Chapter 7
Genetic Risk Factors for Suicidal Behavior

Marco Sarchiapone and Marianna D'Aulerio

Abstract Suicidal behavior comprises a range of heterogeneous entities, from completed suicide to suicide attempts to suicidal ideation (Mann 1998). While the causes of suicide are complex and no simple explanations of the phenomenon exist, it is clear that there is a diathesis component, whereby converging factor such as an acute stressor as well as present and past life circumstances can operate on a backdrop of biological susceptibility. This chapter summarizes the principal research addressing genetic susceptibility to suicide. Even if only the biological vulnerability can be explained, it is acknowledged that the origin and causes of suicidal behavior are a multifactorial act, in which biological aspects are always related to the influence of the environment.

7.1 Introduction

Several researchers have addressed the issue of the origin of suicidal behavior. One of the most useful theoretical models to explain suicidal behavior is the stress-diathesis model. Mann (1998) focused his attention particularly on the role of genetic contribution to suicidal behavior, asserting that genetic make-up as well as acquired susceptibility contributes to a person's constitutional predisposition or diathesis (Wasserman 2000).

The word diathesis, or predisposition, refers to the individual tendency or susceptibility to disease as a result of interaction between genetic vulnerabilities and environmental stress. According to this model, people possessing this predisposition have a greater chance of developing psychological disorders when presented with particular stressful life events. In contrast, people with higher resiliency or low biological vulnerability for a particular disorder need high levels of stress to trigger symptoms of that disorder. According to Mann, the risk for suicidal acts is determined

M. Sarchiapone (✉) · M. D'Aulerio
Medicine and Health Sciences Department, University of Molise, Via De Santis, 86100 Campobasso, Italy
e-mail: Marco.sarchapone@me.com

K.E. Cannon and T.J. Hudzik (eds.), *Suicide: Phenomenology and Neurobiology*,
DOI 10.1007/978-3-319-09964-4_7

not only by a psychiatric illness (the stressor) but also by a diathesis. This diathesis consists of tendencies for greater depression and suicidal ideation, less reason for living, higher rates of lifetime aggression and impulsivity, comorbid borderline personality disorder, substance use disorder or alcoholism, family history of suicidal acts, head injury, smoking, and childhood abuse history (van Heeringen 2012). In particular, Mann (1998) described a predisposition to suicidal acts to be part of a more fundamental predisposition to both externally and self-directed aggression. Aggression and impulsivity are key characteristics, which may be the result of genetic factors or early life experiences.

In a second example of a clinical stress-diathesis model, McGirr and Turecki (2007) suggested that people who attempt or commit suicide have a certain individual predisposition, part of which is given by personality traits, in particular, impulsive-aggressive behaviors. Impulsive-aggressive traits increase suicide risk among a subset of suicides. In this subset, suicide risk does not appear to be a consequence of psychiatric disorder and seems to play a larger role among younger suicides and may mediate familial transmission of suicidal behavior.

7.2 Family, Twin, and Adoption Studies

Family, twin, and adoption studies have demonstrated that the predisposition to suicide includes genetic factors (Petersen et al. 2014) and support the view that the etiology of the familial transmission of suicidal behavior is at least in part genetic, and may be mediated by the transmission of intermediate phenotypes such as impulsive aggression. In addition, there may be environmental causes for familial transmission of intermediate phenotypes and the intergenerational transmission of family adversity (Brent and Melhem 2008).

An association between positive family history and risk of suicide by violent means has been reported (Linkowski et al. 1985), and a large community twin study demonstrated that genetic risk factors accounted for approximately 45 % of the variance in suicidal thoughts and behavior (Statham et al. 1998). Adoption studies also reported increased rates of suicide in the biological rather than adopting relatives of adoptees (Wender et al. 1986).

7.2.1 Family Studies

A number of family studies have implicated familial aggregation in suicidal behavior. Several studies showed a higher rate of suicidal behavior in relatives of suicide victims or attempters compared to relatives of nonsuicidal controls (Brent et al. 1996; Johnson 1998; Malone et al. 1995; Pfeffer et al. 1994; Tsuang 1983). In one of the major studies on the familial transmission of suicide, Roy (1983a, b) demonstrated that almost half (48.6 %) of 243 patients examined with a family history of suicide and with a wide variety of diagnoses (schizophrenia, unipolar and

bipolar affective disorders, depressive neurosis, and personality disorders) had attempted suicide. Runeson and Åsberg (2003) investigated all suicides in Swedish subjects born between 1949 and 1969 (N = 8,396). They found that the rate of suicide was significantly higher in the families of suicide victims than in the families of comparison subjects. In addition, the strongest risk factor for suicide in the families was mental disorder as defined by previous psychiatric inpatient care.

In an effort to further understand the familial transmission of suicide Murphy and Wetzel (1982) collected the family history of suicidal behaviors (suicide, attempted suicide, and suicide threats) in 127 patients hospitalized following a suicide attempt. Patients with personality disorders, frequently reported a family history of these behaviors, most notably attempted suicide. More specifically, 16 % of patients with a diagnosis of primary affective disorder had a family history of suicide and 17 % had a family history of suicide attempts.

7.2.2 Twin Studies

Twin studies aim to evaluate the magnitude by which genetic and environmental factors influence a phenotype in a population. Generally, twin studies investigate the risk of a twin exhibiting suicidal behavior given that the co-twin completed suicide. These studies also compare the suicide risk between monozygotic twin (MZ) pairs to dizygotic twin (DZ) pairs, while assuming that environment factors are similar between MZ and DZ (Zai et al. 2012). Roy and Segal (2001) found an increased concordance for suicide in monogyzotic (MZ) versus dizygotic twins (DZ) (14.9 % vs. 0.7 %), which was consistent with Tsuang's original observations (Tsuang 1977). Moreover, Roy et al. found an even higher concordance rate for suicide attempt in the surviving monozygotic twin of the co-twin's suicide in MZ versus DZ twins (38 % vs. 0 %), supporting the view that the clinical phenotype for concordance included both completed suicide and suicide attempts (Roy et al. 1995).

Voracek and Loibl (2007) conducted a comprehensive and up-to-date review of twin studies in order to evaluate the genetic contributions to suicide risk. The authors collected data from 32 studies, published between 1812 and 2006 in six languages and from 13 different countries. The results showed that concordance for complete suicide was significantly more frequent among monozygotic than zygotic twin pairs. A greater concordance for suicidal behavior for monozygotic twins respect to dizygotic twins was also found by Roy et al. (1997).

7.2.3 Adoption Studies

One recent and important adoption study was conducted on a random sample of 1933 adoptees from the Danish Adoption Register, a register of nonfamilial adoptions of Danish children (i.e., the adoptive parents are biologically unrelated to the adoptee). The rate of attempted suicide in full siblings of adoptees who attempted suicide before

age 60 years was higher than in full siblings of adoptees who had not attempted suicide (incidence rate ratios [IRR] = 3.45; 95 % confidence interval [CI] = 0.94–12.7). After adjustment for history of psychiatric admission of siblings, the increased rate was statistically significant (IRR = 3.88; 95 % CI—1.42–10.6) (Petersen et al. 2014). In their retrospective cohort study on 8,391 adoptees (2,516 with biological parents died from or hospitalized for suicidal behavior and 5,875 with biological parents with a psychiatric hospitalization but never for suicide attempt), Wilcox et al. (2012) reported that exposure to the hospitalization of an adoptive mother because of a psychiatric disorder amplified an adoptee's risk for suicide attempt.

Von Borczyskowski et al. (2006) conducted a study on suicidal behavior in adolescent and young adult international adoptees. A total of 6,065 international adoptees was compared to 7,340 national adoptees and 1,274,312 nonadopted study subjects, all born between 1963 and 1973 and followed up until 2002 using the National Swedish Register. The results demonstrated an increased risk for suicide attempt and suicide death among international adoptees. On the other hand, national adoptees had lower risks than international adoptees, but had increased risks compared to nonadoptees. It seems that biological parents' morbidity explained approximately one-third of the increased risk for national adoptees. Despite the heroic effort of research and the important results obtained with these kind of studies to demonstrate the existence of genetic risk factors for suicidal behavior, it is currently not possible to identify what are these genetic factors which are being transmitted due to several methodological limitations in these approaches (Brent and Mann 2005; Lester 2002).

7.3 Serotonin Pathway

Identifying specific diathesis-related genes has presented many challenges, although the association between mental disorders and suicide is very clear. More than 90 % of suicide completers have a psychiatric disorder, in particular, mood-related disorders (Arsenault-Lapierre et al. 2004; Cavanagh et al. 2003). Patients suffering from bipolar disorder and schizophrenia have greatly increased rates of suicide with approximately 10 % of patients dying of suicide (Hawton et al. 2005a, b).

In particular, the strong association with depression led researchers to focus their attention on the serotonin system. Studies suggested a role of serotonin in suicide. Indeed, a low cerebrospinal fluid (CSF) concentration of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, was associated with increased impulsiveness, impaired control of aggressive behaviors, and suicide attempts (Asberg et al. 1976; Linnoila and Virkkunen 1992; Perroud et al. 2010; Virkkunen et al. 1995). Altered serotonergic function is implicated in the etiology and pathogenesis of several major psychiatric conditions, such as suicidal behavior (Arango et al. 2003). Furthermore, Kim et al (2007a, b) reported data among the overlap of genes in common among suicide, bipolar disorder and schizophrenia, suggesting the presence of disorder-specific pathways.

7.3.1 Tryptophan Hydroxylases (TPH1 and TPH2)

Tryptophan is an essential amino acid for serotonin synthesis and tryptophan hydroxylase (TPH) is the initial and rate-limiting enzyme in the biosynthesis of serotonin. In humans, there are two TPH isoenzymes encoded by two different genes. TPH1 was the first gene to be identified and is located on the short arm of chromosome 11 (11p15.3-p14). The second gene (TPH2) is located on the long arm of chromosome 12 (12q21.1).

Using DNA sample from 56 impulsive and 14 nonimpulsive, alcoholic, violent offenders, and 20 healthy volunteers, Nielsen et al (1994) studied the association between suicidal behavior and TPH1 polymorphism. In the highly impulsive group, the authors observed a significant association between TPH genotype and cerebrospinal fluid 5-HIAA concentration. This association suggests that a genetic variant of the TPH gene may influence 5-HIAA concentration in the cerebrospinal fluid and predisposition to suicidal behavior in some individuals.

Galfalvy et al. (2009) genotyped 343 subjects (Caucasian, African–American, Hispanic) presenting with a Major Depressive Episode for polymorphisms A218C in intron 7 and A-6526G in the promoter region of TPH1. They found that both the AA genotype on intron 7 and the AA genotype on the promoter predicted suicide attempts during the 1-year follow-up and were associated with past attempts of high medical lethality.

In their review, Antypa et al. (2013) confirmed the association between variation on the TPH1 gene and 5-HTTLPR gene and violent suicidal behavior in Caucasian populations. Findings on endophenotypes of suicidality, such as aggression and impulsivity traits, showed positive associations for the TPH1, HTR2A, and MAOA genes, but these studies need further replication, since negative associations were also occasionally reported. Studying the A779C polymorphism of the TPH gene, Arango et al. (2003) found that the less common U or A allele variants were associated with suicide attempt. Other studies have found the U allele to be associated with aggression and lower serotonergic function in vivo.

Zill et al. (2004) first reported an association between TPH2 gene polymorphisms and completed suicide. They identified a second tryptophan hydroxylase isoform (TPH2) in mice, which was exclusively present in the brain. Significant association was detected between one single nucleotide polymorphism and suicide and also haplotype analysis produced support for this association.

Ke et al. (2006) selected the A–G single nucleotide polymorphism (SNP) at the position 40237 relative to 5′-end of TPH2 gene in order to evaluate its association with suicide behavior. The authors recruited 102 MD patients with suicidal behavior (attempters) and 123 MD patients without suicidal behavior (nonattempters). Their results demonstrated that the A allele was significantly less frequent in attempters than in nonattempters ($p = 0.0067$). In addition, individuals with the A/A genotype showed a significantly lower risk of suicide behavior than those with the A/G or G/G genotype (OR = 0.35). These findings suggested that the A–G polymorphism of TPH2 may confer susceptibility to suicidal behavior in MD patients.

While the tryptophan hydroxylase genes represent major candidates in numerous genetic association analyses of suicidal behavior, the results thus far have been inconclusive and occasionally conflicting (Zill et al. 2004).

7.3.2 Serotonin Transporter (5-HTT)

The serotonin transporter (5-HTT) regulates serotonergic transmission by removal of serotonin from the synaptic gap. Several studies reported an association between suicidal behavior and serotonin transporter (5-HTT). Mann et al. (2000) found that binding to 5-HTT was lower in the ventral PFC of suicides compared with nonsuicides in postmortem brains from 220 individuals. Anguelova et al. (2003) conducted a meta-analysis on studies investigating 5-HT receptors and the 5-HTT in suicidal behavior. From this meta-analysis, 26 articles met the inclusion criteria and six different 5-HT receptor loci and the 5-HTT promoter 44 bp insertion/deletion polymorphism were investigated. The combined evidence supports an association between suicidal behavior and a promoter 44 bp insertion/deletion polymorphism of the 5-HTT gene and no such association with 102 T/C polymorphism in the 5-HT2A gene.

Li and He (2007) conducted a separate meta-analysis that analyzed cumulative data from European and Asian population. The findings from this meta-analysis suggested a significant association (*P*-value of 0.0068) between the 5-HTTLPR polymorphism and suicidal behavior, further supporting the hypothesis of the involvement of the brain 5-HTT in the pathogenesis of suicidal behavior.

Several researchers are focused on the association between serotonin transporter (5-HTT) gene and suicidal behavior. Even though some of these studies support this hypothesis, other researchers have failed to demonstrate an association which maybe a result of inadequate statistical power and the use of different populations (Li and He 2006). Further studies are necessary in order to better understand the role of 5-HTT in suicidal behavior.

7.3.3 Serotonin Receptors (5HTR1A, 5HTR1B, 5HTR2A, 5HTR2C)

A number of studies have investigated the link between serotonin receptors and suicidal behavior and have resulted in conflicting results. González-Castro et al. (2013) performed a meta-analysis on the association of 5HTR1A gene with suicidal behavior and found that the rs6295 polymorphism was not associated with suicidal behavior. Similarly, no significant association for polymorphisms rs6295 and rs878567 was found in the case-control study. Similar results were found by Kia-Keating et al. (2007). The combined evidence from 789 case and 1,247 control subjects/participants suggested that there was no significant association between the HTR1B G861C polymorphism and suicidal behavior.

On the other hand, Turecki et al. (1999) and Saiz et al. (2008) have suggested a correlation between 5-HT2 receptors and suicidal behavior. Turecki analyzed postmortem data from 56 subjects who had committed suicide and 126 controls and found that 5-HTR2A binding was greater in the prefrontal cortex of suicidal subjects. Saiz and colleagues compared 193 cases of attempted suicide with 420 control cases in order to examine the association between four serotonergic polymorphisms, A-1438G (rs6311) and T102C (rs6313) of the serotonin 2A receptor gene, and STin2 VNTR and 5-HTTLPR of the SLC6A4 gene, and suicidal behavior. The results demonstrated an excess of the −1438A allele both in impulsive suicide attempts and in suicide attempts with high clinical lethality compared the control group, suggesting that the −1438A allele may predispose for nonimpulsive suicidal behavior.

7.4 Other Pathways

7.4.1 Dopaminergic System

Relatively few studies examining the role of dopamine in suicidal behavior have been published (Arango et al. 2003; Wasserman 2000).

7.4.1.1 Homovanillic Acid

Low level of homovanillic acid (HVA) in cerebrospinal fluid (CSF) were found in suicide attempters that were diagnosed with major depression, and the dopamine system seems to be hypofunctional in major depression (Mann 2003). However, as suggested by Mann (2003), the data are too few to actually understand the role of dopaminergic system in suicidal behavior.

The role of CSF dopamine metabolites in suicidal behavior was reported by Roy et al. (1992), who examined 24-hour urinary outputs of HVA in relation to suicidal behavior in depression. Patients with depression who had attempted suicide had significantly smaller urinary outputs of homovanillic acid, dihydroxyphenylacetic acid (DOPAC), and total body output of dopamine (sum dopamine) than patients with depression who had not attempted suicide. Patients with depression who reattempted suicide during 5-year follow-up had significantly smaller urinary outputs of HVA and sum dopamine than patients who did not reattempt suicide, patients who never attempted suicide, and normal control subjects, and had significantly smaller outputs of DOPAC than patients who never attempted suicide or control subjects. These data add to accumulating evidence for low levels of HVA in cerebrospinal fluid and the suggestion that diminished dopaminergic neurotransmission may play a part in suicidal behavior in depression.

7.4.1.2 Dopamine D2 Receptors

Few studies examining the role of the dopamine receptor DRD2 gene (11q22-q23) in suicide have been published. Finckh et al. (1997) analyzed the polymorphism in exon 8 (E8) of the dopamine D2 receptor gene locus (DRD2) (DRD2 E8). The DRD2 (E8) A/A genotype was associated with increased anxiety and depression scores in alcoholics during the follow up after clinical detoxification treatment. In addition, E8 A/A was associated with increased suicide attempts.

Suda et al. (2009) examined associations between suicide attempts and two kinds of functional polymorphisms in the DRD2 gene: TaqIA and −141C Ins/Del. In this study, 120 suicide attempters and 123 unrelated volunteers were examined. Suda et al. demonstrated significant differences in genotypic and allelic frequencies of −141C Ins/Del and TaqIA polymorphisms between suicide attempters and healthy controls (−141C Ins/Del, $p = 0.01$; TaqIA, $p = 0.036$). The Ins allele of −141C Ins/Del was significantly more frequent in suicide attempters ($p = 0.011$), as well as the A2 allele of TaqIA ($p = 0.017$) suggesting that DRD2 gene polymorphisms may be involved in the biological susceptibility to suicide.

The study on 141C Del variant of the DRD2 asserted that this variant might be a protective factor against the development of alcohol withdrawal symptoms. In addition, this variant might also be a risk factor in a highly burdened subgroup of alcoholics with a paternal and grand paternal history of alcoholism and may contribute to the substantially higher likelihood of suicide in alcoholics (Johann et al. 2005).

7.4.1.3 Tyrosine Hydroxylase

Catacholaminergic dysfunction due to abnormalities in the tyrosine hydroxylase (TH) gene has been implicated in the pathogenesis of suicidal behavior and in mood disorders. Recent evidence suggests that TH gene variants may also increase the risk of suicide attempts in schizophrenic patients, although the interaction with established clinical risk factors is unclear (Hu et al. 2013).

Ordway et al. (1994) studied the concentration of tyrosine hydroxylase in the noradrenageric cell bodies of the locus coeruleus of nine age-matched pairs (antidepressant-free suicide victims and controls). This study found higher concentrations of the enzyme in the samples from suicide victims, thus raising the possibility that the expression of tyrosine hydroxylase in locus coeruleus may be relevant in the pathophysiology of suicide.

In their study, Persson et al. (1997) examined a tetranucleotide repeat polymorphism in the first intron of the tyrosine hydroxylase (TH) locus in 118 adult suicide attempters with diagnosis according to DSM-III-R criteria (major depression, anxiety disorders, adjustment disorders, psychoactive substance abuse disorders, psychotic disorders) and in 78 control adult subjects. The authors reported a high prevalence of carriers of TH-K3 allele in suicide attempters with adjustment disorders and low prevalence of carriers of TH-K1 among all suicide attempters.

These findings suggested that the alleles may reflect predisposition for a common phenotype with altered vulnerability for psychiatric disorders.

7.4.1.4 Catechol-O-Methyltransferase

Catechol-O-methyltransferase (COMT) plays an important role in genetics of suicide risk, because it inactivates dopamine and norepinephrine by the addition of a methyl group from S-adenosylmethionine (Zai et al. 2012). A functional polymorphism on the human COMT gene has been shown to influence aggressive and anger-related traits in various clinical populations. The results found by Baud et al. showed that the high activity genotype (Val/Val) was more frequent in suicide attempters than in normal controls. Moreover, the Val/Val genotype markedly affected the scores on two STAXI subscales—Trait Anger and Anger Control—in female suicide attempters, thus suggesting a possible gender effect of the COMT genotype on a stable personality trait (Baud et al. 2007).

The functional polymorphism (COMT Val108/158Met) affects COMT activity, with the valine (Val) variant associated with higher and the methionine (Met) variant with lower COMT activity. This polymorphism is associated with aggressive and suicidal behavior, although the findings on this relationship have not always been consistent.

Nedic et al. (2011) recruited 312 male and 81 female medication-free patients with alcohol dependence and 487 male and 122 female unrelated, nonsuicidal medication-free Caucasian healthy subjects. Their findings demonstrated that male alcoholic suicide attempters had the higher frequency of Met/Met genotype or Met allele and significantly higher aggression and depression scores compared to male nonattempters. These results confirmed the associations between Met allele and aggressive behavior or violent suicide attempts in various psychiatric diagnoses, and suggested that Met allele of the COMT Val108/158 Met might be used as an independent biomarker of suicidal behavior across different psychopathologies.

7.4.2 Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF), the most abundant neurotrophin in the brain, influences the pathophysiology of anxiety and depression. However, to date the role of BDNF in suicide has not been well investigated.

Plasma BDNF levels in 32 major depressive disorder (MDD) patients who had recently attempted suicide, 32 nonsuicidal MDD patients, and 30 normal controls were examined (Kim et al. 2007a, b). BDNF levels were significantly lower in suicidal MDD patients than nonsuicidal MDD patients or normal controls. These results suggested that a reduction of plasma BDNF level may be related to suicidal behavior in major depression and that BDNF level may be a biological marker of suicidal depression (Kim et al. 2007a, b). BDNF levels were decreased in the

postmortem brain and plasma samples from suicide subjects (Keller et al. 2010). Postmortem brain samples from suicide subjects showed a statistically significant increase of DNA methylation in Wernicke's area at specific CpG sites in BDNF promoter/exon IV compared with nonsuicide control subjects (Keller et al. 2010).

The association between the BDNF gene Val66Met polymorphism and mood disorders was confirmed also by the study of Nedic et al. (2011). They found that the genotype and allele frequencies for the BDNF gene Val66Met polymorphism did not differ when comparing across depression groups (total, bipolar disorder or major depression) and control subjects. Furthermore, it was shown that this BDNF polymorphism was not associated with age of onset or suicidal history in mood disorder patients. In a sample of 813 Caucasian suicide attempters, childhood sexual abuse was associated with violent suicide attempts in adulthood only among BDNF Val/Val individuals and not among BDNF Val/Met or BDNF Met/Met individuals. The result suggested that BDNF Val66Met may modulates the effect of childhood sexual abuse on the violence of suicidal behavior (N. Perroud et al. 2008).

Dwivedi et al. (2003) analyzed whether the expression of BDNF and/or Trk B isoforms were altered in postmortem brain in subjects who commit suicide (hereafter referred to as suicide subjects) and whether these alterations were associated with specific psychopathologic conditions. The sample consisted of 27 suicide subjects and 21 nonpsychiatric control subjects and Brodmann area 9 and hippocampus were the brain areas examined. This study found that BDNF and Trk B were significantly reduced in both prefrontal cortex and hippocampus in suicide subjects as compared with those in control subjects.

Given the importance of BDNF in mediating physiological functions, including cell survival and synaptic plasticity, the reduced expression of BDNF and Trk B in postmortem brain in suicide subjects suggest that these molecules may play an important role in the pathophysiological aspects of suicidal behavior.

7.5 Hypothalamic-Pituitary-Adrenal Axis

Well-established environmental risk factors for suicidal behavior are events causing significant psychological stress, which are particularly difficult to cope with effectively. High stress levels may cause also unfavorable effects in different brain functions, in partilcular on the hypothalamic-pituitary-adrenal (HPA) axis, involved for the regulation of body's response to stress and has complex interactions with brain serotonergic, noradrenergic, and dopaminergic systems. Indeed, the HPA axis is responsible of modulation of cortisol levels, the major stress hormone, and stress plays a major role in the various pathophysiological processes associated with mood disorders and suicidal behavior. Several studies reported association between abnormalities in the HPA axis and suicidal behaviors (Wasserman et al. 2010).

Adrenal steroid hormones are essential to human life and play a central role in maintaining survival in times of stress. Several lines of evidence suggest an association between HPA axis dysregulation, affective disorders, and suicidal behavior

(Arató et al. 1986). As early as 1965, Bunney and Fawcett (1965) reported high levels of urinary 17-hydroxycorticosteroids in depressed suicidal patients.

Leszczyńska-Rodziewicz et al. (2013) studied the polymorphisms of genes involved in the HPA axis (CRHR1, NR3C1, and AVPBR1). This study was performed on 597 patients, 225 of whom had a history of suicide attempts. Even if the haplotype analysis of the AVPR1b gene revealed an association between the GCA haplotype and suicide attempts, this association was not significant after correcting for multiple testing. Nonetheless, the inconsistencies with the previously published results indicate the importance of the further investigation of these polymorphisms with respect to the risk of suicide attempts.

Moreover, the stress response is mediated by corticotrophin-releasing hormone (CRH), which is known to be a regulator of the HPA pathway. Alterations in the HPA system have been related to impulsivity, aggression, and suicidal behavior, common features in schizophrenia (De Luca et al. 2010).

7.6 Genome-Wide and Epigenetic Studies of Suicide

In the last years, genome-wide association studies (GWA study, or GWAS) has been a great contribution to the understanding of suicidal behavior. GWAS aims to study several genetic variants in different individuals and examine the genome for small variations (single nucleotide polymorphisms or SNPs) that occur more frequently in people with a particular disease than in people without the disease. Recent studies provide evidence that epigenetic mechanisms could deliver the missing link between the heritability of suicidal behavior and the interaction between environment and the genome (Bani-Fatemi et al. 2014). These epigenetic mechanisms, which alter gene expression via alternative mechanisms to the coding DNA sequence, result from environmental effects acting on the genome. Studies in rodents indicate that variation in the early environment will trigger these epigenetic modifications and recent data suggest the same may be true in humans. The expression of a number of genes which are involved in normal brain functions have been shown to be under epigenetic control and seem to be dysregulated in suicide (Labonte and Turecki 2010).

The genome-wide linkage survey for genetic loci that influence the risk of suicidal behavior in the context of mood disorders has been reported by Zubenko et al. (2004). Six linkage peaks with maximum multipoint ΔLOD scores that reached genome-wide adjusted levels of significance (2p, 5q, 6q, 8p, 11q, and Xq) were identified and four of these (2p, 6q, 8p, and Xq) exceeded the criterion for "highly significant linkage." The highest ΔLOD score that emerged from this linkage analysis, 5.08, occurred for ARPs with Depression Spectrum Disorder at D8S1145 at cytogenetic location 8p22-p21. These findings provide evidence for suicide risk loci.

Labonté et al. (2013) used a genome-wide approach to investigate the extent of DNA methylation alterations in the brains of suicide completers. The authors

identified 366 promoters that were differentially methylated in suicide completers relative to comparison subjects (273 hypermethylated and 93 hypomethylated). The results demonstrated that promoter DNA methylation levels were significantly greater for several genes in suicide completers relative to control group. Moreover, a significant number of hypomethylated sequences in the promoters of suicide completers were reported, suggesting that DNA methylation patterns may be altered in the brains of suicide completers.

7.7 Conclusions

Suicide is a complex phenomenon. Its multidimensionality, linked to association between social, biological, and psychological factors requires that the understanding of the predisposition to suicide cannot totally explained only by the presences of mental health disorders, even if closely associated to suicidal behavior. Several researchers have established the role of genetic basis of suicidal behavior. However, some of the studies have produced inconsistent findings, often due to difficulties in methods used and difficulties to select the sample. Currently, the more credible studies to explain the role of genetic risk factors for suicidal behaviors are those based on the serotonergic system. The canditate genes (most studied genes are SCL6A4, HTR2A, HTR2C, HTR1A, HTR1B, TPH-1, and TPH-2) pertaining to the serotonergic system have proved to be an important key about the association between suicide behavior and its biological correlates.

References

Anguelova M, Benkelfat C, Turecki G (2003) A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. Mol Psychiatry 8(7):646–653. doi:10.1038/sj.mp.4001336

Antypa N, Serretti A, Rujescu D (2013) Serotonergic genes and suicide: a systematic review. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol 23(10):1125–1142. doi:10.1016/j.euroneuro.2013.03.013

Arango V, Huang Y, Underwood MD, Mann JJ (2003) Genetics of the serotonergic system in suicidal behavior. J Psychiatr Res 37(5):375–386

Arató M, Banki CM, Nemeroff CB, Bissette G (1986) Hypothalamic-pituitary-adrenal axis and suicide. Ann N Y Acad Sci 487(1):263–270. doi:10.1111/j.1749-6632.1986.tb27905.x

Arsenault-Lapierre G, Kim C, Turecki G (2004) Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry 4:37. doi:10.1186/1471-244X-4-37

Asberg M, Träskman L, Thorén P (1976) 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? Arch Gen Psychiatry 33(10):1193–1197

Bani-Fatemi A, Howe AS, De Luca V (2014) Epigenetic studies of suicidal behavior. Neurocase. doi:10.1080/13554794.2013.826679

Baud P, Courtet P, Perroud N, Jollant F, Buresi C, Malafosse A (2007) Catechol-O-methyltransferase polymorphism (COMT) in suicide attempters: a possible gender effect on

anger traits. Am J Med Genet Part B Neuropsychiatr Genet 144B(8):1042–1047. doi:10.1002/ajmg.b.30541

Brent DA, Mann JJ (2005) Family genetic studies, suicide, and suicidal behavior. Am J Med Genet Part C Semin Med Genet 133C(1):13–24. doi:10.1002/ajmg.c.30042

Brent DA, Melhem N (2008) Familial transmission of suicidal behavior. Psychiatr Clin North Am 31(2):157–177. doi:10.1016/j.psc.2008.02.001

Brent DA, Bridge J, Johnson BA, Connolly J (1996) Suicidal behavior runs in families. A controlled family study of adolescent suicide victims. Arch Gen Psychiatry 53(12):1145–1152

Bunney WE Jr, Fawcett JA (1965) Possibility of a biochemical test for suicidal potential: an analysis of endocrine findings prior to three suicides. Arch Gen Psychiatry 13:232–239

Cavanagh JTO, Carson AJ, Sharpe M, Lawrie SM (2003) Psychological autopsy studies of suicide: a systematic review. Psychol Med 33(3):395–405

De Luca V, Tharmalingam S, Zai C, Potapova N, Strauss J, Vincent J, Kennedy JL (2010) Association of HPA axis genes with suicidal behaviour in schizophrenia. Journal of Psychopharmacology (Oxford, England), 24(5), 677–682. doi:10.1177/0269881108097817

Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN (2003) Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 60(8):804–815. doi:10.1001/archpsyc.60.8.804

Finckh U, Rommelspacher H, Kuhn S, Dufeu P, Otto G, Heinz A, Rolfs A (1997) Influence of the dopamine D2 receptor (DRD2) genotype on neuroadaptive effects of alcohol and the clinical outcome of alcoholism. Pharmacogenetics 7(4):271–281

Galfalvy H, Huang Y-Y, Oquendo MA, Currier D, Mann JJ (2009) Increased risk of suicide attempt in mood disorders and TPH1 genotype. J Affect Disord 115(3):331–338. doi:10.1016/j.jad.2008.09.019

González-Castro TB, Tovilla-Zárate CA, Juárez-Rojop I, Pool García S, Genis A, Nicolini H, López Narváez L (2013) Association of 5HTR1A gene variants with suicidal behavior: case-control study and updated meta-analysis. J Psychiatr Res 47(11):1665–1672. doi:10.1016/j.jpsychires.2013.04.011

Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ (2005a) Schizophrenia and suicide: systematic review of risk factors. Br J Psychiatry J Mental Sci 187:9–20. doi:10.1192/bjp.187.1.9

Hawton K, Sutton L, Haw C, Sinclair J, Harriss L (2005b) Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. J Clin Psychiatry 66(6):693–704

Hu J, Chan LF, Souza RP, Tampakeras M, Kennedy JL, Zai C, De Luca V (2013) The role of tyrosine hydroxylase gene variants in suicide attempt in schizophrenia. Neurosci Lett. doi:10.1016/j.neulet.2013.11.025

Johann M, Putzhammer A, Eichhammer P, Wodarz N (2005) Association of the -141C Del variant of the dopamine D2 receptor (DRD2) with positive family history and suicidality in German alcoholics. Am J Med Genet Part B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet 132B(1):46–49. doi:10.1002/ajmg.b.30085

Johnson SH (1998) End-of-life decision making: what we don't know, we make up; what we do know, we ignore. Law Rev 31(1):13–47

Ke L, Qi ZY, Ping Y, Ren CY (2006) Effect of SNP at position 40237 in exon 7 of the TPH2 gene on susceptibility to suicide. Brain Res 1122(1):24–26. doi:10.1016/j.brainres.2006.09.007

Keller S, Sarchiapone M, Zarrilli F et al (2010) INcreased bdnf promoter methylation in the wernicke area of suicide subjects. Arch Gen Psychiatry 67(3):258–267. doi:10.1001/archgenpsychiatry.2010.9

Kia-Keating BM, Glatt SJ, Tsuang MT (2007) Meta-analyses suggest association between COMT, but not HTR1B, alleles, and suicidal behavior. Am J Med Genet Part B Neuropsychiatr Genet 144B(8):1048–1053. doi:10.1002/ajmg.b.30551

Kim S, Choi K-H, Baykiz AF, Gershenfeld HK (2007a) Suicide candidate genes associated with bipolar disorder and schizophrenia: An exploratory gene expression profiling analysis of post-mortem prefrontal cortex. BMC Genom 8(1):413. doi:10.1186/1471-2164-8-413

Kim Y-K, Lee H-P, Won S-D, Park E-Y, Lee H-Y, Lee B-H, Choi S-H (2007b) Low plasma BDNF is associated with suicidal behavior in major depression. Prog Neuropsychopharmacol Biol Psychiatry 31(1):78–85. doi:10.1016/j.pnpbp.2006.06.024

Labonte B, Turecki G (2010) The epigenetics of suicide: explaining the biological effects of early life environmental adversity. Arch Suicide Res Off J Int Acad Suicide Res 14(4):291–310. doi:10.1080/13811118.2010.524025

Labonté B, Suderman M, Maussion G, Lopez JP, Navarro-Sánchez L, Yerko V, Turecki G (2013) Genome-wide methylation changes in the brains of suicide completers. Am J Psychiatry 170 (5):511–520. doi:10.1176/appi.ajp.2012.12050627

Lester D (2002) Twin studies of suicidal behavior. Arch Suicide Res 6(4):383–389. doi:10.1080/13811110214530

Leszczyńska-Rodziewicz A, Szczepankiewicz A, Pawlak J, Dmitrzak-Weglarz M, Hauser J (2013) Association, haplotype, and gene-gene interactions of the HPA axis genes with suicidal behaviour in affective disorders. Sci World J 207361. doi:10.1155/2013/207361

Li D, He L (2007) Meta-analysis supports association between serotonin transporter (5-HTT) and suicidal behavior. Mol Psychiatry 12(1):47–54. doi:10.1038/sj.mp.4001890

Linkowski P, de Maertelaer V, Mendlewicz J (1985) Suicidal behaviour in major depressive illness. Acta Psychiatr Scand 72(3):233–238. doi:10.1111/j.1600-0447.1985.tb02600.x

Linnoila VM, Virkkunen M (1992) Aggression, suicidality, and serotonin. J Clin Psychiatry 53 (Suppl):46–51

Malone KM, Haas GL, Sweeney JA, Mann JJ (1995) Major depression and the risk of attempted suicide. J Affect Disord 34(3):173–185

Mann JJ (1998) The neurobiology of suicide. Nat Med 4(1):25–30

Mann JJ (2003) Neurobiology of suicidal behaviour. Nat Rev Neurosci 4(10):819–828. doi:10.1038/nrn1220

Mann J, Huang Y, Underwood MD et al (2000) A serotonin transporter gene promoter polymorphism (5-httlpr) and prefrontal cortical binding in major depression and suicide. Arch Gen Psychiatry 57(8):729–738. doi:10.1001/archpsyc.57.8.729

Mann JJ, Arango VA, Avenevoli S, Brent DA, Champagne FA, Clayton P, Wenze A (2009) Candidate endophenotypes for genetic studies of suicidal behavior. Biol Psychiatry 65 (7):556–563. doi: 10.1016/j.biopsych.2008.11.021

McGirr A, Turecki G (2007) The relationship of impulsive aggressiveness to suicidality and other depression-linked behaviors. Curr Psychiatry Rep 9(6):460–466

Murphy GE, Wetzel RD (1982) Family history of suicidal behavior among suicide attempters. J Nerv Ment Dis 170(2):86–90

Nedic G, Nikolac M, Sviglin KN, Muck-Seler D, Borovecki F, Pivac N (2011) Association study of a functional catechol-O-methyltransferase (COMT) Val108/158Met polymorphism and suicide attempts in patients with alcohol dependence. Int J Neuropsychopharmacol 14 (03):377–388. doi:10.1017/S1461145710001057

Nielsen DA, Goldman D, Virkkunen M, Tokola R, Rawlings R, Linnoila M (1994) Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. Arch Gen Psychiatry 51(1):34–38

Ordway GA, Smith KS, Haycock JW (1994) Elevated tyrosine hydroxylase in the locus coeruleus of suicide victims. J Neurochem 62(2):680–685. doi:10.1046/j.1471-4159.1994.62020680.x

Perroud N, Salzmann A, Saiz PA, Baca-Garcia E, Sarchiapone M, Garcia-Portilla MP, … European Research Consortium for Suicide (EURECA) (2010) Rare genotype combination of the serotonin transporter gene associated with treatment response in severe personality disorder. Am J Med Genet Part B Neuropsychiatr Genet 153B(8):1494–1497. doi:10.1002/ajmg.b.31118

Perroud N, Courtet P, Vincze I, Jaussent I, Jollant F, Bellivier F, Malafosse A (2008) Interaction between BDNF Val66Met and childhood trauma on adult's violent suicide attempt. Genes Brain Behav 7(3):314–322. doi:10.1111/j.1601-183X.2007.00354.x

Persson M-L, Wasserman D, Geijer T, Jönsson EG, Terenius L (1997) Tyrosine hydroxylase allelic distribution in suicide attempters. Psychiatry Res 72(2):73–80

Petersen L, Sørensen TIA, Kragh Andersen P, Mortensen PB, Hawton K (2014) Genetic and familial environmental effects on suicide attempts: a study of Danish adoptees and their biological and adoptive siblings. J Affect Disord 155:273–277. doi:10.1016/j.jad.2013.11.012

Pfeffer CR, Normandin L, Kakuma T (1994) Suicidal children grow up: suicidal behavior and psychiatric disorders among relatives. J Am Acad Child Adolesc Psychiatry 33(8):1087–1097. doi:10.1097/00004583-199410000-00004

Roy A (1983a) Family history of suicide. Arch Gen Psychiatry 40(9):971–974. doi:10.1001/archpsyc.1983.01790080053007

Roy A (1983b) Family history of suicide. Arch Gen Psychiatry 40(9):971–974

Roy A, Segal NL (2001) Suicidal behavior in twins: a replication. J Affect Disord 66(1):71–74

Roy A, Karoum F, Pollack S (1992) Marked reduction in indexes of dopamine metabolism among patients with depression who attempt suicide. Arch Gen Psychiatry 49(6):447–450. doi:10.1001/archpsyc.1992.01820060027004

Roy A, Segal NL, Sarchiapone M (1995) Attempted suicide among living co-twins of twin suicide victims. Am J Psychiatry 152(7):1075–1076

Roy A, Rylander G, Sarchiapone M (1997) Genetics of suicide. Ann N Y Acad Sci 836 (1):135–157. doi:10.1111/j.1749-6632.1997.tb52358.x

Runeson B, Åsberg M (2003) Family history of suicide among suicide victims. Am J Psychiatry 160(8):1525–1526. doi:10.1176/appi.ajp.160.8.1525

Saiz PA, García-Portilla MP, Paredes B, Arango C, Morales B, Alvarez V, Bobes J (2008) Association between the A-1438G polymorphism of the serotonin 2A receptor gene and nonimpulsive suicide attempts. Psychiatr Genet 18(5):213–218. doi:10.1097/YPG.0b013e3283050ada

Statham DJ, Heath AC, Madden PA, Bucholz KK, Bierut L, Dinwiddie SH, Martin NG (1998) Suicidal behaviour: an epidemiological and genetic study. Psychol Med 28(4):839–855

Suda A, Kawanishi C, Kishida I, Sato R, Yamada T, Nakagawa M, Hirayasu Y (2009) Dopamine D2 receptor gene polymorphisms are associated with suicide attempt in the Japanese population. Neuropsychobiology 59(2):130–134. doi:10.1159/000213566

Tsuang MT (1977) Genetic factors in suicide. Dis Nerv Syst 38(7):498–501

Tsuang MT (1983) Risk of suicide in the relatives of schizophrenics, manics, depressives, and controls. J Clin Psychiatry 44(11):396–400

Turecki G, Brière R, Dewar K, Antonetti T, Lesage AD, Séguin M, Rouleau GA (1999) Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. Am J Psychiatry 156(9):1456–1458

Van Heeringen K (2012) Stress–diathesis model of suicidal behavior. In: Dwivedi Y (ed) The neurobiological basis of suicide. CRC Press, Boca Raton (FL). http://www.ncbi.nlm.nih.gov/books/NBK107203/

Virkkunen M, Goldman D, Nielsen DA, Linnoila M (1995) Low brain serotonin turnover rate (low CSF 5-HIAA) and impulsive violence. J Psychiatry Neurosci JPN 20(4):271–275

Von Borczyskowski A, Hjern A, Lindblad F, Vinnerljung B (2006) Suicidal behaviour in national and international adult adoptees: a Swedish cohort study. Soc Psychiatry Psychiatr Epidemiol 41(2):95–102. doi:10.1007/s00127-005-0974-2

Voracek M, Loibl LM (2007) Genetics of suicide: a systematic review of twin studies. Wien Klin Wochenschr 119(15–16):463–475. doi:10.1007/s00508-007-0823-2

Wasserman D (2000) Suicide: an unnecessary death. Martin Dunitz, London

Wasserman D, Wasserman J, Sokolowski M (2010) Genetics of HPA-axis, depression and suicidality. Eur Psychiatry J Assoc Eur Psychiatr 25(5):278–280. doi:10.1016/j.eurpsy.2009.12.016

Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I (1986) Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch General Psychiatry 43(10):923–929

Wilcox HC, Kuramoto SJ, Brent D, Runeson B (2012) The interaction of parental history of suicidal behavior and exposure to adoptive parents' psychiatric disorders on adoptee suicide

attempt hospitalizations. Am J Psychiatry 169(3):309–315. doi:10.1176/appi.ajp.2011.11060890

Zai CC, de Luca V, Strauss J, Tong RP, Sakinofsky I, Kennedy JL (2012) Genetic factors and suicidal behavior. In: Dwivedi Y (ed) The neurobiological basis of suicide. CRC Press, Boca Raton (FL). http://www.ncbi.nlm.nih.gov/books/NBK107191/

Zill P, Büttner A, Eisenmenger W, Möller H-J, Bondy B, Ackenheil M (2004) Single nucleotide polymorphism and haplotype analysis of a novel tryptophan hydroxylase Isoform (TPH2) gene in suicide victims. Biol Psychiatry 56(8):581–586. doi:10.1016/j.biopsych.2004.07.015

Zubenko GS, Maher BS, Hughes HB, Zubenko WN, Scott Stiffler J, Marazita ML (2004) Genome-wide linkage survey for genetic loci that affect the risk of suicide attempts in families with recurrent, early-onset, major depression. Am J Med Genet Part B Neuropsychiatr Genet 129B(1):47–54. doi:10.1002/ajmg.b.30092