ORIGINAL RESEARCH

Early-onset Alzheimer's disease patient with prion (*PRNP*) p.Val180Ile mutation

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Background: In this study, a known *PRNP* mutation, Val180Ile (c.G538A), was reported in a 58 years old female patient, clinically diagnosed with Alzheimer's disease (AD).

Case report: The patient presented slowly progressive cognitive decline in memory and visuospatial domain. Neuroimaging showed hippocampal atrophy in MRI and mild amyloid positivity in PET scan. Even though her cerebrospinal fluid (CSF) was positive for 14–3-3 protein, no sign of Creutzfeldt-Jakob diseases symptoms was observed. In addition, reduced Aβ42 and elevated total-Tau and phospho-Tau in CSF also proved the AD diagnosis. The mutation may disturb the hydrophobic core of prion protein, and result in abnormal intra-molecular interactions. Due to 23andMe, *PRNP* Val180Ile could not be categorized either as a mutation with complete penetrance, or as neutral variant, and could have a possible role in neurodegeneration. Pathological overlap was observed between prion diseases and other neurodegenerative diseases, including AD or frontotemporal dementia.

Conclusion: Whole exome sequencing and pathway analysis of patient revealed rare or possible risk variants in AD associated genes, such as SORL1 or ABCA7. Along with *PRNP*, AD risk genes may play a role in negative regulation of amyloid formation. Dysfunctions in these genes could possibly be associated in reduced neuroprotection and amyloid clearance.

Keywords: Alzheimer's disease, prion, *PRNP* Val180Ile mutation, Creutzfelt -Jakob disease

Introduction

Human prion diseases are fatal and rare neurodegenerative diseases. The incidence of the disease is approximately one to two cases per million per year.[1] Creutzfeldt-Jakob diseases (CJD) are the most prevalent subtype of human prion disease with rapidly progressive dementia, cerebellar ataxia, myoclonus, and behavioral changes.[2] Although the majority of CJD cases may be sporadic, genetic prion disease could be caused by mutations in the prion protein gene (*PRNP*). Genetic CJD or familial CJD accounted for only 10–15% of all CJD cases.[3] Prion diseases are characterized by an accumulation of an abnormally folded isoform (PrP^{Sc}) of the host-encoded cellular prion protein (PrP^C). Up to now, about 50 different pathogenic mutations in *PRNP* have been addressed, which result in dominant hereditary prion diseases.[4,5] Mutations showed diversity in clinical manifestations depending on each genotype.[6] Prion diseases could also share similarities with additional neurodegenerative diseases, including Alzheimer's disease (AD) or other types of dementia. AD and prion diseases were both verified as age-related diseases with possible genetic causative factors. In cases of genetic mutation, both of them could be inherited autosomal dominantly. In addition, both prion diseases

and AD are based of aggregation of abnormally folding proteins, resulting in neurodegeneration. The abnormal protein assembly could be caused by aging, oxidative stress, abnormal inflammatory process, and reduced defensive mechanisms. The two main hallmarks of AD (senile plaques and neurofibrillary tangles) could also be presented in the brain of CJD patients.[7,8]

PRNP Val180Ile mutation was suggested as one of the causative mutations for familial CJD,[4] and several cases were reported in South Korea.[9] Herein, we reported the clinical phenotypes of a 58-year-old female patient with *PRNP* Val180Ile mutation, who developed progressive cognitive impairment. The disease progression was slow in her and did not present any typical neurologic features of CJD, such as myoclonus or parkinsonian features.

Materials and methods

Whole exome sequencing (WES) was performed on the proband patient by Novogene Inc (https://en.novogene.com; Beijing, China). The DNA was isolated from white blood cells, and 2 μg of genomic DNA was used for the sequencing process. After library preparation, the Illumina platform was used for WES. Whole annotation of data was received as an Excel file, and sequencing data was sent as a .bam file. The Integrative Genomics Viewer (IGV) tool was used to visualize the sequencing data. An extensive analysis of 100 possible causative or risk factor genes of different neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, frontotemporal dementia, dementia with Lewy bodies, or prion diseases) was carried out on the sequencing data (Table S1).

In silico analysis was performed by online tools, including PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), and SIFT (http://sift.jcvi.org/) software, PROVEAN, or ExPASY (https://www.expasy.org/) tools. Structures of normal and mutant prion proteins were constructed by the Raptor X (http://raptorx.uchicago.edu/) software and visualized by Discovery Studio 3.5 Visualizer.[10] Genes, which were binding any mutations (either common or rare) were analyzed by ClueGO v2.0.5. This tool visualized biological networks of gene interactions, which would group the genes into a network with statistical evaluations, based on the annotations in the Gene Ontology.[11]

Case report

A 58-year-old right-handed woman (II-2) with 12 years of education presented progressive memory difficulties in the past year. She reported that the symptoms occurred insidiously, with disorganization and inconsistency in the performance of her duties at work. She regularly misplaced items, showed signs of short-term memory loss, and could not find the way home. Difficulties were also observed in managing her daily activities. No additional family members were reported with similar neurodegenerative disease (Figure 1). Her mother died in her 80s of heart disease (I-1), her father was neurologically normal until his death in his 90s (I-2). One of her brothers (II-4) had died of an accident (in his 40s) and did not present any known neurological abnormality before his death. She had three siblings, one sister (67 years, II-1) and two brothers (62 years and 60 years, II-3 and II-5, respectively), who were healthy and cognitively normal. Negative family history could not be proven, since all living family members refused the genetic test.

Upon cognitive testing, the patient was scored 15/30 on the Mini-Mental State Examination (MMSE) test (impairment in memory, language, visuospatial, and frontal domain) Her initial investigation, electrolytes, renal function, thyroid function, and complete blood count were within normal ranges. The patient's MRI revealed global atrophy with medial temporal lobe and hippocampal atrophy predominance (Figures 2A–C). Aggravated diffuse brain atrophy and small vessel ischemic lesion were observed in follow-up MRI, but no specific abnormality was detected in diffusion-weighted image (DWI, Figures 2A–C). There was no DWI, which implied possible CJD. The Axial 18F-fluorbetaben positron emission tomography (FDG-PET) of the patient shows mild amyloid positivity, and increased diffusion uptake over the bilateral cortices, and increased cerebral cortex (Figure 2D. Electroencephalography (EEG) was also normal without periodic synchronous discharge. The patient was initially
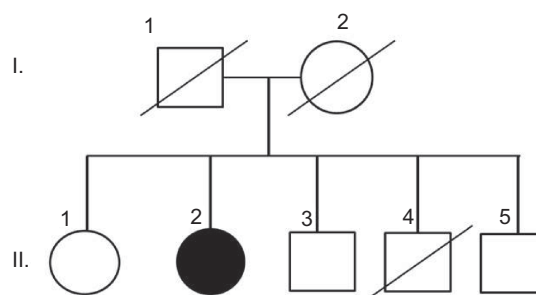
Figure 1 Family history of patient. She did not have any family history of disease.
Notes: Parents I (I-I and I-2) and 3 siblings (II-I, II-3, II-5) of patient (II-2) were unaffected. The 3rd sibling (II-4) died in his 40s.
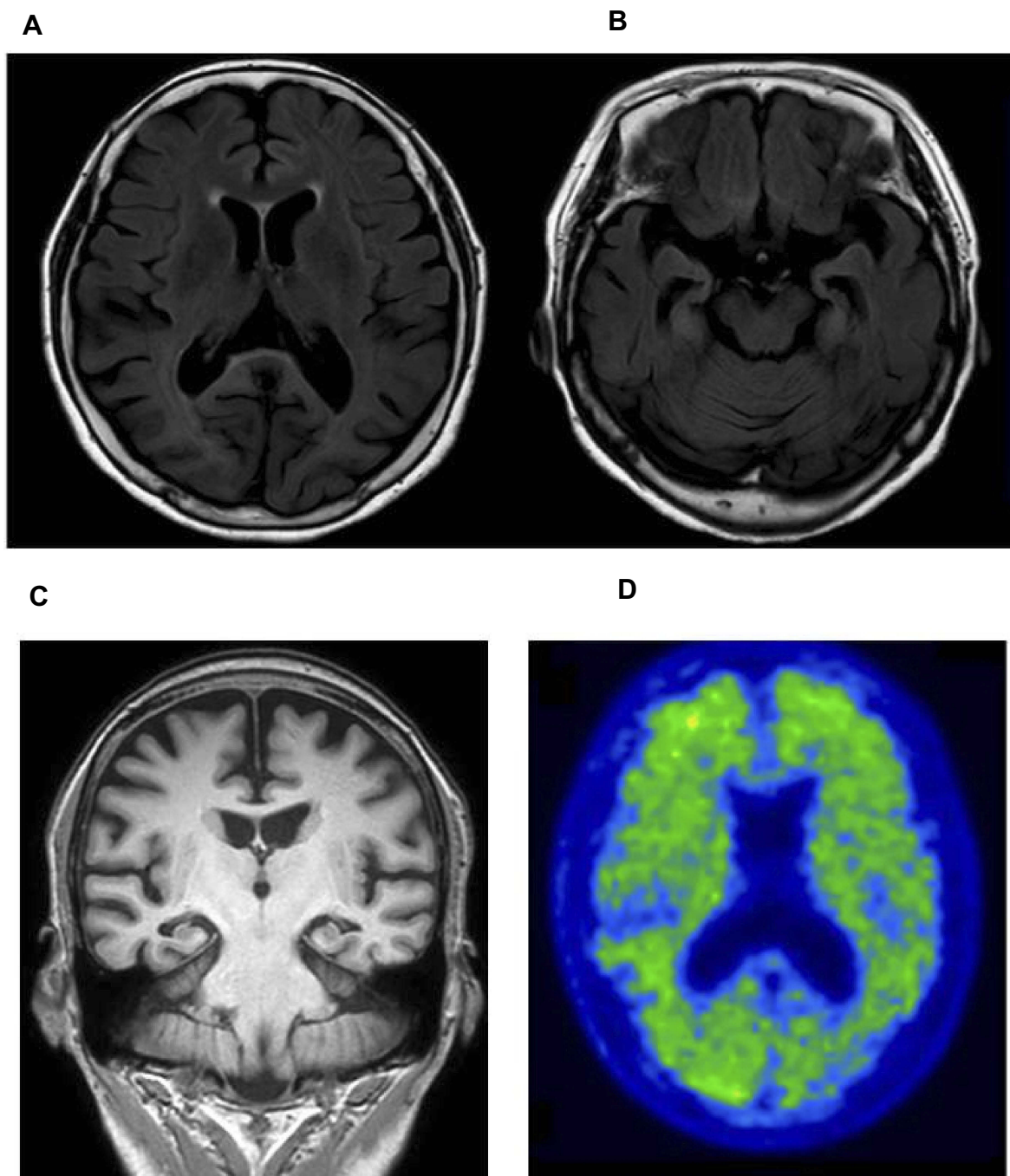
Figure 2 (**A**) Axial FLAIR image of the patient shows moderate atrophy in the bilateral cortices and (**B**) moderate atrophy in the hippocampus. (**C**) Coronal MRI image of patient. (**D**) Axial 18F-fluorbetaben positron emission tomography of the patient shows increased diffusion uptake over the bilateral cortices.

diagnosed as probable Alzheimer's disease by the National Institute on Aging–Alzheimer's Association (NIA–AA) criteria.[12] She was prescribed with an anti-acetylcholinesterase inhibitor, donepezil. One year later, her cognitive deficits were more noticeable. Her husband reported that the patient stopped her daily activities outside her house such as exercise and social activity, and she became unable to perform her activities of daily living.

Her MMSE score was reduced to 13/30. Two years later, the MMSE score was dropped to 10 out of 30, and global clinical dementia rating was 2 and sum of box score was 11. Her visuospatial function impairment became notice-able. She was unable to notice the food on the table, and also developed prosopagnosia. Cerebrospinal fluid (CSF) analy-sis, including cell count, and venereal disease research laboratory (VDRL) test, protein, and glucose, was normal.

However, the CSF 14–3-3 protein was positive. Enzyme-linked immunosorbent assays (ELISA) analyses were performed on Ab42, total tau, and phospho-tau in CSF. Reduced levels of Ab42 (326.8 pg/mL) with elevated total tau (732.9 pg/mL) and phospho-Tau (90.6 pg/μL) protein concentrations were observed. For the accurate disease diagnosis, extensive genetic screening was performed on the patient.

Written informed consent was obtained from the patient for publication of this case report. This report was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1612/376–701).

Results

Whole exome analysis did not reveal any mutations in *APP, PSEN1,* or *PSEN2.* A silent mutation (c.120G>A, p.Gly40, Figure 3A) and a known possible pathogenic mutation in PRNP at codon 180 (c.538G>A; p.Val180Ile Figure 3B) was detected. In addition, several common and rare mutations were found in additional risk genes (Table S1).

Frequencies of PRNP Val180Ile were 0.00019 and 0.000049, in 1000Genomes and EXAC, respectively.

ExAC frequency in East Asia was 0.0003, while in South-East Asia it was 0.0002. Both PolyPhen2 and SIFT revealed the mutation as possibly/probably damaging. PolyPhen2 HumDiv and HumVar scores were 0.937 and 0.887, respectively. SIFT prediction was also damaging, with the score of 0.014, while PROVEAN revealed this mutation as neutral with a score of −0.11. The ExPASY (Figure 4) tool did not reveal significant changes due to Val180Ile. A low increase was found in Kyte and Dootile hydrophobicity scores (V180: 1; I180: 1.033). No significant reduction was seen in bulkiness scores (V180: 17.04, I180: 17.021). In polarity scores (Grantham), low reduction could be seen due to mutation (V180: 7.922; I180: 7.844).

The in silico 3D model predicted that mutation could disturb the protein structure and interactions. A 3D model was performed on normal and mutant prion protein. Our in silico analysis did not predict any significant helix torsion due to Val180Ile, but interactions between α2 and α3 helices changed significantly. Val180 was predicted to be on hydrophobic contact with Cys214 on the α3 helix. Ile180 enhanced the contact of α2–α3 helices, since it could form a hydrogen bond with Glu211 and additional
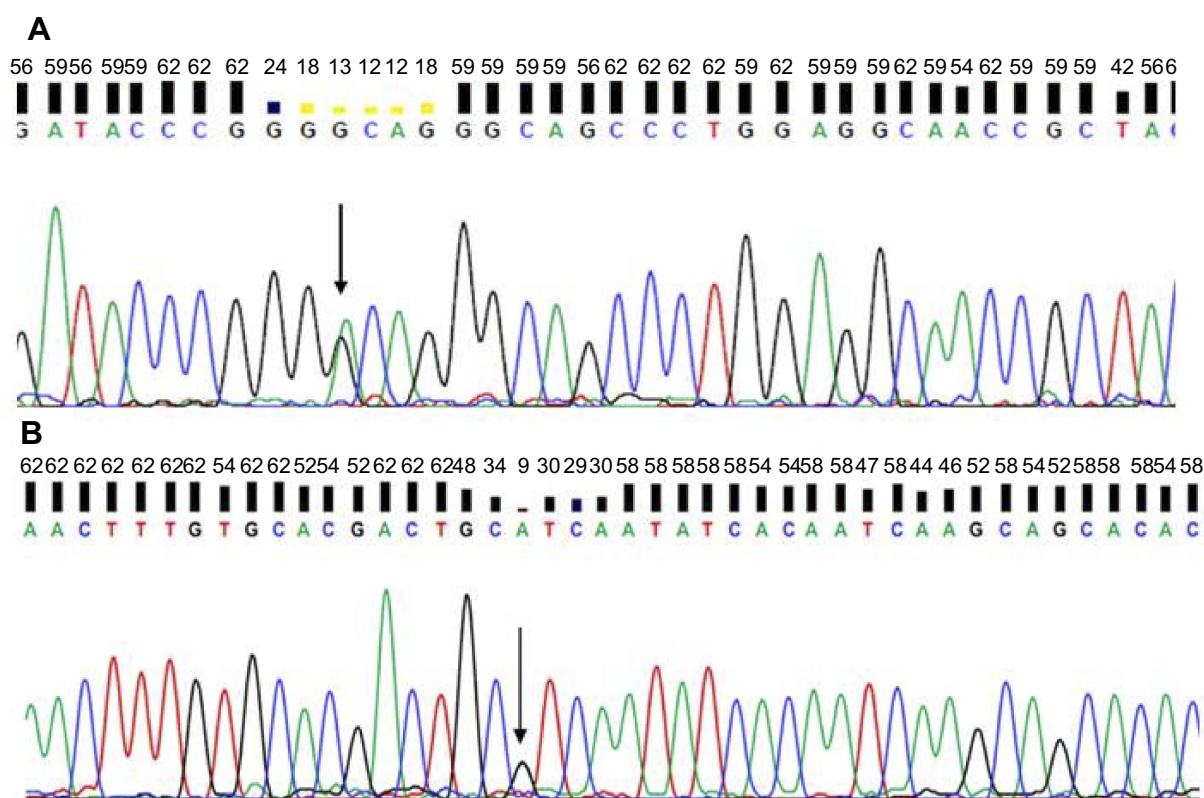
Figure 3 Sequencing data of patient with PRNP. (**A**) G40 and (**B**) V180I.
Note: Arrows indicate mutation.
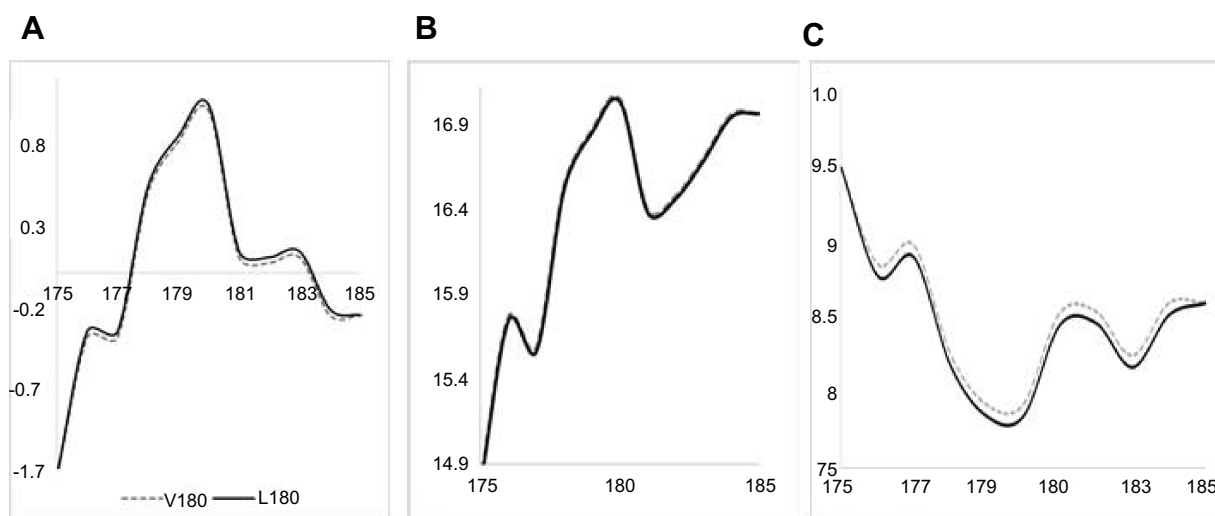
Figure 4 ExPASY prediction for PRNP V180I mutation. (**A**) Kyte Dootile hydrophobicity scores. (**B**) Bulkiness scores. (**C**) Polarity scores.

hydrophobic contact with Val210. Orientation of Ile180 was also changed, which could result in reduced distance and stronger contact between α2–α3 helices (Figure 5).

ClueGo (Figure 6) mapping was also performed on the patient, and revealed a complex network of genes. Pathway analysis suggested that *PRNP* could interact with several genes. *PRNP* could directly play a role negative regulation of amyloid beta formation along with several AD risk genes (such as *ABCA7, SORL1*, and *BACE1*), regulation of calcium mediated signaling with different disease risk genes such as AD (*CR1*), and PD (*BST1, SYT11, PRK2B*). Gene interactions revealed additional possible pathways, in which *PRNP* could contribute, such as lysosome organization, cell response to hydrogen peroxide, or regulation of mitochondrion autophagy.

Discussion

PRNP Val180Ile was commonly observed in East-Asian (Korean, Chinese, and Japanese) patients, but it was also found in a few European CJD cases.[4,12] Val180Ile mutation could be causative mutations for CJD, and its occurrence was rare. There are two previously reported cases of sporadic CJD (sCJD) with *PRNP* Val180Ile mutation in South Korea.[13,14] The clinical and laboratory characteristics of CJD patients with the Val180Ile mutation have been described by Jin et al.[12] The features could include 1) late age of onset, 2) slow disease progression, 3) unique clinical symptoms such as frequent cognitive dysfunction, but no visual or cerebellar symptoms, 4) reduced rate of brain-specific proteins such as neuron-specific enolase (NSE)

and 14–3-3 protein in CSF, and 5) a lack of periodic synchronous discharge in electroencephalogram (EEG) throughout the course of disease. The proband patient in this study did not match any of these features of sCJD, associated with *PRNP* Val180Ile.

The clinical course was distinctively slower than other CJD cases, which were indicated by the absence of the marked drop of MMSE over 4 years (15 to 10 in 4 years). Additionally, the patient was still alive at the time of 48-month follow-up. Cardinal symptoms of CJD such as myoclonic jerk or parkinsonism were not observed. Moreover, the typical MRI abnormalities for sCJD patients with Val180Ile, such as diffuse cortical high-intensity DWI signal, were not revealed in the proband. The florbetaben PET image showed mild diffuse amyloid deposit on bilateral cortices. CSF biomarker of total Ab42, total Tau and phospho-Tau analyses also correlated with AD, which also proved that disease diagnosis.[15] The overall clinical characteristics, laboratory and imaging data corresponded with early onset AD. It remained uncertain whether the *PRNP* mutation was incidentally found in the early onset AD patient or the sCJD with the Val180Ile patient would have atypical clinical course. Furthermore, it remained questionable whether the Val180Ile mutation could always be responsible for the expression of CJD. Nevertheless, several previous reports support the hypothesis that *PRNP* mutation is not always associated with a prion disease. According to the genotype analysis of *PRNP* in a South Korean population, including prion disease patients group (n=22), suspected prion diseases patient group (n=163)
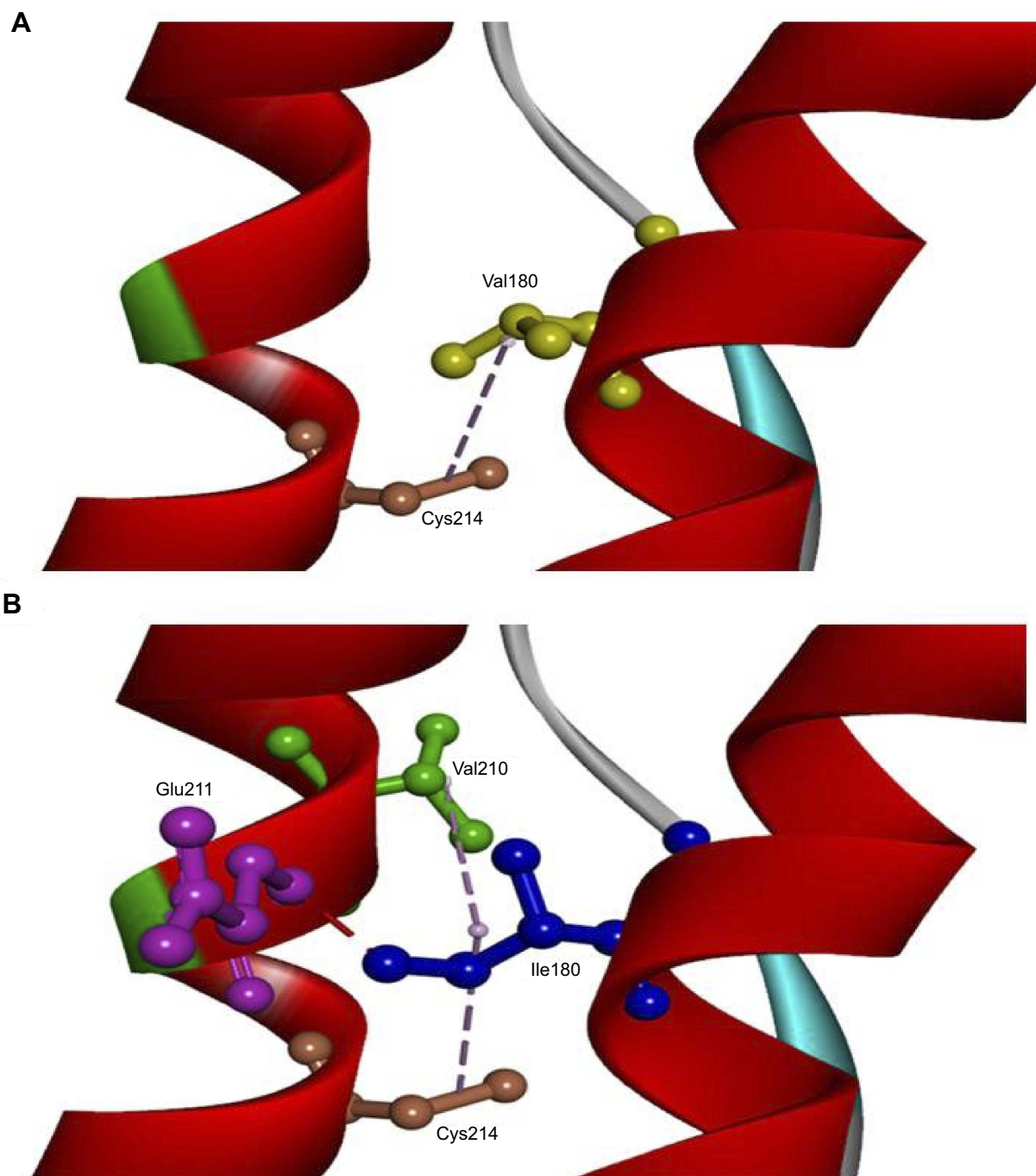
Figure 5 3D model of normal PRNP and PRNP with V180I mutation. (**A**) Val180 (yellow) was predicted to be on hydrophobic contact with Cys214 (orange) on α3 helix. (**B**) Ile180 (blue) enhanced the contact of α2-α3 helices, since it could form a hydrogen bond with Glu211 (purple) and additional hydrophobic contact with Val210 (green). The orientation of Ile180 was also changed, which could result in a reduced distance between α2–α3 helices.

and Korea Association Resource (KARE) data group, three cases of Val180Ile mutations were reported, and two cases from the KARE data group did not display characteristics or symptoms of the neurodegenerative disorder.[16] Prion diseases may share some features such as dementia phenotype and pathological characteristics

with AD. A series of studies suggests the hypothesis that the mutations of *PRNP* also account for other neurodegenerative diseases, including AD. For example, patients with *PRNP* Ser17Gly,[17] Tyr145Ter,[18] Gln160Ter,[19] Tyr163Ter,[20] or Ile215Val[21] were diagnosed with AD or AD-like phenotypes. *PRNP* Val180Ile has low
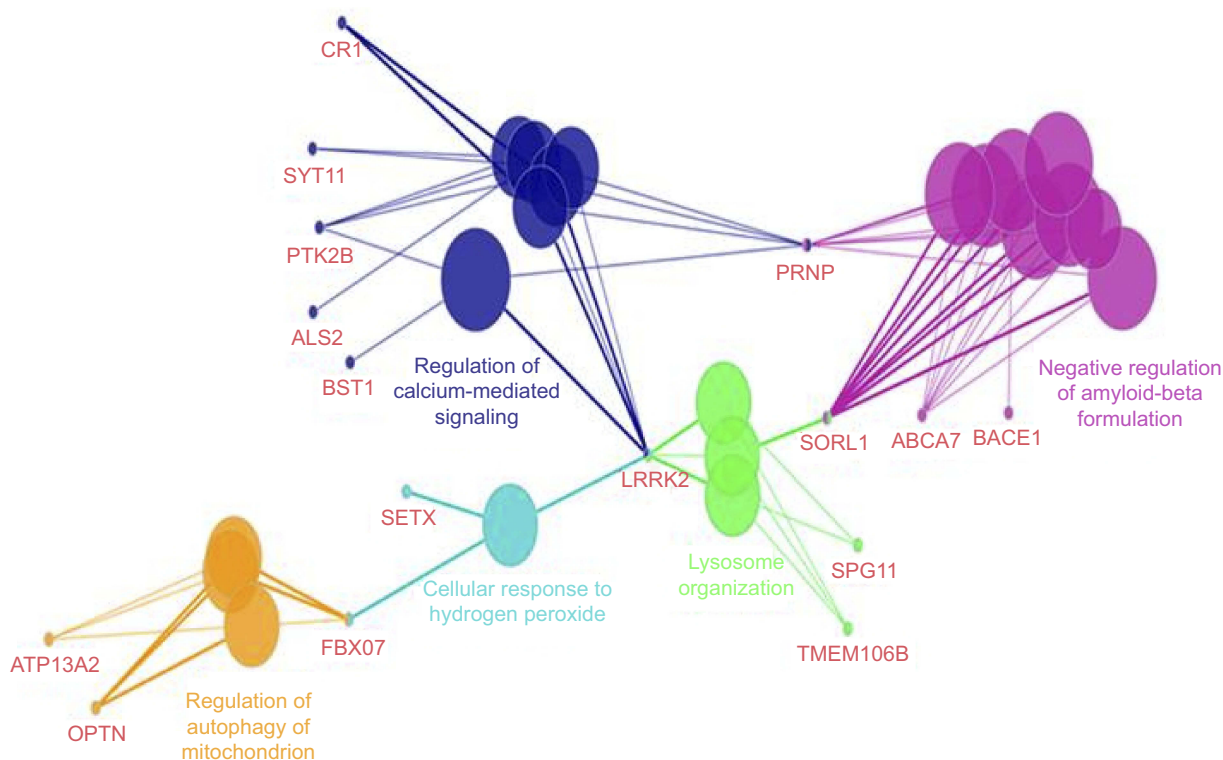
Figure 6 ClueGo mapping of mutations, found in the proband patient.

frequency in the ExAC database (0.00004942, http://exac.broadinstitute.org/). In the 23andMe project, Val180Ile was suggested as a mutation with contradictory pathogenic nature. Even though the pathogenicity of mutation should not be ignored, it was suggested to have low penetrance.[22] Val180Ile was reported in a patient with CJD and Alzheimer's type pathology. In the brain of the patient, several senile plaques appeared with a moderate number of neurofibrillary tangles. The degree of spongiosis was lower than the typical CJD cases. AD and CJD pathology may coexist in a few patients.[23] The rlationship between AD and *PRNP* has been investigated, and prion disease may share some overlap with AD. Both of them are neurodegenerative diseases, based on the abnormal protein conformation and accumulation. In addition, they could have familial and sporadic forms.[17]

PRNP Val180Ile could be involved in a late onset form of CJD or other neurodegenerative diseases. Alzheimer's like phenotypes were also found in several cases of mutation. AD with *PRNP* V180I mutation occurred in patients in their 70s, and disease duration was long, since patients survived for 4–8 years after onset. Imaging data presented hippocampal atropy, and EEG did not present periodic sharp wave complexes.[24] It may be possible that

additional genetic factors or genetic interactions could act as disease-modifiers, and result in earlier disease onset. This proband patient presented similar phenotypes to previous cases, but disease onset was much younger in her. Pathway analysis (Figure 6) with the additional variants in different risk genes revealed a complex network of disease-causing and risk genes, found in the patients (Table S1). Interacting with *SORL1* and *ABCA7*, *PRNP* could play a role in negative regulation of Aβ formation. In the patient, a rare mutation was found in ABCA7 (Ala583Asp) and a possible AD risk mutation was found in SORL1 (Ala528Thr). Both *ABCA7* and *SORL1* could impact the amyloid metabolism, and their role in the early onset form of AD has been investigated.[25,26] Interaction between *SORL1*, and amyloid peptides were proven, since sortilin may play a role in the defense against amyloid aggregation by promoting α-secretase mechanisms. It could also be involved in amyloid trafficking and clearance.[27,28] SORL1 could also protect against prion infection, since the VPS10 domain of sortilin receptor could play a role trafficking prions into lysosomes. However, the abnormal prion proteins could promote the disruption of sortilin in lysosomes, reducing the sortilin levels and lysosomal degradation.[29,30] Prion induced SORL1 dysfunctions may affect the amyloid production

and aggregation. No direct interaction was found between prions and *ABCA7*; however, they may be related through amyloid-associated mechanisms, such as amyloid clearance and microglial mechanisms. Microglia may be protective against amyloid aggregations. ABCA7 was expressed in microglia, resulting in elevated amyloid clearance and phagocytosis.[31] Microglia could also play a possible role in the defense against prion diseases by the clearance of PrP[Sc.32,33] The ability of interaction between Aβ and prion proteins has been proven, and its interaction may be involved in neurodegeneration. Amyloid peptide aggregates may inhibit prion propagation. Normal prion protein may have neuroprotective effects against oxidative stress and amyloid deposition, by inhibiting the β-secretase activity. Normal prion protein could be down-regulated in sporadic AD.[34] It may be possible that *PRNP* Val180Ile could interact with additional AD risk genes, such as with *ABCA7* and/or *SORL1*, which also carried a rare/verified risk mutation. This interaction could result in reduced neuroprotection, amyloid clearance and enhanced amyloid deposition in the patient, which they may also contribute to the earlier disease onset.

Limitations of this study were that we could not perform a brain biopsy on the patient. In addition, even though other affected family members were not affected, a de novo case of mutation could not be verified, since all living family members refused the genetic test. Although *PRNP* Val180Ile mutation has been reported to cause CJD, findings in the presented patient suggest that Val180Ile mutation may not be causative for AD. However, the role of Val180Ile in disease should not be ignored, and it could be a possible risk factor for AD. *PRNP* Val180Ile mutation may reduce the neuroprotective effects in AD patients, and, along with other AD risk genes, it may result in increased Aβ42 production. To confirm the functional role of Val180Ile mutation and its pathogenicity, further investigation may be required.

Acknowledgments

Disclosure

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Supplementary materials

Table S1 Mutations, found in the patient by 100 gene panel analysis

Gene	Mutation	rs ID	1000Genomes	ExAC	SIFT	Polyphen2
ABCA7	A583D	NA	NA	NA	0.08,T	0.924,P
	G1527A	rs3752246	0.825479	0.8405	0.877,T	0.0,B
ALS2	V368M	rs3219156	0.896565	0.9106	0.191,T	0.006,B
ATP13A2	A1072T	rs3170740	0.33127	0.5065	1.0,T	0.001,B
ATXN2	S248N	rs7969300	0.179513	0.0905	0.136,T	0.0,B
BACE1	C481R	rs539765	1	0.9997	1.0,T	0.0,B
BST1	G36A	rs2302468	0.076078	0.0646	0.034,D	0.999,D
	R145Q	rs2302464	0.079074	0.0485	0.118,T	1.0,D
CD33	I198M	rs200827254	0.003195	0.0008	0.061,T	0.04,B
	V294L	rs2271652	0.003195	0.0009	0.305,T	0.001,B
CR1	T1858M	rs3737002	0.248802	0.275	0.021,D	1.0,D
	T2060S	rs4844609	0.995008	0.9853	1.0,T	0.003,B
	T2419A	rs2296160	0.828075	0.8159	1.0,T	0.0,B
CSF1R	H362R	rs10079250	0.153355	0.1192	0.061,T	0.255,B
CTNNA3	R484C	rs200182913	0.0002	0.0002	0.007,D	0.997,D
DSG2	R773K	rs2278792	0.240016	0.2676	0.383,T	0.026,B
EPHA1	M900V	rs6967117	0.960264	0.9366	1.0,T	0.0,B
	V160A	rs4725617	0.94349	0.9284	0.246,T	0.0,B
FBXO7	FM115I	rs11107	0.48742	0.44	1.0,T	0.0,B
GAB2	G135V	rs76853537	0.011981	0.0094	0.537,T	0.003,B
GIGYF2	P460T	rs2289912	0.083067	0.0524	0.375,T	0.756,P
LAMP3	I318V	rs482912	0.496406	0.6483	1.0,T	0.0,B
LRP6	V1062I	rs2302685	0.885583	0.8474	1.0,T	0.0,B
LRRK2	N551K	rs7308720	0.099441	0.0861	0.009,D	1.0,D
	P755L	rs34410987	0.001597	0.0007	0.597,T	0.647,P
	R1398H	rs7133914	0.100439	0.0841	0.1,T	0.992,D
	M2397T	rs3761863	0.551717	0.624	0.466,T	0.0,B
MAPT	Y441H	rs2258689	0.312899	0.2752	0.978,T	0.001,B
MS4A4A	M159V	rs6591561	0.329073	0.2965	0.837,T	0.0,B
MTHFD1L	R58G	NA	NA	NA	0.343,T	0.0,B
NME8	I493T	rs56128139	0.157748	0.2688	0.032,D	0.01,B
NOTCH3	A2223V	rs1044009	0.629393	0.7591	0.175,T	0.001,B
OPTN	K322E	rs523747	0.993411	0.9973	1.0,T	0.0,B
PRNP	V180I	rs74315408	0.0002	4.94E-05	0.014,D	0.937,P
PTK2B	K838T	rs751019	0.364617	0.437	0.439,T	0.014,B
PTPRD	Q447E	rs10977171	0.050919	0.0461	1.0,T	0.991,D
RIN3	T425M	rs3742717	0.292532	0.2385	0.08,T	0.293,B
SETX	S2612G	rs3739927	0.163538	0.0852	0.751,T	0.0,B
	I2587V	rs1056899	0.538738	0.3926	1.0,T	0.0,B
	T1855A	rs2296871	0.443091	0.2758	0.984,T	0.0,B
	F1152C	rs3739922	0.089657	0.0656	0.003,D	0.01,B
	A660G	rs882709	0.213658	0.1211	0.008,D	0.728,P
SIGMAR1	Q2P	rs1800866	0.217252	0.184	0.513,T	0.0,B
SORL1	A528T	rs2298813	0.103235	0.0722	0.306,T	0.962,D
	Q1074E	rs1699107	0.984824	0.9949	1.0,T	0.0,B
	V1967I	rs1792120	0.979433	0.9953	1.0,T	0.0,B
SPG11	F463S	rs3759871	0.47484	0.4659	0.343,T	0.066,B
SYT11	Q48H	rs822522	0.954673	0.988	0.866,T	0.0,B
TM2D3	L6R	rs2939587	0.993411	0.9798	0.466,T	0.0,B
TMEM106B	T185S	rs3173615	0.595048	0.4916	0.214,T	0.043,B

Abbreviations: T, tolerated; P, probably damaging; B, benign; D, damaging.

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