Letter to the Editor

A novel syndromic form of sensory-motor polyneuropathy is linked to chromosome 22q13.31-q13.33

To the Editor:

Hereditary peripheral neuropathies are the most common inherited diseases of the nervous system (1). Several clinical forms are described with Charcot-Marie-Tooth (CMT) disease being the most common with extensive genetic heterogeneity (2,3). Here, we describe a family with an apparently novel syndrome in which sensory-motor polyneuropathy is associated with microcephaly, mental retardation, ophthalmoplegia and syndactyly.

Index is a 46-year-old Saudi male. He was born to healthy first cousin parents and was noted to have syndactyly and strabismus early in infancy. Motor development was normal, but he did have cognitive delays. By 15 years of age, he developed progressive lower extremities weakness and became immobile by 33 years. Weakness of the upper extremities occurred later at the age of 36 years and currently he is challenged to perform even basic hand functions. Sphincter control is normal.

He was short (150 cm) and microcephalic (48 cm) on exam. His facies were largely nondysmorphic (Fig. 1a). He was cognitively impaired with an IQ of 47. Ophthalmoparesis was evident particularly on adduction and downward gaze (Fig. 1b). Pupils were not reactive and oculoccephalic response was absent. Mild facial weakness was noted and mild dysarthria but no tremor or ataxia. There was wasting of calf muscles with foot drop, but the foot arch was largely normal. Deep tendon reflexes were absent and proprioception, touch and temperature sensation were impaired in a length-dependent pattern. There was bilateral syndactyly (Fig. 1c,d) and severe weakness of the wrist movement and mild wasting of the forearms. MRI brain showed mild non-specific brain atrophy. Electrophysiological tests confirmed significant peripheral neurogenic involvement. The compound muscle action potentials were markedly reduced in amplitude but normal in shape, and the sensory nerve action potentials were absent with surface recording and only obtainable with near nerve recording. The sensory and motor conduction velocities were mildly reduced with a range of 34–46 m/s. Motor unit potentials were neurogenic with clear signs of reinnervation but no signs of active denervation. Nerve biopsy showed moderately depleted myelinated axons of all fiber size with no onion bulbs. There was no evidence of active axonal degeneration, but there was some attempt of axonal sprouting (Fig. S2). Muscle biopsy showed neurogenic angulated muscle fibers and mild fiber type grouping; however, there was no evidence of ragged red fibers.

Case 2 is the 45-year-old brother of Case 1. History was similar. Weakness started at the age of 10, was immobile by the age 25, and lost purposeful use of his hand at the age of 30 years, with additional decreased sensation and incontinence. His ability to swallow has deteriorated at the age of 41 and is on strictly soft diet.

Physical examination revealed short stature and microcephaly (50.2 cm) (Fig. 1e). His IQ was 50. There was bilateral exotropia with ophthalmoplegia (Fig. 1f). Facial weakness was evident and gag was difficult to elicit. There was wasting and weakness in forearms and legs with absent reflexes and impaired proprioception. Pain and touch sensation were reduced distally. He had mild webbing of the fingers and two-thirds toe syndactyly (Fig. 1g,h). Conduction studies and EMG were consistent with mainly axonal sensory-motor polyneuropathy with evidence of denervation in upper and lower extremities.

Case 3 is the 34-year-old brother of Case 1 who similarly had strabismus and progressive weakness (upper < lower) that started at the age of 20 years, but he is still able to ambulate albeit with great difficulty. He reports normal sensation, but has been incontinent for urine recently.
Fig. 1. Clinical photographs of the three patients. (a, e, i) Frontal views of the patients showing microcephaly-related dysmorphism. (b, f, j) Severe strabismus shared by all patients. Note the variability of syndactyly where Case 1 has syndactyly of both hands (c, d), Case 2 has two-thirds toe syndactyly (g) and mild syndactyly of hands (h), and Case 3 has only mild syndactyly of hands (l) but not feet (k).

Physical examination revealed normal height (167.7 cm) and weight. He was microcephalic (51 cm) but non-dysmorphic otherwise (Fig. 1i). His IQ was 49. There was bilateral exotropia and ophthalmoparesis (Fig. 1j). Facial weakness was mild. Deep tendon reflexes were absent with atrophy of the distal leg muscles and foot drop. Proprioceptive and touch sensation was impaired distally. There was mild syndactyly of fingers (Fig. 1l). MRI of brain showed diffuse brain atrophy. Neurophysiological testing showed similar findings of sensory-motor axonal polyneuropathy. EMG clearly showed neurogenic motor units.

All patients had normal CK, 7-dehydrocholesterol, liver enzymes, blood electrolytes, plasma amino acids and acylcarnitines, lipid profile, complete blood count, very long chain fatty acids, lactate, pyruvate, cerebrospinal fluid protein analysis, regular and molecular (a-CGH) karyotype on lymphocytes.

The family was enrolled with written informed consent (IRB #2080006). Samples were collected from the three affected brothers and four of the six unaffected siblings; the parents are deceased. Homozygosity mapping was performed as described before (4). One single block of homozygosity was shared by the three affected siblings and not by any of the unaffected siblings to whom we had access on 22q13.31-q13.33 which was confirmed by linkage analysis using easyLINKAGE-Plus v.5.08 (LOD = 2.9017) (Fig. 1S). The locus is flanked by rs6008939 and the distal telomere of 22q and contains 55 genes. In view of the syndactyly phenotype, we hypothesized that the candidate gene is probably involved in sonic hedgehog signaling, so TUBGCP6, a member of the γ-tubulin complex, and TTLL8, a microtubule polyglutamylase, were selected because cargo transport along microtubules is crucial for hedgehog signaling cascades but no mutation was identified (5,6).
X-linked inheritance was excluded by repeating linkage analysis on the X chromosome.

Although this family has type 2 (axonal) CMT-like neurophysiological profile, we are reserved about calling this a syndromic form of CMT because they lack the lower limb skeletal findings that are typical of CMT. In addition, although CNS demyelination has been reported in association with certain CMT subtypes, microcephaly, mental retardation and ophthalmoparesis have never been reported (3). Similarly, syndactyly and microcephaly are the hallmark of craniodigital syndrome but not peripheral neuropathy (7). Therefore, we suggest this is a novel syndrome. The underlying gene is probably involved in the maintenance of peripheral nervous system and brain development. Furthermore, the syndactyly phenotype suggests a developmental role that is not neuro-specific for this gene.

Supporting Information

The following Supporting information is available for this article:
Figure S1. A syndromic form of sensory-motor neuropathy maps to 22q13.31-q13.33. (a) Family pedigree with haplotype analysis for the disease locus at 22q confirms the presence of a shared haplotype among all affected siblings. Parental haplotypes were inferred based on offspring genotypes. (b) easyLINKAGE genomewide analysis reveals linkage to only one locus. (c) Genotyping Console output shows that the 22q block of homozygosity shared by the affected siblings (in black) is not found in the four healthy siblings we examined.

Figure S2. Nerve biopsy. (a) Toluidine blue-stained section from the sural nerve biopsy of the index case. This fascicle shows a moderately marked depletion of myelinated axons of all fiber size and replacement by collagen bundles. Many axons exhibit dense axoplasm (big arrow). Occasional thinly myelinated axons suggesting a demyelinating component are also evident (small arrows); no onion bulbs are seen. Two regenerative axonal clusters are shown in the inset (arrows) (Original magnification, ×400). (b) Transmission electron micrograph of a representative area of the same sural nerve showing some of the residual large myelinating axons with dense axoplasm and condensed organelles in a collagenous endoneurium (matrices). Denervated Schwann cell bands from unmyelinated axons are seen in the background, but better showed in the inset (arrows) (Original magnification ×1200).

Additional Supporting information may be found in the online version of this article.

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References


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Letter to the Editor

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