**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 etal. [20] | Dopper etal. [21] | Moreno et al. [22] | Rohrer et al. [23] |
| Number of asymptomaticcarriers | 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.

**References**

1. Kertesz A, Davidson W, Fox H (1997) Frontal Behavioral Inventory: Diagnostic criteria for frontal lobe dementia. *Can J NeurolSci***24**,29–36
2. Mioshi E, Hsieh S, Savage S,Hornberger M, Hodges JR (2010) Clinical staging and disease progression in frontotemporal dementia. *Neurology***74**,1591-1597.
3. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology***44**, 2308-2314
4. Lebert F,Pasquier F,Souliez L, Petit H (1998) Frontotemporal behavioral scale. *Alzheimer Dis AssocDisord***12**,335-339.
5. Folstein MF,Folstein S, McHugh PR (1975) "Mini Mental State": A practical methods of grading cognitive status of patients for the clinician. *J Psychol Res***12**,189-198.
6. Mattis S (1988)*Dementia Rating Scale*. Psychological Assessment Resources, Odessa, FL.
7. Dubois B.Slachevsky A.Litvan I.Pillon B (2000) The FAB: a Frontal Assessment Battery at bedside. *Neurology***55**,1621-1626.
8. Berg EA (1948) A simple objective for measuring flexibility in thinking.*J Gen Psychol***39**, 15–22.
9. Reitan RM, Wolfson D (1993) *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*, 2nd Edn. Neuropsychology Press, Tuscon, AZ.
10. Grober E,Buschke H, Crystal MD, Bang MA,Dresner R (1988) Screening for dementia by memory testing. *Neurology***38**,900-903.
11. Osterrieth PA (1944) Le test de copied’une figure complex: Contribution al’etude de la perception et de la memoire [The test of copying a complex figure: A contribution to the study of perception and memory] *ArchPsychol***28**,1021–1034.
12. Merck A,Charnallet A,Auriacombe S,Belliard S, Hahn-Barma V,Kremin H,Lemesle B,Mathieux F,Moreaud O, Perrier Palisson D,Roussel M,Sellai F,Siegwart H (2011) La batteried’évaluation des connaissancessémantiques du GRECO (BECS-GRECO): Validation et donnéesnormatives.*RevNeuropsychol (Paris)***3**, 235-255.
13. Peigneux P, Van Der Linden M, Andres-Benito P,Sadzot B, Franck G, Salmon E (2000) A neuropsychological and functional brain imaging study of visuo-imitative apraxia. *Rev Neurol***156**,459-472.
14. Stone VE, Baron-Cohen S, Knight RT (1998) Frontal lobe contributions to theory of mind. *J CognNeurosci***10**, 640-656.
15. Ekman P, Friesen W (1976) *Pictures of facial affect*. Consulting Psychologists Press. Palo Alto.
16. Funkiewiez A,Bertoux M, de Souza LC,Lévy R, Dubois B (2012) The SEA (Social cognition and Emotional Assessment): a clinical neuropsychological tool for early diagnosis of frontal variant of frontotemporal lobar degeneration. *Neuropsychology***26**,81-90.
17. Borroni B, Alberici A, Cercignani M, Premi E, Serra L, Cerini C, Cosseddu M, Pettenati C, Turla M, Archetti S, Gasparotti R, Caltagirone C, Padovani A, Bozzali M (2012) Granulin mutation drives brain damage and reorganization from preclinical to symptomatic FTLD. *Neurobiol Aging***33**, 2506-2520.
18. Premi E, Cauda F, GasparottiR, Diano M, Archetti S, Padovani A, Borroni B (2014) Multimodal FMRI resting-state functional connectivity in granulin mutations: the case of fronto-parietal dementia. *PLoS One***9**, e106500.
19. Pievani M, Paternicò D, Benussi L, Binetti G, Orlandini A, Cobelli M, Magnaldi S, Ghidoni R, Frisoni GB (2014) Pattern of structural and functional brain abnormalities in asymptomatic granulin mutation carriers. *Alzheimers Dement***10**, S354-S363.e1.
20. Jacova C, Hsiung GY, Tawankanjanachot I, Dinelle K, McCormick S, Gonzalez M, Lee H, Sengdy P, Bouchard-Kerr P, Baker M, Rademakers R, Sossi V, Stoessl AJ, Feldman HH, Mackenzie IR (2013) Anterior brain glucose hypometabolism predates dementia in progranulin mutation carriers. *Neurology***81**, 1322-1331.
21. Dopper EG, Rombouts SA, Jiskoot LC, den Heijer T, de Graaf JR, de Koning I, Hammerschlag AR, Seelaar H, Seeley WW, Veer IM, van Buchem MA, Rizzu P, vanSwieten JC (2014) Structural and functional brain connectivity in presymptomatic familial frontotemporal dementia. *Neurology***83**, e19-26.
22. Moreno F, Sala-Llonch R, Barandiaran M, Sánchez-Valle R, Estanga A, Bartrés-Faz D, Sistiaga A, Alzualde A, Fernández E, MartíMassó JF, López de Munain A, Indakoetxea B (2013) Distinctive age-related temporal cortical thinning in asymptomatic granulin gene mutation carriers. *Neurobiol Aging***34**, 1462-1468.
23. Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, van Minkelen R, Rombouts SA, Cardoso MJ, Clegg S, Espak M, Mead S, Thomas DL, De Vita E, Masellis M, Black SE, Freedman M, Keren R, MacIntosh BJ, Rogaeva E, Tang-Wai D, Tartaglia MC, Laforce R Jr, Tagliavini F, Tiraboschi P, Redaelli V, Prioni S,Grisoli M, Borroni B, Padovani A, Galimberti D, Scarpini E, Arighi A, Fumagalli G, Rowe JB, Coyle-Gilchrist I, Graff C, Fallström M, Jelic V, Ståhlbom AK, Andersson C, Thonberg H, Lilius L, Frisoni GB, Pievani M, Bocchetta M, Benussi L, Ghidoni R, Finger E, Sorbi S, Nacmias B, Lombardi G, Polito C, Warren JD, Ourselin S, Fox NC, Rossor MN (2015) Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol***14**, 253-262.