caused through this toxic gain-of-function effect.

Wohlgemuth et al. (2003) reported two unrelated FSHD families wherein the two probands were compound heterozygous for different deletion fragment sizes. Compound heterozygosity was therefore indicated to be compatible with life [10]. Furthermore, this study indicated that susceptibility towards FSHD is therefore not only determined by the size of the deletion fragment alone but also the allelic configuration upon which the deletions are inherited. This investigation proposed a possible phenotypic dosage effect in patients who are compound heterozygous for FSHD-sized 4q35 alleles.

Homozygosity for an FSHD-associated deletion fragment has also been reported to be compatible with life [11]. Tonini et al. (2004) reported an individual homozygous for a 24 kb deletion fragment which was not more severely affected than individuals in the same family harbouring only one deletion fragment indicating that a simplistic dosage effect model is unlikely in this disorder.

Recently, an Italian study, wherein a total of 11 families were included, reported a large cohort of FSHD compound heterozygotes [12]. Neither the severity of the disease, nor the age of onset between the compound heterozygotes and the individuals harbouring a single deletion fragment differed significantly. Homozygosity and compound heterozygosity in FSHD patients do therefore not necessarily result in a more severe phenotype. [9,10,12]. The anticipation that compound heterozygosity should result in a more severe FSHD phenotype is thus not supported in these studies.

A previous study in the South African population identified the presence of an FSHD-associated haplotype co-segregating with a BlnI resistant deletion fragment of 24 kb in three Caucasian families [13,14]. A different FSHD-associated haplotype co-segregated with a 34 kb BlnI resistant deletion fragment in two other Caucasian families [13,14]. This report describes the clinical and genetic findings of the first South African compound heterozygous individual with FSHD who harbours both the 24 and the 34 kb deletion fragments.

2. Materials and methods

This research program was approved by the Ethics Committees of the North-West University (Potchefstroom Campus) and the University of Pretoria. Written informed consent was obtained for each subject prior to their inclusion in the project.

3. Clinical evaluation

The patient discussed in this report is part of a family consisting of eight generations and ca. 690 individuals. The patient, a 52-year-old male, had significant difficulty with the elevation of his arms above his head since the age of approximately 15 years. The right middle finger also had some weakness of extension. At the age of 19 years, he presented with increased fatigue after running long distances or with any form of strenuous exercise. In his mid twenties, bilateral drop feet gradually began to develop. Currently, he is barely able to walk unassisted.

Upon clinical examination, the proband showed moderate facial weakness involving Mm *orbicularis oculi* and *oris* as indicated by the mouth having a pouting

Table 1
Medical Research Council (MRC) scale of muscle strength for the compound heterozygous individual included in this investigation.

Muscle	Right	Left	Muscle	Right	Left
Rhomboids	4	4	Finger extension	3	5
Serratus	3	3	Hip flexion	4	4
Pectoralis	3	3	Hip extension	3–4	3–4
Infraspinatus	4+	4+	Hip adduction	4	4
Supraspinatus	4	4	Hip abduction	4+	4+
Latissimus dorsi	3	3	Knee extension	2–3	2–3
Deltoids	4	4	Knee flexion	3–4	3–4
Biceps	2–3	4	Ankle dorsiflexion	0	0
Triceps	2	3–4	Ankle plantarflexion	5	5
Brachioradialis	0	0	Ankle eversion	0	0
Wrist extension	2–3	4	Ankle inversion	5	5