ALZHEIMER DISEASE

New susceptibility genes uncovered for AD

Alzheimer disease (AD) is a highly heritable neurological disorder. Nevertheless, the genetics underlying late-onset AD, which accounts for most cases of AD, are poorly understood and seemingly complex. For many years, the only well-established genetic risk factor for late-onset cases has been the apolipoprotein E (*APOE*) $\epsilon 4$ allele. Now, two large-scale genome wide association studies, both published in *Nature Genetics*, together report three new susceptibility genes for AD—*CLU*, *CR1* and *PICALM*.

Genome-wide association studies examine single nucleotide polymorphisms (SNPs) in DNA samples from many individuals to discover genetic variants that are associated with disease. Such studies have been successful in identifying risk alleles for several genetically complex disorders, including Parkinson disease and diabetes.

Several genome-wide association studies have been conducted for AD, yet no susceptibility genes have been firmly established aside from *APOE*. The lack of further associations might be attributable to limitations in study design, rather than the absence of other genetic risk factors. “The eight studies for AD that have been published were too small to identify effect sizes of the magnitude likely to be conferred by most susceptibility genes,” explains Julie Williams of Cardiff University, principal investigator of one of the new studies. “To detect such associations, we sought to conduct a large, powerful study.”

Williams and colleagues set up a two-stage genome-wide association study, involving >19,000 participants from across Europe and the US. The researchers assessed 529,205 autosomal SNPs for association in 3,941 individuals with AD and 7,848 controls. Of the six SNPs that reached genome-wide significance (Figure 1), four were related to the *APOE* locus, confirming the association of this gene with AD. The two other SNPs corresponded to two novel associations. One of the SNPs was located on chromosome 8 within an intron of *CLU*, whereas the other SNP was found on

Figure 1 | Scatter plot of the data from the genome-wide association study by Williams and colleagues. The single nucleotide polymorphisms reaching genome-wide significance lie above the red line. Abbreviation: Chr, chromosome. Permission obtained from Nature Publishing Group © Harold, D. *et al. Nat. Genet.* **41**, 1088–1093 (2009).

chromosome 11 in the vicinity of *PICALM*. The associations for both these SNPs were confirmed in an independent group comprising ~2,000 patients with AD and a similar number of aged-matched controls.

Meanwhile, investigators based mainly in France were conducting a similarly scaled, yet independent, two-stage genome-wide association study for AD. The study, led by Philippe Amouyel (Institut Pasteur de Lille), assessed 537,029 SNPs in 2,032 French cases of AD and 12,062 controls. SNPs corresponding to two loci, *APOE* and *CLU*, reached genome-wide significance, while several other SNPs approached this threshold. Results from the replication phase of the study, conducted in 3,978 patients with AD and 3,297 controls from four European countries, confirmed the associations shown by *APOE* and *CLU*, and uncovered a further susceptibility gene, *CR1*, on chromosome 1.

Cross-examination of the data from both studies revealed that suggestive evidence existed in the Williams-led study for an association of *CR1* with AD, while the results from French-based investigation supported an association for *PICALM* and the disease. “This significantly reinforced the validity of our findings,” notes Amouyel.

Many researchers believe that an increase in the level of the 42-amino-acid form of the amyloid β ($A\beta$) peptide—the principal component of the neuritic plaques observed in AD—is a central event in the pathogenesis of AD. The findings from several studies, most notably from those using mouse models of AD, suggest that allelic variation at *CLU*, *CR1* or *APOE* might affect the deposition and/or clearance of $A\beta$. *PICALM* encodes a protein involved in clathrin-mediated endocytosis, and genetic variation at this locus might also influence $A\beta$ biology. Alternatively, a *PICALM* risk allele might exert its effect on synaptic transmission, a process that seems to be impaired in the early stages of AD.

Both groups of researchers are looking to identify other susceptibility genes for AD, through involvement in further genome-wide association studies and by combining existing data. Amouyel’s group also intends to study how *CLU* and *CR1* variants might affect disease progression.

Darran Yates

Original articles Harold, D. *et al.* Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer’s disease. *Nat. Genet.* **41**, 1088–1093 (2009).
Lambert, J. C. *et al.* Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer’s disease. *Nat. Genet.* **41**, 1094–1099 (2009).