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Genetic biomarkers related to the population risks of posttraumatic stress disorder development: single nucleotide variants, gene interactions, and haplotypes

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Abstract

Introduction. Post-traumatic stress disorder (PTSD) encompasses a wide spectrum of psychopathological manifestations that arise after exposure to a severe or life-threatening event. The increasing relevance of PTSD issues is associated with the escalation of military conflicts worldwide. Complex biological mechanisms also play a significant role in the pathogenesis of PTSD, including those changes observed in the hippocampus and other brain structures.

Aim – to identify the most significant genetic markers predisposing the risk of PTSD manifestation, which could contribute to the development of targeted interventions focusing on the preventive measures and treatment strategies of this disorder.

A literature search was conducted in the PubMed database using keywords related to the genetics of PTSD, with a publication time restriction from 2018 to 2023. Out of 623 papers, 20 articles met the inclusion criteria, describing molecular-genetic and statistical data, and the sample size of at least 60 patients with a verified PTSD diagnosis, were reviewed and analyzed in detail. The studies revealed significant associations between PTSD occurrence and single nucleotide variants (SNVs) in the FKBP5 and CRHR1 genes. Particular attention was paid to the interactions between SNVs of different genes and their association with the severity of PTSD clinical manifestations.

Conclusions. Genetic markers, in particular, SNVs in the FKBP5 (rs9470080) and CRHR1 (rs1724402) genes, may play a key role as the risk factors for biological predisposition and the PTSD development. These findings would underlie the targeted interventions integrated into PTSD-related prevention measures and treatment strategies. However, further multicenter and consortium studies with unified design are required to confirm the significance of the identified associations and to specify the epigenetic aspects contributing to the PTSD manifestation and development.

Keywords: ADCYAP1R, CRHR1/2, DRD2/4, FKBP5, NR3C1, post-traumatic stress disorder, SLC6A4.

Conflict of interest: nothing to disclose.

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Генетические маркеры, связанные с рисками развития посттравматического стрессового расстройства: однонуклеотидные варианты, взаимодействие генов и гаплотипов

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Аннотация

Введение. Клиническая картина посттравматического стрессового расстройства (ПТСР) включает широкий спектр психопатологических проявлений, отсроченно возникающих после воздействия тяжелого или угрожающего жизни события. Возрастающая актуальность проблемы ПТСР связана с эскалацией военных конфликтов во всем мире. В патогенезе ПТСР значительную роль также играют сложные биологические механизмы, в том числе изменения, наблюдаемые в гиппокампе и других структурах мозга.

Цель обзора – выявить наиболее значимые генетические маркеры, связанные с риском возникновения ПТСР, что могло бы способствовать разработке таргетных вмешательств, направленных на разработку профилактических мер и стратегий терапии этого расстройства. Нами проведен поиск литературы в базе данных PubMed по ключевым словам, связанным с генетикой ПТСР, с ограничением по времени выхода публикаций с 2018 по 2023 год. Из 623 работ 20 статей, отвечающих критериям включения, с описанием молекулярно-генетических, статистических данных и размером выборки не менее 60 пациентов с верифицированным диагнозом ПТСР, были подробно рассмотрены и проанализированы.

Были выявлены значимые ассоциации между возникновением ПТСР и однонуклеотидными вариантами (ОНВ) в генах FKBP5 и CRHR1 (ось гипоталамо-гипофизарно-надпочечниковой системы и нейроэндокринный путь). Важной исследовательской находкой явилось обнаружение взаимосвязей между однонуклеотидными вариантами определенных генов и тяжестью клинических проявлений ПТСР.

Выводы. Генетические маркеры, в частности однонуклеотидные варианты генов FKBP5 (rs9470080) и CRHR1 (rs1724402), играют ключевую роль как факторы биологической предиспозиции и риска развития ПТСР. Эти данные представляют важное значение для разработки таргетных вмешательств при уточнении мер профилактики и стратегий терапии ПТСР. Однако для подтверждения значимости выявленных ассоциаций «ген – среда» и уточнения эпигенетических аспектов, лежащих в основе манифестации и развития ПТСР, требуется проведение дальнейших мультицентровых и консорциумных исследований по унифицированному дизайну.

Ключевые слова: ADCYAP1R, CRHR1/2, DRD2/4, FKBP5, NR3C1, посттравматическое стрессовое расстройство, SLC6A4.

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Список сокращений
ПТСР – посттравматическое стрессовое расстройство; ОНВ – однонуклеотидный вариант (замена, полиморфизм); ПАВ – психоактивное вещество; ДИ – доверительный интервал; ОШ – отношение шансов.

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is a mental illness originating in the delayed period after exposure to a severe or life-threatening psycho-traumatic event and characterized with a wide range of psychopathological manifestations. These include sudden responses to triggers i.e. phenomena of repeated experience of bright pictures associated with the psycho-traumatic event (flashbacks), fear, anxiety, somatic autonomic manifestations, various degrees of mental confusion, nocturnal sleep disturbances, anxiety dreams and behavioral disorders, viz. alcohol and substance abuse, which reduces overall quality of life and results in the development of social estrangement and social and professional maladaptation, respectively. According to WHO data, the average prevalence of PTSD worldwide is 3.6%, whereas other sources report higher percentages: 8% for women and 4% for men [1]. At the moment, the problem of PTSD has become of greater vitality due to escalation of military conflicts which are a significant factor in the progression of PTSD.

Complex biological mechanisms are involved in the formation of PTSD manifestations. The hippocampus plays an important role in the pathogenic mechanism of PTSD, specifically, the CA3 zone that regulates processes of memory pattern completion and separation that are vital for the formation of behavioral response and emotional processing of new experiences [2, 3]. In some studies, these changes are linked directly with the changes in the neuroplasticity and neurogenesis in the hippocampus that are seen in PTSD, when the regulatory balance between the activity of the mature and the young of the hippocampus is disrupted.

Besides, the studies identified a distributed system of brain structures including the central nucleus of the amygdala, frontal part of the hippocampus and the orbital prefrontal cortex which lies in the basis of the mechanism of imprinting of the type of stress reaction formed at an early age, which also actualizes under the onset of PTSD in adult age [4]. The ongoing long-term activation of the hypothalamo-pituitary-adrenal axis provides the biological foundation for the development of PTSD comorbid sequelae [5].

From the standpoint of existing neurobiological models, the impact of severe and life-threatening stress states and traumas starts up a self-sustaining mechanism of synaptic dysfunction, particularly, in the key neural networks of emotional regulation (the amygdala – ventral medial area of prefrontal cortex – supracallosal gyrus – hippocampus axis) [6]. Other researchers suggest that the changes encompass the thalamus and the cores of the striatum, dorsolateral and dorsomedial areas of prefrontal cortex, posterior cingulate cortex, and the involved sensory areas of cortex [7]. The results of meta-analysis of numerous studies indicate the change in the volume of subcortical areas, which might account for the stability of the clinical performance of PTSD many years since the exposure to the stress factors [8].

These mechanisms are considered the results of gene-environment interactions, and whereas the role of the environment factors seems obvious, the gene basis of PTSD formation requires deeper research [9]. Zhang et al. (2017) [10] summarized results of seven genome-wide association studies (GWAS) on large samples. In these studies, most frequently identified genes were *FKBP5* (involved in the endocrine regulation), *ADCYAP1R1* (regulator of the signal path function), *NR3C1* (glucocorticoid receptor), *DRD2* (dopamine receptor linked to various neuropsychiatric

conditions), *CRHR1* (corticotropin-releasing hormone receptor) and *SLC6A4* (serotonin transporter in plasma membrane). It is of no less importance that these genes are expresses in the aforementioned areas of the brain associated with PTSD mechanisms [10].

We are of the opinion that single-nucleotide variants (SNVs) of these genes and their epistasis and interaction with environment factors might affect formation of susceptibility to development of PTSD.

AIM OF REVIEW

To identify among the aforementioned genes the most significant genetic markers predisposing the risk of PTSD manifestation, which could contribute to the development of targeted interventions focusing on the preventive measures and treatment strategies of this disorder.

MATERIAL AND METHODS

In order to perform the literature search in the optimal way, it was divided in two stages: first, we identified the suitable genes and polymorphisms and then performed a detailed analysis of candidate genes for the PTSD susceptibility using PubMed as the general database. We ran the first stage of search using the following keywords: «PTSD genetic markers», «PTSD genetics», «PTSD genetic polymorphism». The second stage included queries to search for specific genes identified in the first stage: «*FKBP5* and PTSD», «*ADCYAP1R* and PTSD», «*NR3C1* and PTSD», «*DRD2* and PTSD», «*DRD4* and PTSD», «*CRHR1* and PTSD», «*SLC6A4* and PTSD», «*CRHR2* and PTSD». The search yielded 623 publications, of which 20 met our criteria for the detailed analysis: they were published from 2018 to 2023, they were original research comprising molecular, genetic and statistical data, and the data on verification of diagnosis; PTSD was to be the primary condition, the sampling being at least 60 patients.

FK50-BINDING PROTEIN GENE, FKBP5. CORTICOTROPIN-RELEASING HORMONE RECEPTOR 1 AND 2 GENES, CRHR1/2. ALPHA-5-NICOTINE CHOLINORECEPTOR GENE, CHRNA5. ROR-RELATED ORPHAN RECEPTOR ALPHA GENE, RORA

Zhang *et al.* (2020) studied the role of SNVs of several genes including *FKBP5* (*rs3800373, rs1360780, rs9470080* and *rs9296158*), *CRHR1* (*rs4458044* и *rs242924*) and *CRHR2* (*rs8192496* and *rs2267715*) in 1,132 patients with PTSD surviving earthquakes in China. They found that the minor allele A of the polymorphism *rs2267715* in *CRHR2* was associated with a more severe progress of PTSD ($p<0.01$, beta = 1.26, 95%CI = 0.41-2.11). Besides, they saw a statistically significant impact of the SNV *FKBP5-CRHR1* (*rs9470080* × *rs4458044*) on the severity of PTSD in men ($p<0.05$) [11] (Table 1). Boscarino et al. (2022) studied four genetic markers related to PTSD: *FKBP5* (*rs16969968*), *RORA* (*rs8042149*), *CRHR1* (*rs110402*), and *CHRNA5* (*rs16969968*). They found that the link of the first two SNVs with the development of PTSD was statistically significant ($p<0.05$) [12]. Hu *et al.* (2020) reported similar results of the study with a different sampling [13].

In other studies, the groups of Zhang (2020) and Tamman (2019) studies the connections between the SNV of the *FKBP5* gene (*rs3800373, rs9296158, rs1360780, rs9470080*) and the diagnosis of PTSD among veterans of military conflicts. They found that patients with PTSD manifested the alleles A SNV *rs3800373*, G SNV *rs9296158*, C SNV *rs1360780* and C SNV *rs9470080* ($p<0.01$) with higher frequency [11, 14]. Besides, Hu *et al.* (2020) showed that the people with two minor alleles *FKBP5* (*rs9296158, rs3800373, rs1360780* and *rs9470080*) subjected to physical violence in childhood showed higher severity of PTSD symptoms [13].

Li *et al.* (2019) studied four known SVNs of the *FKBP5* gene (rs*3800373, rs9296158, rs1360780* and *rs9470080*) on the sample of 1,140 adult patients with PTSD (Table 1). They found that the *rs9470080* TT genotype was associated with the higher risk of development of PTSD and depression after low-severity stress events ($p<0.05$; OR = 0.13, 95%CI = 0.03-0.63) [15]. Young *et al.* (2018) did not find any connection between the development of PTSD and the interaction of *rs1360780* and psychological traumatization in the childhood [16]. In the study performed on the sample of military veterans diagnosed with PTSD, Kang *et al.* (2019) studied the SNV rs1360780 and found no statistically significant differences between the groups [17]. Jaksic et al. (2019) reported credible associations between the C allele SNV *rs1360780* of the *FKBP5* gene and the diagnosis of PTSD, and the severity of symptoms of the dominant model. However, these connections failed to keep their statistical significance after the Bonferroni correction ($\alpha=0.002$), as well as the connection of PTSD with SNV *rs17689918 CRHR1* [18].

Gelernter *et al.* (2019) performed a search for the whole genome associations using a sample of 146,660 military service veterans and identified the most significant associations with PTSD symptoms ($p<0.001$): *CRHR1* (allele C, *rs1724402*), *CAMKV* (*rs2777888*), *KANSL1* (*rs2532252*) and *TCF4* (*rs2123392*). Besides, the authors identified the statistically significant connections with other SNVs, including *KCNIP4* (*rs4697248*), *HSD17B11* (*rs7688962*), *MAD1L1* (*rs10235664*), *SRPK2* (*rs67529088*) and *LINC01360* (rs*7519147*) [19].

ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE TYPE I RECEPTOR GENE, ADCYAP1R1. SODIUM-DEPENDENT SEROTONIN TRANSPORTER GENE, SLC6A4

In the work performed by the group of (2021), the connection of the SNV of the *ADCYAP1R* gene (rs*2267735*) with the development of PTSD was studied on the sample of 1,132 patients surviving an earthquake. The researchers found the statistically significant connection of interaction of *ADCYAP1R1–FKBP5* (*rs2267735* × *rs1360780*) with the severity of the clinical pattern of PTSD (beta = -1.31, $p<0.05$). Besides, there was identified the statistically significant connection of the interaction of *ADCYAP1R1–CRHR1* (rs*2267735* × *rs242924*) with severity of PTSD in men ($p<0.05$) [20, 21].

Kravić *et al.* (2019) reported absence of significant connections of PTSD with the distribution of genotypes *SLC6A4* (serotonin membrane transporter) and *MAOA* (responsible for

Gene and localization of its expression	References	Cohort	Methods of assessment	Key findings
FKBP5 Hippocampus	Zhang et al. 2020	3890 people (18-62 years); M/F; All races; Military veterans	PCL-4	PTSD(+): A-allele of *rs3800373* (p<0.001; OR=1.3, 95%CI 1.1-1.6), G-allele of *rs9296158* (p<0.001; OR=0.2, 95%CI 0.2-0.3), the C-allele of *rs1360780* (p<0.001; OR=1.3, 95%CI 1.1-1.6), the C-allele of *rs9470080* (p=0.001; OR=2.9, 95%CI 2.4-3.4). PTSD(+) often had *AGCC haplotype* (*rs3800373-rs9296158-rs1360780-rs9470080*) (p<0.01; $\chi 2$=9.1) than PTSD(-).
	Qi et al. 2020	237 people; M/F; Chinese; Child loss experience	CAPS SCID	The distribution of the AGCC haplotype (*rs3800373-rs9296158-rs1360780-rs9470080*) was found to be significantly higher in the probable PTSD group compared to the non-PTSD group.
	Li et al. 2019	1140 people (17-66 years); M/F; Chinese; Earthquake Survivors	PCL-5	PTSD(+): T-allele (*rs9470080*) (p<0.05; OR = 0.1, 95%CI 0.03-0.6). PTSD(+)-depression: AGCT haplotype (*rs3800373-rs9296158-rs1360780-rs9470080*). No significance: *rs3800373, rs9296158* and *rs1360780*.
	Young et al. 2018	266 (18-62 years); M/F; All races; Military veterans	CAPS	PTSD(+): T-allele (*rs1360780*) (OR = 1.91, 95%CI 1.0-3.5).
	Jaksic et al. 2019	719 people; M/F; Caucasian; War survivors	CAPS, BSI, M.I.N.I.	No significance: C-allele (*rs1360780*).
	Kang et al. 2019	239 people; M; Military veterans	CAPS, PCL-4	PTSD(+): C-allele (dominant model) (*rs1360780*) (F=7.3; p<0.01).
	Hu et al. 2020	1042 people; M/F; Caucasian; Military veterans	PCL-5	PTSD(+): C-allele (*rs9470080*) (p<0.05).
	Tamman et al. 2019	577 people; M/F; Military veterans	PCL-5, SCID, CAPS	PTSD(+): G-allele (*rs9296158*), A-allele (*rs3800373*), C-allele (*rs1360780*), C-allele (*rs9470080*) (p≤0.001).
ADCYAP1R Amygdala and hippocampus	Wang et al. 2021	1132 people (18-73 years); M/F; Chinese; Earthquake Survivors	PCL-5	PTSD(+): *ADCYAP1R1-FKBP5* (*rs2267735* × *rs1360780*) associated with severity (beta = -1.3 and P = 0.05); *ADCYAP1R1-CRHR1* (*rs2267735* × *rs242924*) correlated with severity in men (beta = -4.7 and P = 0.02).
DRD2, DRD4 Hippocampus	Yuan et al. 2022	142 people (18-60 years); M/F; Chinese; Earthquake Survivors	SCID, CAPS	PTSD(+): Severe - reduced left CA3 volume - TC heterozygotes (*rs1800497*) (p<0.01).
	Hoxha et al. 2019	719 people; M/F; Caucasian; War survivors	CAPS, BSI	No significance: TaqI (rs1800497 of DRD2) and VNTR in exon 3 (DRD4).
	Zhang et al. 2018	1134 people (16-73 years); M/F; Chinese; Earthquake Survivors	PCL-5	PTSD(+): *DRDxANNK1-COMT* (*rs1800497×rs6269*) (p<0.05). No significance: *DRD2* (*rs1800497*)
	Zhang et al. 2019	1134 people (16-73 years); M/F; Chinese; Earthquake Survivors	PCL-5	PTSD(+): *OXTR–DRD2* (*rs2268498×rs1801028*) (p<0.01; OR = 9.2, 95%CI 3.1-27.5).
CRHR1, CRHR2 Hypothalamus	Zhang et al. 2020	1132 people (18-73 years); M/F; Chinese; Earthquake Survivors	PCL-5	PTSD(+): *CRHR2* A-allele (*rs2267715*) increased severity (p<0.01; beta = 1.3, 95%CI 0.4-2.1), *FKBP5-CRHR1* (*rs9470080×rs4458044* and *rs9296158* × *rs4458044*) was severity in men (p<0.05).
	Boscarino et al. 2022	1074 people; M/F; Caucasian, Non-whites; Military veterans	PCL-5	PTSD(+): *CRHR1* (G-allele; rs110402), *CHRNA5*, (A-allele; *rs16969968*), *RORA* (G-allele; *rs8042149*), *FKBP5* (T-allele; *rs16969968*) (p<0.05).
	Gelernter et al. 2019	146 660 people; M/F; All races; Military veterans	PCL-4	PTSD(+): *CRHR1* C-allele (*rs1724402*) was associated with PTSD (p<0.001)
SLC6A4 Amygdala	Kravić et al. 2019	719 people; M/F; Caucasian; War survivors	CAPS, BSI	No significance: *5-HTTLPR* (high-expressing long allele and low-expressing short allele)
	Taylor et al. 2019	78 people; M; Blast exposure interacts	PCL-5	Homozygous S carriers of *5HTTLPR* showed higher PTS rates than homozygous L carriers (p<0.01).
	Xiao et al. 2019	4072 people (13-18 years); M/F; Chinese; Earthquake Survivors	PCL-4	PTSD(+): A1/A1 of Taq1A (*rs1800497* of *DRD2*) (p<0.01; OR = 2.4, 95%CI 1.4-4.1), PTSD(-): 10/10 of *5-HTTVNTR* (p<0.001; OR = 0.166, 95%CI 0.1-0.3) No significance: *5-HTTLPR* (short or long alleles)
NR3C1 Prefrontal cortex	Castro-Vale et al. 2021	61 people; M; Caucasian; Military veterans	CAPS, SCID	PTSD(+): G-allele (*rs6198*) (p=0.05; OR = 3.6, 95%CI 1.1-11.8). No significance: *rs10052957, rs6189/rs6190, rs6195, rs41423247*.

Note: *PTSD – Post-traumatic stress disorder; PTSD(+) – the group of findings, that showed significantly positive associations with PTSD expressiveness; PTSD(-) – the group of findings, that showed reverse associations with PTSD expressiveness; FKBP5 – FK506 binding protein 5; ADCYAP1R – adenylate cyclase activating polypeptide 1 (pituitary) receptor; DRD2, DRD4 – Dopamine receptor D2/4; CRHR1, CRHR2 – Corticotropin-releasing hormone receptor 1/2; SLC6A4 – Solute carrier family 6 member 4, aka 5-HTT Variants: 5HTTLPR & 5HTTVNTR; NR3C1 – Nuclear receptor subfamily 3, group C, member 1 aka GR; CAPS - Clinician Administrated PTSD Scale; BSI - the Brief Symptom Inventory; PCL-4/5 - PTSD CheckList 4/5, SCID - Structured Clinical Interview for DSM Disorders; M.I.N.I - Mini International Neuropsychiatric Interview.*

Примечания: *ПТСР – посттравматическое стрессовое расстройство; ПТСР(+) – группа данных, показавших достоверную положительную связь с выраженностью ПТСР; ПТСР(-) – группа данных, показавших обратную связь с выраженностью ПТСР; FKBP5 – ген FK506-связывающего белка; ADCYAP1R – ген рецептора к активатору аденилатциклазы 1; DRD2, DRD4 – гены рецепторов дофамина D2/4; CRHR1, CRHR2 – гены рецепторов кортикотропин-рилизинг-гормона 1/2; SLC6A4 – ген транспортера серотонина, также известный как 5-HTT: 5HTTLPR и 5HTTVNTR; NR3C1 – ген глюкокортикоидного рецептора; CAPS – шкала ПТСР, назначаемая клиницистом (Clinician Administrated PTSD Scale); BSI – Brief Symptom Inventory; PCL-4/5 – Контрольный список ПТСР 4/5; SCID – Структурированное клиническое интервью по расстройствам DSM; M.I.N.I - Мини-международное нейропсихиатрическое интервью.*

Table 1. *Summary of the associations between common SNVs, gene interactions, haplotypes and PTSD*

Таблица 1. *Связи однонуклеотидных вариантов, межгенных взаимодействий и гаплотипов с риском развития ПТСР*

serotonin metabolism) in the sample 719 patients with PTSD and conventionally healthy people surviving a military conflict [22]. Taylor *et al*. (2019) studied the connections between the impact of explosion, *5HTTLPR* and PTSD symptoms. The people exposed to the explosion and having the *S*-allele had a more severe progression of PTSD as compared to carriers of the *S*-allele not exposed to the explosion, and to carriers of both *LL* alleles. (p<0.01) [23].

TYPE II AND IV DOPAMINE RECEPTOR GENE, DRD2/4. GLUCOCORTICOID RECEPTOR GENE, NR3C1

The study of Xiao *et al.* (2019) showed that the polymorphisms *DRD2 Taq I* and *5-HTTVNTR* had statistically significant connection to the PTSD diagnosis, whereas the *5-HTTLPR* had none. The genotype A1/A1 of the polymorphism *DRD2 Taq1* had significant association with the increased risk of development of PTSD (OR = 2.39, 95%CI = 1.39-4.12, p<0.01). On the contrary, the genotype 10/10 5-HTTVNTR decreased the risk of PTSD development with statistical significance (OR = 0.17, 95%CI = 0.08-0.34, p<0.001) [24]. Yuan *et al.* (2022) studied the associations between the SNV *rs1800497* (*Taq1A*), severity of PTSD and the volumes of the CA3 zone and the fascia dentata of the hippocampus. Even though they did not find any statistically significant association between the severity of PTSD and the total volume of the hippocampus in patients with the TT genotype, there was found a significant connection between the genotype and severity of PTSD, the most grave clinical pattern was related with reduction of the volume of the left CA3 among the TC heterozygotes (p<0.01) [25].

Hoxha *et al.* (2019) studied associations between the *DRD2* variant (*rs1800497*) and the variable number of tandem repetitions (*VNTR*), located in the third exon *DRD4* with the development of PTSD. The case control study found no significant associations. However, there was identified an association between SNV *DRD2* (*rs1800497*) and deviations in the score of PTSC symptoms per "Brief Symptom Inventory" scale both in the genotype and recessive models, the allele T being the risk allele (p<0.05) [26].

The study of Zhang *et al.* (2018) genotypified the SNVs of three genes *DRD2/ANNK1*, *COMT* and *DBH* in adults exposed to earthquake. The variant *rs1800497* is related to the density of D2 dopamine receptors, and the haplotypes rs6269-rs4633-rs4818-rs4680 impact the level and the activity of the catechol-O-methyl transferase metabolizing catechol amines. The statistical analysis of genetic data identified interaction between *DRD2/ANNK1-COMT* (*rs1800497* × *rs6269*) that was associated with the PTSD diagnosis. However, the analysis involving singular SNVs revealed no significance in the development of PTSD in any of them, as well as the 'gene-environment' interaction [27]. Furthermore, the same study of Zhang et al. (2019) analyzed two SNVs (*rs2268498* in *OXTR* and *rs1801028* in *DRD2*) in the Chinese cohort that was exposed to the earthquake in Wenchuan including 156 cases of PTSD and 978 people in the control group. The interaction between the genotypes *rs2268498* CC/CT and the allele C SNV *rs1801028* was associated with the PTSD diagnosis (p<0.01; OR = 9.18, 95%CI = 3.07 - 27.46) [28] (**Table 1**).

Castro-Vale *et al.* (2021) studies the association between five SNVs of the gene *NR3C1* (*rs10052957, rs6189/rs6190, rs6195, rs41423247* and *rs6198*) and PTSD in veterans of colonial wars in Portugal. The carriership of the variant 9β (allele G) *rs6198* showed the statistically significant association with PTSD within the dominant morel of heredity, and was associated with the severity of the clinical pattern of PTSD [29].

DISCUSSION

From the 20 studies in question, eight studied the SNVs of the glucocorticoid chaperon gene *FKBP5*, with the total sample of 8110 people. All authors studying the SNV *FKBP5* reported significant associations with PTSD for the variant *rs9470080*, regardless of the allele, C or T. However, the results for other variants (*rs9296158, rs3800373, rs1360780*) were ambiguous or statistically insignificant [13–18, 30]. The associations between the two haplotypes (*A-G-C-C* и *A-G-C-T*) and the specifics of progression of PTSD are of special interest due to novelty of results, yet the current data is insufficient to make any firm conclusions [15, 30, 31]; same concerns the results for interactions between the FKBP5 and other genes [14, 20].

As far as the dopamine receptor genes *DRD2/4* are concerned, four studies focused on their SNVs in a total sample of 1995 people and reported, mainly, insignificant associations with PTSD [25–28]. However, the group of Zhang (2018, 2019) found statistically significant interactions between *DRD2/ANKK1-Taq1A-COMT* (rs*1800497* × *rs6269*) and *OXTR–DRD2* (*rs2268498* × *rs1801028*) in a sample of 1134 people (p<0.05) [25, 28]. These results, in their turn, need further research to support their significance.

Among other research, three studies of *CRHR1/2* showed significant associations between separate SNVs and the development of PTSD [11, 12]. The study involving the genome-wide association search by Gelernter *et al.* (2019) on the sample of 146,660 military service veterans, the most significant association with PTSD was found for the C-allele *CRHR1* (*rs1724402*) (p<0.001) [19]. At the same time, the high significance of associations with the development of PTSD was seen in other SNVs: *CAMKV* (*rs2777888*), *KANSL1* (*rs2532252*) and *TCF4* (*rs2123392*) (p<0.001). This additional data had lesser statistical significance as compared with the SNVs mentioned above, but it deserves attention in the light of further research [19]. Based on the comparison of results shown in Table 1, the authors consider discussion of remaining studies unpractical due to contradictory data.

Generally, the presented results show some role of the genes coding the component of the neuroendocrine axis in the etiology of PTSD and the contribution made therein by the neurotransmission of catechol amines and serotonin. The correction of discrepancy in data used for our research is a question of major scientific interest. It is necessary to study the SNVs of the *FKBP5* gene, the haplotypes and the intergenic interactions, as well as earlier neglected SNVs showing high significance of connections with development of PTSD in genome-wide association study, which allows learning the epigenetic aspects of PTSD development, among other things [19, 32]. The answer to the question of the SNV contribution to the development of PTSD is vital for the targeted intervention that could only be performed immediately after the psychological trauma but before the progress of dysfunctions under PTSD would become stable with relevant morphofunctional changes in the patient's brain [33].

CONCLUSIONS

The analysis of the selected papers revealed two highly significant genetic markers related to the development of PTSD: *FKBP5* (*rs9470080*, both the C-allele and the

T-allele) and the C-allele of *CRHR1* (*rs1724402*). These results point at the hypothalamo-pituitary-adrenal axis and the neuroendocrine path as the potential target for the preclinical treatment in order to mitigate the risk and prevent the development of PTSD. Other results, such as the association of the haplotypes of *FKBP5* (*A-G-C-C: rs3800373-rs9296158-rs1360780-rs9470080*; *A-G-C-T: rs3800373-rs9296158-rs1360780-rs9470080*) and *FKBP5-CRHR1* (*rs9470080* × *rs4458044* and *rs9296158* × *rs4458044*) were less significant and studied in less detail. Collated data is of value to identify the vector of our future research. The authors think that genetic testing of patients exposed to psychological trauma might become the foundation for the primary prevention of PTSD in order to impede the cascade of changes in the nervous system leading to the sustainable clinical symptomatology. Although some singular genetic factors of PTSD development are well known, our understanding of the polygenic nature of the illness remains limited, considering insufficient data on epigenetic mechanisms of mental disorders. The priority studies of molecular and genetic foundations of PTSD can ensure a more detailed insight into the pathogenic mechanisms of the disease and development of efficient methods of its prevention and treatment.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study limitations. The study is subject to the typical limitations of review work. The present results are limited by the heterogeneous designs of the studies used for the analysis, as well as by the insufficient sample size to formulate unambiguous conclusions. We observe the need for further research clarifying the significance of risk factors for PTSD, taking into account the polygenic nature and epigenetic mechanisms of the disease.	***Ограничения исследования.*** Исследование подвержено типичным ограничениям обзорной работы. Настоящие результаты ограничены гетерогенными дизайнами исследований, использованных для анализа, а также недостаточным объемом выборки для формулирования однозначных выводов. Мы видим необходимость дальнейших исследований, связанных с уточнением значимости факторов риска развития ПТСР, учитывая полигенную природу и эпигенетические механизмы заболевания.
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Conflict of Interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. T.S. Syunyakov, X. Gonda, A.T. Sak, D.A. Smirnova – formulated the main idea and clarified the hypothesis; guided the study design; provided detailed manuscript editing. A.Ya. Gajduk, A.S. Sustretov, D.A. Kokorev, A.A. Kuznetsov – were responsible for scientific data collection, its systematization and analysis, wrote the first draft of the manuscript. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Т.С. Сюняков, К. Гонда, А.Т. Сак, Д.А. Смирнова – формулировка основной идеи и уточнение гипотезы; руководство оформлением исследования; редактирование рукописи. А.Я. Гайдук, А.С. Сустретов, Д.А. Кокорев, А.А. Кузнецов – сбор литературных данных, их систематизация и анализ, написание текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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