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Genetics of Posttraumatic Stress Disorder: Review and Recommendations for Future Studies

Karestan C. Koenen
Departments of Society, Human Development, and Health and Epidemiology, Harvard School of Public Health and Department of Psychiatry, Boston University School of Medicine, Boston, MA

Posttraumatic stress disorder (PTSD) is common and debilitating. Posttraumatic stress disorder is moderately heritable; however, the role of genetic factors in PTSD etiology has been largely neglected by trauma researchers. The goal of this study is to motivate trauma researchers to reflect on the role genetic variation may play in vulnerability and resilience following trauma exposure. Evidence from family, twin, and molecular genetic studies for genetic influences on PTSD is reviewed. Recommendations for future studies are presented with emphasis on study design and assessment issues particular to the field of trauma and PTSD. Clinical implications of PTSD genetic studies are discussed.

"Genetics is too important to leave to the geneticists"

Plomin & Crabbe 2000 (p. 807)

Posttraumatic stress disorder (PTSD) occurs following exposure to a potentially traumatic life event and is defined by three symptom clusters: reexperiencing, avoidance and numbing, and arousal (American Psychiatric Association, 1994). The majority of Americans will be exposed to a traumatic event, although only a minority will develop PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Still, the disorder is common: At least 1 in 9 American women and 1 in 20 American men will meet criteria for the diagnosis in their lifetime (Kessler et al., 1995, 2005). The disorder is also debilitating: Individuals who develop PTSD have an increased risk of major depression, substance dependence, impaired role functioning, and reduced life course opportunities, including unemployment and marital instability, and health problems (Kessler, 2000). A key question in trauma research is why some individuals develop PTSD following exposure to potentially traumatic events when others appear to experience few negative effects. Genetic factors influence who is at risk for developing PTSD and, therefore, may provide part of the answer to this question.

However, the genetics of PTSD has been largely neglected by most trauma researchers. The result of this neglect is that little progress has been made in identifying variants in specific genes that influence risk of PTSD. This lack of progress is striking when compared to the major advances in other areas of PTSD research such as epidemiology, neuroscience, and treatment. My goal here is to motivate researchers in the field of trauma and PTSD to reflect on the role genetic variation may play in vulnerability and resilience following trauma exposure. My hope is that trauma researchers will consider how they might incorporate genetics into their ongoing and

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Correspondence concerning this article should be addressed to: Karestan C. Koenen, Department of Society, Human Development, and Health; Harvard School of Public Health, 677 Huntington Avenue, Kresge 613, Boston, MA 02115. E-mail: kkoenen@hsph.harvard.edu.

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future studies. Collaboration between nongeneticists with expertise in the phenotypes of trauma exposure and PTSD and geneticists is necessary to advance our knowledge of the genetics of PTSD. Such collaborations also have the potential to impact our understanding of PTSD etiology more broadly and to inform research on prevention and treatment.

EVIDENCE FOR GENETIC INFLUENCES ON RISK FOR POSTTRAUMATIC STRESS DISORDER

Evidence for genetic influences on PTSD comes from family, twin, and molecular genetic studies. If PTSD is genetic, family members of individuals with PTSD should have a higher prevalence of PTSD than do nonrelatives. Twin studies have examined the relative contribution of genetic and environmental influences on the variance in PTSD risk. Recently, candidate gene association studies have sought to identify specific genes that increase risk of having the disorder.

Posttraumatic Stress Disorder in Families

Only a few family studies have specifically examined whether the prevalence of PTSD is higher in relatives of individuals with PTSD (called *probands* in genetic studies) than in relatives of similarly trauma-exposed individuals who did not develop PTSD. The reason for the relative dearth of family studies of PTSD is that the disorder cannot be assessed in relatives who have not experienced a traumatic event. It is unknown whether these unexposed relatives would have been vulnerable to developing PTSD if they had been exposed.

The few existing family studies support an elevated risk of PTSD among relatives with the disorder. Cambodian refugee children whose mother and father both had PTSD were five times more likely to receive the diagnosis than refugee children whose parents did not have PTSD (Sack, Clarke, & Seeley, 1995). Similarly, parents of children who developed PTSD in response to a serious physical injury were more likely to develop PTSD themselves (Hall et al., 2005). Adult children of Holocaust survivors with PTSD had a higher risk of PTSD following trauma compared to adult children of Holocaust survivors without PTSD (Yehuda, Halligan, & Bierer, 2001). The results of these studies suggest vulnerability to developing PTSD runs in families. However, PTSD may run in families for genetic or environmental reasons. Family members are both more genetically similar to each other and share more environmental exposures than do nonrelatives.

Heritable Posttraumatic Stress Disorder

Twin studies are needed to disentangle the role of genetic and environmental factors in risk of developing PTSD. The twin design has been used to calculate the heritability of PTSD; heritability refers to the proportion of the variance in a trait or disorder explained by genetic factors. The basic twin method compares the degree of similarity within identical or monozygotic (MZ) pairs with the degree of similarity within fraternal or dizygotic (DZ) pairs. Monozygotic twins share 100% of their genes and 100% of the shared environment; DZ twins share on average 50% of their genes and 100% of the shared environment. If MZ twins are significantly more similar on a characteristic than are DZ twins, then this phenotype (observed characteristics) is interpreted as being genetically influenced. The heritability estimate is derived by $2(rMZ - rDZ)$, where r = the intraclass twin correlation (Plomin, DeFries, McClearn, & McGuffin, 2001). For categorical phenotypes, such as PTSD diagnosis, the tetrachoric correlation, which assumes an underlying normal distribution of liability, is used to calculate heritability.

Twin studies indicate that genetic influences account for about one third of the variance in PTSD risk (Stein, Jang, Taylor, Vernon, & Livesley, 2002; True et al., 1993). That is, PTSD is approximately 30% heritable, indicating that genetic factors are important in the disorders' etiology. However, twin studies are limited in that they cannot tell us which genes are important in PTSD etiology. Molecular genetic studies are needed to accomplish this aim.

MOLECULAR GENETIC STUDIES OF POSTTRAUMATIC STRESS DISORDER

Human beings are over 99% genetically identical. Research aimed at identifying genes that explain individual differences in risk for PTSD focuses on the tiny fraction (1%) of the DNA sequences that differs among individuals. Almost 90% of human genetic variation is made up of single nucleotide polymorphisms (SNPs, pronounced "snips"), which occur when a single nucleotide (A, T, C or G) in the DNA sequence is altered. An example of a SNP is a change in the DNA sequence from CGTTGG to CGATGG. By definition, the frequency of SNPs must be at least 1% of the population. There are approximately 3 million SNPs in the human genome. Although other types of polymorphisms in the human genome exist, SNPs are most commonly used in molecular genetic studies. Readers interested in learning more about SNPs are encouraged to obtain the SNP Fact Sheet from the Human Genome Project Web site (http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml).

Molecular genetic studies of PTSD have used the case-control candidate gene-association design. The association method detects genes with small effects on risk and has been, until recently, the method of choice for molecular genetic studies of complex disorders (Risch & Merikangas, 1996). Disorders are referred to as *complex* when their etiology is thought to involve a combination of many genes and environmental factors as is the case in PTSD. Association studies correlate a DNA marker's alleles, which are different sequences (SNP) of DNA at a specific position (or locus) on the chromosome, with an outcome. Figure 1 presents a very simple example of the case-control association design. For this hypothetical example, the investigator is interested in whether variation in a specific SNP on a gene thought to be involved in PTSD etiology is associated with PTSD. The investigator tests whether the A allele is more common among PTSD cases. If it is, as is the case in this example, further studies will be done to determine if this SNP is causally implicated in PTSD etiology (called the *causal variant*).

Candidate Genes Influencing PTSD Expression

Given the vast amount of genetic variation (≈25,000 genes; 3 million SNPs), how do investigators choose which genes to study? The choice of candidate genes also raises one of the most important limitations of the candidate gene association design, i.e., the low prior probability of selecting candidate genes that will be associated with the disorder being studied. The challenge of selecting strong candidate genes is one of the motivating factors behind the development of whole genome association studies (WGAS). Rather than hypothesizing genetic association for a specific candidate gene, such studies take an agnostic approach and compare the entire genomes of cases to controls. For more information on WGAS studies, the reader is referred to information on the National Human Genome Research Institute Web site (http://www.genome.gov/17516714),

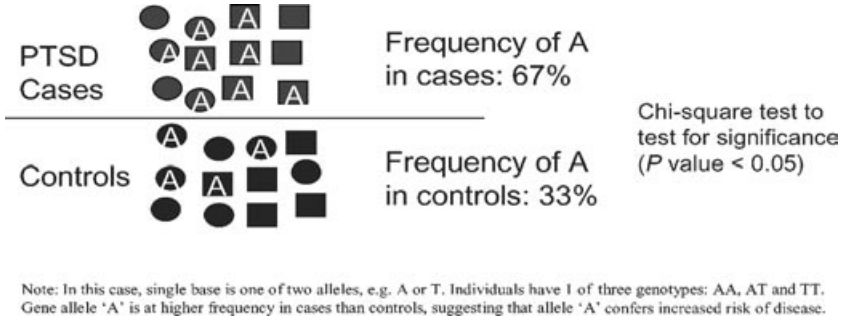

Figure 1. Hypothetical example of posttraumatic stress disorder case control candidate gene-association study involving a single nucleotide polymorphism.

and the excellent review by Hirschhorn and Daly on the promise and challenges of this approach (Hirschhorn & Daly, 2005). As of this writing, no WGAS studies of PTSD have been published.

Despite its limitations, the case control candidate gene association design is still the most widely used method to detect genes associated with vulnerability to PTSD and the most feasible design available to most trauma researchers. Our current understanding of the neurobiology of the disorder drives the selection of candidate genes. Due to space limitations, I will not review PTSD neurobiology here, but reference recent reviews published on this topic (Charney, 2004; Rasmusson, Vythilingam, & Morgan, 2003; Rauch, Shin, & Phelps, 2006). These reviews suggest genes involved in the (a) regulation of the hypothalamic–pituitary–adrenal axis; (b) locus coeruleus/noradrenergic system, and (c) limbic–frontal brain systems, particularly those involved in fear conditioning; might be good candidates for PTSD. Functional polymorphisms or genetic variants that have been shown to impact neurobiological pathways implicated in PTSD are particularly strong candidates. Genes that show different expression profiles in trauma-exposed individuals who do and do not develop PTSD are also good candidates (Segman et al., 2005). For further guidelines on candidate gene selection, the reader is referred to Moffitt et al.'s review of gene-environment interaction in psychiatric disorders (Moffitt, Caspi, & Rutter, 2005). An excellent introduction to the methodological issues in candidate gene association designs in psychiatry is given by Sullivan, Eaves, Kendler, and Neale (2001).

Our genetic code is very similar to that of other mammals; hence, animal studies often suggest potential candidates for human genetic studies. For example, the central role of the lateral nucleus of the amygdala in fear conditioning has been well established by animal models (Davis, Walker, & Myers, 2003). Both the GRP gene, which encodes gastrin-releasing peptide, and stathmin (STMN1), which inhibits microtubule formation, are highly expressed in the amygdala's lateral nucleus and appear to be required for the regulation of fear conditioning in the mouse (Shumyatsky et al., 2002, 2005). Given that enhanced fear conditioning is one of the major neurobiological models for PTSD and that the amygdala is central to this model, GRP and STMN1 are candidate genes for PTSD. Table 1 presents some examples of genes that are posited to be associated with risk of PTSD based on current understanding of the neurobiology of the disorder. Readers interested in learning more about these genes are encouraged to go to the NCBI Online Mendelian Inheritance in Man (OMIM) Web site (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=omim). By using the symbols in Table 1 to search on the OMIM Web site, you can obtain a summary of current research on these genes.

Table 2 summarizes the 10 candidate gene studies of PTSD published to date. Five studies focused on dopamine system genes; four of these examined the association between marker alleles at the D2 dopamine receptor gene (DRD2) and PTSD. The results were conflicting. The first two studies found a positive association with the DRD2A1 allele (Comings et al., 1991; Comings, Muhleman, & Gysin, 1996). The third study found no association with the DRD2A1 allele or with any combination of alleles for the DRD2 locus (Gelernter et al., 1999). The fourth study found a positive association between DRD2A1 and PTSD only in the subset of PTSD cases who engaged in harmful drinking (Young et al., 2002). The final study found a positive association between the dopamine transporter SLC6A3 (DAT1) 3′ polymorphism and chronic PTSD (Segman et al., 2002).

The five remaining studies focused on genes in several other neurobiological pathways. A study of an insertion/deletion polymorphism in the promoter region of the serotonin transporter (SLC6A4) found an excess of s/s genotypes in Korean PTSD patients compared with normal controls (Lee et al., 2005). Kilpatrick et al. (2007) found a significant association between the s/s genotype and PTSD in a sample of hurricane-exposed adults. The s/s genotype was associated with PTSD among those with high hurricane exposure and low social support but not among those with low hurricane exposure and/or high social support (Kilpatrick et al., 2007). No significant association was found between either the Leu7Pro polymorphism in the

Table 1. Examples of Candidate Genes for Posttraumatic Stress Disorder by Neurobiological System

Neurobiological system	Gene name	Gene symbol (Alternate)
HPA axis		
	Glucocorticoid receptor	GCCR
	FK binding protein 5	FKBP5
	Corticotropin-releasing hormone	CRH
	Corticotropin-releasing hormone receptor 1	CRHR1
	Corticotropin-releasing hormone receptor 2	CRHR2
	Corticotropin-releasing hormone binding-protein	CRH-BP
Locus coeruleus/noradrenergic system		
	Noradrenaline transporter	SLC6A2 (NET1)
	Dopamine beta-hydroxylase	DBH
	Catechol-o-methyltransferase	COMT
	Neuropeptide Y	NPY
	Alpha-2C-adrenergic receptor	ADRA2C
Limbic–frontal brain systems		
	Brain-derived neurotrophic factor	BDNF
	Gastrin-releasing peptide receptor	GRP
	Stathmin 1	STMN1
	Dopamine transporter	SLC6A3 (DAT1)
	Dopamine receptor D2	DRD2
	Serotonin transporter	SLC6A4 (5HTTLPR)

neuropeptide Y (NPY) gene (Lappalainen et al., 2002) or polymorphisms in the brain derived neurotrophic factor (BDNF) gene (Zhang et al., 2006) and chronic PTSD. A study of Vietnam war veterans also found no excess of either of two glucocorticoid receptor polymorphisms (N363S and BclI) in PTSD patients (Bachmann et al., 2005).

RECOMMENDATIONS FOR FUTURE CASE-CONTROL CANDIDATE GENES STUDIES

As is apparent from Table 2, our understanding of the genetics of PTSD is still in the early stages. Collaborations between researchers with expertise in the phenotypes of trauma exposure and PTSD and geneticists are needed to move this understanding forward. This section presents recommendations for future PTSD genetic studies. The role of nongeneticist trauma researchers is central to these recommendations, which emphasize the importance of strong study designs and gold-standard assessments of trauma exposure and PTSD.

Power

The statistical power of a candidate gene-association study refers to the probability of detecting a true genetic effect. Power in a genetic study is determined by factors similar to those that influence power in any research design: significance level, sample size, prevalence of the risk factor (e.g., risk genotype) in controls, and the effect size conferred by the risk factor (e.g., risk genotype; see Sullivan et al., 2001) for further discussion of power issues in candidate gene association studies. Several of the PTSD association studies cited in Table 2 had small sample sizes and therefore low power to detect a reasonable effect sizes making their negative results difficult to interpret.

Generalizability

Generalizability or external validity refers to the degree to which inferences made from a specific study can be extended to other people, times, and places. As is evident from Table 2, 6 of the 10 published PTSD candidate gene

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Table 2. Review of Published Case-Control Candidate Gene Associations Studies of Posttraumatic Stress Disorder

First author	Year	Cases *N* (% Male)	Controls *N* (% Male)	Nationality/Race or Ethnicity	Case ascertainment	Chronic PTSD?
Comings	1991	35 (100)	314 (100)	United States/Non-Hispanic White	NNRB/ VA Clinic	Yes
Comings	1996	24 (100)	9 (100)	United States/Non-Hispanic White	VA Clinic	Yes
	1996	13 (100)	11 (100)	United States/Non-Hispanic White	VA Clinic	Yes
Gelernter	1999	52 (100)	87 (100)	United States/Non-Hispanic White	VA Clinic	Yes
Lappalainen	2002	77 (100)	202 (100)	United States/Non-Hispanic White	VA Clinic	Yes
Segman	2002	102 (56)	104 (47)	Israel/Ashkenazi & Non-Ashkenazi Jews	PTSD Research Studies/Mental Health Clinics	Yes
Young	2002	91 (100)	53 (100)	Australia/Non-Hispanic White	Inpatient Unit	Yes
Bachman	2005	118 (100)	42 (100)	Australia/Non-Hispanic White	PTSD Clinic	Yes
Lee	2005	100 (43)	197 (39)	Korea/ Korean	Mental Health Clinics	Yes
Zhang	2006	96 (76)	250 (41)	United States/Non-Hispanic White	VA Clinic	Yes
Kilpatrick	2007	19 (32)	570 (37)	United States/Various	Epidemiologic sample of hurricane exposed adults	No

Review of Published Case-Control Candidate Gene Associations Studies of Posttraumatic Stress Disorder

First author	Year	Trauma Exposed Controls?	Trauma Type	Gene Name (Symbol)	Finding
Comings	1991	No	Combat	Dopamine Receptor D2 (DRD2)	Excess D2A1 allele in PTSD cases $p = .007$
Comings	1996	Yes	Combat	Dopamine Receptor D2 (DRD2)	Excess D2A1 allele in PTSD cases $p = .041$
	1996	Yes	Combat	Dopamine Receptor D2 (DRD2)	Excess D2A1 allele in PTSD cases $p = .002$
Gelernter	1999	No	Combat	Dopamine Receptor D2 (DRD2)	No significant association between D2A1 allele/DRD2 haplotypes and PTSD
Lappalainen	2002	No	Combat	Neuropeptide Y (NPY)	No significant association between Leu7Pro polymorphism and PTSD
Segman	2002	Yes	Various	Dopamine Transporter (DAT1)	Excess 9-repeat allele in PTSD cases $p = .012$

Continued

Table 2. *Continued*

Young	2002	No	Combat	Dopamine Receptor D2 (DRD2)	Excess D2A1 allele only in PTSD cases with harmful drinking $p < .001$
Bachman	2005	Yes	Combat	Glococorticoid Receptor (GCCR)	No significant association between GCCR polymorphisms and PTSD
Lee	2005	No	Various	Serotonin Transporter (SLC6A4)	Excess s allele in PTSD cases $p = .04$
Zhang	2006	Not specified	Not specified	Brain derived neurotrophic factor (BDNF)	No significant association between three BDNF variants and PTSD
Kilpatrick	Under review	Yes	Hurricane	Serotonin Transporter (SLC6A4)	Significant association between s/s genotype and PTSD in adults with high hurricane exposure and low social support

Note. PTSD = posttraumatic stress disorder; NNRB: National Neurological Research Bank, Los Angeles, CA; VA = Veterans Affairs; D2DA1 = Al one allele of DRD2 gene's allele = short version (vs. long) of the serotonin transporter promoter polymorphism.

studies are on exclusively male samples, specifically non-Hispanic White combat veterans recruited from clinics. Clearly, genetic studies of PTSD need to include women, other race/ethnic and age groups, and participants exposed to different types of trauma. However, to be truly generalizable, PTSD genetic studies need to be conducted on epidemiologic samples. The feasibility of incorporating genetics into epidemiologic studies of trauma and PTSD has recently been demonstrated by Acierno and colleagues who collected buccal (cheek cell) DNA samples via mail on a samples of older adults exposed to the 2004 Florida hurricanes (Acierno et al., in press; Galea, Acierno, Ruggiero, Resnick, & Kilpatrick, 2006; Kilpatrick et al., 2007). Collecting, extracting, and storing buccal cell DNA is inexpensive, usually less than $15 a sample (Freeman et al., 1996). The low costs and noninvasiveness of buccal DNA collection means it is now feasible to obtain DNA from epidemiologic samples and store it until funds are available for genotyping.

Population Stratification

The term population stratification is used by geneticists to refer to differences in allele frequencies between cases and controls that occur due to systematic differences in ancestry rather than due to a causal association of genes with disease (Freedman et al., 2004). Population stratification will likely produce a false-positive association between variation in a gene and a disorder if (a) cases and controls differ in racial/ethnic background, (b) racial/ethnic background is associated with differences in allele frequencies, (c) racial/ethnic background is associated with risk for a disorder. The studies in Table 2 addressed the issue of population stratification by matching cases and controls on self-reported race or ethnic background. Although matching on self-reported race/ethnicity is appropriate and reduces risk of population stratification, more sophisticated empirical methods are now available to address this issue. These methods involve genotyping a set of ancestry-informative markers (AIMS) and using them to estimate ancestral proportions by Bayesian cluster analysis implemented in programs such as

Structure (Pritchard, Stephens, & Donnelly, 2000; Pritchard, Stephens, Rosenberg, & Donnelly, 2000). Gelernter and colleagues have published on a set of AIMS shown to be sufficient in distinguishing ancestry of in an American sample accurately (Yang, Zhao, Kranzler, & Gelernter, 2005a, 2005b).

The family-based candidate gene-association design is also used to address the issue of population stratification. In family-based designs, family members serve as controls for each other. Because biological family members have the same ancestral background, these approaches avoid the problem of population stratification. The two most commonly used family-based designs are the discordant sibling–pair design, where one sibling has the disorder (case) and the other does not (control), and the trio design, whereby DNA is collected from both the proband (case) and the proband's parents. For the trio design, the family-based transmission disequilibrium test (TDT) is used to test for genetic association. Because the affected children (probands) must have received susceptibility alleles from their parents, the alleles transmitted from parents to affected children can be viewed as "case" alleles. The nontransmitted alleles are control alleles. The analysis tests whether the case alleles are transmitted with a frequency that would be greater than expected by chance (Spielman & Ewens, 1996). At this writing, no family-based association studies of PTSD have been published.

Family-based designs have traditionally been viewed as unfeasible in PTSD genetics research. However, our group is currently conducting a family-based candidate gene-association study of PTSD in physically injured children (Saxe et al., 2005). Trauma researchers who study children may wish to consider family-based designs because child research requires parental participation and siblings are often available as well. Such designs may also be feasible in scenarios where family members have shared the same trauma exposure such as a natural disaster.

Control Selection

One of the biggest challenges to PTSD candidate gene studies is appropriate control selection. According to epidemiologic principles (Rothman, 2002), controls should be selected from the same underlying population as the cases, representative of all controls with regard to exposure, and identical to the exposed cases except for the risk factor (in this case the genetic variant) under investigation. One practical implication of this last principle, referred to as *exchangeability* between cases and controls, is that controls must be similar to cases in severity of trauma exposure; several PTSD candidate gene studies do not report assessing trauma exposure in controls (Table 2). Violation of the exchangeability principle increases the likelihood that positive associations may be biased due to confounding factors and, in addition to the small sample sizes used in many studies, makes negative associations difficult to interpret.

Two types of study designs commonly used in trauma and PTSD research can facilitate appropriate control selection. The first is the standard epidemiologic study design where a random sample is drawn from an underlying population and assessed for trauma exposure and PTSD. This design was used by Acierno and colleagues in their study of older adults living in Florida counties affected by the 2004 hurricanes (Acierno et al., in press; Kilpatrick et al., 2007). Cases are then individuals in the sample who were diagnosed with PTSD; controls are individuals from the same underlying population exposed to similar traumas, who did not develop PTSD. Although this is one of the most feasible designs for trauma researchers, its limitations include inherently lower reliability in assessing trauma exposure and PTSD retrospectively. Lower measurement reliability will reduce power (Wong, Day, Luan, Chan, & Wareham, 2003).

The second design is the prospective exposed cohort design commonly used to study individuals who are seen in the emergency room following a physical injury (e.g., car accident). In this design, individuals are enrolled in a study upon exposure to a traumatic event and followed over time to see who develops PTSD (cases) and who does not (controls). Cases and controls are therefore acquired from the same underlying population. Some of the strengths of this design include prospective assessments of PTSD and the enhanced feasibility of collecting DNA samples from

participants in the hospital. However, such designs also have limitations in terms of generalizability and projected sample size as compared to retrospective epidemiologic studies.

Case Definition

The PTSD candidate gene-association studies presented in Table 2 have included only cases with current PTSD, where current PTSD involves chronic disorder extending over many years or even decades. When considering disorder etiology, it is useful to distinguish between risk factors for onset or development of the disorder and risk factors for course or chronicity of the disorder. Factors that influence who develops the disorder in the first place may differ from those that influence who recovers from the disorder once it develops. For example, members of disadvantaged ethnic groups are not at higher risk for the development of psychiatric disorders. However, once they develop a psychiatric disorder, their disorders are more chronic than those of non-Hispanic Whites (Breslau, Kendler, Su, Gaxiola-Aguilar, & Kessler, 2005).

Twin studies have relied almost exclusively on diagnoses of lifetime PTSD and, therefore, heritability estimates from such studies explain the proportion of variation in risk for developing PTSD explained by genetic factors. It is not known whether genetic factors explain as much of the variance in chronicity of PTSD or whether the same genes that influence risk for developing PTSD affect PTSD chronicity. Studies are needed that distinguish between genetic influences on risk for developing PTSD versus persistence of the disorder. Both epidemiologic studies that assess lifetime PTSD and prospective exposed-cohort designs where individuals are followed over an adequate time period can be used for this purpose.

Posttraumatic Stress Disorder Comorbidity

Posttraumatic stress disorder is highly comorbid with other psychiatric disorders (Kessler et al., 1995). Much of this comorbidity can be explained by a common genetic diathesis. For example, genetic influences on major depression account for the majority of the genetic variance in PTSD (Koenen et al., 2007). A common genetic diathesis between major depression in PTSD is supported by molecular genetic studies as well. The serotonin transporter promoter s/s polymorphism is implicated in both disorders (Caspi et al., 2003; Lee et al., 2005). Polymorphisms in FKBP5, a glucocorticoid-regulating co-chaperone of stress proteins, which were associated with recurrence of major depressive episodes and response to antidepressant treatment (Binder et al., 2004) have also been associated with peritraumatic dissociation, a risk factor for PTSD, in medically injured children (Koenen, Saxe et al., 2005). Genetic influences common to generalized anxiety disorder and panic disorder symptoms account for approximately 60% (Chantarujikapong et al., 2001) and those common to alcohol and drug dependence (Xian et al., 2000) and nicotine dependence (Koenen, Hitsman, et al., 2005) account for over 40% of the genetic variance in PTSD.

Thus, the limited data available suggest that the same genes involved in other psychiatric disorders, particularly major depression and other anxiety disorders, may influence the risk for PTSD. This has an important implication for PTSD candidate gene studies: The presence of other psychiatric disorders in trauma-exposed controls likely increases the genetic variance shared by cases and controls and attenuates the possibility of finding a positive PTSD-gene association. Psychiatric comorbidity, therefore, needs to be carefully assessed in both cases and controls in PTSD genetic studies. Future genetic studies may benefit from identifying coherent patterns of PTSD comorbidity, such as those proposed by Miller and colleagues in their work on developing a personality-based typology of posttraumatic response (Miller, Kaloupek, Dillon, & Keane, 2004). Using cluster-analyses based on personality assessments, Miller et al. has shown that PTSD comorbidity coheres along the dimensions of externalization and internalization, parallel to those found by Krueger (1999) for comorbidity among common mental disorders. Our ability to find genes for PTSD might improve if PTSD internalizing/externalizing subtypes are considered.

Haplotype Blocks

Almost all of the studies presented in Table 2 have examined the association between a single polymorphism in a gene and PTSD. The limitation of such studies is that the finding of no significant association between that polymorphism and PTSD does not provide strong evidence against that gene playing a role in PTSD etiology. With the publication of the human haplotype map (HapMap), it is now increasingly feasible to assay the majority of common variation in a gene (Altshuler et al., 2005; Daly, Rioux, Schaffner, Hudson, & Lander, 2001; Gabriel et al., 2002). The term *haplotype* is a contraction of the term *haploid genotype* and refers to portions of the genome that contain a set of closely linked alleles (spanning one or many genes) that are inherited as a unit. The tendency of alleles located close to each other on the same chromosome to be inherited together is referred to as *linkage disequilibrium*. The existence of haplotypes means that investigators interested in capturing all common variation in a gene do not have to genotype all the SNPs in the gene. Rather, because blocks of the genome are inherited together, some SNPs will provide redundant information. Thus, a small (er) number of "tagging" SNPs can capture most of the common variation in a gene. Once an investigator has isolated an association signal to, say, a certain haplotype in a particular gene, there are statistical methods that can identify if one or more SNPs are more likely than others to be causally associated.

Table 3 presents the number of tagging SNPs needed to cover common variation in a selection of candidate genes for PTSD. Information in Table 3 was obtained using HAPLOVIEW (Barrett, Fry, Maller, & Daly, 2005; de Bakker et al., 2005). For example, the FKBP5 gene spans just over 115 kb and contains 24 common SNPs in the most recent version of the HapMap. By selecting tag SNPs, based on the linkage disequilibrium profile across this gene in Caucasians, only five SNPs are needed to assay the common genetic variation with a high level of accuracy. In total, six tests are specified to cover all haplotypes. An investigator interested in whether variation in the FKBP5 gene is associated with PTSD can conduct 6 rather than 24 tests. If no association is found (assuming power to detect a reasonable effect size), the investigator has performed a stronger test of whether variation in the FKBP5 gene is associated with PTSD than would be provided in a single polymorphism analysis.

Gene-Gene and Gene-Environment Interaction

Growing evidence supports the role of gene–gene (Schulze et al., 2004) and gene–environment interaction (Moffitt et al., 2005) in psychiatric disorders. Recent studies of significant interactions between variation in the serotonin transporter gene (SCL6A4) and life events in predicting major depression (Caspi et al., 2003) and variation in the monamine oxidase A gene and child maltreatment in predicting antisocial behavior in men (Caspi et al., 2002) are particularly relevant to PTSD. The effect size of a genetic variant on risk for developing PTSD may be conditional on the presence of other genetic variants or on the timing, type, or severity of trauma exposure. Except for the study by Kilpatrick et al. (2007), these possibilities have not been examined in genetic studies of PTSD. Such studies require samples where lifetime trauma exposure is well-characterized.

CLINICAL IMPLICATIONS OF PTSD GENETIC STUDIES

The identification of genetic variants that mediate susceptibility to PTSD has the potential to improve our understanding of why some individuals are particularly vulnerable to the negative long-term consequences of traumatic events. This understanding has the potential to inform the development and targeting of acute pharmacological interventions. There is growing interest in such interventions to prevent the development of PTSD (Pitman & Delahanty, 2005). The potential public health impact of such low-risk and effective pharmacological interventions could be profound. If proved safe and effective, they could be administered to large numbers of people in mass trauma situations (e.g., natural disasters) as a primary prevention strategy. Research on the genetics of PTSD is also beginning to

Table 3. Number of Tagging Single Nucleotide Polymorphisms (SNPs) Needed to Cover Common Variation in Selection of Candidate Genes for Posttraumatic Stress Disorder

Gene	Position	Size kb	#SNPs	# Tag	# tests	Avg R^2
HPA axis dysregulation						
FKBP5	6p21.3-p21.2	115.3	24	5	6	.94
GCCR	5q31	125.7-157.5	57	13	15	.96
CRH-R1	17q12-q22	51.5	21	4	5	.97
CRH-R2	7p21-p15	29.7	14	8	8	.98
CRH-BP	5q11.2-q133	16.6	6	3	3	.95
Locus coeruleus/noradrenergic system						
SLC6A2 (NET1)	16q12.2	47.2	45	12	16	.96
DBH	9q34	22.9	24	10	13	.97
COMT	22q11.21-q11.23	27.2	13	9	10	.98
NPY	7p15.1	7.6	12	4	4	.97
Limbic–frontal brain systems						
BDNF	11p13	66.8	25	3	4	.91
SLC6A3 (DAT1)	5p15.3	52.6	28	12	16	.98
DRD2	11q23	65.5	44	7	8	.98
GRP	18q21	10.6	4	2	2	.90
SLC6A4 (5HTTLPR)	17q11.1-q12	37.8	14	2	3	.90

Note. #SNPs = number of SNPS with major allele frequency > 0.15 in HapMap Caucasians; # tag SNPs = # of SNPs to be genotyped; # tests including multimarker tests; Avg R^2 (common variation explained) = average maximum R^2 between genotyped and untyped SNPs.

address issues of treatment response (Lawford et al., 2003). About 30–50% of PTSD patients do not respond well to sertraline and paroxetine, the only medications currently approved by the Food and Drug Administration (FDA) to treat PTSD (Marshall, Beebe, Oldham, & Zaninelli, 2001; Marshall & Pierce, 2000). Genetic studies have informed the development of more efficacious pharmacological treatments in other disorders and have the potential to do so in PTSD. However, more collaboration between PTSD treatment researchers and geneticists is required for patients to benefit from advances in our knowledge of the genetics of PTSD.

REFERENCES

Acierno, R., Ruggiero, K. J., Galea, S., Resnick, H. S., Koenen, K. C., Rotizsch, J., de Arellano, M., Boyle, J., Kilpatrick, D. G. (2007). Psychological sequelae of the 2004 Florida hurricanes: Implications for post-disaster intervention. American Journal of Public Health, 97 (Suppl. 1), S103-108.

Altshuler, D., Brooks, L. D., Chakravarti, A., Collins, F. S., Daly, M. J., & Donnelly, P. (2005). A haplotype map of the human genome. Nature, 437, 1299–1320.

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: Author.

Bachmann, A. W., Sedgley, T. L., Jackson, R. V., Gibson, J. N., Young, R. M., & Torpy, D. J. (2005). Glucocorticoid receptor polymorphisms and post-traumatic stress disorder. Psychoneuroendocrinology, 30, 297–306.

Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: Analysis and visualization of LD and haplotype maps. Bioinformatics, 21, 263–265.

Binder, E. B., Salyakina, D., Lichtner, P., Wochnik, G. M., Ising, M., Putz, B., et al. (2004). Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nature Genetics, 36, 1319–1325.

Breslau, J., Kendler, K. S., Su, M., Gaxiola-Aguilar, S., & Kessler, R. C. (2005). Lifetime risk and persistence of psychiatric disorders across ethnic groups in the United States. Psychological Medicine, 35, 317–327.

Caspi, A., McClay, J., Moffit, T. E., Mill, J., Martin, J., Craig, I., et al. (2002). Role of genotype in the cycle of violence in maltreated children. Science, 297, 851–854.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I., Harrington, H., et al. (2003). Influence of life stress on

depression: Moderation by a polymorphism in the 5- HTT gene. Science, 301, 386–389.

Chantarujikapong, S. I., Scherrer, J. F., Xian, H., Eisen, S. A., Lyons, M. J., Goldberg, J., et al. (2001). A twin study of generalized anxiety disorder symptoms, panic disorder symptoms and posttraumatic stress disorder in men. Psychiatry Research, 103, 133–145.

Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. American Journal of Psychiatry, 161, 195–216.

Comings, D. E., Comings, B. G., Muhleman, D., Dietz, G., Shahbahrami, B., Tast, D., et al. (1991). The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. Journal of the American Medical Association, 266, 1793–1800.

Comings, D. E., Muhleman, D., & Gysin, R. (1996). Dopamine D2 receptor (DRD2) gene and susceptibility to posttraumatic stress disorder: A study and replication. Biological Psychiatry, 40, 368–372.

Daly, M. J., Rioux, J. D., Schaffner, S. F., Hudson, T. J., & Lander, E. S. (2001). High-resolution haplotype structure in the human genome. Nature Genetics, 29, 229–232.

Davis, M., Walker, D. L., & Myers, K. M. (2003). Role of the amygdala in fear extinction measured with potentiated startle. Annals of the New York Academy of Sciences, 985, 218–232.

de Bakker, P. I., Yelensky, R., Pe'er, I., Gabriel, S. B., Daly, M. J., & Altshuler, D. (2005). Efficiency and power in genetic association studies. Nature Genetics, 37, 1217–1223.

Freedman, M. L., Reich, D., Penney, K. L., McDonald, G. J., Mignault, A. A., Patterson, N., et al. (2004). Assessing the impact of population stratification on genetic association studies. Nature Genetics, 36, 388–393.

Freeman, B., Powell, J., Ball, D., Hill, L., Craig, I., & Plomin, R. (1996). DNA by mail: An inexpensive and noninvasive method for collecting DNA samples from widely dispersed populations. Behavior Genetics, 27, 251–257.

Gabriel, S. B., Schaffner, S. F., Nguyen, H., Moore, J. M., Roy, J., Blumenstiel, B., et al. (2002). The structure of haplotype blocks in the human genome. Science, 296, 2225–2229.

Galea, S., Acierno, R., Ruggiero, K. J., Resnick, H. S., & Kilpatrick, D. G. (2006). Social context and the psychobiology of trauma. Annals of the New York Academy of Sciences, 1071, 231–241.

Gelernter, J., Southwick, S., Goodson, S., Morgan, A., Nagy, L., & Charney, D. S. (1999). No association between D2 dopamine receptor (DRD2) 'A' system alleles, or DRD2 haplotypes, and posttraumatic stress disorder. Biological Psychiatry, 45, 620–625.

Hall, E., Saxe, G., Stoddard, F., Kaplow, J., Koenen, K., Chawla, N., et al. (2006). Posttraumatic stress symptoms in parents of children with acute burns. Journal of Pediatric Psychology, 31, 403–412.

Hirschhorn, J. N., & Daly, M. J. (2005). Genome-wide association studies for common diseases and complex traits. Nature Reviews Genetics, 6, 95–108.

Kessler, R. C. (2000). Posttraumatic stress disorder: The burden to the individual and to society. Journal of Clinical Psychiatry, 61, 4–12.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry, 62, 593–602.

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. Archives of General Psychiatry, 52, 1048–1060.

Kilpatrick, D. G., Koenen, K. C., Ruggiero, K. J., Acierno, R., Galea, S., Resnick, H. S., Roitzsch, J., Boyle, J., Gelernter, J. (2007). Do the serotonin transporter genotype and social support moderate posttraumatic stress disorder and depression in hurricane-exposed adults? American Journal of Psychiatry: (in press).

Koenen, K. C., Fu, Q., Ertel, K., Lyons, M. J., Goldberg, J., Eisen, S. A., True, W., Tsuang, M. T. (2007). Common genetic liability for major depression and posttraumatic stress disorder in men. Journal of Affect Disorder: (in press).

Koenen, K. C., Hitsman, B., Lyons, M. J., Niaura, R., McCaffery, J., Goldberg, J., et al. (2005). A twin registry study of the relationship between posttraumatic stress disorder and nicotine dependence in men. Archives of General Psychiatry, 62, 1258–1265.

Koenen, K. C., Saxe, G., Purcell, S., Smoller, J. W., Bartholomew, D., Miller, A., et al. (2005). Polymorphisms in FKBP5 are associated with peritraumatic dissociation in medically injured children. Molecular Psychiatry, 10, 1058–1059.

Krueger, R. F. (1999). The structure of common mental disorders. Archives of General Psychiatry, 56, 921–926.

Lappalainen, J., Kranzler, H. R., Malison, R., Price, L. H., Van Dyck, D., Krystal, J. H., et al. (2002). A functional neuropeptide Y Leu7Pro polymorphism associated with alcohol dependence in a large population sample from the United States. Archives of General Psychiatry, 59, 825–831.

Lawford, B. R., McD. Young, R., Noble, E. P., Kann, B., Arnold, L., Rowell, J., et al. (2003). D2 dopamine receptor gene

polymorphism: Paroxetine and social functioning in posttraumatic stress disorder. European Neuropsychopharmacology, 13, 313–320.

Lee, H. J., Lee, M. S., Kang, R. H., Kim, H., Kim, S. D., Kee, B. S., et al. (2005). Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. Depression and Anxiety, 21, 135–139.

Marshall, R. D., Beebe, K. L., Oldham, M., & Zaninelli, R. (2001). Efficacy and safety of paroxetine treatment for chronic PTSD: A fixed-dose, placebo-controlled study. American Journal of Psychiatry, 158, 1982–1988.

Marshall, R. D., & Pierce, D. (2000). Implications of recent findings in posttraumatic stress disorder and the role of pharmacotherapy. Harvard Review of Psychiatry, 7, 247–256.

Miller, M. W., Kaloupek, D. G., Dillon, A. L., & Keane, T. M. (2004). Externalizing and internalizing subtypes of combat-related PTSD: A replication and extension using the PSY-5 scales. Journal of Abnormal Psychology, 113, 636–645.

Moffitt, T. E., Caspi, A., & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. Archives of General Psychiatry, 62, 473–481.

Pitman, R. K., & Delahanty, D. L. (2005). Conceptually driven pharmacologic approaches to acute trauma. CNS Spectrums, 10, 99–106.

Plomin, R., Crabbe, J. (2000). DNA. Psychological Bulletin, 126 (6), 806–828.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2001). Behavioral Genetics. New York: Worth.

Pritchard, J. K., Stephens, M., & Donnelly, P. (2000). Inference of population structure using multilocus genotype data. Genetics, 155, 945–959.

Pritchard, J. K., Stephens, M., Rosenberg, N. A., & Donnelly, P. (2000). Association mapping in structured populations. American Journal of Human Genetics, 67, 170–181.

Rasmusson, A. M., Vythilingam, M., & Morgan, C. A., 3rd. (2003). The neuroendocrinology of posttraumatic stress disorder: new directions. CNS Spectrums, 8, 651–656, 665–657.

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—Past, present, and future. Biological Psychiatry, 60, 376–382.

Risch, N. J., & Merikangas, K. (1996). The future of genetic studies of complex human diseases. Science, 273, 1516–1517.

Rothman, K. J. (2002). Epidemiology: An introduction. New York: Oxford University Press.

Sack, W. H., Clarke, G. N., & Seeley, J. (1995). Posttraumatic stress disorder across two generations of Cambodian refugees. Journal of the American Academy of Child and Adolescent Psychiatry, 34, 1160–1166.

Saxe, G. N., Miller, A., Bartholomew, D., Hall, E., Lopez, C., Kaplow, J., et al. (2005). Incidence of and risk factors for acute stress disorder in children with injuries. Journal of Trauma, 59, 946–953.

Schulze, T. G., Buervenich, S., Badner, J. A., Steele, C. J., Detera-Wadleigh, S. D., Dick, D., et al. (2004). Loci on chromosomes 6q and 6p interact to increase susceptibility to bipolar affective disorder in the National Institute of Mental Health Genetics Initiative Pedigrees. Biological Psychiatry, 56, 18–23.

Segman, R. H., Cooper-Kazaz, R., Macciardi, F., Goltser, T., Halfon, Y., Dobroborski, T., et al. (2002). Association between the dopamine transporter gene and posttraumatic stress disorder. Molecular Psychiatry, 7, 903–907.

Segman, R. H., Shefi, N., Goltser-Dubner, T., Friedman, N., Kaminski, N., & Shalev, A. Y. (2005). Peripheral blood mononuclear cell gene expression profiles identify emergent posttraumatic stress disorder among trauma survivors. Molecular Psychiatry, 10, 500–513, 425.

Shumyatsky, G. P., Malleret, G., Shin, R. M., Takizawa, S., Tully, K., Tsvetkov, E., et al. (2005). Stathmin, a gene enriched in the amygdala, controls both learned and innate fear. Cell, 123, 697–709.

Shumyatsky, G. P., Tsvetkov, E., Malleret, G., Vronskaya, S., Hatton, M., Hampton, L., et al. (2002). Identification of a signaling network in lateral nucleus of amygdala important for inhibiting memory specifically related to learned fear. Cell, 13, 905–918.

Spielman, R. S., & Ewens, W. J. (1996). The TDT and other family-based tests for linkage disequilibrium and association. American Journal of Human Genetics, 59, 983–989.

Stein, M. B., Jang, K. J., Taylor, S., Vernon, P. A., & Livesley, W. J. (2002). Genetic and environmental influences on trauma exposure and posttraumatic stress disorder: A twin study. American Journal of Psychiatry, 159, 1675–1681.

Sullivan, P. F., Eaves, L. J., Kendler, K. S., & Neale, M. C. (2001). Genetic case-control association studies in neuropsychiatry. Archives of General Psychiatry, 58, 1015–1024.

True, W. J., Rice, J., Eisen, S. A., Heath, A. C., Goldberg, J., Lyons, M. J., et al. (1993). A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Archives of General Psychiatry, 50, 257–264.

Wong, M. Y., Day, N. E., Luan, J. A., Chan, K. P., & Wareham, N. J. (2003). The detection of gene-environment interaction for continuous traits: Should we deal with measurement error by bigger studies or better measurement? International Journal of Epidemiology, 32, 51–57.

Xian, H., Chantarujikapong, S. I., Shrerrer, J. F., Eisen, S. A., Lyons, M. J., Goldberg, J., et al. (2000). Genetic and environmental influences on posttraumatic stress disorder, alcohol, and drug dependence in twin pairs. Drug and Alcohol Dependence, 61, 95–102.

Yang, B. Z., Zhao, H., Kranzler, H. R., & Gelernter, J. (2005a). Characterization of a likelihood based method and effects of markers informativeness in evaluation of admixture and population group assignment. BioMed Central, Genetics, 6, 50.

Yang, B. Z., Zhao, H., Kranzler, H. R., & Gelernter, J. (2005b). Practical population group assignment with selected informative markers: Characteristics and properties of Bayesian clustering via STRUCTURE. Genetic Epidemiology, 28, 302–312.

Yehuda, R., Halligan, S. L., & Bierer, L. M. (2001). Relationship of parental trauma exposure and PTSD to PTSD, depressive and anxiety disorders in offspring. Journal of Psychiatric Research, 35, 261–270.

Young, B. R., Lawford, B. R., Noble, E. P., Kanin, B., Wilkie, A., Ritchie, T., et al. (2002). Harmful drinking in military veterans with posttraumatic stress disorder: Association with the D2 dopamine receptor A1 allele. Alcohol and Alcoholism, 37, 451–456.

Zhang, H., Ozbay, F., Lappalainen, J., Kranzler, H. R., van Dyck, C. H., Charney, D. S., et al. (2006). Brain derived neurotrophic factor (BDNF) gene variants and Alzheimer's disease, affective disorders, posttraumatic stress disorder, schizophrenia, and substance dependence. American Journal of Medical Genetics B Neuropsychiatric Genetics, 141, 387–393.