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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.

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

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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 (suicid*). 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).

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; Galfalvy et al., 2009; Souery et al., 2001; Tsai et al., 1999), whereas the C allele has been associated with suicide attempts in two studies