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Polymorphisms of Estrogen Receptors and Risk of Depression: Therapeutic Implications

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ABSTRACT

Accumulating evidence suggests the involvement of estrogen in depression. Estrogen can modulate neurotransmitter turnover, enhancing the levels of serotonin and norepinephrine and it is involved in the regulation of serotonin receptor number and function. Across the female reproductive life, fluctuating estrogen levels and low levels have been associated with depressed mood and there is strong support for a beneficial effect of estrogen-containing hormone treatment in depressed peri-menopausal women. Estrogen exerts its biological effects in large part through intracellular activation of its principal receptors, estrogen receptor α (ESR1) and estrogen receptor β (ESR2). Genetic variation in the estrogen receptors may therefore modify estrogen signalling, thus influence a woman's susceptibility to developing depression. This systematic review provides a synthesis of studies which have examined the association between estrogen receptor polymorphisms and depression-related mood disorders across the lifetime. Studies were identified through a search of the literature from January 1980 until March 2012 using MEDLINE, Web of Knowledge, Cochrane Library and PsychINFO databases.

The studies conducted to date have produced inconsistent findings, which likely relates to the large heterogeneity in terms of the populations, study design and depression measures used. It appears unlikely that the common ESR1 variants *rs2234693* and *rs9340799* are associated with moderate depressive symptoms in women; however there is some evidence which indicates a significant association with more severe depressive symptoms, major depressive disorder and anxiety. There are too few studies of ESR2 polymorphisms to draw any definite conclusions; however preliminary evidence suggests that specific variants may modify the risk of depression associated with the use of hormone treatment in women. Few studies have investigated associations in men, and they have focused almost exclusively on ESR1, but all report non-significant findings. Much work is therefore still needed in this field.

If it is confirmed that specific estrogen receptor polymorphisms are associated with the risk of depression, this could have important preventative and therapeutic implications with the potential to develop targeted estrogen receptor agonists and antagonists. Furthermore, it is possible that such therapies may be more effective in treating particular people with depression based on their genetic profile, which is an exciting prospect given that many people do not respond to current antidepressant treatments.

1. INTRODUCTION

1.1 Depression

Depression is a prevalent psychiatric condition affecting up to 20% of the general population[1, 2] and 10-20% are diagnosed with a major depressive disorder (MDD) across their lifetime.[3, 4] It is considered a major public health problem, not only due to its high prevalence, but also because the frequency of comorbidity is high,[5-7] and this further worsens the outcome of these health problems and increases the risk of mortality.[8] Depression has been associated with poorer social functioning and a greater risk for physical symptoms and body pain.[2] The quality of life for the people concerned is severely diminished,[9] creating a substantial burden and cost to the community.[10] Women have a higher prevalence of major depression compared to their male counterparts,[3, 6] indicating that female gender is a risk factor. Evidence from family studies suggests there is a genetic component to depressive disorders, however despite the large number of genetic association studies, very few candidate genes have so far been identified.[11]

1.2 Involvement of estrogen

Accumulating evidence suggests the involvement of estrogen in depression.[12, 13] Depression results, at least in part, from a disruption of the normal brain neurochemistry, which includes a change in the level of neurotransmitters and abnormal functioning of the hypothalamic-pituitary-adrenal axis.[14] Serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine are thought to play key roles[15, 16] and treatments which increase the brain levels of these neurotransmitters can improve depressive symptoms.[17] Estrogen can modulate neurotransmitter turnover, which includes enhancing the levels of serotonin and norepinephrine and it is involved in the regulation of serotonin receptor number and function,[18-20] thus controlling the activity of serotonergic neurons. Across the female reproductive life, fluctuating estrogen levels and low levels have been associated with depressed mood[21-24] and changes in serotonergic activity during the female hormone cycle appear correlated with variations in estrogen levels.[25] The menopause transition, which is characterised by fluctuating and declining estrogen levels, is associated with an increased risk of new onset and recurrent depressive episodes.[26-29] Finally, there is strong support for a

beneficial effect of estrogen-containing hormone treatment (HT) in depressed peri-menopausal women,[30] although its use in postmenopausal women remains less certain.[31, 32]

Estrogen exerts its biological effects in large part through intracellular activation of its principal receptors, estrogen receptor α (ESR1) and estrogen receptor β (ESR2).[33] Genetic variation in the estrogen receptors (ESR) may therefore modify estrogen signalling, thus influence a woman's susceptibility to developing depression. The aim of this review is firstly to provide a synthesis of studies published in the literature which have examined the association between ESR polymorphisms and depression; and secondly to evaluate the overall strength of evidence for such an association. The potential therapeutic implications stemming from this research will then be discussed.

2. METHODOLOGY

A systematic literature search was conducted using the MEDLINE, Web of Knowledge, Cochrane Library and PsychINFO databases, covering the period from January 1980 until March 2012 and combining the terms 'depression' or 'depressive disorder' and 'estrogen receptor polymorphisms' or 'estrogen receptor variants'. Citations were limited to articles and reviews written in English and those involving humans. Studies were also identified by manually searching the reference list of relevant articles, as well as previous reviews on this topic. The studies that were included in this review were those that involved the assessment of a mood disorder (depressive symptoms, MDD, premenstrual dysphoric disorder, puerperal psychosis, and bipolar disorder) or other comorbid affective disorders such as anxiety.

3. ESTROGEN RECEPTOR

ESRs are expressed in a variety of tissues including the brain, where they predominate in limbic-related areas known to be important for emotion, cognition and behaviour.[34, 35] ESR1 is translated from an eight exon gene located on chromosome 6q25.1. It is found in high concentrations in the hypothalamus, hypothalamic preoptic area and the amygdala, and in lower concentrations in the hippocampus and cerebral cortex.[34] The more recently identified ESR2 gene[36] is located on chromosome 14q23.2. It appears to be expressed throughout the brain, although dominant areas are the hippocampus, entorhinal cortex and thalamus.[34] This localisation could indicate that ESR1 plays a more important role than ESR2 in emotive

functions and mood.[34] Indeed, patients with MDD have reduced ESR1 mRNA levels in the amygdala than controls[37] and the effects of estradiol on the serotonin 1A receptor have been shown to be mediated via ESR1.[38] On the other hand, more recent work in ovariectomized rats suggests that estrogen's beneficial effect on depression involves the action of ESR2 in the hippocampus[39] and in mice, estradiol's antidepressant-like effect was also shown to be mediated through ESR2 activation.[40]

Overall, the ESR subtypes share a high degree of sequence homology. With an almost homologous DNA-binding domain (95% identity), they bind to the same DNA response elements. The subtypes also share many functional similarities in terms of substrate binding affinities, including that for estradiol,[36] with 60% identity in the ligand-binding domain. However subtype-selective differences in ligand binding and transcriptional potency have also been reported for novel non-steroidal ligands.[33]

3.1 Signalling

Both ESR subtypes are members of the superfamily of nuclear receptors that regulate transcription in target genes containing estrogen response elements (ERE). In ligand-dependent cell signalling, estrogen, which readily crosses the blood brain barrier, binds to both ESRs inside the cell and the complex then diffuses into the nucleus and binds to a number of specific ERE on various genes. This complex is capable of regulating the expression of hundreds of genes, including genes involved in regulating the synthesis and metabolism of several neurotransmitter systems.[41, 42] The intracellular concentration of the ESRs appears to be correlated to the cellular response to estrogens,[43] with both receptors being upregulated in response to bioavailable estradiol levels.[44] The relative levels of ESR1 and ESR2 in a given cell also influences the estrogen-response. Increased expression of ESR2 can antagonise ESR1 mediated transcription[45, 46] and the two receptors can have opposing effects on gene expression.[47] They can however, also dimerise and work co-operatively.[48]

3.2 Estrogen receptor polymorphisms

Given the putative role for estrogen in depression, variants in the genes coding for the ESR are good candidates to help explain an individual's susceptibility to developing depression. Furthermore, allelic variants in these genes could explain the differential response of women to estrogen-containing HT.[49] Polymorphisms are the presence of more than one allele at a gene locus with a frequency of greater than one percent, and a single nucleotide polymorphism (SNP) more specifically, results from a single nucleotide change at the level of

the DNA sequence. The two most frequently studied polymorphisms are ESR1 *rs2234693* and *rs9340799*, otherwise known as *Pvu*II and *Xba*I due to the creation of the aforementioned restriction site. They are located at position 397 and 351 of intron 1 respectively and are in strong linkage disequilibrium,[50, 51] meaning that certain combinations of alleles occur more frequently in the population than would be expected by random assortment. There is evidence that these polymorphisms are functionally significant, as they may alter transcription factor binding[52] and gene expression.[53] These polymorphisms have also been associated frequently, but not consistently, with a variety of hormone-related health outcomes, such as bone mineral density,[54, 55] vasomotor symptoms,[56] age at menopause,[57] breast cancer[58] and cardiovascular disease,[59, 60] as well as other brain disorders like Alzheimer's disease.[61] These polymorphisms are in strong linkage disequilibrium with the tandem variable repeat TA polymorphism,[62] located in the promoter region of ESR1. The TA-repeat can influence tissue-specific gene expression[63] and has also been associated with bone mineral density[64] and cardiovascular disease.[65] In a similar manner, associations have been reported between various ESR2 polymorphisms and these same health outcomes.[54, 66-73] It therefore seems likely that both ESR1 and ESR2 polymorphisms could also influence an individual's risk of depression.

4. ESTROGEN RECEPTOR POLYMORPHISMS AND DEPRESSION

Table 1 presents a summary of the 19 studies which have examined the association between ESR polymorphisms and mood disorders across the lifetime. The studies vary considerably regarding the populations (ethnicity, age, gender), and the study size and design (case-control, cohort, clinical sample, general population), which may help explain the mixed findings. The assessment of depression also varies, with eight studies focusing on MDD, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and a similar number on depressive symptomatology. This large heterogeneity between studies makes direct comparisons difficult. Only three studies examined depression in later-life, including a study of depressive symptoms in participants aged at least 55 years and our two studies of severe depressive symptoms and MDD in the elderly.[74, 75]

4.1 ESR1 and depression in women

There is no support for an association between mild or moderate depressive symptoms and *rs2234693* or *rs9340799* in women across the lifetime, irrespective of ethnicity, age,

depression evaluation, sample and study design.[56, 76-80] The only two studies to examine other SNPs (*rs728524* and *rs3798577*)[77] and the dinucleotide TA repeat[76] also reported no significant association with depressive symptoms. In accordance with these findings, we reported no significant association between either *rs2234693* or *rs9340799* and mild depressive symptoms among 3525 elderly women.[74] On the other hand, when we examined severe depressive symptoms (CES-D ≥23), we found an increased risk for women TT for *rs2234693* or AA for *rs9340799* (p=0.003 and p=0.009 respectively), compared to women homozygous for the alternative allele.[74] Importantly this association held even after adjustment for numerous potential confounders including past depression.

Of the studies which have examined a diagnosis of MDD in women, equal numbers involved Caucasian and Asian populations. Significant associations were reported with *rs2234693* or *rs9340799* in five of six studies.[74, 75, 81-83] In a Korean case-control study of postmenopausal women, the 43 depressed women were significantly more likely to be heterozygote for *rs2234693* and *rs9340799* compared to the 63 non-depressed controls (p≤0.001).[81] By contrast, among 215 middle-aged Chinese women, the C and G alleles of *rs2234693* and *rs9340799* respectively were more frequent in women with MDD (p=0.004 and p=0.02 respectively).[83] In both studies only non-adjusted results were reported. Our study of the association between *rs2234693* and *rs9340799* with lifetime MDD in older women, supports the findings of Tsai *et al.*[83], even after adjustment for age, education level, the use of antidepressants or HT and bilateral oophorectomy.[75] Furthermore, our study showed that the *rs2234693 GG* genotype was particularly associated with an increased risk of recurrent depressive episodes, regardless of the timing of episodes in relation to the menopause (p=0.02 and p=0.006 for episodes occurring before or after the menopause, respectively). No significant association was found with a single MDD episode. Other ESR1 polymorphisms have also been associated with childhood-onset mood disorders in girls[82] and premenstrual dysphoric disorder.[84] However, no significant association has been found between either the common or rare ESR1 variants and Puerperal Psychosis, or bipolar 1 disorder.[85-87]

4.2 ESR2 and depression in women

Fewer studies have investigated whether ESR2 polymorphisms are associated with depression. Two studies of Asian populations found that the dinucleotide CA length was significantly associated with depression. In a small study of postmenopausal women, those reporting depressive symptoms were more likely to have one extremely short and one long

allele ($p<0.01$),[72] while a slightly larger study of female adolescents reported a higher frequency of short alleles in those diagnosed with first onset MDD ($p<0.001$).[88] Of the other SNPs which have been investigated in more than one study, no significant association has been found between either *rs4986938* or *rs1256049* and severe depressive symptoms in women.[74, 81] However, when we considered the use of HT among elderly women,[74] the A allele of *rs1256049* was associated with an increased risk of severe depressive symptoms among women who were not using HT ($p=0.005$). For women currently taking HT, the A allele was not associated with an increased depression risk. This suggests a gene-environment interaction whereby some genetically predisposed women may benefit most from HT. To date, no other study has explored the potential interaction between ESR genetic variability and HT use in terms of depression risk.

4.3 Estrogen receptor polymorphisms and depression in men

Given that estrogen is the principal female reproductive hormone, and that estrogen-containing hormone treatment is used by menopausal women to relieve symptoms associated with low estrogen levels, it is probably not surprising to find that the majority of studies in this area have focused only on females. The six studies involving men which have examined whether the ESR1 *rs2234693* and/or *rs9340799* polymorphisms were associated with depressive symptoms or MDD, all failed to find a significant association irrespective of age and ethnicity.[74, 76, 79, 82, 83, 87] This was also the case for the ESR1 dinucleotide TA repeat.[76, 89] Our study was the only one to investigate ESR2 polymorphisms in men[74] and we reported no strong evidence of an association with severe depressive symptoms. The AA genotype of *rs4986938* however, was associated with an increased risk that was of borderline significance ($p=0.05$).

4.4 Estrogen receptor polymorphisms and other affective disorders

Five of the studies described above also examined associations with anxiety disorder. Two studies found no significant associations with either depression or anxiety in women,[56, 78] while the others reported significant findings with anxiety only.[76, 79, 89] The Rotterdam study of men and women aged 55 years and older found that a haplotype consisting of the T and A alleles of *rs2234693* and *rs9340799* respectively was associated with an increased risk of anxiety in women ($p=0.02$), and in particular anxiety without comorbid depression symptoms.[79] This is supported by our study of elderly women where we found that the C and G alleles of *rs2234693* and *rs9340799* were associated with a decreased risk of phobia

independently of comorbid depression (p=0.003 and p=0.03 respectively).[90] Conversely, a longitudinal study of children reported higher anxiety scores in those homozygous for the C and G alleles of *rs2234693* and *rs9340799*, if they also had the short TA-repeat polymorphisms (p<0.05).[76] But this is again contradicted by a study in adult male patients where the short TA allele was associated with reduced anxiety scores (p<0.002).[89] In regards to other anxiety disorders, a significant association was found between ESR1 *rs34535804* and an obsessive-compulsive disorder subphenotype in adults (p=0.007),[91] and the A allele of ESR2 *rs1256049* was associated with generalized anxiety disorder in elderly women (p=0.02).[90]

4.5 Summary

Studies which have investigated the association between ESR1 and depression have produced inconsistent findings, which likely relates to the differences in populations and depression measures. It appears unlikely that the ESR1 variants *rs2234693* and *rs9340799* are associated with moderate depressive symptoms in women; however an association with more severe depressive symptoms, MDD and anxiety is possible. There are a lack of studies on later-life depression, which is distinct from depression at younger ages, and likewise, few studies of older postmenopausal women who have low endogenous estrogen levels. There are too few studies of ESR2 polymorphisms to draw any conclusions, although animal data clearly suggests an important role for this receptor in psychiatric disorders (see for review[13]). Results originating from our own study suggest that HT use may modulate the increased risk of late-life depression associated with a specific ESR2 variant, however no subsequent study has yet attempted to replicate these findings. Studies have also failed to test whether the ESR1 and ESR2 receptors could interact to influence the risk of depression, although these receptors can form heterodimers[48]. Such a gene-gene interaction has been shown to modify the risk of Alzheimer's disease[92] and we have recent unpublished results suggesting a significant ESR1-ESR2 interaction on the risk of late-life depression.

Only a small number of studies have investigated the association between ESR polymorphisms (almost exclusively ESR1) and depression in men. All report non-significant findings. A gender-specific association between ESRs and depression could be explained by differences in receptor subtype expression levels in various brain regions, as well as sex dimorphism in brain morphology, neurochemistry and neuronal wiring.[93] However, more research using independent samples is required in this field before definite conclusions can be drawn.

5. THERAPEUTIC IMPLICATIONS

5.1 Therapeutic Potential

If it is confirmed that specific ESR polymorphisms are associated with the risk of depression, this could have important therapeutic implications. This includes the possibility of screening for people who are most at risk of depression and the potential to develop targeted ESR agonists and antagonists. Another exciting prospect is pharmacogenetics, with the possibility of predicting genetically which women would benefit most from HT in terms of depressed mood.

The regulation of ESR1 and ESR2 is complex and the exact mechanisms by which ESR polymorphisms can modify estrogen signalling remain unknown. The most commonly studied variants, ESR1 *rs2234693* and *rs9340799* for example, are silent mutations but they could still have important functional consequences by affecting mRNA structure,[94] stability and receptor synthesis,[95] and they may involve regulatory sequences.[91, 96] Indeed, these polymorphisms have been shown to regulate the expression of the ESR1[53] and alter transcription factor binding[52] and thus could modify estrogen-mediated signaling. Specific alleles of these polymorphisms (C of *rs2234693* and G of *rs9340799*) may be associated with increased serum estradiol levels,[71, 97] but this has not been found consistently.[56, 98] Futhermore, studies which have examined whether these same alleles are associated with more favourable estrogen-dependent outcomes,[91, 99, 100] including the studies of depression and anxiety presented here, have reported conflicting results. The exact reasons for these discrepancies remain to be elucidated, but alterations in ESR1 mRNA expression in the brain may be region, diagnosis and gender-specific.[37, 101] These ESR1 polymorphisms may have reverse effects in different ethnic populations,[102] and there may be differential interactions with other genes and environmental factors. In terms of other SNPs, there is variable evidence for a direct biological significance or an association with human disease.

Further knowledge of the functional consequences of ESR polymorphisms will allow a better understanding of the mechanisms by which they can influence estrogen signalling and thus depression. This will be invaluable for the development of new and effective ESR-subtype selective agonists and antagonists,[103] in particular those that target the brain, while avoiding activation of ESR in other tissues.[104] This will enable future improvements in clinical applications by allowing tailored treatment based on an individual's genetic make-up.

Considering that ESR1 and ESR2 appear to have overlapping but also unique biological functions, it is most likely that receptor subtype-specific coregulators exist. Identification of new coregulators may also provide novel targets for the development of new classes of therapeutic drugs with potential use in the treatment of diseases involving ESR signalling, which could include depression and anxiety.

5.2 Pharmacogenomics

There is a growing body of literature which suggests that individuals have a variable sensitivity to HT, which alters the efficacy or toxicity of such treatments. ESR polymorphisms have been shown to modulate the effect of HT on a variety of health outcomes including bone mineral density,[55, 105] breast cancer,[106] cholesterol levels[51, 107] and cardiovascular disease.[49] Pharmacogenetic studies in osteoporosis for example, suggest that women with the C and G alleles of *rs2234693* and *rs9340799* respectively may have a greater sensitivity to HT,[99] benefiting more from its protective effects. Women homozygous for these alleles have also been shown to be less susceptible to the negative effects of HT on the breast[108] and may have a reduced risk of all-cause deaths with the use of HT.[50] In terms of depression and anxiety, there are only some very preliminary results of an interaction between HT and ESR polymorphisms,[74, 90] but these suggest the possibility that some women may be genetically more susceptible than others to the psycho-protective effects of HT. This is an exciting prospect and could help explain the variable effects of HT when given to peri- and post-menopausal women.

6. CONCLUSION

Much work is still needed to clearly define the role of ESR polymorphisms in depression and the potential for preventative or therapeutic interventions. There is some support for an association between severe depression or MDD and common ESR1 polymorphisms in midlife and older women. There are too few studies to draw conclusions regarding other polymorphisms or associations in men. There is also preliminary evidence that ESR polymorphisms can modify the effect of HT on numerous health outcomes, including depression and anxiety, however this requires replication. If ESR polymorphisms were established to be associated with depression risk, the clinical use of these polymorphisms to help identify people most at risk of depression would be limited, if the effects of these polymorphisms on disease risk were relatively modest. However, an association between ESR

polymorphisms and depression could still have potentially important therapeutic implications, such as the development of ESR-specific targeted hormone therapies. Furthermore, it is possible that such therapies may be more effective in treating particular people with depression based on their genetic profile, but this would first require confirmation through clinical trials. This is an exciting prospect given that over 35% of people do not respond to current antidepressant treatments[109] and antidepressants may be less effective in postmenopausal women in particular,[110, 111] due to the moderating effects of low estrogen levels on serotonergic neurotransmission.[112] Estrogen-based HT and novel non-steroidal ligands would thus be of particular benefit to depressed persons who are unresponsive to other forms of treatment, or it could be given concurrently with antidepressants, which has already proven to be effective in peri- and post-menopausal women.[113-116]

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Table I: Studies across all ages investigating the association between estrogen receptor gene variants and depression measures

Publication	Study characteristics (mean age +/ SD yrs)	Country (ethnicity)	Gene variant	Depression measure (reported prevalence)	Main finding : genetic profile of « depressed » subjects
MILD DEPRESSIVE SYMPTOMS					
Prichard et al., 2002[76]	Longitudinal cohort study of 680 boys and girls followed from 4-6 months until 15-16 yrs	Australia (mostly Caucasian)	*ESR1: rs2234693, rs9340799,* TA-repeat	Depressive symptoms using the DSM-III-R derived scale of depression and the Short Mood Feelings Questionnaire	-No significant associations in boys or girls
Comings et al., 1999[89]	Observational patient-based study, 179 adult male from an Addiction Treatment Unit (40.9 +/- 6.9 yrs)	America (19% African, 15% Hispanic 66% other Caucasian)	*ESR1:* TA-repeat	Depressive symptoms using The Symptom Checklist 90 (SCL-90)	-No significant association
Kravitz et al., 2006[77]	Observational population-based study of 1435 pre- and peri- menopausal women 42-52 yrs (46 yrs)	America (African American, Caucasian, Chinese, Japanese)	*ESR1: rs2234693, rs728524, rs3798577 ESR2: rs1256030*	Depressive symptoms assessed with CES-D ≥ 16 (13-26% depending on ethnic group)	-No significant associations in any ethnic group
Zhou et al., 2012[78]	Case-control population-based study of peri- and post-menopausal women, 78 cases, 72 controls. 40-60 yrs (52 +/- 5 yrs)	China (not stated)	*ESR1: rs2234693, rs9340799*	Depression symptoms based on 17-item Hamilton Depression Rating Scale (HDRS) ≥17 & symptoms for ≥ 2 weeks & decline in functioning	-No significant associations (only examined combined group of women with depression and/or anxiety)
Malacara et al., 2004[56]	Observational population-based study of 177 postmenopausal women ≥45 yrs (53 +/ 5 yrs)	Mexico (not stated)	*ESR1: rs2234693, rs9340799*	Depressive symptoms using the modified 9-item HDRS	-No significant association
Takeo et al., 2005[72]	Observational study of outpatients. 51 postmenopausal women ≥45 yrs.	Japan (Japanese)	*ESR2 :* CA-repeat	Menopausal depressive symptoms assessed using a questionnaire.	-Increased frequency of genotype EL - one extremely short and one long allele ($p<0.01$)

Tiemeier et al., 2005[79]	Observational population-based study of 2268 men & postmenopausal women ≥55 yrs	Netherlands (Caucasian)	*ESR1: rs2234693, rs9340799*	Depressive symptoms assessed with CES-D ≥ 16 (7.8%) and depressive disorder based on DSM-IV (3.2%)	-No significant association in men or women
Yalamanchili, Gallagher, 2012[80]	Secondary analysis of data from a double-blinded placebo-controlled trial of 412 postmenopausal women. 65-77 yrs (71.4 +/- 3.6 yrs).	America (not stated)	*ESR1: rs2234693, rs9340799*	Depressive symptoms using the Geriatric Depression Scale (GDS), Long Form 30, ≥11 (12%)	-No significant associations
SEVERE DEPRESSIVE SYMPTOMS AND MDD					
Mill et al., 2008[82]	Family-based study of 460 affected boy and girl patients aged 7-16 yrs and their families	Hungary (94% Caucasian)	*ESR1: rs2234693,* 10 other SNPs	Childhood onset mood disorder (COMD) meeting DSM-IV criteria, using The Interview Schedule for Children and Adolescents Diagnostic Version	-No significant association with any individual SNPs but haplotype of 3 SNPs *(rs2077647, rs746432, rs532010)* associated with the risk of Childhood onset mood disorder in females only (p=0.05)
Geng et al., 2007[88]	Case-control study of female adolescents, 102 patients, 150 control volunteers, 15-18 yrs (15 yrs)	China (Han Chinese)	*ESR1:* TA-repeat *ESR2:* CA-repeat	First-onset MDD based on DSM-IV	-No significant association with ESR1 -Higher frequency of short ESR2 alleles (p<0.001)
Huo et al., 2007[84]	Case-control population-based study of menstruating women. 91 cases, 56 controls (40 +/ 7 yrs)	America (Caucasian)	*ESR1:* 16 SNPs[1] *ESR2: rs1256030, rs1256061, rs1952586, rs6573553, rs7159462, rs8017441*	History of Premenstrual Dysphoric Disorder and a high self-rated affective symptom score meeting DSM-IV criteria.	-4 SNPs in intron 4 of *ESR1* significantly associated with Premenstrual Dysphoric Disorder: *rs1884051* (p=0.04), *rs3003917* (p=0.02), *rs3020314* (p=0.02), and *rs3020377* (p=0.04) -No significant associations with ESR2
Kishi et al., 2009[87]	Case-control study of adults, 325 patients, 802 controls, 51% women. (40.4 +-/ 14.8 yrs). Menopause status not detailed.	Japan (Japanese)	*ESR1: rs2234693*	MDD based on DSM-IV	-No significant association in men and women.
Tsai et al., 2003[83]	Case-control study of adults, 154 patients, 226 controls, 57% women. (47 +/- 17 yrs). Menopause status not detailed. .	Taiwan (Han Chinese)	*ESR1: rs2234693, rs9340799*	MDD based on 21-item HDRS >18, then diagnosis according to DSM-IV	-In women only, the *rs2234693* C allele (p=0.004), the CC genotype (p=0.01) & *rs9340799* G allele was more frequent (p=0.02)

Kim et al., 2010[81]	Case-control population based study of postmenopausal women, 43 cases, 63 controls. 45-60 yrs (50 yrs)	Korea (Korean)	*ESR1 rs2234693, rs9340799 ESR2: rs1256049, rs4986938*	Depression assessed using the Beck Depression Inventory (BDI) >21 and DSM-IV diagnosis of MDD or depressive disorder	-Higher frequency of *rs2234693* & *rs9340799* heterozygotes (p≤0.001)
Ryan et al., 2011[74]	Observational population-based study of 6017 elderly men and women ≥65 yrs (73.5 +/- 4.9 yrs).	France (likely Caucasian population[2])	*ESR1: rs2234693, rs9340799 ESR2: rs1256049, rs1271572, rs4986938*	-Severe depression defined as severe symptoms, CES-D ≥ 23 or a current diagnosis of MDD according to DSM-IV criteria, based on the MINI (9.4%). -Depressive symptoms, CES-D ≥ 16 (27.3%)	-Among women, higher frequency of *rs2234693* TT (p=0.003) or *rs9340799* AA (p=0.009) -Higher frequency of A allele of *rs1256049* in women not using hormone treatment (p=0.005) -Higher frequency of *rs4986938* AA genotype in men (p=0.05) -No significant association with mild depressive symptoms in either gender.
Ryan et al., 2012[75]	Observational population-based study of 3987 elderly women ≥65 yrs (73 +/- 5.5 yrs).	France (likely Caucasian population[2])	*ESR1: rs2234693, rs9340799*	Lifetime MDD assessed using the MINI according to DSM-IV criteria (11.7%)	-Higher frequency of homozygotes for G allele of *rs9340799* (p=0.009) for recurrent episodes in particular, regardless of the age at first onset relative to the menopause.
PUERPERAL PSYCHOSIS AND BIPOLAR I DISORDER					
Jones et al., 2000[85]	Case-control study of adult men and women. 210 patients (26 women with Puerperal Psychosis), 208 controls (45 +/- 11 yrs)	United Kingdom (Caucasian)	*ESR1: rs2234693, rs9340799*	Bipolar 1 disorder based on DSM-IV and self-reported Puerperal Psychosis based on DSM-IV for parous women	-No significant associations in men or women for Bipolar disorder or Puerperal Psychosis.
Feng et al., 2001[86]	Mixed patient populations. 28 with Bipolar Disorder, 24 females with Puerperal Psychosis, 188 other psychiatric disorders (45 +/- 11 yrs)	United Kingdom (Caucasian, see [85])	*ESR1:* Gene scan, rare variants	Bipolar 1 disorder based on DSM-IV and self-reported Puerperal Psychosis based on DSM-IV for parous women	-No significant associations in men and women.
Kishi et al., 2009[87]	Case-control study of adults, 155 patients, 802 controls, 52% women. (38.8 +-/ 14.2 yrs). Menopause status not detailed.	Japan (Japanese)	*ESR1: rs2234693*	Bipolar based on DSM-IV	-No significant association in men and women

[1]Did not include either *rs2234693* or *rs9340799*; [2]French law prohibits the collection of ethnic-related data however genotype frequencies were similar to those previously observed in Caucasian populations.

CES-D = Center for Epidemiologic Studies Depression Scale; MDD = Major Depressive Disorder; MINI = Mini-International Neuropsychiatry Interview; SNP = single nucleotide polymorphism; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Hamilton Depression Rating Scale (HDRS); GDS = Geriatric Depression Scale; BDI = Beck Depression Inventory; COMD = Childhood onset mood disorder