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Guest Editorial

Genes in context: path to more precise risk prediction in psychiatry?

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Summary

This guest editorial describes the importance of converging genetics and psychosocial epidemiology research methods to understand the biopsychosocial etiology of psychiatric phenotypes.

Keywords

Genetics; epidemiology; psychosocial factors; genomics; polygenic risk score.

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The development of clinically useful prediction models for disease risk is rapidly gaining importance in the contemporary era of precision medicine. Theoretically, a risk prediction model that incorporates major risk factors of a certain disease can help inform prevention and early intervention efforts, and provide biological specificity that could ultimately improve treatment outcomes and prognoses[1,2] while saving time and reducing costs.

Over the past several decades, there have been significant advances in the understanding of risk factors for psychiatric disorders. Prominent theoretical models of the development of psychiatric disorders, such as the biopsychosocial and stress-vulnerability models, attempt to account for a complex interplay between predisposing and precipitating biological, psychological, social and environmental factors.

Psychiatric epidemiology research has traditionally focused on identifying sociodemographic and psychosocial risk factors for psychiatric disorders, such as low socioeconomic status, adverse childhood experiences and cumulative trauma exposure. Furthermore, the impact of family history of psychiatric disorders on risk for these disorders has been well documented in both psychiatric epidemiology and genetics literature. Genome-wide association studies (GWAS) have implicated numerous genetic variants in the etiology of many psychiatric traits. More recently, polygenic risk scores (PRS) derived from large-scale GWAS have demonstrated significant effects in accounting for inter-individual differences in risk.[3] For example, PRS derived from a multi-trait analysis of GWAS (MTAG) across seven different cohorts accounted for 3.8% of the variance in predicting opioid dependence (OUD; we use the term OUD to abbreviate either opioid use disorder or opioid dependence).[4] However, while statistically significant, the predictive utility of this PRS is not clinically meaningful.

Elucidating the interplay between genetic, psychosocial and environmental factors in etiologic models of psychiatric disorders could help explain more variance in these outcomes than either set of factors alone. Considering a combination of both genetic and environmental factors – and how they interact – may help enhance the identification of individuals at risk. Indeed, a burgeoning body of research has investigated PRS-by-environment correlates of complex psychiatric phenotypes such as major depressive disorder, bipolar disorder, and suicidal thoughts and behaviours. Approaches using PRS derived from large-scale GWAS to investigate gene–environment interactions could advance understanding of the complex biopsychosocial etiology of psychiatric disorders and lead to more precise risk prediction models.[3] However, despite recent efforts to examine the intersection between genetic, psychosocial and environmental factors in predicting psychiatric phenotypes, the two fields (i.e. psychiatric epidemiology and genetics) are not integrated nearly as often as they might be.[3]

Across disciplines in medicine, there are current efforts to improve the predictive accuracy for various diseases by combining PRS with traditional risk factors (i.e. *additive* risk models). For example, in an observational study of 352 660 individuals with no history of cardiovascular disease at baseline, incorporating coronary artery disease (CAD) PRS into a pooled cohort equations model (i.e. an algorithm including information on age, sex, race and ethnicity, smoking, total and high-density lipoprotein cholesterol, systolic blood pressure, and diabetes) resulted in a modest, yet statistically significant, enhancement in discriminative accuracy (4.4% net reclassification improvement for cases and −0.4% for non-cases) for incident CAD.[1]

Paralleling such findings on the additive effects of PRS in prediction models in other fields of medicine, incorporating PRS and examining interactions between PRS and environmental and psychosocial factors has the potential to improve the precision of risk prediction in psychiatry. For example, in a 7-year longitudinal study of 1083 European-ancestry veterans without posttraumatic stress disorder (PTSD) at baseline, our group found a significant gene–environment interaction between PRS and attachment style. Specifically, higher PRS only predicted new-onset PTSD among veterans with an insecure attachment style but not among those with a secure attachment style.[5] The variance in the predicted probability of new-onset PTSD explained by PTSD PRS was 19-fold higher among veterans with an insecure *v.* secure attachment style (9.6% *v.* 0.5%).

Furthermore, to examine the interaction between biological and psychosocial/environmental factors in relation to OUD, our team recently analyzed data from 1958 European-ancestry adults who participated in the Yale–Penn Study.[4] Although OUD PRS were positively associated with OUD (odds ratio = 1.42, 95% CI = 1.21–1.66) and explained approximately 8% of the variance of the final multivariable model, socioeconomic factors such as household income and education explained nearly 50% of the variance in OUD. In particular, among individuals in the highest quartile of OUD PRS, those with less than a high school education had a 7.4-fold greater probability of OUD compared with those with a bachelor's degree or higher education. These results suggest that when OUD PRS is used alone, it has low predictive utility; however, when considered in the context of social-environmental factors, it may substantially improve prediction of OUD. We may expect a similar circumstance for many different psychiatric traits.

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Utilisation of sophisticated multivariable analytic methods may also enhance the precision of prediction models in psychiatry. Machine learning models have recently emerged as an effective approach to modeling multi-dimensional data and incorporating PRS in risk prediction models. Relative to conventional regression models, which may lead to biased and less effective prediction, machine learning algorithms employ multivariable, non-parametric methods. This approach is particularly useful when analysing complex data that may not conform to the assumptions of traditional parametric methods. When using these methods, sample sizes are critical in accurately predicting a phenotype of interest. For example, a machine learning prediction model for Crohn's disease created from 1327 individuals yielded an area under curve (AUC) of 0.60; however, in a larger sample ($n = 11\,943$), the AUC increased to 0.86, which is substantially higher than AUCs for prediction of psychiatric phenotypes.[3,6] Thus, future large-scale studies utilising mega biobanks such as the UK Biobank and the VA Million Veteran Program to develop and validate predictive models for psychiatric conditions have the potential to enhance risk prediction in psychiatry. Machine learning is not a cure for insufficient data, and larger, better-powered GWAS, specific to each population studied, are essential.

Some limitations of the current state of genomics knowledge must be noted. For example, the vast majority of GWAS data are from samples comprised predominantly of European ancestry individuals and lack sufficient data from non-European ancestry participants. Risk prediction is generally at least partially population-specific. Thus, future research should focus on obtaining more diverse, population-based samples. Furthermore, currently available mega biobanks have frequently not employed comprehensive measures to assess psychosocial and environmental factors that may shape risk for adverse psychiatric outcomes. Incorporating validated and standardised measures of such factors in GWAS studies would help enhance the precision of risk models that combine genetics and psychosocial and environmental data in predicting risk for psychiatric disorders.

Using PRS, we can now make statistically valid phenotype predictions for many important psychiatric traits. However, we know of no current example where PRS prediction is clinically useful, and clinical utility is an important goal. Given the complex etiology of psychiatric disorders, the concept of precision medicine may currently seem distant and impractical for deployment in clinical settings. Yet, accumulating work from the fields of psychiatric epidemiology and genetics suggest that consideration of genetic risk in the context of psychosocial and environmental factors is a critical step toward informing such efforts, and that considering a larger set of available data – environmental and genetic – may bring the day of practical personalised medicine in psychiatry closer.

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Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

All authors designed the study and collaborated in writing and editing of the manuscript.

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Declaration of interest

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