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Genetic Correlates in Trichotillomania — A Case-Control Association Study in the South African Caucasian Population

Sîan M. J. Hemmings, PhD,[1,2] Craig J. Kinnear, MSc,[1,2] Christine Lochner, PhD,[2] Soraya Seedat, MD, PhD,[2] Valerie A. Corfield, PhD,[1] Johanna C. Moolman-Smook, PhD,[1] and Dan J. Stein, MD, PhD[2,3]

[1] *MRC/US Centre for Molecular and Cellular Biology, University of Stellenbosch, Tygerberg, South Africa*

[2] *MRC Unit on Anxiety and Stress Disorders, University of Stellenbosch, Tygerberg, South Africa*

[3] *Department of Psychiatry, University of Cape Town, Cape Town, South Africa*

Abstract: Background: Trichotillomania (TTM), a prevalent and disabling psychiatric disorder characterized by repetitive hair-pulling, is presently classified as an impulse control disorder (ICD). Some have argued, however, that TTM is an obsessive-compulsive spectrum disorder (OCSD). There is some evidence that both disorders (OCD and TTM) are mediated by serotonergic (5-HT) and dopaminergic pathways. *Methods*: The aim of the present investigation was to assess the role of candidate genes encoding components within the 5-HT and dopaminergic neurotransmitter pathways in mediating TTM. South African Caucasian TTM subjects (n=39), OCD (n=250) and control subjects (n=152) were genotyped for variants in 5-HT and dopaminergic candidate genes. *Results*: Both genotypic and allelic distributions of the 5-HT receptor 2A (*5-HT*$_{2A}$) *T102C* variant were found to be significantly different between the TTM and control subjects (p=0.028 and p=0.024, respectively), and a trend towards significance was noted between the TTM and OCD subjects (p=0.084 and p=0.080 for genotype and allele analyses, respectively), with the *T102T*-genotype found to confer susceptibility to the development of TTM. *Conclusion*: This investigation provides preliminary evidence for the involvement of *5-HT*$_{2A}$ in the molecular aetiology of TTM and supports the need for further replication in a larger dataset. The present data are consistent with previous findings that *5-HT*$_{2A}$ plays a role in mediating impulse dyscontrol.

Introduction

Trichotillomania (TTM) is a disabling psychiatric disorder that affects approximately 1–3% of the general population (1), and is characterized by urges to repeatedly pull out hair, resulting in excessive hair loss and personal distress (2). Although classified as an impulse-control disorder (ICD) (2), several authors have suggested that TTM is best conceptualized as an obsessive-compulsive spectrum disorder (OCSD) on the basis of phenomenological and psychobiological overlaps with obsessive-compulsive disorder (OCD) (3, 4).

A few family studies suggest a biologic overlap between OCD and TTM. Lenane et al. (5) reported an increase in the prevalence of OCD in first degree relatives of TTM probands. In addition, King et al. (6) observed that in relatives of TTM probands the frequency of OCD was greater than in the general population, although this rate was found to be lower than the rate of OCD observed in relatives of OCD probands (7). More recently, Bienvenu et al. (8) found that pathological grooming behaviors were transmitted in families of OCD probands, suggesting that TTM may be considered as part of the familial OCD spectrum of disorders.

TTM, like OCD, responds more robustly to clomipramine, a serotonin (5-HT) reuptake inhibitor (SRI), than to desipramine, a noradrenaline reuptake inhibitor (9). Furthermore, there is evidence that, as in the case of OCD, TTM patients refractory to treatment with SRIs respond to the augmentation of SRIs with dopamine blockers (10, 11). Thus, both the 5-HT and dopamine neurotransmitter systems may be implicated in TTM. Nevertheless, while many trials demonstrate that OCD responds to SRIs, the data on these agents in TTM has proved inconsistent (12, 13). If TTM lies on the OCD spectrum, it may lie some distance away from OCD.

Indeed, in a recently published preliminary study,

Address for Correspondence: Sîan M.J. Hemmings, MRC Unit on Anxiety and Stress Disorders, University of Stellenbosch, POB 19063, Tygerberg 7505, South Africa. E-mail: smjh@sun.ac.za

Baca-Garcia et al. (14) investigated the role that a functional polymorphism in the serotonin transporter (5-HTT) may play in the compulsive-impulsive continuum. The polymorphism they investigated is characterized by a 44bp insertion/deletion in the promoter region of the gene (15). It has been found that the two alleles generated by the polymorphism, the long (*L*) and short (*S*) alleles, affect the functioning of *5-HTT*. *In vitro* studies have indicated that *5-HTT* containing the *L*-allele possess two to three times higher basal transcriptional activity compared to those carrying the *S*-allele (16). The frequency of individuals carrying the *S*-allele was lowest in the group of OCD patients, highest in the group of impulsive suicide attempters, and intermediate in the group of non-impulsive controls.

The aim of the present study was to investigate the role that particular candidate genes encoding components in the 5-HT and dopaminergic pathways may play in mediating the development of TTM. Distribution of genotypic and allelic variants was compared between TTM and OCD patients, and between TTM patients and controls using case-control association analyses in the South African Caucasian population.

In the serotonergic system, variants in genes encoding the 5-HTT and 5-HT_{2A} receptor were investigated. The aforementioned functional polymorphism in the gene encoding *5-HTT* (*5-HTTLPR* [14, 15]) was also investigated in the present study. In *5-HT_{2A}*, a silent polymorphism, occurring in exon 1 of the gene (*T102C*) (17), the function of which is presently under debate, was investigated. Two studies have indicated that the *T102* allele and *T102T* genotype may result in increased expression of 5-HT_{2A} (18, 19), but Bray et al. (20) observed no difference in the expression of the alleles.

In the dopaminergic system, SNPs in genes encoding dopamine receptors 4 (*DRD4*) and 1 (*DRD1*) were investigated. *DRD4* is of interest in molecular studies of psychiatric disorders, due to its involvement in higher brain functions and the modulatory role it plays in dopamine synthesis and turnover in the brain (21, 22). In the present study, a *C* to *T* transition, occurring in the region 5' to the transcription start site at position -521 (*-521C/T* dbSNP rs1800995) (23) was investigated. This polymorphism is thought to affect transcriptional activity of *DRD4*, since the activity of the *T*-allele was reported to be 40% lower than that of the *C*-allele (23).

DRD1 activation in the central nervous system has been found to induce modulated grooming behavior in rodents (24, 25) and may underpin the exacerbation of TTM by dopamine agonists (6). This grooming behavior is enhanced upon administration of DRD1 agonists, particularly after antagonism of serotonergic receptors (26). If *DRD1* mediates certain aspects of grooming behaviors, then genetic variants in *DRD1* that result in decreased function may result in abnormalities in grooming behaviors (e.g., TTM).

Methods

Subject Recruitment

Unrelated South African Caucasian TTM (n=39) and OCD (n=250) patients, and healthy controls (n=152) were recruited through the Medical Research Council (MRC) Unit on Anxiety and Stress Disorders. The patients were referred from a wide variety of sources (including specialist psychiatrists and community-based primary care practitioners), while the controls were recruited from both university and non-university settings. Patients met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (2) for a primary diagnosis of TTM or OCD on the Structured Clinical Interview for Obsessive-Compulsive Spectrum Disorders (SCID-OCSD) (27), and the Structured Clinical Interview for the Diagnosis of Axis I Disorders — Patient Version (SCID — I/P) (28), respectively, as assessed by an experienced clinician. Patients were included irrespective of whether they were at baseline (i.e., not receiving any form of treatment for their primary psychiatric disorder), or were receiving treatment for TTM or OCD The study was approved by the Stellenbosch University's Institutional Review Board, and participation was subject to written informed consent.

Clinical Interview and Self-Report Measures

Specific demographic data, including gender, current age and age at onset of TTM were obtained. The Trichotillomania Behaviour Profile (TBP, available from the first author on request) was administered to

assess hair-pulling phenomenology. In addition, the Massachusetts General Hospital Hairpulling Scale (MGH) (29) was employed to assess the severity of hair-pulling symptoms. OCD symptoms were assessed using the Yale-Brown Obsessive-Compulsive Symptom Checklist and Severity Scale (Y-BOCS) (30).

Polymorphisms analyzed in the 5-HT and dopaminergic candidate genes

Target genomic fragments within the serotonergic (*5-HT$_{2A}$ T102C* and *5-HTTLPR*) and dopaminergic (*DRD4 -521 T/C* and *DRD1 A-48G*) candidates were amplified by means of the polymerase chain reaction (PCR) using published primer sequences and protocols (5-*HT$_{2A}$ T102C* [17]; *5-HTTLPR* [31]; *DRD4 -521C/T* [23] and *DRD1 A-48G* [32]).

All variants except *5-HTTLPR* were genotyped by means of allele-specific restriction enzyme analysis (ASREA). Since *5-HTTLPR* represented an insertion/deletion polymorphism in which the alleles differed by 44bp no ASREA was necessary. Instead, the *5-HTTLPR* PCR product was electrophoresed through a 2% agarose gel, and genotyped accordingly (the long [*L*] allele was characterized as containing the 44bp insertion). Genotypes were assigned as indicated in Table 1.

Assessment of genotypes was conducted blind to diagnosis, and by two independent investigators. Genotypes were only used if the genotyping results obtained by the two independent investigators concurred. In order to ensure genotyping accuracy, replicate samples were included in the PCR-amplification reactions and subsequent genotyping procedures, and only assays that provided 100% concordance between replicates were utilized in the analyses.

Statistical Methods

Statistical tests were performed using the Software Package for Social Sciences (SPSS) version 10.0 (SPSS Inc., Chicago) and the Di Finetti program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Agreement with Hardy-Weinberg equilibrium (HWE) was tested using the Fisher exact test.

Tests for association with the disease status were analyzed under the general genetic (genotypic) and multiplicative (allelic) models. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for the multiplicative model. Odds ratios were calculated assuming the minor allele represents the risk allele.

P-values attained in the present study were corrected for multiple testing (Bonferroni's correction). It is, however, important to remember that p-values depend largely on the sample size; hence, the emphasis is placed on the OR values (calculated for all categorical analyses) and their corresponding 95% CIs, which provide a measure of the strength of association.

Table 1. *Genotyping details for SNPs investigated in the present study*

Gene	Polymorphism	Restriction enzyme	Allele	Fragment size (bp)	Allele detection
5-HT$_{2A}$	*T102C*	*Msp*I[1]	*T*	372	2% agarose
			C	156+216	
5-HTT	*5-HTTLPR*	–	*L*[a]	419	2% agarose
			S[b]	375	
DRD4	*-521 C/T*	*Fsp*I[2]	*C*	380	2.5% agarose
			T	228+152	
DRD1	*A-48G*	*Dde*I[3]	G	259+146	2.5% agarose
			A	146+42+217	

Abbreviations: *5-HT$_{2A}$*: serotonin receptor *2A*; *5-HT$_{1DB}$*: serotonin receptor *1DB*; *5-HTT*: serotonin transporter; *DRD4*: dopamine receptor *4*; *DRD1*: dopamine receptor 1.

1: Promega Corp., Madison, WI, USA; 2: New England Biolabs, Beverly, MA, USA; 3: Roche Applied Science, Basel, Switzerland.

[a] *L* refers to the long allele (containing the insertion)

[b] *S* refers to the short allele (without the insertion)

Table 2. *Genotype and allele counts and frequencies for control, TTM and OCD subjects (percentages are indicated in parentheses)*

Gene	Variant	n_1/n_2	Control						TTM						OCD					
			Genotype			Total	Allele		Genotype			Total	Allele		Genotype			Total	Allele	
			n_{11}	n_{12}	n_{22}		n_1	n_2	n_{11}	n_{12}	n_{22}		n_1	n_2	n_{11}	n_{12}	n_{22}		n_1	n_2
5-HT2A	***T102C***	***C/T***	53 (38.4)	65 (47.1)	20 (14.5)	**138**	171 (62)	105 (38)	10 (28.6)	11 (31.4)	14 (40.0)	**35**	31 (44.3)	39 (55.7)	77 (35.8)	97 (45.1)	41 (19.1)	**215**	251 (58.4)	179 (41.6)
5-HTT	***5-HTTLPR***	***L/S***	39 (39.0)	44 (44.0)	17 (17.0)	**100**	122 (61.0)	78 (39.0)	11 (32.4)	18 (52.9)	5 (14.7)	**34**	40 (58.8)	28 (41.2)	39 (21.4)	78 (42.9)	65 (35.7)	**182**	156 (42.9)	208 (57.1)
DRD4	***-521 C/T***	***T/C***	37 (30.6)	61 (50.4)	23 (19.0)	**121**	135 (55.8)	107 (44.2)	12 (34.3)	16 (45.7)	7 (20.0)	**35**	40 (57.1)	30 (42.9)	57 (29.5)	96 (49.7)	40 (20.7)	**193**	210 (54.4)	176 (45.6)
DRD1	***-48 A/G***	***G/A***	44 (39.3)	51 (45.5)	17 (15.2)	**112**	139 (62.1)	85 (37.9)	13 (36.1)	21 (58.3)	2 (5.6)	**36**	47 (65.3)	25 (34.7)	88 (43.1)	92 (45.1)	24 (11.8)	**204**	268 (65.7)	140 (34.3)

[a]: n_1 refers to the major allele; n_2 refers to the minor allele. ***5-HT$_{2A}$***: serotonin receptor 2A; ***5-HTT***: serotonin transporter; ***DRD4***: dopamine receptor 4; ***DRD1***: dopamine receptor 1.

Results

Demographic and Clinical Variables

Data pertaining to age at interview was available for 143 control and 39 TTM subjects. The mean age at interview among controls was 37.3±11.7 years, 32.6±12.8 years among TTM subjects and 32.7±14.2 years, with no statistically significant difference noted between either TTM and control subjects (p=0.055) or TTM and OCD subjects (p=0.983). Gender was recorded for 146 control, 39 TTM and 250 OCD subjects. Males were underrepresented in the control (23.3% [34/146]) and TTM (10.3% [4/39]) subjects, although the gender ratio was roughly equal in the OCD patient subset (51.2% [128/250] were male). Although no statistically significant differences were noted for gender between the control and TTM groups (p=0.074), a significant difference was noted when gender was compared between the TTM and OCD patient subsets (p<0.001).

The mean age at onset of TTM was 13.4±9.8 years, and for OCD was 17.1±10.4 years. The mean MGH score was 12.1±7.1, while the mean score on the Y-BOCS was 19.9±7.7.

Genetic variables

Hardy-Weinberg equilibrium was found in the control groups for all variants investigated. The genotype and allele frequencies for the variants in the control, TTM and OCD groups are depicted in Table 2.

Statistically significant results were obtained when the *5-HT$_{2A}$* T102C genotype and allele frequencies were compared between the TTM and control groups (p=0.006 and p=0.007 [OR=2.0, 95% CI: 1.3–3.3], respectively). These results remained significant even after correcting for multiple testing (Table 3). Here, significantly more TTM patients were found to possess the *T102T* genotype, compared to controls, indicating that this allele may confer susceptibility to the development of the disorder in a recessive manner (Table 3).

Likewise, statistically significant results were obtained when the *5-HT$_{2A}$* T102C genotype and allele frequencies were compared between the TTM and OCD groups (p=0.021 and p=0.020 [OR=1.7; 95% CI: 1.1–3.3], respectively) (Table 4). Although this significance was lost after correcting for multiple testing, a trend towards significance was still observed (p=0.084 and p=0.080 for genotypic and allelic analyses, respectively). Here, the *T102T* genotype was also found to confer susceptibility to the development of TTM in a recessive manner (Table 4).

No statistically significant associations were observed when the genotype and allele frequencies within the remaining candidate genes were compared between the TTM patients and controls (Table 3), or between TTM and OCD patients (Table 4).

Table 3. *Association analysis investigating the differences in genotype and allele distributions between TTM and control individuals*

Gene	Variant	Genotype p-value	Allele p-value	OR	95% CI
5-HT$_{2A}$	T102C	0.006*	0.007**	2	1.3–3.3
5-HTT	*5-HTTLPR*	0.702	0.751	0.9	0.5–1.7
DRD4	*521C/T*	0.852	0.84	0.9	0.6–1.7
DRD1	*48 A/G*	0.215	0.622	2	0.7–2.0

Abbreviations: OR: odds ratio; CI: confidence interval; *5-HT*$_{2A}$: serotonin receptor 2A; *5-HT*$_{1DB}$: serotonin receptor 1DB; *5-HTT*: serotonin transporter; *DRD4*: dopamine receptor 4; *DRD1*: dopamine receptor 1.
Significant p values are indicated with asterisks.
Corrected p-values: *p=0.028; **p=0.024.

Table 4. *Association analysis investigating the differences in genotype and allele distributions between TTM and OCD individuals*

Gene	Variant	Genotype p-value	Allele p-value	OR	95% CI
5-HT$_{2A}$	T102C	0.021*	0.020**	1.7	1.1–3.3
5-HTT	*5-HTTLPR*	0.501	0.796	0.9	0.6–1.7
DRD4	*521C/T*	0.849	0.672	0.9	0.5–1.4
DRD1	*48 A/G*	0.274	0.946	1	0.6–1.7

Abbreviations: OR: odds ratio; CI: confidence interval; *5-HT*$_{2A}$: serotonin receptor 2A; *5-HTT*: serotonin transporter; *DRD4*: dopamine receptor 4; *DRD1*: dopamine receptor 1.
Significant p values are indicated with asterisks.
Corrected p-values: *p=0.084; **p=0.080.

Discussion

To our knowledge, this is the first published study that investigates the role that candidate genes may play in mediating the development of TTM, and as such, yield important preliminary findings. The genetic data yield preliminary evidence for the involvement of the 5-HT system in mediating the development of TTM. When compared to the healthy control group, an abundance of the 5-*HT*$_{2A}$ *T102T* genotype among TTM patients was detected. The p-value obtained remained significant, even after correction for multiple testing (p=0.024 and p=0.028 for the genotype and allele analyses, respectively). A significantly higher frequency of the *T102T* genotype was also detected among TTM patients when compared to OCD patients, with a trend towards significance even after correction for multiple testing (p=0.080). Thus, the *5-HT*$_{2A}$ T102C polymorphism, or a variant in LD with it, may play a role in mediating impaired impulse control.

The function of this polymorphism is presently under debate. Polesskaya and Sokolov (18) investigated the relationship of the *C102* and *T102* alleles and expression of *5-HT*$_{2A}$ in post-mortem brain tissue of healthy volunteers and patients with schizophrenia, and found that the expression level of *C102* was significantly decreased in relation to that of the *T102* allele. Similarly, Khait et al. (19) assayed platelet *5-HT*$_{2A}$ binding kinetics, and observed that the *T102T* genotype was associated with increased *5-HT*$_{2A}$ receptor density (and thus increased expression). However, Bray et al. (20), using a quantitative allele-specific primer extension assay, observed no

differences in expression between the *C102* and *T102* alleles in several adult cortical regions in a post-mortem assay, and concluded that neither allele affected mRNA expression.

If the *T102* variant is associated with increased expression of the 5-HT_{2A} receptor, then the ensuing alteration in 5-HT transmission may be a risk factor for TTM. Nevertheless, given the uncertainty about the functionality of the variant, it is possible that a different variant, but in LD with it, contributes to the development of the disorder. Indeed, a functional variant in the promoter region, *-1438A/G*, has been found to exhibit a high degree of LD with the *T102C* polymorphism (33, 34).

The present finding is interesting, since the significant difference in the genotype and allele frequencies in *5-HT_{2A} T102C* between the TTM and OCD groups may indicate that, although TTM is classified as an OCSD, the aetiological mechanisms underlying the two disorders differ in some ways. Certainly, this is consistent with a range of literature demonstrating clinical differences between TTM and OCD (35). Further investigations are required to delineate precisely how these two disorders may differ at a molecular level.

The current results are consistent with those obtained from previous pharmacological, clinical, animal and genetic studies, which suggest the involvement of the serotonergic system in impulse dyscontrol (9, 14, 36–38). However, there are important interactions between the 5-HT and dopaminergic systems, for example, Scalzitti et al. (39) reported on the role of *5-HT_{2A}* receptor in the modulation of *DRD1*-mediated grooming behavior in rats. In the present study, no association was noted between the *DRD1 A-48G* variant and the development of TTM. Given the nature of complex disorders, it may well be that the association between the *DRD1 A-48G* variant is only apparent on simultaneous investigation with the *5-HT_{2A}* T102C variant. Because of the small sample sizes, an investigation into the epistatic interactions between the two genes was not viable.

Indeed, a limitation of this study is the relatively small sample of TTM patients. The association detected between the *5-HT_{2A}* T102C polymorphism and TTM may reflect a false positive result. Conversely, the possibility of false negative results for the remaining candidate genes cannot be excluded. A range of other candidate genes ultimately deserve study in TTM, for example, HoxB8 (40) and the gene encoding slit and Trk-like 1 (*SLITRK1*) (41). Likewise, in OCD, researchers are focusing their attention on genes that do not necessarily encode components in the serotonergic or dopaminergic systems (42–45, see 46 for a recent review).

At present there is incomplete consensus as to which test constitutes the most appropriate for correcting for multiple tests in genetic analyses. Applying the Bonferroni correction may well produce a p-value that is too conservative (47, 48), and consequent false negative (Type II error) results, especially where data is not independent. On the other hand, multiple testing does increase the risk of a false positive result; therefore, in the present study it was decided to use the Bonferroni adjustment to correct for multiple tests, adjusting for the number of markers analyzed.

The South African Caucasian population utilized in the investigation are all of Northern European descent, and therefore the confounding factor of population stratification should not influence the results to any large degree. A subset of the South African Caucasian population, the Afrikaners, are believed to be more genetically homogeneous than the general South African Caucasian population, given their history and population dynamics. This has resulted in a relatively small gene pool and an above average frequency of rare genetic illness within the Afrikaner population, due to founder effects (49, 50), and utilizing this sub-population in future genetic studies should help eliminate confounding effect due to population stratification.

In conclusion, the data presented in this investigation reflects preliminary evidence for a link between the *5-HT_{2A}* T102C polymorphism and TTM and warrants further prospective identification of Afrikaner TTM subjects, and non-psychiatric controls, in order to improve the power of the study and limit any possible effect of population stratification.

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