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Split verdict on schizophrenia

It is entirely possible that the paper which concludes this issue of *Nature Genetics* documents little more than a benign, asymptomatic nucleotide substitution in a gene situated on chromosome 21. Then again, it may be telling us something new and potentially very exciting about schizophrenia: the gene in question codes for the β-amyloid precursor protein, and the mutation within it sits very close to the known site of other mutations which are associated with a familial form of Alzheimer's disease (AD). For the moment, there is insufficient evidence to choose between these diverging interpretations, but in the virtual absence of solid leads about the aetiology of schizophrenia, the possibilities are surely worth pursuing.

Schizophrenia is a severely debilitating and surprisingly common disorder, or quite possibly group of disorders, affecting up to 1% of the population. Symptoms include psychosis, hallucinations, delusions, intellectual and social deterioration. A large body of work comparing the incidence of schizophrenia in twin and adoption studies, dating back more than fifty years to Franz Kallmann, supports a strong genetic component for the disease. Although estimates vary, the incidence of schizophrenia among identical twins is roughly 50%, and among fraternal twins the concordance rate is of the order of 10% – significantly more than the 1% risk in the general population. These data provide strong evidence for a hereditary factor(s) in schizophrenia, but it has also been argued, with some conviction, that such findings merely underscore the crucial role that environment plays in shaping human development.

Geneticists working on schizophrenia (and mental disorders in general) have no easy task: for example, there are the problems of diagnosing a highly variable illness, defining the pattern of inheritance of the trait and estimating the penetrance of the defective gene(s). In spite of these obstacles, attention was drawn in 1988 to the long arm of chromosome 5, in the wake of a report of a patient from Canada with a partial trisomy of chromosome 5q presenting with chronic schizophrenia. Using two probes from chromosome 5q, Hugh Gurling and colleagues in London found what appeared to be strong evidence for linkage in seven schizophrenic families - five Icelandic and two British (R. Sherrington *et al. Nature* **336**, 164–167; 1988). Yet a report in the same issue (J.L. Kennedy *et al.* 167–169) failed to observe the same cosegregation in a large kindred from north Sweden. This could have meant simply that schizophrenia is caused by more defects at more than one locus, but during the course of the next couple of years, further reports on 15 Scottish families (D. St. Clair *et al. Nature* **339**, 305–309; 1992), five North American pedigrees (S.D. Detera-Wadleigh *et al. Nature* **340**, 391–393; 1989) as well as others reached the same negative conclusions. Even the British group have concluded that their original findings were probably no more than a statistical anomaly: follow-up studies with new, informative microsatellite markers from the region, in the previously reported families as well as others from Iceland, failed to confirm the original linkage.

With so much attention diverted to the chromosome 5 puzzle over the past few years, it is hardly surprising that little other news has emerged recently. Although there are various reported associations of schizophrenia with, for example, Marfan's syndrome (which maps to chromosome 15) or a chromosome 11 translocation in the vicinity of the dopamine D2 receptor (D. St. Clair *et al. Lancet* **336**, 13–16; 1990) they have not so far been substantiated by linkage studies. Perhaps the most effective, if laborious, strategy is simply to rule out those areas of the genome that do not contain a schizophrenia gene, increasing the odds of detection by a process of elimination. For example, a large European collaboration has been instigated to pool data gathered from 40 affected families. And at a recent clinical meeting in the United States, Ann Pulver of the Johns Hopkins Medical School presented an exclusion map for schizophrenia representing an estimated 30% of the human genome. However, varying estimates of heterogeneity may limit even this strategy.

While progress in schizophrenia has stalled, the same can hardly be said for another significant neuropsychiatric disdorder, Alzheimer's disease. As described in the following *News & Views* story, several mutations associated with early-onset, familial AD have now been found in the gene encoding the β-amyloid precursor (APP) protein. As more are uncovered, the first tentative conclusions can be drawn on their relationship to the associated phenotype, which is not limited to dementia but, as illustrated by the first mutation to be discovered within the amyloid gene, includes cerebral haemorrhage too.

One of the numerous groups which decided to screen their collection of presenile dementia patients for possible *APP* mutations was that of David St. Clair of the Medical Research Council's Human Genetics Unit in Edinburgh, Scotland. As described in this issue (C.T. Jones *et al.* 1, 307-309), St. Clair and colleagues decided to screen more than 100 DNA samples, mostly from Alzheimer's individuals, for sequence changes in the critical region of the APP gene. (Although a perfectly valid experiment, the study was actually designed in part to prepare for the eventual cloning of the chromosome 11 breakpoint previously described by St. Clair's group in another schizophrenia pedigree, and the potential identification of a 'candidate' gene.) Ironically, the one positive result of the *APP* mutation search proved to come not from a demented individual, but from a patient with chronic schizophrenia. The site of the single nucleotide substitution, at codon 713 of the APP gene converting an alanine residue to valine, is just four codons removed from the first cluster of familial AD mutations to be characterized.

Although this finding is undeniably provocative, the story lacks resolution. Although there is a well documented history of the illness in the elderly patient's family, the close relatives are either deceased or cannot be contacted, hence segregation studies have not been possible. Nor was the mutation found in 100 other unrelated schizophrenia individuals whose DNA was subsequently examined (the nucleotide change creates a new restriction site). The authors frankly admit that their discovery may well be no more than a 'rare non-pathogenic variant of no medical significance'.

On the other hand, the altered amino acid sits in a highly conserved region of APP and the polymorphism, if that is all it is, has not been reported in hundreds of controls studied in the wake of the Alzheimer's discovery. Given the growing evidence that mutations within the APP gene can lead to a wide spectrum of different phenotypes, it is very tempting to hypothesize that the codon 713 substitution is causally related to the disorder in this one patient. Though she shows no evidence for Alzheimer's disease, she does suffer from a cognitive defect. It is interesting to note that there are many different subtypes of schizophrenia, including a form which progressively leads to mental decline (formerly known as dementia praecox).

It is now more that six months since St. Clair and colleagues discovered the APP mutation, and although they have submitted news of it to the APP consortium, headed by John Hardy (which seeks to collate news of all mutations discovered within the amyloid gene) it would seem necessary for others to attempt to confirm or refute the finding. It should be possible, in a relatively short space of time, for an answer to emerge as to whether this mutation truly exists in other schizophrenia patients. And if the answer is no, the field will be back where it started (and *Nature Genetics* will have devoted four pages to one of the least informative, but most interesting, restriction fragment length polymorphisms in history). □