Sex Differences in Genetic and Environmental Influences on Obsessive–Compulsive Symptoms in South Korean Adolescent and Young Adult Twins

Yoon-Mi Hur[1] and Hoe-Uk Jeong[2]

[1] *Chonnam National University, Gwangju, Korea*
[2] *Mokpo National University, Mokpo, Korea*

Recent molecular genetic studies provide suggestive evidence for sexual dimorphism in genetics of obsessive-compulsive disorder. However, only a few twin studies have addressed the question of sex differences in genetic and environmental contributions to variation of obsessive–compulsive symptoms. The aim of the present study was to estimate genetic and environmental influences on obsessive–compulsive symptoms in South Korean twins, with a special emphasis on sex difference. In total, 751 adolescent and young adult twin pairs (ages: 13–23 years) completed a Korean version of the 30 items of the Maudsley Obsessional — Compulsive Inventory (MOCI) through a mail survey. A sum of the answers for the 30 items was calculated to represent a total score for obsessive–compulsive symptoms (hereafter, the MOCIT). Males had significantly higher variance of the MOCIT than did females. In males, monozygotic (MZ) twin correlation was significantly higher than dizygotic (DZ) twin correlations (.56 vs. .24), whereas in females, MZ and DZ twin correlations were not significantly different from each other (.39 vs. .36). The general sex-limitation model was applied to the twin data. The results of model-fitting analyses indicated that the unstandardized genetic variance as well as heritability estimate (53% vs. 41%) for the MOCIT was higher in males than in females. However, shared environmental influences did not attain statistical significance perhaps due to insufficient statistical power.

Obsessive–compulsive disorder (OCD) is a complex phenotype with heterogeneous symptom dimensions. Symptoms of OCD include recurrent, distressing, unwanted thoughts, impulses, and images (obsessions) and repetitive behaviors and mental acts (compulsions; American Psychiatric Association, 1994). Symptoms of OCD measured by the questionnaire method have shown to predict a clinical diagnosis of OCD (Heyman et al., 2006). OCD has been shown to be comorbid with tics, Tourette syndrome, and mood and anxiety disorders (Bolton et al., 2007; Miguel et al., 2005). The World Health Organization rates OCD as one of the top 20 most disabling diseases. OCD has similar prevalence rates (approximately 2–3%) cross-culturally around the world (Björgvinsson et al., 2007). The lifetime prevalence rate of OCD among South Koreans has been reported to be 2.1% (Lee, 1994).

Family studies have shown significant increases in the risk of the disorder in relatives of affected probands compared with relatives of controls, supporting genetic etiology of OCD (Nestadt et al., 2000; Pauls et al., 1995). Twin studies also provide evidence for a genetic component in variation of symptoms of OCD. In a recent review of twin studies, van Grootheest et al. (2005) concluded that genetic influences on OCD ranged from 45% to 65% in children and from 27% to 47% in adults when one considered symptom dimensions instead of categorical diagnosis.

While genetic influences on OCD have been relatively well documented, sex differences in genetic factors in OCD have scarcely been studied, and existing studies produced mixed results. Lenane et al. (1990) reported a significantly higher rate of OCD in fathers of OCD children (25%) than in mothers of those children (9%), suggesting marked sex effects on the etiology of OCD. Hudziak et al. (2004) examined genetic and environmental contributions to the Childhood Behavior Checklist Obsessive–Compulsive scale (CBCL-OCS) in the United States and Dutch twins (ages 7–12 years). While Dutch twins demonstrated no sex difference in genetic factors for the score of the CBCL-OCS, the United States twins showed higher genetic influences in boys than in girls (55% vs. 45%). Significant shared environmental

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Address for correspondence: Yoon-Mi Hur, Department of Psychology, Chonnam National University, Gwangju, South Korea. E-mail: ymhur@snu.ac.kr

influences (16%) on CBCL-OCS were observed only in Dutch twins, but the magnitudes of influences were equal in males and females.

Epidemiological studies of OCD have suggested sex difference in the prevalence of OCD. Among children and adolescents, symptoms of OCD are more frequent in males than in females, but the prevalence is reversed in adults (Fireman et al., 2001; Fontenelle & Hasler, 2008; Heyman et al., 2001). Sex differences in clinical features of OCD have also been noted. For example, Lochner et al. (2004) found that males with OCD tended to have an earlier age of onset, and show more tics and worse outcome than did females. Lochner et al. (2004) also noted that female OCD patients had changes in obsessive–compulsive symptoms in the premenstrual/menstrual period, during pregnancy, and with menopause, suggesting that hormones may play a role in symptom variations. Others have claimed that washing rituals and contamination fears were more common in females than in males, whereas checking and symmetry compulsions were more common in males than in females (Castle et al., 1995; Rasmussen & Eisen, 1988). Along with genetic influences on OCD documented by twin and family studies, these clinical and epidemiological research findings indicate the possibility of sex difference in genetic mechanisms for the development of OCD.

The aim of this study was to explore genetic and environmental influences on symptoms of OCD in an unselected sample of South Korean adolescent and young adult twins, with a special emphasis on sex difference. The present investigation is the first to report genetic and environmental factors in symptoms of OCD on the basis of East Asian population. Finding sex difference in the genetic etiology of symptoms of OCD has an important implication for association studies to identify genes for OCD.

Methods

Sample

The sample was drawn from the South Korean Twin Registry (SKTR; Hur et al., 2006). The SKTR is a nationwide volunteer registry of South Korean twins and their families. In 2006, a mail survey including a Korean version of the Maudsley Obsessional — Compulsive Inventory (MOCI) was sent to adolescent and young adult twins registered with the SKTR who were living in Seoul and three counties in South Korea. These areas were selected for the mail survey in 2006 because at the time of the mail survey, permissions for the participation in research had been obtained from the twins in these areas. The overall response rate of the mail survey in 2006 was approximately 32%.

Twins' zygosity in the SKTR was determined from the twins' parents' responses to a zygosity questionnaire that included questions regarding physical similarities and frequency of confusion by family members and others. When compared to the analysis of DNA markers, this questionnaire method to determine zygosity has yielded over 90% accuracy in Asian twin samples (Ooki et al., 1993). To maximize the accuracy in zygosity classification, however, 43 pairs of the twins whose zygosity was ambiguous were excluded from our analyses. The final sample included 751 twin pairs consisting of 186 pairs of male monozygotic twins (MZM), 337 pairs of female MZ twins (MZF), 60 pairs of male dizygotic twins (DZM), 65 pairs of female DZ twins (DZF), and 103 pairs of opposite-sex DZ twins (OSDZ). The number of MZ twins was much higher than that of DZ twins in the present sample, which reflected the twin birth rates in the South Korean population (Hur & Kwon, 2005). The present sample also had an overrepresentation of female twins, partly because some of the young adult male twins were in the military service at the time of the mail survey as males in South Korea have an obligation to army service. The age of the present sample ranged from 13 to 23 years, with a mean of 16.9 years and a standard deviation of 2.4 yrs.

Measure

The Korean version of the MOCI included 30 true-false items designed to measure obsessive–compulsive complaints (Shin et al., 2001). The Korean version was adopted from the MOCI developed by Hodgson and Rachman (1977), and has been extensively studied (Shin et al., 2001). The MOCI encompasses a broad range of obsessive–compulsive symptoms such as checking and cleaning habits, slow repetitive behaviors, and serious doubts about simple daily activities. The MOCI has been shown to reliably discriminate between obsessional patients and normals (e.g., Emmelkamp et al., 1999). Although the authors of the MOCI recommended the use of both the total score and subscale scores (Hodgson & Rachman, 1977), we decided to use the total score only in this study as the reliabilities of the subscales were somewhat low. Thus, the total score of the MOCI (hereafter, MOCIT) used in the present study represents an aggregate of various OCD symptoms. Hodgson and Rachman (1977) showed that the mean score of the MOCIT in obsessional patients was 18.86. The distribution of the MOCIT in the present sample was somewhat positively skewed (skewness = .50 and kurtosis = .15). The internal consistency reliability of the 30 items was .76.

Statistical Methods

To estimate genetic and environmental contributions to the variation of the MOCIT, correlations for the five groups of twins (MZM, MZF, DZM, DZF, and OSDZ) were computed and the general sex-limitation model (Neale & Cardon, 1992) was applied to the twin data. Prior to correlational and model-fitting analyses, effects of zygosity, birth order, sex, and age were examined.

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The general sex-limitation model in the present study included additive genetic (A), and shared (C) and individual specific environmental (E) factors, each of these factors was allowed to vary across sexes to determine sex difference in the magnitude of genetic and environmental influences on obsessive–compulsive symptoms (Neale & Cardon, 1992). The A factors, the sum of the average effect of all genes that influence a trait, correlated at 1.0 and .5 for MZ and same-sex DZ twins, respectively. For OSDZ twins, however, the correlation for the A factors was allowed to vary between 0 and .5, assuming that some of the genes that influence obsessive-compulsive symptoms may be different between males and females. The C factors, those environmental factors that the two members of a twin pair share, correlated at 1.0 for both MZ and DZ twins. Finally, the E factors, environmental factors that are unique to each member of a twin pair and measurement error represented the remaining variance not explained by additive genetic or shared environmental factors.

The raw data option in Mx (Neale et al., 2003) was used for model-fitting analyses. Variations of the general sex-limitation model were made to determine the best fitting model. First, the fit of the general sex-limitation model was compared to that of the saturated model where variances and means of the first- and the second-born MZ and DZ twins were allowed to vary. Next, the fit of the general sex-limitation model was compared to the fit of a series of reduced models. Mx calculates twice the negative log-likelihood (–2LL) of the data. As the difference in –2LL is chi-square distributed with degrees of freedom equal to the difference in degrees of freedom, the likelihood ratio test was used to evaluate alternative models. In all models, age was treated as a covariate to control their main effects on the means.

Results

Descriptive Statistics and Twin Correlations

Table 1 provides descriptive statistics and maximum likelihood correlations for the five groups of twins. Males and females were not significantly different in the mean of the MOCIT. However, males had significantly higher variance of the MOCIT than did females. Age was not significantly related to the MOCIT in any of the two sexes in the present sample. There was no significant mean or variance difference across zygosity groups or between the first- and the second-born twins within each sex, fulfilling the assumptions of twin analyses.

The MZ twin correlation was higher than the DZ twin correlation in both sexes, suggesting genetic influences on the MOCIT. In females, however, the DZ twin correlation was quite close to the MZ twin correlation, suggesting that genetic factors may be less important in females than in males and that shared environmental factors may present. The OSDZ twin correlation was not significantly different from the same-sex DZ twin correlation in males or females. Taken together, these results suggested that the magnitude of genetic and environmental influences on the MOCIT may be different across sexes.

Model-Fitting

Table 2 presents model-fitting results. The difference in fit between the saturated and full general sex-limitation model was not significant ($\Delta\chi^2_{14}$ = 21.9, $p > .10$), indicating that the full general sex-limitation model was acceptable. Therefore, our next step was to compare chi squares in all reduced models to the chi square in the full general sex limitation model. As expected from correlational results, fixing the additive genetic correlation for opposite-sex twins to .5 did not yield a significant change in chi-square (Model 2). Next, the A, C, and E parameters were equated across sexes, which yielded a significant change in chi-square (Model 3). Because correlational analyses showed that genetic influences were higher and shared environmental influences were lower in males than in females, A for females and C for males were removed from Model 2. This procedure again produced a significant change in chi-square (Model 4). Models 5 and 6 showed that either A or C for both sexes could be eliminated from Model 2 without a significant

Table 1

Sample Size, Means and Standard Deviations of Age and MOCIT, and Maximum Likelihood Correlations and Their 95% Confidence Intervals for the Five Groups of Twins

	MZM	DZM	MZF	DZF	OSDZ	Total
N (pairs)	186	60	337	65	103	751
Age Mean (yr)	16.7	16.2	17.2	17.2	16.2	16.9
SD (yr)	2.1	2.2	2.5	2.6	2.1	2.4
MOCI Mean	9.5	10.3	9.5	9.4	9.5	9.5
SD	5.0	4.9	4.4	4.2	4.6	4.6
r^1	.56 (.45 – .65)	.24 (–.01 – .46)	.39 (.30 – .48)	.36 (.14 – .56)	.38 (.20 – .53)	

Note: MZM = male monozygotic twins , DZM = male dizygotic twins, MZF = female monozygotic twins, DZF = female dizygotic twins, OSDZ = opposite-sex dizygotic twins. MOCIT= A total score of the Maudsley Obsessive–Compulsive Inventory.

95% CIs are in parenthesis. [1] Correlations were adjusted for age.

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Table 2

Model-Fitting Results[1]

Model	Description	–2LL	*df*	Δ–2LL	Δ*df*	*p*
1	Full general sex-limitation model	8633.0	1486			
2	r_a for OSDZ = .5	8634.8	1487	1.8	1	.18
3	r_a for OSDZ = .5; $A_{M=}A_f$, $C_{M=}C_f$, $E_{M=}E_f$	8644.0	1490	11.0	4	.03
4	r_a for OSDZ = .5; Drop C_m & A_f	8648.3	1489	15.3	3	.00
5	r_a for OSDZ = .5; Drop A_m & A_f	8639.9	1489	6.9	3	.08
6	r_a for OSDZ = .5; Drop C_m & C_f	8638.6	1489	5.6	3	.13
7	r_a for OSDZ = .5; Drop A_m, A_f, C_m, & C_f	8782.2	1491	149.2	5	.00
8	r_a for OSDZ = .5; Drop A_m & A_f; $E_{M=}E_f$	8701.1	1490	68.1	4	.00
9	**r_a for OSDZ = .5; Drop C_m & C_f; $E_{M=}E_f$**	**8638.8**	**1490**	**5.8**	**4**	**.22**
10	r_a for OSDZ = .5; Drop C_m & C_f; $A_{M=}A_f$	8646.4	1490	13.4	4	.01

Note: r_a = additive genetic correlation. OSDZ = opposite-sex dizygotic twins

Subscripts m and f represent males and females, respectively

A = additive genetic effects, C = shared environmental effects, E = individual specific environmental effects plus measurement error

LL = log likelihood

[1]Age was treated as a covariate in all models. The best fitting model is indicated in bold print.

worsening in fit, although A and C could not be dropped simultaneously (Model 7). E could be constrained to be equal across two sexes when C was removed (Model 9), but not when A was eliminated (Model 8). When A was equated across two sexes after removing C, the resulting chi-square change was significant (Model 10). Taken together, these results suggested that Model 9 was the best fitting model. In Model 9, additive genetic and individual specific environmental factors for the MOCIT were, respectively, 53% (95% confidence intervals, CI: 45%–59%) and 47% (95% CI: 41%–55%) in males, and corresponding estimates were 41% (95% CI: 33%–48%) and 59% (95% CI: 52%–67%) in females. The estimate of unstandardized genetic variance was also substantially higher in males than in females (12.4 vs. 7.7) in the best fitting model, suggesting that the greater phenotypic variance of MOCIT in males than in females may be due to the greater genetic variance in the former than in the latter group.

Discussion

There is growing evidence that sexual dimorphism exists in psychiatric disorders (Zohar et al., 1999). The present study explored sex differences in the genetic etiology of OCD symptoms using South Korean adolescent and young adult twins and found that genetic influences on symptoms of OCD were greater in males than in females (53% and 41%). Our results of sex differences in genetic influences on symptoms of OCD were consistent with the United States twin data but not with Dutch twin data in the Hudziak et al. study (2004). Sex differences in genetic and environmental influences on symptoms of OCD have been examined in Dutch adult twins. However, the results were inconclusive (van Grootheest et al., 2007).

The results of our analyses clearly demonstrated that males had greater total phenotypic and genetic variances in symptoms of OCD than did females. These findings suggest that males and females share some, but not all, of their genetic mechanisms for symptoms of OCD. For example, there may be additional genes operating for symptoms of OCD in males. Another possibility is that although genes may be identical in males and females, the effects specific to males may exist, leading to a larger genetic variance in males than in females. However, the OSDZ twin correlation in our analyses was not significantly lower than same-sex DZ twin correlations. Thus, our results on sex difference in genetic influences need to be interpreted carefully and require replications in a larger twin sample, especially in a sample that includes a large number of OSDZ twins.

Interestingly, recent molecular genetic studies support the existence of sex-specific effects of genes for OCD. For example, Karayiorgou et al. (1997) reported that the low enzyme activity (Met) allele of cathecol-omethyltransferase (COMT) gene was associated with OCD in men, but not in women. This finding has been replicated in several studies (Denys et al., 2006; Karayiorgou et al., 1999et al.,), and confirmed in a recent meta-analysis (Pooley et al., 2007). Sex-specific effects of COMT genes are usually ascribed to transcriptional regulation by estrogens (Xie et al., 1999). For another example, while the serotonin 2A receptor (HTR2A) gene has shown association with OCD primarily in females (Enoch et al., 2001), monoamine oxidase A (MAO-A) gene has been associated with OCD predominantly in males (Karayiorgou et al., 1999).

According to Bilder et al. (2004), the met allele of COMT, via its effect on tonic-phasic dopamine trans-

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mission, predisposes to the stability of mental representations and hence the maintenance of particular patterns of thought and behavior. Several studies support the argument of Bilder et al. (2004). For example, individuals with the met allele of COMT have shown to perform poorly on tests of task shifting (Nolan et al., 2004), have an electrophysiological profile indicative of increased stability of prefrontal neural processing (Gallinat et al., 2003), and demonstrate a greater amygdala–orbitofrontal connectivity in response to negative emotional stimuli that is suggestive of inflexible emotional processing (Drabant et al., 2006). Pooley et al. (2007) argues that the stability and inflexibility of neural processing associated with met-COMT can become excessive, and thereby renders the individual vulnerable to obsessions and compulsions.

In spite of relatively high DZ twin correlation in females, shared environmental influences in the present sample did not attain statistical significance. The failure to detect shared environmental influences is likely due to a lack of statistical power associated with insufficient sample size. Although the results of studies were not consistent, several investigators found that low family socioeconomic status (SES) was a risk factor for the development of OCD and that children with OCD came from larger families than did normal controls (e.g., Guerrero et al., 2003; Heyman et al., 2001). Given the previous finding that streptococcal infection can trigger OCD (Kiessling et al., 1993), the causal shared environmental factor for OCD might be streptococcal infection common in low SES families rather than low SES itself. Fetal exposure to relatively high levels of caffeine, nicotine or alcohol has also been shown to be a predictor of OCD (Santangelo et al., 1994). The present study indicated a hint of shared environmental influences only in females. Future research should, therefore, assess sex differences in shared environmental influences on OCD symptoms in a larger sample, and determine why shared environmental factors exert differential influences in males and females.

Individual specific environmental factors in OCD symptoms found in the present study were 47% in males and 59% in females. Previous studies have suggested that perinatal complications are environmental risk factors for OCD, especially in males (Lensi et al., 1996). Stressful life events have also been shown to be environmental factors that precipitate OCD (Khanna et al., 1988; McKeon et al., 1984). Prior studies have suggested that genes interact with these environmental risk factors (G X E), and that failures to take account of G X E interaction effects in the twin model may lead to an overestimation of the individual specific environmental variance component (Eaves et al., 2003; Rice et al., 2003). Thus, some of the variances of individual specific environmental factors in males and females found in the present study may include G X E component. It would be interesting in the future study to explore environmental risk factors specific to South Korean adolescents and young adults and investigate how these risk factors interact with genetic vulnerability to express symptoms of OCD.

Limitations of the present study need to be addressed. First, due to a lack of statistical power, sex difference was detected only in the genetic estimate in the present sample in spite of a hint of sex difference in shared environmental factors. The results of the present study, therefore, should be taken as preliminary evidence, and further studies with larger samples are clearly necessary to draw a firm conclusion on sex difference in genetic and environmental influences on symptoms of OCD. Secondly, as mentioned earlier, OCD is a heterogeneous disorder with multiple symptom dimensions. Due to low reliabilities of the subscales, we did not divide the total MOCI score into subtypes in the present study. In future research, however, phenotypic subtyping is clearly needed to better understand the genetic etiology of symptoms of OCD. Third, the age span of the twins in the present study is large. Due to a relatively small sample size, we did not divide the total sample into adolescents and young adults. However, it is possible that genetic and environmental influences on symptoms of OCD vary between adolescence and young adulthood. Future research, therefore, should increase sample size and examine continuities and changes in genetic and environmental factors in symptoms of OCD in a longitudinal design. Finally, subjects in the present study were a volunteer sample of South Korean adolescent and young adult twins. The participation rate in this study was modest (approximately 32%). Caution is necessary when one attempts to generalize our results to the whole South Korean population or other human populations as frequencies and effects of the genes involved in OCD have been reported to differ across ethnic groups (Palmatier et al., 1999).

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