Autosomal dominant congenital spinal muscular atrophy: a true form of spinal muscular atrophy caused by early loss of anterior horn cells

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Autosomal dominant congenital spinal muscular atrophy is characterized by predominantly lower limb weakness and wasting, and congenital or early-onset contractures of the hip, knee and ankle. Mutations in TRPV4, encoding a cation channel, have recently been identified in one large dominant congenital spinal muscular atrophy kindred, but the genetic basis of dominant congenital spinal muscular atrophy in many families remains unknown. It has been hypothesized that differences in the timing and site of anterior horn cell loss in the central nervous system account for the variations in clinical phenotype between different forms of spinal muscular atrophy, but there has been a lack of neuropathological data to support this concept in dominant congenital spinal muscular atrophy. We report clinical, electrophysiology, muscle magnetic resonance imaging and histopathology findings in a four generation family with typical dominant congenital spinal muscular atrophy features, without mutations in TRPV4, and in whom linkage to other known dominant neuropathy and spinal muscular atrophy genes has been excluded. The autopsy findings in the proband, who died at 14 months of age from an unrelated illness, provided a rare opportunity to study the neuropathological basis of dominant congenital spinal muscular atrophy. There was a reduction in anterior horn cell number in the lumbar and, to a lesser degree, the cervical spinal cord, and atrophy of the ventral nerve roots at these levels, in the absence of additional peripheral nerve pathology or abnormalities elsewhere along the neuraxis. Despite the young age of the child at the time of autopsy, there was no pathological evidence of ongoing loss or degeneration of anterior horn cells suggesting that anterior horn cell loss in dominant congenital spinal muscular atrophy occurs in early life, and is largely complete by the end of infancy. These findings confirm that dominant congenital spinal muscular atrophy is a true form of spinal muscular atrophy caused by a loss of anterior horn cells localized to lumbar and cervical regions early in development.
Keywords: spinal muscular atrophy; pathology; anterior horn cell; spinal cord; SMA
Abbreviations: LOD = logarithm of odds; SMA = spinal muscular atrophy

Introduction

The spinal muscular atrophies (SMAs) are a heterogeneous group of disorders caused by aberrant development and/or early loss of spinal cord anterior horn cells (Walton and Thomas, 1988). Characteristic clinical features include lower motor neuron weakness and electrophysiological evidence of denervation, in the absence of findings suggestive of a peripheral neuropathy (i.e. no sensory abnormalities, no palpable peripheral nerves, normal nerve conduction and normal sensory action potentials).

By far the most common and best characterized form of SMA is ‘classical’ autosomal recessive 5q-SMA, which is caused almost exclusively by homozygous exon 7 and 8 deletions in SMN1, on chromosome 5q12-q13 (Melki et al., 1990a, b). In 5q-SMA, a wide range in disease severity arises from the presence of variable copy numbers of a partially functional pseudogene (SMN2). In the most severe forms, 5q-SMA0 and 5q-SMA1, loss of anterior horn cells probably begins during the third month of pregnancy (Vassilopoulos and Emery, 1977), resulting in severe to profound weakness at birth (5q-SMA0/1) or during the first few months of life (5q-SMA1) (Dubowitz, 1995), which is generally fatal. In all forms of 5q-SMA there is clear progression in weakness over time.

Other rarer or under-recognized autosomal dominant forms of SMA, also sometimes referred to as dominant distal hereditary motor neuropathies (dHMNs), have also been described. Scapuloperoneal SMA is characterized by slowly progressive scapuloperoneal weakness and atrophy, laryngeal palsy and congenital absence of some muscle groups (DeLong and Siddique, 1992; Isozumi et al., 1996). Other examples include distal SMA with upper limb predominance (Christodoulou et al., 1995), and several predominantly adult-onset SMAs (Richieri-Costa et al., 1981; Nishimura et al., 2004). Each of the dominant SMAs has a characteristic age of onset and pattern of muscle weakness and wasting. The weakness is usually less severe than in 5q-SMA0/1, and the clinical course tends to be static or slowly progressive, rather than rapidly progressive.

Dominant congenital SMA (Reddel et al., 2008), also known as dominant congenital benign SMA (Frijns et al., 1994) or congenital autosomal dominant distal SMA (Adams et al., 1998), has a distinctive clinical phenotype characterized by congenital and/or early-onset contractures of the hip, knee and ankle, and weakness and wasting that predominantly involves the lower limbs (Fleury and Hageman, 1985; Frijns et al., 1994; Adams et al., 1998; van der Vleuten et al., 1998; Mercuri et al., 2004; Reddel et al., 2008). Weakness and/or atrophy of the masseter (Frijns et al., 1994), neck flexor (Frijns et al., 1994; Adams et al., 1998), upper limb (Adams et al., 1998; Reddel et al., 2008) and paraspinal muscles (resulting in scoliosis or kyphoscoliosis) (Fleury and Hageman, 1985; Frijns et al., 1994) has also been described in some dominant congenital SMA kindreds, along with trapezius hypertrophy (Adams et al., 1998), mild scapular winging (Frijns et al., 1994), lumbar hyperlordosis (Fleury and Hageman, 1985; Frijns et al., 1994; Reddel et al., 2008), pes cavus (Adams et al., 1998) and joint hyperlaxity (Frijns et al., 1994). In contrast to autosomal recessive SMA with respiratory distress, marked early-onset diaphragmatic involvement is not a typical feature of dominant congenital SMA, nor is early-onset respiratory involvement. Creatine kinase levels range from normal to twice the upper limit of normal (Frijns et al., 1994; Adams et al., 1998; Reddel et al., 2008).

Muscle MRI and electrophysiology testing can be useful in differentiating dominant congenital SMA from other neuromuscular disorders. Lower limb MRI in both sporadic and familial dominant congenital SMA typically shows marked atrophy of the quadriceps and posterior calf muscles, with relative preservation of the hip adductors, semitendinosus and lateral compartment of the lower leg (Mercuri et al., 2004; Reddel et al., 2008). On EMG, large simple (non-polyphasic) motor units with normal duration, but a decreased recruitment pattern are typical (Reddel et al., 2008), indicating reinnervation. As for all forms of SMA, nerve conduction is within normal limits (Reddel et al., 2008). Muscle histopathology often reveals small grouped or isolated angulated fibres (Fleury and Hageman, 1985; Reddel et al., 2008), features suggestive of denervation (Dubowitz and Sewry, 2007). In the weakest/most atrophied lower limb muscles there is often marked alteration to skeletal muscle architecture, with almost complete replacement by fat in some cases (Fleury and Hageman, 1985). The sural nerve is histopathologically normal (Adams et al., 1998).

The only known genetic cause for dominant congenital SMA at present is TRPV4 (Auer-Grumbach et al., 2010), a transient receptor potential cation channel (subfamily V, member 4) (Nilius et al., 2007; Deng et al., 2010; Nilius and Oswiansik, 2010), which is responsible for typical dominant congenital SMA in a large Dutch kindred (Auer-Grumbach et al., 2010). Linkage studies have excluded the 12q23-q24 TRPV4 locus in other dominant congenital SMA families, indicating genetic heterogeneity (van der Vleuten et al., 1998).

Here we report a four generation family with typical dominant congenital SMA clinical features, MRI, electrophysiology and muscle histopathology findings, segregating in an autosomal dominant pattern of inheritance. Mutations in TRPV4 have been excluded as the cause of dominant congenital SMA in this family by linkage analysis and by direct gene sequencing. Linkage analysis has also been used to exclude other known genetic loci for dominant neuropathies and dominant forms of SMA. The autopsy neuropathology findings in the female proband, who
died at 14 months of age from an unrelated illness, provide unique insight into the pathological basis of this disease, and confirm several hypotheses previously derived from clinical observation.

Patients and methods

The study was approved by the Human Ethics Committee of the Children’s Hospital at Westmead (#2005/042). The family has given informed consent for involvement in this study. The pedigree is shown in Supplementary Fig. 1. All affected family members, except for Subjects I.4 and II.2, were examined by experienced neurologists (K.N., S.R. and S.H.). The proband died unexpectedly at 14 months of age due to meningooccalar septicaemia and a full autopsy was performed, including a detailed neuropathology assessment. Only formalin-fixed paraffin-embedded muscle was available. Muscle fibre typing was performed by immunohistochemical staining for fast myosin (immunoperoxidase-conjugated mouse anti-fast myosin heavy chain clone MY32; Invitrogen).

Linkage analysis and gene sequencing

DNA was available for genetic studies from nine members of the third and fourth generations of the family, as shown in the pedigree (Supplementary Fig. 1).

As dominant congenital SMA caused by TRPV4 mutations is the phenotype that most closely resembles the features present in this kindred, we initially undertook a focused linkage study of the 12q23-q24 locus that contains the TRPV4 gene. The size of the amplicons from the six microsatellite markers that span this region (D12S78, D12S806, D12S1583, D12S1344, D12S129 and D12S1646) was determined using an Applied Biosystems 3730 DNA Analyser. GeneMapper® software version 3.7 (Applied Biosystems) was used to analyse the results. We also sequenced the coding exons and adjacent intronic regions of TRPV4 using genomic DNA from an affected family member (IV.5) as previously described (Rock et al., 2008).

We subsequently performed a family genome-wide linkage study using Illumina CytoSNP12 SNP data; although this chip is designed primarily for copy number variation analysis, it is also suitable for linkage analysis. The program MERLIN (Abecasis et al., 2002) was used to perform parametric multipoint linkage analysis using the Lander–Green algorithm. A fully penetrant dominant disease model and a disease allele frequency of 0.0001 was assumed for the purposes of linkage calculations. The selection and assembly of data files for linkage was performed with LINKDATAGEN (http://bioinf.wehi.edu.au/software; Bahlo and Bromhead, 2009). Mendelian inheritance errors were identified and removed with LINKDATAGEN, and MERLIN was used to remove genotyping errors identified based on inferred unlikely double recombination events between tightly linked markers.

Results

Clinical features

Clinical features in Proband IV.2

The proband (Subject IV.2) was the second of six children born to a non-consanguineous couple of Caucasian ancestry. Decreased foetal movements were noted during the pregnancy. The proband was born at term by uncomplicated vaginal delivery, with normal growth parameters. At birth she had bilateral talipes calcaneovalgus, more severe on the left, with unilateral (left) calf wasting. Her feet were short and broad, with bilateral fixed flexion deformities of the interphalangeal joint in the first toes giving a ‘cocked’ appearance (similar to Subject IV.6’s feet shown in Fig. 1D). There was limited antigravity movement at the hips, knees and ankles. Deep tendon reflexes were reduced at the knee, and absent at the ankle. She had a high-arched palate, but no facial or axial muscle weakness, ophthalmoplegia, ptosis or tongue fasciculations. Muscle bulk, strength and deep tendon reflexes in the upper limbs were normal at birth and throughout infancy.

Ultrasound imaging shortly after birth identified grade 3 acetabular dysplasia of the right hip. A flexion contracture of the left knee was first noted at 11 weeks of age. Her knee contracture and right talipes calcaneovalgus deformity resolved with stretching exercises and serial casting; however, the left foot deformity responded poorly to this treatment and the right hip dysplasia failed to improve with Pavlik harness and abduction pillow therapy. She underwent tendon release surgery of the left foot and surgical relocation of the right hip at the age of 6 months.

A biopsy of the mid right quadriceps muscle, performed at the age of 6 months during foot and hip surgery, showed features suggestive of denervation with patchy small and large group atrophy, which almost exclusively involved type 2 fibres. Most fascicles contained multiple single round atrophic fibres; there were also rare regenerating fibres. On electron microscopy, folds of redundant basal lamina were present in small fibres, consistent with fibre atrophy.

Prior to her death at 14 months, the proband was not yet able to walk and had marked difficulty weight-bearing. She had no facial, bulbar, upper limb, truncal or respiratory involvement and her growth, fine motor and cognitive development were within normal limits.

Clinical presentation of the most severely affected family member (Subject IV.5)

Subject IV.5 (whose clinical features are shown in Fig. 1A–C) was born following an uncomplicated pregnancy, without congenital lower limb contractures. At 6 months of age, lower limb movements were reduced, and he was not yet able to roll or bear weight through his legs. By this time, both feet had developed calcaneovalgus posture at rest, and deep tendon reflexes were absent in the lower limbs. Asymmetry knee contractures developed at the age of 12 months. Bilateral hip contractures developed at the age of 19 months, and bilateral tendon-Achilles contractures developed during the second year of life.

Subject IV.5 first walked at the age of 2 years. At his current age of 4.5 years, he uses bilateral ankle-foot-orthoses, has a wide-based hyperlordotic gait, only walks short distances and falls frequently. He has a positive Gowers’ sign, moderate lower limb weakness and marked generalized lower limb wasting (Fig. 1).

Additional features in Subject IV.5, not shared by other affected family members, include slow and fatigable chewing, difficulties with swallowing and excessive drooling, which first became apparent at the age of 6 months. Barium swallow at age 4 years showed some penetration of thin fluids into the upper airways. Subject IV.5 also has mild expressive language delay and difficulties with
articulation, and was commenced on bi-level non-invasive nocturnal ventilation (BiPAP) at the age of 4 years for sleep-disordered breathing. A progressive asymmetrical pectus carinatum deformity of the anterior chest wall was first noted at 18 months of age, and a mid-thoracic scoliosis developed at 4 years of age.

The clinical history and diagnostic findings in the proband (IV.2), her severely affected brother (Subject IV.5) and two other affected family members [mother (Subject III.2) and female sibling (Subject IV.6) of the proband] are summarized in Supplementary Table 1. 

The lower limb MRI findings in Subject III.2 at age 32 years, which are typical of dominant congenital SMA, are shown in Fig. 2.

Subjects I.4 and II.2 could not be examined, but by verbal report had life-long difficulty walking long distances or standing for long periods, due to rapid fatigue. Subject I.4 used crutches during the later stages of life, prior to her death from cancer aged 73 years. Features of the condition were not present in Subjects III.1, IV.1, IV.3 or IV.4. None of the family had palpable enlargement of the peripheral nerves. SMN1 exon 7 and exon 8 deletions have been excluded in Subject IV.5.

Linkage analysis and sequencing results

Microsatellite analysis showed that affected siblings in generation IV had inherited different maternal haplotypes at the TRPV4 locus, which was inconsistent with linkage to this region. Consistent with this result, no TRPV4 mutations were identified in Subject IV.5.

Parametric multipoint linkage analysis revealed suggestive linkage to six candidate regions within the genome; these were confirmed by manual examination of haplotype segregation with HaploPainter (Thiele and Nurnberg, 2005). However, the logarithm (base 10) of odds (LOD) scores did not reach statistical significance for any of these regions (maximum LOD score 1.81). Interrogation of the published dominant SMA/distal hereditary motor neuropathy genes and loci generated LOD scores of less than –2 (Supplementary Table 2), excluding involvement, in all but one case. The exception was the 14q32 locus for dominant SMA with lower extremity predominance (Harms et al., 2010), which was associated with an overall LOD score of –1.1, still making it an unlikely gene locus in the family. Of note, a LOD score of –6.7 was obtained for the DYNC1H1 gene, which sits within the dominant SMA with lower extremity predominance candidate region, and is associated with a form of Charcot–Marie–Tooth disease with similar features to SMA with lower extremity predominance (Weedon et al., 2011), excluding this as a genetic cause in our family.

All of the recognized dominant Charcot–Marie–Tooth/hereditary motor and sensory neuropathy genes and linked loci also generated LOD scores of less than –2, with the exception of the dominant intermediate Charcot–Marie–Tooth disease type 1A 10q24.1-q25.1 locus, where the LOD score was –1.9, only just over the exclusion threshold. These data are summarized in Supplementary Table 3.

Autopsy findings in Proband IV.2

Limb findings included a dislocated right hip, bilateral acetabular dysplasia and bilateral calcaneovalgus deformities (more marked

Figure 1 Clinical features in dominant congenital SMA. (A–C) Photographs of Subject IV.5, the most severely affected member of this kindred, showing marked wasting of the buttocks, proximal and distal lower limb muscle groups, and hyperlordotic posture due to marked pelvic girdle weakness (A), scoliosis (B), and marked ankle pronation and bilateral pes planus (C). Upper limb musculature is within normal limits. (D) Significant calf wasting in another affected sibling, Subject IV.6. This sibling also has reduced foot length and bilateral ‘cocked’ fixed flexion deformities of the first toe, features also seen in the proband prior to her unexpected death, but not present in their brother, Subject IV.5. Subject IV.6 and the siblings’ mother (Subject III.2) also have medially deviated fifth toes and dysplastic fifth toenails (E), which may be an additional feature of the condition.
Brain examination was unremarkable apart from microscopic findings consistent with septicaemia, along with slight asymmetry of the caudate nuclei, and incomplete rotation of the left hippocampus, both of which are considered developmental variants without clinical significance. There was no neuronal loss or gliosis in the motor cortex or brainstem motor nuclei, and the corticospinal tracts were normal. In the spinal cord the lumbar enlargement was smaller than normal, while the cervical enlargement appeared normal (cervical cord shown in Supplementary Fig. 2). There was atrophy of the lumbar and cervical ventral roots, most severe in the lumbar region where individual roots measured <1 mm in diameter (Fig. 3). The dorsal roots at all levels were macroscopically normal.

Microscopically, there was a marked reduction in the number of large motor neurons in the lower lumbar and sacral ventral horns (L2–S2; L4 cord shown in Fig. 4), medially. An apparent increase in small and medium-sized pyramidal neurons with indistinct Nissl substance was also observed. No chromatolytic or degenerating neurons were seen, and there was no neuronophagia, microglial activation or gliosis. No neuronal inclusions were identified and there was no abnormal tau, phosphorylated neurofilament, TDP-43 or ubiquitin immunoreactivity. In summary, there was no evidence suggestive of active degeneration of anterior horn cells in the lumbosacral cord.

A similar, although less severe reduction in anterior horn cell neurons was present in the cervical spinal cord, whereas in the thoracic and upper lumbar cord (L1) the number of motor neurons appeared normal. The nucleus dorsalis of Clarke and myelination in the spinal white matter and the ventral and dorsal roots were also normal. The sural, phrenic and tibial...
nerves contained a normal number and distribution of myelinated fibres

On muscle histology, there were changes in all muscles consistent with long-standing denervation except the diaphragm, which was normal. In the most severely affected muscles (the lower limb muscles: vastus lateralis, biceps femoris, peronei, gastrocnemius and soleus), there were variable degrees of large and small group atrophy, pericellular and interfascicular fibrosis, and fat replacement, which was most prominent in the vastus lateralis

Figure 3 Spinal cord images. Ventral (A) and dorsal (B) views of lumbosacral cord and cauda equina, and transverse sections of three lumbar segments from proband (C) show markedly atrophic ventral roots and nerves (white arrows) and normal-volume dorsal roots/nerves (red arrows). Gradations on the right in C are 1 mm.

Figure 4 High power spinal cord images. Cresyl violet/Luxol fast blue-stained 15-μm sections from L4 spinal cord segment of proband (A and C), and an age-matched-control (B and D) at ×40 (A and B) and ×400 (C and D) original magnification, showing reduction of anterior horn cell bodies in dominant congenital SMA proband, compared with control, especially the medial ventral horn in A.
Most atrophic fibres expressed fast myosin. Hypertrophic fibres usually stained negative for fast myosin, indicating they were slow fibres. Patchy focal areas of muscle fibre-type grouping of normal-sized fibres were seen in all less severely affected muscles, e.g., the deltoid, shown in Fig. 6. Groups of slow fibres were more common than groups of fast fibres. The triceps was the least affected muscle, other than the diaphragm, and was normal except for occasional atrophic angular fast and slow fibres. Muscle spindles were plentiful, and normal in appearance.

Discussion

The clinical features and investigation results in this kindred are typical of dominant congenital SMA. There is no evidence of linkage to the known dominant SMA, dominant distal hereditary motor neuropathy and dominant Charcot–Marie–Tooth disease genes or loci, suggesting this family has a new genetic form of dominant congenital SMA. However insufficient family DNA samples were available to achieve a significant LOD score to define a new disease locus. The unexpected death of an affected infant from meningococcal disease has provided a rare opportunity to understand the early pathological changes associated with dominant congenital SMA, and to verify longstanding hypotheses about this condition. The most striking neuropathological finding at autopsy was the markedly reduced number of anterior horn cells in the lumbosacral and, to a lesser degree, the cervical spinal cord, in conjunction with thin lumbar ventral nerve roots. The primary pathology that defines spinal muscular atrophy is loss of anterior horn cells and these autopsy findings confirm that dominant congenital SMA is a true form of spinal muscular atrophy.

The presence of congenital contractures in dominant congenital SMA has led to the hypothesis that a clinically significant number of anterior horn cells are lost prenatally (Reddel et al., 2008), and the fact that dominant congenital SMA typically has a static or only slowly progressive postnatal clinical course, suggests that loss of anterior horn cells is largely complete by birth. Early postnatal-onset contractures (as seen in Subject IV.5, in the absence of congenital contractures) may result from a degree of progression in the underlying disease process for a limited period after birth, and/or from inability of the poorly innervated muscles surrounding affected joints to accommodate the demands of growth and/or the loading associated with increased weight-bearing.

Dominant congenital SMA predominantly affects the distal lower limbs, suggesting that the pattern of anterior horn cell loss is likely to be more localized compared with 5q-SMA1, but, until now, it has not been possible to confirm these hypotheses due to a lack of neuropathology data from patients with dominant congenital SMA. At autopsy, infants with 5q-SMA1 have a paucity of motor neurons at all levels of the spinal cord and in the lower brainstem together with swollen ‘ballooned neurons’, chromatolytic motor neurons, gliosis and glial bundles in the anterior roots that indicate persistent neuronal dysfunction and ongoing degeneration (Dubowitz, 1995; Crawford and Pardo, 1996; Araki et al., 2003; Ito et al., 2011). In contrast, in the proband at age 14 months the pattern of selective anterior horn cell loss was limited to the cervical and lumbosacral levels of the spinal cord, and was most marked in the medial regions.
of the anterior horn [i.e. a segmental deficit, limited to one or more columns of the anterior horn, as predicted by Fleury and Hageman (1985)]. This suggests that the gene responsible for dominant congenital SMA in this kindred has a role in the survival of a subpopulation of anterior horn cells, in the medial lumbar and cervical cord, and provides further evidence for a complex regulatory system for anterior horn cell survival that is individualized according to the site and role of the anterior horn cell.

There were no histological abnormalities in the spinal cord, apart from reduced numbers of motor neurons, which strongly suggests the main insult to anterior horn cells in dominant congenital SMA has already occurred by 14 months of age. The presence of fibre grouping of normal-sized fibres in mildly affected muscles also suggests that denervation occurred a reasonable length of time before this child’s death, long enough for reinnervation to occur, and for fibres to return to their normal size. Even though there was no sign of active neuronal degeneration in the spinal cord, the presence of occasional scattered angular fibres, which are generally considered subacute signs of denervation (Dubowitz and Sewry, 2007), suggests there may be a small amount of ongoing denervation that may account for the mild clinical progression after birth observed in some individuals.

Muscle strength is typically preserved early in the course of a range of chronic denervating conditions, because denervated fibres are reinnervated by adjacent intact motor neurons. However, when too few anterior horn cells remain, reinnervation is ineffective, muscle fibres degenerate and weakness develops. The pathological findings in our proband support this paradigm. Even though anterior horn cell loss was clearly seen in the cervical cord, and there was widespread fibre grouping in upper limb muscles, the proband had normal upper limb function, indicating sufficient motor neurons remained to compensate. In contrast, in the severely affected lower limb muscles, effective compensation for the disease process by reinnervation had not occurred, since there was extensive replacement of muscle by fat and fibrous tissue, and atrophic fibres were plentiful. Of note, the denervation changes were very patchy and varied between muscles. In more mildly affected muscles in particular, there were regions with marked fibre grouping immediately adjacent to areas with normal histology. These findings demonstrate the importance of considering the muscle biopsy findings in the full clinical context, as changes of chronic denervation may be missed by chance in a single biopsy. We also recommend caution in extrapolating from aspects such as the nature of the grouped fibres in a biopsy (type 1 versus type 2) or the severity of the denervation changes, as both were highly variable, even within the same muscle.

Sparing of the semitendinosus and adductor muscles on muscle MRI in the thighs has been a striking and consistent finding in all
individuals and families with dominant congenital SMA studied to date, including in the family described in our study (Fleury and Hageman, 1985; Mercuri et al., 2004; Reddel et al., 2008). This suggests that muscle MRI may be a useful, non-invasive test in individuals with lower limb weakness in whom a diagnosis of dominant congenital SMA is being considered, although further studies are required to determine the sensitivity and specificity.

There have also been minor variations in the pattern of muscle weakness in the dominant congenital SMA families reported and our family continues this trend (Fleury and Hageman, 1985; Frijns et al., 1994; Adams et al., 1998; Mercuri et al., 2004; Reddel et al., 2008). For example, most other dominant congenital SMA families have had equinovarus ankle deformities, rather than the calcaneovalgus pattern seen in our kindred. On MRI, tibialis anterior and soleus muscles showed greater disease involvement on muscle MRI in our family suggesting a different pattern of distal muscle involvement (Fleury and Hageman, 1985; Reddel et al., 2008). Another difference is the presence of kyphoscoliosis, scoliosis and hyperlordosis in previously reported families (Fleury and Hageman, 1985; Reddel et al., 2008), whereas these features are present in only the most severely affected member (Subject IV.5) of our kindred. This individual also has respiratory involvement, which is not a commonly described dominant congenital SMA feature. Our family also lacks both the disproportionately short lower limbs in the patients with dominant congenital SMA reported by Mercuri et al. (2004), and the hyperlaxity of the upper limb joints, neck flexor weakness and scapular winging, described by Frijns et al. (1994). The basis for these minor degrees of clinical variation between families is currently unclear but they may stem from genetic heterogeneity, mutation-specific effects or modifier genes.

Currently, the presence of TRPV4 mutation-positive and mutation-negative dominant congenital SMA families indicates at least a degree of genetic heterogeneity. Interestingly, TRPV4 mutations have been identified in Charcot–Marie–Tooth disease type 2C kindreds and in a scapuloperoneal SMA kindred, (Auer-Grumbach et al., 2010; Deng et al., 2010). Charcot–Marie–Tooth disease type 2C is an axonal form of Charcot–Marie–Tooth disease characterized by absence of congenital contractures, onset of weakness and wasting in the lower limb after infancy, and slow progression of weakness and the development of foot contractures over time (Fleury and Hageman, 1985; van der Vleuten et al., 1998; Reddel et al., 2008). All of these features point to a post-natal deterioration of motor nerves, which is in contrast to the time course of neuron loss in dominant congenital SMA. Nevertheless, TRPV4-related dominant congenital SMA, scapuloperoneal SMA and Charcot–Marie–Tooth disease type 2C are clearly allelic disorders, and therefore other genetic causes of Charcot–Marie–Tooth disease type 2 are sensible candidates for dominant congenital SMA.

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**Supplementary material**

Supplementary material is available at *Brain* online.

**References**


