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Nine differentially expressed genes from a post mortem study and their association with suicidal status in a sample of suicide completers, attempters and controls

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ABSTRACT

Several lines of evidence indicate that suicidal behaviour is partly heritable, with multiple genes implicated in its aetiology. We focused on nine genes (S100A13, EFEMP1, PCDHB5, PDGFRB, CDCA7L, SCN2B, PTPRR, MLC1 and ZFP36) which we previously detected as differentially expressed in the cortex of suicide victims compared to controls. We investigated 84 variants within these genes in 495 suicidal subjects (299 completers and 196 attempters) and 1513 controls (109 post-mortem and 1404 healthy). We evaluated associations with: 1) suicidal phenotype; 2) possible endophenotypes for suicidal behaviour. Overall positive results did not survive the correction threshold. However, we found a nominally different distribution of EFEMP1 genotypes, alleles and haplotypes between suicidal subjects and controls, results that were partially replicated when we separately considered the subgroup of suicide completers and post-mortem controls. A weaker association emerged also for PTPRR. Both EFEMP1 and PTPRR genes were also related to possible endophenotypes for suicidal behaviour such as anger, depression-anxiety and fatigue. Because of the large number of analyses performed and the low significance values further replication are mandatory. Nevertheless, neurotrophic gene variants, in particular EFEMP1 and PTPRR, may have a role in the pathogenesis of suicidal behaviour.

1. Introduction

Suicidal behaviour is a significant public health problem and a major cause of death worldwide (Who, 2000). A genetic contribution to its complex aetiology has been demonstrated, twin and adoption studies showing an estimated heritability of 43% (Roy, 1993; Roy et al., 1995; Mcguffin et al., 2001; Voracek and Loibl, 2007).

Most genetic research has focused on serotonergic genes as contributors to the suicidal phenotype (Wang et al., 2015; Rujescu et al., 2007; Geijer et al., 2000), due to neurobiological evidence linking this system with suicidal pathophysiology (Lidberg et al., 2000). However, there is an increasing evidence that genes within other systems, for example the dopaminergic, noradrenergic, or neurotrophic ones, are also likely to affect vulnerability to suicidal behaviour (Suchankova et al., 2013; Rujescu and Giegling, 2010).

In a previous investigation, we adopted a microarray approach in order to screen for new candidate genes and mechanistic pathways. We compared the levels of ~23,000 transcripts in the

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orbitofrontal cortex of suicide victims and controls and identified nine genes (S100A13, EFEMP, PCDHB5, PDGFRB, CDCA7L, SCN2B, PTPRR, MLC1 and ZFP36) that showed differential expression in the cortex of suicide victims in comparison to controls (Thalmeier et al., 2008). These genes play an important role in cellular processes. In brief, both S100A13 and PDGFRB proteins play a role in the central nervous system (CNS) development and mediate neuroprotective functions after injury (Chan et al., 2003; Ishii et al., 2006); the EFEMP1 and PCDHB5 play a role in cell adhesion, such as the development of neural cell-cell connections (Kobayashi et al., 2007; Wu and Maniatis, 1999); the CDCA7L gene encodes a transcription factor that inhibits the monoamine oxidase A (MAOA) promoter (Chen et al., 2005); the SCN2B and PTPRR affect signal transduction in the CNS (Zhang, 2005; Qu et al., 2001); the ZFP36 protein represents a key mediator of inflammation, inhibition of autoimmunity and cancer processes (Al-Souhibani et al., 2010).

Apart from our previous study (Thalmeier et al., 2008), these genes have seldom been studied in relation to psychiatric phenotypes. PDGFRB was found to be associated with psychiatric and not specific symptoms (Tadic et al., 2015), while PTPRR was related to depressive disorder in both a Chinese sample (rs1513105) (Shi et al., 2012) and a genome-wide association study considering Caucasians (rs4760933) (Muglia et al., 2010). Finally, MLC1 was associated with schizophrenia and bipolar disorder (Verma et al., 2005), while a reduction of CDCA7L protein was observed in the brains of MDD subjects (Johnson et al., 2011).

Recently, we reported a modulation of EFEMP1 rs960993 and rs2903838 polymorphisms on Temperament and Character Inventory personality traits, in particular harm avoidance and self-directedness. Interestingly, we could replicate these associations in haploblocks within controls and in the independent sample of suicide attempters for harm avoidance, a phenotype highly associated with suicidal behaviour (Calati et al., 2014). However, the specific mechanisms through which EFEMP1 gene could increases the suicide risk as well as its possible influence on other personality traits closely related to suicidal behaviour (e.g., aggression and anger) are not been investigated. Similarly, if the other above-mentioned genes were involved in the modulation of suicidal behaviour both directly or through intermediate endophenotype remains to be determined.

Therefore, considering all the limitations related to a candidate gene approach, our primary aim was to investigate whether genetic variations in these set of genes (S100A13, EFEMP, PCDHB5, PDGFRB, CDCA7L, SCN2B, PTPRR, MLC1, ZFP36) were associated with suicidal behaviour, in a large sample of suicidal participants (both suicide attempters and suicidal victims) and healthy controls. This sample does not overlap with the previously investigated one (Thalmeier et al., 2008). As secondary aim, in a subsample of subjects, we preliminary explored the association between the single nucleotide polymorphisms (SNPs) under analysis and several personality traits or specific available possible endophenotypes.

2. Methods

2.1. Sample

The total sample was collected from three different sources:

The first sample (sample 1) was composed of 196 suicide attempters and 1404 healthy controls (N tot = 1600). The *suicide attempters* were consecutively referred to general psychiatric wards of the Department of Psychiatry, Ludwig-Maximilians-University of Munich, Germany. Systematic information on suicide attempts was collected through interviews with the patients. The suicide attempts were classified, according to the methods used and the severity of the attempt, as violent (hanging, stabbing, shooting, jump from buildings or in front of vehicles, severe deliberate car accident, electricity, fire) or non-violent (illicit or prescription drugs, rather superficial wrist manipulations, gas suffocation and drowning). The German version of the Intent Score Scale (Pierce, 1981) was used to define impulsive and non-impulsive suicidal behaviour. Current and lifetime diagnoses of mental disorders were assessed using Structured Clinical Interview for DSM-IV (SCID I and SCID II) (First et al., 1990, 1995) close to the time of discharge of the patients. Patients with mental disorders due to a general medical condition or with dementia were excluded. The *healthy controls* were randomly selected and contacted from the city registry of Munich. First, participants were screened via phone, using detailed medical and psychiatric history systemized forms. Second, they were invited to an interview, which consisted of the Structured Clinical Interview for DSM-IV (SCID I and II) (First et al., 1990, 1995). Participants with somatic diseases or a lifetime history of psychiatric disorders or suicidal tendencies were excluded. The present sample represents an enlargement of previously investigated samples (Calati et al., 2008, 2014).

The second sample (sample 2) consisted of 102 suicidal victims and 27 post-mortem controls (N tot = 129) for whom human brain tissue was obtained from the Institute of Forensic Medicine of the Johann Wolfgang Goethe University in Frankfurt am Main, Germany. The research was approved by the University's Internal Review Board. Demographic data of the decedents were obtained from medical records. Post-mortem tissue was derived from the orbitofrontal cortex [Brodmann Area 11].

The third sample (sample 3) was composed of 197 suicidal victims and 82 post-mortem controls (N tot = 279), for whom human brain tissue was obtained from the Institute of Forensic Medicine of the Medical Faculty, University in Ljubljana, Slovenia. The research was approved by the University's Internal Review Board. Demographic data of the decedents were obtained from medical records. Post-mortem tissue was collected in National Institute for Public Health, Department of Medical Microbiology, where DNA from brain tissue was isolated.

The present study was approved by the local ethics committees of each participating source and carried out in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all subjects following a detailed description of the study.

In sum, the whole sample (N = 2008) was composed of a 495 suicidal subjects (299 completers and 196 attempters) and 1513 controls (1404 healthy and 109 post-mortem.

2.2. Aims and instruments

2.2.1. Primary aim

To evaluate whether the SNPs of S100A13, EFEMP1, PCDHB5, PDGFRB, CDCA7L, SCN2B, PTPRR, MLC1 and ZFP36 genes were associated with suicidal behaviour. For this purpose, we considered the whole sample (N = 2008).

2.2.2. Secondary aim

To explore the associations between the same SNPs and several personality traits or possible available endophenotypes. For this purpose, we further investigated the genes with significant signals detected in the primary analysis in a subsample of suicide attempters and healthy controls (N = 1600). We investigated several aspects potentially mediating the genetic contribution to suicidal behaviours. Hereafter we briefly described the instrument used:

1) *The State-Trait Anger Expression Inventory (STAXI):* a 44 item self-report questionnaire that measures the experience and