By Systemic Biases Alzheimer's Genetic Risk Studies Undermined

Genome-wide association studies (GWASs) are often used to study the genetic foundation of various diseases, including Alzheimer's disease (AD). To increase their power to capture associations, the inclusion of parental or family history of AD has been proposed to improve sample size, a process otherwise referred to as GWAS-by-proxy (GWAX).

The Importance of GWAX Biases

The extensive use of GWAX in AD research is attributed to its ability to mine data from middle-aged populations to estimate the incidence of AD and identify risk factors for late-onset outcomes. In fact, GWAX facilitated the discovery of 75 genetic loci for AD risk, thus enhancing knowledge of the disease at the molecular level.

Previous studies have demonstrated that GWAX increases the power of GWAS due to its similar effect size estimates for the top single-nucleotide polymorphisms (SNPs) and high genetic associations with GWAS. However, the GWAX methodology has been frequently associated with measurement errors.

For example, unless clearly defined, children of parents with dementia might not differentiate AD from non-AD in their reports despite exhibiting different genetic backgrounds. Furthermore, combining GWAS and GWAX in the analysis without compensating for heterogeneity can reduce heritability estimates.

Persistent and General Biases

AD GWAX has been associated with persistent selection biases, such as survival and participation biases, in multiple studies. Although these biases are frequently observed in epidemiological and clinical studies, they are rarely discussed in genetic research.

Selection biases are common in large-scale biobanks, such as the United Kingdom Biobank. Thus, GWASs based on the U.K. Biobank and follow-up studies, including Mendelian randomization (MR) and genetic correlation studies, are susceptible to confounding.

Indeed, the present study confirmed the presence of nonrandom selection and reporting by participants, thereby demonstrating genetic associations between survey participation and awareness of parental health history.

GWAX Causes Discrepant Genetic Associations

An analysis of genome-wide data showed only seven traits associated with both GWAS and GWAX. Comparatively, GWAS-based studies reported a protective effect of education, whereas GWAX-based analyses indicated the opposite.

Ten studies observed similar patterns for AD-education genetic associations. Case-control studies and family history-based proxy studies showed negative and positive risk associations, respectively, whereas meta-analyses of both GWAS and GWAX showed intermediate results.

Education is a social factor that promotes longevity, improves the parent-child relationship, and increases general health awareness. However, these factors can also affect AD risk; therefore, education and cognition contribute to various biases observed in AD genetic studies.

GWAX Biases Epidemiologyical Genetic Studies

In the current study, researchers performed two epidemiological applications exploring the genetic associations between cognition and AD. Initially, the researchers predicted late-life cognition using a polygenic risk score (PRS) approach for AD based on GWAS, GWAX, and a mixed meta-analysis, all of which generated negative associations.

The second application involved using an MR approach to estimate the size and direction of the effect of education on AD.

GSUB for AD GWAX and Possible Biases

The authors used a novel GWAS-by-subtraction (GSUB) approach to explore potential mechanisms for the bias in AD GWAX that incorporates improved implementation strategies. GSUB also measures false AD GWAX effects, which are genetic signals that arise from confounding factors that influence family history rather than AD itself.

Using GSUB, the non-AD component was found to be negatively associated with multiple health outcomes, which suggests survival bias, as people reporting parental AD had long-lived parents. Thus, protective alleles associated with longevity-enhancing conditions would misleadingly increase the risk of AD.

Furthermore, children aware of parental AD might be closer to their parents, thereby indicating the confounding effect of socioeconomic stratum and family structure. GSUB also determined that the U.K. Biobank survey may not have discriminated between parental AD and non-AD dementia.

Conclusion

The researchers of the current study report divergence between GWASs and GWAXs, which has the potential to significantly misdirect efforts aimed at diagnosis, treatment, and drug development processes. GSUB, while a promising approach, requires validation and adjustment for biases present in case-control GWASs.

Source:

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