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A Review of Estrogen Receptor α Gene (*ESR1*) Polymorphisms, Mood, and Cognition

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Abstract

OBJECTIVE—There are significant individual differences in the extent to which mood and cognition change as a function of reproductive stage, menstrual phase, postpartum, and hormone therapy. This review explores the extent to which variations or polymorphisms in the estrogen receptor α gene (*ESR1*) predict cognitive and mood outcomes.

METHODS—A literature search was conducted from 1995 to November 2009 through PubMed, EMBASE, and PsychINFO. Twenty-five manuscripts were reviewed that summarize investigations of *ESR1* in mental health.

RESULTS—Among studies investigating *ESR1* in relation to cognition, 11 of 14 case-control studies reported an association between *ESR1* polymorphisms and risk for developing dementia. Three of four prospective cohort studies reported an association between *ESR1* polymorphisms and significant cognitive decline. There are inconsistencies between case-control and cohort studies regarding whether specific *ESR1* alleles increase or decrease the risk for cognitive dysfunction. The relationships between *ESR1* and cognitive impairment tend to be specific to or driven by women and restricted to risk for Alzheimer's disease rather than other dementia causes. Three of five studies examining *ESR1* polymorphisms in relation to anxiety or depressive symptoms found significant associations. Significant associations have also been reported between *ESR1* polymorphisms and childhood-onset mood disorder and premenstrual dysphoric disorder.

CONCLUSIONS—A strong relationship between *ESR1* variants and cognitive outcomes is evident and preliminary evidence suggests a role of the *ESR1* gene in certain mood outcomes. Insights into the discordant results will come from future studies that include haplotype analyses, analyses within specific ethnic/racial populations, and gender-stratified analyses.

Keywords

Estrogen receptor α ; *ESR1*; polymorphisms; cognition; mood; review

Introduction

Biological Plausibility that Estrogen Impacts Cognition and Mood

Estrogen facilitates synaptogenesis, induces growth factor production, protects against oxidative stress, and regulates neurotransmission (e.g., serotonin, norepinephrine and acetylcholine) in brain systems associated with cognition and mood.^{1, 2, 3, 4} The regulatory

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effects of estrogen on choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) are particularly relevant to cognition given the key role of cholinergic transmission in learning, memory, and Alzheimer's disease.^{5, 6, 7} Clinical studies demonstrate effects of estrogen supplementation and withdrawal on mood and cognitive outcomes, but the magnitude and direction of these effects appears to be influenced by the dose, timing and formulation of estrogen treatment.^{8, 9} There is notable variability in clinical response to hormone treatments, including hormone therapy for menopausal symptoms¹⁰ and tamoxifen treatment for breast cancer.^{11, 12} Moreover, there are significant individual differences in the extent to which cognitive function and mood change as a function of reproductive stage^{13, 14} and a high degree of inter- and intra-individual variability in the risk and severity of postpartum depression¹⁵ and premenstrual dysphoric disorder.^{16, 17} This review explores the extent to which individual differences in genes associated with estrogen signaling predict cognitive and mood outcomes.

Estrogen activity in the brain is mediated through activation of intracellular, transmembrane, and membrane-bound estrogen receptors (ERs) along with non-genomic mechanisms. In addition to the transmembrane estrogen G protein coupled receptor GPR30, there are two subtypes of estrogen receptors, ER α and ER β .¹⁸ ER α and ER β receptor subtypes are members of the superfamily of nuclear receptors that regulate transcription in target genes containing estrogen response binding elements. The ER receptor subtypes are encoded by two distinct genes. The ER α gene (*ESR1*) is located on chromosome 6q25.1, and the ER β (*ESR2*) gene is located on chromosome 14q22–24.¹⁹ Both ER α and ER β receptor subtypes are located in brain regions associated with cognitive function and emotion. The ER α receptor is predominantly expressed in the hypothalamus and amygdala, areas involved in autonomic function, emotional regulation, and associative and emotional memory. The ER β receptor is predominantly expressed in the hippocampal formation and entorhinal cortex, brain areas involved in declarative memory.¹⁸ The high level of ER β expression in the hippocampus suggests a role for ER β in cognitive function; however, mental health studies have mainly focused on the ER α gene.

Studies in large populations have reported independent relationships between *ESR2* polymorphisms and risk for depression in adolescents²² and Alzheimer's disease^{20, 21}. These associations must be considered preliminary because *ESR2* studies are few in number. Moreover, subsequent studies have failed to replicate the findings associating *ESR2* polymorphisms and mental health outcomes.^{23, 24, 25} *GPR30* polymorphisms have been studied in relation to breast cancer, but not mental health outcomes.²⁶ For these reasons, the present review focuses on polymorphisms in the *ESR1* gene and their role in mental health.

Genetic Variation in Estrogen Receptor Alpha and Women's Health

Several single nucleotide polymorphisms (SNPs) and variable-number tandem repeat (VNTR) polymorphisms have been identified in *ESR1*.²⁷ Among these identified polymorphisms, only a few have been extensively studied in relation to health outcomes. One well-studied polymorphism is a TA-variable number of tandem repeats (VNTR) in the promoter region that may impact tissue-specific gene expression.²⁸ This TA-repeat polymorphism is in strong linkage disequilibrium with two of the most widely studied SNPs in the *ESR1* gene, PvuII (rs9340799) and XbaI (rs223493), which are located in the first intron of *ESR1* and are in strong linkage disequilibrium with each other.²⁹ See Figure 1 for a schematic figure of the genomic organization of the *ESR1* gene. In linkage disequilibrium, some combinations of alleles occur more frequently in a population than would be expected from random assortment. Therefore, because the PvuII and XbaI are in linkage disequilibrium, one can predict the allele at one SNP given the allele at the other SNP with a high level of confidence. The T and C allele of the PvuII SNP are commonly referred to as the p and P allele, respectively. The A and G allele of XbaI are commonly referred to as the x and X allele, respectively. The X and P are the variant

alleles that lack the respective XbaI and PvuII restriction enzyme recognition site. Currently, there is no definitive evidence concerning the functionality of these SNPs or the biological pathways they affect; however, recent findings support the hypothesis that these SNPs impact estrogen activity by influencing transcription of the *ESR1* gene via altered transcription factor binding.^{30, 31} It is possible that the XbaI and PvuII SNPs as well as the TA-repeat do not affect estrogen signaling directly but may be in linkage disequilibrium with another functional variant in the *ESR1* gene.

The *ESR1* polymorphisms appear to be markers for important clinical outcomes in women such as bone mineral density^{29, 32, 33, 34} and cardiovascular health.^{30, 35, 36, 37} The polymorphisms have been implicated in estrogen-related diseases including breast cancer,^{38, 39, 40} osteoporosis,^{29, 33, 41, 42} endometriosis^{43, 44, 45, 46} and familial premature ovarian dysfunction.⁴⁷ These associations are controversial because of inconsistent findings across studies.^{48, 49} It is difficult to determine which alleles are associated with physiological states that are consistent with optimal estrogen signaling. The majority of studies indicate that the p and x alleles appear to confer risk for breast cancer and osteoporosis, yet reduce risk for endometriosis. The associations between the TA-repeat polymorphism and health outcomes appear to be more consistent. Typically, a lower number of repeats is associated with lower bone mineral density and a higher incidence of osteoporotic fractures.^{29, 33, 42} Additionally, a lower number of repeats confer a greater risk of endometriosis^{43, 44, 45} and premature ovarian dysfunction.⁴⁷

ESR1 associations are frequently found to be ethnic/race specific. For example, a recent meta-analysis concluded that most studies in Asian populations found an association between the PP and/or xx genotypes with increased risk of osteoporosis, whereas the pp and/or xx genotypes were associated with increased risk of osteoporosis in Caucasian populations.⁵⁰ A genetic haplotype is a combination of alleles from different loci along a chromosome that tend to be inherited together. It is reasoned that the specificity of *ESR1* relationships by race or ethnicity may reflect the two-fold higher prevalence of the Px haplotype in Asian populations relative to Caucasian populations.⁴² Two recent molecular studies have supported a relationship between the p allele and risk of osteoporosis. A functional binding site for the transcription factor B-myb was found to be absent with the p allele of PvuII, which, in turn, may reduce *ESR1* transcription rates or produce a functionally different *ESR1* isoform.^{31, 35} Higher plasma estradiol levels were found in postmenopausal women carrying the XP haplotype³¹; however, other studies found no association between serum estradiol levels and *ESR1* polymorphisms.^{51, 52} Taken together, the current literature suggests that *ESR1* transcription activity and/or gene regulation are affected by *ESR1* polymorphisms, but the exact biological mechanism remains to be determined.

There is a striking similarity between the regional distribution of ERs and brain areas affected by Alzheimer's disease (AD) neuropathology including the hippocampus, entorhinal cortex and the basal forebrain.^{1, 53} Decreased levels of ER α have been found in hippocampal neurons in the brains of AD patients.⁵⁴ Mice lacking the ER α (i.e., *ESR1* knockout mice) show impaired performance on cognitive tasks dependent on the hippocampus, a brain region that is critical for memory formation.^{55, 56} This cognitive impairment is reversed with estradiol administration⁵⁶ or with lentiviral delivery of the *ESR1* gene to the hippocampus.⁵⁷ Such evidence that ER α plays a role in cognitive function has fueled a series of studies examining the relationship between *ESR1* genotype and cognitive function. Fewer studies have examined the association between *ESR1* genotype and mood outcomes. The present review aims to facilitate future research in relationships between genetic variation in the *ESR1* gene and mental health by summarizing the current findings.

This review focuses primarily on findings pertaining to the most widely studied polymorphisms, PvuII, XbaI and the TA-repeat; however, findings regarding other *ESR1*

polymorphisms are reported when they were investigated in conjunction with PvuII, XbaI, and/or the TA-repeat. Additionally, we offer potential explanations for discrepant results, discuss potential clinical implications, and suggest areas of focus for future research and methodology that may be advantageous in further characterizing relationships between ER genes and mental health.

Methods

For this systematic review of *ESR1* polymorphisms and mental health, we focused on studies relating *ESR1* polymorphisms to cognitive and mood outcomes. We carried out a literature search from 1995 to November 2009 through PubMed, <http://www.ncbi.nlm.nih.gov/pubmed/>, EMBASE, <http://www.embase.com/> and PsychINFO, <http://www.apa.org/pubs/databases/psycinfo/index.aspx>. We also consulted previous reviews. We selected only publications in the English language and used combinations of the following key words “estrogen receptor polymorphisms” “*ESR1* polymorphisms”, “estrogen receptor alpha”, “rs2234693”, “rs9340799”, “cognition”, “cognitive function”, “memory”, “mood”, “depression”, and “mental disorders.” This resulted in 136 publications for which abstracts were reviewed to identify relevance to the topic of *ESR1* polymorphisms and cognition and mood. From this initial list we identified 25 manuscripts that were published in English and summarize investigations of *ESR1* in mental health as described above. The studies included were heterogeneous in study design, sample size and the statistical covariance of factors other than genetics that influence estrogen signaling (e.g., reproductive stage, age, use of hormone therapy or psychotropic medication). This heterogeneity among *ESR1* studies precluded conducting a formal meta-analysis. We therefore summarize findings by study design in a narrative review. Details of the studies investigating *ESR1* polymorphisms and cognitive function are summarized in Tables 1 and 2. Details of studies investigating *ESR1* polymorphisms and mood outcomes are summarized in Table 3. Figures 2 and 3 present a basic summary of the main findings regarding *ESR1* allele-specific relationships with cognitive and mood outcomes.

ESR1 Polymorphisms and Cognition

Approximately 50% of the genetic risk factors for sporadic Alzheimer’s disease (AD) are yet to be discovered.⁵⁸ Early evidence indicating a relationship between the *ESR1* gene and cognition came primarily from case-control studies. More recently, prospective cohort studies have investigated relationships between *ESR1* and cognitive outcomes longitudinally. The majority of case-control studies indicate a potential relationship between the X and P alleles of XbaI and PvuII and increased risk of cognitive impairment. However, three prospective studies and studies relating ER genes to cognitive function in healthy older adults provide different results. The following sections summarize these results by study design, focusing first on case-control studies and then on prospective studies.

Case-Control Studies

Table 1 summarizes the case-control studies to date examining the link between *ESR1* polymorphisms and cognitive outcomes. Figure 2a shows that 78% of the case-control studies reported an association between *ESR1* polymorphisms and odds of cognitive impairment and that 73% of those positive studies demonstrate a protective effect of the x and p alleles of the XbaI and PvuII SNPs, respectively, against cognitive impairment. Below we describe these case-control studies in greater detail. We also review evidence indicating that the risk of dementia associated with X and P alleles is greater in individuals with the APOE e4 allele, a known risk factor for AD.

The earliest case-control study involved a Japanese sample of sporadic AD patients and healthy older controls.⁵⁹ The frequencies of the X and P alleles were significantly higher in the AD patients versus controls.⁵⁹ In a sample of postmenopausal Danish women, neither the X nor P allele was associated with increased odds of cognitive impairment as assessed by the six-item Orientation-Memory-Concentration test (SDT).⁶⁰ In a secondary, atypical analysis, the X allele was associated with an increased odds of cognitive impairment ($p = .054$) after adjusting for “executive cognitive ability”.⁶⁰ In an Italian sample of AD patients and older controls, findings contrary to previous case-control studies were reported - the xx genotype was associated with increased odds of developing AD.⁶¹ This effect was driven by women and by patients with late-onset AD. No relationship was found with the PvuII SNP.⁶¹ In a mostly female sample of Chinese AD patients and older controls, 16 *ESR1* SNPs were examined and no significant associations were found with the XbaI or PvuII SNP.⁶² However, the odds of developing AD was associated with five SNPs located between intron 3 and intron 7, and age of AD onset was associated with two SNPs located on exon 2 and intron 2. In a subanalysis restricted to females, the five *ESR1* SNPs were significantly associated with increased odds of AD.⁶² Other case-control studies found no association between *ESR1* polymorphisms and odds of developing AD.^{63, 64, 65}

A recent meta-analysis described evidence from eight case-control studies examining whether PvuII and XbaI SNPs increased the odds of developing AD ($n = 8288$) or other forms of dementia ($n = 11036$).⁶⁶ A small but significant association between each SNP and odds of developing AD was found (X carriers: OR 1.2, 95% CI 1.0–1.4, $p = 0.02$; P carriers: OR 1.2, 95% CI 1.0–1.4, $p = 0.01$). In ethnicity-specific analyses, these associations were significant in Asian (X carriers: OR 1.5, 95% CI 1.1–2.0, $p = 0.004$; P carriers: OR 1.5, 95% CI 1.1–2.0, $p = 0.01$), but not European populations (XbaI: OR 1.1, 95% CI 0.9–1.3, $p = 0.37$; PvuII: OR 1.1, 95% CI 0.9–1.3, $p = 0.27$). Conversely, no *ESR1* SNPs were associated with non-AD forms of dementia.⁶⁶ *ESR1* polymorphisms did not relate to odds of all-cause dementia^{66, 67}, vascular dementia⁶⁸, alcohol-associated dementia⁶⁸ or Parkinson’s disease with dementia.⁶⁹ However, the studies may not have been adequately powered to detect these relationships considering that the non-AD dementia groups were often small in size or smaller compared to the AD group. On the contrary, Isoe-Wada and colleagues⁷⁰ reported that the prevalence of the P allele was significantly higher in PD patients with dementia (63%) and AD patients (49%) compared to controls (36%). The prevalence of the X allele was significantly higher in AD patients (29%) compared to controls (17%).⁷⁰

There is some evidence that the odds of developing AD with a particular *ESR1* may be greater in individuals with the APOE e4 allele, a well-established risk factor for AD.^{71, 72, 73} Estrogen mediates the regulation of *APOE* synthesis⁷⁴ and promotes synaptogenesis through an *APOE*-dependent mechanism.⁷⁵ Three studies report no interactive effects of *APOE* and *ESR1* on cognitive function.^{23, 52, 61} Three other studies found a similar significant pattern of interaction.

The first study involved a Japanese sample of older controls and patients with vascular dementia, alcohol-associated dementia, early- and late-onset AD and familial AD.⁶⁸ The frequencies of the P and X alleles were significantly higher in late-onset AD patients with one or more e4 alleles (P 51%, X 30%) compared to healthy elderly controls (P 38%, X 20%).⁶⁸ In an Italian study of sporadic AD patients and older controls, the PP and XX genotypes were associated with increased risk for AD in men only but conferred a substantial increased risk of AD to male and female subjects who carried an APOE e4 allele (OR = 13.3, 95% CI = 1.7–103.6).⁷⁶ A subsequent Italian study reported a higher prevalence of both the PP and XX genotypes and the combined PPXX genotype in sporadic, late-onset AD patients (PPXX 22%) compared to controls (PPXX 9%).⁷⁷ Notably, the cumulative effect of the PPXX genotype and e4 homozygosity conferred a 7-fold increased risk of AD compared to e4-negative subjects.

⁷⁷ A Swedish study reported the opposite pattern of interactions in a clinic-based sample of familial AD patients and controls as well as a community-based sample of female patients with familial AD or sporadic AD and older controls.⁷⁸ In both the clinic- and community-based samples, the combination of the *APOE* e4 allele and the *ESR1* xx or pp genotype was associated with increased risk of familial AD in women, particularly among early- versus late-onset AD patients.⁷⁸ Together, these findings provide some evidence that *ESR1* and *APOE* polymorphisms may interact to influence risk of cognitive decline, but the pattern of those effects varies.

Prospective Cohort Studies

Table 2 summarizes the prospective cohort studies to date examining the link between *ESR1* polymorphisms and cognitive outcomes. As illustrated in Figure 2b, 75% of cohort studies reported significant associations between *ESR1* polymorphisms and cognitive decline. In contrast to the case-control studies, 100% of those positive studies showed a protective effect of the X and P alleles of XbaI and PvuII against cognitive decline.

Two recent prospective studies by the same lead investigator suggest that the p and x alleles are associated with an increased risk of cognitive impairment as measured by the modified Mini-Mental Status Exam (MMSE).^{51, 52} The first study was a prospective cohort study with a six- to eight-year follow-up in a sample of predominantly white, older women.⁵¹ Compared to women with the XX or PP genotype, women with a p or x allele experienced greater cognitive decline over time. In addition, p and x alleles were more frequent in women who developed cognitive impairment (p 62%, x 70%) compared to those who did not (p 56%, x 64%). Most compelling was the finding that women with a pp or xx genotype had a three-fold greater risk of AD or dementia compared to women with a PP or XX genotype.⁵¹ These findings were confirmed in another prospective cohort study of non-demented elderly men and women.⁵² The p and x alleles increased risk for cognitive impairment in women. In men, cognitive impairment was associated with the *ESR1* rs728524 SNP. Levels of circulating estradiol did not relate to any *ESR1* SNPs, and the results were attenuated somewhat after controlling for race.⁵²

Most studies examining *ESR1* polymorphisms in relation to cognitive function have included only a global scale of cognitive function such as the MMSE. A larger battery of cognitive tests was studied in an ethnically diverse sample of 815 midlife women enrolled in the Study of Women's Health across the Nation (SWAN).²³ X and P alleles were associated with better performance on only one cognitive domain, verbal memory, as assessed by the East Boston Memory Test (EBMT). The association with verbal memory was dependent on ethnicity such that Caucasian and African American women who were homozygous for the X allele performed better on the EBMT compared to women without this genotype. Among Caucasian women, those who were homozygous for the P allele performed better than those without this genotype on the delay memory trial. There was no relationship between *ESR1* polymorphisms and any other cognitive measure, including working memory (Digit Span Backwards) and perceptual speed (Symbol Digit Modalities).²³ A prospective cohort study in older, Caucasian adults found no relationship between *ESR1* SNPs and MMSE score or dementia risk.⁶⁷ In a subset of individuals with structural brain scans, women with the p or x allele or haplotypes of the p and x allele had smaller hippocampal and amygdalar volumes compared with women with the P or X allele, and the loss of brain volume increased as the number of risk alleles increased.⁶⁷

Overall Summary of ESR1 Polymorphisms and Cognitive Function

Whereas the majority of case-controlled studies found an association between cognitive decline and the X and P alleles,^{60, 68, 77} prospective cohort studies^{23, 51, 52} generally found an association between cognitive decline and the x and p alleles. Yaffe et al.⁵¹ suggested that

differences in ethnic background across samples, specifically the greater representation of Japanese individuals in the case-control studies, may account for this difference and recommended further research within different ethnic groups. This argument is supported by the meta-analysis showing a link between x and p alleles and AD only in Asian samples.⁶⁶ Ethnicity-specific analyses are also important due to variability in the degree of linkage disequilibrium between *ESR1* polymorphisms across race or ethnic groups.^{42, 50} Variations in *ESR1* allele-specific associations may also be due to the numerous interactions between environmental and genetic risk factors. For example, a case control study²⁵ showed a significant interaction between a SNP on exon 8 of the *ESR2* gene and both the PvuII and XbaI SNPs of *ESR1*. Also, as noted earlier, the *ESR1* and *APOE* genotypes interact to influence risk of dementia.^{68, 76, 77, 78}

Overall, these studies provide evidence that genetic variation in the *ESR1* gene is associated with memory function at midlife and risk of dementia. This evidence is consistent with predictions based upon the presence of *ESR1* mRNA in the amygdala-hippocampal area and entorhinal cortex.⁷⁹ Although a few studies reported relationships in men^{76, 52}, more studies reported relationships in exclusively female samples^{23, 51, 78, 60} or relationships that were driven by women in a mixed gender sample.^{61, 62, 52} Results from a meta-analysis⁶⁶ indicate that the relationship between *ESR1* polymorphisms and cognitive impairment may be specific to AD rather than all-cause dementia. Consistent with this clinical effect, three studies suggest that *ESR1* polymorphisms may impact disease expression. First, a post-mortem study found a trend for an association between the P allele and greater AD pathology (i.e., neurofibrillary tangles) in the brains of 551 Japanese individuals.⁸¹ Second, Corbo et al. reported an association between the PP and XX genotypes and lower MMSE values in women with AD.⁷⁶ Third, age of AD onset has been associated with two *ESR1* SNPs on intron 2 and exon 2.⁶²

***ESR1* Polymorphisms and Mood**

Twin and family-based studies indicate a significant genetic component to Major Depressive Disorder (MDD), and heritability is highest with severe, recurrent and early-onset forms of the disease.^{82, 83, 84, 85} Epidemiologic studies have consistently demonstrated a higher prevalence for MDD in females compared to males.^{86, 87} This sex disparity emerges at puberty.^{88, 89} Multiple lines of evidence have implicated estrogen signaling as contributing to this sex difference.^{90, 91, 92} Females show an increased risk of MDD during the perimenopausal period, a reproductive stage characterized by fluctuations in estradiol.⁹³ Estrogen modulates serotonergic and norepinephrinergic function⁹⁴, both of which are central to affective processing. Lastly, of the two estrogen receptor subtypes, ER α is more predominantly expressed in brain areas that mediate affective and motivational processing including the amygdala and hypothalamus. Furthermore, as noted earlier, smaller amygdala and hippocampal volumes were associated with the p and x alleles of the PvuII and XbaI SNPs in older, healthy women.⁶⁷

Table 3 summarizes the studies to date examining the link between *ESR1* polymorphisms and mood outcomes. Figure 3 illustrates that 60% of studies examining *ESR1* polymorphisms in relation to anxiety or depressive symptoms found significant associations. Each of these positive studies reported that the X and/or P alleles of XbaI and PvuII or longer TA repeat alleles were risk factors for anxiety or depression.

A population-based cohort study of Caucasians aged 55 and older found that the XbaI and PvuII polymorphisms related to anxiety in women but not depressive symptoms or DSM-IV depressive disorder in women or men.⁹⁵ The XP haplotype was associated with an increased risk for anxiety symptoms in women in a dose-dependent manner.⁹⁵ A Chinese study involving patients with MDD and healthy controls reported that a 3-fold higher risk of MDD in women

who were homozygous for the P allele of the PvuII variant compared to women with Pp or pp genotypes.⁹⁶ No such relationships were evident in men. In a sample of adult males treated for substance abuse, the *ESR1* TA-repeat polymorphism was significantly associated with anxiety symptoms.⁹⁷

There is variable evidence of a relationship between *ESR1* polymorphisms and depression or anxiety in female-only samples. There was no evidence of an association between *ESR1* SNPs and depressive symptoms as measured by the Center for Epidemiological Studies Depression Scale (CESD) in a multiracial/multiethnic sample of women participating in SWAN.²⁴ Importantly, women taking antidepressant medication were excluded from these analyses which may represent a form of selection bias if, compared to the study population, there is a higher prevalence of the genetic risk factor among the women excluded due to use of antidepressants. A recent study examined the relationship between premenstrual dysphoric disorder and genetic variation in the *ESR1* gene, the *ESR2* gene, and the catechol-O-methyltransferase (*COMT*) gene, a gene involved in estrogen metabolism.⁹⁸ Four SNPs in intron 4 of *ESR1* showed significantly different allele distributions and genotype distributions between affected women and controls.⁹⁸

Additional studies have investigated *ESR1* polymorphisms and prevalence of a mood disorder and personality traits reflecting dysphoric mood states. PvuII and XbaI variants did not predict odds of developing a childhood-onset mood disorder in a large family-based sample of affected children and their immediate family members.⁹⁹ In females, however, there was an association between childhood-onset mood disorders and a haplotype of three other *ESR1* SNPs in strong linkage disequilibrium (rs746432, rs2077647, rs532010).⁹⁹ No relationship between the PvuII variant and MDD or Bipolar Disorder was found in a Japanese study.¹⁰⁰ No relationship between *ESR1* polymorphisms and suicidal behaviors was found in a German population.¹⁰¹

Summary of *ESR1* Polymorphisms and Mood

The paucity of studies examining *ESR1* genotype and mood outcomes necessitates caution when interpreting the results; however, the findings offer preliminary evidence that the *ESR1* gene may play a role in susceptibility to mood disorders, particularly for females. It becomes especially important to investigate the influence of ER polymorphisms in clinical populations that are prone to mood disorders such as HIV, dementia, chronic inflammatory conditions and cancer patients. Such investigations will bring us closer to the possibility of using genetic markers to identify patients who are at increased risk for mood disorders.

Discussion

There appears to be a strong relationship between *ESR1* polymorphisms and cognitive outcomes. Initial studies investigating *ESR1* variants and mood disorders suggest a similar trend. As with the literature on osteoporotic fracture risk, the literature on cognitive risk factors shows some inconsistencies concerning which particular *ESR1* polymorphisms conferred risk and the directionality of allele-specific effects. Most, but not all, of the case-control studies indicate that the X and P alleles of XbaI and PvuII confer the risk for cognitive impairment. Conversely, three prospective cohort studies in a healthy, older adult population suggest that the x and p alleles confer the risk. Despite these inconsistencies, two findings appear to be reliable; first that the risk for cognitive impairment is found primarily in women and second that the risk is for AD rather than for other causes of dementia. Lastly, many of the studies of *ESR1* polymorphisms and mental health outcomes found that relationships were evident in an exclusively female sample or that females drove such effects in mixed gender samples. Future studies should acquire sufficiently large sample sizes to permit gender-stratified analyses. Additional insights into the discordant results will come from future studies that include haplotype analyses and analyses by ethnic/racial populations.

Investigations involving *ESR1* haplotypes and epistatic relationships appear to produce more reliable and robust results compared to investigations involving single SNP analyses. The majority of studies using haplotype analyses found stronger gene associations when considering combinations of *ESR1* PvuII and XbaI polymorphism genotypes and combinations of *ESR1* genotypes with *APOE* polymorphisms. *ESR1* haplotypes and epistatic relationships may relate more strongly to functional outcomes than single SNP analyses, because they provide more information on other genetic variants that influence estrogen activity through different mechanisms.

Many studies report ethnicity- or race-specific gene associations, which underscore the importance of considering genetic background and population stratification. There is minor racial and ethnic variation in distributions of the PvuII and XbaI genotypes;¹⁰² however, the degree of linkage disequilibrium between *ESR1* polymorphisms may vary between ethnic/race groups. There is a two-fold higher prevalence of the Px haplotype in Asian populations relative to Caucasian populations.⁴² Additionally, the number of TA repeats differs by ethnicity, with estimated major peaks at 14 repeats in European populations and 15 repeats in Asian populations.⁵⁰ Moreover, studies indicate that there are ethnic disparities in the presentation and severity of menopause symptoms, particularly psychosomatic symptoms and hot flashes^{13, 103, 104} suggesting that ethnicity/race may be a factor influencing one's sensitivity to sex hormone fluctuations. The variations in menopausal symptoms and the distribution of *ESR1* genotypes by ethnicity/race underscore the need to control for population stratification or heterogeneity in future studies.

Two major differences between the case-control and cohort studies allow for further speculation into the disparate results. Across all studies, the average age of participants in the cohort studies was somewhat younger than in the case-control studies. Additionally, the majority of case-control studies involved AD outcomes whereas cohort studies involved cognitive decline outcomes. The case-control findings might therefore represent the impact of the SNPs on the more severe form of cognitive impairment in an elderly population, whereas the cohort findings represent the impact of the SNPs on generalized cognitive aging in a mid-life to elderly population. This pattern might then suggest that the optimal level of estrogen signaling is one level in an intact brain (or earlier in life) and a different level in a diseased brain (or later in life). Such a conclusion would be similar to the "healthy cell bias" of estrogen,¹⁰⁵ which proposes that estrogen can only exert neuroprotective effects in a healthy brain that is free of neurodegeneration.

Although the literature on *ESR1* and mood is sparse, there is preliminary evidence that mood varies with *ESR1* genotype. One study found an association between anxiety symptoms and the XP haplotype in women,⁹⁵ while another study demonstrated an increased risk of MDD diagnosis in women homozygous for the P allele.⁹⁶ Other *ESR1* SNPs have been associated with childhood-onset mood disorders⁹⁹ and premenstrual dysphoric disorder.⁹⁸ Among males treated for substance abuse, the TA-repeat polymorphism was associated with anxiety symptoms.⁹⁷ To date, no studies have examined the interaction between estrogen receptor polymorphisms and serotonin signaling genes such as the serotonin transporter gene (*5HTT*). Estrogen regulates serotonergic synthesis, degradation and neuron firing rates in the raphe nuclei.¹⁰⁶ Some studies have found that the clinical response to serotonin reuptake inhibitors (SSRIs) is negatively affected by hypoestrogenic states such as menopause.^{107, 108, 109} A few studies showed improved clinical response to SSRIs in postmenopausal women when the medication regime was supplemented with hormone therapy compared to placebo.^{109, 110, 111}

Given that neurocognitive dysfunction is typically recognized as a core feature of MDD, it is worthwhile to consider the potential interactions among *ESR1* polymorphisms, mood outcomes

and cognitive impairment. A history of depressive symptoms is common in about 20 to 30% of individuals with dementia.¹¹² Hippocampal volume loss, a characteristic of AD, is also reliably observed in patients with MDD.^{113, 114, 115, 116} Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis affects hippocampal and amygdala volume and is evident in both depression and AD each stem in part from.¹¹⁷ Despite these potential links, there is no strong evidence to date that *ESR1* effects on cognitive impairment are related to effects on mood. For example, the x and p alleles were risk factors for memory decline in Caucasian and African American postmenopausal women enrolled in SWAN²³ but were not associated with an increased risk of elevated depression scores.²⁴ Across non-Asian populations, x and p are risk factors for cognitive decline but are associated with decreased risk of depression.

There are many more studies linking mental health outcomes to *ESR1* SNPs than to *ESR2* SNPs. This discrepancy may suggest that ER α receptor is a stronger determinant of mental health outcomes or that there is a publication bias against negative *ESR2* findings. Although the ER α and ER β are similar in structure and function, mechanistic differences between the two receptor subtypes may augment or minimize the effects of polymorphisms on cognition and mood. These differences include the binding and transcription efficacy for non-steroidal ligands¹¹⁸, the levels of circulating 17 β estradiol needed to activate a particular promoter¹¹⁹ and cofactors that help to initiate transcription.¹²⁰ Although *ESR2* is highly polymorphic, there may be fewer functional polymorphisms on the *ESR2* versus *ESR1* gene. To date, one functional *ESR2* polymorphism has been identified in an African American population that influences estrogen binding affinity.¹²¹ Future molecular and genetic association studies with the *ESR2* gene will help to elucidate these possibilities. Finally, no studies have investigated mental health outcomes in relation to the *GPR30* polymorphisms, though *GPR30* is found in the cortex, hippocampus, and locus coeruleus of rodent brain.

Lastly, there is a need for studies focusing on the clinical significance of the *ESR1* polymorphisms in relation to exogenous and endogenous estrogen levels. Bone mineral density has been shown to be more dependent on estradiol levels in men with the X and P alleles compared to men with the xx or pp genotypes.¹²² Additionally, women with the XX or PP genotypes show an augmented response of high-density lipoprotein cholesterol or serum SHBG levels to hormone therapy.³⁵ These findings raise the possibility that *ESR1* genotype might modulate the relationship between endogenous or exogenous estrogen and mental health outcomes. In this way, genetic studies can provide additional insights into inter- and intra-individual differences in the extent to which cognition and mood change with menopause and hormone therapy.

Conclusion

There appears to be strong evidence for a relationship between genetic variants on the *ESR1* gene and cognitive outcomes. The relationships between *ESR1* and cognitive impairment tend to be specific to or driven by women and restricted to risk for Alzheimer's disease rather than other dementia causes. Case-control studies suggest that the X and P alleles of the XbaI and PvuII polymorphisms confer risk, whereas cohort studies suggest that the x and p alleles confer risk. Part of this discrepancy appears to be due to the greater prevalence of Asian cohorts among the case-control studies, as demonstrated in a meta-analysis of case-control studies that demonstrated that X and P are risk factors only in Asian cohorts.⁶⁶ Future studies that include haplotype, ethnicity-specific, and gender-stratified analyses may provide insights into the discrepant results. Most studies examined either Alzheimer's disease or MMSE scores as primary outcomes; only two studies examined comprehensive neuropsychological test batteries. Episodic memory impairment has been shown in numerous studies to be the earliest and strongest neurocognitive predictor of Alzheimer's disease. In the one study to examine *ESR1* polymorphisms in relation to episodic memory performance, the x and p alleles were

uniquely associated with an increased risk of episodic memory impairment in non-demented postmenopausal women. Future studies are needed to evaluate *ESRI* polymorphisms are reliably associated with a lower level of memory performance in non-demented individuals.

Fewer studies have examined *ESRI* variants in relation to mood outcomes, and these studies offer preliminary evidence for a relationship between *ESRI* variants and risk for certain mood disorders including anxiety, depression, childhood-onset mood disorder and premenstrual dysphoric disorder. Future studies are needed to explicitly evaluate whether *ESRI* variants may help to explain the significant individual differences in the extent to which mood and cognition change as a function of reproductive stage, menstrual phase, postpartum, and hormone therapy.

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Figure 1. the genomic organization of the estrogen receptor α gene (*ESR1*) highlighting the positions of the XbaI, PvuII and TA-repeat variants.

Figure 2a.

Figure 2b.

Figure 2.

Figure 2a. (left panel) Summary of findings pertaining to *ESR1* genetic risk factors (RF) for cognitive impairment from case-control studies. Figure 2b. (right panel) Summary of findings pertaining to *ESR1* genetic risk factors (RF) for cognitive impairment from case-control

studies. Although some studies found significant relationships specifically with the XbaI or PvuII SNP and not the other, the main result categories were collapsed into 'X and/or P are RF' and 'x and/or p are RF'. We feel this is justified because the XbaI and PvuII SNPs are in linkage disequilibrium..

Figure 3.

Summary of findings pertaining to *ESR1* genetic risk factors (RF) for anxiety and/or depressive symptoms from case-control and cohort studies. Although some studies found significant relationships specifically with the XbaI or PvuII SNP and not the other, the categories of findings were collapsed into 'X and/or P are RF' and 'x and/or p are RF'. We feel this is justified because XbaI and PvuII are in linkage disequilibrium.

Table 1
Summary of case-control studies investigating *ESR1* polymorphisms and risk of cognitive impairment.

Author (Year)	SNPs Examined	Sample Size (Mean Age $\pm$ SD) & % Female	Ethnicity	Main Finding with <i>ESR1</i> gene
Isoe et al. (1997)	Xbal PvuII	86 sporadic AD patients (76.2 $\pm$ 8.0); 70.9% female 51 older controls (74.9 $\pm$ 6.9); 68.6% female	Asian (Japanese)	Greater prevalence of the X & P alleles in patients vs. controls
Olsen et al. (2006)	PvuII Xbal	208 postmenopausal women with cognitive impairment; 100% female 208 postmenopausal, healthy controls (73.3 $\pm$ 6.4); 100% female	Caucasian (Danish)	Significant association between elevated risk for cognitive impairment and presence of the X allele (OR 1.75; 95% CI 1.05–2.93, $p = .033$). No relationship between PvuII & cognitive impairment
Monastero et al. (2006)	PvuII Xbal <i>APOE</i>	172 probable AD patients; % female not provided 172 older controls (73.3 $\pm$ 8.0)	Caucasian (Italian)	Greater prevalence of the xx genotype in patients vs. controls (OR 1.9, 95% CI 1.2–3.1). No relationship between PvuII & cognitive impairment. No interactive effects of <i>ESR1</i> SNPs and <i>APOE</i> genotype on cognitive impairment.
Ma et al. (2009)	PvuII Xbal 14 other <i>ESR1</i> SNPs	233 AD patients (81.4 $\pm$ 6.7); 84.3% female 245 elderly controls (73.0 $\pm$ 6.3); 75.5% female	Asian (Chinese)	Risk of AD was associated with 5 SNPs located between intron 3 & intron 7 (rs1514348, $p = .027$; rs2347867, $p = .001$; rs6557171, $p = .035$; rs9397456, $p = .024$; rs1801132, $p = .019$), and age of AD onset was associated with 2 SNPs located on exon 2 (rs2077647, $p = .036$) & intron 2 (rs3853248, $p = .011$). No interaction between <i>ESR1</i> SNPs & <i>APOE</i> e4 allele.
Ji et al. (2000)	PvuII Xbal <i>APOE</i> e2, e3, e4	11 familial AD patients (66.3 $\pm$ 7.5); % female not provided 50 early-onset AD patients (60.6 $\pm$ 3.9) 173 late-onset AD patients (78.6 $\pm$ 8.2) 66 VD patients (77.4 $\pm$ 6.9) 17 alcohol-associated dementia patients (67.8 $\pm$ 5.6) 134 healthy elderly control subjects (75.7 $\pm$ 5.5)	Asian (Japanese)	Greater prevalence of the P & X alleles in patients with late-onset AD who carry the <i>APOE</i> e4 allele compared to controls (P 0.51 vs. 0.38; X 0.30 vs. 0.20, all $ps < .01$)
Isoe-Wada et al. (1999)	PvuII Xbal	13 PD patients with dementia (71.9 $\pm$ 5.5); 77% female 71 PD patients without dementia (68.4 $\pm$ 7.5); 72% female 86 AD patients (76.8 $\pm$ 8.0); 70% female 51 older controls (74.9 $\pm$ 6.9); 86% female	Not provided	Compared to controls, the prevalence of the P allele was greater in PD patients with dementia (61.5% vs. 36.3%, $p < .02$) & AD patients (49.4% vs. 36.3%, $p < .05$). Significantly higher prevalence of the X allele in AD patients compared to controls (29.1% vs. 16.7%, $p < .05$).
Mattila et al. (2002)	PvuII	41 patients with pathologically confirmed Parkinson's Disease with Dementia (PDD) (76.0 $\pm$ 6.1); 49% female 59 older controls (76.8 $\pm$ 7.1); 44% female	Caucasian (Finnish)	No association between genotype and risk of PDD or PDD with coexisting AD pathology
Maruyama et al. (2000)	PvuII Xbal	183 patients with clinical AD diagnosis (70 $\pm$ 10.2); 64% female 156 patients diagnosed with AD at autopsy (79.2 $\pm$ 10.4); 55% female 120 older controls (76.6 $\pm$ 15.4); 48% female	Asian (Japanese) Caucasian	No association between genotypes and risk of AD.
Prince et al. (2001)	Xbal	204 sporadic, late-onset AD patients; 61% female 186 older controls; 58% female	Caucasian (Swedish)	No association between the Xbal and risk for sporadic AD
Usui et al. (2006)	PvuII Xbal Myeloperoxidase e Gene –463	205 sporadic AD patients; (69.1 $\pm$ 10.7); 46% female 92 older controls (62.8 $\pm$ 9.0 years); 36% female	Asian (Japanese)	No association between the PvuII, Xbal, or Myeloperoxidase Gene –463 SNPs and risk for sporadic AD

Author (Year)	SNPs Examined	Sample Size (Mean Age $\pm$ SD) & % Female	Ethnicity	Main Finding with <i>ESR1</i> gene
Corbo et al. (2005) 2	PvuII XbaI <i>APOE</i> <i>e2</i> , <i>e3</i> , <i>e4</i>	279 sporadic AD patients (78 $\pm$ 8); 69% female 212 older controls (80 $\pm$ 8); 60% female	Caucasian (Italian)	Significant association between increased risk for AD and PP & XX genotypes in males (OR 3.6, 95% CI 1.2–10.9) and risk of AD was significantly greater for participants who carry the <i>APOE</i> <i>e4</i> allele (OR 13.3, 95% CI 1.7–103.6)
Brandt et al., (1999)	PvuII XbaI <i>APOE</i> <i>e2</i> , <i>e3</i> , <i>e4</i>	193 sporadic, late-onset AD patients (76.1 $\pm$ 8.9); % female not provided 202 older controls (74.6 $\pm$ 7.3)	Caucasian (Italian)	Greater prevalence of both the PP (p = .02) & XX (p = .007) genotypes & the combined PPXX ($\chi^2 = 12$, p = .0001) genotype in patients versus controls. Risk of AD >7 fold in patients with the combined PPXX & <i>APOE</i> <i>e4/e4</i> genotypes (RR 7.6, 95% CI 1.10–62.35; p = .007).
Mattila et al. (2000)	PvuII XbaI <i>APOE</i> <i>e2</i> , <i>e3</i> , <i>e4</i>	Clinic-based sample: 84 familial AD patients (61.6 $\pm$ 8.6); 63% female 81 controls (71.3 $\pm$ 9.4); 67% female Community-based sample: 27 familial AD patients (78.5 $\pm$ 5.7); 100% female 52 sporadic AD patients (81.4 $\pm$ 6.3); 100% female 150 controls (88.6 $\pm$ 3.9); 100% female	Caucasian (Swedish)	An increased risk of familial AD was observed in women who carried the <i>APOE</i> <i>e4</i> allele together with the xx (OR 11.3, 95% CI 2.9–43.8) or pp genotype (OR not provided)
Lambert et al. (2001)	PvuII XbaI ER β exon 8 SNP	186 AD patients (67.9 $\pm$ 12.5); 61% female 405 older controls (62.6 $\pm$ 14.9); 53% female	Caucasian	The frequency of individuals possessing both the XXPP haplotype and the <i>ESR2</i> exon 8 SNP was greater in AD patients vs. controls (OR 0.22; 95% CI 0.05–0.88, p = .02).

Note. Statistical results presented in papers are provided in the table. Statistical significance was determined using an alpha level of $p \leq .05$.

¹ Cognitive impairment was determined by performance on the Six-item Orientation, Memory, Concentration test in Olsen et al. (2006);

² Cognitive impairment was determined by performance on the Mini Mental State Examination (MMSE) in Corbo et al. (2005). Abbreviations: AD Alzheimer's disease, VD Vascular Dementia, PD Parkinson's disease.

Table 2
Summary of prospective cohort studies investigating *ESR1* polymorphisms and cognitive function.

Author (Year)	SNPs Examined	Sample Size (Mean Age $\pm$ SD) & % Female	Ethnicity	Test	Main Finding with <i>ESR1</i> gene
den Heijer et al. (2004)	PvuII XbaI	Cohort study: 6056 older adults & 312 developed dementia (69.0 $\pm$ 8.7); 59% female Imaging substudy: 468 older, non-demented adults; 50% female	Caucasian	MMSE, dementia diagnosis	No association between SNPs & risk of AD or all-cause dementia. Compared to Non-demented women with the PP or XX genotype, non-demented women with the pp or xx genotype had smaller amygdalar (all ps < .05) & hippocampal volumes (p = .10 [PP vs. pp], p = .08 [XX vs. xx]).
Yaffe et al. (2002)	PvuII XbaI	2625 older (> 65 yrs.) women (166 developed cognitive impairment) (70.3 $\pm$ 4.6); 100% female	Caucasian	mMMSE	Significant association between greater MMSE score decline and the p (for PP, Pp, & pp: .6, .8, .9 points, p = .01) or x allele (for XX, Xx, & xx: .7, .7, .9 points, p = .02). Significantly higher frequency of the p allele (OR 1.33, 95% CI 1.03–1.72) and x allele (OR 1.38, 95% CI 1.06–1.81) in women who developed cognitive impairment compared to women who did not.
Yaffe et al. (2009)	4 <i>ESR1</i> SNPs (PvuII, XbaI, rs3798577, rs728524) & 4 <i>ESR2</i> SNPs	1343 older women (73.4 $\pm$ 2.9); 1184 older men (73.7 $\pm$ 2.8); 53% female	Caucasian & African American	mMMSE	Risk of developing cognitive impairment was marginally associated with the p allele (OR 0.65, 95% CI, 0.42–1.01) & significantly associated with the x allele (OR 0.73, 95% CI 0.54–0.99). Significant association between the <i>ESR1</i> rs728524 SNP & cognitive impairment in men (OR = 1.79, 95% CI 1.25–2.57).
Kravitz et al. (2006a)	23 SNPs from the <i>CYP19</i> , <i>CYP11A1</i> , <i>CYP11B1</i> , <i>17HSD</i> , <i>ESR2</i> & <i>ESR1</i> (including PvuII & XbaI) genes	815 mid-life women (49.8 $\pm$ 2.6) from the Study of Women's Health Across the Nation (SWAN); 100% female	Ethnically diverse	Digit Symbol Backwards, Symbol Digit Modalities Test & East Boston Memory Test	Among Caucasian and African American women, those with the XX genotype had higher odds of remembering EBMT story elements compared to those with the xx genotype (OR 1.68, 95% CI 1.15–2.44 [Caucasian women]; OR 1.96, 95% CI 1.18–3.25 [African American women]). Among Caucasian women, those with the PP genotype had higher odds of remembering story elements on the EBMT delayed recall test compared to those with the pp genotype (OR 1.46, 95% CI 1.12–1.91).

Note. Statistical results presented in papers are provided in the table. Statistical significance was determined using an alpha level of $p \leq .05$. Abbreviations: MMSE Mini Mental State Exam, mMMSE Modified Mini Mental State Exam, GMS Geriatric Mental State schedule

Table 3
Summary of studies investigating *ESR1* polymorphisms and mood outcomes.

Author (Year)	SNPs Examined	Sample Size (Mean Age $\pm$ SD) & % Female	Study Type	Ethnicity	Mood Measure	Main Finding with <i>ESR1</i> gene
Tiemeier et al. (2005)	PvuII XbaI	2468 adults (> 55 years) from the Rotterdam population-based cohort study; % female not provided	Population-based association study	Caucasian	Hospital Anxiety & Depression Scale (HADS)	The 'XP' haplotype was associated with increased odds for experiencing anxiety symptoms in women (OR 1.90, 95% CI 1.04–3.48). No associations existed in men or with depressive symptoms.
Comings et al. (1999)	TA-repeat	179 adult males treated for substance abuse (40.9 $\pm$ 6.9); 0% female	Association study	66% Caucasian, 19% African American, 15% Hispanic	Symptom Checklist-90 (SCL-90)	Significant mean differences existed in anxiety scores between genotype groups (LL [1.69 $\pm$ 0.93], SL [1.39 $\pm$ 0.87], SS [1.03 $\pm$ 0.76], $p = .002$). The TA-repeat polymorphism accounted for 7% of the variance in anxiety scores ($p \leq .0004$)
Tsai et al. (2003)	PvuII XbaI	154 patients with MDD (46.8 $\pm$ 17.4); 58% female 226 healthy controls (46.6 $\pm$ 16.6); 56% female	Population-based association study	Asian (Chinese)	21-item Hamilton Depression Rating Scale	Odds of receiving a diagnosis of MDD were almost threefold greater in women with the pp genotype of the PvuII SNP compared to women with the Pp or pp genotype (OR 2.84, 95% CI 1.28–6.31). No associations with the XbaI SNP or in men.
Kravitz et al. (2006)	25 SNPs from the <i>CYP19</i> , <i>CYP11A1</i> , <i>CYP11B1</i> , <i>17HSD</i> , <i>ESR2</i> & <i>ESR1</i> (including PvuII & XbaI) genes	1538 women aged 42–52 from the Study of Women's Health Across the Nation (SWAN); 100% female	Population-based association study	Ethnically diverse	CES-D	No associations between <i>ESR1</i> SNPs & depressive symptoms
Kishi et al. (2008)	PvuII	738 schizophrenia patients (36.6 $\pm$ 18.4); 46% female 155 bipolar patients (45.1 $\pm$ 13.6); 52% female	Case-control	Asian (Japanese)	DSM-IV	No associations between PvuII & schizophrenia, MDD or bipolar disorder

Author (Year)	SNPs Examined	Sample Size (Mean Age $\pm$ SD) & % Female	Study Type	Ethnicity	Mood Measure	Main Finding with <i>ESR1</i> gene
Mill et al. (2008)	11 SNPs in <i>ESR1</i> gene (including PvuII & XbaI)	325 MDD patients (47.5 $\pm$ 16.1); 51% female 802 healthy controls (37.6 $\pm$ 14.3); 56% female	Family-based case-control	Caucasian (Hungarian)	DSM-IV	Significant association between odds of a COMD diagnosis and a haplotype of 3 <i>ESR1</i> SNPs in strong linkage disequilibrium (rs746432, rs2077647, rs532010) specifically in females ($\chi^2 = 6.02$, $p = .05$). No associations existed in men.
Huo et al. (2007)	10 SNPs in <i>ESR1</i> gene (including PvuII & XbaI), 6 SNPs in <i>ESR2</i> gene; <i>COMT</i> Val158Met SNP	91 women with confirmed premenstrual dysphoric disorder (PMDD) (39.5 $\pm$ 5.9); 100% female 56 healthy controls (40.6 $\pm$ 9.0); 100% female	Case-control	Caucasian	Daily visual analog scale of self-rated affective symptoms	Significant association between 4 SNPs in intron 4 of <i>ESR1</i> and odds of PMDD diagnosis specifically in <i>COMT</i> Val homozygotes (all p s < .05)
West-berg et al. (2003)	TA-repeat	172 women of 42 years of age; 100% female	Population-based association study	Caucasian (Swedish)	Karolinska Scales of Personality (KSP)	Significant associations between the TA-repeat polymorphism & KSP scores for the personality factors of non-conformity (53.4 $\pm$ 7.0 [SS] vs. 49.4 $\pm$ 6.3 [LL] & 49.4 $\pm$ 6.8 [SL], $p = .0003$) & psychoticism (50.8 $\pm$ 10.3 [SS] vs. 46.7 $\pm$ 8.8 [LL] & 46.8 $\pm$ 8.8 [SL], $p = .008$)
Prichard et al. (2007)	15 repeat polymorphisms in the <i>DBH</i> , <i>DRD2</i> , <i>MAOA</i> , <i>TFAP2B</i> , <i>NR4A2</i> , <i>LMX1B</i> , <i>AR</i> , <i>ESR1</i> , <i>OXTR</i> , <i>AVPR1A</i>	2096 adults aged 20–24 years from the PATH Through Life Project; 52% female	Population-based association study	Caucasian	A scale comprised of known indicators of anti-social traits	Significant association between a T/G repeat polymorphism in the <i>ESR1</i> gene & antisocial traits in men ($p = .03$)

Note. Statistical results presented in papers are provided in the table. Statistical significance was determined using an alpha level of $p \leq .05$.

Abbreviations: DSM-IV Diagnostic & Statistical Manual of Mental Disorders-IV, CESD Center for Epidemiologic Studies-Depression Scale, SS homozygous for the short allele of TA repeat polymorphism, SL heterozygous for the short allele of TA repeat polymorphism, LL homozygous for the long allele of TA repeat polymorphism.