Title

Serotonin system genes and hoarding with and without other obsessive-compulsive traits in a population-based, pediatric sample: A genetic association study

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Conflicts of Interest

Russell J. Schachar has acted as a consultant for Highland Therapeutics, ehave, and Eli Lilly Canada Inc. and is the Toronto Dominion Bank Financial Group Chair in Child and Adolescent Psychiatry. Vanessa M. Sinopoli, Lauren Erdman, Christie L. Burton, Laura S. Park, Annie Dupuis, Janet Shan, Tara Goodale, S-M Shaheen, Jennifer Crosbie, and Paul D. Arnold have no conflicts of interest to declare.

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Abstract

Background: Hoarding, originally only considered a symptom of obsessive-compulsive disorder (OCD), is now categorized as a separate disorder in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). We studied candidate serotonergic genes and the distinctness of hoarding in children and adolescents and hypothesized that unique gene variants would be associated with hoarding alone.

Methods: We examined obsessive-compulsive (OC) traits, including hoarding, in a total of 5213 pediatric participants in the community. We genotyped candidate serotonin genes (*5-HTTLPR* polymorphism in *SLC6A4* for 2018 individuals and single nucleotide polymorphisms [SNPs] across genes *SLC6A4*, *HTR2A*, and *HTR1B* for 4711 individuals). In a previous study conducted by our group in the same sample, we identified a significant association between *5-HTTLPR* and hoarding in males. In this study, we examined hoarding more closely by testing the association between serotonin gene variants and hoarding traits with and without other accompanying OC traits.

Results: The [L_G + S] variant in *5-HTTLPR* was significantly associated with hoarding alone in males (P-value of 0.009). There were no significant findings for *5-HTTLPR* in females. There were no significant findings after correction for multiple comparisons using SNP array data, but top SNP findings suggested that variation downstream of *HTR1B* may be implicated in hoarding alone in females.

Conclusions: Our results suggest specific serotonin gene variants are associated with hoarding traits alone, differing between sexes. Top findings are in line with our former study, suggesting that individuals with hoarding alone were driving previous results. Our paper supports hoarding disorder's new designation.

Keywords: OCD/Obsessive-Compulsive Disorder; Hoarding; Child/Adolescent; Genetics; Measurement/Psychometrics

1. Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by intrusive and repetitive thoughts and behaviors and is debilitating in nature (American Psychiatric Association [APA], 2013), with an estimated lifetime prevalence of 2-3% worldwide (Angst et al., 2004; Kessler et al., 2005; Murphy et al., 2013).

OCD is phenotypically heterogeneous. A meta-analysis of factor analyses of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) in adults and/or children with OCD reported four symptom dimensions: 1) Symmetry, 2) Forbidden thoughts, 3) Cleaning, and 4) Hoarding (Bloch et al., 2008). Based on mounting scientific evidence (Mataix-Cols & Pertusa, 2012), hoarding is now classified as a separate disorder in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), under the new category "Obsessive-Compulsive and Related Disorders" (APA, 2013).

Hoarding disorder is estimated to affect 2-5% of adults (Samuels et al., 2008) and 2% of adolescents (Ivanov et al., 2013), with little known about its prevalence in children (Burton et al., 2015). It is characterized by difficulty discarding acquired possessions, so as to cause significant clutter and/or financial strain and negatively impact quality of life for patients and their families, and often presents with excessive acquisition of materials (APA, 2013; Burton et al., 2015). Less than 20% of adults with hoarding disorder have OCD, meaning over 80% of adults present with hoarding independent of OCD (Frost et al., 2011). Between 19 and 31% of patients with

pediatric OCD also have hoarding symptoms (Storch et al., 2007, Sheppard et al., 2010; Samuels et al., 2014).

OCD has been identified as familial and heritable, with estimated heritability ranging from 27-47% in adults and 45-65% in children (van Grootheest et al., 2005, Pauls et al., 2014). Hoarding is also familial (Frost & Gross, 1993; Samuels et al., 2002; Samuels et al., 2007a; Pertusa et al., 2008; Steketee et al., 2015) and heritable, with estimates in adult twins ranging from 36-49% (Iervolino et al., 2009; Taylor et al., 2010; Mathews et al., 2014). In adolescence to young adulthood, heritability was shown to range from 29-41% (decreasing with age), with authors noting substantially higher heritability in males versus females in the youngest age group (Ivanov et al., 2017). Among the symptom dimensions of OCD, hoarding was most influenced by unique genetic effects (Iervolino et al., 2011; Burton et al., 2018).

A number of candidate genes have been studied in OCD including *SLC6A4* (solute carrier family 6 member 4), *HTR2A*, and *HTR1B*, respectively corresponding to the serotonin transporter (SERT) and serotonin receptors 5-HT_{2A} and 5-HT_{1B} (Taylor, 2013). Within the promoter of *SLC6A4* lies a heavily researched polymorphism in OCD, *5-HTTLPR* (5-HTT-linked polymorphic region). It exists as a long (L) variant or a short (S) variant (Heils et al., 1996; Lesch et al., 1996). Within the L variant lies single nucleotide polymorphism (SNP) rs25531 (A or G). There are two resulting functional groups: L_A, which yields greater SERT expression and L_G/S, which yields lower SERT expression (Hu et al., 2006). Overall, findings as to which variants across these candidate genes are associated with OCD have been inconsistent (Sinopoli et al., 2017). This may result from failure to adequately address underlying heterogeneity in

OCD, such as presence or absence of hoarding symptoms. For example, some genetic and neuroimaging studies show that the underlying biology of hoarding differs from OCD (van Ameringen et al., 2014). Hoarding symptoms may also differ in their response to the most commonly prescribed medications for OCD, serotonin reuptake inhibitors (SRIs) (Murphy et al., 2004). Patients with OCD and hoarding symptoms respond more poorly to SRIs compared to OCD patients without hoarding symptoms (Bloch et al., 2014), supporting the notion of unique underlying biology. One possibility for this difference in treatment response may be genetic differences between patients with or without hoarding symptoms.

In a recent study, our group examined serotonin candidate gene variants for their association with obsessive-compulsive (OC) trait dimensions in a community pediatric sample and tested whether these associations differed between males and females. Our main finding was that [L_G + S] (versus L_A) was significantly associated with hoarding in males. We also identified a trend for variation downstream of *HTR1B* to be associated with hoarding in females (Sinopoli et al., 2019). Given that recent comprehensive meta-analyses found an association between L_A, as opposed to [L_G + S], and OCD (Taylor, 2013; Taylor, 2016), our results suggest that genetic heterogeneity in the serotonin system may be one factor that underlies the phenotypic heterogeneity observed between OC dimensions and hoarding. What we do not yet know is if hoarding traits alone are driving our previous serotonergic findings. If so, this would suggest that hoarding has genetic correlates that are distinct from OCD and, more specifically, that there are unique serotonin system gene variants that are associated with hoarding alone and not with other OC traits.

In this study, we aimed to further characterize the relationship between hoarding and candidate serotonin gene variants in the same large, pediatric, population-based sample (Sinopoli et al., 2019). We aimed to extend the results of the first study (Sinopoli et al., 2019) and identify if different serotonin system genes variants are associated with each of the following more homogenous, trait-based subgroups: hoarding traits with other OC traits, hoarding traits without other OC traits, and OC traits without hoarding traits. Given that hoarding most often presents independently from OCD and studies suggest biological distinctness of hoarding (Snowdon et al., 2012; van Ameringen et al., 2014), we hypothesized that our previously noted findings, whereby unique serotonergic gene variants were associated with hoarding (as one of the OC trait dimensions), were being driven by individuals with hoarding traits alone. We therefore expected to identify the same genetic variants to be associated with the hoarding only group and not with the hoarding plus OC group or the OC only group. We also hypothesized that our findings would differ between sex groups as seen previously (Sinopoli et al., 2019).

2. Methods

2.1. Participants

As explained in our previous study (Sinopoli et al., 2019), a total of 17,263 children and adolescents, ranging in age from 6-18, were recruited from and evaluated at the Ontario Science Centre in Toronto, Canada for the Thoughts, Actions and Genes (TAG) project further described elsewhere (Crosbie et al., 2013; Burton et al., 2016; Park et al., 2016). Informed consent (and assent where applicable) was acquired for participants and study approval was obtained through

the Research Ethics Board at the Hospital for Sick Children. Complete demographic information and questionnaires were available for 16,718 participants, whereby information was provided via parent-respondent (N=13,680) or self-respondent (N=3,038). Our current study used the same overall sample of individuals used in our previous study (Sinopoli et al., 2019) to further examine hoarding traits in the community. As was the case for our previous study, two smaller, partially overlapping groups of participants were gathered from our initial, overall, population-based sample. Selected individuals had 4 grandparents of European descent. The first group included 2100 individuals who had DNA available to directly genotype *5-HTTLPR* in *SLC6A4*. The second group included 4810 individuals who had genome-wide association study (GWAS) data available and from which SNPs in our candidate genes were obtained.

2.2. Hoarding/obsessive-compulsive features

As described previously (Sinopoli et al., 2019), participants or their parents completed the Toronto Obsessive Compulsive Scale (TOCS) which measures OC traits (Park et al., 2016). Each of the 21 items was scored on a scale of -3 to +3, whereby -3 means the participant performs the behavior far less often than his or her peers and +3 means the participant performs the behavior far more often than his or her peers. The TOCS factors into 6 dimensions: Cleaning/Contamination, Counting/Checking, Symmetry/Ordering, Superstition, Rumination, and Hoarding (Burton et al., 2018). Two items directly pertained to hoarding traits: one examining excessive acquisition of useless objects and another examining difficulty discarding things. We dichotomized each TOCS item, with a score of ≥ 2 indicating presence of the trait and with any other score indicating absence of the trait. We assigned "affected" participants

into the following groups, separately for males and females: 1) Individuals with at least one hoarding trait and at least one other non-hoarding OC trait (Hoarding Plus OC group), 2) Individuals with at least one hoarding trait and without any other non-hoarding OC traits (Hoarding Only group), 3) Individuals with no hoarding traits and at least one OC trait that is not a hoarding trait (OC Only group). Our control group included all individuals with no hoarding or non-hoarding OC traits.

2.3. DNA collection and extraction

Saliva was collected from each participant using Oragene·DNA (OG-500) kits and DNA was extracted using the recommended protocol (DNA Genotek). In addition to the protocol, we centrifuged the samples at 10,000 RPM for 10 min more to remove precipitated carbohydrates. We quantified the DNA using the Quant-iT™ PicoGreen® dsDNA Assay Kit (Invitrogen). To ensure adequate DNA quality, samples were run on agarose gels before being used for the microarrays. DNA samples that had a concentration below 60 ng/µl (if genotyped on the HumanCoreExome-12 v1.0 microarray (Illumina)) and DNA samples of poor quality were excluded.

2.4. Selection of candidate genes

As in our previous study (Sinopoli et al., 2019), we examined candidate serotonin genes *SLC6A4*, *HTR2A*, and *HTR1B* based on their inclusion in a recent OCD meta-analysis and within which lie polymorphisms that have the best evidence of association with OCD (Taylor, 2013).

2.5. *5-HTTLPR*

2.5.1. Direct genotyping

5-HTTLPR variation is not captured using microarrays and so we directly genotyped this polymorphism as detailed in our previous study, carried out with The Centre for Applied Genomics (TCAG) at the Hospital for Sick Children in Toronto (Sinopoli et al., 2019). In brief, genotyping this region involved two steps (Wendland et al., 2006). First, to identify variants as L or S, *5-HTTLPR* was PCR amplified using forward primer 5'-ATGCCAGCACCTAACCCCTAATGT-3' (5'-labeled with HEX fluorescent dye) and reverse primer 5'-GGACCGCAAGGTGGGCGGGA-3' (Gelernter et al., 1997). Second, to identify A or G at rs25531, restriction enzyme MspI (Fermentas, Life Technologies) was used for digestion. Samples were run on an ABI3730XL genetic analyzer using the POP-7 polymer and Dye Set G5 (Applied Biosystems). The Peak Scanner Software v1.0 (Thermo Fisher Scientific) was used to analyze results. *5-HTTLPR* variants were identified as L_A, L_G, or S (which includes the S_A variant and the rare S_G variant). Based on functionality, we sorted our alleles as follows: L_A and [L_G + S]. Alleles were treated as additive in their effect (Hu et al., 2006). Standard quality control (QC) was implemented as previously described (Sinopoli et al., 2019). Individuals were genotyped with a 97% completion rate and reported siblings and individuals of indeterminate ethnicity were removed. In our final, total *5-HTTLPR* sample, we identified 12 individuals carrying the rare S_G variant. We had a final N of 2018 after all QC.

2.5.2. Statistical analyses

Analyses were conducted (similar to what was done previously) using the program, R, version 3.0.1 (https://www.R-project.org). In separate analyses for male and for female subjects, and using an additive model, the expected number of tested alleles (0, 1, 2 [L_G + S] alleles) was used in a logistic regression as a predictor of affected versus control status for each of the 3 trait groups. Age and questionnaire respondent type (parent or self) were used as covariates. To account for multiple comparisons, the final significance threshold was a P-value < 0.017 (0.05 / 3 analyses) for both males and females.

2.6. Candidate gene SNPs

2.6.1. Genotyping

Candidate gene SNPs across *SLC6A4*, *HTR2A*, and *HTR1B* were obtained as previously described (Sinopoli et al., 2019). In short, genotype data was collected using the HumanCoreExome-12 v1.0 microarray (Illumina) and QC included removal of SNPs with a call rate < 0.97 and samples with sex misspecification and ambiguity. Only one member per family was kept for analyses (PI_HAT cutoff = 0.12) and European ethnicity was verified via principal component analysis (PCA) using EIGENSTRAT version 3.2.10 (Price et al., 2006) with HapMap populations CEU and TSI to ensure that our individuals' genetic data clustered with Europeans. Another PCA was conducted to identify and remove outliers within our own population and an additional PCA was conducted without outliers, followed by formation of a scree plot, to identify

seven principal components (PCs) needed to control for population structure in our analyses. We had a final N of 4711 after QC.

Imputation was conducted across *SLC6A4*, *HTR2A*, and *HTR1B* along with ±50 kb flanking DNA using SHAPEIT2 version 2.790 (Delaneau et al., 2014) and IMPUTE2 version 2.3.1 (Howie et al., 2009). 1000 Genomes Phase 3 reference data was used for pre-phasing and for imputation. SNPs were removed for low quality imputation (information score < 0.8) and SNPs with a minor allele frequency (MAF) < 0.05 were excluded. Data were kept as dosage calls for the analyses. Final SNP counts across the 3 candidate genes are shown in Table 1 and are identical to those previously reported (Sinopoli et al., 2019).

[TABLE 1]

2.6.2. Statistical analyses

R, version 3.0.1 (https://www.R-project.org), was used in a set of analyses similar to those previously conducted. Within male and female subjects separately, and using an additive model, logistic regressions were conducted for each SNP using the expected number of tested alleles (0, 1, 2) to predict affected versus control status for each of the 3 trait groups. Analyses were conducted using age, respondent, and the identified PCs (to control for population structure) as covariates. The Genetic Type 1 error calculator (GEC) was used to account for dependent SNPs (Li et al., 2012) and to address multiple comparisons, resulting in a significance threshold P-

value < 6.87e-5 (2.06e-4 / 3 analyses) for males and a significance threshold P-value < 6.77e-5 (2.03e-4 / 3 analyses) for females.

2.7. Sample size considerations

As in our previous study (Sinopoli et al., 2019), the final sample size for *5-HTTLPR* was smaller than the final sample size for our candidate gene SNPs (N of 2018 versus N of 4711). The two groups share a 29% overlap (1516 individuals genotyped for and used in both the *5-HTTLPR* and candidate gene SNP groups). Given that less stringent statistical correction was required for the single variant versus the set of candidate gene SNPs and given that increased labor and cost was required to directly genotype *5-HTTLPR*, the sample size for *5-HTTLPR* was deemed sufficient even though smaller.

3. Results

3.1. *5-HTTLPR* analyses

Demographics for *5-HTTLPR*-genotyped individuals are in Table 2 and are identical to what was previously reported (Sinopoli et al., 2019). As determined through the use of t-tests, there were no significant differences for age between affected males and male controls, or between affected females and female controls. There was a significant difference for respondent between affected males and male controls (absolute t-statistic = 3.09, P-value = 0.002), but not between affected females and female controls. Table 3 shows the affected versus control counts for each of the

three trait groups in our *5-HTTLPR*-genotyped individuals. Table 4 shows the allele frequencies for affected *5-HTTLPR*-genotyped individuals in each of the three trait groups.

[TABLE 2]

[TABLE 3]

[TABLE 4]

As seen in Figure 1, in males, and after correction for multiple comparisons, the [L_G + S] allele was significantly associated with hoarding only (odds ratio, OR, of 1.43; P-value of 0.009). There were no significant differences for females.

[FIGURE 1]

3.2. Candidate gene SNP analyses

Demographics for the candidate gene SNP individuals are in Table 5 and are identical to what was previously reported (Sinopoli et al., 2019). As determined through the use of t-tests, there were no significant differences for age or for respondent between affected males and male controls, or between affected females and female controls. Table 6 shows the affected versus control counts for each of the three trait groups in our individuals genotyped for candidate gene SNPs.

[TABLE 5]

[TABLE 6]

The top 20 SNP findings across the three genes and trait groups, for males and females, are shown in Table 7 and Table 8 respectively. For males, the top SNPs reported were varied across genes and associated trait groups (OR of 0.63 to 1.33; P-value of 7.35e-3 to 2.56e-2) and were not significant after correction for multiple comparisons. For females, the top SNPs reported all corresponded with *HTR1B* and were associated with hoarding only (OR of 1.64 to 1.68; P-value of 5.78e-4 to 9.50e-4). Our findings did not remain significant after correction for multiple comparisons.

[TABLE 7]

[TABLE 8]

4. Discussion

Hoarding is phenotypically and biologically distinct from OCD (Snowdon et al., 2012; van Ameringen et al., 2014). With hoarding now classified as a separate but OCD-related disorder (APA, 2013), we sought to specifically examine serotonin system candidate genes in hoarding, using a sample of children and adolescents from the community to better capture individuals

with hoarding traits who may not also have other OC traits. We previously examined six OC trait dimensions (Cleaning/Contamination, Counting/Checking, Symmetry/Ordering, Superstition, Rumination, Hoarding) and our strongest findings were a significant sex-specific association between the [L_G + S] allele of *5-HTTLPR* and hoarding in males and a sex-specific trend for association between variation downstream of *HTR1B* and hoarding in females (Sinopoli et al., 2019). What remained unanswered in our initial study was if our genetic findings in hoarding were unique to hoarding alone or if they were shared with other OC traits. For this reason, our current study aimed to further examine hoarding in this group to see if hoarding traits independent of other OC traits were driving our previous findings of associations with serotonergic gene variants in hoarding. This would further support the biological distinctness of hoarding from OCD by identifying distinct genetic correlates in hoarding.

We argued that hoarding without other OC traits would be associated with serotonin gene variants that would not be identified when hoarding presents with other OC traits. This is something we were unable to gather from our earlier study because individuals with hoarding alone and individuals with both hoarding and other OC traits were grouped together. Consistent with our hypothesis, we found evidence to support that hoarding in the absence of other OC traits is associated with distinct serotonin gene variants, findings that are not present when examining other OC traits alone or hoarding plus OC traits. Furthermore, as in our previous study, genetic associations differed between sexes, which was also consistent with our hypothesis. Specifically, in males, we found a statistically significant association between [L_G + S] and hoarding only and, in females, we identified a trending association between SNPs downstream of *HTR1B* and hoarding only. Since these were the same associations identified in our former paper

(Sinopoli et al., 2019), it appears individuals with hoarding only were driving our previous findings as suspected.

While our study identifies a statistically significant serotonin gene variant association with hoarding symptoms in the absence of OC symptoms, previous studies have studied the genetics of hoarding within the context of OCD. Samuels and colleagues (2007b) identified suggestive linkage of hoarding obsessions and/or compulsions to a region of chromosome 14 (at marker D14S588) in families with OCD, and also found significant linkage of OCD to a region of chromosome 14 (at marker C14S1937, nearby the first finding) in families with two or more hoarding relatives. Another study conducted in adult OCD patients with and without hoarding did not identify a significant association with *5-HTTLPR* as we did, though the added variance of rs25531 was not considered in this study, nor did the study seek out patients with hoarding symptoms in the absence of OCD (Lochner et al., 2005).

Population-based studies, like ours, allow us to measure the full phenotypic range of traits that are widely distributed in the population as opposed to focusing on the subset of children and adolescents in the clinic. Examining trait-based measures allows us to parse out the effects of specific traits in the presence and absence of other traits, and to address heterogeneity. The Research Domain Criteria (RDoC) project was launched by the National Institute of Mental Health (NIMH) to encourage researchers to study the biological basis of simpler, behavioral traits underling more complex psychiatric disorders. This helps to address heterogeneity and is proposed as a more powerful approach to identifying genetic risk factors for psychiatric traits than the study of categorical diagnoses (NIMH, 2008). Our research underlines the importance

of accounting for precise symptoms and comorbidity and suggests that unique serotonergic mechanisms may be driving hoarding traits in the absence of OCD. Our research also supports previous suggestions that different biological or genetic mechanisms may be implicated in the pathogenesis of OCD depending on sex (Mattina et al., 2016). Overall, a failure to account for underlying heterogeneity may explain some of the past inconsistencies in genetic findings in OCD and related disorders to date (Murphy et al., 2013; Sinopoli et al., 2017).

Like other psychiatric traits and disorders, hoarding is heterogeneous. One important source of heterogeneity is whether hoarding symptoms co-occur with symptoms of OCD. This led us to postulate that our previously identified serotonergic genetic association with hoarding was driven by one of the two subgroups composing the hoarding group in our initial study (hoarding with and hoarding without comorbid OC traits). According to the DSM-5, hoarding disorder should only be diagnosed if the hoarding is not better explained as symptoms of another mental disorder, which includes OCD (APA, 2013). Hoarding behavior may, for example, result from an obsession in someone with OCD (Pertusa et al., 2010; Snowdon et al., 2012; van Ameringen et al., 2014). OCD and hoarding disorder can also be diagnosed as comorbid disorders in the same individual (APA, 2013). One possible explanation of our findings is that our hoarding only group shared phenotypic features and genetic risk factors with hoarding disorder, however this remains speculative given that our population-based questionnaire does not enable us to diagnose DSM-5 disorders (which would require direct interview).

One of the limitations of our study was that our effective sample size was reduced by stratifying into multiple homogenous subgroups. This strategy was of course implemented to better study

phenotypic heterogeneity in hoarding. The second limitation of our paper was that our findings were limited to a subset of variants within serotonin candidate genes, so we cannot say whether or not other genes are implicated in hoarding traits.

5. Conclusion

This paper highlights the importance of addressing phenotypic heterogeneity based on clinical symptoms and sex. Our findings, although requiring replication in larger samples, suggest that hoarding traits, in the absence of OCD traits, are associated with variation in serotonin genes and that this association is both distinct from OCD and dependent on sex. Future studies should be conducted that replicate our serotonin-specific findings in hoarding, including studies in clinical samples of individuals with hoarding disorder as it is currently defined in the DSM-5 (APA, 2013). Studying both hoarding disorder (independent of OCD), OCD (independent of hoarding disorder), and hoarding disorder comorbid with OCD in a larger sample will allow for a more extensive, genome-wide approach to discovery and will help identify if there are unique or shared genetic variants across these groups. Evidence has suggested that OCD patients with hoarding symptoms have a poorer response to conventional OCD treatment when compared to OCD patients without hoarding symptoms (Bloch et al., 2014). Better defining the underlying etiology of hoarding will help inform the design of more effective medications and help appropriately tailor current treatments to individual patients.

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Ethical Considerations

We have obtained written consent and/or assent from all subjects, as appropriate.

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Tables and Figures

Table 1. SNP counts across 3 candidate genes, including all genotyped and imputed SNPs: Common SNPs (MAF ≥ 0.05) are shown for each gene and its flanking regions included in the analyses for males and in the analyses for females. Table obtained from Sinopoli et al. (2019).

Gene	Number of SNPs in Males	Number of SNPs in Females
SLC6A4	121	142
HTR2A	411	361
HTR1B	242	242

Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; *SLC6A4*, solute carrier family 6 member 4 (serotonin transporter gene); *HTR2A*, 5-HT_{2A} receptor gene; *HTR1B*, 5-HT_{1B} receptor gene.

Table 2. *5-HTTLPR*-genotyped individuals: Demographics and group characteristics are shown for total individuals combined, all affected individuals, and control individuals. Table obtained from Sinopoli et al. (2019).

Total Individuals		
	Male	**Female**
N	1050	968
Mean Age (SD)	10.7 (2.5)	11.3 (2.9)
Age Range	6.1 - 17.9	6.3 - 17.9
Respondent: % Parent-report, % Self-report	90.1, 9.9	81.5, 18.5
All Affected Individuals		
	Male	**Female**
N	590	571
Mean Age (SD)	10.6 (2.5)	11.2 (3.0)
Age Range	6.3 - 17.9	6.3 - 17.9
OCD Diagnosis, N (%)	32 (5.4)	30 (5.3)
Mood Disorder Diagnosis, N (%)	12 (2.0)	24 (4.2)
ADHD Diagnosis, N (%)	106 (18.0)	39 (6.8)
Anxiety Disorder Diagnosis, N (%)	74 (12.5)	66 (11.6)
ASD Diagnosis, N (%)	59 (10.0)	12 (2.1)
Tic Disorder Diagnosis, N (%)	28 (4.7)	16 (2.8)
Taking SRI Medication, N (%)	20 (3.4)	19 (3.3)
Respondent: % Parent-report, % Self-report	89.8, 10.2	81.3, 18.7
Allele Frequency: L_A, [L_G + S]	0.48, 0.52	0.52, 0.48
Control Individuals		
	Male	**Female**
N	460	397
Mean Age (SD)	10.8 (2.5)	11.3 (2.9)
Age Range	6.1 - 17.7	6.3 - 17.9
OCD Diagnosis, N (%)	0 (0.0)	0 (0.0)
Mood Disorder Diagnosis, N (%)	3 (0.7)	1 (0.3)
ADHD Diagnosis, N (%)	25 (5.4)	10 (2.5)
Anxiety Disorder Diagnosis, N (%)	3 (0.7)	5 (1.3)
ASD Diagnosis, N (%)	1 (0.2)	0 (0.0)
Tic Disorder Diagnosis, N (%)	2 (0.4)	1 (0.3)
Taking SRI Medication, N (%)	0 (0.0)	0 (0.0)
Respondent: % Parent-report, % Self-report	90.4, 9.6	81.9, 18.1
Allele Frequency: L_A, [L_G + S]	0.52, 0.48	0.53, 0.47

Abbreviations: *5-HTTLPR*, 5-HTT-linked polymorphic region; N, sample size; SD, standard deviation; OCD, obsessive-compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder;

SRI, serotonin reuptake inhibitor; L_A, long variant of *5-HTTLPR* with A allele at SNP rs25531; L_G, long variant of *5-HTTLPR* with G allele at SNP rs25531; S, short variant of *5-HTTLPR*.

Table 3. Trait group counts for *5-HTTLPR*-genotyped individuals: Affected versus control counts for each of the three trait groups.

Hoarding Plus OC		
	Male	**Female**
Affected Individuals	240	240
Control Individuals	460	397
Hoarding Only		
	Male	**Female**
Affected Individuals	147	140
Control Individuals	460	397
OC Only		
	Male	**Female**
Affected Individuals	203	191
Control Individuals	460	397

Abbreviations: OC, obsessive-compulsive.

Table 4. Allele frequencies for *5-HTTLPR*-genotyped individuals: L_A / [L_G + S] breakdown for affected participants in each of the three trait groups.

Hoarding Plus OC		
	Male	**Female**
Allele Frequency: L_A, [L_G + S]	0.46, 0.54	0.53, 0.47
Hoarding Only		
	Male	**Female**
Allele Frequency: L_A, [L_G + S]	0.43, 0.57	0.51, 0.49
OC Only		
	Male	**Female**
Allele Frequency: L_A, [L_G + S]	0.53, 0.47	0.51, 0.49

Abbreviations: OC, obsessive-compulsive; L_A, long variant of *5-HTTLPR* with A allele at SNP rs25531; L_G, long variant of *5-HTTLPR* with G allele at SNP rs25531; S, short variant of *5-HTTLPR*.

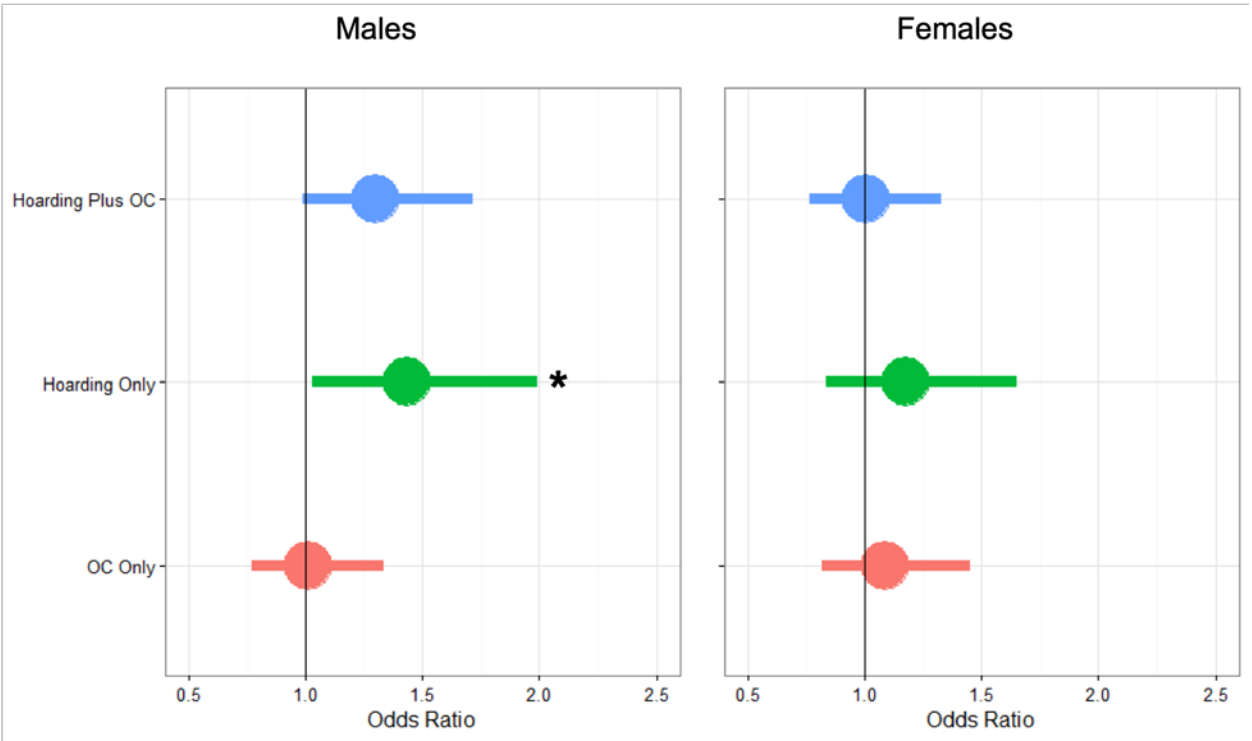

Figure 1. Association between *5-HTTLPR* and trait groups: Forest plots (males on left, females on right). Odds ratios for the [L_G + S] allele are shown as colored points, each representing the effect size estimate for the allele in that trait group relative to controls. The confidence interval for each effect size estimate is represented by the length of each horizontal line. Significant finding is indicated by *. *5-HTTLPR*, 5-HTT-linked polymorphic region; OC, obsessive-compulsive.

Table 5. Individuals genotyped for candidate gene SNPs: Demographics and group characteristics are shown for total individuals combined, all affected individuals, and control individuals. Table obtained from Sinopoli et al. (2019).

Total Individuals		
	Male	**Female**
N	2439	2272
Mean Age (SD)	10.7 (2.6)	11.1 (2.9)
Age Range	6.1 - 17.9	6.1 - 17.9
Respondent: % Parent-report, % Self-report	89.7, 10.3	81.0, 19.0
All Affected Individuals		
	Male	**Female**
N	1025	1043
Mean Age (SD)	11.1 (2.8)	11.8 (3.1)
Age Range	6.1 - 17.9	6.4 - 17.9
OCD Diagnosis, N (%)	28 (2.7)	27 (2.6)
Mood Disorder Diagnosis, N (%)	18 (1.8)	30 (2.9)
ADHD Diagnosis, N (%)	157 (15.3)	44 (4.2)
Anxiety Disorder Diagnosis, N (%)	95 (9.3)	82 (7.9)
ASD Diagnosis, N (%)	65 (6.3)	11 (1.1)
Tic Disorder Diagnosis, N (%)	30 (2.9)	15 (1.4)
Taking SRI Medication, N (%)	30 (2.9)	20 (1.9)
Respondent: % Parent-report, % Self-report	82.8, 17.2	71.9, 28.1
Control Individuals		
	Male	**Female**
N	1414	1229
Mean Age (SD)	10.3 (2.3)	10.6 (2.6)
Age Range	6.1 - 17.7	6.1 - 17.9
OCD Diagnosis, N (%)	0 (0)	0 (0)
Mood Disorder Diagnosis, N (%)	8 (0.6)	2 (0.2)
ADHD Diagnosis, N (%)	95 (6.7)	39 (3.2)
Anxiety Disorder Diagnosis, N (%)	18 (1.3)	22 (1.8)
ASD Diagnosis, N (%)	10 (0.7)	1 (0.1)
Tic Disorder Diagnosis, N (%)	11 (0.8)	5 (0.4)
Taking SRI Medication, N (%)	0 (0)	0 (0)
Respondent: % Parent-report, % Self-report	94.8, 5.2	89.7, 10.3

Abbreviations: SNP, single nucleotide polymorphism; N, sample size; SD, standard deviation; OCD, obsessive-compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; SRI, serotonin reuptake inhibitor.

Table 6. Trait group counts for individuals genotyped for candidate gene SNPs: Affected versus control counts for each of the three trait groups.

Hoarding Plus OC		
	Male	**Female**
Affected Individuals	311	345
Control Individuals	1414	1229
Hoarding Only		
	Male	**Female**
Affected Individuals	154	155
Control Individuals	1414	1229
OC Only		
	Male	**Female**
Affected Individuals	560	543
Control Individuals	1414	1229

Abbreviations: SNP, single nucleotide polymorphism; OC, obsessive-compulsive.

Table 7. Association between serotonin gene SNPs and trait groups in males: Top 20 SNP findings.

SNP	Gene	Tested Allele	MAF	OR	P-value	Trait Group
rs62416430	*HTR1B*	G	0.065	0.63	7.35E-03	OC Only
rs62416429	*HTR1B*	T	0.066	0.65	9.25E-03	OC Only
rs62416428	*HTR1B*	G	0.066	0.65	9.26E-03	OC Only
rs2143824	*HTR1B*	T	0.146	0.76	1.09E-02	OC Only
rs7214991	*SLC6A4*	G	0.373	0.73	1.13E-02	Hoarding Only
rs1487971	*SLC6A4*	T	0.372	0.74	1.49E-02	Hoarding Only
rs7215330	*SLC6A4*	C	0.372	0.74	1.52E-02	Hoarding Only
rs6505167	*SLC6A4*	T	0.108	1.33	1.54E-02	OC Only
rs2770301	*HTR2A*	C	0.228	0.81	1.74E-02	OC Only
rs6505169	*SLC6A4*	A	0.436	0.77	2.32E-02	Hoarding Only
rs7329652	*HTR2A*	G	0.074	0.72	2.39E-02	OC Only
rs9896548	*SLC6A4*	G	0.431	0.76	2.40E-02	Hoarding Only
rs7335941	*HTR2A*	C	0.074	0.72	2.40E-02	OC Only
rs7214248	*SLC6A4*	A	0.328	0.75	2.42E-02	Hoarding Only
rs2025296	*HTR2A*	G	0.097	0.71	2.44E-02	Hoarding Plus OC
rs12945042	*SLC6A4*	T	0.321	0.75	2.46E-02	Hoarding Only
rs7342921	*SLC6A4*	C	0.326	0.75	2.53E-02	Hoarding Only
rs6505165	*SLC6A4*	C	0.434	0.77	2.53E-02	Hoarding Only
rs3794806	*SLC6A4*	G	0.329	0.75	2.55E-02	Hoarding Only
rs7208052	*SLC6A4*	C	0.327	0.75	2.56E-02	Hoarding Only

Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; *SLC6A4*, solute carrier family 6 member 4 (serotonin transporter gene); *HTR2A*, 5-HT_{2A} receptor gene; *HTR1B*, 5-HT_{1B} receptor gene; OC, obsessive-compulsive.

Table 8. Association between serotonin gene SNPs and trait groups in females: Top 20 SNP findings.

SNP	Gene	Tested Allele	MAF	OR	P-value	Trait Group
rs1145827	*HTR1B*	A	0.149	1.68	5.78E-04	Hoarding Only
rs2207053	*HTR1B*	C	0.149	1.67	6.23E-04	Hoarding Only
rs1228806	*HTR1B*	C	0.149	1.67	6.25E-04	Hoarding Only
rs1777763	*HTR1B*	T	0.150	1.67	6.33E-04	Hoarding Only
rs1228805	*HTR1B*	G	0.150	1.67	6.34E-04	Hoarding Only
rs1777762	*HTR1B*	T	0.150	1.67	6.34E-04	Hoarding Only
rs2207056	*HTR1B*	T	0.150	1.67	6.35E-04	Hoarding Only
rs1228797	*HTR1B*	T	0.150	1.67	6.35E-04	Hoarding Only
rs1228798	*HTR1B*	G	0.150	1.67	6.35E-04	Hoarding Only
rs1228800	*HTR1B*	G	0.150	1.67	6.35E-04	Hoarding Only
rs1343334	*HTR1B*	A	0.150	1.67	6.36E-04	Hoarding Only
rs1343336	*HTR1B*	T	0.150	1.67	6.37E-04	Hoarding Only
rs2798528	*HTR1B*	T	0.150	1.67	6.39E-04	Hoarding Only
rs1738506	*HTR1B*	A	0.150	1.67	6.39E-04	Hoarding Only
rs2223832	*HTR1B*	C	0.150	1.67	6.46E-04	Hoarding Only
rs1228804	*HTR1B*	G	0.152	1.66	6.78E-04	Hoarding Only
rs2798529	*HTR1B*	G	0.148	1.66	8.12E-04	Hoarding Only
rs1228802	*HTR1B*	A	0.149	1.64	9.47E-04	Hoarding Only
rs59414600	*HTR1B*	C	0.149	1.64	9.50E-04	Hoarding Only
rs61295513	*HTR1B*	T	0.149	1.64	9.50E-04	Hoarding Only

Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; *HTR1B*, 5-HT_{1B} receptor gene.