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Association between serotonin transporter gene polymorphism and obsessive–compulsive disorder in the Egyptian population

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Abstract

Background Obsessive–compulsive disorder (OCD) is a debilitating disorder that has multifactorial etiology including genetic, neurobiological, cognitive, and environmental influences**.** Genetic studies have focused on the genes of the serotonin system. This study aimed to look for the possible relation between the polymorphism in the promotor region of the serotonin transporter gene and obsessive–compulsive disorder in the Egyptian population.

Results This study included 94 OCD patients and 116 healthy control individuals. Blood samples were collected from all participants for DNA extraction and genotyping. The assessment of patients was done by application of the structured clinical interview according to DSM-V, the dimensional Yale-Brown Obsessive–Compulsive Scale. There was an association between serotonin transporter gene polymorphism and OCD development. The carriage of the short allele was a risk factor for having OCD.

Conclusion Obsessive–compulsive disorder is associated with serotonin transporter gene polymorphism. This will contribute to considering the genetic information of patients for the prediction of best drug response and tolerability by personalizing the choice of treatment.

Keywords Serotonin, Gene polymorphism, Obsessive–compulsive, OCD dimensions' SLC6A4 gene, (5-HTTLPR)

Background

Obsessive–compulsive disorder is a chronic condition associated with recurrent thoughts (obsessions) and/or ritualized behaviors (compulsions) performed to decrease associated anxiety. The estimated prevalence of OCD is about 1–3% of the general population [1].

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The presentation of OCD is heterogeneous with the content of obsessions and compulsions. Symptoms vary across patients so, sometimes patients are divided into different categorical subtypes or dimensions based on their predominant symptom type or comorbid presentation.

The etiology of OCD is multifactorial resulting from interaction between genetic factors and environmental influences. Early family studies and twin studies suggested the genetic contribution to the etiology of OCD [2].

Linkage and association studies examining individual several candidate genes found that multiple genetic variants are involved in the pathophysiology of OCD, each having a tiny effect on the overall genetic risk of OCD. Research studies have paid special attention to serotonin pathway genes due to the therapeutic efficacy of the

drugs that inhibit the reuptake of serotonin in alleviating obsessive–compulsive symptoms [3].

Serotonin transporter (5-HTT) is one of the important variants in OCD etiology. It is encoded by the SLC6A4 gene found on 17q11.2. The function of 5-HTT is mainly terminating the action of serotonin at the synaptic cleft. Alteration of the amount of serotonin transporter can affect serotonin levels [4]. Variations within the polymorphic area of the serotonin transporter (5-HTTLPR) have influences on the transcriptional activity and expression of the serotonin transporter [5].

The identification of specific risk genes involved in OCD etiology was complicated by inconsistent results of the genetic studies [6]. The heterogeneity associated with OCD may explain the inconsistent results [7]. Evidence from candidate gene studies suggests that the genetic vulnerability of OCD may be associated with certain OCD phenotypes according to sex, onset of symptoms, family history of psychiatric disorders especially OCD, presence of comorbidities, and symptom dimensions [8].

To our knowledge, there is no study done to detect the association of serotonin gene polymorphisms in patients with OCD in relation to obsessive–compulsive symptoms dimensions in the Egyptian population.

Aim of the study

This study aimed to explore if serotonin transporter gene polymorphism is related to OCD development and find out if this polymorphism is associated with different obsessive–compulsive symptoms dimensions**.**

Methods

Study design and setting

This study was an unrelated case–control study that included 210 Egyptian individuals which were separated as follows: 94 patients with obsessive–compulsive disorder and 116 healthy individuals without any psychiatric disorder as control. The study was conducted over 2 years in Mansoura University Hospital in the psychiatry department and biochemistry department. The local ethical committee of Mansoura University approved the research (MD.21.09.530). Informed written consent was applied to all study participants before answering any questions or taking blood samples. Inclusion criteria of OCD patients: (1) age < 18 years old, (2) sex: both sexes, (3) patients meeting diagnostic criteria of OCD according to the DSM-5. Exclusion criteria of patient group: (1) patients with any other psychiatric disorder except depression, and anxiety disorder, (2) patients with neurological disorders, head trauma, and severe medical disorders. Criteria of the control group: (1) had no history of neurological and psychiatric disorders, (2) had no family psychiatric history or psychotropic medication history.

Tools

All study participants were interviewed face-to-face in the hospital and subjected to completing a questionnaire that asked for information about social and demographic characteristics including current age, gender, marital status, education, and occupation. Patients were assessed by the following: (1) full history and clinical assessment including chief complaint, the period of illness, family history of any psychiatric disorders, and age of onset (symptoms begin ≤ 18 years old, considered early onset and after 18 years considered late onset) [9]. (2) The Structured Clinical Interview for the DSM-5 clinical version (SCID-5-CV) was used for the diagnosis of obsessive–compulsive disorder and exclusion of any other psychiatric disorder except for depression and anxiety. It helps the clinician step by step throughout the diagnostic process. Interview questions are provided conveniently along each corresponding DSM-5 criterion, which helps in rating each as either present or absent [10]. (3) The Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS) is a semi-structured scale used for the assessment of obsessive–compulsive symptoms dimensions and the severity of these symptoms. The scale includes the following dimensions: (a) harm, aggression, violence obsessions and/or compulsions; (b) sexual, religious obsessions and/or compulsions; (c) symmetry, ordering, arranging obsessions and/or compulsions; (d) contamination, cleaning obsessions and/or compulsions; (e) other miscellaneous obsessions and compulsions as somatic ruminations and superstitions [11] (Table 1).

Laboratory task

Five ml of blood samples were gathered from all subjects into sterile tubes containing EDTA. After gathering, whole blood was transported and maintained in aliquots at 20 °C till use at the biochemistry department of Mansoura University. The extraction and purification of genomic DNA were done by using the QIAamp DNA Blood Mini Kit (QIAGEN, Stanford Valencia, CA, USA) as described by the manufacturer.

Genotyping analysis

The promoter area of the serotonin transporter gene has 44 base pair variable-number of tandem repeat polymorphism; which is associated with varied transcriptional efficiency among the population. It has two alleles; the long (528 base pair) allele and the short (484 base pair) allele. The long allele is more active than the shorter allele by three times [12].

Table 1 Clinical data of OCD patients

	N (%)	Mean ± SD [median (min–max)]
Total	94(100)	
Onset:		
Early (< 18 years)	30(31.9)	23.9 ± 2.6[22(10–58)]
Late (≥ 18 years)	64(68.1)	
Duration (years):		
< 10	56(59.6)	8.99 ± 7.8[20(6–36)]
10 and more	38(40.4)	
Family history:		
No	40(42.6)	
Yes	54(57.4)	
Type of family history:		
OCD	45(47.9)	
Psychosis	3(3.2)	
Affective	2(2.1)	
Substance use	2(2.1)	
Miscellaneous	2(2.1)	
Comorbid psychiatric disorder:		
No	50(53.2)	
Yes	44(46.8)	
Type of comorbid psychiatric disorder		
Depression	17(18.1)	
Anxiety	27(28.7)	
Medical comorbidity	3(3.2)	
Dimensions:		
• Aggression	17(18.1)	
• Sexual and religious	19(20.2)	
• Symmetry	17(18.1)	
• Contamination	20(21.3)	
• Miscellaneous	21(22.3)	
Severity of OCD according to YBOCS:		
• Mild	21(22.3)	±6.1[20(6–36)]
• Moderate	39(41.5)	
• Severe/very severe	34(36.2)	

The process of genotyping using fragment length polymorphism is performed by polymerase chain reaction (PCR). The resulting fragments were amplified from 20 ng of genomic DNA using Applied Biosystems Ampli Taq DNA polymerase kit (from Thermo Fisher) and 10mm of each primer (F-5′GGCGTTGCCGCT CTGAATGC-3′ and (R 5′–GAGGGACTGAGCTGG ACAACCA-3′) which flank the genomic region containing the 5-HTTLPR polymorphism. The PCR conditions were as the following: 10 min at 95 °C, initial denaturation; 30 s at 95 °C, 45 s at 60 °C and 1 min at 72 °C for 35 cycles; finally, 7 min at 72 °C, final extension. The PCR products were resolved by electrophoresis on 2% agarose gels stained with ethidium bromide in order to identify PCR fragments of different sizes: (a) short (S) 486 base pair with 14 repeats; (b) long (L) 529 base pair with 16 repeats; (c) very long (XL) 612/654 base pair with 20/22 repeats [13].

Table 2 Sociodemographic characters of the two studied groups

	Patient group	Control group	*P* value	COR(95%CI)
N	94(100)	116(100)		
Age:				
< 40	68(72.3)	52(44.8)		
40 and more	26(27.7)	64(55.2)	≤ 0.001	1(r)
Mean ± SD	32.9 ± 11.2	42.9 ± 10.8	≤ 0.001	0.3(0.2–0.6)
Sex:				
Male	28(29.8)	56(48.3)	≤ 0.001	1(r)
Female	66(70.2)	60(51.7)		2.2(1.2–3.9)
Occupation:				
Working	41(43.6)	69(59.5)	–	1(r)
Not working	53(56.4)	47(40.5)	≤ 0.001	0.5(0.3–0.9)
Marital status:				
Married	47(50.0)	106(91.4	– ≤ 0.001	1(r)
Unmarried	47(50.0)	10(8.6)		0.1(0.04–0.4)
Education:				
University	46(48.9)	103(88.8)	-	1(r)
2ry or lower	48(51.1)	13(11.2)	≤ 0.001	0.1(0.06–0.2)

Data analysis

The analysis of data was done by using the statistical package of SPSS for Windows, version 25.0. Data were displayed in the form of means ± SD (standard deviation), frequencies, and percentages. Comparisons between quantitative data were calculated by using the Student's *t*-test. The chi-square test and Fischer exact test were used for comparisons between categorical data. The odds ratios (OR), 95% confidence intervals (CI), and significance were measured. Results were statistically significant when values of $p < 0.05$. Nucleotide Polymorphism analysis involved frequency of alleles, genotyping, and Hardy–Weinberg equilibrium (HWE).

Results

In the current study, the mean age of recruited patients was 32.9 ± 11.2 while the mean age of control subjects was 42.9 ± 10.8 which is statistically significant ($p \leq 0.001$) as shown in Table 2.

As regards OCD onset, the mean age of onset was about 23.9 ± 2.6 years. About 31.9% of cases had early onset disorder before 18 years while 68.1% had late onset

disorder after 18 years. The mean period of the disorder was 8.99 ± 7.8 years. The period of disorder was less than 10 years in 59.6% of cases and more than 10 years in 40.4% of cases. As regards family history, about 42.6% of cases did not have a family history of psychiatric disorder while 57.4% of cases had a family history of psychiatric disorders, of which 47.9% had a family history of OCD. About 52.2% of patients had no comorbid psychiatric disorder while 46.8% had comorbid psychiatric disorder, of which 18.1% had comorbid depression and 28.7% had comorbid anxiety. As regards symptom dimensions 17(18.1%) of cases had aggressive obsessions and compulsions, 19(20.2%) had religious, sexual obsessions and compulsions, 17(18.1%) had symmetry obsessions and compulsions, 20(21.3%) had contamination obsessions and compulsions, 21(22.3%) had miscellaneous obsessions and compulsions. The mean severity score of OCD using Yale brown obsessive compulsive was 20.5 ± 6 as shown in Table 1.

The genotype analysis 5-HTTLPR showed that the L allele frequency among OCD patients was 51.1% while in control was 69.4% and S allele frequency was 48.9% in the OCD group while in the control group was 30.6% as shown in Table 3. The carriage of the S allele was significantly higher in the OCD group compared to that of the control group in all genetic models (dominant model OR 2.5080 CI 1.4722 to 4.2725, recessive model OR 3.2424 CI 1.6548 to 6.3531 and additive model OR 2.1731 CI 1.4572 to 3.2409), so the carriage of S allele is a risk factor for the development of OCD as presented in Table 4.

There was a statistically significant difference between the SS genotype of the serotonin transporter gene and the contamination dimension (P value = 0.0014) and between the SS genotype and miscellaneous dimension (P value = 0.02). There was also a statistically significant association between LS genotype and Sexual/religious dimension as presented in Table 5.

There was a statistically significant difference in the genotyping analysis of 5-HTTLPR between female OCD patients and female control (P value = 0.04, P value 0.003) as shown in Table 6.

There was no statistically significant difference in the genotype analysis between OCD patients with comorbid depression and those without comorbid depression (P value = 0.14) (P value = 0.15). There was no statistically significant difference in the genotype analysis between OCD patients with comorbid anxiety and those without comorbid anxiety (P value = 0.7) (P value = 0.4) as shown in Table 7.

Table 3 Descriptive data of 5-HTTLPR alleles among different groups

	Control group *N* (116)%	Patient group *N* (94) %
LL	60 (51.7%)	31 (32.9%)
LS	41 (35.3%)	34 (36.1%)
SS	15 (12.9%)	29 (30.8%)
Hardy–Weinberg		
$\chi 2$	3.269	
P	0.071	
Allele frequency		
L	69.4%	51.1%
S	30.6%	48.9%
Homozygosity	0.65	0.64
Heterozygosity	0.35	0.36
PIC	0.31	0.31

L long allele, *S* short allele, *PIC* polymorphic information content

Table 4 Risk of carriage of the short allele of 5-HTTLPR and development of OCD

	Dominant (DM)	Recessive (RM)	Additive (AM)
Odds ratio	2.5080	3.2424	2.1731
95% CI	1.4722 to 4.2725	1.6548 to 6.3531	1.4572 to 3.2409
z statistic	3.383	3.428	3.806
Significance (*P* value)	0.0007	0.0006	0.0001

Discussion

Obsessive–compulsive disorder is a multifactorial psychiatric disorder that has a severe negative impact on family, social interaction, and work [14]. The underlying etiology of OCD shows differences between societies depending on the genetic foundation. Detection of candidate genes associated with OCD etiology has been complicated by the complex nature of the disorder. The influence of gene-environment interaction shapes the different forms of the disorder. Recently, several research studies have detected variants within genes of monoamines such as dopamine and serotonin. The serotonin system pathway genes are likely involved in the pathophysiology underlying many psychiatric disorders including OCD. This study investigated the possible association between the promoter region of 5-HTT gene polymorphism and the development of OCD. The promoter region contains regulatory regions that regulate transcription and gene expression. It has long and short alleles that are different in the number of repeats and base pairs [15].

In this study, there was a higher frequency of SS genotype in the patient group in comparison with a control group and the carriage of S allele was significant in all genetic model groups. This is in harmony with a

Table 5 Association between genotype of serotonin transporter and OCD dimensions

5-HTTLPR	LL *N* (%)	LS *N* (%)	*P*	OR(95%CI)	SS *N* (%)	*P*	OR(95%CI)
Control	60(51.7)	41(35.3)		r(1)	15(12.9)		r(1)
Aggression	7(41.2)	7(41.2)	0.5	1.5(0.5–4.5)	6(35.3)	0.7	1.3(0.4–4.0)
Sexual/religious	5(26.3)	11(57.9)	0.04	3.2(1.04–10.0)	3(15.8)	0.3	2.4(0.5–11.2)
Symmetry	6(35.3)	7(41.2)	0.4	1.7(0.5–4.4)	4(23.5)	0.2	2.7(0.7–10.7)
Contamination	6(30.0)	5(25.0)	0.8	1.2(0.3–4.3)	9(45.0)	0.0014	6.0(1.8–19.5)
Miscellaneous	7(33.3)	7(33.3)	0.5	1.5(0.5–4.5)	7(33.3)	0.02	4.0(1.2–13.2)

Table 6 Genotype distribution of 5-HTTLPR among male and female cases and control

Males				
	Cases	Control	*P*	OR (95%CI)
5-HTTLPR:				
LL	11(39.)	26(46.4)	–	1(r)
LS	11(39.3)	25(44.6)	0.9	1.04(0.4–2.8)
SS	6(21.4)	5(8.9)	0.1	2.8(0.7–11.3)
Females				
	Cases	Control	*P*	OR (95%CI)
5-HTTLPR:				
LL	20(30.3)	34(56.4)	–	1(r)
LS	23(34.8)	16(26.7)	0.04	2.4(1.1–5.7)
SS	23(34.8)	10(16.7)	0.003	3.9(1.6–9.9)

case–control association study by Denys and his colleagues [16], which suggested an association between OCD with the homozygous SS genotype**.** Also, a previous study by Perez and his colleagues [17] found an increased frequency of the SS genotype in OCD patients.

On the other hand, earlier studies found an association between the LL genotype with OCD [18]. There was a higher frequency of the L allele in female OCD patients in comparison with female controls in a study done by Liu and his colleagues [19]. Other studies found a high frequency of L alleles in OCD patients [20, 21]. The association between the 5-HTTLPR polymorphism and OCD was detected in a number of studies [16, 17, 21]. On the other hand, other studies haven't detected any association between this polymorphism and OCD [22–29].

In this study, there was an association between 5-HTTLPR polymorphism and female patients. This is in harmony with a previous study [16], which suggested an association between the carriage of S allele and OCD in females only.

The association between the S allele and SS genotype with OCD can be explained by the fact that carrying the short variant causes low transcription of the serotonin transporter gene, thus low expression, and low serotonin reuptake while carrying the long variant (L) leads to higher expression of serotonin transporter and more serotonin reuptake [30]. The inconsistent results among studies may be due to factors related to sample size, type of study, heterogeneity of the disorder, other clinical features such as psychiatric comorbidities and lack of stratification of patients to homogenous subgroups. Results of this study suggest studying other polymorphisms within the serotonin transporter gene rather than focusing only on one or two polymorphisms, this will help for a better understanding of the role of serotonin transporter in OCD development.

Strengths of the study

It is one of the earliest studies that investigated the relationship between serotonin transporter gene polymorphism and having OCD in the Egyptian population, also stratified analyses of OCD patients according to their symptom dimensions and sex have been included in the study.

Table 7 Genotype distribution of 5-HTTLPR among patients with or without comorbid depression and anxiety

Genotype of HTTLPR	No (50) *N* (%)	Depression (17)			Anxiety (27)		
		N (%)	*P*	COR (95%CI)	*N* (%)	*P*	COR (95% CI)
LL	20(40%)	3(17.6%)		1(r)	8(29.6%)		1(r)
LS	18(36%)	8(47.1%)	0.14	3.0(0.7–12.9)	8(29.6%)	0.7	(–)
SS	12(24%)	6(35.3%)	0.15	3.3(0.7–15.9)	11(40.7%)	0.4	(–)

Limitations of the study

There are some limitations: (1) Cases were of limited number, so larger samples are needed (2) The study included only one polymorphism within the serotonin transporter gene.

Conclusions

This study suggests an association between the promoter region of serotonin transporter polymorphism and OCD.

Abbreviations

OCD	Obsessive-compulsive disorder
5-HTTLPR	Serotonin transporter-linked polymorphic region
DSM-V	Diagnostic and Statistical Manual of Mental Disorders fifth edition
DY-BOCS	Dimensional Yale-Brown Obsessive Compulsive Scale
SLC6A4	Solute Carrier Family 6 Member 4
SCID-5	Structured clinical interview according to DSM-5
5-HTT	5-Hydroxytryptamine transporter
PCR	Polymerase chain reaction
HWE	Hardy-Weinberg equilibrium
VNTR	Variable number of tandem repeats
SPSS	Statistical Package for the Social Sciences

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Authors' contributions

All authors read and approved the final manuscript.

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Availability of data and materials

Available upon request.

Declarations

Ethics approval and consent to participate

The institutional review board approval was given before the study (MD.21.09.530), and written informed consent was taken from all enrolled subjects before taking blood samples and answering any questions.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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