European Neuropsychopharmacology (2007) **17**, 321–327

www.elsevier.com/locate/euroneuro

Genetics and personality traits in patients with social anxiety disorder: A case-control study in South Africa

Christine Lochner [a,*], Sian Hemmings [b], Soraya Seedat [a], Craig Kinnear [b], Renata Schoeman [c], Kristina Annerbrink [d], Marie Olsson [e], Elias Eriksson [d], Johanna Moolman-Smook [b], Christer Allgulander [f], Dan J. Stein [a,g]

[a] *MRC Unit on Anxiety and Stress Disorders, Department of Psychiatry. University of Stellenbosch, South Africa*
[b] *MRC/US Centre on Molecular and Cellular Biology, University of Stellenbosch, South Africa*
[c] *Department of Psychiatry, University of Stellenbosch, South Africa*
[d] *Department of Pharmacology, Gőteborg University, Sweden*
[e] *Department of Pharmacy, Apoteket AB, Sahlgrenska University Hospital, Gőteborg, Sweden*
[f] *Karolinska Institutet, Sweden*
[g] *Department of Psychiatry, University of Cape Town, South Africa*

Received 16 February 2006; received in revised form 5 June 2006; accepted 27 June 2006

KEYWORDS
Social anxiety disorder;
Genetics;
Serotonin;
Dopamine;
Temperament

Abstract

Background: Social anxiety disorder (SAD) is among the most common of all psychiatric disorders with lifetime prevalence estimates ranging from 7% to 13%. Although there is evidence that SAD has a strong familial basis, there are few studies of potential candidate genes. In addition to a genetic association, there is also the possibility that temperamental risk factors for the disorder may be genetically transmitted. Against this background, our aims were threefold: i.) to compare patients and controls with respect to personality traits, ii.) to genotype a subgroup of these participants to investigate the role of genes encoding components of serotonergic (*5-HT*) and dopaminergic (*DA*) pathways in patients with SAD and iii.) to compare differences in temperament dimensions between carriers of different (dominant vs. recessive) alleles for selected polymorphisms in SAD patients.
Methods: Sixty-three patients ($n=63$; 35 male, 28 female) with a DSM-IV diagnosis of generalized SAD and SPIN-scores >18, and age-matched control participants ($n=150$; 31 male, 119 female) were included in the study. The Temperament and Character Inventory (TCI) was used to measure behaviours associated with specific personality dimensions (i.e. temperament/character). DNA was extracted and genotyped to investigate the role of select candidate genes

* Corresponding author. PO Box 19063, Tygerberg, 7505, South Africa. Tel.: +27 21 938 9179; fax: +27 21 933 5790.
E-mail address: cl2@sun.ac.za (C. Lochner).

doi:10.1016/j.euroneuro.2006.06.010

encoding components in serotonergic and dopaminergic pathways in mediating the development of SAD. To achieve this, the frequency of variants in *5-HT* and *DA* genes was compared between a Caucasian subset of SAD patients ($n=41$) and a convenience sample of Caucasian controls ($n=88$), using case-control association analyses. We also investigated the frequency of variants in *5-HT* and *DA*-related genes across temperament characteristics in SAD patients, using analyses of variance (ANOVA).

Results: Patients scored significantly higher on harm avoidance ($p<0.001$) but lower on novelty seeking ($p=0.04$) and self-directedness ($p=0.004$) compared to controls. In the Caucasian subset, there was a difference between patients and controls in distribution of the *5-HT$_{2A}$ T102C* polymorphism, with significantly more patients harboring *T*-containing genotypes (*T*-containing genotypes: [*T* / *T*+*T* / *C*] vs. [*C* / *C*]) ($\chi^2=7.55$; $p=0.012$). Temperament dimensions did not, however, differ significantly between carriers of different (dominant vs. recessive) alleles for the *5-HT$_{2A}$ T102C* polymorphism in SAD patients.

Conclusions: The results suggest a possible role for the *5-HT$_{2A}$ T102C* polymorphism in the development of SAD. To date genetic findings in SAD have been inconsistent; nevertheless, serotonergic variants, and their associations with temperaments (e.g. reward dependence) deserve further exploration, in the hope that endophenotypes relevant to SAD can ultimately be delineated.

1. Background

Social anxiety disorder (SAD) is a common, disabling condition, characterized by fears that a person will become embarrassed or humiliated in situations where he/she is exposed to perceived public scrutiny in social or performance situations. These fears can either be specific to certain situations, i.e. specific/*discrete* SAD, or SSAD, for instance, public speaking, or eating/drinking in front of others; or they can be generalized across a wide range of situations (i.e. generalized SAD or GSAD), with the latter subtype being associated with more severe disability (Brunello et al., 2000). SAD is a very common anxiety disorder with current prevalence estimates in the range from 4% to 6% and a lifetime risk from 7% to 13% (Wittchen and Fehm, 2001).

Although the etiology of SAD is not yet fully established, twin and family studies suggest that SAD is heritable (Kendler et al., 1992; Lieb et al., 2000; Mancini et al., 1996; Mannuzza et al., 1995; Nelson et al., 2000; Stein et al., 2002). In addition, there is evidence from various studies, including imaging and treatment studies (Furmark et al., 2005, 2004; Rowe et al., 1998; Schneier et al., 2000; Tiihonen et al., 1997) that the serotonin (*5-HT*), and dopamine (*DA*) neurotransmitter systems mediate the symptoms of SAD. Specific variants of *5-HT* and *DA* have been investigated in patients with SAD (e.g. Kennedy et al., 2001; Mathew et al., 2001; Schneier et al., 2000; Stein et al., 1998; Tiihonen et al., 1997; van der Linden et al., 2000), but to date findings have been inconsistent.

The inconsistency across studies may be addressed in part by examining heritable personality dimensions thought to contribute to susceptibility for SAD. In a familial aggregation study of anxiety-related quantitative traits (e.g. behavioral inhibition and related temperamental features) in GSAD, Stein et al. (2001) suggested that these traits were heritable, and proposed that future family and genetic studies of SAD may benefit from including a focus on these quantitative traits (Stein et al., 2001). Certainly, there are several candidate genes encoding proteins that may have a role in subserving brain functions that underlie specific personality traits. A number of studies in both psychiatric and non-psychiatric populations have proposed associations between candidate genes and human personality (Munafo et al., 2003). However, this has not yet been investigated within the context of SAD.

Therefore, the aims of this study were threefold: i.) to compare patients and controls with respect to personality traits, ii.) to genotype a subgroup of these participants to investigate the role of genes encoding components of serotonergic (*5-HT*) and dopaminergic (*DA*) pathways in patients with SAD and iii) to compare differences in temperament dimensions between carriers of different (dominant vs. recessive) alleles for the selected polymorphisms.

2. Methods

2.1. Subjects

The present study was conducted on outpatients assessed at an anxiety disorders research unit. Patients were referred from specialist psychiatrists, primary care practitioners, and advocacy groups. Seventy-five patients ($n=75$: 40 male; 35 female) with generalized SAD were recruited for participation. All patients met DSM-IV criteria for a *primary* diagnosis of SAD on the Structured Clinical Interview for the Diagnosis of Axis I Disorders-Patient Version (SCID-I/P) (First et al., 1998) as assessed by an experienced clinician. However, a cut-off value of >18 on the Social Phobia Inventory (SPIN) was used to confirm SAD diagnoses. In other words, only patients with SPIN-scores higher than 18, i.e. with clinically significant social phobic symptoms (Connor et al., 2000), were included ($n=63$; 35 male, 28 female). The presence of another mood or anxiety disorder did not mean exclusion from the study, provided that it was not the principal diagnosis. The decision to include patients with a primary diagnosis of SAD with/out comorbidity was based upon the fact that secondary depressive episodes are very frequent among patients with anxiety disorders presenting to clinical and research settings (Brawman-Mintzer et al., 1993;