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Gene × Environment Interactions in Complex Behavior: First, Build a Telescope

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Several common alleles that should, because of their functionality, alter stress response have been discovered to do exactly that. They lead to long-lasting differences in depression, anxiety, suicidality, and impulsivity. The short list of genes harboring such alleles includes FKBP5, which has been specifically related to posttraumatic stress disorder (PTSD) (1), the serotonin transporter, brain-derived neurotrophic factor, catechol-*O*-methyltransferase (COMT), monoamine oxidase A, and neuropeptide Y (NPY). In several instances, the allele effect was entirely within stress-exposed individuals; furthermore, an endocrine (testosterone) context dependency was found for monoamine oxidase A (2). For the five of these six genes for which effects of stress-related functional loci have been measured on so-called intermediate phenotypes, in each instance the effect was far more profound (3–7), encouraging the development of a new discipline, “imaging genetics.” Within one study, effects of a functional NPY promoter variant were progressively diluted from the molecular level (brain NPY messenger RNA and plasma peptide concentrations), to brain imaging responses to pain and emotional probes and finally to the more complex level of anxiety (7).

Multi-level analysis with molecular and brain imaging phenotypes is both validating and explanatory; however, there is a different endgame in which we would like to use such genetic markers as clinical predictors. Here there are problems, and to address those problems studies such as the two reports that appear in this issue are required. Gene × environment prediction of complex behavior is expected to be difficult to replicate from one study to the next or one context to the next, for the reason that much can vary or go wrong. However, effects of stress-related functional variants on complex traits such as anxiety, depression, or PTSD are more elusive to replicate. For one thing, it is difficult to quantitate environmental exposures, and the meta-analysis of gene × stress interaction studies conducted in different contexts might easily conflate different levels, types, and timings of exposures. However, failure to replicate is troubling because, as I once heard Neil Risch observe, failure to replicate an observation does not validate the observation, even if it was known that power to replicate some linkage to a complex trait was limited in the first place (8). It is therefore not surprising that people who trust in statistical replication should suffer from serious misgivings, consternation, or disbelief when, as recently happened, a meta-analysis failed to detect a significant $G \times$ stress association for the serotonin transporter locus. Are these people looking for gene × environment interactions on complex phenotypes disappointed because they have been too often “looking in all the wrong places?”

Schwandt *et al.* (9) offer another type of validation and exploration of the effect of the serotonin transporter polymorphism on complex behavior, with an animal model in which they have

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tighter control of variance. Rhesus macaques have an orthologous serotonin transporter polymorphism whose effects on behavior are like that of the human, stress dependent (Barr *et al.* [10]). Here they have studied a gender-specific gene $\times$ environment effect, and the context—social intrusion—is interesting precisely because rhesus macaque males and females respond differently to social intrusion and because there is some evidence for gender-modified differences in the effects of this polymorphism on depression, to which females are more liable.

By contrast, Kolassa *et al.* (11) have shown that the COMT Val158Met locus exerts a strong effect on risk of PTSD, but the effect is dependent on trauma load, in a severe stress context. Having “built the telescope,” they pointed it in the right direction—toward a place and a population that has experienced the extremes of suffering that one human can inflict upon another. They studied some 424 survivors of the Rwandan genocide residing in the Nakivale refugee camp in Southwestern Uganda. At highest traumatic loads, lifetime PTSD approached 100% in these refugee survivors. In this context, Met/Met genotype individuals (the so-called “Worriers” as contrasted with Val/Val “Warriors” [12]), who have been found to have lower pain thresholds and higher anxiety levels, had a high risk of PTSD independent of traumatic load. However, Val/Val and Val/Met genotype individuals were apparently more resilient but nevertheless also suffered from PTSD at higher exposure levels. These “warriors” are resilient but not immune. A single locus such as COMT represents one modulating factor among many and one that can be overwhelmed by highest levels of trauma.

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