Fig. 1 Population frequencies of the APP A673T mutation by country. Created with R package ‘ggplot2’ ‘maps’.

Table 1 Population frequencies of the APP A673T mutation by country

Country	Sample	NO.	Homozygotes /Heterozygotes	Method	Reference
Iceland	1,795 Icelanders	3	Homozygotes	Single track assay SNP genotyping Illumina SNP Chip Genotyping Whole Genome Sequencing and SNP Calling	[21]
Denmark	3487 unrelated Danes	1	NA	Allelic discrimination using the predesigned Taqman single nucleotide polymorphism genotyping assay C_89522366_10 (Life Technologies)	[25]
Norway	544 patients with schizophrenia or bipolar disorder and 204 controls, all Norwegians	3	NA	Single track assay SNP genotyping Illumina SNP Chip Genotyping Whole Genome Sequencing and SNP Calling	[21]
Sweden	283 schizophrenia samples and 310 controls , all with European ancestry	5	NA	Single track assay SNP genotyping Illumina SNP Chip Genotyping Whole Genome Sequencing and SNP Calling	[21]
	8943 US AD cases, 10480 US cognitively normal controls, 862 Swedish AD cases, and 707 Swedish cognitively normal controls	3	Heterozygotes	Infinium HumanExome V1 Beadchip (Illumina, Inc) TaqMan genotyping (Life Technologies).	[29]
Finland	200 schizophrenia patients and 200 controls，all Finnish sample	4	NA	Single track assay SNP genotyping Illumina SNP Chip Genotyping Whole Genome Sequencing and SNP Calling	[21]
	515 Finnish subjects（aged 85 or older）	1	NA	Neuropathologic analyses Sanger method	[22]
USA	8943 US AD cases, 10480 US cognitively normal controls, 862 Swedish AD cases, and 707 Swedish cognitively normal controls	3	Heterozygotes	Infinium HumanExome V1 Beadchip (Illumina, Inc) TaqMan genotyping (Life Technologies).	[29]
	1674 late-onset Alzheimer's disease cases and 2644 elderly control subjects, all North American Whites	0	NA	TaqMan SNP genotyping assay (C_89522366_10; Life technologies, Grand Island, NY, USA)	[28]

China	552 with Alzheimer's disease and vascular dementia, 790 with Parkinson's disease, and 7379 controls, all Asian individuals	0	NA	Applied Biosystems 7500 Fast Real- time PCR TaqMan SNP Genotyping Assays. Sequencing of exon 16 in 10% of the samples Illumina HumaExome BeadChip array with sequencing of random samples	[26]
	1237 healthy longevity subjects (mean age 96.9 years) and 1404 matched younger controls (mean age 44.2 years) , all Chinese	0	NA	Sequencing on an ABI3730xl Genetic Analyzer (ABI, USA) Using high-resolution melting (HRM) on a lightcycler 480 High Resolution Melting Master (Roche, Switzerland) Sequencing of exon 16 in 5% of the HRM sample using an ABI3730xl Genetic Analyzer.	[27]

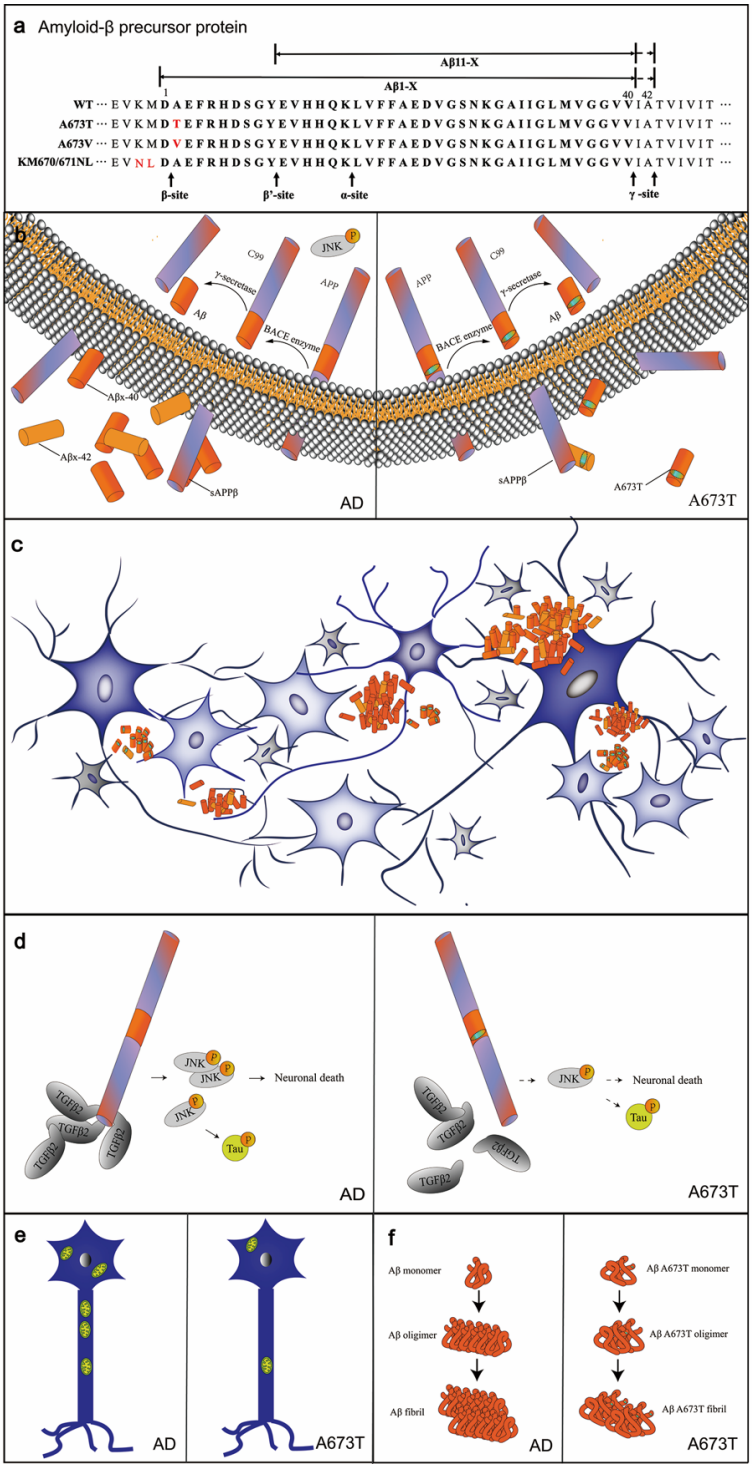

Fig. 2 The mechanisms of A673T protection against AD **a** A673T can reduce C99 generation and decrease the C99/C89 ratio by increasing APP processing by α-secretase and change the cleavage site selection of BACE1 from β-site to β'-site. **b** A673T can reduce both of sAPPβ and C99 levels by reducing the catalytic turnover (Vmax) of APP rather than APP binding affinity (Km) for BACE1. A673T can alter the distribution of C99 in the raft which was codistributed with γ-secretase components, resulting in reduced production of Aβ. **c** A673T promote a decreased propensity for Aβ aggregation. The internalization of microglia highly correlated purely with the aggregation result. **d** A673T has a protective effect on JNK mediated intracellular death signal via APP induced by TGFβ2. **e** Aβ peptide with A2T has a very low plasma membrane binding. A673T can affect mitochondrial axonal transport, thereby protecting against AD. **f** A673T mutant can reduce the formation of Aβ peptide oligomers which are cytotoxic to cultured neurons.

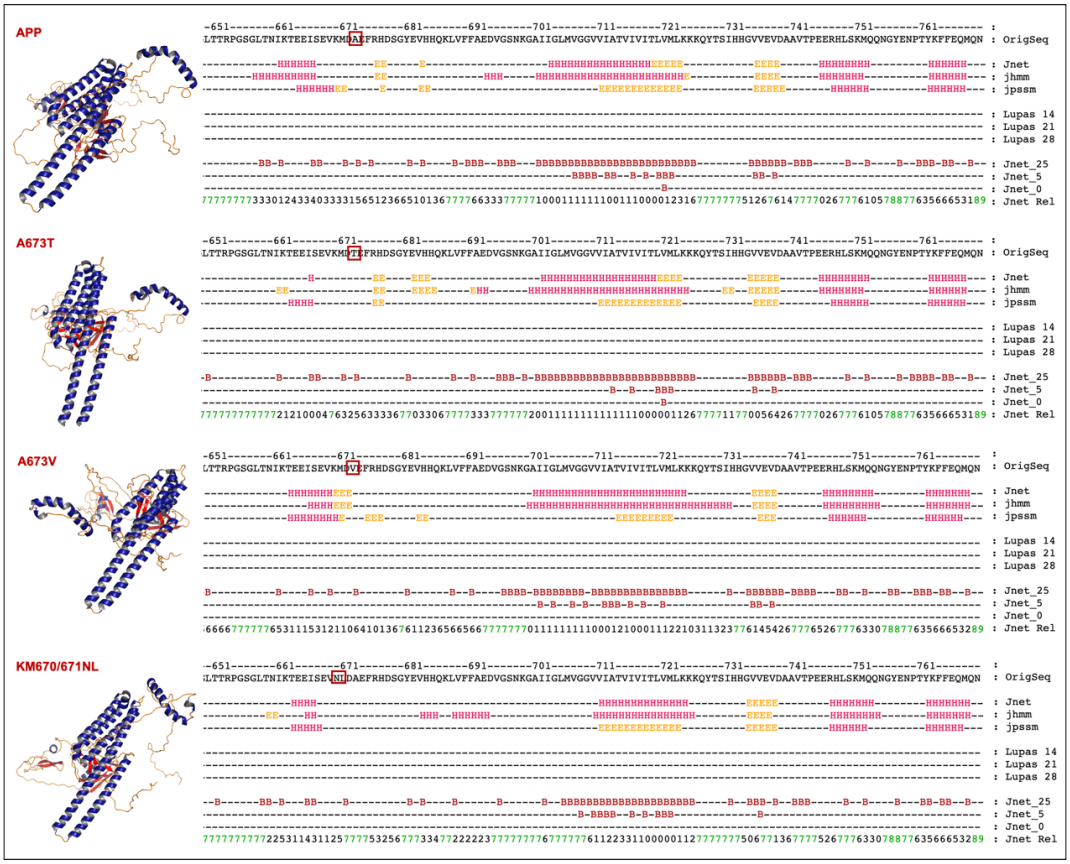

Fig. 3 Structure prediction of wild-type APP peptide and the APP protein with A673T mutation, A673V mutation or KM670/671NL mutation. The molecular visualization system Pymol show possible 3D structure of the APP protein with different mutations in the left. Created with http://raptorx.uchicago.edu/. Jpred 4 prediction results in the right show the probable secondary structure changes of APP caused by mutations in red frames. Created with http://www.compbio.dundee.ac.uk/jpred4/.

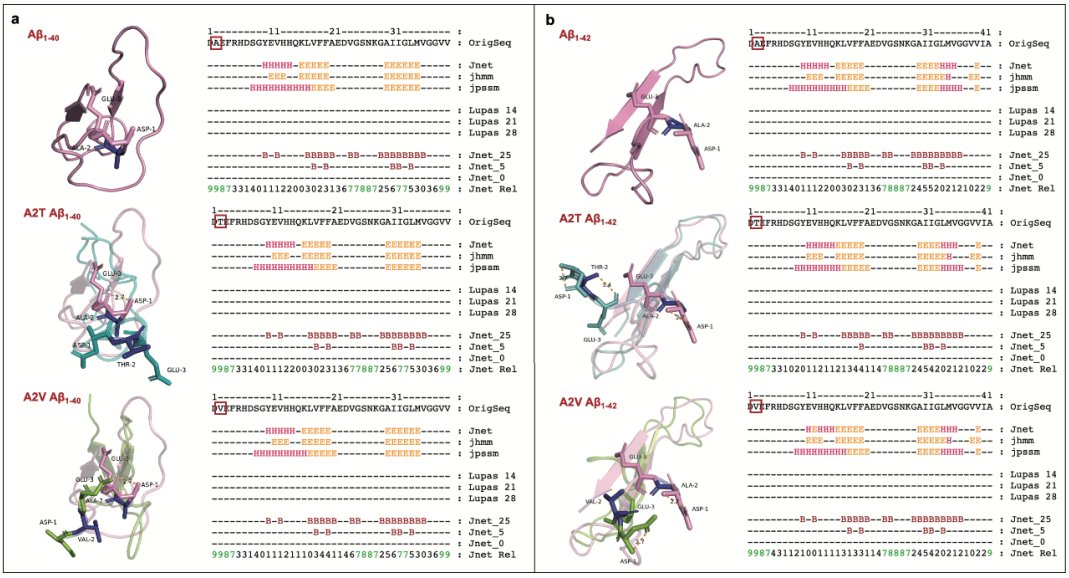

Fig. 4 The molecular visualization system Pymol showed possible 3D structure of wild-type Aβ peptide (pink) and Aβ peptide with A2T mutation (blue) or A2V mutation (green) in the left (a. $A\beta_{1\text{-}40}$ peptide, b. $A\beta_{1\text{-}42}$ peptide). Created with http://raptorx.uchicago.edu/. Jpred 4 prediction results in the right (a. $A\beta_{1\text{-}40}$ peptide, b. $A\beta_{1\text{-}42}$ peptide)showed the probable secondary structure changes of Aβ caused by mutation in red frame. Created with http://www.compbio.dundee.ac.uk/jpred4/.