ORIGINAL ARTICLE

Link between obsessive-compulsive disorder and polymorphisms in HDAC genes

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Objective: Recently, epigenetic mechanisms related to histone modifications including histone deacetylation (HDAC) have been emphasized in psychiatric diseases. Few studies have investigated the relationship of HDAC gene variations to psychiatric diseases, but these gene variations have never been studied in obsessive-compulsive disorder (OCD). The present case-control study aimed to compare symptomatology with HDAC gene variations in patients with OCD.

Methods: Illumina next-generation sequencing of six HDAC genes (HDAC2,3,4,9,10,11) was performed on DNA samples isolated from 200 Turkish subjects recruited from routine clinical practice. Twenty-seven single nucleotide polymorphism (SNPs) in six HDAC genes were scanned with the LightSNiP method.

Results: New variants, all previously unreported in the literature, were identified in the HDAC4, HDAC10, and HDAC11 genes. When control and OCD patient groups were compared, a statistically significant difference was found in HDAC2 rs13212283, HDAC4 rs1063639, and HDAC10 rs1555048 in terms of genotype distribution (p < 0.05). In addition, in the OCD group, a statistically significant relationship was found between some obsessions/compulsions and HDAC2, HDAC3, and HDAC4 polymorphisms (p < 0.05).

Conclusions: Our study shows that the HDAC2, HDAC3, HDAC4, and HDAC10 genes may play a role in the pathogenesis of OCD.

Keywords: Obsessive-compulsive disorder; HDAC genes; histone modification; single nucleotide polymorphism; epigenetics

Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder where repeated obsessions or compulsions are observed continuously or periodically and clearly affect the person’s functioning.1 The clinical presentation of OCD is heterogeneous. Genetic, epigenetic, environmental, psychological, social, and biochemical factors implicated in OCD etiology are thought to play a role in these differences in phenotype.2

A large body of evidence proves cortico-striato-thalamo-cortical circuitry dysfunction to the main pathophysiological feature of OCD.3,4 Structural brain abnormalities in the frontostriatal region have also been detected.5 The most consistent findings from functional imaging studies in OCD relate to abnormally increased activation of the lateral prefrontal cortex, including the orbitofrontal cortex and anterior cingulate.6 Furthermore, impairment is seen in several neuropsychological parameters, such as spatial working memory, spatial recognition, and cognitive processes related to motor initiation and execution, which suggests that OCD may have a relationship with neurodegenerative diseases (e.g., Alzheimer disease [AD]).7,8 A recent study by our group reported that lifetime OCD symptoms were significantly more common in AD patients compared to the control group. This information suggests that previously existing OCD symptoms may lead to a tendency to dementia in later ages in case of a real memory deficiency.9

Candidate gene studies have identified risk variables for OCD within serotonergic (HTR2A, 5HTTLPR, SLC6A4), glutamatergic (SLC1A1, DLGAP3, SAPAP3), and dopaminergic (SLC6A3, DRD4) genes, and genetic linkage studies in OCD have identified chromosomal regions (9p24, 3q27-28, 14q23-32 and sites on chromosomes 1, 6, 7, and 15) that contain genes for the disorder. Genome-wide association studies (GWAS) of OCD have reported significant associations with the genes BTBD3, ASB13, RSP04, DLGAP1, PTTRD, GRIK2, FAIM2, CDH20, MEF2BNB, MEF2B, MEF2BNB-MEF2B, and RFXANK.10

In recent times, epigenetic mechanisms related to gene methylation, histone deacetylation (HDAC), and histone

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acetylation (HAT) have been a focus in psychiatric disorders, and attempts have been made to create treatment strategies for these conditions. Different methylation profiles were found in the promoter regions of the MAOA, GABA, MOG, BDNF, LEPR, OXTR, SLC6A3, and SLC6A4 genes in studies of DNA methylation comparing OCD patients and controls. The balance between HAT/HDAC is thought to be related to neuron death, with diseases occurring when this balance is disrupted. Neuron cell death, causing amyloid precursor protein (APP) activation in AD and amyotrophic lateral sclerosis (ALS), was shown to be associated with HDAC levels in in vitro model studies. HAT has been characterized as an epigenetic mechanism involved in memory formation, and its relevance has been shown in both physiological and pathological conditions. Studies have shown HAT-related heterochromatin structure changes as long-term memories are formed. While several studies investigating the relationship of HDAC gene variations with psychotic and neurodevelopmental disorders have been published, these gene variations have not been studied for a potential role in OCD. Different studies have reported that HDAC4, HDAC3, HDAC10, and HDAC9 single nucleotide polymorphism (SNPs) are associated with schizophrenia, and a deletion on HDAC9 was reported in schizophrenia. Another intronic SNP of HDAC3 (rs2735188), reported by Anney et al., was associated with autism in genome screening of 1,558 families. According to animal studies, HAT has been implicated in mechanisms affecting memory processes in the hippocampus.

In conclusion, variations in exonic and intronic regions of HDAC genes, playing roles in psychotic disorders, affect protein activity and thus cause suboptimal HAT in candidate genes, which is thought to increase OCD risk considerably. Within this context, we designed a case-control study to compare symptomatology and HDAC gene variations in patients with OCD.

Methods

The sample size in the study was determined using G-power. As there was no similar study related to the topic in the literature, we considered an effect size of 0.1, 80% statistical power, a 95% confidence level and 0.05 type 1 error rate; the minimum sample size was calculated as 96 subjects. Our study ultimately included 160 patients and 40 controls.

A total of 160 patients attending the Aydın Government Hospital psychiatry clinic with a previous diagnosis of OCD according to the Structured Clinical Interview in Diagnostic and Statistical Manual of Mental Disorders IV were recruited. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was applied to all patients to determine the severity of obsessive-compulsive (OC) symptoms. OC types were defined using the Y-BOCS symptom checklist. All patients were also administered the Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) applied. The presence of OCPD was determined with the Structured Clinical Interview for DSM-IV Axis II Personality Disorders. As healthy controls, Aydın State Hospital personnel who had not been diagnosed with OCD and did not use any psychotropic drugs or other medications were recruited. Controls were matched with OCD cases in terms of age and sex. All subjects were screened for psychiatric and neurological diseases; the exclusion criteria were psychotic disorder, autism spectrum disorders, bipolar disorder, intellectual disability, substance use disorders, and any organic mental disorder diagnosis. Volunteers participating in the study completed a form created by the researchers to collect sociodemographic and clinical variables, age at disease onset and duration, and information on medical treatment. To prevent any impact on genetic data, patients with comorbid organic diseases or who were on any medication within the preceding 2 months were not included in the study.

DNA isolation

Peripheral blood was used to isolate DNA with the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany), following the manufacturer’s instructions.

DNA concentration and purity

The concentration and purity of the isolated DNA samples were measured using a NanoDrop 1000 Spectrophotometer V3.7 (Thermo Scientific, Waltham, USA).

Illumina sequencing

DNA samples isolated from cases were sequenced for HDAC gene exons (HDAC2: 14 Exon, HDAC: 15 Exon, HDAC4: 27 Exon, HDAC9: 25 Exon, HDAC10: 20 Exon, and HDAC11: 9 Exon) and exon-intron junction points with next-generation sequencing (NGS) methods on the MiSeq Platform (Illumina, San Diego, USA). Raw data were analyzed according to the reference genome (GRCh37[h19]) in a web-based bioinformatics program (https://seq.genomize.com/). The rate at which total count numbers obtained at the end of the analysis encompassed the target regions was assessed as 100% using the Integrative Genomics Viewer (IGV) program. Variations identified according to 50X reading depth per allele (reference allele/alternative allele) were analyzed. Analysis of variations was completed in line with the Standards and Guidelines of the American College of Medical Genetics and Genomics (ACMG). Evaluation of variants in relevant databases (Ensembl, dbSNP, ClinVar, LOVD, UMD-MMR [Universal Mutation Database], HGMD® Professional 2017.3, InSiGHT, PubMed, MMR Variant Database) was made by taking the available information into account.

Identification of variations

The following criteria were applied in the evaluation of detected variations. Allele frequency must be < 5% in any of the following population databases: Exome Sequencing Project (ESP6500), 1000 Genomes Project (1000Genomes), and Exome Aggregation Consortium (ExAC). Exonic changes in all coding regions and

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SNPs were also examined using this test. Differences in allelic distribution of the 27 HDAC genes and associated with some psychiatric diseases were identified with real-time PCR (LightCycler 480, Roche, Basel, Switzerland) using a SNiP panel from the manufacturer. Probes provided by the manufacturer identified single-base changes/SNPs, making polymorphism analysis possible. SNPs were analyzed by melting curve analysis at the end of amplification.

Data analysis

Data analysis was performed with LightCycler 480 software in Tm calling mode or with melting curve genotyping.

Statistical analysis

Statistical analyses were performed in SPSS for Windows 17.0. Differences between the patients and controls in terms of categorical variables, such as demographic and clinical data, were analyzed using chi-square ($\chi^2$) tests, while continuous variables were analyzed with Student's $t$ test. Differences in allelic distribution of the 27 HDAC SNPs were also examined using $\chi^2$ test. The threshold of statistical significance was defined as 0.05.

Ethics statement

This study was approved by the institutional ethics committee of Aydın Adnan Menderes University (#2016/1011). Before the study, all participants provided informed consent.

Results

Sociodemographic and clinical comparisons of the two groups are summarized in Table 1. There were significant differences between the OCD and control groups in terms of age, education level, and marital status ($p = 0.003$, $p = 0.001$, and $p = 0.001$, respectively). There was no significant difference in the sex distribution of the groups ($p > 0.05$). As expected, the differences in tic history and HDRS and HARS scores between the OCD and control groups were also statistically significant ($p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively) (Table 1).

No defined variation was detected in any gene sequence analyses of HDAC2, HDAC3, and HDAC9 in the OCD and control groups.

For the HDAC4 gene, a novel (previously undefined) P855S (c.2563C>T) heterozygote variant and p.T913M (c.2738C>T) heterozygote variant were identified in two different OCD patients. In the control group, one case was identified to have a p.T913M (c.2738C>T) heterozygote variant.

For HDAC10, one OCD patient had the undefined p.A334V (c.1001C>T) heterozygote variant, one OCD patient had the undefined p.V544I (c.1630G>A) heterozygote/p.Q586R (c.1757A>G) heterozygote/p.N612D (c.1834A>G) heterozygote triple variant, three OCD patients had the V4291 (c.1285G>A) heterozygote variant, and one OCD patient had the novel p.P366L (c.1097C>T) heterozygote variant identified. In the control group, one case had a novel p.V544I (c.1630G>A) heterozygote/p.Q586R (c.1757A>G) heterozygote/p.N612D (c.1834A>G) heterozygote triple variant, and one case had the p.H543N (c.1627C>A) heterozygote variant identified.

For the HDAC11 gene, one OCD patient had the undefined p.343H (c.1028C>A) heterozygote variant identified. The 25 polymorphism findings detected with the LightSNiP method are shown in Table 2. Comparisons of the control and OCD group identified statistically significant differences in HDAC2 rs13212283, HDAC4 rs1063639, and HDAC10 rs1555048 genotype distributions ($p = 0.025$, $p = 0.046$, and $p < 0.001$, respectively). There were no statistically significant differences identified for genotype distributions of other SNPs between the groups ($p > 0.05$), nor for allele frequency ($p > 0.05$).

Statistically significant differences were observed for some obsessions and compulsions in OCD patients with HDAC polymorphisms, which are shown in Table 3 ($p < 0.05$).

Discussion

This study is the first to assess the correlation between OCD and HDAC gene variations in Turkish patients. In our research, new variants of HDAC4, HDAC10, and HDAC11 not previously reported in the literature were identified in cases, though without statistical significance. Comparisons of the OCD and control groups identified...
statistically significant differences for the HDAC2 rs13212283, HDAC4 rs1063639, and HDAC10 rs1555048 SNPs. There were statistically significant differences observed for some obsessions and compulsions in OCD patients with HDAC polymorphisms. For sociodemographic features, significant differences were identified for marital status, age, education level, and tic history between OCD subjects.

Based on the assumption that OCD is a neurodevelopmental disease, it is expected that early-onset OCD may display higher heritability and be associated less with environmental stress factors. For late-onset OCD, some genetic and epigenetic mechanisms of stressful life events are believed to be effective in triggering the disease. The neurobiology of OCD is characterized by strong dysfunction in the serotonergic and dopaminergic

| Variable                  | OCD group n (%) | Control group n (%) | df | $\chi^2$ | p-value |
|---------------------------|-----------------|---------------------|----|---------|---------|
| Gender                    |                 |                     |    |         |         |
| Female                    | 132 (82.50)     | 25 (62.50)          | 1  | 0.245   | 0.160   |
| Male                      | 28 (17.50)      | 15 (37.50)          |    |         |         |
| Marital status            |                 |                     |    |         |         |
| Married                   | 71 (44.37)      | 24 (60.00)          | 3  | 4.949   | 0.001   |
| Single                    | 72 (45.00)      | 14 (35.00)          |    |         |         |
| Divorced                  | 5 (3.13)        | 1 (2.5)             |    |         |         |
| Widowed                   | 12 (7.50)       | 1 (2.5)             |    |         |         |
| History of tics           |                 |                     |    |         |         |
| Yes                       | 55 (34.38)      | 0 (0.00)            | 3  | 4.322   | 0.001   |
| No                        | 105 (65.62)     | 0 (0.00)            |    |         |         |
| History of life triggers  |                 |                     |    |         |         |
| Yes                       | 98 (61.25)      | 0 (0.00)            |    |         |         |
| No                        | 62 (38.75)      | 0 (0.00)            |    |         |         |
| OCD onset                 |                 |                     |    |         |         |
| Sudden                    | 56 (35.00)      |                     |    |         |         |
| Slow                      | 104 (65.00)     |                     |    |         |         |
| Obsessions                |                 |                     |    |         |         |
| Aggression                | 18 (11.25)      |                     |    |         |         |
| Contamination             | 46 (28.75)      |                     |    |         |         |
| Symmetry                  | 31 (19.38)      |                     |    |         |         |
| Hoarding                  | 17 (10.62)      |                     |    |         |         |
| Sexual                    | 5 (3.13)        |                     |    |         |         |
| Religious                 | 14 (8.75)       |                     |    |         |         |
| Somatic                   | 9 (5.63)        |                     |    |         |         |
| Compulsions               |                 |                     |    |         |         |
| Repetition                | 50 (31.25)      |                     |    |         |         |
| Cleaning                  | 12 (7.50)       |                     |    |         |         |
| Ritualistic               | 17 (10.63)      |                     |    |         |         |
| Counting                  | 37 (23.12)      |                     |    |         |         |
| Ordering/arranging        | 14 (8.75)       |                     |    |         |         |
| Hoarding                  | 17 (10.62)      |                     |    |         |         |

|                           | Mean ± SD       | Mean ± SD       | F   | df | p-value |
|---------------------------|-----------------|-----------------|-----|----|---------|
| Age                       | 32.13±14.25     | 32.55±8.13      | 15.24| 92 | 0.003** |
| Educational level (years) | 11.77±6.50      | 10.60±10.77     | 6.11 | 94 | 0.001***|
| HDRS                      | 16.51±9.18      | 3.20±3.88       | 25.29| 86 | < 0.001***|
| HARS                      | 20.04±10.76     | 4.03±4.67       | 32.79| 85 | < 0.001***|
| OCD duration              | 10.93±8.33      |                 |     |    |         |
| Y-BOCS total              | 22.54±9.17      |                 |     |    |         |
| Y-BOCS obsession          | 13.10±2.02      |                 |     |    |         |
| Y-BOCS compulsion         | 13.50±9.80      |                 |     |    |         |

df = degrees of freedom; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; OCD = obsessive-compulsive disorder; SD = standard deviation; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

$p < 0.05$, $** p < 0.01$, $*** p < 0.001$.
systems. Accordingly, family, twin, segregation, and linkage studies of OCD have demonstrated roles of genes related to the serotonergic and dopaminergic system. Recently, the focus has shifted to epigenetic mechanisms related to modifications including gene methylation, HDAC, and HAT in psychiatric diseases, and attempts have been made to create treatment strategies that address these mechanisms. Within

Table 2 Genotype distribution of HDAC gene polymorphisms between groups

| Gene/SNP marker | OCD group (n=160) n (%) | Control group (n=40) n (%) | df | χ² | p-value |
|-----------------|-------------------------|---------------------------|----|----|---------|
| **HDAC2**       |                         |                           |    |    |         |
| Genotypes       |                         |                           |    |    |         |
| rs13212283      | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs9488289       | AA (37.50)              | AG (50.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs6558819       | AA (42.50)              | AG (42.50)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs2499618       | AA (47.50)              | AG (47.50)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs13204455      | AA (37.50)              | AG (37.50)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs10499080      | AA (40.00)              | AG (40.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| **HDAC3**       |                         |                           |    |    |         |
| Genotypes       | AA (28.12)              | AG (28.12)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs2530223       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs142519        | AA (27.50)              | AG (27.50)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs2735188       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs11742646      | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs251041        | AA (26.24)              | AG (26.24)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| **HDAC4**       |                         |                           |    |    |         |
| Genotypes       | AA (23.75)              | AG (23.75)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs1063639       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs3791480       | AA (27.50)              | AG (27.50)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| **HDAC9**       |                         |                           |    |    |         |
| Genotypes       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs1726596       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs12531908      | AA (27.50)              | AG (27.50)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs7801162       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs2107595       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| **HDAC10**      |                         |                           |    |    |         |
| Genotypes       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs1555048       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs7290710       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs1076649       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs47284        | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs5771109       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| **HDAC11**      |                         |                           |    |    |         |
| Genotypes       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| rs7634112       | AA (25.00)              | AG (25.00)                |    |    |         |
| Genotypes       | GG (50.00)              | GG (50.00)                |    |    |         |
| df = degrees of freedom; HDAC = histone deacetylation; OCD = obsessive-compulsive disorder; SNP = single nucleotide polymorphism.

* p < 0.05, ** p < 0.01, *** p < 0.001.
| HDAC2    | HDAC2 rs10499080 | HDAC2 rs2499618 | HDAC3 rs2735188 | HDAC3 rs142519 | HDAC3 rs251041 | HDAC4 rs1063639 | HDAC4 rs1726596 | HDAC10 rs1076649 |
|----------|------------------|-----------------|------------------|----------------|----------------|-----------------|-----------------|------------------|
| **Obsessions** |                  |                  |                  |                |                |                 |                 |                  |
| Aggression | 0.230/1/1.000    | 0.118/2/0.946   | 4.766/2/0.149    | 2.163/2/0.921 | 1.010/2/0.592 | 0.546/1/0.710   | 0.584/2/0.770   | 0.121/2/0.939    |
| Contamination | 3.635/1/1.08    | 2.523/2/0.148   | 4.16/2/0.111     | 2.289/2/0.208 | 2.399/2/0.298 | 0.181/1/0.766   | 6.427/2/0.027   | 0.916/2/0.633    |
| Symmetry | 3.635/1/1.08    | 3.336/2/0.199   | 2.707/2/0.222    | 0.896/2/0.644 | 1.970/2/0.373 | 0.033/1/0.592   | 0.859/2/0.634   | 0.899/2/0.643    |
| Hoarding | 2.369/1/1.59    | 7.511/2/0.046*  | 9.105/2/0.003**  | 0.557/2/0.762 | 6.455/2/0.034* | 0.138/1/1.000  | 6.074/2/0.027*  | 2.312/2/0.266    |
| Sexual | 0.983/1/0.666   | 0.567/2/0.686   | 2.513/2/0.331    | 4.161/2/0.111 | 2.399/2/0.298 | 0.181/1/0.766   | 6.427/2/0.027   | 0.916/2/0.633    |
| Religious | 0.238/1/0.722   | 0.771/2/0.677   | 0.671/2/0.654    | 7.000/2/0.042* | 3.953/2/0.141 | 6.830/1/0.007** | 2.120/2/0.229   | 5.064/2/0.073    |
| Somatic | 0.042/1/1.000   | 1.512/2/0.593   | 0.523/2/0.751    | 1.975/2/0.214 | 1.355/2/0.337 | 0.140/1/1.000  | 5.662/2/0.114   | 0.091/2/0.957    |

| **Compulsions** |                  |                  |                  |                |                |                 |                 |                  |
| Repetition | 0.244/1/0.759   | 10.051/2/0.003** | 1.547/2/0.388    | 2.187/2/0.330 | 0.337/2/0.845 | 0.677/1/0.552   | 0.922/2/0.631   | 1.119/2/0.572    |
| Cleaning | 1.606/1/0.339   | 2.402/2/0.157    | 4.16/2/0.111     | 1.625/2/0.423 | 1.267/2/0.520 | 0.181/1/0.766   | 8.283/2/0.011*  | 0.228/2/0.891    |
| Rituals | 0.789/1/0.421   | 2.292/2/0.217    | 0.838/2/0.658    | 1.747/2/0.296 | 2.628/2/0.186 | 0.770/1/1.000  | 0.529/2/0.623   | 1.453/2/0.379    |
| Counting | 0.488/1/0.737   | 7.390/2/0.027*   | 10.71/2/0.001*** | 0.541/2/0.764 | 2.137/2/0.335 | 5.449/1/0.024*  | 1.625/2/0.388   | 0.815/2/0.664    |
| Ordering/arranging | 4.707/1/0.57 | 2.767/2/0.254   | 2.007/2/0.311    | 0.374/2/0.831 | 0.803/2/0.670 | 0.210/1/0.766   | 1.355/2/0.487   | 0.417/2/0.813    |
| Hoarding | 2.369/1/0.597   | 7.511/2/0.023*   | 9.105/2/0.003**  | 0.557/2/0.762 | 6.455/2/0.034* | 0.138/1/1.000  | 6.074/2/0.027*  | 2.312/2/0.266    |

Data presented as $\chi^2$/degrees of freedom (df)/p-value.

HDAC = histone deacetylase; SNPs = single nucleotide polymorphisms.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. 

In conclusion, the present study researched the correlation of HDAC gene polymorphisms with obsessive-compulsive disorder and found significant results. These findings support the hypothesis that HDAC gene variations may play a role in the pathogenesis of OCD.
In addition, a statistically significant relationship was found between increased frequency of repetitive ritual obsessions, hoarding obsessions-compulsions, counting compulsions, and HDAC2, HDAC3, and HDAC4 polymorphisms in the OCD group, suggesting that these polymorphisms may represent a distinct clinical and psychobiological profile in OCD. In OCD, ritual-repetition obsessions are especially thought to be related to problems with the patient’s memory, and studies have focused on this topic in the literature.\textsuperscript{23} It has been reported that symptoms such as symmetry obsession, ordering, ritual repetition, and counting compulsion are observed in patients showing hoarding symptoms more often than in those who do not exhibit hoarding.\textsuperscript{30} Similar inferences were made by Pertusa et al.,\textsuperscript{31} who proposed classifying hoarding as a different form of OC symptoms, unlike symmetry obsession, ordering, ritual repetition, and counting compulsion. Hoarding as a symptom is also linked to Tourette’s syndrome, chronic motor tic disorder, and OCPD.\textsuperscript{31} Therefore, the fact that these findings may stem from a mutual underlying root cannot be neglected. Hoarding is separate from OCD and classified as a different disease group in the DSM-V. On the other hand, it may be suggested that the fundamental nature of hoarding can bring about secondary behavioral disorders, as it may only be natural to expect one to count or arrange the collected items.\textsuperscript{30,31}

On comparison of the presence and absence of obsessions and compulsions individually, the fact that these polymorphisms are observed more frequently in the absence of certain obsessions/compulsions suggests that these polymorphisms may have a protective effect on symptom onset in OCD patients. From this aspect, our study shows that variants identified by both the NGS and LightSNIP methods on the HDAC2, HDAC3, HDAC4, and HDAC10 genes may play a role in OCD pathogenesis and genetic etiology. This is the first study to assess the correlation between OCD and HDAC gene variations. However, further research with larger samples is needed to identify more significant variants and whether the association of these variants with OCD prevails.

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Disclosure

The authors report no conflicts of interest.

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