EDITORIAL COMMENTARY

Autosomal recessive Charcot-Marie-Tooth disease

Over the past decade the genetics behind the majority of cases of Charcot-Marie-Tooth (CMT) disease have been revealed with speed and accompanying astonishment. The findings have been so interesting, and provided so many paradigms, that they are studied by all students of molecular genetics down to undergraduate level. The dominant disorder CMT1 provided the first well documented example of a large scale DNA rearrangement, mediated by flanking long repeat sequences, resulting in a disease causing gene duplication of the myelin protein PMP-22. CMT1 was split into the subclasses a and b, after the identification of mutations in P0, providing an early and excellent example of the "positional candidate gene" approach to gene identification and the X-linked form of CMT provided the first example of a member of the connexin, or gap junction, family of proteins causing a genetic disorder.¹ There were obvious clinical spin offs from these findings, including better clinical definition and mutation screening.

However, advances in the understanding of autosomal recessive CMT have proved more difficult to achieve. This is in part because of the intrinsic problem that recessive families are usually small with few affected members. In the case of CMT this is coupled with genetic heterogeneity, as at least four loci at 8q13–21.1, 11q23, 8q24, and 5q23–33 have been identified. The significant thing about the four loci identified to date is that the studies were either in a single large consanguineous family or a small group of families from an isolated genetic group (for example, Bulgarian gypsies). This makes it very likely that a single gene is responsible for the disorder in that group of families.

The paper by Gabreëls-Festen *et al* published in this issue (pp 000–000), illustrates the methodical approach needed to make progress. They build on two papers arising from the study of two Algerian families. The families have an extraordinary structure; in one family there are 17 offspring, nine affected, from a union between first cousins once removed. This provided enough data to map the gene

locus to 5q23–33.² Another family, this time with three affected siblings in a highly inbred pedigree, were mapped to the same locus. Both families showed characteristic clinical and morphological findings including a delay in walking, the appearance of first signs at about age 5, and early, rapidly worsening, deformation of the feet and spine. However, it was the morphological findings³ from the sural nerve biopsy of one patient, including severe depletion of myelinated fibres with small diameters and thin sheaths, relatively few and small onion bulbs in comparison with CMT1A and Schwann cells with multiple cytoplasmic processes which really provided the clue to Gabreëls-Festen *et al*. The morphological picture was very similar to that found by them in some, apparently unrelated, Dutch families. Combining five families plus a Turkish family, they found linkage to the same chromosome 5 locus. Detailed analysis of the haplotypes suggests that although there is no known relationship between the families they may have come from a common founder. As the Human Genome Project progresses, genes mapping to that region of chromosome 5 will soon be identified, providing suitable candidate genes to test.

This paper provides further proof, were it necessary, of the synergy obtained by careful integration of clinical, pathological, and genetic findings. Long may such a collaborative approach be used in the furtherance of neurology and the advice to patients.

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- 3 LeGuern E, Guilbot A, Kessali M, *et al*. Homozygosity mapping of an autosomal recessive form of demyelinating Charcot-Marie-Tooth disease to chromosome 5q23–q33. *Hum Mol Genet* 1996;5:1685–8.