**Novel and future insights into the complex genetic etiology of Alzheimer’s disease**

Shea J Andrews1; Brian-Fulton Howard2; Alan E Renton2; Eduardo Marcora2; Alison Goate2

1Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, San Francisco, California, USA

2Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai New York, NY, USA

**Summary**

***Background:***

***Recent developments:***

***Where next?***

**Introduction**

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by the aggregation of amyloid β peptides into extracellular plaques and of hyperphosphorylated tau into intracellular neurofibrillary tangles resulting in progressive decline in cognitive function along with concomitant decline in functional ability. Genetic variants play a substantial role in the development of AD and can be conceptualized as occupying a space along two dimensions: minor allele frequency and effect size (Figure 1). At one end of this spectrum, very rare highly penetrant mutations in *APP, PSEN1, and PSEN2* result in autosomal dominant Alzheimer’s disease that typically have an early onset. At the other end of the spectra, common alleles of small effect size contribute to individuals’ genetic liability for disease, but are not individually causal, that are typically identified via genome-wide association studies (GWAS).

In our previous review, we provided an overview of GWAS methodology, the loci discovered by the largest AD GWAS at the time, and of gene prioritization efforts to identify the causal genes at each locus [1]. Since then, two new GWAS of AD have been published that have significantly larger sample sizes and double the number of loci associated with AD (Figure 2). In this Rapid Review, we will summarize the loci and their respective causal genes associated with AD; discuss heritability estimates of AD; and highlight how GWAS summary statistics are being used in downstream analyses. Finally, we will highlight existing knowledge gaps in the genetics of AD and highlight some preliminary studies that are addressing these gaps.

**Genetic loci associated with Alzheimer’s Disease**

Following up on their earlier GWAS [2], Wightman et al [3] performed a meta-analysis of 13 cohorts totaling 1,126,563 individuals (43,725 cases, 46,613 proxy-cases, 717,979 controls, 318,246 proxy-controls) and identified 38 loci associated with AD – seven which were novel. Bellenguez et al similarly expanded their earlier GWAS by increasing their sample size to 788,989 (64,498 cases, 46,828 proxy cases, and 677,643 controls), identifying 75 loci associated with AD – of which 42 are novel.

**References**

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