

# World Journal of *Psychiatry*

*World J Psychiatr* 2021 October 19; 11(10): 681-914



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The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Xu Guo*; Production Department Director: *Yu-Jie Ma*; Editorial Office Director: *Jia-Ping Yan*.

**NAME OF JOURNAL**

*World Journal of Psychiatry*

**ISSN**

ISSN 2220-3206 (online)

**LAUNCH DATE**

December 31, 2011

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Rajesh R Tampi

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

**PUBLICATION DATE**

October 19, 2021

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<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## 'Omics' of suicidal behaviour: A path to personalised psychiatry

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**Author contributions:** Videtic Paska A and Kouter K organized and planned the manuscript; Kouter K wrote a part of MS regarding use of omics in suicidal behaviour research; Epigenomics, proteomics, and building the bridge between personalised medicine and psychiatry; Videtic Paska A wrote the introduction, use of omics in suicidal behaviour research: Genomics, metabolomics; all authors approved the final version of the manuscript; Kouter K and Videtic Paska A declare equal contribution to this manuscript.

**Supported by** the Slovenian Research Agency Research Programme, No. P1-0390, No. J3-7132, and No. Z3-2653.

**Conflict-of-interest statement:** Nothing to declare.

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### Abstract

Psychiatric disorders, including suicide, are complex disorders that are affected by many different risk factors. It has been estimated that genetic factors contribute up to 50% to suicide risk. As the candidate gene approach has not identified a gene or set of genes that can be defined as biomarkers for suicidal behaviour, much is expected from cutting edge technological approaches that can interrogate several hundred, or even millions, of biomarkers at a time. These include the '-omic' approaches, such as genomics, transcriptomics, epigenomics, proteomics and metabolomics. Indeed, these have revealed new candidate biomarkers associated with suicidal behaviour. The most interesting of these have been implicated in inflammation and immune responses, which have been revealed through different study approaches, from genome-wide single nucleotide studies and the micro-RNA transcriptome, to the proteome and metabolome. However, the massive amounts of data that are generated by the '-omic' technologies demand the use of powerful computational analysis, and also specifically trained personnel. In this regard, machine learning approaches are beginning to pave the way towards personalized psychiatry.

**Key Words:** Epigenomics; DNA methylation; Micro-RNA; Genome; Metabolome; Suicide

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**Core Tip:** Suicide is major public health concern worldwide, and at the same time, it is preventable when timely measures are taken. The biological basis of suicidal behaviour is not a product of a single gene, transcript, protein or metabolite; rather, it is represented by intertwined cellular mechanisms, cell types and tissue changes, and based on numerous molecular pathways. The '-omic' technologies might represent the missing link between the current state of psychiatry and future personalised approaches, through the combination of -omics-derived information and the diagnostic process. However, first we need precise, specific and validated biomarkers.

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**Manuscript source:** Invited manuscript

**Specialty type:** Psychiatry

**Country/Territory of origin:** Slovenia

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**Received:** February 27, 2021

**Peer-review started:** February 27, 2021

**First decision:** July 15, 2021

**Revised:** July 16, 2021

**Accepted:** August 30, 2021

**Article in press:** August 30, 2021

**Published online:** October 19, 2021

**P-Reviewer:** Lei XH

**S-Editor:** Fan JR

**L-Editor:** A

**P-Editor:** Guo X



**Citation:** Kouter K, Videtic Paska A. 'Omics' of suicidal behaviour: A path to personalised psychiatry. *World J Psychiatr* 2021; 11(10): 774-790

**URL:** <https://www.wjgnet.com/2220-3206/full/v11/i10/774.htm>

**DOI:** <https://dx.doi.org/10.5498/wjp.v11.i10.774>

## INTRODUCTION

The International Human Genome Sequencing Consortium published the first draft of the human genome in 2001[1,2]. It was completed in 2003, and it provides information on the human genome structure, organization and variation, as well as on the functions of the complete set of human genes. This determination of the 'blueprint' of the human being represented a major breakthrough for biological and medical research, and importantly, it contributed to the development of contemporary technologies for whole-genome studies[3]. Since then, the expectations in the field of molecular genetics of human diseases have been high for the tackling of the basic causes of numerous polygenic and multifactorial diseases. This also applies to psychiatric disorders and suicidal behaviour.

In the era of the continuing evolution of personalised and precision medicine, data on a patient's genetic background represent the foundation for further decisions on their disease diagnosis, treatment and monitoring, and also for disease prevention[4]. A better understanding of the roles of genetic variations in health and disease would benefit greatly in psychiatry, as psychiatric clinical evaluation currently relies on the clinical interview alone.

### Suicidal behaviour

Suicidal behaviour is one of the major global public-health concerns, as every year it accounts for more than 800000 deaths worldwide. In other words, suicides account for 50% of all violent deaths in men, and 71% in women[5]. Suicidal behaviour includes suicide attempts and completed suicides, and its ethology is complex. Many different factors contribute and shape suicidal behaviour, ranging from, but not limited to, biological (genetic, epigenetic), psychological (personality traits), clinical (psychiatric disorders), social and environmental factors[6]. The multifactorial nature of suicidal behaviour demands simultaneous inclusion of many different aspects to deepen our understanding of this phenomena.

The first clues for genetic implications in suicidal behaviour were based on family, twin and adoption studies, and the heritability of suicidal behaviour was estimated to be from 38% to 55% of all attempted and completed suicides[7]. A family history of suicidal behaviour has been recognized as biological, and as a psychological risk factor for suicidal behaviour, independent of psychopathology. This has been supported by small studies[8-12] as well as by a large population study[13]. Impulsive-aggressive behaviour is considered as an endophenotype for suicide, and its familial transmission has been associated with elevated suicide risk in families[14,15]. Twin and adoption studies have provided useful contributions for further estimate of the genetic *vs* environmental factors. Monozygotic twins have shown higher suicide risks than dizygotic twins[13,16], while in studies of suicidal behaviour and adoption, the biological parents had similar effects on suicides in their offspring in non-adopted and adopted situations[17,18].

### Rise of the -omics

Initially, the search for genetic biomarkers of suicidal behaviour was based on a candidate gene approach, which was mainly oriented towards neurotransmitter systems, with stress on the serotonergic system. The reason for this stemmed from neurobiological studies that determined the potential characteristics of suicidal behaviour on different body fluids (*e.g.*, blood, cerebrospinal fluid) and *post-mortem* brain. These studies investigated the roles of the serotonergic, noradrenergic and dopaminergic neurotransmitter systems in suicide, as well as signal transduction pathways and cellular morphology[19].

The first genetic studies of suicidal behaviour showed that two genes involved in the serotonergic pathway appear to be involved in suicide vulnerability: Those for tryptophan hydroxylase 1 and serotonin transporter[20]. However, none of the many studies on candidate gene approaches that followed have provided an answer for the genetic variations that lead to suicidal behaviour. From studies on psychiatric disorders, it became apparent that as in other complex diseases, the genetic contri-

bution to such disorders is polygenic—it arises through numerous variants from an extensive number of loci, each of which has small effect on the ultimate disease risk [21]. This caused the shift from a hypothesis-driven approach towards the hypothesis-free approach, to search for novel candidate genes and variants.

With the more recent technological advances applied to the human genome across different populations, tenths of millions of genetic variants have been found. It has been shown that typically the human genome differs across 4.1 to 5.0 million sites from the reference human genome. The majority of these differences (99.9%) are single nucleotide polymorphisms (SNPs) and short insertions and deletions [22]. Genome-wide association studies (GWAS) have thus emerged, with the use of microarray approaches that can interrogate hundreds of thousands of SNPs.

As suicidal behaviour is also particularly affected by environmental factors, such as early-life adverse events, studies on the epigenetic background have begun to increase over the last decade. DNA methylation studies are the most numerous, and a substantial part of the 28 million CpG dinucleotide DNA methylation sites are now being interrogated through microarray and sequencing approaches [23].

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## USE OF -OMICS IN RESEARCH INTO SUICIDAL BEHAVIOUR

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Large genetics-based studies of suicidal behaviour currently show great diversity for the phenotypes under study, and as suicidal behaviour varies in terms of the degree of lethality and suicidal intent, it is expected that these variables will have an impact on biomarkers. Therefore, studies on completed suicides, as the most homogenous phenotype, might reduce this variability [24]. However, due to limited access to *post-mortem* samples from suicide victims, these studies are relatively few. Therefore, studies other than gen-'omic' have more frequently focused on different suicidal behaviours, as well as suicidal thoughts and ideation. Frequently, suicidal behaviour is included only as an additional phenotype in what are primarily psychiatric disorder studies, which will sometimes obscure any clear genetic contributions to suicidal behaviour *per se*. Additionally, comparisons of the data obtained are often hindered due to variabilities in study design, which range from large population-based studies, to a two-step training and testing sample design, to small case-control studies of only a handful of patients. Despite this apparent diversity and the frequent lack of power to detect small effect sizes, these studies have still contributed importantly to a better understanding of the molecular-biological mechanisms underlying suicidal behaviour.

### Genomics

Only a handful of GWAS have analysed suicide as the primary phenotype [25-29] (Table 1). One of the most unique study designs included more than 4500 DNA samples from consecutive individuals who died by suicide in the state of Utah. These samples were linked to the population database, through which they identified 43 extended families (7-9 generations) with significantly elevated risk for completed suicides. This thus increased the power to identify genomic regions with high-risk variants for suicide, and at the same time reduced the shared environment effects. Out of 207 target genes identified for suicide, 18 were implicated in inflammation and immune functions, which supported previous studies on associations between inflammation and the aetiology of suicide [25,30]. In the second part of this study, they performed follow-up on the identified target regions in an independent population-based analysis, again on completed suicides, and identified four genes: *SP110*, *AGBL2*, *SUCLA2*, and *APH1B*; however, these should be further sequenced to obtain the potential segregating risk variants [25]. A GWAS on a consortium of three different samples did not reveal any SNPs with genome-wide significance ( $P < 1.0 \times 10^{-8}$ ), but still the pathway analysis of the results identified associations with "Cellular Assembly and Organisation", "Nervous System Development and Function", "Cell Death and Survival", "Immunological Disease", "Infectious Disease" and "Inflammatory Response", all of which have been previously shown to be abnormal in suicidal behaviour [26]. In a far smaller study, again, GWAS did not reveal any significant results, but the validation of the GWAS results with a gene expression study identified a cluster of genes involved in neuroimmune function [27].

The most comprehensive study was carried out through a large United Kingdom biobank for a general population cohort that included over 500000 people, and it covered four suicidality phenotypes that were defined as the categories of "thoughts that life was not worth living", "ever contemplated self-harm or suicide", "acts of deliberate self-harm not including attempted suicide", "attempted suicide" and "no

**Table 1 Genome-wide association studies and completed suicide**

Type of -omic	Tissue	Number of samples	Main results	Ref.
Illumina Infinium PsychArray platform v 1.0 (approximately 555000 markers)	Blood	216 suicide cases from extended families	<i>SP110</i> (rs181058279), <i>AGBL2</i> (rs76215382), <i>SUCLA2</i> (rs121908538), <i>APH1B</i> (rs745918508)	Coon <i>et al</i> [25], 2020
Illumina Omni1-Quad Beadchip (1014770 markers)	Not stated	577 suicide attempters and suicides, 1233 non-attempter psychiatric and healthy controls	SNPs in <i>STK3</i> , <i>ADAMTS14</i> , <i>PSME2</i> , and <i>TBX20</i> genes	Galfalvy <i>et al</i> [26], 2015
Affymetrix GeneChip Mapping 50K Xba Array (58900 markers)	Brain tissue	68 suicides, 31 non-suicide deaths	58 SNPs in or near 19 known genes	Galfalvy <i>et al</i> [27], 2013
Illumina HumanOmniExpress (733202 markers) and HumanOmniExpressExome BeadChips (273000 markers)	Not stated	Approximately 746 suicides and 14049 non-suicide controls	No genome-wide significant SNP; <i>GTF2IRD1</i> locus suggested as associated with age at completed suicide	Otsuka <i>et al</i> [28], 2019
Affymetrix United Kingdom BiLEVE Axiom (807411 markers) or the Affymetrix United Kingdom Biobank Axiom (825927 markers) arrays	Blood	> 500000 subjects of different suicide phenotypes and non-suicidal controls	Significant loci for suicidality on chromosomes 9 ( <i>ZCCHC7</i> ), 11 ( <i>CNTN5</i> ) and 13 (rs7989250); genetic correlations between suicidality and depression	Strawbridge <i>et al</i> [31], 2019
Illumina Infinium PsychArray platform (593260 markers), Illumina HumanOmniExpress (733202 markers) and HumanOmniExpressExome BeadChips (273000 markers)	Blood	3413 suicides, 14810 controls	Two genome-wide significant loci involving six SNPs: rs34399104, rs35518298, rs34053895, rs66828456, rs35502061, and rs35256367. Additional 52 variants (mapping to 22 genes) with nominal significance	Docherty <i>et al</i> [29], 2020

suicidality" controls. A "completed suicides" sub-group was also identified based on death certificates. Generally, a polygenic risk score was observed, but the genetic contributions to different suicidality phenotypes implicated distinct genetic contributions to these categories[31].

Another population based study was performed through an extensive DNA bank of suicide deaths that were merged with medical records and sociodemographic data. This was the first study on completed suicide with sufficient power for a GWAS. Two genome-wide significant loci were identified on chromosomes 13 and 15 that were associated with suicide, and the significant heritability based on the SNPs was estimated to be as high as 25% [29], compared to the heritability of a previous population-based study on suicidality, of 7.6% [31]. The only GWAS on an East Asian population for suicide showed the SNP-based heritability to be 35% to 48%, which again confirmed the polygenic nature of the suicide risk[28].

Several other GWAS have been carried out on other suicidal behaviour phenotypes, rather than completed suicide, and they have most often been studied in association with psychiatric disorders. However, due to the variability of the study designs and the lack of in-depth annotation of the significant variations determined with more comprehensive gene function descriptions, any integration of the results is still missing[32].

### Epigenomics

Epigenetics is a rapidly developing field that connects environmental and genetic factors. The term epigenetic regulation broadly covers DNA methylation, histone posttranslational modifications, and regulation by non-coding RNAs[33]. As there is some discussion as to whether non-coding RNAs are truly an epigenetic modification (they show regulation at a post-transcriptional gene expression level), they will be further discussed in the scope of transcriptomics.

DNA methylation is by far the most extensively studied epigenetic modification of suicidal behaviour using candidate gene and -omics approaches. An overview of epigenomic studies that have focused on DNA methylation and suicidal behaviour is given in Table 2. There are multiple approaches to analyse DNA methylation on a genome-wide scale, including whole genome bisulphite sequencing and microarray and antibody-based approaches; these can again make it hard to directly compare studies[34]. The results defined a complex picture of the association of DNA methylation and suicidal behaviour, which included the involvement of differences in cognitive functions[35], cell cycle and cell-cell signalling[36,37], regulation of gene transcription and expression[38], glutamate signalling[39], cell structural integrity and nervous system regulation[40], and neurodevelopment and polyamine metabolism [41].

**Table 2 Overview of epigenomic studies that have examined suicidal behaviour**

Type of -omic	Tissue	Number of samples	Main results	Ref.
Agilent 400K promoter tiling microarrays	Dentate gyrus	46 suicide completers and 16 comparison subjects	Significantly differential methylation of 366 promoters in suicide victims (273 hypermethylated and 93 hypomethylated)	Labonté <i>et al</i> [35], 2013
Illumina Infinium Human Methylation 27 BeadChip	Orbitoprefrontal cortex	25 depressed suicide cases and 28 non-psychiatric sudden death controls	Significantly increased DNA methylation in suicide victims	Haghighi <i>et al</i> [36], 2014
Illumina Human Methylation 450 BeadChip	Prefrontal cortex	23 suicide and 35 non-suicide	Significant altered methylation at four CpGs ( <i>ATP8A1</i> , <i>SKA2</i> , <i>LOC153328</i> and <i>KCNAB2</i> in suicide victims	Guintivano <i>et al</i> [37], 2014
Illumina Human Methylation 450 BeadChip	Prefrontal cortex	Six suicide, six non-suicide	Significantly decreased level of methylation in suicide victims	Schneider <i>et al</i> [38], 2015
Illumina 450 K Infinium microarray	Prefrontal cortex	22 suicide completers and 28 control subjects	Significantly differential methylation of 454 CpGs in suicide completers	Kozlenkov <i>et al</i> [47], 2017
Methylation binding domain-2 (MBD2) sequencing	Prefrontal cortex	22 suicide cases and 17 controls	Significantly decreased methylation in suicide victims, with 115 differentially methylated regions	Nagy <i>et al</i> [39], 2015
Reduced-representation bisulphite sequencing	Prefrontal cortex and hippocampus	Nine suicide victims and nine controls	Significantly decreased methylation of 63 and 2406 CpGs and increased methylation of 43 and 328 CpGs in prefrontal cortex and hippocampus, respectively	Kouter <i>et al</i> [40], 2019
Illumina Infinium Human Methylation 450K BeadChip	Prefrontal cortex	21 suicides and six non-suicides	Significant correlation of 22 CpGs with gene expression in suicide victims	Cabrera-Mendoza <i>et al</i> [41], 2020

Finally here, few studies on epigenetic regulation have so far been carried out that have investigated histones and their posttranslational modification. Most of these have focused on targeting selected genes (*e.g.*, H3K27me3 and TrkB[42]; H3K27me3/H3K4me3 and polyamine system genes[43,44], H3K9me3 and astrocyte connectivity[45]), with limited success. Misztak *et al*[46] (2020) reported a significant increase in H3K27me2 and decrease in H3K9/14ac in the hippocampus and frontal cortex of suicide victims, which might result in lowered brain-derived neurotrophic factor (BDNF) protein levels[46].

### Transcriptomics

Gene transcription can be affected by various biological responses that have tight temporal regulation, which can range from very short (milliseconds) to long-lasting (days) effects[47,48]. Initially, studies used microarray-based approaches to study transcriptomics. As hybridisation-based microarrays have some limitations (*e.g.*, they only allow detection of transcripts complementary to oligonucleotides bound to the array, and they can cause cross-hybridisation), focus has shifted to sequencing-based methods[49]. Additional advantages of sequencing are the possibility to detect alternative splicing, which is especially common in the brain, and the possibility for qualitative analysis[50].

An overview of transcriptomic studies that have examined suicidal behaviour is given in Table 3. The term transcriptomics refers to the study of all of the coding (*i.e.*, producing a code for a protein output) and non-coding (*i.e.*, providing additional regulatory mechanisms) RNA. As the field of non-coding RNAs is particularly diverse, we will focus on micro-RNAs (miRNA) only. The transcriptome of a given cell often exhibits high tissue specificity, which might be why studies have generally focused on transcriptome analysis of the brain. For suicide victims, changes in mRNA expression have been observed for many processes and pathways, which have included cell-cell communication, signal transduction, cell proliferation, development of the central nervous system[51,52], myelination[53] and microglial functions[54]. Changes have also often been observed for neurotransmission [*e.g.*, glutamatergic and gamma-aminobutyric acid (GABA)ergic signalling[53,55]] and for immune system responses and inflammation[52,54,56].

The search for miRNAs that might be used as biomarkers has not been successful yet, although various miRNAs have been identified as differentially expressed in suicide victims. However, such indications have often not been reproduced in other studies. For example, two studies identified miR-330-3p as differently expressed in suicide victims, with one reporting down-regulation in the prefrontal cortex[57], and

Table 3 Overview of transcriptomic studies that have examined suicidal behaviour

Type of -omic	Tissue	Number of samples	Main results	Ref.
U133A Oligonucleotide DNA Microarrays	Prefrontal cortex	19 depressed-suicide victims and 19 controls	No significant results	Sibille <i>et al</i> [105], 2004
Illumina Sentrix HumanRef-8 Expression BeadChips	Orbitofrontal cortex	11 suicide victims and ten controls	Significant downregulation of 59 genes and upregulation of 65 genes in suicide victims	Thalmeier <i>et al</i> [51], 2008
Human Genome U133 Set (HG-U133 A and B) microarray	Prefrontal cortex	16 depressed suicides, eight non suicides and 13 controls	Significantly altered expression of 267 genes, associated with cell cycle control and cell division, myelination, ATP biosynthesis and GABAergic neurotransmission in suicide victims	Klempan <i>et al</i> [53], 2009
HG-U133AB chipset	17 brain areas (amygdala, hippocampus, nucleus accumbens and 14 Brodmann areas)	26 suicide cases and 13 controls	Altogether over 4000 differentially expressed genes, association with cell communication and synaptic transmission in suicide victims	Sequeira <i>et al</i> [55], 2009
RNA-seq	Prefrontal cortex	21 major depressive disorder suicides, 9 MDD non-suicides and 29 controls	Significantly altered expression of 35 genes in suicide victims, association with microglial and immune system functions, and angiogenesis	Pantazatos <i>et al</i> [54], 2017
RNA-seq	Hippocampus	17 MDD suicide victims and 23 control subjects	Significant change in expression of 26 genes in depressed suicide victims, association with inflammation and chromatin regulation	Mahajan <i>et al</i> [56], 2018
RNA-seq	Insula	52 mood disorder suicide victims and 45 non-mood disorder controls	Significant downregulation of 20 genes associated with inflammation response, protein- protein interaction, neurodegeneration, neurodevelopmental and upregulation of 5 genes, associated with intracellular protein transport, inflammation, apoptosis regulation and embryonic development in mood disorder suicide victims	Jabbi <i>et al</i> [52], 2020
RNA-seq	Prefrontal cortex	17 depressed suicide victims and 17 controls	Significant change in cell-type specific expression in depressed suicide victims	Nagy <i>et al</i> [60], 2020
TLDA based miRNA profiler	Prefrontal cortex	18 antidepressant-free MDD suicide victims and 17 controls	Significant downregulation of 21 miRNAs in suicide victims, miRNAs associated with nuclear proteins, transmembrane and signalling proteins	Smalheiser <i>et al</i> [106], 2012
LNA-based miRNA profiler	Prefrontal cortex	Four suicide victims and 4 controls	Significant upregulation of a single miRNA, targeting TrkB-T1, observed in low TrkB-T1 expression suicide victims	Mausson <i>et al</i> [107], 2012
TLDA-based miRNA profiler	Prefrontal cortex	18 suicide victims and 40 control subjects (all mood disorder)	Significant downregulation of 6 miRNAs and upregulation of 2 miRNAs in suicide victims	Smalheiser <i>et al</i> [57], 2014
Small RNA-seq	Prefrontal cortex	Nine suicide victims with depression, nine suicide victims and nine controls	No significant results	Pantazatos <i>et al</i> [54], 2017
TLDA-based miRNA profiler	<i>Locus coeruleus</i>	Nine suicide victims with depression and 11 controls	Significant upregulation of 10 miRNAs and downregulation of 3 miRNAs in suicide victims. Identified miRNAs are targeting multiple genes that were previously associated with psychiatric disorders	Roy <i>et al</i> [58], 2017

the other reporting up-regulation in the *locus coeruleus*[58]; this again indicates the potential importance of tissue specificity.

Recently, focus has been shifting from whole tissue homogenates towards single-cell transcriptome analysis, to better define the complexity of the brain structure and its cellular composition. In doing so, large differences have been seen between subtypes of brain cell populations[59]. Nagy *et al*[60] (2020) analysed the nuclei of the prefrontal cortex in depressed suicide victims, and they identified 26 distinct cell types. The most notable changes were in the deep layer of excitatory neurons and immature oligodendrocyte precursor cells. More specifically, there was association with fibroblast growth factor signalling, steroid hormone receptor cycling, immune function, and cytoskeletal regulation[60].

### Proteomics

The proteome is defined as the complete set of proteins that are expressed by a cell or tissue type, or an organism, under specific conditions, which includes proteins that

result from alternative gene splicing, and posttranslational modifications of proteins [61]. The proteome can thus provide us with a snapshot view of the key players in many cellular processes. Compared to transcriptomics, proteomics has the advantage of providing additional information on RNA-protein translation, protein localisation, protein posttranslational modification, protein localisation, speed of protein production and degradation, and interactions with other proteins[62].

Compared to previously described -omics studies, large-scale studies of proteins are not as common when it comes to suicidal behaviour. An overview of proteomic studies that have examined suicidal behaviour is given in Table 4. Usually, protein samples are first separated (*e.g.*, two-dimensional gel electrophoresis to separate proteins based on molecular weight and isoelectric point), with mass spectrometry used to identify a protein of interest[63].

Various tissue samples have been used to date to study the proteomics of suicidal behaviour, including the prefrontal cortex[64-66], amygdala[65] and cerebellum[67]. Studies have also examined cerebrospinal fluid[68,69] and plasma[70,71], as although these are still invasive, they represent more easily accessible sources of tissue.

A reoccurring pattern can be observed, that is similar to the other -omics studies described above. Here, too, there are connections with many of the previously mentioned cell functions and pathways, with indications of association with glial function, neurodegeneration, oxidative stress, neuronal injury[64], the cytoskeleton, synaptic functions[65], coagulation and inflammation[70], decreased glucose utilisation[69], altered cholesterol metabolism in deliberate self-harm[71], transport functions and cell communication in schizophrenia suicide victims[67], the GABA receptor signalling pathway, and pathways related to other neurotransmitters in mood disorder suicide victims (*e.g.*, serotonin receptor signalling, melatonin signalling, CREB signalling in neurons, dopamine receptor signalling)[66].

Additionally, Cabello-Arreola *et al*[66] (2020) reported a reduction in the protein coded by *KCNQ3* (potassium voltage-gated channel subfamily Q member 3) in suicide victims. This protein serves as a building block for the M-channel, a slow working potassium channel that is involved in the regulation of neuron excitability, which has previously been associated with epilepsy, attention deficit hyperactivity disorder, and psychiatric disorders[72].

Suicidal behaviour is often presented as a comorbidity that is accompanied by other psychiatric disorders that have their own specific aetiologies. A study by Vidal-Domènech *et al*[67] (2020) demonstrated this problem. After comparison of cerebellum protein expression of suicide victims with schizophrenia and healthy controls, 99 proteins were identified as significantly altered. During the further validation of three proteins in a larger group of people, including non-schizophrenia suicide victims, only one of these remained associated with suicidal behaviour. This opens the question of whether the 99 proteins identified indicated associations with schizophrenia, suicidal behaviour, or both[67]. Similar considerations should be taken when interpreting other studies, including with patients with identified psychiatric or other disorders.

### **Metabolomics**

Although the most pronounced changes in suicidal behaviour take place in the brain, the access to the brain itself is generally only through *post-mortem* studies. Finding biomarkers for suicidal behaviour that can be repeatedly and easily monitored in real time is therefore aimed at peripheral tissues, like cerebrospinal fluid, platelets, serum and urine, among others, where the intermediate or end products of metabolism can be measured. Among the first clues for metabolites as potential biomarkers for suicidal behaviour was the finding of Asberg *et al*[73] (1976). In the cerebrospinal fluid of depressed suicide attempters they reported that low levels of 5-hydroxyindoleacetic acid (a metabolite of serotonin degradation) were associated with more attempted suicides and with more violent means, compared to patients with high levels of 5-hydroxyindoleacetic acid[73].

An advanced study of metabolites in large numbers is defined as metabolomics. The patterns of metabolic intermediates can be used to determine dysfunctions in metabolic pathways, which can be linked to symptomatic presentation[74]. Studies of metabolomics and suicidal behaviour alone have not been performed yet, and have instead been incorporated into studies of psychiatric disorders, and most commonly, depression.

In a multicentre study on the severity of depression and suicidal ideation, plasma metabolites and a machine learning approach were used to build a model to discriminate between depressive patients without and with suicidal ideation. In this study, positive correlation between citrate and suicidal ideation was seen, while negative correlation was seen for kynurenine pathway metabolites (especially

Table 4 Overview of proteomic studies examining suicidal behaviour

Type of -omic	Tissue	Number of samples	Main results	Ref.
2D gel electrophoresis	Cerebrospinal fluid	Seven suicide attempter and seven non-attempters	Significantly altered level of a single protein in suicide attempters. Due to limited amount of material the protein could not be identified	Brunner <i>et al</i> [68], 2005
2D gel electrophoresis and MALDI TOF MS	Prefrontal cortex	17 suicide victims and 9 controls	Significantly altered levels of three protein: An isoform of the common astroglia marker glial fibrillary acidic protein (GFAP), manganese superoxide dismutase (SOD2) and $\alpha$ crystallin chain B (CRYAB)	Schlicht <i>et al</i> [64], 2007
DIGE qTOF tandem MS	Prefrontal cortex and amygdala	Six suicide victims and six controls	59 significantly altered protein levels in the cortex and 11 significantly altered proteins in the amygdala. Level of nine proteins were significantly altered in both brain regions, but with varying direction of change (either increased or decreased in suicide victims), suggesting the global change in the brain, yet highlighting the importance of tissue specificity	Kékesi <i>et al</i> [65], 2012
2D gel electrophoresis and-MALDI-TOF MS	Plasma	12 suicide attempters, 12 MDD patients and 12 controls	Significant change in 45 protein, enabling the differentiation between MDD patients exhibiting suicidal behaviour and non-suicidal MDD patients	Yang <i>et al</i> [70], 2016
HPLC and Ion Trap MS	Cerebrospinal fluid	Two suicide victims and two controls	69 proteins with significant change in suicide victims, association with dysregulation of glucose metabolism and oxidative stress response.	Semancikova <i>et al</i> [69], 2018
2D-gel electrophoresis and MALDI MS	Plasma	10 self-harm subjects and 18 controls	Downregulation of apolipoprotein A-IV (Apo A-IV) in deliberate self-harm subjects.	Mathew <i>et al</i> [71], 2019
Liquid chromatography and tandem MS	Cerebellum	Four suicide victims and four controls	99 significantly altered proteins in schizophrenia suicide victims, association with transport function and cell communication. Vacuolar-type proton pump ATPase (VPP1) further validated and associated with suicidal behaviour.	Vidal-Domènech <i>et al</i> [67], 2020
ESI-MS/MS	Dorsolateral prefrontal cortex	Five suicide victims and five controls	33 proteins with significant change in expression (24 decreased and nine increased in the suicide group). Biggest change observed in reduction in protein coded by KCNQ3 (potassium voltage-gated channel subfamily Q member 3) in mood disorder suicide victims.	Cabello-Arreola <i>et al</i> [66], 2020

kynurenine and 3-hydroxykynurenine). Using only citrate and kynurenine, an algorithm for suicidal ideation grade was built[75]. This is of particular interest, as previous studies have associated the tryptophan-kynurenine pathway with brain inflammation and microglial activation, and more recently with suicide[76,77]. In another study of suicidal ideation that was performed on depressed antepartum women, significant inverse associations with suicidal ideation were shown for the neurotransmitter precursors for serotonin and dopamine: 5-hydroxytryptophan and phenylalanine, respectively[78]. Here, again the microglia activation hypothesis might serve as an explanatory mechanism, as it has been linked to alterations in tryptophan signalling and suicidal ideation[77,78]. Of interest, among the metabolomic studies there was also one on cerebrospinal fluid and the serum metabolome. This included treatment-refractory depressed patients, for whom cerebral folate deficiency was shown, although their serum folate levels were normal. In these cases, the metabolomic analysis revealed this reason for the lack of treatment response, which would not have been identified through any other conventional clinical, diagnostic or therapeutic approaches. Administration of folic acid reduced the symptoms of depression, and also the suicidal ideation[74].

Although studies of the metabolome and mental disorders are still in their infancy, these results show great potential for their use, particularly when common treatment approaches do not achieve satisfactory effects.

## BUILDING THE BRIDGE BETWEEN PERSONALISED MEDICINE AND PSYCHIATRY

Throughout this review, we have presented the large body of work that has investigated suicidal behaviour, which has ranged from the genome all the way to the metabolome, thus demonstrating further the complexity of suicidal behaviour. A

biological basis of suicidal behaviour can therefore not be determined by any single gene, transcript, protein or metabolite, as it is the final sum of intertwined cellular mechanisms, cell types and tissue changes.

In these current times of the coronavirus disease 2019 (COVID-19) pandemic, the importance of novel approaches to diagnosis and treatment of people with psychiatric disorders is probably greater than ever. An important advance has been the increased use of telepsychiatry, which uses audiovideo technology to enable live interactions, which can be combined with previously prepared materials to provide the needed counselling, monitoring and therapy[79]. However, when it comes to tailoring the approach to the individual and the use of biological markers to diagnose or monitor treatments, great challenges still remain[80]. Psychiatry remains a field of medicine that is heavily dependent on arbitrary determined thresholds of standards, manuals and questionnaires to diagnose and monitor a patient. Not knowing the definitive cause of complex disorders prevents healthcare personnel from treating each patient in terms of his or her full needs. By personalising the care of people with suicidal behaviour and other psychiatric disorders, psychotherapy and drug treatments will improve from the current estimate of 50% success[81,82].

### **Personalised psychotherapy and pharmacogenomics**

Suicidal behaviour and psychiatric disorders are often associated, but they are not exclusively bound together. While some studies have shown that the majority of suicide victims are, or could be, diagnosed with additional psychiatric disorders, it is estimated that only around 5% to 8% of people with psychiatric disorders will exhibit suicidal behaviour[83]. Thus, more suitable drugs and prescriptions would help a large segment of people with suicidal behaviour (as well as the non-suicidal patients).

Pharmacogenomics is a novel field that is studying the genetic basis of drug metabolism and response. The way we metabolise a drug can be greatly influenced by genetic variations, in terms of genes that code for enzymes, drug transporters and other proteins involved in drug metabolism[84]. The most commonly used phenotype classification system divides patients into subgroups of ultrarapid metabolisers, rapid metabolisers, normal metabolisers, intermediate metabolisers, and poor metabolisers [85].

The suitable choice of psychopharmaceuticals and their dosing is often a long process, with patients reporting side effects before the correct doses and drug combinations can be achieved[86]. Multiple enzymes are associated with differences in drug metabolism, with CYP2D6 and CYP2C19 being the most promising in the field of psychiatry. These both belong to the cytochrome P450 superfamily of enzymes that are responsible for drug metabolism. Based on the Pharmacogenomics Knowledgebase (PharmGKB) database, there are currently 17 antidepressants and 10 antipsychotics on the market. These have medical agency approved guidelines and the labels recommend genetic testing for CYP2D6 and CYP2C19. They then offer either selection or dosage recommendations based on the individual metabolic status[86].

While some studies have shown the association of other genetic variants with pharmacodynamics [*e.g.*, *SLC6A4*, *COMT*, *BDNF*; as detailed in a review by Lett *et al* [87] (2016)], recent guidelines from the International Society of Psychiatric Genetics do not support their use for prescribing psychiatric medications[86].

Despite its limitations (*i.e.*, test result interpretation, cost, high turnaround time, bias through focusing on European ancestry, population allele frequencies) pharmacogenomics has shown great potential, and might therefore be effective and safer for drug prescribing, such that they can be tailored to the personal genetic makeup of the patient[86,88].

### **Use of artificial intelligence**

These -omic-based studies can provide us with large amounts of data. Artificial intelligence is an approach that is beginning to be increasingly used in various fields of medicine, including psychiatry[89]. Through the use of artificial intelligence, computer models can more easily analyse these large datasets, and more importantly, artificial intelligence can lead to predictions of the risk of an event or disease, based on previously analysed data. To date, artificial intelligence has been used in research into suicidal behaviour that has ranged from analysis of social media texts[90] and health records[91], to analysis of the previously described -omics approaches.

Machine learning algorithms have been successfully used to determine whether a person belongs in the group of suicide attempters or non-attempters with 67% accuracy; this was based on only three SNPs: In *HTR1E* (5-hydroxytryptamine receptor 1E); *GABRP* (g-aminobutyric acid type A receptor subunit Pi); and *ACTN2* (actinin  $\alpha$ 2) [92]. Based on gene expression and DNA methylation, Bhak *et al*[93] (2019)

successfully differentiated between suicide attempters and patients with major depressive disorder with 92.6% accuracy, and between suicide attempters and control subject with 86.7% accuracy[93]. Similarly, metabolic profiles can be used to try and differentiate between people. A study by Setoyama *et al*[75] (2016) associated the kynurenine pathway metabolites and citrate with suicidal ideation, which allowed determination of the patients without and with suicidal ideation[75].

An interesting study was reported by Just *et al*[94] (2017), where they used functional magnetic resonance imaging to provide an insightful view of the differences of concept understanding. By measuring the changes in brain activity when presented with words or concepts, the locations and intensity of the responses differed between people with suicidal ideation and the control group; this model differentiated between these two groups with 91% accuracy[94].

Although artificial intelligence comes with several limitations, such as the need for large amounts of unbiased data, precise model development, and technical abilities, it appears to hold promise of better treatment possibilities of individuals. Artificial intelligence should provide better understanding and detection of suicidal behaviour and suicidal ideation, aid in therapy progression and treatment planning, and help with patient monitoring and stratification[95].

### **Challenges of personalised medicine**

Psychiatric disorders are highly heterogeneous, with complex biological underpinning, paired with additional cultural, social and environmental factors[96]. Bragazzi[96] (2013) proposed the use of "psychiatome" to combine the interactions of all of the -omics involved in the development of the psychiatric state of a person. This covers genes, transcription and protein networks, along with brain anatomy, and should incorporate the concept of '5P' medicine: personalised, participatory, predictive, preventive and psycho-cognitive[96]. These -omics might represent part of the missing link between the current state of psychiatry and future personalised approaches, through the addition of -omics-derived information to the diagnostic process. However, for this we need precise, specific and validated biomarkers, which have not yet been identified. Additional limitations of personalized medicine in psychiatry include the question of stigma (*e.g.*, effects on the general population, patients and public health policy makers), ethical aspects (*e.g.*, conflicts of interest, informed consent of patients, data protection), cost-effectiveness and need for additional skillsets for healthcare providers[97].

By including -omics-based data in the diagnostic process, psychiatric disorders can be viewed as spectrum disorders, instead of the current binary "disease or health" approach that is proposed by psychiatric manuals[98]. Here, the end goal is not to reject the classical definition and the diagnostics and care of psychiatric disorders, but to compliment these with better understanding of each patient group[99].

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## **CONCLUSION**

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Suicide is devastating, but at the same time it is preventable if timely measures are taken. Therefore, understanding the biological background of suicide is important, to help develop clinically applicable tools for its detection. However, like in many other cases of complex diseases, we are only just beginning to uncover the biological clues for its development.

Candidate gene approaches and GWAS still lack the identification of any common gene or variant. None of the most researched genes in suicidal behaviour, the serotonergic genes, have been replicated in any GWAS on suicidal behaviour[100]. The replication of results is affected by significant sample differences (*e.g.*, demographic characteristics, primary diagnosis, suicidal behaviour/ideation phenotype) and methodological approaches (*e.g.*, candidate genes, GWAS) across studies. Microarrays are being gradually supplemented and replaced with novel sequencing approaches that can produce faster and cheaper information, which will lead to the generation of more medically useful information, like whole exome sequencing. However, in the case of mental health, we are still far away from any molecular-based tool that is useful for clinical prediction. Only single studies on suicide and whole exome sequencing are currently available[101], and although several hundred thousand SNPs and insertions/deletions have been identified, currently these data provide 'only' a resource for further laborious in-depth analysis to find further biologically meaningful information.

In recent years biomarker research has started to uncover the intriguing roles of extracellular vesicles. These small vesicles are excreted by virtually all cells, and they are involved in cellular communication, as they can travel over short or long distances. Their crossing of the blood-brain barrier gives them particular value in research into the central nervous system, as extracellular vesicles are defined by their origin and their cargo (*e.g.*, proteins, DNA, RNA). This opens new potential for peripheral markers for brain disorders[102]. In the field of mental disorders, only a few studies have been performed, while their involvement in research into suicidal behaviour is currently still untouched[103]. Determination of the origin, number and content of extracellular vesicles, can provide an important contribution to our understanding of brain function in a state of severe stress, such as inflammation or an immune response, both already associated with suicidal behaviour. As the current COVID-19 pandemic represents a significantly increased risk of sociological risk factors for suicidal behaviour, the disease itself triggers inflammation and extremely strong immune responses with a cytokine storm, which can promote increased risk of psychiatric disorders, chronic trauma and stress, which in turn will increase suicide and suicidal behaviour[104]. From this point of view, this represents a unique opportunity to perform molecular-genetic studies on suicidal behaviour using cutting-edge technology.

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## ACKNOWLEDGEMENTS

The authors thank Dr. Christopher Berrie for scientific English editing of the manuscript.

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