Where too much is not a good thing*

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One of 'hot' areas of current research by human geneticists is the basis of inherited diseases in man, and one of the most common such disorder of the peripheral nerves (nerves which bring signals from the brain to the muscles) is Charcot-Marie-Tooth (CMT) disease. The disease was first described in 1886 by two French neurologists, J. M. Charcot and P. Marie and independently by an Englishman, H. H. Tooth. The predominant symptoms of the disease are foot and hand deformities and weakness which result from wasting of muscles. Where the patients are mildly affected, their disease hinders participation in active sports while severely affected persons can be wheel-chair-bound in later life. Several forms of CMT are known with the most common form being usually inherited in a dominant fashion, i.e. passed from generation to generation. These CMT patients have a 50:50 chance of passing the disease on to their children.

There are several autosomal and X-linked loci for CMT, including a locus on chromosome 17 responsible for the most common sub-type, CMT type 1A (CMT1A). The linkage of CMT1A to markers on the proximal short arm of chromosome 17 was first reported by Vance *et al.* (*Exp. Neurol.*, 1989, **104**, 186). Last year Lupski *et al.* (*Cell*, 1991, **66**, 291) made the surprising observation that CMT patients had three copies rather than the usual two, of DNA sequences of a portion of chromosome 17. This led to the hypothesis that CMT was caused by a duplication of DNA sequences. This finding has generated much excitement among human geneticists, because it is unprecedented and could have implications for other genetic diseases.

Recently, a patient with a large duplication of chromosome 17, which was actually visible under the microscope, was identified by Lupski *et al.* (*Nature Genet.*, 1992, **1**, 29) and the hypothesis that CMT was due to gene dosage effect was proven. This finding may have important implications for therapeutic strategies for CMT1A in the long term because it suggests that it may be possible to correct the defect in CMT1A patients by developing methods that modulate expression of the gene(s) which map within the duplication.

There is available presently a mouse model for CMT called *Trembler* (*Tr*). Recently Suter *et al.* reported (*Nature*, 1992, **156**, 241) a point mutation in *Tr* mice in the gene for peripheral myelin protein (PMP-22). 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 CMT1 locus). 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'.

Prajna Patel *et al.* (*Nature Genet.*, 1992, **1**, 159) have now cloned PMP-22 and mapped the gene within the CMT1A duplication. The PMP-22 gene is expressed at high levels in Schwann cells, which wrap around the peripheral nerves and play an important role in the synthesis of the nerve-insulating protein, myelin. These studies suggest that the PMP-22 gene when present in three copies instead of the normal two copies, may lead to the CMT1A condition. While there are likely to be other gene(s) within the CMT1A duplication region, the findings of a point mutation within the PMP-22 gene in the *Trembler* mouse strongly suggest that the PMP-22 gene is likely to play a very important role in CMT1A and that the normalization of the expression of this gene in CMT1A patients who have this duplication may be a possible chemotherapeutic strategy to target in the long term. There is also a reasonable chance that formal proof of the PMP-22 candidacy for CMT1A is at hand. There are few CMT1A patients who do not appear to possess the DNA duplication, and like the *Tr* 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, in which, in addition to CMT symptoms, tremor of hands is also present. The study of such patients will throw more light on the exact role of PMP-22 gene in these neurological disorders.

*"Can we ever have too much of a good thing?" De Cervantes in *Don Quixote*

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