

REVIEW ARTICLE

Investigating the association between genetic factors and the mechanisms underlying post-traumatic stress disorder development

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ABSTRACT

Aim: To investigate the association between the main mechanisms underlying the post-traumatic stress disorder development and polymorphisms in genes encoding regulatory proteins, their receptors, and those regulating the functioning of dopaminergic, serotonergic and other neurobiological systems.

Materials and Methods: As part of the preparation of this review, a search for publications was conducted in the PubMed, Scopus and ResearchGate databases. Keywords relating to the genetic aspects of post-traumatic stress disorder and the functioning of dopaminergic, serotonergic and other neurobiological systems were used to select the relevant literature. The analysis included studies from the last decade that examined single-nucleotide polymorphisms and their impact on the pathophysiological mechanisms that may lead to post-traumatic stress disorder.

Conclusions: The study of polymorphisms in genes associated with the regulation of metabolic changes not only deepens our understanding of the pathogenesis of the disorder but also opens up new avenues for research aimed at identifying risk biomarkers and clarifying the mechanisms of stress reactivity. Further work in this area has the potential to lay the foundations for more accurate predictive models and the development of innovative therapeutic strategies.

KEY WORDS: post-traumatic stress disorder, pathogenesis of PTSD, serotonergic systems, dopaminergic systems, risk biomarkers, personalised approaches

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is one of the most serious problems in modern psychiatry and public health, as its development is linked to exposure of traumatic events, which can occur both in armed conflicts and in civilian life. PTSD is characterised by a range of symptoms that significantly reduce quality of life and affect a person's social functioning and work capacity. According to the DSM-5, the clinical manifestations of this disorder include intrusive memories, sleep disturbances, anxiety, emotional instability and avoidance of activities associated with the traumatic experience [1]. The persistence of symptoms for at least one month is a diagnostic criterion for PTSD, and the clinically administered CAPS-5 scale is used to assess their severity [2]. Research into this disorder is of not only medical but also social significance, as PTSD affects an individual's ability to adapt to society, their capacity for professional activity and their interpersonal relationships.

A nationwide cross-sectional study was recently carried out, involving over three thousand people. Its aim was to investigate the prevalence of stress, anxiety and symptoms of post-traumatic stress disorder amongst Ukrainians as a result of the full-scale russian invasion. The participants were divided into three groups: those who had not changed their place of residence; internally displaced persons; and a third group – those who had moved abroad. According to the results obtained, it was found that 50.8% of those who had not changed their place of residence met the DSM-5 criteria used to diagnose PTSD. For groups of internally displaced persons and those who have left Ukraine, this figure stands at 55.4% and 62.2% respectively. Only 7.2% of those surveyed reported no stress or anxiety, or low levels of either [3]. According to the National Health Service of Ukraine, the number of registered cases of PTSD in the first two months of 2024 was almost equal to the figures for the whole of 2021. In 2023, the incidence rate was more than four times higher than in 2021.

Post-traumatic stress disorder is a complex, multifactorial condition involving various pathogenetic mechanisms and the body's regulatory systems. Dysfunction of the serotonergic and dopaminergic systems, as well as other interrelated neurobiological mechanisms, plays an important role in its development. Serotonin regulates emotional state, sleep and the response to stress, and disturbances in the function of this neurotransmitter's transporters and receptors are associated with increased anxiety and reduced stress resilience. Dopamine, in turn, plays a key role in motivational processes, cognitive control and emotional regulation. An imbalance in its signalling pathways leads to disruption of the reward system and emotional stability, which are characteristic features of PTSD [4, 5]. This is precisely why genetic variants that influence the functioning of these neurobiological systems are regarded as important factors in an individual's vulnerability to developing the disorder.

AIM

The aim of this study was to perform a systematic review of the role of polymorphisms in genes that regulate the functioning of serotonergic, dopaminergic and other neurobiological systems in the development of a genetic predisposition to post-traumatic stress disorder. The main focus was on summarising current data on the relationship between genetic variants and patterns of stress reactivity, determining their contribution to the pathogenesis of PTSD, as well as outlining promising areas for further molecular-genetic research directed at identifying risk biomarkers and developing personalised approaches to prevention and treatment.

MATERIALS AND METHODS

Within the framework of this review, a comprehensive search was carried out for scientific publications in leading international databases – Scopus, PubMed and ResearchGate – which are widely used for medical and biological research. The search strategy was based on the use of key terms related to the genetic factors underlying the development of post-traumatic stress disorder, in particular single-nucleotide polymorphisms (SNPs) in genes that regulate the functioning of serotonergic, dopaminergic and other neurobiological systems. To ensure the analysis remained up to date, the focus was on articles published over the last decade. The review included studies examining the molecular and genetic basis of PTSD, the role of genetic variations in shaping individual susceptibility to stressors, and their impact on hormonal regulation.

This study is in line with the UN Sustainable Development Goals, in particular Goal 3 – 'Good Health and Well-being'. Its significance lies in helping to create a society where everyone has access to high-quality health-care, can maintain their physical and mental health, and has the means to lead a long and active life [6].

ETHICS

All sources used in this literature review are publicly available.

REVIEW AND DISCUSSION

Recent research has confirmed that post-traumatic stress disorder is a complex psychoneurobiological condition involving numerous regulatory systems within the body. The genetic variants that have been studied most extensively are those relating to the functioning of the, dopaminergic and serotonergic systems. The following sections provide an overview of the main findings from studies investigating associations between single-nucleotide polymorphisms of these systems and the risk of developing PTSD.

SEROTONERGIC SYSTEM

Serotonin (5-HT) is one of the key neurotransmitters in the central nervous system, playing a role in regulating a wide range of physiological and psychological processes. Its functional role includes controlling mood, sleep cycles and eating behaviour, as well as modulating responses to stress. Increased serotonin availability in the synaptic space is associated with an improvement in emotional state and a reduction in anxiety levels, which has formed the basis for the development of pharmacological agents that block its reuptake. It is precisely these mechanisms that underlie the action of most modern antidepressants. At the same time, reduced expression of the serotonin transporter (5-HTT) is regarded as one of the key factors in the development of stress-related psychopathological conditions, including post-traumatic stress disorder [7]. Variability in the structure of the genes that regulate the functioning of this system is the subject of active scientific research and may account for individual differences in susceptibility to stress-related psychopathology.

One of the most promising genes in the serotonergic system, which has attracted the attention of researchers, is *SLC6A4*, which encodes the serotonin transporter (5-HTT). This protein is responsible for the reuptake of serotonin from the synaptic space, thereby regulating its concentration and duration of action on postsynaptic

receptors. Disruptions in the functioning of the transporter may lead to an imbalance in serotonergic transmission, which is associated with increased vulnerability to anxiety and depression.

Particular attention is being paid to the study of single nucleotide polymorphisms in the *SLC6A4* gene, which may change the transporter's expression level or functional activity. For example, variations in the promoter region of this gene can influence the amount of protein synthesised and, consequently, the effectiveness of serotonin signalling regulation. Such genetic differences are regarded as potential biomarkers of an individual's susceptibility to developing post-traumatic stress disorder, as they may determine varying levels of stress resilience and emotional regulation. Therefore, research focusing on SNPs of the *SLC6A4* gene offers the prospect of a deeper understanding of the molecular mechanisms underlying PTSD and the development of personalised approaches to its prevention and treatment. A polymorphic region (5-HTTLPR) has been identified, located in the promoter region of the *SLC6A4* gene, with short (S) and long (L) repeats. Carriage of the S allele is associated with reduced expression of 5-HTT compared with the L allele [8, 9]. According to the results of a meta-analysis, it has been established that individuals who are carriers of the S allele show an association with increased sensitivity to stress [10]. Carriers of the S allele were found to have an increased susceptibility to developing anxiety and depressive symptoms, panic disorders and aggressive behaviour [11]. Other studies have also investigated the effect of promoter polymorphisms on serotonin transporter levels. In addition, the role of the rs25531 polymorphism (A/G, LG alleles) in regulating 5-HTT expression levels was also investigated. It turned out that carriers of the S allele exhibited a similar level of 5-HTT expression to that seen in carriers of the L and LG alleles. The studies concluded that impaired regulation of the 5-HTTLPR, and consequently impaired maintenance of extracellular serotonin levels, among individuals who are carriers of the LG and S alleles contributes to an increased risk of stress-related disorders, and in particular PTSD [12, 13]. Some researchers highlight the mediating role of 5-HTTLPR in the interaction between genotype and environment, particularly given that this gene undergoes significant epigenetic changes [14, 15]. *Wankerl et al.* found that individuals who combine two risk factors—the presence of the S allele and adverse prenatal or early childhood influences—exhibit significantly lower levels of serotonin transporter mRNA expression compared with those who do not have these factors. These molecular changes thus form the basis for an increased susceptibility to developing PTSD

in the presence of adverse environmental factors. In particular, in cases of child abuse, the risk of developing PTSD increased by 56.3% [16]. The presence of variants in the promoter region of the serotonin transporter gene, defined as an 'unfavourable genotype', is not an independent factor determining the development of post-traumatic stress disorder. However, the combination of this genotype with traumatic events in childhood or adulthood increases the probability of its occurrence. It has been confirmed that the highest risk of developing PTSD is found in individuals carrying the 5-HTTLPR polymorphism who have also experienced trauma during their lifetime [17].

Serotonin exerts its effects by interacting with specific receptors, consequently, the role of polymorphisms in the genes encoding these receptors is also being actively studied. *Donaldson et al.* investigated the effect of the rs6295 polymorphism of the serotonin 1A receptor (*HTR1A*) gene on the development of depression and PTSD. This polymorphism has been the subject of research as it may influence the regulation of *HTR1A* gene expression. It is located at position -1019 relative to the basal promoter region and is known as the C(-1019)G variant, which is common among population genetic variations. The results showed that carrying the G allele is associated with an increased risk of substance dependence, more frequent psychiatric hospitalisations and suicide attempts [18]. It has also been confirmed that elevated expression of serotonin 1A (5-HT1A) receptors among individuals carrying the G allele of the C(-1019)G polymorphism may lead to an increased risk of developing depressive disorders and a reduced therapeutic response. This effect is most intensely manifested in cases where a person has experienced significant stressful life events [19]. The results of another study also demonstrated a link between the rs6295 polymorphism of the *HTR1A* gene and conditions such as major depressive disorder and bipolar disorder [20]. The results of the meta-analysis revealed a significant association between the C(-1019)G (rs6295) polymorphic locus of the *HTR1A* gene and the development of panic disorder [21]. Other types of serotonin receptors and their genes, particularly 2A and 1B (*HTR2A* and *HTR1B*), were investigated to determine their influence on the development of aggressive behaviour and PTSD symptoms. The results showed that two polymorphisms of the *HTR2A* gene (rs7322347 and rs977003) are associated with the development of post-traumatic stress disorder. Furthermore, the association between the rs7322347 polymorphism and changes in behaviour and the development of aggression was confirmed [5]. Another polymorphism of the serotonergic system, G861C, located in the

serotonin 1B receptor gene (*HTR1B*), was investigated. A significant association of this polymorphic site was found in individuals with major depressive disorder. This is associated with the inhibition of serotonin release in the basal ganglia, which is explained by the activation of second messengers that reduce adenylate cyclase activity and regulate neurotransmitter secretion [22]. Other researchers have investigated the role of the rs6311 (-1438A/G) polymorphism in the promoter region of the *HTR2A* gene in increasing the risk of developing depressive disorders. This association has been confirmed, and the rs6311 polymorphism has been recognised as an important factor contributing to susceptibility to depression [20, 23].

DOPAMINERGIC SYSTEM

Dopamine is one of the key neurotransmitters in the central nervous system, playing a role in regulating motivational processes, emotional reactivity, and cognitive functions. It is synthesised in dopaminergic neurons of the midbrain, particularly in the ventral tegmental area and the substantia nigra, and is transmitted to various brain structures via the activation of specific receptors. There are five main types of dopamine receptors (D1–D5), which belong to two functional families: D1-like (D1, D5) and D2-like (D2, D3, D4). The first activate adenylate cyclase and enhance intracellular signalling, whilst the second inhibit it, maintaining a balance between excitation and inhibition in neural networks. This diversity of receptors enables dopamine to modulate a wide range of mental and behavioural processes. The dopaminergic system functions via several main pathways: the mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular pathways. The mesolimbic pathway is responsible for the formation of motivation and emotional strengthening, the mesocortical pathway for cognitive control and emotional regulation, the nigrostriatal pathway for motor activity, and the tuberoinfundibular pathway for hormonal regulation. The coordinated functioning of these pathways ensures the body's adaptive response to stressors and maintains mental balance. Disruptions in the functioning of the dopaminergic system, particularly an imbalance in the activity of dopamine receptors or transporters, can lead to pathological changes in memory processes and emotional regulation, which is of direct relevance to the development of post-traumatic stress disorder [24].

Disruptions in the regulation of the dopaminergic system are considered to be one of the key mechanisms underlying the pathogenesis of post-traumatic stress disorder. Imbalances in neurotransmitter systems can lead to emotional instability and alter reward

processing, which are characteristic features of PTSD. Particular importance is attached to the mesolimbic dopaminergic pathway, which underpins motivational processes and reward processing. Findings from neurobiological studies indicate that patients with PTSD exhibit reduced responsiveness in the reward system compared with a control group, suggesting that it is dysfunctional. Such dopaminergic dysregulation may be a critical factor in the development of the disorder's symptoms, highlighting the importance of studying changes in dopamine signalling pathways to understand the pathophysiology of PTSD [25]. Because of this, the dopamine D2 receptor gene (*DRD2*) was the subject of the study. It is known that the D2 receptor is involved in the transmission of dopamine signals in presynaptic and postsynaptic neurons; its function is linked to G-protein-coupled receptors (GPCR) and is also associated with the development of PTSD [26]. Genetic variations of the *DRD2* gene are considered to be a factor that may influence an individual's susceptibility to developing post-traumatic stress disorder [27]. Studies show that this gene is associated with a range of psychopathological symptoms, including irritability and schizophrenia [28]. It is suggested that polymorphisms in the *DRD2* gene may alter the typical response to stressful stimuli by influencing cognitive information processing and increasing the risk of developing PTSD and aggressive behaviour [29]. *Niu et al.* investigated the effect of the rs1800497 polymorphism of the *DRD2* gene on susceptibility to PTSD. Two alleles, T (A1) and C (A2), were identified at this polymorphic site. This *DRD2*/ANKK1-Taq1A polymorphic site (rs1800497) is located on chromosome 11 within the ANKK1 gene and in close proximity to the *DRD2* gene. The rs1800497 polymorphism is associated with impaired regulation of dopamine synthesis and reduced expression of D2 receptors in the brain, creating the neurobiological conditions for the manifestation of post-traumatic stress disorder symptoms. The available data suggest that this genotype variant may intensify the severity of clinical manifestations of PTSD, and carriers of the A1 allele show an increased susceptibility to developing the disorder following a traumatic event [30].

The potential influence of polymorphisms in other dopamine receptor genes on the development of PTSD has also been studied intensively. Four polymorphisms of the dopamine D3 receptor (*DRD3*) gene were investigated: rs2134655, rs201252087, rs4646996 and rs9868039. An association between these polymorphic loci and a reduced risk of developing PTSD has been confirmed. Individuals who were carriers of the minor allele for the polymorphisms under investigation showed a statistically significant reduction in the risk

of developing PTSD [25]. Another genetic variant that may be linked to the mechanisms underlying mental disorders such as PTSD is a polymorphism of the dopamine D4 receptor gene (*DRD4*). This gene is characterised by the presence of a variable number of tandem repeats (VNTR), which can range from 2 to 10 copies, with alleles containing 4 and 7 repeats being the most common. A statistically significant association has been identified between this polymorphic site of the *DRD4* gene and PTSD: carriers of the 7-repeat allele have an increased risk of developing this disorder compared with non-carriers. These findings highlight the role of genetic factors in determining vulnerability to PTSD [5]. The dopamine transporter (DAT), which is responsible for dopamine reuptake and maintaining the balance of extracellular dopamine concentrations, is of interest in studies investigating the role of polymorphisms in the gene encoding it (*SLC6A3*) in dopamine metabolism and PTSD development. One of the most extensively studied polymorphisms is the VNTR located in the 3' UTR region of the *SLC6A3* gene. This genetic polymorphism is characterised by the presence of alleles with 9 repeats (9R) and 10 repeats (10R). The presence of the 9R allele in the genotype is associated with reduced DAT expression and increased dopamine levels in the synaptic space. As for carriers of the 10R allele, an increase in affinity for the dopamine transporter and in the efficiency of dopamine reuptake has been observed [31]. Such changes in dopamine metabolism may alter the neuronal response to stressful and traumatic stimulations, thereby impairing the effectiveness of adaptive mechanisms. Dysregulation of this system creates conditions that reduce stress resilience and increases the probability of developing post-traumatic stress disorder, forming the neurobiological basis for its clinical manifestations.

Given the metabolic changes associated with PTSD, researchers have turned their attention to an enzyme known as catechol-O-methyltransferase (COMT), whose function is to inactivate neurotransmitters such as noradrenaline and dopamine in the prefrontal cortex. This enzyme is encoded by the *COMT* gene and is located on chromosome 22q11.21. The rs4680 (Val158Met) polymorphic site of the *COMT* gene is one of the most extensively studied single-nucleotide variants of this gene. It has attracted considerable attention from researchers analysing the neurobiological mechanisms of psychiatric disorders, including post-traumatic stress disorder, obsessive-compulsive disorder and schizophrenia [32]. As a result of the rs4680 single-nucleotide polymorphism, located in exon 4 of the *COMT* gene, an amino acid substitution from valine (Val) to methionine (Met) occurs at codon 158 (Val158Met). Such changes in amino

acid composition result in a four-fold reduction in the activity of the enzyme catechol-O-methyltransferase among individuals who are carriers of the minor allele, compared with homozygotes for the major allele [33]. Such a reduction in enzyme activity leads to changes in neurotransmitter metabolism and, in particular, to an increase in the bioavailability of dopamine, which may have a significant impact on the neurobiological mechanisms governing emotions and stress responses. As a result, carriers of the minor allele show an increased susceptibility to psychiatric disorders, including post-traumatic stress disorder. A research team headed by *Mestrovic H.A.* conducted a study involving military veterans of combat operations with a confirmed diagnosis of PTSD and members of a control group without mental disorders. The aim of this study was to investigate the effect of the Val158Met polymorphism on the activity of catechol-O-methyltransferase and dopamine availability, which are associated with cognitive impairment. An association between this polymorphic variant of the *COMT* gene and the development of PTSD was confirmed; it was also found that cognitive function scores, as assessed using specialised tests (ROCF), were significantly higher among individuals in the control group compared with the group of veterans. For individuals with PTSD who are carriers of the Met allele, the results of cognitive tests were higher than those of Val/Val homozygotes. Thus, the presence of one or two Met alleles of the *COMT* gene at the rs4680 polymorphism exerts a protective effect on working memory mechanisms and cognitive functions in military personnel who have experienced trauma during combat operations and have been diagnosed with PTSD. [34]. *Deslauriers et al.* conducted a study into the role of the Val158Met polymorphism of the *COMT* gene in the development of PTSD among marines and navy personnel of European-American descent. The service personnel were assessed prior to deployment on combat missions in Afghanistan and 4–6 months thereafter; the study evaluated the presence and resolution of fear-potentiated startle, combat experiences and childhood trauma, as well as symptoms of post-traumatic stress disorder. Studies investigating the association between the *COMT* genotype and fear extinction in healthy, non-traumatised individuals found no such association. However, among military personnel who were Met/Met carriers, a statistically significant association was found between combat trauma and reduced fear extinction, compared with Val/Val carriers [35].

OTHER POLYMORPHIC SITES

In addition to the most extensively studied genetic mechanisms related to key neurobiological systems,

the current literature describes the role of a broader spectrum of polymorphisms that may be involved in the mechanisms underlying vulnerability to post-traumatic stress disorder. Such polymorphisms may be associated with social behavior, hormonal regulation, and emotional reactivity, and may play an important role in individual differences in response to traumatic events. Since, despite numerous studies of the complex pathogenic mechanisms underlying the development of PTSD and the role of genetic factors in these mechanisms, no gene has been identified whose structural changes could unequivocally be the cause of PTSD, scientists continue to expand the scope of their research.

One of the genetic factors that may be involved in the development of clinical manifestations of PTSD is polymorphisms in the oxytocin receptor (*OXTR*) gene. A significant association has been identified between the rs53576 polymorphic site of the *OXTR* gene and the pathogenic mechanisms underlying the development of PTSD throughout life [36]. *Zhang et al.* analyzed the effect of polymorphisms in the dopaminergic and oxytocinergic systems on the development of PTSD among a Chinese population that had experienced trauma as a result of an earthquake. This study examined the rs2268498 polymorphism of the *OXTR* gene and the rs1801028 polymorphism of the *DRD2* gene. An increased risk of developing PTSD was found in the presence of the combined effect of the rs2268498×rs1801028 polymorphisms of the genes under study ($P = 0.043$). Thus, this study confirmed the significant role of the interaction between the dopaminergic and oxytocinergic systems in the development of PTSD [37].

It is known that the activity of the monoamine oxidase A enzyme, which breaks down neurotransmitters such as serotonin, dopamine, and epinephrine, may influence the development of aggressive behaviors and PTSD. Four polymorphic sites of the monoamine oxidase A (*MAOA*) gene (rs5906893, rs5906957, rs2283725, rs2072744, and rs979605) were studied, and an association with the onset of antisocial personality disorder was established. [5]. Monoamine oxidase B also plays a role in the breakdown of neurotransmitters. A significant association has been found between the rs1799836 polymorphism of the monoamine oxidase B (*MAOB*) gene and the development of depressive states and the presence of negative emotional personality traits. In addition, an association has been confirmed between this polymorphic locus of the *MAOB* gene and the severity of PTSD in male military personnel and combat veterans [25].

Another factor considered to potentially increase the probability of developing anxiety disorders, particularly post-traumatic stress disorder, is the neuropeptide Y

(*NPY*) gene. The study results showed that individuals who are carriers of the minor allele at the rs16147 polymorphism of the *NPY* gene exhibited an increased susceptibility to developing PTSD [38].

The ADCYAP type I receptor gene (*ADCYAP1R1*) encodes a G-protein-coupled receptor that interacts with the neuropeptide PACAP (pituitary adenylate cyclase-activating peptide) and plays a role in regulating a number of physiological processes, including the body's response to stress. The results of the meta-analysis showed that carrying the C allele at the rs2267735 polymorphism of the *ADCYAP1R1* gene is associated with an increased risk of developing PTSD in the overall study sample and among women and girls, whereas no such association was found among men and boys. The findings suggest a possible role for the *ADCYAP1R1* gene in the development of PTSD, and this effect may differ depending on gender [39].

According to some scientists, inflammatory changes play an important role in the pathogenic mechanisms underlying the development of PTSD. For this reason, the influence of polymorphisms in genes of the inflammatory system was also investigated. Polymorphisms in the promoter region of the *TNFA* gene, which encodes the key pro-inflammatory cytokine tumor necrosis factor α , are associated with an increased susceptibility to post-traumatic stress disorder. In particular, the SNP rs1800629 was found to be significant in terms of the severity of PTSD symptoms, with the GG genotype identified as a risk variant for mental disorders. In addition, significant differences in serum TNF α levels were found between patients with PTSD and the control group, and correlations were identified between elevated expression of this cytokine and a more severe clinical course of PTSD. These findings highlight the potential role of TNF α as a genetic risk factor and a biomarker of functional changes that contribute to the pathogenesis of the disorder [40]. The *IL1B* gene, which encodes the pro-inflammatory cytokine interleukin-1 beta and regulates immune mechanisms, was studied in the context of its association with the development of PTSD. The analysis showed that the minor alleles of SNPs rs1143633C and rs16944A were significantly less common among individuals with PTSD compared to the control group. This association suggests a potential protective effect of these alleles against the development of PTSD, which, in turn, indicates a possible involvement of the *IL1B* gene in the pathogenic mechanisms of the disorder [41].

CONCLUSIONS

Post-traumatic stress disorder is a complex, multifactorial condition that develops as a result of the interaction

of numerous neurobiological and psychosocial mechanisms. Research confirms that imbalances in key neurotransmitter systems, disruptions in hormonal regulation and changes in the functioning of neural networks create conditions that reduce stress resilience and increase vulnerability to the development of PTSD. Importantly, genetic variations do not act in isolation – their impact is amplified when combined with adverse environmental factors, such as childhood trauma or combat experience.

Therefore, PTSD should be regarded as the result of a complex interplay of genetic, biological and social factors. Further research should focus on integrating molecular-genetic data with clinical and psychosocial indicators, which will enable the development of more accurate risk prediction models. A promising area of research is the search for biomarkers that could form the basis for personalised diagnosis and treatment, as well as the development of individualised prevention and treatment strategies that take into account patients' genetic characteristics and life experiences.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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