Neurobiology of Aging 77 (2019) 154–157

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Brief communication

Mutation profile of *APP*, *PSEN1*, and *PSEN2* in Chinese familial Alzheimer's disease

Ying Gao [a,1], Ru-Jing Ren [a,1], Zi-Lin Zhong [b,1], Eric Dammer [c], Qian-Hua Zhao [d], Shan Shan [e,f], Zheng Zhou [e,f], Xia Li [g], Yue-Qi Zhang [a], Hai-Lun Cui [a], Yong-Bo Hu [a], Sheng-Di Chen [a], Jian-Jun Chen [b,***], Qi-Hao Guo [d,**], Gang Wang [a,*]

[a] *Department of Neurology & Neuroscience Institute, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[b] *Shanghai Tenth People's Hospital & Department of Medical Genetics, Tongji University School of Medicine, Shanghai, China*
[c] *Department of Biochemistry, Center for Neurodegenerative Disease, Emory University School of Medicine, Atlanta, GA, USA*
[d] *Department of Neurology & Institute of Neurology, Huashan Hospital, Fudan University, WHO Collaborating Center for Research and Training in Neurosciences, Shanghai, China*
[e] *National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China*
[f] *University of Chinese Academy of Sciences, Beijing, China*
[g] *Alzheimer's Disease and Related Disorders Center, Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

ARTICLE INFO

Article history:
Received 22 April 2018
Received in revised form 5 January 2019
Accepted 21 January 2019
Available online 31 January 2019

Keywords:
Familial Alzheimer's disease
APP
PSEN1
PSEN2
Mutation

ABSTRACT

Causative mutations in the genes encoding amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) account for a majority of cases of familial Alzheimer disease (FAD) inherited in an autosomal-dominant pattern. For the sake of characterizing mutations, index patients from 148 families with FAD were enrolled from mainland China. Sanger sequencing of the genes *APP*, *PSEN1*, and *PSEN2* was performed to characterize the mutation spectrum of the Chinese population. Thirteen of 148 (8.8%) individuals had possible pathogenic *APP*, *PSEN1*, or *PSEN2* variants, including 2 (15.4%) *APP* variants, 8 (61.5%) *PSEN1* variants, and 3 (23.1%) *PSEN2* variants. *PSEN1* variants represented the largest proportion in Chinese FAD, and *PSEN2* variants are responsible for late-onset FAD in China. Analysis of genetic-clinical correlations permitted the conclusion that FAD phenotypes were mainly influenced by specific genetic defects.

1. Introduction

Alzheimer's disease (AD) (MIM#104300) is the predominant cause of dementia. The age of 65 years is often used as a threshold to classify AD patients into early-onset (EOAD) and late-onset (LOAD) groups. Fewer than 1% of AD cases tend to be caused by autosomal dominant mutations in amyloid precursor protein (*APP*) (MIM#104760) (Sherrington et al., 1995), presenilin 1 (*PSEN1*) (MIM#104311) (Levy-Lahad et al., 1995), and presenilin 2 (*PSEN2*) (MIM#600759) genes (Goate et al., 1991). Until now, more than 300 mutations within these 3 genes have been identified to potentially lead to FAD according to the Alzforum database (https://www.alzforum.org/mutations). Among them, *PSEN1* is most frequently mutated with 227 pathologic mutations; in *APP* and *PSEN2*, 27 and 16 pathologic mutations have been identified, respectively. Autosomal dominant AD has a variable clinical phenotype, including typical memory test performance decline, atypical extrapyramidal symptoms, and other neurological features. Both age at onset and clinical features are influenced by causative genes (Ryan et al., 2016).

In an effort to further understand genetic variation within FAD pathogenic genes, we performed a genetic screening of *APP*, *PSEN1*, and *PSEN2* hot spots in 148 index patients with independent family histories including EOAD and LOAD identified at multiple centers and described the genotype-phenotype correlations in the Chinese population.

* Corresponding author at: Department of Neurology & Neuroscience Institute, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, 200025 China. Tel.: +86-21-64454473; fax: +86-21-64454473.
** Corresponding author at: Department of Neurology & Institute of Neurology, Huashan Hospital, Fudan University, WHO Collaborating Center for Research and Training in Neurosciences, Shanghai, China. Tel.: +86-21-64369181; fax: +86-21-64701361.
*** Corresponding author at: Shanghai Tenth People's Hospital & Department of Medical Genetics, Tongji University School of Medicine, Shanghai 200072, China. Tel.: +86-21-65982130; fax: +86-21-65982130.
E-mail addresses: chenjianjun@tongji.edu.cn (J.-J. Chen), dr.guoqihao@126.com (Q.-H. Guo), wg11424@rjh.com.cn (G. Wang).
[1] These 3 authors contributed equally.

0197-4580/$ – see front matter © 2019 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.neurobiolaging.2019.01.018

2. Methods

2.1. Study subjects and clinical examinations

We screened 148 probands from unlinked families in mainland China who were enrolled in (1) the Memory Clinic at the Department of Neurology, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine; (2) the Department of Neurology, Huashan Hospital affiliated to Fudan University School of Medicine; or (3) the Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine. Familial EOAD and LOAD cases were included (Table S1). Sequencing for mutations in *APP*, *PSEN1*, and *PSEN2* genes was performed if 2 first-degree relatives suffered from dementia. The patients had a clinical diagnosis of probable dementia of Alzheimer type according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) (Dubois et al., 2007; McKhann et al., 1984). The analyses also included 100 unaffected individuals of matched geographical ancestry as control individuals. This study was approved by the Research Ethics Committee, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.

2.2. Molecular analyses

APP (exons 16-17), *PSEN1* (exons 3-12), *PSEN2* (exons 4-7) (Jiao et al., 2014; Shi et al., 2015; Youn et al., 2014), and *APOE* (Table S2) were amplified by primer pairs designed online with the Primer3 program (http://primer3.sourceforge.net/). *APOE* genotypes comprising the *APOE* ε2, ε3, and ε4 alleles were assayed (Koch et al., 2002). The gnomAD Database (http://gnomad.broadinstitute.org) was applied to investigate rare variants, defined as variants with a minor allele frequency of <1%. Variants were checked to determine the likelihood of pathogenicity against established databases: the Alzforum database (https://www.alzforum.org/mutations) and the AD/FTD database (http://www.molgen.ua.ac.be/admutations/), as well as online programs: SIFT (http://sift.jcvi.org/www/SIFT_enst_submit.html), Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/), MutationTaster (MutationTaster; http://www.mutationtaster.org), and CADD (http://cadd.gs.washington.edu). The minor allele frequency of <0.01 was standard to classify a variant as rare. Evolutionary conservation of the amino acid sequence including new variants was assessed via the DNASTAR program (http://www.dnastar.com). Then, the high-resolution cryo-EM structure of the human γ-secretase (PDB 5A63) was used for analysis of the potential effect of *PSEN1* variants—NM_000021.3; c.308T>G, p.(Val103Gly) and NM_000021.3; c.529T>G, p.(Phe177Val)—visualizing their position within the 3-dimensional structure using Swiss-PDB Viewer (Bai et al., 2015).

3. Results

3.1. Identified gene mutations of APP, PSEN1, and PSEN2

We identified 12 rare coding variants from 13 independent families (Fig. S1), including 2 (15.4%) variants in *APP*, 8 (61.5%) variants in *PSEN1* found in 65 EOAD cases, and 3 *PSEN2* (23.1%) variants in 83 LOAD cases. Overall, mutants of these 3 genes occupy 8.8% of the cohort.

One novel variant of *APP*—NM_000484.3; c.2083G>A, p.(Val695Met)—3 novel variants of PSEN1—NM_000021.3; c.308T>G, p.(Val103Gly), NM_000021.3; c.415A>T, p.(Met139Leu), and NM_000021.3; c.529T>G, p.(Phe177Val)—and 2 novel PSEN2 variants—NM_000447.2; c.448G>A, p.(Val150Met) and NM_000447.2; c.487C>T, p.(Arg163Cys)—were identified. All families had a clear autosomal-dominant pattern of inheritance of dementia (Fig. S2). Table 1 summarizes all identified mutations.

3.2. Molecular analyses

Multiple orthologous sequence alignments revealed that the APP variant—NM_000484.3; c.2083G>A, p.(Val695Met)—PSEN1 variants—NM_000021.3; c.308T>G, p.(Val103Gly), NM_000021.3; c.415A>T, p.(Met139Leu), and NM_000021.3; c.529T>G, p.(Phe177Val)—and PSEN2 variants—NM_000447.2; c.448G>A, p.(Val150Met) and NM_000447.2; c.487C>T, p.(Arg163Cys)—occurred in conserved residues of their respective proteins (Fig. S3). The γ-secretase structure (PDB 5A63) shows, NM_000021.3; c.308T>G, p.(Val103Gly) and NM_000021.3; c.529T>G, p.(Phe177Val) variants, likely decrease its interaction with other hydrophobic residues, for example, when the aromatic Phe side chain is replaced by a substantially smaller Val side chain (Fig. 1).

3.3. Clinical manifestation

Age at onset was significantly later for patients with *PSEN2* variants (70 ± 6.6 y) than for those with *APP* (55 ± 7.1 y) and *PSEN1* (45 ± 6.5 y) variants. All probands with variants presented with typical amnestic symptoms (Table S3). Of the 13 variant carriers, extrapyramidal signs occurred in one *APP* variant and 3 *PSEN1* variants. Dysarthria and cerebellar signs were observed in *PSEN1* variants NM_000021.3; c.786G>T, p.(Leu262Phe) and NM_000021.3; c.497_499delTTA, p.(Ile167del). Furthermore, 3 patients presented with anxiety and one presented with behavioral changes (Table S3).

4. Discussion

As far as we know, this study involves the largest familial AD patient cohort in Asia so far. The total frequency (8.8%) of the mutations in our cohort is lower than previous reports. The proportion of *APP*, *PSEN1*, and *PSEN2* mutations was 21.3% in China, 17% in Poland, and 22% in Germany (Blauwendraat et al., 2016; Jiao et al., 2014; Żekanowski et al., 2003). Furthermore, Japan, England, and France have reported much higher rates (Campion et al., 1999; Ikeuchi et al., 2008; Janssen et al., 2003). Different definitions of familial AD and racial diversity as well as lifestyle differences can explain this discrepancy. In addition, we recruited patients with at least one demented relative, whereas a minimum of 2 generations of diagnostic criteria were required in other research (Campion et al., 1999; Janssen et al., 2003). We also included a familial LOAD cohort, which is established to have a less than 1% probability of having a genetic mutation (Loy et al., 2014). In addition, there is a greater percentage of *PSEN2* mutations (23.1%) than *APP* mutations (15.4%). Concerning the EOAD series, our analysis demonstrates a lower mutation rate (15.4%) in comparison to a prior Chinese study (21.3%) (Jiao et al., 2014).

Among *APP* variants in our cohort, the new variant NM_000484.3; c.2083G>A, p.(Val695Met) was not present either in publicly available population databases or among any controls; however, the index patient carrying p.(Val695Met) only has a demented mother who began to show memory impairment at the age of 80 years. This variant is predicted to be tolerated by computational approaches (SIFT, Polyphen-2, and CADD). Thus, the pathogenicity of *APP* p.(Val695Met) needs to be further investigated.

Table 1
Summary of mutations in *APP*, *PSEN1*, and *PSEN2* associated with AD

Gene	NM	Exon	Variation		Pathogenicity prediction				gnomAD	Reported in literatures	References
			Nucleotide	Protein	PolyPhen	SIFT	Mutationtaster	CADD			
APP	NM_000484	17	c.2083G>A	p.Val695Met	B:0.314	T:0.22	DC	23.8	NF	No report	
APP	NM_000484	17	c.2149G>A	p.Val717Ile	PBD:0.997	T:0.09	DC	34	NF	Cortical dementia, myoclonus, seizures	Goate et al. (1991) Jiao et al. (2014)
PSEN1	NM_000021	4	c.308T>G	p.Val103Gly	PBD:0.999	APF:0.00	DC	28.2	NF	No report	
PSEN1	NM_000021	4	c.313T>G	p.Phe105Val	PSD:0.797	APF:0.00	DC	24.9	NF	Cortical dementia	Gomez-Tortosa et al., 2010
PSEN1	NM_000021	5	c.415A>T	p.Met139Leu	PBD:0.963	T:0.74	DC	23.1	NF	No report	
PSEN1	NM_000021	6	c.529T>G	p.Phe177Val	PSD:0.844	APF:0.00	DC	28.3	NF	No report	
PSEN1	NM_000021	7	c.676C>T	p.Leu226Phe	PBD:1	APF:0.00	DC	33	NF	Early dysarthria, FTD-like symptoms, myoclonus	Zekanowski et al., 2006 Bagyinszky et al., 2016
PSEN1	NM_000021	8	c.786G>T	p.Leu262Phe	PBD:1	APF:0.00	DC	26	allele count[a]:0.00004	Early dementia, aphasia	Forsell et al., 1997
PSEN1	NM_000021	8	c.856C>G	p.Leu286Val	PBD:0.999	APF:0.00	DC	32	NF	Dementia, extrapyramidal signs, myoclonus	Sherrington et al. (1995) Ikeuchi et al. (2008)
PSEN1	NM_000021	6	c.497_499delTTA	p.Ile167del			DC		NF	Memory deficits, behavioral symptoms, spastic paraparesis	Jiao et al. (2014)
PSEN2	NM_000447	6	c.448G>A	p.Val150Met	PSB:0.762	APF:0.00	DC	23.1	allele count[b]:0.00003	No report	
PSEN2	NM_000447	6	c.487C>T	p.Arg163Cys	PBD:0.998	APF:0.00	DC	35	NF	No report	

Key: PBD, probably damaging; PSD, possibly damaging; APF, affect protein function; T, tolerated; DC, disease causing; NF, not found in gnomAD.
[a] rs637750248.
[b] rs866044092.

Fig. 1. Structure of human γ-secretase is shown in cartoon representation. The structure is colored blue for PSEN1, yellow for presenilin enhancer 2 (PEN-2), magenta for anterior pharynx-defective 1 (APH-1), and green for nicastrin. The key residues are shown as sticks and are colored in red and orange. F177 in PSEN1 participates in a hydrophobic cluster. This region is boxed and shown in close-up view. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Among *PSEN1* mutations, 3 novel variants are classified as probably pathogenic, following the algorithm proposed by Guerreiro et al. (Guerreiro et al., 2010). Furthermore, NM_000021.3; c.308T>G, p.(Val103Gly) and NM_000021.3; c.529T>G, p.(Phe177Val) are here first recognized as probably pathogenic with structural implications. Two variants likely decrease interactions with other hydrophobic residues in gamma secretase and cause structural impairment.

Regarding *PSEN2*, 2 novel variants are classified as probably pathogenic according to Guerreiro et al. (Guerreiro et al., 2010). The variant NM_000447.2; c.448G>A, p.(Val150Met) is described in the gnomAD with an allele frequency of 0.003% in the population. The variant NM_000447.2; c.487C>T, p.(Arg163Cys) was never reported. Nevertheless, the same site variant, NM_000447.2; c.488G>A, p.(Arg163His), was classified as nonpathogenic in the Alzforum database because the proband's 71-year-old mother carrying *PSEN2* p.(Arg163His) had no dementia (Puschmann et al., 2009). Actually, defects in *PSEN2* function may be masked by the normal function of its close homolog *PSEN1*. Consistent with this, *PSEN2* mutation carriers are likely to have a relatively later age of onset (Jayadev et al., 2010; Ryman et al., 2014). Taken together, the pathological effect of p.(Arg163Cys) deserves further attention.

As in our case series (Table S3), *PSEN1* gene variants tend to cause earlier onset and more aggressive clinical phenotypes than ones in *APP* and *PSEN2*. Neurological symptoms were seen in *APP* and *PSEN1* variant carriers, but not *PSEN2*, usually manifesting within several years of symptom onset. Among such symptoms, extrapyramidal signs are the most common. It is noted that the proband with *APP* NM_000484.3; c.2149G>A, p.(Val717Ile) presented a similar manifestation as other Chinese carriers (Zhang et al., 2017), although extrapyramidal signs were not observed in the research by Ryan et al. (Ryan et al., 2016). Some research has implied that *PSEN1* mutations beyond codon 200 are associated with later onset and more severe amyloid angiopathy than mutations before codon 200 (Mann et al., 2001; Shea et al., 2016); however, *PSEN1* NM_000021.3; c.676C>T, p.(Leu226Phe) shows very early onset and atypical symptoms. Thus, codon and type of amino acid are probably both essential in influencing phenotype. Moreover, the heterogeneity of age of onset between the families with p.(Arg163Cys) may suggest that the penetrance and severity of

this mutation are easily influenced by other genetic or environmental factors.

In conclusion, we performed the largest genetic screening of 3 FAD causative genes to date in Asia. Our study expands the mutation spectrum of familial AD. The higher frequency of *PSEN2* in this Chinese study suggests the possibility of including *PSEN2* genetic screening for late-onset FAD in China to improve diagnostic workflow.

Disclosure statement

The authors declare no competing financial interests.

Acknowledgements

The authors are grateful to all subjects who kindly agreed to participate in this study. This study was supported by National Key R&D Program of China (2016YFC1306305), the National Key Basic Research Program of China (973 Program 2015CB964601), the National Natural Science Foundation of China (No. 81671043), Shanghai Technology and Science Key Project in Healthcare (No. 17441902100), and the "Shuguang Program (16SG15)" supported by Shanghai Education Development Foundation and Shanghai Municipal Education Commission.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.01.018.

References

Bai, X.C., Yan, C., Yang, G., Lu, P., Ma, D., Sun, L., Zhou, R., Scheres, S.H.W., Shi, Y., 2015. An atomic structure of human gamma-secretase. Nature 525, 212–217.

Blauwendraat, C., Wilke, C., Jansen, I.E., Schulte, C., Simon-Sanchez, J., Metzger, F.G., Bender, B., Gasser, T., Maetzler, W., Rizzu, P., Heutink, P., Synofzik, M., 2016. Pilot whole-exome sequencing of a German early-onset Alzheimer's disease cohort reveals a substantial frequency of PSEN2 variants. Neurobiol. Aging 37, 208.e11–208.e17.

Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., Thomas-Anterion, C., Michon, A., Martin, C., Charbonnier, F., 1999. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am. J. Hum. Genet. 65, 664–670.

Dubois, B., Feldman, H.H., Jacova, C., Dekosky, S.T., Barberger-Gateau, P., Cummings, J., Delacourte, A., Galasko, D., Gauthier, S., Jicha, G., Meguro, K., O'Brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway, S., Stern, Y., Visser, P.J., Scheltens, P., 2007. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 6, 734–746.

Goate, A., Chartier-Harlin, M.C., Mullan, M., Brown, J., Crawford, F., Fidani, L., Giuffra, L., Haynes, A., Irving, N., James, L., Mant, R., Newton, P., Rooke, K., Roques, P., Talbot, C., Pericak-Vance, M., Roses, A., Williamson, R., Rossor, M., Owen, M., Hardy, J., 1991. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 349, 704–706.

Guerreiro, R.J., Baquero, M., Blesa, R., Boada, M., Bras, J.M., Bullido, M.J., Calado, A., Crook, R., Ferreira, C., Frank, A., Gomez-Isla, T., Hernandez, I., Lleo, A., Machado, A., Martinez-Lage, P., Masdeu, J., Molina-Porcel, L., Molinuevo, J.L., Pastor, P., Perez-Tur, J., Relvas, R., Oliveira, C.R., Ribeiro, M.H., Rogaeva, E., Sa, A., Samaranch, L., Sanchez-Valle, R., Santana, I., Tarraga, L., Valdivieso, F., Singleton, A., Hardy, J., Clarimon, J., 2010. Genetic screening of Alzheimer's disease genes in Iberian and African samples yields novel mutations in presenilins and APP. Neurobiol. Aging 31, 725–731.

Ikeuchi, T., Kaneko, H., Miyashita, A., Nozaki, H., Kasuga, K., Tsukie, T., Tsuchiya, M., Imamura, T., Ishizu, H., Aoki, K., Ishikawa, A., Onodera, O., Kuwano, R., Nishizawa, M., 2008. Mutational analysis in early-onset familial dementia in the Japanese population. The role of PSEN1 and MAPT R406W mutations. Dement. Geriatr. Cogn. Disord. 26, 43–49.

Janssen, J.C., Beck, J.A., Campbell, T.A., Dickinson, A., Fox, N.C., Harvey, R.J., Houlden, H., Rossor, M.N., Collinge, J., 2003. Early onset familial Alzheimer's disease Mutation frequency in 31 families. Neurology 60, 235–239.

Jayadev, S., Leverenz, J.B., Steinbart, E., Stahl, J., Klunk, W., Yu, C.E., Bird, T.D., 2010. Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. Brain 133 (Pt 4), 1143–1154.

Jiao, B., Tang, B., Liu, X., Xu, J., Wang, Y., Zhou, L., Zhang, F., Yan, X., Zhou, Y., Shen, L., 2014. Mutational analysis in early-onset familial Alzheimer's disease in Mainland China. Neurobiol. Aging 35, 1957.e1–1957.e6.

Koch, W., Ehrenhaft, A., Griesser, K., Pfeufer, A., Muller, J., Schomig, A., Kastrati, A., 2002. TaqMan systems for genotyping of disease-related polymorphisms present in the gene encoding apolipoprotein E. Clin. Chem. Lab. Med. 40, 1123–1131.

Levy-Lahad, E., Wasco, W., Poorkaj, P., Romano, D.M., Oshima, J., Pettingell, W.H., Yu, C.E., Jondro, P.D., Schmidt, S.D., Wang, K., Crowley, A.C., Fu, Y.-H., Guenette, S.Y., Galas, D., Nemens, E., Wijsman, E.M., Bird, T.D., Schellenberg, G.D., Tanzi, R.E., 1995. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 269, 973–977.

Loy, C.T., Schofield, P.R., Turner, A.M., Kwok, J.B., 2014. Genetics of dementia. Lancet 383, 828–840.

Mann, D.M., Pickering-Brown, S.M., Takeuchi, A., Iwatsubo, T., 2001. Amyloid angiopathy and variability in amyloid beta deposition is determined by mutation position in presenilin-1-linked Alzheimer's disease. Am. J. Pathol. 158, 2165–2175.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of Health and human services task force on Alzheimer's disease. Neurology 34, 939–944.

Puschmann, A., Ross, O.A., Vilarino-Guell, C., Lincoln, S.J., Kachergus, J.M., Cobb, S.A., Lindquist, S.G., Nielsen, J.E., Wszolek, Z.K., Farrer, M., Widner, H., van Westen, D., Hagerstrom, D., Markopoulou, K., Chase, B.A., Nilsson, K., Reimer, J., Nilsson, C., 2009. A Swedish family with de novo alpha-synuclein A53T mutation: evidence for early cortical dysfunction. Parkinsonism Relat. Disord. 15, 627–632.

Ryan, N.S., Nicholas, J.M., Weston, P.S.J., Liang, Y., Lashley, T., Guerreiro, R., Adamson, G., Kenny, J., Beck, J., Chavez-Gutierrez, L., de Strooper, B., Revesz, T., Holton, J., Mead, S., Rossor, M.N., Fox, N.C., 2016. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. Lancet Neurol. 15, 1326–1335.

Ryman, D.C., Acosta-Baena, N., Aisen, P.S., Bird, T., Danek, A., Fox, N.C., Goate, A., Frommelt, P., Ghetti, B., Langbaum, J.B., Lopera, F., Martins, R., Masters, C.L., Mayeux, R.P., McDade, E., Moreno, S., Reiman, E.M., Ringman, J.M., Salloway, S., Schofield, P.R., Sperling, R., Tariot, P.N., Xiong, C., Morris, J.C., Bateman, R.J., 2014. Symptom onset in autosomal dominant Alzheimer disease: a systematic review and meta-analysis. Neurology 83, 253–260.

Shea, Y.F., Chu, L.W., Chan, A.O., Ha, J., Li, Y., Song, Y.Q., 2016. A systematic review of familial Alzheimer's disease: differences in presentation of clinical features among three mutated genes and potential ethnic differences. J. Formos. Med. Assoc. 115, 67–75.

Sherrington, R., Rogaev, E.I., Liang, Y., Rogaeva, E.A., Levesque, G., Ikeda, M., Chi, H., Lin, C., Li, G., Holman, K., Tsuda, T., Mar, L., Foncin, J.F., Bruni, A.C., Montesi, M.P., Sorbi, S., Rainero, I., Pinessi, L., Nee, L., Chumakov, I., Pollen, D., Brookes, A., Sanseau, P., Polinsky, R.J., Wasco, W., Da Silva, H.A., Haines, J.L., Perkicak-Vance, M.A., Tanzi, R.E., Roses, A.D., Fraser, P.E., Rommens, J.M., St George-Hyslop, P.H., 1995. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 375, 754–760.

Shi, Z., Wang, Y., Liu, S., Liu, M., Liu, S., Zhou, Y., Wang, J., Cai, L., Huo, Y.R., Gao, S., Ji, Y., 2015. Clinical and neuroimaging characterization of Chinese dementia patients with PSEN1 and PSEN2 mutations. Dement. Geriatr. Cogn. Disord. 39, 32–40.

Youn, Y.C., Bagyinszky, E., Kim, H., Choi, B.O., An, S.S., Kim, S., 2014. Probable novel PSEN2 Val214Leu mutation in Alzheimer's disease supported by structural prediction. BMC Neurol. 14, 105.

Żekanowski, C., Styczyńska, M., Pep^{3}ońska, B., Gabryelewicz, T., Religa, D., Ilkowski, J., Kijanowska-Ha^{3}adyna, B., Kotapka-Minc, S., Mikkelsen, S., Pfeffer, A., 2003. Mutations in presenilin 1, presenilin 2 and amyloid precursor protein genes in patients with early-onset Alzheimer's disease in Poland. Exp. Neurol. 184, 991–996.

Zhang, G., Xie, Y., Wang, W., Feng, X., Jia, J., 2017. Clinical characterization of an APP mutation (V717I) in five Han Chinese families with early-onset Alzheimer's disease. J. Neurol. Sci. 372, 379–386.