REVIEW ARTICLE

The genetic factors influencing the development of trichotillomania

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Abstract

Trichotillomania (TTM), an obsessive–compulsive spectrum disorder (OCSD), is a psychiatric condition characterized by repetitive hair pulling. Evidence from family and twin studies suggest a heritable link of TTM. Functional polymorphisms in genes involved in neuronal pathways might influence the susceptibility to TTM. This review is an attempt to compile the genetic factors reported to modify the development of TTM.

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Introduction

Trichotillomania (TTM) is a type of psychiatric disorder which is characterized by repetitive hair pulling (APA 1994). The individual suffering with this disorder pulls out hair in a chronic or compulsive manner from the scalp or eyebrows which results in excessive hair loss as well as personal distress. Hair pulling in individuals suffering from TTM leads to pleasure and relief in tension (APA 2000). TTM affects about 1–3% of the general population (Christenson *et al.* 1991; Rothbaum *et al.* 1993). TTM can be psychologically devastating and lead to several physical complications. The behaviour of hair pulling is one of several grooming behaviours like nail biting and skin picking which occur across species and is considered normal in milder forms (Mansueto *et al.* 2007).

TTM has been classified as an impulse-control disorder (ICD) (APA 1994). However, researchers suggest that based on the phenomenological and psychological overlaps with obsessive--compulsive disorder (OCD), TTM is best described as an obsessive–compulsive spectrum disorder (OCSD) (Swedo and Leonard 1992). Certain behaviours of TTM, such as repetitive motor symptoms, have similarity with other OCSD such as repetitive motor tics in Tourette's syndrome or repetitive compulsive rituals in some OCD symptoms such as tapping or touching (Miguel *et al.* 1997). Even though a relationship between OCD and TTM is proposed based on their similarities, there are important differences between these two anxiety disorders. Compulsions in OCD are generally driven by intrusive thoughts; on the other hand, TTM is not known to be driven by cognitive intrusions. OCD initiates in late adolescence while TTM initiates in early adolescence (Himle *et al.* 1995). Hence, the concept of TTM being an OCSD remains debatable (Eliott and Fuqua 2000).

Familial link

TTM has been found to be a familial and genetically modified psychiatric disorder. Several cases of familial hair pulling have been reported (Sanderson and Hall-Smith 1970; Galski 1983; Kerbeshian and Burd 1991). Relatives of TTM probands have shown higher rate of hair pulling behaviour (Swedo and Rapoport 1991; Christenson *et al.* 1992). The first degree relatives of TTM were found to have increased rates of TTM like behaviour (Swedo and Rapoport 1991; Schlosser *et al.* 1994). Family studies have revealed indirect evidence for a genetic association between OCD and TTM (Lenane *et al.* 1992; King *et al.* 1995). Other psychological grooming behaviours similar to hair pulling such as, nail biting and thumb sucking also show genetic association. For nail biting, 50% of the phenotypic variance were genetically controlled irrespective of gender and for thumb sucking this percentage was 66% for males and 50% for females (Ooki 2005). Such evidence suggest that grooming behaviour like TTM does have a familial link and is also influenced by individual genetics. A lot of work has been done on the genetic susceptibility factors of OCD (Nicolini *et al.* 2009; Norrholm and Ressler 2009). However, molecular genetic studies of TTM are in their relative infancy. According to the best of my knowledge, no review has been published compiling the genetic factors reported to modify the TTM development.

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This review is an attempt to summarize the genetics of TTM and the future directions of research in this field.

Twin study

Although higher than expected rates of TTM have been reported in family studies (as discussed above), only one twin concordance study estimated the heritability rates of TTM (Novak *et al.* 2009). Same-sex American twin pairs with at least one of the twins having TTM were recruited in this study. Among 34 twin pairs, 24 were monozygotic (MZ) and 10 were dizygotic (DZ). MZ and DZ concordance rates were significantly different for three different diagnostic schemes. For MZ, DSM-IV was observed as 0.381 and 0.00 for DZ ($P = 0.047$). Modified DSM was 0.391 for MZ and 0.21 for DZ ($P = 0.021$) and noncosmetic hair pulling was 0.583 for MZ and 0.200 for DZ ($P = 0.046$). The heritability estimates ranged from 0.76 to 0.78. The concordance rates observed in this study are suggestive of a significant role of the genetic factors in the etiology of TTM (Novak *et al.* 2009).

SAP90/PSD9-associated protein (SAPAP)

SAP90/PSD9-associated protein (SAPAP) family proteins interact with other proteins to form a key scaffolding complex at glutamatergic synapses (Scannevin and Huganir 2000). SAPAP protein family has four homologous members. It was shown that mice with a deletion of the *Sapap3* gene showed excessive grooming behaviours (Welch *et al.* 2007). As mouse and human *Sapap3* gene are highly homologous (>90%), it had been hypothesized that *Sapap3* gene might be involved in the etiology of human OCSD (Hollander and Benzaquen 1997; Welch *et al.* 2007). Human *Sapap3* gene is located on chromosome 1p. Family-based association analyses in 383 families from America and Columbia with OCD and/or OCSD including TTM was conducted (Bienvenu *et al.* 2009). Analysing six single-nucleotide polymorphisms (SNPs) in the *Sapap3* gene showed an association with SNP rs6662980 by over-transmission of the G allele ($P = 0.01$, 95% CI = 1.09–5.48) as well as with SNP rs4652869 by under-transmission of the GG genotype ($P = 0.05$, 95% CI = 0.19–2.86) (Bienvenu *et al.* 2009). The haplotype analysis showed an association with rs6662980/rs4652867 GG and TTM ($P = 0.02$) (Bienvenu *et al.* 2009). Another American study comprising 165 cases with TTM and/or OCD and 178 controls sequenced the entire *Sapap3* coding region and flanking intronic sequences (Zuchner *et al.* 2009). Seven nonsynonymous heterozygous polymorphisms were detected (R13C; A148insGPAGA; T156M; A189V; T523K; P606T and K910R). These polymorphisms were significantly over represented (4.2%) in the TTM/OCD cases compared to controls (1.1%) (Zuchner *et al.* 2009). Further analysis suggested that these polymorphisms themselves are not disease causing. However, the possibility of an aggregate of the susceptibility variants contributing to the disease remains open (Zuchner *et al.* 2009).

Serotonergic and dopaminergic pathways

As is the case for OCD, TTM also responds positively to a serotonin (5-HT) reuptake inhibitor (SRI), clomipramine, compared to a noradrenaline reuptake inhibitor, desipramine (Swedo *et al.* 1989). However, increased dosage of SRIs combined with dopamine blockers is considered when treatment with only SRIs fail to initiate a response in TTM patients (Van Ameringen *et al.* 1999; Stein 2000). These suggest that both 5-HT and dopamine neurotransmitter systems might be involved in TTM development. The role of the genes encoding components in the serotonergic (*5-HT*) and dopaminergic pathways were investigated in TTM (Hemmings *et al.* 2006). The functional polymorphisms in the genes encoding *5-HTT* (*5-HTTLPR*) and *5-HT2A* (*T102C*) were chosen as candidate SNPs. The *5-HT2A* gene is located on chromosome 13q and *5-HTT* gene is located on chromosome 17q. Studies have indicated an increased expression of *5-HT2A* due to *T102* allele and *T102T* genotype (Polesskaya and Sokolov 2002; Khait *et al.* 2005), though the actual function of this silent polymorphism is still debatable. SNPs in the gene encoding dopamine receptor 4 (*DRD4*) is of interest in molecular genetic studies of psychiatric disorders since it is involved in higher brain functions and in synthesis and supply of dopamine in the brain (Rubinstein *et al.* 1997; Tarazi and Baldessarini 1999). The *DRD4* gene is located on chromosome 11p. *DRD4 -521C/T* affects the transcriptional activity of *DRD4* by 40% higher expression of the *T* allele compared to the *C* allele (Okuyama *et al.* 1999). SNPs in the gene encoding dopamine receptor 1 (*DRD1*) is also of interest since *DRD1* activation in central nervous system induces modulated grooming behaviours in rodents (Molloy and Waddington 1987; Wachtel *et al.* 1992). The *DRD1* gene is located on chromosome 5q. Functional SNPs in *DRD1* like, *-48 A/G* might be involved in modulating grooming behaviours such as, TTM. Thirty-nine TTM and 250 South African Caucasian OCD patients were investigated for the roles of *-5HT2A* (*T102C*), *5-HTT* (*5-HTTLPR*), *DRD4* (*-521 C/T*) and *DRD1* (*-48 A/G*) against 152 population matched healthy controls (Hemmings *et al.* 2006). *5-HT2AT102C* was found to be associated with TTM compared to controls ($P = 0.006$, OR = 2.0, 95% CI = 1.3–3.3). *T102T* genotype was found to confer susceptible effect in developing TTM. The same genotype *T102T* also showed a trend ($P = 0.084$) towards conferring susceptible effect to TTM when compared to OCD. *5-HTT* (*5-HTTLPR*), *DRD4* (*-521 C/T*) and *DRD1* (*-48 A/G*) did not show any association with TTM (Hemmings *et al.* 2006).

Monoamine pathway

Polymorphisms in genes involved in monoamine function were investigated in 248 OCD/TTM subjects of Caucasian and Afrikaner origin against 312 population matched healthy controls. No association was found with any of the variants and either with TTM or OCD (Lochner *et al.* 2005).

The Slit and Trk-like 1 (SLITRK1)

The Slit and Trk-like 1 (SLITRK1) protein is a neuronal transmembrane protein that controls neurite outgrowth and has roles in extracellular signalling (Mah 2010). The gene encoding SLITRK1 is located on chromosome 13q and has been widely investigated for its association with Tourette's syndrome (O'Rourke *et al.* 2009). The polymorphisms in *SLITRK1* gene were investigated in TTM families of European descent (Zuchner *et al*. 2006). The complete *SLITRK1* gene was screened for variations present in TTM families compared to controls. G to A transition at position 1751 (c.1751G>A) that resulted in substitution of arginine for lysine (R584K) and an A to G transition at position 1777 (c.1777A>G) that replaced serine by glycine (S593G) were detected specific to TTM cases compared to nonTTM controls (Zuchner *et al*. 2006). SLITRK1 protein deficiency has also been shown to cause anxiety-like behaviour in mice (Katayama *et al.* 2010).

Conclusion

Although the genetics of OCD had been well researched by different groups across the globe and also some of the OCSDs, not much work has been done on TTM. TTM represents distressing grooming behaviours as a psychiatric disorder and commands a lot more attention in understanding the heritable and genetic factors that influence the development of the disease. The genetics of TTM are complex and not well understood. The above mentioned candidate genes that have been investigated in TTM need to be studied for disease association in bigger cohorts, and in more populations. A recent study found over-representation of a SNP in the *CDH2* gene in extremely compulsive Dobermans compared to normal ones (Dodman *et al*. 2010). The *CDH2* gene located on chromosome 7, encodes for protein cadherine-2 which is widely expressed and is involved in the mediation of synaptic activity-regulated neuronal adhesion and plays a key role in development of central nervous system (Dodman *et al*. 2010). *CDH2* gene could be a potential candidate gene for an OCSD such as TTM. The limitations of linkage and candidate gene studies could be overcome by genomewide association studies. However, large-scale collaborations are essential to provide enough statistical power for genome wide association studies for finding causative mutations. Understanding of genetic underpinnings and the biological pathways involved should eventually lead to better management and treatment of TTM.

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