Adding to the amyloidoses

Among the amyloidoses — a group of late-onset disorders characterized by the deposition of abnormal protein fibrils at various sites within the body — Alzheimer's disease rightly claims pride of place. Indeed, in recent months, the disease has rarely been out of the headlines, taking into account for example the localization of a second (and apparently more common) early-onset familial Alzheimer's disease (FAD) locus to chromosome 14 (refs 1–4). Moreover, a naturally occurring double mutation in the amyloid precursor protein (APP) gene in a Swedish FAD family[5] leads to six to eightfold over-expression of the 39–42 residue β-amyloid fragment[6,7] when engineered into an amyloid gene and transfected into cultured cells. This provides arguably the most persuasive evidence so far for those postulating a direct link between mutations in the APP gene (and the misprocessing of the protein in general) and the development of Alzheimer's disease. No doubt there will now be yet another race over the next twelve months or so for the eventual identification of the latest FAD gene to be mapped. It will also be interesting to see if the amyloid precursor-like protein, which has just been mapped to chromosome 19 (ref. 8), plays a part in the development of late-onset FAD.

There are, however, a number of other proteins which, when mutated, can give rise to a systemic (as opposed to localized) late-onset condition known as familial amyloid polyneuropathy (FAP)[9]. These disorders are dominantly inherited, characterized by amyloid deposition in various organs including peripheral nerves, and until recently were known to be caused by defects in three distinct genes: transthyretin (prealbumin) on chromosome 18, apolipoprotein AI (apoAI), which maps to chromosome 11 and gelsolin, located on chromosome 9. As described by Merrill Benson and his colleagues on page 252 of this issue of *Nature Genetics*, a new cause of hereditary amyloidosis has now been identified[10].

By far the best characterized culprit in FAP is transthyretin, as more than 30 different mutations in the transthyretin gene have so far been found to cause the disorder, with the majority of them arising in exon 3. The phenotype associated with these mutations is somewhat variable, however, with some cases of numbness and sensory loss beginning in the lower extremities (FAP I), some characterized by early onset of carpal tunnel syndrome (FAP II) and yet more with a milder neuropathy but a significant cardiac myopathy. Despite this battery of genetic data, however, the mechanism of transthyretin deposition is still shrouded in mystery. One possibility is that disulphide bond formation contributes to heterodimer formation and that, as with β-amyloid, missense mutations lead to abnormal conformation and/or greater susceptibility to proteolysis.

The FAP variants caused by mutations in the other two genes — apoAI and gelsolin — are classified as FAP III and FAP IV respectively. The apoAI deposit — an 83-residue N-terminal fragment — was first encountered in a class of FAP notable for a high incidence of renal amyloidosis and gastric ulcer, in which the abnormal protein had originally and mistakenly been identified as transthyretin. The mutation —

a glycine to arginine substitution — occurred at residue 26 of the protein[11]. More recently a second mutation (Leu60Arg) was described in an English family with non-neuropathic amyloidosis and in which slightly larger N-terminal apoAI fragments were detected in the spleen[12].

FAP IV is most frequently found in Finland, where in some regions it affects as many as 1 in 1,000 people. This progressive amyloidosis is characterized by corneal lattice dystrophy and cranial neuropathy, and biochemical evidence had implicated the actin-binding protein gelsolin as the likely defect. The first mutation to be detected was an aspartate to asparagine substitution at residue 187, which leads to the production of a 71-amino acid fragment, interestingly derived from the interior of the molecule. Although this same mutation is also found in non-Finnish families, more recent work has uncovered a second mutation, also involving residue 187 but in which the aspartate is replaced by a tyrosine residue[13].

As discussed by Benson and colleagues in this issue however, a fourth gene must now be added to the list — that encoding the α-chain of fibrinogen. Benson's group examined a family in which three affected members had died from hereditary renal amyloidosis. After examination of the three known genes involved in other forms of hereditary amyloidosis had failed to reveal any putative mutations, the investigators resorted to conventional biochemistry and isolated and purified the amyloid protein deposits from a postmortem kidney. (This was a transplanted kidney the patient had received to combat the amyloidosis.) Partial sequencing of the amyloid peptide fragments revealed that the peptides corresponded to C-terminal sequences from the fibrinogen α chain. Sequencing the genomic DNA and determining the predicted amino acid structure then showed that one allele of the α-fibrinogen gene encoded an arginine to leucine substitution at residue 554, which was also inherited by the propositus' sister and son both of whom also died. Benson and coworkers are currently examining other families with renal amyloidosis, and already have evidence in two of them for a second putative mutation in the α-fibrinogen gene.

It is tempting to speculate on the characteristics shared by this newly extended list of hereditary amyloidosis genes, but about all that one can safely conclude is that they are large plasma proteins synthesized in the liver which are subject to deposition in various other tissues if they contain a pathogenic dominant, single amino acid mutation. However, as noted by the authors, the sizes of the resulting proteolytic amyloid fragments do bear a resemblance, and perhaps this is of significance in explaining the mechanisms of deposition.

The list of candidates is unlikely to end here, however. Other defects can result in a more localized form of amyloidosis: one is in the gene for cystatin C on chromosome 20, which causes a disease known as hereditary cerebral haemorrhage with angiopathy (HCHWA) found largely in Iceland. When a similar rare disorder — HCHWA Dutch type — was encountered in the Netherlands, it was reasonable to expect the same gene defect (given the known migration of people from Holland to Iceland). However, the disorder, which is notable for large amyloid deposits in the brain and death from strokes, is caused by a separate flaw in codon 693 of the APP gene[14]. (Interestingly, the paper that follows the fibrinogen amyloidosis report in this issue describes the localization of a gene responsible for an autosomal dominant syndrome of stroke and dementia, which shares some features with Alzheimer's disease and maps to chromosome 19q)[15]. Yet there are known to be other families suffering from amyloidosis for which no known defect has been identified, and which may represent entirely new forms of FAP.

Fifty years ago, amyloid was thought to be a single entity, but the situation is clearly much more complex. The challenge ahead is to define the pathways by which an array of miscellaneous mutations in a growing number of genes converge to form fibril deposits, and in so doing, possibly define the common structural and/or metabolic features that tie these diseases together. □

1. Schellenberg, G. et al. Science 258, 668–671 (1992).
2. St. George-Hyslop, P. et al. Nature Genet. 2, 330–334 (1992).
3. Van Broeckhoven, C. et al. Nature Genet. 2, 335–338 (1992).
4. Mullan, M. et al. Nature Genet. 2, 340–342 (1992).
5. Mullan, M. et al. Nature Genet. 1, 345–347 (1992).
6. Citron, M. et al. Nature 360, 672–674 (1992).
7. Cai, X-D., Golde, T.E. & Younkin, S.G. Science 259, 514–516 (1993).
8. Wasco, W. et al. Genomics 15, 237–239 (1993).
9. Benson, M.D. J. med. Genet. 28, 73–78 (1991).
10. Benson, M.D. et al. Nature Genet. 3, 252–255 (1993).
11. Nichols, W.C. et al. Genomics 8, 318–323 (1990).
12. Soutar, A.K. et al. Proc. natn. Acad. Sci. U.S.A. 89, 7389–7393 (1992).
13. de la Chapelle, A. et al. Nature Genet. 2, 157–160 (1992).
14. Kevy, E. et al. Science 248, 1124–1126 (1990).
15. Tournier-Lasserve, E. et al. Nature Genet. 3, 256–259 (1993).