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Small Cracks in the Dam: Rare Genetic Variants Provide Opportunities to Delve into Mechanisms of Neuropsychiatric Disorders

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The genetic underpinnings of psychiatric disorders have been explored using common variants (e.g., single nucleotide polymorphisms [SNPs]), but the effect size of such common variants is rather small. While common variants, as a whole, might additively confer substantial risk, there are likely thousands of them, making mechanistic investigation daunting. Recent identification of many rare copy number variants (CNVs), each occurring in less than 1% of a disease population, has opened a new venue to explore mechanistic contribution(s) of limited numbers of genes to neuropsychiatric disorders.

Rare CNVs enriched in cases of schizophrenia, autism spectrum disorders (ASDs), or intellectual disabilities include those at 1q21.1, 3q29, 7q11.23, 15q11–13, 15q13.3, 16p11.2, 17q12, and 22q11.2 (1). A substantial portion of each of these CNV carriers develops neuropsychiatric disorders. For example, one third and one quarter of 22q11.2 hemizygosity carriers are diagnosed with schizophrenia and ASDs, respectively (2). Some of these CNVs might not act alone; 16p11.2 CNV, for example, increases disease risk with a second CNV (3).

Several shared characteristics of rare CNVs have emerged. Each variant is often associated with multiple disorders and ignores the clinical boundaries of neuropsychiatric disorders, but phenotypic features often are more restricted at the individual level. Why this happens defies an easy answer. Improved understanding of this phenomenon is likely to provide an expanded glimpse into the mechanisms of phenotypic variability and incomplete penetrance observed in many neuropsychiatric disorders and may force us to rethink our current methods for classification of psychiatric disorders from a more mechanistic viewpoint.

Despite the robust association between rare CNVs and psychiatric disorders, the exact contributory genes remain elusive, because CNVs are large, involving more than ~1 Mb in most cases. Detailed analysis of the impact of each of the genes encoded in a CNV is essential, but there are not many cases of small deletions and duplications, let alone deletion and duplication of a single gene, in case groups. Further, small CNVs are also found in control subjects (without neuropsychiatric disease), making it difficult to narrow down causative individual genes with statistical reliability (4). Attempts have been made to

identify individual causative genes by associating SNPs on the remaining copy of genes in hemizygous deletion cases with disease. However, the impact of SNPs is small to negligible; such analyses may ascertain how allelic variants in the remaining genes modify disease type and severity but will not necessarily identify genes that cause disease.

Mouse genetics provides an alternative approach for the identification of causative genes and possibly causative mechanisms. In many cases, genes encoded in a given human CNV are conserved and clustered in the murine genome; thus, modeling CNVs in mice is a feasible experimental approach. We are beginning to see genetic mouse models of CNVs. Among them, genetic mouse models of 22q11.2 CNVs have been most intensively studied, partly thanks to identification of their association with schizophrenia in the 1990s. Several mouse lines of 22q11.2 CNVs were developed, which led to reports of many behavioral phenotypes relevant to neuropsychiatric disorders (5). Mouse models for newly identified CNVs have been developed for 7q11.23 (6), 15q11–13 (7), and 16p11.2 (8).

A study reported in this issue by Fejgin *et al.* (9) adds 15q13.3 hemizygosity to this growing list of mouse models of rare CNVs. Hemizygous deletions at 15q13.3 are found in less than 1% of individuals with intellectual disability, ASDs, and schizophrenia, but its odds ratio is larger than 10 for each disease (1); remarkably, it confers the highest known risk factor for epilepsy with an odds ratio of ~68.

As the mouse ortholog of 15q13.3 was deleted and maintained on a single genetic background of the C57BL/6 mouse line in this report, the phenotypic difference between wild-type and hemizygous mice can be attributed to the deletion with confidence. This mouse model recapitulates pleiotropic action of the CNV. Mouse behavioral and physiological phenotypes included heightened levels of seizures and aggression, defects in retention of spatial reference memory, a reduction in auditory-evoked potentials, and increased susceptibility to chemically evoked seizures, thus validating this mouse model and providing an invaluable reagent to probe mechanisms.

Interestingly, some expected phenotypes are not seen in this mouse model. For instance, it has apparently normal anxiety-related behavior, prepulse inhibition, behavioral susceptibility to psychomotor stimulants, working memory, and hippocampus- and amygdala-dependent fear conditioning. It is not clear why these phenotypes relevant to schizophrenia are not present, but previous studies with mouse models of 22q11.2 CNVs suggest that alleles on the genetic background and environmental factors are also powerful modifiers of phenotypic expression (5). The absence of phenotypes should not be taken to imply that the model is invalid until phenotypic expression is examined on different genetic backgrounds and under different environments.

Recapitulating a CNV in a genetic mouse model is the first step and identification of causative individual genes responsible for phenotypes and causative mechanisms is the next step. Many groups are actively investigating the contribution of individual genes encoded in each CNV to the overall phenotypic picture. In the case of 22q11.2 hemizygosity and duplication, which includes more than 30 genes, the generation of mice with segmental

deletions and overexpression within the commonly affected chromosomal region resulted in successful identification of some contributory genes (5).

Typical 15q13.3 hemizygous deletion involves 1.5 Mb, which is modeled in this mouse, but symptomatic atypical deletions, involving only two of the six genes, are found in humans (10). However, the contribution of the four other encoded genes should not be ruled out until proven otherwise. As 15q13.3 deletion includes only six known genes, generation of all single gene deletions for this CNV is realistic and feasible. Detailed, painstaking mouse studies are needed to critically test whether a contiguous set of genes in a CNV causes a phenotype or if contributory genes are not continuously distributed and only some, but not all genes, are causative for a given phenotype (5). If mutant mice of an individual gene exhibit no behavioral phenotypes relevant to neuropsychiatric disorders on multiple genetic backgrounds and under different environments, any interesting biological process mediated by that gene might be an epiphenomenon in terms of disease etiology.

Rare CNVs provide us with cracks on the seemingly formidable barrier toward a mechanistic understanding of neuropsychiatric disorders. Certainly, genetic mouse models provide a dream opportunity to test the general rules that govern genotype-phenotype relation in psychiatric disorders (5). We need to be guarded with interpretative caution against the ensuing flood of information, however.

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