Review

Biological Psychiatry

Common Polymorphisms in the Age of Research Domain Criteria (RDoC): Integration and Translation

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ABSTRACT

The value of common polymorphisms in guiding clinical psychiatry is limited by the complex polygenic architecture of psychiatric disorders. Common polymorphisms have too small an effect on risk for psychiatric disorders as defined by clinical phenomenology to guide clinical practice. To identify polymorphic effects that are large and reliable enough to serve as biomarkers requires detailed analysis of a polymorphism's biology across levels of complexity from molecule to cell to circuit and behavior. Emphasis on behavioral domains rather than clinical diagnosis, as proposed in the Research Domain Criteria framework, facilitates the use of mouse models that recapitulate human polymorphisms because effects on equivalent phenotypes can be translated across species and integrated across levels of analysis. A knockin mouse model of a common polymorphism in the brain-derived neurotrophic factor gene (*BDNF*) provides examples of how such a vertically integrated translational approach can identify robust genotype-phenotype relationships that have relevance to psychiatric practice.

Keywords: Anxiety, BDNF Val66Met, Behavioral dimension, Common polymorphism, Fear learning, Genetic biomarker

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One of the major rationales for the Research Domain Criteria (RDoC) framework is that "diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics" (1). This point is emphasized by how complex the genetic architectures of the major clinical psychiatric disorders have proven to be (2–4). Initially, genome-wide association studies (GWAS) of neuropsychiatric disorders were driven by a model in which common human disorders were the result of a moderate number of common genetic risk factors with genotype relative risk effect sizes in the range of 1.5 to 4.0 (5–7). This common disease/common variant model was attractive because it suggested that with the newly available large-scale genomic technologies, genetic risk factors could be readily identified and then used as biomarkers that would have adequate predictive power to guide clinical practice and would be applicable to a substantial portion of the population (8).

As genome-wide approaches have been applied to very large samples, it has become clear that the genetic risk in human populations for clinical disorders such as autism, schizophrenia, depression, the anxiety disorders, and others is comprised of a complex mix of many distinct and often de novo rare mutations of moderate effect size and thousands of common polymorphisms of very small effect size (3,9–11). The complex polygenic architecture of psychiatric disorders demonstrates that categorical psychiatric diagnoses, defined by clinical phenomenology, capture an extremely wide array of biological complexity, which prevents the practical application of genetic biomarkers to clinical psychiatry.

It may be that the diffuse genetic architecture of psychiatric disorders is due to the inevitable complexity of behavior. However, as posited in the RDoC framework, it may be due instead to the poor mapping of the clinical phenomenology of psychiatric disorders onto the biological pathways that subserve behavior (12). If this is the case, it may be possible to identify effects of common polymorphisms on core aspects of neurobiology and behavior that are of adequate effect size and reliability to guide clinical practice. The challenge then becomes how to identify robust genotype-phenotype relationships and apply them to clinical practice short of diagnosis per se.

The goal of the RDoC framework is to relate the neurobiology underlying different levels of analysis to one another ultimately with implications for behavior and its disorders. That being the case, polymorphisms should be treated as the biological entities they are and studied in detail for their effects on biological function at different levels of analysis. To accomplish this, polymorphisms must be taken out of their human genomic context and introduced into experimental systems that minimize the inevitable off-target genetic and behavioral complexity of human subjects, allow controlled and invasive manipulations across levels of analysis, and facilitate systematic studies on interactions of these polymorphic effects with important biological phenomena such as sex, development, and environmental exposures. In this review, we discuss a vertically integrated translational approach to identifying the effects of common genetic variation on behavior.

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In this approach, human variants are introduced into the genomes of inbred mouse strains, allowing for controlled experiments to understand the phenotypic effects of that variation at different levels of complexity and relate them to one another. That information is then used to develop constrained a priori hypotheses for association testing in humans (Figure 1A). The vertically integrated translational approach is reminiscent of and integrates well with the RDoC framework in that it emphasizes relationships between the biology of different levels of analysis applied to behavioral domains that are relevant to human disorders but can be studied in parallel in humans and nonhuman species (Figure 1B).

Genetic knockout mouse models have been extremely powerful in elucidating the contributions of individual genes to neurobiological function and behavior (13), but their translational value for developing clinical biomarkers is limited because they do not recapitulate the detailed biology of naturally occurring human variants. Genetic knockin technologies allow the targeted introduction of single nucleotide changes into the mouse genome, providing an exact molecular recapitulation of a human variant on an otherwise homogeneous genetic background, which provides construct validity in translation of mouse findings to humans (14). An additional benefit of a mouse model system is that controlled breeding can produce as many animals of each genotype as needed, regardless of the prevalence of the variant in human populations, facilitating analysis of allele-dose effects and factors such as sex and development that may modify the polymorphism's effects. Finally, environmental exposures can be controlled in mouse models, minimizing the confounding effects of diverse experiences in human populations and facilitating controlled studies of how specific exposures interact with the polymorphism.

We have implemented this approach, targeting a common single nucleotide polymorphism (SNP) in the human gene coding for brain-derived neurotrophic factor (*BDNF*), a neurotrophin involved in neuronal growth and survival as well as experience-dependent learning (15–17). The BDNF Valine66-Methionine (Val66Met) SNP (Single Nucleotide Polymorphism Database ID: rs6265) codes for the replacement of an evolutionarily conserved valine with a methionine at position 66 in the BDNF protein. The BDNF Val66Met polymorphism is common in most human populations with the minor allele frequency ranging from .48 in Asian populations to .01 in African populations with European populations in between at .2 (18). In vitro analysis of BDNF Val66Met has demonstrated that the variant BDNF Met protein is less efficiently targeted to the regulated secretory pathway than the BDNF Val protein, which leads to its decreased activity-dependent secretion (19–21). The BDNF SNP has been associated in humans with hippocampal volume, cognitive performance, and psychiatric disorders, including schizophrenia, bipolar disorder, major depression, and anxiety disorders; however, none of these associations has been consistently replicated, limiting their value in refining understanding of BDNF SNP effects and clinical use (22).

BDNF VAL66MET KNOCKIN MOUSE

The prodomain of the BDNF peptide in which the Val66Met polymorphism occurs is highly conserved from mouse to human which implies strong structure-function constraints in this region of the BDNF peptide, and because wild-type inbred mouse strains naturally express the ancestral allele ($BDNF^{Val}$), the same variant nucleotide knocked into the mouse genome causes the same valine to methionine substitution ($BDNF^{Met}$). The $BDNF^{Met}$ allele displayed a dose-dependent effect on regulated BDNF secretion in cultured hippocampal neurons from the variant BDNF mice (i.e., $BDNF^{Val/Val} > BDNF^{Val/Met} > BDNF^{Met/Met}$) despite equal levels of total BDNF protein in the brains of $BDNF^{Val/Val}$ and $BDNF^{Met/Met}$ mice (20). This phenotype recapitulates the cellular phenotype of BDNF Val66Met identified in vitro (19,21) and distinguishes the polymorphic mouse model from BDNF knockout mice, which express their phenotypic effects through reduced BDNF expression. The $BDNF^{Met}$ allele also caused decreased dendritic complexity in hippocampal neurons and decreased total hippocampal volume, the latter providing an external source of validation for

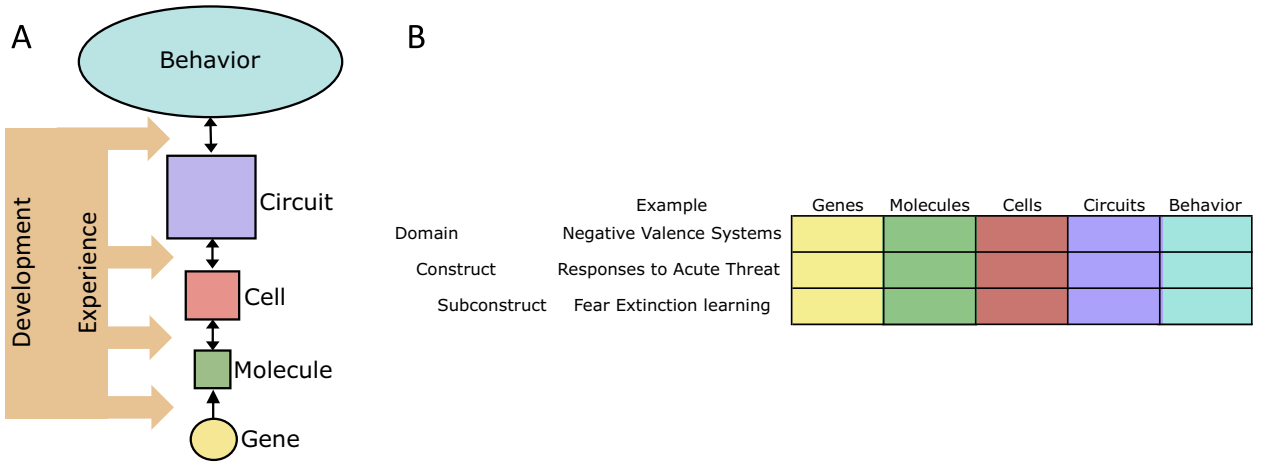

Figure 1. Levels of analysis in behavioral domains. The vertically integrated translational approach **(A)** emphasizes biological effects of polymorphisms across levels of analysis and the modifying effects of development and experience using knockin mouse model systems. Translating to humans is facilitated by the similar organization of the Research Domain Criteria framework **(B)** across levels of analysis.

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