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Clinical Study

A study of a family with the skeletal muscle *RYR1* mutation (c.7354C>T) associated with central core myopathy and malignant hyperthermia susceptibility

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ABSTRACT

Congenital myopathies are early onset hereditary muscle disorders. A sub-group of these is associated with malignant hyperthermia susceptibility. Mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene have been associated with various congenital myopathy phenotypes and may also cause malignant hyperthermia susceptibility. We describe nine affected members of an extended family presenting with a myopathy typically manifesting as upper eye lid ptosis, quadriceps atrophy and patellar dislocation. Three affected members underwent extensive genetic testing and have a *RYR1* exon 46 c.7354C>T gene mutation; two of whom had muscle biopsies – both demonstrated central core myopathy. The only affected family member who underwent testing for malignant hyperthermia susceptibility was shown to be positive. The clinical phenotypes seen among affected family members varies widely in severity, and have features in common with those congenital myopathies associated with malignant hyperthermia susceptibility, raising the possibility that these conditions represent a spectrum of disease.

1. Introduction

Central core disease (CCD) is a dominantly inherited congenital myopathy.[1] It presents as a relatively benign, static or slowly progressive myopathy with hypotonia during early childhood.[2] A large phenotypic variability exists. Diagnosis is based on the presence of cores in skeletal muscle. Mutations in the *RYR1* gene, which encodes the skeletal muscle isoform ryanodine receptor, have been associated with CCD.[3] The *RYR1* gene is fundamental to the process of excitation–contraction coupling and skeletal muscle calcium homeostasis.[3] Statistically significant associations have been demonstrated between certain mutations and clinical phenotype.[4] Patients with CCD are particularly prone to malignant hyperthermia crises under general anaesthesia.

Malignant hyperthermia/malignant hyperthermia susceptibility (MH/MHS) is an autosomal dominant pharmacogenetic disorder of skeletal muscle calcium regulation[5] which manifests principally during general anaesthesia and is an important factor in anaesthetic-induced morbidity and mortality. About one half of all MH reactions can be preceded by numerous uneventful general anaesthetic procedures.[6] MHS is associated with a mild or even subclinical myopathy.[7] MHS is genetically heterogeneous and disease penetrance may vary from patient to patient. It is associated with mutations in the gene *RYR1* with more than 60 mutations in *RYR1* having been identified.[2] These (and those linked with CCD) are clustered in three regions of the protein.[4,5]

2. Methods

The index family (Fig. 1) was recruited following referral to the Southampton Oculoplastics Service at Southampton Eye Unit, Southampton General Hospital, UK. The proband (IV-1) was referred with upper eyelid ptosis. Sixteen affected family members were identified (II-2, II-5, II-7, II-10, II-13, III-2, III-3, III-4, III-6, III-8, III-9, III-10, IV-1, IV-2, IV-3, IV-6) of which nine (II-2, II-10, III-2, III-3, III-4, III-6, IV-1, IV-2, IV-3) participated in this study. Two unaffected members also took part (II-1, III-1). Participants attended specialist clinics (ophthalmology, neurology, orthopaedic, radiology and clinical genetics) for examination purposes. Detailed clinical, biochemical and photographic investigations were performed on all participants. The same specialist in each field performed all clinical examinations. Blood samples were acquired from all participants and tested for: creatine phosphokinase, lactate, human leukocyte antigen B27 subtype (HLA B27), anti-nuclear antibody, extractable nuclear antigen, double stranded DNA, anti-neutrophil cytoplasmic antibody and rheumatoid screen. Three affected members (IV-1, IV-2, IV-3) underwent detailed

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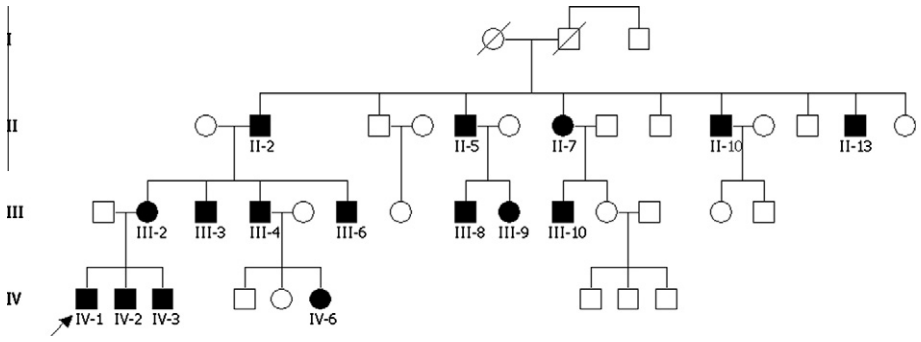

Fig. 1. A family pedigree diagram of four generations (I–IV) of the index family showing the relationships among affected males (solid squares) and females (solid circles) and unaffected individuals (open symbols). Deceased members are indicated by a diagonal rule through the symbol. The arrow shows the position of the proband (IV-1).

radiological examination including radiographic imaging of the chest and ribs, thoracolumbar-sacral spine, pelvis and lower limbs; in addition IV-2 underwent MRI of the spine and musculature. Chromosomal analysis was undertaken on three affected participants (IV-1, IV-2, IV-3) and myotonic dystrophy mutation testing was performed on two affected males (II-2, IV-1). Muscle biopsies (vastus lateralis) were performed on two affected individuals (IV-3, for diagnostic purposes; III-2, for MHS screening including *in vitro* contractile testing [IVCT], which was performed by the Malignant Hyperthermia Unit, St James University Hospital, Leeds, UK). Molecular genetic analysis for MH and CCD was undertaken on IV-3 and III-2 at the Malignant Hyperthermia Unit, St James University Hospital. *RYRI* MH and CCD mutation hot spots were screened. *RYR1* mutation analysis for CCD was performed testing C-terminal *RYR1* exons 47, 48, 95, 100, 101, 102, 103 and 104 by bi-directional fluorescent sequencing for eleven *RYR1* mutations (c.487C>T, c.742G>A, c.1021G>A, c.1840C>T, c.6488G>A, c.6502G>A, c.6617C>T, c.7048G>A, c.7300G>A, c.7304G>A, c.7373G>A). UK families with recurrent MH were screened according to the European Malignant Hyperthermia Group (EMHG) guidelines. Further genetic analysis on participants with *RYR1* exon 46 (IV-1, IV-2, IV-3) was undertaken at the DNA Laboratory, Guy's Hospital, London, UK.

Ethics approval for the study was granted by the local research ethics committee (South and South West Hampshire).

3. Results

This extended non-consanguineous family is of English and Celtic origin. The father (III-1) of the proband has a Polish Jewish background of three generations with Portuguese ancestry. Perinatal history was unremarkable in all family members as was their progressive growth and development. No loss of pregnancy was noted within the family.

Table 1
Clinical features of members of the index family with skeletal muscle *RYR1* mutation (c.7354C>T)

Clinical features	II-1	**II-2**	**II-10**	III-1	**III-2**	**III-3**	**III-4**	**III-6**	**IV-1**	**IV-2**	**IV-3**
Gender	F	M	M	M	F	M	M	M	M	M	M
Short stature	–	–	–	–	–	–	–	–	+	+	+
Macrocephaly	–	+	+	–	+	+	+	+	+	+	+
Facial weakness	–	+	–	–	–	–		–	–	+	+
Male pattern baldness (adult)	–	+	+	+	–	+	+	+	N/A	N/A	N/A
Myopia	+	–	+	+	–	+	–	–	+	+	–
Ptosis	–	+	–	–	+	+	–	+	+	+	+
Low set/posteriorly angulated ears	–	–	–	–	–	–	–	–	–	–	+
Malar hypoplasia	–	–	–	–	+	+	–	+	+	+	+
High arched palate	–	–	–	–	+	+	+	–	+	–	+
Micrognathia + deviated jaw	–	–	–	–	–	–	–	–	–	–	+
Regressive lower jaw	–	–	–	+	–	+	–	–	–	+	–
Absent upper/lower lateral incisors	+	–	–	–		–	+	–	–	+	–
Abnormal upper incisors	+	–	–	–		–	–	–	–	–	–
Conical teeth	–	+	–	–	+	–	–	–	–	+	+
Webbing – neck	–	–	–	–	–	–	–	–	–	+	–
Scoliosis	–	–	–	–	–	+	+	+	+	+	+
Limited forward flexion – hip	–	–	–	–	+	+	–	–	+	+	+
Hip dislocation	–	–	–	–	–	–	+	–	–	–	–
Café au lait patch	–	–	–	–	–	–	–	+	–	–	+
Patella dislocation/locking	–	–	–	–	+	+	+	+	+	+	+
Medial + lateral quadriceps atrophy	–	+	–	–	+	+	+	+	+	+	+
Generalised muscle weakness	–	–	–	–	+	+	–	–	–	–	+
Anaesthetic difficulties	–	–			MHS	N/A*		N/A*	+	–	–
5th finger clinodactyly	–	–	+	–	+	–	+	–	+	+	+
Joint hyperextensibility	–	–	–	–	–	–	+	–	+	–	+
Swallowing difficulties	–	–	–	–	–	–	–	–	–	+	+
Nasal speech	–	–	–	–	+	–	–	–	–	–	–
Muscle cramps after exercise	–	+	–	–	+	–	–	+	+	–	+

Bold type indicates affected persons.
+ = Yes, – = no, MHS = malignant hyperthermia susceptible, N/A = not applicable, *no past anaesthetic, F = female, M = male.