

A genetic screen of the mutations in the Korean patients with early-onset Alzheimer's disease

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Abstract: Early-onset Alzheimer's disease (EOAD) has distinct clinical characteristics in comparison to late-onset Alzheimer's disease (LOAD). The genetic contribution is suggested to be more potent in EOAD. However, the frequency of causative mutations in EOAD could be variable depending on studies. Moreover, no mutation screening study has been performed yet employing large population in Korea. Previously, we reported that the rate of family history of dementia in EOAD patients was 18.7% in a nationwide hospital-based cohort study, the Clinical Research Center for Dementia of South Korea (CREDOS) study. This rate is much lower than in other countries and is even comparable to the frequency of LOAD patients in our country. To understand the genetic characteristics of EOAD in Korea, we screened the common Alzheimer's disease (AD) mutations in the consecutive EOAD subjects from the CREDOS study from April 2012 to February 2014. We checked the sequence of *APP* (exons 16–17), *PSEN1* (exons 3–12), and *PSEN2* (exons 3–12) genes. We identified different causative or probable pathogenic AD mutations, *PSEN1* T116I, *PSEN1* L226F, and *PSEN2* V214L, employing 24 EOAD subjects with a family history and 80 without a family history of dementia. *PSEN1* T116I case demonstrated autosomal dominant trait of inheritance, with at least 11 affected individuals over 2 generations. However, there was no family history of dementia within first-degree relation in *PSEN1* L226F and *PSEN2* V214L cases. Approximately, 55.7% of the EOAD subjects had *APOE* ϵ 4 allele, while none of the mutation-carrying subjects had the allele. The frequency of genetic mutation in this study is lower compared to the studies from other countries. The study design that was based on nationwide cohort, which minimizes selection bias, is thought to be one of the contributors to the lower frequency of genetic mutation. However, the possibility of the greater likeliness of earlier onset of sporadic AD in Korea cannot be excluded. We suggest early AD onset and not carrying *APOE* ϵ 4 allele are more reliable factors for predicting an induced genetic mutation than the presence of the family history in Korean EOAD population.

Keywords: Alzheimer's disease, mutation, presenilin, apolipoprotein-E, sequencing, early onset Alzheimer's disease, genetics

Introduction

Alzheimer's disease (AD) is one of the devastating neurodegenerative disorders and the most frequent cause of dementia. AD is classified into late-onset AD (LOAD) and early-onset AD (EOAD) with the onset age of 65 years being the differentiating border.¹ Although this partition was arbitrary having been based on the retirement age, accumulating evidence demonstrates distinct characteristics of EOAD in comparison to LOAD. The clinical progression of EOAD is more rapid, demonstrating frequent early non-amnesic deficits and intense behavioral, including psychotic, symptoms.^{1–4} The deterioration of functional connectivity of the neural networks is more extensive in EOAD, involving neocortex rather than being confined to medial temporal region

from the earlier disease stage.⁵⁻⁷ Further, to the degree that EOAD affects the subjects who actively work, its social impact is more devastating, and because of this social and economic burden, EOAD needs additional attention.

The genetic contribution to AD pathogenesis is potent in EOAD. The familial occurrence is more frequent in EOAD compared to LOAD, ranging from 32% to 73.3% in referral centers.⁸⁻¹⁰ Also, the frequency of causative mutations in EOAD with autosomal dominant inheritance is much higher, although the frequency is variable between studies (from 11.8% to 71.0%).^{8,9,11} The rate of family history of dementia in first-degree relatives of Korean EOAD patients was similar to that of LOAD (18.7% vs 15.8%) in hospital-based cohort study.¹² This rate is much lower than the incidents previously reported.^{11,13} The recent historical plight of Korea, including a 3-year nationwide war and sustained division of the country, is likely to confound the derivation of an accurate family history of dementia because of the lack of demographic information. To understand the genetic characteristics of EOAD in Korea, we screened the common AD mutations in EOAD subjects from the nationwide cohort, the Clinical Research Center for Dementia of South Korea (CREDOS) study.¹²

The aim of the current study was to estimate the frequency of causative known AD mutations in Korean EOAD patients through checking the mutations in *APP*, *PSEN1*, and *PSEN2* genes, including serially recruited 104 subjects with EOAD.

Materials and methods

Subjects

The subjects who developed clinical symptoms of AD before 65 years of age were consecutively recruited from 8 institutes as a part of a hospital-based cohort study conducted by the CREDOS from April 2012 to February 2014. Comprehensive neurological, neuropsychological, laboratory, and brain magnetic resonance imaging (MRI) evaluations were performed as previously described.¹² All EOAD patients met the revised clinical criteria of probable AD from the National Institute on Aging-Alzheimer's Association (NIA-AA)¹⁴ at initial evaluation and follow-up. Blood samples were collected from 104 unrelated EOAD patients who gave written informed consent for this study. An attempt was made at establishing familial aggregation of pathogenic mutations in these patients with EOAD. The EOAD subjects showing pathologic mutations were investigated to determine whether or not the disease exhibited any familial aggregation. All protocols were approved by the institutional review boards of each hospital and were in accordance with the principles expressed in the Declaration of Helsinki.

Genetic analysis

Genomic DNA was extracted from the leukocytes using commercially available Puregene kit (Qiagen, Valencia, CA, USA). The causative mutations of AD in the *APP* (exons 16-17), *PSEN1* (exons 3-12), and *PSEN2* (exons 3-12) genes along with the flanking intron sequences were screened, because the causative AD mutations are mainly located in these regions.¹⁵

Statistics

Two group comparisons between the subjects with and without a family history of dementia were performed using independent sample *t*-test (Statistical Package for the Social Sciences [SPSS] Version 19.0; SPSS Inc, Chicago, IL, USA).

Results

Demographic characteristics

The demographic and clinical characteristics are summarized in Table 1. The mean age at onset (AO) was 56.3±5.6 years. The family history of dementia was noted in 24 patients, among whom maternal history was observed in 19 (18.3%) and paternal history in 5 (4.9%) patients. There was no difference between the EOAD subjects with and without family history in terms of sex, AO, education, severity of dementia, mini-mental state examination, clinical dementia rating, and *APOE* genotype.

Mutation analyses

Four AD causative mutations were identified when genetic mutations in *APP* (exons 16-17), *PSEN1* (exons 3-12), and *PSEN2* (exons 3-12) were investigated. Two mutations were noted in *PSEN1* gene, T116I and L226F.

Table 1 Clinical characteristics of the subjects

	All (n=104)	Family history (n=24)	No family history (n=80)
Sex, F	63 (60.6%)	17 (70.8%)	46 (57.5%)
Age, years	60±5.4	61.0±6.0	59.4±5.2
Age at onset, years	56.3±5.6	57.2±6.3	56.1±5.4
Education, years	9.0±4.5	9.3±4.8	9.0±4.5
MMSE	18±6.9	18.3±6.5	17.9±7.0
CDR	1.1±0.7	1.1±0.7	1.1±0.8
CDR-SOB	5.8±4.5	5.5±4.0	5.9±4.7
<i>APOE</i> genotype			
ε2ε3	2 (1.9%)	1 (4.2%)	1 (1.3%)
ε3ε3	44 (42.3%)	10 (41.7%)	34 (42.5%)
ε3ε4	46 (44.2%)	8 (33.3%)	38 (47.5%)
ε4ε4	12 (11.5%)	5 (20.8%)	7 (8.8%)

Note: Data are presented as mean ± standard deviation or n (%).

Abbreviations: CDR, clinical dementia rating; CDR-SOB, clinical dementia rating-sum of boxes; F, female; MMSE, mini-mental state examination.

Table 2 The EOAD subjects with identified genetic mutations

Mutation	Pathogenic	Sex/AO/APOE	FH	Presenting symptoms	MMSE/CDR at imaging	Imaging	CSF
<i>PSEN1</i> T116I	Causative (La Bella et al ¹⁷)	Female/38/ε2ε3	Yes	Memory loss	23/0.5	MRI: atrophy in med T FDG-PET: ↓ met in bi T & P	tTau/Aβ42, 4.53; pTau181/Aβ42, 0.43
<i>PSEN1</i> L226F	Causative (Zelanski et al; ¹⁶ Bagyinszky et al ²²)	Female/37/ε3ε3	No	Memory loss	21/1	MRI: atrophy in med T & P FDG-PET: ↓ met in bi T & P	ND
<i>PSEN2</i> R62C	Unclear (Slegers et al; ²¹ Ertekin-Taner et al; ²⁰ Brouwers et al ¹⁹)	Male/49/ε3ε3	No	Obsessive compulsive behavior	24/1	MRI: diffuse atrophy SPECT: ↓ perfusion in F & T	ND
<i>PSEN2</i> V214L	Probably involved in disease (Youn et al ¹⁸)	Female/54/ε3ε3	No	Memory loss, anomia	15/1	MRI: atrophy in med T FDG-PET: ND	tTau/Aβ42, 1.66; pTau181/Aβ42, 0.20

Abbreviations: EOAD, early-onset Alzheimer's disease; AO, age at onset; bi, bilateral; CDR, clinical dementia rating; F, frontal; FDG-PET, fluorodeoxy glucose positron emission tomography; FH, family history; med, medial; met, metabolism; MMSE, mini-mental state examination; ND, not done; P, parietal; SPECT, single-photon emission computed tomography; T, temporal; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.

Both were previously identified as causative mutations in AD in the Western countries,^{16,17} and another 2 were observed in *PSEN2* gene, R62C and V214L (Table 2). V214L was reported as a probable pathogenic mutation in our country based on in silico analysis.¹⁸ In regards to *PSEN2* R62C, there has been a report in relation to AD.¹⁹ However, its pathogenic connection with AD has been refuted by its identification in non-AD subjects.^{20,21} No mutations were identified in exons 16 and 17 of *APP* gene in our EOAD subjects.

The EOAD patients with *PSEN1* L226F do not have a family history of dementia. In the patient with *PSEN2* V214L mutation, first-degree relatives did not have dementia, and only the grandmother was reported to have an unknown subtype of dementia at the age of 70 years. In contrast, subject with *PSEN1* T116I mutation had paternal history of dementia with autosomal dominant trait (Figure 1). However, the family history for individuals of earlier generation was not available. Screening for genetic mutation in family members could be performed in *PSEN1* L226F, both biological parents and 2 elderly siblings. They neither revealed clinical symptoms of dementia on evaluation nor carried the mutation at

PSEN1, thus demonstrating that *PSEN1* L226F in the patient is most likely from de novo mutation.²²

The *APOE* genotype of the subjects was ε3ε3 in 3 subjects and ε2ε3 in 1 subject.

Discussion

In a study of 104 Korean EOAD patients, we identified 3 causative mutations by screening the genetic mutations in exons 16–17 of *APP* and coding regions of *PSEN1* and *PSEN2*. This incidence was much lower compared to prior reports, where 71% (24 of 34 families with AO <61 years)¹¹ and 54.6% (6 of 11 families with AO <65 years)⁹ of EOAD patients with autosomal dominant inheritance trait, and 68% of EOAD patients with a family history within first-degree relationship (21 of 31 probands with AO <61 years)²³ were found to have a causative mutation in *PSEN1*, *PSEN2*, or *APP*. A familial EOAD was defined as having one another EOAD patient within first-degree relationship with additional AD patient in this study, which is broader than the definition of autosomal dominant inheritance, which requires 3 affections over 2 generations.²⁴ Despite this, a causative mutation was found in only 1 case (4.2% of 24 familial cases). Most of the studies which reported higher frequency of genetic mutations were very likely to be influenced by the selection bias of including the subjects with genetic susceptibility.⁸ This recent investigation evaluating an unselected consecutive population over a 10-year period demonstrated that pathogenic mutations comprised 2 of 17 EOAD (11.8%, AO <65 years) cases with autosomal dominant inheritance.⁸ The Iberian African study recruited a larger number of unrelated EOAD patients regardless of family history from 9 different institutions (AO <65 years) and demonstrated a mutation frequency (6 of 74 familial EOAD patients) of 8.1%,¹⁰ in which the definition of family history was the same as ours. The frequency of genetic mutation from the recent unbiased screening

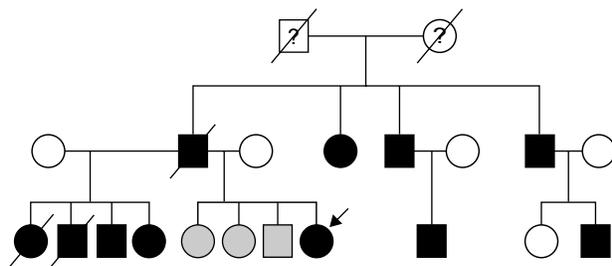


Figure 1 Genealogy tree of the EOAD patients with *PSEN1* T116I mutation. The symbols filled with black represent the patients with clinical Alzheimer's disease, while the gray symbols correspond to the family members with mild cognitive impairment (MCI). The arrow indicates the proband being studied here. The history of dementia was not available in first generation of the genealogy tree.

Abbreviation: EOAD, early-onset Alzheimer's disease.

studies is much closer to ours than the previously reported statistics. This study was conducted as a nationwide cohort study, and we tried to recruit every EOAD subject willing to give their consent and who met our inclusion criteria from April 2012 to February 2014. We believe that this approach minimizes the selection bias and is helpful in estimating the frequency of genetic mutation in the Korean EOAD population, and by extension in clinical practice.

There have been a few Asian studies on genetic screening of AD mutations. In a Japanese study, among 45 familial AD and 29 sporadic EOAD (AO <60 years) cases, 3 causative mutations were identified in EOAD patients (AO, 40–55 years) from 3 families (*PSEN1* 772A>G and *PSEN1* 1158C>A) and 1 sporadic case (*PSEN2* 1262C>T).²⁵ A Chinese group screened AD mutations employing 54 familial EOAD (AO <65 years) cases from 32 families.²⁶ Four *PSEN1* (p.A434T, p.I167del, p.F105C, and p.L248P) mutations in 4, and 1 *APP* (p.V717I) mutation in 2 unrelated families were identified (AO, 33–50 years). All the recognized causative mutations were different from those observed in our study. An exact comparison of those results with ours is inappropriate due to the different design of the study. However, in terms of the frequency of mutation, our result of 1 in 24 familial EOAD cases is somewhat lower than the other Asian studies, while 2 in 80 EOAD cases without a family history of dementia is comparable.

There were only a few Korean studies on genetic screening or case reports of AD mutations. In 1996, Hong et al published a case report on *PSEN1* H163R in a Korean family with EOAD, which is a quite common causative mutation for AD.²⁷ In 2008, Park et al published a genetic screening study, but they employed only 6 EOAD patients. *PSEN1* G206S and M233T and *APP* V715M causative mutations were found in 3 unrelated patients including 1 without family history.²⁸ In 2010, Kim et al published a study on *PSEN1* M139I in a family with EOAD.²⁹ In 2012, a novel mutation, *PSEN1* H163P, was reported in a probably de novo case of AD, which was suggested as a probable pathogenic variant associated with EOAD.³⁰ The first *PSEN2* mutation in Korea, *PSEN2* V214L, was discovered in 2014, which was suggested to be involved in AD or another type of dementia due to three-dimensional (3D) modeling.¹⁸ Based on these studies, the authors raised the importance of genetic mutation screening in the Korean EOAD populations. We have, however, found 3 probable causative mutations among the 104 EOAD subjects. Thus, the specificity of presently available genetic screening technique in assessing EOAD patients is diminished. Hence, genetic screening techniques including more delicate

guidelines are needed. Although we could not compute the statistical significance because of the small number of mutation cases, a positive family history seems not to be critical in predicting the presence of AD causative mutation in the Korean EOAD patients. We found 2 patients without an overt family history of a first-degree relative having had a genetic mutation, *PSEN1* L226F and *PSEN2* V214L, while only 1 patient in a familial case did note a recent Korean history, which impairs the precise tracking of family history of dementia. Instead, earlier AO was thought to be a more consistent factor in determining the necessity of checking genetic AD mutations in Korean EOAD patients. An AO of 58 years had been suggested as a cutoff point for genetic analysis based on Western data.^{9,23} AO was 31, 35, and 34 years in EOAD subjects with genetic mutation, and 62- and 55-year-old patients with AO did not carry causative mutations in a prior Korean study.²⁸ Similarly, AO was 38, 37, and 54 years in our EOAD patients with causative mutation. Although we cannot provide the valuable cutoff age for genetic study in our population due to the low frequency of mutation, the AO threshold should be lower than in the Western countries.

Our prior cohort analysis demonstrated higher frequency of *APOE* ϵ 4 allele in EOAD patients than in LOAD patients, since its occurrence was 49.3% vs 40.8%, respectively.¹² Consistent with this finding, a Chinese study identified that 55.7% of the EOAD subjects had *APOE* ϵ 4 allele. This was much higher than the reported allele frequency of *APOE* ϵ 4 in EOAD patients from other countries.^{9,26} In contrast, none of the EOAD patients who were positive for causative mutation carried *APOE* ϵ 4. These findings are consistent with prior reports demonstrating that the EOAD subjects carrying causative AD mutations are less likely to carry *APOE* ϵ 4 allele.^{9,11} Taken together, not carrying *APOE* ϵ 4 allele is suggested to be another factor to consider in the genetic mutation screening of EOAD. Additionally, the possibility is raised that EOAD in Korea is more likely to be an earlier manifestation of sporadic AD, based on the more prevalent *APOE* ϵ 4 allele carriership in addition to the lower frequency of genetic mutation.^{31,32}

We cannot exclude the likelihood that the protocol of genetic screening in this study might impair the additional detection of AD genetic mutations. The targeted sequencing of *APP*, *PSEN1*, and *PSEN2* genes including the sites with frequent AD causative mutations has been employed in prior genetic screening studies in EOAD. However, a recent study performing exome sequencing revealed that novel mutation is present in *APP* outside the common mutation sites.³¹

In the current study, we targeted part of *APP*, *PSEN1*, and *PSEN2* where most of the causative mutations were identified, which might miss the rare mutation of AD outside these regions, exons 10 and 12 of *PSEN1* and exon 9 of *PSEN2*.^{33,34} Moreover, we could not check the copy number of *APP*, which might not detect genomic *APP* duplication.³⁵ Thus, further study to perform exome sequencing may be helpful, since several additional genes were confirmed or suggested to be involved in AD progression.

Conclusion

In conclusion, we identified the 3 definitely or probably pathogenic AD mutations, *PSEN1* T116I, *PSEN1* L226F, and *PSEN2* V214L, employing 24 EOAD patients with a family history and 80 without a family history of dementia. The frequency of such mutations was lower compared to the results reported from other countries. The study design having been based on a nationwide cohort minimizes the selection bias, thereby leading to a lower frequency of genetic mutation. However, the greater possibility of earlier onset of sporadic AD in Korea cannot be excluded. In addition, we suggest that earlier AO in the absence of *APOE* ϵ 4 allele is more valuable in estimation of the necessity of genetic mutation testing than the presence of family history in Korean EOAD patients.

Acknowledgments

This work was supported by grants from the Korea Health Technology R&D Project (HI10C2020, HI14C1942, and HI14C3331) through the Korea Health Industry Development Institute (KHIDI), Korea Ministry of Health & Welfare, and the Original Technology Research Program for Brain Science through the National Research Foundation of Korea funded by the Korean Government (MSIP; No 2014M3C7A1064752). Genetic screening has been performed by Department of Bionano Technology, Gachon University. For the current study, blood samples were collected from the patients with informed consent at Soonchunhyang University Bucheon Hospital, Republic of Korea; Dong-A University Medical Center, Busan, Republic of Korea; Gachon University, Gil Medical Center, Incheon, Korea; Pusan National University Hospital, Busan, Republic of Korea; Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea; Ilsan Hospital, National Health Insurance Corporation, Goyang, Republic of Korea; Myongii Hospital, Goyang, Republic of Korea; Inha University School of Medicine, Incheon, Republic of Korea. The Ethical Committee of the Soonchunhyang University Bucheon Hospital, Seoul National University College of Medicine & Neurocognitive

Behavior Center, and Seoul National University Bundang Hospital approved the current study.

Disclosure

The authors report no conflicts of interest in this work.

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