Association between Estrogen Receptor Gene Polymorphisms and Depression in Post-Menopausal Women: A Preliminary Study

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INTRODUCTION

Women are vulnerable to depression especially along with menopause.1 Women who had reproductive cycle event-related depression such as premenstrual dysphoric disorder, perimenopausal depression and postpartum depression reported a stronger family history of mental illness than other depressed women.2 It suggests unique characteristics and perhaps a more biologically driven illness for this subgroup of depressed women.2

Post-menopausal women experience variable biological and psychological changes. The effect of reduced levels of estrogen can effect on post-menopausal depression. Estrogen triggers physiological responses by binding to the estrogen receptor (ER). Two subtypes of ER, ERα and ERβ are now known. We investigated the significance of ERα and ERβ polymorphisms and post-menopausal depression in this study. Forty three women with post-menopausal depression and 63 post-menopausal women without depression as normal controls were recruited. Polymerase chain reaction-restriction fragment length polymorphism method was used to investigate genotypes of ERα and ERβ polymorphisms. Genotypes of PvuII and XbaI polymorphism of ERα receptor were significantly different in patients with post-menopausal depression comparing with controls. Genotypes of ERβ did not show association with post-menopausal depression. Our study showed that ERα receptor polymorphism had an association with depression in post-menopausal women. It suggests that investigation of ER genes and their functions might be important for understanding pathophysiological mechanism of post-menopausal depression.

Key Words Menopause, Depression, Estrogen, Receptor, Polymorphism.
METHODS

Forty three women with post-menopausal depression and 63 post-menopausal women without depression as normal controls in Korean population were recruited for this study. All of them were between 45 and 60 years and were not under psychiatric treatment. Post-menopausal women who have intact uterus and more than 1 ovary, no sex steroid hormone use in the previous 3 months, absence of pregnancy, and previous regular menstrual cycle were enrolled. In addition to menstruation history, serum FSH, LH, and estradiol (E2) were tested to confirm postmenopausal period in all the women. Postmenopausal women with Beck Depression Inventory (BDI) scores over 21 (39.17±11.04) were evaluated and included as postmenopausal depression group if they were diagnosed as major depressive disorder or depressive disorder, NOS by DSM-IV criteria by psychiatrist. They were not under psychiatric treatment. All the normal controls were under BDI score 21 (8.61±2.25) and they were evaluated by psychiatrist to be determined as they did not have any kind of depressive disorder. They were also performed by other scales such as Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and State-Trait Anxiety Inventory. Subjects with neurological disorder, endocrine disorder, and other psychiatric disorder were excluded in this study. Written informed consent was obtained from all the subjects.

Genomic DNA from the peripheral blood was extracted using DNA Isolation kit (Bioneer, Daejeon, Korea) following the manufacturer’s protocol. ERα genotypes were determined with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method reported earlier with some modification. After PCR, 1.3-kb fragments were digested by PvuII and XbaI. The primers for analysis of ERβ genes such as the PvuII (T/C; rs2234693) in the 5’ region of the gene and XbaI (A/C; rs9340799) polymorphisms located upstream from exon 1 of ERα may influence the tissue specific expression of the ERα gene. The two common polymorphisms such as the PvuII (T/C; rs2234693) in the 5’ region of the gene and XbaI (A/C; rs9340799) polymorphisms in intron 1 are in strong linkage disequilibrium with this repeat. Also, PvuII single nucleotide polymorphism (SNP) polymorphism (PCR-RFLP) method reported earlier.

DISCUSSION

The two subtypes of ER (ERα and ERβ) differ with respect to tissue distribution and coregulator interactions. The two common polymorphisms such as the PvuII (T/C; rs2234693) in the 5’ region of the gene and XbaI (A/C; rs9340799) polymorphisms in intron 1 are in strong linkage disequilibrium with this repeat. Also, PvuII single nucleotide polymorphism (SNP) pro-

| Table 1. Genotypes of estrogen receptor polymorphisms in patients with post-menopausal depression and normal controls |
|-----------------|-----------------|-----------------|-----------------|
|                  | Patients (N=43) | Controls (N=63) | p value        |
|------------------|-----------------|-----------------|-----------------|
| PvuII, N(%)      |                 |                 |                |
| PP               | 11 (25.6)       | 18 (28.6)       | 0.001*         |
| Pp               | 26 (60.5)       | 18 (28.6)       |                |
| pp               | 6 (13.9)        | 27 (42.8)       |                |
| XbaI, N(%)       |                 |                 |                |
| XX               | 7 (16.3)        | 6 (9.5)         | 0.000†         |
| Xx               | 34 (79.1)       | 18 (28.6)       |                |
| xx               | 2 (4.6)         | 39 (61.9)       |                |
| AluI, N(%)       |                 |                 |                |
| AA               | 22 (51.2)       | 39 (61.9)       | 0.345          |
| Aa               | 21 (48.8)       | 23 (36.5)       |                |
| aa               | 0 (0.0)         | 1 (1.6)         |                |
| Rsal             |                 |                 |                |
| RR               | 19 (44.2)       | 35 (55.6)       | 0.442          |
| Rr               | 20 (46.5)       | 25 (39.7)       |                |
| rr               | 4 (9.3)         | 3 (4.7)         |                |

*χ²=13.204, df=2, †χ²=35.894, df=2

not associated with genotypes of ERα and ERβ polymorphism.
duces a binding site for a specific transcription factor that may affect gene expression. The functional polymorphism of ERb was not identified yet, and there are two common SNPs such as AluI at position 1730 (G/A; rs4986938) in the 3’ untranslated region and Rsal silent mutation at position 1082 (G/A; rs1256049) in exon 5.

In this study, ERa receptor polymorphisms were strongly associated with depression in post-menopausal women. Considering PvulI and XbaI position of ERα might influence expression of ERα gene as mentioned above, these results showed the importance of functions of ERα polymorphisms in post-menopausal depression. Otherwise, ERβ polymorphism was not associated with post-menopausal depression. The two polymorphisms examined in this study have not functional expression. Further research of ERβ should be evaluated in post-menopausal depression along with identification of functional polymorphisms.

To our knowledge, this is the first case-control study of ER polymorphisms and post-menopausal depression. The influence of the ER polymorphism on physical and emotional symptoms of post-menopausal women has been insufficiently studied.

A few previous studies were performed to examine the relationship of ER receptor polymorphisms and postmenopausal depression. Malacara et al. reported that ERα polymorphisms (PvuII and XbaI) was not associated with emotional symptoms in post-menopausal women. In a cohort study, Tiemeier et al. also examined the same ERα polymorphisms and found no association with depressive symptoms in women over 55 years. Instead, they found an association of an ERα with anxiety symptoms unlike our results. Kravitz et al. analyzed 4 SNPs of ERα and ERβ in pre- and perimenopausal depression and found no association with depressive symptoms and those SNPs, although their SNPs were different with our study except PvuII of ERα. Majority of the subjects in previous study were Caucasians and they did not include normal control samples. Ethnic and socio-cultural and environmental factors are involved in the appearance or symptoms of post-menopausal depression.

Considering relatively small sample size of our study, which may affect deviation of H-W-E and different genotype distribution of ERα polymorphisms in Korean population, further studies with larger samples and different ethnic populations are recommended to elucidate the function of ER polymorphisms and depression in post-menopausal period. Also, given that a single polymorphism in a single gene could not exert any major impact on the activity of the sex steroids and on aspects of the phenotype that are under the influence of these hormones, diverse genetic studies with genes involving estrogen function is needed to elucidate pathophysiologic mechanism of postmenopausal depression.

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