RECENT DEVELOPMENTS IN THE GENETICS OF LATE-ONSET ALZHEIMER'S DISEASE

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Twenty years ago, the □4 allele in the gene encoding apolipoprotein E (APOE) was first reported as a genetic risk factor for late-onset Alzheimer's disease, the most common of all late-onset dementias. This finding, together with evidence from twin studies and genetic analyses of early-onset familial Alzheimer's disease, has spurred a flurry of projects aimed at deciphering additional genetic determinants underlying susceptibility for Alzheimer's. These projects culminated in applying high-throughput genotyping and, most recently, high-throughput DNA sequencing (e.g. in the context of whole exome or whole genome sequencing) technologies. The former, conducted mostly in the context of genome-wide association studies (GWAS), have pinpointed common polymorphisms in more than 20 separate loci showing genetic association with Alzheimer's disease risk at genome-wide significance, i.e. P-values <5x10-8. Examples of such Alzheimer's GWAS loci include the genes encoding bridging integrator 1 (BIN1), clusterin (CLU), and ATP-binding cassette, sub-family A, member 7 (ABCA7; for more information and these and other loci consult the 'AlzGene' database created and maintained by our group [www.alzgene.org]). With the exception of APOE-□4, however, the individual effect on disease risk of these variants is small with odds ratios typically well below 1.2-fold per risk allele. Thus, collectively, polymorphisms in these and other established GWAS loci only account for a fraction of the total heritability estimated to underlie the observed phenotypic variance. Some researchers believe the hitherto unexplained (or: "missing") heritability to be caused by the effects of rare functional DNA sequence variants, e.g. those eliciting amino-acid substitutions or differential transcript splicing. To this end, recent whole exome and whole genome sequencing studies have revealed novel associations between Alzheimer's risk and rare variants located in the genes encoding triggering receptor expressed on myeloid cells 2 (TREM2) or phospholipase D family, member 3 (PLD3). While it is still premature to reach any definitive conclusions as to whether rare variant associations will effectively close the missing heritability gap, both empirical and theoretical considerations based on these most recent findings suggest that the situation may be more complex. At the meeting, I will present examples of some of the most recent findings in Alzheimer's disease genetics and discuss their potential relevance with respect to furthering our understanding of the underlying genetic risk architecture and their potential connection to the "amyloid hypothesis" that has dominated thinking in the field for far more than two decades.