ALZHEIMER DISEASE

Alzheimer disease risk genes: 29 and counting

Lars Bertram and Rudolph E. Tanzi

The risk of Alzheimer disease is substantially influenced by genetic factors. A new genome-wide association study of more than 600,000 individuals identifies nine novel Alzheimer disease risk genes, raising the total count of independent risk loci to 29.

Refers to Jansen, I. E. et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer disease risk. *Nat. Genet.* https://doi.org/10.1038/s41588-018-0311-9 (2019).

Alzheimer disease (AD) is a debilitating neurodegenerative disorder that is characterized by progressive decline in cognitive functioning and ultimately leads to dementia and death. Pathogenetically, AD is triggered by the aberrant deposition of amyloid-β (Aβ) as amyloid plaques, leading to neurofibrillary tangle formation, neuroinflammation, synaptic dysfunction, neuronal loss and, ultimately, onset of cognitive decline. Importantly, the molecular events causing neuronal cell death precede the onset of cognitive symptoms by a decade or more[1], which indicates that therapeutics targeting neuropathology, once available, will need to be administered before the onset of symptoms. The identification of predictive AD biomarkers and genetic risk factors will, therefore, be essential for an 'early prediction–early detection–early intervention' approach to preventing AD-related dementia.

Use of genetic linkage analysis followed by positional cloning led to the discovery of rare mutations in the three genes that encode the Aβ precursor protein (*APP*) and presenilins 1 and 2 (*PSEN1* and *PSEN2*), which cause fully penetrant monogenic forms of AD[2]. However, the vast majority of AD probably has a polygenic background driven by numerous genomic variants, the identification of which is the main aim of genome-wide association studies (GWAS). Until now, the last bona fide GWAS in AD was published over 5 years ago[3]. That study included ~75,000 individuals and enabled the identification of 20 AD risk loci, of which 11 were novel at the time. In January 2019, a new AD GWAS was published in *Nature Genetics*[4] and included a sample size more than eightfold greater than that of the 2013 GWAS by accumulating the genetic data of ~635,000 individuals. This vast increase in number enabled the identification of nine novel AD risk loci, increasing the current total in the new AD GWAS to 29 (not counting the three monogenic genes) (TABLE 1).

As expected, the reported loci included many that had already been highlighted in 2013 (REF.[3]), but the new GWAS data also failed to confirm several of those previously reported (for example, *MEF2C*, *NME8*, *CELF1* and *FERMT2*). In addition, the analyses by Jansen et al.[4] confirmed that one locus (*CD33*; originally identified in a GWAS by our group more than 10 years ago[5]) is associated with AD risk at genome-wide significance ($P<5\times10^{-8}$). Also new on the list is *ADAM10*, which encodes the key enzyme that cleaves APP to preclude Aβ generation and has previously been shown to contain rare variants segregating with AD status in families[6]. Another newly identified locus was *APH1B*, which, along with the presenilins, is a component of the γ-secretase complex, responsible for cleaving APP to produce Aβ.

In addition to merely increasing sample size (and along with it, statistical power), the new GWAS by Jansen et al.[4] also breaks new ground on several other fronts. First, the largest portion of the new data set — nearly 48,000 individuals with AD and 330,000 controls without AD — consisted of genome-wide data from the UK Biobank (UKB) project. UKB is a prospective cohort study with deep genetic and phenotypic data collected from ~500,000 individuals across the United Kingdom[7]. At baseline, UKB participants were aged between 49 years and 69 years, and were therefore mostly too young to have developed AD, incidence of which peaks after the age of 65 years. To circumvent this problem, Jansen et al.[4] utilized a method based on 'proxy phenotyping', which makes use of parental AD status as recorded in UKB medical records. This approach was recently proposed[8] to be a valid approximation of future AD status in UKB individuals for whom genotype data were available but who had not (yet) developed AD themselves.

Second, Jansen et al.[4] used an impressive array of computational tools with the aim of integrating high-resolution transcriptomics and epigenomics data to aid the molecular and functional interpretation of their results. These analyses revealed that most DNA variants associated with AD are located in non-coding portions of the genome, especially in regions that have effects on gene transcription. This finding is in line with GWAS results from other complex phenotypes and has important bearings on the design of future genomic studies: if most of the functionally relevant variation occurs outside genes, technologies that focus on coding regions only (such as exon variant genotyping or whole-exome sequencing) are unlikely to be suitable for deciphering the genetic basis of AD and other conditions. Instead, more emphasis should be placed on the regions between genes (for example, by using whole-genome sequencing) and their functional implications and interactions (for example, by using epigenomic and transcriptomic profiling). Furthermore, and in line with previous work, the in silico modelling performed by Jansen et al.[4] emphasizes the role of the innate immune system and neuroinflammation as crucial components in the pathogenesis of AD. To this end, the authors used their data to establish DNA variant enrichments for immune system-related tissues (whole blood, spleen and liver) and, perhaps more importantly, for a key population of immune cells in the brain (microglia).

Third, although no direct association signals were observed for the genes that cause early-onset monogenic AD (*APP*, *PSEN1* and *PSEN2*), the GWAS variants identified by Jansen et al.[4] show highly significant enrichment in other genes involved in the regulation of APP catabolic processes. This is the

first time that APP metabolism has emerged as a main functional category in genetic analyses of polygenic late-onset AD. Fourth, the new GWAS data provide important new clues about the phenotypic connections between AD and other traits. For instance, the authors used Mendelian randomization analyses to show that the previously observed protective effects of increased cognitive ability and higher educational attainment on AD risk are, indeed, causally related. Last but not least, the results of this study were published in preprint form (on the bioRxiv database) before entering the peer-review process. The authors should be commended for this decision, as it has effectively enabled the community to work with their exciting new findings for almost a year before formal publication.

Despite its seminal scope and unique analytical angles, the study by Jansen et al.[4] still leaves some important questions unanswered. For instance, even though our knowledge of the genomic basis of AD was vastly increased by their results, the new data were unable to markedly increase the proportion of phenotypic variance explained by genetics, a situation often described as the 'missing heritability problem' in complex traits[9]. However, if the phenotypic variance cannot be sufficiently explained by 'simple' DNA variants of the type measured in this and other GWAS (for example, single base changes and small insertion–deletions), the elusive heritability must be hidden elsewhere, for instance in other types of genomic variants (necessitating other genotyping and sequencing methods) and/or in genetic interactions among loci (necessitating novel analytical approaches)[9]. These still elusive factors could also be the reason for a second conundrum not resolved by the study of Jansen et al.[4], namely, that even their highly refined map of AD genomics did not appreciably improve clinical predictive ability over previous, less informative sets of variants[10]. Last, delineating the precise molecular mechanisms linking 'genomic dysfunction' with 'cognitive dysfunction' (for example, via 'immune system dysfunction') is still a work in progress and will require the development and application of novel methods effectively linking readouts from 'omics'-based studies to cellular function in vivo.

Table 1 | **AD risk genes newly identified in GWAS by Jansen et al.**

Chr	Position[a]	Lead SNP	Nearest gene	*P* value	AD effect[b]	Potential link to AD pathogenesis
1	161155392	rs4575098	*ADAMTS4*	2.05×10^{-10}	Risk	Neuroprotection: extracellular matrix protease
3	57226150	rs184384746	*HESX1*	1.24×10^{-8}	Risk	Homeobox gene; development
4	11026028	rs6448453	*CLNK*	1.93×10^{-9}	Risk	Innate immunity; neuroinflammation
7	145950029	rs114360492	*CNTNAP2*	2.10×10^{-9}	Risk	Neuronal development
15	59022615	rs442495	*ADAM10*	1.31×10^{-9}	Protection	Sheddase; APP processing
15	63569902	rs117618017	*APH1B*	3.35×10^{-8}	Risk	γ-Secretase; APP processing
16	31133100	rs59735493	*KAT8*	3.98×10^{-8}	Protection	Transcriptional regulation
18	56189459	rs76726049	*ALPK2*	3.30×10^{-8}	Risk	Signal transduction
19	46241841	rs76320948	*AC074212.3*	4.64×10^{-8}	Risk	Unknown

Data from TABLE 1 in REF.[4] except the 'Potential link to AD pathogenesis' column, which represents a summary of the authors' review (and interpretation) of the literature. AD, Alzheimer disease; APP, Aβ precursor protein; Chr, chromosome; GWAS, genome-wide association study; SNP, single-nucleotide polymorphism. [a]Chromosomal position in base pairs (both hg19). [b]Summary of the predominant effect across data sets as provided in primary publication.

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Competing interests
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