•Forum•

Challenges to psychiatry's symptom-based diagnostic system

Influence of cross-disorder analyses on the diagnostic criteria of mental illnesses

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Summary: Cross-disorder studies are identifying shared genetic variations among common mental illnesses – including schizophrenia, bipolar disorder, and major depression – which are classified as independent disorders in the current diagnostic system. These cross-disorder studies are challenging the traditional system of diagnosing mental disorders based on clinical symptoms, but it remains to be seen whether or not they will lead to an improved method of classifying psychiatric disorders that can, in turn, lead to better outcomes for individuals suffering from these conditions.

Key words: cross-disorder analyses; mental illness; genetics; diagnoses

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Mental illnesses are the result of cerebral dysfunctions of unknown etiology which manifest as cognitive, affective, motivational, and behavioral impairments.[1] Despite their origin in the brain, specific diagnostic biomarkers for mental disorders have not yet been identified, so clinicians must rely on clinical presentations to classify the conditions. Present understanding of the pathogenesis of mental illnesses mainly arises from genetic studies that are, paradoxically, largely focused on mental disorders as classified by the traditional symptom-based diagnostic system.

Genetic findings have identified several potential genes related to mental illness, many of which occur in multiple mental illnesses. The unexpected similarity of the genetic variations in persons with different types of mental disorders has increased the popularity of cross-disorder genetic analysis. For example, a cross-disorder genome-wide association study (GWAS)[2] found shared genetic variations on genes in regions of chromosomes 3p21 and 10q24, and single-nucleotide polymorphisms (SNPs) within two L-type voltage-gated calcium channel subunits (*CACNA1C* and *CACNB2*) among individuals with schizophrenia, bipolar disorder, autism spectrum disorder, major depressive disorder, and attention deficit-hyperactivity disorder. Another cross-disorder analysis of six different neurodevelopmental disorders (intellectual disabilities, autism spectrum disorder, attention deficit-hyperactivity disorder, schizophrenia, bipolar disorder, and epilepsy) found that among 241 genes involved in cerebral development, 7 genes are directly related to neurodevelopmental disorders and 10 genes are indirectly related to mental disorders.[3] Such studies suggest that the conceptual independence of mental disorders classified in current diagnostic systems may not reflect the underlying brain pathology.

How serious is this challenge to the present diagnostic system for mental illnesses? Some relatively rare conditions have already been reclassified when a specific genetic etiology was discovered. The best example is Rett syndrome which was diagnosed as a pervasive developmental disorder in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[4] but re-classified as a neurological disorder in the more recent fifth edition of the diagnostic manual (DSM-5)[5] because research found it was caused by a single X-chromosome mutation in the methyl-CpG-binding protein 2 (MECP2).[6]

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We think it premature to take such examples as evidence that the time has come to discard the current symptom-based diagnostic systems. It cannot be assumed that shared genetic variations indicate a similar pathogenesis. For example, the identified shared genetic variations on SNPs within two L-type voltage-gated calcium channel subunits of *CACNA1C* and *CACNB2* for five diagnostically separate mental illnesses[2] may only indicate that one step in the long pathological process for the conditions is shared. There is no evidence that these SNPs within *CACNA1C* and *CACNB2* are key causative genes of the five mental illnesses, and, therefore, no justification for the claim that the conditions belong to one diagnostic group. In fact, the voltage-gated calcium channel coded by these genes is a macromolecular assembly located in the membrane of excitable cells distributed throughout the brain, heart, smooth muscle, and endocrine system that play important roles in multiple vital activities including gene expression, muscle contraction, and hormone release. *CACNA1C* is related to maintaining heart rhythm,[7] and *CACNB2* is related to the production and differentiation of T cells in lymphocytes, which is important in maintaining the integrity of the immune system;[8] their relationship to brain functioning is unclear. Malfunctions of this voltage-gated calcium channel occur in cardiovascular diseases, diabetes, tumors, and cerebrovascular diseases.[9,10] Thus, the identified genetic variations in SNPs within *CACNA1C* and *CACNB2* for the five mental disorders are probably not limited to these conditions, and, moreover, the results for the five mental disorders may be confounded by the co-occurrence of specific physical illnesses.

The other major finding in the field about the seven genes that are directly related to six types of neurodevelopmental disorders[3] is also of limited diagnostic value. Many (and probably most) neuropsychiatric disorders are associated with abnormalities in the neurodevelopmental process that manifest at different times over the lifetime. Finding that several of the disorders that manifest early in life have some genetic determinants of the neurodevelopmental process in common does not prove that they should be included in a single diagnostic group. The genetic fingerprint for disorders will depend on knowing the entire genetic profile for each unique condition. Differential diagnoses will focus on the genetic components that are different from other conditions, not on the components that are shared with other conditions.

The causes of mental illness still largely remain *terra incognita*. It is clear that currently defined mental disorders with similar clinical presentations may be the outcome of different pathogenetic processes and, conversely, that similar pathogentic processes may present with very different clinical symptoms. New genetic analysis are shedding some light on the issue, but it remains unclear what part of the puzzle we are seeing. Despite the presence of some genetic similarities between schizophrenia, bipolar disorder, major depressive disorder, attention deficit-hyperactivity disorder, and autism spectrum disorder, there are more differences than similarities between these conditions.

Cross-disorder analyses are justifiably making us reconsider the phenomenology-based diagnostic system of mental illnesses that has been used for more than a century. But the results of these genetic analyses need several rounds of refinement and demonstrated clinical benefits (e.g., improved outcomes when targeting treatments to genetically classified disorders) before we can justify replacing the current diagnostic system with genetic marker-based diagnoses. Much of the work to date has been based on secondary analyses of single-disorder studies. Future studies need to simultaneously include individuals with specific conditions of interest (and specific comorbid conditions) and adjust for physical conditions that could potentially confound the genetic findings.

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Conflict of interest statement

The authors report no conflict of interest related to this manuscript.

跨病种研究对精神疾病诊断标准的影响

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概述：许多跨病种研究逐渐发现在不同的常见精神疾病之间——包括精神分裂症、双相情感障碍、和抑郁症，存在共同的遗传变异，而目前诊断系统中已经将这些疾病分为独立的精神障碍。这些跨病种研究对基于临床症状的精神障碍诊断传统系统是一种挑战，但是这否能够成为精神疾病分类的一种改进方法从而改善这些承受痛苦的患者的预后仍有待观察。

关键词：跨障碍分析；精神疾病；遗传学；诊断

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