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ALZHEIMER DISEASE:

New light on an old *CLU*

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Abstract

Genome-wide association studies (GWAS) have uncovered over two dozen candidate Alzheimer disease susceptibility genes; however, the results of these studies showed limited overlap. Two independently performed GWAS involving cohorts from europe and the US have now identified three additional putative Alzheimer disease genes that show modest but remarkably consistent effects across data sets.

Alzheimer disease (AD) is a fatal neurodegenerative disorder characterized neuropathologically by the extracellular accumulation of amyloid-β (Aβ) plaques, and the intracellular accumulation of hyperphosphorylated tau protein in the form of neurofibrillary tangles. AD is highly heritable, but its genetic architecture is complex, making genetic analysis difficult. 11 genome-wide association studies (GWAS) have been published, and have identified over two dozen novel AD candidate loci.[1] Until recently, however, little or no overlap was observed between the results of different studies. Two large-scale GWAS conducted by Lambert *et al*. and Harold *et al*. have now pinpointed three novel putative susceptibility genes for AD—*CLU*, *CR1* and *PICALM*—which exert modest effects on AD risk, but show strong correlation with AD risk when all available data are combined. Notably, the most prominent result in both studies was the association between AD risk and the clusterin-encoding *CLU* gene, which is located on the short arm of chromosome 8. Owing to its functional relationship with apolipoprotein E (*APOE*), *CLU* (also known as apolipoprotein J) was previously studied as a candidate gene in AD. These earlier studies, which probed for a potential association between *CLU* and AD risk, however, lacked power due to insufficient sample sizes and other methodological issues, precluding earlier recognition of this locus as an AD risk gene.

"…*CLU, CR1* and *PICALM* were identified as risk factors for AD…"

Numerous studies utilizing conventional genetic linkage and positional cloning experiments have revealed that mutations in the genes encoding amyloid precursor protein, presenilin 1 and presenilin 2 can lead to altered production of Aβ, which is sufficient to cause rare, early-onset (~50 years of age) familial forms of AD. The vast majority of AD cases, however, are of later onset (>65 years of age), and this latter form of AD is widely believed to be

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influenced by an array of low-penetrance, common risk alleles. These alleles probably affect a variety of pathways, many of which are believed to be involved in the production, aggregation and removal of Aβ. Although the total number of AD risk genes (and their precise identity) remains unclear, good evidence exists to suggest that, in combination, these genes have a substantial impact on disease predisposition and age of onset. In the search for these late-onset AD genetic risk factors, hundreds of loci have been assessed in well over 1,200 genetic association studies. A common misconception in the field is that, overall, these studies have not yielded any consistent results besides the discovery of an association between the *APOE* ε4 allele and AD. In fact, over 30 different loci have been identified that seem, on systematic meta-analysis of the available data, to be associated with AD risk (for an up-to-date overview, see the 'AlzGene' database[4]). The novel genes highlighted in the recent studies by Lambert *et al*. and Harold *et al*. could, therefore, be thought merely to extend this list by three additional loci.[2,3] Several characteristics, however, set these new studies apart from most other previous AD genetic studies. As a result, *CLU*, *CR1* and *PICALM* are placed high on the current 'Top Results' list on AlzGene, which ranks AD genetic studies according to a combination of criteria, including effect size, *P* value, degree of heterogeneity, and assessment for reporting biases.[4]

First, and most importantly, *CLU*, *CR1* and *PICALM* were identified as risk factors for AD by means of a genome-wide association approach. GWAS simultaneously probe hundreds of thousands of genetic markers, in an essentially unbiased and hypothesis-free manner. The fact that both novel GWAS independently found *CLU* to be associated with increased AD risk is particularly interesting, given the vast number of genetic markers that were assessed. Second, the overarching theme of previous genetic association studies in complex diseases has been the lack of independent replication. In view of the probable small effect sizes exerted by any one of these loci, the inconsistencies might be at least partially explained by a lack of power due to insufficient sample size of the individual studies. Lambert *et al*. and Harold *et al*. overcame this limitation by combining large data sets for both their initial genome-wide analyses and the follow-up genotyping. The two-stage GWAS conducted by Lambert and colleagues involved nearly 15,000 participants from Europe, and the study conducted by Harold *et al*. included a similar number of individuals (>16,000) from Europe and the US. In addition, both studies have already provided independent replication for each other's main findings, although only *CLU* showed genome-wide significant association within each study individually. Third, additional independent replication of the new GWAS results for two of the three novel loci, *CR1* and *PICALM*, was actually already (and unknowingly) provided by previously published AD GWAS.[5-7] Last, when all the available genetic evidence is classified using recently proposed guidelines for the cumulative assessment of genetic association data, all three loci show strong epidemiological credibility, a characteristic shared by only half a dozen other loci on the AlzGene 'Top Results' list.

CLU has long been considered to be a candidate gene for AD and, accordingly, a wealth of functional data has accrued over the past 15 years. On the basis of these data, the leading hypothesis proposes that clusterin, a 75 kDa chaperone protein that is expressed at high levels in the brain, binds to and promotes the clearance of Aβ, a function potentially shared with *APOE*. *APOE* is believed to aid the export of Aβ out of the brain into plasma; clusterin, however, is also believed to aid the re-entry of Aβ back into the brain. Excessive re-entry would be predicted to lead to enhanced Aβ levels in the brain, effectively impairing its clearance.[8]

The potential roles of *CR1* and *PICALM* in AD are less well established. *CR1* encodes complement component (3b/4b) receptor 1, the main receptor of complement C3b protein. Like clusterin, C3b binds Aβ and could promote its clearance.[9] *PICALM* encodes phosphatidylinositol-binding clathrin assembly protein, a protein that is involved in VAMP2

trafficking—a process involved in synaptic neurotransmitter release.[10] Neurotransmitter release is compromised early in the brains of individuals with AD, and Harold *et al*. speculate that the association between AD risk and *PICALM* might be linked to the production of Aβ via clathrin-mediated endocytosis.[3] These potential molecular mechanisms all require further investigation; however, the consistency of the novel genetic results identified by Lambert *et al*. and Harold *et al*. clearly warrant intensive genetic fine mapping and resequencing to identify the actual pathogenic variants.

"…only *CLU* showed genome-wide significant association within each study…"

In conclusion, the two recently published GWAS seem to have pinpointed at least one—and potentially more—bona fide AD risk genes. It must be pointed out, however, that the effects of these genes on AD risk are quite modest. Indeed, these effects are more than an order of magnitude lower than the effect of the *APOE ε4* allele on AD risk. Further studies will be needed to clarify the functional basis of these associations. Only after this objective is accomplished can we be sure that we have identified novel AD risk genes. Identification of novel AD risk genes is necessary if we are to improve our capacity for early prediction and, hopefully, prevention of this devastating disease.

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