行政院國家科學委員會補助專題研究計畫成果報告

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FE65 基因多型性變異與老年性阿滋海默症相關性之本土研究

The association of FE65 polymorphism with sporadic late onset Alzheimer disease in Taiwan.

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□赴國外出差或研習心得報告一份

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□國際合作研究計畫國外研究報告書一份

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一、中文摘要

蛋白質 FE65 可與 Amyloid Precursor Protein 之細胞內段結合，並進而改變乙型類澱粉之代謝；近來許多研究探討 FE65 基因多型性變異與老年偶發性阿滋海默症的關係。這是台灣首次進行相關的研究，我們收集了 66 位老年偶發性阿滋海默症的病患，及 78 位年齡、教育程度相當之正常參與者，其中絕大多數是"11"基因型，只有一位正常者具有"12" 基因型；因此，就台灣族群而言，FE65 基因多型性變異與老年偶發性阿滋海默症的發生並無顯著關係。

關鍵詞：FE65、基因多型性變異、阿滋海默症

Abstract

The FE65 protein binds to the intracellular domain of the amyloid precursor protein (APP), and may regulate the metabolism of Aβ. A genetic polymorphism in intro 13 of the FE65 gene has been reported to be associated with the sporadic late-onset Alzheimer's disease (AD) recently. This is a similar investigation in Taiwan. We collect 66 AD patients, and 78 control subjects nearly matched with age and education level. Most of them have the same "11" genotype, and only one "12" genotype in the control group. In conclusion, there is no association between the FE65 polymorphism and sporadic late-onset Alzheimer's disease.

Keywords: FE65, polymorphism, Alzheimer's disease

二、緣由與目的

The FE65 protein binds to the YENTPY sequence in the cytoplamic domain of APP. This motif is believed to be involved in the modulation of trafficking of APP and the production of Aβ. Therefore, the Fe65 may play the key "adaptor" role that links multiprotein complex to the intracellular domain of APP. Human FE65 gene is more than 10Kb in length and contains 14 exons. Sequence study reveals a polymorphism with a trinucleotide deletion (CTA) and nearly complete linkage disequilibrium with A→G substitution in intron 13. Recently, there are some investigations to survey the association between the FE65 polymorphism and AD, but without consensus. We launch this project to find the relationship between FE65 gene polymorphism and the incident risk of AD in Taiwan, and seek more clinical evidences to clarify the possible of FE65 in the pathogenesis of AD.

三、結果與討論

1. Subjects

In one-year period, 66 patients compatible with the diagnosis of clinical probable Alzheimer's disease according to the criteria of NINCDS-ADRDA were included. Seventy-eight normal control subjects also took apart in this study. The demographic data was show in the following table.1.

There is no significant difference in sex ratio and age distribution between AD and control groups. But the education year is slight higher in the AD group. The *P*-value is 0.049 calculated with one-way ANOVA.

Table.1 Demographic data of subjects in the study:

Group	Male	Female	Number total	Age	Education years*
AD	**32**	**34**	**66**	**75.24±8.46#** **(53-94)※**	**7.95±5.20** **(0-20)**
Control	**34**	**43**	**78**	**75.79±8.66** **(40-93)**	**6.23±5.08** **(0-16)**

 # Mean±SD; ※ ()=Range; *One-way ANOVA analysis

2. **FE65 polymorphism**

All the subjects had donated the venous blood to extract the DNA. We analyzed the FE65 gene polymorphism of each subject according to the protocol cited in previous method with some modification. Restriction enzyme ***SpeI*** would cut the 178bp PCR product into 2 segments (106bp and 72bp) in the allele 1, but not in the allele 2 with ***cta*** deletion. To our surprise, almost the 144 subjects have "11" allele and only one "12" allele polymorphism in the control group (Talbe.2). The allele 2 frequency is as low as 0.35%. We also find that there is no association between the Fe65 gene type and the incidence of AD. The odds ratio (OR) is 1.013 (Chi square). It doesn't support the hypothesis even corrected with the education factor (p=0.49, General linear model).

Table.2 Fe65 polymorphism

Genotype	"11"	"12"	"22"	
AD	**66**	**0**	**0**	**66**
Control	**77**	**1**	**0**	**78**
Total	**143**	**1**	**0**	**144**

3. Discussion:

(1). According to the previous studies of Fe65 polymorphism, the allele "2"(deletion in intro13) frequency is about 10% to 20%, and there is uncertain relationship between the incidence of AD and this gene polymorphism. Our study shows that the allele2 scarcely existed in our population (less than 1%). This difference may be due to the race factor. We also get the conclusion that there is no significantly protective effect of allele 2 in the occurrence of AD in our population.

(2). In contrast to our original planning, we don't categorize the subjects into different age or ethic groups, and discuss the interaction with APOE polymorphism, because the rare frequency of allele 2 in our population.

(3). It is not easy to persuade to patient and caregiver to donate venous blood for DNA

analysis. They become cautious and even withdrawn, especially they have to read and sign the consents, which contain lots of special terms. We need to spend a lot of time to explain the whole procedure to the subjects.

四、計畫成果自評

1. From this study, we get the conclusions that the allele2 of FE65 polymorphism is rare existed in our population, and there is no strong relationship between this polymorphism and sporadic AD. We hope to get it published, because there is no similar study in Taiwan, and eccentric distribution of polymorphism frequency in our population.

2. Small sample size may bother the statistic power in our study. We hope to collect more cases, stratified them with young and old and elder groups, and see the interaction between APOE polymorphism.

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