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Estrogen associated gene polymorphisms and their interactions in the progress of Alzheimer's disease

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ABSTRACT

The extensive neuroprotective effects of estrogen against Alzheimer's disease (AD) have been proven in numerous laboratory studies. However, in clinical studies, the exact role of estrogen in AD is still ambiguous. Some evidences even suggested the high levels of estrogen or estrogen replacement treatment increased the risk of AD. Thus, there must be other factors affecting the neuroprotective effects of estrogen. Multiple enzymes and receptor proteins are involved in the biosynthesis, metabolism and signaling pathways of estrogen, and mediate the beneficial effects of estrogen on AD. Previous studies have suggested some polymorphisms of genes encoding these enzymes and proteins are associated with the risk of AD. In addition to the genes associated with estrogen biosynthesis and metabolism and the genes encoding estrogen receptor proteins, some other genes also modulate the effects of estrogen on AD, or interact with other estrogen-associated genes on the progress of AD. The gene-hormone and gene-gene interactions may be key to unraveling the conflicting results regarding the effect of estrogen on AD. In this paper, we will review and discuss the associations between polymorphisms of these genes and their interactions and the susceptibility to AD. A better understanding of these estrogen-associated genes is significant to explore the pathogenesis of AD.

Contents

Abbreviations: AD, Alzheimer's disease; Aβ, β amyloid peptide; ERT, estrogen replacement therapy; ESR, estrogen receptor; E1, estrone; E2, estradiol; E3, estriol; CYP, cytochrome P450; CYP11A1, cytochrome P450 cholesterol side chain cleavage enzyme; HSD-3β, 3β-hydroxysteroid dehydrogenase; CYP17, 17α-hydroxylase/17, 20-lyase; DHEA, dehydroepiandrosterone; 17β-HSD, 17β-hydroxysteroid dehydrogenase; SULTs, sulfotransferases; UGTs, UDP-glucuronosyltransferases; COMT, catechol-O-methyltrasferase; GSTs, glutathione-S-transferases; ApoE, apolipoprotein E; AAO, age-at-onset; VNTR, variable-number tandem repeat; RFLP, restriction fragment length polymorphism; MMSE, Mini-Mental State Examination; NCD, non-coding deletion; HDL, high density lipoprotein; FAD, familial Alzheimer's disease; VLDLr, very low density lipoprotein receptors; LDLr, low density lipoprotein receptor; LRP, lipoprotein receptor related protein; seladin-1, selective Alzheimer's disease indicator-1; FNC, fetal neuroepithelial cell; ChAT, choline acetyltransferase; BuChE, butyrylcholinesterase; ACh, acetylcholine; ChE, cholinesterase; AChE, acetylcholinesterase.

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1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by progressive cognitive impairment sufficient to affect functional capacities and cause altered behavior and language deficit. It is the most common dementia and the major cause for senile dementia. Among people aged over 60, the estimated global prevalence of dementia was 24.3 million in 2001. This number is predicted to double every 20 years, and will reach over 80 million by 2040 (Ferri et al., 2005).With the increase of life expectancy, AD has become a global problem. AD affects patients' quality of life, places a great burden on caregivers, and has serious socioeconomic implications. The annual cost per person with dementia exceeds that for patients with cancer or cardiovascular disease (Hampel et al., 2011). Thus, understanding the pathogenesis and risk factors for AD is of great significance.

In previous studies, AD has been found to be more prevalent in women (Andersen et al., 1999; Bachman et al., 1992; Fratiglioni et al., 1997) and this increase in prevalence has drew the attention of researchers because of the effect of estrogen, which declines rapidly after menopause. Numerous laboratory studies have demonstrated the neuroprotective effects of estrogen against AD. Estrogen may protect against the age-related atrophy of hippocampus, a key area of the brain involved in memory function (Eberling et al., 2003). In addition, estrogen enhances the outgrowth and survival of neurons in culture (Brinton et al., 1997). Previous studies have also reported that estrogen can induce an increase of dendritic spines and synapses in hippocampal CA1 pyramidal cells (Woolley et al., 1997). Using neuronal cell lines, previous studies demonstrated the antioxidant and anti-apoptosis functions of estrogen (Ba et al., 2004; Chiueh et al., 2003). Estrogen regulates multiple neurotransmitter systems, including cholinergic, serotonergic and dopaminergic systems, which have degenerative changes in patients with AD (Craig and Murphy, 2009). The deposition of extracellular β amyloid peptide (Aβ) and the presence of neurofibrillary tangles are the neuropathological hallmarks of AD. Estrogen can inhibit the formation of Aβ plaques (Morinaga et al., 2007, 2011; Yue et al., 2005), accelerate Aβ degradation (Merlo and Sortino, 2012), and protect against Aβ-induced neuronal death (Yao et al., 2007). Previous studies have also shown that estrogen prevents the hyperphosphorylation of tau protein, which forms neurofibrillary tangles (Alvarez-de-la-Rosa et al., 2005).

Taken together, these observations demonstrate that estrogen exerts a broad range of protective effects against AD progression. Therefore, estrogen replacement therapy (ERT) is regarded as a potential treatment for AD. However, in an actual patient population, the precise role of estrogen in AD is still ambiguous. First, not all studies have shown gender differences in the prevalence and incidence of AD. Some recent studies, especially those performed in America, have suggested that males and females have a similar prevalence of AD after controlling for age (Hebert et al., 2001), and the incidence did not differ significantly between genders up to an advanced age (Edland et al., 2002; Ruitenberg et al., 2001). Second, serum levels of estrogen are not always significantly lower in patients with AD compared to controls; some studies reported comparable or even higher levels of estrogen in patients with AD (Cunningham et al., 2001; Paoletti et al., 2004). Furthermore, menopause status and the decline of estrogen levels are not necessarily associated with cognitive impairments (Herlitz et al., 2007). Some previous studies suggested that estrogen levels were not related to cognitive performances in women (Thal et al., 2003; Yaffe et al., 1998). Finally, early studies suggested that estrogen deficiency increased the risk of AD, and that ERT was useful in preventing AD (Paganini-Hill and Henderson, 1994; Yaffe et al., 2000b). However, other evidences showed that high concentrations of estrogen were not necessarily associated with beneficial effects on AD or cognitive ability (den Heijer et al., 2003), but resulted conversely in an increase in the risk of AD and the rate of cognitive decline (Geerlings et al., 2003; Ravaglia et al., 2007; Yaffe et al., 1998). The adverse effects of ERT on the incidence of cognition and dementia was supported by the Women's Health Initiative Memory Study (Espeland et al., 2004; Shumaker et al., 2004), a large multicenter, randomized, double-blind, placebo-controlled clinical trial, which cautioned regarding the application of ERT in AD.

These controversial results indicate that the level of estrogen is not the only factor that determines the effect of estrogen on AD. The synthesis, metabolism and signaling pathways of estrogen are complex. Multiple enzymes and receptor proteins are involved in this process, and affect the levels and physiological effects of estrogen. Thus, the genes encoding these enzymes and proteins may interfere with the effects of estrogen on AD, contribute to the failure of ERT, and furthermore, increase the risk of AD. In addition to these estrogen biosynthesis and metabolism genes and estrogen receptor (ESR) protein genes, some other genes also modulate the effects of estrogen on AD, or interact with other estrogen-associated genes, thereby, contributing to the progression of AD. These gene-hormone and gene-gene interactions may be key to unraveling the conflicting results regarding the effect of estrogen on AD.

A few previous studies reviewed the associations between estrogen related genes and the susceptibility of AD, which mainly focused on aromatase (CYP19, an estrogen synthesis gene), catechol-O-methyltrasferase (COMT, an estrogen metabolism gene), and the ESR1 gene (Hiltunen et al., 2006; Serretti and Olgiati, 2012; Sundermann et al., 2010). We will systematically review the associations between the risk of AD and the estrogen

synthesis and metabolism genes, ESR genes and genes affecting the neuroprotective effects of estrogen. We will not only summarize the current literatures regarding the relationship between estrogen associated genes and AD, but we will also analyze the probable factors and gene–gene interactions that may cause the inconsistent results.

A comprehensive systematic review was performed using MEDLINE and EMBASE databases from inception to December 2012. We used combinations of the following items: estrogen, gene, polymorphism, mutation, variation, Alzheimer's disease, AD, synthesis, metabolism, 17α-hydroxylase/17, 20-lyase, CYP17, aromatase, CYP19, catechol-O-methyltrasferase, COMT, CYP1A1, glutathione-S-transferase, GST, GSTM1, GSTM3, GSTM4, GSTO1, GSTO2, GSTP1, GSTT1, GSTZ1, estrogen receptor, ER, ESR, ERα, ER1, ERβ, ER2, ESRα, ESR1, ESRβ, ESR2, apolipoprotein E, ApoE, seladin-1, acetylcholine, ACh, choline acetyltransferase, ChAT, butyrylcholinesterase, BuChE, BCHE, neprilysin and NEP. We did not use any language restrictions. The references of all relevant articles were also searched.

2. Biosynthesis and metabolism of estrogen

Estrogen is a group of chemically similar hormones, which involve in the estrous cycle of human and other animals, and are necessary for development of female characteristics and reproduction. The major forms of estrogen contain estrone (E1), estradiol (E2) and estriol (E3), with E2 being the predominantly biological one. The secretion and delivery of estrogen in brain consist of three pathways, including (1) peripheric organs such as ovaries produce estrogens which then release into blood and finally bind to neuronal ESRs; (2) paracrine: estrogens are locally synthesized through the aromatization of androgen and transported to adjacent targeted neurons, and (3) autocrine: the same individual neuron cells, in which the ESRs and aromatase co-expressed, are not only the resource of estrogens but also the targets (Rajoria et al., 2011).

The biosynthesis and metabolic pathway of estrogen is complex, and involves several enzymes. Considering that the focus of our review is estrogen-associated genes, including the genes that encode for these estrogen biosynthesis and metabolism enzymes, we introduce the pathway of estrogen synthesis and metabolism briefly (see Fig. 1), and focus on the effects of the related enzymes.

First, the cytochrome P450 (CYP) cholesterol side chain cleavage enzyme (CYP11A1) catalyzes the initial step in steroid biosynthesis, and promotes the conversion from cholesterol into pregnenolone. Next, the 3β-hydroxysteroid dehydrogenase (HSD-3β) enzyme catalyzes pregnenolone conversion into progesterone. The 17α-hydroxylase/17, 20-lyase (CYP17) has both 17α-hydroxylase and 17, 20-lyase activities. The CYP17 enzyme catalyzes two key reactions in the production of estrogen (Vasaitis et al., 2011). The 17α-hydroxylase catalyzes the conversion from pregnenolone to 17α-hydropregnenolone, and progesterone to 17α-hydroprogesterone, respectively. Then, the 17, 20-lyase further converts the 17α-hydropregnenolone to dehydroepiandrosterone (DHEA), and 17α-hydroprogesterone to androstenedione. The HSD-3β enzyme also converts DHEA to androstenedione. There are bidirectional reactions between androstenedione and testosterone. Androstenedione can be converted into testosterone via 17β-hydroxysteroid dehydrogenase (17β-HSD) type 5, while testosterone can be converted into androstenedione via the activity of 17β-HSD type 2 (Milani et al., 2009). Aromatase, encoded by CYP19 gene, is another important enzyme, which catalyzes the last stage of the estrogen biosynthesis pathway. It catalyzes the aromatization of androstenedione and testosterone into E1 and E2, respectively. Moreover, 17β-HSD plays a critical role in the bidirectional reactions between E1 and E2. The 17β-HSD type 1 promotes the formation of E2 from E1, and conversely, the 17β-HSD type 2 catalyzes the conversion of E2 to E1.

After the biosynthesis of estrogens, estrogens exert their biological effects via their interactions with ESRs. There are two well-known ESRs, ESR alpha (ESR1) and ESR beta (ESR2), which

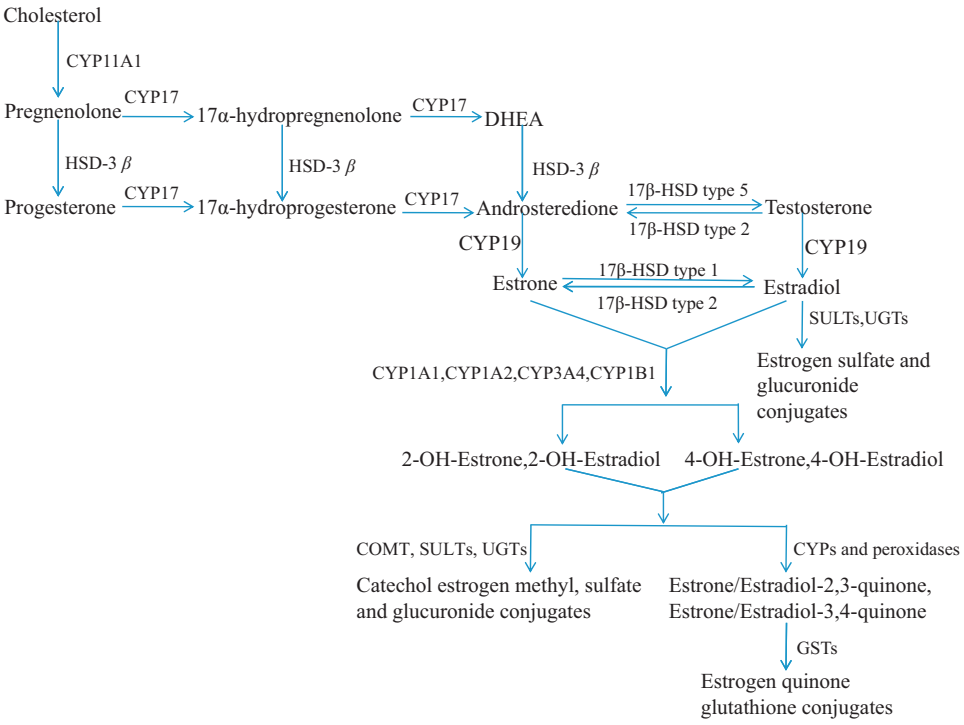

Fig. 1. The pathway of estrogen synthesis and metabolism. It is focused on the effects of the related enzymes. CYP, cytochrome P450; CYP11A1, cytochrome P450 cholesterol side chain cleavage enzyme; HSD-3β, 3β-hydroxysteroid dehydrogenase; CYP17, 17α-hydroxylase/17, 20-lyase; DHEA, dehydroepiandrosterone; 17β-HSD, 17β-hydroxysteroid dehydrogenase; SULTs, sulfotransferases; UGTs, UDP-glucuronosyltransferases; COMT, catechol-O-methyltrasferase; GSTs, glutathione-S-transferases.

mediate the effects of estrogen on AD. We introduce these receptors in detail in another section in this review. With respect to the metabolism of estrogen, the formation of estrogen conjugates is a key component in estrogen metabolism (Raftogianis et al., 2000). The major conjugative pathway for estrogen is the formation of sulfates, followed by glucuronides, which are catalyzed by sulfotransferases (SULTs) and UDP-glucuronosyltransferases (UGTs), respectively. Furthermore, both E1 and E2 can be hydroxylated by CYP isoforms, including CYP1A1, CYP1A2, CYP3A4 and CYP1B1, to form catechol estrogen, including 2-OH-E1/E2 and 4-OH-E1/E2, which are then catalyzed by catechol-O-methyltrasferase (COMT), SULTs and UGTs to form catechol estrogen methyl, sulfate and glucuronide conjugates. In addition, via the activity of CYPs and peroxidases, 2-OH-E1/E2 and 4-OH-E1/E2 can be converted into E1/E2-2,3-quinone and E1/E2-3,4-quinone, which are further catalyzed by glutathione-S-transferases (GSTs) to form estrogen quinone glutathione conjugates. Considering the effects of catechol estrogen on DNA damage, the inactivation of catechol estrogen via the formation of conjugates is critical for estrogen metabolism. Among these conjugates, methyl conjugates catalyzed by COMT are the predominant metabolites, and further conjugation safeguards are dependent on the detoxification of catechol estrogen quinones via conjugation to glutathione. The associations between COMT and GSTs, which are important estrogen metabolism associated enzymes, and AD, are reviewed in another section in this review.

3. Associations between estrogen biosynthesis and metabolism associated gene polymorphisms and the risk of AD

The synthesis and metabolism of estrogen are regulated by several related enzymes. These enzymes are critical for maintaining the levels of estrogen and mediating the neuroprotective effects of estrogen against AD. Extensive studies have investigated the effects of genes encoding estrogen biosynthesis as well as metabolism related enzymes on AD susceptibility, which are reviewed in another section in this review and are summarized in Table 1.

3.1. Genes associated with estrogen synthesis

3.1.1. CYP17

The CYP17 gene, which is located on chromosome 10q24.3, encodes the cytochrome P450c17α enzyme. This enzyme plays a key role in the biosynthesis of estrogen. Two previous studies have analyzed the associations between CYP17 gene polymorphisms and the risk of AD. The early one was conducted among 66 AD patients and 86 controls, and the polymorphism at the restriction enzyme site (MspAI) was analyzed. The result showed no association between this polymorphism and the risk of AD (Wang et al., 2005). The other one investigated the contribution of CYP17 gene polymorphism to the susceptibility of AD among women with Down syndrome. The study analyzed 7 single nucleotide polymorphisms (SNPs) in the CYP17 gene, including one at the 3′ end, 5 in the transcribed region and one in the promoter. The result suggested there were four SNPs (rs3740397, rs10786712, rs6163, and rs743572) that increased the risk of AD among females with Down syndrome (Chace et al., 2012).

3.1.2. CYP19

The CYP19 gene, another critical gene for the synthesis of estrogen, is located on 15q21.2, and encodes the enzyme aromatase, which is responsible for the final step in the biosynthesis of estrogen and catalyzes the conversion from androgen to estrogen. The CYP19 gene consists of a 30 kb coding region and a 93 kb regulatory region (Bulun et al., 2003). This large regulatory region consists of 10 tissue-specific promoters, which are expressed in the gonads, bone, brain, and other tissues for the biosynthesis of estrogen. Previous findings have suggested that the local increase in aromatase levels in the brain plays a critical neuroprotective role in preventing aging-associated neurodegenerative disorders (Garcia-Segura et al., 2003). Thus, aromatase has received increasing attention for its important regulation on the neuroprotective effects of estrogen. Moreover, the CYP19 gene, as a candidate risk factor, has also been widely studied. Several studies have demonstrated the associations between CYP19 gene polymorphisms and the risk of AD.

Iivonen and colleagues first reported the relationship between CYP19 gene polymorphisms and the susceptibility to AD (Iivonen et al., 2004). Nine SNPs (rs1004984, rs730154, rs1902586, rs1008805, rs767199, rs727479, rs1065778, rs1143704 and rs10046) spanning this gene were tested among 394 AD patients and 469 controls. Allele and genotype frequencies for three SNPs (rs767199, rs727479, and rs1065778) were significantly different between AD patients and controls. Following this study, another study analyzed 18 SNPs in the 5′UTR and the entire coding region among 227 AD patients and 131 controls, and the result showed the rs2899472 was significantly associated with AD risk, after controlling for age, sex, and apolipoprotein E (ApoE) gene (Huang and Poduslo, 2006). Furthermore, this study demonstrated there was gene-gene interaction between CYP19 and ApoE on the susceptibility to AD. Previous studies have also suggested a gender difference in the associations between CYP19 gene and the risk of AD. The study measured the SNPs (rs1004984, rs1902586, rs1008805, rs767199, rs1065778, rs10046, and rs700519), which were analyzed in studies of Iivonen et al. and Huang and Poduslo, and as well as an indel (rs11575899) and a microsatellite (TTTA repeat) (Butler et al., 2010). It was found the rs1065778, rs10046, indel and microsatellite were associated with AD, and this association was only present in females. Another study supported gender specificity in the association between CYP19 gene and AD (Corbo et al., 2009). It was reported that the T allele of the rs4646 on CYP19 was associated with an earlier onset of age in women but not in men. More interestingly, a recent study suggested a polymorphism of CYP19 gene (rs2899472) might be associated with $A\beta_{1\text{-}42}$ levels in normal subjects (Han et al., 2010); this result requires confirmation in further studies.

In contrast, other studies did not observe the associations between the CYP19 gene polymorphisms and the risk of AD (Giedraitis et al., 2009; Li et al., 2008). Thus, the genetic variants of CYP19 gene might be risk factors for AD. However, until now, no specific inference could be drawn regarding the association between CYP19 gene and AD. In addition to the effects on the susceptibility to AD, the role of CYP19 gene in age-at-onset (AAO) and pathological characteristics of AD warrant further studies.

3.2. Genes associated with estrogen metabolism

3.2.1. CYP1A1

The CYP1A1 gene is located on chromosome 15q24.1, and is an important gene related to the hydroxylation of estrogen. Two polymorphisms in the CYP1A1 gene, m1 (a C substituted for T in the 3′-noncoding region, causing a MspI restriction site) and m2 (a substitution of valine for isoleucine in codon 462 of exon 7) were most frequently reported, and suggested to be associated with an increased risk for breast cancer (Huang et al., 1999). These two polymorphisms were also analyzed to identify their associations with the risk of AD in few previous studies (Nicholl et al., 1999; Wang et al., 2005), however, no evidence of an association was found.

3.2.2. COMT

The COMT gene, which is located on chromosome 22q11.2, has 6 exons, spans 27 kb, and encodes 271 amino acids. The most

frequently investigated SNP on the COMT gene is a functional SNP on exon 4 (rs4680). It is characterized by a high activity allele G (valine) and a low activity allele A (methionine) in codon 158 (Valine158Methionine, Val158Met). Because it mediates O-methylation, COMT plays an important role in inactivating estrogen (Nock et al., 2006). Studies have suggested that the rs4680 polymorphism significantly affects the serum levels of estrogen. Females with the COMT A allele have higher E2 levels compared to women with the G allele (Worda et al., 2003). Interestingly, in males, the G allele was associated with higher levels of E2 (Thornton et al., 2011). Taken together, these data suggest the existence of gender specific effects of the polymorphism of COMT gene on estrogen.

Several studies have analyzed the associations between the Val158Met variant of COMT gene and the risk of AD. Unexpectedly, nearly all of these studies did not find an association between this polymorphism alone and the susceptibility to AD (Lanni et al., 2012; Martinez et al., 2009; Wang et al., 2005). However, only one study, conducted by Forero et al., found an initial association between COMT polymorphism and sporadic AD in males, but this association was lost after the Bonferroni correction (Forero et al., 2006). Recently, another study suggested that the A allele showed a trend association with late onset of AD (Bicalho et al., 2012). Furthermore, a recent study analyzed the effects of other SNPs of the COMT, including rs737866, rs933271, rs1544325, rs4646312, rs740601, and rs4646316, and found no association between these polymorphisms and the risk of AD or psychological symptoms in AD (Pereira et al., 2012). Another study showed that the COMT gene polymorphism increased the risk of psychosis in AD, but in general, was not associated with the risk of AD (Borroni et al., 2004). Although the role of Val158Met polymorphism as an independent risk factor for AD was not identified, the synergistic effects between this polymorphism and ApoE ε4 status on AD have been demonstrated in previous studies. This estrogen associated gene-gene interaction on AD is reviewed in another section in this review.

3.2.3. GSTs

GSTs are enzymes that conjugate a wide range of electrophilic xenobiotic compounds to glutathione. It is suggested that GSTs metabolize estrogen and deactivate estrogen-derived metabolites (Karageorgi et al., 2011). GST enzymes are involved in DNA protection against oxidative damage, including inducing free radical and metabolite production via the metabolism of estrogen (Karageorgi et al., 2011). As the important protective enzymes that catalyze the detoxification of estrogen, previous studies have suggested the associations between GSTs and AD. In the CNS, the oxidative burden may be magnified by reductions in GSTs levels or activity. Studies showed compared to controls, patients with AD had the significantly decreased activity of GSTs in the amygdala, hippocampus and parahippocampal gyrus, inferior parietal lobule, and nucleus basalis of Meynert. GST protein levels were also depleted in most brain regions in AD (Lovell et al., 1998).

Human cytosolic GSTs include members of the following 7 classes: Alpha (GSTA), Mu (GSTM), Pi (GSTP), Theta (GSTT), Kappa (GSTK), Zeta (GSTZ), and Omega (GSTO). Several genes of different GST classes were analyzed to determine the associations between these genes and AD.

3.2.3.1. GSM1 and GSM3. GSM1 gene has been relatively widely studied. The deletion polymorphism of GSTM1 gene results in important phenotypic consequences, and is related to the inactivity of GSTM1, which causes severe oxidative stress (Bolt and Thier, 2006). There have been a total of 7 studies investigating the relationship between GSTM1 gene polymorphisms and the susceptibility to AD (Bernardini et al., 2005; Ghosh et al., 2012; Green et al., 1995; Nicholl et al., 1999; Piacentini et al., 2012b; Pinhel et al., 2008; Stroombergen and Waring, 1999). However, only one study, which was performed in an Italian population, demonstrated that the GSTM1 null genotype was associated with an increased risk of AD (Piacentini et al., 2012b).

With respect to GSTM3, a few previous studies have shown an association between GSTM3 and AD. The decreased levels of GSTM3 was reported in AD-affected hippocampus (Blalock et al., 2004), and the GSTM3 transcript levels in blood mononuclear cells of AD patients were also lower than that in normal subjects (Maes et al., 2007). Considering that GSTM3 specifically accumulates in senile plaques, neurofibrillary tangles, and microglia (Tchaikovskaya et al., 2005), the effects of GSTM3 gene polymorphisms on the susceptibility to AD were analyzed in some studies. The functional polymorphism, rs7483, has been the most frequently studied. It was reported that this polymorphism was associated with the risk of AD, particularly robust in women and ApoE ε4 negative subjects (Maes et al., 2010). Two other studies did not find the independent effect of rs7483 on the risk of AD (Bullock et al., 2013; Hong et al., 2009). However, it was suggested that there was a gene-gene interaction between this polymorphism and the rs1111875 in the gene cluster of the hematopoietically expressed homebox, the insulin-degrading enzyme, and the kinesin family member 11 (Bullock et al., 2013).

For other polymorphisms on GSTM3 gene, Hong and the colleagues analyzed the rs1332018 and rs1799735 in 363 AD patients and 358 normal controls (Hong et al., 2009). The result showed that the rs1799735 polymorphism was associated with the risk of AD, particularly in ApoE ε4 allele non-carriers. These data suggested that the GSTM3 gene might be a risk factor for AD, and there was a gene-gene interaction between GSTM3 gene and other genes on the susceptibility to AD.

3.2.3.2. GSTO1 and GSTO2. The GSTO1 and GSTO2 genes comprise the GST Omega class. The GSTO1 gene is located on chromosome 10q25.1. The variants of GSTO1 gene may reduce enzyme activity and further influence the susceptibility to oxidative stress (Kolsch et al., 2004). Previous study showed the GSTO1 gene expression was significantly lower in AD hippocampus compared to controls (Li et al., 2003). Several studies have investigated the association between GSTO1 gene and the risk of AD. The missense mutation, a C→A transversion in exon 4 (rs4925) was the most frequently studied SNP of the GSTO1 gene (Allen et al., 2012; Capurso et al., 2010; Kolsch et al., 2004; Kuwano et al., 2006; Li et al., 2003, 2006; Ozturk et al., 2005; Piacentini et al., 2012a). However, among these studies, only one observed a significant difference in rs4925 genotype distribution between AD patients and age- and sex-matched healthy controls. The frequency of A allele was much higher in AD patients than that in controls (OR = 3.789; 95% CI, 2.442-5.878) (Capurso et al., 2010). Although evidences did not support the rs4925 as an independent risk for AD, several studies suggested it might influence the AAO of AD. Two studies demonstrated that the A allele was associated with delayed AAO of AD (Li et al., 2003, 2006), however, conversely, another study showed the A allele resulted in earlier AAO of AD (Kolsch et al., 2004).

The other SNPs of GSTO1 gene, including rs11509437, rs11509438 (Piacentini et al., 2012a), rs1804834 (Capurso et al., 2010; Kolsch et al., 2004), rs11191972, rs2164624 (Kuwano et al., 2006; Li et al., 2003, 2006) and rs1147611 (Li et al., 2003, 2006) were also analyzed in previous studies. The result revealed that the rs11509437 was associated with the increased risk of AD (Piacentini et al., 2012a).

The GSTO2 gene, the second most actively transcribed gene of the GSTO class, lies 7.5 kb downstream of GSTO1 gene, and is located in the linkage region within the GSTO1 gene. Thus, the studies on the association between GSTO2 gene and AD obtained

similar results with GSTO1 gene. To date, no evidence has supported the GSTO2 gene polymorphisms influence the susceptibility to AD (Allen et al., 2012; Kuwano et al., 2006; Li et al., 2003; Nishimura et al., 2004; Ozturk et al., 2005; Piacentini et al., 2012a). However, it was suggested that the GSTO2 gene might influence the AAO of AD (Li et al., 2003, 2006).

3.2.3.3. GSTP1 and GSTT1. The GSTP1 gene, which is located on chromosome 11q13, is polymorphic. Two SNPs, an A→G transition at nucleotide 313 (exon 5, codon 105) and a C→T transition at nucleotide 341 (exon6, codon114), have been identified. These variants encode for the Ile^{105}→Val^{105} and Ala^{114}→Val^{114} substitutions. According to these amino acid substitutions, four allelic polymorphisms were described: the GSTP1*A encodes for Ile^{105}/Ala^{114}; the *B encodes for Val^{105}/Ala^{114}; the *C encodes for Val^{105}/Val^{114}, and the *D encodes for Ile^{105}/Val^{114} (Bernardini et al., 2005). The associations between these two SNPs and four allelic polymorphisms of GSTP1 gene and AD were previously studied. The earliest study showed that compared to control group, AD patients showed higher frequencies of the mutant genotypes (A313G and C341 T). When estimating the GSTP1 haplotype distribution, the GSTP1*A/GSTP1*B and GSTP1*A/GSTP1*C haplotypes were less frequent in AD patients, while the GSTP1*B/GSTP1*B and GSTP1*C/GSTP1*D haplotypes were more frequent in AD patients (Zuntar et al., 2004). Following this study, another study demonstrated that there was a significant association of the GSTP1*C allelic variant with late-onset AD. Furthermore, as a preliminary result, it was suggested that there was an interaction between the GSTP1*C allele and ApoE ε4 allele on the increased risk of AD (Bernardini et al., 2005). Other study supported this finding and showed the *C allele was significantly associated with the faster decline of cognitive ability (Spalletta et al., 2007). In addition, the Ile^{105}→Val^{105} variant was also higher in AD patients, mainly in subjects carrying the ApoE ε4 allele (Pinhel et al., 2008). These evidences suggest the GSTP1 gene could be considered to be a candidate gene for AD. Moreover, there may be a gene-gene interaction between GSTP1 gene and ApoE gene on the susceptibility to AD.

The GSTT1 gene was relatively less well-studied. Previous studies mainly analyzed the influence of GSTT1 gene deletion, which abolishes enzyme activity, on the susceptibility to AD. It was suggested that the deletion of the GSTT1 gene was a risk factor of AD (Ghosh et al., 2012; Pinhel et al., 2008; Stroombergen and Waring, 1999), and this null polymorphism predicted earlier AAO of AD (Spalletta et al., 2007). However, some other studies did not observe the association between the deletion of GSTT1 gene and the risk of AD (Bernardini et al., 2005; Piacentini et al., 2012b). Thus, the influences of GSTT1 gene on the susceptibility to AD are still ambiguous.

The other GST enzyme genes, GSTM4 and GSTZ1, were involved in a few genome-wide association studies (Emahazion et al., 2001; Li et al., 2008; Reiman et al., 2007); however, the results were all negative (see Table 1).

4. ESR genes and AD

4.1. ESR1 gene

The ESR1 gene is located on chromosome 6q25.1. Previous studies have identified several SNPs and variable-number tandem repeat (VNTR) polymorphisms in the ESR1 gene. Among these identified SNPs, rs2234693 (PvuII) and rs9340799 (XbaI), which are located in intron 1 of the ESR1 gene, 397 and 351 bp upstream of exon 2, respectively, are the most studied. The PvuII (C to T substitution) and XbaI (G to A substitution) are both restriction fragment length polymorphism (RFLP), and they are in strong linkage disequilibrium (Becherini et al., 2000). The P and p are commonly used to denote the C and T allele of PvuII, respectively. The X and x are used to refer to G and A allele of XbaI, respectively. The uppercase and lowercase letters indicate the absence and presence of the restriction sites, respectively. The relatively well-studied (TA)n VNTR polymorphism, which is located in the promoter region, 1 kb upstream of the exon 1, is also in strong linage disequilibrium with the PvuII and XbaI sites (Becherini et al., 2000). We mainly reviewed the studies on the associations between PvuII and XbaI polymorphisms and the risk of AD. The effects of the (TA)n VNTR polymorphism and other SNPs of ESR1 gene on AD are also discussed. The profiles of these studies were summarized in Table 1.

4.1.1. PvuII and XbaI polymorphisms

Considering that the genotypic frequencies of PvuII and XbaI polymorphisms differ significantly between Caucasian and Asian populations (Luckhaus and Sand, 2007), we separately reviewed the previous studies according to the ethnicity of the subjects. The earliest study involving Caucasian patients was performed in an Italian population in 1999. The PvuII and XbaI polymorphisms were measured among 193 patients with late-onset AD and 202 age and education matched control subjects (Brandi et al., 1999). The result showed that the prevalence of PP ($p = 0.02$), XX ($p = 0.007$) and PPXX ($p = 0.0001$) genotypes were all significantly increased in patients with AD compared to controls. Another study supported this result and found a gender specific effect of the PvuII and XbaI polymorphisms on the risk of AD. The PP and XX genotypes were susceptible factors for AD only in males (OR = 3.6, 95%CI = 1.2–10.9) among the Italian population (Corbo et al., 2006). Although the PvuII and XbaI polymorphisms were not related to the risk of AD in females, the PP and XX genotypes were associated with lower values of Mini-Mental State Examination (MMSE) ($p = 0.0007$) in female subjects. Recently, a study performed in a large Spanish population (1113 AD patients and 1109 controls) also supported that the P allele of PvuII polymorphism increased the risk of AD (OR = 1.29, $p = 0.008$) (Boada et al., 2012). Some studies found that other alleles or genotypes of the PvuII and XbaI were linked with AD. For example, the frequency of Pp was increased in female AD patients from Finland (Mattila et al., 2000). In another study in an Italian sample, the xx, but not the pp genotype, was associated with the increased susceptibility to AD (Monastero et al., 2006).

However, some other studies did not find positive results. In two studies performed among UK and Italian based Caucasian (Lambert et al., 2001; Porrello et al., 2006), the PvuII and XbaI polymorphisms were not associated with the risk of AD. In a Swedish population, the XbaI polymorphism was also not associated with AD (Prince et al., 2001). In a large prospective cohort studies, 6056 Dutch Caucasian subjects aged 55 years and older were investigated (den Heijer et al., 2004). During mean 5.8 years follow-up, 230 developed AD. After controlling for confounding factors, there was no association between the PvuII and XbaI polymorphisms and the risk of AD, either in men or women.

For the studies performed among Asian population, the earliest one was performed in Japan. The frequencies of both P and X allele were higher in AD patients than those in controls (Isoe-Wada et al., 1999). Following this study, two others conducted in Asian population also showed the P and X alleles and the PPXX genotype were more frequent in AD patients compared to controls (Ji et al., 2000; Lin et al., 2003). Inconsistent with these findings, some other studies did not observe an association between the alleles or genotypes of PvuII and XbaI polymorphisms and AD (Dresner-Pollak et al., 2009; Ma et al., 2009; Maruyama et al., 2000; Usui et al., 2006).

According to these results, the PvuII and XbaI polymorphisms of ESR1 gene may be linked with the susceptibility to AD. However,

Table 1
The associations between polymorphisms of estrogen synthesis and metabolism genes and ESR genes and the risk of AD.

Gene	Polymorphisms tested	Author (year)	Ethnicity	*N* (% females)		Risk/protective polymorphisms (other findings)
				AD	Controls	
CYP17	MspA1-promoter	Wang (2005)	Asian (Taiwan)	66 (50%)	86 (49%)	ns
CYP19	8 SNPs, TTTA repeat	Butler (2009)	Caucasian (UK)	207 (56%)	233 (52%)	rs1065778, rs10046, rs11575899 and TTTA repeat in females
	rs12907866, rs17601241, rs4646	Corbo (2009)	Caucasian (Italy)	319 (80%)	110 (64%)	ns (The T allele of the rs4646 was associated with an earlier onset of age only in women)
	18 SNPs in the 5′UTR and the entire coding region	Huang (2006)	Caucasian (USA)	227 (69%)	131 (59%)	rs2899472 (The rs1008805 and rs727479 were associated with AD among the ApoE ε4 allele carriers)
	Nine SNPs	Ivonen (2004)	Caucasian (Finland)	394 (70%)	469 (60%)	rs767199, rs727479, rs1065778
	rs1062033,rs2008691, rs700518	Li (2008)	Caucasian (Canada)	753 (58%)	736 (64%)	ns
	rs767199, rs2008691, rs700518	Giedraitis (2009)	Caucasian (Sweden)	86 (0%)	404 (0%)	ns
COMT	rs4680	Borroni (2004)	Caucasian (Italy)	181 (66%)	208 (62%)	ns
		Lanni (2012)	Caucasian (Italy)	276 (67%)	248 (57%)	ns (There was interaction between the G allele and ApoE ε4 allele on the risk of AD)
		Martinez (2009)	Caucasian (Spain)	345 (71%)	253 (60%)	ns (The GG/AG genotype and ApoE ε4 allele synergistically increased the risk of AD)
		Bicalho (2012)	Hispanic (Brazil)	169 (71%)	97 (69%)	ns (The A allele had a trend association with later onset of AD)
		Forero (2006)	Hispanic (Colombia)	102 (70%)	168 (58%)	ns
		Wang (2005)	Asian (Taiwan)	66 (50%)	86 (49%)	ns (An synergistic effect was found between GG genotype and ApoE ε4 allele on the risk of AD)
	6 SNPs	Pereira (2012)	Hispanic (Brazil)	98 (66%)	113 (73%)	ns
CYP1A1	rs4646903, rs1048943	Nicholl (1999)	Caucasian (UK)	23 (61%)	23 (61%)	ns
	rs4646903	Wang (2005)	Asian (Taiwan)	66 (50%)	86 (49%)	ns
GSTM1	Insertion-deletion	Piacentini (2012)	Caucasian (Italy)	168 (39%)	143 (43%)	deletion
		Bernardini (2005)	Caucasian (Italy)	210 (63%)	228 (64%)	ns
		Nicholl (1999)	Caucasian (UK)	23 (61%)	23 (61%)	ns
		Green (1995)	Caucasian (USA)	79 (—)	121 (—)	ns
		Stroombergen (1999)	Caucasian (UK)	43 (60%)	225 (55%)	ns
		Pinhel (2008)	Hispanic (Brazil)	41 (78%)	24 (75%)	ns
		Ghosh (2012)	Asian (India)	50 (44%)	100 (38%)	ns
GSTM3	rs7483	Bullock (2012)	Caucasian (Europe)	1757 (—)	6294 (—)	ns
		Maes (2010)	Caucasian (USA)	347 (55%)	146 (61%)	rs7483, especially in women and ApoE ε4 negative subjects
	rs7483,rs1332018, rs1799735	Hong (2007)	Caucasian (Germany)	363 (67%)	358 (53%)	rs1799735, especially in the group of ApoE ε4 allele non-carriers
GSTM4	rs560018	Emahazion (2001)	Caucasian (Scotland)	237 (—)	328 (—)	ns
GSTO1	rs4925	Allen (2012)	Caucasian (USA)	3493 (—)	4617 (—)	ns
		Ozturk (2005)	Caucasian (USA)	1116 (—)	735 (61%)	ns
	rs4925,rs1804834	Capurso (2010)	Caucasian (Italy)	103 (60%)	157 (50%)	rs4925
		Kolsch (2004)	Caucasian (Germany)	244 (72%)	280 (55%)	ns (The A allele of rs4925 led to earlier AAO)
	rs4925, rs11509437, rs11509438	Piacentini (2012)	Caucasian (Italy)	119 (60%)	114 (60%)	rs11509437
	rs4925, rs1119197, rs2164624, rs1147611	Li (2003 and 2006)	Caucasian (USA)	1773 (—)	1041 (—)	ns (The A allele of rs4925 was associated with the delayed AAO)
	rs4925, rs11191972, rs2164624	Kuwano (2006)	Asian (Japan)	1526 (72%)	1666 (60%)	ns
GSTO2	rs156697	Allen (2012)	Caucasian (USA)	3493 (—)	4617 (—)	ns
		Piacentini (2012)	Caucasian (Italy)	119 (60%)	114 (60%)	ns

Table 1 (*Continued*)

Gene	Polymorphisms tested	Author (year)	Ethnicity	*N* (% females)		Risk/protective polymorphisms (other findings)
				AD	Controls	
	rs157077, rs156697, rs2297235	Li (2003)	Caucasian (USA)	1773 (—)	1041 (—)	ns (The −183T allele of rs2297235 was associated with later AAO)
	rs2297235	Ozturk (2005)	Caucasian (USA)	1116 (67%)	735 (61%)	ns
		Kuwano (2006)	Asian (Japan)	1526 (72%)	1666 (60%)	ns
		Nishimura (2004)	Asian (Japan)	172 (60%)	163 (61%)	ns
GSTP1	rs1695	Giedraitis (2009)	Caucasian (Sweden)	86 (0%)	404 (0%)	ns
		Pinhel (2008)	Hispanic (Brazil)	41 (78%)	24 (75%)	Val variant, mainly in the subjects carrying ApoE ε4 allele
	rs1695, rs1138272	Bernadini (2005)	Caucasian (Italy)	210 (63%)	228 (64%)	GSTP1*C allelic variant (There was an interaction between the GSTP1*C allele and ApoE ε4 allele on increased risk of AD)
		Zuntar (2004)	Caucasian (Croatia)	56 (59%)	231 (30%)	ns
GSTT1	Insertion-deletion	Bernadini (2005)	Caucasian (Italy)	210 (63%)	228 (64%)	ns
		Piacentini (2012)	Caucasian (Italy)	119 (60%)	114 (60%)	ns
		Stroombergen (1999)	Caucasian (UK)	43 (60%)	225 (55%)	deletion
		Pinhel (2008)	Hispanic (Brazil)	41 (78%)	24 (75%)	deletion
		Ghosh (2012)	Asian (India)	50 (44%)	100 (38%)	deletion
GSTZ1	rs8004558	Li (2008)	Caucasian (Canada)	753 (58%)	753 (58%)	ns
		Reiman (2007)	Caucasian (USA, Netherlands)	861 (—)	550 (—)	ns
ESR1	PvuII, XbaI PvuII, XbaI, (TA)n VNTR	Brandi, 1999	Caucasian (Italy)	193 (—)	202 (—)	PP, XX and PPXX (Risk of AD increased 7.6 fold in homozygous ApoE ε4 subjects with PPXX genotype)
		Corbo (2006)	Caucasian (Italy)	279 (69%)	212 (60%)	PP and XX only in males (PP and XX genotypes were associated with lower MMSE values in women. There was interaction between PP and/or XX genotypes and ApoE ε4 allele on the risk of AD)
		den Heijer (2004)	Caucasian (Netherlands)	230 (70%)	5744 (59%)	ns (The pp or xx genotype was associated with smaller hippocampal and amygdalar volumes on MRI in women)
		Lambert (2001)	Caucasian (UK)	186 (61%)	405 (53%)	ns (There was an interaction between ESR1 and ESR2 gene polymorphisms on the risk of AD)
		Maruyama (2000)	Caucasian (UK)	156 (55%)	120 (48%)	ns
		Mattila (2000)	Caucasian (Sweden)[a]	84 (63%)	81 (67%)	ns (In female subjects, the risk of FAD increased among subjects carrying the pp or xx genotype together with ApoE ε4 allele)
			Caucasian (Sweden)[b]	79 (100%)	150 (100%)	
			Caucasian (Finland)	51 (69%)	59 (44%)	Pp in females
		Monastero (2006)	Caucasian (Italy)	172 (65%)	172 (65%)	xx
		Porello (2006)	Caucasian (Italy)	131 (56%)	109 (53%)	ns (In females, the p and x alleles interacted with ApoE ε4 allele to increase the risk of AD)
		Isoe (1999)	Asian (Japan)	86 (70%)	51 (86%)	P and X alleles
		Ji (2000)	Asian (Japan)	234 (—): FAD 11, EOAD 50, LOAD 173	134 (—)	P and X allele in LOAD group (In LOAD, the PP genotype and P allele were more frequent in ApoE ε4 carriers)
		Lin (2003)	Asian (China)	30 (80%)	125 (50%)	P and X
		Maruyama (2000)	Asian (Japan)	183 (70%)	133 (64%)	ns
		Usui (2006)	Asian (Japan)	205 (54%)	92 (36%)	ns
		Ma (2009)	Asian (China)	233 (84%)	245 (76%)	ns
		Dresner-Pollack (2009)	Asian (Israel)	118 (100%)	68 (100%)	ns

Table 1 (*Continued*)

Gene	Polymorphisms tested	Author (year)	Ethnicity	*N* (% females)		Risk/protective polymorphisms (other findings)
				AD	Controls	
	PvuII, rs3844508	Merce Boada (2012)	Caucasian (Spain)	1113 (70%)	1109 (53%)	P allele of PvuII; G allele of rs3844508[d]
	XbaI	Prince (2001)	Caucasian (Sweden)	204 (61%)	186 (58%)	ns
	47 SNPs	Li (2008)	Caucasian (Canada)	753 (58%)	736 (64%)	ns
	39 SNPs	Goumidi (2011)	Caucasian (France)	1007 (67%)	647 (63%)	ns
	14 SNPs	Ma (2009)	Asian (China)	233 (84%)	245 (76%)	rs1514348, rs2347867, rs6557171, rs9397456, rs1801132 (The rs2077647 and rs3853248 were associated with AAO)
	NCD1[c]	Merce Boada (2012)	Caucasian (Spain)	1113 (70%)	1109 (53%)	deletion in females
ESR2	rs4986938	Lambert (2001)	Caucasian (UK)	186 (61%)	405 (53%)	ns
	CA repeat in intron 5	Forsell (2001)	Caucasian (Sweden)	336 (64%)	110 (66%)	allele 5 (18 repeats of CA)
	IVS3-1842A > G, rs1271573,rs1256043, rs1256059, rs4986938	Pirskanen (2005)	Caucasian (Finland)	387 (70%)	467 (60%)	rs1271573 and rs1256043 in females
	rs4986938,rs1255998, rs1255953	Luckhaus (2006)	Caucasian (Austria, Germany)	126 (65%)	111 (63%)	ns (There was an interaction between rs4986938 and rs1255953 on the risk of AD)
	rs4986938, rs867443, rs10144225, rs7154455, rs1952586	Goumidi (2011)	Caucasian (France)	1007 (67%)	647 (63%)	ns
	rs4986938	Dresner-Pollack (2009)	Asian (Israel)	118 (100%)	68 (100%)	ns

ns means no significant association between the polymorphisms and the risk of AD among the entire subjects.
Abbreviations: ESR, estrogen receptor; MMSE, Mini-Mental State Examination; FAD, familial Alzheimer's disease; EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease; ApoE, apolipoprotein E; VNTR, variable-number tandem repeat; NCD1, non-coding deletion 1; AAO, age-at-onset.
—, no data provided.
[a] Clinic-based sample: all the 84 AD patients were FAD.
[b] Community-based sample: in the 79 AD patients, 27 were FAD.
[c] a 2244 base pair interstitial deletion within intron 6.
[d] Protective polymorphism.

there are still some inconsistencies. Several factors may contribute to the controversial results. First, ethnicity is an important factor that affects the distribution of the alleles and genotypes of the PvuII and XbaI polymorphisms. A meta-analysis study analyzed the evidences of the associations between the PvuII and XbaI polymorphisms and the risk of AD ($n = 8288$) or other forms of cognitive impairments ($n = 11036$) (Luckhaus and Sand, 2007). The results showed the frequencies of X and P alleles differed remarkably between Asian (0.20 and 0.38, respectively) and European populations (0.35 and 0.44, respectively). The X and P allele statuses were significantly associated with the risk of AD in the Asian group (for X carriers, OR = 1.5, 95%CI 1.1–2.0, $p = 0.004$; for P carriers, OR = 1.5, 95%CI 1.1–2.0, $p = 0.006$), but not in the European population. Second, some previous studies have demonstrated gender specific effects of the PvuII and XbaI polymorphisms on the risk of AD (Corbo et al., 2006; Mattila et al., 2000; Monastero et al., 2006). The prospective cohort studies also proved that the p and x allele increased the risk of cognitive decline in women but not in men (Yaffe et al., 2009, 2002). Therefore, we speculate that the various gender ratios in different studies partially caused the inconsistent results when the studies simultaneously analyzed the associations among both males and females. We recommend analyzing the effects of ESR1 gene separately for males and females in future studies. Third, the pathogenic mechanisms of AD are very complex and involve several factors and their interactions, including the gene-gene and gene-environment co-activities. Several studies reported there were interactions between the PvuII and XbaI polymorphisms and the ApoE gene ε4 allele status on the susceptibility to AD (Brandi et al., 1999; Corbo et al., 2006; Mattila et al., 2000; Porrello et al., 2006). In addition, ESR1 and ESR2 gene polymorphisms were suggested to synergistically influence the risk for AD (Lambert et al., 2001). These multifactor interactions may be a key point to investigate the effects of estrogen-associated genes on AD.

The ESR1 gene polymorphisms are not only associated with the risk of AD, but also related to the AD pathological manifestations. A previous study showed that the P allele had a dose-dependent effect on the stage of neurofibrillary tangles in males with AD. However, this association was not observed for the XbaI polymorphism or among female patients (Kazama et al., 2004). The PvuII and XbaI polymorphisms were also related to changes in brain structure. Using voxel-based morphometry, researchers investigated the effect of XbaI polymorphism on gray matter volumes among 20 healthy postmenopausal women, and found that the X allele was associated with smaller gray matter volumes of the cerebral and cerebellar cortex (Boccardi et al., 2008). In a prospective cohort study, among 468 participants who underwent a brain MRI, the pp or xx genotype was associated with smaller hippocampal and amygdalar volumes on MRI in females. However, there was no relationship between these two polymorphisms and brain volumes in men (den Heijer et al., 2004). These results suggested that there might be gender-specific differences in the associations between ESR1 gene polymorphisms and the manifestations of AD, which should be noted in future studies. Interestingly, despite the debate in cross-sectional studies, all of the three prospective cohort studies reported the associations between the p and x alleles and cognitive decline or smaller brain volume in females (den Heijer et al., 2004; Yaffe et al., 2009, 2002).

Although the results were inconsistent, we still believe that the ESR1 gene is important for understanding the mechanisms of AD, considering that the associations between the PvuII and XbaI polymorphisms and the risk of AD have been proposed to be specific. Studies have shown that the allele status and genotype of the PvuII and XbaI polymorphisms were not associated with

vascular dementia (Ji et al., 2000), alcohol-associated dementia (Ji et al., 2000) or Parkinson's disease with dementia (Mattila et al., 2002). The meta-analysis study also reported that the genotypes of these two polymorphisms were not associated with non-AD forms of dementia or cognitive impairment (Luckhaus and Sand, 2007).

Currently, the function of the PvuII and XbaI polymorphisms and how they affect the risk of AD are still unclear. Previous study showed these two polymorphisms influenced the levels of estrogen. In females, but not in males, the px haplotype significantly decreased the plasma level of estrogen (Schuit et al., 2005), although the mechanism underlying this phenomenon remains unknown. Studies have suggested that the PvuII and XbaI polymorphisms have influences on the transcriptional activity of ESR1 gene. It has been reported that the PX haplotype construct in HeLa cells showed a lower expression compared to the px construct, although the difference was not significant (Lambert et al., 2001). It was hypothesized that the PvuII and XbaI polymorphisms might regulate the expression of ESR1 gene via the altered binding of transcription factors and effect on the splicing of the ESR1 gene (Herrington et al., 2002; Schuit et al., 2005).

4.1.2. Other polymorphisms of ESR1 gene

The relationships between other polymorphisms of ESR1 gene and AD have also been investigated. A genome-wide association study of AD was conducted among 753 AD patients and 736 controls to identify the SNPs associated with the risk or AAO of AD. This study analyzed 47 SNPs of ESR1 gene, and the result showed that rs3844508 had a trend of association with the risk of AD (Li et al., 2008). This polymorphism was also measured in another study, in which a new polymorphism, ESR1 non-coding deletion 1 (ESR1-NCD1), a 2244 base interstitial deletion within intron 6, was also measured (Boada et al., 2012). The result was that the G allele of the rs3844508 reduced the risk of AD in males, and the deletion ESR1-NCD1 was a susceptible factor for AD in women. In a mostly female Chinese sample, 16 SNPs of ESR1 gene, including the PvuII and XbaI polymorphisms, were investigated (Ma et al., 2009). Although the PvuII and XbaI polymorphism were not associated with AD, there were associations between five SNPs clustered between intron3 and intron 7 (rs1514348, rs2347867, rs6557171, rs9397456 and rs1801132) and the risk of AD. Furthermore, two SNPs located on exon2 and intron 2 (rs2077647 and rs3853248) were associated with the AAO of AD. Recently, 39 SNPs of ESR1 gene were tested among 1007 AD patients and 647 controls from France. However, no significant association was found (Goumidi et al., 2011). Furthermore, the association between the (TA)n VNTR polymorphism and the risk of AD was evaluated in one study; however no positive association was observed (Dresner-Pollak et al., 2009).

4.2. ESR2 gene

The ESR2 gene is located on chromosome 14q22-24. Compared to ESR1, the ESR2 was identified much later (Mosselman et al., 1996). Therefore, the associations between ESR2 gene polymorphisms and AD were relatively less studied. To the best of our knowledge, there were a total of six studies that investigated the relationship between ESR2 gene and the risk of AD.

The earliest study was conducted in 186 AD patients and 405 controls. Patients and controls were recruited from a UK population. In this study, a polymorphism in the 3′-nontranslated region (rs4986938, A to G) of the ESR2 gene was tested. The result showed that this polymorphism did not appear to play a significant role in the susceptibility to AD in the total sample nor in either gender (Lambert et al., 2001). Shortly after this study, another study investigated whether the CA repeat in intron 5 of the ESR2 gene (Tsukamoto et al., 1998) was associated with AD in 336 AD patients and 110 healthy age-match controls (Forsell et al., 2001). Fourteen different alleles were found. When the frequencies of these alleles analyzed separately, the frequency of allele 5 (155 bp, 18 repeats of CA) was higher in controls compared to AD patients (13.6% compared to 8.0%, OR = 0.55, $p = 0.014$), suggesting that allele 5 may be a protective factor against AD.

Recently, four studies explored the effects of several SNPs of ESR2 gene on AD. One investigated 5 SNPs, including SNP1 = IVS3-1842A > G, SNP2 = IVS3-1880C > T (rs1271573), SNP3 = IVS4 + 1231C > T (rs1256043), SNP4 = IVS7 + 584C > T (rs1256059) and SNP5 = 3′UTR*39A > G (rs4986938) in 387 AD patients and 467 controls. These studies found that the allele T and the genotype T/T of SNP2 and SNP3 were associated with an increased risk of AD in women (Pirskanen et al., 2005). In another study, 3 exonic SNPs (rs4986938, rs1255998 and rs1255953) located in the 3′UTR were studied in 126 AD patients and 111 healthy controls. The allele distribution of these 3 SNPs was similar between AD patients and controls. However, there were interactions between rs4986938 and rs1255953 on the risk of AD (Luckhaus et al., 2006). The rs4986938 and other 4 SNPs (rs867443, rs10144225, rs7154455 and rs1952586) were analyzed in two other studies, but no positive association was found (Dresner-Pollak et al., 2009; Goumidi et al., 2011).

In summary, on the basis of these previous studies, studies regarding the associations between ESR2 gene polymorphisms and AD were insufficient and inconclusive. The rs4986938 has been the most frequently reported SNP. Only one of the five studies, which tested this polymorphism, suggested that it might be associated with AD. However, some studies suggested this polymorphism was related to the risk of vascular dementia in women (Dresner-Pollak et al., 2009) and the risk of AD in female patients with Down syndrome, which is a disorder that demonstrates similar pathological changes to AD (Zhao et al., 2011). In addition, a prospective study suggested two SNPs of ESR2 gene (rs1256065 and rs1256030) were associated with the risk of cognitive impairment in females, and the rs1255998 and rs1256030 were associated with cognitive impairment in males (Yaffe et al., 2009). Further studies are warranted investigating the association between the ESR2 gene and AD.

5. Estrogen, ApoE and AD

5.1. Estrogen and ApoE

ApoE is a 35 kD, 299 amino acids long lipid-associated protein. It is a ligand for members of the low density lipoprotein receptor family, and participates in the transport of cholesterol and other lipids (Mahley, 1988). ApoE is principally expressed in liver, and second-most expressed in brain (Srivastava et al., 1996). ApoE is also expressed in other tissues, such as heart, lung, kidneys and spleen. In the nervous system, ApoE is synthesized primarily in non-neuronal cell type, such as astroglia and microglia, and under specific conditions, in neurons (Kim et al., 2009). In the CNS, ApoE protein is mainly present on high density lipoprotein (HDL)-like lipoprotein particles, and is the predominant apolipoprotein of HDL-like lipoproteins, which have been reported to be the only lipoproteins in the CNS (Kim et al., 2009). ApoE is important in cholesterol transport and clearance in CNS. The cholesterol delivered to neurons from ApoE-containing lipoprotein particles is required for synapse formation, and after nerve regeneration, ApoE clears and redistributes the cholesterol and lipid debris (Hauser et al., 2011).

The ApoE gene is mapped to 19q13.2, and consists of 4 exons and 3 introns. In human, there are 3 major isoforms of ApoE, known as ApoE ε2, ApoE ε3, and ApoE ε4 (Hallman et al., 1991). These three isoforms differ from each other by only one amino acid substitution at residue positions 112 and 158; the ε2 allele has a

Cys at position 112 and 158, the ε3 allele has a Cys at 112 and Arg at 158, and the ε4 allele has an Arg at both positions. However, the functional consequences of these differences are profound and critical. As a generally acknowledged genetic risk factor for late-onset sporadic AD, the ApoE ε4 allele is strongly associated with an increased risk of AD. The potential mechanisms involve several pathogenic factors of AD, including regulating the aggregation and clearance of Aβ, modulating the neurotoxicity and tau phosphorylation, and affecting synaptic plasticity and neuroinflammation. The roles of ApoE in AD have been well reviewed (Hauser et al., 2011; Kim et al., 2009; Verghese et al., 2011). Our review is focused on previous evidences of the interactions between estrogen and ApoE gene on AD.

AD, as a common complex disorder, is different from single-gene diseases in that there are several genetic and environmental pathogenic factors. Both estrogen and ApoE genotype play broad roles in the pathogenesis of AD. Current evidences indicate that estrogen and the ApoE allele status do not influence AD alone, but interact with each other on the susceptibility and progression of AD. The neuroprotective effects of estrogen may rely on the genotype of ApoE gene. Previous cross-sectional studies have shown that ApoE ε4 negative females taking ERT exhibited the best performance on cognitive tests among postmenopausal women. In contrast, women who were ε4 allele carriers did not receive benefits from ERT (Burkhardt et al., 2004). In ApoE ε4 negative women, ERT reduced the risk of familial AD (FAD) by 80% (OR = 0.2, 95%CI = 0.1–0.5), but in female ApoE ε4 carriers, ERT was not associated with the susceptibility to AD (Rippon et al., 2006). Furthermore, prospective studies have suggested that estrogen use attenuated the risk of cognitive decline by almost half compared to non-users among ε4 negative women; however, among ε4 positive women, estrogen use did not demonstrate benefits to prevent cognitive impairments, but accelerated the rate of cognitive decline (Kang and Grodstein, 2012; Yaffe et al., 2000a). These results suggested that the ApoE genotype may be a key determinant of ERT efficacy in cognitive improvement and the prevention of AD, and the controversial results on ERT clinical trials could be partially explained by modulation of the ApoE genotype.

5.1.1. Estrogen regulates the expression of ApoE gene

Studies reported that estrogen regulated the mRNA and gene expression levels of ApoE, and this regulation might be tissue-specific (Srivastava et al., 1996). Brain ApoE mRNA levels increased significantly following E2 administration, while hepatic ApoE mRNA levels did not. In brain, the product of ApoE is mainly in astroglia and microglia. It has been shown that estrogen treatment elevated the ApoE mRNA levels in both astrocyte and microglia in mixed cultures (Stone et al., 1997). Interestingly, recent studies have reported the different regulatory effects of the two ESR subtypes, ESR1 and ESR2, on ApoE expression levels in cultured hippocampal neurons in vitro and in the hippocampus in vivo. The activation of ESR1 up-regulated, while the activation of ESR2 down-regulated the ApoE mRNA and protein expression levels (Wang et al., 2006). In addition, the ESR2 levels were higher in the ApoE ε4 microglia compared to the ApoE ε3 microglia (Brown et al., 2008). Hence, considering the down-regulatory effects of ESR2 on ApoE expression, this may at least partially explain the lower levels of ApoE protein observed in ApoE ε4 mouse brains, as well as in the hippocampus and frontal cortex of ApoE ε4 positive AD patients (Bertrand et al., 1995; Ramaswamy et al., 2005). Estrogen is not only related to ApoE gene expression, but also to ApoE receptor levels. ApoE receptors comprise a family of receptors, including the very low density lipoprotein receptors (VLDLr), low density lipoprotein receptor (LDLr), lipoprotein receptor related protein (LRP), ApoE receptor, megalin and GP330. In the CNS, LDLr and LRP are two receptors that bind to and induce the endocytosis of ApoE-containing lipoproteins (Holtzman et al., 1995). It was shown that E2 replacement significantly increased LRP expression in the hippocampus, olfactory bulb and neocortex in ovariectomized mice, and decreased LDLr protein expression in the olfactory bulb (Cheng et al., 2007). Furthermore, the effect of estrogen on ApoE expression differed between allelic statuses of ApoE gene. The increase in the transcriptional level in response to estrogen was most significant in the presence of the ε4 allele, followed by the ε2 allele (Lambert et al., 2004).

5.1.2. The ApoE-dependent neuroprotective mechanisms of estrogen against AD

Estrogen involves multiple pathogenic mechanisms of AD, in which the ApoE gene may play critical roles.

The enhancement of synaptic sprouting is one important neuroprotective effects of estrogen against AD. Estrogen affects the levels of synapse density in the hippocampal CA1 region (Woolley and McEwen, 1992). Using the entorhinal cortex lesion model, which is a deafferentation model for AD, studies have found that ovariectomy decreased sprouting to the inner layer of dentate gyrus (Stone et al., 1998). E2 replacement subsequently returned the sprouting to the inner layer and increased the synaptogenesis in the outer layer. However, this sprouting enhancing effect was not observed in ApoE-knock-out mice. Studies have also shown that estrogen can only induce the synaptic sprouting effect where ApoE protein is needed. In response to deafferentation of the entorhinal cortex, hippocampal slice culture system showed mossy fiber sprouting into the dentate gyrus. However, in an ApoE knockout mice culture system, this sprouting response was defective; no sprouting was observed in the dorsal region, while sprouting was retained in the ventral region (Teter et al., 1999). When treated with E2, the sprouting in dorsal but not ventral region increased by 75%. This finding demonstrated that the increase in neuronal sprouting induced by estrogen was in the same region where sprouting was required for ApoE. These studies suggested that the synaptic sprouting effect of estrogen is dependent on ApoE.

Both ApoE and estrogen play remarkable roles in neurite outgrowth. Reports have suggested that the influence of ApoE on neurite outgrowth is differentially modulated by the ApoE genotype. The ApoE ε3 allele increases neurite outgrowth, while the ε4 allele has no effect or even decreases neurite outgrowth (Nathan et al., 2004, 2002). Considering the close relationship between estrogen and ApoE, researchers hypothesized that the ApoE genotypes influence the neurite outgrowth effect of estrogen. To test this hypothesis, the interaction between estrogen and ApoE isoforms on neurite outgrowth were measured in cortical neurons of adult mice. In the presence of ApoE ε2 allele, E2 increased the neurite length more than that in the presence of ApoE ε3 allele. However, E2 had no effect on neurite outgrowth when the ApoE allele was not present or only when the ApoE ε4 allele was present. These data demonstrated that the influences of estrogen on neurite growth were via an ApoE-dependent mechanism and regulated by the ApoE genotype (Nathan et al., 2004). Although estrogen increased the expression of both ApoE ε3 and ε4 alleles, only the ε3 isoform facilitated neurite outgrowth. There was a synergistic effect between E2 and the ApoE ε3 allele, but not with the ApoE ε4 allele, on neurite outgrowth. It was reported that the neurite extent increased by approximately 30% with the ApoE ε3 allele alone, and up to 70% when the ApoE ε3 allele was combined with E2 (Nathan et al., 2004).

In addition to neurite outgrowth, the anti-inflammatory activity is another critical protective effect of estrogen on attenuating the neurodegenerative process (Bruce-Keller et al., 2000; Vegeto et al., 2001). It was reported that the anti-inflammatory effects of estrogen were regulated by the ApoE

genotype. Compared to the ApoE ε3 mice, the anti-inflammatory activity of E2 significantly reduced in the ApoE ε4 targeted replacement mice (Brown et al., 2008). This interaction between the ApoE genotype and the anti-inflammatory activity of estrogen was found for nitrite, TNFα and IL-6 production by immune activated microglia. This ApoE genotype-specific anti-inflammatory activity of estrogen warrants further studies.

5.2. The gene–gene interactions between ESRs and ApoE on the risk of AD

We have reviewed the previous studies on the associations between ESR1 and ESR2 gene polymorphisms and the risk of AD. The results are still controversial. AD is a multi-factorial disease. There are gene-gene interactions that contribute to the susceptibility to AD. For the close relationship between estrogen and ApoE gene, several studies considered the modulation of ApoE genotype when analyzed the associations between ESR gene polymorphisms and AD. The results suggested that the ApoE gene, as a widely accepted risk factor for late-onset AD, regulated the associations between ESR genes and AD (summarized in Table 1). This genomic interaction at least in part explained the inconsistent results of the influences of ESR gene polymorphisms on the risk of AD.

The earliest study investigating the regulation of ApoE gene was conducted in an Italian population. The prevalence of PPXX genotype of the PvuII and XbaI polymorphisms were significantly higher in AD patients than those in controls, which was equivalent to a relative risk of 2.84 for PPXX carriers (Brandi et al., 1999). When analyzing the cumulative contribution of ApoE gene to the ERS1 gene polymorphisms, the authors found that ApoE ε4 allele increased the risk in individuals carrying PPXX genotype. The relative risk of AD for the PPXX individuals with homozygous ApoE ε4 allele elevated to 7.6.

Another study conducted in an Italian population supported this genomic synergistic effect of ESR and ApoE genes on the risk of AD. However, this interaction was only found in males. In males, the ApoE ε4 allele conferred an additional risk of AD to subjects who were PP and XX genotypes of the PvuII and XbaI polymorphisms. Furthermore, PP and/or XX genotypes reduced the plasma ApoE levels significantly compared to other genotypes. When analyzed separately by gender, this effect of ESR1 gene on the plasma ApoE levels was also only found in males (Corbo et al., 2006). This gender-specific interaction between the PvuII and XbaI polymorphisms of ESR1 gene and ApoE ε4 allele on the risk of AD was demonstrated by other studies. Both the PvuII and XbaI polymorphisms were not associated with AD. However, among the ApoE ε4 allele carriers, the p and x allele significantly increased the risk of AD in females but not in males (Porrello et al., 2006). One study suggested this gender-specific genomic interaction between ESR1 and ApoE genes on the risk of AD was also present in FAD. Among a Swedish FAD sample, the genotype of ESR1 gene alone was not associated with FAD. However, in females, both xx and pp genotypes interacted with the ApoE ε4 allele to synergistically increase the risk of FAD (Mattila et al., 2000).

Similar to the associations between ESR1 gene polymorphisms and the risk of AD, the interaction between ESR1 and ApoE genes on AD was also inconsistent. There were studies that did not support this interaction. One study suggested that although the xx genotype increased the risk of AD, there was no interaction between the PvuII and XbaI polymorphisms and ApoE genotypes on the susceptibility to AD (Monastero et al., 2006). The other study showed neither of these two polymorphisms of ESR1 gene nor the interaction between ESR1 and ApoE genes was associated with AD (Dresner-Pollak et al., 2009). For other polymorphisms on ESR1 gene, only one study analyzed if there was an interaction between other 39 SNPs of the ESR1 gene and ApoE ε4 allele on the risk of AD, and no positive result was found (Goumidi et al., 2011). We speculate that there may be other confounding factors influencing the results, similar to gender and ethnicity, which require further investigations.

The interaction between the polymorphisms of ESR2 gene and ApoE ε4 allele status was less studied, and only two studies were found. One study analyzed the influence of ApoE genotype on the association between rs4986938 of ESR2 gene and the risk of AD. No interaction was found (Dresner-Pollak et al., 2009). The other one also did not observe the interaction between 5 SNPs of ESR2 gene (rs4986938, rs867443, rs10144225, rs7154455 and rs1952586) and ApoE genotype on the risk of AD (Goumidi et al., 2011).

5.3. Interaction between estrogen synthesis and metabolism associated genes and ApoE gene

In addition to ESR1 gene, several previous studies have suggested the regulatory effect of ApoE genotype on the relationships between estrogen synthesis and metabolism associated genes and the susceptibility to AD.

The COMT gene was not suggested to be an independent risk factor for AD. However, several studies have shown an interaction between the COMT gene and the ApoE ε4 allele on the susceptibility to AD. The study by Wang and colleagues showed that when analyzed separately, the COMT gene alone was not associated with the risk of AD. However, the high activity allele G of the Val158Met polymorphism had a synergistic effect with ApoE ε4 on the increased risk of AD. The OR value of AD among subjects carrying one ε4 allele was 2.6, and increased to 3.6 among subjects with both GG genotype of COMT gene and one ε4 allele (Wang et al., 2005). Another study tested the Val158Met polymorphism of COMT gene among 345 AD patients and 253 controls, and found similar result (Martinez et al., 2009). Neither allele nor genotype of COMT gene was associated with AD, however, the synergistic effect between COMT gene and the ε4 allele was found. For subjects carrying at least one ε4 allele without COMT G allele, the risk of AD was 2.61; while for the ε4 allele carriers with GG or AG genotype, the OR value increased to 5.96 and 6.71, respectively. This synergistic effect was particularly remarkable for females. Recently, studies have suggested a gene-gene interaction between the COMT gene and ApoE ε4 allele was not only present in AD, but also in the risk of mild cognitive impairment and the memory decline. Subjects carried both ε4 allele and GG genotype of the Val158Met polymorphism showed a significantly increased risk for mild cognitive impairment (Lanni et al., 2012). In a normal population, participants with both the ε4 allele and the COMT G allele had the lowest scores on the test of semantic memory (Donges et al., 2012).

The CYP19 gene is a candidate risk gene for AD. Previous study has demonstrated the ApoE ε4 allele status modulates the association between CYP 19 gene and AD. Huang and Poduslo tested 18 SNPs of CYP19 among 227 AD patients and 131 controls (Huang and Poduslo, 2006). The result showed that the T allele of rs2899472 increased the risk of AD (OR = 1.67), while in ApoE ε4 positive subjects, the OR value of this SNP increased to 2.08. Furthermore, two other SNPs (rs1008805 and rs727479) were significantly associated with AD among the ε4 allele carriers, but not among the ε4 allele non-carriers.

The interactions between the GST enzyme genes and ApoE ε4 allele were also observed in previous studies. In the study of Pinhel and colleagues, the GSTP1 $Ile^{105} \rightarrow Val^{105}$ variant and the null polymorphism of GSTT1 gene were proved to be the risk factors for AD. This susceptibility to AD was enlarged among subjects carrying ApoE ε4 allele (Pinhel et al., 2008). In addition, the subjects carrying both GSTP1*C allelic variant and ApoE ε4 allele had a significantly increased risk of AD (Bernardini et al., 2005).

6. Other estrogen-associated genes

6.1. Estrogen, selective AD indicator-1 (seladin-1) and AD

The seladin-1 gene was first identified by Greeve and colleagues (Greeve et al., 2000). They were interested in that AD selectively impaired specific neurons in distinct brain regions, such as the large pyramidal neurons of the inferior temporal cortex, the hippocampus, the amygdala, and the entorhinal cortex. The underlying mechanisms were still unknown. Greeve and colleagues aimed to identify the genes that were differentially expressed in the selective vulnerable brain regions by comparing gene expression between the inferior temporal lobes and fronto-parietal cortices using an mRNA display approach. Among more than 30 differentially expressed cDNAs, a novel cDNA that had an expression that was significantly reduced in inferior temporal lobes was found. This new gene was designated as seladin-1 gene, which is located on chromosome 1p31.1-p33. The seladin-1 gene consists of 9 exons and 8 introns, and encodes an open reading frame of 516 amino acid residues. Seladin-1 is located in the endoplasmic reticulum, and to a lesser extent, in the Golgi apparatus. Apart from the brain, in peripheral tissues, the highest expression levels of seladin-1 mRNA were detected in adrenal gland, and moderate expression was found in liver, lung, spleen, and prostate.

Greeve and colleagues also demonstrated that the biological functions of seladin-1 were associated with the pathogenic mechanisms of AD. Seladin-1 conferred resistance against Aβ and oxidative stress induced apoptosis (Greeve et al., 2000). In PC12 clones that were selected for resistance against AD-associated Aβ-induced toxicity and H_2O_2-mediated oxidative stress, the mRNA levels of seladin-1 were several fold higher compared to the wild-type cells, and the protein levels were two fold higher in those protected cells. These effects of seladin-1 may be associated with the inhibition of caspase-3 activation, which is a key modulator of the apoptotic process. Following the study of Greeve and colleagues, another study showed that the down-regulation of seladin-1 gene transcription in brain regions that are selectively impaired in AD was associated with hyperphosphorylated tau (Iivonen et al., 2002). In addition to anti-apoptosis, seladin-1 exhibits another critical biological property involved in the pathogenesis of AD; seladin-1 modulates the metabolism of cholesterol. The identification of the ApoE gene as a major risk factor of AD suggested the importance of cholesterol homeostasis in preventing AD. Seladin-1 was demonstrated to be identical to the gene encoding the 3-beta-hydroxysterol delta-24-reductase, a cholesterol synthesizing enzyme, which catalyzes the synthesis of cholesterol from desmosterol. The seladin-1 gene overexpression increases the amount of membrane cholesterol, which is important in protecting the neuronal cells against toxic insults and inhibits the production of Aβ (Peri et al., 2011; Peri and Serio, 2008b).

Researchers have suggested that the seladin-1 might be a downstream effector of the activation of ESRs in the CNS. Using a unique human cell model, the gonadotropin-releasing hormone secreting neuroblast long-term cell cultures from human fetal olfactory epithelium, studies demonstrated that estrogen influenced the expression of the seladin-1 gene. The fetal neuroepithelial cell (FNC) expresses both ESR1 and ESR2. Thus, it is a good model to study the role of estrogen in neurons. Using quantitative real-time RT-PCR, the expression of seladin-1 mRNA in FNC was evaluated to identify if it was modulated by estrogen. E2 and ESR1 agonists significantly increased the level of seladin-1 mRNA (Benvenuti et al., 2005). The ESR1 appeared to be the main mediator, because the ESR2 agonist had much weaker effects on the mRNA levels of seladin-1. Another study supported the critical role of seladin-1 in the neuroprotective effects of estrogen. Using a small interfering RNA methodology, the mRNA and protein levels were significantly reduced in FNC. Silencing the expression of seladin-1 caused the loss of the protective effects of E2 against Aβ and oxidative stress induced toxicity and caspase-3 activation. The computer-assisted analysis revealed the presence of half-palindromic estrogen responsive elements upstream the coding region of the seladin-1 gene. A 1490-bp region was cloned in a luciferase reporter vector and then co-transfected with the ESR1 in Chinese hamster ovarian cells. Exposure to E2 increased the luciferase activity (Luciani et al., 2008). All these evidences demonstrated the close relationship between estrogen and seladin-1. Seladin-1 also plays an important role in regulating the neuroprotective effects of estrogen. The functions of seladin-1 on AD and the associations between seladin-1 and estrogen have been reviewed in detail elsewhere (Peri et al., 2011; Peri and Serio, 2008a,b). Our review is focused on the association between seladin-1 gene polymorphisms and the risk of AD.

The potential genetic contribution of seladin-1 gene to AD was only analyzed in a few studies. One previous study reported that the polymorphisms of the seladin-1 gene were associated with the risk of AD (Lamsa et al., 2007). Four SNPs (rs638944, rs600491, rs718265, and rs7374) on the seladin-1 gene were tested in 414 AD patients (mean age 71.8 ± 7.4 years, 70% females) and 459 controls (mean age 69.6 ± 5.1 years, 60% females) from Finland. When researchers compared the allelic and genotypic distribution between all of the cases and controls, no difference was found. However, after stratification according to gender, males with the T allele of rs600491 showed a significantly increased risk of AD. Moreover, the rs638944 and rs600491 were strongly linked. The study found that the TC haplotype was a protective factor of AD, with a frequency of 0.22 in cases and 0.30 in controls. In contrast, the GC haplotype was a risk factor, with a frequency of 0.10 in cases and 0.05 in controls. These results were supported by a recent study that examined the rs600491 SNP of seladin-1 gene in 295 AD patients and 204 cognitive healthy controls (Feher et al., 2012). When all patients and controls were compared together, no difference in the rs600491 genotype distribution was found. However, after stratification according to gender, there was a significant association between the T/T genotype and the risk of AD in males. These findings suggested a gender specific effect of seladin-1 gene polymorphism on the susceptibility to AD. For FAD, a study investigated exons 1-9 of the seladin-1 gene among Italian patients with FAD. The result showed the genotypes of seladin-1 gene were not associated with AD risk (Tedde et al., 2008).

On the basis of these previous studies, the studies on seladin-1 gene polymorphisms and AD are still insufficient. It is still unknown whether there is a gene-gene interaction between seladin-1 gene and other estrogen-associated genes on the risk of AD.

6.2. Choline acetyltransferase (ChAT) and butyrylcholinesterase (BuChE) genes

One of the characteristic biochemical deficits of AD is the decline of the number of basal forebrain cholinergic neurons. Cholinergic synaptic function is particularly susceptible to Aβ protein induced toxicity (Small et al., 2001), which may accelerate the loss of cholinergic neurons and then cause a decrease in the levels of the neurotransmitter, acetylcholine (ACh). The ACh neurotransmission in the hippocampus and cerebral cortex plays an important role in cognitive functions. The synthesis of ACh is regulated by ChAT, a rate-limiting enzyme, which is regarded as the specific indicator of cholinergic neurons. The hydrolysis of synaptic ACh, which is regulated by cholinesterase (ChE) enzymes, is also critical for cholinergic neurotransmission. To date, the primary therapeutic approach of AD is to reduce the ACh synaptic degradation using ChE inhibitors. There are two types of ChE,

acetylcholinesterase (AChE) and BuChE, which are found to be differentially expressed. In CNS, BuChE is mainly found in glial cells and endothelial cells, while AChE is in neurons and axons. Although the majority of ChE in brain is AChE, there is a particularly high expression of BuChE in the neurons in the hippocampus, thalamus and amygdala, the key areas of AD. Furthermore, previous studies have suggested that in AD the AChE activity is progressively reduced; however, BuChE is conversely significantly increased in AD. These three enzymes, ChAT, AChE and BuChE, synergistically regulated the levels of ACh and the function of cholinergic neurons. For the important role of these three enzymes in the pathology of AD, many previous studies have investigated the associations between the polymorphisms of ChAT, AChE and BuChE genes and the risk of AD. Although AChE is the major ChE, only few studies explored the effects of polymorphisms of AChE gene on AD, and all the results were negative (Clarimon et al., 2003a; Cook et al., 2005; Piccardi et al., 2007; Scacchi et al., 2009). In contrast, several studies suggested the influences of ChAT and BuChE gene polymorphisms on AD. Furthermore, ChAT and BuChE gene expression and functions were reported to be closely related to estrogen. In this review, we mainly focused on the associations between ChAT and BuChE gene polymorphisms and the risk of AD, and the relationships between estrogen and these two genes.

The association between estrogen and cholinergic neurotransmission has been extensively discussed. The effect of estrogen on enhancing and preserving cholinergic functions in CNS is one of the potential mechanisms of estrogen protection against AD (Norbury et al., 2003). We consider the influence of estrogen on the synthesis and hydrolysis ACh enzymes as a key mechanism for the estrogen regulation of the cholinergic neurotransmission. Genetic studies have shown that estrogen modulates the mRNA and expression levels of ChAT gene. Using quantitative in situ hybridization techniques, it was reported that the estrogen replacement resulted in a significant increase of ChAT immunoreactivity and the celluar mRNA levels of ChAT in the medial septum and nucleus basalis magnocellularis in adult rats (Gibbs et al., 1994). With NG108-15 neuronal cells, a cell culture model of cholinergic neurons, studies found estrogen dose-dependently increased the expression of ChAT gene (Yamamuro and Aizawa, 2010). Recently, a study showed that estrogen also increased the transcription of ChAT in the motoneurone-like cell line NSC-34 and in the spinal cord (Johann et al., 2011). These evidences demonstrated that ChAT gene was closely associated with estrogen; the mRNA and expression levels of ChAT gene were dramatically regulated by estrogen.

With regard to BuChE, evidences suggested a gene-gene interaction between the BuChE gene and other estrogen-associated genes. The study of Combarros and colleagues investigated the genotype of the 5′UTR polymorphism (rs1062033) of CYP19 gene and the BuChE gene K variant in 187 AD patients and 172 unrelated controls from Spain (Combarros et al., 2005). When the risk was considered for the single CYP19 polymorphism, a marginally significant association was observed between the presence of the C/C genotype and AD (OR = 1.54, 95%CI = 0.97–2.44, $p = 0.053$). In contrast, there was a significant decrease in the risk for AD among subjects with BuChE K allele compared to non-K carriers (OR = 0.56, 95%CI = 0.32–0.97, $p = 0.022$). When these two polymorphisms were analyzed together, the association between CYP19 genotype and the risk of AD was dependent on the BuChE K allele status. Among the K allele carriers, the CYP19 genotype was still not associated with AD. However, in the K allele non-carriers, the presence of CYP19 C/C genotype significantly increased the susceptibility to AD (OR = 1.81, 95%CI = 1.06–3.08, $p = 0.020$), and this association did not change after the adjustment for sex, age and ApoE genotype. Furthermore, Combarros and his colleagues investigated the interaction between ESR1 and BuChE gene polymorphisms on AD (Combarros et al., 2007). The study included 183 AD patients and 169 control individuals. All the subjects were analyzed for the PvuII polymorphism and BuChE K allele status. The ESR1 PvuII polymorphism alone was not associated with AD. However, among BuChE K allele carriers, the P allele of PvuII polymorphism significantly decreased the risk for AD.

These studies suggested that ChAT and BuChE might be the mediators of the effects of estrogen on AD. The ChAT and BuChE genes were also affected by or interacted with estrogen. As estrogen-associated genes, we summarized the previous results of the associations between ChAT and BuChE gene polymorphisms and the risk of AD in Table 2.

For ChAT gene, the most extensively studied polymorphism was A120 T (rs3810950) in exon5. In Caucasian populations, this polymorphism was reported to be associated with the risk of AD in 2 studies (Grunblatt et al., 2009; Mubumbila et al., 2002) out of a total of 6 studies (Cook et al., 2005; Grunblatt et al., 2009; Harold et al., 2003; Mubumbila et al., 2002; Ozturk et al., 2006; Schwarz et al., 2003). In Asian populations, 2 (Kim et al., 2004; Lee et al., 2012; Tang et al., 2008) out of 4 studies (Ahn Jo et al., 2006; Kim et al., 2004; Lee et al., 2012; Tang et al., 2008) showed an association between the A allele of rs3810950 and the risk of AD.

In addition to rs3810950, some other SNPs were also investigated, mainly including rs1880676 (Ahn Jo et al., 2006; Grunblatt et al., 2009; Harold et al., 2003; Ozturk et al., 2006), rs2177369 (Cook et al., 2005; Piccardi et al., 2007; Scacchi et al., 2009), and rs868750 (Harold et al., 2003; Ozturk et al., 2006), and the results were still ambiguous. Interestingly, several studies suggested gene-gene interactions between ChAT polymorphisms and ApoE ε4 status. The association between ChAT gene and the risk of AD became stronger (Grunblatt et al., 2009; Lee et al., 2012; Ozturk et al., 2006), or even only existed among ApoE ε4 allele carriers (Grunblatt et al., 2009).

With regard to BuChE gene, the K variant (rs1803274) is the most promising polymorphism, which is located at the C terminus and essential for BuChE protein tetramerization (Lane and He, 2013). This polymorphism is associated with lower serum levels and enzymatic activity of the BuChE. Unexpectedly, there were a larger number of the studies on the associations between polymorphisms of BuChE gene and the risk of AD than the studies on the AChE gene, and nearly all of these studies analyzed the K variant (Table 2). Although the results were inconsistent, these studies suggested that the age, ethnicity, and the ApoE ε4 allele status might regulate the relationship between the K variant and AD. In Caucasian populations, several studies demonstrated that the K allele was more frequent in AD patients compared to controls (Beyer et al., 2005; Lehmann et al., 1997; McIlroy et al., 2000; Panegyres et al., 1999; Wiebusch et al., 1999). This susceptible effect of the K variant increased in subjects with ApoE ε4 allele (Panegyres et al., 1999; Wiebusch et al., 1999) or even only existed in ApoE ε4 carriers (Lehmann et al., 1997; Tilley et al., 1999). Furthermore, the OR value of the K variant to AD increased with the age (Beyer et al., 2005; Lehmann et al., 1997; McIlroy et al., 2000; Tilley et al., 1999; Wiebusch et al., 1999). However, some other studies found the opposite results that the frequency of K variant was associated with the decrease of the risk of AD among all subjects (Bizzarro et al., 2010), or in ApoE ε4 non carriers (Alvarez-Arcaya et al., 2000; Bizzarro et al., 2010). Other studies did not find the associations between the polymorphism of BuChE gene and the risk of AD (Bertram et al., 2000; Brindle et al., 1998; Cook et al., 2005; Crawford et al., 1998; Grubber et al., 1999; Kehoe et al., 1998; Piccardi et al., 2007; Prince et al., 2001; Russ et al., 1998; Scacchi et al., 2009; Singleton et al., 1998), even after controlling for age and the ApoE ε4 status (Crawford et al., 1998; Russ et al., 1998; Singleton et al., 1998). For Asian populations, nearly all of the

Table 2
The associations between ChAT, BuChE and NEP gene polymorphisms and the risk of AD.

Gene	Polymorphisms tested	Author (year)	Ethnicity	*N* (% females)		Risk/protective polymorphisms (other findings)
				AD	Controls	
ChAT	14 variants	Harold (2003)	Caucasian (UK)	508 (—)	118 (—)	ns
	19 SNPs	Grünblatt (2009)	Caucasian (Australia)	41 (—)	464 (—)	rs3810950 (The rs1880676 was associated with the risk of AD only among ApoE ε4 allele carriers)
	rs3810950	Mubumbila (2002)	Caucasian (France, Germany)	122 (71%)	112 (44%)	AA genotype
	rs1880676, rs3810950, rs868750	Ozturk (2006)	Caucasian (USA)	1001 (67%)	708 (61%)	A allele of rs868750, especially in non ε4 carriers
	rs2177369, rs3810950	Cook (2005)	Caucasian (UK)	215 (—)	320 (—)	GG genotype of rs2177369[a]
	rs3810950, rs868749	Schwarz (2003)	Caucasian (Germany)	242 (65%)	143 (70%)	ns
	rs2177369	Scacchi (2008)	Caucasian (Italy)	471 (69%)	254 (60%)	GG genotype
		Piccardi (2007)	Caucasian (Italy)	158 (73%)	118 (64%)	ns
	rs3810950, rs1880676	Ahn (2006)	Asian (Korea)	316 (72%)	264 (63%)	ns (In non-ApoE ε4 allele carriers, A allele increased the risk of AD)
	rs3810950	Kim (2004)	Asian (Korea)	246 (70%)	561 (72%)	AA genotype
		Tang (2008)	Asian (China)	273 (75%)	271 (60%)	ns (A allele was associated with earlier AAO and worse cognitive function)
		Lee (2012)	Asian (Korea)	736 (73.5%)	1386 (64.5%)	A allele (A allele was associated with earlier AAO, and there was gene-gene interaction between A allele and ApoE ε4 on the risk of AD)
BuChE	rs1803274	Lehmann (1997)	Caucasian (UK)	149 (58%)	104 (75%)	ns (K allele was associated with LOAD in ApoE ε4 carriers, and the OR value increased with age)
		Panegyres (1999)	Caucasian (Australia)	38 (—)	30 (—)	K allele, especially in ApoE ε4 carriers
		McIlroy (2000)	Caucasian (Ireland)	175 (65%)	187 (69%)	K allele, especially in subjects >75 years
		Beyer (2005)	Caucasian (Spain)	206 (62%)	181 (60%)	K allele, and the risk accumulated with age
		Combarros (2005)	Caucasian (Spain)	187 (70%)	172 (74%)	K allele[a] (There was an interaction between CYP19 gene and BuChE gene on the risk of AD)
		Bizzarro (2010)	Caucasian (Italy)	167 (62%)	129 (52%)	K allele[a]
		Hiltunen (1998)	Caucasian (Finland)	78 (74%)	97 (66%)	ns (K allele frequency was reduced in AD patients carrying ApoE ε4 allele under 75 years of age)
		Kehoe (1998)	Caucasian (UK)	181 (60%)	71 (52%)	ns
		Russ (1998)	Caucasian (UK)	203 (—)	122 (—)	ns
		Singleton (1998)	Caucasian (UK)	119 (—)	83 (—)	ns
		Crawford (1998)	Caucasian (USA)	391 (31%)	201 (60%)	ns
		Brindle (1998)	Caucasian (USA, Canada)	188 (64%)	165 (44%)	ns
		Tilley (1999)	Caucasian (UK)	177 (62%)	118 (31%)	ns (K allele and ApoE ε4 allele interacted on the increased risk of AD in the >75 year age group)
		Grubber (1999)	Caucasian (USA)	245 (58%)	241 (52%)	ns
		Alvarez—Arcaya (2000)	Caucasian (Spain)	249 (68%)	250 (75%)	ns (In non-ApoE ε4 carriers, the K variant decreased the risk of AD only in women)
		Mattila (2000)	Caucasian (Finland)	80 (64%)	67 (45%)	ns (Among ApoE ε4 allele carriers, the non K allele status increased the risk of AD)
		Bertram (2000)	Caucasian (USA)	460 (—)	367 (—)	ns
		Prince (2001)	Caucasian (Sweden)	204 (61%)	186 (58%)	ns
		Cook (2005)	Caucasian (UK)	215 (—)	320 (—)	ns
		Piccardi (2007)	Caucasian (Italy)	158 (73%)	118 (64%)	ns

Table 2 (*Continued*)

Gene	Polymorphisms tested	Author (year)	Ethnicity	*N* (% females)		Risk/protective polymorphisms (other findings)
				AD	Controls	
	rs1803274, rs3495	Wiebusch (1999)	Caucasian (Canada)	135 (53%)	70 (36%)	K allele, especially in ApoE ε4 carriers and older patients
	rs1803274, rs1355534	Scacchi (2009)	Caucasian (Italy)	471 (69%)	254 (60%)	ns
	rs1803274	Ki (1999)	Asian (Korea)	78 (78%)	74 (—)	ns
		Yamamoto (1999)	Asian (Japan)	203 (—)	288 (—)	ns
		Lee (2000)	Asian (China)	89 (53%)	101 (45%)	ns
		Kim (2001)	Asian (Korea)	164 (—)	239 (—)	ns
		Bi (2001)	Asian (China)	38 (—)	40 (—)	ns
		Raygani (2004)	Asian (Iran)	105 (57%)	129 (65%)	K allele, especially in ApoE ε4 carriers and older patients
NEP	rs701109	Clarimon (2003)	Caucasian (Spain)	118 (75%)	91 (52%)	C allele among subjects aged 75 years and under
	rs989692, rs2196521, rs1025192, rs1816558, rs3773885, rs3773882, rs3736187	Helisalmi (2004)	Caucasian (Finland)	390 (70%)	468 (60%)	T allele of the rs989692, A allele of rs3736187
	21 SNPs and GT repeat	Wood (2007)	Caucasian (USA)	298 (54%)	298 (54%)	rs1836915 and rs6776185
	rs989692, rs3736187	Vepsalainen (2009)	Caucasian (Finland)	379 (69%)	456 (61%)	rs989692, rs3736187
	rs1836914, rs989692, rs9827586, rs6797911, rs61760379, rs3736187, rs701109	Miners (2012)	Caucasian (Italy)	1057 (—)	424 (—)	rs6797911
	CA and GT repeats, a 480 base pair fragment in the promoter region	Lilius (2003)	Caucasian (Sweden)	315 (—) EOAD: 163 LOAD: 152	109 (—)	ns
	GT repeat, −1075A > G, −1284G > C	Sakai (2004)	Asian (Japan)	240 (72%)	163 (72%)	GT repeat
	8 SNPs	Shi (2005)	Asian (China)	257 (60%)	242 (53%)	-204G→C, IVS17-294C→T, IVS22 + 36C→A
	AC and TG repeats in the upstream region of exon 1, CA repeat in the 3rd intron, TG repeat in the 22nd intron	Oda (2002)	Asian (Japan)	201 (67%)	208 (54%)	ns
	GT repeat	Sodeyama (2001)	Asian (Japan)	75 (—)	89 (—)	ns
	rs701109, −204G/C	Fu (2009)	Asian (China)	236 (72%)	332 (61%)	ns

ns means no significant association between the polymorphisms and the risk of AD among the entire subjects.
Abbreviations: AD, Alzheimer's disease; ChAT, choline acetyltransferase; BuChE, butyrylcholinesterase; NEP, neprilysin; ApoE, apolipoprotein E; AAO, age-at-onset; EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease.
[a] Protective polymorphism.

related studies (Bi et al., 2001; Ki et al., 1999; Kim et al., 2001; Lee et al., 2000; Yamamoto et al., 1999) did not observe an association between the K variant and the risk of AD regardless of age and ApoE ε4 status. Only one study demonstrated that the K allele increased the risk of AD, and the OR value increased with age and the presence of the ApoE ε4 allele (Raygani et al., 2004). Further studies are required to determine if the ethnicity really influences the association between the K allele and AD.

From these evidences, we can see that the ChAT and BuChE genes are closely associated with estrogen, and induce the effects of estrogen on cholinergic neurotransmission. As estrogen-associated genes, the polymorphisms of ChAT and BuChE genes may influence the susceptibility to AD, in which the ApoE genotype most likely plays a regulatory role.

6.3. Estrogen and neprilysin

The regulation of estrogen on the level of Aβ, which has been extensively studied, is one of the main ways that estrogen prevents AD. The potential molecular mechanisms may involve many aspects. Here, we focus on the association between estrogen and Aβ degrading enzyme, neprilysin. We speculate that estrogen promotes Aβ degradation mainly through this enzyme.

Neprilysin is a zinc-dependent cell surface metalloendopeptidase. It degrades both monomeric and oligomeric forms of Aβ40 and Aβ42, and is regarded as the primary Aβ degrading enzyme in the brain. Considering that estrogen was proved to affect the levels of Aβ, studies have analyzed the associations between estrogen and neprilysin. The results showed estrogen regulated neprilysin activity in the brain. The ovariectomy significantly decreased the activity of neprilysin, and estrogen replacement increased neprilysin levels to control values (Huang et al., 2004). Recently, in neuroblastoma SH-SY5Y cells, studies showed that estrogen and two selective ESR1/ESR2 agonists up-regulated neprilysin expression. There are two estrogen responsive elements identified in the neprilysin gene, that bind to ESR1 and ESR2 and then activate ESR-dependent gene expression (Liang et al., 2010). These data suggest estrogen influences neprilysin expression levels, which then regulate the Aβ degradation. It may be a potentially novel mechanism for the neuroprotective activity of estrogen. As an important estrogen-associated gene, we reviewed the previous studies on the associations between neprilysin gene polymorphisms and the risk of AD in Table 2.

Neprilysin gene is located on chromosome 3q25.1-q25.2. Several SNPs and dinucleotide-repeats of neprilysin gene were analyzed. In Caucasian populations, studies suggested that some SNPs were associated with the risk of AD, including rs989692 (Helisalmi et al., 2004; Vepsalainen et al., 2009), rs3736187 (Helisalmi et al., 2004; Vepsalainen et al., 2009), rs1836915 (Wood

et al., 2007), rs6776185 (Wood et al., 2007) and rs6797911 (Miners et al., 2012). One study suggested that age influenced the association between neprilysin gene polymorphism and the risk of AD. The study analyzed rs701109 polymorphism and suggested it was not associated with AD among the entire sample. However, among subjects aged 75 years and younger, the C allele of this polymorphism increased the risk of AD (Clarimon et al., 2003b). Only one study conducted among a Caucasian population did not found the positive result. This study investigated three putative important regions, including two dinucleotide-repeats and a 480 base pair fragment (Lilius et al., 2003). Among Asian populations, three of the studies did not observe the link between neprilysin gene polymorphisms and the risk of AD (Fu et al., 2009; Oda et al., 2002; Sodeyama et al., 2001). Two studies showed that GT repeat polymorphism and three other SNPs (-204G→G, IVS17-294C→T, and IVS22 + 36C→A) were associated with the risk of AD (Sakai et al., 2004; Shi et al., 2005).

From these evidences, we observed that neprilysin is a key mediator in the effects of estrogen on Aβ degradation. Neprilysin gene may be a susceptible factor to AD.

7. Conclusions

In summary, we reviewed the associations between the risk of AD and polymorphisms of the genes with close relationships to estrogen. These gene polymorphisms or gene-gene interactions influence the neuroprotective effects of estrogen. In addition to estrogen synthesis and metabolism associated genes and ESR genes, we also summarized important genes that are involved in the potential mechanisms of estrogen against the pathogenic progression of AD, including the enhancement of neurite outgrowth and synaptic sprouting, anti-apoptosis and anti-inflammation, regulation of cholinergic neurotransmitter systems, and promotion of Aβ degradation (see Fig. 2). The roles of estrogen in the progression of AD may be dependent on the genotype status of these genes. One of the most notable of these genes is ESR1 gene. It is the most studied estrogen-related gene. Most of the studies demonstrated that ESR1 gene independently or synergistically functions with other genes to affect the risk of AD. In addition, over half of the relevant studies suggested that polymorphisms of GSTM3, GSTT1, ChAT and NEP genes were risk factors for AD. Until now, evidences from previous studies did not support the roles of COMT, GSTM1, GSTO1, GSTO2, ESR2 and BuChE genes on the susceptibility of AD. Previous reviews are consistent with our results demonstrating that ESR1 gene was associated with the risk of AD, while COMT gene might not be related to the susceptibility of AD (Serretti and Olgiati, 2012; Sundermann et al., 2010). A past review published in 2006 suggested that CYP19 gene polymorphisms increased the risk of AD (Hiltunen et al., 2006). However, more recent studies we reviewed did not support this result. The association between CYP19 gene and AD requires additional studies. Only one or two studies have examined the relationships between CYP17, CYP1A1, GSTM4 and GSTZ1 genes and the risk of AD, and all of these few studies obtained negative results. As a recently identified gene, seladin-1 gene polymorphism has been suggested to be a risk factor for AD in males, which needs to be confirmed.

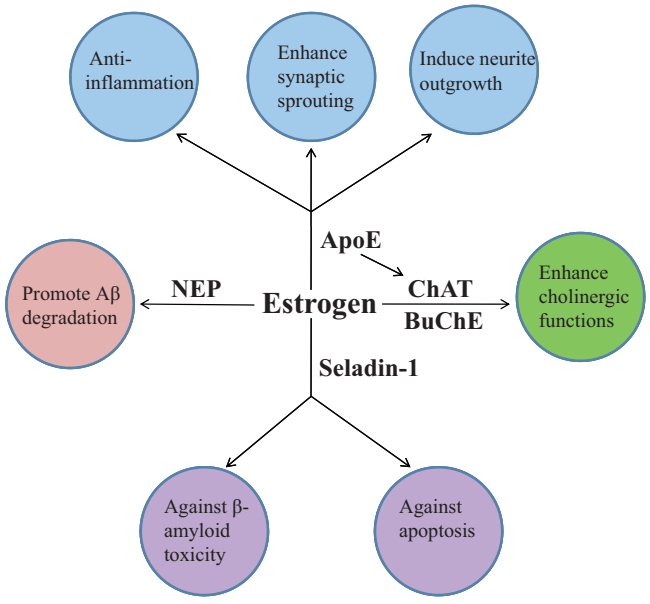

Fig. 2. The critical genes involved in the potential mechanisms of estrogen against the pathogenic progress of AD. ApoE gene interacts with ChAT and BuChE genes on regulating cholinergic functions. ApoE, apolipoprotein E; ChAT, choline acetyltransferase; BuChE, butyrylcholinesterase; NEP, neprilysin.

In our review, we analyzed the probable causes of discrepant findings on the associations between estrogen-related genes and the risk of AD. The potential causes include: (1) ethnicity: For each gene in Tables 1 and 2, we separately listed the previous studies according to the ethnicity of the subjects. The study results of ESR1 and BuChE genes were influenced by ethnicity. For other genes, Caucasians were the main study subjects, and studies on other ethnicities were insufficient. (2) Gender: Gender is always an important factor in studies on estrogen. From our review, the associations between CYP19 and ESR1 genes and the risk of AD were more obvious in females. Hence, the various gender ratios of subjects in different studies most likely caused the inconsistent results. (3) Gene–gene interaction: We emphasized the gene-gene interactions in our review, particularly for the regulatory effects of ApoE gene. Previous studies showed the large part of estrogen-related genes, including CYP19, COMT, GSTM3, GSTP1, ESR1, ChAT and BuChE, might influence the risk of AD in synergy with other genes, mainly ApoE gene. We recommend that the ApoE ε4 status should be considered in further studies on the associations between estrogen or its related genes and AD.

8. Further studies and clinical applications

ERT is regarded as a potential treatment or prevention of AD. However, the inconsistent results of ERT hinder its application in clinical practice. We think ERT may be not suitable for every patient. Further studies should try to determine who benefits from ERT. In this review, we introduced the associations between the risk of AD and the genes that may modulate the neuroprotective effects of estrogen on promoting Aß degradation and ameliorating amyloid toxicity, as well as anti-inflammation, anti-apoptosis, enhancing synaptic sprouting, regulating cholinergic functions, and inducing neurite outgrowth. The ApoE gene is involved in more than one aspect, and has been most extensively studied in clinical trials on ERT. Moreover, previous evidences suggested that ERT may prevent AD or improve cognitive function only in ApoE ε4 negative patients. However, for other genes, there is a lack of studies regarding the method by which the polymorphisms in these genes regulate the effects of estrogen. Further studies should not only confirm the associations between these genes and the risk of AD, but also analyze the effects of estrogen against AD under different genotypes of these genes. It can help to identify the patients who are most likely to benefit from ERT.

Furthermore, estrogens exert their biological effects via interactions with ESRs. Recent studies demonstrated ESR1 was more important for the anti-Aβ role of estrogen (Carroll and Pike, 2008; Cordey and Pike, 2005; Merlo and Sortino, 2012). Studies suggested that the development of subtype-selective ligands that specifically target different ESRs might be a better approach for the

treatment of AD (Nilsson et al., 2011). We believe there will be additional studies on developing these ESR subtype-selective ligands. Considering that ESR gene polymorphisms may be risk factors for AD, we suggest further studies investigating the different roles of ESR1 and ESR2 or subtype-selective ligands under different genotypes of ESR genes.

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