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Chapter 4

Genetics of Posttraumatic Stress Disorder — Candidate Genes and Their Implication in the Disease-Associated Molecular Pathomechanisms

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Abstract

Posttraumatic stress disorder (PTSD) is a complex psychiatric disorder (DSM-V code: 309.81; ICD-10 codes: F43.1). PTSD is an anxiety disorder developed in a person experiencing, witnessing, or learning about an extreme physically or/and psychologically distressing event. Its incidence and the number of this disease-affected people are threateningly increasing in contemporary society. Therefore, the development of prognostic strategies and novel efficient methods on early diagnostics and treatment of PTSD is currently considered as one of the most important healthcare problems worldwide.

Results of epidemiologic, clinical, and experimental studies suggest implication of both environmental and genetic factors in pathomechanisms of PTSD and that, most probably, PTSD belongs to complex disorders with polygenic inheritance. Whereas the environmental factors triggering PTSD are well defined, less is known about PTSD-associated genetic variations and molecular etiopathomechanisms.

Several studies, including our own reports, suggest the involvement of neuro-immune alterations in the pathophysiology of PTSD. These include changes in neuronal plasticity, synaptic connectivity, humoral and cellular immune-mediated responses, and apoptosis rate leading to cognitive deficit and behavioral changes in patients with PTSD accompanied with development of low-grade inflammatory reactions. Currently, many research groups working on elucidation of molecular mechanisms of PTSD are exploring whether these changes have genetic background or are induced by other external or internal environmental factors.

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In the present chapter, we provide overview and discussion of the existing data, including our own results, on variations in genes encoding neuro-immune and apoptotic mediators and regulators and related transcription factors in PTSD patients. Potential role of these genetic variations in generation and development of PTSD is considered and the implication of relevant candidate genes in mechanisms responsible for disease progression is proposed.

Keywords: Apoptosis, candidate genes, complement system, posttraumatic stress disorder, synaptic plasticity

1. Introduction

Posttraumatic stress disorder (PTSD; DSM-V code: 309.81; ICD-10 codes: F43.1) is a complex, severe, and chronic psychiatric illness [1–2]. PTSD is an anxiety disorder developed in a person experiencing, witnessing, or learning about an extreme physically and/or psychologically distressing event [3–7]. Its incidence and the number of disease-affected people are threateningly increasing in contemporary society. They usually remain out of society, become drug addicted, alcoholic, and often commit suicide [8–10]. Therefore, development of prognostic strategies, novel efficient methods on early diagnostics and treatment of PTSD is currently considered as one of the most important health care problems worldwide.

Results of epidemiologic, clinical, and experimental studies suggest implication of both environmental and genetic factors in pathomechanisms of PTSD, and that, most probably, PTSD belongs to the complex disorders with polygenic inheritance. PTSD is also unique in its exposure to an environmental (traumatic) event as the first criterion for diagnosis. Whereas the environmental factors triggering PTSD are well defined, less is known about PTSD-associated genetic variations and molecular etiopathomechanisms [11–17]. Although it is beyond the scope of many studies to comprehensively discuss the genetics of PTSD, it should be noted that there is an emerging literature on genetic variations in those neurobiological systems which drive responses to trauma and, consequently, are risk factors to develop PTSD. Many studies on detection of candidate genes association with PTSD are being carried up to date [18–26].

In the present chapter, we provide overview and discussion of the existing data, including genetic variants of serotonergic and dopaminergic systems, hypothalamic–pituitary–adrenal (HPA) axis, and other genes related to neurotransmission, neuromodulation, and stress physiology. Here, we have also included our own results on variations in genes encoding neuro, immune, and apoptotic mediators and regulators, and related transcription factors in PTSD patients. Potential role of these genetic variations in generation and development of PTSD is considered and the implication of relevant candidate genes in mechanisms responsible for disease progression is proposed.

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2. Genetic Studies of PTSD

2.1. Neuroendocrine system candidate genes

Many studies indicate association between PTSD and polymorphisms of number of genes, suggesting a polygenic nature of PTSD. Several studies indicate that functional abnormalities in neuroendocrine system detected in PTSD patients are conditioned with hereditary factor [21–26]. Thus, as it follows from Table 1, PTSD is associated with the genetic mutations in a number of genes encoding neurotransmitters, hormones and their enzymes, hormone receptors and transporters.

Candidate genes	Cytogenetic location	Studied SNPs	Source
Dopaminergic system			
Dopamine D2 receptor *(DRD2)*	11q23	rs1800497	[24-30]
Dopamine D3 receptor *(DRD3)*	3q13.3	rs2134655, rs201252087, rs4646996, rs9868039	[31]
Dopamine D4 receptor *(DRD4)*	11p15.5	VNTR	[32]
Dopamine transporter type 1 *(SLC6A3, DAT1)*	5p15.3	VNTR	[33]
Dopamine beta-hydroxylase *(DBH)*	9q34	rs1611115	[37, 38]
Catechol-O-methyltransferase *(COMT)*	22q11	rs4680 rs4633C	[39-41]
Serotonergic system			
Serotonin transporter *(SLC6A4, SERT)*	17q11	rs4795541, rs25531	[42-45]
Serotonin type-2A receptor *(HTR2A)*	13q14.2	rs6311	[46, 47]
Tryptophan hydroxylase 1 *(TPH1)*	11p15.1	rs2108977	[48]
Tryptophan hydroxylase 2 *(TPH2)*	12q21.1	rs11178997	[41, 48]
GABAergic system			
Gamma-aminobutyric acid receptor alpha-2 *(GABRA2)*	4p12	rs279836, rs279826	[49]
Hypothalamic-pituitary-adrenal axis			
Cannabinoid receptor 1 *(CNR1)*	6q15		[50]

Candidate genes	Cytogenetic location	Studied SNPs	Source
Glucocorticoid receptor GCCR *(NR3C1)*	5q31.3	rs41423247 rs258747	[51, 52]
Corticotropin-releasing hormone receptor-1 *(CRHR1)*	17q21.31	rs12944712	[53]
Pituitary adenylate cyclase 1 receptor *(ADCYAP1R1, PAC1)*	7p14.3	rs2267735	[54, 55]
FK506 binding protein 5 *(FKBP5)*	6p21	rs9296158, rs3800373, 1360780, rs9470080	[56-62]
Neurotrophic factor			
Brain-derived neurotrophic factor *(BDNF)*	11p14.1	rs6265	[30, 63-66]
Other genes			
Apolipoprotein E *(ApoE)*	19q13	rs429358, rs7412	[67]
Monoamine oxidase B *(MAOB)*	Xp11.3	rs1799836	[70]
Neuropeptide Y *(NPY)*	7p15.3	rs16139	[71]
Phosphoribosyl transferase domain-containing protein 1 *(PRTFDC1)*	10p12.1	rs6482463	[73]
Regulator of G-protein signalling 2 *(RGS2)*	1q31.2	rs4606	[74]

Table 1. Neuroendocrine system candidate genes in PTSD

2.1.1. Dopaminergic system

Dopaminergic system dysregulation has long been implicated in the pathophysiology of PTSD. A positive association between the risk for development of PTSD and Taq1A (rs1800497) polymorphism of the dopamine D2 receptor gene was found [24–30]. The dopamine D3 receptor (*DRD3*) gene's 4 SNPs (rs2134655, rs201252087, rs4646996, and rs9868039) showed evidence of association with PTSD [31]. Also, positive association was revealed between tandem repeat polymorphism of dopamine transporter gene and PTSD, as well as between dopamine D4 transporter gene long allele and severity of PTSD symptoms [32]. Recent publications reported that carriers of the 9R of allele of the gene, encoding the dopamine transporter (*SLC6A3, DAT, or DAT1*), had increased the risk of PTSD [33–36]. This finding suggests that genetically determined features of *DAT* may contribute to the development of PTSD among trauma survivors. Genetic variants in dopamine beta-hydroxylase (*DBH*) gene represent a likely candidate for examining genetic contributions to PTSD because of the role this enzyme plays in converting dopamine to norepinephrine as a part of catecholamine synthesis [37, 38]. A significant association between one or more copies of the rs4680 allele of

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COMT and PTSD has been reported. Thus, regulation of COMT and subsequent catecholamine neurotransmitter cascades may be an important factor in fear processing for those with PTSD and similar psychiatric disorders [39, 40]. Moreover, a recent study has shown a significant association of the *COMT* allele rs4633C with total PTSD, and severity scores of D category (negative alterations in cognitions and mood) of DSM-V categories [41].

2.1.2. Serotonergic system candidate genes

Dysregulation of brain serotonergic systems has been implicated in the pathophysiology of PTSD; indeed, this pathway represents the most studied candidate in PTSD. The most studied polymorphism in this system is located in the promoter region of the serotonin transporter encoding gene (*SLC6A4, 5-HTTLPR*). Several studies indicated that this risk was associated with rs4795541, rs25531 genotypes, and PTSD [35, 42–45]. Serotonin receptor 2A rs6311 polymorphism has also been found to be associated with PTSD [46–47].

Goenjian and colleagues' studies have suggested association of *TPH1, TPH2*, and *5HTTLPR* with PTSD and depressive symptoms [48]. It was shown that the *TPH-2* allele rs11178997T and *COMT* allele rs4633C together accounted for 7% of the variance in severity scores of PTSD. Carriers of these *COMT* and *TPH-2* alleles may be at increased risk for PTSD. These findings provided biological support for dividing DSM-IV category C symptoms into DSM-V categories C and D [41].

2.1.3. GABAergic system

Inhibitory neurotransmitter, gamma-aminobutyric acid receptor gene (*GABAA*) has been studied in relation to PTSD. Three polymorphisms in the *GABAA* receptor subunit alpha 2 (*GABRA2*) had significant interactions with childhood trauma to predict PTSD [49].

2.1.4. HPA axis candidate genes

PTSD is also characterized by dysfunction of the stress response system, such that activity of the HPA axis is altered. Recent studies reported associations between PTSD and cannabinoid receptor (*CNR1*) gene variants NM_016083 and NM_033181; [50], glucocorticoid receptor (*NR3C1*, rs41423247, and rs258747) gene [51, 52], and between SNP in corticotropin-releasing hormone receptor-1 (*CRHR1*, rs12944712) and PTSD [53]. Also neuropeptide pituitary adenylate cyclase-activating polypeptide is regulating the stress response. Recently, a genetic variant in the PAC1 receptor (*ADCYAP1R1*; rs2267735) was found to be associated with PTSD [54, 55]. Of particular interest were the findings that a genetic variation of the glucocorticoid receptor cochaperone protein, FKBP5, moderates risk of developing PTSD in childhood abuse cases [56–61]. Binder and colleagues found that 4 SNPs in *FKBP5* (rs9296158, rs3800373, 1360780, rs9470080) interacted with child abuse severity to predict adult PTSD symptoms [62].

2.1.5. Neurotrophic factor candidate genes

Brain derived neurotrophic factor (BDNF) is involved in the neural plasticity underlying the extinction of fear and recovery from stress, both disrupted in PTSD. Based on its role in

hippocampal-dependent learning and the neurobiology of anxiety and depression, the *BDNF* gene has been studied in relation to PTSD. A significant interaction between *DRD2* Taq1A (rs1800497) and Val66Met (rs6265) predicts PTSD severity [30]. Interestingly, a recent study in humans and rats suggested that *BDNF* overexpression may be a critical stress response underlying PTSD by showing that the Val66Met allele confers vulnerability to PTSD via startle data and plasma BDNF levels [63–66].

2.1.6. Other candidate genes

Apolipoprotein E (ApoE) is involved in stress dysregulation. A significant association between the ApoE2 allele and impaired memory and greater re-experiencing symptoms has been found in combat-exposed PTSD patients [67–69]. The monoamine oxidase B gene (*MAOB*) rs1799836 polymorphism has been studied in relation with PTSD because *MAOB* expression in platelets has been implicated in several psychopathologies and may represent a biomarker for vulnerability to psychiatric illness [70]. Recent studies of the link between neuropeptide Y (NPY) and PTSD were published [71]. However, another study did not find any association between polymorphism in *NPY* (Leu7Pro; rs16139) and PTSD in a population of Caucasian combat veterans [72]. Nievergelt and colleagues found evidence for phosphoribosyl transferase domain-containing protein 1 (*PRTFDC1*) as a potential novel PTSD gene, but this finding needs further replication [73]. Finally, it was reported that the regulator of G-protein signaling 2 (RGS2) belongs to a protein family that has been widely involved in neural plasticity, particularly associated with learning and memory, and may play a critical role in PTSD-associated cognitive dysfunction. In PTSD patients experiencing high stress and low social support, an association with *RGS2* (rs4606) was found [74].

2.2. Complement system candidate genes

The complement system is major effector of the immune response, which acts on the interface of innate and adaptive immunity, and is a key component and trigger of many immunoregulatory mechanisms. Changes in the functional activity of the complement cascade contribute to the pathology of many human diseases [75–77], including mental disorders [78–83], and are also detected during physiological stress [84, 85]. It has already been demonstrated that complement system alterations are involved in PTSD pathogeneses, particularly hypoactivation state of the complement alternative pathway in PTSD patients, which positively and significantly correlates ($p < 0.05$) with total (frequency and intensity) PTSD symptom cluster of re-experiencing, avoidance, and hyperarousal, and with PTSD total symptom score [13]. Now, our interest is focused on studying the genetic basis of complement system regulators, particularly the role and genetic variants of complement factors B, H, and I (*CFB, CFH*, and *CFI*, accordingly) in PTSD. The distributions of genotypes for *CFB, CFH*, and *CFI* SNPs in both patients and control groups were in compliance with Hardy–Weinberg equilibrium ($p > 0.05$). The allele and phenotype frequencies of *CFB, CFH*, and *CFI* genetic variants in the groups of PTSD patients and controls are shown in Table 2.

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Gene (SNP)	Genotypes			Alleles		Carriage
***CFB* rs12614**	CC	CT	TT	C	T	T
PTSD	87 (0.58)	59 (0.4)	3 (0.02)	233 (0.78)	65 (0.22)	62 (0.42)
Controls	125 (0.55)	89 (0.4)	12 (0.05)	339 (0.75)	113 (0.25)	101 (0.45)
p				0.32		0.56
OR				0.84		1.13
95% CI:				0.59-1.19		0.75-1.72
***CFB* rs1048709**	GG	GA	AA	G	A	A
PTSD	134 (0.918)	11 (0.075)	1 (0.007)	279 (0.955)	13 (0.045)	12 (0.08)
Controls	167 (0.92)	14 (0.08)	0 (0)	348 (0.96)	14 (0.04)	14 (0.08)
p				0.7		0.87
OR				1.16		0.94
95% CI:				0.54-2.50		0.42-2.09
***CFH* rs424535**	TT	TA	AA	T	A	A
PTSD	56 (0.38)	47 (0.32)	44 (0.3)	159 (0.54)	135 (0.46)	91 (0.62)
Controls	74 (0.344)	108 (0.502)	33 (0.154)	256 (0.6)	174 (0.4)	141 (0.6)
p				0.145		0.47
OR				1.25		1.17
95% CI:				0.93-1.69		0.76-1.81
***CFH*rs1061170**	CC	CT	TT	C	T	T
PTSD	30 (0.21)	53 (0.36)	63 (0.43)	113 (0.39)	179 (0.61)	83 (0.47)
Controls	24 (0.11)	104 (0.46)	97 (0.43)	152 (0.34)	298 (0.66)	128 (0.57)
p				0.17		1.0
OR				0.81		1.92
95% CI:				0.60-1.10		1.05-3.52
***CFH* rs800292**	CC	CT	TT	C	T	T
PTSD	117 (0.8)	25 (0.17)	4 (0.03)	259 (0.89)	33 (0.11)	29 (0.2)
Controls	166 (0.74)	55 (0.24)	4 (0.02)	387 (0.86)	63 (0.14)	59 (0.26)
p				0.29		0.16
OR				0.78		1.43
95% CI:				0.50-1.23		0.87- 2.37
***CFI* rs10033900**	TT	TC	CC	T	C	C
PTSD	38 (0.3)	62 (0.4)	49 (0.3)	138 (0.46)	160 (0.54)	111 (0.75)
Controls	69 (0.31)	99 (0.44)	57 (0.25)	237 (0.53)	213 (0.47)	156 (0.69)

Gene (SNP)	Genotypes			Alleles		Carriage
p				0.089		0.279
OR				1.29		0.77
95% CI:				0.962-1.73		0.486-1.23
***CFI*rs1000954**	GG	GA	AA	G	A	A
PTSD	98 (0.66)	40 (0.27)	10 (0.07)	236 (0.8)	60 (0.2)	50 (0.34)
Controls	84 (0.488)	75 (0.436)	12 (0.076)	243 (0.71)	101 (0.29)	87 (0.51)
p				**0.02**[a]		**0.006**[b]
OR				0.61		2.03
95% CI:				0.42-0.88		1.29-3.2
***CFI* rs4469075**	CC	CG	GG	C	G	G
PTSD	19 (0.13)	60 (0.42)	65 (0.45)	98 (0.34)	190 (0.66)	79 (0.55)
Controls	17 (0.1)	76 (0.5)	71 (0.4)	110 (0.3)	218 (0.7)	93 (0.57)
p				1.0		0.75
OR				0.98		1.32
95% CI:				0.7-1.37		0.64– 2.70

[a] $p_{corrected}$ values for comparison of mutant allele frequency between PTSD patients and controls.

[b] $p_{corrected}$ values for comparison of mutant allele carriage between PTSD patients and controls.

Table 2. Distribution of genotypes, alleles and carriage of minor alleles of CFB, CFH and CFI polymorphisms in patients with PTSD and controls.

According to the results obtained, the *CFI* rs1000954*A allele was more frequent in controls than in patients (0.29 vs. 0.20, $p_{nominal} = 0.008$, OR = 0.61, 95 %CI: 0.42-0.88). Also, the carriers of this allele were overrepresented in the group of controls compared to patients (0.51 vs. 0.34, $p_{nominal} = 0.002$, OR = 2.03, 95% CI: 1.29–3.2). In case of other selected polymorphisms, no significant association with PTSD was found ($p > 0.05$).

2.3. Candidate genes of apoptosis

Apoptosis is a genetically programmed, morphologically distinct form of cell death that can be triggered by a variety of physiological and pathological stimuli [86]. According to various apoptotic stimuli, apoptosis can be induced by two major pathways: the intrinsic pathway (mitochondria-dependent pathway) and the extrinsic pathway (death receptor-dependent pathway) [87]. Recent studies reported that neuronal apoptosis of amygdala, hippocampus, and medial prefrontal cortex (mPFC) have a certain relationship with the pathogenesis of PTSD [88]. However, the role of apoptosis in the pathogenesis of PTSD is not yet entirely clear.

Apoptosis is the process of strict control multigene, known in the process of apoptosis with a series of apoptosis-related genes, such as Bcl-2 family, caspase family, C-myc oncogenes, and

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tumor suppressor gene P53, etc. The Bcl-2 family proteins play a crucial role in the process of apoptosis and are considered to be the final passage of apoptosis. Bcl-2 family proteins regulate mitochondrial structure and functional stability with the help of other apoptosis protein synergy. According to the recent study, the increase of the Bcl-2 and Bax expression and the imbalance in the Bcl-2/Bax ratio were few of the mechanisms causing mPFC neuronal apoptosis, which may be one of the reasons of PTSD development in rat [88].

According to our study, the rs956572*A minor allele of the *BCL2* gene was overrepresented in patients with PTSD compared to healthy subjects (0.64 vs. 0.41, $p_{nominal}$ = 6.02E-11, OR = 2.59, 95% CI: 1.94–3.44). In addition, the carriers of this allele were more in the group of patients compared to controls (0.87 vs. 0.65, $p_{nominal}$ = 4.11E-7, OR = 3.53, 95% CI: 2.14–5.81). Further, we found that the rs1801018*G minor allele of the *BCL2* gene was more frequent among controls compared to patients (0.5 vs. 0.4, $p_{nominal}$ = 0.0036, OR = 0.66, 95% CI: 0.50–0.87). Also, the carriers of the rs1801018*G minor allele were more frequent in controls than in patients (0.79 vs. 0.61, $p_{nominal}$ = 8.6E-5, OR = 2.41, 95% CI: 1.54–3.75). After Bonferroni correction, difference in allele frequency between the patient and the control groups minor alleles remained significant (Table 3).

Gene (SNP)	**Genotypes**			**Alleles**		**Carriage**
***ANXA5* rs11575945**	CC	CT	TT	C	T	T
PTSD	63 (0.79)	14 (0.17)	3 (0.04)	140 (0.875)	20 (0.125)	17 (0.21)
Controls	53 (0.71)	21 (0.28)	1 (0.01)	127 (0.85)	23 (0.15)	22 (0.29)
p				1.4[a]		0.75[b]
OR				0.79		0.65
95% CI:				0.41 - 1.5		0.31 - 1.35
***ANXA11* rs1049550**	GG	GA	AA	G	A	A
PTSD	83 (0.415)	101 (0.505)	16 (0.08)	267 (0.67)	133 (0.33)	117 (0.59)
Controls	68 (0.34)	97 (0.485)	35 (0.175)	233 (0.58)	167 (0.42)	132 (0.66)
p				**0.013[a]**		0.12[b]
OR				0.695		1.38
95% CI:				0.52 - 0.93		0.92 - 2.07
***BCL2* rs956572**	GG	GA	AA	G	A	A
PTSD	27 (0.135)	89 (0.445)	84 (0.42)	143 (0.36)	257 (0.64)	173 (0.87)
Controls	71 (0.355)	94 (0.47)	35 (0.175)	236 (0.59)	164 (0.41)	129 (0.65)
p				**1.20E-10[a]**		**8.22E-07[b]**
OR				2.59		3.53
95% CI:				1.94 - 3.44		2.14 - 5.81
***BCL2* rs1801018**	AA	AG	GG	A	G	G

Gene (SNP)	Genotypes			Alleles		Carriage
PTSD	78 (0.39)	83 (0.415)	39 (0.195)	239 (0.6)	161 (0.4)	122 (0.61)
Controls	42 (0.21)	114 (0.57)	44 (0.22)	198 (0.5)	202 (0.5)	158 (0.79)
p				**0.0072**[a]		**0.00017**[b]
OR				0.66		2.41
95% CI:				0.5 - 0.87		1.54 - 3.75

[a] $p_{corrected}$ values for comparison of mutant allele frequency between PTSD patients and controls.

[b] $p_{corrected}$ values for comparison of mutant allele carriage between PTSD patients and controls.

Table 3. Distribution of genotypes, alleles and carriage of minor alleles of *ANXA5, ANXA11* and *BCL2* polymorphisms in patients with PTSD and controls.

The externalization of phosphatidylserine is one of the leading indicators of apoptosis. The annexins are multigene family of Ca^{2+}-regulated phospholipid-dependent and membrane-binding annexin proteins [89]. One member of the annexin gene family, annexin A5, is known as a Ca^{2+}-dependent, phospholipid-binding protein that inhibits protein kinase C (PKC) signaling. Although annexin A5 has been used for the detection of apoptosis, it shows high affinity for surface-exposed phosphatidylserine during apoptosis and may directly involve in apoptotic pathway [90]. Another member of annexins family is annexin A11, which is involved in calcium signaling, apoptosis, vesicle trafficking, cell growth, and the terminal phase of cell division [91].

According to the results obtained, the blood level of annexin-A5 was significantly lower in PTSD and which may also be one of the factors responsible for development of PTSD-associated low-grade inflammation [92, 93]. The results of annexin family proteins encoding genes association with PTSD are shown in Table 3. The *ANXA11* gene rs1049550*A allele was more frequent among controls than in patients (0.42 vs. 0.33, $p_{nominal} = 0.013$, OR = 0.695, 95% CI: 0.52–0.93). There were no significant differences of carriers of rs1049550*A minor allele in the group of patients compared to controls.

2.4. Candidate genes of synaptic plasticity

Synaptic plasticity change, which is a fundamental characteristic of the nervous system, underlies numerous aspects of cognition. Plasticity is essential for the recovery of the nervous system after injury, stroke, and other pathological processes and can permit remarkable functional recovery even after devastating damage, especially in a young and otherwise healthy brain. However, the very mechanisms of plasticity that permit development, learning, resilience, memory, and recovery can also contribute to behavioral dysfunction and to psychopathology [94].

Complexins are small, cytosolic proteins that bind to the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex to regulate synaptic vesicle exocytosis. Complexin 1 and 2 are the two major isoforms in the brain [95, 96]. Significant alterations of

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complexins 2 expression levels are seen in a number of neurological and psychiatric disorders, including bipolar disorder [97–99], major depression [98, 100], Huntington's disease (HD) [101, 102], schizophrenia [97, 100, 103–107], Parkinson's disease [108], Alzheimer's disease [109], and PTSD [93].

Neurotrophin family are traditionally recognized for their nerve growth promoting function and are recently identified as crucial factors in regulating neuronal activity in the central and peripheral nervous systems. The family members including brain-derived neurotrophic factor (*BDNF*), nerve growth factor (*NGF*), and its receptor (*NGFR*) are the essential mediators of synaptic and morphological plasticity, neuronal growth, survival, and differentiation; especially in the developing brain, thought may play an important role in pathogenesis of PTSD. [110]

We have reviewed data related neurotransmitter/neuroendocrine systems that are known to be involved in the pathophysiology of PTSD and that may contribute to the symptoms and cognitive dysfunctions in these patients. In Table 4, we have collected our data concerning candidate genes of the proteins involved in synaptic plasticity which may contribute to PTSD.

Gene (SNP)	**Genotypes**			**Alleles**		**Carriage**
***BDNF* rs6265**	GG	GA	AA	G	A	A
PTSD	150 (0.75)	48 (0.24)	2 (0.01)	348 (0.87)	52 (0.13)	50 (0.25)
Controls	129 (0.645)	67 (0.335)	4 (0.02)	325 (0.81)	75 (0.19)	71 (0.36)
p				**0.03**[a]		**0.02**[b]
OR				0.65		1.65
95% CI:				0.44 - 0.95		1.07 - 2.54
***CPLX2* rs1366116**	CC	CT	TT	C	T	T
PTSD	34 (0.39)	36 (0.41)	17 (0.2)	104 (0.6)	70 (0.4)	53 (0.61)
Controls	45 (0.6)	24 (0.32)	6 (0.08)	114 (0.76)	36 (0.24)	30 (0.4)
p				**0.006**[a]		**0.02**[b]
OR				2.2		0.43
95% CI:				1.4 – 3.6		0.2 - 0.8
***CPLX2* rs3892909**	CC	CT	TT	C	T	T
PTSD	16 (0.18)	45 (0.52)	26 (0.3)	77 (0.44)	97 (0.56)	71 (0.82)
Controls	15 (0.2)	41 (0.55)	19 (0.25)	71 (0.47)	79 (0.53)	60 (0.8)
p				1.7[a]		2.4[b]
OR				1.13		0.9
95% CI:				0.73 – 1.76		0.4 – 1.97
***NTNG1* rs628117**	AA	AG	GG	A	G	G
PTSD	47 (0.36)	66 (0.5)	19 (0.14)	160 (0.6)	104 (0.4)	85 (0.64)

Gene (SNP)	**Genotypes**			**Alleles**		**Carriage**
Controls	36 (0.34)	43 (0.41)	26 (0.25)	115 (0.55)	95 (0.45)	69 (0.66)
p				0.2[a]		0.8[b]
OR				0.79		1.06
95% CI:				0.55 – 1.14		0.62 - 1.82
***NGF* rs6330**	CC	CT	TT	C	T	T
PTSD	66 (0.33)	106 (0.53)	28 (0.14)	238 (0.6)	162 (0.4)	134 (0.67)
Controls	130 (0.65)	58 (0.29)	12 (0.06)	318 (0.8)	82 (0.2)	70 (0.35)
p				**2.04E-09[a]**		**4.20E-10[b]**
OR				2.64		3.77
95% CI:				1.9 - 3.6		2.5 - 5.7
***NGF* rs4839435**	GG	GA	AA	G	A	A
PTSD	130 (0.65)	66 (0.33)	4 (0.02)	326 (0.8)	74 (0.2)	70 (0.35)
Controls	85 (0.425)	97 (0.485)	18 (0.09)	267 (0.67)	133 (0.33)	115 (0.58)
p				**4.00E-06[a]**		**1.20E-05[b]**
OR				0.46		0.4
95% CI:				0.33 - 0.63		0.27 - 0.6
***NGFR* rs11466155**	CC	CT	TT	C	T	T
PTSD	109 (0.545)	82 (0.41)	9 (0.045)	300 (0.75)	100 (0.25)	91 (0.46)
Controls	110 (0.55)	75 (0.375)	15 (0.075)	295 (0.74)	105 (0.26)	90 (0.45)
p				1.37[a]		2[b]
OR				0.94		0.98
95% CI:				0.68 - 1.29		0.66 - 1.45
***NGFR* rs734194**	CC	CT	TT	C	T	T
PTSD	164 (0.82)	34 (0.17)	2 (0.01)	362 (0.9)	38 (0.1)	36 (0.18)
Controls	109 (0.545)	74 (0.37)	17 (0.085)	292 (0.73)	108 (0.27)	91 (0.46)
p				**2.74E-10[a]**		**8.82E-09[b]**
OR				0.284		0.263
95% CI:				0.19 - 0.42		0.17 - 0.42
***CHN1* rs14228**	CC	CT	TT	C	T	T
PTSD	79 (0.395)	86 (0.43)	35 (0.175)	244 (0.61)	156 (0.39)	121 (0.6)
Controls	82 (0.41)	62 (0.31)	56 (0.28)	226 (0.565)	174 (0.435)	118 (0.59)
p				0.39[a]		1.52[b]
OR				0.83		0.94
95% CI:				0.63 - 1.1		0.63 - 1.4

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Gene (SNP)	Genotypes			Alleles		Carriage
***CHN1* rs2646153**	AA	AG	GG	A	G	G
PTSD	50 (0.25)	86 (0.43)	64 (0.32)	186 (0.465)	214 (0.535)	150 (0.75)
Controls	57 (0.285)	90 (0.45)	53 (0.265)	204 (0.51)	196 (0.49)	143 (0.72)
p				0.4[a]		0.86[b]
OR				1.2		0.84
95% CI:				0.9 - 1.6		0.54 – 1.3
***FOS* rs7101**	CC	CT	TT	C	T	T
PTSD	12 (0.06)	71 (0.355)	117 (0.585)	95 (0.24)	305 (0.76)	188 (0.94)
Controls	94 (0.47)	85 (0.43)	21 (0.1)	273 (0.68)	127 (0.31)	106 (0.53)
p				**4.04E-37**[a]		**1.31E-21**[b]
OR				6.9		13.9
95% CI:				5.1 - 9.4		7.3 - 26.5
***FOS* rs1063169**	GG	GT	TT	G	T	T
PTSD	161 (0.8)	36 (0.18)	3 (0.02)	358 (0.9)	42 (0.1)	39 (0.2)
Controls	92 (0.46)	80 (0.4)	28 (0.14)	264 (0.66)	136 (0.34)	108 (0.54)
p				**1.50E-15**[a]		**1.70E-12**[b]
OR				0.23		0.21
95% CI:				0.16 - 0.33		0.13 - 0.32
***JUN* rs11688**	GG	GA	AA	G	A	A
PTSD	34 (0.17)	113 (0.565)	53 (0.265)	181 (0.45)	219 (0.55)	166 (0.83)
Controls	47 (0.24)	111 (0.56)	42 (0.2)	205 (0.51)	195 (0.49)	153 (0.77)
p				0.09[a]		0.11[b]
OR				1.27		0.67
95% CI:				0.96 - 1.68		0.4 - 1.1
***IER5* rs6425663**	GG	GT	TT	G	T	T
PTSD	29 (0.145)	78 (0.39)	93 (0.465)	136 (0.34)	264 (0.66)	171 (0.86)
Controls	20 (0.1)	74 (0.37)	106 (0.53)	114 (0.285)	286 (0.715)	180 (0.9)
p				0.09[a]		0.17[b]
OR				0.77		1.53
95% CI:				0.57 - 1.04		0.83 - 2.8

[a] $p_{corrected}$ values for comparison of mutant allele frequency between PTSD patients and controls.

[b] $p_{corrected}$ values for comparison of mutant allele carriage between PTSD patients and controls.

Table 4. Distribution of genotypes, alleles and carriage of minor alleles of *BDNF*, *CPLX2*, *NTNG1*, *NGF*, *NGFR*, *CHN1*, *FOS*, *JUN*and *IER5* polymorphisms in patients with PTSD and controls.

According to the data obtained, the rs6265*A allele of the*BDNF* gene was more frequent in controls than in patients (0.19 vs. 0.13, $p_{nominal}$ = 0.03, OR = 0.65, 95% CI: 0.44–0.95). Also, the carriers of rs6265*A minor allele were overrepresented in the group of controls compared to patients (0.36 vs. 0.25, $p_{nominal}$ = 0.02, OR = 1.65, 95% CI: 1.07–2.54). In contrast, the rs1366116*T minor allele of the *CPLX2* gene was more frequent among patients compared to controls (0.4 vs. 0.24, $p_{nominal}$ = 0.002, OR = 2.2, 95% CI: 1.4–3.6). Also, the carriers of this allele were more in the group of patients compared to controls (0.61 vs. 0.4, $p_{nominal}$ = 0.008, OR = 0.43, 95% CI: 0.2–0.8). Further, we found that the rs6330*T allele of the *NGF* gene was overrepresented in patients with PTSD compared to healthy subjects (0.4 vs. 0.2, $p_{nominal}$ = 1.02E-9, OR = 2.64, 95% CI: 1.93–3.61). Also, the carriers of the rs6330*T minor allele (CT + TT) were more frequent in patients than in controls (0.67 vs. 0.35, $p_{nominal}$ = 2.1E-10, OR = 3.77, 95% CI: 2.49–5.70). On the contrary, the frequency (0.33 vs. 0.2, $p_{nominal}$ = 2.0E-6, OR = 0.46, 95% CI: 0.33–0.63) and carriers (0.58 vs. 0.35, $p_{nominal}$ = 6.0E-6, OR = 0.40, 95% CI: 0.27–0.60) of the rs4839435*A minor allele of the *NGF* gene were higher in controls than in PTSD patients. The *NGFR* rs734194*T minor allele frequency again was higher in controls than in patients (0.27 vs. 0.1, $p_{nominal}$ = 1.37E-10, OR = 0.28, 95% CI: 0.19–0.42). The same applies to the carriers of the *NGFR* rs734194*T allele (0.46 vs. 0.18, $p_{nominal}$ = 4.41E-9, OR = 0.26, 95% CI: 0.17–0.42). Also, rs7101*T allele of the *FOS* gene was more frequent in patients than in controls (0.76 vs. 0.31, $p_{nominal}$ = 2.02E-37, OR = 6.90, 95% CI: 5.05–9.43). The carriers of rs7101*T minor allele were overrepresented in the group of patients compared to controls (0.94 vs. 0.53, $p_{nominal}$ = 6.57E-22, OR = 13.89, 95% CI: 7.28–26.51). In contrast, the rs1063169*T minor allele of the *FOS* gene was more frequent among controls compared to patients (0.34 vs. 0.1, $p_{nominal}$ = 7.48E-16, OR = 0.23, 95% CI: 0.16–0.33). Also, the carriers of this allele were more in the group of controls compared to patients (0.54 vs. 0.2, $p_{nominal}$ = 8.51E-13, OR = 0.21, 95% CI: 0.13–0.32). After Bonferroni correction, difference in allele frequency between the patient and the control groups for these minor alleles remained significant.

3. Conclusion

As found in several mental disorders, the risk for PTSD following traumatic event has limited genetic heritability. The genetic understanding of PTSD through candidate gene studies is premature at this point, although several genes hold promise as potential biomarkers. Identifying and understanding the genetics of PTSD will enrich our ability of diagnosis of PTSD. In Figure 1, we summarized the candidate genes responsible for generation and development of PTSD.

Several studies indicated the association between PTSD and polymorphisms of number of genes of dopaminergic, serotonergic, and GABAergic systems, HPA axis, and other genes related to neurotransmission, neuromodulation, etc. We also compiled a list of genes that have been reported in the literature to be significantly associated with PTSD, also adding our own results on variations in genes encoding neuro-, immune and apoptotic mediators and regulators, and related transcription factors. Profound understanding of risks in PTSD is possible through classic and convergent genomic approaches and this will lead to development of

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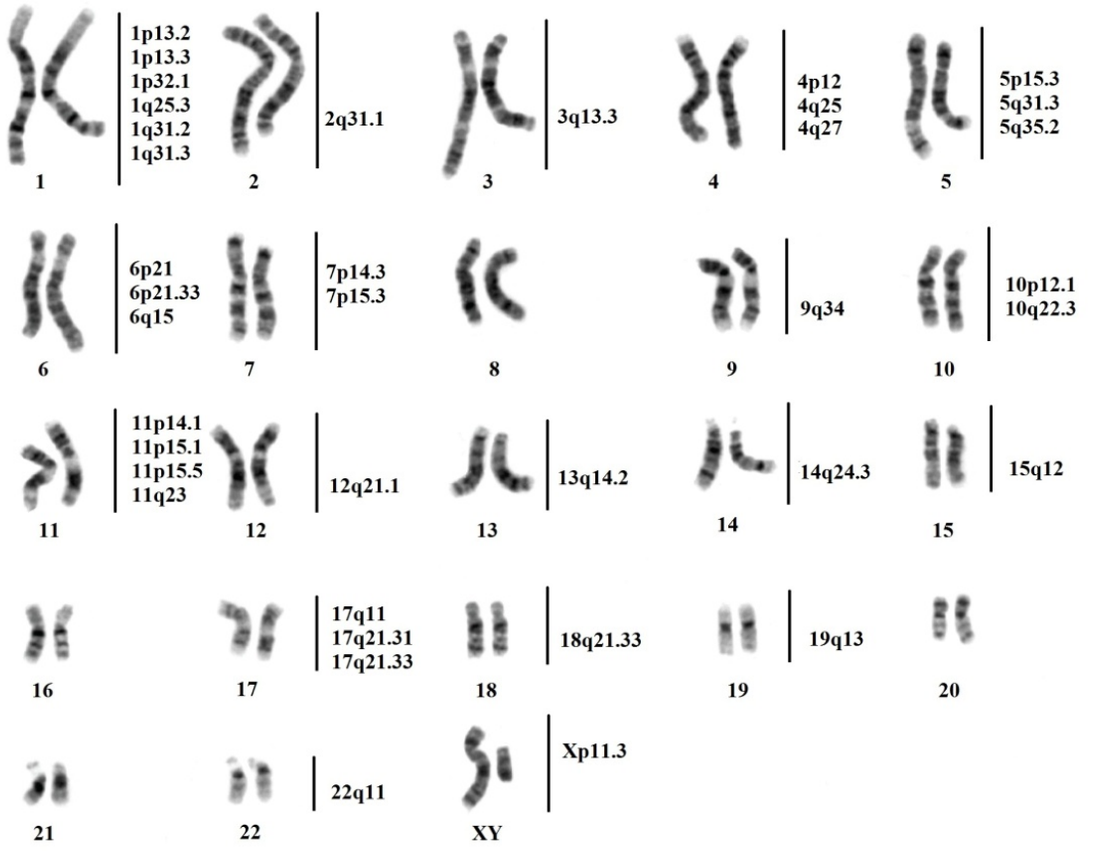

Figure 1. Candidate genes responsible for development of PTSD.

targeted treatment and prevention approaches. Overall, such researches highlight the potential usefulness of the assessment of target genes' alteration in diagnosis of PTSD.

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