Suicidal behaviour: genes, environmental stress and temperamental traits

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Genetics and gene-environment interaction in suicide.

ABSTRACTS: Multiple risk factors have been involved in the risk for suicide and multiple trajectories have been hypothesized leading to suicidal behaviour. Consistent evidence suggests the involvement of heritable factors, as well as a critical role of life stress and early adversity. In the present article we will review the evidence for the involvement of genetic, environmental as well as personality traits in the risk for suicide, together with recent evidence supporting an interaction between these different factors.

Temperamental traits of impulsive aggression, neuroticism and introversion have also been implicated in suicidal risk. However, it is unlikely that these factors, themselves, can explain suicide. As regard genetic effects, suggestive evidence has been reported for serotonin transporter gene (SLC6A4), serotonin receptor 2A (5HTR2A), Tryptophan hydroxylase (TPH1, TPH2), Catechol-o-methyl transferase (COMT) and Brain derived neurotrophic factor (BDNF). Other interesting genes are dopamine receptor D2 (DRD2), Cortico-trophin-releasing hormone 1 (CRHR1). Studies addressed to investigate the combined effect of genetic predisposition and environmental influences reported positive findings for SLC6A, 5HTR2A, BDNF and Regulator of G-protein signaling 2 (RGS2). Finally, among genes influencing suicide-related traits, the Mono-amine oxidase A (MAOA) and the COMT showed interactive effects with early adverse events on impulsivity and anger in suicidal individuals. In conclusion, there is evidence of a genetic liability for suicidal behaviour, be modulated by environmental risk factors as well as individual psychological characteristics, such as temperamental traits. Future studies are required to address this complexity by an integrated approach.

Key words: suicide, life events, childhood trauma, temperamental traits, gene, gene-environment interaction.

Introduction

Suicide or suicide completion is the act of taking one's own life voluntarily.

Suicide-related behaviour is a general term used to refer to self-injury, suicide attempt and suicide. According to Silverman et al. (2007), self-injury with no or undetermined intent to die refers to "self-harm" and "undetermined suicide-related behaviour" respectively. When clear or some degree of intent to die is present, we refer to "suicide attempt" when self-harm does not result in death and "suicide" when it has a fatal outcome. Suicide-related ideations and communications with some intent to die (suicidal threat and suicidal plans) may be also present independently from manifest self-destructive acts.

Suicide is a major public health problem, representing the 10th leading cause of death worldwide (Levi et al., 2003). The incidence rate for completed suicide vary considerable in different countries, from 1.1 per 100,000 inhabitants in Azerbaijan to 51.6 per 100,000 inhabitants in Lithuania (WHO, 2002). The highest suicide rates are found in Eastern European countries (Belarus, Estonia and Lithuania and Russian federation); low rates are found mainly in Latin America (Colombia, Paraguay) and some countries in Asia (Philippines and Thailand 5.6), while Countries in other parts of Europe, in North America, and parts of Asia and the Pacific tend to fall somewhere in between these extremes (as examples: Finland 28.4/ 100,000, France 20.0/ 100,000, USA 13.9/100,000). According to the World Health Organization (WHO) World Mental Health (WMH) Surveys (conducted 2001–2007); the 12-months prevalence estimate of suicide attempts

is 0.3% (Borges et al., 2010). In most countries, men have a higher reported rate of completed suicide, whereas women have a higher rate of attempted suicide (Schmidtke et al., 1996). Suicide rates are highest in elderly people in most countries. However, over the past 50 years, rates have risen in young people, in particular in men (Wasserman et al., 2005; Wasserman & Wasserman, 2009), and decreased in elderly people (Pritchard & Hansen, 2005).

Over 90% of suicides had recognizable psychiatric illness at the time of their death (Tanney, 2000), mostly mood disorders, borderline personality disorder, post-traumatic stress disorder and schizophrenia (Bolton & Robinson, 2010). Nevertheless, the association between suicide and psychiatric disorders is not linear, therefore independent risk factors should account for the individual risk for suicide.

In the present article we aimed to review the current knowledge of genetic factors involved in suicidal behaviours, in particular completed suicide and suicide attempt, and their interaction with environmental risk factors. Moreover, we also took into account the few studies addressing the interplay between genetic predisposition, suicide-related temperamental traits and suicidal risk.

Methods

Literature search

Genetic studies in suicidal behaviour were located through several literature-search strategies. Up to March 2011, appropriate search terms (gene, genetics,

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heritability, suicide, suicide attempt, completed suicide, suicidality, suicidal behaviour, suicidal ideation, suicide intent) were entered in the essential electronic literature databases (Pub Med, PsycINFO and Web of Science). The same terms were entered in conjunction with other terms for gene-environment studies (stress, trauma, life events, adverse events, sexual abuse, physical abuse, emotional abuse, emotional neglect, physical neglect) and interaction studies on related suicidal traits (aggression, violence, impulsivity, impulsive behaviour, anger, hostility, neuroticism, negative emotionality). The reference lists of all retrieved studies were perused for possibly citing earlier studies of topical relevance.

Study inclusion criteria

The literature search was limited to English-language reports. Any study reporting data on genetic polymorphisms for a type of suicidal behaviour (i.e. completed suicide, suicide attempt or suicidal ideation), regardless of the study design, was eligible for inclusion in the review.

Study details

Regarding genes independently involved in suicidal behaviour, we reported only those investigated at least in two independent studies. Using the above extensive literature search strategies and applying the above wide criteria for study inclusion, 123 reports were detected on

genetic variants involved in suicidal behaviours; 20 were detected for gene-environment interactions and 2 for interactive studies taking into account suicide-related traits.

Risk factors for suicidal behaviours

At the level of population, according to the data derived from the World Mental Health (WMH) Surveys (Borges et al., 2010), risk factors for suicidal behaviour include female sex, younger age, lower education and income, unmarried status, unemployment, presence of diverse 12-month DSM-IV mental disorders, parent psychopathology and childhood adversities.

Mental disorder is the most important risk factor for suicidal behaviour. Indeed, more than 90% of suicidal individuals suffer from mental disorders (Bertolote et al., 2004). Mood disorders are present in 30%, substance abuse in 18%, schizophrenia in 14%, and personality disorders in 13.0% of suicides. According to the National Comorbidity Survey study (Kessler et al., 1994), subjects at higher risk for suicide attempts were those affected by mood disorders (OR=12.9), Bipolar disorder (OR=29.7), substance abuse disorder (OR=5.8), anxiety disorders (OR=3.2), particularly generalized anxiety disorder, panic disorder and post-traumatic stress disorder (respective ORs:

5.6, 5.6 and 6.0), non-affective psychosis (OR=5.7) and antisocial personality disorder (OR=5.7). Moreover, comorbid conditions exponentially increased the risk of suicidal behaviour from 6.1 to 19.7 (OR) in subjects with 2 or more psychiatric disorders (Kessler et al., 1999).

Investigators have proposed many models to explain or predict suicide. One such explanatory and predictive model is the stress-diathesis model (Mann et al., 1999). According to this model, one stressor is almost invariably the onset or acute worsening of a psychiatric disorder, but other risk factors, such as familiar and genetic components and other psychosocial factors can also contribute. As will be reviewed below, the role of heritable factors in suicidal behaviour is well established, as demonstrated by family studies, post-mortem brain autopsies and modern molecular investigations in suicide attempters (Currier & Mann, 2008). Nevertheless, the neurobiology of suicide is complex, and differential genetic and environmental pathways to suicide have recently been proposed. According to Kendler et al. (2010), genes may influence the risk for suicide in a mediational model through their impact on response to stress, risk of psychiatric illness and/or personality traits related to suicide. Specifically, genes would mediate the effect of stress on the risk of developing or exacerbating psychopathological symptoms and suicidal ideation, as we will discuss below in more detail. Early severe trauma, such as sexual abuse or parental loss, may act directly on suicidality or through the risk for psychiatric disorders, also depending on genetic predisposition. Recent adversity would influence suicide risk mainly through interaction with genetic predisposition to stress reactivity and/or psychiatric disorders. Finally, it has also been hypothesized a gene x environment x development interaction, in which the effect of genetic predisposition would be modulated by environmental factors depending on the individual developmental stage (for details see Kendler, 2010).

In the following paragraphs, we will focus on environmental and genetic factors that have been implicated in suicidal behaviour. A separate paragraph will be dedicated to intermediate phenotypes related to suicide, i.e. personality traits associated with suicidal behaviours. Subsequently, we will summarize the findings of recent molecular studies addressing the interaction between genes and environmental stressors in suicide. Genetic studies on personality traits related to suicidal risk will also be briefly reviewed.

Environmental risk factors

The role of trauma, stress, and negative life events as risk factors for suicidal ideation and behaviour has been long recognized (Paykel et al., 1975). Several possible pathways between exposure to trauma have been suggested in the literature, including the mediating role of posttraumatic symptoms, depression, psychiatric comorbidity, and the impact on personality and cognitive development. Much attention has been paid to early trauma as risk factors for suicide in adolescence and adulthood, such as physical and sexual abuse, and parental neglect (Brodsky & Stanley, 2008; Bruffaerts et al., 2010; Perepletchikova & Kaufman, 2010; Roy, 2001; Sarchiapone et al., 2007). Other familial factors, such as parental suicide, parental psychiatric disorder, alcohol abuse and socioeconomic indicators have been associated with increased suicide risk in the offspring (von Borczyskowski et al., 2010).

Although some studies have found a relationship between physical abuse, neglect and suicidal behaviour, most studies showed a much greater effect of a history of sexual abuse on suicidal behaviour (Molnar et al., 2001), with an increased risk in those reporting more than one type of abuse (Anderson et al., 2002). The role of child sexual abuse in suicide has been confirmed by a recent meta-analysis of the literature (Maniglio, 2010). Childhood traumas have been hypothesized to induce neurobiological alterations correlated with suicide and aggression (Roy, 2002). A consistent finding

from neurobiological studies is that low serotonergic functioning is associated with increased impulsivity and self-destructive behaviour (Mann et al., 2001). Evidence from nonhuman primate studies supports the hypothesis that early trauma (maternal deprivation) contribute to the presence of biological correlates of suicidality in humans (Higley et al., 1992). For instance, in a previous study we found significant correlations between childhood traumas and traits of aggression in suicide attempters (Sarchiapone, Jausent et al., 2009). Recent evidence suggests that early adversity may induce neurobiological alteration by affecting gene function via epigenetic programming, i.e. genes' expression alteration (Labonte & Turecki, 2010). Stressful life events commonly reported shortly preceding suicidal behaviour are job problems, family discord, somatic illness, financial trouble, unemployment, separation, death and illness in family (Heikkinen et al., 1994). As mentioned above, acute stress may also elicit suicidal behaviours in interaction with an existing genetic predisposition. Moreover, recent stressors have been reported having a stronger impact in subjects that had also experienced childhood trauma, particularly sexual abuse in both childhood and adulthood (retraumatization) (Krysinska et al., 2009). This is consistent with the evidence that exposure to certain stressors early in life increases the sensitivity of the organism to later stress (Heim & Nemeroff, 2001), probably through persisting neurobiological alterations induced by early trauma in systems regulating response to stress, impulsivity and aggression. Finally, other severe traumas that have been associated with suicidality are military combat, criminal victimization, natural disasters, torture and even contact with traumatized individuals (secondary traumatization) (Krysinska et al., 2009).

Genetic risk factors

There is evidence that heritable factors play an important role in suicidality. Since the 1970's, a number of family- and family history-studies have shown

that suicide aggregates in families (Baldessarini & Hennen, 2004), even independently from the familial transmission of psychiatric disorders (Brent et al., 1996). From twin studies, the estimates of heritability for suicide range between 21–55% (Voracek & Loibl, 2007). However, although transmission of suicide risk is to a certain extent independent from psychiatric disorders, increased rates of suicidal ideation in the relatives of suicide probands are largely explained by increased familial rates of axis I and axis II disorders (Brent et al., 1996; Johnson et al., 1998) and comorbid mental disorders in probands strengthen the concordance for suicidal behaviours among relatives (Goodwin et al., 2004). According to large Scandinavian register data, the strongest risk factor for suicide attempt is mental illness necessitating hospital admission as well as family history of mental illness (Agerbo et al., 2002; Mortensen et al., 2000). Therefore, we may assume the existence of a genetic overlap between psychiatric diseases and suicidal behaviour, together with the existence of genes affecting independently the two disorders.

Studies of molecular genetics have poorly addressed the genetic specificity of suicide. This is not surprising, since more than 90% of suicidal subjects are concurrently affected by a mental illness (Tanney, 2000). Moreover, studies have often employed pure case-control designs (i.e. psychiatric suicidal subjects vs. healthy controls); such designs cannot establish whether the genetic differences detected depend on comorbid psychiatric illness or suicide itself, unlike designs based on non-suicidal psychiatric controls that are less biased from this point of view. To our knowledge, a first attempt to specifically disentangle similarities and differences of genetic effects in suicide and mood disorders has been only recently made by Brezo et al. (2010). Brezo et al. evaluated a large cohort, followed for 22 years, for both suicidal behaviour and mood disorders, focusing on genes involved in the regulation of the

serotonergic system. Further details will be provided and discussed below.

In the last two decades, the studies of molecular genetics in suicidal behaviour have mostly focused on genes encoding for neurotransmitters and their receptors, with strongest evidence for the serotonin (5-HT) system, but also for genes involved in stress systems (Hypothalamic-pituitary-adrenal axis), cell signaling and neuroprotective/growth factors. The 5-HT system has been widely investigated, because of the observed clinical benefit of antidepressant drugs on clinical syndromes with an increased risk of suicide and because of evidence coming from postmortem studies, which have reported fewer serotonin transporters in the prefrontal cortex, hypothalamus and brainstem of suicide victims (Purselle & Nemeroff, 2003). Thereafter, a large number of studies investigated the role of 5-HT transporter gene (SLC6A4) in suicide. In particular, studies focused a promoterlength polymorphism in SLC6A4 (5-HTTLPR). The short variant (S-allele) of this polymorphism was found to have lower transcription efficiency and less transporter expression compared to the long variant (L-allele) (Heils et al., 1996). Many studies reported positive association with suicidal behaviour and two meta-analyses of the literature confirmed a positive association between the S-allele in 5-HTTLPR and suicidal behaviour, in particular violent suicide attempt (Anguelova et al., 2003; Lin & Tsai, 2004). However, many negative studies have also been published (Akar et al., 2010; Baca-Garcia et al., 2010; Chen et al., 2007; Chong et al., 2000; Contreras et al., 2010; Courtet et al., 2003; De Luca et al., 2008; De Luca, Tharmalingam, King et al., 2005; Geijer et al., 2000; Gerra et al., 2004; Helbecque et al., 2006; Mann et al., 2000; Maurex et al., 2010; Mergen et al., 2006; Pungercic et al., 2006; Roy et al., 2001; Rujescu et al., 2001; Saiz et al., 2008a; J. Segal et al., 2009; Wang et al., 2009; Zalsman, Anderson et al., 2005; Zalsman et al., 2001; J. Zhang et al., 2008).

Moreover, only few studies employing psychiatric controls reported positive findings, mostly in major depression, schizophrenia (Campi-Azevedo et al., 2003) and alcohol dependence (Preuss et al., 2001). A further variant in the SLC6A4 gene (VNTR in intron 2, STin2) was found to be associated with increased risk of suicidal behaviour both schizophrenia and major depression (De Luca, Zai et al., 2006; Lopez de Lara et al., 2006). Overall, the SLC6A4 gene seems to be mostly associated with some features of suicidal behaviour, such as severity and lethality (Vincze et al., 2008; Wasserman et al., 2007), violence and repetition (Bayle et al., 2003; Bellivier et al., 2000; Campi-Azevedo et al., 2003; Courtet et al., 2004; Gorwood et al., 2000; Neves et al., 2008; Shen et al., 2004).

Other genes involved in the regulation of the 5-HT systems have also been investigated. Interesting results have been obtained for the serotonin receptor 2A (5HTR2A) (Arias et al., 2001; Bonnier et al., 2002; Vaquero-Lorenzo et al., 2008), though the major findings have been obtained in violent-impulsive suicide attempt (Giegling et al., 2006; Saiz et al., 2008a). However, many negative studies have been reported as well

(Arias et al., 2001; Bondy et al., 2000; Brezo et al., 2010; Correa et al., 2004; De Luca, Likhodi et al., 2007; De Luca et al., 2008; De Luca et al., 2009; Du et al., 1999; Ertugrul et al., 2004; Etain et al., 2004; Fanous et al., 2009; Geijer et al., 2000; Khait et al., 2005; Ono et al., 2001; Preuss et al., 2000; Tan et al., 2002; Turecki et al., 1999; Videtic et al., 2006; Yoon & Kim, 2008, 2009; Zalsman, Frisch et al., 2005; J. Zhang et al., 2008). An enzyme involved in the synthesis of 5-HT, tryptophan hydroxylase 1 (TPH1) has recently been reported not to be associated with suicidal behaviour in schizophrenia according to a meta-analysis of the literature (Saetre et al., 2010). However, a previous meta-analysis on psychiatric disorders in general reported a positive association with suicidality (Rujescu et al., 2003). The neuronal tryptophan hydroxylase gene (TPH2) has also been associated with suicidal behaviours (Lopez de Lara et al., 2007; Perez-Rodriguez et al., 2010; Yoon & Kim, 2009; Zhou et al., 2005; Zill et al., 2004), though inconsistently (Brezo et al., 2010; Campos et al., 2010; De Luca, Hlousek et al., 2006; De Luca et al., 2004; De Luca et al., 2008; De Luca, Voineskos et al., 2005; Mann et al., 2008; Mouri et al., 2009; Must et al., 2009; Perroud, Neidhart et al., 2010; Zill et al., 2007). Many other genes involved in serotonergic neuro-transmission have been investigated, but mostly negative findings have been obtained with few exceptions: Serotonin receptor 1A (5HTR1A) (Lemonde et al., 2003; Sawiniec et al., 2007), Serotonin receptor 1B (5HTR1B) (New et al., 2001), though a meta-analysis of the literature disconfirmed the finding (Kia-Keating et al., 2007), and Serotonin receptor 6 (5HTR6) (Azenha et al., 2009). However inconsistency was reported also for 5HTR1A (Brezo et al., 2010; Nishiguchi et al., 2002; Serretti et al., 2009; Serretti, Mandelli et al., 2007; Videtic et al., 2006; Wang et al., 2009; Yoon & Kim, 2009) and 5HTR6 (Brezo et al., 2010; Okamura et al., 2005).

A recent work investigated eleven 5-HT genes in a large cohort of children followed for 22 years, in order to identify common and specific genetic risk factors for depressive disorders and suicide attempt, acting directly or as moderators in gene-environment interactions with childhood sexual or childhood physical abuse (Brezo et al., 2010). Two genes were found associated with suicide attempt: TPH1 in a specific way and independently from mood disorders, and 5HTR2A, that was associated with both depression and suicide attempt. Nevertheless, 5HTR2A was directly associated with depressive disorders, while through interactions with histories of sexual and physical abuse with suicide attempt.

The dopaminergic and noradrenergic systems have also been investigated because of their involvement in the regulation of stress responses and depressive disorders. Briefly, suggestive evidence has been obtained for Dopamine receptor 2 (DRD2) (Finckh et al., 1997; Johann et al., 2005; Suda et al., 2009), despite a recent negative study (Baca-Garcia et al., 2010). No positive evidence has been reported for Tyrosine hydroxylase (TH) (Giegling et al., 2008; Hattori et al., 2006), though positive association with severity of suicide attempt was reported (De Luca et al., 2008). Dopadecarboxylase (DDC) was not found to be associated with suicidal behaviour (Baca-Garcia et al., 2010; Giegling et al., 2008) though some association with violent suicide attempt has been found (Giegling et al., 2008). No association was reported for other candidate dopaminergic genes such as Dopamine receptor D4 (DRD4) (Persson et al., 1999; Zalsman et al., 2004) and Dopamine receptors D1, D3 and D5 (DRD3, DRD5) (Baca-Garcia et al., 2010). Regarding the noradrenergic neurotransmission, studies focusing on Adrenergic receptor 2A (ADRA2A) have mainly demonstrated no association with suicidal behaviour (Baca-Garcia et al., 2010; Martin-Guerrero et al., 2006; Sequeira et al., 2004), with the exception of one study finding an association with

completed violent suicide in females of an Asian sample (Fukutake et al., 2008). Pertaining to the GABAergic system, two studies have investigated the GABA receptor A3 but negative findings were obtained (Baca-Garcia et al., 2010; Baca-Garcia et al., 2004).

Genes involved in the metabolism of monoamines have also been investigated. Suggestive evidence have been obtained for Catechol-o-methyl transferase (COMT) as evidenced by a first meta-analysis of the literature (Kia-Keating et al., 2007), though we did not find significant evidence by a recent meta-analysis of the literature (Calati et al., 2010). Monoamine oxidase A (MAOA) has been associated with completed suicide (Du et al., 2002) and violent suicide attempt in males (Courtet et al., 2005), whilst most of the studies reported negative findings (Baca-Garcia et al., 2010; Brezo et al., 2010; De Luca, Tharmalingam et al., 2006; De Luca, Tharmalingam, Sicard et al., 2005; Huang et al., 2004; Kunugi et al., 1999). To our knowledge, Monoamine oxidase B (MAOB) has been investigated to a lower extent and two negative reports were published (Baca-Garcia et al., 2010; Brezo et al., 2010).

Other interesting genes are those related to Corticotrophin-releasing hormone (CRH), regulators of the hypothalamic-pituitary-adrenal pathway and response to stress. The CRH gene was found to be associated with suicide attempt in patients with schizophrenia (De Luca et al., 2010). Studies in other populations have, however, failed to find a positive association (Baca-Garcia et al., 2010; Wasserman et al., 2008). The Corticotrophin-releasing hormone receptor 1 (CRHR1) was found to be associated with suicide attempt in 2 studies (De Luca et al., 2010; Wasserman et al., 2009), and to interact with life stressors in increasing suicide risk in a third study (Wasserman et al., 2008), though inconsistencies have been reported (Baca-Garcia et al., 2010). The gene encoding for receptor type 2 (CRHR2) was found to be associated with severity of suicide attempt (De Luca et al., 2007) but not with suicide attempt itself

(Baca-Garcia et al., 2010; De Luca et al., 2010).

Genes involved in neuroprotection and cell proliferation as well as inflammatory processes have received particular interest, given their involvement in neurodegenerative/neuropsychiatric disorders (Duman, 2009). Interesting data have been obtained for the Brain derived neurotrophic factor gene (BDNF) (Iga et al., 2007; Kim et al., 2008; Sarchiapone et al., 2008) member of the "neurotrophin" family of growth factors. Associations have been reported also with high lethality (Schenkel et al., 2010; Vincze et al., 2008) and violent suicide attempts (Neves et al., 2010), though negative reports have also been published (Baca-Garcia et al., 2010; Hong et al., 2003; Hwang et al., 2006; Kohli et al., 2010). The Nerve growth factor receptor (NGFR), a low affinity receptor for several neurotrophins including BDNF, has also been associated with suicide attempt in depressed patients (Kunugi et al., 2004), though other studies did not confirm the finding (Baca-Garcia et al., 2010; McGregor et al., 2007). Nitric oxide (NO) displays many properties of a neurotransmitter and it is involved in neurotoxicity associated with stroke and neurodegenerative diseases. The neuronal NO synthase gene (NOS1) has been found to be associated with both completed and attempted suicide (Cui et al., 2010; Rujescu et al., 2008), though findings are inconsistent (Baca-Garcia et al., 2010). Finally, the proinflammatory cytokine Tumor necrosis factor (TNF) has been reported to be associated with completed suicide in one study (Omrani et al., 2009), but not in a previous one focusing on suicide attempt (Saiz et al., 2008b). In the nervous system, estrogens are involved in a number of processes which regulate synaptic plasticity including synaptogenesis and neurogenesis, and have been linked to neuropsychiatric disorders (Craig & Murphy, 2007). Attention has been focused on Estrogen receptor 1 (ESR1) (Sundermann et al., 2010). To our knowledge, three studies have so far investigated associations

between suicidal behaviour and genetic variants in the ESR1 gene, but negative findings were reported (Baca-Garcia et al., 2010; Giegling, Rujescu et al., 2008; Tsai et al., 2003). Many other genes have been investigated in suicidal behaviour but inconsistent or poor evidence has been obtained.

Suicide-related personality traits

As is the case with most complex traits the role of genes in suicidal behaviour remains elusive. It has been hypothesized that genes may have an indirect effect on suicide risk through intermediate phenotypes, such as impulsive-aggressive traits (Savitz et al., 2006). It has to be underlined that a circular relationship may exist between genetic factors, suicide-related traits and suicidal behaviour. Indeed the results of candidate gene association studies suggest that genetic vulnerability factors for various related psychiatric phenotypes (major psychiatric disorders and personality traits) partly overlap with personality traits predisposing to suicidal behaviour (see also Baud, 2005). However, disentangling the effects the genetic factors influencing these different pathological conditions, appears to be a difficult task.

Studies are increasingly shifting from risk factors that predict the emergence of suicidality in the short term to such biologically determined risk factors as personality traits and temperaments. Four main constellations of personality characteristics are associated with suicidal behaviour: impulsivity, hostility-aggression, introversion, and anxiety-neuroticism.

Impulsivity and aggressive traits have been long recognized as risk factors for suicidal behaviour (Eisenthal, 1967; Klerman, 1987) and seem to play a larger role among younger suicides (Gorlyn, 2005). Impulsive-aggressive traits have been linked to abnormalities in monoaminergic functioning; in particular, lowered 5-HT transmission and enhanced dopamine and noradrenalin functioning (Oquendo & Mann, 2000). Impulsive-aggressive traits have a genetic background, suggesting that it may be an endophenotype associated with the 5-HT genes

and also with the emergence of suicidality (Courtet et al., 2004). The role of neuroticism, namely the tendency to experience feelings such as anxiety, anger, guilt and depressed mood, has been widely recognized as well as a trait correlated with suicidal behaviour (Brezo et al., 2006), though it has also been linked to a variety of psychopathological conditions (Lahey, 2009), mostly characterized by high levels of suicidality. Introversion, defined as the tendency toward being predominantly concerned with and interested in one's own mental life, and therefore to be more reflective and to enjoy limited relationships, has been postulated as a core personality trait pre-disposing to concomitant depression and suicidality (Janowsky, 2001). Inter-individual variability in the levels of both neuroticism and introversion has been mainly linked to the 5-HT system (Lester, 1989; Netter & Rammsayer, 1989). An early study reported the 5-HTTLPR polymorphism associated with high levels of neuroticism (Lesch et al., 1996). This finding has been the subject of numerous replication studies and several recent meta-analyses. To date, there is a substantial consensus concern-

ing the role of the serotonin system in neuroticism and anxiety-related traits (for a review see Canli, 2008).

At the opposite, "resilience" may be a personality trait protective for suicidal behaviours. Resilience is the capacity for successful adaptation to change, to thrive in the face of adversity or recover from negative events. It is a measure of stress coping ability or emotional stamina (Connor, 2006). We have repeatedly reported of poor resilience in suicidal individuals with substance abuse (Cuomo et al., 2008; Roy, Sarchiapone et al., 2007) and suicidal prisoners (Sarchiapone, Carli et al., 2009). Measures of low resilience have also been associated with suicide risk in adolescents (Nruham et al., 2010; Park et al., 2010), depressed elderly men (Hobbs & McLaren, 2009) and veterans (Brenner et al., 2009; Pietrzak et al., 2010). Moreover, evidence has been reported that childhood trauma may affect resilience and increase suicidal ideation, as a further link between traumatic events, personality and suicidality (Segal, 2009).

Gene-environment interaction in suicidal behaviour

Genes and life-stress

The first evidence of an interaction between genetic factors and environmental factors date back in 2003 with the publication of the study by Caspi et al. (2003). The study was performed on a large birth cohort of 847 Caucasian subjects followed from the age of 3 to 26, and genotyped for the 5-HTTLPR polymorphism.

Stressful life events occurring after the 21st birthday and before the 26th birthday were assessed with the aid of a life-history calendar. Past-year depressive symptoms, suicide attempts and recurrent suicidal thoughts were assessed at age 26. Results of the analyses showed a significant interaction between 5-HTTLPR polymorphism and stressful life events on depressive symptoms, major depression and suicidal ideation/attempt. In particular, life events predicted suicide ideation/ attempt among homozygous for the S-allele and heterozygous subjects, but not among homozygous for the L-allele. Nevertheless, a following study by Zalsman et al. (2006) failed to find a significant interaction between 5-HTTLPR and life events in suicidal behaviour in a sample of 191 patients affected by major depression, though succeeding in replicating the interaction on major depression and depressive severity. However, differences in samples size and characterization (847 vs. 191 subjects, population cohort vs. major depressives), genotyping (biallelic 5-HTTLPR vs. triallelic LA/ LG/S sub-type with rs25531), evaluation of life events and suicidal behaviour (past-year suicide attempt/ideation vs. lifetime suicide attempt) may have influenced the results obtained in this following study. In a further study on a sample of 850 school-aged children (Cicchetti et al., 2010), the 5-HTTLPR genotype has been found to be associated with suicidal ideation in maltreated children only (both emotionally abused/ neglected and physically/ sexually abused). Nevertheless, the effect of genotype was not significant when

considering children severely abused, i.e. exposed to three or four maltreatment subtypes. On the other hand, considering more recent stressful events, these have been reported to predict 1 to 10 years later depression and suicidality on a large twin sample (Coventry et al., 2010), but interaction with 5-HTTLPR was found, neither considering the 5-HTTLPR length polymorphism nor the triallelic 5-HTTLPR sub-type with rs25531.

Of note, Zalsman et al. (2006) also investigated separately childhood and recent events reporting no significant effect on both depression and suicidal behaviour. On the other hand, an earlier study had reported a significant impact of childhood abuse on major depression in interaction with the 5-HTTLPR genotype (Kaufman et al., 2004). Therefore, Gibb et al. (2006) performed a preliminary analysis on a small sample of psychiatric patients (n=30), of which 15 (50%) had a positive history of suicide attempt. Subjects were evaluated for childhood trauma by the Childhood trauma questionnaire (CTQ). The authors were able to demonstrate a significant interaction between the 5-HTTLPR polymorphism, physical and sexual abuse in suicidal behaviour. In a following study in substance dependence (Roy, Hu et al., 2007), the risk of suicide attempt was found to increase with increasing reports of childhood trauma scores, and such increase was exaggerated among those with low expression forms of the 5-HTTLPR genotype. However, recently Brezo et al. (2010), in their longitudinal study aimed to detect specific genetic effects on mood disorders and suicide, investigated 9 single nucleotide polymorphisms in SLC6A4 and found an interactive effect between rs3794808 and childhood physical abuse on the risk for mood disorders, but not suicidal behaviour.

In 2006, Wasserman et al. (2006) focused on another 5-HT gene in suicidal behaviour: the 5HTR1A. The sample under investigation was composed by 272 suicidal attempters and their parents (trios) evaluated for life events, prior suicidal behaviour and genotyped for

the rs6295 (-1019C/G) polymorphism. The authors could not replicate the finding of an over transmission of the G-allele in suicide attempters (Lemondé et al., 2003), though they could detect a strong trend for its over transmission in subjects characterized by high level of previous traumatic and/or stressful life events. However, a subsequent study on suicide victims reported more life events in those homozygous for the C-allele in the same 5HTR1A polymorphism (Videtic et al., 2009). As regards 5HTR2A, Brezo et al. (2010) in their extensive analysis of eleven 5-HT genes in mood disorders and suicide attempt, reported a significant effect on suicidal risk but only through interaction with sexual and physical abuse.

Only a few studies have analyzed other genes involved in serotonergic neurotransmission in interaction with stressful life events in suicidal behaviour. To our knowledge, only one and two studies respectively investigated TPH1 and TPH2. Zhang et al. (2010) reported a significant interaction between TPH2 (rs7305115) and negative life events in the preceding year on suicidal risk in a sample of patients affected by major depression, whilst Mann et al. (2008), considering another variant (rs4131347) and childhood abuse, failed to find interactive effects on suicidality in major depressive patients. To our knowledge, the only study investigating TPH1 did not find positive interaction with physical or sexual abuse (Brezo et al., 2010). Huang et al. (2004) focused on the MAOAgene and childhood adversity, but no interactive effects were detected on suicidal behaviour, though an association with childhood abuse and impulsive traits in males was detected. As stated before, a gene of recent interest for suicide is BDNF. In 2008, Perroud et al. (2008) evaluated a large sample of suicide attempters for age at onset, violence and repetition of suicidal behaviour, together with childhood trauma and the Val66Met polymorphism in BDNF. The authors reported an interaction between BDNF (Val/Val genotype) and sexual abuse on violent suicide.

They also found severity of childhood maltreatment associated with suicide repetition and younger age at onset. The same year, on a sample of 170 depressed patients, we reported a significant interaction between BDNF genotype and childhood emotional abuse on the risk of suicide attempt (Sarchiapone et al., 2008), supporting the evidence of an increased risk of suicide in Valallele carriers exposed to childhood trauma. Wasserman et al. (2008) investigated the potential interaction between life events and polymorphisms within two genes involved in the regulation to stress response of the hypothalamic-pituitary-adrenocortical (HPA) axis: the Corticotrophin-releasing hormone (CRH) and the Corticotrophin-releasing hormone receptor 1 (CRHR1) in a sample of 542 trios with suicide attempter offspring, evaluated for life events prior to a suicide attempt. No significant findings were obtained, except for a trend of over transmission of a variant in CRHR1 (rs4792887) in suicide attempters exposed to low levels of stressors. Recently, Roy et al. (2010) investigated the involvement of the genetic variants in another gene involved in HPA-axis regulation: FK506 binding protein 5 (FKBP5). FKBP5 was

found associated with suicide attempt both independently and in inter-action with childhood trauma.

A further gene of interest may be Regulator of G-protein signaling 2 (RGS2), encoding for a regulator factor of neuronal signaling. RGS2 was reported positive in suicidal behaviour in a study in the Japanese population (Cui et al., 2008). Recently, on a sample of individuals exposed to the 2004 Florida hurricane, the rs4606 polymorphism in RGS2 was found to be associated with increased levels of suicidal ideation, indicating a potential role of this genetic variant in the risk for suicidal behaviour in stress-exposed subjects (Amstadter et al., 2009).

Genes, suicide-related traits and life-stress

Genes have been hypothesized acting indirectly on suicide risk through intermediate phenotypes, such as personality traits correlated with suicidal tendencies. Therefore, many studies focused on the genetic bases of suicide have investigated impulsive aggression, neuroticism and negative emotionality as potential endophenotypes of suicidal tendencies. Within the context of suicidal behaviours, violent suicide attempt and measures of violence and aggression have been mainly

associated with 5-HTTLPR (Bayle et al., 2003; Zalsman et al., 2001), COMT (Baud et al., 2007; Calati et al., 2010; Rujescu et al., 2003), Mono-amine oxidase A (MAOA) (Courtet et al., 2005) and DOPA decarboxylase (DDC) (Giegling, Moreno-De-Luca et al., 2008). Impulsive suicide and impulsive traits have been again associated with 5-HTTLPR (Courtet et al., 2004) and COMT (Calati et al., 2010), but also with TPH1 (Galfalvy et al., 2009). Contrasting evidence has been obtained for 5HT2A, associated, on a hand, with non-impulsive suicide (Saiz et al., 2008a), low impulsive aggression (Zalsman et al., 2010) and anxiety-related traits (Serretti et al., 2007), and high levels of anger, aggression (Giegling et al., 2006) on the other. Other genes of interest are Tachykinin receptor 1 gene (TACR1) (Giegling et al., 2007), ABCG1 transporter (Gietl et al., 2007), Nitric-oxide (NOS) (Rujescu et al., 2008), and Axonal guidance gene SLIT2 (Sokolowski et al., 2010), all associated with measures of aggression.

Only few studies have investigated a potential 3-way interaction between genetic predisposition, personality traits and life events. To our knowledge, only two studies have so far reported positive evidence. Huang et al. (2004) investigated the MAOA gene, childhood abuse and aggressive-impulsive traits in a sample of psychiatric patients compared with healthy controls. The authors did not find a significant association with suicide attempt, but they reported an association with a history of abuse and high impulsivity in male individuals. The authors suggest a potential interaction between this genetic variant and childhood abuse in the risk of developing impulsive tendencies in male individuals.

A recent study investigated the role of nine candidate genes (5-HTTLPR, TPH1, TPH2, 5HTR1A, 5HTR2A, 5HTR1B, MAOA, COMT and BDNF) and childhood maltreatment in modulating anger-related traits in suicide attempters (Perroud et al., 2010). A functional polymorphism in the COMT gene was

found to modulate the association between sexual abuse and anger-traits. In the presence of sexual abuse, individuals carrying the Val high-activity allele displayed greater disposition toward anger than individuals homozygous for the Met allele. Notably, none of the serotonin-related genes influenced the effect of childhood abuse on anger traits.

Conclusions

Many different social, environmental, genetic and neurobiological factors are linked to the risk for suicide. However, on their own, these factors are unlikely to explain suicide, which is more likely to be dependent on the interaction between a genetic predisposition and exposure to environmental risk factors.

Differential pathways have been hypothesized, from indirect effects of genes on risk of developing psychiatric disorders and/or abnormal temperamental traits associated with suicidal behaviour that may be in turn elicited by acute stressors, to direct effects of early adversities on neurobiological systems regulating stress response. Recent evidence also suggests that early adversity may induce neurobiological alteration by affecting gene function via epigenetic programming. An additional contribution may be derived from behavioural traits correlated with suicide risk, such as impulsive-aggression, neuroticism and negative emotionality, which may either be explained by the genetic risk for suicide or independently interact with other genetic and environmental risk factors. To date, only few studies have addressed the complex interplay between genes, stressful events and, even less, temperamental traits.

In the present review of the literature we summarized the current knowledge of genetic factors that have been involved in suicidal behaviours and studies addressing the investigation of their interplay with environmental risk factors as well as suicide-related temperamental traits. We performed a broad search of the literature, applying only few restriction criteria (English language and reporting of any kind of genetic polymor-

phisms within genes), independently from study designs, size and ethnic composition of samples, and specific suicidal behaviour (i.e. completed vs. attempted). Moreover, for both brevity and clarity purposes, we have not gone into detail of specific polymorphisms, of samples investigated (all psychiatric vs. psychiatric probands compared to healthy controls, and specific composition of samples in terms of psychiatric diagnosis), and we made no assessment of the methodological quality of studies.

Therefore, the reader should take into account that both positive and negative findings reported may have different loadings depending on specific suicidal behaviour, study design, investigated populations and polymorphisms considered.

In conclusion, there is evidence of a genetic liability for suicidal behaviour, which may be modulated by environmental risk factors as well as individual psychological characteristics, such as temperamental traits. Given the complexity of suicidal behaviours and multiple sources of influence, future studies are required to address this complexity with novel methods of investigation and analysis, in order to identify the different trajectories leading to suicidal behaviour, possibly by combining evidence derived from different disciplines such as epidemiology, social science, psychology, genetics and neurobiology. Technologies and methods for studying genetics in complex disorders are evolving quickly, and an integrated approach will yield new insights.

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References

- Agerbo, E., Nordentoft, M., & Mortensen, P. B. (2002). **Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study.** *Bmj*, 325(7355), 74.
- Akar, T., Sayin, A., Bakkaloglu, Z., Cabuk, D. K., Kucukyildirim, S., Demirel, B., et al. (2010). **Investigation of serotonin transporter gene promoter (5-HTTLPR) and intron 2 (variable number of tandem repeats) polymorphisms with suicidal behavior in a Turkish population.** *DNA Cell Biol*, 29(8), 429–434.
- Amstadter, A. B., Koenen, K. C., Ruggiero, K. J., Acierno, R., Galea, S., Kilpatrick, D. G., et al. (2009). **Variation in RGS2 is associated with suicidal ideation in an epidemiological study of adults exposed to the 2004 Florida hurricanes.** *Arch Suicide Res*, 13(4), 349–357.
- Anderson, P. L., Tiro, J. A., Price, A. W., Bender, M. A., & Kaslow, N. J. (2002). **Additive impact of childhood emotional, physical, and sexual abuse on suicide attempts among low-income African American women.** *Suicide Life Threat Behav*, 32(2), 131–138.
- Anguelova, M., Benkelfat, C., & Turecki, G. (2003). **A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior.** *Mol Psychiatry*, 8(7), 646–653.
- Arias, B., Gasto, C., Catalan, R., Gutierrez, B., Pintor, L., & Fananas, L. (2001). **The 5-HT(2A) receptor gene 102T/C polymorphism is associated with suicidal behavior in depressed patients.** *Am J Med Genet*, 105(8), 801–804.
- Azenha, D., Alves, M., Matos, R., Santa, J. F., Silva, B., Cordeiro, C., et al. (2009). **Male specific association between the 5-HTR6 gene 267C/T SNP and suicide in the Portuguese population.** *Neurosci Lett*, 466(3), 128–130.
- Baca-Garcia, E., Vaquero-Lorenzo, C., Perez-Rodriguez, M. M., Gratacos, M., Bayes, M., Santiago-Mozos, R., et al. (2010). **Nucleotide variation in central nervous system genes among male suicide attempters.** *Am J Med Genet B Neuropsychiatr Genet*, 153B(1), 208–213.
- Baca-Garcia, E., Vaquero, C., Diaz-Sastre, C., Jimenez-Trevino, L., Saiz-Ruiz, J., Fernandez-Piqueras, J., et al. (2004). **Lack of association between polymorphic variations in the alpha 3 subunit GABA receptor gene (GABRA3) and suicide attempts.** *Prog Neuropsychopharmacol Biol Psychiatry*, 28(2), 409–412.
- Baldessarini, R. J., & Hennen, J. (2004). **Genetics of suicide: an overview.** *Harv Rev Psychiatry*, 12(1), 1–13.
- Baud, P. (2005). **Personality traits as intermediary phenotypes in suicidal behavior: genetic issues.** *Am J Med Genet C Semin Med Genet*, 133C(1), 34–42.
- Baud, P., Courtet, P., Perroud, N., Jollant, F., Buresi, C., & Malafosse, A. (2007). **Catechol-O-methyltransferase polymorphism (COMT) in suicide attempters: a possible gender effect on anger traits.** *Am J Med Genet B Neuropsychiatr Genet*, 144B(8), 1042–1047.

- Bayle, F. J., Leroy, S., Gourion, D., Millet, B., Olie, J. P., Poirier, M. F., et al. (2003). **5HTTLPR polymorphism in schizophrenic patients: further support for association with violent suicide attempts.** *Am J Med Genet B Neuropsychiatr Genet*, 119B(1), 13–17.
- Bellivier, F., Szoke, A., Henry, C., Lacoste, J., Bottos, C., Nosten-Bertrand, M., et al. (2000). **Possible association between serotonin transporter gene polymorphism and violent suicidal behavior in mood disorders.** *Biol Psychiatry*, 48(4), 319–322.
- Bertolote, J. M., Fleischmann, A., De Leo, D., & Wasserman, D. (2004). **Psychiatric diagnoses and suicide: revisiting the evidence.** *Crisis*, 25(4), 147–155.
- Bolton, J. M., & Robinson, J. (2010). **Population-attributable fractions of Axis I and Axis II mental disorders for suicide attempts: findings from a representative sample of the adult, noninstitutionalized US population.** *Am J Public Health*, 100(12), 2473–2480.
- Bondy, B., Kuznik, J., Baghai, T., Schule, C., Zwanzer, P., Minov, C., et al. (2000). **Lack of association of serotonin-2A receptor gene polymorphism (T102C) with suicidal ideation and suicide.** *Am J Med Genet*, 96(6), 831–835.
- Bonnier, B., Gorwood, P., Hamon, M., Sarfati, Y., Boni, C., & Hardy-Bayle, M. C. (2002). **Association of 5-HT(2A) receptor gene polymorphism with major affective disorders: the case of a subgroup of bipolar disorder with low suicide risk.** *Biol Psychiatry*, 51(9), 762–765.
- Borges, G., Nock, M. K., Haro Abad, J. M., Hwang, I., Sampson, N. A., Alonso, J., et al. (2010). **Twelve-month prevalence of and risk factors for suicide attempts in the world health organization world mental health surveys.** *J Clin Psychiatry*.
- Brenner, L. A., Homaifar, B. Y., Adler, L. E., Wolfman, J. H., & Kemp, J. (2009). **Suicidality and veterans with a history of traumatic brain injury: precipitants events, protective factors, and prevention strategies.** *Rehabil Psychol*, 54(4), 390–397.
- Brent, D. A., Bridge, J., Johnson, B. A., & Connolly, J. (1996). **Suicidal behavior runs in families. A controlled family study of adolescent suicide victims.** *Arch Gen Psychiatry*, 53(12), 1145–1152.
- Brezo, J., Bureau, A., Merette, C., Jomphe, V., Barker, E. D., Vitaro, F., et al. (2010). **Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: a 22-year longitudinal gene-environment study.** *Mol Psychiatry*, 15(8), 831–843.
- Brezo, J., Paris, J., & Turecki, G. (2006). **Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review.** *Acta Psychiatr Scand*, 113(3), 180–206.
- Brodsky, B. S., & Stanley, B. (2008). **Adverse childhood experiences and suicidal behavior.** *Psychiatr Clin North Am*, 31(2), 223–235.
- Bruffaerts, R., Demyttenaere, K., Borges, G., Haro, J. M., Chiu, W. T., Hwang, I., et al. (2010). **Childhood adversities as risk factors for onset and persistence of suicidal behaviour.** *Br J Psychiatry*, 197(1), 20–27.
- Calati, R., Porcelli, S., Giegling, I., Hartmann, A. M., Moller, H. J., De Ronchi, D., et al. (2010). **Catechol-o-methyltransferase gene modulation on suicidal behavior and personality traits: review, meta-analysis and association study.** *J Psychiatr Res*.
- Campi-Azevedo, A. C., Boson, W., De Marco, L., Romano-Silva, M. A., & Correa, H. (2003). **Association of the serotonin transporter promoter polymorphism with suicidal behavior.** *Mol Psychiatry*, 8(11), 899–900.
- Campos, S. B., Miranda, D. M., Souza, B. R., Pereira, P. A., Neves, F. S., Bicalho, M. A., et al. (2010). **Association of polymorphisms of the tryptophan hydroxylase 2 gene with risk for bipolar disorder or suicidal behavior.** *J Psychiatr Res*, 44(5), 271–274.
- Canli, T. (2008). **Toward a neurogenetic theory of neuroticism.** *Ann N Y Acad Sci*, 1129, 153–174.
- Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). **Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene.** *Science*, 301(5631), 386–389.
- Chen, C. K., Lin, S. K., Huang, M. C., Su, L. W., Hsiao, C. C., Chiang, Y. L., et al. (2007). **Analysis of association of clinical correlates and 5-HTTLPR polymorphism with suicidal behavior among Chinese methamphetamine abusers.** *Psychiatry Clin Neurosci*, 61(5), 479–486.
- Chong, S. A., Lee, W. L., Tan, C. H., Tay, A. H., Chan, A. O., & Tan, E. C. (2000). **Attempted suicide and polymorphism of the serotonin transporter gene in Chinese patients with schizophrenia.** *Psychiatry Res*, 97(2–3), 101–106.
- Cicchetti, D., Rogosch, F. A., Sturge-Apple, M., & Toth, S. L. (2010). **Interaction of child maltreatment and 5-HTT polymorphisms: suicidal ideation among children from low-SES backgrounds.** *J Pediatr Psychol*, 35(5), 536–546.
- Connor, K. M. (2006). **Assessment of resilience in the aftermath of trauma.** *J Clin Psychiatry*, 67 Suppl 2, 46–49.
- Contreras, J., Hernandez, S., Quezada, P., Dassori, A., Walss-Bass, C., Escamilla, M., et al. (2010). **Association of serotonin transporter promoter gene polymorphism (5-HTTLPR) with depression in Costa Rican schizophrenic patients.** *J Neurogenet*, 24(2), 83–89.
- Correa, H., Campi-Azevedo, A. C., De Marco, L., Boson, W., Viana, M. M., Guimaraes, M. M., et al. (2004). **Familial suicide behaviour: association with probands suicide attempt characteristics and 5-HTTLPR polymorphism.** *Acta Psychiatr Scand*, 110(6), 459–464.
- Courtet, P., Buresi, C., Abbar, M., Baud, P., Boulenger, J. P., Castelnaud, D., et al. (2003). **No association between non-violent suicidal behavior and the serotonin transporter promoter polymorphism.** *Am J Med Genet B Neuropsychiatr Genet*, 116B(1), 72–76.
- Courtet, P., Jollant, F., Buresi, C., Castelnaud, D., Mouthon, D., & Malafosse, A. (2005). **The monoamine oxidase A gene may influence the means used in suicide attempts.** *Psychiatr Genet*, 15(3), 189–193.
- Courtet, P., Picot, M. C., Bellivier, F., Torres, S., Jollant, F., Michelon, C., et al. (2004). **Serotonin transporter gene may be involved in short-term risk of subsequent suicide attempts.** *Biol Psychiatry*, 55(1), 46–51.
- Coventry, W. L., James, M. R., Eaves, L. J., Gordon, S. D., Gillespie, N. A., Ryan, L., et al. (2010). **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*, 153B(3), 757–765.
- Craig, M. C., & Murphy, D. G. (2007). **Estrogen: effects on normal brain function and neuropsychiatric disorders.** *Climacteric*, 10 Suppl 2, 97–104.
- Cui, H., Nishiguchi, N., Ivleva, E., Yanagi, M., Fukutake, M., Nushida, H., et al. (2008). **Association of RGS2 gene polymorphisms with suicide and increased RGS2 immunoreactivity in the postmortem brain of suicide victims.** *Neuropsychopharmacology*, 33(7), 1537–1544.
- Cui, H., Supriyanto, I., Asano, M., Ueno, Y., Nagasaki, Y., Nishiguchi, N., et al. (2010). **A common polymorphism in the 3'-UTR of the NOS1 gene was associated with completed suicides in Japanese male population.** *Prog Neuropsychopharmacol Biol Psychiatry*, 34(6), 992–996.
- Cuomo, C., Sarchiapone, M., Giannantonio, M. D., Mancini, M., & Roy, A. (2008). **Aggression, impulsivity, personality traits, and childhood trauma of prisoners with substance abuse and addiction.** *Am J Drug Alcohol Abuse*, 34(3), 339–345.
- Currier, D., & Mann, J. J. (2008). **Stress, genes and the biology of suicidal behavior.** *Psychiatr Clin North Am*, 31(2), 247–269.
- De Luca, V., Hlousek, D., Likhodi, O., Van Tol, H. H., Kennedy, J. L., & Wong, A. H. (2006). **The interaction between TPH2 promoter haplotypes and clinical-demographic risk factors in suicide victims with major psychoses.** *Genes Brain Behav*, 5(1), 107–110.
- De Luca, V., Likhodi, O., Kennedy, J. L., & Wong, A. H. (2007). **Differential expression and parent-of-origin effect of the 5-HT2A receptor gene C102T polymorphism: analysis of suicidality in schizophrenia and bipolar disorder.** *Am J Med Genet B Neuropsychiatr Genet*, 144B(3), 370–374.

- De Luca, V., Mueller, D. J., Tharmalingam, S., King, N., & Kennedy, J. L. (2004). **Analysis of the novel TPH2 gene in bipolar disorder and suicidality.** *Mol Psychiatry*, 9(10), 896–897.
- De Luca, V., Strauss, J., & Kennedy, J. L. (2008). **Power based association analysis (PBAT) of serotonergic and noradrenergic polymorphisms in bipolar patients with suicidal behaviour.** *Prog Neuropsychopharmacol Biol Psychiatry*, 32(1), 197–203.
- De Luca, V., Tharmalingam, S., & Kennedy, J. L. (2007). **Association study between the corticotropin-releasing hormone receptor 2 gene and suicidality in bipolar disorder.** *Eur Psychiatry*, 22(5), 282–287.
- De Luca, V., Tharmalingam, S., King, N., Strauss, J., Bulgin, N., & Kennedy, J. L. (2005). **Association study of a novel functional polymorphism of the serotonin transporter gene in bipolar disorder and suicidal behaviour.** *Psychopharmacology (Berl)*, 182(1), 128–131.
- De Luca, V., Tharmalingam, S., Muller, D. J., Wong, G., de Bartolomeis, A., & Kennedy, J. L. (2006). **Gene-gene interaction between MAOA and COMT in suicidal behavior: analysis in schizophrenia.** *Brain Res*, 1097(1), 26–30.
- De Luca, V., Tharmalingam, S., Sicard, T., & Kennedy, J. L. (2005). **Gene-gene interaction between MAOA and COMT in suicidal behavior.** *Neurosci Lett*, 383(1–2), 151–154.
- De Luca, V., Tharmalingam, S., Zai, C., Potapova, N., Strauss, J., Vincent, J., et al. (2010). **Association of HPA axis genes with suicidal behaviour in schizophrenia.** *J Psychopharmacol*, 24(5), 677–682.
- De Luca, V., Viggiano, E., Dhoot, R., Kennedy, J. L., & Wong, A. H. (2009). **Methylation and QTD analysis of the 5-HT2A receptor 102C allele: analysis of suicidality in major psychosis.** *J Psychiatr Res*, 43(5), 532–537.
- De Luca, V., Voineskos, D., Wong, G. W., Shinkai, T., Rothe, C., Strauss, J., et al. (2005). **Promoter polymorphism of second tryptophan hydroxylase isoform (TPH2) in schizophrenia and suicidality.** *Psychiatry Res*, 134(2), 195–198.
- De Luca, V., Zai, G., Tharmalingam, S., de Bartolomeis, A., Wong, G., & Kennedy, J. L. (2006). **Association study between the novel functional polymorphism of the serotonin transporter gene and suicidal behaviour in schizophrenia.** *Eur Neuropsychopharmacol*, 16(4), 268–271.
- Du, L., Faludi, G., Palkovits, M., Demeter, E., Bakish, D., Lapierre, Y. D., et al. (1999). **Frequency of long allele in serotonin transporter gene is increased in depressed suicide victims.** *Biol Psychiatry*, 46(2), 196–201.
- Du, L., Faludi, G., Palkovits, M., Sotonyi, P., Bakish, D., & Hrdina, P. D. (2002). **High activity-related allele of MAO-A gene associated with depressed suicide in males.** *Neuroreport*, 13(9), 1195–1198.
- Duman, R. S. (2009). **Neuronal damage and protection in the pathophysiology and treatment of psychiatric illness: stress and depression.** *Dialogues Clin Neurosci*, 11(3), 239–255.
- Eisenthal, S. (1967). **Suicide and aggression.** *Psychol Rep*, 21(3), 745–751.
- Ertugrul, A., Kennedy, J. L., Masellis, M., Basile, V. S., Jayatilake, K., & Meltzer, H. Y. (2004). **No association of the T102C polymorphism of the serotonin 2A receptor gene (HTR2A) with suicidality in schizophrenia.** *Schizophr Res*, 69(2–3), 301–305.
- Etain, B., Roussea, A., Roy, I., Henry, C., Malafosse, A., Buresi, C., et al. (2004). **Lack of association between 5HT2A receptor gene haplotype, bipolar disorder and its clinical subtypes in a West European sample.** *Am J Med Genet B Neuropsychiatr Genet*, 129B(1), 29–33.
- Fanous, A. H., Chen, X., Wang, X., Amdur, R., O'Neill, F. A., Walsh, D., et al. (2009). **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*, 150B(3), 411–417.
- Finckh, U., Rommelspacher, H., Kuhn, S., Dufeu, P., Otto, G., Heinz, A., et al. (1997). **Influence of the dopamine D2 receptor (DRD2) genotype on neuroadaptive effects of alcohol and the clinical outcome of alcoholism.** *Pharmacogenetics*, 7(4), 271–281.
- Fukutake, M., Hishimoto, A., Nishiguchi, N., Nushida, H., Ueno, Y., Shirakawa, O., et al. (2008). **Association of alpha2A-adrenergic receptor gene polymorphism with susceptibility to suicide in Japanese females.** *Prog Neuropsychopharmacol Biol Psychiatry*, 32(6), 1428–1433.
- Galfalvy, H., Huang, Y. Y., Oquendo, M. A., Currier, D., & Mann, J. J. (2009). **Increased risk of suicide attempt in mood disorders and TPH1 genotype.** *J Affect Disord*, 115(3), 331–338.
- Geijer, T., Frisch, A., Persson, M. L., Wasserman, D., Rockah, R., Michaelovsky, E., et al. (2000). **Search for association between suicide attempt and serotonergic polymorphisms.** *Psychiatr Genet*, 10(1), 19–26.
- Gerra, G., Garofano, L., Santoro, G., Bosari, S., Pellegrini, C., Zaimovic, A., et al. (2004). **Association between low-activity serotonin transporter genotype and heroin dependence: behavioral and personality correlates.** *Am J Med Genet B Neuropsychiatr Genet*, 126B(1), 37–42.
- Gibb, B. E., McGeary, J. E., Beevers, C. G., & Miller, I. W. (2006). **Serotonin transporter (5-HTTLPR) genotype, childhood abuse, and suicide attempts in adult psychiatric inpatients.** *Suicide Life Threat Behav*, 36(6), 687–693.
- Giegling, I., Hartmann, A. M., Moller, H. J., & Rujescu, D. (2006). **Anger- and aggression-related traits are associated with polymorphisms in the 5-HT-2A gene.** *J Affect Disord*, 96(1–2), 75–81.
- Giegling, I., Moreno-De-Luca, D., Rujescu, D., Schneider, B., Hartmann, A. M., Schnabel, A., et al. (2008). **Dopa decarboxylase and tyrosine hydroxylase gene variants in suicidal behavior.** *Am J Med Genet B Neuropsychiatr Genet*, 147(3), 308–315.
- Giegling, I., Rujescu, D., Mandelli, L., Schneider, B., Hartmann, A. M., Schnabel, A., et al. (2007). **Tachykinin receptor 1 variants associated with aggression in suicidal behavior.** *Am J Med Genet B Neuropsychiatr Genet*, 144B(6), 757–761.
- Giegling, I., Rujescu, D., Mandelli, L., Schneider, B., Hartmann, A. M., Schnabel, A., et al. (2008). **Estrogen receptor gene 1 variants are not associated with suicidal behavior.** *Psychiatry Res*, 160(1), 1–7.
- Gietl, A., Giegling, I., Hartmann, A. M., Schneider, B., Schnabel, A., Maurer, K., et al. (2007). **ABCG1 gene variants in suicidal behavior and aggression-related traits.** *Eur Neuropsychopharmacol*, 17(6–7), 410–416.
- Goodwin, R. D., Beautrais, A. L., & Fergusson, D. M. (2004). **Familial transmission of suicidal ideation and suicide attempts: evidence from a general population sample.** *Psychiatry Res*, 126(2), 159–165.
- Gorlyn, M. (2005). **Impulsivity in the prediction of suicidal behavior in adolescent populations.** *Int J Adolesc Med Health*, 17(3), 205–209.
- Gorwood, P., Batel, P., Ades, J., Hamon, M., & Boni, C. (2000). **Serotonin transporter gene polymorphisms, alcoholism, and suicidal behavior.** *Biol Psychiatry*, 48(4), 259–264.
- Hattori, H., Shirakawa, O., Nishiguchi, N., Nushida, H., Ueno, Y., & Maeda, K. (2006). **No evidence of an association between tyrosine hydroxylase gene polymorphisms and suicide victims.** *Kobe J Med Sci*, 52(6), 195–200.
- Heikkinen, M., Aro, H., & Lonnqvist, J. (1994). **Recent life events, social support and suicide.** *Acta Psychiatr Scand Suppl*, 377, 65–72.
- Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., et al. (1996). **Allelic variation of human serotonin transporter gene expression.** *J Neurochem*, 66(6), 2621–2624.
- Heim, C., & Nemeroff, C. B. (2001). **The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies.** *Biol Psychiatry*, 49(12), 1023–1039.
- Helbecque, N., Sparks, D. L., Hunsaker, J. C., 3rd, & Amouyel, P. (2006). **The serotonin transporter promoter polymorphism and suicide.** *Neurosci Lett*, 400(1–2), 13–15.
- Higley, J. D., Suomi, S. J., & Linnoila, M. (1992). **A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys.** *Biol Psychiatry*, 32(2), 127–145.
- Hobbs, M., & McLaren, S. (2009). **The interrelations of agency, depression, and suicidal ideation among older adults.** *Suicide Life Threat Behav*, 39(2), 161–171.

- Hong, C. J., Huo, S. J., Yen, F. C., Tung, C. L., Pan, G. M., & Tsai, S. J. (2003). Association study of a brain-derived neurotrophic-factor genetic polymorphism and mood disorders, age of onset and suicidal behavior. *Neuropsychobiology*, 48(4), 186–189.
- Huang, Y. Y., Cate, S. P., Battistuzzi, C., Oquendo, M. A., Brent, D., & Mann, J. J. (2004). An association between a functional polymorphism in the monoamine oxidase a gene promoter, impulsive traits and early abuse experiences. *Neuropsychopharmacology*, 29(8), 1498–1505.
- Hwang, J. P., Tsai, S. J., Hong, C. J., Yang, C. H., Lin, J. F., & Yang, Y. M. (2006). The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression. *Neurobiol Aging*, 27(12), 1834–1837.
- Iga, J., Ueno, S., Yamauchi, K., Numata, S., Tayoshi-Shibuya, S., Kinouchi, S., et al. (2007). 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*, 144B(8), 1003–1006.
- Janowsky, D. S. (2001). Introversion and extroversion: implications for depression and suicidality. *Curr Psychiatry Rep*, 3(6), 444–450.
- Johann, M., Putzhammer, A., Eichhammer, P., & Wodarz, N. (2005). Association of the –141C Del variant of the dopamine D2 receptor (DRD2) with positive family history and suicidality in German alcoholics. *Am J Med Genet B Neuropsychiatr Genet*, 132B(1), 46–49.
- Johnson, B. A., Brent, D. A., Bridge, J., & Connolly, J. (1998). The familial aggregation of adolescent suicide attempts. *Acta Psychiatr Scand*, 97(1), 18–24.
- Joiner, T. E., Jr., Johnson, F., & Soderstrom, K. (2002). Association between serotonin transporter gene polymorphism and family history of attempted and completed suicide. *Suicide Life Threat Behav*, 32(3), 329–332.
- Kaufman, J., Yang, B. Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J. H., et al. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci U S A*, 101(49), 17316–17321.
- Kendler, K. S. (2010). Genetic and environmental pathways to suicidal behavior: reflections of a genetic epidemiologist. *Eur Psychiatry*, 25(5), 300–303.
- Kessler, R., McGonagle, K., Zhao, S., Nelson, C., Hughes, M., Eshleman, S., et al. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry*, 51(1), 8–19.
- Kessler, R. C., Borges, G., & Walters, E. E. (1999). Prevalence of and risk factors for lifetime suicide attempts in the national comorbidity survey. *Archives of General Psychiatry*, 56(7), 617–626.
- Khait, V. D., Huang, Y. Y., Zalsman, G., Oquendo, M. A., Brent, D. A., Harkavy-Friedman, J. M., et al. (2005). Association of serotonin 5-HT_{2A} receptor binding and the T102C polymorphism in depressed and healthy Caucasian subjects. *Neuropsychopharmacology*, 30(1), 166–172.
- Kia-Keating, B. M., Glatt, S. J., & Tsuang, M. T. (2007). Meta-analyses suggest association between COMT, but not HTR1B, alleles, and suicidal behavior. *Am J Med Genet B Neuropsychiatr Genet*, 144B(8), 1048–1053.
- Kim, B., Kim, C. Y., Hong, J. P., Kim, S. Y., Lee, C., & Joo, Y. H. (2008). Brain-derived neurotrophic factor Val/Met polymorphism and bipolar disorder. Association of the Met allele with suicidal behavior of bipolar patients. *Neuropsychobiology*, 58(2), 97–103.
- Klerman, G. L. (1987). Clinical epidemiology of suicide. *J Clin Psychiatry*, 48 Suppl, 33–38.
- Kohli, M. A., Salyakina, D., Pfennig, A., Lucae, S., Horstmann, S., Menke, A., et al. (2010). Association of genetic variants in the neurotrophic receptor-encoding gene NTRK2 and a lifetime history of suicide attempts in depressed patients. *Arch Gen Psychiatry*, 67(4), 348–359.
- Krysinska, K., Lester, D., & Martin, G. (2009). Suicidal behavior after a traumatic event. *J Trauma Nurs*, 16(2), 103–110.
- Kunugi, H., Hashimoto, R., Yoshida, M., Tatsumi, M., & Kamijima, K. (2004). 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*, 129B(1), 44–46.
- Kunugi, H., Ishida, S., Kato, T., Tatsumi, M., Sakai, T., Hattori, M., et al. (1999). A functional polymorphism in the promoter region of monoamine oxidase-A gene and mood disorders. *Mol Psychiatry*, 4(4), 393–395.
- Labonte, B., & Turecki, G. (2010). The epigenetics of suicide: explaining the biological effects of early life environmental adversity. *Arch Suicide Res*, 14(4), 291–310.
- Lahey, B. B. (2009). Public health significance of neuroticism. *Am Psychol*, 64(4), 241–256.
- Lemond, S., Turecki, G., Bakish, D., Du, L., Hrdina, P. D., Bown, C. D., et al. (2003). Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J Neurosci*, 23(25), 8788–8799.
- Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, 274(5292), 1527–1531.
- Lester, D. (1989). A neurotransmitter basis for Eysenck's theory of personality. *Psychol Rep*, 64(1), 189–190.
- Levi, F., La Vecchia, C., Lucchini, F., Negri, E., Saxena, S., Maulik, P. K., et al. (2003). Trends in mortality from suicide, 1965–99. *Acta Psychiatr Scand*, 108(5), 341–349.
- Lin, P. Y., & Tsai, G. (2004). Association between serotonin transporter gene promoter polymorphism and suicide: results of a meta-analysis. *Biol Psychiatry*, 55(10), 1023–1030.
- Lopez de Lara, C., Brezo, J., Rouleau, G., Lesage, A., Dumont, M., Alda, M., et al. (2007). Effect of tryptophan hydroxylase-2 gene variants on suicide risk in major depression. *Biol Psychiatry*, 62(1), 72–80.
- Lopez de Lara, C., Dumais, A., Rouleau, G., Lesage, A., Dumont, M., Chawky, N., et al. (2006). STin2 variant and family history of suicide as significant predictors of suicide completion in major depression. *Biol Psychiatry*, 59(2), 114–120.
- Maniglio, R. (2010). The role of child sexual abuse in the etiology of suicide and non-suicidal self-injury. *Acta Psychiatr Scand*.
- Mann, J. J., Brent, D. A., & Arango, V. (2001). The neurobiology and genetics of suicide and attempted suicide: a focus on the serotonergic system. *Neuropsychopharmacology*, 24(5), 467–477.
- Mann, J. J., Currier, D., Murphy, L., Huang, Y. Y., Galfalvy, H., Brent, D., et al. (2008). No association between a TPH2 promoter polymorphism and mood disorders or monoamine turnover. *J Affect Disord*, 106(1–2), 117–121.
- Mann, J. J., Huang, Y. Y., Underwood, M. D., Kassir, S. A., Oppenheim, S., Kelly, T. M., et al. (2000). A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch Gen Psychiatry*, 57(8), 729–738.
- Mann, J. J., Waternaux, C., Haas, G. L., & Malone, K. M. (1999). Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry*, 156(2), 181–189.
- Martin-Guerrero, I., Callado, L. F., Saitua, K., Rivero, G., Garcia-Orad, A., & Meana, J. J. (2006). The N251K functional polymorphism in the alpha(2A)-adrenoceptor gene is not associated with depression: a study in suicide completers. *Psychopharmacology (Berl)*, 184(1), 82–86.
- Maurex, L., Zaboli, G., Ohman, A., Asberg, M., & Leopardi, R. (2010). The serotonin transporter gene polymorphism (5-HTTLPR) and affective symptoms among women diagnosed with borderline personality disorder. *Eur Psychiatry*, 25(1), 19–25.
- McGregor, S., Strauss, J., Bulgin, N., De Luca, V., George, C. J., Kovacs, M., et al. (2007). p75(NTR) gene and suicide attempts in young adults with a history of childhood-onset mood disorder. *Am J Med Genet B Neuropsychiatr Genet*, 144B(5), 696–700.
- Mergen, H., Demirel, B., Akar, T., & Senol, E. (2006). Lack of association between the serotonin transporter and tryptophan hydroxylase gene polymorphisms and completed suicide. *Psychiatr Genet*, 16(2), 53.

- Molnar, B. E., Berkman, L. F., & Buka, S. L. (2001). **Psychopathology, childhood sexual abuse and other childhood adversities: relative links to subsequent suicidal behaviour in the US.** *Psychol Med*, 31(6), 965–977.
- Mortensen, P. B., Agerbo, E., Erikson, T., Qin, P., & Westergaard-Nielsen, N. (2000). **Psychiatric illness and risk factors for suicide in Denmark.** *Lancet*, 355(9197), 9–12.
- Mouri, K., Hishimoto, A., Fukutake, M., Shirowa, K., Asano, M., Nagasaki, Y., et al. (2009). **TPH2 is not a susceptibility gene for suicide in Japanese population.** *Prog Neuropsychopharmacol Biol Psychiatry*, 33(8), 1546–1550.
- Must, A., Tasa, G., Lang, A., Vasar, E., Koks, S., Maron, E., et al. (2009). **Variation in tryptophan hydroxylase-2 gene is not associated to male completed suicide in Estonian population.** *Neurosci Lett*, 453(2), 112–114.
- Netter, P., & Ramsayer, T. (1989). **Serotonin-ergic effects on sensory and motor responses in extraverts and introverts.** *Int Clin Psychopharmacol*, 4 Suppl 1, 21–26.
- Neves, F. S., Malloy-Diniz, L., Romano-Silva, M. A., Campos, S. B., Miranda, D. M., De Marco, L., et al. (2010). **The role of BDNF genetic polymorphisms in bipolar disorder with psychiatric comorbidities.** *J Affect Disord*.
- Neves, F. S., Silveira, G., Romano-Silva, M. A., Malloy-Diniz, L., Ferreira, A. A., De Marco, L., et al. (2008). **Is the 5-HTTLPR polymorphism associated with bipolar disorder or with suicidal behavior of bipolar disorder patients?** *Am J Med Genet B Neuropsychiatr Genet*, 147B(1), 114–116.
- New, A. S., Gelernter, J., Goodman, M., Mitropoulou, V., Koenigsberg, H., Silverman, J., et al. (2001). **Suicide, impulsive aggression, and HTR1B genotype.** *Biol Psychiatry*, 50(1), 62–65.
- Nishiguchi, N., Shirakawa, O., Ono, H., Nishimura, A., Nushida, H., Ueno, Y., et al. (2002). **Lack of an association between 5-HT1A receptor gene structural polymorphisms and suicide victims.** *Am J Med Genet*, 114(4), 423–425.
- Nrugham, L., Holen, A., & Sund, A. M. (2010). **Associations between attempted suicide, violent life events, depressive symptoms, and resilience in adolescents and young adults.** *J Nerv Ment Dis*, 198(2), 131–136.
- Okamura, K., Shirakawa, O., Nishiguchi, N., Ono, H., Nushida, H., Ueno, Y., et al. (2005). **Lack of an association between 5-HT receptor gene polymorphisms and suicide victims.** *Psychiatry Clin Neurosci*, 59(3), 345–349.
- Omrani, M. D., Bushehri, B., Bagheri, M., Salari-Lak, S., Alipour, A., Anoshae, M. R., et al. (2009). **Role of IL-10 -1082, IFN- γ +874, and TNF- α -308 genes polymorphisms in suicidal behavior.** *Arch Suicide Res*, 13(4), 330–339.
- Ono, H., Shirakawa, O., Nishiguchi, N., Nishimura, A., Nushida, H., Ueno, Y., et al. (2001). **Serotonin 2A receptor gene polymorphism is not associated with completed suicide.** *J Psychiatr Res*, 35(3), 173–176.
- Oquendo, M. A., & Mann, J. J. (2000). **The biology of impulsivity and suicidality.** *Psychiatr Clin North Am*, 23(1), 11–25.
- Park, Y. J., Ryu, H., Han, K., Kwon, J. H., Kim, H. K., Kang, H. C., et al. (2010). **Suicidal ideation in adolescents: an explanatory model using LISREL.** *West J Nurs Res*, 32(2), 168–184.
- Paykel, E. S., Prusoff, B. A., & Myers, J. K. (1975). **Suicide attempts and recent life events. A controlled comparison.** *Arch Gen Psychiatry*, 32(3), 327–333.
- Perepletchikova, F., & Kaufman, J. (2010). **Emotional and behavioral sequelae of childhood maltreatment.** *Curr Opin Pediatr*, 22(5), 610–615.
- Perez-Rodriguez, M. M., Weinstein, S., New, A. S., Bevilacqua, L., Yuan, Q., Zhou, Z., et al. (2010). **Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls.** *J Psychiatr Res*, 44(15), 1075–1081.
- Perroud, N., Courtet, P., Vincze, I., Jaussent, I., Jollant, F., Bellivier, F., et al. (2008). **Interaction between BDNF Val66Met and childhood trauma on adult's violent suicide attempt.** *Genes Brain Behav*, 7(3), 314–322.
- Perroud, N., Jaussent, I., Guillaume, S., Bellivier, F., Baud, P., Jollant, F., et al. (2010). **COMT but not serotonin-related genes modulates the influence of childhood abuse on anger traits.** *Genes Brain Behav*, 9(2), 193–202.
- Perroud, N., Neidhart, E., Petit, B., Vessaz, M., Laforge, T., Relecom, C., et al. (2010). **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*, 153B(4), 909–918.
- Persson, M. L., Geijer, T., Wasserman, D., Rockah, R., Frisch, A., Michaelovsky, E., et al. (1999). **Lack of association between suicide attempt and a polymorphism at the dopamine receptor D4 locus.** *Psychiatr Genet*, 9(2), 97–100.
- Pietrzak, R. H., Goldstein, M. B., Malley, J. C., Rivers, A. J., Johnson, D. C., & Southwick, S. M. (2010). **Risk and protective factors associated with suicidal ideation in veterans of Operations Enduring Freedom and Iraqi Freedom.** *J Affect Disord*, 123(1–3), 102–107.
- Preuss, U. W., Koller, G., Bahlmann, M., Soyka, M., & Bondy, B. (2000). **No association between suicidal behavior and 5-HT2A-T102C polymorphism in alcohol dependents.** *Am J Med Genet*, 96(6), 877–878.
- Preuss, U. W., Koller, G., Soyka, M., & Bondy, B. (2001). **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*, 50(8), 636–639.
- Pritchard, C., & Hansen, L. (2005). **Comparison of suicide in people aged 65–74 and 75+ by gender in England and Wales and the major Western countries 1979–1999.** *Int J Geriatr Psychiatry*, 20(1), 17–25.
- Pungercic, G., Videtic, A., Pestotnik, A., Pajnic, I. Z., Zupanc, T., Balazic, J., et al. (2006). **Serotonin transporter gene promoter (5-HTTLPR) and intron 2 (VNTR) polymorphisms: a study on Slovenian population of suicide victims.** *Psychiatr Genet*, 16(5), 187–191.
- Purselle, D. C., & Nemeroff, C. B. (2003). **Serotonin transporter: a potential substrate in the biology of suicide.** *Neuropsychopharmacology*, 28(4), 613–619.
- Roy, A. (2001). **Childhood trauma and hostility as an adult: relevance to suicidal behavior.** *Psychiatry Res*, 102(1), 97–101.
- Roy, A. (2002). **Urinary free cortisol and childhood trauma in cocaine dependent adults.** *J Psychiatr Res*, 36(3), 173–177.
- Roy, A., Gorodetsky, E., Yuan, Q., Goldman, D., & Enoch, M. A. (2010). **Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide.** *Neuropsychopharmacology*, 35(8), 1674–1683.
- Roy, A., Hu, X. Z., Janal, M. N., & Goldman, D. (2007). **Interaction between childhood trauma and serotonin transporter gene variation in suicide.** *Neuropsychopharmacology*, 32(9), 2046–2052.
- Roy, A., Rylander, G., Forslund, K., Asberg, M., Mazzanti, C. M., Goldman, D., et al. (2001). **Excess tryptophan hydroxylase 17 779C allele in surviving cotwins of monozygotic twin suicide victims.** *Neuropsychobiology*, 43(4), 233–236.
- Roy, A., Sarchiapone, M., & Carli, V. (2007). **Low resilience in suicide attempters.** *Arch Suicide Res*, 11(3), 265–269.
- Saiz, P. A., Garcia-Portilla, P., Paredes, B., Arango, C., Morales, B., Alvarez, V., et al. (2008b). **Association study of the interleukin-1 gene complex and tumor necrosis factor alpha gene with suicide attempts.** *Psychiatr Genet*, 18(3), 147–150.
- Sarchiapone, M., Carli, V., Cuomo, C., & Roy, A. (2007). **Childhood trauma and suicide attempts in patients with unipolar depression.** *Depress Anxiety*, 24(4), 268–272.
- Sarchiapone, M., Carli, V., di Giannantonio, M. D., & Roy, A. (2009). **Risk factors for attempting suicide in prisoners.** *Suicide Life Threat Behav*, 39(3), 343–350.
- Sarchiapone, M., Carli, V., Roy, A., Iacoviello, L., Cuomo, C., Latella, M. C., et al. (2008). **Association of polymorphism (Val66Met) of brain-derived neurotrophic factor with suicide attempts in depressed patients.** *Neuropsychobiology*, 57(3), 139–145.

- Sarchiapone, M., Jaussent, I., Roy, A., Carli, V., Guillaume, S., Jollant, F., et al. (2009). **Childhood trauma as a correlative factor of suicidal behavior - via aggression traits. Similar results in an Italian and in a French sample.** *Eur Psychiatry*, 24(1), 57–62.
- Savitz, J. B., Cupido, C. L., & Ramesar, R. S. (2006). **Trends in suicidology: personality as an endophenotype for molecular genetic investigations.** *PLoS Med*, 3(5), e107.
- Sawiniec, J., Borkowski, K., Ginalska, G., & Lewandowska-Stanek, H. (2007). **Association between 5-hydroxytryptamine 1A receptor gene polymorphism and suicidal behavior.** *Przegl Lek*, 64(4–5), 208–211.
- Schenkel, L. C., Segal, J., Becker, J. A., Manfro, G. G., Bianchin, M. M., & Leistner-Segal, S. (2010). **The BDNF Val66Met polymorphism is an independent risk factor for high lethality in suicide attempts of depressed patients.** *Prog Neuropsychopharmacol Biol Psychiatry*, 34(6), 940–944.
- Schmidtke, A., Bille-Brahe, U., DeLeo, D., Kerkhof, A., Bjerke, T., Crepet, P., et al. (1996). **Attempted suicide in Europe: rates, trends and sociodemographic characteristics of suicide attempters during the period 1989–1992. Results of the WHO/EURO Multicentre Study on Parasuicide.** *Acta Psychiatr Scand*, 93(5), 327–338.
- Segal, D. L. (2009). **Self-reported history of sexual coercion and rape negatively impacts resilience to suicide among women students.** *Death Stud*, 33(9), 848–855.
- Segal, J., Schenkel, L. C., Oliveira, M. H., Salum, G. A., Bau, C. H., Manfro, G. G., et al. (2009). **Novel allelic variants in the human serotonin transporter gene linked polymorphism (5-HTTLPR) among depressed patients with suicide attempt.** *Neurosci Lett*, 451(1), 79–82.
- Sequeira, A., Mamdani, F., Lalovic, A., Anguelova, M., Lesage, A., Seguin, M., et al. (2004). **Alpha 2A adrenergic receptor gene and suicide.** *Psychiatry Res*, 125(2), 87–93.
- Serretti, A., Calati, R., Giegling, I., Hartmann, A. M., Moller, H. J., Colombo, C., et al. (2007). **5-HT2A SNPs and the Temperament and Character Inventory.** *Prog Neuropsychopharmacol Biol Psychiatry*, 31(6), 1275–1281.
- Serretti, A., Calati, R., Giegling, I., Hartmann, A. M., Moller, H. J., & Rujescu, D. (2009). **Serotonin receptor HTR1A and HTR2C variants and personality traits in suicide attempters and controls.** *J Psychiatr Res*, 43(5), 519–525.
- Serretti, A., Mandelli, L., Giegling, I., Schneider, B., Hartmann, A. M., Schnabel, A., et al. (2007). **HTR2C and HTR1A gene variants in German and Italian suicide attempters and completers.** *Am J Med Genet B Neuropsychiatr Genet*, 144B(3), 291–299.
- Shen, Y., Li, H., Gu, N., Tan, Z., Tang, J., Fan, J., et al. (2004). **Relationship between suicidal behavior of psychotic inpatients and serotonin transporter gene in Han Chinese.** *Neurosci Lett*, 372(1–2), 94–98.
- Silverman, M. M., Berman, A. L., Sanddal, N. D., O'Carroll P, W., & Joiner, T. E. (2007). **Rebuilding the tower of Babel: a revised nomenclature for the study of suicide and suicidal behaviors. Part 2: Suicide-related ideations, communications, and behaviors.** *Suicide Life Threat Behav*, 37(3), 264–277.
- Sokolowski, M., Wasserman, J., & Wasserman, D. (2010). **Association of polymorphisms in the SLIT2 axonal guidance gene with anger in suicide attempters.** *Mol Psychiatry*, 15(1), 10–11.
- Suda, A., Kawanishi, C., Kishida, I., Sato, R., Yamada, T., Nakagawa, M., et al. (2009). **Dopamine D2 receptor gene polymorphisms are associated with suicide attempt in the Japanese population.** *Neuropsychobiology*, 59(2), 130–134.
- Sundermann, E. E., Maki, P. M., & Bishop, J. R. (2010). **A review of estrogen receptor alpha gene (ESR1) polymorphisms, mood, and cognition.** *Menopause*, 17(4), 874–886.
- Tan, E. C., Chong, S. A., Chan, A. O., & Tan, C. H. (2002). **No evidence for association of the T102C polymorphism in the serotonin type 2A receptor with suicidal behavior in schizophrenia.** *Am J Med Genet*, 114(3), 321–322.
- Tanney, B. L. (2000). **Psychiatric diagnoses and suicidal acts.** In *Comprehensive Textbook of Suicidology* (pp. 311–341). New York: Guilford.
- Tsai, S. J., Wang, Y. C., Hong, C. J., & Chiu, H. J. (2003). **Association study of oestrogen receptor alpha gene polymorphism and suicidal behaviours in major depressive disorder.** *Psychiatr Genet*, 13(1), 19–22.
- Turecki, G., Briere, R., Dewar, K., Antonetti, T., Lesage, A. D., Seguin, M., et al. (1999). **Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide.** *Am J Psychiatry*, 156(9), 1456–1458.
- Vaquero-Lorenzo, C., Baca-Garcia, E., Diaz-Hernandez, M., Perez-Rodriguez, M. M., Fernandez-Navarro, P., Giner, L., et al. (2008). **Association study of two polymorphisms of the serotonin-2A receptor gene and suicide attempts.** *Am J Med Genet B Neuropsychiatr Genet*, 147B(5), 645–649.
- Videtic, A., Pungercic, G., Pajnic, I. Z., Zupanc, T., Balazic, J., Tomori, M., et al. (2006). **Association study of seven polymorphisms in four serotonin receptor genes on suicide victims.** *Am J Med Genet B Neuropsychiatr Genet*, 141B(6), 669–672.
- Videtic, A., Zupanc, T., Pregelj, P., Balazic, J., Tomori, M., & Komel, R. (2009). **Suicide, stress and serotonin receptor 1A promoter polymorphism -1019C>G in Slovenian suicide victims.** *Eur Arch Psychiatry Clin Neurosci*, 259(4), 234–238.
- Vincze, I., Perroud, N., Buresi, C., Baud, P., Bellivier, F., Etain, B., et al. (2008). **Association between brain-derived neurotrophic factor gene and a severe form of bipolar disorder, but no interaction with the serotonin transporter gene.** *Bipolar Disord*, 10(5), 580–587.
- von Borczyskowski, A., Lindblad, F., Vinnerljung, B., Reintjes, R., & Hjern, A. (2010). **Familial factors and suicide: an adoption study in a Swedish National Cohort.** *Psychol Med*, 1–10.
- Voracek, M., & Loibl, L. M. (2007). **Genetics of suicide: a systematic review of twin studies.** *Wien Klin Wochenschr*, 119(15–16), 463–475.
- Wang, S., Zhang, K., Xu, Y., Sun, N., Shen, Y., & Xu, Q. (2009). **An association study of the serotonin transporter and receptor genes with the suicidal ideation of major depression in a Chinese Han population.** *Psychiatry Res*, 170(2–3), 204–207.
- Wasserman, D., Cheng, Q., & Jiang, G. X. (2005). **Global suicide rates among young people aged 15–19.** *World Psychiatry*, 4(2), 114–120.
- Wasserman, D., Geijer, T., Sokolowski, M., Frisch, A., Michaelovsky, E., Weizman, A., et al. (2007). **Association of the serotonin transporter promoter polymorphism with suicide attempters with a high medical damage.** *Eur Neuropsychopharmacol*, 17(3), 230–233.
- Wasserman, D., Geijer, T., Sokolowski, M., Rozanov, V., & Wasserman, J. (2006). **The serotonin 1A receptor C(-1019)G polymorphism in relation to suicide attempt.** *Behav Brain Funct*, 2, 14.
- Wasserman, D., Sokolowski, M., Rozanov, V., & Wasserman, J. (2008). **The CRHR1 gene: a marker for suicidality in depressed males exposed to low stress.** *Genes Brain Behav*, 7(1), 14–19.
- Wasserman, D., & Wasserman, C. (2009). *Oxford Textbook of Suicidology and Suicide Prevention: A Global Perspective*. New York: Oxford University Press.
- Wasserman, D., Wasserman, J., Rozanov, V., & Sokolowski, M. (2009). **Depression in suicidal males: genetic risk variants in the CRHR1 gene.** *Genes Brain Behav*, 8(1), 72–79.
- WHO. (2002). *World report on violence and health*. Geneva: World Health Organization.
- Yoon, H. K., & Kim, Y. K. (2008). **Association between serotonin-related gene polymorphisms and suicidal behavior in depressive patients.** *Prog Neuropsychopharmacol Biol Psychiatry*, 32(5), 1293–1297.
- Yoon, H. K., & Kim, Y. K. (2009). **TPH2 -703G/T SNP may have important effect on susceptibility to suicidal behavior in major depression.** *Prog Neuropsychopharmacol Biol Psychiatry*, 33(3), 403–409.

Zalsman, G., Anderson, G. M., Peskin, M., Frisch, A., King, R. A., Vekslerchik, M., et al. (2005). **Relationships between serotonin transporter promoter polymorphism, platelet serotonin transporter binding and clinical phenotype in suicidal and non-suicidal adolescent inpatients.** *J Neural Transm*, 112(2), 309–315.

Zalsman, G., Frisch, A., Baruch-Movshovits, R., Sher, L., Michaelovsky, E., King, R. A., et al. (2005). **Family-based association study of 5-HT(2A) receptor T102C polymorphism and suicidal behavior in Ashkenazi inpatient adolescents.** *Int J Adolesc Med Health*, 17(3), 231–238.

Zalsman, G., Frisch, A., Bromberg, M., Gelernter, J., Michaelovsky, E., Campino, A., et al. (2001). **Family-based association study of serotonin transporter promoter in suicidal adolescents: no association with suicidality but possible role in violence traits.** *Am J Med Genet*, 105(3), 239–245.

Zalsman, G., Frisch, A., Lewis, R., Michaelovsky, E., Hermesh, H., Sher, L., et al. (2004). **DRD4 receptor gene exon III polymorphism in inpatient suicidal adolescents.** *J Neural Transm*, 111(12), 1593–1603.

Zalsman, G., Huang, Y. Y., Oquendo, M. A., Burke, A. K., Hu, X. Z., Brent, D. A., et al. (2006). **Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression.** *Am J Psychiatry*, 163(9), 1588–1593.

Zalsman, G., Patya, M., Frisch, A., Ofek, H., Schapir, L., Blum, I., et al. (2010). **Association of polymorphisms of the serotonergic pathways with clinical traits of impulsive-aggression and suicidality in adolescents: A multi-center study.** *World J Biol Psychiatry*.

Zhang, J., Shen, Y., He, G., Li, X., Meng, J., Guo, S., et al. (2008). **Lack of association between three serotonin genes and suicidal behavior in Chinese psychiatric patients.** *Prog Neuropsychopharmacol Biol Psychiatry*, 32(2), 467–471.

Zhang, Y., Zhang, C., Yuan, G., Yao, J., Cheng, Z., Liu, C., et al. (2010). **Effect of tryptophan hydroxylase-2 rs7305115 SNP on suicide attempts risk in major depression.** *Behav Brain Funct*, 6, 49.

Zhou, Z., Roy, A., Lipsky, R., Kuchipudi, K., Zhu, G., Taubman, J., et al. (2005). **Haplotype-based linkage of tryptophan hydroxylase 2 to suicide attempt, major depression, and cerebrospinal fluid 5-hydroxyindoleacetic acid in 4 populations.** *Arch Gen Psychiatry*, 62(10), 1109–1118.

Zill, P., Buttner, A., Eisenmenger, W., Moller, H. J., Bondy, B., & Ackenheil, M. (2004). **Single nucleotide polymorphism and haplotype analysis of a novel tryptophan hydroxylase isoform (TPH2) gene in suicide victims.** *Biol Psychiatry*, 56(8), 581–586.

Zill, P., Preuss, U. W., Koller, G., Bondy, B., & Soyka, M. (2007). **SNP- and haplotype analysis of the tryptophan hydroxylase 2 gene in alcohol-dependent patients and alcohol-related suicide.** *Neuropsychopharmacology*, 32(8), 1687–1694.