**Psychological impact of predictive genetic testing for inherited Alzheimer’s disease and frontotemporal dementia: the IT-DIAfN protocol**

**SUPPLEMENTAL DIGITAL CONTENT 1**

**METHODS**

*The IT-DIAfN Protocol – further details*

Prenatal counselling and diagnosis were not included in the protocol. Reasons for requesting the predictive genetic testing were qualitatively collected.

The expected time frame between blood sample and genetic disclosure was no longer than two months. Participants were allowed to withdraw from the protocol at any stage and could be readmitted by starting again with pre-test consultation.

For logistic reasons, the IRCCS Fondazione Besta carried out T1 follow-up assessment by phone. As a consequence, only qualitative information about possible life changes were collected and no psychological assessment was available for 7 participants.

*Psychological assessment – further details*

Personality traits were assessed by the Big Five Questionnaire,1 and anxious symptoms by the State-Trait Anxiety Inventory.2

Depressive symptoms were evaluated by two scales. The HDRS was a clinician-administered scale, ranging between 0 and 52. A score of 0–7 is generally accepted to be within the normal range. The BDI was a self-administered scale, ranging between 0 and 63. Scores less than 9 indicated minimal symptoms associated to low mood, while higher scores were indicative of depressive symptoms of increasing intensity.

The SF-12 is a health-related quality of life questionnaire consisting of twelve questions and two summary scores to assess physical (Physical Component Summary) and mental (Mental Component Summary) health. For both dimensions, the score ranged from 0 to 100, with higher scores representing better health.

The WHOQOL-short version is a 26-items questionnaire consisting of four domains: physical health, psychological health, social relationships, and environmental health. The score ranges from 0 to 100; the higher the score, the greater the participant's perception of well-being in that domain.

Coping strategies were rated by the Brief COPE.3

The RSA measures the ability to adapt to psychosocial adversities. It evaluates six intra- and interpersonal protective dimensions of resilience: perception of self, planned future, social competence, family cohesion, social resources, structured style, personal competence. The RSA consists of 33 items, each ranging from 1 to 7. For each dimension, higher scores reflect higher levels of protective factor of resilience.

The MHLOC scale evaluated the degree to which people believed that health and disease were primarily consequence of individual behaviours, fate, or under the control of powerful others. Three domains were derived: internal, chance external, and powerful others external. For all domains, the range score is 6-36: the higher the score, the higher the participant's belief for that dimension.

**REFERENCES**

1. Caprara GV, Barbaranelli C, Borgogni L. *Big Five Questionnaire*. Firenze: O.S. Organizzazioni Speciali; 1993.
2. Spielberger CD. *State-Trait Anxiety Inventory: Bibliography*. 2nd ed. Palo Alto CA: Consulting Psychologists Press; 1989.
3. Carver CS. You want to measure coping but your protocol’s too long: Consider the Brief COPE. *Int J Behav Med.* 1997;4:92-100.

**Supplementary table 1.** Sociodemographic and psychological features of 20 healthy at-risk relatives (see ‘Second consultation’ box in figure 1) included in IT-DIAfN protocol by genetic disclosure at baseline.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Genetic disclosure** | |  |  |
|  | *disclosed*  n=15 | *not disclosed*  n=5 | Pa | Pb |
| ***Sociodemographics*** |  |  |  |  |
| Age (years) | 40.3±9.6 | 39.2±19.9 | 0.672 | - |
| Gender (F) | 10 (66%) | 2 (40%) | 0.292 | - |
| Education |  |  |  |  |
| Middle | 1/14 (7%) | 1 (20%) |  |  |
| High | 4/14 (29%) | 4 (80%) |  |  |
| University | 9/14 (64%) | 0 (0%) | 0.047 | - |
| Years to expected disease onset | 15.5+14.3 | 13.5+19.4 | 0.866 | - |
| Family diagnosis |  |  |  |  |
| Alzheimer’s Disease | 5 (33%) | 4 (80%) |  |  |
| Frontotemporal Dementia | 10 (67%) | 1 (20%) | 0.069 | - |
| ***Psychological scales*** |  |  |  |  |
| *Personality* |  |  |  |  |
| BigFive Q. - Extraversion | 38.1±9.2 | 45.0±8.1 | 0.230 | 0.237 |
| BigFive Q. - Agreebleness | 45.9±7.9 | 42.6±4.8 | 0.553 | 0.868 |
| BigFive Q. - Conscientiousness | 40.1±10.8 | 47.2±6.4 | 0.168 | 0.216 |
| BigFive Q. - Neuroticism | 38.9±9.8 | 34.2±6.1 | 0.349 | 0.691 |
| BigFive Q. - Openness | 41.6±11.4 | 45.0±5.2 | 0.735 | 0.711 |
| *Anxiety* |  |  |  |  |
| State -Trait Anxiety Inventory - State | 32.1±9.3 | 29.4±6.3 | 0.672 | 0.232 |
| State -Trait Anxiety Inventory - Trait | 40.5±9.5 | 43.0±6.5 | 0.395 | 0.975 |
| *Depression* |  |  |  |  |
| Beck Depression Inventory | 6.1±6.0 | 6.2±5.5 | 0.933 | 0.796 |
| Hamilton Depression Rating Scale | 3.5±3.5 | 3.0±4.1 | 0.672 | 0.541 |
| *Quality of Life* |  |  |  |  |
| SF-12 Physical Composite Score | 51.9±7.0 | 57.6±2.6 | 0.042 | 0.111 |
| SF-12 Mental Composite Score | 44.5±10.5 | 37.8±12.8 | 0.266 | 0.564 |
| WHOQOL – physical health | 74.7±13.8 | 84.8±8.0 | 0.142 | 0.364 |
| WHOQOL – psychological health | 61.3±11.5 | 64.6±9.2 | 0.612 | 0.353 |
| WHOQOL – social health | 66.1±16.7 | 66.6±19.6 | 0.612 | 0.890 |
| WHOQOL – environmental health | 63.7±15.7 | 67.4±10.5 | 0.672 | 0.056 |
| *Coping Strategies* |  |  |  |  |
| Brief COPE – problem focused | 18.9±3.3 | 17.2±3.1 | 0.343 | 0.849 |
| Brief COPE – emotion focused | 25.4±4.6 | 22.4±3.1 | 0.156 | 0.341 |
| Brief COPE - dysfunctional coping | 23.4±3.3 | 23.6±3.5 | 0.893 | 0.929 |
| *Resilience* |  |  |  |  |
| RSA – self | 20.6±4.1 | 24.0±3.8 | 0.219 | 0.164 |
| RSA – future | 10.7±2.7 | 12.8±4.0 | 0.343 | 0.840 |
| RSA – structured style | 15.4±2.0 | 15.4±2.3 | 0.964 | 0.879 |
| RSA – social competence | 23.1±4.2 | 24.4±5.2 | 0.444 | 0.559 |
| RSA – family cohesion | 23.3±4.9 | 25.4±3.7 | 0.391 | 0.439 |
| RSA – social resource | 30.5±4.0 | 29.2±7.4 | 0.687 | 0.791 |
| RSA – personal competence | 31.6±6.2 | 36.8±7.0 | 0.219 | 0.514 |
| *Health-related beliefs* |  |  |  |  |
| MHLOC - internal | 24.8±3.0 | 23.8±5.5 | 0.497 | 0.176 |
| MHLOC – chance | 19.9±7.4 | 20.4±3.5 | 0.933 | 0.820 |
| MHLOC – powerful others | 21.1±2.7 | 19.2±2.8 | 0.266 | 0.204 |

achi-square or Mann-Whitney test bage- and education-adjusted analysis of covariance

SF: Short Form, WHOQOL: World Health Organization Quality of Life, RSA: Resilience Scale for Adults, MHLOC: Multidimensional Health Locus of Control

**Supplementary table 2.** Psychological features of 20 healthy at-risk relatives (see ‘Second consultation’ box in figure 1) included in IT-DIAfN protocol by years to expected disease onset at baseline.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Years to expected disease onset** | |  |  |
|  | <4  n=7 | 5-23  n=13 | Pa | Pb |
| *Personality* |  |  |  |  |
| BigFive Q. - Extraversion | 40.0±10.3 | 39.8±9.1 | 1.000 | 0.135 |
| BigFive Q. - Agreebleness | 44.4±10.2 | 45.5±5.5 | 0.877 | 0.533 |
| BigFive Q. - Conscientiousness | 40.7±9.4 | 42.5±10.9 | 0.757 | 0.236 |
| BigFive Q. - Neuroticism | 38.3±11.5 | 37.5±8.0 | 1.000 | 0.471 |
| BigFive Q. - Openness | 40.0±14.1 | 41.6±11.6 | 0.588 | 0.896 |
| *Anxiety* |  |  |  |  |
| State -Trait Anxiety Inventory - State | 29.0±5.9 | 32.7±9.7 | 0.485 | 0.986 |
| State -Trait Anxiety Inventory - Trait | 37.1±7.1 | 43.2±9.1 | 0.115 | 0.231 |
| *Depression* |  |  |  |  |
| Beck Depression Inventory | 4.1±4.7 | 7.2±6.1 | 0.241 | 0.591 |
| Hamilton depression Rating Scale | 2.4±2.6 | 3.9±4.0 | 0.588 | 0.199 |
| *Quality of Life* |  |  |  |  |
| SF-12 Physical Composite Score | 55.4±2.9 | 52.2±7.9 | 0.485 | 0.413 |
| SF-12 Mental Composite Score | 46.9±3.7 | 40.7±13.3 | 0.485 | 0.197 |
| WHOQOL – physical health | 84.0±8.8 | 73.5±14.0 | 0.081 | 0.421 |
| WHOQOL – psychological health | 67.1±8.2 | 59.5±11.3 | 0.115 | 0.172 |
| WHOQOL – social health | 71.1±20.5 | 63.6±15.0 | 0.275 | 0.332 |
| WHOQOL – environmental health | 73.1±14.3 | 60.1±12.6 | 0.046 | 0.230 |
| *Coping Strategies* |  |  |  |  |
| Brief COPE – problem focused | 19.0±3.7 | 18.1±3.1 | 0.432 | 0.880 |
| Brief COPE – emotion focused | 26.3±3.3 | 23.7±4.8 | 0.261 | 0.504 |
| Brief COPE - dysfunctional coping | 24.1±3.7 | 23.0±3.1 | 0.432 | 0.602 |
| *Resilience* |  |  |  |  |
| RSA – self | 23.4±3.4 | 20.4±4.3 | 0.120 | 0.876 |
| RSA – future | 11.0±4.0 | 11.4±2.7 | 0.592 | 0.313 |
| RSA – structured style | 15.4±2.1 | 15.4±2.0 | 0.592 | 0.826 |
| RSA – social competence | 23.7±4.0 | 23.3±4.7 | 0.967 | 0.167 |
| RSA – family cohesion | 24.9±4.7 | 23.3±4.6 | 0.536 | 0.880 |
| RSA – social resource | 29.7±6.6 | 30.4±3.9 | 0.773 | 0.837 |
| RSA – personal competence | 35.3±7.2 | 31.7±6.2 | 0.536 | 0.744 |
| *Health-related beliefs* |  |  |  |  |
| MHLOC - internal | 25.9±3.0 | 23.9±3.9 | 0.351 | 0.067 |
| MHLOC - chance | 21.3±3.9 | 19.3±7.7 | 0.536 | 0.808 |
| MHLOC – powerful others | 22.7±2.1 | 19.5±2.5 | 0.014 | 0.041 |

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SF: Short Form, WHOQOL: World Health Organization Quality of Life, RSA: Resilience Scale for Adults, MHLOC: Multidimensional Health Locus of Control

**Supplementary table 3.** Sociodemographic and psychological features of 16 healthy at-risk relatives (see ‘Third consultation/Blood draw’ box in figure 1) included in IT-DIAfN protocol by genetic status at baseline.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Genetic status** | |  |  |
|  | *carriers*  n=6 | *non-carriers*  n=10 | Pa | Pb |
| ***Sociodemographics*** |  |  |  |  |
| Age (years) | 41.8±9.9 | 40.1±9.6 | 0.635 | - |
| Gender (F) | 4 (67%) | 6 (60%) | 0.790 | - |
| Education |  |  |  |  |
| Middle | 1 (17%) | 0/9 (0%) |  |  |
| High | 1 (17%) | 4/9 (44%) |  |  |
| University | 4 (66%) | 5/9 (56%) | 0.300 | - |
| Years to expected disease onset | 16.4+14.7 | 13.4+14.8 | 0.713 | - |
| ***Psychological scales*** |  |  |  |  |
| *Personality* |  |  |  |  |
| BigFive Q. - Extraversion | 37.8±5.5 | 39.1±11.0 | 0.958 | 0.998 |
| BigFive Q. - Agreebleness | 49.5±6.1 | 43.7±7.8 | 0.093 | 0.224 |
| BigFive Q. - Conscientiousness | 37.0±11.0 | 42.4±10.1 | 0.263 | 0.520 |
| BigFive Q. - Neuroticism | 42.7±7.0 | 36.9±10.4 | 0.181 | 0.470 |
| BigFive Q. - Openness | 42.7±4.3 | 41.6±14.0 | 0.958 | 0.858 |
| *Anxiety* |  |  |  |  |
| State -Trait Anxiety Inventory - State | 32.3±9.3 | 31.8±9.4 | 0.792 | 0.317 |
| State -Trait Anxiety Inventory - Trait | 39.5±7.1 | 40.2±10.9 | 0.875 | 0.828 |
| *Depression* |  |  |  |  |
| Beck Depression Inventory | 4.2±4.8 | 6.7±6.6 | 0.562 | 0.783 |
| Hamilton depression Rating Scale | 2.0±1.8 | 4.1±4.0 | 0.428 | 0.540 |
| *Quality of Life* |  |  |  |  |
| SF-12 Physical Composite Score | 55.0±5.5 | 50.5±7.3 | 0.220 | 0.416 |
| SF-12 Mental Composite Score | 43.3±9.7 | 45.8±10.9 | 0.492 | 0.652 |
| WHOQOL – physical health | 70.2±13.0 | 78.8±13.9 | 0.263 | 0.494 |
| WHOQOL – psychological health | 68.7±8.8 | 58.7±12.4 | 0.147 | 0.219 |
| WHOQOL – social health | 66.5±12.9 | 66.8±18.7 | 0.875 | 0.851 |
| WHOQOL – environmental health | 64.0±19.7 | 65.6±14.4 | 0.792 | 0.972 |
| *Coping Strategies* |  |  |  |  |
| Brief COPE – problem focused | 17.0±3.7 | 19.3±3.6 | 0.224 | 0.088 |
| Brief COPE – emotion focused | 25.7±4.5 | 25.1±4.7 | 0.776 | 0.789 |
| Brief COPE - dysfunctional coping | 21.3±3.6 | 24.1±3.1 | 0.145 | 0.375 |
| *Resilience* |  |  |  |  |
| RSA – self | 21.8±5.3 | 20.7±3.8 | 0.776 | 0.981 |
| RSA – future | 11.3±3.8 | 11.1±3.1 | 1.000 | 0.691 |
| RSA – structured style | 16.2±2.1 | 15.1±1.8 | 0.529 | 0.256 |
| RSA – social competence | 26.8±2.9 | 21.3±3.6 | 0.008 | 0.032 |
| RSA – family cohesion | 25.2±4.2 | 22.8±5.5 | 0.529 | 0.708 |
| RSA – social resource | 30.8±2.6 | 30.4±4.6 | 0.776 | 0.674 |
| RSA – personal competence | 33.2±8.4 | 32.2±6.4 | 0.955 | 0.893 |
| *Health-related beliefs* |  |  |  |  |
| MHLOC - internal | 22.7±2.7 | 26.1±2.3 | 0.056 | 0.033 |
| MHLOC - chance | 20.3±5.7 | 19.6±8.2 | 1.000 | 0.830 |
| MHLOC – powerful others | 19.5±2.6 | 21.9±2.4 | 0.073 | 0.093 |

achi-square or Mann-Whitney test bage- and education-adjusted analysis of covariance

SF: Short Form, WHOQOL: World Health Organization Quality of Life, RSA: Resilience Scale for Adults, MHLOC: Multidimensional Health Locus of Control

**Supplementary table 4.** Sociodemographic and psychological features of 15 healthy at-risk relatives (see ‘Genetic test disclosure’ box in figure 1) included in IT-DIAfN protocol by T12 follow-up at baseline.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 1. **T12 follow-up** | |  |  |
|  | 1. *completed* 2. n=10 | 1. *not completed* 2. n=5 | 1. Pa | 1. pb |
| 1. ***Sociodemographics*** |  |  |  |  |
| 1. Age (years) | 1. 41.0±10.0 | 1. 39.0±9.8 | 1. 0.679 | 1. - |
| 1. Gender (F) | 1. 5 (50%) | 1. 5 (100%) | 1. 0.053 | 1. - |
| 1. Education |  |  |  |  |
| 1. Middle | 1. 1 (10%) | 1. 0/4 (0%) |  |  |
| 1. High | 1. 3 (30%) | 1. 1/4 (25%) |  |  |
| 1. University | 1. 6 (60%) | 1. 3/4 (75%) | 1. 0.769 | 1. - |
| 1. Years to expected disease onset | 1. 13.5+14.3 | 1. 19.4+15.0 | 1. 0.371 | 1. - |
| 1. Family diagnosis |  |  |  |  |
| 1. Alzheimer’s Disease | 1. 4 (40%) | 1. 1 (20%) |  |  |
| 1. Frontotemporal Dementia | 1. 6 (60%) | 1. 4 (80%) | 1. 0.439 | 1. - |
| 1. ***Psychological scales*** |  |  |  |  |
| 1. *Personality* |  |  |  |  |
| 1. BigFive Q. - Extraversion | 1. 39.0±11.1 | 1. 36.4±4.3 | 1. 0.859 | 1. 0.595 |
| 1. BigFive Q. - Agreebleness | 1. 44.7±8.1 | 1. 48.4±7.6 | 1. 0.513 | 1. 0.428 |
| 1. BigFive Q. - Conscientiousness | 1. 40.1±11.3 | 1. 40.0±10.7 | 1. 0.953 | 1. 0.878 |
| 1. BigFive Q. - Neuroticism | 1. 37.2±10.7 | 1. 42.4±7.2 | 1. 0.310 | 1. 0.358 |
| 1. BigFive Q. - Openness | 1. 42.7±12.9 | 1. 39.4±8.7 | 1. 0.768 | 1. 0.481 |
| 1. *Anxiety* |  |  |  |  |
| 1. State -Trait Anxiety Inventory - State | 1. 30.9±9.9 | 1. 34.4±8.6 | 1. 0.254 | 1. 0.476 |
| 1. State -Trait Anxiety Inventory - Trait | 1. 42.1±10.3 | 1. 37.2±7.4 | 1. 0.440 | 1. 0.392 |
| 1. *Depression* |  |  |  |  |
| 1. Beck Depression Inventory | 1. 5.6±6.4 | 1. 7.2±5.5 | 1. 0.440 | 1. 0.989 |
| 1. Hamilton depression Rating Scale | 1. 4.1±4.0 | 1. 2.2±1.9 | 1. 0.513 | 1. 0.261 |
| 1. *Quality of Life* |  |  |  |  |
| 1. SF-12 Physical Composite Score | 1. 51.5±6.3 | 1. 52.6±9.1 | 1. 0.768 | 1. 0.272 |
| 1. SF-12 Mental Composite Score | 1. 43.4±9.8 | 1. 46.8±12.6 | 1. 0.371 | 1. 0.805 |
| 1. WHOQOL – physical health | 1. 77.1±15.1 | 1. 69.8±10.7 | 1. 0.254 | 1. 0.244 |
| 1. WHOQOL – psychological health | 1. 59.6±12.9 | 1. 64.8±7.8 | 1. 0.440 | 1. 0.482 |
| 1. WHOQOL – social health | 1. 66.8±18.7 | 1. 64.8±13.7 | 1. 0.679 | 1. 0.958 |
| 1. WHOQOL – environmental health | 1. 61.0±17.0 | 1. 69.2±12.3 | 1. 0.310 | 1. 0.598 |
| 1. *Coping Strategies* |  |  |  |  |
| 1. Brief COPE – problem focused | 1. 19.7±2.2 | 1. 16.8±5.1 | 1. 0.304 | 1. 0.077 |
| 1. Brief COPE – emotion focused | 1. 25.1±5.2 | 1. 26.3±3.0 | 1. 0.945 | 1. 0.962 |
| 1. Brief COPE - dysfunctional coping | 1. 23.5±3.7 | 1. 23.0±2.4 | 1. 0.733 | 1. 0.673 |
| 1. *Resilience* |  |  |  |  |
| 1. RSA – self | 1. 21.2±4.1 | 1. 19.3±4.1 | 1. 0.539 | 1. 0.611 |
| 1. RSA – future | 1. 10.5±2.6 | 1. 11.3±3.4 | 1. 0.839 | 1. 0.398 |
| 1. RSA – structured style | 1. 15.0±1.6 | 1. 16.5±2.5 | 1. 0.304 | 1. 0.101 |
| 1. RSA – social competence | 1. 21.8±4.0 | 1. 26.5±2.6 | 1. 0.076 | 1. 0.021 |
| 1. RSA – family cohesion | 1. 23.1±5.4 | 1. 23.8±3.7 | 1. 0.945 | 1. 0.520 |
| 1. RSA – social resource | 1. 30.0±4.4 | 1. 31.8±2.6 | 1. 0.454 | 1. 0.474 |
| 1. RSA – personal competence | 1. 32.1±6.2 | 1. 30.5±6.9 | 1. 0.733 | 1. 0.962 |
| 1. *Health-related beliefs* |  |  |  |  |
| 1. MHLOC - Internal | 1. 25.2±3.1 | 1. 24.0±3.1 | 1. 0.594 | 1. 0.530 |
| 1. MHLOC - Chance | 1. 20.5±7.3 | 1. 18.6±8.3 | 1. 0.679 | 1. 0.948 |
| 1. MHLOC – powerful others | 1. 21.9±2.4 | 1. 19.6±2.9 | 1. 0.129 | 1. 0.117 |

achi-square or Mann-Whitney test bage- and education-adjusted analysis of covariance

SF: Short Form, WHOQOL: World Health Organization Quality of Life, RSA: Resilience Scale for Adults, MHLOC: Multidimensional Health Locus of Control

**Supplementary figure 1.** Spaghetti-plot of raw longitudinal data (T0: baseline; T12: 12-months follow-up) on the RSA planned future and Hamilton Depression Rating Scale in 10 healthy at-risk relatives (see ‘Follow-up’ box in figure 1) included in IT-DIAfN protocol. Dotted lines indicate carriers.

|  |  |
| --- | --- |
|  |  |

**Supplementary figure 2.** Differences between baseline (T0) and 12-months follow-up (T12) on psychological scales in 10 at-risk relatives (see ‘Follow-up’ box in figure 1) included in the IT-DIAfN protocol. Means and C.I., p on Wilcoxon test.

|  |  |  |  |
| --- | --- | --- | --- |
| p=0.553 | p=0.074 | p=0.303 | p=0.888 |
| p=0.202 | p=0.400 | p=0.108 | p=0.799 |
| p=0.126 | p=0.674 | p=0.831 | p=0.075 |
| p=0.105 | p=0.271 | p=0.371 | p=0.675 |
| p=0.234 | p=0.057 | p=0.440 | p=0.240 |
| p=0.097 |  |  |  |