

Evidence for compound heterozygosity causing mild and severe forms of autosomal recessive spinal muscular atrophy

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Abstract

Spinal muscular atrophy is an autosomal recessive disease of motor neurone degeneration which shows a variable phenotype. Two candidate genes show deletions in affected subjects but with no distinction between different forms of the disease. We report an unusual family in which mild and severe SMA coexists and patients are deleted for the SMN gene. The father is affected with late onset SMA; therefore this family shows pseudodominant inheritance. When typed using closely linked flanking markers the severely affected son does not share the same haplotype as his sib, who is deleted for SMN but shows no signs yet of SMA. This supports the hypothesis that differences in SMA phenotype can be explained by a multiple allele model.

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Key words: spinal muscular atrophy (SMA); survival motor neurone gene (SMN); compound heterozygosity.

The autosomal recessive group of proximal spinal muscular atrophies (SMA) of childhood (types I-III), in which there is widespread death of motor neurones leading to weakness and wasting of voluntary muscle,¹ have all been mapped to the same region of chromosome 5q13.^{2,3} Two candidate genes which show deletions in patients have been cloned from the region. The survival motor neurone gene (SMN) is deleted in >95% of affected people⁴ and the neuronal apoptosis inhibitory protein gene (NAIP) is deleted in 45% of severely affected (type I) patients but only 18% of mildly affected patients (types II and III).⁵ Recently, adult onset SMA, sometimes referred to as type IV, has also been linked to this region by the finding that some patients with disease onset as late as the fourth decade show identical deletions in exon 7 and 8 of the SMN gene to children with severe forms of the disease.⁶ Other patients with type IV SMA have been found not to be deleted for SMN suggesting that this milder form is genetically heterogeneous.⁷ Thus there is a remarkable degree of phenotypic heterogeneity in this disease but the genetic basis of severity has not been elucidated. It has been suggested that the extent of deletions underlies the age of onset and severity of the disease. Alternatively, given that these genes exist in multiple copies in the region, gene dosage may be relevant to the pathogenesis of motor neurone death.

We have analysed the candidate genes in a family in which proximal, symmetrical lower motor neurone weakness with absent reflexes appears to be segregating as an autosomal dominant trait. Autosomal dominant SMA, in contrast to the recessive form of the disease, is usually an indolent, distal disease of weakness and wasting which characteristically has a late onset.⁸

Case reports

The family pedigree is shown in fig 1. The affected subjects consist of the father, who was asymptomatic until the age of 27, when he developed weakness which progressed over a 10 year period until he was wheelchair bound. His older son is currently asymptomatic at the age of 5 years and has not been investigated with muscle biopsy or EMG. The younger son was floppy from birth and came to the attention of paediatricians at the age of 6 months because he was unable to sit upright unsupported. At that time he was noted to have poor head control, diminished tendon reflexes, and proximal muscle weakness. He was never able to stand and is currently wheelchair bound. Muscle biopsy has confirmed morphological changes consistent with SMA.

All available family members including the paternal grandmother were typed for the deletions in the SMN and NAIP genes using the polymerase chain reaction as previously described.^{4,5} Closely linked flanking microsatellite markers were used to assess which chromosome had been inherited by each child. These typings are shown in fig 1.

Discussion

The clinical features as described conform to a diagnosis of type II SMA in the affected child and to type IV SMA in the father. Both are deleted for exons 7 and 8 of the SMN gene which makes it overwhelmingly likely that this family has chromosome 5 linked autosomal recessive SMA. Variation in the severity of the disease within a family has been described but such an extreme difference as exists here is unusual. The apparent autosomal dominant transmission is explained by the father being a homozygote and the mother being a heterozygote. Offspring of this pairing will thus have a 1 in 2 chance of being homozygous for the disease mutation and pseudodominant transmission will occur. Pseudodominant inheritance in SMA families has previously been

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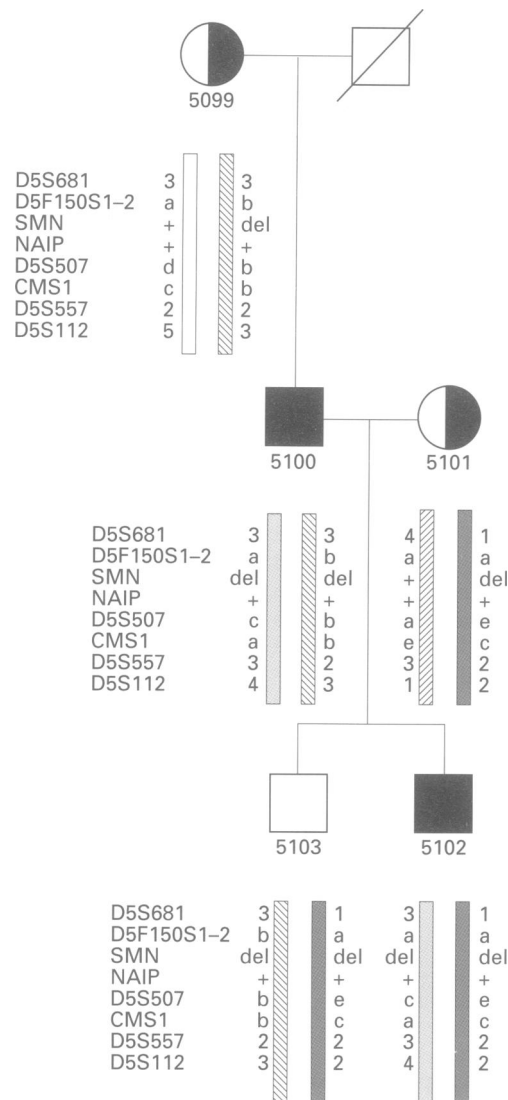


Figure 1 Haplotype analysis of markers in the SMA candidate region and analysis of deletions in the SMN gene. The affected father (5100) has given different chromosomes to his severely affected son (5102) and to his other son (5103) who may be unaffected or, more likely, presymptomatic.

described.^{9,10} An unexpected finding was the discovery of deletions in the SMN gene in the asymptomatic child. One interpretation of this is that this child is currently presymptomatic and that he will develop, similarly to his father, a mild form of SMA, later in life. Alternatively, this child may never develop the disease at all; rare incidences of unaffected sib pairs discordant for the disease but both deleted for SMN have recently been described.¹¹⁻¹³

As shown in fig 1, both sibs have inherited the same chromosome from their mother and the origin of the difference in phenotype must therefore have come from their father. Thus the father, who is mildly affected, is a compound heterozygote for a mild and a severe disease causing allele with the mild allele compensating for the effect of the severe allele. This is the first clear demonstration of compound heterozygosity as an explanation of the difference in severity between the subtypes of SMA. In other cases where members of the same family have been deleted for SMN but shown a gross

difference in phenotype they have shared identical haplotypes, suggesting that genetic influences outside the immediate SMA region may contribute to the variation in phenotype in these families.¹¹⁻¹³

This family provides strong support for the multiple allele model of SMA, proposed by Becker, which predicted both the rare occurrence of pseudodominance and the appearance of extreme differences in phenotype in one family.^{14,15} The model depends on the presence of a common normal allele which in combination with any of a number of rare mutant alleles will give the various forms of the disease. Unusual pedigrees such as the one described in this study arise when a person carrying two of the rare mutant alleles produces offspring with a heterozygous carrier. Alternatively, given the intrinsic instability of this region of the genome, it may be the case that the father is carrying similar alleles but that one of these has undergone an additional mutation during spermatogenesis. In this way his offspring may show discordance owing to germline mosaicism. In keeping with the idea of germline instability, it has been shown that de novo deletions do occur.^{16,17}

Deletions in the SMN gene have proved to be specific for autosomal recessive SMA but no explanation at the molecular genetic level exists for the observed differences in phenotype. In families where conventional autosomal recessive inheritance is observed, all affected offspring will have inherited the same disease carrying chromosomes. In this family two sibs, both with identical deletions in the SMN gene, have inherited different disease carrying chromosomes from their father.

In summary, this family is unusual because there are two generations with affected subjects. Furthermore there is an extreme polarisation in the severity of the observed phenotype. Further analysis of the molecular genetic difference between the affected subjects may help in elucidating the basis of this phenotypic difference.

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