



Trio study and meta-analysis support the association of genetic variation at the serotonin transporter with early-onset obsessive–compulsive disorder



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H I G H L I G H T S

- We studied triallelic 5-HTTLPR in early-onset obsessive–compulsive disorder (OCD).
- 103 trios of OCD-affected children and both their parents were investigated.
- Over-transmission of the L_A allele to affected offspring was observed.
- Meta-analysis confirmed association of the L_A allele with OCD.
- Our data support the 5-HTTLPR L_A allele as a risk variant for early-onset OCD.

A R T I C L E I N F O

Article history:

Received 31 May 2014

Received in revised form 18 July 2014

Accepted 21 July 2014

Available online 2 August 2014

Keywords:

Obsessive–compulsive disorder

Serotonin transporter

5-HTTLPR

Transmission disequilibrium test

Meta-analysis

A B S T R A C T

Despite compelling evidence for major genetic contributions to the etiology of obsessive–compulsive disorder (OCD), few genetic variants have been consistently associated with this debilitating illness. Molecular genetic studies in children and adolescents with OCD are of particular interest, since early onset of the disease has been observed to be associated with increased familiarity. We replicate here for the first time in early-onset OCD patients, a previously reported association of OCD with the common gain-of-function L_A allele at the serotonin transporter linked polymorphic region known as 5-HTTLPR in a collection of parent-offspring trios. The present meta-analysis of this recently refined serotonin transporter gene variant revealed further support for the L_A allele conferring increased genetic susceptibility to OCD. We conclude that the 5-HTTLPR is currently the single best supported risk variant for OCD, in regards of early-onset OCD, albeit of modest effect size and the possibility that the conferred risk might not be specific to OCD.

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1. Introduction

Obsessive–compulsive disorder (OCD) is a debilitating neuropsychiatric disorder marked by recurring, anxiety-laden intrusive thoughts (obsessions) and repetitive behaviors (compulsions). OCD patients suffer from recurrent, persistent thoughts, ideas, impulses, and behavioral patterns imposing themselves on the patients against their will and perceived by them as distressing and excessive [2]. Obsessive–compulsive symptoms heritability

has been estimated to be between 0.27 and 0.47 in adults and between 0.45 and 0.65 in children [22]. One of the most frequently investigated candidate genes for OCD is the serotonin transporter (*SLC6A4*) with its transcriptional control insertion/deletion polymorphism known as the 5-HTTLPR. Traditionally, 5-HTTLPR alleles have been divided into long (L) alleles with high expressing function and short (S) alleles with low expressing function. Recently the L alleles at the 5-HTTLPR were subdivided into truly high-expressing L_A and low-expressing L_G alleles, calling for a re-appreciation of previous research [11]. Hu et al. showed that as many as one in three L alleles (depending on ethnicity) are actually low-expressing (L_G) and thus functionally equivalent to the short (S) variant [11]. This improved understanding of 5-HTTLPR functionality enabled them to identify a significant association of the gain-of-function L_A allele with OCD in an unrelated case-control sample and a collection of trios. Although three subsequent replication attempts were statistically non-significant, all showed increased odds ratio for association of the L_A allele with OCD [20,24,28].

While OCD onset occurs most often in adolescence and early adulthood (median age of onset 19 years reported in the National Comorbidity Survey Replication), symptoms can occur already in young children [12]. Early-onset OCD has been associated with higher prevalence of OCD in first-degree relatives, suggesting higher familiarity in this group [reviewed in 18,26]. In addition, some differences in gender distribution, the nature of OCD symptoms and the illness course, as well as pattern of co-morbidity are present between early and late-onset OCD [13]. A stratified meta-analysis has pointed toward a possible particular association of the 5-HTTLPR long (L) allele with early-onset OCD and OCD in Caucasians [3]. This finding and the known especially high familiarity in early-onset OCD prompted us to further evaluate the role of the refined 5-HTTLPR in a separate sample including only children and adolescents with OCD and both of their biological parents.

Here, we replicate for the first time the originally reported association of the L_A allele with OCD [11] in a collection of early-onset OCD trios and further demonstrate a strong association of this allele with OCD in a meta-analysis for the L_A allele.

2. Materials and methods

2.1. Study group and genotyping

We collected a total of 103 trios from OCD-affected children and from both of their biological parents. The study sample included patients who had received treatment for OCD at the Departments of Child and Adolescent Psychiatry at the Universities of Würzburg, Marburg, Freiburg or Technical University of Aachen, according to protocols approved by the local institutional review boards and after obtaining informed written consent. All included patients with OCD were children and adolescents with an age at onset of less than 18 years, and all participants of the included trios were of European ancestry. All OCD probands fulfilled the diagnostic criteria for OCD according to DSM-IV [1]. Criteria for OCD were assessed by interviewing the children and parents with the respective versions of “Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter” (Kinder-DIPS) [21]. Severity and further characteristics of OCD were examined by interviewing the patients with the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (with a summary score above 16 points determined to be the cut-off for clinical impairment caused by OCD symptomatology) [16].

Criteria for co-morbid disorders were assessed with Kinder-DIPS, which screens for a wide range of psychiatric disorders in children and adolescents. These include affective-, anxiety-, eating- and tic disorders, attention-deficit/hyperactivity disorder (ADHD),

conduct-, oppositional disorder, as well as a screening component for substance use, abuse, psychosis and somatic diseases. Screening for autistic spectrum disorders was carried out with CASCAP-D [4]. Diagnostic assessments of present and lifetime Tourette’s syndrome and tic disorders were performed with the adapted German version [10] of the Child and Adult Schedule for Tourette and Other Behavioral Syndromes (STOBS) [14]. Exclusion criteria were: lifetime history of psychotic disorder, Tourette’s syndrome, autistic disorder, alcohol dependence and mental retardation (IQ < 70). Co-morbid disorders in the probands included ADHD (10.9%), mood (affective) disorders (5.8%), anorexia nervosa (2.5%), tics (10.9%, no Tourette’s syndrome), phobias (5.9%) and other anxiety disorders (1.7%). Probands with co-morbid disorders were included in the study only when OCD symptoms predominated. The mean age \pm SD of the OCD-affected children was 12.84 ± 2.91 years. Mean age of disease onset \pm SD was 11 ± 3.19 years.

Psychiatric disorders in parents of the OCD probands were assessed systematically with the lifetime version of the schedule for affective disorders and schizophrenia (SADS-L) [7]. On average 3.8% of the mothers and 2.1% of the fathers of the probands met the criteria for OCD. Other psychiatric disorders observed in the parents included most commonly anxiety (28.3% in mothers and 12.8% in fathers) and affective (17% in mothers and 19.1% in fathers) disorders. Less frequently diagnosed disorders in the parents were eating disorders, tics, alcohol abuse and ADHD. This collection is an extension and re-evaluation of a previously published, non-significant association analysis of the original (bi-allelic) 5-HTTLPR in OCD [25]. Genomic DNA was extracted from whole blood at the local sites and genotyped as described previously [27] under a protocol approved by the Institutional Review Board of the National Institute of Mental Health Division of Intramural Research Programs in Bethesda, MD (protocol number 96-M-0124). No-template controls and duplicate samples consistently yielded expected results; there were no Mendel errors; founder genotypes did not deviate from Hardy-Weinberg equilibrium (exact test, $P = 0.57$). The transmission disequilibrium test (TDT) was performed on child-parents trios [17]. The software package PLINK was used for the TDT analysis [15].

2.2. Meta-analysis

Relevant studies were identified by searching the database PUBMED (<http://www.ncbi.nlm.nih.gov/pubmed/>) for the terms (“obsessive-compulsive disorder” OR “OCD”) AND (“5-HTTLPR” OR “serotonin transporter”). From the search results all published original articles, which investigated the association of the refined 5-HTTLPR with OCD (both early- and late-onset) as of 30th April 2014 were included, and combined with the data from the current study. Since both case-control and family-based studies were included in the meta-analysis, and patient populations were not identical between studies, a random-effects model with the DerSimonian-Laird estimator of between-study variance (T^2) was used. The results obtained were very similar using other estimators (e.g. restricted maximum likelihood or empirical Bayes). Variability due to between-study heterogeneity was estimated to be $I^2 = 29\%$ (95% CI = 0–90; $Q_{(5)} = 7.02$, $P = 0.219$). The studies were also analyzed with fixed-effects meta-analyses. Funnel plot and a “trim and fill” analysis were used to assess whether there was any evidence of publication bias [5,6]. The analysis was conducted with the metafor package in R (www.r-project.org) [23].

3. Results

We observed a significant over-transmission of the L_A allele at the 5-HTTLPR to affected offspring in our OCD-affected

Table 1
Transmission disequilibrium test for association of 5-HTTLPR with early-onset OCD.

Allele	Transmitted	Non-transmitted	P-value
5-HTTLPR L _A allele	68	39	0.0054

child-parents trios (transmitted:non-transmitted, 68:39, $\chi^2 = 7.86$, $df = 1$, $P = 0.0054$, odds ratio 2.06) (Table 1). Our results thus support the notion of increased susceptibility to OCD being conferred by gain-of-function variation within the 5-HTTLPR of *SLC6A4*.

As a next step, we included these data in a meta-analysis of all published studies of the refined 5-HTTLPR and OCD (Fig. 1). We conducted random-effects inverse-variance weighted meta-analysis of the effect estimates across all studies, and observed a significant meta-analysis P value of 0.003 for association of the L_A allele with OCD (odds ratio 1.33, 95% confidence interval 1.10–1.61, Fig. 1). We used random-effects modeling under the assumption of a distribution of effects given that the studies originate from multiple centers that used different recruitment and ascertainment strategies. Fixed-effects meta-analyses yielded almost identical results (odds ratio 1.31, 95% confidence interval 1.14–1.52, $P = 0.00021$). No significant heterogeneity of effects was detected in the meta-analysis. There was some asymmetry in the funnel plot assessing publication bias (Supplementary Figure S1) and the trim and fill analysis indicated that one study was missing. If the missing study is included in an updated analysis the odds ratio decreases slightly from 1.33 to 1.27 (95% confidence interval 1.03–1.56, $P = 0.0225$), but the overall conclusions remain the same.

Supplementary Figure S1 related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neulet.2014.07.038>.

4. Discussion

Molecular genetic studies in children and adolescents with OCD are of special interest, because formal genetic studies showed strong relationship between increased familiarity and an early

onset of OCD. Furthermore, early-onset OCD can be distinguished from later onset OCD by a different pattern of comorbidity and some differences in gender distribution, as well as differences in the nature of OCD symptoms and the illness course [13]. Our trio study in a children and adolescents OCD sample constitutes the first replication of the initial report on the refined 5-HTTLPR and OCD in adults [11].

The L-allele at the 5-HTTLPR has been repeatedly associated with OCD, even though not all studies have replicated these findings [13]. The report of Hu et al., 2006 showing that the 5-HTTLPR L-allele is subdivided into truly high-expressing L_A and low-expressing L_C alleles, and that the L_A allele is associated with OCD, has pointed out the need for a reappraisal of previous association studies results [11]. Although three subsequent reports to the Hu et al. study [11] did not associate the L_A allele with OCD at statistical significance [20,24,28], all three studies showed an increased odds ratio for this gain-of-function allele consistent with the original observation and with our results (Fig. 1). Differences in results between our study and previous replication attempts of the Hu et al. report [11] may be related to phenotypic and/or genotypic heterogeneity, polygenic contribution or additional functional variation within *SLC6A4*. It has been suggested that younger age of onset may represent a discrete, more aetiological-based OCD subgroup that can be used as a factor to reduce heterogeneity and provide more power for genetic investigation [13]. From the previous replication attempts of the association of the 5-HTTLPR L_A allele with OCD, only the study of Voyiaziakis et al. [24] investigated retrospectively an early-onset OCD sample with at least two affected siblings in a large multicenter US family study pedigree design. In contrast, our sample consisted of OCD-affected child-parents trios, including a higher number of sporadic OCD cases. Some differences in symptoms presentation have been described between familial and sporadic early-onset OCD [9] and it is possible that they are related to differences in the gene variants conferring risk to the disease.

A recent meta-analysis, assessing published reports on the association of the refined 5-HTTLPR with OCD, found an association of the 5-HTTLPR L_A allele with the disease (odds ratio 1.251, 99% confidence interval 1.048–1.492, $P = 0.001$) [19]. We conducted a

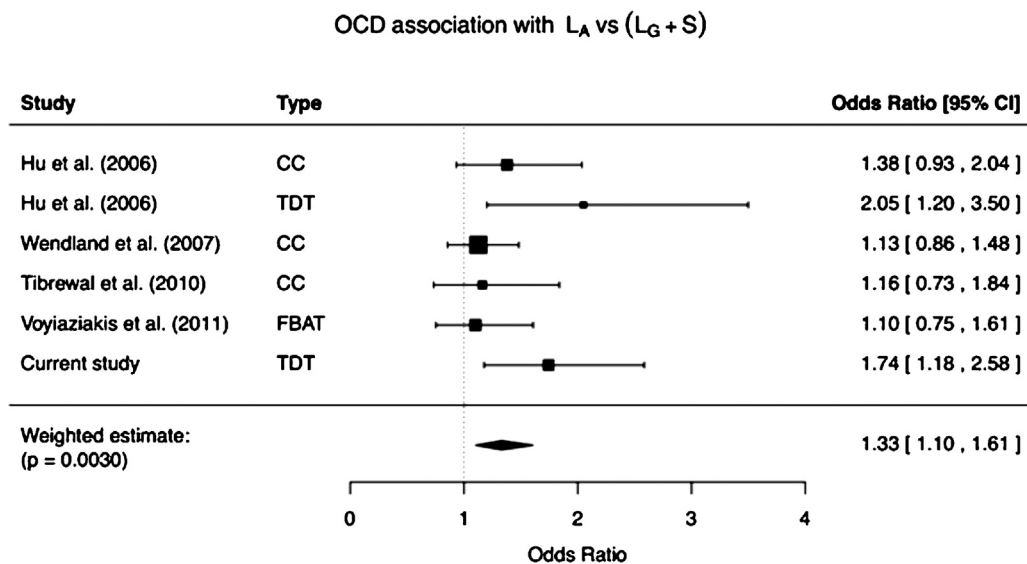


Fig. 1. Summary and meta-analysis of all published association analyses of the serotonin transporter 5-HTTLPR gain-of-function L_A allele and obsessive-compulsive disorder. Black bars in the forest plot represent 95% confidence intervals for odds ratio; the sample size is reflected in symbol size. The sample for the present report consisted of European-ancestry early-onset (<18 years of age) probands; demographic and phenotypic characteristics for the remaining studies are as follows: Hu et al. (2006) [11] – case-control; European-ancestry individuals, early- and adult-onset probands; Hu et al. (2006) [11] – trios; predominantly European-ancestry families, early- and adult-onset probands; Wendland et al. (2007) [28] – European-ancestry individuals, early- and adult-onset probands; Tibrewal et al. (2010) [20] – Asian-ancestry individuals, early- and adult-onset probands; Voyiaziakis et al. (2011) [24] – primarily European-ancestry families, early-onset probands and at least two affected siblings per family. Abbreviations: CC, case-control; TDT, transmission disequilibrium test; FBAT, family-based association testing; CI, confidence interval.

meta-analysis combining the previously published data with the results of the present study on an early-onset OCD sample, and confirmed a strong association of the 5-HTTLPR L_A allele with OCD. Together, these data suggest that in comparison to other genetic findings the gain-of-function L_A allele currently represents the most strongly and consistently associated common susceptibility allele for OCD. The notion of serotonin transporter gain-of-function being a risk factor for OCD is further supported by the rare gain-of-function coding variant known as Ile425Val that is associated with a complex, predominantly OCD-like neuropsychiatric phenotype [29]. Several non-coding *SLC6A4* variants, including rs25532 and rs16965628, have been found to modulate 5-HTTLPR functionality. When the presumably higher-expressing alleles at the 5-HTTLPR triallelic polymorphism, rs25532 and rs16965628 were studied together as a haplotype, it was significantly overrepresented in OCD probands, while no significant effect was observed when the three polymorphisms were studied as individual loci. These findings also corroborated the hypothesis of increased serotonin transporter functioning association with OCD [30]. These genetic observations are also in line with the well-documented therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs), which directly target the serotonin transporter protein encoded by *SLC6A4* [8].

Due to the heterogeneity of OCD, studying genetic profiles of OCD in subtypes of the disorder and across different classes of obsessive-compulsive symptoms may provide valuable additional information for genetic predisposition to the disease [13]. Our study replicated for the first time the association of the L_A allele with OCD using an early-onset OCD sample. Future studies of risk haplotypes, including the L_A 5-HTTLPR, in OCD subtypes, including early-onset OCD, and their possible association with symptoms constellations, may provide additional insight into the genetic predisposition to OCD.

Conflict of interest

Dr. Jens R. Wendland is currently a full-time employee of Pfizer. Prof. Susanne Walitza has received research funding from Vifor Pharma, Switzerland and was on the speakers' bureau of Eli Lilly, Janssen-Cilag and Astra Zeneca.

Acknowledgments

This research was supported by the Intramural Research Program of the NIH, National Institute of Mental Health (contract MH000336-30) and by the Swiss National Science Foundation (project number 130237). We would like to thank Prof. Steven Taylor for his help with the meta-analysis.

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