Familial Alzheimer's disease: Research on 630 pedigrees in the Greek population

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Abstract

The *PSENs/APP* mutation distribution in Greek patients with familial Alzheimer's disease (FAD) remains unclear. The research on FAD can make a significant contribution to the prevention, diagnosis and treatment of Alzheimer's disease (AD). We aimed to analyze the sociodemographic and clinical features of Greek FAD pedigrees which have an increased possibility to carry *PSENs/APP* mutations. In total, 630 pedigrees with AD from Outpatient Memory Clinics of University Departments of Neurology (School of Medicine of AUTh) and also from Greek Association of Alzheimer Disease and Related Disorders for the years 2014-2018 were examined. The inclusion criteria in order to increase the possibility of the pedigrees to carry *PSENs/APP* mutations were according to the Dominantly Inherited Alzheimer's Network (DIAN) and more specifically we tried to find families with at least 2 patients in different generations and the age of symptom onset ≤ 60. Additional clinical resources, like the neuropsychological assessment, the cerebrospinal fluid, the apolipoprotein ε and magnetic resonance imaging of at least one symptomatic person per family were included. In total, 53 families (218 symptomatic people) were met the criteria and were further analyzed by DIAN. 12 families (46 symptomatic people) were approved by the Committee of this Research Center in order to perform genetic testing for PSEN 1, PSEN 2, and APP mutations. 63% of the symptomatic people of these pedigrees were women. The mean number of people with early onset of AD as well as of the affected generations was 2.4 (range: 2-4). The mean age of symptoms onset in these pedigrees was 59.8 and the mean age of symptoms onset of people with early onset of NA was 55.4 years. In conclusion, the selection of FAD pedigrees is a very difficult process due to the specific inclusion criteria of this study. This study emphasizes the importance of a careful sampling method in genetic research.

Keywords: Alzheimer's disease, familial Alzheimer's disease, pedigrees, *PSENs/APP* mutations

JEL Classifications: I10, I18, I19

Introduction

Alzheimer's Disease (AD) is a devastating disease that affects more than 50 million people worldwide. This number is expected to double every 20 years, reaching 80 million in 2030 and more than 150 million in 2050. The statistics related to AD and its effect on patients, their families, and the entire healthcare system are staggering (Alzheimer's Association website, 2018). The number of patients with AD in Greece is currently more than 150.000 (200.000 according to the ADI report) causing a huge amount of costs per year, and thus has an immense social impact and heavy economic burden (Minister of Health, 2016).

AD can be categorized as sporadic AD or familial AD (FAD) and based on family history. The sporadic cases of AD are without family history; however, FAD requires the person with AD to have at least one first-degree relative diagnosed with AD or mild cognitive impairment (MCI) due to AD (Cacace et al., 2016). Of the single-gene forms of dementia, most follow an autosomal dominant inheritance pattern, including genetic AD. Although the majority of cases are sporadic, a markedly FAD component has been reported in 60% of early-onset (<65 years) AD patients (Bird, 2008), and this autosomal dominant mode of inheritance is found in about 1-5% of AD (Bekris et al., 2010). However, a FAD family history pattern may be complicated by reduced penetrance and variable expressivity. Both reduced penetrance and variable expressivity result from genetic, epigenetic, and stochastic factors that are not completely understood (UCSF Memory and Aging Center, 2012).

AD with autosomal dominant inheritance means a pathogenic variant (disease-causing mutation) in one copy (allele) of a gene causes the signs and symptoms of AD. FAD includes autosomal dominant AD, that arises from mutations in one of the three flowing genes (Tanzi,2013): the amyloid precursor protein gene (APP), presenilin 1 gene (PSEN1), and presenilin 2 gene (PSEN2). These mutations are nearly 100% penetrant and the onset of dementia symptoms typically occurs at a relatively young and predictable age across generations (Ryman et al., 2014). These mutations have been targeted by the Dominantly Inherited Alzheimer Network (https://dian.wustl.edu/) and other cohorts around the world. The Dominantly Inherited Alzheimer Network (DIAN) is a multinational, longitudinal study of FAD families providing critical insight into the order and timing of the AD pathological cascade (Aschenbrenner et al., 2019).It was established in 2008 and it is an international research partnership involving institutions in the United States, Australia, Europe, Asia and South America focusing on the operation of Observational Studies and a long-term effort to observe changes that occur in individuals with FAD.

FAD constitute a critically important area of study on AD research, although it represents a minority of all AD cases for the following reasons:

1. It encompasses the physiological and pathological features of all cognitive stages from preclinical to MCI to dementia.
2. Pathological characteristics of genetic forms are similar to the more common sporadic ones, and research on FAD contributes to advances in the basic scientific understanding of these diseases.
3. It represents an ideal population, with a possible predictable age at onset (AAO), which is relatively young and has minimal complications, and facilitates exploration of the pathogenesis of AD (Jia et al., 2020).

4. It is important to focus on people with subjective cognitive impairment and there is an association between early subjective memory changes and mutation carriers of FAD (Weston et al.,2018).
5. There is an increasing need to analyse the genetics of FAD in order to answer the question of whether shared genetic risk factors may explain the similar phenotype among late-onset apparently sporadic AD, FAD, and other neurodegenerative dementias (frontotemporal dementia, cortico-basal degeneration, progressive supranuclear palsy, and Creutzfeldt-Jakob disease) (Sassi et al., 2014).
6. It promotes the development of transgenic animal models with which anti-dementia drugs are tested and also it promotes clinical trials with putative disease-modifying drugs, which have the potential to delay or even prevent AD in asymptomatic people, in addition to slowing progression in those with symptoms (Mega et al., 2020).

The inherited component for AD risk has focused on close relatives and consideration of the full family history may improve the accuracy and utility of risk estimates (Cannon-Albright et al., 2019). Family history which can be used as a diagnostic tool and help guide decisions about genetic testing for the patient and at-risk family members (Genetic Alliance, 2009). The main way used to collect family history information and to identify genes in inherited disorders like FAD has been the examination of an extensive pedigree (Jimenez-Escrig et al., 2005). According to the Guide of Genetic Alliance (2010) family history can be a powerful screening tool and has often been referred to as the best "genetic test".

The *PSENs/APP* mutation distribution in Greek patients with FAD remains unclear (Finckh et al., 2005). This study tries to detect linkage between given family history information on a pedigree and the probability of these family members being mutation carriers for FAD. It analyzes the demographic and clinical features of Greek FAD pedigrees which have an increased possibility to carry *PSENs/APP* mutations and focuses on enhancing the understanding of the pedigrees with or without PSENs/APP mutations. This study is an ongoing study and the initial aim is to analyze and present the preliminary results of the demographic and clinical features of Greek FAD pedigrees which have an increased possibility to carry PSENs/APP mutations based on specific criteria. This is the first step for expanding the present research field and enhancing the understanding of the pedigrees with or without PSENs/APP mutations.

METHODS

Study design

This study focused on affected individuals with a family history suggestive of FAD. The family history in the form of pedigree and also additional clinical resources, like the neuropsychological assessment, the cerebrospinal fluid, the apolipoprotein ε and magnetic resonance imaging (MRI) of at least one symptomatic person per family were examined. This study included participants with MCI and AD. The diagnosis of MCI patients met the diagnostic criteria of Petersen et al (1999) whereas patients with AD met the criteria of DSM V (American Psychiatric Association, 2013).

The inclusion criteria for this study in order to increase the possibility of the pedigrees to carry *PSENs/APP* mutations were according to the Dominantly Inherited Alzheimer's Network (DIAN) Expanded Registry Exploratory Genetic Counseling and Testing (GCT) Program. Pedigrees with individuals who met the following criteria were included: (1) of Greek ethnicity, (2) at least one first-degree

relative in addition to the patient himself/herself within the family who exhibited objective cognitive decline suggestive of AD in a different generation that the patients, (3) age at symptom onset (AAO) ≤ age 60 for the two different generations, (4) a written informed consent need to have been obtained from each individual when he/she had participated on the neuropsychological evaluation. The exclusion criteria were the following: (1) other causes of cognitive impairment supported by MRI or laboratory tests (vitamin B12, folic acid, etc) and (2) individuals who had a medical or psychiatric disorder that would interfere with the completion of the assessments.

A separate Scientific Advisory Board of Ethical Committee of GAADRD was involved in the oversight of the study. This study has been included for assessment in the Agenda of 65th Session and has been approved on 6 February of 2021.

Participants

The participants of this study have visited, for a neuropsychological evaluation, the Outpatient Memory Clinics of University Departments of Neurology (School of Medicine of Aristotle University of Thessaloniki) and the Greek Association of Alzheimer Disease and Related Disorders (GAADRD) between 2014 and 2018. During the neuropsychological assessment, participants were asked if they have a family history of dementia. For each family with a positive family history, the health professional (geneticists, neurologists) created the family pedigree. In this neuropsychological assessment, the affected individuals and their relatives signed an informed consent form for the use of their clinical data also for other studies.

Procedure

In total, 630 pedigrees from this database for the 5 years were further examined for the inclusion criteria by the research team of this study (psychologist, neurologist and genetic counselor). In the first step, the pedigrees were examined for AAO≤ age 60. In the second screening, a telephone interview was conducted by the research team in order to collect missing information on the pedigrees and to include only families with 2 affected generations. In this telephone interview, participants were asked if they accept to participate in this specific study. After the first and second screening of the total number of pedigrees, the research team decided on the final number of pedigrees that will be sent to the DIAN Network for further examination. The DIAN Committee accepted a number of pedigrees for further genetic testing according to the criteria that were stated above on 5th of January 2021.

This study design is described also in figure 1.

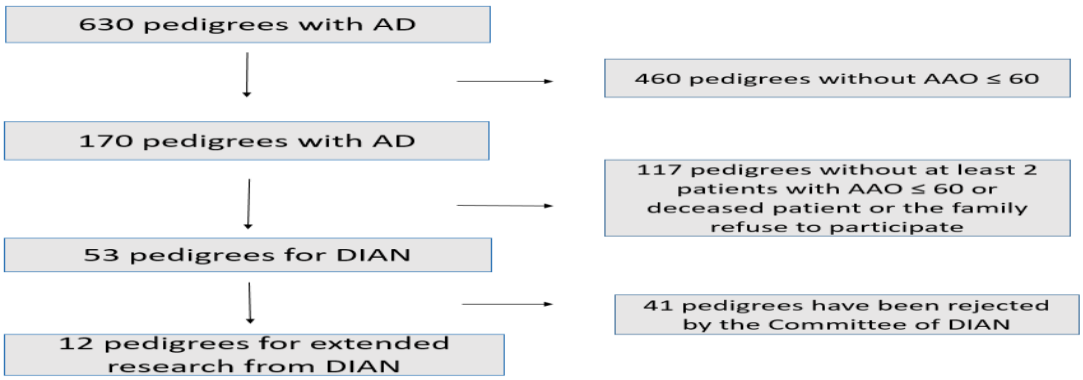

Figure 1. Flowchart of the enrolled pedigrees

Statistical analysis

Statistical analysis was performed using SPSS software (ver. 19.0; IBM Corp., Armonk, NY, USA). A P-value of <0.05 was considered statistically significant. Quantitative variables such as affected generations, affected family members, age, AAO, years of education, and cognitive assessment scores are expressed as the mean ± SD and the range.

RESULTS

The examination of the 630 pedigrees has as a result a total of 170 pedigrees including an individual with AAO ≤ age 60. These pedigrees were further examined through a telephone interview for the inclusion criteria of at least one first-degree relative in addition to the patient himself/herself within the family who exhibited objective cognitive decline suggestive of AD in a different generation than the patients. After the telephone interview, 53 families, including in total 218 symptomatic people, met the above criteria (Table 1 and 2). The 67,8% of them were women. Of the 218 symptomatic people, 110 individuals were early-onset family members (50,5%). The AAO in the pedigree in total was 64 years and the AAO on early-onset family members in the pedigree was 57,4 years.

After further analysis by DIAN, 12 families including 46 symptomatic people were approved by the Committee of this Research Center in order to perform genetic testing for PSEN 1, PSEN 2 and APP mutations (Table 3 and 4). 63% of the symptomatic people of the 12 pedigrees were women. Of the 46 individuals, 29 were early-onset family members (63%), which is a significantly higher percentage than the number of the same individuals in the 53 pedigrees. The mean number of people with early onset of AD as well as of the affected generations was 2.4 (range: 2-4), whereas in the 53 pedigrees were 2 generations. The mean age of symptoms onset in the 12 pedigrees was 59,8 years old while in the 53 pedigrees was 64 years. Also, the mean age of symptoms onset of people with early onset of AD was 55,4 years than 57,4 years in the previous pedigrees.

One also significant difference between the comparison of these pedigrees is that the average age of the 53 participants was 65,4 years and the AAO of them was 56,2 whereas the 12 participants were 63,3 years old and the AAO on their 53,4.

Table 1: Demographic and clinical characteristics of the 53 pedigrees

CHARACTERISTICS	TOTAL NUMBER OF PARTICIPANTS	AVERAGE	PERCENTAGE (%)
Number of people with symptoms	218	4,1(range:2-8)	
Females	148	2,7(range:0-6)	67,8
Males	70	1,3(range:0-6)	32, 2
Early onset family members	110	2(range:1-4)	50,5
Affected generations		2,4(range:2-4)	
AAO in the pedigree in total		64(range:45-85)	
AAO on early onset family members in the pedigree		57,4(range:45-65)	

Table 2. Demographic and clinical characteristics of the 53 participants/patients

CHARACTERISTICS	TOTAL NUMBER OF PARTICIPANTS	AVERAGE	PERCENTAGE (%)
Number of participants	53		
Females	41		77,3
Males	12		22,7
Age		65,4(range:50-73)	
AAO		56,2(range:45-65)	
Years of education		11,1(range:6-21)	
Minimental State Examination (MMSE) score		19,7(range:1-28)	

Table 3. Demographic and clinical characteristics of the 12 pedigrees

CHARACTERISTICS	TOTAL NUMBER OF PARTICIPANTS	AVERAGE	PERCENTAGE (%)
Number of people with symptoms	46	3,8(range:2-4)	
Females	29	2,4(range:0-6)	63
Males	17	1,4(range:0-3)	37
Early onset family members	29	2,4(range:2-4)	63
Affected generations		2,4(range:2-4)	
AAO in the pedigree in total		59,8(range:50-69)	
AAO on early onset family members in the pedigree		55,4(range:50-60)	

Table 4. Demographic and clinical characteristics of the 12 participants

CHARACTERISTICS	TOTAL NUMBER OF PARTICIPANTS	AVERAGE	PERCENTAGE (%)
Number of participants	12		
Females	9		75
Males	3		25
Age		63,3(range:50-69)	
AAO		53,4(range:48-58)	
Years of education		11(range:6-18)	
Minimental State Examination (MMSE) score		17,3(range:1-28)	

DISCUSSION

A family history is important to establish a pattern of transmission and identify potential diseases such as AD that an individual may be at increased risk for the disease in the future. The identification of deterministic genes associated to FAD enables members of families with positive history for dementia to consider to undergo the relevant genetic testing (Mega et al., 2020). The recent availability of clinical trials of experimental drugs for inherited AD can explain this change of demand for genetic testing (Bateman et al., 2017). In addition, the understanding of the complex relationship between genotype and phenotype in dementia families is highly relevant in terms of therapeutic strategies including targeting specific genes (Kwok et al., 2020).

Our study is focused on sociodemographic and clinical characteristics on pedigrees which can increase the possibility of a family with positive AD history having a FAD and carrying *PSENs/APP* mutations. In the present study, some characteristics of pedigrees of FAD families were determined which are in line with the most researches on FAD. In order to increase the possibility to find carriers of *PSENs/APP* mutations, there is a need to have at least one first-degree relative in addition to the patient himself/herself within the family who exhibited objective cognitive decline suggestive of AD in a different generation that the patients, and also the age at symptom onset for both individuals need to be before 60s in these two different generations (Moulder et al., 2013; LanoiseleÂe et al., 2017;Aschenbrenner et al., 2020).

However, there are many studies using different inclusion criteria for finding families with FAD. In the study of byJia et al. (2020), 1330 patients with AD or MCI in 404 pedigrees were enrolled from the Chinese Familial Alzheimer's Disease Network in order to be determined for PSENs/APP mutations. In this research, the only inclusion criteria were the presence of at least one first-degree relative in addition to the patient himself/herself within the family who exhibited objective cognitive decline suggestive of AD. In addition, Mega et al. (2020) in their study evaluated the feasibility and acceptability of the genetic counseling and testing process, as undertaken according to the Italian Dominantly Inherited Alzheimer's and Frontotemporal Network (IT-DIAfN) protocol. In this study the suggestive family history was defined based on the presence of (i) at least three affected first-degree relatives in two generations, irrespectively of the age at onset, or (ii) at

least two affected first-degree relatives in two generations, with at least one with onset at ≤ 65 years, or (iii) one affected family member with onset at ≤ 60 years or with a suggestive clinical phenotype (e.g. dementia with atypical presentation, recurring presence in other relatives, peculiar geographic origin). Also, 170 families were included in the study of LanoiseleÂe et al. (2017) when at least two first-degree relatives suffered from early-onset AD with an age of onset <65 years in two generations. In this study, they included also 129 sporadic cases of AD with an AOO below age 51. It is crucial to underline that 53 families have members with mutations for FAD and from these 17 families were sporadic cases.

In-depth genetic studies in additional FAD kindreds displaying a marked discrepancy in age at symptom onset in family members of different generations (Reitz et al., 2020). Thus, it will be highly valuable to disentangle the etiology of differences in age at onset through more in-depth studies including a large cohort of FAD families.

It is crucial to underline that there are many studies focused on cognitively unimpaired or mildly impaired individuals who learned they had genetic markers of AD. Milne et al ,(date) found that participants expected that they will routinely learn risk reduction strategies for delaying symptoms of AD, learn about effective therapies and have access to follow up care (Stites, 2018). Early identification of increased risk may allow the individual and health professional to take steps to reduce risk by implementing lifestyle changes, introducing medical interventions, and/or increasing disease surveillance (Genetic Alliance, 2009).

Finally, the entire procedure, including genetic testing and repeated assessments is highly demanding, especially in terms of human resources. The procedure is expected to be accomplished within a research environment by a multidisciplinary team in centers with specific expertise. Nowadays, there is an increasing need of an optimized genetic counseling protocol which could be eventually transferred to clinics and could be used in routine clinical practice (Bocchetta et al., 2016). Of note, in a previous study on inherited dementia, we revealed that a high proportion of patients belonging to high-risk pedigrees asked for genetic counselling; requests decreased according to the estimated family risk (Fostinelli et al., 2018).

Limitations

Our study has some limitations. It is an ongoing study in which we need to finalize the number of FAD pedigrees with and without PSENs/APP mutations after the genetic testing. The results of the present study should be considered preliminary because the 12 selected participants have not yet been tested for FAD mutations. Also, the AAO and family history data were collected based on the recall of some of the participants in this study. Family members who passed away and patients who refused to participate may have affected the results.

Also, we need to analyze further the hereditary and clinical profile of FAD, the genetic features, and to compare genetic heterogeneity and/or homogeneity between Greek and other ethnic groups with FAD, with and without PSENs/APP mutations.

The testing process in FAD can be improved on the basis of further evaluation of genetic counseling protocols in larger cohorts and

different settings. Effectiveness and selection bias of patients and at-risk relatives pursuing the genetic testing (i.e. psychological characteristics that promoted self-selection of individuals who are able to deal with the counselling process and test result) deserves to be further explored (research in preparation).

Last but not least, Alzheimer's Disease is a disease with no sure cure. And while there are things that someone can do in order to avoid in a big percentage the sporadic form, the familiar form of the disease is different in the terms of prevention and the progression of the disease is rapid. Thus, genetic screening in populations with mild cognitive impairment or probable familiar AD could arise several bioethical issues which need further research.

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