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Commentary: “Genomics of PTSD – Sequencing Stress and Modeling Misfortune”

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Posttraumatic stress disorder (PTSD) is a commonly occurring mental health consequence of exposure to extreme, life threatening stress. Importantly, although exposure to traumatic stress is, by definition, requisite for the development of PTSD, individual susceptibility to PTSD (conditioned on trauma exposure) varies widely. Twin studies over the past two decades provide persuasive evidence for genetic influences on PTSD risk (1), and the past decade has witnessed the start of a concerted effort to detect specific genetic susceptibility variants for PTSD. Yet, with the possible exception of one gene, *FKBP5*, identified early on as a mechanistic candidate (2) and fairly persistently replicated since, the PTSD genetics landscape is littered with the remains of non-replicated association studies (for a recent review see (3)). Why has it been so difficult to detect and replicate risk genes for PTSD? How and when will credible genetic risk (and resilience) factors for PTSD be discerned? Some of the issues involved are shared with other psychiatric disorders, and some are unique to PTSD.

First, many psychiatric disorders (e.g., schizophrenia) have required very large sample sizes (i.e., tens to hundreds of thousands) to reach a point of adequate power to identify reasonably large sets of replicable risk loci. There is no reason to expect that PTSD will require smaller numbers; indeed, there are reasons (see below) to expect that even larger sample sizes will be required. To date, most published PTSD GWAS have been small, but the coming together of investigators to share data in efforts such as the Psychiatric Genomics Consortium PTSD (PGC-PTSD) group promises to change this status quo.(4) Not only do such collaborations enable the field to harness the collective sample sizes of the various investigative teams, but they also provide valuable opportunities for researchers to come together to discuss analytical and other methodological issues that can facilitate standardization, ultimately leading to a set of best practices.

Second, the PTSD phenotype is – like most if not all of the other mental disorder diagnostic entities – not a single disease at all, but rather a heterogeneous collection of symptoms that occur after exposure to a traumatic event. Experts have succinctly pointed out that there are

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DISCLOSURES

Drs. Stein reports having received consulting fees from Actelion, Dart Neuroscience, Janssen, Neurocrine, and Pfizer Pharmaceuticals in the past 2 years. He also has an equity interest in Resilience Therapeutics and stock options with Oxeia Pharmaceuticals and Resilience Therapeutics.

79,794 different symptom combinations that can yield a DSM-IV PTSD diagnosis.(5) This has ballooned to 636,120 for DSM-5 PTSD, which was one of the diagnoses whose criteria were most aggressively (or egregiously, depending on your perspective) changed in this latest edition. The point being that much work is to be done to map the topography of what is and isn't PTSD. And if PTSD is the uber-state, what are its provinces and towns – the domains and subtypes of PTSD that will almost certainly have differing genetic risk profiles? Can GWAS (or exome sequencing or whole genome sequencing, which capture not only common but also rare variation) find what is *shared* among these different symptom constellations? Maybe. Does treating the phenotype as uniform maximize the ability of these technologies to find this mutual genetic ground? Or would a more powerful approach be to provide as input the different constitutive domains (e.g., re-experiencing symptoms, hyperarousal symptoms, etc.) and put them into a multivariate GWAS, recognizing that this tactic, too, will require some statistical legerdemain to identify what those domains should be given the multitude of decisions about grouping that would need to be made?(6) How would we know which was better? Would it be finding *more* associated variants using one approach or the other? Would it be finding *stronger effects* for specific symptoms (e.g., in univariate GWAS that looked at each domain separately) than for the disorder? The good news is that there are an ever-growing number of polygenic epidemiological approaches that will enable us to parse GWAS data into phenotypically sensible lanes amenable to subtype hypothesis testing.(7) The bad news is that the more subtypes that truly exist, the larger will be the sample sizes needed to detect them. And, needless to say, these approaches will require the collation of rich phenotypes that go beyond perfunctory trauma-exposed “case” or “control” characterizations that have been the stuff of most PTSD studies to date.

Then we come to issues that are, if not unique to PTSD, certainly accentuated in its case. The nature of the environment-gene interplay creates particular challenges in modeling PTSD. Simply put, you can't develop PTSD if you are never exposed to “sufficient” trauma. ICD-11 (“exposure to extremely threatening or horrific event or series of events”) and DSM-5 (“exposure to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence”) do their best to provide guidance around what types and extent of trauma are needed to develop PTSD. But what is sufficiently threatening undoubtedly varies among individuals, and it is that threshold that we believe defines (at least in part) genetic risk for PTSD. To make matters more complicated, exposure to traumatic events is neither uniform across the population or random, nor is every sufficiently traumatic event associated with the same conditional risk for PTSD.(8) How, then, to model risk given such a state of affairs? The field has so far done very little to tackle these modeling problems. To date, most case-control GWAS having taken the eminently reasonable first step of requiring “trauma exposure” for all subjects. But this has largely been done without regard to the type, timing, or number of exposures. This could result in cases being at higher risk for PTSD because they have had more exposure than controls to events that can yield PTSD, not because they are at increased genetic risk given exposure. Such a scenario would bias the association toward the null hypothesis and thus diminish the likelihood of finding genes for PTSD. A worthwhile next step might be for case-control studies in PTSD to stratify by severity or type (or both) of trauma exposure, and then meta-analyze across trauma strata. Given sufficient power, these types of approaches will help us

determine the best metrics for classifying and quantifying trauma exposure. Taking these next steps will require very large sample sizes that are now feasible through the coming together of multiple research groups in collaborative entities such as the PGC-PTSD.

The field has also been somewhat pre-occupied with hunting for gene-environment (GxE) interactions. But GxE interactions – which may be rare -- are not at all needed to explain the interplay of genes and trauma in PTSD. By definition, PTSD involves both G and E, but not necessarily GxE. Accordingly, a solid reckoning of additive effects of trauma and genes is most definitely required. As our sample sizes grow and as best practices coalesce around the collection of finer-grained information about E, the field will need to grapple with how to best account for these effects, paying especially close attention to how they are modeled in our association analyses (e.g., which covariates to include, if any)(9) and, as a consequence, how they are reflected in the summary statistics and polygenic risk scores we share for meta- and cross-trait analyses, respectively. In our excitement to share data and cross replicate, these non-trivial nuances of analytical modeling should not be ignored.

Last but not least, the field is resigned to (and excited by) the fact that genetic variant data will not tell the whole story, and that epigenetic mechanisms undoubtedly contribute to individual differences in risk for PTSD and in its various phenotypic manifestations. The excitement stems from the realization that no other psychiatric disorder is as ripe for studying epigenetic mechanisms as is PTSD, it being a prototypical environmentally influenced mental disorder. The resignation stems from the awareness that trauma is not only an environmental exposure to be modeled in concert with genetic data, but that trauma exposure may alter expression of the very risk genes we study. Whereas these relationships can, and have been, expertly modeled and interrogated at the candidate gene level (see, once again, *FKBP5*),(10) how to do so at GWAS or genome-wide interaction (GEWIS) (or their rare variant equivalent) scale is a daunting premise.

This commentary has posed more questions than it has provided answers, with the aim of identifying speed bumps along the road to further PTSD genomic discovery. The expertise reflected in the papers published in this issue provides reassurance that the field is being driven by thoughtful, talented researchers with the right skill sets to drive us rapidly and safely to the finish line. The challenges posed by the dependency of PTSD on trauma exposure has forced the field to consider E when searching for G. As a result, PTSD will lead the way among the mental disorders in uncovering credible genomic factors that, in combination with environmental exposures, influence risk for mental health and illness.

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