favour of a gene dosage mechanism recently came to light when Lupski *et al.* (*Nature Genet.* 1, 29–33; 1992) reported decreased NCVs (reminiscent of CMT patients) in an individual with a partial trisomy of chromosome 17p, which included all of the CMT1A candidate region.

However, the impetus for the current flood of papers came less from studies in humans than from a mouse model for CMT called *Trembler* (*Tr*). *Tr* mice move awkwardly and suffer from seizures and tremors; at the cellular level they suffer from hypomyelination in the peripheral nervous system and continuing Schwann cell proliferation. In a recent paper in *Nature*, U. Suter *et al.* (**356**, 241–244; 1992) described a point mutation in *Tr* mice in the gene for peripheral myelin protein-22 (*pmp-22*) and have subsequently found a second allelic mutation (both occur in membrane-spanning regions of pmp-22) in *Trembler-J* (*Tr*^{J}) mice (*Proc. natn. Acad. Sci. U.S.A.* **89**, 4382–4386; 1992). Not only is *Trembler* a legitimate model for CMT on phenotypic grounds, but *Tr* maps to murine chromosome 11, in a region syntenic with human chromosome 17p (and the CMT1A locus). Taken together, the evidence was sufficiently persuasive that Suter *et al.* predicted that 'the human PMP-22 gene will be found on the proximal short arm of chromosome 17, identifying *PMP-22* as a candidate gene for the Charcot-Marie-Tooth disorder'.

Evidently the same thought occurred to several groups who have now confirmed that prediction and their findings are published in this issue of *Nature Genetics* (P.I. Patel *et al.* page 159; L.J. Valentijn *et al.* page 166; V. Timmerman *et al.* page 171; N. Matsunami *et al.* page 176). In each case, the groups have produced direct evidence that *PMP-22* maps to the duplicated region in CMT1A, using methods such as pulsed field gel electrophoresis, fluorescent *in situ* hybridization and dosage analysis. In particular, Patel *et al.* have cloned the human PMP-22 gene, noting strong homology with *pmp-22* and finding expression in the spinal cord and femoral nerve. *PMP-22* maps firmly in the middle of the duplication, again suggesting that overexpression of the gene is the cause, at least in part, of CMT1A.

Settling the issue may not be straightforward, however. The onset of disease symptoms differs markedly in *Tr* mice (caused by a point mutation) compared to humans (predominantly a duplication). It is possible that transgenic mice, the obvious means with which to test the dosage hypothesis, will not live long enough to manifest the disease, which in humans does not usually appear until the second decade. And what about other genes in the region, of which there could be be 30 or more? Some of these genes may contribute to the CMT phenotype as well as other disorders that map in close proximity to CMT1A (for example an REM sleep deficit associated with Smith-Magenis syndrome).

There is, however, a reasonable chance that formal proof of the *PMP-22* candidacy for CMT1A is at hand. There are a few CMT1A patients who do not appear to possess the DNA duplication, and like the *Tr* (*Tr*^{J}) mice, they may harbour a defect within the PMP-22 gene. *PMP-22* defects may also give rise to similar neurological disorders such as Roussy-Levy syndrome, which compounds CMT symptoms with tremor of the hands. Such studies are undoubtedly in progress. □

Pioneer proteins

Norrie disease is a rare but extremely severe neurodevelopmental disorder characterized by congenital blindness, mental retardation and progressive hearing loss. The locus maps to the short arm of the X chromosome which has revealed a multitude of genes that can give rise to hereditary blindness. One of these, choroideremia, was isolated by positional cloning almost two years ago, and now in this issue, two European groups report the isolation of a candidate gene for Norrie disease using a similar approach (W. Berger *et al.* page 199; Z-Y. Chen *et al.* page 204). Several Norrie patients are found to have deletions including or contained within the putative Norrie gene.

Unfortunately, for the moment, the predicted sequence has not proved particularly helpful in elucidating its likely function. The Norrie gene appears to encode a novel polypeptide—otherwise referred to as a 'pioneer protein' by some investigators—with no relatives in the databases. Not that discerning homology is necessarily that informative, but in this case there are virtually no clues from the predicted protein structure as to its normal role. The protein is small (133 amino acids), relatively polar and conserved in evolution. Indeed, study of a related gene in *Drosophila* may prove to be more fruitful. □