Psychiatry Research 271 (2019) 554–558

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Genetic variability in the serotoninergic system and age of onset in anorexia nervosa and obsessive-compulsive disorder

Maria Teresa Plana[a,*], Teresa Torres[b], Natalia Rodríguez[b], Daniel Boloc[c], Patricia Gassó[b,d], Elena Moreno[a], Amalia Lafuente[b,d,e], Josefina Castro-Fornieles[a,c,d,e], Sergi Mas[b,d,e], Luisa Lazaro[a,c,d,e,*]

[a] Department of Child and Adolescent Psychiatry and Psychology, Institute of Neurosciences, Hospital Clinic de Barcelona, C/ Villarroel 170, E-08036 Barcelona, Spain
[b] Department of Clinical Foundations, Pharmacology Unit, University of Barcelona, Barcelona, Spain
[c] Department of Medicine, University of Barcelona, Barcelona, Spain
[d] The August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain
[e] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Carlos III Health Institute, Spain

ARTICLE INFO

Keywords:
Anorexia nervosa
Obsessive-compulsive disorder
Age of onset
Genetic pleiotropy
Single nucleotide polymorphisms
Serotonin: 5HTR2A

ABSTRACT

The age of onset of some psychiatric disorders may have etiopathogenic and clinical effects and may influence outcome. Following on from previous work by our group where we showed that early onset anorexia nervosa (AN) and obsessive-compulsive disorder (OCD) shared a common genetic background, the aim of the present study is to assess genetic pleiotropy related to the serotonergic system (SLC6A4, 5HTR2A, 5HTR2C, TPH2, SLC18A1), in a common phenotype such as very-early age of onset. One hundred and sixteen adolescents diagnosed with AN and 74 adolescents diagnosed with OCD participated in the present study. We confirmed the existence of a genetic overlap between OCD and AN. Specifically, we described genetic pleiotropy for age at onset across these disorders, associating two SNPs (rs6311, rs4942587) of the HTR2A with the very-early onset phenotype.

1. Introduction

Several studies have investigated the potential relationships between anorexia nervosa (AN) and obsessive compulsive disorder (OCD), based on the phenotypic features that the two disorders share, such as repetitive and ritualistic behaviours, excessive habit formation, and cognitive rigidity (Godier and Park, 2014). In both groups of patients high levels of obsessive characteristics have been found (Halmi et al., 2005). In a categorical evaluation of personality and in adult samples, the most prevalent personality disorder in restrictive type AN and OCD patients were Cluster C personality disorder (Marañón et al., 2004; Samuels et al., 2000), even in first degree relatives (Calvo et al., 2009). Moreover, several studies have demonstrated high rates of comorbidity between these disorders and these conditions co-occur more frequently than expected by chance (Wentz et al., 2009; Cederläf et al., 2015).

AN and OCD also share common neurobiological abnormalities such as dysregulation of the serotonergic system and impaired control in frontostriatal systems (Marsh et al., 2009). These findings have been supported by epidemiological (Altman and Shankman, 2009), longitudinal (Bulik et al., 1997) and family studies (Strober et al., 2007). Cavallini et al. (2000) provided support for a common genetic liability between eating disorders and OCD, and, a genetic association study recently identified a genetic overlap (Mas et al., 2013).

The study of genetic overlapping, or pleiotropy, is a common strategy in diseases that exhibit significant co-heritability. These studies define the relationship between complex traits, and provide new insights into the disease mechanism. If these approaches focus on specific phenotypes or symptoms common to both diseases, they could point us towards more specific associations as well. Moreover, it has been hypothesized that concrete symptoms exhibits less phenotypic complexity than a fully-fledged disorder such as OCD or AN and it is more likely to have reduced genetic complexity and greater locus specific heritability (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

The age of onset of some psychiatric disorders may determine etiopathogenic and clinical effects and may influence outcome. Differentiating between early and late onset disorders may help to discern further the type of symptoms and the likely comorbidities, and may aid in prognosis.

* Corresponding authors at: Department of Child and Adolescent Psychiatry and Psychology, Institute of Neurosciences, Hospital Clinic de Barcelona, C/ Villarroel 170, E-08036 Barcelona, Spain.
E-mail addresses: sergimash@ub.edu (M.T. Plana), llazaro@clinic.cat (L. Lazaro).

https://doi.org/10.1016/j.psychres.2018.12.019
Received 30 July 2018; Received in revised form 5 November 2018; Accepted 3 December 2018
Available online 06 December 2018
0165-1781/

Different studies have point out clinical differences between very early onset and early onset. Van Noort et al. (2018) has found that, early onset anorexia nervosa patients displayed more restrictive eating behavior, received more tube-feeding and had less problems with self-esteem and perfectionism compared with adolescent onset of AN. They may also lack features such as body dissatisfaction and present higher incidence of other psychiatric diagnoses, worse outcome and more readmissions than late adolescence onset patients samples (Castro et al., 2004). Moreover, very early onset patients with AN (< 13 years old) present lower percentages of ideal body weight and have lost weight more rapidly (Peebles et al., 2006). In etiological theories of AN, genetic and environmental influences differ between prepubertal and pubertal twins, with an increased genetic risk for the transmission of eating pathology after puberty (Klump et al., 2010).

A study in OCD patients found that the very early onset group was characterized by a longer duration of illness, higher rates of comorbid tics, more frequent ordering and repeating compulsions and greater parent-reported psychosocial difficulties (Nakatani et al., 2011). De Mathis et al. (2008) also found that lower age at onset was associated with a higher probability of having comorbidity with tics, anxiety, somatoform, eating and impulse-control disorders.

No genetic association studies have been conducted with regard to the age of onset in AN. In OCD, some results have confirmed the association between serotonin-receptor 2A (HTR2A), early onset OCD in children and adolescents and increased severity of OCD symptoms (Walitza et al., 2012).

Following on from previous work by our group (Mas et al., 2013) where we showed that early onset AN and OCD shared a common genetic background, we hypothesized that this genetic pleiotropy could be more specific if we consider a common and more homogenous phenotype of both disorders, such as the existence of very-early onset patients. The aim of the present study is to assess genetic pleiotropy of very-early onset diseases (AN and OCD) related to the serotonergic system (*SLC6A4, 5HTR2A, 5HTR2C, TPH2, SLC18A1*).

2. Materials and methods

2.1. Subjects

One hundred and sixteen adolescents diagnosed with AN and 74 adolescents diagnosed with OCD were consecutively recruited from the Department of Child and Adolescent Psychiatry and Psychology at the *Hospital Clínic* in Barcelona. A complete description of the sample can be found in a previous study (Mas et al., 2013). Briefly, all subjects met DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for these disorders. The diagnoses were made using the department's own clinical interview, which is designed to assess the patient's current psychopathology and developmental history. Specifically, the interview examines the following conditions on the basis of DSM-IV criteria: developmental disorders, schizophrenia and other psychotic disorders, mood disorders, disruptive behavior disorders, anxiety disorders, and eating disorders. The age range of subjects was 10 to 18 years. Patients with mental retardation and other neurological disorders were excluded, as were non-Caucasians. Twelve patients from the OCD group had comorbid AN.

Patients were divided based on the age of onset of the disorder into “very early onset” and “early onset” . In accordance with Peebles et al. (2006), very-early onset AN patients were defined as aged < 13 and early onset patients from 13 to 18 years. In OCD patients, no cut-off age at onset was found to clearly divide the sample in homogeneous subgroups. However, cluster analyses revealed that differences started to emerge at the age of 10 and were more pronounced at the age of 17, suggesting that these were the best cut-off points for this sample (de Mathis, 2008). Accordingly, in OCD patients with onset at age < 10 were defined as very-early onset and those from 10 to 18 years as early onset.

All procedures were approved by the hospital's Ethics Committee. Written informed consent was obtained from all parents, and verbal informed consent was given by all subjects (patients and controls) following an explanation of the procedures involved.

2.2. Clinical assessment

Eating symptomatology was assessed using the Spanish version (Castro et al., 1991) of the Eating Attitudes Test (EAT-40) (Garner & Garfinkel, 1979), which assesses different aspects of eating and body shape attitudes. Obsessive–compulsive symptomatology was assessed using the Leyton Obsessional Inventory-Child Version (LOI-CV) (Berg et al., 1986), a 20-item self-report questionnaire. The inventory also estimates the level of interference with daily activities caused by obsessive–compulsive symptoms. Perfectionism was assessed with the Child and Adolescent Perfectionism Scale (CAPS) (Castro et al., 2004). The CAPS is a 22-items self-administered questionnaire based on a multidimensional conceptualization of perfectionism. It has two scales: the self-oriented perfectionism (SOP) and the socially prescribed perfectionism (SPP). Symptoms related to depression were assessed by means of validated instruments with proven reliability. The Children's Depression Inventory (CDI) (Kovacs & Beck, 1981) is a 21-item self-report questionnaire that is used to assess the presence and severity of depressive symptomatology.

2.3. Sample preparation

Blood samples were collected from the individuals in EDTA (K2EDTA BD Vacutainer EDTA tubes; Becton Dickinson, Franklin Lakes, New Jersey), and genomic DNA was extracted with the MagNA Pure LC DNA isolation Kit III and an LC MagNA Pure system (Roche Diagnostics GmbH, Mannheim, Germany). The DNA concentration was determined by absorbance (ND1000, NanoDrop, Wilmington, Delaware).

2.4. SNP selection, genotyping and quality control

A total of 44 SNPs were selected in 5 candidate genes of the serotonin system (*SLC6A4, 5HTR2A, 5HTR2C, TPH2, SLC18A1)* (covering target loci and upstream and downstream regions) by tagging analysis (as implemented in Haploview 4.1) at an r^2 threshold of 0.8 to capture 98% of the most common HapMap phase II variants based on the CEU panel (minor allele frequency > 0.1) (range 91–100% for individual genes). The 44 SNPs were genotyped by the GoldenGate assay with the Veracode genotyping system (Illumina, San Diego, USA) at the Madrid Node of the Spanish National Genotyping Centre (CeGen). For quality control, eight samples were genotyped in duplicate for all the SNPs analyzed, with a 100% concordance rate.

2.5. Statistics

Sample size and statistical power were calculated using Quanto1.2 software (http://hydra.usc.edu/gxe). Given the sample size, and assuming a 5% level of significance, we were able to detect odds ratio values of > 2.0 with > 83% statistical power when polymorphisms with allele frequencies of > 0.1 were analyzed. Data were analyzed using SPSS17.0 (statistical analysis software, SPSS Inc., Chicago, IL, USA). Means and standard deviations were computed for continuous variables. To estimate the independent contribution of each SNP to susceptibility to disease, genotype frequencies were assessed by means of multivariate methods based on logistic regression analysis and analyzed under a codominant model using the SNPassoc R package (González et al., 2007). To avoid false positive results due to multiple testing, Bonferroni correction was applied and the significance threshold was set to $p < 0.001$.

Table 1
Demographic and clinical characteristics of the participants in the present study, divided according to the age of onset as very-early onset ($N = 65$) and early-onset patients ($N = 125$).

	Very Early	Early	Statistics
N (%)	65 (34,2)	125 (65,8)	
Sex, Male/Female	18/47	24/101	$X^2 = 1.8$, $p = 0.181$
Age, Mean (SD)	14,4 (2,2)	16,3 (1,4)	$t = -7.1$, $p < 0,001$
Age at onset, Mean (SD)	10,3 (2,9)	13,6 (2,5)	$t = -5.1$, $p < 0,001$
Diagnoses			$X^2 = 3.2$, $p = 0.07$
AN, *N* (%)	34 (52,3)	82 (65,6)	
OCD, *N*(%)	31 (47,7)	43 (34,4)	
Comorbidities, *N*(%)	32 (49,4)	61 (48,8)	$X^2 = 0.1$, $p = 0.955$
First Degree Relatives, *N*(%)	36 (55,3)	68 (54,4)	$X^2 = 0.1$, $p = 0.897$
Second Degree Relatives, *N*(%)	54 (83,9)	100 (80,0)	$X^2 = 0.3$, $p = 0.607$
Clinical Symptomatology			
EAT-40 (only AN), Mean (SD)	43.1 + 26.7	42.6 + 25.4	$t = 0.084$, $p = 0.933$
LOI-CV, Mean (SD)	21.6 + 13.1	25.1 + 14.5	$t = -1.356$, $p = 0.177$
CAPS-SOP, Mean (SD)	39.2 + 11.2	41.6 + 11.4	$t = -1.149$, $p = 0.253$
CAPS-SPP, Mean (SD)	22.2 + 8.0	23.3 + 9.0	$t = -0.665$, $p = 0.507$
CDI, Mean (SD)	15.0 + 9.9	16.8 + 9.2	$t = -1.057$, $p = 0.293$

AN: Anorexia nervosa; OCD: Obsessive-compulsive disorder; EAT: Eating Attitudes Test; LOI-CV: Leyton Obsessional Inventory-Child Version; CAPS SOP: Child and Adolescent Perfectionism Scale Self-Oriented Perfectionism; CAPS SPP: Child and Adolescent Perfectionism Scale Socially Prescribed Perfectionism; CDI: Childhood Depression Inventory.

3. Results

3.1. Sociodemographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of the study participants, divided according to age of onset as very-early onset ($N = 65$) or early-onset patients ($N = 125$). A total of 116 cases of AN and 74 cases of OCD participated in this study. In the AN group, the 97,4% of the sample was girls ($N = 113$) and the 2,6% boys ($N = 3$), with the onset before 13 years old of 29,3% ($N = 34$) of patients. The eating disorder was restrictive in 78,5% ($N = 91$) of patients and purgative in 21.6% ($N = 25$). The assessment revealed that 75% ($N = 87$) of patients showed no current comorbidity, whereas 17,2% had a depressive disorder ($N = 20$), and 7,8% had a generalized anxiety disorder ($N = 9$). Mean lowest BMI in the acute phase of AN was 16.1 (SD, 1.5) kg/m^2. In the OCD group, the 47,3% of the sample was girls ($N = 37$) and the 52,7% boys ($N = 39$). Onset was very early in 41,9% ($N = 31$) of patients. Overall, 56,8% ($n = 42$) of patients showed no comorbidity while 43,2% ($n = 32$) had a lifetime history of eating disorder (16,2%, $n = 12$), anxiety disorder (13,5%, $n = 10$), attention deficit disorder (5,4%, $n = 4$), tics/Tourette syndrome (4,1%, $n = 3$), bipolar disorder (2,7%, $n = 2$), and negative defiant disorder (1,4%, $n = 1$).

There were no significant differences in sex, comorbidity and family history of psychiatric disorders between very early onset and early onset in either the AN group or the OCD group. Neither there were significant differences in eating, obsessive-compulsive and depressive symptomatology and perfectionism, between very early onset and early onset in AN group. Patients with early onset OCD had more obsessive-compulsive symptomatology ans social prescribed perfectionism than patients with very early onset OCD.

3.2. Genetic analysis

Table 2 shows the candidate genes of the serotonin neurotransmission pathway and the selected genetic polymorphisms included in the present study.

The results of the genetic association study according to the age of onset are summarized in Fig. 1. Two SNPs in the HTR2A gene showed significant results after applying multiple testing corrections ($p < 0.001$). Table 3 shows the details of the genotype distribution and the genetic association test of the two significant SNPs in the overall sample. As it can be observed, carriers of the G allele of the rs494287 are more frequent among Early onset patients (AG + GG, 52.2%) than Very-early onset cases (AG + GG, 35%). Regarding rs6311, T carriers are more frequent among Very early onset patients (TT + CT 83.3%) versus Early onset (TT + CT 62.8%). In order to explore the specificity of the associations observed, we stratified the sample according to the diagnosis (AN or OCD). If the significant associations are due to true pleiotropy, we may expect similar trends for each SNP to be obtained when both disorders are analyzed separately. A genetic association analysis in this stratified sample was performed with the two significant SNPs (Table 3). Genotype distribution in the Very-early onset and Early onset categories was not significantly different between AN and OCD and the associations showed the same direction and similar strength. However, the associations only remained significant in the AN group; only a tendency towards association was observed in the OCD patients. The lack of significance in the OCD group is probably a consequence of the loss of statistical power due to the sample size reduction after diagnoses stratification (OCD, $N = 84$).

4. Discussion

In this study we confirmed the existence of a genetic overlap between OCD and AN. Specifically, we described genetic pleiotropy for

Table 2
Candidate genes and selected SNPs for the present study.

Gene	SNPs
5HTR2A	rs4942577, rs9567733, rs7333412, rs9567736, rs9567737, rs2296972, rs2770298, rs731779, rs1002513, rs927544, rs4942587, rs2296973, rs731245, rs985934
5HTR2C	rs6318, rs518147, rs1801412, rs3813929, rs3813928, rs6311, rs6313
SLC18A1	rs4921691, rs10099144, rs10088489, rs11204097, rs6586896, rs4922132, rs2132699, rs2279709, rs11783752, rs7013199
SLC6A4	rs7214991, rs2066713, rs4251417, rs25531, rs17825877
TPH2	rs3935748, rs11178993, rs4570625, rs10748185, rs6582072, rs7299582, rs11179018, rs11179027, rs10879351, rs10879357, rs7133320, rs11179050

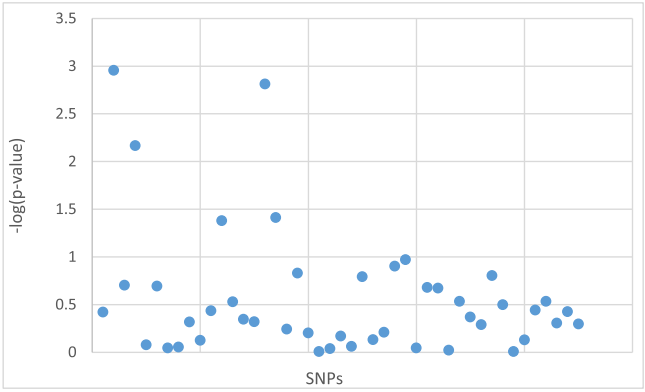

Fig. 1. Association results for single nucleotide polymorphisms in candidate genes. The Y-axis indicates –log of the likelihood ratio tests computed for 44 valid SNPs. The X-axis indicates various SNPs ordered by gene.

Table 3
Genotype distribution of significant SNPs according to dominant model, in the overall sample and stratified by diagnoses.

All	Very early onset		Early onset					
rs4942587	*N*	%	*N*	%	OR	lower	upper	*p*-value
A/A	39	65.0	54	47.8	1.00			0.001
A/G	15	25.0	55	48.7	2.65	1.31	5.35	
G/G	6	10.0	4	3.5	0.48	0.13	1.82	
rs6311								
C/C	10	16.6	42	37.2	1.00			0.001
C/T	33	55.0	38	33.6	0.37	0.16	0.81	
T/T	17	28.3	33	29.2	0.92	0.38	2.24	
Anorexia								
rs4942587	*N*	%	*N*	%	OR	lower	upper	*p*-value
A/A	21	61.8	41	50.0	1.00			0.007
A/G	8	23.5	39	47.6	2.50	0.99	6.30	
G/G	5	14.7	2	2.4	0.20	0.04	1.15	
rs6311								
T/T	4	11.8	28	34.1	1.00			0.002
C/T	23	67.6	30	36.6	0.19	0.06	0.61	
C/C	7	20.6	24	29.3	0.49	0.13	1.88	
Obssessive compulsive disorder								
rs4942587	N	%	*N*	%	OR	lower	upper	*p*-value
A/A	18	69.2	13	41.9	1.00			0.03
A/G	7	26.9	16	51.6	3.16	1.01	9.89	
G/G	1	3.8	2	6.5	2.77	0.23	33.88	
rs6311								
C/C	6	23.1	14	45.2	1.00			0.07
C/T	10	38.5	8	25.8	0.34	0.09	1.30	
T/T	10	38.5	9	29.0	0.39	0.10	1.43	

age at onset across these disorders, associating two SNPs (rs6311, rs4942587) of the HTR2A with the very-early onset phenotype.

Psychiatric disorders such as OCD and AN are heterogeneous, with multiple symptoms that sometimes overlap. The main hypothesis of this study was that patients with very-early onset OCD and AN would share common pathogenic mechanisms and could add more specific genetic associations due to the reduced heterogeneity between groups.

We focused our studies on the serotonin system because it is a major monoamine neurotransmitter to the central nervous system and is essential to a wide range of functions including mood behavior, eating patterns, cognition, sleep, reproduction and motor disorders. Genetic variants affecting serotonin neurotransmission have been separately associated with both diseases, OCD and AN, suggesting the involvement of this system in specific behavioral traits such as perfectionism and obsessionality (Enoch et al., 1998).

HTR2A encodes the 5-HT2A receptor and is located on chromosome 13q14. The most studied polymorphism of this gene is rs6311, a promoter variant named −1438 G/A. This polymorphism decreases the use of a transcription start site and affects translational efficiency, changing RNA and protein expression (Smith et al., 2013). Meta-analyses of case control genetic association studies, conducted separately for OCD (Taylor, 2013, 2016) and AN (Gorwood et al., 2003; Martaskova et al., 2009), have confirmed the significant associations of these disorders with the A allele of rs6311. However, the results from individual studies testing these associations vary and in some cases conflict with each other (Sinopoli et al., 2017; Baker et al., 2017). As in the case of other variants, the findings seem to indicate that rs6311 is associated with specific symptoms (probably common to OCD and AN) and characterize a subgroup of patients reflecting sex, age at onset and presence of comorbidities (Sinopoli et al., 2017).

Our results are in agreement with these observations and confirm previous results in OCD. The rs6311 variant of the 5HTR2A has been consistently associated with early onset OCD (Walitza et al., 2012, 2002; Enoch et al., 2001), while conflicting results are reported in adult populations (Sinopoli et al., 2017). Moreover, these significant associations were obtained in populations that included only patients who could be considered very early onset OCD (Walitza et al., 2012, 2002) (average age of onset 11.1 ± 3.2 and 12.1 ± 2.1 years). No similar studies have been conducted with very-early onset AN.

The other genetic variant identified in our study is rs4942587, an intronic variant. It has been identified as an eQTL variant, meaning that it has some effect on the gene expression, or at least is in linkage disequilibrium with a variant with this effect. However, we cannot rule out a possible role for rs4942587 in modulating gene expression by acting on novel untranslated regions and alternative exons, as recent findings have identified new transcripts and exon-intron boundaries in the HTR2A (Ruble et al., 2016).

The role of serotonin in the age of onset of AN and OCD, does not rule out the possible effect that other systems could have in the same phenotype or the effect that the serotonin system could have in other shared phenotypes such as personality disorders. Several personality traits are detected in AN and OCD patients, mainly perfectionism, neuroticism, negative emotionality, harm avoidance, and Cluster C personality disorders in AN patients (Cassin, 2005; Marañón et al., 2004) and neuroticism and Cluster C personality in OCD patients (Samuels et al., 2000). In our study, psychometric evaluations to detect comorbidities with personality disorders were not performed due to the sample age, only perfectionism with the Child Adolescent Perfectionism Scale (CAPS) was assessed (no differences were detected between very-early and early onset disorders, see Table 1). Regarding genetic pleiotropy of personality disorders, Cluster C personality disorder is not associated with the 5-HTTLPR polymorphism of the serotonin transporter (Jacob et al., 2004). However, neuroticism is associated with the 5-HTTLPR polymorphism specifically in patients with Cluster C personality disorder (Jacob et al., 2004). In contrast, genetic variations in the *COMT* gene, involved in dopamine metabolism, contribute to the genetic pleiotropy of neuroticism across anxiety-related phenotypes (Hettema et al., 2008).

The main limitation of the present study is the sample size. Another important limitation of our study is that we have not performed an evaluation of the puberty of the patients using the Tanner scale, which has motivated the choice of age criteria for each group. However, we believe that the relatively narrow phenotype under study (very early onset disease) is an important strength. The sample represented a homogeneous clinical population, not just because early-onset OCD can be considered a separate subtype of the condition (Taylor, 2011), but also because the adolescent AN group did not include any eating disorders not otherwise specified, in order to obtain a sample of eating disorder patients with a similar degree of severity and thus to reduce the heterogeneity.

In conclusion, in spite of the small sample size, the preliminary results we report here reveal that the genetic background related to the serotonin system, that has been separately associated with AN and OCD, affects a common phenotype of the two diseases, such as the existence of a very-early onset subgroup of patients.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.019.

References

Altman, S.E., Shankman, S.A., 2009. What is the association between obsessive-compulsive disorder and eating disorders? Clin. Psychol. Rev. 29 (7), 638–646.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Press, Washington DC.

Baker, J.H., Schaumberg, K., Munn-Chernoff, M.A., 2017. Genetics of anorexia nervosa. Curr. Psychiatry Rep. 19 (11), 84.

Berg, C.J., Rapoport, J.L., Flament, M., 1986. The Leyton obsessional inventory—child version. J. Am. Acad. Child. Adolesc. Psychiatry 25, 84–91.

Bulik, C.M., Sullivan, P.F., Fear, J.L., Joyce, P.R., 1997. Eating disorders and antecedent anxiety disorders: a controlled study. Acta Psychiatr. Scand. 96, 101–107.

Calvo, R., Lázaro, L., Castro-Fornieles, J., Font, E., Moreno, E., Toro, J., 2009. Obsessive-compulsive personality disorder traits and personality dimensions in parents of children with obsessive-compulsive disorder. Eur. Psychiatry 24 (3), 201–206.

Cassin, S.E., von Ranson, K.M., 2005. Personality and eating disorders: a decade in review. Clin. Psychol. Rev. 25 (7), 895–916.

Castro, J., Toro, J., Salamero, M., 1991. The eating attitudes test: validation of the Spanish version. Eval. Psicol. 7, 175–190.

Castro, J., Gila, A., Puig, J., Rodriguez, S., Toro, J., 2004. Predictors of rehospitalization after total weight recovery in adolescents with anorexia nervosa. Int. J. Eat Disord. 36 (1), 22–30.

Cavallini, M.C., Bertelli, S., Chiapparino, D., Riboldi, S., Bellodi, L., 2000. Complex segregation analysis of obsessive-compulsive disorder in 141 families of eating disorder probands, with and without obsessive-compulsive disorder. Am. J. Med. Gen. 96, 384–391.

Cederlöf, M., Thornton, L.M., Baker, J., Lichtenstein, P., Larsson, H., Rück, C., et al., 2015. Etiological overlap between obsessive-compulsive disorder and anorexia nervosa: a longitudinal cohort, multigenerational family and twin study. World Psychiatry 14 (3), 333–338 Oct.

Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat. Genet. 45, 984–994.

de Mathis, M.A., do Rosario, M.C., Diniz, J.B., Torres, A.R., Shavitt, R.G., Ferrão, Y.A., et al., 2008. Obsessive-compulsive disorder: influence of age at onset on comorbidity patterns. Eur. Psychiatry 23 (3), 187–194.

Enoch, M.A., Greenberg, B.D., Murphy, D.L., Goldman, D., 2001. Sexually dimorphic relationship of a 5-HT2A promoter polymorphism with obsessive-compulsive disorder. Biol. Psychiatry 49 (4), 385–388.

Enoch, M.A., Kaye, W.H., Rotondo, A., Greenberg, B.D., Murphy, D.L., Goldman, D., 1998. 5-HT2A promoter polymorphism -1438 G/A, anorexia nervosa, and obsessive-compulsive disorder. Lancet 351 (9118), 1785–1786.

Garner, D.M., Garfinkel, P.E., 1979. The eating attitudes test: an index of the symptoms of anorexia nervosa. Psychol. Med. 9, 273–279.

Godier, L.R., Park, R.J., 2014. Compulsivity in anorexia nervosa: a transdiagnostic concept. Front. Psychol. 5 (778), 18.

González, J.R., Armengol, L., Solé, X., Guinó, E., Mercader, J.M., Estivill, X., et al., 2007. SNPassoc: an R package to perform whole genome association studies. Bioinformatics 23, 644–645.

Gorwood, P., Kipman, A., Foulon, C., 2003. The human genetics of anorexia nervosa. Eur. J. Pharmacol. 480 (1–3), 163–170.

Halmi, K.A., Tozzi, F., Thornton, L.M., Crow, S., Fichter, M.M., Kaplan, A.S., et al., 2005. The relation among perfectionism, obsessive-compulsive personality disorder and obsessive-compulsive disorder in individuals with eating disorders. Int. J. Eat Disord. 38 (4), 371–374.

Hettema, J.M., An, S.S., Bukszar, J., van den Oord, E.J., Neale, M.C., Kendler, K.S., et al., 2008. Catechol-O-methyltransferase contributes to genetic susceptibility shared among anxiety spectrum phenotypes. Biol. Psychiatry 64 (4), 302–310.

Jacob, C.P., Strobel, A., Hohenberger, K., Ringel, T., Gutknecht, L., Reif, A., et al., 2004. Association between allelic variation of serotonin transporter function and neuroticism in anxious cluster C personality disorders. Am. J. Psychiatry 161 (3), 569–572.

Klump, K.L., Burt, S.A., Spanos, A., McGue, M., Iacono, W.G., Wade, T.D., 2010. Age differences in genetic and environmental influences on weight and shape concerns. Int. J. Eat. Disord. 43 (8), 679–688.

Kovacs, M., Beck, A.T., 1981. An empirical-clinical approach toward a definition on childhood depression. In: Schulterbrand, JG, Raskins, A (Eds.), Depression in Childhood: Diagnosis, Treatment and Conceptual Models. Academy Press, New York.

Marañón, I., Echeburua, E., Grijalvo, J., 2004. Prevalence of personality disorders in patients with eating disorders: a pilot study using the IPDE. Eur. Eat Disord. Rev. 12, 217–222.

Marsh, R., Maia, T.V., Peterson, B.S., 2009. Functional disturbances within frontostriatal circuits across multiple childhood psychopathologies. Am. J. Psychiatry 166, 664–674.

Martásková, D., Slachtová, L., Kemlink, D., Záhoráková, D., Papezová, H., 2009. Polymorphisms in serotonin-related genes in anorexia nervosa. The first study in Czech population and metaanalyses with previously performed studies. Folia Biol. 55 (5), 192–197 Praha.

Mas, S., Plana, M.T., Castro-Fornieles, J., Gassó, P., Lafuente, A., Moreno, E., et al., 2013. Common genetic background in anorexia nervosa and obsessive compulsive disorder: preliminary results from an association study. J. Psychiatr. Res. 47 (6), 747–754.

Nakatani, E., Krebs, G., Micali, N., Turner, C., Heyman, I., Mataix-Cols, D., 2011. Children with very early onset obsessive-compulsive disorder: clinical features and treatment outcome. J. Child Psychol. Psychiatry 52 (12), 1261–1268.

Peebles, R., Wilson, J.L., Lock, J.D., 2006. How do children with eating disorders differ from adolescents with eating disorders at initial evaluation? J. Adolesc. Health 39 (6), 800–805.

Ruble, C.L., Smith, R.M., Calley, J., Munsie, L., Airey, D.C., Gao, Y., et al., 2016. Genomic structure and expression of the human serotonin 2A receptor gene (HTR2A) locus: identification of novel HTR2A and antisense (HTR2A-AS1) exons. BMC Genet. 17, 16.

Samuels, J., Nestadt, G., Bienvenu, O.J., Costa Jr., P.T., Riddle, M.A., Liang, K.Y., et al., 2000. Personality disorders and normal personality dimensions in obsessive-compulsive disorder. Br. J. Psychiatry 177, 457–462.

Sinopoli, V.M., Burton, C.L., Kronenberg, S., Arnold, P.D., 2017. A review of the role of serotonin system genes in obsessive-compulsive disorder. Neurosci. Biobehav. Rev. 80, 372–381.

Smith, R.M., Papp, A.C., Webb, A., Ruble, C.L., Munsie, L.M., Nisenbaum, L.K., et al., 2013. Multiple regulatory variants modulate expression of 5-hydroxytryptamine 2A receptors in human cortex. Biol. Psychiatry. 73 (6), 546–554.

Strober, M., Freeman, R., Lampert, C., Diamond, J., 2007. The association of anxiety disorders and obsessive compulsive personality disorder with anorexia nervosa: evidence from a family study with discussion of nosological and neurodevelopmental implications. Int. J. Eat. Disord. 40, S46–S51.

Taylor, S., 2011. Early versus late onset obsessive-compulsive disorder: evidence for distinct subtypes. Clin. Psychol. Rev. 31, 1083–1100.

Taylor, S., 2013. Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies. Mol. Psychiatry 18 (7), 799–805.

Taylor, S., 2016. Disorder-specific genetic factors in obsessive-compulsive disorder: a comprehensive meta-analysis. Am. J. Med. Genet. B Neuropsychiatr. Genet. 171B (3), 325–332.

van Noort, B.M., Lohmar, S.K., Pfeiffer, E., Lehmkuhl, U., Winter, S.M., Kappel, V., et al., 2018. Clinical characteristics of early onset anorexia nervosa. Eur. Eat. Disord. Rev. 26 (5), 519–525 Vienna.

Walitza, S., Bové, D.S., Romanos, M., Renner, T., Held, L., Simons, M., et al., 2012. Pilot study on HTR2A promoter polymorphism, -1438G/A (rs6311) and a nearby copy number variation showed association with onset and severity in early onset obsessive-compulsive disorder. J. Neural. Transm. 119 (4), 507–515 Vienna.

Walitza, S., Wewetzer, C., Warnke, A., Gerlach, M., Geller, F., Gerber, G., et al., 2002. 5-HT2A promoter polymorphism -1438 G/A in children and adolescents with obsessive-compulsive disorders. Mol. Psychiatry 7 (10), 1054–1057.

Wentz, E., Gillberg, I.C., Anckarsäter, H., Gillberg, C., Råstam, M., 2009. Adolescent-onset anorexia nervosa: 18-year outcome. Br. J. Psychiatry 194 (2), 168–174.