RESEARCH PAPER

Cognitive impairment in the preclinical stage of dementia in FTD-3 *CHMP2B* mutation carriers: a longitudinal prospective study

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Received 2 August 2012
Revised 11 October 2012
Accepted 13 October 2012
Published Online First 10 November 2012

ABSTRACT

Objective and methods A longitudinal study spanning over 8 years and including 17 asymptomatic individuals with *CHMP2B* mutations was conducted to assess the earliest neuropsychological changes in autosomal dominant neurodegenerative disease frontotemporal dementia (FTD) linked to chromosome 3 (FTD-3). Subjects were assessed with neuropsychological tests in 2002, 2005 and 2010.

Results Cross-sectional analyses showed that the mutation carriers scored lower on tests of psychomotor speed, working memory, executive functions and verbal memory than a control group consisting of not-at-risk family members and spouses. Longitudinal analyses showed a gradual decline in psychomotor speed, working memory capacity and global executive measures in the group of non-demented mutation carriers that was not found in the control group. In contrast, there were no significant group differences in domain scores on memory or visuospatial functions. On an individual level the cognitive changes over time varied considerably.

Conclusion Subjects with *CHMP2B* mutation show cognitive changes dominated by executive dysfunctions, years before they fulfil diagnostic criteria of FTD. However, there is great heterogeneity in the individual cognitive trajectories.

INTRODUCTION

Frontotemporal dementia (FTD) comprises a both clinically and neuropathologically heterogeneous group of neurodegenerative diseases, which predominantly affect the frontal and temporal lobes. FTD is an important cause of early-onset dementia, and a positive family history of dementia can be found in 30–50% of cases.[1]

A large Danish family with autosomal dominant FTD caused by mutation in the *CHMP2B* gene on chromosome 3 has been followed closely by a multinational and multidisciplinary research group for more than two decades. Clinical and pathological features of demented family members were first described in 1987,[2] and in 2002 clinical details of 22 cases were reported.[3] In 1995 linkage to chromosome 3 was established,[4] and in 2005 the *CHMP2B* mutation was identified.[5] The clinical phenotype has been described as dominated by early changes in behaviour and personality typical of the behavioural variant of FTD, leading to the term FTD-3. As the disease has a subtle onset and often slow progression, the exact age at onset and therefore duration can be difficult to determine. However, the estimated average age of onset is 58 years of age and the mean duration 10 years, but with great variability.[6] At the stage of clinical dementia, CT scans of FTD-3 patients typically show global cortical atrophy.[7] However, a serial MRI study of nine presymptomatic mutation carriers showed increased atrophy rates in the inferior temporal cortex, superior frontal cortex and the insular cortex when compared to non-carriers,[8] supporting the notion that the disease starts in the anterior brain regions before it spreads to other parts of the brain.

Neuropsychological data on FTD-3 have hitherto only been presented in single-case reports[3] and as preliminary data in a cross-sectional study of family members correlated to haplotypes.[9] While case studies of clinically demented family members have shown severe and generalised cognitive impairment except for preserved episodic memory, the study of preclinical symptoms indicated a pattern of predominantly frontal lobe involvement in subjects with the mutation, years before overt dementia symptoms could be detected.

In this study we present cross-sectional and longitudinal neuropsychological data collected over an 8-year period on non-demented family members with and without the *CHMP2B* mutation. The purpose of the study was to characterise the earliest neuropsychological changes in FTD-3 and thereby contribute to the understanding of this unique cause of neurodegeneration. Specifically, we hypothesise that differences will be found in the direction of poorer performances among family members with the *CHMP2B* mutation.

METHODS

Subjects

Subjects were recruited via a family contact group that distributes information within the FTD-3 family. Family members aged 40–70 and their spouses were invited to participate. Subjects were excluded if they had a formal diagnosis of dementia or a history of other neurological or severe psychiatric illness (such as major depression or psychosis). All family members were anonymously tested for the CHMP2B mutation, and neither the

Table 1 Number of participants

Group	2002	2005	2010	Total number of subjects included	Included in 2002+2005+2010
Mutation carriers	16	10	13	19	9
Non-mutation carriers	23	22	24	32	14
Spouses	17	15	9	22	5
Total	56	47	46	73	28

subjects nor any member of the research group who had contact with the subjects were informed of the genetic status of individual participants. Individuals who expressed a wish to know their genetic status, were referred to formal genetic counselling and testing at the Copenhagen Memory Clinic.

A total of 51 FTD-3 family members (19 mutation carriers and 32 non-carriers) and 22 spouses participated in the study that took place in 2002, 2005 and 2010. Not all subjects were able and willing to participate in all three sessions. Subjects were excluded when they either turned 70 years of age or when they were formally diagnosed with dementia; new subjects over the age of 40 were enrolled as they volunteered. Altogether, 149 neuropsychological examinations were conducted in relation to the study. The number of participants at the three different test sessions is shown in table 1. Of the 16 mutation carriers tested in 2002, two were excluded between 2002 and 2005 due to a dementia diagnosis. Dementia diagnoses were based on a formal clinical assessment unrelated to the testing in the present study. One new mutation carrier was enrolled in 2005 and two in 2010. One carrier was only tested in 2002 and 2010. Five of the 13 mutation carriers tested in 2010 showed clinical dementia signs at that time, but a formal evaluation leading to the diagnosis of FTD-3 dementia was first carried out within the following 2 years. Nine mutation carriers, 14 non-mutation carriers and five spouses were tested at all three sessions.

Genetic testing

Genetic testing was performed at the Institute of Neurology, University College London, UK, and at the Section of Neurogenetics, University of Copenhagen, Denmark. To identify mutation carriers (G to C transversion at position 31449 in *CHMP2B*, GenBank accession number NG_007885), DNA was isolated from EDTA blood samples by standard methods. The mutation was identified by direct sequencing using BigDye Terminator V.1.1 Cycle Sequencing Kit (Applied Biosystems) with the primers 5′-TTT TGT TTT TAC TAG GAG GTG C-3′ or 5′-TTG TAG CCT TTG AAG TAG AGG C-3′ according to the manufacturer's instructions.

Neuropsychological test battery

A battery of internationally employed neuropsychological tests was administered covering six different cognitive domains, but with an emphasis on frontal lobe functions. In order to keep the test session within a reasonable amount of time, we mainly included tests that are short and easily administered.

Episodic memory

Episodic memory was measured using two standard tests: the Logical Memory immediate and delayed recall of stories from the Wechsler Memory Scale Revised (WMS-R)[10] and recall of the Rey Complex Figure after a 3 min delay.[11]

Psychomotor speed

Psychomotor speed was measured using two standard tests: the Symbol Digit Modalities Test (SDMT)[12] and the Trail Making Test parts A and B.[13]

Visuospatial abilities

Visuospatial functions were assessed by the ability to copy Rey's Complex Figure and to draw a clock with the hands set at five past two. Clock drawing was scored using the criteria described in the CLOX test.[14]

Executive functions

A global measure of executive functions, including two separate subscales, was obtained using a combination of tests measuring various aspects of this domain. Deductive reasoning was measured by a 20-item version of the Cognitive Estimation Test,[15] and the Picture Arrangement Test from the Wechsler Adult Intelligence Scale (WAIS)[16] was included as a measure of the ability to integrate and organise information.

Fluency

Fluency tests measure the ability to produce and organise new material. Verbal fluency was measured as the production of words in 1 min within certain categories (animals and fruits/vegetables) and given a starting letter (s and d). Non-verbal fluency was measured using the five-point drawing test.[17]

Working memory

Attention and working memory were assessed by the Letter-Number Sequencing from the WAIS-III[18] and the Graded Difficulty Arithmetic Test.[19]

General intellectual level was assessed using the Danish Adult Reading Test (DART), a Danish equivalent of the National Adult Reading Test (NART).[20] Education index scores were calculated as the sum of years of schooling (7–12) and a level of education index (range 1–5).[21]

Data collection

In 2002, 2005 and 2010, family members and their spouses were invited to family gatherings and information meetings at an inn in Jutland, Denmark, close to the family's origin and where many of the family members still live. As a part of these meetings the neuropsychological testing took place. Five clinical neuropsychologists, who each administered a segment of the short test battery, did the testing. Four of the neuropsychologists were the same at all three meetings, minimising tester influence on results. The subjects moved between five test stations, each session lasting 15–20 min. The neuropsychologists were blind to the subjects' familial and genetic status.

Individuals who were willing to participate in the neuropsychological testing but were unable to attend the meetings were visited and tested by one of the neuropsychologists during the following months when this could be arranged. However, since the participants were healthy, working people with busy family lives, who were geographically spread over the country, this was not always possible.

The study was approved by the local Ethics Committee of Copenhagen and Frederiksberg (KF 01–094/02). Written informed consent was obtained from all participants.

Data analysis

Initial analysis showed that the non-mutation carriers and the spouses did not differ significantly with respect to age, education, estimated intelligence or neuropsychological measures. The two groups were therefore combined into one control group. Individual scores for the six cognitive domains were calculated as follows. First, the raw score data for each test score entering the respective domains were transformed to z-scores. These z-scores were based on the means and SDs of all available values across all subjects at all three time points, that is, from the total of all 149 examinations. Second, the z-scores for the separate tests in each of the six domains were summed and then again z-transformed using the means and SDs of the six summed scores.

The differences between the mutation carriers and controls with regard to demographic variables as well as test and domain scores obtained at first testing were analysed by independent sample t test. Differences on clock drawing, Rey copy and the visuospatial domain scores were assessed with the Mann–Whitney U test because of skewed distributions of scores in the control group. To minimise the risk of low test scores being due to low premorbid intellectual functioning, subjects with a DART score below 12 (n=4) were excluded from the cross-sectional part of the study, but not from the longitudinal part. Since it must be regarded as highly unlikely that the mutation carrier group would perform better than the control group, we have set the significance level, α, at 0.05 one-tailed. Effect sizes for significant differences have been estimated using Cohen's 'd' calculated using the SDs of the control group. Inspection of the distributions for the six domain scores at the three intervals did not reveal any substantial departures from normality, and in only two cases (visuospatial in 2000 and 2002) did Kolmogorov–Smirnov tests show any significant departure from normality. We therefore considered the use of a parametric procedure, namely the mixed model analysis of variance, to be justified.

In order to evaluate cognitive changes over time, the six domain scores were analysed using a mixed-model analysis of variance, with Group (mutation and control) as a between-subject variable and Year (2002, 2005 and 2010) as a repeated measure. Where Mauchley's test for sphericity was significant, the appropriate degrees of freedom were adjusted using the Greenhouse–Geisser epsilon.

RESULTS

Cross-sectional analysis: mutation carriers vs. controls at first testing

Demographic data for the two groups, measured at the time when the subjects were first included into the study, are shown in table 2. No significant differences were found with respect to age, gender, educational level or DART scores between the 17 mutation carriers and the 51 controls.

Group comparisons of cognitive domain scores are shown in table 3. Significant differences were found in two domains: visuospatial (p=0.01) and psychomotor speed (p=0.04). There was a trend towards significance for executive functions (p=0.06) and working memory (p=0.07). In each case, the mutation group performed worse than the control group and the effect sizes ranged from 0.47 to 1.2, that is, what Cohen characterised as 'medium' to 'large'.[22] Comparison on single test performances showed that the mutation group performed significantly poorer than the control group on six of the 14 measures: Picture Arrangement, Symbol Digit Modalities Test, Letter–Number Sequencing, Logical Memory, Design Fluency and Trail Making Test B. Cohen's d for these comparisons ranged from 0.43 to 0.76.

Longitudinal analysis: mutation carriers and controls followed over 8 years

Nine mutation carriers and 19 controls were tested at all time points. The groups did not differ significantly with respect to background variables (table 2) or cognitive domain scores at the first visit in 2002. In order to describe the pattern of neuropsychological changes in the years preceding the clinical onset of dementia, domain scores from the two groups at the three time points were analysed.

Means for all six cognitive domains for the two groups are shown in figure 1. In the analysis of the Memory domain a significant effect of Year was found ($F(2,52)=5.35$, $p=0.008$), but there was no significant effect of Group and no significant interaction. Similarly, in the analysis of the Visuospatial domain there was a significant effect of Year ($F(2,52)=4.58$, $p=0.015$) but no significant effect of Group or interaction. In the Psychomotor Speed domain the effects of Year ($F(1,26)=10.55$, $p=0.001$), Group ($F(1,26)=4.62$, $p=0.041$) and the interaction between them ($F(2,52)=5.67$, $p=0.012$) were all significant. Likewise for the Executive domain, there were significant effects of Year ($F(1.6,40.4)=4.11$, $p=0.033$), Group ($F(1,26)=6.8$, $p=0.015$) and the interaction between them ($F(1.26,40.4)=7.4$, $p=0.004$), and again for the Working Memory domain the effect of Year ($F(2,52)=6.53$, $p=0.003$), Group ($F(1,26)=8.7$, $p=0.007$), and the interaction ($F(2,52)=3.42$, $p=0.004$) were significant. For the Fluency domain there was only a significant effect of interaction between Year and Group ($F(2,52)=6.94$, $p=0.008$).

In order to elucidate the above interactions we conducted series of post-hoc t tests comparing the carrier and control groups on all six domains at each year of assessment separately. As stated above, the two groups did not differ significantly on any domains in 2002. In 2005, the carrier group performed significantly worse on the Executive, Fluency and Working Memory domains ($p<0.05$) and near-significantly worse on the Psychomotor Speed domain ($p=0.052$). This pattern was repeated in the results from 2010 where the two groups differed significantly on the same four domains ($p<0.02$).

Table 2 Demographic characteristics, first testing (mean, SD)

Group	Age	Education	DART	Gender (M/F)
Mutation carriers, all participants (n=17)	51.1 (7.5)	12.6 (2.0)	27.2 (5.1)	10/7
Control group, all participants (n=51)	51.1 (7.7)	12.2 (2.2)	30.4 (7.2)	24/27
Mutation carriers, tested at all three sessions (n=9)	51.6 (5.0)	12.2 (2.2)	25.4 (8.6)	6/3
Control group, tested at all three sessions (n=19)	49.4 (5.9)	12.4 (2.1)	29.1 (7.7)	10/9

All group comparisons are non-significant.
DART, Danish Adult Reading Test.

Table 3 Performance on first testing

Cognitive domain/test	Mutation carriers (n=17)	Control group (n=51)	p Value	Cohen's d
Psychomotor speed	−0.11 (0.54)	0.22 (0.70)	0.04	0.47
Symbol Digit Modalities Test	40.8 (7.6)	46.1 (12.3)	0.02	0.43
Trail Making A	36.3 (11.8)	31.9 (12.7)	0.11	
Trail Making B	86.0 (35.5)	71.9 (28.3)	0.05	0.50
Memory	0.00 (0.69)	0.18 (0.74)	0.20	
Logical memory (WMS-R), total recall	41.4 (12.4)	47.8 (12.2)	0.03	0.52
Rey Complex Figure test, 3 min recall	20.4 (5.8)	19.7 (6.5)	0.34	
Visuospatial function	−0.08 (0.65)	0.26 (0.62)	0.01	0.55
Rey Complex Figure test, copy	34.8 (1.3)	35.2 (1.2)	0.14	
Clock drawing free hand	12.7 (1.9)	13.6 (1.7)	0.45	
Executive functions	−0.39 (0.40)	0.17 (0.49)	0.06	1.14
Working memory	−0.59 (0.75)	0.25 (0.70)	0.07	1.2
Letter number sequencing (WAIS-3)	9.2 (2.1)	10.4 (2.2)	0.03	0.55
Graded difficulty arithmetic test	13.1 (5.0)	14.1 (5.1)	0.25	
Fluency	0.03 (0.51)	0.05 (0.64)	0.44	
Verbal fluency, category	42.8 (9.2)	41.0 (7.8)	0.22	
Verbal fluency, lexical	26.1 (7.5)	24.8 (7.7)	0.28	
Design fluency (a.m.Regard)	22.4 (5.2)	26.1 (8.0)	0.04	0.46
Other executive measures				
Picture arrangement, WAIS	18.0 (6.0)	22.4 (5.8)	0.01	0.76
Cognitive estimations, 20 items (errors)	7.8 (5.5)	6.8 (5.3)	0.25	

Domain scores are reported as z-scores (mean and SD). Single test scores are reported as raw scores (mean and SD).

Individual profiles

Figure 2 shows changes in the individual cognitive profiles for the nine mutation carriers who were tested in all 3 years. Demographic data and clinical observations are listed in table 4. In order to maintain the subjects' anonymity, gender is not listed, and age and education are listed as range scores. For carriers 1 and 2 no cognitive decline could be discerned over the eight-year period, and dementia has still not been diagnosed in either of these two carriers. After having recovered from a depressive episode, carrier 2 was referred for dementia

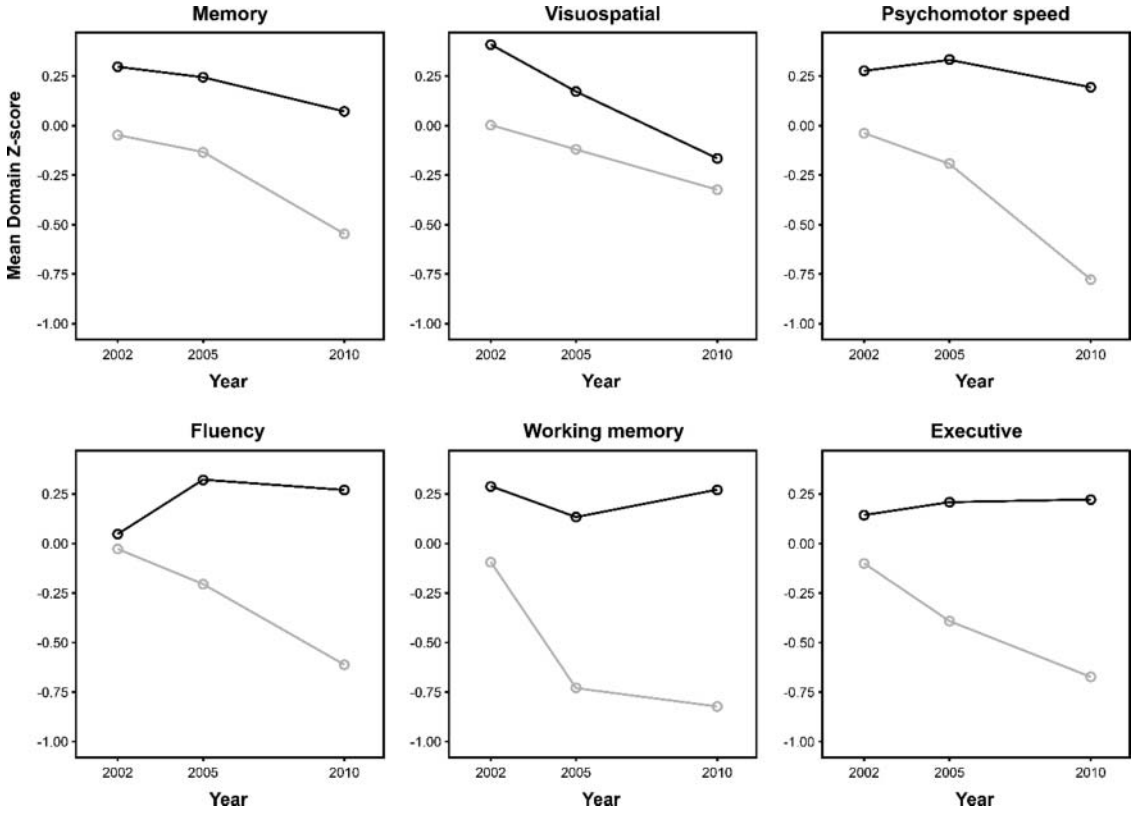

Figure 1 Profile plots for the six cognitive domains. Domain z-scores are shown on the y-axis. Control group (n=19), mutation carriers (n=9).

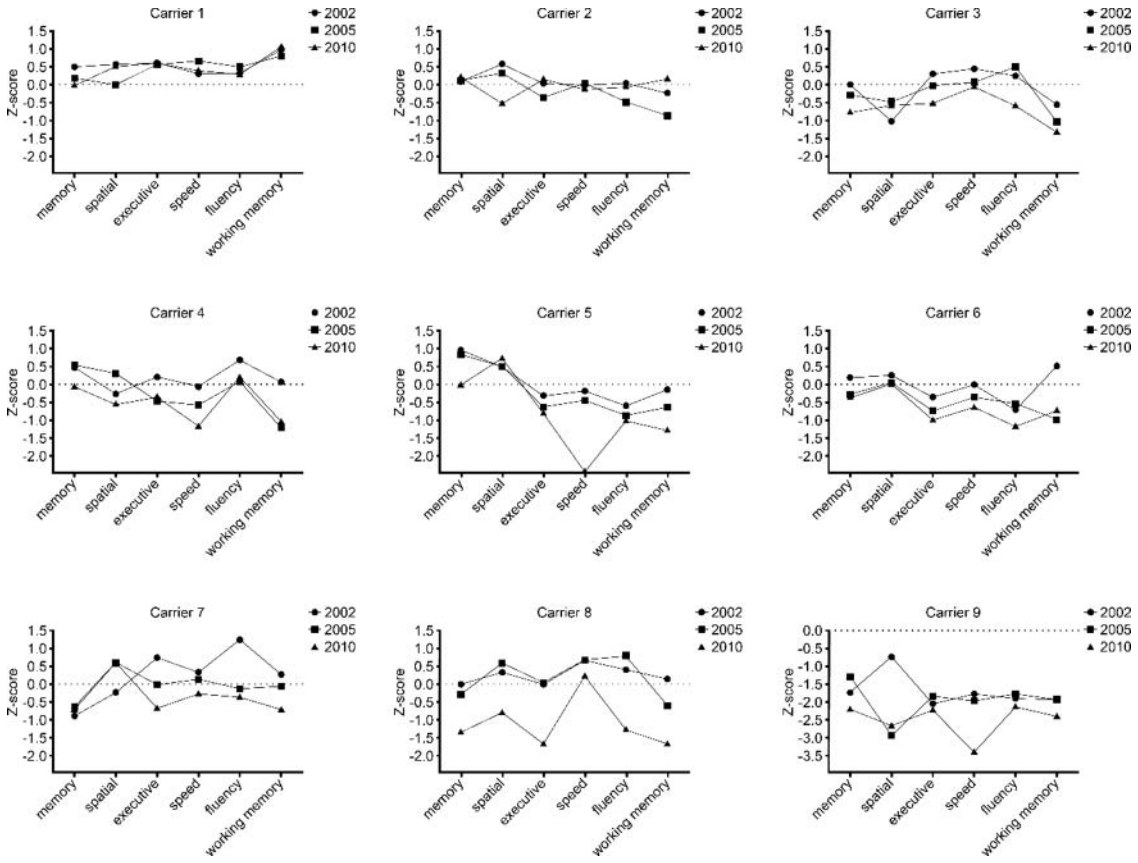

Figure 2 Cognitive profiles for the nine mutation-carriers tested at all three time points. Cognitive domain scores are shown as z-scores on the y-axis.

evaluation in the summer of 2012. An evaluation programme, including neurological examination, behavioural assessment, detailed neuropsychological testing, and a PET-FDG scan did not show any definite signs of early dementia. For carriers 3 and 4, a decline was moderate but detectable in most domains. From a clinical perspective, carrier 3 was the one with the most profound behavioural changes, and was formally diagnosed with FTD-3 shortly after the testing. For carriers 5, 6, 7 and 8, a much more marked cognitive decline is visible, and all four have a profile characteristic of FTD with dominant impairment in working memory and executive functions. Carrier 5 also showed a severe impairment in psychomotor speed. All three showed discrete clinical signs of early dementia at the last testing. Carrier 7 was formally diagnosed one year later and carrier 5, two years later. Carrier 8 showed a marked decline in most domains from 2005 to 2010, and was diagnosed with FTD-3 half a year after the last testing. Apart from executive dysfunctions, she also had profound memory problems and severe anomia, not reflected in our test battery. Carrier 9 was dyslexic and performed poorly on most cognitive tests already in 2002. A further decline is reflected during the 8-year period, but a formal referral to dementia evaluation was not made until 2011.

Table 4 Background information for mutation carriers whose cognitive profiles are shown in figure 2

Carrier	Age group, 2002	Education	Comments
1	2	13	No suspicion of symptoms by subject or family.
2	2	13	Discrete behavioural changes noted by family in 2010. Depression in winter 2011–12. Formal evaluation in summer 2012: no clear signs of dementia.
3	2	15	Severe behavioural changes. Dementia diagnosed in 2010.
4	3	11	No reported symptoms.
5	1	13	No reported symptoms in 2010. Dementia diagnosed in 2012.
6	3	10	No reported symptoms.
7	3	14	Discrete cognitive and behavioural changes. Dementia diagnosed in 2011.
8	2	13	General impairment and severe language problems. Behavioural changes. Diagnosed with dementia in 2011.
9	4	8	Low premorbid level. Clinically demented. Diagnosed in 2011.

Age: 1: 41–45, 2: 46–50, 3: 51–55, 4: 56–60. Exact age is not listed to keep data blinded to participants. Education: Years of schooling (7–12)+level of education (1–5).

DISCUSSION

Our study shows than cognitive impairment can be detected several years before the development of manifest dementia symptoms in *CHMP2B* mutation carriers. Cross-sectional analysis showed that asymptomatic mutation carriers as a group scored lower on several neuropsychological tests of psychomotor speed, working memory, executive functions and verbal memory compared to a control group consisting of family members without the *CHMP2B* mutation and spouses. This could reflect either an early effect of the mutation, a less than perfect matching of groups in spite of insignificant

differences in demographic variables, or a combination of the two. In the 8-year longitudinal analysis we saw a gradual decline in psychomotor speed, working memory capacity and global executive measures in the group of non-demented mutation carriers that was not found in the control group. In contrast there were no significant group differences with regard to changes on domain scores of memory or visuospatial functions. This clearly supports the classification of *CHMP2B*-related dementia as a form of FTD, with a neuropsychological profile very different from what we see in, for instance, Alzheimer's disease. How these specific neuropsychological changes relate to the underlying molecular pathology caused by mutant *CHMP2B* is not currently clear, but the recent development of a mouse model of *CHMP2B* mutation may provide insight in the future.[23] In recent studies of presymptomatic FTD-3 family members (only partly overlapping with our group) on generalised brain atrophy[24] and brain tissue perfusion changes as measured with MRI,[25] changes tend not to be confined to the anterior parts of the brain. Nevertheless, the present study indicates that the functional effect measured by neuropsychology tends to be more 'frontal'.

The early impairment in the psychomotor speed domain might suggest a subcortical element in the disease. However, the decline on this domain reflects a reduced performance on the SDMT and Trail Making B. Both tests are known to be among the most sensitive measures of overall brain damage, and both measure divided attention as well as psychomotor and mental processing speed. Impaired performance on these tests, but not on Trail Making A, might therefore suggest that the executive components play a significant role. With regard to memory, the two groups performed equally on the domain score, but the mutation carriers did score lower on the logical memory test than the control group. A low score on this test might of course reflect impairment in verbal memory per se, but the test is also very sensitive to attention deficits as it requires that the subjects reproduce two stories that are read to them only once. As indicated above, interpretation of neuropsychological test scores is often not straightforward, as most tests draw on several cognitive functions. For instance, impaired scores on a memory test might reflect problems in attention or executive functions. In our study, we attempted to minimise this problem by constructing domain scores based on several test scores. Another issue to consider when comparing scores on neuropsychological tests is whether the tests are similar with regard to sensitivity. If, for instance, the memory tests were much less sensitive than the executive tests, this could explain our result. However, most tests included in this study have high sensitivity, as we wanted to be able to detect early and subtle neuropsychological changes. In particular, it should be noted that the memory domain included the WMS-Logical Memory and Rey Complex Figure tests, both of which are cognitively demanding. Copying the Rey Figure can also be considered a complex visuospatial task, but both this and the clock drawing test can be viewed as all-or-none tests, with skewed distributions among healthy individuals. As such they might not have been the best choice as measures of visuospatial functions.

In retrospect, a sensitive naming test would have improved our test battery. Anomia is a common early symptom in FTD and has also been reported in several FTD-3 cases when the patients have come to neuropsychological testing as part of a formal diagnostic assessment. The only language measures included in this study are the two verbal fluency tests. These tests tap the individual's ability to generate (search and organise) words according to either a semantic category or a starting letter/phonological sound. As such they are sensitive to executive as well as language dysfunctions. We found no difference on any of the verbal fluency tests between the mutation carriers and the controls at first testing, and when looking at changes in individual profiles over time, the fluency measures in general seem more stable than the other two executive measures (working memory and global executive functions). This indicates that language is usually spared in the preclinical phase of FTD-3, but this clearly needs to be investigated further.

Changes in personality and behaviour are the hallmarks of FTD, and several reports of such changes early in the disease course was the reason that this family disease was first classified as an FTD variant.[3 4] A systematic assessment of the earliest behavioural changes in CHMP2B mutation carriers would of course be tremendously interesting, but was unfortunately not possible to carry out within this design. Valid information about behavioural changes must be obtained from systematic interview with a near relative using, for instance, the Frontal Behavioural Inventory (FBI)[26] or the Cambridge Behavioural Inventory (CBI).[27] In 2002 we did in fact administer the FBI to all subjects who came as a couple, but realised that there were too many missing data to make this effort meaningful. Other approaches to characterise the behavioural changes in FTD-3 are presently being considered.

We have shown that early cognitive deficits most often are found in either working memory tests or other executive measures, but cannot point to specific tests that are better than others at detecting the early symptoms of FTD-3. It is possible that future studies, applying newer executive measures, such as the Hayling and Brixton Tests,[28] as well as more extensive language measures and tests of social cognition, will prove to be better at detecting early dementia in *CHM2B* mutation carriers.

To our knowledge this is the only longitudinal study of preclinical neuropsychological data of a genetically defined sample of future FTD patients. Despite the overall picture of cognitive deficits predominantly involving frontal lobe functions, thus supporting the classification of *CHMP2B*-related dementia as a form of FTD, our study also shows great individual variation in the phenotypic presentations in patients with *CHMP2B* mutations. In this family we see typical behavioural forms of FTD with minimal cognitive impairment as well as patients with severe cognitive symptoms but minimal early changes in affect and behaviour. The individual cognitive profiles also vary: some patients show a typical dysexecutive syndrome, while others develop dementia with a more general cognitive decline, and in a few patients severe anomia has been noticed. In some patients we see very slow and gradual progression with mild cognitive symptoms many years before the patients fulfil the clinical diagnosis of dementia, and in other cases the disease course is much more rapid with a more sudden and severe cognitive decline. Such variations in phenotypic presentations have also been reported in several other autosomal dominant dementias,[1] including between individuals in the same family with the same genetic mutation,[29 30] which shows that there is no direct relationship between the underlying mutation and the range and extent of clinical presentations in patients with neurodegenerative diseases. This is likely to be explained by a combination of environmental and genetic causes. For instance, differences in expression level of the non-mutated *CHMP2B* allele is one of many possible factors that could influence disease phenotype.

In conclusion, we present the first longitudinal preclinical neuropsychological test data for *CHMP2B* mutation carriers revealing, over an 8-year period, a gradual decline in psychomotor speed, working memory capacity and global executive

measures with relative sparing of episodic memory and visuo-spatial functions, supporting the classification of *CMHP2B* related dementia as a form of FTD.

Acknowledgements The authors thank Birgitte Fagerlund, Anne Melsen, Rune Nielsen, Hanne Udesen, Asmus Vogel and Tine Wøbbe for help with data collection. The FReJA group wishes to thank Direktør Einar Hansen og hustru Fru Vera Hansens fund for financial support.

Contributors All authors have been involved in the planning and conduction of the study, as well as the analysis and interpretation of data. JS, AG, JB, PJ and TWT have primarily been responsible for the clinical data. TTN, JEN and AI have been responsible for the genetic analysis. All authors have been engaged in drafting the article and revising it critically for important intellectual content. All authors have approved the submitted, revised version.

Funding This work was supported by Direktør Einar Hansen og hustru Fru Vera Hansens fond, the Danish MRC (grant 22-04-0458) and the Medical Research Council UK.

Competing interest None.

Ethics approval The local Ethics Committee of Copenhagen and Frederiksberg (KF 01-094/02).

Provenance and peer review Not commissioned; externally peer reviewed.

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J Neurol Neurosurg Psychiatry 2013 84: 170-176 originally published online November 10, 2012
doi: 10.1136/jnnp-2012-303813