Genetics and Suicide

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Eugene Lin and Shih-Jen Tsai

Abstract

Strong evidence suggests a genetic susceptibility to suicidal behavior, including familial heritability and common occurrence in twins. In the recent advent of scientific research, the genome-wide association study (GWAS), an alternative to the candidate-gene approach, is widely utilized to examine hundreds of thousands of SNPs by high-throughput genotyping technologies. In addition to the candidate-gene approach, the GWAS approach has recently been employed to study the determinants of suicidal behavior. Several recent findings have demonstrated that some SNPs and genes are closely associated with suicidal behavior. This chapter addresses recent molecular genetic studies in suicidal behavior. First, we surveyed the SNPs and genes identified as genetic markers that are correlated and associated with suicidal behavior in the candidate-gene association studies. Next, we reviewed the SNPs and genes that have been suggested as contributors to suicidal behavior in the GWAS studies. Finally, we summarized the limitations and future directions. Future research with independent replication in large sample sizes is needed to confirm the role of the SNPs and genes identified in the candidate-gene and GWAS studies in suicidal behavior.

E. Lin
Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan

Vita Genomics, Inc., Taipei, Taiwan

S.-J. Tsai (✉)
Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Shih-Pai Road, Sec. 2, Taipei 11217, Taiwan

Division of Psychiatry, National Yang-Ming University, Taipei, Taiwan
e-mail: tsai610913@gmail.com

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8.1 Introduction

Numerous studies over the last three decades have reported that abnormalities in the functioning of the central serotonergic system are linked to the pathogenesis of suicidal behavior (Ryding et al. 2008). To date, most of the molecular genetic studies focused on the serotonergic pathway as the basis of established biological correlations of suicidal behavior, and thus, the candidate genes were primarily related to the serotonergic system (Bondy et al. 2006). Genetic association studies using genetic variants such as single nucleotide polymorphisms (SNPs) have shown that genes contribute to suicide risks and have suggested several genes such as *serotonin transporter* related to suicidal behavior, but not all reports support these findings (Tsai et al. 2011).

In addition, evidence from other research designs (such as adoption, family, geographical, immigrant, surname, and twin studies of suicide) suggested genetic contributions to suicide risk (Baldessarini and Hennen 2004). Further, the contribution of additive genetic factors is estimated to be 30–50 % for suicidal behavior including ideation, plans, and attempts (Voracek and Loibl 2007). Twin and family studies also documented a higher concordance rate for suicide in monozygotic than dizygotic twins (24.1 % vs. 2.8 %) and nearly fivefold greater relative risk of suicidal acts in the relatives of individuals who die by suicide, even after adjusting for psychiatric disorder.

8.2 Candidate-Gene Association Studies

Genes that code for proteins involved in regulating serotonergic neurotransmission have been major candidate genes for the association studies of suicidal behavior. Among them, genes for serotonergic receptors, serotonin transporter, tryptophan hydroxylase, and other monoaminergic systems have received the most research attention.

8.2.1 Brain-Derived Neurotrophic Factor Pathway

The protein encoded by the *brain-derived neurotrophic factor* (*BDNF*) gene is a member of the neurotrophin family and plays an important role in neuronal survival and brain plasticity (Dwivedi 2010). In the past decade, evidence is accumulating to suggest *BDNF* and its relevant genes such as the *neurotrophic tyrosine kinase receptor type 2* (*NTRK2*) and *nerve growth factor receptor* (*NGFR*) genes in the pathogenesis of suicidal behavior and major depression from clinical studies and postmortem studies. The functional Val66Met (rs6265) SNP in *BDNF* has attracted much attention in suicide research. However, evidence for assessing the risk of *BDNF* Val66Met in suicidal behavior is currently controversial. *BDNF* Val66Met has been reported to predispose to suicidal behavior in Japanese, Taiwanese, Korean, and Italian populations (Tsai et al. 2011). On the contrary, this association with suicide behavior has not been replicated in Taiwanese, Slovenian, Caucasian, and German studies (Tsai et al. 2011). Regarding the conflicting findings in these studies, a meta-analysis may

help to elucidate the role of *BDNF* Val66Met in suicidal behavior. Zai et al. (2012) performed the meta-analysis of BDNF Val66Met in suicidal behavior using data from 12 studies and suggested that *BDNF* Val66Met is involved in suicidality.

In addition to the aforementioned findings, a report failed to find an association between the *BDNF* SNPs and suicidal behavior but found the associations of SNPs in *NTRK2* with suicide attempt in depressed German patients, which were also replicated in the African American population (Kohli et al. 2010). McGregor et al. (2007) also investigated three SNPs in *NGFR* for an association with suicide behavior in childhood-onset mood disorder, and the results did not support an association of the *NGFR* SNPs with suicide risk.

8.2.2 Dopaminergic System

Genes in the dopaminergic system could be candidates for suicidal behavior study due to the fact that the striatal dopaminergic activity is related to impulsivity, a character of suicidal behavior. In a Japanese report, Suda et al. (2009) implicated possible involvement of the TaqIA and − 141C insertion/deletion variants of the *dopaminergic D2 receptor* (*DRD2*) gene in the biological susceptibility to suicidal behavior. Furthermore, this finding is in line with an earlier report that linked the *DRD2* − 141C insertion/deletion variant with attempted suicide in German alcoholics (Johann et al. 2005).

Catechol-O-methyltransferase (COMT), the postsynaptic enzyme that metabolizes released dopamine, is a critical enzyme in the metabolic degradation of dopamine in the prefrontal cortex. Kia-Keating et al. (2007) conducted a meta-analysis using six studies and demonstrated evidence of a modest significant association between the *COMT* Val158Met SNP and suicidal behavior. In addition, two following studies identified the role of *COMT* Val158Met in suicidal behavior among the male subjects in Korean (Lee and Kim 2011) and Caucasian (Pivac et al. 2011) populations. These findings are in line with a report associating *COMT* Val158Met with attempted suicide in Caucasian alcoholics (Nedic et al. 2011).

Monoamine oxidase (MAO) is a mitochondrial outer membrane enzyme that degrades biogenic amines, including neurotransmitters such as dopamine. The *MAOA* gene contains a functional variable number tandem repeat (or VNTR) in the upstream regulatory region (*MAOA*-uVNTR). Hung et al. (2012) indicated that there was no association between *MAOA*-uVNTR and suicidal behaviors in the meta-analysis using data from seven case-control association studies. However, Antypa et al. (2013) found that the *MAOA* rs909525 SNP was associated with suicidality after examining the following markers: *MAOA* rs909525, *MAOA* rs6323, *MAOA* rs2064070, and *MAOB* rs1799836.

8.2.3 Hypothalamic–Pituitary–Adrenal (HPA) Axis

The HPA axis is a neuronal and endocrine system that regulates the body's response to stress. Dysregulation of the HPA axis may be related to the risk of suicidal

behavior owing to the fact that stress plays a major role in the various pathophysiological processes associated with suicidal behavior (Pompili et al. 2010). De Luca et al. (2010) tested the HPA axis-related genes including the *corticotrophin-releasing hormone* (*CRH*), the *corticotrophin-releasing hormone receptor 1* (*CRHR1*), *CRHR2*, *CRH binding protein* (*CRHBP*), and *melanocortin 2 receptor* (*MC2R*) genes in a cohort of schizophrenia subjects with attempted suicide. The genotype analyses yielded a significant association between *CRHBP* and suicide attempt. They also demonstrated a significant interaction between *CRHR1* and *CRHBP* in influencing suicide attempt and the severity of suicidal behavior, suggesting that SNPs in the HPA-axis-related genes could be associated with suicidal behavior in schizophrenia. Wasserman et al. (2008) also reported *CRHR1* rs4792887 for suicidality in depressed males exposed to low stress. In addition, Roy et al. (2012) showed an interaction between *CRHBP* and childhood trauma on suicidal behavior. Moreover, there was an additive effect with the *FK506 binding protein 5* (*FKPB5*) gene.

The protein encoded by *FKBP5* is a member of the immunophilin protein family, which plays a role in causing subsensitivity of the glucocorticoid receptor. In a study with seven *FKBP5* SNPs in families with bipolar offspring, Willour et al. (2009) suggested that *FKBP5* may influence attempted suicide and number of depressive episodes in the bipolar subjects. In addition, Supriyanto et al. (2011) reported that the haplotypes (comprised of rs3800373 and rs1360780) in *FKBP5* were associated with completed suicide in the Japanese population. Furthermore, Roy et al. (2012) showed that an interaction between *FKBP5* and childhood trauma may increase the risk for attempting suicide.

8.2.4 Serotonergic Receptors

Suicide genetic studies mostly investigated the *5-hydroxytryptamine receptor 1A* (*HTR1A*) and *5-hydroxytryptamine receptor 2A* (*HTR2A*) genes that encode two of the serotonin receptors, which have opposing functions in a variety of cellular and behavioral processes.

HTR1A C-1019G (rs6295) has attracted considerable interest in suicidal behavior research because this SNP influences serotonergic neurotransmission. Angles et al. (2012) performed a meta-analysis of a possible correlation between *HTR1A* C-1019G and suicidal behavior with 4 studies and found no association. Similarly, González-Castro et al. (2013) performed another meta-analysis with nine studies and confirmed no association.

There are many genetic association studies of the *HTR2A* gene with suicidal behavior. Li et al. (2006) have made a good summary of these reports with a meta-analysis of 73 association studies for *HTR2A* and suicidal behavior. They detected a significant association between *HTR2A* A-1438G and suicidal behavior. However, they failed to find a significant association of *HTR2A* T102C with suicidal behavior.

In addition, a meta-analysis utilizing seven studies demonstrated no significant association between the G861C (rs6296) SNP in the *5-hydroxytryptamine receptor 1B* (*HTR1B*) gene and suicidal behavior (Kia-Keating et al. 2007).

8.2.5 Serotonin Transporter

The *solute carrier family 6 member 4* (*SLC6A4*) gene codes for the serotonin transporter. Following serotonin release, the serotonin transporter is the major site of serotonin reuptake into the presynaptic neuron. By regulating the reuptake of the released serotonin, the serotonin transporter is central to fine-tuning the serotonergic neurotransmission.

Among the genetic variants in *SLC6A4*, a 44-base pair (bp) insertion–deletion in the promoter region (serotonin-transporter-linked polymorphic region; 5-HTTLPR) polymorphism and a 17-bp VNTR in the second intron of *SLC6A4* have been extensively studied for an association with suicidal behavior. Li and He (2007) reviewed 39 studies that examined the association between the functional 5-HTTLPR polymorphism and suicidal behavior in groups with psychiatric diagnoses. Their report suggested a significant association ($P = 0.0068$) with S allele as the risk allele for suicidal behavior. For the *SLC6A4* VNTR polymorphism, they demonstrated no significant association for both the 10-repeat allele and 12-repeat allele, either in allelic or genotypic analysis.

8.2.6 Tryptophan Hydroxylase

The encoded proteins by the *tryptophan hydroxylase 1* (*TPH1*) and *tryptophan hydroxylase 2* (*TPH2*) genes are the rate-limiting enzymes in the biosynthesis of serotonin. In humans, as well as in other mammals, there are two isoforms of TPH, referred to as TPH1 and TPH2.

Numerous studies have tested for an association between the genetic variants in *TPH1* and suicidal behavior but produced contradictory results. Li and He (2006) reported a meta-analysis with published 22 studies. They demonstrated a significant overall association between suicidal behavior and the *TPH1* A218C/A779C SNPs, suggesting the involvement of *TPH1* in the pathogenesis of suicidal behavior. In contrast, a following meta-analysis is conflicting and does not support *TPH1* A218C/A779C being a susceptibility locus for suicidal behavior (Saetre et al. 2010). However, a recent meta-analysis with 37 studies provided evidence that *TPH1* A218C/A779C may be a risk factor to manifest suicidal behavior at the clinical level (González-Castro et al. 2014).

The *TPH2* gene has attracted much attention for its role in suicidal behavior pathophysiology since its identification. Several studies have tested *TPH2* in recent years for associations with suicidal behavior with positive findings, although some studies found negative findings (Tsai et al. 2011). A meta-analysis of these studies may help to clarify the role of *TPH2* in suicidal behavior. González-Castro et al. (2014) performed a meta-analysis with 37 studies and could not find an association with suicidal behavior with regard to the *TPH2* SNPs (including G-703T, A-473T, and G19918A).

8.2.7 Gene–Gene Interaction

Because suicidal behavior may be related to multiple genes, several studies have investigated gene–gene interaction in suicidal behavior. Studies have tested the gene–gene interaction between *MAOA* and *COMT* in suicide attempt history in families with at least one member having bipolar disorder (De Luca et al. 2005) and in patients with schizophrenia (De Luca et al. 2006); however, these studies found no additive effect in conferring suicidal behavior risk. Another report showed no association among the *HTR2C* and *MAOA* intergenic haplotype combination and suicide attempt in bipolar patients (De Luca et al. 2008).

Moreover, Murphy et al. (2011) identified a three-locus gene–gene interaction (including *HTR1B* rs6296, *SLC1A2* rs4755404, and *NTRK2* rs1659400) as a significant predictor of suicidal behavior after controlling for possible confounders such as age, gender, alcohol abuse, and schizophrenia. They also found four SNPs (including *SLC1A2* rs4755404, *SLC1A3* rs2269272, *HTR1B* rs6296, and *NTRK2* rs1659400), which showed evidence of association with suicidal behavior compared to a non-attempter control group.

Souza et al. (2011) evaluated whether genetic variants in *HTR3A* and *HTR3B* were susceptibility SNPs for suicidal behavior in Caucasian subjects with schizophrenia. Although *HTR3A* and *HTR3B* may not play a major role in the susceptibility for suicidal behavior, there were two nominally significant gene–gene interactions.

8.3 Genome-Wide Association Study

The genome-wide association study (GWAS) is an alternative to the candidate-gene approach (Christensen and Murray 2007). Unlike the candidate-gene approach, there is no a priori hypothesis about the involved genes in the GWAS studies, which examine common genetic variations (500,000 to 2 million SNPs) across the entire human genome in an attempt to identify genetic associations with observable traits by using high-throughput genotyping technologies.

8.3.1 GWAS by Perlis and Colleagues

In a GWAS study, Perlis et al. (2010) examined the association between common genome-wide variation and lifetime suicide attempts in bipolar I and II disorder as well as major depressive disorder. Strongest evidence of association for suicide attempt in bipolar disorder was observed for the rs1466846 SNP without known gene within 400 kb. In major depression, strongest evidence of association was shown for the rs2576377 SNP in the ABI family member 3 binding protein (*ABI3BP*) gene. Replication samples did not provide further support for these two SNPs.

However, they conducted a meta-analysis incorporating all available mood disorder subjects ($N=8737$) and identified ten SNPs in four loci, including the sorbin and SH3 domain containing 1 (*SORBS1*) and protein kinase C epsilon (*PRKCE*) genes.

The *SORBS1* gene has been indicated in insulin signaling (Perlis et al. 2010). Knockout mice for the *PRKCE* gene have been shown to exhibit reduced anxiety behavior. In addition, a study found differences in expression of multiple protein kinases, including the one encoded by the *PRKCE* gene, in individuals with depression relative to control subjects.

8.3.2 GWAS by Willour and Colleagues

Willour et al. (2012) conducted a GWAS study that compared the genotypes of 1201 bipolar subjects with a history of suicide attempts to the genotypes of 1497 bipolar subjects without a history of suicide attempts. Genotyping was performed using the Affymetrix 6.0 array. Their analysis produced an association with the rs300774 SNP at the threshold of genome-wide significance ($P=5.07\times10(-8)$). The associated rs300774 SNP is within a large linkage disequilibrium block that includes the SH3 and SYLF domain containing 1 (*SH3YL1*), acid phosphatase 1 (*ACP1*), and family with sequence similarity 150 member B (*FAM150B*) genes.

Expression in the *ACP1* gene was significantly elevated in bipolar subjects who have completed suicide (Willour et al. 2012). Furthermore, the protein encoded by the *ACP1* gene is a tyrosine phosphatase that influences the Wnt signaling pathway regulated by lithium, indicating *ACP1* as a functional candidate for involvement in suicidal behavior. Little is known about the potential functional contribution in the brain for *SH3YL1* and *FAM150B*.

8.3.3 GWAS by Perroud and Colleagues

Suicidal ideation or suicidal plans that emerge during the course of antidepressant treatment have received considerable public attention. A small subset of patients with major depressive disorder develops this uncommon adverse event. Perroud et al. (2012) conducted a GWAS study to identify SNPs involved in increasing suicidal ideation during antidepressant treatment, where the subjects ($n=706$) were either treated with escitalopram ($n=394$) or nortriptyline ($n=312$). They utilized high-quality Illumina Human610-quad chip genotyping data. There were 244 subjects who experienced an increase in suicidal ideation during follow-up.

Perroud et al. (2012) revealed that the rs11143230 SNP ($P=8.28\times10(-7)$) in the guanine deaminase (*GDA*) gene was significantly associated with increasing suicidality. The *GDA* gene encodes an enzyme responsible for the hydrolytic deamination of guanine and found to be differentially expressed in thalami from patients with schizophrenia.

8.3.4 Limitations in GWAS

With respect to the aforementioned GWAS studies, there were several limitations. First, the small size of the sample does not allow drawing definite conclusions. Small sample sizes can result in none of the findings reaching genome-wide significance due to insufficient statistical power (Spencer et al. 2009). In future work, independent replications in large sample sizes are needed to confirm the role of the polymorphisms found in these GWAS studies.

In addition, most of the loci found in the GWAS studies are not immediately informative because they are noncoding variants, which have incomplete annotation and unknown mechanisms (Ward and Kellis 2012). Therefore, extensive experimental work is needed to uncover the molecular mechanisms responsible for suicidal behavior. Moreover, the GWAS studies did not replicate across studies or populations, causing us to question the validity of novel associations, especially when the loci found are noncoding (Nebert et al. 2008).

8.4 Future Perspective

Future research may benefit from examining gene–gene interactions with novel computational techniques such as generalized multifactor dimensionality reduction (Lin et al. 2009). It is essential to address these interactions in order to describe complex traits in genetics. Epistasis analysis for gene–gene interactions has been advocated for deciphering complex mechanisms, particularly when each involved factor only demonstrates a minor marginal effect. Association studies based on individual SNPs or haplotypes, using a locus-by-locus or region-by-region approach, may overlook associations that can only be found when gene–gene interactions are investigated (Lane et al. 2012). To assess gene–gene interactions, there are many promising methods available, including regression models, multifactor dimensionality reduction, generalized multifactor dimensionality reduction, Bayesian approaches, and artificial neural network algorithms.

In addition, epigenetic approaches, which are modulated by environmental factors, should be considered to obtain clinically meaningful prediction of suicide owing to the fact that suicide may involve effects of the environment, genes, and their interaction. Guintivano et al. (2014) conducted an epigenome-wide association study using Illumina Infinium Human Methylation (HM) 450 BeadChip and generated a prediction model for suicidal behaviors with the rs7208505 SNP in the *spindle and kinetochore-associated complex subunit 2* (*SKA2*) gene. However, their results were limited by the small size of the cohort. Future epigenetic studies with a much larger cohort of patients are needed to better assess sensitivity and specificity of the proposed predictive models and biomarkers.

Other approaches such as transcriptomics should also be employed to identify and prioritize biomarkers of relevance to suicidality. Le-Niculescu et al. (2013) investigated whole-genome gene expression profiling in the blood samples using Affymetrix HG-U133 Plus 2.0 GeneChips and found four biomarkers (including the

spermidine/spermine N1–acetyltransferase 1 (*SAT1*), *phosphatase and tensin homolog* (*PTEN*), *myristoylated alanine-rich protein kinase C substrate* (*MARCKS*), and *mitogen-activated protein kinase kinase kinase 3* (*MAP3K3*) genes) to be predictive of suicidality in bipolar disorder and psychosis. However, their results should be interpreted with caution because of small sample sizes, and future transcriptome-based studies with large sample sizes should be carried out to further evaluate their findings.

Furthermore, studies in future work can examine the contributions of genetic markers by whole-genome sequencing (Ng and Kirkness 2010) or exome sequencing (Bamshad et al. 2011). It has been suggested that gene variants with relatively large effects on drug efficacy or side effects are rare rather than common ones because of additive effects of significant loci (Tucker et al. 2009). Rare variants can only be discovered through whole-exome and whole-genome sequencing or family-based studies, instead of GWAS studies. Whole-genome sequencing represents a new era of scientific research and provides the most comprehensive collection of an individual's genetic variation owing to the reduced cost and the increased throughput of next-generation sequencing technologies. Exome sequencing, which selectively sequences the nucleotides of protein-coding exons in an individual, has recently been introduced as an alternative and efficient approach for Mendelian disorders and common diseases (Bamshad et al. 2011). In summary, combining whole-genome approaches with novel computational tools may potentially lead to a better understanding on suicide.

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