

The Genetic Studies of Obsessive-Compulsive Disorder and Its Future Directions

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Obsessive-compulsive disorder (OCD) is characterized by recurrent and persistent thoughts (obsessions), and repetitive behaviors or mental acts (compulsions). In Korea, an epidemiological study reported that the lifetime prevalence of OCD in the population was greater than two percent. The exact cause of OCD is still unknown. Evidence from familial, twin and segregation studies supports the role of a genetic component in the etiology of OCD. In addition, there is growing evidence that OCD has a specific neurochemical and neuro-anatomical basis. According to this evidence, researchers have selected various candidate genes which have been implicated in the neurophysiology of OCD, and differences of allelic variants in OCD patients and controls have been analyzed. In this review we will introduce the results of previous genetic studies of OCD which have been performed in other populations, including twin studies, family studies, segregation analyses, linkage analyses, and association studies. In addition to these studies, we will present the results of our genetic studies of OCD performed in Korea.

Key Words: Obsessive-compulsive disorder, genetic component

Obsessive-compulsive disorder (OCD) is characterized by recurrent and persistent thoughts (obsessions), and repetitive behaviors or mental acts (compulsions). Most patients with OCD have a chronic course of the illness and show a wide range of functional impairment in occupational and social areas. One epidemiological study reported that about 3% of the general population

in the U.S. has experienced OCD.¹ This prevalence is 20 times higher than previously expected. This result suggests that OCD is more common than schizophrenia or panic disorder, which are both well-known by the general population. In Korea, an epidemiological study² reported that the lifetime prevalence of OCD in urban and rural populations were 2.29% and 2.14%, respectively. The causes of OCD are still unclear, but there is growing evidence that OCD has some specific neurobiological bases, and that one of these is a genetic component. The familial tendency of OCD has been observed since the 1930s using genetic studies of OCD. These included twin, family, segregation, and association studies, and revealed that some specific genes have an effect on the development of OCD.³ Therefore, we reviewed in this paper studies concerning the genetics of OCD using various ethnic groups, including Koreans.

TWIN STUDIES

Many researchers have used twin studies to estimate the relative importance of genetic and environmental factors in the development of OCD. If the concordance rate of a certain disorder between monozygotic (MZ) twins is 100%, we can conclude that the disorder is most likely purely genetic. If the MZ concordance rate is less than 100%, it means that the disorder is likely caused by a mixture of genetic and environmental factors. Also, if the concordance rate between MZ twins is much higher than that of dizygotic twins (DZ), it can be considered that a genetic component contributes substantially to the pathophysiology of the disorder.³ Inouye et al.⁴ reported an 80%

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concordance rate of obsessional neurosis among ten pairs of Japanese MZ twins, as compared to a 50% concordance rate among four pairs of DZ twins. Carey and Gottesman⁵ found an 87% concordance rate of obsessive symptoms and features between MZ twins (47% in DZ twins) from the Maudsley Twin Register. In addition, the response to clomipramine⁶ or sertraline⁷ has appeared to be more similar in MZ twins than for DZ twins. Most recently, van Grootheest et al.⁸ reviewed past twin researches. They concluded that only the studies which used a dimensional approach and analyzed the data with Structural Equation Modeling have convincingly shown that obsessive-compulsive (OC) symptoms are heritable in children, with genetic influences in the range of 45% to 65%. In adults, studies suggest a genetic influence on OC symptoms, ranging from 27% to 47%. In summary, although most twin studies have important limitations, such as inconsistent diagnostic criteria and small sample sizes, all the results consistently found higher concordance rates for MZ twins than for DZ twins. However, the fact that the MZ concordance rate is not 100% indicates that environmental factors, such as birth complications and other physiological vulnerabilities, may have an impact on the development of OCD.⁹

FAMILY STUDIES

Because family is not only a unit for genetic transmission, but also a transmission of environmental and cultural backgrounds, familial aggregation is not sufficient to prove that the disorder is genetically transmitted. The family study method compares the rates of illness in families with those in the general population. There are two types of methods in family study: the family history method and the family study method.

Family history method

The family history method is used to determine the prevalence of a disease in relatives by relying on a single informant to report diagnostic information on all first-degree relatives. Lewis et al.¹⁰ reported a rate of 32.7% for pronounced obsessive traits in a sample of 306 first-degree relatives of

patients with OCD. Rasmussen and Tsuang¹¹ presented a family history of a clinical sample of 44 patients who met the DSM-III criteria for OCD. They reported that 4.5% of parents of the OCD patients met the full criteria for OCD and another 11.4% of parents had significant OC traits. A number of first-degree relatives of these patients also had probable OCD or obsessive traits. Riddle et al.¹² reported that 71% of the clinically referred children with OCD had a parent with either OCD or OC symptoms.

Family study method

The family study method uses a strategy of obtaining diagnostic data by directly interviewing all available relatives. This method relies on a personal assessment of all first-degree relatives to obtain diagnostic information. In 1992, Bellodi et al.¹³ reported that the morbidity risk for OCD in patients' families accounted for 3.4%. When 21 patients with an age of onset under 14 years were examined, the morbidity risk in first-degree relatives reached 8.8%, compared with 3.4% among the relatives of 71 later-onset probands.¹³ Using a structured interview, Paul et al.¹⁴ directly interviewed all available first-degree relatives of 100 probands with OCD. They found that the rates of OCD and subthreshold OCD were significantly greater among relatives of probands with OCD (10.3% and 7.9%, respectively) than among the comparison subjects (1.9% and 2.0%, respectively). Nestadt et al.¹⁵ also reported that the lifetime prevalence of OCD was significantly higher in cases with OCD relatives when compared with control relatives (11.7% vs. 2.7%). Probands with tics or OC personality disorder were not more likely to have relatives with OCD than those without these features. Recently, two direct interview family studies of OCD were published. Fyer et al.¹⁶ reported that a significantly higher risk for OCD, but not other anxiety disorders, was found in relatives of OCD probands when compared to relatives of controls. There was no relationship between the proband age at onset of OCD and the strength of familial aggregation. However, the same group¹⁷ found that, when relative diagnoses were derived without the benefit of proband informant reports, no evidence of familial OCD

transmission was found. When diagnoses were made including information from the proband about the relative, evidence of familial OCD was found, but only when the diagnostic threshold was lowered to include cases with probable OCD or OCD symptoms. Evidence for familial transmission of OCD was found only when diagnoses were made using information from the affected proband about their relatives. Therefore, they concluded that their own inconsistent results suggest that OCD may be heterogeneous with regard to familial transmission.

SEGREGATION ANALYSES

Once familial aggregation of OCD is established by twin studies and family studies, the next step is to determine whether the patterns within families are consistent with genetic models. Although segregation analysis cannot prove the existence of genes, if the analyses reveal that the patterns within families closely follow a pattern predicted from basic Mendelian principles, genetic factors are likely an essential factor in the cause of the disorder.³ Five complex segregation analyses have implicated a major locus in a proportion of families with OCD.¹⁸⁻²² Nicolini et al.²³ collected data from 24 OCD probands and reported that either an autosomal dominant or recessive model could not be rejected. Cavallini et al.²⁰ applied a complex segregation analysis to a sample of 107 Italian families with probands with OCD using regressive logistic models to test for possible models of genetic transmission. For the 107 OCD families, the best fit was a dominant model of transmission (with a higher penetrance for females), but this did not include an expanded phenotype (OCD + Tourette's syndrome + chronic motor tics). In addition, Alsobrook et al.²² performed complex segregation analyses with families ascertained through an OCD-affected proband. Their segregation analyses used four factor-analytic symptom dimensions to subset the family sample based upon the probands' symptom factor scores to resolve the phenotypic heterogeneity observed among individuals with OCD. Analyses limited to families' probands with high symmetry and ordering symptoms led to rejection of the

polygenic model, indicating the involvement of a major locus. However, they also could not identify a specific Mendelian model. Nestadt et al.¹⁸ performed complex segregation analyses of the 153 families (80 case and 73 control) included in the Johns Hopkins OCD Family Study. They found strong evidence that OCD involved a major gene and conformed to a Mendelian-dominant model, with significant sex effects and residual familial effects. Recently, Hanna et al.¹⁹ studied 52 families (35 case and 17 control families) through pediatric probands (10 - 17 years). Their results of complex segregation analyses provided evidence for a major susceptibility locus in OCD when age at onset was incorporated into the model. These results suggest that the mode of inheritance may be influenced by the residual effects of an affected parent, which provides further evidence for the etiologic heterogeneity of OCD. The dominant Mendelian model provided a somewhat better fit than the other Mendelian models.

In summary, the previous five segregation studies indicate that the familial transmission of OCD is caused by genetic factors. Although some studies suggested a possible dominant model, the mode of transmission is generally difficult to model. This might be due to the fact that OCD is an etiologically and clinically heterogeneous condition. Thus, several genes may influence the behavioral component of OCD, and a mixed model involving several genes of major effect on a multigenic background seems to fit the mode of transmission of OCD.

LINKAGE ANALYSES

Once it has been demonstrated that genetic transmission accounts for at least some of the familiarity of a disorder, the next logical step is to locate the susceptibility genes. The purpose of a linkage study is to demonstrate that a DNA-marker with known chromosomal localization congregates with a disease in families.³ Weissbeck et al.²⁴ studied a three-generation family transmitting OCD and tic disorders and reported that the highest LOD score found was 1.3 in the 4p13 chromosome region. To date, several genome-wide linkage studies of OCD have been pub-

lished. Hanna and his colleagues²⁵ analyzed a genome scan in 56 individuals from seven families ascertained through pediatric OCD probands; 27 of the 56 subjects had a lifetime diagnosis of definite OCD. Their genome scan consisted of 349 microsatellite markers with an average between-marker distance of 11.3 cM. They found that the maximum multipoint LOD score with a dominant model was 2.24 on 9p24. This result was also replicated by Willour et al.²⁶ when they genotyped 50 pedigrees with OCD using microsatellite markers spanning the 9p24 candidate region. They also reported that a 9p24 signal was observed in both parametric and nonparametric linkage analyses. Recently, Shugart et al.²⁷ conducted a genome-scan analysis of 219 families collected as part of the OCD Collaborative Genetics Study. Using the broad OCD definition, they observed the strongest evidence for linkage was on chromosome 3q27-28. Covariate-linkage analyses implicated a possible role of gene on chromosome 1 in increasing the risk for an earlier-onset form of OCD.

ASSOCIATION STUDIES

Whereas linkage analysis focuses merely on the position of a tested marker, an association study tests whether a particular allele of a marker, a specific genotype, or a haplotype is statistically associated with affected individuals when compared to unaffected controls. Two design strategies are employed in association studies: population case-control designs and family-based association designs. Currently, the major approach used in identifying OCD susceptibility genes has been to compare the distribution of genotypes or alleles of genes implicated in the neurophysiology of OCD using population- or family-based association studies.²⁸

Genes related to serotonin neurotransmission

Studies performed over the last decade have implicated the involvement of the serotonin (5-HT) system in the pathophysiology of OCD. The number of [³H] paroxetine binding sites in blood platelets has been found to be significantly lower

in OCD patients than in normal controls.²⁹ It has also been reported that m-chlorophenylpiperazine (m-CPP), a serotonergic agent, exacerbates OC symptoms.^{30,31} In addition, the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of OCD has led to the hypothesis of a serotonergic dysfunction in OCD. Therefore, most widely-investigated candidate genes of OCD are genes related to serotonergic neurotransmission.

Serotonin transporter gene

Since the serotonin transporter (5-HTT) is the primary target of action of SSRIs, the 5-HTT gene located on chromosome 17q12 may be a good candidate for OCD treatment. The serotonin transporter gene has a functional biallelic polymorphism in the promoter region,³² consisting of an insertion (long allele, L) or a deletion (short allele, S) of 44 bp, which has been shown to have a significant effect on blood serotonin concentration.³³ McDougle et al.³⁴ used a family-controlled transmission disequilibrium test (TDT) with a set of 34 European-American family trios of OCD and found that the association and linkage disequilibrium between the 5-HTT linked the promoter region (5-HTTLPR) gene L allele with OCD. They also reported that a poor response to SSRIs might be related with the L allele. Bengel et al.³⁵ recruited 75 Caucasian OCD patients and 397 ethnically-matched individuals from a non-patient control group and found that the patients with OCD were more likely than controls to carry two copies of the L allele (46.7% vs. 32.3%). However, Kinner et al.³⁶ did not find any significant association between the distribution of the 5-HTTLPR genotypes and OCD in 54 OCD patients of Afrikaner descent and 82 ethnically-matched control individuals. Camarena et al.³⁷ analyzed the 5-HTTLPR polymorphic system in 115 Mexican OCD patients and 136 controls. They could not find a significant association between the L allele and OCD in both case-control and family-based designs, including haplotype-based haplotype relative risk (HHRR) and TDT. Many other studies performed in various populations including Jewish,³⁸ German,³⁹ French,⁴⁰ etc.⁴¹ also did not find a significant association between 5-HTTLPR polymorphism and OCD.

In Korea, there has been only one study of the association between 5-HTTLPR and OCD. We

genotyped and phenotyped both 124 OCD patients and 171 normal controls but could not find any association between 5-HTTLPR polymorphism and the development of OCD. However, in the OCD group, patients with the L/L + S/L genotype had higher scores for the religious/somatic factor derived from 13 main contents of the Yale-Brown obsessive-compulsive symptom (Y-BOCS) checklist than those with the S/S genotype.⁴² The frequencies for the 5-HTTLPR genotype in our sample revealed a higher percentage (63 - 64%) of the S/S genotype and a very lower percentage (3%) of the L/L genotype, which were quite different from those determined from a Western population, where a higher percentage (32 - 47%) of the L/L genotype and a relatively lower percentage (14 - 15%) of the S/S genotype were found.³⁵

Recently, other single-nucleotide variants have been detected within HTTLPR,⁴³ and one of them is an A→G SNP which is located 1,629 bp upstream of the transcription start point. Because this G is a sequence variation that always occurs in the context of the L allele of HTTLPR in which it alters AP2 transcription factor binding and suppresses transcription, the A and G alleles are referred to as L_A and L_G. Therefore, the two L alleles L_A and L_G, together with the S allele, comprise a triallelic locus of 5-HTTLPR,⁴⁴ and unrecognized L_G alleles in S/L and L/L genotypes can create the appearance of S allele dominance because certain L_G-containing genotypes tend not to be high expressing.⁴⁴ Hu et al.⁴⁴ reported that the gain-of-function L_AL_A genotype was approximately twice as common in 169 whites with OCD than in 253 ethnically matched controls, which means it has a moderate (1.8 fold) effect on the risk of OCD. They also analyzed a TDT test using 175 trios consisting of probands with OCD and their parents, and they found that the L_A allele was overtransmitted to the patients with OCD by twofold.

Serotonin receptor genes

Among many serotonin receptor subtypes, the 5-HT_{2A} receptor has been the most important in the etiology and treatment of OCD. The activation of postsynaptic 5-HT_{2A} and 5-HT_{2C} receptors may be important in the improvement of OCD symptoms after treatment with an SSRI.⁴⁵ Studies in OCD patients showed blunted prolactin and

cortisol responses to 5-HT₂ receptor agonists.⁴⁶ Enoch et al.⁴⁷ recruited and genotyped 101 Caucasian OCD patients (48 females, 53 males) and 138 control subjects (77 females, 61 males) and found that the -1438A allele frequency was higher only in female OCD patients and not in male patients. Walitza et al.⁴⁸ performed an association analysis of 5-HT_{2A} polymorphism in 55 German children and adolescents with OCD, and also in 223 controls, and confirmed the association between the -1438A allele of the 5-HT_{2A} gene and juvenile OCD. Meira-Lima et al.⁴⁹ examined the allelic and genotypic frequencies of the T102C and C516T variants of the 5-HT_{2A} gene in 79 Brazilian OCD patients and 202 control subjects. Although they did not find any significant differences in the frequencies of allele and genotype for the T102C 5-HT_{2A} gene polymorphism, they found a significant association between C516T 5-HT_{2A} gene polymorphism and OCD. Tot et al.⁵⁰ analyzed 58 Turkish OCD patients and 83 controls. Although they could not find significant differences in genotype distribution for either T102C or -1438 G/A polymorphism of 5-HT_{2A} between the two groups, they found that the TT genotype for T102C and AA genotype for -1438 G/A polymorphism of 5-HT_{2A} were significantly higher in the patients with severe OCD compared to those with moderate to severe OCD. Other studies did not find a significant association between -1438 A/G polymorphism^{28,38,51} or T102 polymorphism²⁸ and OCD.

Some researchers have found that the activation of the 5-HT_{2C} receptor induces self-grooming in rats.⁵² This result supports the hypothesis that selective stimulation of central 5-HT_{2C} receptors exacerbates symptoms in OCD. It has also been reported that m-CPP, which stimulates 5-HT_{2C} receptor, exacerbates OC symptoms.^{30,31} These studies provide support for the possible involvement of 5-HT_{2C} receptors in the etiology of OCD. Cavallini et al.⁵³ investigated the role of the Cys23Ser mutation of the 5-HT_{2C} receptor gene in OCD by performing an association study comparing a sample of 109 Italian OCD patients with a sample of 107 healthy control subjects. However, they did not find any allelic or genotypic association between OCD and the 5-HT_{2C} receptor gene. Frisch et al.³⁸ also performed a similar study in

Jewish OCD patients and did not find any significant association between 5-HT_{2C} receptor polymorphism and OCD.

The 5-HT_{1D} β receptor appears to be particularly interesting in the pathophysiology of OCD. The 5-HT_{1D} β receptor is a terminal autoreceptor involved in the regulation of 5-HT synthesis and release, and is expressed mostly in the limbic region and in the striatum. Gross-Isseroff et al.⁵⁴ reported that sumatriptan, a selective 5-HT_{1D} β agonist, caused significant OCD symptom exacerbation. In addition, Stern et al.⁵⁵ found that the continuous administration of sumatriptan could reduce depression and OC symptoms in three refractory OCD patients. To date, only eight studies of the association between the 5-HT_{1D} β gene and OCD have been reported. Two family-based association studies by Mundo et al.^{56,57} reported that the G861 allele of the 5-HT_{1D} β gene was preferentially transmitted to OCD patients. However, other family-based studies by Camarena et al.,⁵⁸ Di Bella et al.,⁵⁹ and Walitza et al.³⁹ did not replicate this result. The other two case-control studies^{28,60} also did not find any association between 5-HT_{1D} β G861C polymorphism and OCD. In Korea, we investigated the association 5-HT_{1D} β G861C and OCD but could not find any significant associations (unpublished).

Tryptophan hydroxylase (TPH) gene

TPH is the rate-limiting enzyme in the synthesis of 5-HT. Therefore, it has been considered that the variant in TPH may influence serotonin turnover and behaviors controlled by serotonin, such as OCD.⁶¹ To date, only three studies of the association between the TPH1 or 2 genes and OCD have been published. Frisch et al.³⁸ found no association between TPH1 and Jewish OCD patients. Walitza et al.³⁹ also did not find transmission disequilibrium for alleles of the SNP rs1800532 (TPH1 gene) in patients with early onset OCD using a TDT test. The TPH2 gene has been recently found and received attention because its mRNA was detected exclusively in the brain.⁶² Mossner et al.⁶³ investigated the association between TPH2, the gene of the novel brain-specific TPH2, in OCD and its role in childhood and adolescent-onset OCD. In analysis of the SNPs, rs4570625 and rs456946 of TPH2, they

found a significant preferential transmission of haplotype G-C to OCD. They also found a trend of preferential transmission of the C allele of SNP rs4565946 to the early-onset of OCD.

Genes related to dopamine neurotransmission

As mentioned above, the most prevailing hypothesis on the mechanism of OCD is the serotonin hypothesis. However, about 40% of OCD patients do not respond to SSRIs, and some patients show no convincing functional abnormalities related to serotonin.⁶⁴ Furthermore, the serotonin system varies and is interrelated with other neurotransmitters or neuronal circuits.⁶⁴ Therefore, apart from the main hypothesis suggesting serotonin abnormalities, some authors have proposed that dopamine could participate in the pathophysiology of OCD.⁶⁵ When high concentrations of dopamine-related drugs, such as amphetamine and bromocriptine, were administered in animal studies, stereotypic behaviors similar to the obsessive behaviors in OCD patients were observed.⁶⁵ Administration of dopamine receptor inhibiting drugs in combination with an SSRI reduced obsessive symptoms in OCD patients who had previously shown resistance to treatment with an SSRI alone.⁶⁶ Similarly, there have been reports that OC symptoms have emerged during treatment with clozapine, a dopamine receptor D₄ (DRD₄) antagonist.⁶⁷ This evidence obtained from neuroanatomical and pharmacological data suggests that the dopaminergic neurotransmitter system may also be implicated in mediating OCD.

Dopamine transporter gene (DAT1)

The DAT1 gene is located on chromosome 5p15.3 and has 40 bp variable numbers of tandem repeats (VNTR, with 3 - 11 repeats) on the 3'-untranslated region.⁶⁸ There is some possibility that these VNTR have an effect on the gene expression and the level of DAT1 protein in the brain.⁶⁹ However, there have only been a few studies examining the association between DAT1 and OCD. Frisch et al.³⁸ reported that there was no association between the DAT1 gene and OCD in Jews, and Hemmings et al.²⁸ also did not find any difference in the distribution of DAT1 VNTR between the OCD and control groups. In Korea,

we investigated the differences of genotype distributions of the DAT1 gene between 115 OCD patients and 160 normal controls.⁷⁰ Because a previous study showed that the 10-repeats allele is reported to increase DAT1 gene expression compared with the 7-, 9-, and 11-repeats alleles,⁷¹ we classified the genotype of DAT1 into 10/10-repeats and non-10/10-repeats groups. However, we did not find any significant association between the DAT1 gene and OCD. Also, there were no significant differences in total Y-BOCS scores, global assessment of functioning scores, and total Hamilton depression rating scale scores between the patients with 10/10-repeats and non-10/10-repeats genotypes in OCD patients. Considering our results, in consideration with the combined results of the two previous studies, suggest that DAT1 gene polymorphism is not likely to confer susceptibility to OCD.

Dopamine receptor genes

Because of the phenomena of emerging OC symptoms after treatment with clozapine, the DRD4 gene has been the focus of genetic studies of OCD. The DRD4 gene was characterized by the insertion of 2-10 of 48 bp imperfect tandem repeats in the encoding region of the third exon.⁷² Billet et al.⁷³ genotyped more than 118 Canadian OCD patients for DAT1 (40 bp VNTR), DRD2 (TaqIA), DRD3 (MscI), and DRD4 (48 bp VNTR). They found significant differences in allele frequencies between patients and controls only for the DRD4 gene. However, Frisch et al.³⁸ reported that there were no significant differences of genotype distributions of DRD4 between OCD and control patients. Hemmings et al.²⁸ also reported negative results in an Afrikaner population. Meanwhile, Millet et al.⁷⁴ found different results from both a French family-based and population-based association studies. In their study, an extended transmission-disequilibrium test for preferential allele transmission in OCD showed an absence of transmission of 2-repeats allele of DRD4 gene (48 bp VNTR). In a population-based association study, they found a significantly lower frequency of 2-repeats allele in OCD than in controls. Recently, a study showed a significantly lower frequency of the DRD4 VNTR 7-repeat allele of early onset OCD than that of late-onset OCD in

South African Caucasians, but not in Afrikaners.⁷⁵ In Korea, we classified the DRD4 genes (48 bp VNTR) of 115 OCD patients to the short genotype (genotype with at least one copy of the 2-repeats) and long genotype (genotype without a 2-repeats). We could determine that the short genotype frequency of DRD4 was significantly higher in OCD patients than in normal control groups.⁷⁶ However, contrary to a previous study by Hemmings et al.,⁷⁵ we found no difference in genotype frequencies between the early-onset OCD (age of onset < 17) group and the late-onset OCD (age of onset ≥ 17) group.⁷⁶ In conclusion, there are still inconsistent results of the association between the DRD4 gene and OCD, but some studies⁷⁴ (including ours⁷⁶) suggest the possibility that the 2-repeats allele or a nearby genetic variation could have a protective effect against OCD symptoms.

There have only been a few studies on the DRD2 gene in OCD. Nicollini et al.⁵¹ performed an association analysis of the DRD2 and DRD3 gene in 67 OCD patients and 54 controls. Although they did not observe any significant associations between these genes and OCD, they found a higher frequency of A2/A2 of DRD2 in OCD patients with tics (N = 12). As mentioned above, Billet et al.⁷³ also did not find a significant association between DRD2 and OCD. Most recently, Denys et al.⁷⁷ examined 150 OCD patients (56 males) and 150 controls (79 males). They could not find any significant differences in genotype distribution of DRD2 between the two groups. However, when they stratified the sample by gender, they found higher frequency of the DRD2 A2 allele in male OCD patients compared to male controls. However, their sample size of male OCD patients seemed too small to draw a definite conclusion, and further analysis of larger samples is warranted to confirm their data.

To date, there have been only three studies concerning the associations between the DRD3 gene and OCD. All of these studies showed no association between the Ser9Gly variant of DRD3 gene and OCD.^{51,73,78}

Genes related to the metabolism of neurotransmitters

Catechol-O-methyltransferase (COMT) is an en-

zyme involved in the inactivation of catecholamines, including adrenaline, noradrenaline, and dopamine. A polymorphism in the human COMT gene (G472A) results in a valine (Val) to methionine (Met) amino acid substitution (Val158Met) and also reduces the activity of the enzyme to one quarter of that encoded by the Val allele.⁷⁹ The alleles are codominant, and heterozygotic patients (Val/Met genotype) have intermediate levels of COMT activity in comparison to homozygous individuals.⁸⁰ There have been several studies about the possible role of the COMT gene in OCD. Karayiorgou and colleagues performed population-based⁸¹ and family-based association⁸² studies and reported that in both studies the low activity allele (Met158) is significantly associated with susceptibility to OCD in males only. Contrary to these results, Schindler et al.⁸³ used a family-based population analysis and demonstrated a tendency for an association between homozygosity (Met/Met or Val/Val) at the COMT locus and OCD. Alsobrook et al. collected 56 OCD probands and their parents, and reported a mildly significant association with the low-activity COMT allele in female probands of OCD, but not in male probands. Their findings of gender dimorphism contradict previous results by Karayiorgou and colleagues.^{81,82} Meanwhile, some researchers have reported that the heterozygous genotype (Val/Met) was significantly more common than expected in the Afrikaner OCD population.⁸⁴ However, other researchers could not find any significant associations between the COMT gene and OCD.^{49,85,86} In Korea, we analyzed the genotype of COMT in 124 OCD patients and 170 normal controls, but we did not find any differences of genotype distribution between the two groups (unpublished).

MAOA is another important enzyme that degrades biogenic amines (noradrenaline, serotonin, and, to a lesser degree, dopamine). There are two polymorphisms which are related to the level of enzymatic activity.⁸⁷ The first polymorphism, which is located 1.2 kb upstream of the MAOA coding sequences, consists of a 30 bp repeated sequence present in 2-, 3-, 3.5-, 4-, or 5-repeats, and it has been designated MAOA-uVNTR. This polymorphism is functional, in that 3.5-, 4- and 5-repeats are transcribed 2-3 times more efficiently

than those with 3- and 2-repeats.⁸⁸ The second polymorphism is a T to C substitution on exon 14 (EcoRV), and the T allele is related to lower enzyme activity.⁸⁷ Camarena et al.⁸⁹ examined the MAOA-A/EcoRV polymorphism in a sample of 122 OCD patients and 124 healthy subjects and found that the T allele was associated with OCD in female patients by family-based and population-based association studies. However, Hemmings et al.²⁸ did not find any association between EcoRV of the MAOA gene and OCD. In Korea, we recruited 121 OCD patients (81 males and 40 females) and 276 controls (138 males and 138 females). In Korea, we found that male OCD patients had a higher frequency of 3-repeats of MAOA-uVNTR than normal male controls (64.2% in OCD vs. 47.8% in control, unpublished), but we did not find this association in female OCD patients. Although more larger-scale studies are warranted, our results (including several previous studies^{82,89}) indicate the possibility of an association between the MAOA gene and OCD and its gender dimorphic effects.

Other genes

In addition to monoamines, there have been other putative neurotransmitters or neurotrophic factors playing a role in the development of OCD, such as glutamate, GABA, and brain-derived neurotrophic factor (BDNF).

Using the family based association test, Arnold et al.⁹⁰ tested for an association of the glutamate receptor, ionotropic, N-methyl-d-aspartate 2B (GRIN2B) with OCD in 130 families and found that GRIN2B may be associated with a susceptibility to OCD. Regarding glutamate receptor ionotropic kainate 2 (GRIK2) and 3 (GRIK3), Delorme et al.⁹¹ performed a case-control study in 156 patients and 141 controls, and also a transmission disequilibrium test in 124 parent-offspring trios. Although there were no associations of GRIK3 S301A or GRIK2 rs2227281 (intron 14) and rs2227283 (exon 15) with OCD in the case-control or family-based analyses, the GRIK2 SNP 1867 allele (rs2238076) in exon 16 was transmitted less than expected in OCD.

Recently, there has been increasing evidence that the major inhibitory neurotransmitter, GABA,

may also be functionally involved in OCD. Zai et al.⁹² investigated five polymorphisms in the GABA type B receptor 1 (GABBR1) gene in 159 OCD probands and their families using the TDT, and they found a trend with an over-transmission of the -7265A allele at the A-7265G polymorphism in OCD.

Hall et al.⁹³ evaluated a possible role of the BDNF gene in 164 triads with OCD and suggested that the Met66 allele, which affects the sequence of the proBDNF protein, is undertransmitted and likely confers a protective effect against OCD.

FUTURE DIRECTIONS

The genetic research of OCD has been much advanced during the past decade. However, like in other psychiatric disorders, the genetic study of OCD has several limitations that should be overcome. First, OCD is not a homogenous condition, and there might be various underlying etiological mechanisms of OCD. Therefore, the ability to define genetically valid subgroups of OCD is crucial for genetic studies of OCD. Miguel et al.⁹⁴ suggested several strategies for identifying valid OCD phenotypes as follows. 1) The categorical approaches: early-onset OCD phenotype, tic-related OCD phenotype and sensory phenomena as a component of the OCD phenotype, and 2) the dimensional approaches: OCD symptom dimensions and quantitative personality traits related to OCD. Another approach to identify more homogenous OCD subtypes is to find endophenotypes, including brain-based markers (i.e., neuroimaging and neurophysiological findings). Second, the genotypes' distribution of genes is not the same according to ethnicity. As mentioned above, genotype distributions of various genes in Asians (including Koreans) are quite different from those in the Western population. Therefore, it could not be assumed that the results from Western populations would be replicated in Asian populations, including Koreans. In addition, most genetic studies of OCD did not have a sufficient sample size to draw clear conclusions. Therefore, if more large-scale studies using large sample sizes would be performed in various populations, it would be helpful to understanding the genetic contribution

to OCD.

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