Using the Strategy of Genome-Wide Association Studies to Identify Genetic Markers of Suicidal Behavior: A Narrative Review

Использование стратегии полногеномного поиска ассоциаций (GWAS) для идентификации генетических маркеров суицидального поведения: описательный обзор литературы

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Review

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ABSTRACT

BACKGROUND: Several studies involving various suicidal phenotypes based on the strategy of the search of genome-wide associations with single nucleotide polymorphisms have been performed recently. These studies need to be generalized.

AIM: To systematize the findings of a number of genome-wide association studies (GWAS) for suicidal phenotypes, annotate the identified markers, analyze their functionality, and possibly substantiate the hypothesis holding that these phenotypes reflect a nonspecific set of gene variants that are relevant as relates to stress-vulnerability as a key endophenotype of suicidal behavior (SB).

METHODS: A search on the PubMed and related resources using the combinations "suicide AND GWAS" and "suicidal behavior AND GWAS" was performed. It yielded a total of 34 independent studies and meta-analyses.

RESULTS: For the 10 years since such studies emerged, they have undergone significant progress. Estimates of the SNP heritability of SB in some cases are comparable with estimates of heritability based on the twin method. Many studies show a high genetic correlation with the genomic markers of the most common mental disorders (depression, bipolar disorder, schizophrenia, post-traumatic stress disorder). At the same time, a genomic architecture specific to SB is also encountered. Studies utilizing the GWAS strategy have not revealed any associations of SB with candidate genes that had been previously studied in detail (different neurotransmitters, stress response system, polyamines, etc.). Frequently reported findings from various studies belong in three main groups: 1) genes involved in cell interactions, neurogenesis, the development of brain structures, inflammation, and the immune responses; 2) genes encoding receptors for neurotrophins and various components of the intracellular signaling systems involved in synaptic plasticity, embryonic development, and carcinogenesis; and 3) genes encoding various neuro-specific proteins and regulators.

CONCLUSION: In general, GWAS in the field of suicidology mainly serve the purpose of a deeper understanding of the pathophysiology of suicidal behavior. However, they also demonstrate growing capability in terms of predicting and preventing suicide, especially when calculating the polygenic risk score among certain populations (psychiatric patients) and in combination with tests of different modalities. From our point of view, there exists a set of markers revealed by the GWAS strategy that seems to point to a leading role played by stress vulnerability, an endophenotype that is formed during early development and which subsequently comes to play the role of key pathogenetic mechanism in SB.

АННОТАЦИЯ

ВВЕДЕНИЕ: В последние годы накапливаются данные, полученные с использованием стратегии поиска ассоциаций различных суицидальных фенотипов с однонуклеотидными полиморфизмами, которые нуждаются в обобщении.

ЦЕЛЬ: Систематизировать находки полногеномного поиска ассоциаций (GWAS) по суицидальным фенотипам, аннотировать выявленные маркеры, проанализировать их функциональность и найти возможные подтверждения гипотезы о том, что они отражают неспецифический набор генных вариантов, имеющих отношение к стресс-уязвимости как к ключевому эндофенотипу суицидального поведения.

МЕТОДЫ: Поиск материала осуществляли в базе данных PubMed по ключевым словосочетаниям «suicide AND GWAS», «suicidal behavior AND GWAS» с использованием взаимосвязанных источников, что позволило выявить 34 независимых исследования и метаанализа.

РЕЗУЛЬТАТЫ: За 10 лет с момента своего появления исследования этого типа продемонстрировали значительный прогресс. Оценки SNP-наследуемости суицидального поведения (СП) в ряде случаев приближаются к оценкам наследуемости близнецовым методом. Во многих исследованиях выявляется высокая генетическая корреляция с геномными маркерами наиболее распространённых психических расстройств (депрессия, биполярное расстройство, шизофрения, посттравматическое стрессовое расстройство), но в то же время обнаруживается и специфическая для СП геномная архитектура. Исследования в рамках стратегии GWAS не выявляют ассоциаций СП с наиболее детально исследованными ранее генами-кандидатами (медиаторные системы мозга, система стресс-реагирования, полиамины и др.). Повторяющиеся геномные находки относятся к трем основным группам: 1) гены, вовлечённые в межклеточные взаимодействия, формирование структур мозга, нейрогенез, воспаление и иммунные реакции; 2) гены, кодирующие рецепторы к нейротрофинам и различные компоненты внутриклеточных сигнальных систем, участвующих в синаптической пластичности, эмбриональном развитии и канцерогенезе; 3) гены, кодирующие различные нейроспецифические белки и регуляторы.

ЗАКЛЮЧЕНИЕ: Стратегия GWAS в сфере суицидологии в основном служит целям более глубокого понимания патофизиологии СП, но при этом демонстрирует растущий потенциал в плане предикции и превенции суицидов, особенно при расчёте полигенного риска, среди определённых контингентов (психиатрические пациенты) и в сочетании с тестами других модальностей. Выявляемый средствами GWAS набор наиболее часто повторяющихся маркеров, с нашей точки зрения, отражает ведущую роль в генезе СП феномена стресс-уязвимости — формируемого в процессе раннего развития эндофенотипа, который впоследствии играет роль ключевого патогенетического механизма суицида.

Keywords: *suicidal behavior; genome-wide associative studies; genomic markers; stress vulnerability*
Ключевые слова: *суицидальное поведение; полногеномные ассоциативные исследования; геномные маркеры; стресс-уязвимость*

INTRODUCTION

The research on the genetics of suicide has a long history. The tendency for suicide to run in families has been recognized for a considerable time, and this understanding has consistently served as a basis for acknowledging the role of heredity in this vexing phenomenon, as supported by dedicated studies [1]. Behavioral genetics (psychogenetics) seeks to tackle the challenge of determining the relative contributions of genes and the environment to specific behaviors, psychological traits, or mental disorders [1, 2]. During the pre-genomic era, research on the genetics of suicide used family and twin studies, as well as studies involving adopted children. Those types of studies estimated the heritability of suicidal behavior (SB) to be between 43% and 55%, attributing the remaining influence to environmental factors in their broadest sense (family, upbringing, peers, life stress, social factors, etc.) [3, 4].

In the subsequent phase of the investigation of heredity contributors to SB following the sequencing of the human genome and the advent of cost-effective methods for identifying gene variants, such as the polymerase chain reaction, the genetics of suicide has developed for a long time along the candidate-gene approach [2]. From the perspective of pathophysiology and psychobiology, crucial brain systems such as the serotonergic system, the catecholamine system, the GABAergic system, the excitatory amino acid system, and the stress response system, along with other neurobiological mechanisms, play a central role in SB. These systems influence the diathesis–stress and the associated predisposing traits and behavior patterns that can lead to impulsive or deliberate self-harming actions [5]. Despite hundreds of studies conducted in this area, only a few identified associations, such as those with the genes for tryptophan hydroxylase 2 (*TPH2*), serotonin transporter (*5-HTT*), and the brain-derived neurotrophic factor (*BDNF*), have been confirmed in independent studies [6]. Factors contributing to the frequent discrepancies in the results include small and not-always-monoethnic samples and the heterogeneity of phenotypes [6]. SB accompanies various psychopathologies; some suicides are committed in the context of depression, bipolar disorder, alcohol or drug addiction, and schizophrenia (SCZ) [7]. This is particularly significant for Russian psychiatry, as preventing suicides in clinical populations remains a challenge and has been the focus of targeted studies funded by the state. Notably, only a small proportion of patients with these disorders commit suicide, indicating that the inheritance of SB can be differentiated from the inheritance of mental disorders. This necessitates an in-depth study of the genetic markers of suicide as they compare with markers of the aforementioned psychopathologies and some personality traits, such as aggressiveness or impulsivity [7].

In recent years, the focus of research has shifted from the candidate gene strategy to genome-wide association studies (GWAS) [8]. Unlike the candidate gene approach, GWAS involve a hypothesis-unencumbered search for associations between specific traits, pathologies, or behaviors and a broad array of polymorphisms across the human genome [8]. Central to this approach are single nucleotide polymorphisms (SNPs), the most common genetic variations in the human genome, their proximity to known coding regions, their potential functional significance, and their overall contribution to the heritability of particular pathologies or behaviors. The "Common Disease-Common Variants" hypothesis underlies the GWAS strategy, suggesting that familial pathologies with heritability around 40% can be attributed to the very weak effects of hundreds or thousands of polymorphisms, each with allele frequencies of approximately 40% in the population [8]. Many other considerations from population genetics, the identification of direct and indirect effects, and accounting for linkage disequilibrium and correlations between polymorphisms have led to the understanding that analysis from 500,000 to 1 million SNPs simultaneously, given a sufficiently large monoethnic sample, should result in successful identification of the relevant markers [8]. The tools employed in these studies, such as diagnostic arrays, are commercially available from companies like Illumina, Inc. and Affymetrix, Inc.

The design of studies within this strategy typically involves case-control studies, where populations that either exhibit or do not exhibit a particular behavior or trait (categorical variant) or show a continuum of a trait or behavior (dimensional variant) are compared across a large number of markers. Factors such as phenotype homogeneity and statistical data processing methods, which rely on non-trivial approaches and specialized software when p-values $<7.2\times10^{-8}$ are set as a significance criterion for the entire genome, play a crucial role [9]. Additionally, the GWAS approach employs special techniques such as the multilocus analysis, and analysis from the perspective of protein-protein interactions or probable biochemical pathways, where a set of SNPs is identified based on their potential relation to metabolic processes [8]. From

the identified independent risk markers associated with a particular disorder (ranging from several dozen to several hundreds), a polygenic risk score (PRS) is calculated based on data from the largest or most informative GWAS to date [10]. The importance of the PRS lies in its potential predictive value for certain individuals under particular conditions. Thus, the effectiveness of GWAS significantly depends on data accumulation, sample pooling, comparison with existing databases (repositories of biomedical knowledge), and the statistical analysis methods used. Another important task is to calculate the heritability of the pathology considering all identified markers: known as SNP heritability (h^2_{snp}). Overall, the GWAS strategy enables the exploration of the "genomic architecture" of any complex trait, behavior, or disorder.

Despite the limitations, assumptions, and uncertainties inherent in the method and data processing, GWAS have demonstrated their effectiveness in revealing the genomic architecture of various diseases, such as macular degeneration. They have also led to advances in pharmacogenetics, particularly in psychiatry and addiction medicine [11]. In suicidology, GWAS have also gained wide acceptance despite a significant limitation: a completed suicide (CS) is a relatively rare event globally, occurring in just 0.014% of the population [12], which makes it difficult to classify the occurrence as common. However, it should be borne in mind that the prevalence of suicide attempts (SA) is tens of times higher, and that suicidal ideation (SI), according to various data, can occur in 20-30% of people depending on the sample [13]. These forms of suicidality are not linearly related; while SI and SA can predict future SI and SA to some extent, they have little correlation with future CS [14, 15]. This underscores the need to study genetic markers for each type of SB separately, complicating the task of generalizing GWAS results in suicidology. In response to this, the organization of the Suicide Working Group and the International Suicide Genetics Consortium (ISGC) within the international Psychiatric Genomics Consortium (PGC) appears entirely justified. These groups comprise researchers who collect and curate accumulating data, exchange information, conduct individual GWAS, refine phenotypes, and perform meta-analyses.[1]

Given the challenges associated with the phenomenon of suicide, various approaches are employed in the genetics of suicidality research. Recently, there has been increased attention to both widespread and rare genomic variations, including probable *de novo* mutations, utilizing methodologies like whole exome sequencing (WES) [16]. This approach involves sampling a relatively small number of extended families exhibiting SB across multiple generations [17]. Another interesting combined approach is "convergent functional genomics", which identifies genetic markers through RNA in the blood. This method uses reverse transcription and predicts suicide risk based on several independent lines of evidence, including genetic data, psychological questionnaires, functional tests (such as dexamethasone supression test), and biomarkers profile [18]. Despite these advances, "classical" GWAS remain the strategies most used for studying the genetic architecture of SB.

The results of GWAS projects related to suicidal phenotypes have been summarized multiple times. For instance, in 2014, a group led by M. Sokolowski analyzed 8 studies published at the time. They found no consistent patterns and noted that genome-wide findings were rarely replicated in independent studies [19]. Nevertheless, the potential of such studies was highlighted, especially when it comes to identifying polygenic effects and calculating PRS. Additionally, considerable attention was drawn to a significant predominance of the genes involved in neurogenesis among the findings [19]. In 2020, we conducted a comprehensive review of 15 individual studies on this subject, meticulously annotating all the mentioned genes and scrutinizing the observed associations through the lens of the pathogenetic model of stress vulnerability, which serves as the foundation for understanding SB [20]. Our analysis yielded a significant conclusion: GWAS in the field of SB fail to uncover associations with neurotransmitter systems or the stress response system as pathophysiologically predicted: however, they allow one to identify numerous associations with the genes implicated in the processes of nervous system development and formation, neuroplasticity, intercellular interactions, cell adhesion and proliferation, intracellular signaling systems, and immune responses. We speculated that this validates the diathesis–stress models (vulnerability–stress model), which offer the most logical explanations for SB [4, 21]. According to these models, vulnerability stems

[1] Psychiatric Genomics Consortium (PGC): Suicide Working Group [cited November 2023]. Available from: https://pgc.unc.edu/for-researchers/working-groups/suicide-working-group/

from adverse factors during early development (such as severe stress, multiple adversities and traumatic events), with suicide seen as a consequence of later-life stressors impacting the already "set stage" [21, 22]. Central to these concepts are the interactions between genetic factors and environmental ones, as well as the timing and sensitive periods of development during which these influences occur [20].

Given that stress exerts a pervasive influence affecting various bodily systems, it is unsurprising to uncover associations with a broad spectrum of genetic markers linked to diverse bodily functions, each potentially contributing to vulnerability. This may encompass disruptions in cellular mechanisms during brain structure formation, as well as dysfunctions in other systems such as the neurohumoral regulation system, metabolic functions, and immune responses [20]. We suggested that an unusual set of genetic markers, often inexplicable from the perspective of SB pathophysiology, reflects a degree of susceptibility to early traumatic stress, leading to deviations from normal neural development, cellular imbalances in brain regions, disturbances in synaptogenesis and neuroplasticity, and subsequent structural abnormalities detectable through neuroimaging techniques [20].

Indeed, recent evidence suggests that individuals in various age groups with histories of SI and SA may display deviations from normal cortical and subcortical maturation. Common findings include reduced volumes of the ventral and dorsal regions of the prefrontal cortex, decreased surface areas in the right frontal cortex, and disruptions in the connections between the inferior frontal gyrus and temporal lobes and other brain regions [23–25]. Despite inconclusive findings and remaining challenges in distinguishing between groups displaying SB and those exhibiting depression or bipolar disorder, mounting evidence indicates that SB may indeed stem from the abnormalities of specific brain structures responsible for self-control, risk-taking, impulsivity, affective symptoms, and decision-making errors [23, 24]. These observations underscore the growing interest in further exploration to attempt to identify the genetic markers associated with suicidality, including through GWAS.

It is worth noting that since the publication of our review [20], several new GWAS results focusing on SB and utilizing increasingly larger sample sizes have emerged, alongside new overarching analytical studies. A recent comprehensive review specifically addressed the genetics and epigenetics of SB in all its forms (including non-suicidal self-injury, SI, SA, and CS), encompassing various genetic methodologies [26]. The authors analyzed data from 31 classical GWAS; 7 genome-wide studies employing copy number variation (CNV) as markers; 4 whole-exome studies identifying rare markers; 39 studies assessing PRS; 4 linkage studies (analyzing linked inheritance); 438 studies using the candidate gene strategy, of which 53 assessed gene-environment interaction (GxE); 7 studies that utilized Mendelian randomization; 16 whole-epigenomic association studies (EWAS); 36 studies aimed at identifying DNA methylation of candidate genes; 13 studies on non-coding RNAs; and 6 studies on identifying histone modifications [26]. In this comprehensive review, the authors primarily focused on listing the diverse cellular and neurometabolic pathways identified among the signals from GWAS, paying less attention to their functionality and implications for understanding the pathophysiology of SB.

This review aims to systematize the findings of GWAS on suicidal phenotypes, annotate the identified markers, analyze their functionality, and potentially confirm the previous hypothesis that they reflect a nonspecific set of gene variants associated with stress vulnerability as a key endophenotype of suicidal behavior. Additionally, the review aims to achieve a higher level of generalization and pathogenetic explanation of SB beyond merely listing the technical processes or genes involved in the associations presented [26]. Given the continuous influx of new research in this field, one of the goals was to encompass as many publications as possible in existence by the end of 2023, primarily focusing on original GWAS and meta-analyses. Such a review could serve as a valuable information resource for similar studies conducted in Russia.

METHODS

Sources of information, search strategy and selection criteria

The research represents the result of a monitoring of all recent original studies and reviews regarding the use and efficacy of GWAS in the field of suicidology since 2014. Conducted from January to December 2023, this work involved directly annotating all markers and constructing an informative table of sources. We conducted searches on the PubMed platform using the keywords "suicide AND GWAS" and "suicidal behavior AND GWAS". Additionally, we considered interrelated sources, including references from original studies, previously published reviews (including

our own), and analytical articles by leading experts in the field. The analysis encompassed all sources identified as of December 2023, totaling 34 original papers. We included studies on all suicidal phenotypes, irrespective of the definitions of SB, SA, and SI. Our focus was solely on "classical" GWAS, primarily aimed at conducting GWAS using SNPs as markers. This review is not a systematic one and does not purport to be. According to its design and stated objective, it aims to validate previously put forth hypotheses regarding the association of suicidal phenotypes with genomic markers that may sometimes be challenging to elucidate.

Analysis of the results

The publications identified and selected for analysis were studied in full text, including additional information posted on the journal's websites. The necessary information was copied and tabulated. The obtained data were considered from the following angles:

1. Increased attention to the sample, its characteristics, methods for accounting for SB and ideation;
2. Accounting exclusively for genome-wide markers (some GWAS projects used the candidate gene strategy on the same sample as an additional measure, which led to an excessive number of genes mentioned);
3. A broad approach to marker analysis, i.e. inclusion of polymorphisms in the list not only exclusively at a significance level of $p < 7 \times 10^{-8}$, but also nominal (presumptive), i.e. at values of the order of $p < N \times 10^{-7\text{-}6}$;
4. Special attention paid to the SNP inheritance indicator;
5. Mandatory annotation of the closest genes and comparative analysis of their reproducibility on the entire data set.

The sources of the information on the functional role of the mentioned genes were the resources Gene Cards[2], National Library of Medicine[3], and UniProt[4]. All 34 analyzed publications [27–60] are summarized in Table S1 in the Supplementary.

RESULTS

Evolution of methodology and performance of GWAS on suicidal phenotypes

While initial studies of this type were primarily incidental ramifications of pharmacogenetic projects, where certain patients exhibited increased suicidal tendencies during treatment, subsequent projects have deliberately focused on exploring SB or SI [27–29]. Thus, while in the studies [27–29] the suicidal phenotype emerged as a series of responses to single queries regarding SI from widely used questionnaires on depressive symptoms, in latter works [30–32], direct inquiries about SB from structured diagnostic interviews were employed. In the studies reviewed, SI was characterized as a phenotype in 15 (45.5%) works; SA — in 25 (75.8%); and CS — in 9 (27.3%). Notably, a significant portion of the studies (n=14) accounted for both SI and SA simultaneously, sometimes including CS as well, resulting in a cumulative percentage exceeding 100%.

Various tools were utilized by authors to identify and delineate these phenotypes, ranging from individual questions extracted from diverse depression scales to comprehensive assessment instruments like the Columbia Suicide Severity Rating Scale, the Beck Scale for Suicide Ideation, the Beck Suicide Intent Scale, and sections dedicated to suicidal tendencies in psychiatric diagnostic tools such as SCAN, CIDI 2.1, SCID, and MINI (refer to Table S1 in the Supplementary). In recent years, some authors have developed proprietary methodologies based on gradations of suicidality, as demonstrated in the work by Zai et al. [53]. These approaches, employing ordinal scales ranging from 0 to 4–5 based on the presence and severity of SI and SB, contribute to the construction of the concept of ordinal suicidality [26]. Furthermore, several studies draw on medical databases (national or regional mortality registries, mental health records, and data from frontline health assessments or alcohol consumption among large cohorts), while in certain instances online surveys meant to gauge participants' psychological well-being or specialized surveys targeting military personnel or war veterans are utilized (refer to Table S1 in the Supplementary).

Hence, a wide variety of phenotypes is used in GWAS studies on suicidality, extending beyond the primary indicators of SI, SA, and CS. This undoubtedly impacts the findings of GWAS and their reproducibility. Consequently, specialists from the Suicide Working Group of the PGC have taken to developing a protocol to standardize these phenotypes. Given that some GWAS also incorporate the notions of non-suicidal self-harm, it is imperative to

[2] Available from: https://www.genecards.org/
[3] Available from: https://www.ncbi.nlm.nih.gov/gene/
[4] Available from: https://www.uniprot.org

distinctly delineate suicidal tendencies from other forms of self-injury and establish uniform definitions.

Upon considering factors such as sample size and characteristics, the following conclusion seems appropriate. In initial studies focusing on patients with depression and bipolar disorder (BD), sample size was dictated by the design of the pharmacogenetic objectives, ranging from 400 to 2,000 individuals, with 10–25% exhibiting increased SI during treatment. Subsequent studies tailored to specific populations (e.g., patients with SCZ, depression, or familial cohorts) included sample sizes ranging from several dozen to several thousand participants. Nearly all studies, especially those that yielded negative results, seemed to suggest that enhanced success could be attained through larger sample sizes. A logical development was the combination of cohorts based on disorder presence and suicidal manifestations, with the use of large databases of genotyped individuals (for example, UK BioBank) proving to be pivotal. In the most recent meta-analysis, the sample size exceeded 40,000 individuals (collected from 22 cohorts) with varied manifestations of suicidality, alongside over 900,000 controls [60] (refer to Table S1 in the Supplementary). Genotyping was conducted using different variants of arrays manufactured by Illumina, Inc. and Affymetrix, Inc.

The focus of our analysis lies on the performance of GWAS, as characterized by the identification of associations with specific markers, their reproducibility, and their functional genomics significance. While early studies spanning 2015–2019 typically failed to detect significant genome-wide associations, and the identified markers were considered putative (nominal), a breakthrough occurred with the study by Strawbridge et al. [42]. Leveraging large cohorts and biobank data, the identification of markers became more frequent, with the set significance criteria (p <5–7x10^{-8}). Across experiments, the likelihood of detecting such markers increased with larger numbers of cases and controls (refer to Table S1 in the Supplementary). Notably, meta-analyses conducted by Mullins et al. [56], Kimbrel et al. [59], and Docherty et al. [60] proved the most efficient in this regard.

Concurrently, all studies confirmed these previously observed patterns, as documented in prior review papers [19, 20, 26]. Specifically, this means that GWAS in the field of SB have failed to confirm any associations with the anticipated (canonical) genes related to monoamine and other neurotransmitter systems, the stress response system, the neurotrophin system, and other systems previously investigated within the candidate gene strategy. At the same time, numerous associations with genes whose products initially appeared challenging to correlate with the pathophysiology of SB have been revealed. This complexity can be understood through the analysis of metabolic pathways, an enrichment analysis based on functional attributes, and protein-protein interactions. Such a generalization is presented, for example, in the work by Galfalvy et al., which identified broad clusters such as the "cell assembly and organization", "development and function of the nervous system", "cell death and survival", "immune diseases", "infectious diseases", and "inflammatory response" [40].

Polygenic risk scores calculation and GWAS reproducibility

PRS calculation is a widely used technique that was employed in many of the studies reviewed. Sokolowski et al. in their work, since no marker achieved genome-wide significance in GWAS, used a combined approach, where PRS were calculated for a set of genes "ontologically related to neurological functions, developmental processes, and synaptic processes" [35]. On that basis, a set of 590 polygenes associated with SA was presented. They revealed associations with processes such as cell adhesion and migration, as well as intracellular signaling systems, particularly those associated with small GTPases and receptor tyrosine kinases. All these systems are somehow related to the death and survival of neurocytes and synaptic plasticity; that is, the development and formation of the central nervous system, including under various external (stressful) influences [35]. The same work presented a list of 16 genes associated with SA which were previously recognized as markers of SB namely: *BDNF, CDH10, CDH12, CDH13, CDH9, CREB1, DLK1, DLK2, EFEMP1, FOXN3, IL2, LSAMP, NCAM1, NGF, NTRK2,* and *TBC1D1*. Among these markers are genes encoding known nerve growth factors, their receptors, cadherin proteins (the main factors responsible for cell adhesion), transcription factors, as well as other factors of cell growth and differentiation.

In this context, it appears interesting to analyze Table S1 in the Supplementary in terms of the reproducibility of the results of different GWAS. Our review of the first 15 GWAS on suicidal phenotypes from 2009 to 2015 identified 4 genes as recurrent across different independent studies (*NTRK2, FOXN3, LSAMP,* and *CTNNA3*) [20]. To date, based on the analysis of 34 studies, we have identified

27 repeating genes, including 8 genes involved in cell-cell interactions, neurogenesis, and immune responses: namely, *LSAMP* (a cell adhesion protein involved in axon targeting during central nervous system development), *CDH13* (cadherin 13, a member of the major Ca-dependent cell-cell adhesion regulators family that inhibits axon growth during differentiation), *CNTN5* (contactin, a member of the immunoglobulin superfamily that is involved in cell interactions), *NCAM1* (a cell adhesion protein, which is a member of the immunoglobulin superfamily), *DCC* (netrin receptor 1, an adhesion molecule and axon growth directing factor), *SEMA3A* (semaphorin 3A, which is secreted immunoglobulin that can act as a neurorepellent or neuroattractant and is necessary for the normal development of neurons), *NLGN1* (neuroligin, a neuronal surface protein and synaptic plasticity factor), and *CTNNA3* (a vinculin/alpha-catenin family protein involved in intercellular interactions). Additionally, 2 genes have been identified whose products are associated with the state of the intercellular matrix: *HS3ST1* (heparan sulfate sulfotransferase, an enzyme synthesizing the heparan anticoagulant) and *ABI3BP* (a heparin and glycosaminoglycan binding protein). Hence, most of the genes (*n*=10) are in some manner linked to intercellular interactions, which are crucial in the early development of nervous tissue and the maintenance of its condition throughout an individual's life.

The second most numerous group (*n*=8) included genes encoding neurotrophin receptors and constituents of intracellular signaling systems, which are also involved in synaptic plasticity, neurogenesis, embryonic development, and carcinogenesis: namely, *GFRA1* (a receptor for neurotrophins GDNF and NTN), *NTRK2* (a membrane tyrosine kinase and receptor for neurotrophin BDNF), *RHEB* (a universal GTP-binding protein involved in the regulation of the cell cycle and carcinogenesis in humans), *STK3* (a serine/threonine protein kinase involved in the regulation of apoptosis and that inhibits proliferation and tumor growth), *SOX5* (a transcription factor related to the SRY gene and key factor determining the male sex that is involved in embryonic development), *PDE4B* (phosphodiesterase 4B, an intracellular signaling factor), *RGS18* (a regulator of the G protein-dependent signaling system), and *ZNF406* (the zinc finger of ZFAT that is involved in the regulation of transcription and the immune response).

The third group consists of 9 genes which are primarily linked by the fact that their products are neurospecific proteins or are associated with nervous tissue functions. They are genes such as *BRINP3/FAM5C* (a retinoic acid-induced neurospecific protein), *LRRTM4* (a leucine repeat-rich transmembrane protein of the nervous tissue), *LINC01392* (non-coding RNA of unknown function), *MHC* (a major histocompatibility complex), *SLC6A9* (a glycine transporter), *FURIN* (a subtilisin-like protein convertase), *CACNG2* (a subunit of the calcium voltage-dependent channel), *FOXN3* (a forkhead/winged helix transcription factor presumably involved in the elimination of transcription errors), and *LUZP2* (a leucine zipper protein presumably involved in the pathogenesis of Alzheimer's disease).

Over the past decade, there has been significant progress achieved in the reproducibility of GWAS results in suicidology. Growing evidence suggests that the identified markers are linked not to neurochemical processes and the main neurotransmitter systems, but to mechanisms involving the formation of cellular components in the nervous tissue, neuroplasticity, the maintenance of neuronal and glial cell interactions, neurocyte survival and death, signaling systems, and immune responses. These mechanisms are likely connected to structural impairments in the developing brain during early stress exposure, contributing to vulnerability-stress, which is a key transdiagnostic endophenotype that may underlie both SB and various mental disorders, many of which are associated with stress [61].

Gene-environment interactions according to GWAS

In the genetics of SB, gene-environment interactions are crucial, since the trait itself is not what is inherited but the vulnerability to environmental factors. This constatation is supported by several of the GWAS that have assessed such interactions. For example, Wendt et al. identified several genome-wide markers that were different between men and women, demonstrating the interaction of suicidality with various environmental psychotraumatic factors, the levels of social support, and one's socioeconomic status [54]. Significant gene-environment (GxE) associations were uncovered with neuroimaging data between these markers, particularly with the volume of the hippocampus, amygdala, and the structural features of the white matter bundles integrating the brain structures involved in goal-setting behavior. One polymorphism, including association with the *CHST14* gene (carbohydrate sulfotransferase involved in the synthesis of mucopolysaccharides), was shown to interact with physical and sexual abuse experienced

in childhood and later life. The authors concluded that these identified relationships and interactions highlight the relevance of synaptic plasticity as a potential target for addressing suicidality and post-traumatic conditions [54].

Several recent studies have used GWAS to identify genetic markers and associations of suicidality with various physiological and psychobiological characteristics. For instance, Levey et al. utilized data from a study on suicide risks among U.S. Army servicemen, employing an approach that allowed them to assess the severity of suicidal thoughts and actions (ordinal suicidality) [45]. They found associations with the *LDHB* gene (lactate dehydrogenase, anaerobic metabolism), the *FAH* gene (tyrosine catabolism), and the *ARNTL2* gene (regulation of circadian rhythm) [45]. Brick et al. discovered an association with the *SEMA3A* gene, which encodes the semaphorin 3A protein, a secreted immunoglobulin necessary for normal neuronal development [46]. This gene is also linked to comorbid alcohol dependence, depression, inflammatory processes, and asthma. Notably, a significant genetic correlation with neurocognitive functions, specifically facial expression identification tasks, was observed [46]. Russel et al. used Mendelian randomization to identify an association between components of the immune system (interleukin 6 and the C-reactive protein) and various forms of self-harm (non-suicidal and suicidal), highlighting the relationship between these behaviors [50]. Campos' study produced similar results, showing a genetic correlation between suicidal thoughts and non-suicidal self-harm [51]. Polimanti et al. identified a link between suicidal thoughts and various addictions mediated by markers on chromosome 16 [52].

Our analysis bolsters previously posited hypotheses about the role of identified genetic markers in the formation of the cellular and regulatory mechanisms of vulnerability–stress. It also highlights the relationship between suicidal phenotypes and various pathogenetically based phenomena, such as the immune reactions found in multiple mental disorders, self-harming behavior, and addictions. This underscores the importance of examining the overlaps amongst various mental illnesses, which are significant risk factors for suicide.

Genetic correlation with mental disorders according to GWAS

The question of which common polygenes carry the risk of fostering the development of depression (or other mental disorders) and SB simultaneously, and whether it is possible to differentiate polygenic influences that increase the risk of suicide within mental disorders from those actually associated with the disorders themselves, is crucial. This question is addressed in numerous studies [35, 36, 38–40, 43, 47, 48, 52, 53, 55, 56, 58, 60]. Almost all studies of this type have identified common genotypes for SI, SA, CS, and clinical phenotypes. For instance, Sokolowski et al. as early as in 2016 [35] identified 750 genes associated with the development of nervous tissue that are more specific to SA than to psychiatric diagnoses. They also showed, using the PGC databases for SCZ, BD, and depression, that PGC-SCZ polygenes are associated with SA in both diagnosed and undiagnosed patients, and characterized the overlap markers between PGC-SCZ and patients with SA without diagnoses. These 590 markers were believed to be primarily associated with neuronal development genes, emphasizing the importance of common vulnerability genes for SA and mental disorders, particularly SCZ, even in the absence of a formal diagnosis [35].

Mullins et al., using data from several clinical cohorts (including those with depression, BD, and SCZ), calculated the PRS for SA in each condition and conducted a meta-analysis [43]. They found that a genetic predisposition to major depression increases the risk of SA in patients with depression, BD, and SCZ. The authors suggest that the genetic etiology of SA may be both unique and partly shared with major depression. In other words, individuals who commit SA carry a burden of depression risk alleles, rather than merely a higher genetic load that is responsible for the mental disorder they are diagnosed with.

The predictive value of PRS in psychiatry remains low; previous studies have shown that PRS for severe depression explains only about 2% of the differences in patient statuses [62]. However, based on the work of Mullins et al., PRS appears to be a promising indicator for assessing suicide risk among psychiatric patients, especially as the volume of international databases grows and more genetic material from various ethnic groups is collected [43].

The studies by Docherty et al. [49] and Li et al. [58] are particularly illustrative in this context. Docherty et al., using data from 3,413 cases of CS in Utah, U.S., and over 14,000 controls of European origin, identified several highly significant genome-wide markers (see Table S1 in the Supplementary). They also established genetic correlations with various psychiatric and psychological traits and variables, including (in order of increasing effect size)

alcohol consumption, autism spectrum disorders, childhood IQ, loneliness, depressive symptoms, impaired self-control (disinhibition), and diagnoses of depression and SCZ [49]. Li et al., using the same dataset and conducting a meta-analysis with 8,315 cases and over 2.45 million controls of European origin, found positive genetic correlations between CS and depression, anxiety, stress, sleep disorders, SCZ, and pain syndrome, as well as negative correlations with smoking and education/intelligence levels [58]. Additionally, in the same study, when analyzing further cohorts, positive genetic correlations were found between CS and BD, post-traumatic stress disorder, generalized anxiety disorder, autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), chemical dependencies, neuroticism, serum triglyceride and cholesterol levels, and negative correlations with subjective well-being, intracranial volume, and cognitive functions [58].Thus, based on GWAS, PRS are increasingly demonstrating a degree of predictive power logically explained by our understanding of risk factors and the pathogenesis of SB.

SNP heritability indices according to GWAS data

It should be noted that as the sample size increases and large cohorts from various databases are included in the analysis, SNP heritability indices are also refined (see Table S1 in the Supplementary). They fluctuate within fairly significant boundaries: from 1–2% [33, 57] to 24–48% [44, 45, 49] (the latter already approaches the estimates obtained by the twin method [3]). At the same time, most studies provide estimates of about 5–10% [42, 43, 48, 51, 56, 58, 60]. Moreover, if the h^2_{snp} values for SA often remain within the 5–7% range, then for CS they already reach 24.5% [49], which can be regarded as a consequence of greater certainty of the phenotype. This bridges the gap between heritability estimates from behavioral genetics and molecular genetics, which is characteristic of mental disorders [63], and which has called into question the value of SNP heritability assessment in general [64]. This phenomenon, known as "missing heritability problem", has several potential explanations [65]. In particular, it has been suggested that many common variants with negligible effects remain undiscovered, that rare variants with large effects undetectable by standard GWAS genotyping are too influential, and that behavioral genetic approaches may overestimate heritability in general [65]. Interestingly, the highest h^2_{snp} estimates (around 35–48%) were obtained from monoethnic samples (Japan) [44], while meta-analyses of multiethnic cohorts yield average values [56, 58, 60].

Meta-analyses of GWAS results

The results of recent meta-analyses are of the greatest interest. Thus, in the work by Mullins et al. [56], there were 29,782 SA cases and 519,961 controls, all from the ISGC database. The analysis methods used allowed the researchers to exclude the genetic influences on SA mediated by mental disorders. Two loci achieved genomic significance for SA: the major histocompatibility complex (MHC) and an intergenic locus on chromosome 7. The latter remained associated with SA even after excluding the influence of mental disorders and was replicated in an independent cohort. This locus was also linked to risky behavior, smoking, and sleep disorders [56]. This meta-analysis identified six genes previously mentioned in earlier studies (see Table S1 in the Supplementary). In the meta-analysis by Li et al. [58], there were 10 such genes. The authors highlighted the *NLGN1* gene, which encodes neuroligin, a postsynaptic neuronal protein. Proteins from this family act as ligands for the presynaptic agents β-neurexins and are involved in the formation and remodeling of synapses in the central nervous system [58]. Additionally, the *ROBO2* gene, variants of which are associated with morning chronotype, smoking, and mathematical abilities, was of interest. Noteworthy in this regard is also the *ARNTL2* gene from the study by Levey et al. [45], which is also associated with circadian rhythms [58].

Kimbrel et al. conducted a large-scale meta-analysis as part of the Million Veterans Program, which was initiated to address the sharp rise in suicides among U.S. veterans of wars and military conflicts [59]. The analysis included data from 633,778 genotyped veterans, 19% of whom had some form of SB, with cohorts from the ISGC collection used as a replication sample. A notable feature of this meta-analysis was the clear division by ancestry (European, African, Asian, and Latin American groups), allowing for the identification of markers common to all groups, as well as those specific to each group. The meta-analysis identified over 200 highly significant individual markers, including new ones such as *ESR1* (the estrogen receptor), *TRAF3* (the tumor necrosis factor receptor), *METTL15* (mitochondrial methyltransferase), and *MKNK1* (the protein kinase involved in the stress response) [59]. Functional enrichment analysis using the FUMA GWAS catalog identified markers that are universal across all ethnic groups, are expressed in the

brain and pituitary gland, and are associated with synaptic mechanisms, axonal interactions, ubiquitination, parathyroid hormone synthesis, the dopaminergic, glutamatergic, and oxytocin synapses in the brain, intracellular cAMP-dependent pathways, and cell adhesion. The highest genetic correlation (r >0.75) was observed between SB and depression, as well as post-traumatic stress disorder, while the correlation with SCZ and BD was significantly lower (r=0.36–0.29).

The most comprehensive meta-analysis to date was performed by Docherty et al., in which the phenotype was SA [60]. The ISGC sample included data on 43,871 SA cases from 22 cohorts with the number of controls approaching a million, taking into account ancestry, with a significant proportion of the controls being clinically assessed for mental disorders. As a result, 12 loci were identified at p <5×10^{-8}. The closest genes to these loci included *DRD2* (dopamine receptor type 2), *SLC6A9* (the glycine transporter), *FURIN* (subtilisin-like protein convertase), *NLGN1* (neuroligin), *SOX5* (the transcription factor), *PDE4B* (phosphodiesterase B), and *CACNG2* (the calcium voltage-gated channel subunit). These markers were consistent with those previously identified in other studies (see Table S1 in the Supplementary). The authors found common genetic variability between SA with ADHD, smoking, and risk tolerance, even after accounting for the influence of comorbid BD and post-traumatic stress disorder. Additionally, multiple analyses identified 519 significant gene sets affecting areas such as epigenetic mechanisms, genome regulation and transcription, cellular stress response mechanisms, DNA repair, and immune responses [60]. The study also revealed a significant genetic overlap with the genes associated with various mental and somatic conditions, particularly smoking, ADHD, risk tolerance (linked to impulsivity and risk-taking behavior), and pulmonary pathology. The authors stressed that many findings in the meta-analysis regarding the involvement of genes associated with epigenetic regulation, as well as the overlap with mental disorders, support the concept of diathesis–stress as the leading pathogenetic mechanism of suicide [60].

DISCUSSION

Interpretating the data

Based on the analysis of 34 original studies and meta-analyses, we have identified and annotated 27 recurring genomic markers associated with various suicidal phenotypes. When considering each of these markers individually, their direct involvement in SB remains challenging to explain. However, as genes and their products increasingly appear across multiple studies, we believe they can be fitted into a certain pathogenetic framework. This framework is most logically linked to the impact of stress and the concept of vulnerability–stress, often regarded as the primary endophenotype of SB [5, 20, 21]. The presence of associations with the genes involved in neural tissue formation, neuroplasticity, synaptogenesis, cellular interactions, and immune responses, coupled with accumulating epigenetic and neuroimaging evidence, provides a logical explanation of suicide as a consequence of early traumatic experiences and subsequent interactions with existing stressors [20]. Equally logical within this framework is the role of mental disorders, whose genetic architecture partially overlaps with that of SB and is similarly influenced by vulnerability–stress and gene-environment interactions [61]. While this framework is not exhaustive or universally applicable, it offers a means to analyze future GWAS findings in terms of their alignment with this concept, thereby facilitating the interpretation of the diverse data generated in such studies.

Suicide represents a profoundly complex and multifaceted polyetiological behavioral phenomenon stemming from a combination of neurobiological, psychiatric, psychological, and social factors. A contentious, unresolved issue revolves around whether SA constitutes an independent, evolutionarily formed behavior or a complication of mental disorders such as depression, borderline personality disorder, or SCZ. Large-scale meta-analyses conducted within the ISGC underscore the existence of a distinct genomic architecture unique to SA [66]. Conversely, studies of extensive cohorts employing traditional psychogenetic methods assert that parental mental illness explains nearly half of the genetic transmission of the habit of suicide attempts, albeit without impacting transmission through upbringing [67]. Moreover, while suicide itself is partially inherited, the genetic overlap between SA and CS underscores the presence of two distinct groups: those that attempt suicide and those that commit it [67].

Therefore, elucidating the genomic architecture of SB as a transdiagnostic phenotype across major psychopathologies, including depression and other disorders, alongside the psychological constructs underpinning SA, offers insight into SB mechanisms, especially given the fact that vulnerability–stress can be an endophenotype of both SB and mental

disorders. As research into the genetics of suicide employing GWAS strategies progresses and evolves, with advancements in analysis methods, accumulation of genomic data, and the integration of multi-omics data (epigenomics, proteomics, metabolomics, microbiomics) [68], the issue of summarizing these findings within the context of suicide pathogenesis remains paramount.

Limitations

This review primarily adopts a descriptive approach, and the search strategy utilized is limited, potentially impacting the scope of the analyzed data. This, alongside the exclusive focus on SNPs while disregarding other markers, constitutes the primary limitation of the review.

Practical utility of GWAS for suicide

Currently, anticipating the predictive efficacy of genetic markers in the general population remains challenging. However, this prospect appears to be more feasible in high-risk cohorts, such as patients of psychiatric clinics. Particularly, PRS assessments offer increasingly robust predictive capacities, potentially extending to the individual level, contingent upon the identification of specific marker sets and their comparison with continuously expanding genetic databases. Despite various uncertainties and diverse analytical approaches, GWAS findings in suicidology progressively, as sample sizes grow and ethnic diversity is considered, alongside the augmentation of international genetic databases, allow one not only to confirm some pathogenetic hypotheses, but also provide hope for practical implementation (when combined with diverse test modalities) to predict and prevent suicides, which constitutes the ultimate objective of research in this field.

Prospects for further research

Based on the results of our review, we can opine that the enhanced effectiveness of suicide studies using the GWAS approach points toward several directions. First of all, they are the standardization of phenotypes based on more accurate definitions of all manifestations of SB; the use of the most clinically proven suicide risk scales, an increase in sample sizes and their standardization in terms of ethnicity and origin; the homogeneity of clinical samples and their detailed psychiatric verification; the stratification of samples by age with a focus on adolescents and young adults, men and women; the integration of genetic data with psychological constructs of suicide; and the widespread use of international databases of genetic information.

CONCLUSION

In our opinion, the set of most frequently recurring markers identified by GWAS reflects the leading role in the genesis of SB of the vulnerability–stress phenomenon — an endophenotype formed in early development, which subsequently plays the role of key pathogenetic mechanism of suicide.

The GWAS strategy in suicidology primarily serves the purpose of better understanding the pathophysiology of SD, but it also shows the growing potential of suicide prediction and prevention, especially when calculating PRS, among certain populations (psychiatric patients) and in combination with other test modalities.

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Supplementary data

Supplementary material to this article can be found in the online version:
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