

Table S1: CAG expansion in our study sample

| No. | Subject ID | Enroll-HD Centres | CAG expansion |
|------------|-------------------|--------------------------|----------------------|
| 1 | HD-3 | LIRH Foundation Rome | 44 |
| 2 | HD-4 | LIRH Foundation Rome | 46 |
| 3 | HD-5 | LIRH Foundation Rome | 46 |
| 4 | HD-6 | LIRH Foundation Rome | 43 |
| 5 | HD-7 | LIRH Foundation Rome | 48 |
| 6 | HD-9 | LIRH Foundation Rome | 43 |
| 7 | HD-13 | LIRH Foundation Rome | 49 |
| 8 | HD-14 | LIRH Foundation Rome | 44 |
| 9 | HD-15 | LIRH Foundation Rome | 43 |
| 10 | HD-16 | LIRH Foundation Rome | 42 |
| 11 | HD-17 | LIRH Foundation Rome | 45 |
| 12 | HD-19 | LIRH Foundation Rome | 44 |
| 13 | HD-21 | LIRH Foundation Rome | 41 |
| 14 | HD-22 | LIRH Foundation Rome | 41 |
| 15 | HD-24 | LIRH Foundation Rome | 42 |
| 16 | HD-25 | LIRH Foundation Rome | 42 |
| 17 | HD-27 | LIRH Foundation Rome | 43 |
| 18 | HD-28 | LIRH Foundation Rome | 46 |
| 19 | HD-29 | LIRH Foundation Rome | 41 |
| 20 | HD-32 | LIRH Foundation Rome | 43 |
| 21 | HD-33 | LIRH Foundation Rome | 43 |
| 22 | HD-34 | LIRH Foundation Rome | 49 |
| 23 | HD-36 | LIRH Foundation Rome | 44 |
| 24 | HD-37 | LIRH Foundation Rome | 44 |
| 25 | HD-38 | LIRH Foundation Rome | 43 |
| 26 | HD-39 | LIRH Foundation Rome | 42 |

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|----|-------|----------------------|----|
| 27 | HD-42 | LIRH Foundation Rome | 41 |
| 28 | HD-45 | LIRH Foundation Rome | 45 |
| 29 | HD-46 | LIRH Foundation Rome | 44 |
| 30 | HD-50 | LIRH Foundation Rome | 41 |
| 31 | HD-51 | LIRH Foundation Rome | 45 |
| 32 | HD-52 | LIRH Foundation Rome | 42 |
| 33 | HD-53 | LIRH Foundation Rome | 44 |
| 34 | HD-56 | LIRH Foundation Rome | 47 |
| 35 | HD-57 | LIRH Foundation Rome | 47 |
| 36 | HD-58 | LIRH Foundation Rome | 45 |
| 37 | HD-60 | LIRH Foundation Rome | 44 |
| 38 | HD-62 | LIRH Foundation Rome | 47 |
| 39 | HD-63 | LIRH Foundation Rome | 44 |
| 40 | HD-65 | LIRH Foundation Rome | 41 |
| 41 | HD-66 | LIRH Foundation Rome | 45 |
| 42 | HD-67 | LIRH Foundation Rome | 45 |
| 43 | HD-69 | LIRH Foundation Rome | 43 |
| 44 | HD-71 | LIRH Foundation Rome | 44 |
| 45 | HD-73 | LIRH Foundation Rome | 47 |
| 46 | HD-74 | LIRH Foundation Rome | 48 |
| 47 | HD-76 | LIRH Foundation Rome | 45 |
| 48 | HD-77 | LIRH Foundation Rome | 44 |
| 49 | HD-78 | LIRH Foundation Rome | 44 |
| 50 | HD-79 | LIRH Foundation Rome | 42 |
| 51 | HD-80 | LIRH Foundation Rome | 49 |
| 52 | HD-81 | LIRH Foundation Rome | 43 |
| 53 | HD-82 | LIRH Foundation Rome | 44 |
| 54 | HD-83 | LIRH Foundation Rome | 40 |
| 55 | HD-84 | LIRH Foundation Rome | 46 |
| 56 | HD-85 | LIRH Foundation Rome | 41 |

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|-----------------------------------|--------|---------------------------------|----------------|
| 57 | HD-86 | IRCCS Besta Milan | 40 |
| 58 | HD-87 | IRCCS Besta Milan | 40 |
| 59 | HD-89 | IRCCS Besta Milan | 41 |
| 60 | HD-91 | IRCCS Besta Milan | 43 |
| 61 | HD-92 | IRCCS Besta Milan | 43 |
| 62 | HD-93 | IRCCS Besta Milan | 40 |
| 63 | HD-94 | Sant'Andrea University Hospital | 44 |
| 64 | HD-95 | Sant'Andrea University Hospital | 42 |
| 65 | HD-96 | Sant'Andrea University Hospital | 43 |
| 66 | HD-97 | Sant'Andrea University Hospital | 42 |
| 67 | HD-98 | Sant'Andrea University Hospital | 42 |
| 68 | HD-99 | Sant'Andrea University Hospital | 44 |
| 69 | HD-100 | Sant'Andrea University Hospital | 45 |
| 70 | HD-101 | Sant'Andrea University Hospital | 41 |
| 71 | HD-102 | Sant'Andrea University Hospital | 45 |
| 72 | HD-103 | Sant'Andrea University Hospital | 45 |
| 73 | HD-104 | Sant'Andrea University Hospital | 42 |
| 74 | HD-105 | Sant'Andrea University Hospital | 47 |
| 75 | HD-106 | Sant'Andrea University Hospital | 40 |
| Mean repeat number (\pm SD) | | | 43,7 \pm 2.3 |

Table S2: Correlations between CAG expansions and clinical variables

| CLINICAL VARIABLES | CAG expansion | |
|-----------------------|---------------|--------------|
| | <i>r</i> | <i>p</i> |
| CRIq_Edu | -0,348 | 0,002 |
| CRIq_WA | -0,320 | 0,005 |
| CRIq_LA | -0,219 | 0,059 |
| CRIq_Tot | -0,372 | 0,001 |
| ΔTFC | -0,008 | 0,946 |
| ΔTMS | -0,088 | 0,454 |
| cUHDRS_t0 | -0,040 | 0,736 |
| cUHDRS_t1 | -0,035 | 0,764 |
| cUHDRS_t2 | -0,039 | 0,738 |

CRIq_Edu: Cognitive Reserve Index Educational; CRIq_WA: Cognitive Reserve Index Working activity; CRIq_LA: Cognitive Reserve Index Leisure activities; CRIq_Tot: Cognitive Reserve Index Total score; ΔTFC: the difference between the Total Functional Capacity score at t2 and t0; ΔTMS: the difference between the Total Motor Score at t2 and t0; cUHDRS_t0: composite Unified Huntington's Disease Rating Scale at baseline; cUHDRS_t1: composite Unified Huntington's Disease Rating Scale at 1-year follow-up; cUHDRS_t2: composite Unified Huntington's Disease Rating Scale at 2-year follow-up.

Table S3: Correlations between CAG expansions and cognitive variables at three timepoints

| COGNITIVE TEST | | CAG expansion | |
|----------------|------|---------------|----------|
| | | <i>r</i> | <i>p</i> |
| BASELINE | MMSE | -0,020 | 0,865 |
| | SDMT | 0,054 | 0,647 |
| | VFT | -0,102 | 0,382 |
| | SCR | -0,004 | 0,974 |
| | SWR | -0,018 | 0,876 |
| I follow-up | MMSE | 0,030 | 0,797 |
| | SDMT | 0,051 | 0,665 |
| | VFT | -0,027 | 0,817 |
| | SCR | 0,006 | 0,963 |
| | SWR | -0,019 | 0,874 |
| II follow-up | MMSE | -0,1 | 0,397 |
| | SDMT | -0,013 | 0,914 |
| | VFT | -0,126 | 0,280 |
| | SCR | 0,052 | 0,655 |
| | SWR | -0,026 | 0,824 |

MMSE: Mini Mental State Examination; SDMT: Symbol Digit Modality Test; VFT: Categorical Verbal Fluency Test; SCR: Stroop Color Reading Test; SWR: Stroop Word Reading Test.

Table S4.1: Clinical and cognitive scores in impaired and normal cognitive reserve total index groups.

| | | CRIq_Tot impaired Group (n=32) Mean \pm SE | CRIq_Tot normal Group (n=43) Mean \pm SE | p |
|---|---------------|--|--|----------|
| Clinical variables | Δ _TFC | -1.69 \pm 0.2 | -1.33 \pm 0.23 | 0.311 |
| | Δ _TMS | 10.5 \pm 1.39 | 7.44 \pm 1.48 | 0.149 |
| | cUHDRS_t0 | 73.24 \pm 8.5 | 85.27 \pm 7.47 | 0.293 |
| | cUHDRS_t1 | 62.84 \pm 8.84 | 77.55 \pm 8.14 | 0.229 |
| | cUHDRS_t2 | 49.96 \pm 9.72 | 69.15 \pm 9.20 | 0.162 |
| Cognitive variables - <i>Baseline</i> | MMSE | 25.53 \pm 0.5 | 27.01 \pm 0.4 | 0.069 |
| | SDMT | 23.03 \pm 2.26 | 26.55 \pm 2.06 | 0.257 |
| | VFT | 13.4 \pm 1.01 | 14.37 \pm 0.73 | 0.431 |
| | SCR | 47.21 \pm 2.86 | 50.69 \pm 2.81 | 0.399 |
| | SWR | 65 \pm 4.1 | 73.39 \pm 3.76 | 0.140 |
| Cognitive variables - <i>1 year follow-up</i> | MMSE | 24.87 \pm 0.66 | 26.04 \pm 0.48 | 0.064 |
| | SDMT | 22.41 \pm 2.37 | 25.64 \pm 2.09 | 0.314 |
| | VFT | 12.31 \pm 1.15 | 14.53 \pm 0.77 | 0.101 |
| | SCR | 43.25 \pm 2.62 | 49.23 \pm 2.99 | 0.153 |
| | SWR | 61.37 \pm 3.91 | 70.67 \pm 3.96 | 0.107 |
| Cognitive variables - <i>2 years follow-up</i> | MMSE | 24.16 \pm 0.73 | 26.04 \pm 0.45 | 0.067 |
| | SDMT | 21.28 \pm 2.06 | 24.98 \pm 2.35 | 0.261 |
| | VFT | 11.65 \pm 0.87 | 13.18 \pm 0.71 | 0.176 |
| | SCR | 42.46 \pm 3.54 | 47.23 \pm 3.1 | 0.316 |
| | SWR | 55.66 \pm 4.46 | 67.63 \pm 4.19 | 0.067 |

Table S4.2: Clinical and cognitive scores in impaired and normal cognitive reserve education groups

| | | CRIq_Edu impaired Group (n=14) Mean ± SE | CRIq_Edu normal Group (n=61) Mean ± SE | p |
|---|------------------|---|---|----------|
| Clinical variables | Δ_TFC | -1.64 ± 0.34 | -1.44 ± 0.20 | 0.659 |
| | Δ_TMS | 9.14 ± 1.69 | 8.66 ± 1.22 | 0.857 |
| | cUHDRS_t0 | 77.07 ± 15.01 | 80.848 ± 6.05 | 0.796 |
| | cUHDRS_t1 | 73.14 ± 15.58 | 70.848 ± 6.55 | 0.883 |
| | cUHDRS_t2 | 61.28 ± 16.56 | 60.898 ± 7.46 | 0.982 |
| Cognitive variables - <i>Baseline</i> | MMSE | 25.84 ± 0.91 | 26.59 ± 0.34 | 0.385 |
| | SDMT | 26.21 ± 4.1 | 24.78 ± 1.64 | 0.719 |
| | VFT | 13.5 ± 1.66 | 14.06 ± 0.64 | 0.717 |
| | SCR | 47.85 ± 4.3 | 49.52 ± 2.29 | 0.751 |
| | SWR | 66.5 ± 6.41 | 70.57 ± 3.13 | 0.575 |
| Cognitive variables - <i>1 year follow-up</i> | MMSE | 24.92 ± 1.22 | 25.96 ± 0.41 | 0.319 |
| | SDMT | 25.57 ± 4.12 | 23.96 ± 1.68 | 0.690 |
| | VFT | 11.92 ± 2.07 | 13.96 ± 0.67 | 0.238 |
| | SCR | 45.64 ± 4.39 | 46.91 ± 2.34 | 0.812 |
| | SWR | 67.42 ± 6.33 | 66.54 ± 3.21 | 0.904 |
| Cognitive variables - <i>2 years follow-up</i> | MMSE | 24.84 ± 1.21 | 25.623 ± 0.44 | 0.488 |
| | SDMT | 24.5 ± 3.89 | 23.15 ± 1.79 | 0.747 |
| | VFT | 11.85 ± 1.59 | 12.68 ± 0.58 | 0.565 |
| | SCR | 46.21 ± 4.55 | 44.96 ± 2.68 | 0.837 |
| | SWR | 63.21 ± 6.84 | 62.36 ± 3.53 | 0.916 |

Table S4.3: Clinical and cognitive scores in impaired and normal cognitive reserve working activity index groups.

| | | CRIq_WA impaired Group (n=29) Mean \pm SE | CRIq_WA normal Group (n=46) Mean \pm SE | p |
|---|---------------|--|--|-------|
| Clinical variables | Δ _TFC | -1.52 \pm 0.28 | -1.46 \pm 0.22 | 0.867 |
| | Δ _TMS | 10.14 \pm 1.71 | 7.87 \pm 1.31 | 0.293 |
| | cUHDRS_t0 | 76.92 \pm 9.31 | 82.17 \pm 7.1 | 0.652 |
| | cUHDRS_t1 | 69.2 \pm 9.73 | 72.58 \pm 7.74 | 0.786 |
| | cUHDRS_t2 | 54.78 \pm 10.93 | 64.86 \pm 8.64 | 0.471 |
| Cognitive variables - <i>Baseline</i> | MMSE | 25.67 \pm 0.55 | 26.95 \pm 0.38 | 0.067 |
| | SDMT | 24.1 \pm 2.59 | 25.65 \pm 1.9 | 0.625 |
| | VFT | 14.89 \pm 1.04 | 13.37 \pm 0.72 | 0.219 |
| | SCR | 51.69 \pm 3.49 | 47.65 \pm 2.45 | 0.335 |
| | SWR | 68.44 \pm 4.43 | 70.67 \pm 3.65 | 0.702 |
| Cognitive variables - <i>1 year follow-up</i> | MMSE | 25.17 \pm 0.73 | 26.15 \pm 0.46 | 0.239 |
| | SDMT | 23.65 \pm 2.59 | 24.68 \pm 1.99 | 0.752 |
| | VFT | 13.31 \pm 1.13 | 13.76 \pm 0.83 | 0.746 |
| | SCR | 47.37 \pm 3.34 | 46.23 \pm 2.65 | 0.790 |
| | SWR | 66.17 \pm 4.26 | 67.04 \pm 3.83 | 0.883 |
| Cognitive variables - <i>2 years follow-up</i> | MMSE | 24.57 \pm 0.78 | 26.04 \pm 0.47 | 0.092 |
| | SDMT | 22.03 \pm 2.63 | 24.26 \pm 2.06 | 0.506 |
| | VFT | 12.31 \pm 1 | 12.67 \pm 0.66 | 0.753 |
| | SCR | 43.79 \pm 3.75 | 46.08 \pm 3 | 0.636 |
| | SWR | 60.03 \pm 4.89 | 64.09 \pm 4.07 | 0.531 |

CRIq_Tot: Cognitive Reserve Index Total score; CRIq_Edu: Cognitive Reserve Index Educational; CRIq_WA: Cognitive Reserve Index Working activity;
 Δ TFC: the difference between the Total Functional Capacity score at t2 and t0; Δ TMS: the difference between the Total Motor Score at t2 and t0;
cUHDRS_t0: composite Unified Huntington's Disease Rating Scale at baseline; cUHDRS_t1: composite Unified Huntington's Disease Rating Scale at 1-year follow-up; cUHDRS_t2: composite Unified Huntington's Disease Rating Scale at 2-year follow-up.
MMSE: Mini Mental State Examination; SDMT: Symbol Digit Modality Test; VFT: Categorical Verbal Fluency Test; SCR: Stroop Color Reading Test; SWR: Stroop Word Reading Test.
SE: standard error; NS: not significant.