Presymptomatic testing for autosomal dominant spinocerebellar ataxia type 1

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Abstract

Presymptomatic testing was done on four people from a large family in which an autosomal dominant form of spinocerebellar ataxia was segregating. Earlier genetic analysis had shown that in this family the disorder was tightly linked to an informative microsatellite polymorphism on chromosome 6p. Two subjects with prior risks of 50% of developing the disease had final risks after testing of 2%; the other two with prior risks of 25% had final risks of 1%. Chromosome 6p linked spinocerebellar ataxia may now be added to Huntington's disease as a late onset disorder in which genetic linkage may be used to carry out presymptomatic testing.

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The inherited spinocerebellar ataxias are progressive neurological disorders characterised by degeneration of cerebellum, spinal cord, and brain stem. They are clinically and genetically heterogeneous.¹ Among the dominantly inherited forms is a subtype, SCA1, which has been linked to the short arm of chromosome 6, near to the HLA locus.²⁻⁵ Subjects with SCA1 have progressive ataxia of gait, dysarthria, and dysphagia. Age at onset of symptoms is between 20 and 50 years. The disease progresses over several decades, ultimately resulting in death.⁶

Not all types of dominantly inherited spinocerebellar ataxia are linked to chromosome 6.^{7,8} Thus before using genetic markers to track the SCA1 gene through at risk families, it is necessary to carry out a formal linkage analysis of cosegregation of gene and marker within that family. This requires a large family and a highly informative marker. Recently, a dinucleotide repeat polymorphism with multiple alleles at the D6S89 locus⁹ has been shown to

be tightly linked to SCA1.¹⁰⁻¹² This system is useful not only for confirming linkage within a family but also for using in presymptomatic testing.

Part of an extended Scottish family (family 2 in reference 1) with SCA1 is shown in the figure. The mean age of onset of disease was 39 years. Testing for D6S89 alleles in DNA samples from nine affected and 50 unaffected members gave a maximum lod score of 3.4 at $\theta=0$, representing odds of 2500:1 that the marker and SCA1 are genetically linked in this family.¹³

Four subjects (arrowed in the figure; sexes concealed for reasons of confidentiality), who had no signs of SCA1 at ages 30, 33, 36, and 52, requested presymptomatic testing. Two (III.1 and III.8) had affected parents and a 50% prior risk (unadjusted for age). The other two (III.3 and III.4) had a father who had died of other causes at a comparatively early age and who were therefore at 25% risk. All four went through a genetic counselling protocol similar to that used in preclinical testing for Huntington's disease.¹⁴

D6S89 genotypes were determined after polymerase chain reaction amplification by methods previously described.⁹ Inspection of the pedigree shows that allele 3 is in phase with the SCA1 gene, and that none of the four probands had inherited this allele. Thus each had their prior risk substantially reduced. The exact residual risk depends on assumptions made about the recombination rate between the D6S89 and SCA1 loci. At a recombination fraction of 5%,¹¹ III.1 and III.8 have a residual risk of developing SCA1 of 5%, while for III.3 and III.4 it is 2.5%. At the more likely recombination fraction of 2%^{12,13} the figures are 2% and 1%, respectively.

Presymptomatic testing for late onset autosomal dominant disorders has to date been largely confined to Huntington's disease. This is a genetically homogeneous entity with invariably severe outcome. A battery of polymorphic markers on chromosome 4p permits a reasonable estimate of the residual risk of developing the disease after DNA testing. However, since the prospects for those found to carry the gene are so gloomy, it is essential that pre-test counselling be carried out according to internationally agreed protocols.¹⁵ The same imperative applies to the dominantly inherited ataxias, but with the additional requirement that a prior linkage analysis be carried out in the family at risk.

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Pedigree of the family in which SCA1 is segregating. Affected people are shaded and probands arrowed. Genotypes at the D6S89 locus are shown beneath the pedigree symbols.

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