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RESEARCH SUMMARY

Determining an individual’s genetic susceptibility in complex diseases like Alzheimer’s disease (AD) is challenging as multiple variants each contribute a small portion of the overall risk. Polygenic Risk Scores (PRS) are a mathematical construct or composite that aggregates the small effects of multiple variants into a single score. Potential applications of PRS include risk stratification, biomarker discovery and increased prognostic accuracy. A systematic review demonstrated that methodological refinement of PRS is an active research area, mostly focused on large case-control genome-wide association studies (GWAS). In AD, where there is considerable phenotypic and genetic heterogeneity, we hypothesized that PRS based on endophenotypes and pathway-relevant genetic information would be particularly informative. In the first study, data from the NIA Alzheimer’s Disease Neuroimaging Initiative (ADNI) was used to develop endophenotype-based PRS based on amyloid (A), tau (T), neurodegeneration (N) and cerebrovascular (V) biomarkers, as well as an overall/combined endophenotype-PRS. Results indicated that combined phenotype-PRS predicted neurodegeneration biomarkers and overall AD risk. By contrast, amyloid and tau-PRSs were strongly linked to the corresponding biomarkers. Finally, extrinsic significance of the PRS approach was demonstrated by application of AD biological pathway-informed PRS to prediction of cognitive changes among older women with breast cancer (BC). Results from PRS analysis of the multicenter Thinking and Living with Cancer (TLC) study indicated that older BC patients with high AD genetic susceptibility within the immune-response and endocytosis pathways have worse cognition following chemotherapy±hormonal therapy rather than hormonal-only therapy. In conclusion, PRSs based on biomarker- or pathway-specific genetic information may provide mechanistic insights beyond disease susceptibility, supporting development of precision medicine with potential application to AD and other age-associated cognitive disorders.

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