**Supplementary Material**

**Supplementary Table 1. Demographics, genetic and clinical features for each patient.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Pt** | **Gene** | **Diagnosis** | **Sex** | **Age at PET** | **Age at Diagnosis** | **Age at Onset** | **Disease duration at PET** | **Years of Education** | **ACE-R /100** |
| **A** | MAPT | bvFTD | F | 51 | 51 | 46 | 5.5 | 16 | 43 |
| **B** | MAPT | bvFTD | F | 61 | 60 | 52 | 9 | 16 | 44 |
| **C** | GRN | bvFTD | F | 71 | 70 | 66 | 4.8 | 10 | 33 |
| **D** | GRN | nfPPA | M | 66 | 65 | 63 | 2.4 | 10 | 76 |
| **E** | C9orf72 | bvFTD | M | 56 | 56 | 54 | 2.8 | 10 | 53 |
| **F** | C9orf72 | bvFTD | F | 51 | 51 | 47 | 4.5 | 10 | 41 |
| **G** | C9orf72 | bvFTD | M | 59 | 58 | 56 | 3 | 9 | 46 |

*Abbreviations: Pt=patient; bvFTD=behavioural variant frontotemporal dementia; nfPPA=non-fluent primary progressive aphasia; F=Female; M=Male; ACE-R= Addenbrooke’s Cognitive Examination Revised*

**Supplementary Table 2. Demographics of the two age- and sex-matched control groups compared to each patient in radioligand-specific tests. Age, years of education, and ACE-R scores were compared between the two groups of controls with independent-samples t-tests, while sex was compared with the Chi-square test.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Group control** | **N** | **Sex** **(F/M)** | **Age****(mean ± SD)** | **Education****(mean ± SD)** | **ACE-R** **(mean ± SD)**  |
| **[11C]PK11195** | 15 | 8/7 | 68.8±5.5 | 14.4±2.8 | 93.3±4.4 |
| **[18F]AV-1451** | 15 | 7/8 | 67.3±7.6 | 15.4±2.3 | 95.7±3.2 |
| **Difference controls****(p-value)** | **-** | 0.72 | 0.56 | 0.32 | 0.11 |

*Abbreviations: F/M= female/male; SD=standard deviation; ACE-R= Addenbrooke’s Cognitive Examination Revised*

**Supplementary Table 3. [11C]PK11195 binding potential (BPND) values and Z-scores (Z) for brain regions with statistically significant increased BPND in each patient (Pt) compared to controls at p < 0.05 uncorrected (tests surviving FDR correction are in bold). Mean and standard deviation (SD) BPND values for controls are also reported.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Region** | **Controls BPND** | **Pt A** | **Pt B** | **Pt C** | **Pt D** | **Pt E** | **Pt F** | **Pt G** |
| **Name** | **#** | **Mean** | **SD** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** |
| Hippocampus R | 1 | 0.01 | 0.07 | 0.28 | **3.81** | - | - | - | - | - | - | - | - | - | - | - | - |
| Hippocampus L | 2 | 0.04 | 0.07 | - | - | 0.29 | **3.75** | - | - | - | - | - | - | - | - | - | - |
| Amygdala R | 3 | 0.01 | 0.07 | 0.37 | **4.95** | 0.21 | 2.72 | - | - | - | - | 0.22 | 2.87 | - | - | - | - |
| Amygdala L | 4 | 0.06 | 0.04 | 0.34 | **6.35** | 0.34 | **6.40** | - | - | - | - | - | - | - | - | - | - |
| Anterior temporal lobe medial part R | 5 | 0.04 | 0.06 | 0.23 | **3.11** | - | - | - | - | - | - | 0.35 | **5.10** | 0.19 | 2.50 | - | - |
| Anterior temporal lobe medial part L | 6 | 0.04 | 0.06 | 0.25 | **3.14** | 0.22 | 2.68 | - | - | - | - | - | - | - | - | - | - |
| Anterior temporal lobe lateral part R | 7 | 0.10 | 0.07 | 0.26 | 2.42 | 0.33 | **3.46** | - | - | - | - | - | - | - | - | - | - |
| Anterior temporal lobe lateral part L | 8 | 0.03 | 0.05 | 0.27 | **4.70** | 0.26 | **4.38** | - | - | - | - | 0.19 | 3.11 | 0.27 | **4.70** | - | - |
| Parahippocampal and ambient gyri R | 9 | 0.05 | 0.05 | 0.27 | **4.08** | 0.19 | 2.56 | - | - | - | - | 0.22 | 3.05 | - | - | - | - |
| Parahippocampal and ambient gyri L | 10 | 0.07 | 0.05 | 0.28 | **3.79** | 0.41 | **6.23** | - | - | - | - | 0.22 | 2.73 | - | - | - | - |
| Middle and inferior temporal gyrus R | 13 | 0.01 | 0.04 | - | - | 0.14 | **3.32** | - | - | 0.11 | 2.56 | - | - | - | - | - | - |
| Middle and inferior temporal gyrus L | 14 | -0.02 | 0.03 | 0.14 | **6.02** | 0.08 | **3.77** | 0.08 | **3.70** | - | - | 0.08 | **3.95** | 0.10 | **4.50** | - | - |
| Fusiform gyrus R | 15 | -0.01 | 0.02 | 0.11 | **5.07** | 0.20 | **9.27** | 0.05 | 2.41 | 0.19 | **8.68** | 0.16 | **7.42** | 0.09 | **4.14** | - | - |
| Fusiform gyrus L | 16 | -0.01 | 0.05 | 0.16 | **3.36** | 0.24 | **4.84** | - | - | 0.10 | 2.21 | 0.37 | **7.33** | - | - | 0.11 | 2.37 |
| Insula L | 20 | 0.02 | 0.05 | - | - | - | - | - | - | - | - | 0.16 | 2.92 | - | - | - | - |
| Middle frontal gyrus L | 28 | -0.05 | 0.06 | - | - | - | - | - | - | - | - | - | - | 0.09 | 2.28 | - | - |
| Middle frontal gyrus R | 29 | -0.01 | 0.05 | - | - | 0.08 | 1.84 | - | - | - | - | - | - | 0.11 | 2.63 | - | - |
| Nucleus accumbens L | 36 | 0.11 | 0.07 | - | - | 0.33 | **3.06** | - | - | - | - | - | - | - | - | - | - |
| Nucleus accumbens R | 37 | 0.08 | 0.08 | 0.45 | **4.84** | - | - | - | - | - | - | - | - | - | - | - | - |
| Putamen L | 38 | 0.06 | 0.05 | - | - | - | - | 0.29 | **4.85** | 0.16 | 1.98 | - | - | - | - | - | - |
| Putamen R | 39 | 0.08 | 0.04 | 0.15 | 1.83 | 0.18 | 2.59 | 0.19 | 3.07 | 0.15 | 1.98 | - | - | - | - | - | - |
| Pallidum L | 42 | 0.03 | 0.10 | 0.27 | 2.40 | - | - | 0.25 | 2.13 | - | - | - | - | 0.27 | 2.40 | - | - |
| Straight gyrus L | 52 | 0.18 | 0.07 | 0.43 | **3.55** | - | - | - | - | - | - | - | - | - | - | - | - |
| Straight gyrus R | 53 | 0.16 | 0.09 | 0.44 | **3.20** | - | - | - | - | - | - | - | - | - | - | - | - |
| Anterior orbital gyrus L | 54 | 0.04 | 0.06 | - | - | - | - | - | - | - | - | - | - | 0.37 | **5.27** | - | - |
| Anterior orbital gyrus R | 55 | 0.07 | 0.06 | - | - | - | - | - | - | - | - | - | - | 0.27 | **3.15** | 0.23 | 2.56 |
| Inferior frontal gyrus L | 56 | 0.09 | 0.05 | - | - | - | - | - | - | - | - | - | - | 0.23 | 2.83 | - | - |
| Inferior frontal gyrus R | 57 | 0.12 | 0.06 | - | - | 0.25 | 2.31 | - | - | - | - | - | - | 0.23 | 2.03 | - | - |
| Superior frontal gyrus L | 58 | 0.07 | 0.05 | - | - | - | - | - | - | - | - | - | - | - | - | 0.18 | 2.48 |
| Superior frontal gyrus R | 59 | 0.04 | 0.06 | - | - | - | - | - | - | - | - | - | - | - | - | 0.17 | 2.11 |
| Lingual gyrus L | 64 | 0.15 | 0.07 | - | - | - | - | - | - | - | - | - | - | - | - | 0.29 | 2.10 |
| Lingual gyrus R | 65 | 0.11 | 0.06 | - | - | - | - | - | - | - | - | - | - | - | - | 0.23 | 1.96 |
| Cuneus L | 66 | 0.17 | 0.05 | - | - | - | - | - | - | - | - | - | - | 0.35 | **3.74** | 0.27 | 2.12 |
| Cuneus R | 67 | 0.12 | 0.05 | - | - | - | - | - | - | - | - | - | - | - | - | 0.23 | 1.88 |
| Medial orbital gyrus L | 68 | 0.12 | 0.06 | 0.25 | 1.97 | - | - | - | - | - | - | - | - | 0.36 | **3.82** | - | - |
| Lateral orbital gyrus L | 70 | 0.13 | 0.06 | - | - | - | - | 0.28 | 2.42 | - | - | - | - | 0.52 | **6.22** | - | - |
| Lateral orbital gyrus R | 71 | 0.13 | 0.06 | - | - | - | - | - | - | - | - | - | - | 0.52 | **6.27** | - | - |
| Posterior orbital gyrus L | 72 | 0.10 | 0.07 | 0.29 | 2.55 | - | - | - | - | - | - | - | - | - | - | - | - |
| Posterior orbital gyrus R | 73 | 0.14 | 0.06 | - | - | - | - | - | - | - | - | - | - | 0.27 | 2.32 | - | - |
| Substantia nigra L | 74 | 0.22 | 0.07 | - | - | - | - | - | - | - | - | - | - | 0.44 | 2.91 | - | - |
| Substantia nigra R | 75 | 0.15 | 0.07 | - | - | - | - | 0.60 | **6.47** | - | - | - | - | - | - | - | - |
| Subgenual frontal cortex L | 76 | 0.01 | 0.07 | 0.30 | **4.13** | - | - | - | - | - | - | - | - | - | - | - | - |
| Subcallosal area L | 78 | 0.17 | 0.12 | - | - | - | - | - | - | - | - | 0.43 | 2.10 | - | - | - | - |
| Subcallosal area R | 79 | 0.23 | 0.16 | - | - | - | - | 0.68 | 2.91 | - | - | - | - | - | - | - | - |
| Presubgenual frontal cortex L | 80 | 0.15 | 0.10 | 0.35 | 1.87 | - | - | - | - | - | - | - | - | - | - | - | - |
| Presubgenual frontal cortex R | 81 | 0.10 | 0.08 | 0.25 | 1.83 | - | - | - | - | - | - | - | - | - | - | - | - |
| Superior temporal gyrus anterior part L | 82 | 0.09 | 0.09 | 0.32 | 2.53 | - | - | - | - | - | - | - | - | - | - | - | - |
| Superior temporal gyrus anterior part R | 83 | 0.11 | 0.10 | 0.29 | 1.93 | 0.30 | 1.99 | - | - | - | - | 0.35 | 2.48 | - | - | - | - |

*Abbreviations: L=Left; R=Right*

**Supplementary Table 4. [18F]AV1451 binding potential (BPND) values and Z-scores (Z) for brain regions with statistically significant increased BPND in each patient (Pt) compared to controls at p < 0.05 uncorrected (tests surviving FDR correction are in bold). Mean and standard deviation (SD) BPND values for controls are also reported.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Region** | **Controls****BPND** | **Pt A** | **Pt B** | **Pt C** | **Pt D** | **Pt E** | **Pt F** | **Pt G** |
| **Name** | **#** | **Mean** | **SD** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** | **BPND** | **Z** |
| Hippocampus L | 2 | 0.07 | 0.08 | - | - | - | - | 0.34 | 3.12 | - | - | - | - | - | - | - | - |
| Amygdala R | 3 | 0.06 | 0.07 | 0.35 | **4.11** | - | - | - | - | - | - | - | - | - | - | - | - |
| Amygdala L | 4 | 0.05 | 0.08 | 0.24 | **2.51** | - | - | - | - | - | - | - | - | - | - | - | - |
| Anterior temporal lobe medial part R | 5 | 0.00 | 0.06 | 0.25 | **4.39** | 0.14 | 2.42 | - | - | - | - | 0.15 | 2.59 | - | - | - | - |
| Anterior temporal lobe medial part L | 6 | 0.01 | 0.06 | 0.37 | **6.62** | - | - | 0.11 | 1.86 | - | - | 0.27 | **4.80** | - | - | - | - |
| Anterior temporal lobe lateral part R | 7 | 0.05 | 0.08 | 0.35 | **3.67** | 0.24 | 2.27 | - | - | - | - | 0.22 | 2.03 | - | - | - | - |
| Anterior temporal lobe lateral part L | 8 | 0.04 | 0.08 | 0.42 | **4.85** | 0.21 | 2.20 | - | - | - | - | 0.32 | **3.55** | - | - | - | - |
| Parahippocampal and ambient gyri R | 9 | 0.03 | 0.06 | 0.29 | **4.11** | 0.16 | 2.11 | - | - | - | - | - | - | - | - | - | - |
| Parahippocampal and ambient gyri L | 10 | 0.04 | 0.06 | 0.27 | **3.66** | 0.19 | 2.37 | 0.17 | 2.17 | - | - | - | - | - | - | - | - |
| Middle and inferior temporal gyrus R | 13 | 0.01 | 0.06 | 0.16 | **2.56** | 0.17 | 2.68 | - | - | - | - | 0.12 | 1.82 | - | - | - | - |
| Middle and inferior temporal gyrus L | 14 | 0.01 | 0.05 | 0.29 | **6.01** | 0.13 | 2.67 | 0.15 | 3.04 | - | - | 0.28 | **5.83** | - | - | - | - |
| Fusiform gyrus R | 15 | 0.02 | 0.08 | 0.30 | **3.63** | 0.21 | 2.43 | - | - | - | - | - | - | - | - | - | - |
| Fusiform gyrus L | 16 | 0.03 | 0.06 | 0.34 | **5.60** | - | - | - | - | - | - | 0.27 | **4.36** | - | - | - | - |
| Insula L | 20 | 0.02 | 0.05 | 0.15 | 2.41 | - | - | - | - | - | - | - | - | - | - | - | - |
| Lateral remainder of occipital lobe L | 22 | -0.04 | 0.06 | - | - | 0.09 | 2.04 | - | - | - | - | - | - | - | - | - | - |
| Cingulate gyrus anterior part L | 24 | 0.13 | 0.06 | 0.27 | 2.32 | - | - | - | - | - | - | - | - | - | - | - | - |
| Cingulate gyrus anterior part R | 25 | 0.09 | 0.05 | - | - | 0.19 | 1.84 | - | - | - | - | - | - | - | - | - | - |
| Cingulate gyrus posterior part L | 26 | 0.07 | 0.05 | 0.16 | 1.84 | 0.18 | 2.17 | - | - | - | - | - | - | - | - | - | - |
| Cingulate gyrus posterior part R | 27 | 0.05 | 0.05 | 0.15 | 1.91 | - | - | - | - | - | - | - | - | - | - | - | - |
| Middle frontal gyrus L | 28 | -0.06 | 0.05 | 0.06 | 2.29 | 0.16 | **4.22** | - | - | - | - | 0.07 | 2.58 | - | - | - | - |
| Middle frontal gyrus R | 29 | -0.02 | 0.06 | - | - | 0.20 | 3.57 | - | - | - | - | - | - | - | - | - | - |
| Posterior temporal lobe L | 30 | -0.01 | 0.06 | 0.13 | 2.33 | 0.13 | 2.32 | - | - | - | - | - | - | - | - | - | - |
| Posterior temporal lobe R | 31 | -0.01 | 0.05 | 0.09 | 1.95 | 0.11 | 2.48 | - | - | - | - | - | - | - | - | - | - |
| Inferiolateral remainder of parietal lobe L | 32 | -0.01 | 0.07 | 0.13 | 2.16 | 0.16 | 2.69 | - | - | - | - | - | - | - | - | - | - |
| Inferiolateral remainder of parietal lobe R | 33 | 0.01 | 0.05 | - | - | 0.16 | 3.10 | - | - | - | - | - | - | - | - | - | - |
| Caudate nucleus L | 34 | 0.21 | 0.10 | 0.40 | 1.85 | - | - | - | - | - | - | - | - | - | - | - | - |
| Caudate nucleus R | 35 | 0.18 | 0.11 | - | - | 0.43 | 2.34 | - | - | - | - | - | - | - | - | - | - |
| Nucleus accumbens L | 36 | 0.16 | 0.07 | 0.62 | **6.35** | 0.30 | 1.99 | 0.43 | 3.78 | - | - | - | - | - | - | - | - |
| Nucleus accumbens R | 37 | 0.19 | 0.12 | 0.42 | 1.92 | 0.42 | 1.86 | - | - | - | - | - | - | - | - | - | - |
| Putamen L | 38 | 0.26 | 0.08 | - | - | 0.40 | 1.85 | - | - | - | - | - | - | - | - | - | - |
| Thalamus L | 40 | 0.23 | 0.06 | 0.34 | 1.84 | - | - | 0.39 | 2.59 | - | - | - | - | - | - | - | - |
| Pallidum L | 42 | 0.18 | 0.09 | 0.42 | **2.64** | 0.39 | 2.34 | - | - | - | - | 0.45 | 2.97 | - | - | - | - |
| Pallidum R | 43 | 0.21 | 0.13 | - | - | 0.47 | 2.03 | - | - | - | - | - | - | - | - | - | - |
| Straight gyrus L | 52 | 0.15 | 0.07 | 0.50 | **4.72** | - | - | - | - | - | - | - | - | - | - | - | - |
| Straight gyrus R | 53 | 0.13 | 0.07 | 0.38 | **3.68** | - | - | - | - | - | - | - | - | - | - | - | - |
| Anterior orbital gyrus L | 54 | 0.01 | 0.07 | 0.15 | 1.92 | - | - | - | - | - | - | - | - | - | - | - | - |
| Anterior orbital gyrus R | 55 | 0.01 | 0.06 | 0.15 | 2.18 | - | - | - | - | - | - | - | - | 0.22 | 3.34 | - | - |
| Inferior frontal gyrus L | 56 | 0.06 | 0.06 | 0.22 | **2.87** | 0.23 | 3.03 | - | - | - | - | - | - | - | - | - | - |
| Inferior frontal gyrus R | 57 | 0.09 | 0.07 | - | - | 0.27 | 2.70 | - | - | - | - | - | - | - | - | - | - |
| Superior frontal gyrus L | 58 | 0.04 | 0.05 | 0.20 | **2.94** | 0.15 | 2.11 | - | - | - | - | 0.17 | 2.46 | - | - | - | - |
| Superior frontal gyrus R | 59 | 0.04 | 0.07 | - | - | 0.23 | 2.95 | - | - | - | - | - | - | - | - | - | - |
| Superior parietal gyrus L | 62 | 0.01 | 0.06 | - | - | 0.15 | 2.48 | - | - | - | - | - | - | - | - | - | - |
| Medial orbital gyrus L | 68 | 0.08 | 0.07 | 0.30 | **3.35** | - | - | - | - | - | - | - | - | - | - | - | - |
| Medial orbital gyrus R | 69 | 0.08 | 0.08 | 0.24 | 2.11 | 0.26 | 2.25 | - | - | - | - | - | - | - | - | - | - |
| Lateral orbital gyrus L | 70 | 0.05 | 0.07 | 0.36 | **4.50** | 0.18 | 1.87 | - | - | - | - | - | - | 0.29 | 3.43 | - | - |
| Lateral orbital gyrus R | 71 | 0.04 | 0.07 | 0.19 | 1.99 | - | - | - | - | - | - | - | - | 0.34 | 3.97 | - | - |
| Posterior orbital gyrus L | 72 | 0.04 | 0.05 | 0.33 | **5.26** | - | - | - | - | - | - | - | - | - | - | - | - |
| Posterior orbital gyrus R | 73 | 0.07 | 0.08 | 0.30 | **2.79** | - | - | - | - | - | - | - | - | - | - | - | - |
| Substantia nigra L | 74 | 0.26 | 0.11 | - | - | - | - | - | - | - | - | 0.54 | 2.56 | - | - | - | - |
| Substantia nigra R | 75 | 0.22 | 0.13 | 0.49 | 2.13 | - | - | - | - | - | - | - | - | - | - | - | - |
| Subgenual frontal cortex L | 76 | -0.01 | 0.08 | 0.24 | **3.09** | - | - | - | - | - | - | - | - | - | - | - | - |
| Subgenual frontal cortex R | 77 | -0.05 | 0.05 | 0.12 | **3.49** | 0.06 | 2.30 | - | - | - | - | - | - | - | - | - | - |
| Subcallosal area L | 78 | 0.14 | 0.12 | 0.39 | 2.05 | - | - | 0.47 | 2.63 | - | - | - | - | - | - | - | - |
| Subcallosal area R | 79 | 0.11 | 0.08 | 0.31 | 2.35 | 0.34 | 2.79 | - | - | - | - | - | - | - | - | - | - |
| Presubgenual frontal cortex L | 80 | 0.11 | 0.09 | 0.32 | 2.29 | - | - | - | - | - | - | - | - | - | - | - | - |
| Presubgenual frontal cortex R | 81 | 0.02 | 0.07 | 0.19 | 2.24 | 0.25 | 3.10 | - | - | - | - | - | - | - | - | - | - |
| Superior temporal gyrus anterior part L | 82 | 0.08 | 0.08 | 0.38 | **3.72** | - | - | - | - | - | - | 0.39 | **3.87** | - | - | - | - |

*Abbreviations: L=Left; R=Right*

**Supplementary Figure 1. Axial slices of the [11C]PK11195 (left) and [18F]AV-1451 (right) binding potential (BPND) maps for each patient (A-G). For comparison, the last row shows the corresponding average BPND maps across 15 controls.** **Patients A and B are MAPT mutation carriers; cases C and D are patients with GRN mutations; and patients E, F and G are C9orf72 mutation carriers. The BPND maps were spatially normalised to ICBM 152 2009a space, masked and smoothed (isotropic 6mm full width at half maximum Gaussian). The BPND maps are overlaid on the ICBM 152 2009a T1 MR template and the slices are reported in the neurological display convention (left on the left). The BPND scale applies to both radioligands.**

