Preclinical signs of impairment in persons at high risk of frontotemporal dementia related to chromosome 3 (FTD3): Preliminary findings in neuropsychological tests

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BACKGROUND

We have studied a large kindred in Jutland with autosomal dominant frontotemporal dementia linked to chromosome 3, the only such family yet known.

1985-7: Initial studies (Gydesen et al., 1987)

1995: Linkage to the pericentromeric region of chromosome 3 (Brown et al., 1995)

2002: Publication of full clinical details (Gydesen et al., 2002)

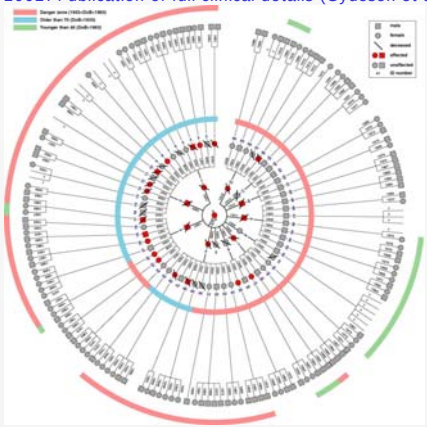

Figure 1. Pedigree

Of the 60 grandchildren, 55 or 58 are offspring of gene carriers.

We estimate that now about 300 individuals are at risk of developing the disease

Figure 2. The family farm of the Jutland pedigree. The original case, born 1876, was a farmer's wife and raised her 12 children on this farm when the photograph was taken c. 1905.

OBJECTIVE

The phenotype in the early phase of the disease is not yet known, and we studied well subjects at risk of developing the disease to detect early signs

METHODS

At risk members of the family and their spouses between 40 and 70 years of age were invited to participate in neuropsychological assessment performed without knowledge of status. 38 family members and 20 spouses participated. Some of the subjects have not yet been haplotyped, and we report preliminary results from comparisons of 20 test measures in 3 well-matched subject groups:
11 high risk subjects, 16 low risk subjects, and 19 spouses.

RESULTS

T-tests without corrections for multiple comparisons showed:

1) No significant differences between the two control groups;

2) A total of 8 significant differences (2 at the .002 level) between high risk family members and controls, all with the high risk subjects impaired.

Trail Making B was impaired relative to both control groups, and significant differences between high risk subjects and one control group (but not both) were found in cognitive estimations, letter-number sequences (a measure of working memory control), immediate (but not delayed) story recall, and one further test (table 1)

CONCLUSION

The pattern of subtle impairments found in the high risk family members is compatible with predominantly frontal involvement. These preliminary results must be confirmed in the full data set and replicated in further cross-sectional and longitudinal analyses in a follow-up, which has been planned for this Autumn.

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Table1. Background variables, estimated intelligence, and results from neuropsychological tests with significant differences between high risk family members and controls.

The two control groups did not differ significantly in any test.

	High risk N=11	Controls 1 (Low risk) N=16	Controls 2 (Spouses) N=19	Comparison 1 (Risk vs. controls 1) p-value	Comparison 2 (Risk vs. controls 2) p-value
Age	53.3 (7.6)	54.3 (8.9)	51.4 (7.3)	NS	NS
Education	11.8 (1.9)	11.6 (2.5)	11.8 (2.1)	NS	NS
DART (IQ estimation)	27.3 (5.8)	28.1 (8.1)	28.5 (5.8)	NS	NS
Design Fluency Regard)	21.1 (6.1)	24.4 (9.8)	27.2 (7.3)	NS	< .05
Clox 2 (copy)	14.1 (.5)	14.3 (.8)	14.5 (.5)	NS	< .05
Trail Making B	103.9 (45.2)	72.5 (27.5)	76.3 (23.6)	< .05	< .05
Cognitive estimations 20 questions)	11.0 (5.1)	7.0 (7.8)	5.5 (3.5)	NS	< .05
Text recall immediate)	19.4 (5.9)	26.6 (5.7)	25.0 (7.9)	< .01	NS
Letter-number sequences (WMS-III)	8.8 (2.3)	11.4 (1.7)	10.2 (2.3)	< .01	NS

Non-significant test results

Neuropsychological tests without significant group differences:

CalCap total RT, correct responses, and false responses; Graded arithmetic (GDA); QS multiplication; Clox 1 (free drawing); Rey copy and 3-min retention; Letter fluency; Category fluency; SDMT; Trail Making A; WAIS Picture Arrangement; Text recall (delayed).

Figure 3. Peter Johannsen, with PET images of case III-22 (MMSE 26) and case III-20 (MMSE 0), both showing severe hypoperfusion of nearly all cortical regions

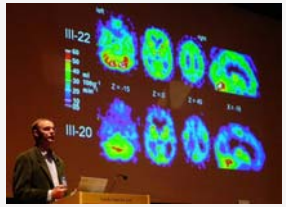

Figure 4. Gaia Skibinski, gene hunter

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