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Genomic Updates in Understanding PTSD

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Abstract

Twin studies as well as more recent genetics-based heritability analyses demonstrate that up to 40 to 50% of the variance in predicting PTSD following trauma is heritable. However, most of the specific gene pathways and mechanism that mediate risk vs. resilience for PTSD following trauma exposure have yet to be elucidated. This review will examine the latest results from large scale Genome-wide association studies as well as other approaches aimed at understanding mechanisms of development of and recovery from PTSD.

Keywords

Gene-by-environment interaction; stress; anxiety; PTSD; Depression; epigenetic; trauma

Introduction: Current state of Psychiatric Genomics and Consortium Efforts

Post-traumatic stress disorder (PTSD) is unique among psychiatric disorders in that it is contingent on traumatic environmental experience(s). Thus, how these environmental experiences shape the brain circuits involved in the traumatic response - dependent on emotional memory and synaptic plasticity - play a fundamental role in the etiology of the disorder. While many individuals throughout their lifetime will experience trauma, only a subset (5-15%) will go on to develop PTSD. (Kessler et al., 1995) Furthermore, twin studies and other approaches to understanding genetic susceptibility to disease suggest that PTSD is a heritable illness. Finally, the latest large-scale consortium efforts to examine the genomics of PTSD have confirmed its heritability using genomic analyses across tens of thousands of subjects. (Duncan et al., 2018) Together these facts highlight the pressing need to understand

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the genetic differences that may predispose certain individuals to react maladaptively to traumatic experiences and develop PTSD.

Several primary criteria define PTSD, as outlined in the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-V), they include: 1) exposure to a trauma, 2) re-experiencing of that trauma, 3) avoidance of trauma-related stimuli, 4) negative thoughts or feelings that began or were worsened after the trauma, 5) trauma-related arousal and reactivity, and 6) general distress and functional impairment related to these symptoms. (American Psychiatric Association, 2013) In the DSM-V, PTSD was placed into a new category of "Trauma-and Stressor-Related Disorders," reflecting the definitional necessity of traumatic experience(s).

Genome-wide association studies (GWAS) for psychiatric disorders, including PTSD, are at an exciting inflection point as sample sizes needed to identify loci significantly associated with the disease are being aggregated. Modern GWAS analyses typically include tens of thousands to hundreds of thousands of samples and perform a simple statistic at each of the~1 million queried Single Nucleotide Polymorphisms (SNPs – the common variation in single A, C, G, T nucleotides within DNA). While requiring very large, international, consortia-based sample sizes, they provide unparalleled power to discover new, unbiased genetic factors associated with illness.

These genetic association approaches are beginning to uncover gene pathways that may be important drivers of disease. There has been significant progress with several common disorders including autism, bipolar disorder, and schizophrenia. These GWAS studies have revealed hundreds of genetic loci significantly associated with psychiatric disease, and follow-up work are now identifying novel biological pathways that underlie pathology. (Consortium, 2014; Craddock and Sklar, 2013; Green et al., 2013; Klaus et al., 2018; Kwon et al., 2013; Sekar et al., 2016; Sklar et al., 2011; Voineagu et al., 2011; Wang et al., 2009).

Simultaneously with the above discovery studies, sophisticated statistical algorithms are being developed to enhance our understanding of the mountains of genetic data being produced. Just a few examples of the work being done include improved methods to leverage summary association statistics for a variety of analyses, methods to determine shared genetic risk across disorders, tissue-specific expression of risk-variants, functional genomic elements enriched for heritable SNPs, putative allele-specific transcription factor binding events, and optimized linear models for the analysis of large datasets. (Bulik-Sullivan et al., 2015a; Finucane et al., 2018, 2015; Loh et al., 2018; Pasaniuc and Price, 2017; Reshef et al., 2017) These advances across medicine are reshaping our ability to understand and treat disease.

In the past few decades, the field of psychiatry has stagnated with regards to drug discovery, as many of the targets studied via candidate gene approaches have failed to demonstrate efficacy. Retrospective analyses of candidate genes across medicine have demonstrated that the lack of statistical rigor has resulted in a great deal of effort towards the study of genes that may not be robustly associated with disease in human populations, with several analyses

of schizophrenia confirming this as well. (Farrell et al., 2015; Johnson et al., 2017; Kowalska et al., 2017).

In PTSD, drug development centered on well-understood candidate genes have failed to demonstrate efficacy in clinical trials. An important example of this is *CRFR1* (corticotropic releasing factor receptor 1) antagonists, for which a 2017 trial of an antagonist in women with PTSD failed to demonstrate efficacy in the primary endpoint of a reduced Clinician-administered PTSD scale score. (Dunlop et al., 2017) This does not mean that this gene is not important to the disease, but rather, we do not understand the complexity of gene regulation and the specific components of human biology related to such genes to make inferences based on prior candidate genetic studies. Indeed, in a small sub-analysis of the *CRFR1* antagonist trial, it was seen that individuals GG homozygous at *rs110402*, a SNP in the third intron of *CRFR1*, responded favorably to treatment with the drug, when there was a history of childhood maltreatment, compared to a matched placebo group. The patients in this group demonstrated improvements in the secondary outcome measure of the PTSD symptom scale-self report total score. While this was a very small sub-group within the larger study, the result suggests that gene-by-environment interactions may play an important role in determining the molecular pathways most relevant to disease in PTSD.

GWAS approaches promise to identify genetic loci of disease susceptibility amenable to drug targeting, biomarker development, and disease stratification. Additionally, the large sample sizes required for these efforts have stimulated the formation of large consortia to produce the datasets required to achieve well-powered results, which have the side benefit of enhancing collaboration across the field. Collaborative organizations such as PTSD working group of the psychiatric genomics consortium (PGC-PTSD) as well as the Million Veteran Program (MVP) have led this effort.

Smaller GWAS cohorts in the study of PTSD have revealed a variety of putative associations, however, none of these have yet robustly replicated across multiple datasets. (Nievergelt et al., 2018) The PGC-PTSD has established a multi-institution, multi-pronged approach to generating the large datasets required to characterize the phenotypic heterogeneity and biological underpinnings of the disorder. In particular, specific working groups have been established: psychophysiology, physical health, imaging, GWAS, copy number variation, epigenomics, transcriptomics, microbiome, and finally a systems biology working group aimed at analyses across these datasets.

In this review, we will focus on the latest iteration of the genetic association investigation carried out by the PGC-PTSD, and highlight areas for continued investigation, in particular, integration of environmental measures into our understanding of disease risk, and ongoing “big data” efforts that will elucidate biomarkers, disease subtypes, and environmental indices that will be informative for downstream studies.

Post-traumatic Stress Disorder heritability estimates and epidemiology

The two principle facets of PTSD are 1) undergoing a traumatic experience and 2) having an underlying susceptibility to disease. One could imagine that susceptibility to be driven by

genetic predispositions, environmental influences on developmental processes (e.g., early life stress, or stress experienced in utero), or the combination of both. Disentangling these interactions at the level of specific polymorphisms via genetic association studies is in its infancy, as we will discuss later on. However, epidemiological approaches can be very informative as to the magnitude of the role genetics play in heritability and to which environmental associations we should pay attention.

Twin studies were the first approach to defining genetic heritability of PTSD, by comparing the incidence of PTSD in pairs of monozygotic and dizygotic twins. Studies found a 46% heritability in a combined sample of male and female twins, and 72% in an all-female sample of twins. (Sartor et al., 2012, 2011) Twin studies have also demonstrated that genetic variation contributes to the risk of trauma exposure. A 2002 study suggested that risk for experiencing assaultive traumas (such as sexual assault or robbery) were moderately heritable, while non-assaultive traumas (such as natural disasters and car accidents) did not have a detectable genetic component. (Stein et al., 2002) While initially controversial, with the concern of 'blaming the victim', at the level of epidemiological studies, such findings suggest that factors such as risk-seeking behavior or inattention to danger could help to explain heritability of trauma exposure. Together these data suggest there is genetic susceptibility both to experiencing particular social trauma and to developing PTSD in the aftermath of trauma exposure.

The incidence of PTSD is directly related to the type, severity, and pervasiveness of trauma in a population. People who have experienced more trauma are at higher risk for the eventual development of PTSD. For this reason, GWAS approaches have taken the approach of using trauma-matched controls–so that the associated variants will better delineate the risk alleles that characterize the 5-15% of the population susceptible to PTSD. Longitudinal epidemiological studies of military personnel have further characterized risk versus resilience.

Studies in military personnel who had directly experienced combat in the Vietnam War demonstrated a 19% lifetime risk for PTSD, 10-year post-war rates as high as 28%, and as many as 11% of veterans continued to demonstrate PTSD symptoms up to 40 years after combat. (Dohrenwend et al., 2006; Marmar et al., 2015) In studies of soldiers who have served in Iraq or Afghanistan, the incidence of PTSD is proportional to the severity of the trauma experienced. However, a ceiling is observed in that the maximal incidence appears to be about 25-30% in such studies, suggesting a threshold after which the dose-response effect of trauma-severity on population risk does not continue to increase. Another result from these longitudinal studies has been the characterization of the diversity of outcomes post-trauma, including spontaneous recovery (recovery without any treatment) and delayed PTSD (the development of more severe symptoms sometime after the initial traumatic experience). (Smid et al., 2009)

Another important observation from epidemiological studies is that the lifetime risk of PTSD in women is double that of men. (Norris, Foster, & Weisshaar, 2002) An active area of inquiry is to understand whether this enhanced risk stems from increased exposure to traumatic events (i.e., sexual abuse and rape), or whether there may be a differential sex-

dependent genetic predisposition to PTSD. The data are mixed, and it remains possible that both a higher exposure to particular traumatic events and genetic predisposition may both play a role. The majority of studies suggest that even when differences in trauma experience are accounted for, sex differences in PTSD incidence persist. The most convincing evidence coming from studies of matched trauma histories, wherein the greater female risk for PTSD cannot be accounted for by greater exposure to trauma, and this finding appears to be stable across a variety of types of trauma. (Breslau et al., 1999; Breslau and Anthony, 2007) However, conflicting evidence was reported in a 2006 study of intimate partner violence, suggesting that once differences in trauma exposure are accounted for, the increased risk for PTSD in females disappears. (Cortina and Kubiak, 2006) Indeed, the authors of this study make valid criticisms of the questionnaires that are used to quantify types of trauma and suggest that improvements could be made to gather data that better reflects the reality of the female trauma experience. More work is required to generate the large, representative datasets needed to answer these questions. (Yehuda et al., 2015)

While all of these interesting genetic facets of PTSD are detectable at an epidemiological level, the first step in unraveling which genes play important roles in disease, is to understand the gene variants with a main effect on PTSD risk, independent of environmental variables. In the past 10 years, several candidate gene associations have elucidated sex-specific and gene-by-environment (GxE) interactions with trauma. More recently consortium efforts have gained momentum to aggregate the number of samples needed for GWAS to identify strongly associated variants.

Candidate Gene Studies

As mentioned previously, recent analyses of candidate gene studies have suggested that in general, these prior studies were underpowered, have led to many false positives, and thus far rarely replicate in larger, well-powered genetic studies. (Farrell et al., 2015; Johnson et al., 2017; Kowalska et al., 2017). That said, we believe that it is informative to provide a brief discussion of prior candidate gene analyses in PTSD, for a historical account, as well as to illustrate how to identify functional aspects of genes once GWAS has validated new targets. Several candidate gene association studies have demonstrated associations with PTSD. Two of the most prominent associated genes have been *ADCYAP1R1* and *FKBP5*, which have been found to confer risk for PTSD symptomology in a sex-specific and a GxE manner, respectively. These genes, discussed briefly below, provide examples of mechanistic studies aimed at understanding the association of a risk variant SNP with PTSD as a function of environment or other biological factors (sex and estrogen status). However, variants in these genes have not yet been observed to have a main effect on PTSD risk in large scale GWAS analyses.

A polymorphism in *ADCYAP1R1* (the receptor for pituitary adenylate cyclase-activating polypeptide or *PACAP*), has been associated with PTSD in women, but not men. We previously identified a SNP in a putative estrogen response element of *ADCYAP1R1* which predicted PTSD diagnosis, and whole blood methylation of this gene's CpG island correlated with PTSD symptom severity. (Ressleret al., 2011a) Furthermore, the initial SNP association has been replicated at a GxE level by several groups. (Almli et al., 2013; Pohlack

et al., 2015; Uddin et al., 2013; Wang et al., 2013) Neuroimaging approaches demonstrated further that this *ADCYAP1R1* risk variant is associated with increased amygdala and hippocampal activation in response to threat stimuli, as well as reduced functional connectivity between these two regions in women. (Stevens et al., 2014) Mechanistic work has further demonstrated allele-specific binding of estradiol to the estrogen response-element within the gene, with reduced binding to the risk allele, increased expression of *ADCYAP1R1* in mice treated with estradiol, and showed that women with the risk allele also harbor lower *ADCYAP1R1* expression. (Mercer et al., 2016) PACAP peptide and *ADCYAP1R1* biology has been extensively covered elsewhere. (Ramikie and Ressler, 2016)

Similar to *ADCYAP1R1,* a polymorphism in the glucocorticoid receptor element of FK506 Binding Protein 51 (*FKBP5*) has been shown to associate with PTSD in the context of childhood maltreatment. (Binder et al., 2008) Further studies demonstrated that the locus harboring the risk variant was epigenetically regulated in an allele-dependent manner, both at the level of chromatin structure and DNA methylation. In particular, it was seen that changes in whole blood methylation of the variant glucocorticoid receptor element were dependent on the history of childhood maltreatment. (Klengel et al., 2013) *FKBP5* polymorphisms have also been linked with a variety of additional psychopathologies, including aggressive behavior, depression recurrence and response to antidepressant treatment, and suicide risk. (Bevilacqua et al., 2012; Binder et al., 2004; Roy et al., 2010) FKBP5 biology has also been covered extensively elsewhere. (Zannas and Binder, 2014)

The main criticisms of the above candidate gene by environment studies (cGxE), is that these approaches are not demonstrating main effects on PTSD diagnosis in large-cohort GWAS investigations and are prone to bias. It is possible, and may be likely, that the large GWAS studies in PTSD are still insufficiently powered to capture these polymorphisms, especially given that they may need to be studied in a gene x environment context. Nonetheless, there are clear limitations. In the case of *FKBP5*, for example, while it appears to be strongly associated with a variety of outcomes, it is unclear to what extent *FKBP5* represents a druggable target or possesses sufficient predictive power to be useful clinically. In terms of identifying GxE interactions, while the critical importance of certain environmental variables in the development of psychopathology has been convincingly demonstrated epidemiologically, methods to statistically integrate genetic and environmental variables need to be developed. We discuss several possibilities later on. However, the most immediate need is to elucidate the genetic architecture of PTSD using large-scale GWAS, at the sufficiently powered samples sizes to identify variants that are significantly associated with PTSD diagnosis.

Genome-wide association studies of PTSD

To date, published GWAS results have largely been underpowered to detect genomewide significant loci that have replicated within and across studies, though some have yielded genome-wide significant loci ($p < 5 \times 10^{-8}$) in the discovery cohort. See Nievergelt et al. for a review of the gene variants that have reached genome-wide significance in any study. The largest published PTSD GWAS to-date is the freeze 1 dataset of the PGC-PTSD, which comprised 11 multiethnic cohorts with 5000 cases versus 15000 mostly trauma-exposed

controls (87.7% trauma-exposed). This analysis was not sufficiently powered to identify PTSD associated SNPs at a genome-wide significant p-value (Duncan et al., 2018). The next iteration of the psychiatric genomics consortium's PTSD GWAS dataset, freeze 2, will include 32,000 cases and 100,000 trauma-exposed controls. (Nievergelt et al., 2018) This sample size is approaching the level at which genome-wide significant loci have been discovered for other psychiatric disorders, such as schizophrenia.

A number of analyses were carried out with the initial PGC-PTSD study that elucidated some interesting aspects of the underlying genetic architecture of disease, including heritability and cross-disorder genetic overlap. The authors'estimated overall molecular heritability of PTSD to be ~15%, however, they found much higher estimates for females compared to males. Female heritability was calculated to be 29% whereas heritability for males was not significantly greater than 0%. In contrast to twin studies, these heritability estimates for PTSD are much lower. Previous work has estimated heritability for PTSD in the ranges of 13-34%, 46%, and 72%. (Sartor et al., 2012, 2011; True et al., 1993) However, the underpowered sample size of the initial PGC-PTSD study resulted in a low heritability z-score of 3.0 – a score influenced by the sample size, SNP-based heritability, and the proportion of causal variants. (Hill et al., 2016) Thus, the heritability estimates are more speculative than they will be in a larger dataset. Notably, investigations of heritability estimates in other traits, specifically schizophrenia and height, have suggested that heritability can be more fully accounted for by gene variation if all SNPs are included in the analysis, but this requires larger sample sizes. (Loh et al., 2015; Yang et al., 2010)

Analysis of other well-powered datasets suggests not only that genetics can indeed account for a large fraction of heritability, but also that most complex traits are extremely polygenic. Recent advances in analytical approaches of GWAS data, suggests that the inflation of GWAS test statistics in well-powered datasets may be the result of polygenicity rather than genomic inflation. (Bulik-Sullivan et al., 2015b) The next iteration of the PGC-PTSD dataset will likely provide a clearer picture of the molecular heritability of PTSD.

To analyze cross-disorder genetic correlation, the PGC-PTSD authors were similarly limited by the size of the dataset, and so limited their comparisons to schizophrenia, major depressive disorder, and bipolar disorder. Notably, using different polygenic risk score approaches, significant overlap was observed between PTSD and all three other psychiatric disorders, consistent with the shared heterogeneity of risk across disorders. (Duncan et al., 2018)

Integrating the Genetic and Environmental Components of Disease

A multitude of epidemiological evidence clearly indicates the importance of distinct environmental influences on risk for PTSD – in particular, childhood adversity has been very strongly linked with a variety of future psychopathologies. (Bremner et al., 1993; Lang et al., 2006) Understandably, there have been extensive efforts in the field to discover the genetic underpinnings that may render one susceptible to early life adversity, however, statistical approaches have lagged behind our ambitions. Previously, a paucity of rigorous, genome-wide approaches to GxE have resulted in investigators selecting candidate genes for cGxE studies. In PTSD, cGxE investigations with relatively small sample sizes have yielded

some intriguing results. In particular, genes such as *FKBP5*, conferring sensitivity to early life stress and gender-specific susceptibility to stress have been identified (Almli et al., 2013; Binder et al., 2008; Boscarino et al., 2012; Collip et al., 2013; Dias and Ressler, 2013; Lavebratt et al., 2010; Ressler et al., 2011b; Stevens et al., 2014; Zimmermann et al., 2011). However, these cGxE investigations have come under scrutiny – in particular, more sophisticated statistical modeling and an appreciation for the effect sizes seen in large-scale GWAS for exemplary psychiatric disorders suggest that studies to date have been underpowered and insufficiently modeled to generate rigorous genetic associations. (Ashley-Koch et al., 2015; Eaves and Verhulst, 2014; Matthew C Keller, 2014; Moore and Thoemmes, 2016)

In the field of PTSD genetics, the contingency of PTSD on exposure to trauma makes it particularly salient to include environmental measures of trauma into statistical models of genetic association. However, there are many statistical challenges to this approach, many of which have not been sufficiently accounted for in analyses to date. Covered extensively elsewhere, specific difficulties include properly scaling measurement variables, controlling for the effects of covariates on interaction, and a deeper understanding of potential nonlinear relationships between predictors and the outcome of interest that may masquerade as true associations. (Border and Keller, 2017; M C Keller, 2014; Moore and Thoemmes, 2016) Furthermore, it is now being appreciated that the candidate gene variants that have historically been employed in GxE studies are not likely to be significant drivers of disease in human populations. (Farrell et al., 2015; Johnson et al., 2017)

In principle, it may be possible that certain genetic associations will not be detectable without including an environmental component in the statistical model. A simple example would be a type of cross-over interaction, wherein alleles that increase the risk for a certain disorder in a particular environment may confer protection to that same disorder in another environment. (Sharma et al., 2015) A concrete example would be if a polymorphism in a gene interacts with early life stress, such that in the context of early life stress, one allele confers protection to future psychopathology while the other confers risk; however, in the context of a “less” stressful early life experience, those relationships are reversed. Some in the field argue this type of interaction is unlikely, however, more investigation is required to rule this possibility out. (Duncan et al., 2014) Furthermore, given the small effects any particular genetic variant exerts on disease risk, as we have observed for schizophrenia and other psychiatric disorders with well powered GWAS’, it is likely that much larger sample sizes and a more sophisticated statistical approach will be required to properly answer this question.

However contentious GxE studies have been, the contribution of environmental variables to psychopathology is clear and unbiased approaches to identify molecular correlates of environmental influences are needed. Some clever approaches have been developed that mitigate the statistical hurdles of genome-wide or candidate GxE studies. One method developed just this year called EAGLE (environment-ase through generalized linear modeling) – utilizes RNA sequencing data combined with environmental measures in order to infer GxE interactions at the level of exonic, allele-specific gene expression at heterozygous loci.The authors developed a hierarchical Bayesian model, that utilized within-

sample allelic differences in RNA-seq reads to allow for each test to have an internal control. This method allows for one to infer the relationship between an environmental factor and allele-specific expression of a particular gene. (Knowles et al., 2017)

Another solution to evaluating genetic risk is to use polygenic risk scores (PRS) to model genetic variation rather than to focus on specific polymorphisms. This abrogates the risk associated with multiple testing of alleles by aggregating risk or resilience across many alleles that have independently been shown to associate with disease, thus greatly improving predictive power. An excellent example of this comes from a recent paper on early life complications and schizophrenia risk, mediated by the polygenic risk score (PRS) for schizophrenia. Here, the PRS was calculated as a function of the loci that had reached genome-wide significance for a main effect on schizophrenia risk. Schizophrenia PRS was used to approximate genetic risk for disease and its interaction with early life complications. (Ursini et al., 2018) PRS for schizophrenia interacted with early life complications (ELCs), with greater degrees of ELCs correlating strongly with increased odds ratios for future schizophrenia development. In general, ELCs were not predictive of case-control status (i.e., a diagnosis of schizophrenia); however, in the context of high-risk PRS, ELCs predicted an increased odds ratio of schizophrenia development – demonstrating a tractable genetic signature of risk to ELCs. To further parse apart the specific contribution of risk variants, the authors developed a “placental PRS (PPRS).” Here, the authors hypothesized that the genetic risk conferred by early life stress would be mediated by those risk variants that are both highly and differentially expressed with respect to delivery complications in the placenta. This PPRS score, turned out to interact with a history of ELCs to correlate with schizophrenia diagnosis in adulthood. (Ursini et al., 2018)

This is an excellent example linking a clinical phenomenon (ELCs) with future psychopathology. For many years it was appreciated how ELCs seemed to play a role in the development of schizophrenia – in particular, obstetric complications have long been associated with a risk for schizophrenia development; however, our ability to identify particular gene pathways and tissues mediating risk has been limited. (Cannon et al., 2002; Jones et al., 1998; Nicodemus et al., 2008; Zornberg et al., 2000) This study offers an example of how PRS can be used to investigate GxE interactions in a statistically tractable fashion.

Across psychiatric disorders, such an approach can greatly benefit the clinical utility of genetic information, as caregivers may be able to put more effort into mitigating environmental risk factors for those at greater risk of disease. In PTSD, the role of early life stress, or specific high impact trauma types have been strongly linked to PTSD risk. (Bremner et al., 1993; Heim and Nemeroff, 2002, 2001; Kaufman et al., 2000; Lang et al., 2006; Stovall-McClough and Cloitre, 2006) Well-powered GWAS results for PTSD and the identification of risk loci would allow the construction of PRS scores that can be used to parse genetic vulnerability to specific types of trauma, and other environmentally relevant variables.

Future Directions

The first and foremost goal in the coming years will be the construction of large datasets of genetic and environmental information in order to generate high-quality analyses of genetic risk for PTSD. These datasets will lay the foundation for future investigations into basic research as well as applied research and drug development.The freeze 2 dataset and the next iteration of the Million Veterans Programs will provide the sample sizes needed to elucidate risk variants significantly associated with PTSD.

At the level of basic biology, understanding genetic risk in an unbiased manner will allow us to parse apart the specific cells and tissues that play roles in mediating disease risk. Already, sophisticated algorithms have been developed that allow one to assign GWAS risk loci to tissues, either through imputing gene expression alterations through an understanding of which variants influence gene expression or by using the GWAS risk loci themselves. (Finucane et al., 2018, 2015; Hormozdiari et al., 2018; Pasaniuc and Price, 2017) Single cell transcriptomic and epigenetic data will greatly expand our understanding of the unique expression profiles of all cells throughout the body. This information will allow us to localize risk loci to particular cell types within the body, and hopefully associate particular types of genetic risk with specific outcomes and disease subtypes. In the same way that risk for early life birth complications and future schizophrenia risk was parsed by tissue-specific gene expression profiles, it's likely that massive single-cell transcriptomic atlases of the human brain will similarly aid us in localizing the genetic risk for PTSD and other psychiatric disorders to specific neural circuits and tissues. This type of information can be tremendously useful to home in on particular tissues and cell types in terms of GxE associations. And finally, genome-editing technologies may then enable us to functionally query these variants with causal experiments.

Even after GWAS studies reveal genome-wide significant hits, an open question in the field remains – how to use this information to identify pathways that are actually relevant to PTSD. Recent analyses have suggested that genetic heritability is even more polygenic that just our genome-wide significant hits suggests. Analyses of schizophrenia GWAS have suggested that heritability and disease risk is quite widespread. One analysis from Loh, et al. 2015 demonstrated that >71% of 1 megabase regions in the genome harbor at least one variant that contributes to risk of disease. Another study from Boyle, et al. 2017 demonstrated that most genomic regions contributing to the heritability of schizophrenia are in fact broadly expressed and are not genes that are particularly enriched in the brain. This led the authors to propose the "Omnigenic model" of disease risk which is as follows: while disease risk is likely to be driven by aberrations in relevant biological processes which we have an understanding of (i.e. synaptic pruning in schizophrenia), gene networks are so densely interconnected, that any gene that is widely expressed will have some nonzero influence on core gene function; core genes being those directly responsible for the biological processes underlying disease (i.e. extinction of fear in PTSD). Furthermore, since widely expressed genes outnumber core genes, the majority of heritability on a genome-wide scale will be driven by variation in these peripheral gene networks (Boyle et al., 2017; Loh et al., 2015).

This insight raises several interesting possibilities: for any given disease, to what extent is heritability driven by variation in core vs non-core genes? Are there variants that influence core gene expression but don't necessarily confer risk? How do we define core genes? These insights demonstrate that much work is needed to truly understand the associations that GWAS will provide for us. Nonetheless, the international studies aimed at understanding the genomic underpinnings of PTSD, a disorder with clear heritable risk, are making rapid progress, and the biological basis of PTSD is indeed tractable.

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Highlights:

- Over 40% of the risk for PTSD may be genetically heritable.
- Large-scale genome wide association studies offer the current best approaches.
- Incorporating environment into genetic models is critical for stress-related disorders.
- It is hoped that genetic discoveries will lead to novel targets for intervention in PTSD.