**Supplementary Material**

**SUPPLEMENTARY METHODS 1: STATISTICAL ANALYSIS**

To compare demographic and cognitive features,statistical analyses were performed using SPSS software version 20.0 (SPSS Inc.). The Mann-Whitney U test was used to compute the differences between groups. Wilcoxon pairwise-t-test was used for longitudinal analysis on neuropsychological data. Results were considered significant for *p*<0.05.

**SUPPLEMENTARY METHODS 2: COGNITIVE ASSESSMENT**

The behavioral assessment included: The Frontal Behavioral Inventory [1], the Frontotemporal Dementia Rating Scale [2], Neuropsychiatric Inventory [3], and the Frontal Dysfonctionnement Scale [4].

The neuropsychological battery included: for General intellectual abilities the Mini-Mental State Examination [5] and the Mattis Dementia Rating scale [6]; for Executive functions the Frontal Assessment Battery [7], the Wisconsin Card Sorting Test [8]and the Trail Making test A and B [9]; for verbal and spatial memory the Free and Cued Recall test [10]and Rey-Osterrieth Complex Figure Test [11]respectively; for language the Categorical fluency (animals), Phonetic fluency (P letter), and the Becs-Greco naming [12]; for praxies the Praxies Evaluation Battery [13]; for Visuospatial abilities the copy of Rey-Osterrieth Complex Figure Test [11]and for social cognition the Faux pas test [14]for Theory of mind and the Ekman test[15], as part of the SEA battery [16]for emotion recognition.

**Supplementary Table 1.** Neuropsychological and behavioral tests results.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **TESTS** | **T0** | | **T20** | |
| ***aGRN+***  **(n=16)** | ***GRN-***  **(n=17)** | ***aGRN+***  **(n=14)** | ***GRN-***  **(n=14)** |
| **Global efficiency**  **Mini-Mental State Examination** (/30) | 29.3±1.1 | 28.7±1.4 | 29.6±0.6 | 28.9±1.4 |
| **Mattis Dementia Rating Scale**(/ 144) | 141.0±4.5 | 142.3±1.5 | 142.8±1.5 | 141.4±3.2 |
| **Verbal and spatial memory** |  |  |  |  |
| **Free and Cued Recall Test** |  |  |  |  |
| Identifications (/16) | 16.0±0.0 | 16.0±0.0 | 16.0±0.0 | 16.0±0.0 |
| Immediate cued recall (/16) | 15.8±0.6 | 15.8±0.8 | 15.6 ±0.6 | 15.2±1.0 |
| Immediate free recall (/48) | 34.9±4.9 | 35.5±3.2 | 36.6±5.2 | 34.2±4.9 |
| Immediate total recall (/48) | 47.0±1.0 | 47.2±1.1 | 46.9±1.3 | 46.8±2.1 |
| Delayed free recall (/16) | 13.8±1.3 | 13.9±1.3 | 14.3±1.3 | 14.0±1.6 |
| Delayed total recall (/16) | 15.9±0.3 | 16.0±0.0 | 16.0±0.0 | 15.9±0.3 |
| **Rey Complex Figure memory** |  |  |  |  |
| Time (seconds) | 140.2±35.0 | 135.6±48.1 | 132.0±50.4 | 124.1±30.5 |
| Score | 22.5±6.3 | 24.3±6.6 | 24.0±6.7 | 24.0±5.6 |
| **Digit span**  Forward | 6.4±1.1 | 6.4±1.2 | 6.4±1.2 | 6.6±1.2 |
| Backward | 5.0±1.1 | 4.6±1.0 | 5.7±2.6 | 4.7±1.2 |
| **Wisconsin Card Sorting Test** |  |  |  |  |
| Score (/20) | 18.1±4.2 | 19.5±0.9 | 19.7±0.7 | 18.7±3.4 |
| Categories (/6) | 5.6±1.2 | 6±0.0 | 6.0±0.0 | 5.8±1.0 |
| Time (seconds) | 179.4±76.8 | 178.4±67.3 | 177.3±59.2 | 194.5±97.7 |
| **Frontal Assessment Battery** |  |  |  |  |
| Total score (/18) | 17.5±1.1 | 17.4±1.1 | 17.9±0.3 | 17.4±0.9 |
| Similarities (/3) | 3.0±0.0 | 2.9±0.3 | 3.0±0.0 | 2.8±0.4 |
| Phonological fluency (/3) | 2.8±0.4 | 2.8±0.6 | 2.9±0.3 | 2.8±0.4 |
| Grasping (/3) | 3.0±0.0 | 3.0±0.0 | 3.0±0.0 | 3.0±0.0 |
| Motor sequences (/3) | 2.9±0.3 | 2.9±0.3 | 3.0±0.0 | 2.9±0.3 |
| Conflicting instructions (/3) | 2.9±0.3 | 3.0±0.0 | 3.0±0.0 | 2.9±0.3 |
| Go-no-go (/3) | 2.9±0.5 | 3.0±0.0 | 3.0±0.0 | 2.9±0.3 |
| **Trail Making Test** |  |  |  |  |
| Part A | 27.9±14.8 | 25.8±8.1 | 24.4±9.3 | 25.1±7.0 |
| Part B | 59.9±37.8 | 50.4±12.8 | 53.9±14.3 | 55.0±22.4 |
| B – A | 31.5±25.2 | 25.8±8.1 | 30.4±13.3 | 30.1±19.1 |
| **Language** |  |  |  |  |
| **Verbal Fluency** (/2 minutes) |  |  |  |  |
| Semantic (animals) | 35.4±8.9 | 35.8±8.7 | 36.4±6.7 | 36.6±8.7 |
| Phonological (P) | 23.5±7 | 24.1±7.8 | 24.8±7.5 | 23.0±5.2 |
| **Oral confrontation Naming** (/40) | 39.9±0.3 | 39.9±0.2 | 39.6±0.7 | 40.0±0.0 |
| **Emotion Recognition and social cognition** |  |  |  |  |
| **Ekman test** |  |  |  |  |
| Total score (/35) | 30.8±2.4 | 30.4±3.6 | 30.9±1.6 | 30.5±3.0 |
| Happiness (/5) | 5.0±0.0 | 5.0±0.0 | 5.0±0.0 | 5.0±0.0 |
| Surprise (/5) | 4.4±0.7 | 4.5±0.6 | 4.2±1.1 | 4.4±1.0 |
| Disgust (/5) | 4.6±0.7 | 4.2±1.1 | 4.5±0.5 | 4.5±0.9 |
| Neutral (/5) | 4.6±0.9 | 4.6±1.0 | 5.1±1.0 | 4.5±1.0 |
| Fear (/5) | 3.6±1.3 | 3.5±0.9 | 3.6±1.2 | 3.5±1.2 |
| Anger (/5) | 4.4±0.7 | 4.4±0.8 | 4.8±0.5 | 4.3±0.8 |
| Sadness (/5) | 4.1±1.2 | 4.1±1.2 | 4.1±1.0 | 4.3±0.8 |
| **Faux pas recognition test** |  |  |  |  |
| Score (/30) | 27.7±2.9 | 26.1±4.4 | 27.7±3.0 | 25.9±4.2 |
| Faux pas control test (/10) | 9.9±0.5 | 9.8±0.7 | 9.7±1.1 | 9.6±0.8 |
| **Praxies assessment** |  |  |  |  |
| Manual dexterity (/36) | 36.0±0.0 | 35.8±0.7 | 35.8±0.6 | 35.5±1.1 |
| Kinetic melody (/24) | 23.8±0.8 | 23.8±0.7 | 23.9±0.3 | 23.8±0.7 |
| Meaningless gestures imitation(/36) | 35.9±0.3 | 36.0±0.0 | 36.0±0.0 | 35.9±0.3 |
| Intransitive gestures pantomime (/36) | 35.8±0.8 | 36.0±0.0 | 35.8±0.8 | 36.0±0.0 |
| Transitive gesturespantomime (/36) | 35.8±0.8 | 35.9±0.5 | 35.90±0.5 | 35.4±2.4 |
| **Visual-constructive abilities** |  |  |  |  |
| **Rey Complex Figure Copy** |  |  |  |  |
| TotalScore (/36) | 35.3±0.9 | 34.6±1.4 | 35.0±1.3 | 35.2±1.2 |
| Time (seconds) | 150.2±54.2 | 124.1±31.6 | 143.3±42.8 | 119.2±28.1 |
| **Behavioral assessment**  Frontal Battery Inventory scale (/72) | 2.0±0.5 | 2.0±3.9 | 2.0±2.5 | 2.0±4.2 |
| Neuropsychiatric Inventory (/36) | 4.5±5.0 | 5.0±6.4 | 5.0±4.8 | 5.0±7.8 |
| Frontemporal Dementia Rating Scale (/28) | 0.2±0.5 | 0.2±0.6 | 0.0±0.0 | 0.3±0.6 |
| Frontotemporal Behavioral scale (/4) | 1±1.2 | 1.0±1.4 | 0.6±1.2 | 1.0±1.3 |

Mean±SD are reported; all the scores of a*GRN+* individuals were normal.

There were no statistical differences in the cognitive scores at baseline between the two groups. Longitudinal analysis did not find any difference between groups.

**Supplementary Table 2.** *GRN* mutations.

|  |  |  |  |
| --- | --- | --- | --- |
| Mutations | | | |
|  | **c.DNA** | **Protein** | **Exon** |
| 1 | c.907del | p.Ala303Profs\*58 | 9 |
| 2 | c.1494\_1498del | p.Glu498Aspfs\*12 | 12 |
| 3 | c.813\_816delCACT | p.Tyr272Serfs\*10 | 8 |
| 4 | c.1201C>T | p.Gln401\* | 11 |
| 5 | c.380\_381del | p.Pro127Argfs\*2 | 5 |
| 6 | c.1231\_1232dup | p.Ala412fs\*1 | 11 |
| 7 | complete *GRN* deletion | p.0 | - |
| 9 | c.1157G>A | p.Trp386\* | 10 |
| 10 | c.443\_444del | p.Gly148Valfs\*11 | 5 |
| 11 | c. 1A>G | Met1 | 2 |

**Supplementary Table 3.** List of the exclusion criteria for the study

|  |
| --- |
| Age < 18 or > 75 |
| Pregnancy |
| Neurological or psychiatric disorders |
| Diabetes and inflammatory/immunological disorders |
| MRI contraindications  (Metal-containing implants and foreign bodies, tattoos, intrauterine dispositive) |
| PET contraindications  (diabetes, urinary incontinence) |

**Supplementary Table 4.** Regions with significant annualized percentage of metabolic changes in a*GRN+* compared to *GRN-.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Region | Ke | Coordinates (x, y, z) | T | Mean % annual changevalues | Maximal %  annual changevalues |
| L Frontal middle | 111 | -40, 6, 60 | 4.91 | -2.92 | -7.02 |
| L Frontal inferior orbital | 163 | -20, 22, -22 | 4.67 | -2.45 | -6.64 |
| L Thalamus | 98 | -10, -18, 2 | 3.93 | -2.56 | -8.66 |
| L Temporal inferior | 91 | -28, 0, -42 | 4.54 | -3.17 | -7.02 |
| R Frontal superior orbital | 59 | 18, 32, -24 | 4.10 | -2.50 | -7.15 |

MNI coordinates and % annual change, mean and maximal values are reported.

Ke, cluster extent, number of voxels.

**Supplementary Table 5.** Demographic data among the different studies.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Our study | Borroni et al. [17] | Premi et al. [18] | Pievani et al. [19] | Jacova et  al. [20] | Dopper et  al. [21] | Moreno et al. [22] | Rohrer et al. [23] |
| Number of asymptomatic  carriers | 16 | 9 | 17 | 5 | 9\* | 28 | 13 | 45 |
| Mean age (y) | 41.9±8.2 | 40.1±11.7 | 41.6±9.0 | 45.0±10.0 | 51.5±13.5 | 54.0±8.0 | 54.0±12.0 | 55.0 |
| Mean estimated distance to age at onset (y) | 20±10 | - | - | 12.0±7.0 | 7.0±12.0 | 8.6±7.0 | - | - |

\* including 5 cognitively impaired.

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