

## SINGLE NUCLEOTIDE POLYMORPHISMS AND SUICIDAL BEHAVIOUR

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### SUMMARY

The World Health Organization estimates that almost one million deaths each year are attributable to suicide, and suicide attempt is close to 10 times more common than suicide completion. Suicidal behaviour has multiple causes that are broadly divided into proximal stressors or triggers and predisposition such as genetic. It is also known that single nucleotide polymorphisms (SNPs) occur throughout a human DNA influencing the structure, quantity and the function of proteins and other molecules. Abnormalities of the serotonergic system were observed in suicide victims. Beside 5-HT1A and other serotonin receptors most studied are the serotonin transporter 5' functional promoter variant, and monoamine oxidase A and the tryptophan-hydroxylase 1 and 2 (TPH) polymorphisms. It seems that especially genes regulating serotonergic system and neuronal systems involved in stress response are associated with suicidal behaviour. Most genetic studies on suicidal behaviour have considered a small set of functional polymorphisms relevant mostly to monoaminergic neurotransmission. However, genes involved in regulation of other factors such as brain-derived neurotropic factor seems to be even more relevant for further research.

**Key words:** suicide – genetics – depression – serotonin – neurotransmitters

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### INTRODUCTION

The World Health Organization estimates that almost one million deaths each year are attributable to suicide, and suicide attempt is close to 10 times more common than suicide completion (Nock et al. 2008, WHO 2012). Further it is estimated that more than 20 million disability- adjusted life-years (years of healthy life lost through premature death or disability) are lost because of suicide worldwide (Levi et al. 2003). It is also estimated that 1.5 million will die from suicide in 2020 worldwide (Levi et al. 2003). Suicide alone represents the 10th leading cause of death worldwide (Levi et al. 2003).

Suicidal behaviour has multiple causes that are broadly divided into proximal stressors or triggers and predisposition (Mann & Currier 2010). If triggers could be mainly attributed to environmental factors, predisposition could be associated with stressors on one side such as childhood adversities and genetic predisposition such as specific combination of different genetic variants on the other. Psychiatric illness is a major contributing factor and more than 90% of suicide victims have a psychiatric illness (Lönnqvist et al. 1995). The most prevalent mental disorders analysed by the psychological autopsy method among suicide victims are depressive syndromes (Lönnqvist et al. 1995). Increasing amount of data about suicidal behaviour indicates that suicide is familial and that familial transmission of suicidal behaviour cannot be explained by the transmission of psychiatric disorder alone (Brent & Mann 2005, Mann & Currier 2010). Estimates of heritability for suicide range between 21–50%, and 30–55% for a broader phenotype of suicidal

behaviour and ideation (Voracek & Loibl 2007). The global suicide rate is calculated to around 14 suicides per 100,000 inhabitants. However, the highest annual rates are in Eastern Europe, where 10 countries report more than 27 suicides per 100 000 persons per selected year (WHO 2012). Suicide rate in Slovenia has been among the highest in the world for over two decades: around 30 per 100000 inhabitants per year with a tendency to decline in last years (Oravec et al. 2006). It could be speculated that specific genetic polymorphisms are involved in observed differences (Marušič 2005). It is also known that single nucleotide polymorphisms (SNPs) occur randomly throughout a human DNA. They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNPs in the human genome. The data on SNPs associated with suicidal behaviour will be presented with a special focus on the data obtained from the suicide victims of Slovenian origin.

### SEROTONINERGIC SYSTEM

Abnormalities of the serotonergic system were observed in suicide victims in the population with high suicide rates (Videtič et al. 2000). It seems that genetic polymorphisms involved in the regulation of serotonergic systems could influence the response to stress in some individuals. One of the most abundant serotonin receptors in the mammalian brain is the autoreceptor 1A (5-HT1A). Increased 1A receptor production could enhance the negative feedback inhibition of serotonergic Raphe neurons and lead to a lower serotonergic neurotransmission, causing a predisposition to depression and suicide (Alber et al.

2011). The observation that the G allele increase the HTR1A receptor gene expression, and therefore reduces serotonergic neurotransmission that might predispose to suicidal behaviour, made the promoter polymorphism -1019C>G a very promising candidate gene. Promoter polymorphism -1019C>G on suicide victims and controls all of Slovenian origin was analysed taking into account stressful life events in a month prior to suicide (Videtič et al. 2000). Differences in the distributions of genotype and allele frequencies were not significant between suicide victims and control group. However, more stressful life events in the month prior to the suicide were reported for the subgroup with CC genotype in comparison to subgroup with CG/GG genotypes (Videtič et al. 2000).

Beside 5-HT1A receptor, most studied in respect to suicidal behaviour is the serotonin transporter 5' functional promoter variant, serotonin 5-HT1B and 5-HT2A receptors, and monoamine oxidase A (Rujescu et al. 2007, Mann & Currier 2010). Not only the binding of serotonin but also the synthesis could be influenced by nucleotide polymorphisms. Tryptophan-hydroxylase (TPH) is the key enzyme in biosynthesis of serotonin (Arango et al. 2003). Two isoforms of TPH has been discovered, namely TPH1 and TPH2. TPH2 was only found in central nervous system, mostly in the brain stem. The most extensive study was done by Zill and co-workers that did the screening of 10 SNPs in the fifth and sixth intron. They reported that different haplotypes could be important risk factor for suicidal behaviour (Zill et al. 2004). In the DNA sequence for TPH2 a very rare functional polymorphism that changes amino acid arginine to histidine (Arg441His; in the DNA 1463 G>A) has been determined with 80 per cent lower function of the enzyme (Zhang et al. 2005).

In another study, different SNPs were analysed on suicide victims and controls all of Slovenian origin (Zupanc et al. 2011). Association between suicide and aforementioned polymorphism with high impact on the enzyme activity was not observed because this SNP was not polymorphic in studied population. However association was found with another studied SNP (Rs1843809) (Zupanc et al. 2011) with less known impact on the enzyme function.

Further, less serotonin transporter mRNA and fewer binding sites in the serotonin raphe nuclei were observed as a part of the serotonin system dysfunction in suicide victims (Huang et al. 2004). On the contrary, it was reported recently that selected polymorphisms of the serotonin transporter gene and also serotonin receptor genes are not associated with the genetic susceptibility to completed suicide under acute influence of alcohol or among alcohol-dependent individuals in a population with high suicide rates (Zupanc et al. 2010). Nevertheless it is known that other abnormalities in the function of the systems responsive to stress are associated with suicidal behaviour.

## CATECHOL-O-METHYL-TRANSFERASE

The metabolism of other neurotransmitters could be impaired in suicide victims by the altered function of the enzymes involved in the degradation of neurotransmitters. Catecholamine degradation is regulated with the activity of the enzyme catechol-O-methyltransferase (COMT), which catalyses the transfer of a methyl group to catecholamines and degrades dopamine, noradrenaline and adrenaline. A common functional polymorphism (COMT Val108/158Met), a G to A nucleotide transition that results in amino acid substitution from valine (Val) to methionine (Met) on position 158 in the membrane-bound or in position 108 in the soluble form of COMT (rs4680) is known. The Met form is associated with the low-activity of COMT, while the Val form of COMT is related to a high-activity (Russ et al. 2000). It has been observed that Met/Met genotype leads to a threefold to fourfold decrease in COMT enzymatic activity compared to Val/Val genotype (Kia-Keating et al. 2007). Data on the role of the COMT Val108/158Met polymorphism and suicidal behaviour are inconclusive (Kia-Keating et al. 2007, Calati et al. 2010) and recent meta-analysis suggested that COMT variants may not be directly implicated in suicidal behaviour (Calati et al. 2011). However, similarly to some previous reports (Nolan et al. 2000; Ono et al. 2004), eave more recently, differences in the frequency of the Met/Met genotype were observed between in male control subjects and male suicide victims, suggesting that this genotype of the COMT Val108/158Met might be a protective factor against suicide (Pivac et al. 2011). In contrast to male subjects, no significant differences in the frequency of the COMT Val108/158Met variants were detected between female control and female suicide victims groups (Pivac et al. 2011). In accordance to this report, it has been reported that COMT is a potent moderator of sexual dimorphism, since estrogen reduces COMT enzyme activity, thus reducing the effect of COMT genotype in women relative to men (Dickinson & Elvevag 2009).

## NEUROTROPHINS

Not only on the level of neurotransmitters and central nervous system functioning but also structural changes could be observed in patients with mental disorders associated with increased suicide risk such as depression, schizophrenia and bipolar disorder, indicating that other mechanisms could be involved in suicidal behaviour. Indeed it is known that neuronal activity plays a pivotal role in synaptic plasticity and that neurotrophins are potent factors for synaptic modulation. For example, brain-derived neurotrophic factor (BDNF) influences a variety of neural processes during the development such as: neurogenesis, neuronal survival and maturation of neural development

pathways (Russo-Neustadt 2003). The BDNF Val66Met variant is a known functional polymorphism (rs6265), consisting of the substitution of valine with methionine in codon 66. It has been shown that the Met allele is associated with the reduced BDNF activity (Egan et al. 2003). Further, a recent meta-analysis including 12 studies showed a trend for the Met-carrying genotypes and Met allele conferring risk for suicide (Zai et al. 2011). Among included studies the study with the largest sample size indicated that the combined Met/Met and Met/Val genotypes of the BDNF Val66Met variant could be the risk factor for violent suicide in female subjects and for suicide in victims exposed to childhood trauma (Pregelj et al. 2011).

Also genes regulating other systems could be involved in suicidal behaviour. Abnormalities in the hypothalamic adrenal (HPA) axis in suicidal behaviour and also major depression were reported. Further the HPA axis has bidirectional relationships with the serotonergic and noradrenergic systems contributing to the complexity of the neurobiology of suicidal behaviour (Mann & Currier 2010). Indeed altogether it is estimated that 4,000 genes are involved in communication between brain cells.

## CONCLUSIONS

It seems that especially specific gene variants regulating the serotonergic system and other neuronal systems involved in stress response are associated with suicidal behaviour. Most genetic studies on suicidal behaviour have considered a small set of functional polymorphisms relevant mostly to monoaminergic neurotransmission. However, genes involved in regulation of other factors such as BDNF seems to be even more relevant for further research.

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