Absence of linkage between chromosome 21 loci and familial amyotrophic lateral sclerosis

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Abstract

Familial amyotrophic lateral sclerosis (FALS) has recently been shown to be linked to chromosome 21 markers in a subset of families. However, we were unable to show linkage between FALS and chromosome 21 markers which flank the putative FALS locus in UK families.

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Recently, linkage has been reported between familial amyotrophic lateral sclerosis (FALS) and chromosome 21 markers in a subset of families.¹ Multipoint analysis yielded a significant location score 10 cM telomeric to *D21S58*. However, no significant two point lod scores were obtained. We have investigated whether a similar linkage occurs in FALS cases collected in the UK. In our study, microsatellite polymorphisms were used to ensure a high level of informativity.

At present, we have identified more than 30 UK families with the characteristic features of an autosomal dominant mode of inheritance with DNA available from at least one affected subject. Entry criteria for this study are that at least one member of the family should show typical upper and lower motor neurone signs. Eight families were used which consisted of 13 affected and 35 unaffected subjects. Five microsatellite polymorphisms were investigated which flank the FALS locus identified by Siddique *et al*¹ and are in order from the centromere: *D21S120*, *D21S214*, *D21S210*, *IFNAR*, and *D21S156*. DNA was amplified by PCR in the presence of ³²P α -dCTP and primer pairs for the five loci and separated on 6% polyacrylamide. Two point lod scores were determined using the program MLINK with published allele frequencies (GDB). An age dependent penetrance curve was used (0.78 at 80 years).

The lod score table (table) shows significant exclusion of linkage at a recombination fraction of 0.001 for *D21S210*, *D21S214*, and *IFNAR* and a significant exclusion of linkage for *D21S156* out to a recombination fraction of 0.004. No significant linkage or exclusion was

Figure Multipoint analysis of chromosome 21 loci in familial amyotrophic lateral sclerosis.

obtained with *D21S120*. Multipoint analysis was performed using the program LINKMAP (LINKAGE version 5.1).² The genetic distances between the markers were derived from a published genetic linkage map of chromosome 21.³ Multipoint analysis indicated significant exclusion of the FALS locus from a genetic distance of approximately 4 cM around *D21S214*, 3 cM around *D21S210*, 6 cM around *IFNAR*, and 13 cM around *D21S156* (figure). Siddique *et al*¹ estimated that 55% of FALS families showed linkage to chromosome 21, but using a test of heterogeneity, HOMOG version 2.8,⁴ we found no evidence of heterogeneity. In conclusion, we were unable to show a linkage between FALS and chromosome 21 markers close to the APP locus, *IFNAR* and *D21S156* (21q22.3) which flank the FALS locus identified by Siddique *et al*.¹ No positive location scores were obtained around the previously reported FALS locus (21q22.1-q22.2).

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Pairwise lod scores between FALS and five chromosome 21 loci.

Chromosome location	Recombination fraction									
	0	0.001	0.005	0.01	0.05	0.1	0.2	0.3	0.4	
<i>D21S214</i>	-4.79	-2.00	-1.31	-1.01	-0.39	-0.18	-0.04	-0.01	0	
<i>D21S210</i>	-4.72	-2.20	-1.51	-1.22	-0.58	-0.35	-0.17	-0.1	-0.05	
<i>D21S120</i>	0.49	0.49	0.48	0.47	0.41	0.34	0.2	0.09	0.02	
<i>IFNAR</i>	-5.25	-2.19	-1.49	-1.19	-0.49	-0.21	-0.01	0.02	0.00	
<i>D21S156</i>	-5.63	-2.56	-1.86	-1.55	-0.82	-0.5	-0.22	-0.08	-0.02	

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