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EDITORIAL

Novel Alzheimer's disease risk genes: exhaustive investigation is paramount

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This year marks the 10th anniversary of the publication of two genome-wide association studies (GWAS) that heralded a change in the field of complex genetics of late-onset Alzheimer's disease (AD) [1, 2]. Until then, only *APOE ε4* was unquestionably recognized as a genetic risk factor for AD because of its large effect on disease risk: the so-called low-hanging fruit. These two papers, however, instilled confidence in the ability of the GWAS design to also detect genetic risk loci with smaller effects on AD susceptibility [1, 2]. Since then, a widespread adoption of the GWAS approach has resulted in the identification of many AD risk genes and loci that proved to be consistent across studies. The GWAS data in turn have led to an explosion of subsequent studies of epidemiological or bioinformatic nature, e.g. correlating GWAS-identified SNPs with biomarker phenotypes, or construing information about pathophysiological pathways based on the associated SNPs, or combining alleles at associated SNPs across the genome into polygenic risk profiles. But underneath all this is the realization that GWAS typically provide indirect association signals due to the use of 'tag' SNPs. The still undetected genetic variants that directly modulate disease risk at GWAS loci could have a considerably different strength of effect, or uncover molecular mechanisms and pathways involved in AD risk that diverge from current knowledge. This realization has boosted in-depth molecular investigations in genes and loci identified in Alzheimer's disease GWAS.

The review cluster in this issue of *Acta Neuropathologica* provides detailed discussions of three of these AD risk genes (*SORL1*, *CD33* and *ABCA7*) for which significant advances have been made in identifying genetic variants that directly modulate Alzheimer's disease risk [3–5]. A fourth paper gives a bird's-eye view of the new genetic landscape of AD, and uses recent experimental evidence on AD genes to give a different interpretation of the GWAS data in the shape of a new model of AD pathogenesis [6].

Several important messages can be gathered from these reviews. Both *SORL1* and *ABCA7*, which were reported as Alzheimer's disease risk genes based on the association of common variants, were subsequently shown to harbor numerous rare deleterious variants which were detected more often in AD patients than in cognitively healthy individuals [3, 5]. While logical in hindsight, these were important breakthroughs stirring the prevailing notion that the genetic architecture of complex AD was dominated by *APOE ε4* and common variants with small effects. The protective role of the sorLA protein in AD had already been studied extensively, but the functionality of some of its protein domains was still incompletely understood [3]. The effect ABCA7 may exert on AD risk is still uncertain [5]. The rare predicted loss-of-function variants in *ABCA7* and *SORL1* can now guide the design of experimental investigation of their molecular effect in the context of AD.

The multitude of different rare variants in *SORL1* and *ABCA7*, combined with the strength of their risk increasing effect, means that their impact at the population level is not negligible. In their review, Campion and colleagues report that 3.6% of all AD patients and up to 4.8% of early onset AD patients carry a protein truncating mutation or rare predicted pathogenic missense mutation in *SORL1* [3]. Another 4.4% of European AD patients carry a rare *ABCA7* protein truncating mutation (overlap between *SORL1* and *ABCA7* carriers assumed to be minimal) [5]. Odds ratios well exceed those of common variant associations in GWAS. This begs the question whether current polygenic risk profiling efforts (for scientific purpose) would not benefit from incorporating information on carrier status of rare risk variants. Campion and colleagues do caution against current implementation

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of genetic screening for these variants in a clinical setting, in the absence of functional and segregation data [3]. This is clearly exemplified by the protein truncating variants in *ABCA7* [5]. At first glance these protein truncating variants are considered to lead to 50% loss of protein due nonsense mediated mRNA decay, but cDNA sequencing of several different *ABCA7* variants revealed both escape from nonsense mediated mRNA decay and unknown splicing events that could restore the reading frame. The extent to which this occurs differs from carrier to carrier, troubling straightforward interpretation of the impact of such variants on individual disease risk.

While neither rare variants in *SORL1* nor in *ABCA7* can account for the GWAS association signals at these loci, common functional polymorphisms explaining the GWAS signals in *ABCA7* as well as in *CD33* have been identified, as reviewed [4, 5]. In *ABCA7*, a common protein truncating variant caused by a large deletion explains the GWAS association signal in African Americans, and a pathogenic repeat expansion explains the GWAS association signal in Europeans (reviewed in Ref. [5]). Corroborated by both earlier and more recent evidence in different loci [7, 8], these findings illustrate that the repertoire of genetic variation to be investigated as risk factors for AD should be broadened. Technologies such as long-read sequencing will facilitate this in the years to come.

Intriguingly, while *CD33* was among the first GWAS-identified genes in which a functional risk variant was detected, its association with AD in GWAS is not always replicated. The functional polymorphism affects *CD33* exon 2 splicing efficiency. The AD-protective allele results in an increase of an isoform lacking exon 2, which encodes the IgV domain involved in ligand binding. This observation has led to the formulation of a loss of function hypothesis for *CD33* in AD risk. In their review, however, Estus and colleagues propose a new gain of function hypothesis based on recent experimental evidence [4]. While additional evidence will be required to reconcile all existing data in this new model, progress on CD33 exemplifies that in silico pathway-based analyses that lack this level of detail are unlikely to accurately approximate the pathogenesis of AD.

A similar message can be derived from the review of Dourlen et al. [6]. In their timely synopsis of the genetic landscape of AD, they first discuss the new AD risk genes in relation to the amyloid cascade hypothesis, including genes involved in APP metabolism and Aß peptide production, Aß peptide degradation and clearance, and Aß peptide toxicity, as well as tau toxicity. Evidence from high-throughput molecular approaches on novel AD genes, however, motivated Dourlen et al. to propose a new paradigm for AD pathogenesis in which they assign a central role to the focal adhesion pathway and dysregulation of synaptic plasticity. As they point out in their review, this pathway would not have been identified when relying on in silico analyses of GWAS gene lists alone [6].

Ideally, this new model will spark debate and stimulate efforts to verify or refute it, which in turn will yield further insights. An attractive feature of the model is its circular nature and the notion behind it that individual patients may have different entry points into the vicious cycle, requiring personally adapted treatment strategies. The next challenge will be to delineate identifiable subgroups of individuals that are likely to share an entry point into the vicious cycle of AD pathology. Genetically defined subtypes could be a promising start.

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