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Chapter 11 Genetic Factors and Suicidal Behavior

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11.1. INTRODUCTION

Approximately 1 million people worldwide die by suicide each year. With a prevalence rate of 0.0145% and suicide accounting for 1.5% of death by all causes, it is the 10th leading cause of mortality worldwide (Hawton and van Heeringen 2009). Suicide is complex, multifactorial behavioral phenotype. Suicide is also familial: a family history of suicide increases risk of suicide attempts and completed suicide. In this chapter, we will examine the family, twin, and adoption studies that establish the existence of both genetic and environmental bases of suicidal behavior. We will then review the major candidate gene findings. Lastly, we will discuss recent developments in genetic studies of suicide and comment on future experiments that may help resolve the challenges that are hindering genetic research into the pathophysiology of suicide.

11.2. FAMILY,TWIN, AND ADOPTION STUDIES

11.2.1. Family Studies

Family studies of suicide are designed to explore the extent to which suicidal behavior permeates families. A number of family studies have indicated familial aggregation of suicidal behavior. Most studies have shown a higher rate of suicidal behavior in relatives of suicide victims or attempters compared to relatives of non-suicidal controls (Tsuang 1983; Pfeffer et al. 1994; Malone et al. 1995; Brent et al. 1996; Johnson et al. 1998). Population registries in Denmark and Sweden have provided large data-sets to explore the familiality of suicide. Four such studies have been carried out, all reporting increased rates of suicide in offspring of suicidal parents compared to offspring of non-suicidal parents (Agerbo et al. 2002; Qin et al. 2002, 2003; Runeson and Asberg 2003). One of the investigations provides evidence that this observed increase may not be due to grief, since suicide rates of individuals who lost their parent(s) to suicide were higher compared to individuals who lost their parent(s) to homicides or accidents (Runeson and Asberg 2003).

While population registry studies have the advantage of high statistical power, they may lack details in psychiatric diagnoses and suicidal behavior. In a study of suicide records dating from 1880 to 1980 in an Amish community, Egeland and Sussex (1985) found 26 reported suicides that aggregated within four families who also had a high incidence of mood disorders. The authors also found other families that were affected by multiple mood disorders but had no history of suicidal behavior. This suggests that the presence of mood disorders may be one risk factor for suicide, but additional factors likely play a role. Similarly, Tsai et al. (2002) showed that there was an increased risk for suicide in relatives of bipolar suicide victims compared to relatives of bipolar disorder patients who were not suicidal. Tsuang et al. (1985) and Powell et al. (2000) both found higher rates of suicides within families of psychiatric inpatients who completed suicide than within families of psychiatric inpatients who were not suicidal, regardless of the inpatient's psychiatric diagnosis. These results are in agreement with the finding that the suicide attempt rate in families of suicide attempters is higher compared to families of nonattempters, despite both attempters and nonattempters having similar mood disorder profiles (Brent et al. 2002, 2003). These studies also suggest that the trend for familiality of suicide completion may be at least partially independent of the familiality of psychiatric diagnoses.

Brent et al. (1996) examined adolescent suicide victims and matched non-suicidal controls from chart reviews. They found an increased rate of suicide attempts in first-degree relatives of suicide victims compared to those of non-suicidal controls. Fourteen additional studies also reported increased rate of suicide attempts or completion in families of suicide completers (Gould et al. 1996; Cheng et al. 2000; Kim et al. 2005) and probands with a history of suicide attempt (Garfinkel et al. 1982; Roy 1983, 2001, 2002, 2003; Linkowski et al. 1985; Mitterauer 1990; Pfeffer et al. 1994; Bridge et al. 1997; Johnson et al. 1998; Goodwin et al. 2004; Mann et al. 2005). These studies suggested the existence of a common suicide phenotype that includes both attempt and completion. Suicidal ideation, in contrast, may present as a separate suicide phenotype. The rate of suicidal ideation in relatives of suicidal probands was not increased after controlling for the presence of psychiatric disorders in relatives (Brent et al. 1996; Kim et al. 2005).

The rate of familial suicide attempts was higher in suicide attempters compared to nonattempters, but the rate of suicide attempts was not higher in families of suicidal ideators compared to nonideators (Pfeffer et al. 1994). These observations suggest that suicidal ideation may segregate more with psychiatric diagnoses than suicide attempt/completion. Suicidal ideation and suicide attempt/completion may be partly independent phenotypes and do not fit strictly on a severity scale of suicidal behaviors.

The family studies we have reviewed are retrospective studies. Lieb et al. (2005) carried out a prospective study to examine the risk of suicidal ideation or attempts in the offspring of depressed mothers who had attempted or contemplated suicide. They found a greater than 50% increase in the risk for suicidal ideation or attempt relative to offspring whose mothers had never attempted suicide. From the aforementioned discussion, family studies support a genetic component of suicidal behavior. They provide evidence that the inheritance of suicidal behavior include both suicide attempt and suicide completion. Also, they show that the familial transmission may be independent of that of psychiatric disorders despite the fact that most suicide attempters/completers have underlying neuropsychiatric diagnoses.

11.2.2. Twin Studies

Twin studies are designed to evaluate the magnitude by which genetic and environmental factors influence a phenotype in a population. For the purpose of this review, twin studies investigate the risk of a twin exhibiting suicidal behavior given that the co-twin completed suicide. They 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. The earliest studies were case reports from the 1800s, including concordant twins described by Dr. Benjamin Rush in 1812. Nonetheless, these findings cannot be confirmed because the state of monozygosity and (same sex) dizygosity was not ascertained until the 1930s. Additional case reports were published regarding suicide concordance rates in MZ and DZ twin pairs. Kallman (1953) reported a MZ concordance rate of 5.6% (1/18) versus a DZ concordance rate of 0% (0/21). Harvald and Hauge (1965) examined the Danish national twin registry and found 4 concordant MZ pairs out of 21 compared to no concordance within 75 DZ pairs. Kaprio et al. (1995), in comparison, reported no concordance in suicide within 34 MZ twin pairs and 2 concordant DZ pairs out of 119 in the Finnish national twin registry. In the United States, Roy et al. (1991) reported 7 concordant MZ pairs for suicide completion out of 62 compared to 2 concordant DZ twin pairs out of 114 collected from a national twin registry, the Minnesota Twin Loss Study, and other sources.

Roy et al. (1995) furthered the findings to include suicide attempts in the analysis. They found 10 of 26 surviving MZ co-twins had attempted suicide, while none of the nine surviving DZ co-twins had a history of suicide attempts. This suggests that suicide attempts and completions may share a common genetic component. Roy and Segal (2001) continued on to collect a sample from the United States and Canada consisting of 13 MZ and 15 DZ pairs. The difference between the MZ (4/13) and the DZ (0/15) concordance rates for suicide completion or attempt was significant. Unfortunately, these studies did not include psychiatric conditions and many cases of suicide attempts and suicidal ideation may have been missed. Nevertheless, the variability in reported heritability may likely have resulted from the small size of individual samples, which would have limited the extent of these analyses. The latest estimate for the heritability of suicide attempt/completion is 43% (95% confidence interval [CI]: 27%–60%; McGuffin et al. 2010).

Larger population-based twin studies have been conducted. A telephone interview study (Statham et al. 1998) where the authors included 5995 respondents of European ancestry showed increased concordance within MZ pairs compared to DZ pairs across suicide phenotypes that include the presence of any suicidal thoughts, persistent thoughts/plan/minor attempt, and serious suicide attempt. They estimated the heritability of suicidal ideation to be 43%, suicide plan/attempt 44%, and that of serious suicide attempt to be 55%. Fu et al. (2002) took into consideration psychopathology and reported the heritability of suicidal ideation to be 36% and that of suicide attempt to be 17% from 3372 male twin pairs belonging to the Vietnam Era Twin Registry. Glowinski et al. (2001) carried out a similar study on suicides attempted by 3416 female adolescent twins from a U.S. twin registry and found lifetime suicide attempt concordance rates to be 25% and 13% for MZ and DZ pairs, respectively. After taking into account shared and non-shared environmental factors, genetic factors were found to explain 48% of the variance in suicide attempt. More recently, Cho et al. (2006) investigated the rates of self-reported suicidal ideation or attempt on U.S. adolescent twins within 12 months prior to the interviews. As with previous reports, they found higher concordance rates for either suicidal ideation or suicide attempt in MZ pairs (23% and 38%, respectively) than in DZ pairs (17% and 17%, respectively). The investigators also found that aggression and depression may explain more of the variance in

suicidality in females compared to males, while alcohol use and binge drinking seem to explain a larger portion of the variance in suicidal behavior in males than in females (Cho et al. 2006).

In all of the aforementioned four large-scale studies, the authors consistently found that psychiatric diagnoses (including major depressive disorder, conduct disorder, anxiety disorder, and alcohol dependence) and environmental factors (including childhood sexual and physical abuse) were associated with higher risk of attempting suicide. As with family studies, twin studies support a genetic basis of suicidal behavior and suggest that the genetic component of suicidal behavior may be independent of the heritability of psychiatric disorders. Furthermore, at least part of the heritability of suicidal behavior may overlap with suicidal ideation, suicide attempt, and suicide completion.

11.2.3. Adoption Studies

There are relatively few adoption studies that investigate the effect of environment on suicidal behavior. Using the Danish Adoption Registry, Schulsinger et al. (1979) matched 57 adoptees who committed suicide with 57 adoptees without history of suicidal behavior. Of the 269 biological relatives of suicidal adoptees, 12 committed suicide, while only 2 of the 269 biological relatives of non-suicidal adoptees committed suicide. None of the relatives of the adopted families in the study were affected by suicide. These observations support a genetic component of suicide. From the same registry, Wender et al. (1986) compared 71 adoptees with affective disorder to 71 adoptees who did not report significant affective disorder symptoms. They found higher frequencies of suicide in those related to affective disorder adoptees, especially those of the “affect reaction” subtype, compared to the relatives of unaffected adoptees. This suggests that the mechanism of suicide may involve the regulation of impulsive behavior.

11.3. REVIEW OF CANDIDATE GENES

Candidate gene studies have been the predominant methodology used in published genetic studies of suicidal behavior. Most of the published studies are recorded in Suicidal Behaviours: Genetic Association Studies Database (SBGAS) maintained by the McGill Group for Suicide Studies (URL: http://gmes.mcgill.ca/).

11.3.1. Serotonergic System

The serotonin neurotransmission system has received the most attention in candidate gene studies of suicidal behavior due largely to the role of serotonin in mood regulation and studies showing altered serotonin function in suicide victims (Virkkunen et al. 1989; Koller et al. 2003). Specifically, low cerebrospinal fluid concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5HIAA) has been found in numerous studies of suicidal patients (Asberg 1997), especially in high-lethality attempters (Placidi et al. 2001).

11.3.1.1. Tryptophan Hydroxylases *TPH1* and *TPH2*

The synthesis of serotonin (5-hydroxytryptamine [5-HT]) is catalyzed by the rate-limiting enzymes, the more broadly expressed TPH1 and the neuron-specific TPH2. The 29 kb human *TPH1* gene is localized on chromosome 11p15.3-p14 (Boularand et al. 1995). Several common single-nucleotide polymorphisms (SNPs) have been described in the upstream regulatory region and in intron 7 (Rotondo et al. 1999). Although functional variants have not been reported in the coding region of the *TPH1* gene (Han et al. 1999), the A (U) allele of the intron-7 A779C (rs1799913) marker has been associated with higher cerebrospinal fluid levels of the serotonin metabolite 5HIAA (Nielsen et al. 1994), and the CC genotype of the intron-7 A218C (rs1800532) marker has been associated with lower TPH1 protein levels in the prefrontal cortex (Ono et al. 2002). TPH1 expression in the anterior pituitary among other brain areas suggests a role in the hypothalamic–pituitary–adrenal (HPA) axis (Zill et al. 2009).

Since the first published finding by Nielsen et al. (1994) that the C-allele of the A779C polymorphism was associated with suicide attempts in alcoholic violent offenders/arsonists, over 40 papers have investigated this gene for association with suicide attempt, suicide completion, and suicidal ideation. Rujescu et al. (2003) conducted the first meta-analysis of A218C genotype data from seven studies on Caucasians and found that the A-allele (odds ratio [OR] = 1.33; 95% CI: 1.17–1.51) and both the AA and AC genotypes (OR = 1.48; 95% CI: 1.22–1.79) conferred risk for suicide attempt/completion. However, the suicide attempters have a mixture of different psychiatric diagnoses. Thus, the influence of other psychiatric diagnoses on these findings remained uncertain. More recently, Saetre et al. (2010) carried out a meta-analysis of studies in which the suicide cases were matched with controls for psychiatric diagnoses. They did not find A218C/A779C to be significantly associated with suicide (OR = 0.96; 95% CI: 0.80–1.16). The reason behind the discrepant results between these two meta-analyses could be that the first meta-analysis utilized

healthy controls, while the latest meta-analysis employed controls matched with suicide cases for psychiatric disorders (e.g., schizophrenia suicide attempters versus schizophrenia nonattempters). Saetre et al. (2010) instead found a significant association between A218C with schizophrenia, suggesting that the association detected in the previous meta-analysis may have been confounded by the suicide cases' comorbid psychiatric conditions. It may also explain the lack of significant difference in TPH1 expression between suicide and non-suicidal groups (Zill et al. 2009; Perroud et al. 2010a). Despite numerous studies of *TPH1* polymorphisms in suicidal behavior, taken together, the results have not been meaningful. Nonetheless, the role of *TPH1* gene in suicide cannot be dismissed without examining additional polymorphisms, including those in its upstream regulatory region (Sun et al. 2005).

Unlike TPH1 being expressed in both the central nervous system and the periphery, TPH2 is the predominant form of tryptophan hydroxylase expressed in the brain (Walther et al. 2003). There have been conflicting results in the literature over the difference in expression of the more recently discovered, neuron-specific TPH2 between non-suicidal controls and suicide completers. Some papers have reported an increased expression of the *TPH2* gene in suicide victims (Bach-Mizrachi et al. 2008; Perroud et al. 2010a), while others did not observe this difference in TPH2 expression between suicide victims and non-suicidal controls (De Luca et al. 2006a). The different brain regions examined could have contributed to the mixed gene expression findings. The 93.6 kb gene, located at 12q21.1, has been examined frequently since the first report of the G-allele of the rs1386494 marker being nominally associated with suicide completion in a German sample (Zill et al. 2004). Many subsequent studies examining multiple polymorphisms yielded mostly negative findings (De Luca et al. 2004a, 2005b; Zill et al. 2007; Mann et al. 2008; Mouri et al. 2009; Must et al. 2009), except for studies in depressed patients (Ke et al. 2006; Lopez de Lara et al. 2007; Yoon and Kim 2009). Unfortunately, even though multiple *TPH2* markers have been investigated, the analyzed polymorphisms often do not overlap among the studies, making interpretation of the findings difficult. It might be possible that *TPH2* gene expression changes with depression status, but not with suicide behavior *per se*. It might also be possible that the brain region–specific expression changes observed in suicide victims may be influenced by epigenetic changes in the *TPH2* gene promoter region.

11.3.1.2. Serotonin Transporter 5HTT(*SLC6A4* Gene)

The gene coding for 5HTT (*SLC6A4*, 37.8 kb at 17q11.1-q12) is another frequently examined candidate for studying the genetics of suicide. It is the primary target of many commonly prescribed antidepressant medications. 5HTT expression has been shown to be decreased in prefrontal cortical regions of suicide completers (Arango et al. 1995; Mann et al. 1996; Austin et al. 2002), but a number of study findings disputed these earlier reports (Mann et al. 1996; Little et al. 1997; Perroud et al. 2010a). Underlying psychiatric conditions and medications could have contributed to the mixed findings.

Two polymorphisms, in particular, a 44 nucleotide insertion/deletion polymorphism (serotonin transporter linked polymorphic region, HTTLPR) in the promoter region ~1kb from the transcription start site and a 17 base pair (bp) variable number tandem repeat (VNTR) polymorphism in intron 2 (STin2), affect the function of 5HTT. More specifically, the HTTLPR genotypes carrying the short (S) allele (SS or LS) are associated with decreased transcriptional activity of the promoter (Collier et al. 1996) and reduced reuptake of serotonin compared to the long–long (LL) genotype (Heils et al. 1996). Also, the STin2 region has been shown to be an enhancer element in transgenic reporter mouse embryos, where the 12-repeat allele of STin2 was associated with increased reporter gene expression (MacKenzie and Quinn 1999). Since the first published report of *5HTT* gene and suicide attempt by Bellivier et al. (1997), over 40 papers have been published on this topic. Included is a recent comprehensive meta-analysis of studies up to January 2006 showing the long allele to be associated with decreased risk for suicide in the entire sample (OR = 0.88; 95% CI: 0.80–0.97) (Li and He 2007). The authors did not find STin2 to be associated with suicidal behavior from pooling five study samples and stratifying the meta-analysis by sex, ethnicity, diagnostic groups, and method of case–control pairing (i.e., whether suicide cases and controls were matched for psychiatric diagnosis) (Li and He 2007). In nine studies where the suicide attempters were paired with suicide nonattempters with the same psychiatric conditions, carriers of the long allele were associated with decreased risk for suicide (OR = 0.83; 95% CI: 0.73–0.95). The results from the meta-analysis of four studies found that the HTTLPR short allele carrying genotypes were not significantly associated with suicide completion (OR = 1.07; 95% CI: 0.48–2.37). This could possibly be due to reduced sample sizes and the fact that the control groups consisted of nonpsychiatric subjects. More recent studies of 5HTT in suicide found the short allele to be associated with violent suicide attempts (Wasserman et al. 2007; Neves et al. 2008, 2010).

It is important to note that the HTTLPR polymorphism has been associated with numerous neuropsychiatric disorders including depression (Kiyohara and Yoshimasu 2010), bipolar disorder (Cho et al. 2005), child aggression (Beitchman et al. 2006), and alcohol dependence (Feinn et al. 2005) as well as neuroticism (Sen et al. 2004). All of these disorders have in turn been associated with increased suicidality (Persson et al. 1999b). Similarly, STin2 has been associated with schizophrenia (Fan and Sklar 2005). In addition, the *5HTT* gene has been associated with response to antidepressants (Smits et al. 2004; Porcelli et al. 2011). Thus, it would be crucial to include the administration of serotonin reuptake inhibitors as a covariate when analyzing this gene in suicide. Also, the SNP rs25531 has been linked with the long allele of HTTLPR. It involves an A to G substitution that has been associated with lower 5HTT expression (Nakamura et al. 2000; Hu et al. 2006). This additional level of complexity at this locus may have contributed to some of the mixed findings in earlier genetic studies involving this gene. Studies including the rs25531 polymorphism, however, did not find significant association between the HTTLPR and suicidal behavior (De Luca et al. 2006c, 2008a; Chen et al. 2007; Segal et al. 2009). In the presence of childhood trauma, the short allele has been associated with suicide (Gibb et al. 2006; Roy et al. 2007), suggesting that gene–environment interaction could play an important role in suicidal behavior. Functional effects of the 10-repeat, 12-repeat, and other alleles of STin2 as well as its interaction with HTTLPR need to be verified in humans (Ali et al. 2010). The interaction between STin2 and childhood trauma should be explored. Additional polymorphisms across the *5HTT* gene, especially those in the HTTLPR region (Nakamura et al. 2000; Sakai et al. 2002), have been largely unexplored in most published studies (De Luca et al. 2006c; Zhang et al. 2008).

11.3.1.3. Serotonin Receptors (*HTR1A, HTR1B, HTR2A, HTR2C*, etc.)

Over 10 studies have reported negative findings with respect to *HTR1A* in suicidal behavior, beginning with Nishiguchi et al. (2002) who reported nonsignificant results with two infrequent missense variants in Japanese suicide completers versus healthy controls. Most studies since then have concentrated on the promoter C-1019G (rs6295) polymorphism, which is located within the consensus sequence for a transcriptional repressor called nuclear DEAF-1 related (Lemonde et al. 2003), with the C-allele having higher binding affinity than the G-allele. Thus, the G-allele represents the un-repressed or high-expression variant. Lemonde et al. (2003) also found the high-expression G-allele to be overrepresented in suicide completers of French Canadian ancestry compared to healthy controls. This may explain the low serotonin levels observed in suicide completers. These positive findings were not replicated however in other samples of suicide completers (Huang et al. 2004; Ohtani et al. 2004; Serretti et al. 2007b; Videtic et al. 2009b) or suicide attempters (Huang et al. 2004; Serretti et al. 2007b; Wang et al. 2009).

The 1.17 kb intronless *HTR1B* gene located at 6q13 is also another frequently studied gene in suicide research due to the aggressive and impulsive behavioral phenotypes observed in knockout mice lacking the expression of the homologous *Htr1b* gene (Saudou et al. 1994; Brunner and Hen 1997; Zhuang et al. 1999; Bouwknecht et al. 2001). It has also been associated with antisocial behavior in alcohol-dependent individuals (Soyka et al. 2004). Since high level of impulsive aggression has been reported in psychological autopsy of suicide victims compared to psychiatric controls (Dumais et al. 2005; McGirr et al. 2008), *HTR1B* was considered a candidate gene for suicidal behavior. A meta-analysis of six studies with various study designs did not yield a significant finding of suicidal behavior with the G861C polymorphism (rs6296) (Kia-Keating et al. 2007).

Later publications did not find G861C to be associated with suicidal behaviors. The T-261G (rs11568817) and A-161T (rs130058) polymorphisms, which have been shown to alter 5HT1B expression in cell lines (Sun et al. 2002; Duan et al. 2003a), were found to be associated with suicidal ideation in depressed patients (Wang et al. 2009). However, other investigations into these and other polymorphisms, namely, A1180G, C129T (Huang et al. 1999; Zouk et al. 2007), T-261G (Zouk et al. 2007), A-161T (Hong et al. 2004; Tsai et al. 2004; Videtic et al. 2006; Zouk et al. 2007), and G371T (De Luca et al. 2008a), did not yield significant results. An exception was a marginal overrepresentation of the A-161T T-allele in suicide victims compared to healthy controls (Zouk et al. 2007). The different study designs and different markers investigated in each study made comparison among these studies challenging. For instance, Zouk et al. (2007) examined suicide victims versus healthy controls while Wang et al. (2009) examined the severity of suicidal behavior within a group of patients. The suicide cases in Zouk et al. (2007) were Caucasians of various psychiatric diagnoses, while the sample recruited by Wang et al. (2009) consisted of a group of Han Chinese major depressive patients without history of alcoholism, drug abuse, drug-induced bipolar disorder, or depressive disorders. It remains to be explored whether the presence of certain psychiatric conditions affects the association of *HTR1B* with suicidal behavior. Of interest, obsessive–compulsive disorder and bipolar disorder have been associated with *HTR1B* in several studies (Mundo et al. 2000, 2001, 2002). Nonetheless, the results from the literature thus far suggest that *HTR1B* may not play a major role in suicidal behavior.

The serotonin 2A receptor (*HTR2A*) gene is localized to 13q14-q21 and is 62.66 kb in length. The majority of studies to date reported 5HT2A expression or binding to be increased in suicide victims (Cheetham et al. 1988; Lowther et al. 1994; Turecki et al. 1999; Arango et al. 2003). Increased 5HT2A levels have also been reported in platelets of suicidal patients (Pandey 1997). A SNP in the promoter region of *HTR2A*, A-1438G (rs6311), as well as an exon 1 SNP, T102C (Ser34Ser, rs6313), have been extensively studied in numerous psychiatric disorders. The C102 allele has been associated with a 20% decrease in 5HT2A receptor levels in the temporal cortex (Polesskaya and Sokolov 2002). Li et al. (2006) carried out a metaanalysis of T102C of 25 studies published up to July 2005 on suicidal behavior, and they did not find significant association with suicide attempt versus non-suicidal patients (seven studies; OR = 0.98; 95% CI: 0.83–1.16). Other matching strategies yielded positive findings where the T102 was found to be a protective allele. These methods included comparing individuals with suicidal ideation to a combined group of patients lacking ideation and healthy controls (five studies; OR = 0.77; 95% CI: 0.62–0.95), or comparing individuals with suicidal ideation and attempts to psychiatric controls without attempt or ideation and healthy controls (20 studies; OR = 0.88; 95% CI: 0.77–1.00). In the same paper, the meta-analysis of A-1438G of seven studies in suicidal behavior showed that A-allele carrying genotypes were protective against suicide (OR = 0.67; 95% CI: 0.50–0.89) (Li et al. 2006). More recent studies with T102C and A-1438G yielded mostly negative findings. Only one study thus far has investigated the tag SNPs, SNPs selected to minimize overlapping genetic information, spanning *HTR2A* for association with suicidal ideation. This study used a sample of 270 families affected by schizophrenia or schizoaffective disorder (Fanous et al. 2009). They did not observe significant association between any of the tag SNPs or their haplotypes and suicidal ideation. Phenotypic heterogeneity from analyzing these tag SNPs in suicide attempters and completers may have contributed to the mixed results for this gene.

Suicidal behavior has been hypothesized to be partly X-linked. This is because of the seemingly different rates of suicidal ideation (2 females:1 male), suicide attempts (4 females:1 male), and suicide completion (1 female:3 males) between the two sexes (Stefulj et al. 2004a,b; Bondy et al. 2006). Turecki et al. (2003) first investigated the X-linked *HTR2C* gene where the authors did not find the G-995A (rs3813928) polymorphism to be significant in suicide completion. Subsequent studies focused on a missense polymorphism Ser23Cys (rs6318, G68C) in the coding region of the gene and most did not find this polymorphism significant. However, Videtic et al. (2009a) found the G-allele to be associated with risk for suicide in their Slovenian sample. The *HTR2C* gene is large (326.1 kb), and thus additional polymorphisms need to be investigated. Also, changes in mRNA editing have been reported in suicide victims (Gurevich et al. 2002). In addition to the *HTR2C* gene, Turecki et al. (2003) also explored for possible association between suicide completion and the *HTR1D*, *HTR1E*, *HTR1F*, *HTR5A*, and *HTR6* genes. They did not find any of the tested markers in these genes to be associated with suicide risk.

11.3.1.4. Monoamine Oxidases–*MAOA* and *MAOB*

MAOA is a mitochondrial enzyme that degrades monoamines including dopamine, norepinephrine, and serotonin. It is the major target of the monoamine oxidase inhibitor (MAOI) class of antidepressants. Elevated activity of the MAOA enzyme in the hypothalamic region of suicide victims has been reported (Sherif et al. 1991). The *MAOA* gene is localized to Xp11.23-p11.4. A 30 bp repeat in the promoter region has been associated with levels of expression (Sabol et al. 1998) where alleles 2 (with 3.5 repeats) and 3 (with four repeats) were associated with higher *in vitro* transcriptional activity. These alleles have also been associated with higher 5HIAA levels (Jonsson et al. 2000; Williams et al. 2003) and lower response to serotonin (as measured by increase in circulating prolactin levels upon fenfluramine administration) (Manuck et al. 2000). Two additional polymorphisms, EcoRV (rs1137070) and Fnu4HI (rs6323), have been associated with changes in enzyme activity (Hotamisligil and Breakefield 1991). The promoter VNTR has been examined in more than eight studies, with Ho et al. (2000) finding the 132 bp allele 3 to be associated with risk for suicide attempts in bipolar disorder patients. The authors also analyzed and found the Fnu4HI (rs6323) T-allele to be associated with suicide risk in the same sample (Ho et al. 2000). Courtet et al. (2005) found in a sample of hospitalized suicide attempters with various diagnoses that alleles 2 and 3 were overrepresented in violent attempters. Other polymorphisms in this 90.66 kb gene should be interrogated for possible association with suicidal behavior. Only one study (Brezo et al. 2010) explored the 115.8 kb *MAOB* gene, which is adjacent to *MAOA*, in association with suicide attempts. The authors did not report any significant findings with two examined *MAOB* polymorphisms.

11.3.2. Dopaminergic System

The dopamine system has not been a major target for suicide genetic research. There have been few studies looking into altered dopamine (and norepinephrine) levels in brain tissues of suicide victims (Arango et al. 1993) and

cerebrospinal fluid (CSF) of suicide attempters (Roy et al. 1986; Jones et al. 1990; Lester 1995). Dopamine has also been associated with impulsivity, a personality trait that is implicated in suicide (van Gaalen et al. 2006; Oswald et al. 2007).

11.3.2.1. Tyrosine Hydroxylase

Tyrosine hydroxylase (*TH*) is a small 7.9 kb gene located on chromosome 11p15.5. A nominally significant finding was reported between the putatively functional 252 bp eight-repeat allele of the tetranucleotide repeat (Albanese et al. 2001) in the promoter region of *TH* and suicide attempters compared to healthy control subjects (Persson et al. 1997). Another research group did not replicate these positive findings with suicide attempt in bipolar disorder patients (Ho et al. 2000). Giegling et al. (2008) investigated three SNPs in the DOPA decarboxylase (*DDC*) gene in addition to the Val81Met (rs6356) and a 3′ polymorphism (rs3842727) in the *TH* gene. They did not find positive results with either gene. Gerra et al. (2005) explored the relationship between the gene coding for the dopamine transporter *SLC6A3* and did not find the VNTR in the 3′ untranslated region of the gene to be associated with male suicide-attempting heroin addicts compared to controls. The VNTR in exon 3 of the dopamine *DRD4* gene has also been investigated in two studies (Persson et al. 1999a; Zalsman et al. 2004) with negative findings.

11.3.2.2. Catechol-*O*-Methyltransferase

Catechol-*O*-methyltransferase (*COMT*) deactivates dopamine and norepinephrine by the addition of a methyl group from *S*-adenosylmethionine. The 27.2 kb gene is mapped to 22q11.1-q11.2. The Val158Met (rs4680) polymorphism has been investigated in many psychiatric disorders. The Met allele has been associated with lower thermostability and resultant lower COMT enzymatic activity (Weinshilboum and Raymond 1977; Lachman et al. 1998). Two meta-analyses have been conducted. Kia-Keating et al. (2007), using data from six previous studies (Ohara et al. 1998a; Nolan et al. 2000; Russ et al. 2000; Liou et al. 2001; Rujescu et al. 2003; Ono et al. 2004), found the low-functioning Met allele to be associated with suicide risk. However, the results could be influenced by the different sex ratios among the studies. It is important to note that several groups have reported the sex-specific association of suicidal behavior with Val158Met (Nolan et al. 2000; Ono et al. 2004). Calati et al. (2011) presented an updated meta-analysis with four additional samples (De Luca et al. 2005a, 2006b; Baud et al. 2007; Zalsman et al. 2008), and they did not report Val158Met to be significant. Similar to the Kia-Keating et al.'s (2007) paper, this meta-analysis could be influenced by different case–control matching strategies employed by each included study or insufficient number of studies. In addition, both meta-analyses reported a significant effect of sex ratios (Kia-Keating et al. 2007; Calati et al. 2011). Sex-specific analysis of this and additional *COMT* polymorphisms (e.g., Nackley et al. 2006) in suicide are warranted.

11.3.2.3. Dopamine Receptor *DRD2*

Four suicide phenotype studies of the dopamine receptor *DRD2* gene (11q22-q23) have been published. Finckh et al. (1997) reported an exon 8 polymorphism in the 3′ untranslated region where the AA genotype appeared to be overrepresented in the alcoholic patients with history of suicide attempts. Subsequent studies investigated a putatively functional promoter insertion/deletion polymorphism (–141 Ins/Del, rs1799732; Arinami et al. 1997), with Johann et al. (2005) reporting the Del allele conferring risk for suicide attempt or ideation in alcoholics. Suda et al. (2009) recently reported the Ins allele as well as the A2 allele of the TaqIA polymorphism to be overrepresented in the suicide attempters compared to the healthy controls. A third paper by Ho et al. (2000) did not find –141C Ins/Del to be associated with suicide attempt in their sample of bipolar and unipolar disorder patients. Additional *DRD2* polymorphisms, particularly the putatively functional C957T (rs6277, Duan et al. 2003b), rs12364238, and rs1076560 (Zhang et al. 2007) markers, should be explored in suicidal behavior. Caution must be given when analyzing *DRD2* markers as, similar to *5HTT*, many of these *DRD2* markers have been implicated in a number of psychiatric disorders (Noble 2003).

11.3.3. Hypothalamic–Pituitary–Adrenal Axis

The Hypothalamic Pituitary Adrenal (HPA) axis is a very important component of the stress response system. HPA axis abnormalities, as indicated by nonsuppression in the dexamethasone suppression test, have been implicated in suicidal behavior (McGirr et al. 2010; Pompili et al. 2010). One study has explored two polymorphisms (rs1870393 and rs3176921) in the corticotrophin-release hormone (*CRH*) gene in suicide attempt using a family-based study design (Wasserman et al. 2008). The authors reported negative findings. Wasserman et al. (2008) also investigated two polymorphisms in the gene coding for the CRH receptor (*CRHR1*) (rs4792887 and rs1396862) and found the T-

allele of rs4782887 to confer risk for suicide attempts, particularly in males who had experienced low-level stressful life events. In the same year, Papiol et al. (2007) reported a similar study genotyping two different *CRHR1* SNPs (rs110402 and rs242937) in their sample of suicide attempters and healthy controls. They did not find these SNPs to be associated with suicide attempt. Papiol et al. (2007) also reported negative findings with two SNPs (rs2270007 and rs2240403) in the CRH receptor 2 gene (*CRHR2*), in contrast to a nominal association of a GT-repeat polymorphism in *CRHR2* with severity of suicidal behavior measured in bipolar disorder subjects in a nuclear family sample (De Luca et al. 2007). Papiol et al. (2007) also did not find one putative functional SNP (rs1360780; Binder et al. 2004) in FK506-binding protein (*FKBP5*) gene to be associated with suicide attempt, but Willour et al. (2009) reported significant association of four markers in *FKBP5* with bipolar disorder depending on suicide attempt status. Papiol et al. (2007) did not find two SNPs (rs7728378 and rs1875999) in the gene encoding CRH-binding protein (*CRHBP*) to be significant, the results that are not consistent with a more recent report of an association between *CRHBP* and suicide attempt history in schizophrenia patients (De Luca et al. 2010). Although our group (De Luca et al. 2010) did not find the glucocorticoid receptor gene (*NR3C1*) to be associated with suicide attempt history in schizophrenia patients, increased methylation of specific *NR3C1* promoter CpG sites have been reported in the hippocampi of suicide victims with history of childhood trauma (McGowan et al. 2009), the results that may account for the observed decreased expression of glucocorticoid receptors in these brain regions (Labonte and Turecki 2010).

11.3.4. Brain-Derived Neurotrophic Factor and Tropomyosin-Related Kinase B

Decreased brain-derived neurotrophic factor (BDNF) levels have been reported in suicide victims (Dwivedi et al. 2003; Karege et al. 2005; Kim et al. 2007; Dwivedi 2010). Of the regional SNPs, the Val66Met (rs6265) polymorphism has received more attention in genetic studies of suicide. Initial studies of this functional polymorphism did not find it to be associated with suicide attempts (Hong et al. 2003; Huang and Lee 2007). However, Vincze et al. (2008) found an overrepresentation of the Val allele in violent bipolar suicide attempters versus healthy controls. The majority of recent studies reported the Met allele to be associated with suicide attempt in the context of various psychiatric diagnoses, including schizophrenia (Huang and Lee 2007), bipolar disorder (Kim et al. 2008), and depression (Iga et al. 2007; Sarchiapone et al. 2008). Additional studies did not report the Val66Met to be associated with suicide (Zarrilli et al. 2009; Kohli et al. 2010; Spalletta et al. 2010) or worsening of suicidal behavior during a drug trial in treatment-resistant depressed adolescents (Brent et al. 2010). Overall, a recent meta-analysis by our group of 11 published studies found the Met allele to be associated with risk for suicide ($p = 0.032$; $OR_{Met} = 1.16$; 95% CI: 1.01–1.32; Zai et al. 2011).

The association of *BDNF* may be influenced by its downstream receptor tropomyosin-related kinase B (*NTRK2*; Kunugi et al. 2004). Kunugi et al. (2004) was first to report an association between Ser205Leu of *NTRK2* and depressed suicide. McGregor et al. (2007) did not replicate this finding in young adults who had childhood depression and had been prospectively followed for over 20 years. More recently, multiple polymorphisms in the *NTRK2* gene have been consistently associated with suicidal behavior. Perroud et al. (2009) found *NTRK2* to be associated with suicidal ideation in the Genome-based Therapeutic Drugs for Depression (GENDEP) study and Kohli et al. (2010) recently supported these findings by showing that multiple polymorphisms in *NTRK2* were associated with suicide attempt history in two ethnically distinct depression samples. Gene–gene interaction may be able to refine the association findings in suicide and identify pathways involved in this devastating outcome. In addition, the observed changes in BDNF expression levels in suicide could be epigenetically determined. Keller et al. (2010) reported hypermethylation at specific CpG sites in the *BDNF* promoter region that correlated with decreased BDNF expression. Similarly, hypermethylation at specific CpG dinucleotides in the *NTRK2* gene promoter have been linked to reduced frontal cortical expression of a TrkB protein isoform in postmortem brain studies in suicide victims (Ernst et al. 2009). Further discussion of methylation and other epigenetic mechanisms is provided later.

11.3.5. Adrenergic Receptor A2A

The levels of adrenergic α-2A receptor have been found increased in the postmortem brain tissues of depressed suicide victims (De Paermentier et al. 1997; Garcia-Sevilla et al. 1999). However, these findings need further replication (Gross-Isseroff et al. 2000). Its gene, adrenergic receptor A2A (*ADRA2A*), is 3.65 kb in length and mapped to chromosomal region 10q24-q26. The Asn251Lys (rs1800035) polymorphism has been reported as functional because the Lys allele increases the ligand-mediated G-protein coupling and enhances downstream signaling in the inhibition of adenylate cyclase and activation of MAPK (Small et al. 2000). Neither Ohara et al. (1998b) nor Sequeira et al. (2004) found significant results with a promoter polymorphism (C-1291G, rs1800544) in Japanese suicide attempters with mood disorders and French Canadian suicide victims, respectively. A more recent study by Fukutake

et al. (2008), however, reported the C-1291 allele to be associated with risk for female suicide completion in their Japanese sample.

11.3.6. Other Genes

Poulter et al. (2008) found increased anterior prefrontal *GABRA1* gene promoter methylation that was consistent with their previous finding of decreased anterior prefrontal GABRA1 levels in major depressive suicide victims (Merali et al. 2004). There is increasing evidence of altered expression of GABA (γ-aminobutyric acid) system components in suicide, yet genetic studies of GABA system genes in suicide are still lacking. One study investigating polymorphisms in the $GABA_A$ receptor α3 subunit gene *GABRA3* (Baca-Garcia et al. 2004), and another study on the glutamate decarboxylase genes *GAD1* and *GAD2*, did not find a significant association with suicidal behavior (De Luca et al. 2004b). Nonetheless, recent reports of altered GABA receptor subunit mRNA expression in depressed suicide victims (Sequeira et al. 2009; Poulter et al. 2010) encourage exploration of additional GABA system genes in suicide (Lee et al. 2009). In particular, the altered expression levels point to examination of polymorphisms in regulatory regions.

Signaling molecules have been investigated in suicidal behavior. The rs1130214 and rs2494746 markers in the gene coding for the intracellular signaling molecule protein kinase B (AKT1) were associated with suicide attempt and violent attempt, respectively (Magno et al. 2010). Previously, angiotensin-receptor blockers were identified as a possible risk factor for suicide (OR = 3.52) (Callreus et al. 2007). Four studies have explored the role of the angiotensin-converting enzyme (*ACE*) gene in suicidal behavior. Two studies found the low-functioning insertion allele (Rigat et al. 1990) to be associated with suicide completion (Hishimoto et al. 2006; Fudalej et al. 2009). One study found the deletion allele to be overrepresented in suicide attempters and completers compared to controls (Sparks et al. 2009), while another did not find this marker associated with suicide attempt history in depressed patients (Hong et al. 2002). Other genes that have been implicated in suicidal behavior and are awaiting replication include apolipoprotein E (*APOE*) (Hwang et al. 2006), cholecystokinin (*CCK*; Shindo and Yoshioka 2005), 14-3-3 epsilon (Yanagi et al. 2005), spermine/spermidine *N*-acetyltransferase (*SAT1*; Sequeira et al. 2006), regulator of G-protein signaling (*RGS2*; Cui et al. 2008), and neuronal nitric oxide synthase (*NOS1*; Rujescu et al. 2008; Cui et al. 2010).

11.3.7. Genome-Wide Studies of Suicide

Zubenko and coworkers reported a genome-wide linkage study of suicide attempts in 81 families where the probands were affected by recurrent early-onset major depression (Zubenko et al. 2004). Using 389 microsatellite markers, they reported significant linkage in chromosomal regions 2p, 5q, 6q, 8p, 11q, and Xq. Hesselbrock et al. (2004) reported another genome scan of suicide using 336 microsatellite markers across the genomes of multiplex families affected by alcoholism from the Collaborative Study on the Genetics of Alcoholism (COGA). When they conducted a nonparametric analysis on 59 pairs of siblings who had both attempted suicide(s), they found the marker D2S1790 near chromosomal region 2p11 to be linked (Hesselbrock et al. 2004). The findings on 2p12 were later replicated in a sample of 162 bipolar disorder pedigrees (Willour et al. 2007). This study on bipolar disorder patients also found linkage with markers D6S1035, D6S1277, and D6S1027 on chromosome 6q25-q26 (Willour et al. 2007). The marker D6S1035 was found to be linked to bipolar disorder/recurrent major depressive disorder diagnosis in a large sample of 154 families from the National Institute of Mental Health genetics initiative (Cheng et al. 2006); however, two other markers at 6q24-q25, D6S1848 and D6S2436, were found to be linked to suicide completion in this bipolar disorder sample. Recent advances have allowed for large-scale genotyping of SNPs across the genome in large samples to carry out genome-wide hypothesis-generating studies. Unfortunately, using genome-wide significance threshold of 5×10^{-8} did not yield significant findings from any of the published studies thus far, indicating that the genetic architecture underlying suicidal behavior is complex with multiple genes of moderate effect. Perroud et al. (2012) published a genome-wide association study of treatment-associated suicidality on the GENDEP sample of 706 major depression patients treated with escitalopram or nortriptyline. These patients were assessed for increased suicidality during 12 weeks of treatment using a composite score calculated from the 3rd item of the HDRS-17, the 10th item of the Montgomery-Asberg Depression Rating Scale, and the 9th item of the Beck Depression Inventory. The authors found rs11143230 downstream of the guanine deaminase (cypin) (*GDA*) gene to be most significantly associated with increased suicidality during antidepressant treatment. They also found rs358592 in the voltage-gated potassium channel (*KCNIP4*) gene and rs4732812 upstream of the elongation protein 3 homolog (*ELP3*) gene to be most significantly associated with increased suicidality during escitalopram treatment. The rs6812841 marker was most significantly associated with increased suicidality during nortriptyline treatment. Since cypin interacts with the

postsynaptic density protein-95 (PSD-95), and PSD-95 is involved in glutamatergic neurotransmission, glutamate signaling may be involved in suicidality. The authors also extracted genotypes for SNPs in 33 candidate genes for suicide, and they found the *NTRK2* gene to be the most significant in the escitalopram-treated group and the *CRHR2* gene to be the most significant in the nortriptyline-treated group (Perroud et al. 2010b). A genome-wide association study was conducted using two bipolar disorder and two major depressive disorder patient conglomerate samples totaling 8737 patients of which 2805 had a lifetime history of at least one suicide attempt (Perroud et al. 2010b). The strongest association signal came from the intergenic marker rs1466846 for suicide attempt in the bipolar disorder discovery sample, and rs2576377 in the Abl-interactor family member 3 binding protein (*ABI3BP/TARSH*) gene for suicide attempt in major depression discovery sample. However, these findings were not replicated in the bipolar disorder or major depression replication samples. The authors selected 19 candidate genes for suicide and found only nominal results with *FKBP5* and *NGFR* genes (Perlis et al. 2010). The authors further conducted a random effects meta-analysis of markers with $p < 1 \times 10^{-3}$ across all four mood disorder samples, half of the 10 most significant markers reside in the gene coding for sorbin and SH3-domain containing-1 (SORBS1), which has been implicated in insulin signaling. Willour et al. (2011) reported a genome-wide association study using the same samples of bipolar disorder patients. After metaanalysis of markers with $p < 1 \times 10^{-3}$ from the first sample in both bipolar disorder samples, they found the most significant signal with rs300774 in an intergenic region at 2p25 in linkage disequilibrium with the *SH3YL1*, *ACP1*, and *FAM150B* genes. Further investigations in postmortem prefrontal cortical brain samples from suicide completers revealed significantly higher ACP1 expression in suicide victims compared to non-suicidal victims (Willour et al. 2011). More recently, another genome-wide association study of suicidality was reported on major depression sample from the RADIANT study (Schosser et al. 2011). In addition to analyzing the discrete variable of serious suicide attempt, genotypes were also analyzed using the SCAN interview, which captures suicide severity from suicide ideation to attempt. None of the top findings from the RADIANT sample were replicated in the German replication sample. However, meta-analysis of top findings from the RADIANT and Sequenced Treatment Alternatives to Relieve Depression (STAR*D) samples revealed an association with rs1377287 in the solute carrier family 4 member 4 (*SLC4A4*) gene. Recent advances in genotyping technologies have enabled us to collect large amounts of genetic information. However, more work needs to be done in terms of better characterization of suicidal behavior and clearer understanding of how gene markers work in pathways to clarify these preliminary whole-genome findings.

11.4. METHODOLOGICAL AND PHENOTYPIC CONSIDERATIONS

With most of the genetic findings of suicidal behavior being nominal or mixed, it has become apparent that there are numerous issues that need to be resolved as we move toward more comprehensive and large-scale genome-wide studies. These issues of suicide genetic studies, as well as more recent research strategies, are discussed later.

11.4.1. Gene–Gene Interactions

Genes rarely work alone. Relatively low ORs derived from meta-analyses of various candidate genes discussed earlier suggest that multiple genes are involved in the complex phenotype of suicide. Only a handful of studies looked at the combined effect of two or more genes in suicidal behavior. Our group (De Luca et al. 2010) reported a nominally significant interaction between *CRHR1* rs16940665 and *CRHBP* rs1875999 in the severity of suicidal behavior in a sample of 231 schizophrenia patients. Investigation into the interaction between *MAOA* and *COMT* polymorphisms in suicide attempt did not yield significant findings in schizophrenia or bipolar disorder patients (De Luca et al. 2005a, 2006b). The interaction between the X-linked genes *MAOA* and *HTR2C* also was not significant (De Luca et al. 2008b). Vincze et al. (2008) found *BDNF* and *5HTT* polymorphisms to be independently associated with violent suicide in their bipolar disorder sample, but they did not find a significant interaction between these two genes in suicidal behavior. Perroud et al. (2009) recently found a significant interaction between *BDNF* and *NTRK2* polymorphisms in suicidal ideation in their GENDEP clinical trial sample. Additional interactions between genes should be explored, using software including the generalized multifactor dimensionality reduction (GMDR; Lou et al. 2007) and HELIXTREE (Golden Helix, Inc.; e.g., Zai et al. 2009). With large datasets from genome-wide association and gene expression microarray studies, pathway analysis using ingenuity pathway analysis (IPA; e.g., Inada et al. 2008; Charlesworth et al. 2010) could be a viable option for more comprehensive analysis of gene pathways in suicidal behavior.

11.4.2. Gene–Environment Interactions

Suicidal behavior is considered a complex phenotype that involves both genetic predispositions and distal/proximal environmental factors (Roy et al. 2009). Personal history of childhood abuse has been repeatedly implicated as a risk factor for suicidal behavior (Brodsky et al. 1997; Melhem et al. 2007; Brezo et al. 2008b; Carballo et al. 2008). Some epidemiological studies have estimated that sexual abuse may explain 20% of the risk variance in suicide (Brent and Melhem 2008). Using data collected for the Dunedin Multidisciplinary Health and Development study, Caspi et al. (2003) found that individuals carrying the HTTLPR short (S) allele and who experienced childhood (during 3–11 years of age) maltreatment or increasing number of stressful life events (at 21–26 years of age), assessed using the life-history calendar, were more prone to suicidal ideation or attempts. Gibb et al. (2006) reported similar findings of increased risk of suicide attempts in 30 psychiatric inpatients who were HTTLPR S-allele carriers and who had experienced physical or sexual abuse but not emotional abuse. Roy et al. (2007) also reported in a sample of African-American substance-dependent patients that those carrying the low-expressing *5HTT* genotypes (SS, SLg, and LgLg) and having experienced higher levels of childhood trauma (as assessed by the Childhood Trauma Questionnaire) were at increased risk for suicide attempts. The interaction between S-allele carrying genotypes and maltreatment was also observed in suicidal ideation in low-income children (Cicchetti et al. 2010). A recent study did not replicate the findings on suicidal ideation in 3243 subjects from 2230 families with HTTLPR (Coventry et al. 2010). Possible explanation for the discrepancy between this study and the others could be that stressful life events assessed for this study were restricted to 12 months leading up to the study rather than history of childhood trauma as assessed in most of the other studies. Nonetheless, further investigations using various study designs are required to resolve these mixed findings. Also, measurement of life events needs to be standardized and likely more information will be obtained if the life events are quantified (Risch et al. 2009; Uher et al. 2011; Mandelli et al. unpublished).

While individuals carrying the *MAOA* VNTR low-functioning allele were more prone to antisocial behavior and conduct disorder (Caspi et al. 2002), they were not prone to suicidal behaviors (Caspi et al. 2003). Brezo et al. (2010) recently reported on a large longitudinal study wherein a cohort of 1255 youths was followed for 22 years and assessed for the development of mood disorders and suicidal behaviors. The authors then examined variants within 11 serotonin system genes for association with these psychiatric phenotypic outcomes. They also explored the possible interaction between these gene variants and childhood physical/sexual abuse on these outcomes. They reported that the *TPH1* rs10488683 marker was associated directly with suicide attempt and three markers in *HTR2A* were associated with suicide attempt with history of abuse (Brezo et al. 2010). Thus, given these initial reports, it appears that incorporation of stressful life events and/or maltreatment is a useful strategy for enhancing genetic studies of suicide.

11.4.2.1. Effects of Medication or Substance Use

Bipolar subjects with comorbid substance use disorders (SUD) had a 39.5% rate of lifetime attempted suicide, compared to those without SUD at a rate of 23.8% (Dalton et al. 2003). A forensic study on suicide victims with respect to alcohol intake prior to suicide showed that while HTTLPR, *TPH1* A218C, and *ACE* insertion/deletion variants were not associated with the presence of alcohol in the blood of suicide victims at time of death, *TPH2* rs1386483 TT genotype appeared underrepresented in the group of suicide victims where alcohol was detected. This suggests that the *TPH2* marker may protect against suicide related to alcohol consumption (Fudalej et al. 2009).

The majority of suicidal behavior occurs in depressed patients, but the role of antidepressants in suicide remains controversial. Some reports suggest that certain antidepressants increase the risk of suicide (Teicher et al. 1990; Khan et al. 2003), but others argue against it (Gibbons et al. 2007). Perroud et al. (2009) published the first paper examining the effects of candidate gene variants on the emergence or worsening of suicidal behavior, as measured by the Beck Depression Inventory (BDI) and Montgomery-Åsberg Depression Rating Scale (MADRS), during 12 weeks of antidepressant treatment in the GENDEP clinical trial on 796 major depressive disorder patients. The authors analyzed genes implicated in the mechanism of the antidepressants escitalopram and nortriptyline, namely, *TPH1*, *TPH2*, *HTR1A*, *HTR2A*, *5HTT*, *ADRA2A*, *SLC6A2*, *BDNF*, and *NTRK2*. The *BDNF* markers rs962369 and rs11030102 were significantly associated with suicide ideation, as was the rs1439050 marker in the BDNF receptor gene *NTRK2*. They also found haplotypes containing Val66 to be associated with an increase in suicidal ideation. In male patients taking nortriptyline, the authors found *ADRA2A* rs11195419 A-allele carriers to have increased suicidal ideation at a 12 week follow-up compared to GG genotype carriers. This finding highlights the importance of genetic findings in the context of medication treatment. Brent et al. (2010) also looked at the changes in suicidality in treatment-resistant depressed adolescents after 12 weeks of being on another antidepressant medication alone or in combination with cognitive behavioral therapy. They found *FKBP5* to be associated with suicide events (worsening or emergence of suicidal behavior during the study treatment period). Laje et al. (2007) reported findings from screening

of SNPs within 68 candidate genes; they found markers in the glutamate receptor genes glutamate receptor, ionotropic, kainite 2 (*GRIK2*) and glutamate receptor, ionotropic, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate 3 (*GRIA3*) to be associated with suicide ideation emerging during selective serotonin reuptake inhibitor (SSRI) treatment in patients from the STAR*D clinical trial, while the genes *BDNF* or *NTRK2* were not associated. In the same sample, Perlis et al. (2007) found the cAMP response element–binding protein (*CREB1*), which acts upstream of *BDNF*, to be associated in males only. Laje et al. (2009) followed up with the first genome-wide association study (GWAS) in the same sample using the Illumina Human-1 BeadChip that samples 109,365 SNPs. They reported the proteoglycan-like sulfated glycoprotein papilin gene *PAPLN* and the interleukin receptor gene *IL28RA* to be genome-wide significant (Laje et al. 2009). An important limitation of the GWAS approach is the extensive correction required for massive multiple testing. In the statistical effort to reduce false positive findings, important true positives may be missed.

11.4.2.2. Epigenetic Mechanism

We have noted earlier in this chapter that there is a strong genetic component in suicidal behavior. It is possible that part of this strong genetic component is determined by DNA modification, that is, epigenetics (Petronis 2010). The epigenetic factors may include modifications of histone proteins and cytosine residues at CpG dinucleotides within promoter regions of genes. While epigenetic signatures are heritable, they can be modified by the environment, as demonstrated in rodent models of maternal nursing behavior (Weaver et al. 2004) and physical exercise (Collins et al. 2009). In the maternal behavior model, maternal licking and grooming of the pups was shown to alter the epigenetic profile at the glucocorticoid receptor (*NR3C1*) gene promoter, as well as change the binding of a specific transcription factor (EGR1) to the *NR3C1* promoter, alter hippocampal NR3C1 expression, and alter HPA stress response in the pup. Physical exercise has also been shown to alter histone modification patterns in the dentate gyrus (Collins et al. 2009). These epigenetic modifications in turn change promoter activity via differential binding to transcription factors and silencers. In a human postmortem study, McGowan et al. (2009) extended these findings to humans, wherein suicide victims who had experienced child abuse had increased cytosine methylation at the binding site for EGR1 compared to suicide victims without history of abuse. The authors went on to demonstrate in cell culture experiments that the observed specific methylation interfered with EGR1 binding, leading to decreased *NR3C1* promoter activity (McGowan et al. 2009). In view of these mechanisms, the gene–environment interactions noted earlier could be partly mediated by an epigenetic mechanism (Tsankova et al. 2007). Other postmortem brain studies have shown hypermethylation in CpG islands of promoters of other genes, including *rRNA* (McGowan et al. 2008), *GABRA1* (Poulter et al. 2008), *NTRK2* (Ernst et al. 2009), spermine oxidase (*SMOX*; Fiori and Turecki 2010), and *BDNF* (Keller et al. 2010). Given that hypermethylation leads to decreased promoter activity, the observations could explain the decreased expression of these gene products reported in suicide victims. Thus, epigenetic investigation of other suicide candidate genes may clarify some of the inconsistencies in genetic findings of suicidal behavior. Further investigations including differential allele expression should also be carried out (De Luca et al. 2011).

11.4.3. Better Characterization of Suicidal Behavior

As previously mentioned, suicidal behaviors range from suicidal ideation through attempts of varying degrees of intentionality and lethality to suicide completion. Even though family studies have pointed to overlapping genetic basis among these three behaviors, their differences may explain in part the inconsistencies in the results reported in genetic studies.

11.4.3.1. Consideration of the Psychiatric Disorder Context

Another possible explanation for the mixed candidate gene findings could be that different research groups used different case–control matching strategies. Many studies matched suicide victims with healthy control subjects. These studies would not be able to distinguish possible associations between the genetic variants and psychiatric disorders from associations between these same genetic variants and suicide. Preexisting psychiatric disorders likely play a significant role (Arsenault-Lapierre et al. 2004). For instance, over 90% of a random sample of suicide victims have at least one Axis I psychiatric diagnosis upon psychological autopsy (Henriksson et al. 1993; Cavanagh et al. 2003). Over half of the suicide victims suffered from a depressive disorder though the prevalence is higher in females compared to males. Alcohol dependence, on the other hand, was observed more often in male victims (39%) than in females (18%). Eighty-eight percent of these victims had two or more diagnoses. Ernst et al. (2004) studied the 10% of suicide completers with no Axis I diagnoses (n = 16) detected in their psychological autopsy sample and compared them with living controls. They concluded that most of the individuals who committed suicide and appeared

psychiatrically normal after a psychological autopsy may have had an underlying psychiatric process that the psychological autopsy method, as commonly carried out, failed to detect.

A possible way to overcome this methodological problem would be to match suicide attempters with suicide nonattempters who have the same underlying psychiatric disorders, but the comparability of these groups is based on the assumption that the genetic mechanism of suicide attempts is the same for all psychiatric disorders. Both borderline personality disorder and major depressive disorder have high rates of suicide, but suicide attempters with borderline personality disorder display significantly more impulsive aggression than attempters with major depression alone. The former group also made their first suicide attempts at significantly younger ages than the latter group of patients (Soloff et al. 2000). Although not without its challenges, patients with suicide attempts and borderline personality disorder can be matched with borderline personality disordered patients without suicide attempts. One challenge in this regard is the fact that recurrent suicidal behavior is regarded as a common diagnostic feature of borderline personality disorder; thus, patients without suicide attempts are less common and it is therefore more difficult to obtain a large sample size.

11.4.3.2. Intermediate Phenotypes

Gene expression profiling will be increasingly used to look for new candidate genes for suicide. Klempan et al. (2009) recently published replicated findings of reduced *SAT1* gene expression across 12 postmortem cortical regions of depressed suicide victims compared to nonpsychiatric controls from the Quebec Suicide Brain Bank. Sequeira et al. (2009) reported findings from the first gene expression microarray analysis on samples from the same brain bank. Down-regulation of the metabotropic glutamate receptor (GRM3) was found in the prefrontal and parietal cortices of suicide victims with or without depression compared to controls. They also found altered expression of multiple subunits of the $GABA_A$ receptor in suicide victims with depression compared to non-suicidal controls. $GABA_A$ receptor expression was also altered in depressed suicide victims compared to suicide victims without history of depression. These findings suggest that the altered expression of $GABA_A$ subunit genes may be specific for major depression and not directly related to suicide (Sequeira et al. 2009). If these results are replicated in independent samples, expression changes may serve as a candidate intermediate phenotype that may disentangle the confounds between suicide and depression.

van Heeringen et al. (2003) found reduced 5HT2A receptor binding in the frontal cortical region of a sample of suicide attempters compared to normal controls. Also, impulsivity was correlated to 5HTT binding in suicide attempters, but not in controls (Lindstrom et al. 2004). A single-photon emission computed tomography (SPECT) split-dose activation study undertaken after a verbal fluency test found decreased prefrontal cortical activation in recent depressed suicide attempters compared to healthy controls (Audenaert et al. 2002). *BDNF* Val66Met was recently associated with 5HTT binding in multiple brain regions, with the ValVal genotype associated with higher 5HTT availability than the Met-containing genotypes in both male suicide attempters and healthy controls (Henningsson et al. 2009). It appears that genetic studies of brain imaging data, as well as postmortem studies (e.g., Hercher et al. 2009, 2010) with respect to suicidal behavior, should take into account potential confounders, including underlying psychiatric diagnoses and medication.

The mechanism of suicidal attempt and completion may be mediated by personality traits (e.g., Brezo et al. 2006, 2008a). In particular, family studies have pointed to impulsive aggression or Cluster B personality disorder to be an intermediate phenotype of suicide (Brent et al. 1996; Johnson et al. 1998; Kim et al. 2005; Zouk et al. 2006; Diaconu and Turecki 2009; McGirr et al. 2009). The more suicidal behaviors aggregate within families, the higher the level of aggressive behavior observed in both the probands and their offspring (Brent et al. 2003; Melhem et al. 2007). Twin studies have demonstrated the genetic heritability of aggressive trait to be ~45% (Rushton et al. 1986; Coccaro et al. 1997). Impulsivity has been associated with a promoter polymorphism in *HTR1A* (Benko et al. 2010) and *HTR2A* (Nomura et al. 2006). *HTR2A* (Giegling et al. 2006; Serretti et al. 2007a) and *MAOA* (Manuck et al. 2000) have also been associated with anger and aggression. Whether or not previous associations reported between suicide and *HTR1B* (Zouk et al. 2007), *HTR2A* (Preuss et al. 2001; Giegling et al. 2006), and *MAOA* (Manuck et al. 2000; Courtet et al. 2005) were due to an underlying association between these genes and aggressive behavior remains to be further scrutinized.

Several personality traits, namely, neuroticism, hopelessness, and extroversion as measured using standardized instruments including the NEO-PI-R, have been found to be associated with suicide ideation, attempt, and completion (Brezo et al. 2006; Heisel et al. 2006; Stankovic et al. 2006). Within the domain of neuroticism, the depression facet

was associated while self-consciousness was inversely related to suicidal ideation (Chioqueta and Stiles 2005). Using available follow-up data for up to 7 years from the Collaborative Longitudinal Personality Disorders study, Yen et al. (2009) found negative affect to be a significant predictor of suicide attempt, even after accounting for gender, childhood sex abuse, major depressive disorder, and SUD. Genetic studies of these suicide-related personality traits may clarify some of the mixed findings in suicide.

Suicidal behavior has also been suggested to be partly associated with impaired problem solving (Sakinofsky et al. 1990) and learning and decision making. As such, Jollant et al. (2005) compared performance on the Iowa Gambling Task (Bechara et al. 1999) between suicide attempters and nonattempters, and found attempters to perform significantly worse than nonattempters, irrespective of psychiatric disorder or violence of the attempts. Subsequently, Jollant et al. (2007) investigated polymorphisms in the serotonergic system (*TPH2*, *5HTT*, *TPH1*, and *MAOA*) in the Iowa Gambling Taskin suicide attempters. While overall performance on the task was not significantly different among the genotype groups of each polymorphism, the suicide risk genotype carriers improved significantly less than the other genotype carriers over the course of the task (Jollant et al. 2007). The results suggest that these genetic risk variants influence the rigidity in the decision-making process and the inability to learn from negative outcomes from earlier decisions in suicide attempters. It is important to note that performance on the Iowa Gambling Task was correlated to emotional lability and anger expression but not impulsivity (Jollant et al. 2005). Interestingly, the AA genotype of the A218C marker in *TPH1* has been associated with reduced anger control in suicide attempters (Baud et al. 2009). The recently published modified Stroop test may offer more accurate predictive information for suicidal behavior (Malloy-Diniz et al. 2009; Cha et al. 2010); however, the long-term predictive value of this test remains to be evaluated.

11.5. CONCLUDING REMARKS

Family, twin, and adoption studies have established a genetic basis of suicidal behavior. However, suicide candidate gene studies have been plagued by inconsistent findings. To move forward, a consensus needs to be reached for the definition of different types of suicidal behaviors. Researchers are increasingly using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to better categorize suicidal behaviors. This instrument requires the suicidal act to be self-directed with intent to die (Posner et al. 2007). Intermediate phenotypes, including impulsive aggression, major depression, borderline personality disorder, cognitive inflexibility, and stress sensitivity, should be used to clarify the various aspects of suicidal behavior (Mann et al. 2009). Study design should control for sex (e.g., in analysis of *COMT*) and underlying psychiatric disorders. Genes should be studied more comprehensively by analyzing coding and promoter polymorphisms as well as tag markers across each gene to assess their role in suicidal behavior and related phenotypes. The traditional candidate gene approach remains very important since understanding the biology starts with one gene at a time (Neale and Sham 2004).

With the rapid development of genome-wide technology, GWAS are turning out some novel genes as in the study by Laje et al. (2009). Analysis of genetic findings should include genes that are functionally related, using software such as FORGE (Pedroso et al. in press), GMDR, and IPA. Key environmental contributors need to be considered as part of the experimental design. These would include distal childhood trauma (sexual abuse, adverse life events), more proximal acute stress, as well as support systems. The effect of environmental stressors may be mediated through epigenetic regulation of gene expression (with microarrays analyzed using weighted correlation network analysis (WGCNA); Zhang and Horvath 2005) including methylation and hydroxymethylation of CpG sites in gene promoter regions (Irizarry et al. 2009). Thus, epigenetic examination of risk gene promoters will provide complementary data that may account for part of the variance in gene expression levels and suicide susceptibility that cannot be explained by polymorphisms alone.

Overall, suicide is a complex phenotype with multiple contributing genetic and environmental factors. Multidisciplinary examination into suicidal behavior will enable us to elucidate the pathophysiological mechanism underlying suicide. Understanding this mechanism may lead to better treatments and prevention in those at risk.

REFERENCES

1. Agerbo E, Nordentoft M, Mortensen P.B. Familial, psychiatric, and socioeconomic risk factors for suicide in young people: Nested case–control study. Br Med J. 2002;325(7355):74. [PMC free article: PMC117126] [PubMed: 12114236]

2. Albanese V, Biguet N.F, Kiefer H, Bayard E, Mallet J, Meloni R. Quantitative effects on gene silencing by allelic variation at a tetranucleotide microsatellite. Hum Mol Genet. 2001;10(17):1785–1792. [PubMed: 11532988]
3. Ali F.R, Vasiliou S.A, Haddley K, Paredes U.M, Roberts J.C, Miyajima F. et al. Combinatorial interaction between two human serotonin transporter gene variable number tandem repeats and their regulation by CTCF. J Neurochem. 2010;112(1):296–306. [PMC free article: PMC2848977] [PubMed: 19860858]
4. Arango V, Ernsberger P, Sved A.F, Mann J.J. Quantitative autoradiography of alpha 1- and alpha 2-adrenergic receptors in the cerebral cortex of controls and suicide victims. Brain Res. 1993;630(1–2):271–282. [PubMed: 8118693]
5. Arango V, Huang Y.Y, Underwood M.D, Mann J.J. Genetics of the serotonergic system in suicidal behavior. J Psychiatr Res. 2003;37(5):375–386. [PubMed: 12849930]
6. Arango V, Underwood M.D, Gubbi A.V, Mann J.J. Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. Brain Res. 1995;688(1–2):121–133. [PubMed: 8542298]
7. Arinami T, Gao M, Hamaguchi H, Toru M. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Hum Mol Genet. 1997;6(4):577–582. [PubMed: 9097961]
8. Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: A meta-analysis. BMC Psychiatry. 2004;4:37. [PMC free article: PMC534107] [PubMed: 15527502]
9. Asberg M. Neurotransmitters and suicidal behavior. The evidence from cerebrospinal fluid studies. Ann N Y Acad Sci. 1997;836:158–181. [PubMed: 9616798]
10. Audenaert K, Goethals I, Van Laere K, Lahorte P, Brans B, Versijpt J. et al. SPECT neuropsychological activation procedure with the Verbal Fluency Test in attempted suicide patients. Nucl Med Commun. 2002;23(9):907–916. [PubMed: 12195096]
11. Austin M.C, Whitehead R.E, Edgar C.L, Janosky J.E, Lewis D.A. Localized decrease in serotonin transporter-immunoreactive axons in the prefrontal cortex of depressed subjects committing suicide. Neuroscience. 2002;114(3):807–815. [PubMed: 12220580]
12. Baca-Garcia E, Vaquero C, Diaz-Sastre C, Jimenez-Trevino L, Saiz-Ruiz J, Fernandez-Piqueras J. et al. Lack of association between polymorphic variations in the alpha 3 subunit GABA receptor gene (*GABRA3*) and suicide attempts. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28(2):409–412. [PubMed: 14751442]
13. Bach-Mizrachi H, Underwood M.D, Tin A, Ellis S.P, Mann J.J, Arango V. Elevated expression of tryptophan hydroxylase-2 mRNA at the neuronal level in the dorsal and median raphe nuclei of depressed suicides. Mol Psychiatry. 2008;13(5):507–513. 465. [PMC free article: PMC2361383] [PubMed: 18180753]
14. Baud P, Courtet P, Perroud N, Jollant F, Buresi C, Malafosse A. Catechol-*O*-methyltransferase polymorphism (COMT) in suicide attempters: A possible gender effect on anger traits. Am J Med Genet B Neuropsychiatr Genet. 2007;144B(8):1042–1047. [PubMed: 17510945]
15. Baud P, Perroud N, Courtet P, Jaussent I, Relecom C, Jollant F. et al. Modulation of anger control in suicide attempters by TPH-1. Genes Brain Behav. 2009;8(1):97–100. [PubMed: 19220488]
16. Bechara A, Damasio H, Damasio A. R, Lee G. P. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci. 1999;19(13):5473–5481. [PubMed: 10377356]
17. Beitchman J. H, Baldassarra L, Mik H, De Luca V, King N, Bender D. et al. Serotonin transporter polymorphisms and persistent, pervasive childhood aggression. Am J Psychiatry. 2006;163(6):1103–1105. [PubMed: 16741214]
18. Bellivier F, Laplanche J. L, Leboyer M, Feingold J, Bottos C, Allilaire J.F. et al. Serotonin transporter gene and manic depressive illness: An association study. Biol Psychiatry. 1997;41(6):750–752. [PubMed: 9067001]
19. Benko A, Lazary J, Molnar E, Gonda X, Tothfalusi L, Pap D. et al. Significant association between the C(–1019)G functional polymorphism of the HTR1A gene and impulsivity. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(2):592–599. [PubMed: 19725031]
20. Binder E. B, Salyakina D, Lichtner P, Wochnik G. M, Ising M, Putz B. et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet. 2004;36(12):1319–1325. [PubMed: 15565110]
21. Bondy B, Buettner A, Zill P. Genetics of suicide. Mol Psychiatry. 2006;11(4):336–351. [PubMed: 16462816]
22. Boularand S, Darmon M. C, Ravassard P, Mallet J. Characterization of the human tryptophan hydroxylase gene promoter. Transcriptional regulation by cAMP requires a new motif distinct from the cAMP-responsive element. J Biol Chem. 1995;270(8):3757–3764. [PubMed: 7876116]

23. Bouwknecht J. A, Hijzen T. H, van der Gugten J, Maes R. A, Hen R, Olivier B. Absence of 5-HT(1B) receptors is associated with impaired impulse control in male 5-HT(1B) knockout mice. Biol Psychiatry. 2001;49(7):557–568. [PubMed: 11297712]
24. Brent D. A, Bridge J, Johnson B. A, Connolly J. Suicidal behavior runs in families. A controlled family study of adolescent suicide victims. Arch Gen Psychiatry. 1996;53(12):1145–1152. [PubMed: 8956681]
25. Brent D. A, Melhem N. Familial transmission of suicidal behavior. Psychiatr Clin North Am. 2008;31(2):157–177. [PMC free article: PMC2440417] [PubMed: 18439442]
26. Brent D, Melhem N, Turecki G. Pharmacogenomics of suicidal events. Pharmacogenomics. 2010;11(6):793–807. [PMC free article: PMC2921883] [PubMed: 20504254]
27. Brent D. A, Oquendo M, Birmaher B, Greenhill L, Kolko D, Stanley B. et al. Familial pathways to early-onset suicide attempt: Risk for suicidal behavior in offspring of mood-disordered suicide attempters. Arch Gen Psychiatry. 2002;59(9):801–807. [PubMed: 12215079]
28. Brent D. A, Oquendo M, Birmaher B, Greenhill L, Kolko D, Stanley B. et al. Peripubertal suicide attempts in offspring of suicide attempters with siblings concordant for suicidal behavior. Am J Psychiatry. 2003;160(8):1486–1493. [PubMed: 12900312]
29. Brezo J, Bureau A, Merette C, Jomphe V, Barker E. D, Vitaro F. et al. Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: A 22-year longitudinal gene-environment study. Mol Psychiatry. 2010;15(8):831–843. [PubMed: 19381154]
30. Brezo J, Paris J, Hebert M, Vitaro F, Tremblay R, Turecki G. Broad and narrow personality traits as markers of one-time and repeated suicide attempts: A population-based study. BMC Psychiatry. 2008a;8:15. [PMC free article: PMC2294113] [PubMed: 18325111]
31. Brezo J, Paris J, Turecki G. Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: A systematic review. Acta Psychiatr Scand. 2006;113(3):180–206. [PubMed: 16466403]
32. Brezo J, Paris J, Vitaro F, Hebert M, Tremblay R. E, Turecki G. Predicting suicide attempts in young adults with histories of childhood abuse. Br J Psychiatry. 2008b;193(2):134–139. [PubMed: 18669998]
33. Bridge J. A, Brent D, Johnson B. A, Connolly J. Familial aggregation of psychiatric disorders in a community sample of adolescents. J Am Acad Child Adolesc Psychiatry. 1997;36(5):628–636. [PubMed: 9136497]
34. Brodsky B. S, Malone K. M, Ellis S. P, Dulit R. A, Mann J.J. Characteristics of borderline personality disorder associated with suicidal behavior. Am J Psychiatry. 1997;154(12):1715–1719. [PubMed: 9396951]
35. Brunner D, Hen R. Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. Ann N Y Acad Sci. 1997;836:81–105. [PubMed: 9616795]
36. Calati R, Porcelli S, Giegling I, Hartmann A. M, Moller H.J, De Ronchi D. et al. Catechol-*o*-methyltransferase gene modulation on suicidal behavior and personality traits: Review, meta-analysis and association study. J Psychiatr Res. 2011;45(3):309–321. [PubMed: 20667552]
37. Callreus T, Agerskov Andersen U, Hallas J, Andersen M. Cardiovascular drugs and the risk of suicide: A nested case-control study. Eur J Clin Pharmacol. 2007;63(6):591–596. [PubMed: 17468865]
38. Carballo J.J, Harkavy-Friedman J, Burke A. K, Sher L, Baca-Garcia E, Sullivan G. M. et al. Family history of suicidal behavior and early traumatic experiences: Additive effect on suicidality and course of bipolar illness? J Affect Disord. 2008;109(1–2):57–63. [PMC free article: PMC3491751] [PubMed: 18221790]
39. Caspi A, McClay J, Moffitt T. E, Mill J, Martin J, Craig I. W. et al. Role of genotype in the cycle of violence in maltreated children. Science. 2002;297(5582):851–854. [PubMed: 12161658]
40. Caspi A, Sugden K, Moffitt T. E, Taylor A, Craig I. W, Harrington H. et al. Influence of life stress on depression: Moderation by a polymorphism in the *5-HTT* gene. Science. 2003;301(5631):386–389. [PubMed: 12869766]
41. Cavanagh J. T, Carson A. J, Sharpe M, Lawrie S. M. Psychological autopsy studies of suicide: A systematic review. Psychol Med. 2003;33(3):395–405. [PubMed: 12701661]
42. Cha C. B, Najmi S, Park J. M, Finn C. T, Nock M. K. Attentional bias toward suicide-related stimuli predicts suicidal behavior. J Abnorm Psychol. 2010;119(3):616–622. [PMC free article: PMC2994414] [PubMed: 20677851]
43. Charlesworth J. C, Curran J. E, Johnson M. P, Goring H. H, Dyer T. D, Diego V. P. et al. Transcriptomic epidemiology of smoking: The effect of smoking on gene expression in lymphocytes. BMC Med Genomics. 2010;3:29. [PMC free article: PMC2911391] [PubMed: 20633249]
44. Cheetham S. C, Crompton M. R, Katona C. L, Horton R. W. Brain 5-HT2 receptor binding sites in depressed suicide victims. Brain Res. 1988;443(1–2):272–280. [PubMed: 3359270]

45. Chen C. K, Lin S. K, Huang M. C, Su L. W, Hsiao C. C, Chiang Y. L. et al. Analysis of association of clinical correlates and 5-HTTLPR polymorphism with suicidal behavior among Chinese methamphetamine abusers. Psychiatry Clin Neurosci. 2007;61(5):479–486. [PubMed: 17875025]
46. Cheng A. T., Chen T. H, Chen C. C, Jenkins R. Psychosocial and psychiatric risk factors for suicide. Case–control psychological autopsy study. Br J Psychiatry. 2000;177:360–365. [PubMed: 11116779]
47. Cheng R, Juo S. H, Loth J. E, Nee J, Iossifov I, Blumenthal R. et al. Genome-wide linkage scan in a large bipolar disorder sample from the National Institute of Mental Health genetics initiative suggests putative loci for bipolar disorder, psychosis, suicide, and panic disorder. Mol Psychiatry. 2006;11(3):252–260. [PubMed: 16402137]
48. Chioqueta A. P, Stiles T. C. Personality traits and the development of depression, hopelessness, and suicide ideation. Pers Individual Diff. 2005;38(6):1283–1291.
49. Cho H, Guo G, Iritani B. J, Hallfors D. D. Genetic contribution to suicidal behaviors and associated risk factors among adolescents in the U.S. Prev Sci. 2006;7(3):303–311. [PubMed: 16775759]
50. Cho H.J, Meira-Lima I, Cordeiro Q, Michelon L, Sham P, Vallada H. et al. Population-based and family-based studies on the serotonin transporter gene polymorphisms and bipolar disorder: A systematic review and meta-analysis. Mol Psychiatry. 2005;10(8):771–781. [PubMed: 15824745]
51. Cicchetti D, Rogosch F. A, Sturge-Apple M, Toth S. L. Interaction of child maltreatment and 5-HTT polymorphisms: Suicidal ideation among children from low-SES backgrounds. J Pediatr Psychol. 2010;35(5):536–546. [PMC free article: PMC2910938] [PubMed: 19779024]
52. Coccaro E. F, Bergeman C. S, Kavoussi R. J, Seroczynski A. D. Heritability of aggression and irritability: A twin study of the Buss–Durkee aggression scales in adult male subjects. Biol Psychiatry. 1997;41(3):273–284. [PubMed: 9024950]
53. Collier D. A, Stober G, Li T, Heils A, Catalano M, Di Bella D. et al. A novel functional polymorphism within the promoter of the serotonin transporter gene: Possible role in susceptibility to affective disorders. Mol Psychiatry. 1996;1(6):453–460. [PubMed: 9154246]
54. Collins A, Hill L. E, Chandramohan Y, Whitcomb D, Droste S. K, Reul J. M. Exercise improves cognitive responses to psychological stress through enhancement of epigenetic mechanisms and gene expression in the dentate gyrus. PLoS One. 2009;4(1):e4330. [PMC free article: PMC2628725] [PubMed: 19180197]
55. Courtet P, Jollant F, Buresi C, Castelnau D, Mouthon D, Malafosse A. The monoamine oxidase A gene may influence the means used in suicide attempts. Psychiatr Genet. 2005;15(3):189–193. [PubMed: 16094253]
56. Coventry W. L, James M. R, Eaves L. J, Gordon S. D, Gillespie N. A, Ryan L. et al. Do 5HTTLPR and stress interact in risk for depression and suicidality? Item response analyses of a large sample. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(3):757–765. [PMC free article: PMC3319106] [PubMed: 19911410]
57. Cui H, Nishiguchi N, Ivleva E, Yanagi M, Fukutake M, Nushida H. et al. Association of *RGS2* gene polymorphisms with suicide and increased RGS2 immunoreactivity in the postmortem brain of suicide victims. Neuropsychopharmacology. 2008;33(7):1537–1544. [PubMed: 17728697]
58. Cui H, Supriyanto I, Asano M, Ueno Y, Nagasaki Y, Nishiguchi N. et al. A common polymorphism in the 3′-UTR of the *NOS1* gene was associated with completed suicides in Japanese male population. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(6):992–996. [PubMed: 20470850]
59. Dalton E. J. Cate, Carter T. D, Mundo E, Parikh S. V, Kennedy J. L. Suicide risk in bipolar patients: The role of co-morbid substance use disorders. Bipolar Disord. 2003;5(1):58–61. [PubMed: 12656940]
60. De Luca V, Likhodi O, Van Tol H. H, Kennedy J. L, Wong A. H. Gene expression of tryptophan hydroxylase 2 in post-mortem brain of suicide subjects. Int J Neuropsychopharmacol. 2006a;9(1):21–25. [PubMed: 15941494]
61. De Luca V, Mueller D. J, Tharmalingam S, King N, Kennedy J. L. Analysis of the novel *TPH2* gene in bipolar disorder and suicidality. Mol Psychiatry. 2004a;9(10):896–897. [PubMed: 15197398]
62. De Luca V, Muglia P, Masellis M, Jane Dalton E, Wong G. W, Kennedy J. L. Polymorphisms in glutamate decarboxylase genes: Analysis in schizophrenia. Psychiatr Genet. 2004b;14(1):39–42. [PubMed: 15091314]
63. De Luca V, Souza R. P, Zai C. C, Panariello F, Javaid N, Strauss J. et al. Parent of origin effect and differential allelic expression of BDNF Val66Met in suicidal behaviour. World J Biol Psychiatry. 2011;12(1):42–47. [PubMed: 20726824]
64. De Luca V, Strauss J, Kennedy J. L. Power based association analysis (PBAT) of serotonergic and noradrenergic polymorphisms in bipolar patients with suicidal behaviour. Prog Neuropsychopharmacol Biol Psychiatry. 2008a;32(1):197–203. [PubMed: 17869399]
65. De Luca V, Tharmalingam S, Kennedy J. L. Association study between the corticotropin-releasing hormone receptor 2 gene and suicidality in bipolar disorder. Eur Psychiatry. 2007;22(5):282–287. [PubMed: 17532191]

66. De Luca V, Tharmalingam S, Muller D. J, Wong G, de Bartolomeis A, Kennedy J. L. Gene–gene interaction between *MAOA* and *COMT* in suicidal behavior: Analysis in schizophrenia. Brain Res. 2006b;1097(1):26–30. [PubMed: 16725119]
67. De Luca V, Tharmalingam S, Sicard T, Kennedy J. L. Gene–gene interaction between *MAOA* and *COMT* in suicidal behavior. Neurosci Lett. 2005a;383(1–2):151–154. [PubMed: 15936529]
68. De Luca V, Tharmaligam S, Strauss J, Kennedy J. L. 5-HT2C receptor and MAO-A interaction analysis: No association with suicidal behaviour in bipolar patients. Eur Arch Psychiatry Clin Neurosci. 2008b;258(7):428–433. [PubMed: 18504633]
69. De Luca V, Tharmalingam S, Zai C, Potapova N, Strauss J, Vincent J. et al. Association of HPA axis genes with suicidal behaviour in schizophrenia. J Psychopharmacol. 2010;24(5):677–682. [PubMed: 18838498]
70. De Luca V, Voineskos D, Wong G. W, Shinkai T, Rothe C, Strauss J. et al. Promoter polymorphism of second tryptophan hydroxylase isoform (TPH2) in schizophrenia and suicidality. Psychiatry Res. 2005b;134(2):195–198. [PubMed: 15840421]
71. De Luca V, Zai G, Tharmalingam S, de Bartolomeis A, Wong G, Kennedy J. L. Association study between the novel functional polymorphism of the serotonin transporter gene and suicidal behaviour in schizophrenia. Eur Neuropsychopharmacol. 2006c;16(4):268–271. [PubMed: 16274962]
72. De Paermentier F, Mauger J. M, Lowther S, Crompton M. R, Katona C. L, Horton R. W. Brain alpha-adrenoceptors in depressed suicides. Brain Res. 1997;757(1):60–68. [PubMed: 9200499]
73. Diaconu G, Turecki G. Family history of suicidal behavior predicts impulsive–aggressive behavior levels in psychiatric outpatients. J Affect Disord. 2009;113(1–2):172–178. [PubMed: 18504057]
74. Duan J, Sanders A. R, Molen J. E, Martinolich L, Mowry B. J, Levinson D. F. et al. Polymorphisms in the 5′-untranslated region of the human serotonin receptor 1B (*HTR1B*) gene affect gene expression. Mol Psychiatry. 2003a;8(11):901–910. [PubMed: 14593427]
75. Duan J, Wainwright M. S, Comeron J. M, Saitou N, Sanders A. R, Gelernter J. et al. Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. Hum Mol Genet. 2003b;12(3):205–216. [PubMed: 12554675]
76. Dumais A, Lesage A. D, Alda M, Rouleau G, Dumont M, Chawky N. et al. Risk factors for suicide completion in major depression: A case–control study of impulsive and aggressive behaviors in men. Am J Psychiatry. 2005;162(11):2116–2124. [PubMed: 16263852]
77. Dwivedi Y. Brain-derived neurotrophic factor and suicide pathogenesis. Ann Med. 2010;42(2):87–96. [PMC free article: PMC3708652] [PubMed: 20166812]
78. Dwivedi Y, Rizavi H. S, Conley R. R, Roberts R. C, Tamminga C. A, Pandey G. N. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry. 2003;60(8):804–815. [PubMed: 12912764]
79. Egeland J. A, Sussex J. N. Suicide and family loading for affective disorders. JAMA. 1985;254(7):915–918. [PubMed: 4021024]
80. Ernst C, Deleva V, Deng X, Sequeira A, Pomarenski A, Klempan T. et al. Alternative splicing, methylation state, and expression profile of tropomyosin-related kinase B in the frontal cortex of suicide completers. Arch Gen Psychiatry. 2009;66(1):22–32. [PubMed: 19124685]
81. Ernst C, Lalovic A, Lesage A, Seguin M, Tousignant M, Turecki G. Suicide and no axis I psychopathology. BMC Psychiatry. 2004;4:7. [PMC free article: PMC400739] [PubMed: 15053834]
82. Fan J. B, Sklar P. Meta-analysis reveals association between serotonin transporter gene STin2 VNTR polymorphism and schizophrenia. Mol Psychiatry. 2005; 10(10):928–938. 891. [PubMed: 15940296]
83. Fanous A. H, Chen X, Wang X, Amdur R, O'Neill F. A, Walsh D. et al. Genetic variation in the serotonin 2A receptor and suicidal ideation in a sample of 270 Irish high-density schizophrenia families. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(3):411–417. [PMC free article: PMC2844884] [PubMed: 18712714]
84. Feinn R, Nellissery M, Kranzler H. R. Meta-analysis of the association of a functional serotonin transporter promoter polymorphism with alcohol dependence. Am J Med Genet B Neuropsychiatr Genet. 2005;133B(1):79–84. [PubMed: 15635638]
85. Finckh U, Rommelspacher H, Kuhn S, Dufeu P, Otto G, Heinz A. et al. Influence of the dopamine D2 receptor (DRD2) genotype on neuroadaptive effects of alcohol and the clinical outcome of alcoholism. Pharmacogenetics. 1997;7(4):271–281. [PubMed: 9295055]
86. Fiori L. M, Turecki G. Genetic and epigenetic influences on expression of spermine synthase and spermine oxidase in suicide completers. Int J Neuropsychopharmacol. 2010;13(6):725–736. [PubMed: 20059804]

87. Fu Q, Heath A. C, Bucholz K. K, Nelson E. C, Glowinski A. L, Goldberg J. et al. A twin study of genetic and environmental influences on suicidality in men. Psychol Med. 2002;32(1):11–24. [PubMed: 11883722]
88. Fudalej S, Fudalej M, Kostrzewa G, Kuzniar P, Franaszczyk M, Wojnar M. et al. Angiotensin-converting enzyme polymorphism and completed suicide: An association in Caucasians and evidence for a link with a method of self-injury. Neuropsychobiology. 2009;59(3):151–158. [PubMed: 19439995]
89. Fukutake M, Hishimoto A, Nishiguchi N, Nushida H, Ueno Y, Shirakawa O. et al. Association of alpha2A-adrenergic receptor gene polymorphism with susceptibility to suicide in Japanese females. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(6):1428–1433. [PubMed: 18547701]
90. Garcia-Sevilla J. A, Escriba P. V, Ozaita A, La Harpe R, Walzer C, Eytan A. et al. Up-regulation of immunolabeled alpha2A-adrenoceptors, Gi coupling proteins, and regulatory receptor kinases in the prefrontal cortex of depressed suicides. J Neurochem. 1999;72(1):282–291. [PubMed: 9886080]
91. Garfinkel B. D, Froese A, Hood J. Suicide attempts in children and adolescents. Am J Psychiatry. 1982;139(10):1257–1261. [PubMed: 7124975]
92. Gerra G, Garofano L, Pellegrini C, Bosari S, Zaimovic A, Moi G. et al. Allelic association of a dopamine transporter gene polymorphism with antisocial behaviour in heroin-dependent patients. Addict Biol. 2005;10(3):275–281. [PubMed: 16109590]
93. Gibb B. E, McGeary J. E, Beevers C. G, Miller I. W. Serotonin transporter (5-HTTLPR) genotype, childhood abuse, and suicide attempts in adult psychiatric inpatients. Suicide Life Threat Behav. 2006;36(6):687–693. [PubMed: 17250473]
94. Gibbons R. D, Brown C. H, Hur K, Marcus S. M, Bhaumik D. K, Mann J.J. Relationship between antidepressants and suicide attempts: An analysis of the Veterans Health Administration data sets. Am J Psychiatry. 2007;164(7):1044–1049. [PubMed: 17606656]
95. Giegling I, Hartmann A. M, Moller H.J, Rujescu D. Anger- and aggression-related traits are associated with polymorphisms in the *5-HT-2A* gene. J Affect Disord. 2006;96(1–2):75–81. [PubMed: 16814396]
96. Giegling I, Moreno-De-Luca D, Rujescu D, Schneider B, Hartmann A. M, Schnabel A. et al. Dopa decarboxylase and tyrosine hydroxylase gene variants in suicidal behavior. Am J Med Genet B Neuropsychiatr Genet. 2008;147(3):308–315. [PubMed: 17948905]
97. Glowinski A. L, Bucholz K. K, Nelson E. C, Fu Q, Madden P. A, Reich W. et al. Suicide attempts in an adolescent female twin sample. J Am Acad Child Adolesc Psychiatry. 2001;40(11):1300–1307. [PMC free article: PMC1474069] [PubMed: 11699804]
98. Goodwin R. D, Beautrais A. L, Fergusson D. M. Familial transmission of suicidal ideation and suicide attempts: Evidence from a general population sample. Psychiatry Res. 2004;126(2):159–165. [PubMed: 15123395]
99. Gould M. S, Fisher P, Parides M, Flory M, Shaffer D. Psychosocial risk factors of child and adolescent completed suicide. Arch Gen Psychiatry. 1996;53(12):1155–1162. [PubMed: 8956682]
100. Gross-Isseroff R, Weizman A, Fieldust S. J, Israeli M, Biegon A. Unaltered alpha(2)-noradrenergic/imidazoline receptors in suicide victims: A postmortem brain autoradiographic analysis. Eur Neuropsychopharmacol. 2000;10(4):265–271. [PubMed: 10871708]
101. Gurevich I, Tamir H, Arango V, Dwork A. J, Mann J.J, Schmauss C. Altered editing of serotonin 2C receptor pre-mRNA in the prefrontal cortex of depressed suicide victims. Neuron. 2002;34(3):349–356. [PubMed: 11988167]
102. Han L, Nielsen D. A, Rosenthal N. E, Jefferson K, Kaye W, Murphy D. et al. No coding variant of the tryptophan hydroxylase gene detected in seasonal affective disorder, obsessive–compulsive disorder, anorexia nervosa, and alcoholism. Biol Psychiatry. 1999;45(5):615–619. [PubMed: 10088048]
103. Harvald B, Hauge M. Hereditary factors elucidated by twin studies. In: Neel J. V, Shaw M. W, Schull W. J, editors. Genetics and the Epidemiology of Chronic Disease. Washington, DC: U.S. Department of Health, Education, and Welfare; (1965) pp. 61–76.
104. Hawton K, van Heeringen K. Suicide. Lancet. 2009;373(9672):1372–1381. [PubMed: 19376453]
105. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D. et al. Allelic variation of human serotonin transporter gene expression. J Neurochem. 1996;66(6):2621–2624. [PubMed: 8632190]
106. Heisel M. J, Duberstein P. R, Conner K. R, Franus N, Beckman A, Conwell Y. Personality and reports of suicide ideation among depressed adults 50 years of age or older. J Affect Disord. 2006;90(2–3):175–180. [PubMed: 16380165]
107. Henningsson S, Borg J, Lundberg J, Bah J, Lindstrom M, Ryding E. et al. Genetic variation in brain-derived neurotrophic factor is associated with serotonin transporter but not serotonin-1A receptor availability in men.

Biol Psychiatry. 2009;66(5):477–485. [PubMed: 19500776]
108. Henriksson M. M, Aro H. M, Marttunen M. J, Heikkinen M. E, Isometsa E. T, Kuoppasalmi K. I. et al. Mental disorders and comorbidity in suicide. Am J Psychiatry. 1993;150(6):935–940. [PubMed: 8494072]
109. Hercher C, Canetti L, Turecki G, Mechawar N. Anterior cingulate pyramidal neurons display altered dendritic branching in depressed suicides. J Psychiatr Res. 2010;44(5):286–293. [PubMed: 19765721]
110. Hercher C, Parent M, Flores C, Canetti L, Turecki G, Mechawar N. Alcohol dependence-related increase of glial cell density in the anterior cingulate cortex of suicide completers. J Psychiatr Neurosci. 2009;34(4):281–288. [PMC free article: PMC2702445] [PubMed: 19568479]
111. Hesselbrock V, Dick D, Hesselbrock M, Foroud T, Schuckit M, Edenberg H. et al. The search for genetic risk factors associated with suicidal behavior. Alcohol Clin Exp Res. 2004;28 5 Suppl:70S–76S. [PubMed: 15166638]
112. Hishimoto A, Shirakawa O, Nishiguchi N, Hashimoto T, Yanagi M, Nushida H. et al. Association between a functional polymorphism in the renin–angiotensin system and completed suicide. J Neural Transm. 2006;113(12):1915–1920. [PubMed: 16736244]
113. Ho L. W, Furlong R. A, Rubinsztein J. S, Walsh C, Paykel E. S, Rubinsztein D. C. Genetic associations with clinical characteristics in bipolar affective disorder and recurrent unipolar depressive disorder. Am J Med Genet. 2000;96(1):36–42. [PubMed: 10686549]
114. Hong C. J, Huo S. J, Yen F. C, Tung C. L, Pan G. M, Tsai S. J. Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. Neuropsychobiology. 2003;48(4):186–189. [PubMed: 14673216]
115. Hong C. J, Pan G. M, Tsai S. J. Association study of onset age, attempted suicide, aggressive behavior, and schizophrenia with a serotonin 1B receptor (A-161T) genetic polymorphism. Neuropsychobiology. 2004;49(1):1–4. [PubMed: 14730192]
116. Hong C. J, Wang Y. C, Tsai S. J. Association study of angiotensin I-converting enzyme polymorphism and symptomatology and antidepressant response in major depressive disorders. J Neural Transm. 2002;109(9):1209–1214. [PubMed: 12203048]
117. Hotamisligil G. S, Breakefield X. O. Human monoamine oxidase A gene determines levels of enzyme activity. Am J Hum Genet. 1991;49(2):383–392. [PMC free article: PMC1683299] [PubMed: 1678250]
118. Hu X. Z, Lipsky R. H, Zhu G, Akhtar L. A, Taubman J, Greenberg B. D. et al. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive–compulsive disorder. Am J Hum Genet. 2006;78(5):815–826. [PMC free article: PMC1474042] [PubMed: 16642437]
119. Huang Y. Y, Battistuzzi C, Oquendo M. A, Harkavy-Friedman J, Greenhill L, Zalsma G. et al. Human 5-HT1A receptor C(-1019)G polymorphism and psychopathology. Int J Neuropsychopharmacol. 2004;7(4):441–451. [PubMed: 15469667]
120. Huang Y. Y, Grailhe R, Arango V, Hen R, Mann J.J. Relationship of psychopathology to the human serotonin1B genotype and receptor binding kinetics in postmortem brain tissue. Neuropsychopharmacology. 1999;21(2):238–246. [PubMed: 10432472]
121. Huang T. L, Lee C. T. Associations between brain-derived neurotrophic facto *G196A* gene polymorphism and clinical phenotypes in schizophrenia patients. Chang Gung Med J. 2007; 30(5):408–413. [PubMed: 18062171]
122. Hwang J. P, Yang C. H, Hong C. J, Lirng J. F, Yang Y. M, Tsai S. J. Association of APOE genetic polymorphism with cognitive function and suicide history in geriatric depression. Dement Geriatr Cogn Disord. 2006;22(4):334–338. [PubMed: 16954688]
123. Iga J, Ueno S, Yamauchi K, Numata S, Tayoshi-Shibuya S, Kinouchi S. et al. The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with psychotic feature and suicidal behavior in Japanese major depressive patients. Am J Med Genet B Neuropsychiatr Genet. 2007;144B(8):1003–1006. [PubMed: 17510948]
124. Inada T, Koga M, Ishiguro H, Horiuchi Y, Syu A, Yoshio T. et al. Pathway-based association analysis of genome-wide screening data suggest that genes associated with the gamma-aminobutyric acid receptor signaling pathway are involved in neuroleptic-induced, treatment-resistant tardive dyskinesia. Pharmacogenet Genomics. 2008;18(4):317–323. [PubMed: 18334916]
125. Irizarry R. A, Ladd-Acosta C, Wen B, Wu Z, Montano C, Onyango P. et al. The human colon cancer methylome shows similar hypo- and hypermethylation at conserved tissue-specific CpG island shores. Nat Genet. 2009;41(2):178–186. [PMC free article: PMC2729128] [PubMed: 19151715]
126. Johann M, Putzhammer A, Eichhammer P, Wodarz N. 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 B

Neuropsychiatr Genet. 2005;132B(1):46–49. [PubMed: 15389757]
127. Johnson B. A, Brent D. A, Bridge J, Connolly J. The familial aggregation of adolescent suicide attempts. Acta Psychiatr Scand. 1998;97(1):18–24. [PubMed: 9504698]
128. Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R. et al. Impaired decision making in suicide attempters. Am J Psychiatry. 2005;162(2):304–310. [PubMed: 15677595]
129. Jollant F, Guillaume S, Jaussent I, Castelnau D, Malafosse A, Courtet P. Impaired decision-making in suicide attempters may increase the risk of problems in affective relationships. J Affect Disord. 2007;99(1–3): 59–62. [PubMed: 17010445]
130. Jones J. S, Stanley B, Mann J.J, Frances A. J, Guido J. R, Traskman-Bendz L. et al. CSF 5-HIAA and HVA concentrations in elderly depressed patients who attempted suicide. Am J Psychiatry. 1990;147(9):1225–1227. [PubMed: 1696794]
131. Jonsson E. G, Norton N, Gustavsson J. P, Oreland L, Owen M. J, Sedvall G. C. A promoter polymorphism in the monoamine oxidase A gene and its relationships to monoamine metabolite concentrations in CSF of healthy volunteers. J Psychiatr Res. 2000;34(3):239–244. [PubMed: 10867119]
132. Kallman F. J. Heredity in Health and Mental Disease: Principles of Psychiatric Genetics in the Light of Comparative Twin Studies. New York: Norton; 1953.
133. Kaprio J, Romanov K, Lonnqvist J, Koskenvuo M. Suicide in twins: The Finnish twin cohort study. Psychiatr Genet. 1995;5:S102.
134. Karege F, Vaudan G, Schwald M, Perroud N, La Harpe R. Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. Brain Res Mol Brain Res. 2005;136(1–2):29–37. [PubMed: 15893584]
135. Ke L, Qi Z. Y, Ping Y, Ren C. Y. Effect of SNP at position 40237 in exon 7 of the *TPH2* gene on susceptibility to suicide. Brain Res. 2006;1122(1):24–26. [PubMed: 17011525]
136. Keller S, Sarchiapone M, Zarrilli F, Videtic A, Ferraro A, Carli V. et al. Increased BDNF promoter methylation in the Wernicke area of suicide subjects. Arch Gen Psychiatry. 2010;67(3):258–267. [PubMed: 20194826]
137. Khan A, Khan S, Kolts R, Brown W. A. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: Analysis of FDA reports. Am J Psychiatry. 2003;160(4):790–792. [PubMed: 12668373]
138. Kia-Keating B. M, Glatt S. J, Tsuang M. T. Meta-analyses suggest association between COMT, but not HTR1B, alleles, and suicidal behavior. Am J Med Genet B Neuropsychiatr Genet. 2007;144B(8):1048–1053. [PubMed: 17525973]
139. Kim B, Kim C. Y, Hong J. P, Kim S. Y, Lee C, Joo Y. H. Brain-derived neurotrophic factor Val/Met polymorphism and bipolar disorder. Association of the Met allele with suicidal behavior of bipolar patients. Neuropsychobiology. 2008;58(2):97–103. [PubMed: 18843195]
140. Kim Y. K, Lee H. P, Won S. D, Park E. Y, Lee H. Y, Lee B. H. et al. Low plasma BDNF is associated with suicidal behavior in major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(1):78–85. [PubMed: 16904252]
141. Kim C. D, Seguin M, Therrien N, Riopel G, Chawky N, Lesage A. D. et al. Familial aggregation of suicidal behavior: A family study of male suicide completers from the general population. Am J Psychiatry. 2005;162(5):1017–1019. [PubMed: 15863812]
142. Kiyohara C, Yoshimasu K. Association between major depressive disorder and a functional polymorphism of the 5-hydroxytryptamine (serotonin) transporter gene: A meta-analysis. Psychiatr Genet. 2010;20(2):49–58. [PubMed: 20016401]
143. Klempan T. A, Rujescu D, Merette C, Himmelman C, Sequeira A, Canetti L. et al. Profiling brain expression of the spermidine/spermine *N*1-acetyltransferase 1 (*SAT1*) gene in suicide. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(7):934–943. [PubMed: 19152344]
144. Kohli M. A, Salyakina D, Pfennig A, Lucae S, Horstmann S, Menke A. et al. Association of genetic variants in the neurotrophic receptor-encoding gene NTRK2 and a lifetime history of suicide attempts in depressed patients. Arch Gen Psychiatry. 2010;67(4):348–359. [PMC free article: PMC3696349] [PubMed: 20124106]
145. Koller G, Bondy B, Preuss U. W, Bottlender M, Soyka M. No association between a polymorphism in the promoter region of the *MAOA* gene with antisocial personality traits in alcoholics. Alcohol Alcohol. 2003;38(1):31–34. [PubMed: 12554604]
146. Kunugi H, Hashimoto R, Yoshida M, Tatsumi M, Kamijima K. A missense polymorphism (S205L) of the low-affinity neurotrophin receptor *p75NTR* gene is associated with depressive disorder and attempted suicide. Am J Med Genet B Neuropsychiatr Genet. 2004;129B(1):44–46. [PubMed: 15274039]

147. Labonte B, Turecki G. The epigenetics of suicide: Explaining the biological effects of early life environmental adversity. Arch Suicide Res. 2010;14(4):291–310. [PubMed: 21082447]
148. Lachman H. M, Nolan K. A, Mohr P, Saito T, Volavka J. Association between catechol *O*-methyltransferase genotype and violence in schizophrenia and schizoaffective disorder. Am J Psychiatry. 1998;155(6):835–837. [PubMed: 9619160]
149. Laje G, Allen A. S, Akula N, Manji H, John Rush A, McMahon F. J. Genome-wide association study of suicidal ideation emerging during citalopram treatment of depressed outpatients. Pharmacogenet Genomics. 2009;19(9):666–674. [PMC free article: PMC2819190] [PubMed: 19724244]
150. Laje G, Paddock S, Manji H, Rush A. J, Wilson A. F, Charney D. et al. Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. Am J Psychiatry. 2007;164(10):1530–1538. [PubMed: 17898344]
151. Lee R, Petty F, Coccaro E. F. Cerebrospinal fluid GABA concentration: Relationship with impulsivity and history of suicidal behavior, but not aggression, in human subjects. J Psychiatr Res. 2009;43(4):353–359. [PubMed: 18490031]
152. Lemonde S, Turecki G, Bakish D, Du L, Hrdina P. D, Bown C. D. et al. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci. 2003;23(25):8788–8799. [PubMed: 14507979]
153. Lester D. The concentration of neurotransmitter metabolites in the cerebrospinal fluid of suicidal individuals: A meta-analysis. Pharmacopsychiatry. 1995;28(2):45–50. [PubMed: 7542785]
154. Li D, Duan Y, He L. Association study of serotonin 2A receptor (*5-HT2A*) gene with schizophrenia and suicidal behavior using systematic meta-analysis. Biochem Biophys Res Commun. 2006;340(3):1006–1015. [PubMed: 16405867]
155. Li D, He L. Meta-analysis supports association between serotonin transporter (5-HTT) and suicidal behavior. Mol Psychiatry. 2007;12(1):47–54. [PubMed: 16969368]
156. Lieb R, Bronisch T, Hofler M, Schreier A, Wittchen H. U. Maternal suicidality and risk of suicidality in offspring: Findings from a community study. Am J Psychiatry. 2005;162(9):1665–1671. [PubMed: 16135626]
157. Lindstrom M. B, Ryding E, Bosson P, Ahnlide J. A, Rosen I, Traskman-Bendz L. Impulsivity related to brain serotonin transporter binding capacity in suicide attempters. Eur Neuropsychopharmacol. 2004;14(4):295–300. [PubMed: 15163439]
158. Linkowski P, de Maertelaer V, Mendlewicz J. Suicidal behaviour in major depressive illness. Acta Psychiatr Scand. 1985;72(3):233–238. [PubMed: 4072720]
159. Liou Y. J, Tsai S. J, Hong C. J, Wang Y. C, Lai I. C. Association analysis of a functional catechol-*o*-methyltransferase gene polymorphism in schizophrenic patients in Taiwan. Neuropsychobiology. 2001;43(1):11–14. [PubMed: 11150892]
160. Little K. Y, McLauglin D. P, Ranc J, Gilmore J, Lopez J. F, Watson S. J. et al. Serotonin transporter binding sites and mRNA levels in depressed persons committing suicide. Biol Psychiatry. 1997;41(12):1156–1164. [PubMed: 9171906]
161. Lopez de Lara V. A, Detera-Wadleigh S, Cardona I, Kassem L, McMahon F. J. Nested association between genetic variation in tryptophan hydroxylase II, bipolar affective disorder, and suicide attempts. Biol Psychiatry. 2007;61(2):181–186. [PubMed: 16806105]
162. Lou X. Y, Chen G. B, Yan L, Ma J. Z, Zhu J, Elston R. C. et al. A generalized combinatorial approach for detecting gene-by-gene and gene-by-environment interactions with application to nicotine dependence. Am J Hum Genet. 2007;80(6):1125–1137. [PMC free article: PMC1867100] [PubMed: 17503330]
163. Lowther S, De Paermentier F, Crompton M. R, Katona C. L, Horton R. W. Brain 5-HT2 receptors in suicide victims: Violence of death, depression and effects of antidepressant treatment. Brain Res. 1994;642(1–2):281–289. [PubMed: 8032889]
164. MacKenzie A, Quinn J. A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. Proc Natl Acad Sci U. S. A. 1999;96(26):15251–15255. [PMC free article: PMC24806] [PubMed: 10611371]
165. Magno L. A, Miranda D. M, Neves F. S, Pimenta G. J, Mello M. P, De Marco L. A. et al. Association between AKT1 but not AKTIP genetic variants and increased risk for suicidal behavior in bipolar patients. Genes Brain Behav. 2010;9(4):411–418. [PubMed: 20132317]
166. Malloy-Diniz L. F, Neves F. S, Abrantes S. S, Fuentes D, Correa H. Suicide behavior and neuropsychological assessment of type I bipolar patients. J Affect Disord. 2009;112(1–3):231–236. [PubMed: 18485487]

167. Malone K. M, Haas G. L, Sweeney J. A, Mann J.J. Major depression and the risk of attempted suicide. J Affect Disord. 1995;34(3):173–185. [PubMed: 7560545]
168. Mann J.J, Arango V. A, Avenevoli S, Brent D. A, Champagne F. A, Clayton P. et al. Candidate endophenotypes for genetic studies of suicidal behavior. Biol Psychiatry. 2009;65(7):556–563. [PMC free article: PMC3271953] [PubMed: 19201395]
169. Mann J.J, Bortinger J, Oquendo M. A, Currier D, Li S, Brent D. A. Family history of suicidal behavior and mood disorders in probands with mood disorders. Am J Psychiatry. 2005;162(9):1672–1679. [PubMed: 16135627]
170. Mann J.J, Currier D, Murphy L, Huang Y. Y, Galfalvy H, Brent D. et al. No association between a TPH2 promoter polymorphism and mood disorders or monoamine turnover. J Affect Disord. 2008;106(1–2):117–121. [PMC free article: PMC2756663] [PubMed: 17604842]
171. Mann J.J, Henteleff R. A, Lagattuta T. F, Perper J. A, Li S, Arango V. Lower 3H-paroxetine binding in cerebral cortex of suicide victims is partly due to fewer high affinity, non-transporter sites. J Neural Transm. 1996;103(11):1337–1350. [PubMed: 9013420]
172. Manuck S. B, Flory J. D, Ferrell R. E, Mann J.J, Muldoon M. F. A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. Psychiatry Res. 2000;95(1):9–23. [PubMed: 10904119]
173. McGirr A, Alda M, Seguin M, Cabot S, Lesage A, Turecki G. Familial aggregation of suicide explained by cluster B traits: A three-group family study of suicide controlling for major depressive disorder. Am J Psychiatry. 2009;166(10):1124–1134. [PubMed: 19755577]
174. McGirr A, Diaconu G, Berlim M. T, Pruessner J. C, Sable R, Cabot S. et al. Dysregulation of the sympathetic nervous system, hypothalamic–pituitary–adrenal axis and executive function in individuals at risk for suicide. J Psychiatry Neurosci. 2010;35(6):399–408. [PMC free article: PMC2964370] [PubMed: 20731961]
175. McGirr A, Renaud J, Bureau A, Seguin M, Lesage A, Turecki G. Impulsive–aggressive behaviours and completed suicide across the life cycle: A predisposition for younger age of suicide. Psychol Med. 2008;38(3):407–417. [PubMed: 17803833]
176. McGowan P. O, Sasaki A, D'Alessio A. C, Dymov S, Labonte B, Szyf M. et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009;12(3):342–348. [PMC free article: PMC2944040] [PubMed: 19234457]
177. McGowan P. O, Sasaki A, Huang T. C, Unterberger A, Suderman M, Ernst C. et al. Promoter-wide hypermethylation of the ribosomal RNA gene promoter in the suicide brain. PLoS One. 2008;3(5):e2085. [PMC free article: PMC2330072] [PubMed: 18461137]
178. McGregor S, Strauss J, Bulgin N, De Luca V, George C. J, Kovacs M. et al. *p75(NTR)* gene and suicide attempts in young adults with a history of childhood-onset mood disorder. Am J Med Genet B Neuropsychiatr Genet. 2007;144B(5):696–700. [PubMed: 17357149]
179. McGuffin P, Perroud N, Uher R, Butler A, Aitchison K. J, Craig I. et al. The genetics of affective disorder and suicide. Eur Psychiatry. 2010;25(5):275–277. [PubMed: 20462744]
180. Melhem N. M, Brent D. A, Ziegler M, Iyengar S, Kolko D, Oquendo M. et al. Familial pathways to early-onset suicidal behavior: Familial and individual antecedents of suicidal behavior. Am J Psychiatry. 2007;164(9):1364–1370. [PMC free article: PMC3804909] [PubMed: 17728421]
181. Merali Z, Du L, Hrdina P, Palkovits M, Faludi G, Poulter M. O. et al. Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABA(A) receptor subunits in frontal cortical brain region. J Neurosci. 2004;24(6):1478–1485. [PubMed: 14960621]
182. Mitterauer B. A contribution to the discussion of the role of the genetic factor in suicide, based on five studies in an epidemiologically defined area (Province of Salzburg, Austria) Compr Psychiatry. 1990;31(6):557–565. [PubMed: 2265540]
183. Mouri K, Hishimoto A, Fukutake M, Shiroiwa K, Asano M, Nagasaki Y. et al. TPH2 is not a susceptibility gene for suicide in Japanese population. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(8):1546–1550. [PubMed: 19748542]
184. Mundo E, Richter M. A, Sam F, Macciardi F, Kennedy J. L. Is the 5-HT(1Dbeta) receptor gene implicated in the pathogenesis of obsessive–compulsive disorder? Am J Psychiatry. 2000;157(7):1160–1161. [PubMed: 10873927]
185. Mundo E, Richter M. A, Zai G, Sam F, McBride J, Macciardi F. et al. 5HT1Dbeta receptor gene implicated in the pathogenesis of obsessive–compulsive disorder: Further evidence from a family-based association study. Mol Psychiatry. 2002;7(7):805–809. [PubMed: 12192628]

186. Mundo E, Rouillon F, Figuera M. L, Stigler M. Fluvoxamine in obsessive–compulsive disorder: Similar efficacy but superior tolerability in comparison with clomipramine. Hum Psychopharmacol. 2001;16(6):461–468. [PubMed: 12404554]
187. Must A, Tasa G, Lang A, Vasar E, Koks S, Maron E. et al. Variation in tryptophan hydroxylase-2 gene is not associated to male completed suicide in Estonian population. Neurosci Lett. 2009;453(2):112–114. [PubMed: 19356604]
188. Nackley A. G, Shabalina S. A, Tchivileva I. E, Satterfield K, Korchynskyi O, Makaro S. S. et al. Human catechol-*O*-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. Science. 2006;314(5807):1930–1933. [PubMed: 17185601]
189. Nakamura M, Ueno S, Sano A, Tanabe H. The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. Mol Psychiatry. 2000;5(1):32–38. [PubMed: 10673766]
190. Neale B. M, Sham P. C. The future of association studies: Gene-based analysis and replication. Am J Hum Genet. 2004;75(3):353–362. [PMC free article: PMC1182015] [PubMed: 15272419]
191. Neves F. S, Malloy-Diniz L. F, Romano-Silva M. A, Aguiar G. C, de Matos L. O, Correa H. Is the serotonin transporter polymorphism (5-HTTLPR) a potential marker for suicidal behavior in bipolar disorder patients? J Affect Disord. 2010; 125(1–3):98–102. [PubMed: 20096463]
192. Neves F. S, Silveira G, Romano-Silva M. A, Malloy-Diniz L, Ferreira A. A, De Marco L. et al. Is the 5-HTTLPR polymorphism associated with bipolar disorder or with suicidal behavior of bipolar disorder patients. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(1):114–116. [PubMed: 17579356]
193. Nielsen D. A, Goldman D, Virkkunen M, Tokola R, Rawlings R, Linnoila M. Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. Arch Gen Psychiatry. 1994;51(1):34–38. [PubMed: 7506517]
194. Nishiguchi N, Shirakawa O, Ono H, Nishimura A, Nushida H, Ueno Y. et al. Lack of an association between 5-HT1A receptor gene structural polymorphisms and suicide victims. Am J Med Genet. 2002;114(4):423–425. [PubMed: 11992564]
195. Noble E. P. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. Am J Med Genet B Neuropsychiatr Genet. 2003;116B(1):103–125. [PubMed: 12497624]
196. Nolan K. A, Volavka J, Czobor P, Cseh A, Lachman H, Saito T. et al. Suicidal behavior in patients with schizophrenia is related to COMT polymorphism. Psychiatr Genet. 2000;10(3):117–124. [PubMed: 11204347]
197. Nomura M, Kusumi I, Kaneko M, Masui T, Daiguji M, Ueno T. et al. Involvement of a polymorphism in the 5-HT2A receptor gene in impulsive behavior. Psychopharmacology (Berl) 2006;187(1):30–35. [PubMed: 16767413]
198. Ohara K, Nagai M, Suzuki Y. Low activity allele of catechol-*o*-methyltransferase gene and Japanese unipolar depression. Neuroreport. 1998a;9(7):1305–1308. [PubMed: 9631418]
199. Ohara K, Nagai M, Tani K, Tsukamoto T, Suzuki Y. Polymorphism in the promoter region of the alpha 2A adrenergic receptor gene and mood disorders. Neuroreport. 1998b;9(7):1291–1294. [PubMed: 9631415]
200. Ohtani M, Shindo S, Yoshioka N. Polymorphisms of the tryptophan hydroxylase gene and serotonin 1A receptor gene in suicide victims among Japanese. Tohoku J Exp Med. 2004;202(2):123–133. [PubMed: 14998306]
201. Ono H, Shirakawa O, Kitamura N, Hashimoto T, Nishiguchi N, Nishimura A. et al. Tryptophan hydroxylase immunoreactivity is altered by the genetic variation in postmortem brain samples of both suicide victims and controls. Mol Psychiatry. 2002;7(10):1127–1132. [PubMed: 12476329]
202. Ono H, Shirakawa O, Nushida H, Ueno Y, Maeda K. Association between catechol-*O*-methyltransferase functional polymorphism and male suicide completers. Neuropsychopharmacology. 2004;29(7):1374–1377. [PubMed: 15127078]
203. Oswald L. M, Wong D. F, Zhou Y, Kumar A, Brasic J, Alexander M. et al. Impulsivity and chronic stress are associated with amphetamine-induced striatal dopamine release. Neuroimage. 2007;36(1):153–166. [PubMed: 17433881]
204. Pandey G. N. Altered serotonin function in suicide. Evidence from platelet and neuroendocrine studies. Ann N Y Acad Sci. 1997;836:182–200. [PubMed: 9616799]
205. Papiol S, Arias B, Gasto C, Gutierrez B, Catalan R, Fananas L. Genetic variability at HPA axis in major depression and clinical response to antidepressant treatment. J Affect Disord. 2007;104(1–3):83–90. [PubMed: 17467808]
206. Pedroso I, Lourdusamy A, Rietschel M, Nöthen M. M, Cichon S, McGuffin P, Al-Chalabi A, Barnes M. R, Breen G. Common genetic variants and gene-expression changes associated with bipolar disorder are over-

represented in brain signaling pathway genes. Biol Psychiatry (in press) [PubMed: 22502986]
207. Perlis R. H, Huang J, Purcell S, Fava M, Rush A. J, Sullivan P. F. et al. Genome-wide association study of suicide attempts in mood disorder patients. Am J Psychiatry. 2010;167(12):1499–1507. [PMC free article: PMC3795390] [PubMed: 21041247]
208. Perlis R. H, Purcell S, Fava M, Fagerness J, Rush A. J, Trivedi M. H. et al. Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. Arch Gen Psychiatry. 2007;64(6):689–697. [PubMed: 17548750]
209. Perroud N, Aitchison K. J, Uher R, Smith R, Huezo-Diaz P, Marusic A. et al. Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. Neuropsychopharmacology. 2009;34(12):2517–2528. [PubMed: 19641488]
210. Perroud N, Neidhart E, Petit B, Vessaz M, Laforge T, Relecom C. et al. Simultaneous analysis of serotonin transporter, tryptophan hydroxylase 1 and 2 gene expression in the ventral prefrontal cortex of suicide victims. Am J Med Genet B Neuropsychiatr Genet. 2010a;153B(4):909–918. [PubMed: 20052688]
211. Perroud N, Uher R, Ng M. Y, Guipponi M, Hauser J, Henigsberg N. et al. Genome-wide association study of increasing suicidal ideation during antidepressant treatment in the GENDEP project. Pharmacogenomics J. 2010b;12(1):68–77. [PubMed: 20877300]
212. Persson M. L, Geijer T, Wasserman D, Rockah R, Frisch A, Michaelovsky E. et al. Lack of association between suicide attempt and a polymorphism at the dopamine receptor D4 locus. Psychiatr Genet. 1999a;9(2):97–100. [PubMed: 10412189]
213. Persson M. L, Runeson B. S, Wasserman D. Diagnoses, psychosocial stressors and adaptive functioning in attempted suicide. Ann Clin Psychiatry. 1999b;11(3):119–128. [PubMed: 10482121]
214. Persson M. L, Wasserman D, Geijer T, Jonsson E. G, Terenius L. Tyrosine hydroxylase allelic distribution in suicide attempters. Psychiatry Res. 1997;72(2):73–80. [PubMed: 9335198]
215. Petronis A. Epigenetics as a unifying principle in the aetiology of complex traits and diseases. Nature. 2010;465(7299):721–727. [PubMed: 20535201]
216. Pfeffer C. R, Normandin L, Kakuma T. Suicidal children grow up: Suicidal behavior and psychiatric disorders among relatives. J Am Acad Child Adolesc Psychiatry. 1994;33(8):1087–1097. [PubMed: 7982859]
217. Placidi G. P, Oquendo M. A, Malone K. M, Huang Y. Y, Ellis S. P, Mann J.J. Aggressivity, suicide attempts, and depression: Relationship to cerebrospinal fluid monoamine metabolite levels. Biol Psychiatry. 2001;50(10):783–791. [PubMed: 11720697]
218. Polesskaya O. O, Sokolov B. P. Differential expression of the “C” and “T” alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. J Neurosci Res. 2002;67(6):812–822. [PubMed: 11891796]
219. Pompili M, Serafini G, Innamorati M, Moller-Leimkuhler A. M, Giupponi G, Girardi P. et al. The hypothalamic–pituitary–adrenal axis and serotonin abnormalities: A selective overview for the implications of suicide prevention. Eur Arch Psychiatry Clin Neurosci. 2010;260(8):583–600. [PubMed: 20174927]
220. Porcelli S, Drago A, Fabbri C, Gibiino S, Calati R, Serretti A. Pharmacogenetics of antidepressant response. J Psychiatry Neurosci. 2011;36(2):87–113. [PMC free article: PMC3044192] [PubMed: 21172166]
221. Posner K, Oquendo M. A, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of suicidal events in the FDA’s pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035–1043. [PMC free article: PMC3804920] [PubMed: 17606655]
222. Poulter M. O, Du L, Weaver I. C, Palkovits M, Faludi G, Merali Z. et al. $GABA_A$ receptor promoter hypermethylation in suicide brain: Implications for the involvement of epigenetic processes. Biol Psychiatry. 2008;64(8):645–652. [PubMed: 18639864]
223. Poulter M. O, Du L, Zhurov V, Palkovits M, Faludi G, Merali Z. et al. Altered organization of GABA(A) receptor mRNA expression in the depressed suicide brain. Front Mol Neurosci. 2010;3(3) [PMC free article: PMC2854532] [PubMed: 20407580]
224. Powell J, Geddes J, Deeks J, Goldacre M, Hawton K. Suicide in psychiatric hospital in-patients. Risk factors and their predictive power. Br J Psychiatry. 2000;176:266–272. [PubMed: 10755075]
225. Preuss U. W, Koller G, Soyka M, Bondy B. Association between suicide attempts and 5-HTTLPR-S-allele in alcohol-dependent and control subjects: Further evidence from a German alcohol-dependent inpatient sample. Biol Psychiatry. 2001;50(8):636–639. [PubMed: 11690601]

226. Qin P, Agerbo E, Mortensen P. B. Suicide risk in relation to family history of completed suicide and psychiatric disorders: A nested case–control study based on longitudinal registers. Lancet. 2002;360(9340):1126–1130. [PubMed: 12387960]
227. Qin P, Agerbo E, Mortensen P. B. Suicide risk in relation to socioeconomic, demographic, psychiatric, and familial factors: A national register-based study of all suicides in Denmark, 1981–1997. Am J Psychiatry. 2003;160(4):765–772. [PubMed: 12668367]
228. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest. 1990;86(4):1343–1346. [PMC free article: PMC296868] [PubMed: 1976655]
229. Risch N, Herrell R, Lehner T, Liang K. Y, Eaves L, Hoh J. et al. Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression: A meta-analysis. JAMA. 2009;301(23):2462–2471. [PMC free article: PMC2938776] [PubMed: 19531786]
230. Rotondo A, Schuebel K, Bergen A, Aragon R, Virkkunen M, Linnoila M. et al. Identification of four variants in the tryptophan hydroxylase promoter and association to behavior. Mol Psychiatry. 1999;4(4):360–368. [PubMed: 10483053]
231. Roy A. Family history of suicide. Arch Gen Psychiatry. 1983;40(9):971–974. [PubMed: 6615160]
232. Roy A. Characteristics of cocaine-dependent patients who attempt suicide. Am J Psychiatry. 2001;158(8):1215–1219. [PubMed: 11481153]
233. Roy A. Family history of suicide and neuroticism: A preliminary study. Psychiatry Res. 2002;110(1):87–90. [PubMed: 12007597]
234. Roy A. Distal risk factors for suicidal behavior in alcoholics: Replications and new findings. J Affect Disord. 2003;77(3):267–271. [PubMed: 14612227]
235. Roy A, Agren H, Pickar D, Linnoila M, Doran A. R, Cutler N. R. et al. Reduced CSF concentrations of homovanillic acid and homovanillic acid to 5-hydroxyindoleacetic acid ratios in depressed patients: Relationship to suicidal behavior and dexamethasone nonsuppression. Am J Psychiatry. 1986;143(12):1539–1545. [PubMed: 2431628]
236. Roy A, Hu X. Z, Janal M. N, Goldman D. Interaction between childhood trauma and serotonin transporter gene variation in suicide. Neuropsychopharmacology. 2007;32(9):2046–2052. [PubMed: 17356577]
237. Roy A, Sarchiopone M, Carli V. Gene–environment interaction and suicidal behavior. J Psychiatr Pract. 2009;15(4):282–288. [PubMed: 19625883]
238. Roy A, Segal N. L. Suicidal behavior in twins: A replication. J Affect Disord. 2001;66(1):71–74. [PubMed: 11532534]
239. Roy A, Segal N. L, Centerwall B. S, Robinette C. D. Suicide in twins. Arch Gen Psychiatry. 1991;48(1):29–32. [PubMed: 1984759]
240. Roy A, Segal N. L. and, Sarchiapone M. Attempted suicide among living co-twins of twin suicide victims. Am J Psychiatry. 1995;152(7):1075–1076. [PubMed: 7793447]
241. Rujescu D, Giegling I, Gietl A, Hartmann A. M, Moller H. J. A functional single nucleotide polymorphism (V158M) in the *COMT* gene is associated with aggressive personality traits. Biol Psychiatry. 2003;54(1):34–39. [PubMed: 12842306]
242. Rujescu D, Giegling I, Mandelli L, Schneider B, Hartmann A. M, Schnabel A. et al. *NOS-I and -III* gene variants are differentially associated with facets of suicidal behavior and aggression-related traits. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(1):42–48. [PubMed: 17579350]
243. Runeson B, Asberg M. Family history of suicide among suicide victims. Am J Psychiatry. 2003;160(8):1525–1526. [PubMed: 12900320]
244. Rushton J. P, Fulker D. W, Neale M. C, Nias D. K, Eysenck H. J. Altruism and aggression: The heritability of individual differences. J Pers Soc Psychol. 1986;50(6):1192–1198. [PubMed: 3723334]
245. Russ M. J, Lachman H. M, Kashdan T, Saito T, Bajmakovic-Kacila S. Analysis of catechol-*O*-methyltransferase and 5-hydroxytryptamine transporter polymorphisms in patients at risk for suicide. Psychiatry Res. 2000;93(1):73–78. [PubMed: 10699230]
246. Sabol S. Z, Hu S, Hamer D. A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet. 1998;103(3):273–279. [PubMed: 9799080]
247. Saetre P, Lundmark P, Wang A, Hansen T, Rasmussen H. B, Djurovic S. et al. The tryptophan hydroxylase 1 (*TPH1*) gene, schizophrenia susceptibility, and suicidal behavior: A multi-centre case–control study and meta-analysis. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(2):387–396. [PubMed: 19526457]

248. Sakai K, Nakamura M, Ueno S, Sano A, Sakai N, Shirai Y. et al. The silencer activity of the novel human serotonin transporter linked polymorphic regions. Neurosci Lett. 2002;327(1):13–16. [PubMed: 12098489]
249. Sakinofsky I, Roberts R. S, Brown Y, Cumming C, James P. Problem resolution and repetition of parasuicide. A prospective study. Br J Psychiatry. 1990;156:395–399. [PubMed: 2346841]
250. Sarchiapone M, Carli V, Roy A, Iacoviello L, Cuomo C, Latella M. C. et al. Association of polymorphism (Val66Met) of brain-derived neurotrophic factor with suicide attempts in depressed patients. Neuropsychobiology. 2008;57(3):139–145. [PubMed: 18600033]
251. Saudou F, Amara D. A, Dierich A, LeMeur M, Ramboz S, Segu L. et al. Enhanced aggressive behavior in mice lacking 5-HT1B receptor. Science. 1994;265(5180):1875–1878. [PubMed: 8091214]
252. Schosser A, Butler A. W, Ising M, Perroud N, Uher R, Ng M. Y. et al. Genome wide association scan of suicidal thoughts and behaviour in major depression. PLoS One. 2011;6(7):e20690. [PMC free article: PMC3130038] [PubMed: 21750702]
253. Schulsinger F, Kety S. S, Rosenthal D, Wender P. H. A family study of suicide. In: Schou M, Stromgren S, editors. Origin, Presentation and Treatment of Affective Disorders. London U.K.: Academic Press; 1979. pp. 277–287.
254. Segal J, Schenkel L. C, Oliveira M. H, Salum G. A, Bau C. H, Manfro G. G. et al. Novel allelic variants in the human serotonin transporter gene linked polymorphism (5-HTTLPR) among depressed patients with suicide attempt. Neurosci Lett. 2009;451(1):79–82. [PubMed: 19103261]
255. Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. Am J Med Genet B Neuropsychiatr Genet. 2004;127B(1):85–89. [PubMed: 15108187]
256. Sequeira A, Gwadry F. G, Ffrench-Mullen J. M, Canetti L, Gingras Y, Casero R. A Jr. et al. Implication of SSAT by gene expression and genetic variation in suicide and major depression. Arch Gen Psychiatry. 2006;63(1):35–48. [PubMed: 16389195]
257. Sequeira A, Mamdani F, Ernst C, Vawter M. P, Bunney W. E, Lebel V. et al. Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. PLoS One. 2009;4(8):e6585. [PMC free article: PMC2719799] [PubMed: 19668376]
258. Sequeira A, Mamdani F, Lalovic A, Anguelova M, Lesage A, Seguin M. et al. Alpha 2A adrenergic receptor gene and suicide. Psychiatry Res. 2004;125(2):87–93. [PubMed: 15006432]
259. Serretti A, Calati R, Giegling I, Hartmann A. M, Moller H.J, Colombo C. et al. 5-HT2A SNPs and the Temperament and Character Inventory. Prog Neuropsychopharmacol Biol Psychiatry. 2007a;31(6):1275–1281. [PubMed: 17590256]
260. Serretti A, Mandelli L, Giegling I, Schneider B, Hartmann A. M, Schnabel A. et al. HTR2C and *HTR1A* gene variants in German and Italian suicide attempters and completers. Am J Med Genet B Neuropsychiatr Genet. 2007b;144B(3):291–299. [PubMed: 17192951]
261. Sherif F, Marcusson J, Oreland L. Brain gamma-aminobutyrate transaminase and monoamine oxidase activities in suicide victims. Eur Arch Psychiatry Clin Neurosci. 1991;241(3):139–144. [PubMed: 1790159]
262. Shindo S, Yoshioka N. Polymorphisms of the cholecystokinin gene promoter region in suicide victims in Japan. Forensic Sci Int. 2005;150(1):85–90. [PubMed: 15837012]
263. Small K. M, Forbes S. L, Brown K. M, Liggett S. B. An asn to lys polymorphism in the third intracellular loop of the human alpha 2A-adrenergic receptor imparts enhanced agonist-promoted Gi coupling. J Biol Chem. 2000;275(49):38518–38523. [PubMed: 10948191]
264. Smits K. M, Smits L. J, Schouten J. S, Stelma F. F, Nelemans P, Prins M. H. Influence of SERTPR and STin2 in the serotonin transporter gene on the effect of selective serotonin reuptake inhibitors in depression: A systematic review. Mol Psychiatry. 2004;9(5):433–441. [PubMed: 15037864]
265. Soloff P. H, Lynch K. G, Kelly T. M, Malone K. M, Mann J.J. Characteristics of suicide attempts of patients with major depressive episode and borderline personality disorder: A comparative study. Am J Psychiatry. 2000;157(4):601–608. [PubMed: 10739420]
266. Soyka M, Preuss U. W, Koller G, Zill P, Bondy B. Association of 5-HT1B receptor gene and antisocial behavior in alcoholism. J Neural Transm. 2004;111(1):101–109. [PubMed: 14714219]
267. Spalletta G, Morris D. W, Angelucci F, Rubino I. A, Spoletini I, Bria P. et al. BDNF Val66Met polymorphism is associated with aggressive behavior in schizophrenia. Eur Psychiatry. 2010;25(6):311–313. [PubMed: 20430595]
268. Sparks D. L, Hunsaker J. C, Amouyel P, Malafosse A, Bellivier F, Leboyer M. et al. Angiotensin I-converting enzyme I/D polymorphism and suicidal behaviors. Am J Med Genet B Neuropsychiatr Genet.

2009;150B(2):290–294. [PubMed: 18521860]
269. Stankovic Z, Saula-Marojevic B, Potrebic A. Personality profile of depressive patients with a history of suicide attempts. Psychiatr Danub. 2006;18(3–4):159–168. [PubMed: 17099606]
270. Statham D. J, Heath A. C, Madden P. A, Bucholz K. K, Bierut L, Dinwiddie S. H. et al. Suicidal behaviour: An epidemiological and genetic study. Psychol Med. 1998;28(4):839–855. [PubMed: 9723140]
271. Stefulj J, Buttner A, Kubat M, Zill P, Balija M, Eisenmenger W. et al. 5HT-2C receptor polymorphism in suicide victims. Association studies in German and Slavic populations. Eur Arch Psychiatry Clin Neurosci. 2004a;254(4):224–227. [PubMed: 15309390]
272. Stefulj J, Buttner A, Skavic J, Zill P, Balija M, Eisenmenger W. et al. Serotonin 1B (5HT-1B) receptor polymorphism (G861C) in suicide victims: Association studies in German and Slavic population. Am J Med Genet B Neuropsychiatr Genet. 2004b;127B(1):48–50. [PubMed: 15108179]
273. Suda A, Kawanishi C, Kishida I, Sato R, Yamada T, Nakagawa M. et al. Dopamine D2 receptor gene polymorphisms are associated with suicide attempt in the Japanese population. Neuropsychobiology. 2009;59(2):130–134. [PubMed: 19390224]
274. Sun H. F, Chang Y. T, Fann C. S, Chang C. J, Chen Y. H, Hsu Y. P. et al. Association study of novel human serotonin 5-HT(1B) polymorphisms with alcohol dependence in Taiwanese Han. Biol Psychiatry. 2002;51(11):896–901. [PubMed: 12022963]
275. Sun H. F, Fann C. S, Lane H. Y, Chang Y. T, Chang C. J, Liu Y. L. et al. A functional polymorphism in the promoter region of the tryptophan hydroxylase gene is associated with alcohol dependence in one aboriginal group in Taiwan. Alcohol Clin Exp Res. 2005;29(1):1–7. [PubMed: 15654285]
276. Teicher M. H, Glod C, Cole J. O. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry. 1990;147(2):207–210. [PubMed: 2301661]
277. Tsai S. J, Hong C. J, Yu Y. W, Chen T. J, Wang Y. C, Lin W. K. Association study of serotonin 1B receptor (A-161T) genetic polymorphism and suicidal behaviors and response to fluoxetine in major depressive disorder. Neuropsychobiology. 2004;50(3):235–238. [PubMed: 15365222]
278. Tsai S. Y, Kuo C. J, Chen C. C, Lee H. C. Risk factors for completed suicide in bipolar disorder. J Clin Psychiatry. 2002;63(6):469–476. [PubMed: 12088157]
279. Tsankova N, Renthal W, Kumar A, Nestler E. J. Epigenetic regulation in psychiatric disorders. Nat Rev Neurosci. 2007;8(5):355–367. [PubMed: 17453016]
280. Tsuang M. T. Risk of suicide in the relatives of schizophrenics, manics, depressives, and controls. J Clin Psychiatry. 1983; 44(11):396–397. 398–400. [PubMed: 6643403]
281. Tsuang M. T, Boor M, Fleming J. A. Psychiatric aspects of traffic accidents. Am J Psychiatry. 1985;142(5):538–546. [PubMed: 3985193]
282. Turecki G, Briere R, Dewar K, Antonetti T, Lesage A. D, Seguin M. et al. 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. 1999;156(9):1456–1458. [PubMed: 10484964]
283. Turecki G, Sequeira A, Gingras Y, Seguin M, Lesage A, Tousignant M. et al. Suicide and serotonin: Study of variation at seven serotonin receptor genes in suicide completers. Am J Med Genet B Neuropsychiatr Genet. 2003;118B(1):36–40. [PubMed: 12627464]
284. Uher R, Caspi A, Houts R, Sugden K, Williams B, Poulton R. et al. Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: Replications and implications for resolving inconsistent results. J Affect Disord. 2011;135(1–3):56–65. [PMC free article: PMC3752793] [PubMed: 21439648]
285. van Gaalen M. M, van Koten R, Schoffelmeer A. N, Vanderschuren L. J. Critical involvement of dopaminergic neurotransmission in impulsive decision making. Biol Psychiatry. 2006;60(1):66–73. [PubMed: 16125144]
286. van Heeringen C, Audenaert K, Van Laere K, Dumont F, Slegers G, Mertens J. et al. Prefrontal 5-HT2a receptor binding index, hopelessness and personality characteristics in attempted suicide. J Affect Disord. 2003;74(2):149–158. [PubMed: 12706516]
287. Videtic A, Peternelj T. T, Zupanc T, Balazic J, Komel R. Promoter and functional polymorphisms of HTR2C and suicide victims. Genes Brain Behav. 2009a;8(5):541–545. [PubMed: 19496825]
288. Videtic A, Pungercic G, Pajnic I. Z, Zupanc T, Balazic J, Tomori M. et al. Association study of seven polymorphisms in four serotonin receptor genes on suicide victims. Am J Med Genet B Neuropsychiatr Genet. 2006;141B(6):669–672. [PubMed: 16856120]
289. Videtic A, Zupanc T, Pregelj P, Balazic J, Tomori M, Komel R. Suicide, stress and serotonin receptor 1A promoter polymorphism -1019C>G in Slovenian suicide victims. Eur Arch Psychiatry Clin Neurosci.

2009b;259(4):234–238. [PubMed: 19224112]
290. Vincze I, Perroud N, Buresi C, Baud P, Bellivier F, Etain B. et al. Association between brain-derived neurotrophic factor gene and a severe form of bipolar disorder, but no interaction with the serotonin transporter gene. Bipolar Disord. 2008;10(5):580–587. [PubMed: 18657242]
291. Virkkunen M, De Jong J, Bartko J, Linnoila M. Psychobiological concomitants of history of suicide attempts among violent offenders and impulsive fire setters. Arch Gen Psychiatry. 1989;46(7):604–606. [PubMed: 2472123]
292. Walther D. J, Peter J. U, Bashammakh S, Hortnagl H, Voits M, Fink H. et al. Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science. 2003;299(5603):76. [PubMed: 12511643]
293. Wang S, Zhang K, Xu Y, Sun N, Shen Y, Xu Q. An association study of the serotonin transporter and receptor genes with the suicidal ideation of major depression in a Chinese Han population. Psychiatry Res. 2009;170(2–3):204–207. [PubMed: 19897250]
294. Wasserman D, Geijer T, Sokolowski M, Frisch A, Michaelovsky E, Weizman A. et al. Association of the serotonin transporter promotor polymorphism with suicide attempters with a high medical damage. Eur Neuropsychopharmacol. 2007;17(3):230–233. [PubMed: 17029913]
295. Wasserman D, Sokolowski M, Rozanov V, Wasserman J. The *CRHR1* gene: A marker for suicidality in depressed males exposed to low stress. Genes Brain Behav. 2008;7(1):14–19. [PubMed: 17376150]
296. Weaver I. C, Cervoni N, Champagne F. A, D'Alessio A. C, Sharma S, Seckl J. R. et al. Epigenetic programming by maternal behavior. Nat Neurosci. 2004;7(8):847–854. [PubMed: 15220929]
297. Weinshilboum R. M, Raymond F. A. Inheritance of low erythrocyte catechol-*o*-methyltransferase activity in man. Am J Hum Genet. 1977;29(2):125–135. [PMC free article: PMC1685255] [PubMed: 848488]
298. Wender P. H, Kety S. S, Rosenthal D, Schulsinger F, Ortmann J, Lunde I. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch Gen Psychiatry. 1986;43(10):923–929. [PubMed: 3753159]
299. Williams R. B, Marchuk D. A, Gadde K. M, Barefoot J. C, Grichnik K, Helms M. J. et al. Serotonin-related gene polymorphisms and central nervous system serotonin function. Neuropsychopharmacology. 2003;28(3):533–541. [PubMed: 12629534]
300. Willour V. L, Chen H, Toolan J, Belmonte P, Cutler D. J, Goes F. S. et al. Family-based association of FKBP5 in bipolar disorder. Mol Psychiatry. 2009;14(3):261–268. [PMC free article: PMC4317355] [PubMed: 18180755]
301. Willour V. L, Seifuddin F, Mahon P. B, Jancic D, Pirooznia M, Steele J. et al. A genome-wide association study of attempted suicide. Mol Psychiatry. 2011 advance online publication: [doi: 10.1038/mp. 2011.4] [PMC free article: PMC4021719] [PubMed: 21423239]
302. Willour V. L, Zandi P. P, Badner J. A, Steele J, Miao K, Lopez V. et al. Attempted suicide in bipolar disorder pedigrees: Evidence for linkage to 2p12. Biol Psychiatry. 2007;61(5):725–727. [PubMed: 17046723]
303. Yanagi M, Shirakawa O, Kitamura N, Okamura K, Sakurai K, Nishiguchi N. et al. Association of 14-3-3 epsilon gene haplotype with completed suicide in Japanese. J Hum Genet. 2005;50(4):210–216. [PubMed: 15838597]
304. Yen S, Shea M. T, Sanislow C. A, Skodol A. E, Grilo C. M, Edelen M. O. et al. Personality traits as prospective predictors of suicide attempts. Acta Psychiatr Scand. 2009;120(3):222–229. [PMC free article: PMC2729360] [PubMed: 19298413]
305. Yoon H. K, Kim Y. K. TPH2 -703G/T SNP may have important effect on susceptibility to suicidal behavior in major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(3):403–409. [PubMed: 19162119]
306. Zai C. C, Manchia M, De Luca V, Tiwari A. K, Chowdhury N. I, Zai G. C. et al. The brain-derived neurotrophic factor gene in suicidal behaviour: A metaanalysis. Int J Neuropsychopharmacol. 2011;30:1–6. Advance online publication. doi:10.1017/S1461145711001313.
307. Zai C. C, Tiwari A. K. De, Luca V, Muller D. J, Bulgin N, Hwang R. et al. Genetic study of BDNF, DRD3, and their interaction in tardive dyskinesia. Eur Neuropsychopharmacol. 2009;19(5):317–328. [PubMed: 19217756]
308. Zalsman G, Frisch A, Lewis R, Michaelovsky E, Hermesh H, Sher L. et al. DRD4 receptor gene exon III polymorphism in inpatient suicidal adolescents. J Neural Transm. 2004;111(12):1593–1603. [PubMed: 15565493]
309. Zalsman G, Huang Y. Y, Oquendo M. A, Brent D. A, Giner L, Haghighi F. et al. No association of COMT Val158Met polymorphism with suicidal behavior or CSF monoamine metabolites in mood disorders. Arch Suicide Res. 2008;12(4):327–335. [PMC free article: PMC3773865] [PubMed: 18828035]

310. Zarrilli F, Angiolillo A, Castaldo G, Chiariotti L, Keller S, Sacchetti S. et al. Brain derived neurotrophic factor (BDNF) genetic polymorphism (Val66Met) in suicide: A study of 512 cases. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(4):599–600. [PubMed: 18759323]
311. Zhang Y, Bertolino A, Fazio L, Blasi G, Rampino A, Romano R. et al. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. Proc Natl Acad Sci USA. 2007;104(51):20552–20557. [PMC free article: PMC2154469] [PubMed: 18077373]
312. Zhang B, Horvath S. A general framework for weighted gene co-expression network analysis. Stat Appl Genet Mol Biol. 2005;4 Article 17. [PubMed: 16646834]
313. Zhang J, Shen Y, He G, Li X, Meng J, Guo S. et al. Lack of association between three serotonin genes and suicidal behavior in Chinese psychiatric patients. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(2):467–471. [PubMed: 17964050]
314. Zhuang X, Gross C, Santarelli L, Compan V, Trillat A.C, Hen R. Altered emotional states in knockout mice lacking 5-HT1A or 5-HT1B receptors. Neuropsychopharmacology. 1999;21(2 Suppl):52S–60S. [PubMed: 10432489]
315. Zill P, Buttner A, Eisenmenger W, Moller H.J, Bondy B, Ackenheil M. Single nucleotide polymorphism and haplotype analysis of a novel tryptophan hydroxylase isoform (TPH2) gene in suicide victims. Biol Psychiatry. 2004;56(8):581–586. [PubMed: 15476687]
316. Zill P, Buttner A, Eisenmenger W, Muller J, Moller H.J, Bondy B. Predominant expression of tryptophan hydroxylase 1 mRNA in the pituitary: A postmortem study in human brain. Neuroscience. 2009;159(4):1274–1282. [PubMed: 19233335]
317. Zill P, Preuss U.W, Koller G, Bondy B, Soyka M. SNP- and haplotype analysis of the tryptophan hydroxylase 2 gene in alcohol-dependent patients and alcohol-related suicide. Neuropsychopharmacology. 2007;32(8):1687–1694. [PubMed: 17251907]
318. Zouk H, McGirr A, Lebel V, Benkelfat C, Rouleau G, Turecki G. The effect of genetic variation of the serotonin 1B receptor gene on impulsive aggressive behavior and suicide. Am J Med Genet B Neuropsychiatr Genet. 2007;144B(8):996–1002. [PubMed: 17510950]
319. Zouk H, Tousignant M, Seguin M, Lesage A, Turecki G. Characterization of impulsivity in suicide completers: Clinical, behavioral and psychosocial dimensions. J Affect Disord. 2006;92(2–3):195–204. [PubMed: 16545465]
320. Zubenko G.S, Maher B.S, Hughes H.B, Zubenko W.N, Scott Stiffler J, Marazita M.L. 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 B Neuropsychiatr Genet. 2004;129B(1):47–54. [PubMed: 15274040]

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