The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders

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Research into the causes of psychopathology has largely focused on two broad etiologic factors: genetic vulnerability and environmental stressors. An important role for familial/heritable factors in the etiology of a broad range of psychiatric disorders was established well before the modern era of genomic research. This review focuses on the genetic basis of three disorder categories—posttraumatic stress disorder (PTSD), major depressive disorder (MDD), and the anxiety disorders—for which environmental stressors and stress responses are understood to be central to pathogenesis. Each of these disorders aggregates in families and is moderately heritable. More recently, molecular genetic approaches, including genome-wide studies of genetic variation, have been applied to identify specific risk variants. In this review, I summarize evidence for genetic contributions to PTSD, MDD, and the anxiety disorders including genetic epidemiology, the role of common genetic variation, the role of rare and structural variation, and the role of gene–environment interaction. Available data suggest that stress-related disorders are highly complex and polygenic and, despite substantial progress in other areas of psychiatric genetics, few risk loci have been identified for these disorders. Progress in this area will likely require analysis of much larger sample sizes than have been reported to date. The phenotypic complexity and genetic overlap among these disorders present further challenges. The review concludes with a discussion of prospects for clinical translation of genetic findings and future directions for research.

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Genes and stress are the two most widely acknowledged contributors to psychopathology. The ‘diathesis-stress’ hypothesis has been the leading etiologic model for psychiatric disorders for decades (although alternatives have been proposed, see Boyce, this issue). The essence of this model is that genes and adversity, independently and in combination, increase the liability to disorder, which in turn results once a threshold of sufficient liability is crossed. In this review, I will focus on the ‘diathesis’ (that is, genetic) component as it relates to disorders that are most commonly thought of as stress-related disorders: posttraumatic stress disorder (PTSD), major depressive disorder (MDD), and anxiety disorders. In reality, stress (especially early adversity and later stressful life events) has been identified as a risk factor for a broader range of psychiatric disorders, including bipolar disorder (Gilman *et al*, 2015) and schizophrenia (Matheson *et al*, 2013). However, the role of stressful

environments and the physiology of stress response systems have been most closely linked to depressive, anxiety, and traumatic stress disorders.

The role of genes in psychiatric illness was suggested well before the modern genomic era through family and twin studies. All psychiatric disorders that have been studied by these methods have been reported to be familial and heritable to varying degrees. More recently, molecular genetic studies have begun to identify specific DNA variations associated with neuropsychiatric disorders and related phenotypes. In the sections that follow, I briefly introduce and summarize the methods and study designs used in psychiatric genetics. I will then review in more detail the status of genetic studies of PTSD, MDD, and anxiety disorders, including evidence that the heritable component of these disorders overlaps and is shared to varying degrees with other disorders. Finally, I will discuss prospects for clinical translation of these findings and future directions for research.

THE TOOLKIT OF PSYCHIATRIC GENETICS

Defining the genetic contribution to psychiatric disorders (as with other complex disorders) typically involves a series of

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Figure 1. Summary of psychiatric genetic methods. (Adapted from Smoller *et al*, 2015.)

questions and study designs as depicted in Figure 1 and reviewed in Smoller *et al* (2015), from which this section is adapted. The first question is usually whether the disorder aggregates in families. To answer this, *family studies* compare the prevalence of disorder among first-degree relatives of affected individuals (probands) with that among either first-degree relatives of unaffected controls or to the population prevalence. When the ratio of these prevalences, known as the familial recurrence ratio, is significantly greater than 1.0, we conclude that the disorder is familial. Because family members share both genetic and environmental influences, family studies by themselves cannot establish a genetic contribution. *Twin studies* can be used to distinguish genetic and environmental components by comparing disorder concordance rates between genetically identical (monozygotic, MZ) and non-identical (dizygotic, DZ) twin pairs. Assuming that environmental risk factors do not differ systematically for MZ vs DZ twins, a significantly increased concordance in MZ vs DZ pairs implies a role for genetic variation. Variance component modeling methods are often used to dissect genetic, shared environmental, and individual-specific variance components. The ratio of the genetic variance component to the full phenotypic variance provides the heritability of the phenotype. Typically, additive (narrow-sense) heritability is reported (denoted h^2) (Visscher *et al*, 2008). Heritability may range from 0 (no contribution of genetic variation to phenotypic variation) to 100% (phenotypic variation entirely attributable to genetic variation).

Once a trait or disorder is shown to be heritable, molecular genetic studies can be undertaken to localize and identify the genetic influences at the level of DNA variation. *Linkage studies* aim to map the chromosomal location of disease genes. Co-inheritance of a DNA marker with the disease of interest in families is evidence that a disease-related gene is 'linked to' (physically close to) that DNA marker. However, linkage studies are best-suited to Mendelian disorders where disease is caused by one or more rare mutations of large effect. In contrast, psychiatric disorders are complex disorders thought to result from the contribution of many, often common and low-penetrance, susceptibility loci in combination with environmental risk factors. For complex disorders, *association studies* are more powerful for identifying risk loci and have become the dominant strategy for genetic studies of psychiatric disorders. Association studies typically utilize a case-control design to determine whether specific genetic variants (alleles) are more common among affected (cases) than among unaffected individuals (controls). For continuous traits, association analysis examines whether specific alleles are associated with quantitative variation in the trait of interest.

Association studies have been used to evaluate different classes of DNA variation relevant to psychopathology. The *genetic architecture* of a phenotype refers to entire complement of underlying genetic risks factors including their number, allele frequencies, and effect sizes of contributing variants. The allelic spectrum underlying complex

phenotypes includes at least three major classes of DNA variation: common single-nucleotide variants (common SNVs or 'SNPs', allele frequencies $\geq 1\%$), rarer single-nucleotide variation (rare SNVs, allele frequencies $< 1\%$), and structural variations, including copy number variants (CNVs), insertion/deletions, and balanced translocations. In addition to inherited variation, rare pathogenic variants can occur *de novo*, arising in a parental gamete, a fertilized embryo, or the developing fetus. In general, penetrance is inversely related to allele frequency because selection pressure suppresses the frequency of highly penetrant deleterious loci. Thus, rare pathogenic variants are typically more highly penetrant (ie, have a larger effect size) than common variants. More recently, a potential role for somatic mutation (in which a mutation arises in a subpopulation of developing or mature cells including neurons) has been suggested for neuropsychiatric phenotypes (Insel, 2014).

In general, two strategies for association analysis of SNVs are widely used: *candidate gene studies* and *genome-wide association studies* (GWAS). The first relies on genes that have been implicated in a phenotype based on prior evidence. Biological candidate genes are usually selected based on prior evidence from animal models (eg, knockout mice) or human studies (eg, genes that are targets of psychotropic medications). More recently, loci identified from GWAS (see below) have become popular candidates. Biological candidate gene studies have well-documented limitations. Perhaps most importantly, they are derived from existing hypotheses about the biological basis of psychiatric disorders. Because our knowledge of disorder biology is incomplete, the prior probability that any given candidate gene is truly relevant is low. Not surprisingly, then, candidate gene studies have a poor track record of replication and many candidate gene associations are likely to be spurious (Sullivan, 2007). In addition, by their very nature, association studies of biological candidates can at best validate existing hypotheses rather than discover novel risk loci.

In contrast, GWAS enable a so-called 'unbiased' search for risk loci by examining variants across the genome instead of limiting the search to hypothesized candidates. GWAS of common SNPs became possible with the development of DNA microarrays that interrogate up to 1 million or more SNPs across the genome. Alleles of many SNPs in a given genomic region are correlated and inherited together (due to linkage disequilibrium, or LD). Therefore, a given SNP may provide information about other correlated SNPs, so that only a subset of the millions of SNPs in the genome need to be genotyped directly to cover genome-wide variation. The conventional threshold for 'genome-wide significance' is a P -value less than 5×10^{-8} , a Bonferroni correction for the effective number (one million) of independent statistical tests that are conducted in a typical GWAS. More recently, advances in DNA sequencing technologies have enabled exome-wide (and even genome-wide) analysis of rare variants.

Very large sample sizes (on the order of 25 000 or more cases) are needed to adequately power genome-wide analyses

of either common or rare variants. In the case of common variants, the requirement for large samples is due to the small effect sizes expected—typically an allelic odds ratio of less than 1.20. In the case of rare variants, effect sizes may be larger, but their rarity again entails large sample sizes to allow detection of a sufficient number of risk variant carriers (Moutsianas *et al*, 2015; Zuk *et al*, 2014). *Gene–environment interaction* ($G \times E$) studies examine whether the effect of a genetic variant is modified by an environmental exposure. To date, most $G \times E$ association studies have focused on a limited set of biological candidate genes and have been underpowered to detect robust effects (Duncan *et al*, 2014b). The availability of established genetic risk alleles (eg, from recent genome-wide studies) has created a new set of candidate variants that can be examined in $G \times E$ studies.

GWAS data can also be used to study genetic effects beyond the simple association of a single variant or gene with a disorder or trait. *Pathway (or gene set enrichment) analyses* can implicate sets of genes—for example, genes in a given biological pathway. Pathway analyses can be more powerful than single marker tests because they aggregate association signals across groups of genes. By implicating functionally related genes, they can also provide insights into the biological mechanisms by translating association signals into sets of cellular functions or molecular pathways that may underlie disease pathogenesis. So-called *polygene risk scores* (PRS) provide another index of aggregate genetic effects. Psychiatric disorders are now known to be highly polygenic—that is the genetic component includes hundreds or thousands of individual rare and common variants. The large majority of common risk alleles will not show genome-wide significant evidence of association given available sample sizes. A PRS can be derived from a GWAS by selecting all SNPs that exceed a nominal P -value threshold (eg, $P < 0.05$). These SNPs are then used to generate a score that is simply a sum of the allele count weighted by the effect size (eg, log odds ratio) for each SNP. In other words, the PRS provides a single measure of genetic loading for common risk alleles for a given phenotype. The PRS can then be used as a predictor or a covariate in future studies of a disease in independent samples for which GWAS data are available. GWAS data for a given phenotype can also be used to estimate the variance attributable to common variation (so-called SNP-Chip heritability, h^2_{SNP}). A variety of approaches have been developed to estimate such heritability (Bulik-Sullivan *et al*, 2015; Ge *et al*, 2015; Yang *et al*, 2011; Zaitlen *et al*, 2014). Aggregate cross-disorder effects of common variants can be estimated using PRS and bivariate analyses of h^2_{SNP} (Wray *et al*, 2014).

Establishing that a genetic variant, gene, or gene set is associated with a disorder of interest is only the first step in answering the question of how specific genes contribute to the disorder. A wide range of molecular, cellular, and clinical research studies may be needed to characterize the pathogenetic mechanisms involved. These include studies of gene expression, animal and cellular models in which genes may be experimentally altered to study functional

effects, and clinical neuroscience studies (eg, neuroimaging and neurophysiology) examining the effect of genetic variation on brain structure and function.

The next section briefly highlights findings from psychiatric genetic research, most notably the discovery of scores of genetic associations that exceed stringent genome-wide thresholds for statistical significance.

PROGRESS IN PSYCHIATRIC GENETICS

In the 1980s and 1990s, linkage studies implicated a large number of chromosomal regions that might harbor risk loci for a range of psychotic, mood, and anxiety disorders. However, linkage findings were difficult to replicate, and by the late 1990s, it became clear that association studies would be more powerful than linkage studies for discovering common, low penetrance risk alleles. During the next decade, hundreds of candidate gene association studies were reported, but replication of findings from these studies proved elusive.

A turning point for psychiatric genetics occurred with the advent of large GWAS. Whereas few if any loci could be confidently said to be associated with a psychiatric disorder before 2008, GWAS has, at this writing, yielded nearly 200. In 2007, the international Psychiatric Genomics Consortium (PGC) was formed as investigators came together to share GWAS data sets and pursue centralized analyses (Sullivan, 2010). To date, large GWAS by the PGC and other groups have identified numerous genome-wide significant loci, including more than 100 for schizophrenia alone (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Another success story has been the identification of large (>100 kilobases) CNVs that confer risk to a range of neuropsychiatric disorders, including ASD, SCZ, and, to a lesser extent, BD (Green *et al*, 2015; Malhotra and Sebat, 2012). Recently, exome sequencing studies and family-based studies of rare mutations have implicated rare SNVs in ASD (Geschwind and State, 2015) and SCZ (Purcell *et al*, 2014). As expected, the common variants have modest effect sizes (allelic odds ratios ~ 1.05 – 1.2) while those for rare CNVs and mutations can be more substantial (odds ratios of ~ 2.0 – 30.0). Studies of common variants, rare mutations, and structural variations have also documented genetic overlap among a range of psychiatric disorders (Smoller, 2013). Beyond the growing catalog of established risk variants, pathway analyses have begun to implicate functional sets of genes in multiple disorders, including genes involved in immune function, glial cell function, calcium channel signaling, glutamatergic neurotransmission, histone methylation, structural elements of the postsynaptic density, and targets of the fragile X mental retardation protein (FMRP) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Duncan *et al*, 2014a; Lee *et al*, 2012; Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium *et al*, 2015; Nurnberger *et al*, 2014; Pedroso *et al*, 2012; Purcell *et al*, 2014; Schizophrenia Working Group

of the Psychiatric Genomics Consortium, 2014; Uddin *et al*, 2014).

However, progress in genetic studies of the stress-related disorders reviewed here has been slower. The following sections will review genetic findings for the three categories of stress-related disorders: traumatic-stress disorders (ie, PTSD), MDD, and anxiety disorders (generalized, panic, and phobic disorders). For each, I will first review their genetic epidemiology (family and twin studies), studies of common SNVs, rare SNVs, and structural variation, and finally G × E studies.

GENETICS OF POSTTRAUMATIC STRESS DISORDER

PTSD occurs in a subset of individuals exposed to traumatic events and comprises four clusters of symptoms: intrusive re-experiencing of the trauma, avoidance of stimuli associated with the trauma, negative cognitions and mood associated with the trauma, and excessive arousal or reactivity. In DSM-5 (American Psychiatric Association, 2013), PTSD was moved from the anxiety disorder group to a new category of ‘trauma- and stressor-related disorders’. While a majority (50–85%) of Americans experience a traumatic event during their lifetimes, the lifetime prevalence of PTSD is approximately 7% (Kessler and Wang, 2008), indicating that a minority of individuals exposed to trauma develop the disorder. Genetic studies may provide important clues to these individual differences in vulnerability.

Family and Twin Studies

Because the expression of PTSD requires exposure to a significant trauma, estimating the familial aggregation of PTSD is complicated by the need to account for varying degrees of trauma exposure among relatives. Thus, in a standard case–control design, it is impossible to determine whether relatives who have not experienced significant trauma might have otherwise been affected. Risk of PTSD has been shown to be elevated among offspring of parents with PTSD in some but not in all studies (Leen-Feldner *et al*, 2013). The largest study (Roth *et al*, 2014) comprised a cohort of 6924 mothers and their children and found a significant increase in offspring PTSD in a dose–response relationship with maternal posttraumatic stress symptoms (ORs 1.2–1.6). Interestingly, parent–offspring transmission was largely mediated through an increase in trauma exposure among offspring of mothers with PTSD. PTSD-related twin studies have addressed the complex genetic relationship between trauma exposure and disorder risk by distinguishing their heritable components. Genetic factors can contribute to PTSD liability in at least four ways: by influencing the liability to (criterion A) trauma exposure; by influencing PTSD risk independent of trauma exposure; by influencing other risk factors for PTSD (eg, personality traits, or comorbidities); or by a pleiotropic effect on two or more of these.

A series of twin studies treating trauma exposure as the phenotype of interest has documented the heritability of this pre-condition for PTSD. In a study of the Vietnam Era Twin Registry (True *et al*, 1993) all individual DSM-III-R PTSD symptoms were heritable ($h^2=0.32$ – 0.45). In addition, combat exposure was itself similarly heritable ($h^2=0.35$). PTSD and combat exposure were also genetically correlated. In a civilian twin sample, Stein *et al* (2002) found evidence for the heritability of PTSD symptoms ($h^2=0.28$ – 0.36) and assaultive trauma ($h^2=0.20$) but not non-assaultive trauma. The genetic correlation between PTSD symptoms and assaultive trauma was substantial ($r_g=0.76$). Interestingly, this genetic correlation declined as the number of assaultive traumas reached high levels, consistent with the hypothesis that large doses of trauma can cause PTSD regardless of genetic vulnerability (Jang *et al*, 2007). In a large population-based twin sample in which the heritability of PTSD was 0.46, even larger estimates were observed for the heritability of high-risk trauma ($h^2=0.60$), and the genetic correlation between high-risk trauma and PTSD was again substantial ($r_g=0.89$) (Sartor *et al*, 2012).

Thus, twin studies have documented moderately heritabilities for PTSD (in the range of 30–50%) and high-risk trauma exposure (in the range of 30–60%) and that genetic influences on them are highly overlapping. The mechanism underlying genetic effects on trauma exposure remains unclear, though they may be mediated by personality traits (such as risk-taking) that increase the probability of exposure to dangerous environments.

Common Variation

Candidate gene studies. Efforts to identify specific genetic variants contributing to the heritability of PTSD have overwhelmingly focused on biological candidate genes (Cornelis *et al*, 2010). In particular, genes involved in monoaminergic neurotransmission and elements of the HPA axis have been commonly investigated. The most widely studied polymorphism has been a variable number tandem repeat (VNTR) in the promoter region of the serotonin transporter gene (*SLC6A4*), which encodes the target of serotonin reuptake inhibitors. This functional polymorphism, referred to as the 5HTTLPR, is common in European ancestry populations, with a frequency of approximately 45% for the so-called short (S) allele that is associated with reduced transcription of *SLC6A4*. Association studies of the 5HTTLPR and PTSD have been inconclusive, and a recent meta-analysis of 12 studies found no evidence of association overall, though homozygosity for the S allele was associated with PTSD in samples classified as having high-trauma exposure (Gressier *et al*, 2013).

Nominally significant associations have been reported between PTSD symptoms and other neurotransmitter- and neuropeptide-related genes including *HTR2A*, *SLC6A3*, *DRD3*, *NPY*, *CNR1*, and *RGS2* (Cornelis *et al*, 2010; Sah and Geraciotti, 2013; Wolf *et al*, 2014a). Recent data from the Grady Trauma Project, a study of predominantly

African-American inner-city individuals with high trauma exposure ($N=2698$), found evidence for association between PTSD and variants in the proinflammatory C-reactive protein gene (*CRP*) (Michopoulos *et al*, 2015). Risk SNPs were also associated with serum CRP levels which, in turn, were associated with PTSD symptoms and fear-potentiated startle. In the same cohort, a variant in the opioid receptor-like 1 gene (*OPRL1*) was associated with PTSD symptoms and fear-potentiated startle as well as amygdala-insula connectivity by fMRI (Andero *et al*, 2013). This gene encodes the amygdala nociceptin (NOP)/orphanin FQ receptor (NOP-R) and rodent studies have demonstrated its importance to fear conditioning. Amygdala expression of the mouse ortholog *opr1l* was reduced after fear conditioning in a PTSD-like mouse model. Further, injection of an NOP-R agonist into the central amygdala impaired fear consolidation (Andero *et al*, 2013). Of note, administration of the opioid agonist morphine shortly after trauma exposure has been found to reduce the incidence of PTSD (Holbrook *et al*, 2010), further supporting a role for opioidergic systems in PTSD.

More compelling results have been reported for two genes related to neuroendocrine function. Pituitary adenylate cyclase-activating polypeptide (PACAP) is a hypothalamic neuropeptide with modulatory effects on a broad range of neurohormones including stimulation of corticotropin releasing hormone (CRH) secretion (Vaudry *et al*, 2009). In mice, deletion of the PACAP receptor PAC-R1 is associated with decreases in anxiety behavior and fear conditioning. Ressler *et al* (2011) reported that variation in *ADCYAP1R1*, the gene encoding PAC-R1, is associated with PTSD in females. In particular, an SNP (rs2267735) in a putative estrogen response element (ERE) was associated with PTSD risk as both a main effect and a gene–environment interaction with trauma. While several subsequent association analyses did not support a main effect of rs2267735 with PTSD (Chang *et al*, 2012), gene–environment interactions for this SNP have been observed with childhood adversity and high levels of lifetime trauma in females (Almli *et al*, 2013; Uddin *et al*, 2013). Further analyses revealed associations between the PTSD risk allele at this SNP and expression of PAC-R1 in human brain, increased amygdala reactivity to threat stimuli, reduced amygdala/hippocampal connectivity, and decreased hippocampal activation during contextual fear conditioning by fMRI (Pohlack *et al*, 2015; Ressler *et al*, 2011; Stevens *et al*, 2014).

Perhaps the most most comprehensively-studied candidate to date has been the FK506 binding protein 5 gene, *FKBP5*. Binder, Ressler and colleagues (Binder *et al*, 2004, 2008; Fani *et al*, 2013; Klengel *et al*, 2013; Mehta *et al*, 2011) have demonstrated a role for *FKBP5* variation in stress-related phenotypes and disorders. However, the evidence linking this gene to PTSD suggests that its effect is mainly in the form of $G \times E$, and so it is discussed in the $G \times E$ section below. In general, candidate gene and GWAS studies have not supported a main effect of *FKBP5* variation (Binder *et al*, 2008; Logue *et al*, 2013; Nievergelt *et al*, 2015; Solovieff *et al*, 2014).

For the most part, candidate gene studies of PTSD, like those for the other stress-related disorders reviewed here, have been underpowered, making both positive and negative findings difficult to interpret. One of the largest candidate gene studies, comprising 845 PTSD cases and 1693 trauma-exposed controls from the Nurses Health Study II, examined 3742 SNPs spanning more than 300 genes (Solovieff *et al*, 2014). With one exception, no genes showed significant evidence of association. The exception was *SLC18A2* (aka *VMAT2*) whose product transports monoamine neurotransmitters into synaptic vesicles. An intronic SNP (rs323276) was associated with PTSD after correction for multiple testing of candidate SNPs and phenotypes. In an independent African-American sample drawn from the Detroit Neighborhood Health Study, a 9-SNP haplotype containing the rs323276 risk allele was again associated with PTSD, though rs323276 itself was not associated. In another study of a similar set of 295 candidate genes, no main effect associations were identified in a sample of 810 National Guard soldiers (Liberzon *et al*, 2014).

Genome-wide association studies. The first GWAS of PTSD, in military veterans and their intimate partners, reported a genome-wide significant association between PTSD (295 cases and 196 controls) and an SNP (rs8042149) in the retinoid-related orphan receptor gene (*RORA*) (Logue *et al*, 2013). While this SNP was not significantly associated in two replication samples in the same publication, further analysis of *RORA* SNPs in a subset of the discovery and replication samples ($N=540$) reported an association between rs17303244 and a fear component of PTSD (Miller *et al*, 2013). Examination of rs8042149 among individuals assessed for PTSD symptoms after hurricane exposure detected an association with PTSD symptom severity (Amstadter *et al*, 2013). However, associations between *RORA* SNPs (including rs8042149) were not detected in two larger independent replication samples from the Nurses' Health Study II and a cohort of Iraq and Afghanistan-era US veterans (Guffanti *et al*, 2014).

Genome-wide significant associations have also been reported with PTSD in the Toll-like 1 gene (*TLL1*), the cordon-bleu WH2 repeat protein gene (*COBL*) (Xie *et al*, 2013), and in the lincRNA gene *AC068718.1* (Guffanti *et al*, 2013). In a sample of 3215 trauma-exposed individuals, no significant association between the *COBL* SNP rs406001 with PTSD symptoms was found, but a significant interaction between this SNP with childhood trauma was reported (Almli *et al*, 2014).

Nievergelt *et al* (2015) recently conducted a GWAS of PTSD in a multi-ethnic cohort ($N=3494$) of male combat-exposed US Marines and Sailors from the Marine Resiliency Study. A total of 940 met criteria for partial or full PTSD. Meta-analysis of GWAS results across ethnicities identified a genome-wide significant SNP (rs6482463) in intron 3 of the phosphoribosyl transferase domain containing 1 gene (*PRTFDC1*). However, there was no clear evidence of

association in a smaller replication sample of veterans and their intimate partners.

A single study surveyed SNPs across the mitochondrial genome (Flaquer *et al*, 2015) in light of the key role of mitochondria in cellular stress responses to a range of external challenges (Manoli *et al*, 2007). Mitochondrial dysfunction has been linked to abnormalities in synaptic plasticity and cellular resilience and has been implicated in mood and other psychiatric disorders (Manji *et al*, 2012). Flaquer *et al* reported association between PTSD and two mitochondrial SNPs (mtSNPs): mt8414C → T, a missense variant located in *MT-ATP8*, and mt12501G → A a synonymous variant located in *MT-ND5*. Both genes are involved in the regulation of reactive oxygen species. Finally, a GWAS of dissociative symptoms associated with PTSD, and another recent GWAS of PTSD among combat veterans reported no genome-wide significant hits (Ashley-Koch *et al*, 2015; Wolf *et al*, 2014b).

Rare and Structural Variation

To date, no systematic search for rare SNVs or structural variation related to PTSD has been reported.

Gene–Environment Interaction

With the exception of substance use disorders, PTSD is the only psychiatric disorder for which an environmental exposure is required by definition. In addition other environmental exposures, including childhood maltreatment, poverty, and low social support, have been shown to increase the risk of PTSD among trauma-exposed individuals (DiGangi *et al*, 2013b; Ozer *et al*, 2003). In a 2013 systematic review, Digangi *et al* (2013a) examined the 28 candidate gene association studies of PTSD that compared cases and trauma-exposed controls. They concluded that, in addition to low statistical power, $G \times E$ studies of PTSD have suffered from a range of limitations including a restricted focus on a small number of polymorphisms and inadequate consideration of the timing, chronicity, or differential effect sizes of multiple exposures. Notable $G \times E$ associations in PTSD with at least some replication in independent samples have included interactions between childhood adversity and the PACAP receptor (described above) (Almli *et al*, 2013; Ressler *et al*, 2011; Uddin *et al*, 2013) as well as a promoter region polymorphism in the β_2 adrenergic gene (*ADRB2*) (Liberzon *et al*, 2014).

The most extensive $G \times E$ analyses have focused on *FKBP5* and have elucidated a mechanism by which genetic variation in *FKBP5* may interact with early adversity to increase the risk of stress-related disorders. The gene product of *FKBP5* acts as a co-chaperone in the Hsp-90-steroid receptor complex and inhibits glucocorticoid receptor (GR) activity by several mechanisms including reducing GR binding affinity and nuclear translocation (Zannas and Binder, 2014). *FKBP5* transcription is itself rapidly induced by GR activation through steroid-response elements in the *FKBP5*

promoter region. These reciprocal effects create an ultra-short negative feedback loop that modulates GR sensitivity (Zannas and Binder, 2014). Several studies have reported that variation in *FKBP5* moderates the effect of adversity and trauma on risk of PTSD (Binder *et al*, 2004, 2008; Fani *et al*, 2013; Klengel *et al*, 2013; Mehta *et al*, 2011; Xie *et al*, 2010). In particular, the *FKBP5* SNP rs1360780, located in an enhancer region 488 bp away from a glucocorticoid response element (GRE) in intron 2, appears to be functionally related to GR-mediated expression of *FKBP5* (Klengel *et al*, 2013). The minor T allele enhances *FKBP5* transcription in response to GR activation by inducing chromatin-mediated conformational changes that enhance contact between the intron 2 GRE and the transcription start site (TSS). Exposure to early-life adversity and trauma leads to GR activation and, in the presence of the T (risk) allele, induces excessive hippocampal *FKBP5* expression resulting in sustained cortisol levels. This effect is accompanied by demethylation of a GRE in intron 7 that also interacts with the TSS, further amplifying *FKBP5* expression in the presence of GR activation (Zannas and Binder, 2014). Thus, *FKBP5* genotype interacts with childhood trauma to induce epigenetically-mediated hippocampal glucocorticoid resistance. This effect was not observed with adult trauma. Klengel *et al* (2013) demonstrated that this $G \times E$ is associated with increased risk for stress-related disorders including PTSD and depression. In addition, *FKBP5* risk variants have been associated with neuroimaging markers implicated in stress-related disorders, including amygdala and hippocampal volume and reactivity (Fani *et al*, 2013; Holz *et al*, 2015; Pagliaccio *et al*, 2014; White *et al*, 2012). Several important features of this story are worth highlighting. First, they provide some of the most direct evidence of both statistical and biological gene–environment interaction. Second, they highlight the importance of developmental sensitive periods in $G \times E$ studies: the *FKBP5* risk allele effects on gene expression and PTSD risk appear to interact specifically with childhood but not later-life adversity.

Genetic and $G \times E$ studies of PTSD face an important challenge which is often under-appreciated. Trauma exposure is a precondition for the expression of PTSD. However, we need to distinguish two types of adversity exposure that have different etiologic roles. We might call the first type ‘index traumas’—that is, traumatic events that fulfill Criterion A of the DSM diagnostic criteria as causes of PTSD (see Figure 2). The second type, which I’ll call ‘risk exposures’, would include traumas and other adversities (eg, early or chronic stressors) that are risk factors for PTSD (Koenen *et al*, 2007; Ozer *et al*, 2003) but were not sufficient to cause PTSD. The outcome of main-effect genetic studies and $G \times E$ studies of PTSD will depend on how these two types of trauma are ascertained in case–control studies. In addition, as noted earlier, genetic influences on trauma exposure and PTSD overlap. This gene-by-environment correlation (rGE) suggests that some of the genetic variants influencing PTSD risk may act through their effect on exposure to causal traumas. That is, a genetic variant may

increase the risk for PTSD by increasing the risk of exposure to index traumatic events. Genetic association studies of PTSD often compare cases with controls matched on trauma exposure. By design, then, such analyses would have limited ability to detect the fraction of PTSD risk alleles whose effect is mediated by increasing exposure to an 'index trauma'. At the same time, studies that include controls unscreened for index trauma exposure would have reduced power to detect loci that act independent of an effect on trauma exposure compared with studies in which controls are matched for trauma exposure. In examining $G \times E$ for risk exposures, matching cases and controls with respect to index traumas becomes less relevant. $G \times E$ studies of PTSD where the environmental exposure is an index trauma could compare cases with varying severity of index trauma, for example. On the other hand, $G \times E$ studies of risk exposures could examine controls matched (or not) for index trauma. However, the interpretation of both main effect and $G \times E$ studies are further complicated by the fact that index traumas and risk exposures are correlated (Koenen *et al*, 2007). Unfortunately, it is often difficult to determine whether a trauma exposure is a sufficient cause or merely risk-enhancing and few studies have endeavored to distinguish these two classes.

Figure 2. Complexity of causal relationships between genetic risk and environmental trauma/adversity. Only a subset of possible relationships are depicted. Genes (G) may (path a) influence PTSD directly or (b) by increasing the risk of index traumas (T_i) which in turn cause PTSD (c). In addition, index traumas may increase PTSD risk independent of genetic effects (d). In addition, trauma/adversity may act as risk exposures (R_e) that amplify risk (e and f) but are not a primary cause of PTSD. These risk exposures may themselves be under genetic influence (d). Finally, T_i and R_e may be correlated and each may modify the effect of risk genes (representing gene–environment interactions).

Summary

Twin studies have documented that both trauma exposure and PTSD itself are moderately heritable and genetically correlated. To date, however, the molecular genetic basis of PTSD remains largely uncharted (Table 1). Candidate gene studies have focused primarily on a subset of genes involved in serotonergic, dopaminergic, and neuroendocrine function with decidedly mixed results. GWAS have identified a handful of common variants associated with PTSD, but none have been widely replicated. More convincing evidence has been reported for a $G \times E$ between early adversity and variation in *FKBP5*, and functional studies have provided the basics of a mechanistic account of how this genetic variation alters stress responses by epigenetic alterations of gene expression and downstream effects on glucocorticoid function. In general, common variant studies of PTSD have been underpowered to detect the relatively modest effects that have been validated in large-scale GWAS studies of other complex phenotypes. In addition, the role of rare and structural variation remains unexplored.

In the coming years, progress in identifying the genetic basis of PTSD is expected to take a leap forward with analyses of larger samples. In particular, the PGC's PTSD Workgroup is bringing together GWAS data sets from around the world and participating sites have genotyping completed or underway for approximately 20 000 cases and 50 000 controls (Logue *et al*, 2015).

GENETICS OF DEPRESSION

MDD is a common condition with lifetime prevalence estimates from US population-based studies of 11% among adolescents (Avenevoli *et al*, 2015) and more than 16% among adults (Kessler and Wang, 2008). In addition, depressive disorders including MDD and dysthymia are the second leading cause of disability worldwide (Ferrari *et al*, 2013). A variety of stressful life events have been shown to increase the risk for depression (Hammen, 2005; Kessler, 1997) including poverty (Brooks-Gunn and Duncan, 1997; McLeod and Shanahan, 1996), negative family relationships and parental divorce (Gilman *et al*, 2003; Repetti *et al*, 2002), and childhood maltreatment (Chapman *et al*, 2004; Widom *et al*, 2007). Unlike PTSD, MDD and depressive symptoms

TABLE 1 Summary of Stress-Related Disorder Genetics

	PTSD	MDD	Anxiety disorders
Approximate familial recurrence risk ratio (λ)	Undefined	3	4–6
Approximate heritability (h^2 from twin studies)	0.32–0.46	0.40	0.30–0.50
Common variation: leading candidate genes	<i>ADCYAP1R1</i> , <i>SLC18A2</i>	Many reported but conflicting findings	Many reported but conflicting findings
Common variation: leading GWAS findings	<i>RORA</i> , <i>TLL1</i> , <i>COBL</i> , <i>PRTFDC1</i> , <i>AC068718.1</i>	<i>PCLO</i> , <i>CACNA1C</i> , <i>SYNE1</i> , <i>SIRT1</i> , <i>LHPP</i>	<i>TMEM132D</i> (panic disorder)
Rare and structural variation	None	Limited data	7q11.23 del, <i>FMR1</i> triplet repeat
Leading $G \times E$ findings	<i>FKBP5</i> $\times$ childhood trauma; <i>ADCYAP1R1</i> $\times$ childhood and lifetime trauma	<i>FKBP5</i> $\times$ childhood trauma, <i>CRHR1</i> $\times$ childhood trauma	Many reported but conflicting findings

have been investigated extensively in genetic studies, with genetic epidemiologic studies dating back to the 1920s (Tsuang and Faraone, 1990). Recent genomic studies have implicated several risk loci, although few have been replicated, as detailed below.

Family and Twin Studies

A meta-analysis of high quality family studies confirmed that MDD aggregates in families, with a summary odds ratio of 2.84 (95% CI: 2.31–3.49) among first-degree relatives of affected probands compared with those of controls (Sullivan *et al*, 2000). More recent family studies have produced similar recurrence risk ratio estimates (Merikangas *et al*, 2014). Twin studies have shown that the familial aggregation of MDD is largely due to genetic factors, with a heritability of approximately 40% (Kendler *et al*, 2006; Sullivan *et al*, 2000), though higher estimates (up to 70%) have been reported in clinically-ascertained or longitudinal twin samples (Kendler *et al*, 1993b; McGuffin *et al*, 1996).

Family and twin studies have also examined subtypes of MDD that may confer greater familial risk (Smoller and Perlis, 2004). In particular, increased familial recurrence risk and heritability have been associated with earlier-onset and recurrent depression (Bland *et al*, 1986; Kendler *et al*, 1999a, 2005; Weissman *et al*, 1984) as well as greater depression severity or impairment (Klein *et al*, 2002; Lyons *et al*, 1998), though these findings have not been universally observed.

Common Genetic Variation

Candidate gene studies. Before the availability of GWAS, common variation studies of MDD were largely limited to biological candidate genes in neurotransmitter, neuropeptide, and neuroendocrine systems related to antidepressant targets or implicated in animal models. The results of these studies have been mixed and most have been underpowered to detect the modest effects expected for common variants. Meta-analyses of biological candidate gene studies have provided some support for association between MDD and specific variants (Gatt *et al*, 2015). In particular, nominal associations have been reported in meta-analyses for variants in several serotonergic genes (*HTR2A*, *SLC6A4*, *HTR1A*, *TPH2*) (Gao *et al*, 2012; Kishi *et al*, 2013; Lopez-Leon *et al*, 2007; Zhao *et al*, 2014), as well as *APOE*, *DRD4*, *GNB3*, *SLC6A3*, and *MTHFR* (Clarke *et al*, 2010; Lopez-Leon *et al*, 2007; Wu *et al*, 2013). Of note, however, none of these genes has been implicated in large GWAS (Wray *et al*, 2012). As Flint and Kendler (2014) have demonstrated, candidate gene meta-analyses of MDD have been underpowered and the data thus far are consistent with a lack of significant findings in any meta-analysis. Using a different approach, Lee *et al* (2012) examined 188 MDD candidate genes and 178 biological gene sets related to these genes in a pathway analysis encompassing three GWAS data sets. Genes involved in glutamatergic synaptic neurotransmission were

significantly associated with MDD after correction for multiple testing.

GWAS. The first GWAS of MDD comprised 1738 cases and 1802 controls (Sullivan *et al*, 2009). Although no genome-wide significant loci were detected, 11 of the top signals localized to a 167-kb region encompassing *PCLO*, which encodes piccolo, a presynaptic protein involved in monoaminergic neurotransmitter release. A larger series of replication samples did not support this association but an exploratory analysis of the subset of samples most similar to the discovery sample yielded nearly significant association for a non-synonymous *PCLO* SNP (rs2522833). Although subsequent candidate gene studies have implicated this or other *PCLO* SNPs in depression (Hek *et al*, 2010; Minelli *et al*, 2012), bipolar disorder (Choi *et al*, 2011), and HPA axis function (Kuehner *et al*, 2011; Schuhmacher *et al*, 2011), the gene has not shown association in independent GWAS of MDD. A subsequent GWAS (Kohli *et al*, 2011) reported a significant recessive association for an SNP (rs1545843) in *SLC6A15*, a gene involved in transporting neutral amino acids. Risk alleles were also correlated with reduced hippocampal *SLC6A15* expression and reduced hippocampal volume and neuronal integrity measured by magnetic resonance spectroscopy. Mice susceptible to chronic stress were also found to have reduced hippocampal *SLC6A15* expression. Subsequent research suggested that the putative risk allele is associated with enhanced cortisol secretion on the dexamethasone/CRH test and impairments in memory and attention in patients with MDD (Schuhmacher *et al*, 2013). Of note, however, this locus has not been supported in subsequent larger depression GWAS (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium *et al*, 2013; Wray *et al*, 2012) or in GWAS meta-analyses of hippocampal volume by the international ENIGMA consortium (Hibar *et al*, 2015).

More than 15 GWAS of MDD have now been reported, but success in establishing risk variants has been limited (Dunn *et al*, 2015). The largest case-control GWAS to date was reported by the PGC, comprising a discovery sample of 9240 cases and 9519 controls (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium *et al*, 2013). No SNPs reached genome-wide significance in this sample or in a joint analysis with independent replication samples. The study found that loci accounting for as little as 0.5% of the phenotypic variance in MDD could be excluded with 90% power. Secondary analyses of depressive subtypes (by sex, recurrent depression, recurrent early-onset, and latent class analysis of 'typical' MDD) also produced no significant findings, though smaller sample sizes limited the power of these analyses.

A GWAS meta-analysis of 17 independent samples ($N = 34\,549$) from the CHARGE Consortium (Hek *et al*, 2013) examined depressive symptoms measured by the Center for Epidemiologic Studies Depression Scale (CES-D). No genome-wide significant associations were identified in the discovery sample. However, one locus on chromosome

5q21 did show significant evidence of association when top SNPs from this analysis were meta-analyzed with an independent replication sample (total $n = 51\,258$). Because the CES-D assesses depressive symptoms in the past week, it may be that phenotypic misclassification contributed to the largely null results of this study. Other loci that appear to influence depression risk have emerged from cross-disorder genetic studies (discussed in more detail later), including *SYNE1* (Green *et al*, 2013) (a gene associated with BPD) and *CACNA1C* (also associated with BPD and SCZ) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Green *et al*, 2010).

The most compelling GWAS results for MDD were recently reported by the CONVERGE Consortium using low-coverage whole genome sequencing (CONVERGE Consortium, 2015). In a sample of 5303 Han Chinese women with recurrent MDD and 5337 controls, they identified two genome-wide significant loci: one on chromosome 10 near *SIRT1* and a second in an intron of *LHPP*. These loci were replicated in an independent Chinese sample, and in a combined analysis of the discovery and replication samples, the top *SIRT1* SNP (rs12415800) and the top *LHPP* SNP (rs35936514) achieved P -values of 2.37×10^{-10} and 6.43×10^{-12} , respectively. The investigators attributed their success to reducing heterogeneity by focusing on a Chinese sample with severe MDD. Indeed, the *SIRT1* association was even stronger when cases were restricted to those with the more severe melancholic subtype despite a smaller sample size. The associated SNPs are much less common in European ancestry samples and were not associated in the larger PGC-MDD mega-analysis (European ancestry), suggesting that these loci may have population-specific effects.

In addition to single locus analyses, gene set enrichment analyses of GWAS data for MDD have begun to implicate numerous biological pathways (Kao *et al*, 2012; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015; Song *et al*, 2013). The largest of these, by the PGC, included GWAS data on more than 60 000 individuals across multiple psychiatric disorders (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015). With respect to MDD, enriched pathways included those involved in protein phosphatase type 2A regulator activity, cell junction organization, and histone modification.

Rare and Structural Variation

Depressive symptoms are among the phenotypic manifestations of several medical genetic syndromes caused by rare mutations in specific genes. These include autosomal dominant disorders such as Huntington disease (gene: *HTT*) and acute intermittent porphyria (*HBMS*), recessive inborn errors of metabolism such as homocystinuria (*CBS*) and other recessive disorders such as Wolfram syndrome (*WFS1*), X-linked disorders such as Fabry disease (*GLA*), and mitochondrial disorders such as MELAS (*MT-TL1* and *MT-*

ND5) (Anglin *et al*, 2012; Ebert *et al*, 2010). An excess of expanded triplet repeat alleles in *HTT* was also reported in a study examining more than 11 000 chromosomes from MDD cases and controls, with a reported carrier frequency of 3 per 1000 among MDD patients (Perlis *et al*, 2010).

Pre-dating the recent era of common variant and rare variant association studies, a large number of linkage analyses of MDD were reported. Although linkage studies are less powerful than association analysis for studying common risk variants, they can detect rare variant loci that segregate in families. Linkage signals have been reported for 15 of the 22 autosomes, with some regions observed in independent studies (Flint and Kendler, 2014), but none of these have led to the identification of specific mutations. Few rare variant association studies have been reported for non-syndromic forms of MDD (Kato, 2015) and no well-powered whole exome or whole genome studies are available. In sum, then non-syndromic forms of MDD have not been convincingly associated with rare SNVs, though efforts to identify such variants have been limited.

Several genome-wide studies have examined rare CNVs in relation to MDD. An initial report (Glessner *et al*, 2010) identified a 646-kb duplication in 5 of 1693 cases but none of 4506 controls. The duplication, on chromosome 5q35.1, encompassed exons of *SLIT3*, *CCDC99*, and *DOCK2*; however, subsequent studies have not observed enrichment of this duplication. In one study, though, exome sequencing of 40 families ascertained for probands with ASD identified putatively damaging *SLIT3* mutations in two families in which carriers presented with MDD (Cukier *et al*, 2014). The gene is of interest because of its role in axon guidance. Another study found a significantly greater burden of copy number deletions of >100 kb in cases with recurrent MDD ($N = 3106$) compared with controls ($N = 459$ screened and 5619 unscreened controls) (Rucker *et al*, 2013), but this was not supported in a re-analysis of the same cases with more stringent CNV calling algorithms (Rucker *et al*, 2015). Additional studies have also failed to find significant evidence for enrichment of CNVs in recurrent MDD (O'Dushlaine *et al*, 2014) or among patients who attempted suicide (Perlis *et al*, 2012). Finally, whole genome sequencing in a sample of children and adolescents referred to a neuropsychiatric evaluation clinic and observed two gene-disrupting CNVs in children with MDD and anxiety (Brand *et al*, 2014). Larger-scale studies will be needed to clarify whether CNVs represent a risk factor for MDD.

Gene-Environment Interaction

There is no question that both genes and environment influence risk for depression, and recent evidence suggests that exposure to stressful life events is, itself, heritable (Power *et al*, 2013). However, $G \times E$ studies ask the more specific question of whether the joint effect of genetic variation and environmental risk factors is significantly different from the product of their individual effects. The existence of important $G \times E$ effects could help account for the largely

negative findings of main effect candidate gene and GWAS studies. Perhaps the most influential and controversial association finding related to depression was a report that stressful life events interact with the 5HTTLPR to increase the risk of depression (Caspi *et al*, 2003). That study examined 847 members of the longitudinal Dunedin Multi-disciplinary Health and Development Study at age 26 and found a dose-response interaction between the 5HTTLPR short allele and number of stressful life events over the past 5 years on past-year major depressive episodes, depressive symptoms, and suicide attempt. The same interaction was seen when considering childhood maltreatment as the environmental exposure. These findings seemed to fit with convergent evidence from animal models (Champoux *et al*, 2002; Holmes *et al*, 2003). They also spawned a large number of similar studies and attempts at replication, though findings have been mixed. In fact, meta-analyses of the 5HTTLPR $G \times E$ have come to conflicting conclusions. Weighing against the validity of an interaction, the two meta-analyses that used more stringent study inclusion criteria did not support the interaction (Munafo *et al*, 2009; Risch *et al*, 2009) while those with more liberal criteria (and using one-tailed P -values) did (Karg *et al*, 2011; Sharpley *et al*, 2014). In addition, the most direct effort to replicate the original findings (using a similar measure in a longitudinal birth cohort from New Zealand) found no evidence for the interaction even after conducting 104 separate regression models (Fergusson *et al*, 2011). Some have suggested that the inconsistent picture of $G \times E$ studies of the 5HTTLPR is attributable to heterogeneity of measurement and outcomes across studies, and that the effect is predominantly seen in females, young people, and studies using structured diagnostic interviews to assess exposures and depression (Uher and McGuffin, 2008). Nevertheless, the fact that better-powered replication studies have been less likely to detect the interaction and that evidence of publication bias exists have cast doubt on the robustness of the finding (Duncan *et al*, 2014b).

Many other candidate gene $G \times E$ studies of depression have been reported, largely focusing on monoaminergic and HPA axis genes (Dunn *et al*, 2011; Mandelli and Serretti, 2013). Of these, the strongest evidence has emerged for genes involved in stress hormone function—in particular, *CRHR1* and *FKBP5*. *CRHR1* is a G protein-coupled receptor that has a key role in stress responses through its role in the HPA axis as well as by mediating CRH effects on extrahypothalamic sites. An extensive preclinical literature has supported a role for *CRHR1* in depressive and anxiety behaviors (Heim *et al*, 2009). *CRHR1* SNPs have also been associated with anxious temperament and emotion circuit activity in a rhesus macaque model (Rogers *et al*, 2013) as well as MDD and cortisol reactivity in human studies (Ishitobi *et al*, 2012; Mahon *et al*, 2013; Sheikh *et al*, 2013). In a predominantly African-American sample, Bradley *et al* (2008) reported an interaction between variants in intron 1 of *CRHR1* and a history of child abuse for risk of depressive symptoms, with supportive evidence in a smaller clinical sample of

predominantly European-American women. Several subsequent studies have supported a *CRHR1* genotype $\times$ childhood maltreatment effect for depression (Heim *et al*, 2009; Laucht *et al*, 2013; Ressler *et al*, 2010) and cortisol reactivity (Heim *et al*, 2009; Sumner *et al*, 2014; Tyrka *et al*, 2009). As reviewed above, childhood adversity or trauma has also been shown to interact with *FKBP5* variation to increase the risk for stress-related disorders including depression (Appel *et al*, 2011; Zimmermann *et al*, 2011).

As noted earlier, candidate gene studies have limitations that may be overcome by well-powered genome-wide studies. To date, however, genome-wide $G \times E$ studies have only begun to appear. Using a PRS derived from the PGC-MDD meta-analysis, Peyrot *et al* (2014) observed a PRS-by-childhood trauma interaction for risk of depression in an European sample. Specifically, the penetrance of polygenic loading for MDD was greater among those with a history of childhood trauma. A US population-based study of older adults ($N=8761$) found no interaction between the MDD PRS and recent stressful life events on depressive symptoms, though the life events measure was limited and the outcome measure (CES-D) captures only current symptoms (Musliner *et al*, 2014).

Summary

MDD aggregates in families and is moderately heritable ($\sim 40\%$). The voluminous body of biological candidate gene studies has implicated several loci but none of these genes has been supported by unbiased genome-wide studies. In fact, the largest GWAS mega-analysis of MDD failed to identify any genome-wide significant common variants. More recently, two genome-wide significant loci were identified in a sample of Han Chinese women with recurrent MDD.

The difficulty in identifying loci associated with depression from large-scale GWAS suggests that the genetic architecture of depression is highly complex. In particular, the common variant component of MDD is likely to be extremely polygenic with thousands of contributing variants of individually small effect (Chang *et al*, 2014; Major Depressive Disorder Working Group of the Psychiatric GC *et al*, 2013). The h^2_{SNP} of MDD has been estimated at 0.21–0.32 (Cross-Disorder Group of the Psychiatric Genomics Consortium *et al*, 2013; Lubke *et al*, 2012), confirming that common variants are causally related to risk. However, simulations accounting for disorder prevalence and heritability indicate that GWAS of MDD would need to have sample sizes up to five-fold larger than those for SCZ to have comparable power to identify risk loci (Wray *et al*, 2012; Yang *et al*, 2010). Experience with GWAS of complex traits suggests that there is typically a sample size threshold or inflection point beyond which the number of genome-wide significant loci increases linearly (Levinson *et al*, 2014). For SCZ, the inflection point was observed at approximately 15 000 cases. Extrapolating from these results, the inflection point for MDD is not likely to be reached before GWAS

include 75 000 to 100 000 cases. These predictions will soon be put to the test as analyses on this scale are currently being planned by the PGC. However, as recently discussed (Levinson *et al*, 2014), sample size requirements could even be greater in the presence of misdiagnosis or if MDD is more genetically heterogeneous than SCZ. Thus, strategies to enhance the genetic homogeneity of MDD samples may be needed to advance our understanding of the genetic basis of depression. Numerous variables have been proposed to index more genetically homogeneous subtypes of MDD, including age of onset, recurrence, comorbid anxiety, chronicity, severity, suicidality, postpartum onset, and others. In addition, a recent large twin study suggested that MDD risk may reflect three orthogonal genetic factors, influencing, respectively, a general liability to internalizing disorders, core symptoms of MDD, and neurovegetative symptoms (Kendler *et al*, 2013). The recent successful GWAS by the CONVERGE Consortium supports the utility of examining more homogeneous subtypes of depression.

Larger-scale genome-wide studies will also facilitate studies of gene–environment interplay (Dunn *et al*, 2015). For example, risk loci established by GWAS would provide a set of robust candidate variants for G × E studies. In addition, genome-wide G × E analyses may be useful for discovering novel interactions. Finally, the contribution of rare and structural variation remains to be seen.

GENETICS OF ANXIETY DISORDERS

According to epidemiologic surveys, anxiety disorders represent the most common class of psychiatric disorders, though these estimates include PTSD and obsessive-compulsive disorder (OCD) which are no longer grouped with anxiety disorders in DSM-5 (Kessler and Wang, 2008). The burden of these disorders is substantial, owing in part to their early onset and persistence (Costello *et al*, 2005). Early stress and trauma are important risk factors for anxiety disorders (Gibb *et al*, 2007; Stein *et al*, 1996) and dysregulation of HPA axis function has been demonstrated in generalized, panic, and phobic anxiety disorders (Abelson *et al*, 2007; Dieleman *et al*, 2015).

Family and Twin Studies

The risk of anxiety disorders is approximately 4–6 times higher in first-degree relatives of affected probands compared with relatives of unaffected probands (Hettema *et al*, 2001). In twin studies, heritability estimates have been in the range of 30–50% (Hettema *et al*, 2001; Scaini *et al*, 2012, 2014; Smoller *et al*, 2009; Tambs *et al*, 2009a) though higher estimates (~40–65%) have been reported from analyses that include repeated assessments and correct for diagnostic unreliability (Kendler *et al*, 1999b). In addition, family and twin studies have suggested that genetic contributions cross the boundaries among anxiety disorders and between normal and pathologic anxiety. First-degree relatives of probands with one anxiety disorder are at risk for a range of other

anxiety disorders, and twin studies have documented genetic overlap among most if not all anxiety disorders (Hettema *et al*, 2005; Roberson-Nay *et al*, 2012; Smoller *et al*, 2008a; Tambs *et al*, 2009b). Factor analyses of twin data show genetic overlap of phobic fears that do not respect DSM boundaries (Loken *et al*, 2014). In fact, the shared genetic component among panic disorder (PD), phobias, generalized anxiety disorder (GAD), OCD, and PTSD is substantially larger than their disorder-specific genetic components (Tambs *et al*, 2009b).

Common Genetic Variation

As with PTSD and MDD, the majority of genetic association studies of the anxiety disorders have been candidate gene studies based on a limited number of biological hypotheses. These have commonly focused on genes related to monoaminergic neurotransmitter systems, neuropeptides, and HPA axis function. Of the anxiety disorders, PD has received the most attention.

Panic disorder. In candidate gene studies of PD, several loci have shown nominal association in independent samples. These include the 5HTTLPR polymorphism of *SLC6A4*, the val158met polymorphism (rs4680) of *COMT*, and a promoter length polymorphism of *MAOA*; however, conflicting results have been reported and the direction of allelic effect has been inconsistent. Nominally significant results have also been reported between panic disorder or panic attacks with variants in other monoaminergic genes (eg, *HTR1A* and *HTR2A*), GABA receptor genes (*GABRB3* and *GABRA5*) stress hormone genes (*CRHR1*), neuropeptidergic/neurotrophic genes (*BDNF*, *NPSR1*, *ACE*), and many others, but a recent comprehensive meta-analysis of the 23 most widely-studied candidate variants found no robust associations (Howe *et al*, 2015).

The relevance of several of these genes has been supported by imaging-genetic studies in which putative anxiety or panic risk alleles have been associated with reactivity or structural differences in the amygdala or related components of fear circuitry including functional variants in *SLC6A4* (5HTTLPR), *MAOA* (μVNTR), *BDNF* (val66met), *COMT* (val158met), *HTR1A* (–1019C/G), *NPRS1* (Asn¹⁰⁷Ile), and *RGS2* (rs4606) (Domschke and Dannlowski, 2010); again, however, association results are inconsistent. The most widely-studied of these has been the 5HTTLPR for which the short allele has been associated with amygdala reactivity in response to emotional faces in numerous studies. However, the most recent meta-analysis of 35 studies failed to support this association (Bastiaansen *et al*, 2014).

Another approach has been to focus on biologic systems that may be specific to PD. For example, heightened sensitivity to carbon dioxide (CO₂) is an established biological correlate of PD. Inhaled CO₂ triggers panic attacks in a majority of individuals with PD, but only a minority of unaffected controls (Battaglia and Ogliari, 2005). In rodents, CO₂ inhalation reduces amygdala pH, inducing acidosis and

fear behaviors (Coryell *et al*, 2007; Wemmie *et al*, 2003; Ziemann *et al*, 2009). More specifically, the rodent amygdala acts as a chemosensor for the detection of hypercarbia, a function mediated by the acid sensing ion channel-1a subunit (ASIC1a) (Ziemann *et al*, 2009). Disrupting the *asic1a* gene in mice decreases acidosis-induced fear behavior, which can be restored through transgenic expression of *asic1a* in the amygdala (Ziemann *et al*, 2009). Similar findings have been reported for *asic1a* at the level of the bed nucleus of the stria terminalis (Taughner *et al*, 2014). We previously reported evidence of linkage between PD and a region of chromosome 12q encompassing the human ortholog of *asic1a* (*ACCN2*) (Smoller *et al*, 2001). More recently, we observed association between variants in *ACCN2* and PD that appeared to be stronger in cases with the respiratory subtype of PD (Smoller *et al*, 2014). In healthy volunteers, PD-associated alleles were also associated with amygdala volume and amygdala reactivity to emotional faces (Smoller *et al*, 2014). In a subsequent report, an intronic *ACCN2* SNP was associated with respiratory rate and anxiety sensitivity (but not panic symptoms) in response to inhalation of CO₂-enriched air among healthy volunteers (Savage *et al*, 2015).

In the first GWAS of PD (*N*=200 cases/200 controls) (Otowa *et al*, 2009), genome-wide significant variants were reported in *TMEM16B* and *PKP1*, but these findings were not supported in a replication attempt by the same investigators in a larger independent sample (Otowa *et al*, 2010). However, more robust support has emerged for transmembrane protein 132D (*TMEM132D*). An initial GWAS found association of a *TMEM132D* SNP (rs7309727) as well as a haplotype combining this and another SNP (rs11060369). Risk genotypes were associated with higher *TMEM132D* mRNA expression in human post-mortem frontal cortex, results further supported by a mouse model in which high anxiety-related behavior was associated with a *Tmem132d* SNP and correlated with expression of *Tmem132d* mRNA in the anterior cingulate cortex (Erhardt *et al*, 2011). In a subsequent meta-analysis of eight independent case-control samples, genome-wide significant associations of rs7309727 and the haplotype of rs7309727-rs11060369 were reported when the analysis was restricted to European ancestry cases with primary PD (Erhardt *et al*, 2012). The function of this gene is not fully understood, but it has been suggested that it has a role in threat processing (Haaker *et al*, 2014).

Other anxiety disorder-related phenotypes. Fewer candidate gene studies and no GWAS have been reported for social anxiety disorder (SAD), phobic disorders, or GAD. Nominally significant associations with social anxiety or SAD have been reported for several candidate loci including *COMT* (Hettema *et al*, 2015), catenin- $\delta 2$ (*CTNND2*) (Nivard *et al*, 2014), and *CNTNAP2* (Stein *et al*, 2011) and several loci involved in circadian rhythm function (Sipila *et al*, 2010). Given the strong genetic correlations among anxiety disorders, several studies have examined broad phenotypes

including multiple anxiety disorders with nominal associations reported for glutamic acid decarboxylase 1 (*GAD1*) (Donner *et al*, 2012; Hettema *et al*, 2006a), *DRD2* (Sipila *et al*, 2010), *COMT*, *BDNF* (Enoch *et al*, 2008), and *PPARGC1A* (Hettema *et al*, 2011).

In addition to the genetic and phenotypic overlap among anxiety disorder phenotypes, the boundary between pathologic and subsyndromal anxiety is indistinct, consistent with the hypothesis that anxiety disorders represent more extreme variations of a continuously distributed set of traits. For the most part, studies of the genetics of anxiety related traits have focused on temperamental and personality traits associated with a liability to develop various anxiety disorders in children and adults, including behavioral inhibition (BI), neuroticism, introversion, and harm avoidance (Smoller *et al*, 2015). For example, BI, a stable temperamental tendency to be cautious and behaviorally restrained in novel social and non-social situations, is a familial and developmental risk factor for SAD and other anxiety disorders (McGrath *et al*, 2012). We found that genetic variants in *RGS2*, a gene implicated in mouse models of anxious temperament (Yalcin *et al*, 2004), are associated with BI in childhood, introversion in adults and amygdala and insular cortex activation in response to emotional faces, brain phenotypes implicated in liability to social and other anxiety disorders (Smoller *et al*, 2008b). The relevance of *RGS2* to pathologic anxiety is supported by several studies that have reported association to a variety of anxiety disorders, including GAD, PD, and PTSD (Amstadter *et al*, 2009; Hohoff *et al*, 2015; Koenen *et al*, 2009; Leygraf *et al*, 2006; Mouri *et al*, 2009; Otowa *et al*, 2011) as well as SSRI response in patients with SAD (Stein *et al*, 2014), although studies to date have been small and negative results have been reported (Hettema *et al*, 2015).

GWAS of anxiety-related traits have not yet established any genome-wide significant loci. Indeed, meta-analyses of up to 17 000 subjects have found no genome-wide significant associations for neuroticism or harm avoidance (de Moor *et al*, 2012; Service *et al*, 2012). A GWAS of phobic anxiety measured by the 8-item Crown-Crisp index in more than 11 000 health professionals also failed to identify significant associations (Walter *et al*, 2013). Estimates of h^2_{SNP} from aggregate genome-wide SNP data have been substantially lower than those reported in twin studies: 6% for neuroticism, 1–19% for anxiety-related behaviors as measured by the Anxiety-Related Behaviors Questionnaire, and 17% for phobic anxiety (Trzaskowski *et al*, 2013; Vinkhuyzen *et al*, 2012; Walter *et al*, 2013). These results suggest that common variants influencing these traits exist, but have very modest effects, consistent with the hypothesis that anxiety-related personality traits are highly polygenic and that environmental influences have a substantial role.

Rare and Structural Variation

Anxiety is a prominent feature of Williams syndrome, a neurodevelopmental disorder caused by a copy number

deletion of approximately 3 megabases on chromosome 7q. Individuals with Williams syndromes exhibit high rates of GAD and specific phobias (though not SAD), suggesting that one or more genes influencing non-social anxiety may reside in the deleted region (Leyfer *et al*, 2009). Similarly high rates of anxiety disorders (along with psychotic and mood disorders) are seen in individuals with 22q11.2 deletion syndrome (also known as DiGeorge or velocardiofacial syndrome) (Fung *et al*, 2010; Schneider *et al*, 2014; Zarchi *et al*, 2014). Few studies have examined the role of CNVs in more common, non-syndromic anxiety disorders, however. A study of PD in a Japanese sample (535 cases and 1520 controls) found no association of rare CNVs, but a statistical excess of common duplications in the 16p11.2 region (Kawamura *et al*, 2011).

Several neurodevelopmental genetic syndromes due to rare mutations have been reported to include prominent anxiety symptoms including Rett syndrome (due to mutations in *MECP2*) (Cianfaglione *et al*, 2015) and Fragile X syndrome (due to triplet repeat expansion of *FMR1*) in which social avoidance is particularly common (Wadell *et al*, 2013). Carriers of the *FMR1* premutation also have elevated rates of social and other anxiety disorder phenotypes (Boyle and Kaufmann, 2010).

As noted earlier, linkage analyses can detect rare mutations of large effect in affected pedigrees. Numerous linkage studies of anxiety disorders have been reported, though results have been inconsistent. A meta-analysis of anxiety disorder linkage studies comprising 162 families found modest, but not genome-wide significant, evidence of linkage at 24 different chromosomal regions (Webb *et al*, 2012). To date, efforts to identify rare SNVs associated with anxiety disorders by sequencing methods have been limited. Following the association of *TMEM132D* in GWAS analyses of PD, the gene was resequenced in 300 anxiety disorder cases (85% with a diagnosis of PD) and 300 healthy controls (Quast *et al*, 2012). An overrepresentation of putatively functional coding variants in controls was reported, suggesting that rare alleles in *TMEM132D* may have a protective effect. This finding awaits further replication and functional analyses.

Gene-Environment Interaction

Very few $G \times E$ studies have been reported for panic, phobic, or generalized anxiety disorders. These have been largely limited to the same candidate genes studied in main effect association analyses, with some nominally significant associations reported but conflicting results and inadequate power overall (Amstadter *et al*, 2010; Blaya *et al*, 2010; Choe *et al*, 2013; Laucht *et al*, 2009; Reinelt *et al*, 2014).

Summary

Anxiety disorders are familial and moderately heritable. To date, however, efforts to identify the specific DNA variations contributing to the heritability of these disorders have yet to

establish any unequivocal susceptibility loci. Genetic studies of anxiety face a number of obstacles. First, the line between normal and pathologic anxiety is often unclear, and the phenotypic and genetic boundaries between clinical anxiety syndromes are indistinct. Second, the discovery of anxiety-related genetic variants has been hampered by the relatively small sample sizes of existing studies and focus on a limited set of biological candidate genes. Like other psychiatric disorders, anxiety disorders are likely to be highly polygenic, involving thousands of genetic variants of modest effect. Identifying such variants may require genome-wide studies on a large scale. At the same time, genetic research on anxiety can make use of several resources that are less well developed for other psychiatric disorders. In particular, well-established experimental animal models capture key aspects of human anxiety and fear behavior, and neuroimaging studies have made substantial progress in mapping the structural and functional components of anxiety/fear circuitry (Smoller, 2011). These resources create opportunities for focusing genetic studies on relevant biological pathways as well as platforms for evaluating the functional significance of risk loci that may be identified in the future.

CROSS-PHENOTYPE GENETICS OF STRESS-RELATED DISORDERS

Family and twin studies have documented familial coaggregation and co-heritability of multiple psychiatric disorders (Smoller, 2013). Of relevance here, substantial familial and genetic overlap has been found between stress-related disorders and between these disorders and other psychiatric phenotypes (Figure 3). As noted earlier, family and twin studies have shown cross-disorder familial risk and high degrees of genetic correlation among the anxiety disorders, supporting the hypothesis that liability to these disorders involves a general anxiety diathesis (Hettema *et al*, 2005; Loken *et al*, 2014; Smoller *et al*, 2008a; Tambs *et al*, 2009b). In addition, offspring of parents with anxiety have a nearly three-fold increased odds of having depressive disorders compared with non-psychiatric control offspring (Micco *et al*, 2009). Conversely, first-degree relatives of individuals with MDD are at increased risk of BPD, ADHD, and anxiety disorders (Faraone and Biederman, 1997; Smoller, 2013; Smoller and Finn, 2003). Twin studies have shown that familial co-aggregation is largely due to heritable factors. For example, in twin samples, genetic variation underlying the risk of MDD and GAD overlaps completely (Kendler *et al*, 2007; Roy *et al*, 1995). Significant genetic correlations have also been reported between MDD and, respectively, PTSD (0.77–1.0), BPD (0.65), alcohol dependence (0.40–0.60), ADHD (0.67–0.77), and nicotine dependence (0.21), and neuroticism (0.43) (Cole *et al*, 2009; Edwards and Kendler, 2012; Kendler *et al*, 1993a; Kendler and Myers, 2010; Koenen *et al*, 2008, 2003; McGuffin *et al*, 2003; Sartor *et al*, 2012). Anxiety symptoms and ADHD symptoms also show

substantial genetic correlations (0.45–0.58) (Michellini *et al*, 2015). In addition, shared genetic factors have been found between MDD and non-psychiatric disorders including obesity and migraine headache (Afari *et al*, 2010; Ligthart *et al*, 2010; Schur *et al*, 2009).

Molecular genetic studies have recently extended the study of cross-disorder effects to the level of DNA variation. The phenomenon of pleiotropy—the association of one genetic locus to more than one phenotype—is widespread in many areas of medicine including autoimmune, metabolic, and cardiovascular diseases (Solovieff *et al*, 2013). In the realm of neuropsychiatric disorders, pleiotropic effects have been identified for common and rare SNVs and rare CNVs and other structural variants (Smoller, 2013). For example, a GWAS meta-analysis including more than 60 000 cases and controls identified several loci with genome-wide significant effects across five disorders: MDD, SCZ, BPD, ASD, and ADHD (Cross Disorder Group of the Psychiatric GWAS Consortium, 2013). In particular, genes involved in calcium channel signaling were associated with all five disorders. A subsequent analysis of SNP heritability found significant genetic correlations between MDD and SCZ (0.43), BPD (0.47), and ADHD (0.37), respectively, supporting prior evidence from family and twin studies (Cross-Disorder Group of the Psychiatric Genomics Consortium *et al*, 2013). PRS analyses have also documented common variant overlap between MDD and anxiety symptoms as well as neuroticism (Demirkan *et al*, 2011; Luciano *et al*, 2012; Middeldorp *et al*, 2011) and between PTSD and BPD (Nievergelt *et al*, 2015; Solovieff *et al*, 2014). In addition, pathway analyses by the PGC have revealed enrichment of multiple biological pathways across MDD, BPD, and SCZ (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015). In particular, pathways related histone methylation, synapse-related genes, and genes involved in immune and neurotrophic function exhibited shared enrichment across these disorders.

Cross-disorder effects of rare SNVs and structural variants have been well documented for neurodevelopmental disorders (especially ASD, SCZ, and intellectual disability) (Fromer *et al*, 2014; Smoller, 2013), but less so for stress-related disorders. Recurrent MDD is one of several psychiatric disorders (including psychotic disorders and ASD) linked to the balanced translocation between chromosomes 1 and 11 (1;11)(q42.1;q14.3) that disrupts *DISC1* (Blackwood *et al*, 2001). As noted earlier, CNVs have shown little evidence of association with stress-related disorders, although the 22q11.2 deletion may be variably expressed in a broad range of psychopathologies including depression and anxiety disorders (Squarcione *et al*, 2013).

While it is clear that genetic influences on stress-related and other disorders overlap to varying degrees, the biological basis of this overlap is largely unknown. Filling this gap may require investigation at multiple levels including characterization of pleiotropic allelic effects in model systems (cellular and animal models) and human clinical neuroscience (eg, neuroimaging and neurophysiology). Nevertheless,

several notable examples of such research are beginning to emerge. The pleiotropic effect of *FKBP5* variants on stress-related disorders—resulting from transcriptional and epigenetic effects on HPA axis dysregulation—has already been discussed. Another relevant example involves experimental animal model studies in which human genetic variation can be introduced, creating ‘humanized mice’. The functional val66met polymorphism of *BDNF* alters intracellular trafficking activity-dependent BDNF secretion and has been associated with a range of neuropsychiatric phenotypes including mood and anxiety disorders and PTSD, as well as brain structural variation (eg, hippocampal volume), although genetic association studies have had mixed results (see Notaras *et al*, 2015 for review). Casey *et al* (2013) have demonstrated that mice engineered to express the human Met allele exhibit a range of phenotypes relevant to stress-related disorders including increased anxiety-related behaviors and resistance to SSRI treatment. They further found that the Met allele is associated with impaired fear extinction in mice and humans and neuroimaging measures of amygdala-prefrontal cortical imbalance in humans.

Summary

Convergent evidence from genetic epidemiologic, molecular genetics, and neuroscience studies has demonstrated overlapping genetic influences on stress-related and other psychiatric disorders. These studies are beginning to highlight shared biological underpinnings that transcend diagnostic boundaries. They are also consistent with the rationale behind the Research Domain Criteria (RDOC) initiative whose goals are to develop ‘new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures’ by studying ‘basic dimensions of functioning...across multiple levels of analysis, from genes to neural circuits to behaviors, cutting across disorders as traditionally defined’ (Insel and Cuthbert, 2009). Genetic studies are essential to such a bottom-up approach and may facilitate the goal of an etiology-based nosology.

PROSPECTS FOR CLINICAL TRANSLATION

Although few specific genetic risk variants for stress-related disorders have been established, progress in this area may provide important opportunities for translation to clinical and public health applications. In particular, genetic discoveries may facilitate advances in therapeutics, risk prediction, and diagnostic classification.

Pharmacologic treatments for stress-related disorders are still based on serendipitous discoveries and biological insights that are half a century old. The discovery that a specific gene or set of genes confers risk for illness raises the possibility that drugs targeting that gene or pathway may have therapeutic effects. A principal advantage of unbiased genome-wide studies and pathway analyses is their capacity

Figure 3. Cross-disorder genetic relationships for stress-related disorders. (a) Genetic correlations derived from twin studies. (Chantarujikapong *et al*, 2001; Hettema *et al*, 2006b; Sartor *et al*, 2012). (b) Common variant overlap derived from GWAS (numbers represent genetic correlations, PRS: polygene risk score) (Cross-Disorder Group of the Psychiatric Genomics Consortium *et al*, 2013; Nievergelt *et al*, 2015; Solovieff *et al*, 2014). (c) Example loci with effects reported across multiple disorders (Cross Disorder Group of the Psychiatric GWAS Consortium, 2013; Green *et al*, 2013). ADHD, attention deficit/hyperactivity disorder; AG, agoraphobia; BPD, bipolar disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; PD, panic disorder; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder; SCZ, schizophrenia.

to identify novel targets for therapeutic development. For several complex disorders, including cardiovascular and autoimmune diseases, GWAS findings include known targets of effective drugs, providing a proof-of-concept that genetic discoveries have therapeutic relevance (Okada *et al*, 2014; Plenge *et al*, 2013). Notably, among the strongest associations emerging from SCZ GWAS are variants in *DRD2*, the target of all approved antipsychotic drugs. Nevertheless, some risk loci present more ‘drug-able’ targets than others. The most promising are risk variants that represent gain-of-function mutations and protective variants that cause loss-of-function effects (Flannick *et al*, 2014; Kathiresan, 2015). Inhibition of these gene products might be expected to be therapeutic. A prominent example are mutations in *PCSK9*, an enzyme involved in the degradation of LDL receptors. Loss-of-function variants in *PCSK9* are associated with reduced LDL cholesterol concentrations and risk of coronary disease, while rare gain-of-function mutations are associated with increased LDL and premature heart disease (Dadu and Ballantyne, 2014). In 2015, the first *PCSK9* inhibitors obtained FDA approval for the treatment of hypercholesterolemia. The translation of genetic findings to therapeutic strategies for stress-related disorders must await robust genetic associations—though as reviewed above, several loci (eg, *FKBP5*, *ADCYAP1R1*) and pathways (neurotrophic, opioidergic, and glucocorticoid receptor function) have been implicated in stress responses and fear behavior. Several of these findings converge on biological systems that may be responsive to therapeutic modulation (Andero and Ressler, 2012). However, even with validated genetic associations in hand, the road to therapeutic translation may be long and costly, beginning with functional studies (eg, in cellular or experimental animal models) needed for target validation (Smoller, 2014).

Apart from providing new molecular targets, genetic findings may also translate to improved therapeutic options by identifying new phenotypic targets: etiologically-based subgroups (eg, based on early age of onset, comorbidities, and other factors) that may be useful for matching patients to effective treatments (Smoller, 2014). Relatedly, pharmacogenetic approaches aim to identify genetic profiles that can be used to select the most effective and least toxic therapies for a given patient—a central goal of ‘precision medicine’. While validated genetic predictors of treatment response have been identified in other areas of medicine, none has yet been established for stress-related disorders (Smoller, 2014).

A second hope for translation of genetic findings is the prospect for early identification of risk and the development of primary or secondary prevention strategies. However, given the polygenicity and modest penetrance of most genetic risk variants, individual common variants will have insufficient predictive value to be clinically useful for risk prediction or diagnosis (Keyes *et al*, 2015). Multilocus predictors, including PRS that include thousands of common variants, can capture greater proportions of risk, but their clinical utility is likely to remain limited for common disorders (Chatterjee *et al*, 2013). However, PRS may be more useful in the epidemiologic context, functioning as a summary measure of genetic vulnerability in studies that may reveal environmental main or interaction effects. Such approaches could identify modifiable exposures that should be prioritized for prevention or intervention strategies, particularly among genetically at-risk individuals. Risk stratification for stress-related disorders may also be more feasible if rare, highly penetrant risk variants are discovered or with the development of integrative methods that can incorporate common and rare variants, other biomarkers and environmental risk factors.

Finally, as noted earlier, genetic findings may inform efforts, along the lines of the RDOC initiative, to move beyond a psychiatric nosology based on symptom-based, categorically-defined syndromes. We have seen that family, twin, and genomic studies have demonstrated substantial genetic correlations among stress-related and other disorders as well as with subsyndromal dimensions of symptoms and personality and neuroimaging phenotypes. Nevertheless, the project of creating a bottom-up, etiologically-based nosology may be a long, iterative process and is unlikely to supplant our syndromic approach for clinical purposes without a much more developed evidence base than is foreseeable in the near term. In addition, this effort will need to address several challenges along the way. For example, while many psychiatric phenotypes are more accurately modeled as quantitative dimensions, continuous with normal variation, adapting this to the needs of clinical decision making may be difficult. Moreover, the complexity and multiplicity of causes and phenotypes will continue to complicate nosologic boundaries.

CONCLUSIONS

Stress-related disorders, like other psychiatric disorders, are familial and heritable. However, efforts to identify the specific genetic variants underlying this heritability have thus far met with limited success. Throughout this review, I have highlighted several recurrent themes that have contributed to this state-of-the-science. These include an over-reliance on candidate gene studies, and the lack of sufficient power to detect the kind of modest main and $G \times E$ effects expected for complex phenotypes. In addition, the role of rare and structural variation remains largely unexplored, making it difficult to characterize the full allelic spectrum underlying disorder risk.

These conclusions immediately suggest directions for future research. First, candidate gene studies will be most informative when they have adequate power to detect small effect sizes and are supported by compelling, convergent biological evidence (such as that accumulated for *FKBP5*). Second, there is a need for the kind of large-scale unbiased genome-wide searches that have already proven successful for other psychiatric disorders including ASD, SCZ, and BPD. As noted earlier, genetic associations for depression, PTSD, and anxiety disorders may require even larger samples to achieve power comparable to that required for SCZ—on the order of tens of thousands of cases. Fortunately, analyses approaching this scale are now becoming feasible for MDD and PTSD through the PGC. Third, as GWAS establishes variants with significant main effects, environmental modifiers of these effects can be examined in $G \times E$ studies. In parallel, genome-wide $G \times E$ studies may reveal novel components of the stress–diathesis relationship.

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