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SHORT COMMUNICATION

Genetic variability within the *S100B* gene influences the personality trait self-directedness

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Summary Elevated serum levels of S100B have proven useful as an indicator of brain-injury but have also been shown in patients diagnosed with psychiatric disorders. Recently, associations were found between variations in the *S100B* gene and schizophrenia as well as bipolar affective disorder. The aim of the present study was to investigate whether some of these genetic variations influence general aspects of human behaviour as portrayed by normal dimensions of personality. Two single nucleotide polymorphisms within the *S100B* gene, 2757C>G and 5748C>T, were genotyped in two population based cohorts consisting of 42-year-old women (n = 270) and 51-year-old men (n = 247), respectively. The two polymorphisms were analysed with respect to personality traits assessed using the Temperament and Character Inventory (TCI). In men, the 2757C>G polymorphism was found to significantly influence the TCI dimension self-directedness with higher scores in 2757G homozygotes. A similar tendency towards association was seen in the female cohort; however, this correlation did not remain significant after correction for multiple comparisons. Furthermore, the 5748C>T polymorphism was highly associated with self-directedness in men. Self-directedness is an overall estimate of adaptive strategies to adjust behaviour to conceptual goals as well as coping strategies and is strongly correlated to general mental health and absence of personality disorder. These preliminary findings suggest that the *S100B* gene may be implicated not only in certain pathological brain conditions but also in processes involved in normal behaviour.

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Introduction

The highly conserved factor S100B belongs to the S100 family of Ca^{2+}-binding proteins and the *S100B* gene is located on chromosome 21 at 21q22.3. It is a low molecular mass protein (21 kDa) that is abundant in the central nervous system. The effects of S100B involve regulation of transcription factors, cell growth and differentiation, protein phosphorylation and the inflammatory response (Donato et al., 2009). S100B is secreted by astrocytes and released into the extracellular space where its actions depend on the concentration at which it is released. At nanomolar concentrations, S100B has been shown to have neurotrophic effects while at micromolar concentrations it is believed to produce toxicity due to apoptosis and necrosis as well as stimulating secretion of proinflammatory mediators (Li et al., 2000).

Brain-injury often results in diffusion of S100B across the disrupted blood–brain barrier and the protein has thus served as a serum biomarker of the severity of such events. During the past decade, several studies have reported elevated serum levels of S100B in a number of psychiatric disorders such as major depression (Schroeter et al., 2008) and schizophrenia (Rothermundt et al., 2001).

The reported relevance of S100B for brain functions and our previous findings regarding associations between personality traits and variations in genes related to inflammation (Suchankova et al., 2009) prompted us to investigated the possible influence of different genotypes in *S100B* on personality traits in two cohorts. The polymorphisms chosen constitute a haplotype of two single nucleotide polymorphisms (SNPs) within *S100B*, 2757C>G SNP (rs1051169) and 5748C>T SNP (rs9722) that has been shown to be more frequent in schizophrenic patients when compared to healthy controls (Liu et al., 2005).

Methods

Subjects

The female and male cohorts are both population-based cohorts and the subjects were originally recruited for studies on obesity, anthropometrics and cardiovascular risk factors. Clinical data and further details on these two cohorts have been reported previously (Rosmond et al., 1998; Baghaei et al., 2003). At the time of investigation all women and men were 42 and 51 years old, respectively. No man or woman was excluded from the study due to somatic or psychiatric disease. All participants gave their informed consent and the study protocol was approved by the ethical committee at the University of Gothenburg.

Cohort I

Women (n = 1464) born on odd days in the year of 1956 and living in Gothenburg, Sweden, were recruited from the National Population Register. The first phase of the study involved a questionnaire in which the women were asked to fill out self-measurements of height, weight, waist and hip circumferences; 1137 women (78%) responded to the questionnaire. Based on the self-reported measurements, the ratio over the waist and hips (WHR) was calculated and three subgroups chosen on the basis of low, median or high WHR with 150 subjects in each group were selected for further studies. The distribution of WHR measurements for these women appeared normal and was similar to that of the total cohort (Baghaei et al., 2003). In the second phase, the 450 women were invited to a health examination to which 270 (60%) volunteered to participate in. Blood samples were obtained from all 270 women for genotyping. Completed questionnaires of the Temperament and Character Inventory (TCI) (Cloninger et al., 1993) were returned by 201 women.

Cohort II

The recruitment process for the male cohort was very similar to the one used for the female cohort. All men (n = 1302), born during the first six months of 1944 and living in Gothenburg, Sweden, were recruited in 1992 from the National Population Register. The questionnaires with self-reported anthropometric measurement were returned by a total of 1040 (80%) men. Three subgroups chosen on the basis of low, median or high WHR with 150 subjects in each group were selected for further studies. The health examination took place in 1995; 284 (63%) volunteered to participate and out of these 247 (55%) gave blood for genotyping. Completed questionnaires of TCI were returned by 151 men.

Genotyping

The SNPs that were assessed are both located in the *S100B* gene, the 2757C>G is a synonymous SNP found in exon 2 and the 5748C>T SNP is located in the 3′UTR. Venous blood was collected from each participant and genomic DNA was extracted from blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Both studied polymorphisms were analysed using polymerase chain reaction (PCR) as the amplifying step followed by genotype assessment by sequenom chip-based MALDI-TOF mass spectrometry. The PCR products for the Sequenom analysis were generated using HotstarTaq polymerase from Qiagen. A total volume of 5 μL containing 100 mM of each primer, 1.625 mM $MgCl_2$, approximately 20 ng genomic DNA and 500 μM of each dNTP was used. An initial 15 min denaturing step at 94 °C was followed by 45 cycles of 20 s at 94 °C, 30 s at 56 °C and 1 min at 72 °C. Finally the samples were incubated at 72 °C for 3 min. The PCR primer sequences used for Sequenom analysis were ACGTTGGATGCAATATTCTGGAAGGGAGGG/ACGTTGGATGGGGAAAGCTCATTGTTGATG and ACGTTGGATGGATTAGAAAGCAGCCAAACC/ACGTTGGATGCTACTAGGCTGCAAGCCCTT for 2757C>G and 5748C>T, respectively. The extension primer for 2757C>G was CATTGTTGATGAGCTCCTT and GGCTGCTTTCTTGCATGACC for 5748C>T.

Personality assessment

The TCI is a psychometric instrument based on a 238-items true/false questionnaire (Cloninger et al., 1993). It includes the four temperament dimensions: novelty seeking (impulsive vs. reflective), harm avoidance (anxious vs. calm), reward dependence (warm vs. aloof), and persistence (steadfast vs. fickle). In addition, the inventory also measures three character dimensions: self-directedness (resourceful vs. helpless), cooperativeness (empathic vs. hostile), and self-transcendence (self-forgetful vs. acquisitive).