BEHAVIORAL DISORDERS

Genetic Polymorphisms: A Cornerstone of Translational Biobehavioral Research

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A new generation of interdisciplinary research seeks to use common functional genetic polymorphisms to model emergent variability in brain chemistry that regulates behaviorally relevant brain structure and function. This genetically mediated variability is then being mapped onto trajectories of risk for psychopathology, especially that precipitated by environmental adversity. This Perspective highlights a recent paper in *Science* that provides a powerful example of how a common functional genetic polymorphism can serve as a translational bridge between human and mouse research, extending our understanding of biological pathways that mediate individual differences in behavior and in risk for psychopathology.

Our developing understanding of the nature and extent of human genetic variation has spurred translational research that is systematically mapping links between common functional genetic polymorphisms, variability in brain chemistry, and individual differences in brain structure and function that shape how we respond to challenges in our environment (*1*). In turn, the relevance of such neurogenetic pathways of behavioral variability are being examined in the context of risk for psychopathology (*2*), especially in response to environmental adversity (*3*). The neural circuits that support adaptive physiological and homeostatic functions, as well as complex behaviors, are critically dependent on synaptic plasticity, a process through which neuronal connections are sculpted in response to activity-dependent stimulation. Such activity- or stimulus-dependent plasticity is orchestrated, in part, by a constellation of growth or trophic factors. Among these, brain-derived neurotrophic factor (BDNF) not only regulates cell survival, proliferation, and synaptic growth in the developing central nervous system but also is a critical element in modulating activity-dependent synaptic changes, such as hippocampal long-term potentiation. Thus, variability in BDNF function may contribute to alterations in hippocampal function and subsequently to hippocampal-dependent learning and memory. In this Perspective, I first provide a highly select overview of research into the biological and behavioral effects of a common genetic polymorphism that results in altered BDNF signaling. I then highlight a recent study by Soliman *et al.* reported in *Science* Express (*4*), which illustrates how we can build translational bridges across human and mouse research through genetic variation, extending our understanding of biological pathways that mediate individual differences in behavior and in risk for psychopathology (Fig. 1).

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THE HUMAN *BDNF* GENE

In 2003, Daniel Weinberger and colleagues, who earlier had pioneered the application of noninvasive human imaging to mapping the neurobiological signatures of common genetic polymorphisms (*5*, *6*), reported that a common nonsynonymous single-nucleotide polymorphism (SNP) in the human *BDNF* gene resulted in variable BDNF protein function and memory-related hippocampal activation (*7*). The SNP, a guanine-to-adenine change at nucleotide 196, produces a valine (Val)–to–methionine (Met) amino acid substitution at codon 66 (Val66Met) in the BDNF prodomain. The group found that in comparison with the more common Val allele, the Met allele resulted in abnormal intracellular trafficking of pro-BDNF, which is enzymatically cleaved to form the active BDNF protein, and in the secretion of BDNF protein when cultured hippocampal neurons were chemically activated. Consistent with the role of BDNF in the hippocampal plasticity that underlies learning, people who carried the Met allele had disrupted hippocampal function [as measured with functional MRI (fMRI)] and poorer episodic memory relative to people homozygous for the Val allele. Subsequent studies from this group demonstrated that human Met allele carriers also exhibited specific deficits in episodic memory–related hippocampal function (*8*) and smaller hippocampal volumes (*9*) relative to Val allele homozygotes. Thus, these early studies implicated the BDNF Val66Met polymorphism in the mediation of individual differences in memory-related hippocampal processes and, potentially, psychopathologies related to hippocampal function.

THE BDNF MET MOUSE

In 2006, Francis Lee and colleagues sought to apply transgenic approaches in mice to begin addressing gaps in our knowledge of how the documented in vitro effects of the BDNF Val66Met polymorphism on intracellular trafficking and activity-dependent secretion lead to the in vivo effects on hippocampal structure and function and episodic memory. Targeted disruption of endogenous gene expression or function in mice has yielded countless advances in our understanding of basic genetic, molecular, and cellular processes that may contribute to the regulation of human behavior as well as the emergence and pathophysiology of human disease (*10*). In contrast to most transgenic mouse studies, however, Lee and colleagues designed a BDNF Met allele "knock-in" in which transcription of the *BDNF*-Met nucleotide at codon 66 is regulated by endogenous mouse *bdnf* gene promoters (*11*). Thus, Lee and colleagues created a mouse model that reproduced the human BDNF Val66Met polymorphism rather than broadly disrupting the functioning of the mouse *bdnf* gene. Remarkably, the variant BDNF Met mice expressed many of the phenotypic effects of the Met allele in humans, including diminished activity-dependent BDNF secretion, reduced hippocampal volume, and impaired hippocampal-dependent learning and memory. In additional analyses not possible in humans, Lee and colleagues found that, relative to control animals, the BDNF Met mice displayed significantly reduced dendritic arborization and complexity of hippocam-

pal neurons, molecular effects that may drive the reduced hippocampal volume seen in BDNF Met mice and reported in humans with the Met allele. Moreover, BDNF Met mice exhibited increased anxiety-related behaviors in response to stressful provocation, and this bias was not normalized by treatment with the antidepressant fluoxetine. This latter observation is clinically important, because fluoxetine is a selective serotonin reuptake inhibitor (SSRI), and one putative mechanism underlying the mood-stabilizing effects of SSRIs is serotonin-mediated BDNF expression and resulting neurogenesis, especially in the hippocampus (*12*). Thus, the BDNF Met transgenic mouse model has not only confirmed the effects of the human BDNF Met allele on hippocampal-dependent processes, but also provided novel evidence of a cellular mechanism (that is, decreased dendritic arborization and complexity) that may link the molecular effects of the variant to the human macrostructural neural effects documented with MRI and the related deficits in learning and memory. Furthermore, the ineffectiveness of fluoxetine in reversing the anxiety profile of BDNF Met mice is consistent with abnormal activity-dependent BDNF signaling associated with the Met allele.

Fig. 1. Meeting of the minds. The recent study of Soliman *et al.* illustrates the opportunity to build translational bridges across human and mouse research through genetic variation, extending our understanding of biological pathways that mediate individual differences in behavior and in risk for psychopathology.

A NEW BRIDGE

A recent paper in *Science* Express (*4*) reports the results of coordinated human and mouse research on the BDNF Met allele from the laboratories of B. J. Casey and Francis Lee, respectively. These studies have converged to illuminate another behaviorally relevant neurobiological pathway that could translate to advancements in our understanding of the pathophysiology and treatment of mood and anxiety disorders. Building on the earlier observation of increased anxiety-related behaviors in BDNF Met mice, the team of investigators examined parallel effects of the BDNF Met allele on the extinction of conditioned fear responses and the underlying neurobiological circuits supporting this behavior. This extinction involves a process through which animals learn that a previously conditioned stimulus no longer predicts an aversive outcome (for example, an electric shock), a pathway that may be disrupted in human mood and anxiety disorders.

Although general arousal and the acquisition of conditioned fear responses were unaffected by the BDNF Met allele in both humans and mice, extinction of the conditioned fear response was significantly impaired relative to the BDNF Val allele in humans and wild-type *bdnf* gene in mice. Using methodologies suited to each population (MRI in humans and tissue-specific gene expression in mice), the team explored underlying neurobiological mechanisms of this behavioral deficit. During extinction learning in humans, fMRI revealed that, as compared to people with the Val allele, the BDNF Met allele was associated with decreased activity in the ventromedial prefrontal cortex (vmPFC), which is critical in facilitating fear extinction, and increased activity in the amygdala, which is critical for the acquisition and expression of fear conditioning. Structural MRI data from the humans further revealed that this dysfunctional pattern of vmPFC and amygdala activities mapped onto microstructural alterations in the frontotemporal white matter fibers that connect these brain regions. Because BDNF contributes to the development of the central nervous system and previous work has associated the Met allele with reduced gray matter volume in the hippocampus and prefrontal cortex, the authors also examined regional gray matter volume in their sample population. In contrast to the effects on frontotemporal white matter, the BDNF Met allele was not associated with differences in amygdala gray matter volumes as compared to the Val allele, although there was a nonsignificant trend toward decreased hippocampal volumes. Gray matter volumes in prefrontal regions were not examined. The authors interpret these patterns of BDNF Met allele effects on brain function and structure to suggest that the deficit in fear extinction probably reflects the impact of BDNF signaling on the activity-dependent plasticity that supports learning within the frontoamygdalar circuitry. Consistent with this interpretation, examination of c-*fos*, an immediate early gene that indexes activity-dependent neuronal activity, in regions of the mouse brain analogous to the human vmPFC, revealed blunted patterns of c-*fos* gene expression in BDNF Met mice relative to controls. Moreover, deficits in extinction learning have been previously linked to reduced dendritic complexity of neurons in the vmPFC analog of BDNF Met mice (*13*).

The parallel behavioral and neurobiological effects reported by Soliman *et al.* across humans and mice reveal a striking pattern of impaired frontoamygdalar circuit function and related fear extinction associated with abnormal BDNF signaling. This remarkable translational research is possible because the variability in BDNF function is driven by a common polymorphism in the human *BDNF* gene that has been faithfully reproduced

Table 1. Select effects of the BDNF Val66Met polymorphism across levels of analysis common or unique to humans and mice. At each level of analysis, the BDNF Met allele is associated with relative dysfunction in comparison with the BDNF Val allele in humans or the wild-type gene in mice. Italics highlight important gaps in our knowledge that can be addressed using techniques available in humans (epidemiological gene-by-environment interaction studies of psychopathology) or mice (single-unit multielectrode recording in behaving animals) or common to both species (behavioral stress reactivity). NA, not available. *Results from in vitro studies of cultured rat hippocampal neurons transfected with BDNF Val or Met alleles. †Also observed in transfected rat hippocampal neurons.

Level of analysis		
	Homo sapiens	*Mus musculus*
Gene	*BDNF*	*bdnf*
DNA sequence	G → A SNP at nucleotide 196	*G* → A knock-in at nucleotide 196
Amino acid	Val → Met at codon 66	Met at codon 66
Molecular		• Regulated secretion † • *c-fos* expression • Intracellular trafficking*
Cellular	NA	• Dendritic arborization • Dendritic complexity
Physiological	NA	*Long-term potentiation?*
Circuit	• Hippocampal volume • Hippocampal activation • vmPFC activation • Amygdala activation • Frontoamygdalar connectivity	• Hippocampal volume
Behavioral	• Episodic memory • Fear extinction • *Stress reactivity?*	• Contextual memory • Fear extinction • *Stress reactivity?*
Clinical	*Gene-by-environment interaction—mediated risk?*	

in the mouse gene. It is through the common language of DNA that effective translational bridges can be constructed between research in humans and nonhuman animal models that seek to identify detailed biological pathways that mediate variability in behaviorally relevant brain function and in the related risk for psychopathology. As illustrated in Table 1, our appreciation of the molecular, cellular, and systems pathways that mediate the behavioral effects of variability in BDNF function is critically dependent on cross-species translational research, and such research is propelled by modeling variability at the level of individual genes.

LOOKING FORWARD

Like all avenues of experimentation in this nascent and rapidly evolving field of transdisciplinary research, there are many more questions than answers about the BDNF Val66Met polymorphism. For example, the phenotypic effects of any single or even multiple genetic polymorphisms are dependent on the broader genetic background of the individual (*14*), yet the potential moderating effects of human geographical ancestry or of mouse inbred strain have not been sufficiently examined with the BDNF Val66Met polymorphism. Thus, the reported phenotypic effects in either humans or mice may not be consistently manifest across populations. The phenotypic effects of the BDNF Met allele also may be influenced by genetic polymorphisms that affect complementary signaling pathways. For example, a recent study reported a significant interaction between the human BDNF Met allele and a common functional polymorphism that affects serotonin signaling in predicting structural differences in frontoamygdalar circuitry (*15*). It will be important to develop transgenic mouse models that allow for more detailed examination of the cellular and molecular impact of such gene-gene interactions. The moderating effects of genetic background and gene-gene interactions are important for understanding not only the basic biology of the BDNF Val66Met polymorphism but also its potential utility in predicting risk for and treatment of psychopathology, another area that requires much additional research. Although current and prior research suggests an important role for the BDNF Met allele in the development of psychopathology, especially mood and anxiety disorders, the findings in human studies are, at best, inconclusive (*16*). As with other common functional polymorphisms implicated in risk for psychopathology, it will be paramount to further bridge human and mouse neuroscience research with epidemiological studies that can model and test gene-by-environment interaction effects, which have emerged as a critical element in mediating risk for psychopathology (*3*). In fact, the demonstrated bias in fear extinction rooted in altered frontoamygdalar circuitry associated with the BDNF Met allele clearly suggests the importance of examining the impact of this variant in how individuals respond to environmental stress exposure. Finally, the increasing application of genome-wide association methods to human neuroscience studies holds great promise for revealing many currently unknown genetic substrates of variability in behaviorally relevant neurobiological pathways. The promise of such research to usefully inform our understanding of psychopathology, however, is likely to be fully realized through translational approaches that target biological pathways and intermediate behaviors, such as those highlighted in the current work of Soliman *et al*. (*17*).

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