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King–Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene

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Abstract

King–Denborough syndrome (KDS), first described in 1973, is a rare condition characterised by the triad of dysmorphic features, myopathy, and malignant hyperthermia susceptibility (MHS). Autosomal dominant inheritance with variable expressivity has been reported in several cases. Mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene have been implicated in a wide range of myopathies such as central core disease (CCD), the malignant hyperthermia (MH) susceptibility trait and one isolated patient with KDS.

Here we report clinical, pathologic and genetic features of four unrelated patients with KDS. Patients had a relatively uniform clinical presentation but muscle biopsy findings were highly variable. Heterozygous missense mutations in *RYR1* were uncovered in three out of four families, of which one mutation was novel and two have previously been reported in MH. Further RyR1 protein expression studies performed in two families showed marked reduction of the RyR1 protein, indicating the presence of allelic *RYR1* mutations not detectable on routine sequencing and potentially explaining marked intrafamilial variability.

Our findings support the hypothesis that *RYR1* mutations are associated with King–Denborough syndrome but that further genetic heterogeneity is likely.

Keywords: Congenital myopathies; King–Denborough syndrome; Central core disease; Malignant hyperthermia susceptibility (MHS); Skeletal muscle ryanodine receptor (RYR1) gene

1. Introduction

King–Denborough syndrome (KDS) was first described by King and Denborough in 1973 [1] and is characterised by a susceptibility to malignant hyperthermia (MH),

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delayed motor development, short stature, cryptorchidism, skeletal abnormalities, and variable dysmorphic features. Skeletal abnormalities include scoliosis, kyphosis, lumbar lordosis, and pectus carinatum/excavatum. Additional findings such as vertebral fusion, eventration of the diaphragm and spinal cord tethering have been reported in few individuals with suggestive clinical features [2,3]. Variable dysmorphic features include ptosis, down-slanting palpebral fissures, malar hypoplasia, high-arched palate, dental crowding/malocclusion, micrognathia, low-set ears, and webbing of the neck [2]. Some of these features overlap with Noonan syndrome and it has been suggested that there may be a link between the two syndromes [4]. However, whilst moderate CK elevations and a MH reaction have been reported in isolated cases with a clinical but genetically unconfirmed diagnosis of Noonan syndrome [5,6], kyphoscoliosis is uncommon in the latter and heart defects are not usually a feature in KDS.

Various diagnostic studies support the conclusion that King–Denborough syndrome is, at least in part, a myopathy. Resting CPK levels are elevated in some KDS patients [1,7] and muscle biopsies have shown a variety of myopathic features, most commonly fibre size variation and few, small, or atrophic type I muscle fibres [2,8]. Central cores, the diagnostic hallmark of central core disease (CCD) and also often seen in MH patients, are uncommon in KDS.

Many patients with KDS have a family history of MH and/or of dysmorphic features; thus, it has been suggested that KDS is inherited in an autosomal dominant manner [7]. However, siblings with apparently unaffected parents and a severe phenotype with prenatal onset have been subsequently reported [9–11], suggesting either recessive inheritance, mosaicism or highly variable penetrance. There also seems to be a predominance of males with KDS [2] but the reason for this finding is uncertain.

At this time, the genetic basis for KDS is unclear in the majority of patients. One prior case was published demonstrating a *de novo* mutation in the skeletal muscle ryanodine receptor (*RYR1*) [12] gene. *RYR1* encodes the principal sarcoplasmic calcium release channel with a crucial role in excitation–contraction coupling and has been associated with several neuromuscular conditions, including MH [13], central core disease (CCD) [14], multiminicore disease (MmD) [15] and centronuclear myopathy (CNM) ([16].

Here we describe the clinical, pathologic and genetic features of four patients with features suggestive of KDS and provide evidence for prominent *RYR1* involvement but also possible genetic heterogeneity.

2. Patients

Patients with King–Denborough syndrome (KDS) were included in this study and selected for *RYR1* screening based on a combination of suggestive dysmorphic features and presence of a myopathy with or without a personal or family history of malignant hyperthermia (MH). The main clinical, histopathological and genetic features of our patients are summarised in Table 1.

2.1. Patient 1

The patient is a 6-year-old male who first presented for neurologic evaluation at age five. The chief complaints at presentation were an unusual gait and frequent falls. He also complained of exercise intolerance and frequent myalgias after exercise. His past history was significant for delayed gross motor development (he did not walk until age four). His pregnancy, birth, and early postnatal histories as far as known were unremarkable. The family history was significant in that the patient's father (who was unavailable for interview or examination) was also reported to have gait abnormalities, facial dysmorphisms, and had experienced a previous malignant hyperthermia reaction.

On examination height (115 cm) and weight (23.6 kg) were on the 20th and 66th percentiles, respectively. Facial dysmorphisms were noted including mild bilateral ptosis, hypertelorism, mild webbing of the neck, and a round facies with full cheeks (Fig. 1A). Motor examination revealed mild truncal hypotonia, mild upper and lower proximal weakness (MRC 4+/5), and an abnormal gait featuring prominent lumbar lordosis. The remainder of his neurologic examination, along with his cardiac and pulmonary examinations, was unremarkable.

Laboratory investigations included a CPK level elevated at 424 IU/L. Microarray analysis showed a normal male complement without any known pathogenic copy number variations. X-rays of the spine showed an exaggerated lordosis in the sagittal plane and twenty-two degrees of thoracolumbar scoliosis. The muscle biopsy was largely unremarkable with the exception of rare atrophic types I and II fibres (Fig. 2A and D). In addition, no abnormalities were detected by electron microscopy (data not shown). Sequencing of the *RYR1* gene revealed a heterozygous mutation of c.6617C>G in exon 40 of *RYR1* resulting in an amino acid substitution of p.Thr2206Arg. This mutation has been detected in 3 previously reported cases of malignant hyperthermia [17,18]. Western blot analysis of protein extracted from the biopsy sample revealed a 84% reduction in RyR1 levels as compared to an unaffected control (Supplemental Fig. S1).

2.2. Patient 2

This 14-year-old boy was referred for further assessment following a presentation with scoliosis, recurrent patella dislocations from the age of 8 years and symptoms and signs of mild hip girdle weakness. CK levels were slightly elevated at 250 IU/l (normal laboratory range 25–195 IU/l).

In the family history he was the youngest of 3 children. His oldest brother had suffered an anaesthetic reaction