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Three of a kind

As the year draws to a close, it is tempting to look back and ponder some of the major developments in genetics that have occurred during the past 12 months. In contrast to last year, when the discovery of expanding trinucleotide repeats galvanized research into the mechanism of hereditary disease, this year's crowning achievements rest, arguably, in the fine resolution of genetic and physical linkage maps of chromosomes — impressive technological feats whose true worth will be realized in time. But there are many other curious disease origins which remain a puzzle, and this month's issue features three such groups of papers that revisit territory familiar to readers of *Nature Genetics* —Alzheimer's disease, Charcot-Marie-Tooth disease and genetic imprinting. In this issue, important new developments in all three stories are revealed.

The September editorial suggested that after something of a lull, there were signs that the imprinting field was making news once more. Yet this was not to anticipate the three papers in this issue (pages 259, 265 and 270) that report that the gene for the small nuclear ribonucleoprotein polypeptide N (*SNRPN*) maps to the critical region of 1 megabase (Mb) or more on chromosome 15 implicated in Prader-Willi syndrome, which is commonly associated with a deletion of the paternal chromosome 15q11–13. More importantly, the mouse homologue (*Snrpn*) is found to be imprinted — the gene is expressed only from the paternal allele, while the maternal copy of the gene transcriptionally silent. As such, *Snrpn* becomes only the fourth known murine gene to exhibit such imprinting behaviour (after insulin-like growth factor 2 and its receptor, and *H19*) and *SNRPN* a prime candidate for at least contributing to the Prader-Willi phenotype.

Very little is known about the function of the SmN polypeptide, other than that it is likely to be involved in the splicing of mRNA. Its expression is largely confined to the brain, which is certainly consistent with the diverse developmental defects of Prader-Willi syndrome. As shown by Cattanach and colleagues on page 270, *Snrpn* is *not* expressed in a mouse model for Prader-Willi syndrome which they have constructed containing a maternal duplication for the central part of mouse chromosome 7. Meanwhile, new findings from Robert Nicholls and coworkers show that deletion of another identified gene, the human homologue of the mouse pink-eye dilution (*p*) locus, may be responsible for the hypo-pigmentation commonly seen in Prader-Willi and Angelman syndromes, as well as a distinct albinism disorder[1]. The further pursuit of the possible roles of these two loci in these 'imprinting sydromes' will be fascinating to watch.

1992 has seen a considerable focus in Alzheimer's research on β-amyloid, the proteolytic fragment of the amyloid precursor protein (APP) which is deposited in neuritic plaques in elderly patients, and in particular on genetic alterations that may predispose to the same eventuality. A handful of mutations within the *APP* gene have been found[1], which have led to the proposal of an 'amyloid cascade' hypothesis to explain the aetiology of Alzheimer's disease.

But despite the evidence for *APP* defects producing some forms of early-onset familial Alzheimer's disease (FAD), and for another locus for late-onset FAD on chromosome 19, the genetic heterogeneity of FAD clearly extends beyond these two loci. Such suspicions were finally confirmed in a recent report from Gerry Schellenberg and colleagues[2], who mapped a second early-onset FAD to chromosome 14. In this issue three other groups present their own data which leave no doubt as to the significance of this result (pages 330, 335 and 340).

The possibility of an FAD locus existing on chromosome 14 can be traced back to 1983, when a faint hint of linkage was reported with the G_m locus, but never substantiated. The subsequent mapping of the gene for α1 antichymotrypsin (a constituent of amyloid plaques) to chromosome 14, and the description of a familial 14;21 Robertsonian translocation associated with FAD in a single family ensured that chromosome 14 was never fully discounted by those striving to find other FAD loci. But it was not until a supply of highly polymorphic microsatellite markers derived from chromosome 14q became available that the linkage was revealed. Using such probes, Peter St George Hyslop and collaborators finally found convincing evidence in September for linkage in six independent FAD kindreds (some of which had previously shown some evidence for linkage to chromosome 21). Christine Van Broeckhoven's group reports an extensive analysis of two FAD pedigrees that had also shown tentative linkage to chromosome 21, but which can now be definitely classified as chromosome 14-linked. Both groups suggest that their earlier findings were probably spurious. Mike Mullan and colleagues were studying the candidacy of the α1-antichymotrypsin (AACT) gene several months ago before extending their search on chromosome 14. Their data also suggest that the majority of early-onset FAD is attributable to a gene on chromosome 14. Although *AACT* has been excluded, some predict that the true locus will be intimately involved with amyloid processing. Conversely, the ultimate identification of the new gene may lead to an entirely new approach to the origins (genetic and otherwise) of Alzheimer's disease. Meanwhile, the search for at least one more early-onset FAD locus continues.

In June, *Nature Genetics* published four papers announcing that the gene for peripheral myelin protein, *PMP-22*, maps to the duplication on chromosome 17 found in individuals with Charcot-Marie-Tooth disease type 1A (CMT1A). Given that a mutation in the murine *Pmp-22* gene exists in *Trembler* mice — a good model for CMT1A — it was suggested that either overexpression of *PMP-22* as a consequence of the duplication, or (in very rare cases) a mutation in the same gene, could give rise to CMT. Both possibilities are addressed in papers in this issue (page 288, 292). First, James Lupski and his Baylor colleagues identify a complex repetitive element that flanks the duplicated DNA segment (of approximately 1.5 Mb) and which, probably through a process of unequal crossing over, is likely to generate the duplication. In CMT patients, they find three copies of the repeat, supporting this idea. (A corollary of this event is that the same region might become deleted. Such a patient, with a pressure-sensitive neuropathy, has recently been identified by Phillip Chance and colleagues.)

Is *PMP-22* the critical gene in producing the CMT phenotype? According to the accompanying paper from Frank Baas and coworkers, the answer is a resounding 'Yes'. They recently identified a CMT pedigree in which affected individuals showed genetic linkage to the same region on chromosome 17 that is typically duplicated in CMT1A, but did not themselves possess the duplication. Not only did the group detect a missense mutation within the *PMP-22* gene in this severely affected family that segregates with the disease, but the mutation is identical to the murine *Trembler-J* mutation. (The Baylor group have also identified a *PMP-22* point mutation in CMT.) Thus, *PMP-22* would appear to share with the *APP* gene the dubious distinction of promoting disease by either increased dosage (individuals with trisomy 21 are more prone to develop Alzheimer's disease) or specific mutations. And as Baas and colleagues point out, there is also a persuasive analogy with the related X-linked gene for proteolipid protein, *PLP*, another component of myelin: it seems that both specific mutations and, more rarely, a duplication of this region can give rise to Pelizaeus-Merzbacher disease. Although it is still possible that other genes in the duplicated 1.5 Mb interval contribute to CMT disease, *PMP-22* will now receive the lion's share of the attention. □

1. Rinchik, E.M. *et al. Nature* (in the press).
2. Schellenberg, G. *et al. Science* **258**, 668–671 (1992).