**Supplementary Table 1.** The demographic and clinical characteristics in pathogenic/likely pathogenic *APP* mutations.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exon** | **Mutation** | **Families and Origin** | **Affected** | **Gender, M/F** | **Mean AAO, y (range)** | **Onset symptom** | **Amnesia** | **Non-amnestic clinical phenotype** | **neurological symptoms** | | **BPSD** | ***APOE*** | **Non-dementia symptoms** | | **Disease duration**  **(range)** | **References** |
| 16 | KM670/671NL | n=3 Sweden | 43 | - | 53.8  (44-61) | n=28 amnesia  n=4 BPSD | 28 | n=9 Disorientation  n=14 Language impairment  n=5 BPSD | n=10 myoclonus  n=10 seizures | | Delusion/  hallucination  depression  aggressiveness | n=2 ε2/ε3  n=1 ε4/ε4 | - | | 7.9  (3-13) | [1-3] |
| A673V | n=1 Italy | 1 | 1/0 | 36.0 | -- | 1 | Language impairment  Apraxia/ agnosia  BPSD | myoclonus  Spastic paraplegia | | depression  aggressiveness | n=1 ε3/ε3 | - | | - | [4] |
| D678H | n=3 Taiwan | 6 | 2/4 | 51.0  (47-55) | n=5 amnesia | 6 | n=5 Disorientation  n=2 Visuospatial disorder  n=1 Language impairment  n=2 Apraxia/ agnosia  n=5 BPSD | - | | Delusions/  hallucination  anxiety | n=5 ε3/ε3 | - | | - | [5, 6] |
| D678N | n=1 Japan  n=2 China | 4 | 1/3 | 56.0  (42-64) | n=1 amnesia | 4 | n=1 Disorientation  n=1 Visuospatial disorder  n=1 Language impairment  n=3 Apraxia/ agnosia  n=2 BPSD | n=2 EPS | | apathy  irritability  aggressiveness | n=1 ε2/ε3 | - | | - | [7-9] |
| E682K | n=1 Belgium | 1 | 0/1 | 47 | n=1 depression | 1 | n=1 Language impairment  n=1 Apraxia/ agnosia | - | | depression | n=1 ε3/ε3 | - | | - | [10] |
| K687N | n=1 German  n=1 China | 2 | 0/2 | 51.5  (51-52) | - | 2 | n=1 Disorientation  n=2 Visuospatial disorder  n=2 Language impairment  n=1 Apraxia/ agnosia  n=1 Dyscalculia | - | | - | n=1 ε2/ε3 | - | | - | [11, 12] |
| K687Q | n=2 China | 2 | 2/0 | 57.5  (52-63) | n=2 amnesia | 2 | n=1 Visuospatial disorder  n=1 Dyscalculia | - | | - | n=1 ε2/ε3  n=1 ε3/ε3 | - | | - | [13] |
| 17 | A692G | n=1 Dutch  n=1 UK | 5 | 4/1 | 47.4  (39-54) | - | 5 | n=3 Disorientation  n=1 Visuospatial disorder  n=3 Language impairment  n=4 Apraxia/ agnosia  n=1 Dyscalculia  n=1 BPSD | n=2 EPS  n=1 myoclonus  n=2 seizures | | depression | - | n=1 headache | | 9.4  (8-11) | [14, 15] |
| E693del | n=3 Japan | 6 | 1/5 | 51.3  (35-59) | n=3 amnesia | 5 | n=1 Disorientation  n=1 Visuospatial disorder  n=1 Apraxia/ agnosia  n=4 BPSD | n=2 EPS  n=3 ataxia  n=3 Spastic paraplegia  n=2 pathologic reflex | | mutism  depression | n=3 ε3/ε3 |  | | - | [16-19] |
| E693G | n= 1 Sweden  n=1 USA | 14 | 4/2 | 57.4  (52-65) | n=9 amnesia  n=1 headache | 10 | n=10 Disorientation  n=5 Language impairment  n=6 Apraxia/ agnosia  n=9 BPSD | n=5 EPS  n=3 myoclonus  n=1 seizures | | Delusions/  hallucination  anxiety  suspiciousness  mutism  apathy  aggressiveness  depression | - | n=1 headache  fatigue  n=2 sleep disturbance | | 8.6  (3-16) | [20, 21] |
| T714A | n=1 Denmark  n=1 Iran  n=1 Poland | 5 | 1/4 | 49.2  (44-58) | n=2 amnesia  n=1 distraction | 5 | n=2 Disorientation  n=2 Visuospatial disorder  n=5 Language impairment  n=3 Apraxia/ agnosia  n=4 BPSD | n=1 EPS  n=1 seizures | | delusions  anxiety  aggression  depression | - |  | | - | [22-25] |
| T714I | n=1 Austria  n=1 USA | 3 | 2/1 | 34 | n=1 amnesia  n=1 visual dysfunction | 3 | n=2 Disorientation  n=2 Visuospatial disorder  n=1 Apraxia/ agnosia  n=3 BPSD | n=2 EPS  n=1 myoclonus  n=2 seizures  n=1 spastic paraplegia  n=1 pathologic reflex  n=1 frontal release signs | | aggression  depression | n=1 ε3/ε3 |  | | 4.0  (3-5) | [26, 27] |
| V715A | n=1 German  n=1 Poland | 2 | 0/2 | 45.0  (42-48) | n=1 amnesia | 2 | n=2 Visuospatial disorder  n=2 Language impairment  n=1 Apraxia/ agnosia | - | | - | - |  | | - | [25, 28] |
| V715M | n=1 France  n=1 Korea  n=1 China | 3 | 2/1 | 44.0  (41-47) | n=1 amnesia | 3 | n=1 Disorientation  n=1 Visuospatial disorder  n=2 Language impairment  n=3 Apraxia/ agnosia  n=1 BPSD | n=1 EPS  n=1 seizures | | apathy | n=1 ε3/ε3 | n=1 blepharospasm | | 10.0  (6-14) | [29-31] |
| I716F | n=1 Austria  n=1 Spain | 2 | 2/0 | 38.0  (31-45) | n=1 amnesia  n=1 depression | 2 | n=1 Disorientation  n=1 Visuospatial disorder  n=2 Language impairment  n=1 Apraxia/ agnosia  n=1 BPSD | n=1 EPS  n=1 myoclonus  n=2 seizures  n=1 ataxia | | depression | n=1 ε3/ε3 |  | | 7.0  (3-10) | [32-34] |
| I716M | n=1 German | 1 | 1/0 | 64 | - | 1 | n=1 Disorientation  n=1 Apraxia/ agnosia  n=1 BPSD | - | | avolition | - |  | | - | [35] |
| I716T | n=1 | 1 | 1/0 | - | - | 1 | n=1 BPSD | - | | - | - |  | | - | [36] |
| I716V | n=1 USA | 1 | 0/1 | 53 | - | 1 | n=1 Visuospatial disorder  n=1 Language impairment | - | | - | - |  | | - | [37] |
| V717F | n=1 Hungary | 2 | 0/1 | - | n=1 amnesia | 2 | n=1 Disorientation  n=2 Language impairment  n=1 Apraxia/ agnosia  n=1 BPSD | n=1 EPS  n=1 myoclonus  n=2 seizures | | aggression | - |  | | - | [38] |
| V717G | n=1 UK | 1 | 1/0 | 44 | n=1 amnesia | 1 | - | - | | - | - |  | | - | [39] |
| V717I | n=2 Australia  n=9 China  n=3 Japan  n=1 UK  n=2 USA | 69 | 27/41 | 52.6  (37-62) | n=15 amnesia  n=1 disorientation  n=1 dyscalculia  n=1 headache  n=2 vertigo | 48 | n=36 Disorientation  n=2 Visuospatial disorder  n=15 Language impairment  n=45 Apraxia/ agnosia  n=11 Dyscalculia  n=44 BPSD | n=19 EPS  n=8 myoclonus  n=7 seizures  n=13 ataxia  n=13 spastic paraplegia  n=3 pathologic reflex  n=3 frontal release signs | Delusions/  hallucination  depression  aggression  anxiety  Irritability  apathy | | n=1 ε2/ε3  n=2 ε2/ε4  n=20 ε3/ε3  n=9 ε3/ε4  n=4 ε4/ε4 | | n=1  sleep disturbance  n=2 vertigo  n=2 headache  n=3 cerebrovascular accident  n=1 hydrocephalus | 9.9  (3-18) | [40-48] |
| V717L | n=1 UK  n=1 USA  n=1 Japan | 6 | 2/3 | 42.8  (35-51) | n=3 amnesia  n=1 distraction  n=1  working executive dysfunction | 6 | n=1 Disorientation  n=3 Visuospatial disorder  n=2 Language impairment  n=5 Apraxia/ agnosia  n=4 BPSD | n=1 EPS  n=1 myoclonus  n=1 seizures  n=3 pathologic reflex | | hallucination  aggression  anxiety  Irritability  depression | n=2 ε3/ε3 |  | | - | [49-51] |
| T719N | - | - | - | - | - | - | - | - | | - | - |  | | - | - |
| T719P | n=1 Italy | 1 | 0/1 | 43 | n=1 amnesia | 1 | n=1 Apraxia/ agnosia  n=1 BPSD | n=1 EPS | | Irritability  aggression | n=1 ε3/ε3 |  | | - | [52] |
| M722K | n=1 China | 1 | 0/1 | 42 | n=1 amnesia | 1 | n=1 Disorientation  n=1 Language impairment  n=1 Apraxia/ agnosia  n=1 BPSD | - | | depression | n=1 ε3/ε4 |  | | - | [53] |
| L723P | n=1 Australia | 1 | 1/0 | 45 | - | 1 | n=1 Language impairment  n=1 Apraxia/ agnosia  n=1 BPSD | - | | hallucination  persecutory delusions  aggression | - |  | | - | [54] |
| K724N | n=1 Belgium | 1 | 0/1 | 55 | n=1 amnesia | 1 | n=1 Apraxia/ agnosia  n=1 BPSD | - | | anxiety  depression  apathy | n=1 ε3/ε4 |  | | - | [55] |

Abbreviations: AAO, age at onset; BPSD, behavioral and psychological disorders of dementia; EPS, extrapyramidal symptoms

**Supplementary Table 2.** The effects on APP processing in pathogenic/likely pathogenic *APP* mutations.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exon** | **Mutation** | **APP processing** | | | | | **References** | |
| **Aβ40** | **Aβ42** | **Aβ42/Aβ40** | **Total Aβ** | **Source** | |  | |
| 16 | KM670/671NL | Increased 7x  Increased 3.4x | Increased 8x  Increased 3x | Not increased  Not increased | Increased 4x~5x  Increased 3x | Hek293  N2A | | [30, 53, 56] | |
| A673V | Slightly increased  Increased 1.7x | Slightly increased  Increased 2x | Not increased  Not increased | Slightly increased  Increased 1.8x | COS7  CHO | | [4, 57] | |
| D678H | Slightly increased | Increased 2.4x | Increased 1.7x | Increased | Hek293 | | [5, 57] | |
| D678N |  | Not increased |  | Not increased | Hek293 | | [57] | |
| E682K | Slightly increased  Increased 1.7x  Increased 1.7x | Increased 3x  Increased 2.5x  Increased 3x | Increased  Slightly increased  Increased 1.7x | Increased  Increased 1.8x  Increased 2x | Hek293  CHO  primary neurons | | [10, 58] | |
| K687N | Increased 2x | Increased 2x | Not increased | Increased 2x | Hek293 | | [11] | |
| K687Q |  |  |  |  |  | |  | |
| 17 | A692G | Increased 1.6x  Increased 1.8x  Increased 2x | Increased 2x  Increased 2x  Increased 2x | Slightly increased  Not increased  Not increased | Increased 1.7x  Increased 1.8x  Increased 2x | Hek293  CHO  primary neurons | | [10, 56] | |
| E693del | Decreased 40% | Decreased 40% | Not increased | Decreased | Hek293 | | [16] | |
| E693G | Not increased | Slightly decreased | Decreased 20% | Not increased | Hek293 | | [56] | |
| T714A |  |  |  |  |  | |  | |
| T714I | Decreased 68%  Decreased 80% | Increased 3.5x  Increased 1.6x | Increased 11x  Increased 8.2x |  | Hek293T  primary neurons | | [26, 59] | |
| V715A | Decreased 45% | Increased | Increased 3x  Increased 4x |  | primary neurons  Hek293 | | [28, 59] | |
| V715M | Decreased 50%  Decreased 70% | Not increased | Increased 1.7x  Increased 4x | Decreased 50% | Hek293  primary neurons | | [30, 59] | |
| I716F | Decreased 50% | Increased 2x | Increased 4x | Decreased 50% | CHO | | [32] | |
| I716M |  |  |  |  |  | |  | |
| I716T | Decreased 20% | Increased 2.7x | Increased 12x | Not increased | CHO | | [60] | |
| I716V | Not increased  Not increased  Increased 2.4x | Increased  Increased 1.7x  Increased 3x | Increased 1.9x  Increased 1.6x  Slightly increased | Not increased  Increased 2.4x | primary neurons  Hek293  CHO | | [37, 59] | |
| V717F | Decreased 40% | Increased 1.8x | Increased 3x | Decreased 30% | Hek293 | | [56] | |
| V717G | Decreased | Increased | Increased |  | COS | | [61] | |
| V717I | Decreased 25%  Decreased 50% | Increased 2.7x  Slightly increased | Increased 1.8x  Increased 1.9x  Increased 3x | Not increased | Hek293T  primary neurons  CHO | | [26, 32, 37, 56, 59] | |
| V717L | Decreased 25% | Increased | Increased 4x |  | primary neurons | | [59] | |
| T719N | Slightly decreased | Increased 5x | Increased 5x |  | N2A | | [62] | |
| T719P |  |  |  |  |  | |  | |
| M722K | Slightly decreased | Slightly increased | Increased 1.7x |  | N2A | | [53] | |
| L723P |  |  | Increased 1.9x |  | CHO | | [54] | |
| K724N | Decreased 30% | Increased 2x | Increased 2.6x  Increased 3x |  | Hek293T  primary neurons | | [55] | |

**Supplementary Table 3.** The demographics and the frequencies of clinical features in V717I mutation and other mutations.

|  |  |  |  |
| --- | --- | --- | --- |
|  | V717I | All *APP* mutations | P Value |
| AAO (years), mean ± SD | 52.9 ± 5.5 | 51.1 ± 6.8 | 0.106 |
| Gender (M/F) | 26/36 | 54/71 | 0.869 |
| Amnesia (n, %) | 49, 79.0% | 115, 88.5% | 0.083 |
| Non-amnestic clinical phenotype (n, %) |  |  |  |
| Disorientation | 36, 58.3% | 66, 35.8% | 0.344 |
| Visuospatial disorder | 2, 3.2% | 21, 16.2% | 0.010\* |
| Language impairment | 15, 24.2% | 47, 36.2% | 0.097 |
| Apraxia/ agnosia | 45, 72.6% | 85, 65.4% | 0.319 |
| Dyscalculia | 11, 17.7% | 14, 10.8% | 0.179 |
| BDSP | 44, 71.0% | 85, 65.4% | 0.441 |
| Neurological symptoms (n, %) |  |  |  |
| EPS | 18, 22.2% | 37, 29.1% | 0.958 |
| Myoclonus | 9, 14.8% | 26, 17.7% | 0.607 |
| Seizures | 8, 13.1% | 29, 19.7% | 0.256 |
| Ataxia | 13, 21.3% | 17, 13.4% | 0.165 |
| Spastic paraplegia | 13, 21.3% | 17, 13.4% | 0.165 |
| Pathologic reflex | 3, 4.9% | 9, 7.1% | 0.569 |
| Frontal release signs | 3, 4.9% | 4, 3.1% | 0.549 |

SD, standard deviation; BPSD, behavioral and psychological disorders of dementia; EPS, extrapyramidal symptoms. Clinical features are all shown as numbers and proportions (%). \*, statistically significant for P < 0.05

**Supplementary Table 4.** The demographics and the frequencies of clinical features in V717I mutation and other mutations.

|  |  |  |  |
| --- | --- | --- | --- |
|  | V717I | Other variants | P Value |
| AAO (years), mean ± SD | 52.9 ± 5.5 | 51.2 ± 6.9 | 0.087 |
| Gender (M/F) | 26/36 | 28/35 | 0.777 |
| Amnesia (n, %) | 49, 79.0% | 66,97.1% | 0.001\* |
| Non-amnestic clinical phenotype (n, %) |  |  |  |
| Disorientation | 36, 58.3% | 30, 44.1% | 0.112 |
| Visuospatial disorder | 2, 3.2% | 19, 27.9% | 1.310×10-4 \* |
| Language impairment | 15, 24.2% | 32, 47.1% | 0.007\* |
| Apraxia/ agnosia | 45, 72.6% | 40, 58.8% | 0.100 |
| Dyscalculia | 11, 17.7% | 3, 4.4% | 0.014\* |
| BDSP | 44, 71.0% | 41, 60.3% | 0.201 |
| Neurological symptoms (n, %) |  |  |  |
| EPS | 18, 22.2% | 19, 28.8% | 0.929 |
| Myoclonus | 9, 14.8% | 17, 19.8% | 0.433 |
| Seizures | 8, 13.1% | 21, 24.4% | 0.090 |
| Ataxia | 13, 21.3% | 4, 4.7% | 0.012 \* |
| Spastic paraplegia | 13, 21.3% | 4, 4.7% | 0.012 \* |
| Pathologic reflex | 3, 4.9% | 6, 7.0% | 0.360 |
| Frontal release signs | 3, 4.9% | 1, 1.2% | 0.273 |

SD, standard deviation; BPSD, behavioral and psychological disorders of dementia; EPS, extrapyramidal symptoms. Clinical features are all shown as numbers and proportions (%). \*, statistically significant for P < 0.05



**Supplementary figure 1. The demographics and the frequencies of clinical features in V717I mutation and all *APP* mutations.** A. The AAO and B. The gender of V717I mutation and all *APP* mutations. C. The frequencies of amnesia and non-amnestic clinical phenotype. D. The frequencies of neurological symptoms. (\* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001).



**Supplementary figure 2. The demographics and the frequencies of clinical features in V717I mutation and other mutations.** A. The AAO and B. The gender of V717I mutation and other mutations. C. The frequencies of amnesia and non-amnestic clinical phenotype. D. The frequencies of neurological symptoms. (\* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001).

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