The Genetics of Suicidal Behavior

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INTRODUCTION

It is important to understand the heritability of an illness or behavior in order to determine the effects of genetic factors on the etiology of that illness or behavior. The heritability of an illness can be identified by the genetic model of the illness (“genetic modeling”); in other words, the generational segregation of the heredity of an illness. Nonetheless, the genetic modeling of psychopathology has not been precisely identified. The inheritance of suicidal behavior is complicated; it is thought to be related to the interaction of multiple genes and the interaction among genes and the environment. The genetic factor in suicidal behavior was studied initially in family, twin, and adoption studies. In subsequent years, candidate genes for suicidal behavior were identified as the result of advances in techniques like gene mapping (with which the chromosomal location of suicidal behavior can be predicted), and association and linkage analysis.

Genetic factors seem to play role in 30%-50% of cases with suicidal behavior, independent of other psychological disturbances or psychological stressors (Roy et al., 1995; Mc Guffin et al., 2001). Researchers argue that some individuals are genetically vulnerable to suicidal behavior and that this genetic vulnerability might be related to inherited personality characteristics such as impulsiveness and aggression (Brent et al., 2005). The genetic factors underlying vulnerability to suicidal behavior should be studied in greater detail.

The present study aimed to review research that investigated the genetic factors related to the neurobiology of suicidal behavior and to discuss their findings. As such, we searched the Turkish and English language psychiatric literature. We scanned keywords in the abstracts...
of papers published between 1979 and 2008 via such databases as PubMed, EMBASE, ISI Web of Science, UL-AKBIM Turkish Medicine Index, and Turkish Psychiatry Index. Review studies, meta-analyses, and studies that significantly contributed to the suicide literature were examined. Herein we first discuss twin studies, adoption studies, and family studies that strongly support the role of genetic factors in suicidal behavior. Then, we discuss recent findings on suicide-related genes.

**Twin Studies**

Twin studies were the first to show the genetic basis of suicidal behavior. Initially, twin studies were conducted with small samples, but then larger samples were used and multiple variables were examined in more recent twin studies. Statham et al. (1998) conducted a study with 5995 twins that were grouped as follows: those with suicidal ideation, those that had mildly severe suicide attempts, and those with severe suicidal attempts. The concordance rates for monozygotic twins were higher than those of dizygotic twins, for all 3 groups. Statham et al. (1998) also found that if 1 twin had a severe suicidal attempt the concordance rate of those monozygotic twins were 17-fold greater than those of other twins. The concordance rate ranged between 13.2% and 25% for monozygotic twins and between 0.7% and 12.8% for dizygotic twins in other studies (Roy et al., 1991; Glowinski et al., 2001; Roy and Segal, 2001). The diagnostic risk factors of suicidal behavior and suicidal attempts were identified in all these studies as follows: history of major depression, adult antisocial personality disorder, post-traumatic stress disorder, panic disorder, and substance dependence. In summary, successful suicides and suicide attempts were more prevalent among monozygotic twins than dizygotic twins, which points to a genetic basis of suicidal behavior and its relationship to psychiatric disorders.

**Adoption Studies**

Adoption studies also support the genetic basis of suicidal behavior and provide important information on the role of environmental factors in suicidal behavior. There are 2 main studies in this area: 1 was conducted by Schulsinger et al. (1979) with 269 adopted individuals that had attempted suicide. The researchers noted attempted suicides in the history of 12 adoptees’ biological relatives; whereas there were only 2 individuals in the control group whose biological relatives had attempted suicide. The other study was conducted by Wender et al. (1986), who compared the frequency of suicidal behavior among the biological relatives of adopted individuals that had major depression and among adopting families. The prevalence rate of suicidal behavior was 15 times higher among the biological relatives than the adopting families. Moreover, the researchers compared the frequency of suicidal behavior among the biological relatives of adopted individuals that had diagnosed with an affective disorder and healthy adoptees. They found that suicide attempts were more prevalent among the biological relatives of adoptees with an affective disorder (Wender et al., 1986). Adoption studies emphasize the role of genetic factors in suicidal behavior and at the same time, they highlight possible environmental factors that suicidal behavior, which require further investigation.

**Family Studies**

Family studies indicate that suicidal behavior clusters around family members. The relationship between familial predisposition to suicidal behavior and psychiatric illnesses, particularly major depression, has been widely studied. The risk of suicide was 8-fold greater in the first-degree relatives of psychiatric patients compared to those of normal people (Tsuang, 1983). One study, Egeland and Sussex (1985), which examined the 100 year-back family records indicated that a family history of suicide in family members of people who completed suicide attempts seems to be more important than psychopathology. Predisposition of family members to suicidal behavior was thought to be transmitted through psychopathology, but the findings of Egeland and Sussex highlighted for the first time that the role of genetics in suicide could be independent of psychiatric illness. Subsequent studies also show that more people with a family history of attempted suicide attempt suicide than people with a family history of psychopathology in the absence of attempted suicide, and that there is high rate of psychopathology among the children of parents that committed suicide (Mitterauer et al., 1988; Qin et al., 2003; Runeson and Asberg, 2003). Moreover, the children of parents with a personal history of suicidal behavior or a history of suicidal behavior in their siblings are prone to the risk of suicidal behavior (Brent et al., 2003). In conclusion, the literature indicates that a family history of suicide is a major risk factor for suicidal behavior, independent of psychopathology.

**Studies of Candidate Genes**

In the past, knowledge about the role of genetics in psychiatric illnesses was restricted to findings of twin,
adoptation, and family studies. With the advent of the Human Genome Project, we can now determine the nucleotide configuration of a variety of genes (candidate genes) related to illness. A series of changes, polymorphisms, occur in the DNA of these candidate genes. Studies on suicidal behavior report differences in polymorphisms, in terms of location and mechanism, and correlational analyses are mostly conducted on a single nucleotide polymorphism (SNP). SNP refers to a change of one base of DNA into another base. Studies report negative findings (Du et al., 2000a; Ohtani et al., 2004; Stefulj et al., 2005). One meta-analysis study indicated that there is no positive relationship between the A218C polymorphism and suicidal behavior (Lalovic and Turecki, 2002); however, some meta-analyses report a positive relationship between the A218C polymorphism and suicidal behavior (Rujescu et al., 2003a; Bellivier et al., 2004). There are methodological differences, different diagnostic categories and samples, and different ethnic backgrounds among these studies, and thus no conclusive results can be reached. Findings related to TPH2 have attracted more attention.

**TPH2**

The TPH2 gene is the second isoform of TPH and is located on the 12q15 chromosome (Walther et al., 2003). TPH2 could be a better candidate gene for suicide studies due to its specificity to brain tissue. The relationship between TPH2 and suicide has been recently studied; 2 studies investigated suicidal behavior and mRNA level in the TPH2 gene in the dorsolateral prefrontal cortex (De Lucas et al., 2004; Zill et al., 2007). Zill et al. (2007) reported higher mRNA levels in depressive patients that had attempted suicide than in depressive patients without a history of suicidal behavior. De Lucas et al. (2004) did not observe any such difference between the 2 groups of patients; however, these studies are criticized for measuring mRNA levels only at the terminal points of serotonin neurons. In a more recent post-mortem study, Bach-Mizrachi et al. (2006) measured mRNA levels in the dorsal and median raphe nucleus (located in the body of serotonin neurons) and observed that mRNA levels were higher in suicide cases than in depression cases without a history of attempted suicide. High levels of TPH2 mRNA in depressive patients that committed suicide might be related to a homeostatic process in response to decreasing levels of serotonin. The role of genetic variation of TPH2 activity and on suicidal behavior should be examined in more detail. Although some studies recently identified a variety of polymorphisms of the TPH2 gene, consistent data does not exist (Mann et al., 2008).

**Serotonin Transporter Receptors**

SERTs reuptake serotonin from synaptic gaps and thus play a role in balancing serotonergic neurotransmission. Several studies indicate a relationship between suicidal behavior and changes in the attachment of SERTs in the ventral prefrontal cortex of the brain, which is responsible for inhibition and restriction functions of
brain (Mann et al., 2000). For that reason the gene of this receptor has been extensively studied. SERTs are coded by the SLC6A4 gene located on the 17th chromosome. Most polymorphisms occur in the SERT-related promoter area (5HTTLPR), which has short (S) and long (L) alleles (Lesch et al., 1996). S alleles lead to a decrease in transcription of DNA information on RNA and thus leads to low gene expression, lowering the reuptake of serotonin. S alleles are related to anxiety-related personality characteristics (Lesch et al., 1996). Moreover, their relationship to impulsivity and suicidal behavior has been studied. Studies of functions of brain different ethnic groups suggested that S alleles are related to completed suicides, violent suicide attempts (Courtet et al., 2004), and the frequency and lethality of suicidal behavior (Campi-Azevedo et al., 2003).

In a study that investigated the relationship between 5HTTLPR polymorphism, and impulsivity and compulsivity, patients with obsessive-compulsive disorder were reported to have fewer S alleles and patients with impulsive suicidal behavior had more S alleles (Baca-Garcia, 2005). This finding suggests that S alleles are not completely related to the clinical picture of psychiatric disorders, but linked to some symptoms of these disorders. There are inconsistent findings on the role of SERT genes on suicidal behavior. Meta-analyses indicate that S alleles might be related to violent suicidal behavior (Anguelova et al., 2003; Arango et al., 2003; Ertuğrul et al., 2004; Khait et al., 2005) and A-1438G polymorphism (Bonnier et al., 2002).

5-HT1A

Antidepressants can desensitize 5-HT1A receptors in the raphe nucleus and thus increase serotonin transmission. Therefore, the 5-HT1A receptor gene becomes a candidate gene for depressive patients, although it is related more to anxiety. The most common polymorphism of the 5-HT1A receptor gene is C-1019G (Wu and Comings, 1999). A recent study reports that homozygote C-1019G alleles were at higher levels in depressive patients that committed suicide and that this polymorphism increases expression of the 5-HT1A receptor gene in cortical areas (Lemonde et al., 2003). Yet, other studies did not observe any relationship between C-1019G polymorphism and suicidal behavior (Mann, 2003; Huang et al., 2004a).

5-HT1B and Other Serotonin Receptor Genes

The 5-HT1B gene is thought to be linked to suicide, aggression, major depression, alcohol abuse, and substance abuse. This receptor inhibits serotonin release in neuron terminals; in other words, it inhibits neuronal firing, acting as a somatodendritic auto receptor. The 5-HT1B receptor is affected mostly by G861C polymorphism and rarely by F124C polymorphism (Nöthen et al., 1994). The G861C allele is correlated with alcoholism and antisocial personality characteristics (Lappalainen et al., 1998), and substance abuse (Mann, 2003). The gene’s 161T polymorphism has been recently identified and researchers report no relationship between this polymorphism and suicidal behavior in patients with schizophrenia (Hong et al., 2004) or major depression (Tsai et al., 2004).
There are a limited number of studies on other serotonin receptors. Researchers observed no relationship between suicidal behavior and 5-HT2C (Stefulj et al., 2004), 5-HT6 (Okamura et al., 2005), or 5-HT7 (Turecki et al., 2003). In summary, there are positive findings about the 5-HT2A receptor, but in general, there seems to be no relationship between serotonin receptors and suicidal functions of brain functions, the 5-HT1B receptor is related to alcoholism and antisocial personality characteristics, and thus it should be examined in greater detail in terms of suicidal behavior involving impulsive and violent acts.

**The Tyrosine Hydroxylase Gene**

Tyrosine hydroxylase (TH) is another candidate gene, which is used in neurotransmitter biosynthesis; however, few studies have examined its relationship to suicidal behavior. In one study TH-K3 allele polymorphism was linked to suicidal behavior in patients with adjustment disorder and previous suicide attempts (Persson et al., 1997), but this was not supported by the findings of another study of cases that committed suicide (Hattori et al., 2006). Another study investigated the relationships between the DOPA decarboxylase gene and the TH gene, and suicidal behavior and aggression (Giegling et al., 2008). The DOPA decarboxylase gene was reported to be related to suicidal behavior and aggression, whereas no relationship was observed between the TH gene and suicidal behavior.

**Monoamine Oxidase-A (MAO-A)**

MAO-A is a mitochondrial membrane enzyme that plays a key role in monoamine metabolism. The MAO-A gene is located on the short branch of the X chromosome and it is related to the sex of the organism. The activity of this enzyme is thought to be linked to aggressive behavior. Aggressive and impulsive suicide attempts in men are suggested to be secondary to MAO-A polymorphism (Du et al., 2002). There are several polymorphisms of this enzyme and the most common is MAO-A-uVNTR polymorphism (Sabol et al., 1998). MAO-A-uVNTR polymorphism might be related to impulsive aggression in healthy men (Manuck et al., 2000), but this finding was not supported by subsequent studies (Garpenstrand et al., 2002). MAO-A-uVNTR polymorphism is thought to be related to a childhood history of sexual and physical abuse, and impulsivity (Huang et al., 2004b). Low BOS 5-HIAA levels in this polymorphism are said to be related to bipolar disorder, major depression, alcoholism, impulsive aggression, and antisocial personality characteristics (Mann, 2003; Williams et al., 2003; Hattori et al., 2005).

**Catechol-O-Methyl Transferase (COMT)**

COMT is responsible for monoamine degradation. The COMT gene is located on the 22q11 chromosome. It has 2 polymorphisms that have H (high activity) and L (low activity) alleles due to Val and Met changes in the 108/158 position. The Val/Val genotype provides higher enzyme activity, while Met/Met results in the lowest enzyme activity (Lachman et al., 1996). Previous studies report a correlation between COMT polymorphism and some phenotypes of psychiatric illnesses. L alleles are related to aggression and suicidal behavior according to some studies (Rujescu et al., 2003b; Ono et al., 2004), but this is not supported by others (Liou et al., 2001). The relationship between gene polymorphisms of this enzyme and personality characteristics has been studied and researchers report that personality styles like avoidance of harm and anger are related to L alleles (Rujescu et al., 2003b; Hashimoto et al., 2007; Baud et al., 2007). Findings on COMT gene polymorphisms indicate that this gene is not related to a predisposition to suicidal behavior, though it might affect the phenotype of suicidal behavior. Its relationship to suicidal behavior, anger, and personality styles should be investigated in greater detail.

**The Dopaminergic and Other Systems**

Dopamine receptors are related more to alcoholism than to suicidal behavior VNTR polymorphism of the D4 receptor (DRD4) is related to some personality characteristics, such as the search for excitement (Ebstein et al., 1996), but there were no significant findings on its relationship to suicidal behavior (Kluger et al., 2002; Munafò et al., 2003).

**GABA**

Post-mortem studies indicate an increased level of activity of GABA(A) alpha 1 and GABA(A) beta 3 receptors in some areas of the cortex in the brains of suicide victims (Choudary et al., 2005). Thus, GABA receptor sub-groups might be biological indicators of suicidal behavior (Choudary et al., 2005).

**Cholecystokinin**

The most common polymorphism of cholecystokinin is CCK-196G/A. This polymorphism was observed in males that committed suicide (Shindo et al., 2005).
Neurotrophins

Recent studies have investigated the relationship between suicide and neurotrophins, which play a significant role in neuronal continuity and synaptic plasticity in the brain. Brain-derived neurotrophic factor (BDNF) is a well-known type of neurotrophin (Huang and Reichardt, 2001). In a post-mortem study researchers identified low BDNF mRNA levels in the prefrontal cortex and hippocampus of suicide victims (Dwivedi et al., 2003), but the results functions of brain did not point to a candidate gene. The most common polymorphism of BDNF is Val66Met. In one study researchers did not observe any relationship between this polymorphism and suicidal behavior in patients with bipolar and unipolar depression (Hong et al., 2003). In another study BDNF-Val66Met polymorphism was linked to violent suicide attempts in people with a history of childhood trauma (Perroud et al., 2008). Neurogenesis could play a role in the etiopathogenesis of suicide functions of brain, but this issue requires further investigation.

The Endocannabinoid System

Endocannabinoids (ECs) are substances activated via cannabinoid receptors. They are composed of amides, esters, and unsaturated fats in the central nervous system, particularly the cerebral cortex, basal ganglion, and limbic structures (Mechoulam et al., 1991). Two receptors are known: cannabinoid 1 (CB1) and cannabinoid 2 (CB2). CB2 is located mostly in peripheral structures and is related to the immune system. CB1 is located primarily in the brain and is related to G protein. ECs regulate the release of neurotransmitters via CB1 receptors (Matias et al., 2006). One study showed an increase in the density of CB1 and an increase in G protein activation (activated by GB1) in the dorsolateral prefrontal cortex of suicide victims that had been diagnosed with major depression (Hungund et al., 2004). This finding indicates a relationship between the EC system and suicidal behavior. Similar results were obtained from alcoholic suicide victims (Vinod et al., 2005). The pathophysiology of CB1 receptor level increases in the EC system is not fully understood. Anomalies in the cyclic AMP cycle were identified in the prefrontal cortex of suicide victims that had been diagnosed with major depression (Dwivedi et al., 2004). This anomaly is thought to be related to an increase in CB1 density. Increases in CB1 activate G protein and inhibit adenylyl cyclase (found in the cyclic AMP cycle), creating some abnormalities (Vinod and Hungund, 2006).

CONCLUSION

Polymorphism studies have contributed much to our understanding of the molecular basis of suicidal behavior, although these findings cannot be considered definitive. In fact, we encounter similar difficulties in the understanding of genetics of both psychopathologies and suicidal behaviour, difficulties in providing a clinical definition of suicidal behavior, the complexity of heritability, and limitations in methodology of genetic studies confound reported findings (Atabey et al., 2004). Moreover, epigenetic alterations that might change gene expression have not as yet been identified (Atabey et al., 2004). Despite these limitations, new studies on the genetics of suicidal behavior continue to enhance our understanding of suicidal behavior. We know that suicidal behavior is transmitted to new generations independent of psychopathology or psychological stressors. Individuals that are genetically prone to suicide might exhibit suicidal behavior in response to psychopathology and adverse life events. Studies have demonstrated the relationship between suicidal behavior and the genetic mechanism of such phenotypes as anger and impulsivity, which clarifies the concept of a tendency for suicidal behavior.

The most important neurochemical findings of suicide come from studies of the serotonergic system; recent findings indicate a relationship between the TPH2 gene and suicidal behavior. S alleles of SERT genes are related to violent suicidal functions of brain behavior. Despite significant findings regarding the 5-HT2A receptor, suicidal behavior and serotonin receptors do not seem to be significantly related. There are interesting results concerning the enzymes responsible for neurotransmitter degradation. Studies have indicated that MAO-A provides information about the phenotype of suicidal behavior in men. Findings related to this enzyme highlight the relationship between suicidal behavior and such phenotypes as impulsivity and aggression, and antisocial personality characteristics. The COMT gene suggests a relationship between suicide, and anger and impulsivity. Studies on BDNF and the EC system suggest that there are some changes in the messaging system inside cells in suicide cases. In conclusion, findings related to biological changes remain unclear, but they do provide a roadmap that could lead to a deeper understanding of suicidal behavior.
REFERENCES


