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PATHO-GENETICS OF POSTTRAUMATIC STRESS DISORDER

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SUMMARY

Clinical genetic studies propose a moderate genetic contribution to the pathogenesis of PTSD with a heritability of about 30-35%. The present brief review will give an overview of molecular genetic research in PTSD yielding support for specific vulnerability genes. Additionally, evidence for gene-environment (GxE) interactions between susceptibility genes of PTSD and traumatic experiences will be reported. Recent studies suggest a pivotal role of epigenetic mechanisms such as DNA methylation in mediating the impact of trauma in the pathogenesis of PTSD. Future approaches to further unravel the genetic underpinnings of PTSD might comprise genome-wide association studies (GWAS), the investigation of the genetic influence on intermediate phenotypes of PTSD (e.g., imaging genetics) as well as pharmaco- and psychotherapy-genetic studies. Genetic research in PTSD will be discussed with respect to its potential benefit regarding innovative and individually tailored therapeutic approaches in PTSD.

Key words: *PTSD – association – gene-environment interaction – epigenetics – imaging genetics – pharmacogenetics*

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is an anxiety disorder characterized by symptoms of re-experiencing the trauma such as flash-backs, intrusions or night-mares, avoidance behavior and hyperarousal persisting for more than 1 month post experiencing or witnessing extreme traumatic events involving actual or perceived threat of death or serious injury or threat to one's physical integrity (American Psychiatric Association 1994).

Given methodological problems regarding definition of the traumatic stressor as well as regarding valid instruments and timing of assessment, the life-time prevalence of PTSD is difficult to determine. However, in the US general population the lifetime prevalence of PTSD has been estimated at 7% (Kessler et al. 2005) and as high as 35% in people who experienced the war in Bosnia and Herzegovina (Priebe et al. 2010).

The etiology of posttraumatic stress disorder (PTSD) is considered to be multifactorial with an interaction of traumatic environmental factors as well as genetic factors, since - as exemplarily shown by Kessler et al. (1995) - about 75% of the investigated population experienced a traumatic event in their lifetime, while only 7.8% of this sample developed PTSD.

CLINICAL GENETICS

An influence of genetic factors on the pathogenesis of PTSD has been demonstrated by clinical genetic studies such as family studies and twin studies: First degree relatives of patients with PTSD show an increased risk of developing PTSD themselves (Sack et al. 1995), with some evidence for maternal imprinting mechanisms (Yehuda et al. 2008). Twin studies in e.g. Vietnam war veterans have revealed a heritability of PTSD of ~ 30-35% (Koenen et al. 2002, True et al. 1993), while a recent twin study suggests a heritability of 70% (Sartor et al. 2012), i.e. about one third to up to 70% of the entire variance in the pathogenesis of PTSD can be attributed to genetic factors with the remainder of the variance being explained by environmental factors, particularly with regard to the persistence of PTSD symptoms (Roy-Byrne et al. 2004). Distinct genetic risk factors for the latent internalizing (41%) and externalizing (69%) comorbidity dimensions of PTSD have been suggested (Wolf et al. 2010). In accordance with a considerable clinical comorbidity between PTSD and major depressive disorder, alcohol dependence, nicotine dependence, panic disorder and generalized anxiety disorder, there seems to be a great overlap between genetic risk factors for these disorders (Chantarujikapong et al. 2001, Davidson et al. 1998, Goenjian et al. 2008, Koenen et al. 2003, Koenen et al. 2005, Koenen et al. 2008a, McLeod et al. 2001, Pervanidou 2008, Sartor et al. 2011, Scherrer et al. 2008, Xian et al. 2000, for review see Afifi et al. 2010).

MOLECULAR GENETICS

Single risk genes contributing to this overall genetic risk of PTSD have been identified by to date over 40 molecular genetic studies (for review see Broekman et al. 2007, Cornelis et al. 2010, Koenen 2007, Nugent et al. 2008): evidence has been provided for the serotonin transporter (5-HTT) gene promoter region (5-HTTLPR) to be associated with acute stress disorder symptoms, as well as PTSD severity score and PTSD as a categorical nosological entity (Lee et al. 2005, Mercer et al. 2012, Wang et al. 2011). Association of variation in the serotonin 2A receptor (5-HT2A) gene has been reported

to be a risk factor for PTSD in a trauma-exposed African-American sample (Mellman et al. 2009). Genes related to the hypothalamus-pituitary-adrenal axis and therefore supposed to be involved in the mediation of stress response have constituted another major focus in molecular genetic association analyses in PTSD: the FKBP5 gene - coding for a co-chaperone protein influencing glucocorticoid receptor sensitivity - has been found to be associated with PTSD (Binder et al. 2008, Boscarino et al. 2011), plasma cortisol and PTSD severity among survivors of the World Trade Center attacks (Sarapas et al. 2011) and specific types of hypothalamic-pituitary-adrenal axis dysfunction within PTSD (Mehta et al. 2011). Furthermore, corticotropin-releasing hormone type 1 receptor gene (CRHR1) variants were observed to predict posttraumatic stress symptoms onset and course in pediatric injury patients (Amstadter et al. 2011). Finally, a variant in a putative oestrogen response element within the ADCYAP1R1 gene, coding for the receptor of the pituitary adenylate cyclase-activating polypeptide (PACAP), was associated with PTSD particularly in females (Ressler et al. 2011). Further evidence has accumulated for variation in genes involved in the dopaminergic system to increase vulnerability to PTSD: association with PTSD has been reported for the catechol-O-methyltransferase (COMT) gene (Boscarino et al. 2011) and the dopamine D2 receptor (DRD2) gene (Voisey et al. 2009), with some support for DRD2 variation to specifically mediate severe co-morbid psychopathology (anxiety, depression) and social dysfunction in PTSD subjects (Lawford et al. 2006). The dopamine transporter (DAT1) gene has also been found to be associated with PTSD, with, however, also contradictory reports of no association (Bailey et al. 2010, Drury et al. 2009, Segman et al. 2002, Valente et al. 2011). Still unreplicated evidence has been published for a possible role of the endocannabinoid receptor 1 (CNR1) and the gamma-aminobutyric acid receptor subunit alpha-2 (GABRA2) genes to confer susceptibility to PTSD (Lu et al. 2008, Nelson et al. 2009).

GENE-ENVIRONMENT (GXE) INTERACTION STUDIES

In addition to the identification of vulnerability genes, the complex-genetic nature of PTSD necessitates the investigation of the interplay of genetic factors with environmental factors regarding the pathogenesis of PTSD or resilience towards stress-related disorders, respectively (see Gillespie et al. 2009, Koenen et al. 2008b, Koenen et al. 2009b, Nugent et al. 2011, Yehuda et al. 2010). Thus, increasing effort has been put into so-called gene-environment-interaction (GxE) analyses: several studies have suggested variation in the serotonin transporter (5-HTT) gene promoter region and traumatic events to interactively increase the risk for PTSD with, however, contradictory results regarding the direction of allelic association (5-HTTLPR long vs. short alleles) (Grabe et al. 2009; Kilpatrick et al. 2007, Koenen et al. 2011a, Kolassa et al. 2010a, Thakur et al. 2009, Xie et al. 2009) and evidence for a moderating influence of county-level environment (Koenen et al. 2009a). 5-HTT gene variation and childhood trauma have furthermore been found to interactively increase the risk for PTSD-related phenotypes like anxiety sensitivity (Klauke et al. 2011, Stein et al. 2008). Further attention has been paid to gene-environment interactions related to the HPA axis as this neurobiochemical pathway has been shown to be crucially involved in response to stressful or traumatic experiences (see review by Mehta & Binder 2012). In the largest GxE study in PTSD so far, Binder et al. reported genetic variation in the FKBP5 gene and child abuse severity to interactively predict PTSD symptoms in adulthood (Binder et al. 2008), which could be replicated in an independent sample (Xie et al. 2010). In a sample of Croatian war veterans, an interaction between dopamine beta-hydroxylase (DBH) gene variation and combat history on PTSD status was reported, with DBH plasma activity being suggested to possibly constitute a biomarker for PTSD susceptibility (Mustapic et al. 2007). Further GxE interaction in PTSD has been observed for variation in the RGS2 (Amstadter et al. 2009a), GABRA2 (Nelson et al. 2009) and COMT (Amstadter et al. 2009b, Kolassa et al. 2010b) genes (for review see Koenen 2005, Koenen et al. 2009b).

EPIGENETICS

Recently, epigenetic mechanisms such as methylation or acetylation have been shown to critically influence gene regulation and mediate adaptation to environmental influences (Jaenisch & Bird 2003), with the latter presumably being of particular relevance for the pathogenesis of PTSD (Dudley et al. 2011, Yehuda et al. 2011, Yehuda & Bierer 2009). In animal models, it has been suggested that epigenetic processes might constitute flexible and temporally dynamic mechanisms of adjustment to stressful environmental influences (Chertkow-Deutsher et al. 2010, Lesch 2011, Roth & Sweatt 2011): e.g., increased methylation of the brain-derived neurotrophic factor (BDNF) gene resulting in reduced gene expression in the prefrontal cortex has been observed after maltreatment in rats (Roth et al. 2011) and greater 5-HTT gene methylation was associated with enhanced behavioral stress reactivity following early life stress in primates (Kinnally et al. 2011). Very recent studies have identified a differential methylation status in genes involved in the immune system to be associated with PTSD (Smith et al. 2011, Uddin et al. 2010). Also, higher methylation in the MAN2C1 gene (Uddin et al. 2011) or lower 5-HTT DNA methylation, respectively (Koenen et al. 2011b), and greater exposure to potentially traumatic events have been shown to interactively increase the risk for PTSD.

PERSPECTIVES

Clinical and molecular genetic studies point to a moderate influence of genetic factors and provide strong support for considerable gene-environment interaction in the etiology of PTSD. First epigenetic studies demonstrated methylation patterns to mediate the impact of aversive experiences on a biological level to increase vulnerability to PTSD.

Future avenues to further unravel the complex-genetic underpinnings of PTSD might comprise genome-wide studies, imaging genetics and other intermediate phenotype approaches as well as pharmaco- and psychotherapy-genetic studies in PTSD.

Novel candidate genes of PTSD might arise from large-scale molecular target screenings in validated animal models of stress response (Zhang et al. 2006) and genome-wide association studies (GWAS) in patients with PTSD, where the entire genome is interrogated for association with the disorder applying a hypothesis-free approach (Cornelis et al. 2010).

A first imaging genetic study examining the impact of genetic variants on relevant neuronal activation patterns as an intermediate phenotype of PTSD revealed a significant influence of serotonin transporter (5-HTT) gene variation on activity of brain regions involved in the cognitive control of emotion (amygdala, prefrontal cortex) in patients with PTSD (Morey et al. 2011). Besides the cortico-limbic interaction during cognitive or emotional processing, further promising intermediate phenotypes of PTSD might comprise the function of hypothalamic-pituitary-adrenal axis or the locus coeruleus-noradrenergic system, a smaller hippocampal volume, a large cavum septum pellucidum, more neurological soft signs, lower general intellectual ability and poorer performance in the specific cognitive abilities of executive function, attention, declarative memory, and processing of contextual cues, which have been shown to be heritable and related to PTSD (Grossman et al. 2002, Kremen et al. 2007, Kremen et al. 2012, Skelton et al. 2012).

Pharmaco- and psychotherapy-genetic studies analyze the genetic control of inter-individual variation in treatment response. To date, two such studies have been published with respect to PTSD: significant improvement in social functioning during pharmacotherapy with paroxetine was found to be influenced by DRD2 gene variation (Lawford et al. 2003), while 5-HTTLPR low-expression alleles (S or L(G)) were reported to confer impaired treatment response to cognitive behavioral therapy in PTSD (Bryant et al. 2010).

Genetic research in PTSD is hoped to finally result in the development of novel therapeutic approaches such as innovative drugs based on vulnerability genes identified by molecular genetic studies or in the application of resilience-increasing psychotherapeutic techniques counteracting genetic susceptibility (cf. Haglund et al. 2007). In the light of recent findings regarding epigenetic processes crucially shaping the risk for PTSD, future studies might additionally want to explore epigenetic x environment (EpiGxE) interactions as well as the potential benefit of psychotropic drugs acting on epigenetic mechanisms such as valproate (histone deacetylase inhibitor), the MAO-A inhibitor tranylcypromine (demethylation inhibitor) or S-adenosyl-methionine (methyl group donor) in the treatment of PTSD as previously suggested for e.g. affective disorders (Hamm & Costa 2011, Papakostas 2009, Schmidt et al. 2011). Furthermore, advances in genetic research hold great promise with regard to the development of a more personalized, individualized medicine. Increasing identification of genetic risk factors in pharmaco- and psychotherapy-genetic studies might allow for an early definition of non-responders to a particular therapeutic intervention and thus for a more targeted choice of the most efficient therapeutic agent or psychotherapeutic approach. This would help tremendously to lower the individual patient's suffering as well as the economic burden of healthcare cost related to the treatment of PTSD (Bowirrat et al. 2010, Ramey-Hartung et al. 2008).

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