Journal of Molecular and Genetic Medicine

ISSN: 1747-0862

Ren et al., J Mol Genet Med 2017, 11:1
DOI: 10.4172/1747-0862.1000249

Case Report Open Access

Clinical and Genetic Analysis of Early-Onset Alzheimer's Disease in Two Chinese Han Families with Presenilin-1 Mutations

Ren Z*, Xia M*, Chen Z, Shi Y, Ma Q, Bai Y* and Zhang J*

Department of Neurology, People's Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China

**These authors contributed equally to this manuscript*

Abstract

Alzheimer's disease is an autosomal dominant neurodegenerative disease manifested by core symptoms of cognitive decline and memory impairment. This progressive disorder with an insidious onset typically appears in older individuals, but may also affect young people, even in their 30s. It is well established that mutations in amyloid precursor protein (APP), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) cause Alzheimer's disease. *PSEN1* mutation is more common in Familial Alzheimer's disease compared with *PSEN2* and APP. Two patients fulfilling the NINCDS-ADRDA criteria for probable and definite Alzheimer's disease were assessed. Two *PSEN1* mutations (p.L392P and p.M233L) were identified from 2 probable early-onset familial Alzheimer's disease (EOFAD) families, respectively. The p.L392P and p.M233L mutations were associated with prominent early onset, rapidly progressive dementia, and neurologic symptoms. Both p.L392P and p.M233L were predicted or confirmed to be pathogenic, and the p.L392P mutation in *PSEN1* is the first report in China.

Keywords: Early-onset; Alzheimer's disease; *PSEN1*; Genetic mutations; Rapidly progressive; Chinese population

Introduction

Alzheimer's disease (AD) has become a great burden to society. Currently, the global prevalence of AD is approximately 35.6 million individuals, and projected to rise substantially to 2 billion people over the age of 60 by 2050 [1]. APP, *PSEN1* and *PSEN2* mutations show high correlations with AD, which is characterized by core symptoms of progressive decline in cognitive function, memory loss, behavior changes, reduced ability to carry out daily living activities, and neurodegeneration-induced psychiatric symptoms [2]. These symptoms worsen over time. *PSEN1* mutations show an earlier age at onset (AOO), and are easily affected by atypical features during the clinical course. Patients with *PSEN2* mutations have a delayed AOO, with the longest disease duration, they present more commonly with disorientation. APP mutations have a close relationship with aggression and APP duplication presented more frequently with apraxia [3]. Interestingly, *PSEN1* mutations account for approximately 75% to 80% of families [4]. More than 230 mutations in *PSEN1* have been reported in Alzforum - a network for cure [5]. We screened the three genes in two early-onset Alzheimer's disease (EOAD) patients and part of their family members. Two *PSEN1* mutations (p.M233L and p.L392P) were identified, with phenotypic and genotypic features characterized in detail.

Material and Methods

The pro-bands fulfilled NINCDS-ADRDA [6] criteria for probable and definite Alzheimer's disease. Clinical and molecular investigations were carried out after informed consent was obtained from participating family members. The study protocol was approved by the Institutional Review Board of People's Hospital of Zhengzhou University.

1. In the first family, the proband (Figure 1: A1-II-3) was a 50-year-old man who had a more than three years duration of memory impairment. Executive function was almost lost and thus he resigned from his job, couldn't find his way home, and had urinary incontinence as well as little interest in speaking and movement, he became a stooge of his wife. His diet was changed from noodles to anything available. Neuropsychological examinations revealed serious decreases of overall mental parameters: The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA) yielded scores of 8/30 and 4/30, respectively.

2. In the second family, the proband (Figure 1: B1-II-3) was a 49-year-old farmer, and he had suffered from progressive memory loss for three years and behavior change for one year before treatment. He could not remember events that just happened, and became strong-willed. At that time, he repeated his words but did not cooperate in completing the neuropsychological evaluation.

In this study, eight members from the two families and 100 control subjects were recruited.

DNA sequencing and genotyping

Genomic DNA was isolated according to standard procedures from peripheral blood leukocytes of all enrolled members. Genomic DNA was extracted from peripheral blood leukocytes with the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Polymerase chain reaction (PCR) was performed on the exon regions of *PSEN1* (NG_007386.2) [7], *PSEN2* (NG_007381.1) [8], and APP (NG_007376.1) [9], The *PSEN1* (exons 3~12), *PSEN2* (exons 3~12), APP (exons 16~17). The sequences of all exons are shown in the (Supplementary Tables 1-3). Polymerase chain reaction (PCR) reactions have a total volume of 50 μl containing 25 μl polymerase (Bioindustry, TaKaRa, BIO INC, Japan), 16 μl sterile water,5 μl DNA (100 ng/μl) and optimized primer mix. PCR amplifications were carried out over 30 cycles (denaturation 94°C; annealing appropriate temperature, extension 72°C), with a final extension (10 min) at 72°C. After PCR amplification, PCR products

***Corresponding author:** Dr. Jiewen Zhang and Dr. Yingying Bai, Department of Neurology, People's Hospital of Zhengzhou University, Zhengzhou, 450003, Henan, P.R. China, Tel: 86 371 65580782, Fax: 8637165981119; E-mail: zhangjiewen9900@126.com and stupidmelon@126.com

Received January 14, 2017; **Accepted** February 10, 2017; **Published** February 14, 2017

Citation: Ren Z, Xia M, Chen Z, Shi Y, Ma Q, et al. (2017) Clinical and Genetic Analysis of Early-Onset Alzheimer's Disease in Two Chinese Han Families with Presenilin-1 Mutations. J Mol Genet Med 11: 249 doi:10.4172/1747-0862.1000249

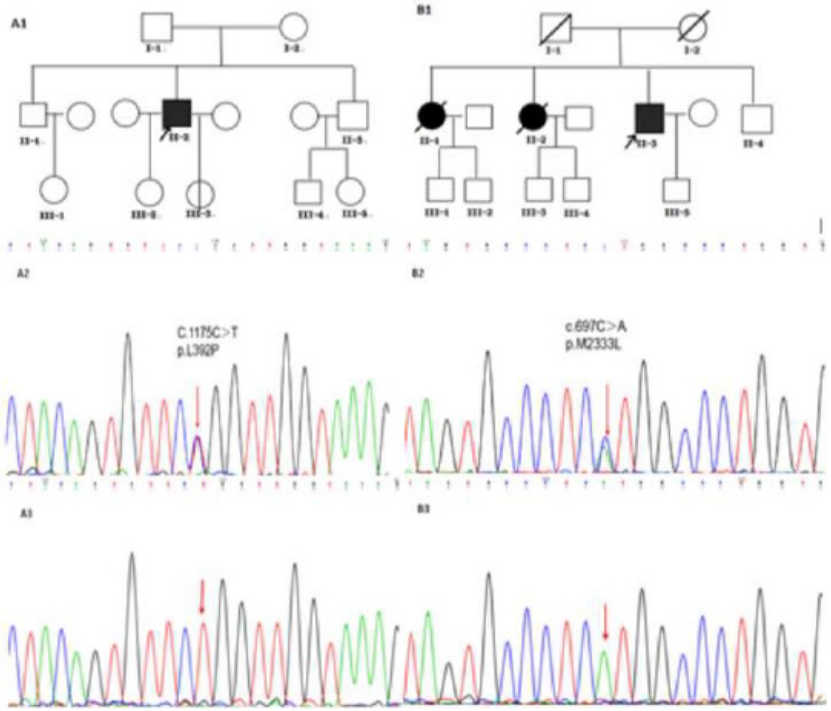

Figure 1: (A1) Pedigree of the first patient of Alzheimer's disease with *PSEN1* Leu392 Pro-mutation. (B1) Pedigree of the second Alzheimer's disease patient with *PSEN1* Met233Leu mutation. The arrow indicates the pro-band: Circle, female; square, male; black symbol, affected family member; slashed symbol, deceased family member; straight symbol, pre-symptomatic mutation carrier. Blood samples were available from the pro-band (A1-II-2, B1-II-3) and family members (A1: I-1, I-2, II-1, II-3, I II-3; B1: III-5). (A2, A3) DNA sequencing chromatograph of the exon 11 of the *PSEN1* gene; (B2, B3) DNA sequencing chromatograph of the exon 7 of the *PSEN1* gene.

of the proband and other 6 members of the families were subjected to electrophoresis on a 2% low-melting agarose gel before phenol-chloroform extraction and ethanol precipitation.

Purified PCR products were directly sequenced on an ABI3100 automated sequencer (Applied Biosystems, Foster City, CA, USA). Sequencing reads and list were compared using Chromas software and NCBI blast. Protein analysis referred to database Uniprot.

Results

Case reports

Case 1: The proband of the first pedigree had an onset age of 48 and suffered from progressive memory problem and poor judgment, interfering with his social and professional activities. His cognitive status deteriorated gradually at the age of 49, behavior and psychiatric disturbances, including cowardly, anxiety, depression, restlessness, aspontaneity and emotional bluntness were developed. Neuropsychological examinations revealed deficits in recent memory, orientation in time and space, concentration, visuospatial ability, understanding, word naming, finding appropriate words and verbal fluency. He has been a night shift employee working with ink as a newspaper sorter for thirty years, and has had severe anxiety disorders due to life pressure for ten years. Further evaluation demonstrated a severe overall mental decline that mainly affected his visuospatial ability and execution, as well as recall, language, attention, and calculation. Therefore, speech was substantially impaired in this patient, with a marked change of verbal comprehension and autistic tendencies. In addition, the patient's history outlined an insufficient performance in daily self-care activities (ADL = 45/100, Barthel index), For instance, he had moderate dressing apraxia and timing of toilet, and simply could not execute any other project in the ADL system. The Clinical Dementia Rating (CDR) test revealed severe dementia. He also had some degree of anxiety and depression.

The patient cooperated to complete the electroencephalogram (EEG) and Polysomnography. EEG showed intermittently generalized slow delta-theta activity, and the polysomnography detected an abnormal sleep pattern. He also suffered from insomnia.

Four generations of the pedigree were questioned, with no common reply. As the Figure 1: A1 shows, I-1 is a retired teacher at the age of 69 and I-2 is a retired cotton mill worker at the age of 71, II-1 and II-3 are both construction workers, both of which had no complaint of discomfort. III members do not exceed than 30 years old.

Case 2: The second patient was a farmer. At 46, he couldn't remember what happened recently and couldn't even remember where he placed his money. He paid no attention to personal hygiene, with almost no clothing changing. He once lost his way home at the age of 48. He could not remember his recent actions, and became stubborn and couldn't understand words of his families. He became indifferent, timid, crying, depressed and overly cautions. Multiple childish behaviors, e.g. wearing bricks as pearls, were observed. He showed increased sleep and urination frequencies. Neuropsychological assessment showed executive dysfunction, anomia and memory loss. Physical examinations showed nothing markable except for brainstem reflex.

Development of progressive memory loss in the proband's sister (Figure 1: B1-II-1) started at the age of 47. Then, she could not complete her daily work, and died at the age of 53 after being bedridden for ten months. II-2 had similar symptoms at the age of 42, and six years later she passed away. II-4 was a boy with congenital mental retardation, detailed evaluation of his overall situation was not possible.

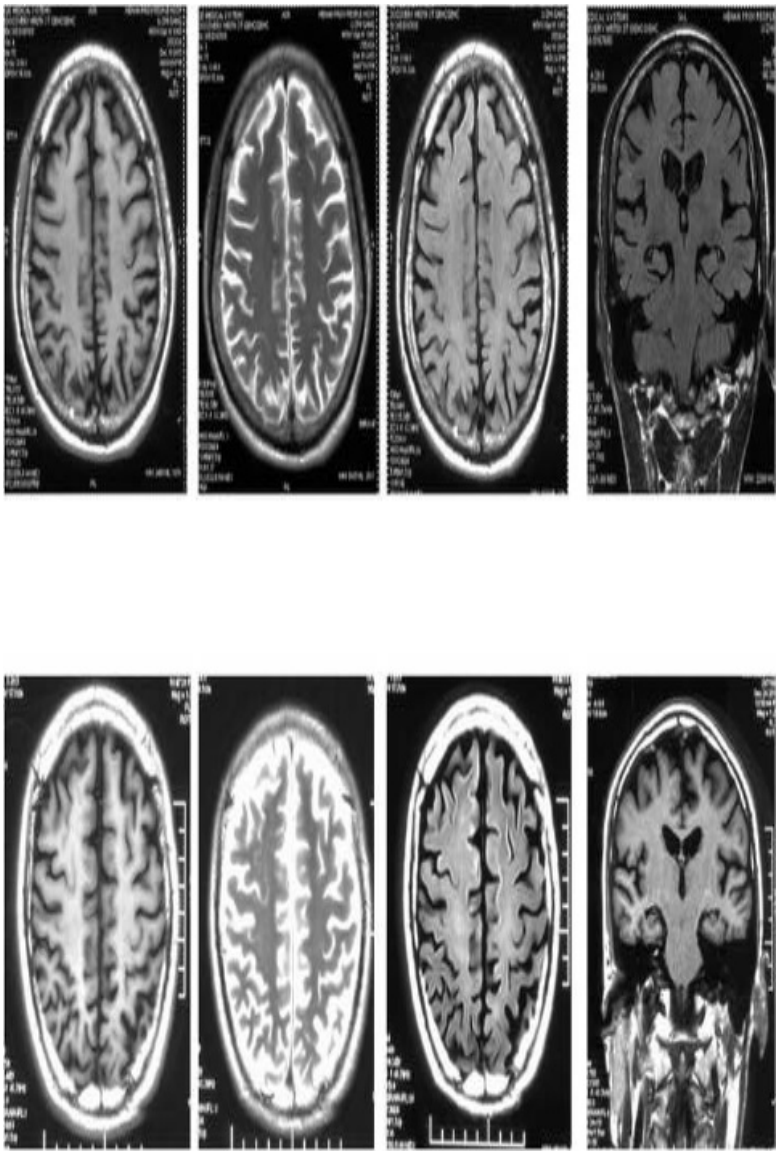

Figure 2: The Brain MRI of the two patients. Upper: The first patient, Down: The second patient. Sequence: T1WI, T2WI, T2 flair, Hippocampus coronal. Shows: Atrophy in both cerebral cortex and hippocampus.

Auxiliary examinations

Laboratory tests including routine blood tests, biochemical and virus, TORCH, folic acid and B12, homocysteine, and function tests of liver, kidney and thyroid of the two patients were generally within the normal limits.

Imageological examinations

At time of accepting treatment, brain magnetic resonance imaging (MRI) in both patients displayed decreased volumes of bilateral parietal and temporal lobes, especially the hippocampus. Both cases were compatible with a clinical diagnosis of probable dementia of the Alzheimer's type (Figure 2).

Mutation analysis

All exons of the three genes were amplified by standard PCR on genomic DNA of the proband. Mutation number was based on the cDNA (GenBank entry NG_007386.2).

In the first patient's genetic sequence, the position 391 +2 corresponds to the C of the CCG translation into T of the CTG, Sanger sequencing yielded a CCG to CUG nucleotide substitution in codon 392 of the *PSEN1* gene, causing an amino acid substitution of Leu to Pro (L392P). The structures ofpresenilin1 with Leu 123 residue and Pro mutation were generated by the Raptor 3D prediction program (Figure 3). The genetic sequences of immediate family members were assessed, and only III-3 had the same mutation.

The position 232 +1 corresponds to the A of the ATG translation into C of the CTG, Sanger sequencing showed an AUG to CUG nucleotide substitution in codon 233 of the *PSEN1* gene, causing an amino acid substitution of methionine to leucine (M233L). Regrettably, we were only able to collect the data of III-5, he had no mutation in the same position.

Discussion

The two patients with early onset AD had *PSEN1* mutations, which

are more common in familial Alzheimer's disease compared with *PSEN2* and APP mutations. The p.M233L mutation in *PSEN1* was previously assessed, with the carriers showing an average age at onset of 37 years (range from 28 to 45years), with progressive memory loss and aggressive disease courses [10]. Poryet et al. [11] described a patient with the mutation p.M233L, who had plaques and neurofibrillary tangles on brain biopsy. *PSEN1*'s codon 233 is highly conserved, and has four different mutations, including p.M233V, p.M233I, p.M233T and p.M233L, which are all pathogenic. The above patient with the p.M233L mutation showed prominently early onset, rapidly progressive dementia, and cognitive and personality symptoms.

To our knowledge, p.L392P was identified here for the first time in China [12]. In the present study, clinical and genetic characteristics of early-onset dementia caused by a Leu392Pro mutation were determined, based on all *PSEN1* mutations; a 100% penetrance was obtained [13].

This is the first description of a Chinese family with ADFOAD including mutation analysis. We detected a known NG_007386.2:c.1175C>T mutation in *PSEN1* that causes a substitution of a leucine for proline at position 392. This mutation was first reported in an Italy family affected by EOFAD with psychiatric symptoms at onset [14]. In this Chinese family, the proband's earliest complaint was a memory loss, and he was fired for incompetence. He had repetitive and poor speech within 6 months of disease onset. He lost the ability to take care of himself, especially for eating and dressing. Therefore, he became a burden to his wife, with almost no activity performed by him. On EEG, spike waves appeared, but he had no epilepsy sign or movement impairment. These findings indicate that the p.L392P mutation is associated with psychiatric syndrome, emotional symptoms and chronic disease course.

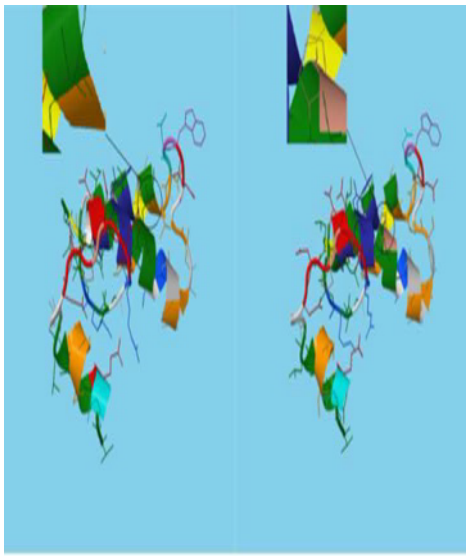

Figure 3: Secondary structures of *PSEN1* with native Leu 392 residue and pro-mutation. The structures of presenilin 1 with native Leu 392 residue and pro mutation were generated by Raptor 3D prediction program. The wild-type and mutant residues were colored with pink and green. Mutation p.L392P altered the side chain of residue at position 392.

Different mutations were reported in the same codon 392, a Leucine (CTG) to a Valine (GTG) substitution. The L392V mutation was shown to be pathogenic in previous studies, with similar clinical manifestations, including memory complaints, extrapyramidal features, myoclonus and generalized seizures, and early age of onset, presented in all affected members [15,16].

Next, a comparison was carried out of clinical features in patients with the Leu to Pro mutation at various *PSEN1* gene segments [14,17-23]. As shown in Table 1, the same mutation in different domains had distinct functions. Nevertheless, the majority of patients had emotional changes and memory loss. They had similar ages at onset, ranging from 24 to 47 years with a mean age of 35.00 (± 8.07) years; mean duration was 9.67 (± 5.35) years. These findings indicate that the same amino acid mutation at different positions in *PSEN1* may lead to distinct clinical manifestations.

For the Chinese patient with the Leu to Pro mutation, disease progression was more faster than in previously reported patients. 2 years after onset, he became very indifferent and totally dependent. During the 2 years, no cerebrovascular or trauma events worsened his condition. Compared with previously reported cases, this patient showed a relatively faster disease progression. Perhaps cognitive decline did not attract enough attention in China until obvious dysfunction appeared.

For these two families, a contradistinction cannot be made regarding the characteristics of the members. The first proband had a positive family history but all the affected relatives had died at the time of investigation. The second one had no origin in parents, but transmitted the mutation to his offspring. Although we are unsure whether these were two FAD families, the two above mutations are likely to be familial. In addition, the changes of cerebrospinal fluid biomarkers were not assessed. Therefore, this study has some limitations.

Condor	Exon	Onset	Gender	Duration	The main clinical features
		Age (yrs)		(Years)	
85	4	26	Male	-	Unmotivated, withdrawn, agnosia and disorientation spastic gait tremor
113	4	39	Female	11	Unusual familiarity, depressed mood, personality changes defective judgment, impulsive spending and stereotyped behavior.
PSEN1 166	6	24	Female	11	Memory loss, depression, ataxia, and spasticity generalized seizures began
219	7	47	Female	7	Memory and cognitive function empty words
235	7	29	Male	4+	Progressive memory and language impairment, tonico-clonic seizures, myoclonus and Babinski
248	7	42	Female	-	Progressive memory deficits
286	8	35	Female	19	Memory disturbances, affecting language, praxis and visuospatial functions behavior and parkinsonian
392	11	38	Male	6+	Memory deficits, worsening of mood, loss of social contact

Table 1: The comparison about the mutation in Leu to Pro in different conders in the *PSEN1* exons.

Conclusion

In conclusion, we assessed two possible EOFAD Chinese families, and detected two missense *PSEN1* mutations (p.M233L and p.L392P). The p.M233L mutation caused progressive memory loss, sharply declined ability to carry out daily life activities, and aggressive disease course. Here, the p.L392P mutation was reported in China for the first time, with rapid disease progression, psychiatric syndrome, emotional symptoms, and serious memory cognitive decline. Mutations in *PSEN1* are common in AD, and have an early onset.

Disclosure Statement

The authors have no actual or potential conflicts of interest.

Acknowledgements

This research was supported by State Key Clinical Specialty Construction Project in 2012. The authors wish to express their sincere gratitude to the patient and their family for their time and support.

References

1. Abbott A (2011) Dementia: A problem for our age. Nature 475, S2–S4.
2. Alzheimer's Association (2013) Alzheimer's disease: Facts and figures. Alzheimer's Dement 9(2): 208-245.
3. Bettens K, Sleegers K, Broeckhoven CV (2010) Current status on Alzheimer's disease molecular genetics: From past, to present, to future. Hum Mol Genet 19(R1): R4-R11.
4. Xia MS, Chen Y, Shi Y, Huang J, Xu T, et al. (2015) Probable novel PSEN2 Pro123Leu mutation in a Chinese Han family of Alzheimer's disease. Neurobiol Aging 36(12): e3313-3338.
5. http://www.alzforum.org/
6. https://en.wikipedia.org/wiki/NINCDS-ADRDA_Alzheimer%27s_Criteria
7. GenBank (2008) Homo sapiens presenilin 1 (PSEN1), Ref-Seq-Gene on chromosome 14. Reference Sequence: NG_007386.2.
8. GenBank (2008) Homo sapiens presenilin 2 (PSEN2), Ref-Seq-Gene on chromosome 1. Reference Sequence: NG_007381.1.
9. GenBank (2008) Homo sapiens amyloid beta precursor protein (APP), RefSeqGene on chromosome 21. Reference Sequence: NG_007376.1.
10. Jiang HY, Li GD, Dai SX, Bi R, Zhang DF, et al. (2015) Identification of PSEN1 mutations p.M233L and p.R352C in Han Chinese families with early-onset familial Alzheimer's disease. Neurobiol Aging 36(3): e1603-1606.
11. Portet F, Dauvilliers Y, Campion D, Raux G, Hauw JJ, et al. (2003) Very early onset AD with a de novo mutation in the presenilin 1 gene (Met 233 Leu). Neurology 61: 1136–1137.
12. http://www.molgen.ua.ac.be/ADMutations/
13. Sinning M, Rooyen JPV, Venegas-Francke P, Vasquez C, Behrens MI, et al. (2010) Clinical and genetic analysis of a Chilean family with early-onset autosomal dominant Alzheimer's disease. J Alzheimers Dis 21(3): 757-761.
14. Tedde A, Forleo P, Nacmias B, Piccini C, Bracco L, et al. (2000) A presenilin-1 mutation (Leu392Pro) in a familial AD kindred with psychiatric symptoms at onset. Neurology 55: 1590-1591.
15. Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, et al. (1995) Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature 376(31): 775-778.
16. Campion D, Flaman JM, Brice A, Hannequin D, Dubois B, et al. (1995) Mutations of the presenilin 1 gene in families with early-onset Alzheimer's disease. Human Mol Gen 4: 2373-2377.
17. Ataka S, Tomiyama T, Takuma H, Yamashita T, Shimada H, et al. (2004) A novel presenilin-1 mutation (Leu85Pro) in early-onset alzheimer disease with spastic paraparesis. Arch Neurol 61: 1773-1776.
18. Raux G, Gantier CR, Thomas–Anterion J, Boulliat P, Verpillat D, et al. (2000) Dementia with prominent frontotemporal features associated with L113P presenilin 1 mutation. Neurology 55: 1577–1578.
19. Moehlmann TE, Xia WX, Edbauer D, Murrell J, Capell A, et al. (2002) Presenilin-1 mutations of leucine 166 equally affect the generation of the Notch and APP intracellular domains independent of their effect on Abeta 42 production. Proc Natl Acad Sci USA 99(12): 8025-8030.
20. Smith MJ, Gardner RJM, Knight MA, Forrest SM, Beyreuther K, et al. (1999) Early-onset Alzheimer's disease caused by a novel mutation at codon 219 of the presenilin-1 gene. NeuroReport 10: 503–507.
21. Campion D, Brice A, Dumanchin C, Puel M, Baulac M, et al. (1996). A novel presenilin 1 mutation resulting in familial Alzheimer's disease with an onset age of 29 years. Neuro Report 7: 1582-1584.
22. Jiao B, Tang B, Liu X, Xu J, Wang Y, et al. (2014) Mutational analysis in early-onset familial Alzheimer's disease in Mainland China. Neurobiol Aging 35(8): e1951-1956.
23. Sanchez-Valle RA, Llado M, Ezquerra-Rey MJ, Rami L, Molinuevo P (2007) A novel mutation in the PSEN1 gene (L286P) associated with familial early-onset dementia of Alzheimer type and lobar haematomas. Eur J Neurol 14(12): 1409-1412.