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Calcium Homeostasis Modulator 1 Gene P86L Polymorphism and Susceptibility to Alzheimer's Disease

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Alzheimer's disease (AD) is a complex neurodegerative disease causing problems with memory, thinking and behavior, although those problems vary among individuals and from early to late stage. The cause of AD is still unknown; however, there has been much effort to reveal the mechanism to AD pathology using different tools such as animal models, gene expression profiling and genome-wide association studies (GWAS) [1-3]. Among the different genetic and environmental factors contributing to AD, it has been revealed that genetic factors attribute to about 70 percent of AD [4]. Considerable progress has been made to identify genetic factors of AD susceptibility including the early-onset mutations of genes encoding amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin1 (PSEN2) and a large number of the late-onset mutations of genes mainly including ATP Binding Cassett Transporter7 (ABCA7), Apolipoprotein E (APOE), Bridging Integrator 1 (BIN1), Clusterin (CLU) and Sortilin-Related Receptor 1 (SORL1) [5]. AD involves with the progressive extracellular deposition of amyloid β-peptide (Aβ) in the brain and generally the over-production of the 40- or 42-aa-long Aβ is suggested to be correlated with neuronal dysfunction [6]. Studies of AD have shown that abnormal amyloid metabolism induces an upregulation of neuronal calcium signaling, leading to an initial decline in memory and subsequent apoptosis. It has been proposed that there is a potential connection between Aβ, calcium and pathogenesis of AD as Aβ oligomers can form calcium-permeable channels in membranes [7]. In addition, Aβ oligomers lead to calcium influx and cell death through increased calcium permeable channel formation [8]. Based on these evidences regarding the role for calcium dysregulation in the pathogenesis of AD, research progress has been made to identify susceptibility genes to AD that may be involved in the regulation of calcium homeostasis.

A study from Dreses-Werringloer et al. [9] has demonstrated that a non-synonymous single nucleotide polymorphism (SNP) in calcium homeostasis modulator 1 (CALHM1), the Pro86Leu (P86L, C>T, rs2986017), was associated with calcium permeability and soluble amyloid precursor protein alpha (sAPPα) accumulation and the P86L polymorphism was significantly associated with AD in independent case-control studies of 3404 participants. Since 2008, many epidemiological studies have showed an association between P86L polymorphism in CALHM1 and AD risk [10,11]; however, there are still controversies of the effect of P86L polymorphism in AD due to inconsistent results across published studies. For instance, Aqdam et al. [10] and Boada et al. [12] have showed that the *P86L* polymorphism of CALHM1 gene has associated with late-onset AD (LOAD) in Iranian and Spain population, respectively. In contrast, Nacmias et al. [13] and Fehér et al. [14] have reported that there was no association between the CALHM1 variation and AD risk with both early-onset AD (EOAD) and LOAD in subjects from Italian and Hungarian population, respectively. All of these studies have suggested that further study is needed with a bigger sample size to confirm their results. As a consequence, the first meta-analysis of the association study between P86L SNP and risk of AD was reported in 2010 by Lambert et al. [15]. This meta-analysis data of 7,873 AD cases and 13,274 controls in Caucasian origin have revealed that the CALHM1 P86L polymorphism was not a potential genetic determinant of AD; however, the *P86L* polymorphism in CALHM1 interaction with ApoE ε4 allele was found to have significant association with the risk of early-onset AD. Since the first meta-analysis by Lambert et al. [15] in 2010, several studies have been published regarding the correlation between P86L SNP and AD susceptibility; therefore, we performed an updated meta-analysis by adding the latest data to obtain a more precise estimation of the relationship.

In our previous meta-analysis, we included a total of sixteen studies (twenty-four subgroup studies consisting of 9795 cases and 15,335 controls) to evaluate the *P86L* polymorphism of CALHM1 for the risk of AD [16]. This meta-analysis was searched and selected using the PubMed, Science Direct, Scopus and Google Scholar databases up to Jun 2015 using the search terms "CALHM1" and "polymorphism or SNP or variant" in combination with "Alzheimer's disease". A meta-analysis with pooled odds ratios and 95% confidence intervals was carried out to assess the associations between *P86L* polymorphism and the risk for AD under four genetic models (heterozygous, homozygous, dominant and recessive) with fixed or random effects models. These results confirmed that the homozygote model was significantly associated with increased risk for AD in overall and Caucasians. Our genotype distribution in the control group followed the Hardy-Weinberg equilibrium (HWE) and showed all genetic models were statistically correlated with increased risk of AD. Three genetic models (homozygote, heterozygote and recessive) in the fixed effect model (CC vs. TT, pooled OR: 1.33, 95%: 1.16-1.53; CC vs. TC, pooled OR: 1.16, 95%: 1.04-1.29; TT vs. CC/TC, pooled OR: 1.26, 95%: 1.04-1.44) and the dominant genetic model in the random effect model (TT/TC vs. CC, pooled OR: 1.19, 95%: 1.06-1.34) were significantly associated with increased risk for AD. The conflicting results between Lambert et al. and our meta-analysis have occurred and this could be due to the number of included studies and the subjects from different ethnic groups. In our meta-analysis, we used additional studies involving 3883 subjects from seven studies and additionally included four Asian studies unlike Lambert et al. which only consisted of Caucasians [16]. It has been suggested that genotype frequencies according to ethnicity were different, which means these different genotypes may be lead to elucidate different results. Our results showed that some of the genetic models were significantly correlated with increased risk for AD in overall and Caucasian populations.

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Even though the results from these two meta-analysis studies are inconsistent, Rubio-Moscardo et al. [17] has demonstrated that rare genetic variants, p.R154H and p.G330D, in CALHM1 disturb calcium homeostasis and may contribute to the risk of EOAD based on the sequencing date of all CALHM1coding genes obtained from three independent series consisting of 284 EOAD patients and 326 controls and calcium imaging analyses. Moreover, the overexpression of CALHM family members in the nematode *Caenorhabditis elegans* touch neurons is sufficient to trigger necrotic-like neuronal death [18]. These evidences and our meta-analysis have presented that there is a significant relationship between CALHM1 and the risk of AD. Although our meta-analysis has some limitations in terms of ethnicity, a number of included studies and age, the P86L polymorphism analysis of CALHM1 gene in our data may be useful potential biomarker for genetic association study in patients with AD. Furthermore, future studies should be needed to determine the association between the P86L polymorphism and AD risk in large-scale of Asian populations.

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