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COMMENTARY

Unveiling genetic substrates of brain–heart comorbidities: Integration of both common and rare variants

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In the latest issue of *Nature*, Huang et al. examined the role of common variants in rare neurodevelopmental conditions (NDCs) and discovered that common variant predisposition for NDCs is correlated with the rare variant component of risk. Their findings suggest that future studies should investigate the possible role of indirect genetic effects on cognition-related phenotypes in rare NDCs, by means of considering the contribution of both common and rare variants.[1] In this commentary, we aim to highlight their key findings in the NDCs context, and then provide research prospects for further exploration of such common variant predisposing for cardiac comorbidity in patients with psychoneurological disorders, in view of the increasingly recognized brain–heart networks.

Rare conditions involving the central nervous system have attracted great attention during the past decades due to its high morbidity in the global population. Genetic research has largely improved the diagnosis of rare NDCs. However, a monogenic diagnosis can only be achieved in about one third of the patients, while the genetic predisposition of the majority is considered complicated. A recent study suggested that common variants can also contribute to an increased risk for rare NDCs.[2] To better understand the interplay between common and rare variants in the context of these conditions, Huang et al. conducted a large-scale GWAS and constructed polygenic scores for NDCs and relevant traits using the Deciphering Developmental Disorders study-derived GWAS and external GWAS datasets. They found that patients with a monogenic diagnosis have less polygenic risk than undiagnosed patients, which supports the acknowledged liability threshold model

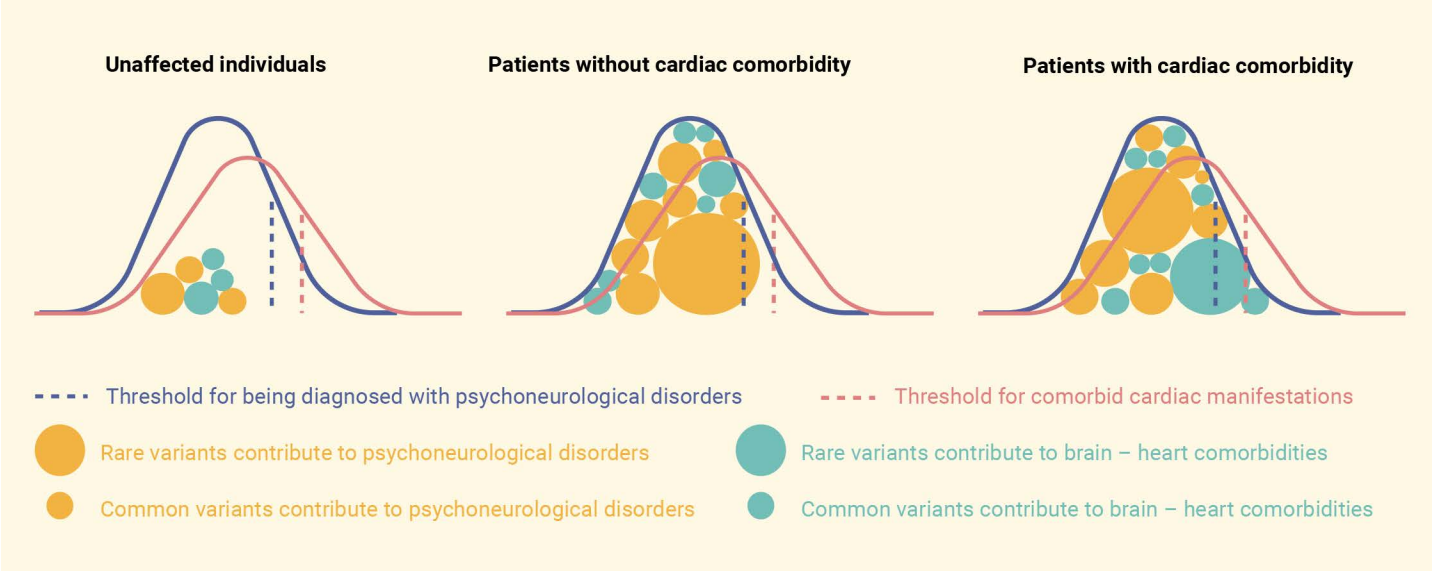

Figure 1. Schematic illustration of how common and rare genetic variants act synergistically to modify the risk of brain–heart comorbidities The dotted blue and red lines indicate thresholds for psychoneurological disorders and cardiac comorbidity, respectively. Circles represent different genetic factors. The size of circles represents the impact of common or rare variants on disease risk, where bigger size indicates variants with stronger effects. The left panel indicates unaffected individual due to genetic burden not reaching any threshold. The middle and right panels indicate patients of psychoneurological disorders without (genetic burden reached the dotted blue line but not the red one) or with (genetic burden reached both the dotted blue and red lines) cardiac comorbidity, respectively.

for NDCs. According to the model, common genetic variants with small effect sizes and rare genetic variants with much stronger effects can act synergistically to modify organ function and therefore lead to variable effects on phenotypic traits. Thus, prominent clinical manifestations could only be observed when the genetic burden reaches the threshold. Besides, their results also revealed that NDCs are genetically correlated with multiple brain-related traits, which is partially, though not entirely, driven by genetic effects. This could explain the findings from previous studies that the common variant contribution behind NDCs overlaps with polygenic risk for schizophrenia and for predisposition to reduced educational attainment and cognitive performance.

It is worth noting that cardiac dysfunction has been increasingly observed as comorbidities in patients of multiple neurodevelopmental disorders with different genetic substrates. The brain–heart axis represents a constellation of physiologic interactions between the cardiovascular and central nervous systems. Due to their intimate inter-organ networks, patients with neurodevelopmental disorders also have higher risks of developing cardiac comorbidities. This is the so-called brain-heart comorbidity. In fact, since enunciated by Claude Bernard over 150 years ago, the intimate connection of the brain with other organs has been reviewed constantly with emerging evidence (e.g. gut-to-brain neuromodulation[3]). Among the multiple organ axes that have been confirmed to be disease-associated, the brain–heart axis has attracted great attention in recent years, as cardiovascular health and mental health are still the most important issues in the field of medical research in the 21st century. Cardiac manifestations have received increasing attention in patients with psychoneurological disorders with different genetic substrates, including schizophrenia, major depressive disorders, Alzheimer's disease or Huntington's disease. Some studies have attributed this to

adverse drug reactions or the prevalence of other risk factors, such as dyslipidemia and diabetes that are related to unhealthy lifestyles in this population. However, there is a growing consensus that the brain–heart axis and its related genetic factors may have an important role in explaining the overlap between brain dysfunction and cardiac manifestations. Thus, recent studies have shown that neuroimmune modulation and inflammation could be contributors to cardiovascular comorbidities in patients with psychoneurological disorders. For example, patients with stress-related mental disorders tend to develop cardiac dysfunction via increased levels of soluble CD40 ligand (sCD40L) and soluble vascular cell adhesion molecule (sVCAM-1). In addition, some stress-mediated proinflammatory cytokines, such as tissue necrosis factor alpha (TNF-α) and interleukin-6, can cause prolongation of the action potential duration and QT interval.[4] Though this theory is well acknowledged, it might underappreciate the role of genetic effects in brain–heart axis regulation, as multiple lines of evidence have suggested the overlapped genetic factors essentially underlying the brain–heart comorbidities. In 2023, a pioneering study by Zhao et al. combined magnetic resonance imaging (MRI) and genetic data analysis to investigate the genetic basis of brain–heart association. By uncovering the genetic co-localizations and correlations between heart structure or function and brain clinical end points, they suggested that risks of brain diseases may have implications for adverse heart metrics.[5] Moreover, by exploring the molecular mechanism that contributes to NDCs, a recent study confirmed the role of *CAMK2D* mutation in the co-occurrence of neurological symptoms and dilated cardiomyopathy. These findings support the shared genetic predisposition for both heart and brain disorders. Under such circumstances, the up-to-date genetic findings presented by Huang et al. could not only expand our knowledge of the genetic etiology of NDCs, but also offer new strategies to unveil the genetic basis underlying cardiac comorbidities following NDCs or other psychoneurological disorders.

To this end, when performing genetic evaluation for patients with psychoneurological disorders, it is important to be aware that some of the variants, especially common variants identified to affect the expression of genes co-expressed in brain and heart (e.g., ion channel-encoding genes, spliceosome genes), might not only have a role in a single phenotype, but rather in a broader range of pathological changes attributing to brain–heart comorbidities. In order to objectively evaluate the genetic risk of cardiac comorbidities following psychoneurological disorders, the rare variant burden score (RVBS) based on rare variants with large effect sizes and polygenic score (PGS) based on common variants with small effect sizes should be integrated with appropriate weights so as to assure the suitable liability threshold for specific phenotypic traits. When the aggregate genetic burden reaches the threshold for psychoneurological disorders (dotted blue line) or even cardiac comorbidity (dotted red line), it renders clinicians a clue for assessing whether a patient of psychoneurological disorders will develop cardiac comorbidities or not (Figure 1). In this way, clinicians could make decisions on whether further steps such as real-time cardiac electrical activity monitoring with portable devices should be implemented.

It is worth mentioning that several lines of future challenges still remain when evaluating the genetic substrates of brain-heart comorbidities. First, clarifying the molecular mechanisms is essential for translating genetic findings into clinical applications. Therefore, it is important to be aware that the functional interpretation of GWAS-identified genetic variants remain a significant task for future research. Some well acknowledged functional genomics tools, such as CRISPR-based assays or single-cell RNA sequencing, could be used to rigorously investigate the genotype – phenotype association by prioritizing the genes or variants that can significantly affect the severity of both psychoneurological and cardiac manifestations. Second, though large-scale GWAS studies provide a great opportunity to elucidate the inherited pattern and new susceptibility genes, applying these findings to individual patient care remains challenging due to the complex interaction between genetic and environmental factors, and the variability in genetic backgrounds across ethnicity. Third, most GWAS studies were confined to the recognition of specific loci or regions. To further investigate the reason behind, more concrete research regarding both the functional genes and the regulatory genes associated with the co-occurrence of two or more phenotypes is required. Therefore, aside from the identification of pathogenic variants within protein-coding regions, variants that fall into specific *cis*-regulatory or *trans*-regulatory elements may also be emphasized.

Overall, the study by Huang et al. highlighted the contribution of common variants in NDCs, which is probably due to their interference with the penetrance of rare deleterious variants. Their findings effectively answered the emerging question regarding interaction between common and rare variants in rare genetic conditions. The liability threshold theory, as highlighted by Huang et al., could prompt the research digging deeper into the brain – heart comorbidities. Nevertheless, future studies are still needed to understand the molecular mechanisms for genotype–phenotype association. This is especially important when exploring the possible role of common genetic variants with direct or indirect effects on brain–heart comorbidities. As can be expected, precisely clarifying the genetic etiology of cardiac comorbidities in patients with psychoneurological disorders will help us to better understand the genetic basis for brain–heart comorbidities.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.