REVIEW

Serotonergic genes and suicide: A systematic review

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Abstract
Suicide is one of the leading causes of death in the world. Its aetiology is complex and diverse, however, epidemiological studies show that suicidal behavior is partly heritable. Neurobiological evidence implicates serotonergic dysfunction in suicidality, stimulating genetic research to focus on genes related to the serotonergic system. In this paper, we review evidence from studies examining the association between various serotonergic genes (Tryptophan Hydroxylase genes: TPH1; TPH2, Serotonin Transporter gene: 5-HTTLPR in SLC6A4, Serotonin Receptor genes: HTR1A, HTR2A, HTR1B, HTR2C and Monoamine Oxidase A gene: MAOA) and suicidal behavior. The data show associations between variation on the TPH1 gene and 5-HTTLPR gene and violent suicidal behavior in Caucasian populations, with the least inconsistencies. Results are mixed for the TPH2 gene and serotonin receptor genes, but for some genes, studies that include haplotypic analyses or that examine a larger coding region of the genes tend to provide more reliable results. Findings on endophenotypes of suicidality, such as aggression and impulsivity traits, show positive associations for the TPH1, HTR2A, and MAOA genes, but need further replication, since negative associations are also occasionally reported. Since genes can only partially explain suicidal risk, several studies during the past decade have tried to incorporate environmental factors in the susceptibility model. Studies to date show that variation on the 5-HTTLPR, MAOA and HTR2A gene can interact with stressful life events to increase risk for suicidal behavior. Limitations of case-control studies are discussed and future considerations are put forward with regard to endophenotypic measurements and gene-environment interactions.

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KEYWORDS
Suicidal behavior; Serotonin genes; Endophenotypes; Gene-environment interaction
1. Introduction

Suicide, the act of deliberately killing oneself, is among the most frequent causes of death in the world, with about one million people ending their lives every year. According to the World Health Organization (WHO) (2012), the highest suicide rates are found in Europe, with European countries filling the top nine places with the highest rates in the world. The average estimated prevalence rate of suicide in Europe is 13.9 per 100,000 people. The highest suicide rates are observed in the Commonwealth of Independent States, followed by countries that have recently entered the European Union, such as Lithuania, Hungary, and Slovenia. Men are five times more likely to commit suicide compared to women, and this pattern is consistent across all European countries (WHO, 2012).

The causal trigger that may lead an individual to the act of suicide greatly varies, but a number of common risk factors have been proposed. Risk factors for suicide can be conceptualized in two dimensions, resulting in the commonly endorsed “diathesis-stress” model of suicide (Mann, 2003). Distal factors, such as genetic loading, perinatal and early-life experiences, neurobiological disturbances and personality characteristics constitute an individual’s “diathesis” for suicide. Proximal factors, such as acute stressful events, psychiatric disorders, environmental or societal factors constitute the “stress” component. Hence, the components of the diathesis render the individual more vulnerable under conditions of stress.

A significant determinant of a person’s diathesis is the individual’s genetic susceptibility toward suicidal behaviors. There is sufficient epidemiological evidence from family, twin and adoption studies showing that suicidal tendencies (both in terms of attempts and completion) run in families, independent of the presence of a psychiatric disorder (Brent et al., 1996; Brent and Mann, 2005). Twin-studies report heritability estimates that range between 21-50%, and up to 55% for a broader phenotype that includes suicidal ideation or planning (Voracek and Loibl, 2007).

Knowledge on the exact neurobiological and genetic systems responsible for suicidal vulnerability is far from clear, however, a number of candidate genes have been examined during the last decades (Wasserman et al., 2009). The serotonin system has received much attention, since disruptions in serotonergic neurotransmission have been well documented in suicidal patients, especially in the form of low cerebrospinal fluid levels of a serotonin metabolite (5-hydroxy-indole-acetic-acid) in suicide attempters (Lidberg et al., 2000; Mann and Malone, 1997; Roy et al., 1986).

In this review, we aim to provide an overview of the current results on the association of serotonergic genes with suicidal behavior. We discuss data from studies that have examined suicide attempters or suicide completers or, in rare cases, both. We acknowledge that these two phenotypes, although they have several underlying neurobiological mechanisms in common, still differ to a significant extent. Both phenotypes fall under the umbrella of “suicidal behavior” or “suicidality”, however, the exact phenotype of suicidal “completion”, “attempt” or “ideation” will be mentioned when discussing individual studies, for the sake of potential discrepancies in findings that can be subsequently noted. We discuss data on genes that influence the metabolism of serotonin, as well as reports on gene-environment interactions and suicide.

2. Experimental procedures

In order to identify eligible studies for the present review, we searched PubMed and MedLine for published literature. The main serotonergic genes examined for this review were selected from recent reviews and meta-analyses on the topic (e.g. Bondy et al., 2006). The name of each gene was entered (e.g. Tryptophan Hydroxylase or TPH1) together with the stem of the word suicide (suicide). This was done for each serotonergic gene separately, and different formulations of name of the gene were also entered in order to detect any missed reference. Reviews and meta-analyses were also inspected and are discussed in this review when appropriate. We also checked cross-references manually for the identification of other studies. All research reports reviewed here were written in the English language.

3. Serotonergic genes

During the last decades, several studies have demonstrated abnormalities in the functioning of the serotonergic system that are related to the pathogenesis of suicidal behavior (Ryding et al., 2008). Consequently, genes that code for proteins that regulate the neurotransmission of serotonin have been considered as candidates in association studies of suicidal behavior.

3.1. Tryptophan hydroxylase

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the synthesis of serotonin (5-HT); it converts the amino-acid tryptophan to 5-hydroxy-tryptophan, which is then decarboxylated into 5-HT (Nielsen et al., 1994). The TPH1 gene is located on chromosome 11p15.3-p14. It is suggested that TPH1 plays a role in the peripheral serotonin generation, primarily expressed in the enterochromaffin cells of the gut and in the pineal gland, where it produces 5-HT as a precursor of melatonin synthesis (Walther and Bader, 2003), but also a minor effect on brain 5-HT has been suggested. A more recent identification was the one of the TPH2 gene, which is located at chromosome 12q15, comprises 11 exons and covers a region of 93.5 kb (Walther et al., 2003). TPH2 is highly expressed in the raphe nuclei in the brain, the main locus of serotonin synthesis (Walther et al., 2003).

3.1.1. TPH1 gene

The TPH1 gene was the first serotonergic gene to be examined in relation to suicide. The studies examining variants within the TPH1 gene (those investigated in at least two studies) are presented in Table 1. Originally, variation on a polymorphism in intron 7 with an A to C substitution at nucleotides 779 (A779C) was related to a history of violent suicide attempts (Nielsen et al., 1994). Following that initial finding, three studies reported positive associations between the A779C variant and suicide attempt or completion; two studies found the C allele as the risk variant (Nielsen et al., 1998; Roy et al., 2001) and one study showed increased frequency of the A allele in suicide attempters (Mann et al., 1997).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Variant</th>
<th>Sample</th>
<th>Suicide outcome</th>
<th>Result</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nielsen et al. (1994)</td>
<td>A779C</td>
<td>36 SA+ alcoholic offenders, 34 SA−, 20 controls</td>
<td>Suicide attempt</td>
<td>CC&lt;sup&gt;b&lt;/sup&gt; attempts, ( p=0.016 )</td>
<td>Caucasian (Finnish)</td>
</tr>
<tr>
<td>Mann et al. (1997)</td>
<td>A779C</td>
<td>29 MDD SA+, 22 MDD SA−</td>
<td>Suicide attempt</td>
<td>A allele&lt;sup&gt;b&lt;/sup&gt; attempts (( p&lt;0.009 ))</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Nielsen et al. (1998)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A779C</td>
<td>102 SA+ alcoholic offenders, 83 SA−, 232 Controls</td>
<td>Suicide attempt</td>
<td>C allele&lt;sup&gt;b&lt;/sup&gt; attempts (( p=0.001 )) in impulsive offenders only</td>
<td>Caucasian (Finnish)</td>
</tr>
<tr>
<td>Furlong et al. (1998)</td>
<td>A218C</td>
<td>125 MD SA+, 114 SA−</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Caucasian (British)</td>
</tr>
<tr>
<td>Bellivier et al. (1998)</td>
<td>A218C</td>
<td>52 BD SA+, 87 BD SA−</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Caucasian (French)</td>
</tr>
<tr>
<td>Tsai et al. (1999)</td>
<td>A218C</td>
<td>41 MDD SA+, 17 SA−</td>
<td>Suicide attempt</td>
<td>AA&lt;sup&gt;b&lt;/sup&gt; attempts (( p&lt;0.05 )) vs. SA− and controls</td>
<td>Chinese</td>
</tr>
<tr>
<td>Kunugi et al. (1999)</td>
<td>A218C</td>
<td>46 MD SA+, 208 controls</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Japanese</td>
</tr>
<tr>
<td>Rotondo et al. (1999)</td>
<td>A6526G</td>
<td>97 offenders SA+, 70 offenders SA−, 153 controls</td>
<td>Suicide attempt</td>
<td>A allele&lt;sup&gt;b&lt;/sup&gt; attempts (( p&lt;0.001 ))</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Du et al. (2000)</td>
<td>A218C</td>
<td>47 SV, 83 Control</td>
<td>Completed suicide</td>
<td>No association</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Bennett et al. (2000)</td>
<td>A218C, A779C</td>
<td>165 SA+, 99 controls</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Geijer et al. (2000)</td>
<td>A218C</td>
<td>132 SV, 132 controls</td>
<td>Completed suicide</td>
<td>No association</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Ono et al. (2000)</td>
<td>A218C, A6526G</td>
<td>27 SCZ SA+, 190 SCZ SA−, 236 controls</td>
<td>Suicide attempt</td>
<td>C allele&lt;sup&gt;b&lt;/sup&gt; attempts (( p=0.01 ))</td>
<td>Japanese</td>
</tr>
<tr>
<td>Paik et al. (2000)</td>
<td>A218C</td>
<td>24 Monozygotic twin of completers, 158 control</td>
<td>Co-twin completed suicide</td>
<td>No association</td>
<td>Korean</td>
</tr>
<tr>
<td>Roy et al. (2001)</td>
<td>A779C</td>
<td>231 SA+, 281 controls</td>
<td>Suicide attempt</td>
<td>AA genotype&lt;sup&gt;b&lt;/sup&gt; attempts (( p&lt;0.003 )) stronger with violent attempts</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Abbar et al. (2001)</td>
<td>A218C</td>
<td>101 SV, 129 controls</td>
<td>Completed suicide</td>
<td>No association with single SNPs, haplotype 6526G-5806T-218C&lt;sup&gt;b&lt;/sup&gt;completed suicide</td>
<td>Caucasian (Canadian)</td>
</tr>
<tr>
<td>Turecki et al. (2001)</td>
<td>A218C, A6526G, G5806T</td>
<td>167 MD SA+, 167 controls</td>
<td>Suicide attempt</td>
<td>A allele&lt;sup&gt;b&lt;/sup&gt; attempts (( p=0.03 ))</td>
<td>Caucasian (European)</td>
</tr>
<tr>
<td>Souery et al. (2001)</td>
<td>A218C</td>
<td>49 SA+, 112 controls</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Jewish</td>
</tr>
<tr>
<td>Ohtani et al. (2004)</td>
<td>A218C, A779C</td>
<td>80 AD SA+, 241 AD SA−</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Caucasian (German)</td>
</tr>
<tr>
<td>Koller et al. (2005)</td>
<td>A779C, A6526G, G5806T</td>
<td>297 SA+, 329 SA−, 184 controls</td>
<td>Suicide attempt</td>
<td>No association with single SNPs, haplotype TCAA of -7180/-7065/-6526/218/779&lt;sup&gt;b&lt;/sup&gt; attempts</td>
<td>Chinese</td>
</tr>
<tr>
<td>Liu et al. (2006)</td>
<td>5 SNPs (incl. A779C and A218C)</td>
<td>297 SA+, 329 SA−, 184 controls</td>
<td>Suicide attempt</td>
<td>CC&lt;sup&gt;c&lt;/sup&gt; attempts in elderly (&gt; 65 years old)</td>
<td>Caucasian (Croatian)</td>
</tr>
<tr>
<td>Stefulj et al. (2006)</td>
<td>A218C</td>
<td>247 SV, 320 controls</td>
<td>Completed suicide</td>
<td>No association</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Wilson et al. (2009)</td>
<td>A218C</td>
<td>71 BPD SA+, 29 BPD SA−, Controls</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Caucasians</td>
</tr>
<tr>
<td>Galfalvy et al. (2009)</td>
<td>A218C, A-6526G</td>
<td>160 MDD SA+, 183 MDD SA−</td>
<td>Suicide attempt</td>
<td>AA genotype of both SNPs (( p&lt;0.01 ))&lt;sup&gt;b&lt;/sup&gt; attempts</td>
<td>Caucasians (mainly)</td>
</tr>
<tr>
<td>Saetre et al. (2010)</td>
<td>5 SNPs (incl. A779C and A218C)</td>
<td>340 SCZ SA+, 398 SCZ SA−</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Caucasians</td>
</tr>
</tbody>
</table>

Abbreviations: SA+: suicide attempters; SA−: patients without a history of suicide attempt; SV: Suicide victims; MDD: Major Depressive Disorder; AD: alcohol dependent; SCZ: Schizophrenic; BPD: Borderline Personality Disorder; MD: Mood disorder; BD: Bipolar Disorder; SNP: Single Nucleotide Polymorphism.

<sup>a</sup>Replication data given.
<sup>b</sup>Associated with.
Most subsequent research focused mainly on the A218C, which is in close, but not complete, linkage disequilibrium (LD) with the A779C in Caucasians (Rotondo et al., 1999). The A allele of the A218C has been identified to be more frequent in suicide attempters compared to non-attempters in four studies (Abbar et al., 2001; Gafalvy et al., 2009; Souery et al., 2001; Tsai et al., 1999), whereas the C allele has been associated with suicide attempts in two studies (Paik et al., 2000; Stefulj et al., 2006). Other common variants within the promoter region, such as the T-7180G, C-7065T, A-6526G and G-5806T, have been identified (Rotondo et al., 1999). The A allele of the A-6526G, found to be in LD with A779C, was associated with suicide attempts in two studies involving Caucasian samples (Gafalvy et al., 2009; Rotondo et al., 1999). One study found a risk haplotype associated with suicide completion (6526G-5806T-218C) (Turecki et al., 2001), whereas another study found an association between the haplotype TCAAA of -7180/-7065/-6526/218/779 SNPs and suicide attempts (Liu et al., 2006).

A number of non-replications have also been reported. Null associations were found between genetic variants in the TPH1 and suicide completers in Caucasian populations (Bennett et al., 2000; Du et al., 2000) as well as in Asian populations (Ohtani et al., 2004; Ono et al., 2000). Studies examining suicide attempters with different psychiatric diagnoses also yielded negative associations (Furlong et al., 1998; Koller et al., 2005; Saetre et al., 2010; Wilson et al., 2009; Zalsman et al., 2001).

Several meta-analyses were occasionally conducted in order to better estimate the association of the TPH1 variation and suicidality. The first meta-analysis, by Lalovic and Turecki (2002) selected 17 studies and found no reliable effect of association, whereas Rujescu et al. (2003a) and Bellivier et al. (2004) examined seven and nine studies, respectively, and found a significant association between the A allele of the A218C SNP and suicide risk in Caucasians. Li and He (2006) confirmed the significant association between suicidal behavior and the A779C/A218C polymorphisms by including 22 studies and stronger associations were observed in the Caucasian samples. In the most recent meta-analysis, Saetre et al. (2010) found no effect of the TPH1 A218C/A779C polymorphisms on suicidal behavior, however, the authors did not distinguish between Caucasian and Asian populations in the meta-analysis. Finally, a recent study examined the association between 143 single nucleotide polymorphisms (SNPs) in 11 serotonergic genes and suicide attempts and an association was found only for a TPH1 variant (rs10488683) (Brezo et al., 2010).

The results linking variation in the TPH1 gene with suicidality are mixed, although observations are more in favor of association in Caucasian populations. Ten studies reported an association between A218C/A779C and suicide outcomes in Caucasians, but the implicated risk allele is not always consistent.

3.1.2. TPH2 gene

The TPH2 gene, being the predominant TPH isoform in the brain, has been examined as a candidate gene of suicidal risk. Studies have examined the expression of TPH2 mRNA at the neuronal level in several brain areas and its relationship to suicidal behavior. An elevated expression of TPH2 mRNA was found in the dorsal and median raphe nuclei of suicidal depressed participants in comparison to matched controls (Bach-Mizrachi et al., 2006) and in the prefrontal cortex of suicide victims (Perroud et al., 2010a). However, the genetic variant (rs10748185) that explained variation in TPH2 expression in the Perroud et al. study was not associated with suicidal behavior. Another study did not find any differences between the suicide group and controls in postmortem brain expression of TPH2 mRNA levels, although greater amounts of TPH2 mRNA were observed in the suicides (De Luca et al., 2006).

A number of studies have examined the differences in genotype and haplotype distributions of TPH2 variants between suicide victims and controls. Initially, 10 SNPs in the TPH2 gene were investigated in 263 suicide victims and 266 healthy control subjects of Caucasian origin, and significant single SNP and haplotype associations were found (Zill et al., 2004). Similarly, Lopez de Lara et al. (2007) genotyped 14 SNPs in 259 depressed subjects of French-Canadian origin, 114 of whom committed suicide during their depressive episode. The authors found that two upstream and two intronic SNPs of the TPH2 gene were associated with suicide, while two SNPs (rs4448731 and rs4641527) were significant predictors of completed suicide. Along the same lines, Zhou et al. (2005) examined 16 SNPs within TPH2 and observed an increased frequency of a risk haplotype in suicide attempters, in two populations (Finnish whites and African Americans). Furthermore, the risk haplotype identified by Zhou et al., was associated with suicidal and parasuicidal behaviors in another sample (Perez-Rodriguez et al., 2010). Similarly, Lopez et al. (2007) investigated 4 SNPs (rs11178997, rs1386494, rs1007023, rs9325202) and observed a haplotypic association with suicide attempts, in a sample of 2018 members of 670 families with Bipolar Disorder.

Besides these positive associations between TPH2 haplotypes and suicidal outcomes, a few studies failed to detect associations. Mouri et al. (2009) examined 15 SNPs within the TPH2 gene but failed to find any association in a case-control study of 234 completed suicide and 260 control subjects in a Japanese population. No associations were found in two further studies examining 14 SNPs (Must et al., 2009) and 8 SNPs (Campos et al., 2010) of the TPH2, in Caucasian samples.

Other studies focused on single SNPs of the TPH2 gene with equivocal results. Fudalej et al. (2010) found that the TT genotype of the rs1386483 SNP of the TPH2 was more frequent in suicide victims compared to controls, particularly in those with a history of repeated attempts. Another TPH2 SNP (rs1843809) was associated with completed alcohol-related suicide (Zupanc et al., 2011). Yoon and Kim (2009) found that the G allele of the TPH2 -703G/T (rs4570625) promoter polymorphism was more frequent in a suicidal depressed group compared to a control group, in a Korean sample, but Stefulj et al. (2011) did not replicate this finding in a sample of suicide victims (Caucasians). Further, the G allele of the rs7305115 SNP was associated with attempted suicide in two Chinese samples of depressed patients (Ke et al., 2006; Zhang et al., 2010). Moreover, the A allele of the rs4290270 SNP was more frequent in a cohort.
of 369 suicidal participants, than in 436 patients with major depression or in 373 controls (Grohmann et al., 2010). Other studies, however, did not find an association between TPH2 variants and history of suicide attempt(s) in mood disorder patients (Mann et al., 2008), bipolar patients (Campos et al., 2010; De Luca et al., 2004) schizophrenic patients (De Luca et al., 2005) or alcohol-dependent patients (Wozosek et al., 2011; Zill et al., 2007).

To date, different variants within TPH2 have been investigated, but there is no consistent association between a single variant and suicide (either completed or history of attempt). Ethnic variability and genetic variation on multiple loci may explain the discrepant findings. Studies examining haplotypes of the TPH2 gene tend to yield more consistent results than single-SNP association studies, but failures to replicate also exist.

3.2. Serotonin transporter gene

The serotonin transporter (5-HTT) is terminating serotonergic action through the uptake of serotonin from the synaptic cleft, and its density is an important index of serotonergic function (Lesch et al., 1994). The serotonin transporter gene (SLC6A4) is located on chromosome 17 and has a common functional promoter polymorphism (5-HTTLPR), consisting of a short allele (S) and a long allele (L). The short allele has been associated with lower transcriptional efficiency and less transporter expression, binding and reuptake (Lesch et al., 1994). Another variation (Lg) within the promoter region (rs25531) was subsequently associated with a similar lower expression to the S allele (Wendland et al., 2006). The serotonin transporter is a possibly putative candidate gene since it regulates serotonin turnover and its levels in the synaptic cleft (Lesch et al., 1996). Indicative of its role, research from postmortem studies has shown that depressed suicide victims have fewer serotonin transporters in cortical areas such as the prefrontal cortex, hypothalamus and brainstem (Purselle and Nemeroff, 2003). Furthermore, 5-HTT availability in the brain was lower in a group of male suicide attempters carrying the S allele compared to matched controls (Bah et al., 2008).

The 5-HTTLPR has been investigated quite extensively as a candidate gene of suicidal vulnerability (Table 2). Results summarized from the last meta-analysis show a strong positive association between the S allele of the 5-HTTLPR and suicidal behavior (Li and He, 2007). Stronger differences were observed between suicide attempters and non-attempter patients as compared to healthy controls, indicating that an association between the variant and suicide independent from psychiatric diagnosis. Since this meta-analysis, several studies have continued the further investigation of the role of the 5-HTTLPR in suicidal behavior. Five studies found an association between the SS genotype/ S allele and increased lethality of the suicide attempt (Saiz et al., 2011; Wasserman et al., 2007a), or violent attempts (Neves et al., 2010; Neves et al., 2008). Furthermore, in a large study of 5688 psychiatric patients and controls, only three female suicide attempters were carriers of the very rare LgLg genotype (functionally similar to SS) (Perroud et al., 2010b).

Some contradictory evidence posing the L allele as the risk allele exists, in Asian samples. The L allele was more frequent in male schizophrenic suicide attempters than in patients with no suicidal history, in a Chinese sample (Hung et al., 2011). An interaction was found between the L allele of the 5-HTTLPR and the G allele of the rs11568817 polymorphism of the HTR1B gene on suicidal ideation, in another Chinese sample (Wang et al., 2009).

A number of negative associations between the 5-HTTLPR and suicidality have also been reported (Akar et al., 2010; Segal et al., 2009) in spite of violent attempts or completion being assessed. Another study found no association in a small sample of borderline patients (Maurex et al., 2010). Other studies found null associations but assessed suicidal ideation only (Coventry et al., 2010; Wang et al., 2009), or did not specify the type of suicidal behavior exhibited (Contreras et al., 2010).

In sum, despite the negative results reported by several studies, a substantial amount of research (and meta-analyses) show a significant association between the S allele of the 5-HTTLPR and violent suicidal behavior. Results are less consistent in non-Caucasian samples, with a preliminary indication that the L allele could be a susceptibility variant in Asian populations. Research from the 5-HTTLPR and suicide indicates the necessity for employing well-defined phenotypes, in particular, assessing the degree of lethality/violence of the suicidal behavior.

3.3. Serotonin receptor genes

Up to 13 distinct serotonin receptors have been identified that serve serotonin neurotransmission. These are G-protein-coupled receptors, and are divided into separate classes (from 5-HT1 to 5-HT7), and subtypes within each class (e.g. 5HT1A), on the basis of their structure and functionality (Hoyer et al., 2002). The serotonin receptor system is extremely complex, subject to genetic and epigenetic influences and posttranslational modifications (for a detailed review, (Hoyer et al., 2002)).

3.3.1. The 5-HT1A receptor

The 5-HT1A receptor is an important mediator of serotonergic signaling in the brain. As a G protein-coupled receptor, it is an autoreceptor of the raphe nuclei regulating the serotonin synthesis and neurotransmission and is also distributed in regions that receive input from the raphe nuclei (such as the frontal cortex, amygdala, hippocampus) (Savitz et al., 2009). Considering its dynamic role in affecting serotonergic neurotransmission, this receptor has been examined in suicide research. In an initial post-mortem study, it was found that depressed suicide victims had a reduced number of 5-HT1A receptors and lower receptor affinity in the hippocampus and amygdala, compared to controls (Cheetham et al., 1990).

Consequently, the HTR1A gene, located on the long arm of chromosome 5 (5q11.2-13), was suggested as a candidate gene for suicidal susceptibility during the last decade. Table 3 shows a summary of results on this gene. The first study by Lemonde et al. (2003) showed an association between suicide attempters and the C(-1019)G (or rs6295) variant, where attempters were four times more likely to
### Table 2  
Studies investigating the serotonin transporter polymorphism (5-HTTLPR) and suicide (studies presented in chronological order).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Suicide outcome</th>
<th>Result</th>
<th>Ethnicity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li and He (2007)</td>
<td>39 studies: 3096 cases, 5936 controls</td>
<td>Attempters/completers</td>
<td>S allele OR: 0.88, p=0.0068</td>
<td>mixed</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Li and He (2007)</td>
<td>32 studies (sample size na)</td>
<td>Attempters/completers</td>
<td>S allele OR: 0.87, p=0.001</td>
<td>Europeans</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Li and He (2007)</td>
<td>7 studies (sample size na)</td>
<td>Attempters/completers</td>
<td>S allele OR: 1, p=0.97</td>
<td>Asians</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Wasserman et al. (2007a)</td>
<td>85 SA+</td>
<td>Lethality of suicide attempts</td>
<td>SS lethality vs. SL&amp;LL p=0.0026</td>
<td>Caucasian/Ukranian</td>
<td></td>
</tr>
<tr>
<td>Neves et al. (2008)a</td>
<td>77 BD SA+, 90 BD SA−, 187 Controls</td>
<td>Suicide attempt</td>
<td>SA+ vs. SA− ns, S allele&lt;sup&gt;b&lt;/sup&gt; violent SA, p=0.0001</td>
<td>Brazilian</td>
<td></td>
</tr>
<tr>
<td>Segal et al. (2009)</td>
<td>94 MDD SA+, 94 controls</td>
<td>Suicide attempt</td>
<td>No association</td>
<td>Brazilian</td>
<td></td>
</tr>
<tr>
<td>Wang et al. (2009)</td>
<td>420 MDD patients</td>
<td>Suicide ideation (scale)</td>
<td>No association</td>
<td>Chinese</td>
<td></td>
</tr>
<tr>
<td>Neves et al. (2010)a</td>
<td>86 BD SA+, 112 BD SA−, 103 controls</td>
<td>Suicide attempt</td>
<td>S allele&lt;sup&gt;b&lt;/sup&gt; violent SA p=0.0001</td>
<td>Brazilian</td>
<td></td>
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<tr>
<td>Akar et al. (2010)</td>
<td>86 SA+, 96 SV, 181 controls</td>
<td>Attempt/completion</td>
<td>No association</td>
<td>Turkish</td>
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<tr>
<td>Maurex et al. (2010)</td>
<td>77 BPD</td>
<td>Suicide attempt (scale)</td>
<td>No association</td>
<td>Caucasian</td>
<td></td>
</tr>
<tr>
<td>Coventry et al. (2010)</td>
<td>3666 community sample</td>
<td>Suicide ideation (scale)</td>
<td>No association</td>
<td>Europeans</td>
<td></td>
</tr>
<tr>
<td>Contreras et al. (2010)</td>
<td>99 SCZ SB+, 74 SCZ SB−</td>
<td>SB not specified</td>
<td>No association</td>
<td>Costa-Rican</td>
<td></td>
</tr>
<tr>
<td>Saiz et al. (2011)</td>
<td>227 SA+, 686 SA−, 420 controls</td>
<td>Suicide attempt</td>
<td>S allele&lt;sup&gt;b&lt;/sup&gt; lethality</td>
<td>Caucasian</td>
<td></td>
</tr>
<tr>
<td>Hung et al. (2011)</td>
<td>60 SCZ SA+, 108 SCZ SA−</td>
<td>Suicide attempt</td>
<td>L allele&lt;sup&gt;b&lt;/sup&gt; attempts</td>
<td>Chinese</td>
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</tr>
</tbody>
</table>

Abbreviations: na: not available; SA+: suicide attempters; SA−: patients without a history of suicide attempt; BD: Bipolar Disorder; MDD: Major Depressive Disorder; BPD: Borderline Personality Disorder; SV: Suicide victims; SB: suicidal behavior; SCZ: Schizophrenic; na: not available.

*<sup>a</sup>Possible overlap in samples (not specified).

<sup>b</sup>Associated with.
carry the GG genotype. This finding was supported by an increased methylation of the promoter region of the HTR1A gene in the prefrontal cortex of depressed patients who had committed suicide and were carrying the GG genotype of the C(-1019)G (Albert et al., 2008). Another group found that the G allele was more frequent in suicide victims compared to controls and was also related to a higher number of stressful life events in the suicide victim group (Rad et al., 2012). However, several other studies did not find this overrepresentation of the G allele in suicide attempters (Serretti et al., 2007c; Videtic et al., 2009b; Wasserman et al., 2006; Wrzosek et al., 2011). Three studies observed differential variation of the C(-1019)G in suicide attempters with high exposure to stressful life events (Rad et al., 2012; Videtic et al., 2009b; Wasserman et al., 2006) but the overrepresentation of the risk allele has not been consistent. Two other polymorphisms within HTR1A gene (Pro161Leu and Gly272Asp) were not associated with suicide in Japanese victims (Nishiguchi et al., 2002); variation in these polymorphisms are mainly observed in Asian populations.

Furthermore, a recent meta-analysis on the C(-1019)G included four studies comprising a total of 957 patients with suicidal behavior and 957 controls and concluded that there is no evidence of association between this variant and suicide (Angles et al., 2012). Results linking variation on the HTR1A gene with suicidal behavior are mostly negative, although interaction with stressful life events could be further investigated.

### 3.3.2. The 5-HT2A receptor

The 5-HT2A receptor has a complex distribution and function. One of its functions is that it mediates the inhibition of norepinephrine neurons via GABAergic cells in the locus coreleus leading in an increased availability of serotonin in the synapse (Serretti et al., 2007b). Post mortem studies have investigated the number of 5-HT2A receptors in the cortex of suicidal victims, but results have been heterogeneous (Stockmeier, 2003). Oquendo et al. (2006) observed no significant differences in 5-HT2A binding in the prefrontal cortex of suicides and controls, although suicide participants had lifetime aggression scores that correlated positively with HTR2A binding in all prefrontal areas examined. Evidence from PET and SPECT techniques demonstrate a reduction in 5-HT2A binding in anxious and depressed suicide attempters but an increase in impulsive attempters (Audenaert et al., 2006). Interestingly, SSRIs can normalize both increased and decreased levels of 5-HT2A binding (Audenaert et al., 2006).

The 5-HT2A receptor gene (HTR2A), located on chromosome 13q14q21, has been considered a possibly important candidate gene for suicidal risk. The most extensively examined polymorphisms are the A-1438G (rs6311 C/T) and T1028 (rs6313) within this gene; summary results for these two SNPs are provided in Table 4. After a series of studies implicating the HTR2A gene in suicide, as well as null associations, a meta-analysis by Li et al. (2006), included 25 reports and concluded that there was no significant association between the T1028/A-1438G polymorphisms and suicidal behavior. De Luca et al. (2007) found that the ratio of the C/T allele expression of the
<table>
<thead>
<tr>
<th>Authors</th>
<th>Variant</th>
<th>Sample</th>
<th>Suicide outcome</th>
<th>Result</th>
<th>Ethnicity</th>
<th>Notes</th>
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<td></td>
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<td>17 studies</td>
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<td>8 studies</td>
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<tr>
<td>Fanous et al. (2009)</td>
<td>T102C</td>
<td>1425 persons with a SCZ family member</td>
<td>Attempt/completion</td>
<td>No association</td>
<td>Caucasian</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>De Luca et al. (2007)</td>
<td>T102C</td>
<td>10 SV, 10 controls</td>
<td>Parent of origin</td>
<td>No association</td>
<td>Not reported</td>
<td></td>
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<tr>
<td>Wrzosek et al. (2011)</td>
<td>T102C</td>
<td>38 AD SA+, 110 AD SA−</td>
<td>Suicide attempt</td>
<td>CC&lt;sup&gt;a&lt;/sup&gt; attempts in females</td>
<td>Caucasian</td>
<td></td>
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<tr>
<td>Vaquero-Lorenzo et al. (2008)</td>
<td>T102C</td>
<td>441 SA+, 339 SA−, 410 controls</td>
<td>Suicide attempt</td>
<td>CC&lt;sup&gt;a&lt;/sup&gt; attempts</td>
<td>Caucasian</td>
<td></td>
</tr>
<tr>
<td>Giegling et al. (2006)</td>
<td>A-1438G</td>
<td>203 SA+, 363 controls</td>
<td>Suicide attempt</td>
<td>A allele&lt;sup&gt;a&lt;/sup&gt; attempts</td>
<td>Caucasian (German)</td>
<td></td>
</tr>
<tr>
<td>Saiz et al. (2011)</td>
<td>A-1438G</td>
<td>227 SA+, 686 SA−, 420 controls</td>
<td>Suicide attempt</td>
<td>GG&lt;sup&gt;a&lt;/sup&gt; impulsive attempts</td>
<td>Caucasian</td>
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</table>

Abbreviations: SV: suicide victims; SA+: suicide attempters, SA−: patients without a history of suicide attempt; MDD: Major Depressive Disorder; AD: Alcohol Dependent; SCZ: Schizophrenic.

<sup>a</sup>Associated with.
T102C was significantly decreased in the prefrontal cortex of 10 suicide victims compared to 10 non-suicidal participants, but found no association between the polymorphism and suicidal behavior. In a subsequent report on partly the same sample the authors found that the methylation of the C allele in the pre-frontal cortex of heterozygous suicide victims did not differ from that of the non-suicidal group (De Luca et al., 2009). Several other studies failed to find an association between the T102C and suicide ideation (Fanous et al., 2009) or suicide attempts (Yoon and Kim, 2009). In a more recent paper involving a larger sample, Yoon and Kim (2009) reported null results for the HTR2A A-1438G (and HTR1A C-1019G, TPH2 -703G/T variants). A negative association was also reported for the C-1420T of the HTR2A gene in a sample of 226 suicide victims and 225 healthy control subjects (Videtic et al., 2006).

Some positive associations have been observed with HTR2A markers and suicide outcomes. Giegling et al. (2006), found that the HTR2A variants rs594342-rs6311: G-C and rs6311 C were associated with increased non-violent and impulsive suicidal behavior respectively. Moreover, the CC genotype of the T102C SNP has been found to be more frequent among suicide attempters (Vaquero-Lorenzo et al., 2008; Wrozsek et al., 2011), whereas no association was found with the C1354T polymorphism (Vaquero-Lorenzo et al., 2008). Furthermore, Saiz et al. (2011) found that the -1438G allele was associated with impulsive suicidal attempts in a Cauca-sian sample, but no overall differences were found between attempters, non-attempters and controls.

Inconsistent results have been found with regard to the HTR2A variants, as well as the risk allele involved. In line with the notion that genetic variation on one locus influences genetic transcription on another, a combined expression of the minor allele G at -783 with G-allele at -1438, resulted in a reduced promoter activity (Myers et al., 2007). Other factors are likely to moderate or influence the expression of such genetic risk, one of them being stressful life events [see section “Gene-environment interactions”].

3.4. Other serotonergic genes

Few studies have examined the association between variation on other serotonin receptor genes, such as the HTR2C and HTR1B. With regard to the HTR1B gene, variation on the rs11568817 alone and together with rs130058 forming a haplotype, were significantly related to suicidal ideation in a group of Chinese patients with major depression (Wang et al., 2009). Further, no association has been found between the HTR1B gene and suicide in a sample of 696 patients (Huang et al., 1999), in a sample of German suicide attempters (Rujescu et al., 2003b), and in suicide victims of German and Slavic origin (Stefulj et al., 2004). Zupanc et al. (2010) found no association between several serotonin receptor genes (HTR1B 861G/C and -161A/T, and HTR1F -78C/T and HTRA2 -1420C/T) and completed alcohol-related suicide. Variation on the HTR2C was not associated with suicidal behavior in Han Chinese participants (Zhang et al., 2008). Finally, in a study that examined 18 selected genes (COMT, HTR2A, HTR1A, HTR1B, TPH1, MAO-A, TPH2, DBH, CNR1, BDNF, ABCG1, GABRA5, GABRG2, GABRB2, SLC1A2, SLC1A3, NTRK2, CRHR1), in a sample of 159 patients with Axis-I psychiatric disorders, associations were observed with suicidal attempts and four SNPs (rs4755404, rs2269272, rs6296 and rs1659400) in genes SLC1A2, SLC1A3, HTR1B and NTRK2, respectively (Murphy et al., 2011). An interaction between the NTRK2 gene and history of childhood abuse was also found on subsequent suicidal acts.

4. Treatment emergent suicidality (TESI)

The risk of pharmacologically induced suicidality has been recently observed. Particular caution has been proposed in relation to antidepressant-induced suicidality during initiation of treatment in young patients (Seemüller et al., 2010). The identification of patients at high risk of becoming suicidal during the course of antidepressant treatment has lead to the investigation of potential risk factors for TESI, including genetic vulnerability. Musil et al. (2012) examined a range of serotonergic genes including (TPH1, TPH2, MAOA, SLC6A4, and BDNF) in an inpatient study of 22 patients with TESI, 117 non-TESI suicidal patients, and 130 non-suicidal patients. Only the TPH2 rs1386494 polymorphism was associated with TESI, which has been previously associated with attempted (Lopez et al., 2007) and completed suicide (Zill et al., 2004). Two studies adopted genome-wide association approaches for the detection of genetic markers as risk factors for TESI, but no “genomewide” significant marker was found (La je et al., 2009; Menke et al., 2012). Of note, these studies suffered from a quite small number of suicide cases (n<100), thus, larger samples are warranted.

5. Genes involved in the metabolism of serotonin

Genetic studies have concentrated on genes within the serotonergic system, on the basis of neurobiological evidence that implicates serotonin in suicidal behavior. However, genes of other systems, for example the dopaminergic or noradrenergic, have also been associated with suicidal behavior [for an extensive review please see Rujescu and Giegling (2010)]. It is not within the scope of the present paper to report on all such studies, however, we will review evidence for the MAOA gene, due to its key role in the metabolism of serotonin (Shih et al., 1999).

5.1. MAOA gene

Monoamine oxidase A (MAOA) is a mitochondrial enzyme that plays an important role in the metabolism of monoamines of the central and peripheral nervous systems. MAOA oxidizes biogenic amines such as serotonin, epinephrine, and norepinephrine, and low MAOA activity results in elevated levels of these neurotransmitters in the brain (Shih et al., 1999). Knockout-MAOA mice have a severe imbalance in serotonin and norepinephrine synthesis, which is reflected in an increase of aggressiveness (Scott et al., 2008). Similarly, inactivating mutations in human MAOA gene lead to impulsive aggression in males (Brunner et al., 1993).

The most extensively studied part of the MAOA gene involves a regulatory variable number tandem repeat
(VNTR) in the promoter region that appears to be associated with variability in impulsivity and aggression (Manuck et al., 2000). In relation to suicide, results tend to be negative with a recent meta-analysis by Hung et al. (2012), (7 studies: 1452 suicide cases, 1198 controls) concluding that there is no association between this polymorphism and suicidal behaviors, even when each gender was examined separately. Few studies have distinguished between violent and non-violent attempts in relation to MAOA variation, for example, a higher frequency of the high-expressing allele was found in Caucasian males who had made a violent suicide attempt compared to those with a non-violent attempt, whereas no association was observed with suicide without this distinction (Courtet et al., 2005).

Although results from studies to date hint towards no evidence of a direct association between the MAOA gene and suicidality, several studies provide evidence of its involvement in aggression, impulsivity and other endophenotypic measures of suicide.

6. Endophenotypes of suicidal behavior

Vulnerability markers that are inherent to the phenotype have been proposed as “endophenotypes”, filling in the gap between genes and the elusive disease process (Gottesman and Gould, 2003). Anger, aggression and impulsivity traits have been proposed as endophenotypes of suicidal behavior (Mann et al., 2009; Wasserman et al., 2007b) and meet the majority of the endophenotype criteria, since prior research has demonstrated their state-independence, heritability, and co-segregation within families (Brent et al., 2003; Melhem et al., 2007; Oquendo et al., 2004). Other endophenotypes, such as disadvantageous decision-making, altered skin-conductance and neuroimaging correlates, have also been proposed, but the extent to which these measures fulfill all the endophenotype criteria remains to be determined (Courtet et al., 2011; Mann et al., 2009).

Several associations have been reported between aggression-related traits and serotonergic genes. Giegling et al. (2006) found that several markers in the HTR2A gene (rs643627; rs594242; rs6311) were related to anger, aggression and suicide-related behavior in a sample of suicide attempters and controls (Giegling et al., 2006). On the other hand, HTRA2 markers (rs643627, rs594242, rs6311, and rs6313) were not strongly associated with personality characteristics (as measured with the Temperament and Character Inventory) in suicide attempters and controls (Serretti et al., 2007a), indicating that other, non-aggression-related, personality characteristics are less likely to mediate suicidal behavior. Furthermore, variation on the HTR1B promoter A-161T locus had a significant effect on levels of aggression in a sample of suicide victims (Zouk et al., 2007). Baud et al. (2009), found an association between the TPH1 218AA genotype and increased levels of anger in a group of suicide attempters suffering from different psychiatric disorders (n=544). Similarly, Rujescu et al. (2002) observed associations with anger-related traits and TPH1 SNPs (A218C and A779C) in a group of healthy volunteers and suicidal participants. In a recent study, we observed a similar moderation by three MAOA polymorphisms on anger traits of suicide attempters, whereas association between MAOA markers and suicidal status was weaker (Antypa et al., 2012). The association between genetic variation and anger traits is interesting, since anger personality traits have been linked to characteristics of the suicide attempt, such as the degree of impulsiveness of the attempt (Giegling et al., 2009).

Impulsivity is another component often entrenched in suicidal acts and has also been suggested as a suitable endophenotype of suicide in genetic research (Turecki, 2005). Participants with the GG genotype of the C(-1019)G SNP showed significantly higher impulsiveness scores compared to GC or CC carriers on several aspects of impulsiveness (using the Behavioral Inhibition Scale) (Benko et al., 2010). The relationship between genetic variation and aggression- or impulsivity-traits is in conceptual agreement with the specific associations between violent suicidal behavior and lethality of suicide attempts previously observed with certain genes (e.g. TPH1).

Nevertheless, inconsistent results have also been found with impulsivity/agression traits as endophenotypic outcomes of suicide in genetic research. For example, serotonergic receptor HTR1A and HTR2C variants were only marginally related to anger and aggression-related traits in suicide attempters and controls (Serretti et al., 2007c) and not associated with other personality traits (Serretti et al., 2009). Similarly, no association was found between the 5-HTTLPR and impulsivity and history of aggressive behavior in a sample of suicide attempters (Baca-Garcia et al., 2004).

Impulsivity and aggression are closely related characteristics, however not all suicides are impulsive, yet a certain degree of action (or “aggression” toward oneself) is necessary to qualify as a suicidal act. Several measures of aggression or impulsivity exist, but it remains to be determined which ones are the most closely related to the suicidal phenotype and the most sensitive in detecting genetic effects in suicide research. Complementary approaches measuring impulsivity/aggression across several levels of expression, e.g. through self-report scales as well as neuropsychological laboratory tests or neuroimaging techniques, could assist in the detection of better endophenotypes of suicidality.

Finally, impaired decision-making has been proposed to represent a potential neuropsychological endophenotype of suicidal behavior. It has been quantitatively defined in the Iowa gambling task and related to the functioning of the left lateral orbitofrontal cortex (Jollant et al., 2005; Jollant et al., 2010). Genetic polymorphisms previously associated with suicidal behavior, including the 5-HTTLPR, TPH1, and MAOA, modulated the learning process necessary in the Iowa gambling task for making advantageous choices in suicide attempters (Jollant et al., 2007).

7. Gene-environment interactions

Suicidal behavior is often a result of stressful life circumstances, either experienced recently or in the distal past. Recent environmental factors explain possibly an important amount of causality in suicidal behavior, with low social support and low income or unemployment among the most frequent risk factors (Li et al., 2011; Qin et al., 2003).
Serotonergic genes and suicide

Childhood trauma also confers to suicidal risk (Sarchiapone et al., 2009). Children with history of sexual or physical abuse have an increased risk of suicidal behavior during adulthood (Brezo et al., 2007). Genetically predisposed individuals are particularly vulnerable to adverse environmental exposure and have an increased risk for pathological states, including suicidal behavior.

In the well-known study by Caspi et al. (2003) the authors found that suicidal ideation was significantly higher for participants carrying the S5 genotype of the 5-HTTLPR with a history of an increased number of stressful life events (>3 life events) (Caspi et al., 2003). Further, the 5-HTTLPR genotype moderated the association between childhood physical and sexual abuse in predicting history of suicide attempt(s) in a mixed psychiatric inpatient sample (Gibb et al., 2006) and in a sample of patients with substance dependence (Roy et al., 2007). There is increasing evidence indicating that it is important to take into account genetic and environmental risk factors in suicide risk assessment.

With regard to the HTR2A gene, Ben-Efraim et al. (2012) recently conducted a family-based study, including 660 offspring with a history of suicide attempt(s), and both their parents and examined 49 SNPs, covering about 98% of the common variation in the coding region. They found a G × E interaction between the exon 1 of the rs6313 variant and stressful life events, determined by an overtransmission of the CT genotype and an undertransmission of the TT genotype. A significant parent-of-origin association was found in this interaction in females, which showed an over-dominant inheritance pattern. A further G × E was observed with the rs7322347 variant in female participants, and rs6310 and rs6305 variants were associated with suicidal attempts in the total sample. The findings of that study indicate that it is important to take into account heterogeneity patterns, as well as environmental factors that can influence gene expression. Furthermore HTR2A variants (rs6561333, rs7997012 and rs1885884) were associated with history of suicide attempts through interactions with sexual and physical abuse histories, in a large (n=1255) cohort study (Brezo et al., 2010).

The effects of early-life stress on the serotonergic system and its development may confer its risk to suicidality through an increase in impulsive or aggressive tendencies (Sarchiapone et al., 2009). Along these lines, variation within the MAOA gene has been consistently associated with increased aggression or impulsivity under conditions of life stress. Caspi et al. (2002) reported that maltreated boys carrying the low expression allele of the MAOA-uVNTR were more likely to develop antisocial problems. Similar G × E interactions, implicating the low expression MAOA-uVNTR genotype, have been found in adolescent boys demonstrating violent behaviors under psychosocial risky conditions (Nilsson et al., 2006) and in males showing increased impulsivity if abused in the past (Huang et al., 2004). However, one study failed to detect a G × E interaction with the MAOA and violent behaviors (Haberstick et al., 2005).

Genes and early- or late-environmental stressors may cause neurobiological modifications in the serotonin system, which may in turn influence other systems, such as that of the hypothalamic-pituitary-adrenal (HPA) axis. Animal and human studies show that serotonergic system is involved in the regulation of the stress response, and dysfunctions in this system may impair the functionality of the HPA axis (Firk and Markus, 2007). Consequently, HPA regulatory genes have been recently proposed as candidates for suicide risk. In brief, G × E interactions were found with several SNPs of the corticotropin-releasing hormone receptor-1 (CRHR1), a regulatory gene of the HPA axis, in a family-based study of Caucasian offspring with history of suicide attempts (Ben-Efraim et al., 2011). Two other HPA axis genes, the CRHBP and the FKBP5 were also recently shown to interact with childhood trauma and increase risk for suicidal behavior in a sample of African Americans (Roy et al., 2012). Moreover, there is recent evidence showing that variation on genes within the glutamatergic system (i.e. GRIN2B) increase risk for severe suicide attempts in individuals with serious childhood/adolescent physical assault history (Sokolowski et al., 2012).

Converging perspectives have been put forward on how stress may influence neurobiology and gene expression in order to increase risk for suicide. A thorough review of the neurodevelopmental origins of suicidal behavior recently examined animal and human data demonstrating that early life events influence the epigenetic processes of genes involved in the serotonergic and stress-response systems (Turecki et al., 2012). Changes in biological, emotional and cognitive phenotypes are likely to result from stress and increase the risk for suicidality (please see Turecki et al. (2012) for a review). Similarly, Roy et al. (2009) argued that distal risk factors can create a risky biological and psychological background, which will render the individual vulnerable to suicide when subsequently faced with a proximal stressor. Figure 1 shows an integrative model from evidence suggesting that genetic variations, through epigenetic and early-life environmental influences, may cause neurobiological and cognitive alterations that lead to personality changes, and eventually, suicidal behavior.

8. Conclusions and future considerations

There has been a noteworthy effort during the past decade to examine the association between genes of the serotonergic system and suicidal behavior. In summary, there is a substantial amount of evidence linking the TPH1 gene with suicidal behavior in Caucasian populations. There has been a shift of attention in the latest years examining the contribution of the TPH2 gene instead, which however does not provide conclusive results from investigations involving single SNP variants. Studies that include haplotypic analyses or that examine a greater region of the TPH2 gene tend to provide more reliable results. A promising association is observed between the S (Lg) allele of the 5-HTTLPR and violent suicide attempts. Well-designed studies with homogeneous populations and well-defined phenotypes are necessary to further certify this association. If the results continue to be consistent in linking the S (and Lg) allele with violent suicide attempts and increased risk of lethality, this information could be of potential clinical use. Results are
less promising for the serotonin receptor genes, although there is recent indication that the variation on the HTR2A interacts with stressful life events to influence risk for suicide. Findings on endophenotypic measures of suicidality, such as aggression and impulsivity traits, provide positive results for the TPH1, HTR2A, MAOA, genes but need further replication and clarification, since negative associations are also occasionally reported. Gene-environment interactions reported to date provide support for the possible moderating role of the 5-HTTLPR, MAOA and HTR2A and deserve further investigation.

Uncovering the genetic profile that underlies complex phenotypes, such as suicidal behavior, remains a challenge. There are several common pitfalls that the case-control association studies are often subject to, such as small sample sizes, ethnic stratification between cases and controls, or overlap between suicidal behavior and psycho-pathology. These are common methodological issues that, if possible, should be addressed in each study separately, and taken into account when meta-analytic methods are performed. Acknowledging these shortcomings, some more general methodological and conceptual issues need to be addressed in the field of genetics of suicide.

Suicidal behavior is a heterogeneous phenotype, with different biological processes underlying suicidal ideation, suicidal attempts and completed suicide. The identification of more narrow and specific endophenotypes would greatly assist in the detection of biological and genetic pathways leading to suicidal risk. Several endophenotypes have already been suggested, such as aggression, anger and impulsivity traits, neurocognitive disturbances, or cortisol response to stress (Mann et al., 2009). It remains to be determined which of them fulfill all the suggested endophenotype criteria (Gottesman and Gould, 2003) and constitute a better marker of suicidal behavior. Results to date look promising and further research is warranted in this area.

The serotonergic system, although largely implicated in the suicidal phenotype, is not the only one that contributes to such maladaptive behavior. Other systems, such as the noradrenergic and the dopaminergic systems, along with HPA axis function, are all involved in the regulation of stress response and form part of the underlying biological disturbances that characterize suicidality (Rujescu and Giegling, 2010). Other genes that play a role in neuronal survival and plasticity, such as the brain-derived neuro-trophic factor, may also contribute to suicidal vulnerability (Sarchiapone et al., 2008).

Consequently, improvement is also necessary in the genetic and statistical approaches that integrate genetic markers from various biological systems and link them to phenotypes of suicide. Candidate gene approaches often produce conflicting results and technical improvements have led to genome-wide association (GWAS) studies in order to locate candidate genes from the whole genome. However, results to date from GWAS studies are unsatisfactory with most studies showing no evidence of association at a genome-wide significant level (Schosser et al., 2011) or only marginally (Willour et al., 2011). In addition, the genetic loci that emerge from GWAS studies are often hard to replicate (Perlis et al., 2010). Such approaches are still in their infancy, not to mention that they still have to meet the computational challenge of multifactorial designs, such as the integration of environmental factors.

It is well accepted that the genetic basis of suicide explains this phenotype only partially. The environment plays a potentially equal role in rendering the individual vulnerable to suicide. Increasing attention has been paid during the last years on this interplay of genetic and environmental factors and a number of stressors have been proposed (Roy et al., 2009). Since different types of life stressors may influence suicidal risk, and in different ways (early life adversity or more recent stressors; Figure 1),
these factors should be jointly assessed and examined, whenever possible, in future studies. Furthermore, gender is another variable that has a great impact on suicide rates and types of method used (Moller-Leimkuhler, 2003). Genetic studies have shown a gender effect on suicidal behavior (e.g. Videtic et al., 2009a), and neurobiological differences in brain serotonin receptors have also been documented (Biver et al., 1996).

Considering that suicidal behavior is partly heritable, it would be an important step to be able to understand the genetic architecture of such risky, and often detrimental, behaviors. A better insight of how genes interact with non-genetic factors, such as environmental stress, and how these processes differ for each gender, would facilitate early detection of suicidal risk, and development of effective screening tools for its prevention and management.

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Contributors

N. Antypa conducted the literature search and wrote the first draft of the review. A. Serretti provided comments and suggestions during the writing process. D. Rujescu provided further comments and feedback on the manuscript.

Conflict of interest

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Serotonergic genes and suicide


