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Close linkage of three neuronal genes on distal mouse Chromosome 15

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The mouse neurological mutant motor endplate disease (*med*) is located on distal Chromosome (Chr) 15. We recently identified mutations in the voltage gated sodium channel, *Scn8a*, that is encoded by the *med* locus (Burgess et al. 1995; Kohrman et al. 1996a,b). In the course of evaluating candidate genes for *med*, we refined the map positions of four genes that were previously assigned to this region either by *in situ* hybridization or by low-resolution genetic mapping: contactin (*Cntn1;* Gennarini et al. 1989), peripherin (*Prph*; Pendleton et al. 1991; Moncla et al. 1992), the calcium channel beta subunit 3 (*Cchb3*; Chin et al. 1995), and natural resistance-associated macrophage protein 2 (*Nramp2;* Gruenheid et al. 1995).

The genetic polymorphisms used in this study are described in Table 1. One hundred and eighty progeny from the intersubspecific backcross [(C57BL/6J-*med*^{tg} × CAST/Ei)F_1 × C57BL/6J] (Kohrman et al. 1995) were analyzed (Fig. 1). The observed gene order and distances are: *D15Mit34*–2.2 ± 1.1 cM–*Cntn1*–5.0 ± 1.6 cM–*D15Mit44, Nramp2, Prph, Cchb3*–0.6 ± 0.6–*med*^{tg} (*Scn8a*)–1.7 ± 1.0 cM–*D15Mit16*–1.1 ± 0.8 cM–*D15Mit35.*

To position these genes with respect to the rest of the chromosome, we typed *Scn8a* on The Jackson Laboratory BSS interspecific backcross (Rowe et al. 1994). *Scn8a* mapped to a position approximately 40 cM distal to the centromere, between *D15Bir17* and *D15Mit16* (*Hoxc*). Complete haplotype data for this cross are available electronically at http://www.jax.org/resources/documents/cmdata.

Our results demonstrate that the brain sodium channel gene. *Scn8a,* the neuronal calcium channel beta subunit, and the neurofilament protein peripherin map within a 1-cM interval. The close linkage of these neuron-specific genes suggests that they might be regulated by shared *cis*-acting elements. These three genes, along with *Nramp 2, Cntn1,* and the *Hoxc* cluster, have been mapped to a conserved linkage group of human Chr 12q11–12q13 (Burgess et al. 1995; Collin et al. 1994; Moncla et al. 1992; Vidal et al. 1995; Berglund and Ranscht 1994). We have determined the gene order for six mouse loci in this linkage group, but the arrangement of the human genes has not been determined. The recently described YAC contig spanning human Chr 12 (Krauter et al. 1995) will facilitate comparative mapping of the human loci and identification of potential neuronal regulatory regions.

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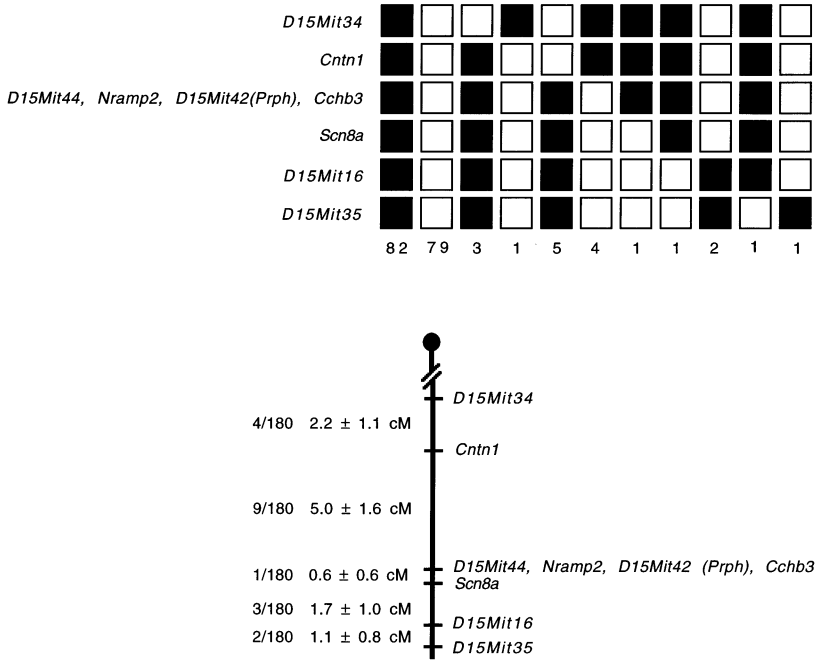

Fig. 1. Genetic map of distal mouse Chr 15. Genomic DNA from 180 backcross animals was typed for the indicated gene loci as described in the text. Each column represents one haplotype derived from the heterozygous backcross parent. The number of mice with each haplotype is indicated at the bottom of the column. Solid symbols, C57BL/6J alleles; open symbols, CAST/Ei alleles. The derived genetic map is shown with distances in cM.

Table 1. Polymorphic loci on mouse Chromosome 15. Alleles for three strains are listed. nd, not done.

Locus	Probe/Primers	Enzyme	C57BL/6J	CAST/Ei	SPRET	Reference
Cchb3	rat cDNA mB1.7	TaqI	6.0	6.0, 4.8	nd	M. Uhler
Cntn1	mouse cDNA	TaqI	8.7, 3.8, 3.5, 2.1	19.0, 5.0, 1.7	nd nd	B. Ranscht and E. O. Berglund
Nramp2	SCA3/SCA5	PCR	0.35	0.22	nd	Gruenheid, 1995
Prph	mouse cDNA 5g	TaqI	8.8	1.8	nd	Landon et al., 1989
Prph	D15Mit42	PCR	0.188	0.170	nd	Dietrich, 1994
Scn8a	6-7	TaqI	1.7	nd	2.3	Kohrman et al., 1995
Scn8a	*med*^{tg}	PCR	neg	neg	neg	Kohrman et al., 1995

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