EDITORIAL OPEN ACCESS

Unraveling the genetic complexity of Alzheimer disease with Mendelian Randomization

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Genome-wide association studies (GWASs) have changed the way we conceive human genetics and have led to the discovery of thousands of risk variants involved in disease etiology. However, despite tremendous advances made in understanding the genetic architecture underlying disease, there remains an underinvestigated component of risk, namely phenotypic traits that can predispose or protect individuals to disease. The availability of large amounts of GWAS data affords the opportunity to investigate the relationship between myriad traits.[1]

In the current issue of *Neurology® Genetics*, Raghavan et al.[2] aim at determining the putative causal relationship between educational attainment and Alzheimer disease (AD). The authors use Mendelian Randomization, the gold standard for causality in genetic studies, as a statistical approach that uses genetic data in the form of SNPs to study whether an exposure exerts a causal effect in an outcome. This promising methodology sits at the interface between observational epidemiology and interventional trials and aims at addressing the question of whether an observational association between a risk or protective factor and a disease of interest is consistent with a causal effect by focusing usually only on genome-wide significant SNPs. One of the key strengths of this method is that it relies on genetic variants that are fixed at conception and remain constant over the lifespan of an individual and that are randomized during gametogenesis, which means that genetic variants are not associated with all the confounder factors that affect an observational study.[3]

In a simple way, SNPs genome-wide associated with a certain exposure modify the risk of that exposure, which in turn affects the disease of interest. Raghavan et al. not only consider SNP genome-wide related to educational attainment as instrumental variables but also use genetic regions surrounding individually associated SNPs to nominate genes that might contribute to the disease.

The authors identify a causal inverse relationship between educational attainment and AD and demonstrate that an increase of 4.2 years of educational attainment is associated with 37% reduction in AD, exerting a notable protective effect. When focusing on individual loci, the authors identify 6 regions that significantly replicate the causal association and nominate the following genes: the leucine-rich repeat-containing 7 (*LRCC7*), the prostaglandin E receptor 3 (*PTGER3*), and the neuronal growth regulator precursor (*NEGR1*) genes as the main drivers of this relationship.

Mendelian Randomization has the potential to significantly contribute to our understanding of environmental and protective factors in Alzheimer disease; however, this method depends on assumptions, and the plausibility of these assumptions must be assessed. To verify the consistency of their findings, the authors perform a set of sensitivity analyses to account for confounding effects that

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might be violating any core assumption. No evidence of reverse causation, horizontal pleiotropy, or heterogeneity is identified.

The reported findings should be interpreted in the context of existing evidence from other research studies using different designs, and clinical guidelines should not be elaborated uniquely based on Mendelian Randomization results. To make a definite conclusion that might be helpful from the clinical perspective to guide disease prevention, replicating these findings in non-European populations with variable educational background and experiences remains key.

Author contributions

Both authors contributed equally to the initial manuscript preparation, manuscript editing, and commentary.

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