FRONTO-TEMPORAL DEMENTIA

a clinical and genetic-epidemiological study

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FRONTO-TEMPORAL DEMENTIA

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FRONTO-TEMPORALE DEMENTIE

een klinische en genetisch-epidemiologische studie

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CONTENTS

* For reason of uniformity, the term 'hereditary Pick disease' (chapter 8) and 'frontal lobe dementia' (chapter 4) in earlier, published, papers has been consistently changed into 'fronto-temporal dementia' (FTD), as used in the later papers. Accordingly the terminology in chapter 2-10 is uniform.

The main results in this thesis are reported in the following papers:

Familiaire vormen van frontotemporale dementie.
Stevens M, Van Swieten JC, Van Duijn CM, Tibben A, Niermeijer MF.
Nederlands Tijdschrift voor Geneeskunde 1995;139:871-875.

Preparing for presymptomatic DNA-testing for early onset Alzheimer disease / Cerebral Haemorrhage and Hereditary Pick Disease.
Tibben A, Stevens M, De Wert GMWR, Niermeijer MF, Van Duijn CM, Van Swieten JC.
Journal of Medical Genetics 1997;34:63-72.

Apolipoprotein E gene and sporadic frontal lobe dementia.
Stevens M, Van Duijn CM, De Knijff P, Van Broeckhoven C, Heutink P, Oostra BA, Niermeijer MF, Van Swieten JC.
Neurology 1997;48:1526-1529.

Hereditary frontotemporal dementia is linked to chromosome 17q21-q22: a genetic and clinico-pathological study of three Dutch families.
Heutink P*, Stevens M*, Rizzu P, Bakker E, Kros JM, Tibben A, Niermeijer MF, Van Duijn CM, Oostra BA, Van Swieten JC (*both authors contributed equally to this study).
Annals of Neurology 1997;41:150-159.

Familial aggregation in fronto-temporal dementia.
Stevens M, Van Duijn CM, Kamphorst W, De Knijff P, Heutink P, Van Gool WA, Scheltens Ph, Ravid R, Oostra BA, Niermeijer MF, Van Swieten JC.
Neurology 1998, in press.

Clinical heterogeneity in fronto-temporal dementia linked to chromosome 17.
Stevens M, Kamphorst W, Kros JM, Van Duijn CM, Heutink P, Ravid R, Kuyt LP, Tibben A, Oostra BA, Niermeijer MF, Van Swieten JC.
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Once revealed, no more to be concealed: pitfalls in genetic research on neurodegenerative disease: the case of fronto-temporal dementia.
Stevens M, De Wert GMWR, Niermeijer MF, Van Swieten JC, Tibben A.
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Chapter 1

General introduction:

review and objectives of the study

GENERAL INTRODUCTION

1.1 HISTORICAL REVIEW OF PICK'S DISEASE

At the turn of the nineteenth century into the 20th century many leading neurologists were active to devise new pathological or clinical classifications of the large group of dementing illnesses in later life, the 'dementia senilis'. Until then that eponym included every psychiatric, behavioral and cognitive disturbance, occurring after middle age and leading to complete deterioration of the mental functions.

In 1892, Arnold Pick (1851-1924), professor in neurology and psychiatry at the German University of Prague, reported a patient with a two-year history of progressive 'feeble-mindedness', behavioral disturbances and eventually aphasia.[1] Focal temporal atrophy of the brain was found at autopsy. Pick subsequently described a few more cases with frontal and temporal atrophy and considered this focal pathology as a localized type of 'senile dementia' and not a distinct disease-entity.[2] However he suggested a possible clinical-pathological relation without being specific.

Alois Alzheimer (1911) described the microscopical findings to become associated with 'Pick's disease'[3]: neuronal loss, spongiosis and gliosis in the frontal and temporal cortex, argentophilic granules in the neuronal cytoplasm pushing the nucleus towards the cell body (Pick bodies), and swollen neurons (Pick cells) in the absence of neurofibrillary tangles and plaques.

Van Mansvelt (1953), in a review, classified Pick's disease according to the localization of atrophy into three types: frontal, temporal and mixed.[4] Pick bodies were reported in only one third of the cases. For a diagnosis of Pick's disease at that time, Pick bodies were not essential. Constantinidis (1974) classified frontotemporal atrophy into three types based on the presence of Pick bodies and Pick cells: (1) cases with Pick bodies and swollen neurons, (2) cases with only swollen neurons, and (3) cases without Pick bodies and Pick cells.[5]

Fronto-temporal dementia in the absence of Pick bodies became also described by Brun as 'frontal lobe degeneration of non-Alzheimer type'.[6]

Neary reported 15 cases with 'dementia of frontal lobe type'.[7] Recently, the Manchester and Lund groups introduced the term 'fronto-temporal dementia' (FTD) to include new entities as 'dementia of non-Alzheimer type', 'dementia lacking distinctive histologic features' and 'dementia of frontal lobe type', whereas the diagnosis Pick's disease is set aside for fronto-temporal dementia with Pick bodies.[8,9]

1.2 EPIDEMIOLOGY

Since the recent nature of the definition of FTD, including Pick's disease, and continuing use of old classifications of early onset dementias, accurate figures on prevalence and incidence of FTD and Pick's disease are not available. Moreover, the few clinical and post-mortem studies on FTD often give no data on the proportional occurrence of this condition within the total group of demented patients. Heterogeneous case-finding and diagnostic methodologies do not allow any reliable epidemiological figures before the second half of this century, and in recent years only estimates are possible (see chapter 3 of this thesis). Pick's disease, as defined by Tissot including Pick bodies, was found in a post-mortem study in a ratio of 1 : 10 to Alzheimer's disease.[10] In a Swedish pathology department series 20 cases with FTD (=12%) in 158 cases with organic dementia were seen between 1967-1987, and four cases of Pick's disease were diagnosed.[6] FTD was found in 3% of an autopsy series (n=460) with dementia, and in 10% of cases younger than 70 years.[9] Another such series (n=345) gave a figure of 9% for FTD without Pick bodies and 1% for Pick's disease.[11] In other studies Pick's disease has also been diagnosed in a minority of FTD cases.[9-12]

1.3 FAMILIAL OCCURRENCE

Pick's disease in a 56-year-old woman with psychosis, behavioral changes and mutism, having a mother dying of dementia at 50 years prompted Gans (1923) to propose a genetic connection, similar as he had found in a reported family with dementia in a grandfather, father and two

cousins.[13,14] Dementia with a long prodromal history of personality and behavioral changes in multiple cases in one or multiple generations became reported between 1930-1940.[15-19]

Sanders and Schenk reported an autosomal dominant transmission in a family of 4 generations with 17 affected persons; the diagnosis was confirmed by neuropathological study in 4 cases.[20,21]

A significant difference in age of onset of dementia in two families and a tendency toward an earlier age of onset in successive generations was also observed.[22]

A family history positive for dementia has been reported in 19-60% in recent studies (see also chapter 3 of this thesis).[14,23-25] However, the relationship with the index case in the family was not always specified. Possibly related non-Alzheimer dementias transmitted in families became also reported.[26,27]

1.4 CLINICAL HETEROGENEITY IN FRONTO-TEMPORAL DEMENTIA
(usually sporadic or genetic status undetermined)

The age of onset of FTD is usually between 40 and 60 years, with a peak around 55 years.[4,7,23,28,29] Occasionally an earlier (< 30 years) or later onset (> 70 years) were observed.[4,15,29,30] The mean duration of illness varied between 5 and 10 years in large pathologically verified series.[7,9,11,22,23,28] Women seemed more often affected than men in older reports, whereas the ratio is about 1 : 1 in recent series.[4,7,10,23]

FTD can be clinically differentiated from Alzheimer's disease (AD).[7,28,31] A structured questionnaire using clinical information has shown distinct profiles for FTD and AD.[32] Changes in behavior, especially disinhibition, roaming and hyperorality are significantly more frequent in FTD than AD, whereas early amnesia is consistent with AD. Speech changes may also differentiate FTD from AD.[28,33,34]

Loss of initiative, disinhibition, and stereotypic and perseverative behavior are prominent early features in FTD. Loss of insight, lack of judgement and of emotional concern develop invariably. Some clinical symptoms may predominate, like an apathetic, a disinhibited or a

stereotypic form.[31] Social withdrawal is a prominent feature in some patients.[29] Changes in eating habits (preference for sweets) and considerable weight gain are frequent (60-80%).[7,23,29,35]

Speech production becomes gradually reduced in all patients. Some experience word-finding problems.[29,36] Stereotypic phrases and echolalia frequently occur before mutism eventually develops.[7,30]

Early psychiatric symptoms like psychotic episodes, delusions and hallucinations were observed in one series (6/20) of FTD[23], but not in others.[7,28]

Neuropsychological testing shows distractibility and impaired attention. Orientation in time and place, and memory for recent events remain intact, although formal memory testing is frequently impaired. Impulsivity, impersistence, loss of abstract thinking, reduced verbal fluency, perseveration and difficulties in set shifting (for example in the Wisconsin Card Sorting test) are characteristic features in FTD. Comprehension is usually intact.[7,29] Selective language deficits and word retrieval problems are incidentally found.[37] Visuospatial functions generally remain intact.

These features are included in the consensus statement of criteria for FTD proposed by the Manchester and Lund groups (Appendix).[8]

1.5 NEUROIMAGING

An enlarged Sylvian fissure in a patient with progressive language deficits and behavioral changes was the first reported CT anomaly (1982).[38] Subsequent (3 years) neuropathology showed frontal and temporal degeneration with Pick bodies. The CT pattern of frontal and temporal atrophy became confirmed in other pathologically confirmed cases of Pick's disease and clinical series of FTD.[9,28,29,36,39] However, the CT scan may be normal, especially in the initial phase of the disease.[28]

A frontotemporal or anterior hypoperfusion on SPECT, found in clinical series of FTD, correlated strongly with the pathological diagnosis.[7,29,33,40,41] An asymmetric pattern of perfusion has been reported in some cases.[42] A decreased glucose metabolism on PET scan was reported in cases with a neuropathological diagnosis of Pick's disease.[43,44]

1.6 GENETIC STUDIES

A search for a possible prion mutation as cause for hereditary FTD was negative.[45,46]

The first attempt of gene localization (Wilhelmsen) demonstrated linkage to chromosome 17 in a family with autosomal dominant inheritance of disinhibition-dementia-parkinsonism-amyotrophy complex, characterized by initial behavioral changes followed by cognitive decline and parkinsonism.[39,47] The locus was mapped to a 12 cM region on 17q21-22. Subsequently, progressive subcortical gliosis (2 families) and autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration (one family) were mapped to this region (Table 1).[48,49] These conditions show clinical and pathological similarities with respect to the age of onset, presenting and subsequent symptoms and most affected brain regions, but there are also differences as discussed in chapter 8.[39,50,51] In 1997 an international conference proposed 'fronto-temporal dementia and parkinsonism linked to chromosome 17' (FTD-17) as the new term including all such families with evidence for linkage to a 2 cM region on 17q21-q22 (Table 1).[52]

An early study on the distribution of apolipoprotein E genotypes in FTD cases, established as a risk factor in Alzheimer's disease, showed no association of a specific Apo E allele with FTD.[53,54,55] However, our studies suggested an association of ApoE4 with FTD, most pronounced in the cases with a negative family history for dementia.[25,56]

1.7 MOLECULAR PATHOLOGY

Until now neither electron-microscopical nor biochemical analyses have given a clue on a possible disease mechanism in FTD. The recently introduced designation of tauopathy for one form of familial FTD-17 does suggest such a mechanism and seems attractive by the localization of a gene involved in tau synthesis in the chromosomal region of interest.[57-59] How attractive this hypothesis might be, it is still too early to explain any possible molecular pathology. Recently a possible classification based on different types of tau pathology was described. Immunoblotting of tau protein extracted from filaments shows variable bands, enabling differentiation of some types of FTD-17 and Alzheimer's disease.[58]

Table 1.

Clinical and pathological characteristics of families with fronto-temporal dementia and parkinsonism linked to chromosome 17.[52]

Characteristics	Original nomenclature							
	DDPAC	PPND	FMST	PDP	HFTD	Duke	HDD	AusF
Number of cases/ total relatives	13/33	35/303	41/383	18/60	113/475	16/41	21/475	26/172
Mean age of onset (yr)	45	43	49	53	46-63	55	62	53
Mean duration (yr)	13	8.6	10	13	8.2-8.7	9.2	8	9
Clinical symptomatology								
dementia	+	+	+	+	+	+	+	+
frontal symptoms	+	+	nm	+	+	+	+	+
disinhibition	+	nm	nm	+	+	+	+	+
loss of initiative	nm	+	nm	+	+	+	nm	+
parkinsonism	+	+	+	-	+	+	+	+
Distribution of degeneration								
frontal cortex	+	+	+	+	+	+	+	+
temporal cortex	+	+	+	+	+	+	+	+
basal ganglia	+	+	+	+	+	+	+	+
substantia nigra	+	+	+	+	+	+	+	+
Microscopic neuropathology								
neuronal loss	+	+	+	+	+	+	+	+
gliosis	+	+	+	+	+	+	+	+
spongiosis	+	-	+	+	+	nm	+	+
ballooned cells	+	+	+	nm	+	nm	-	+
Ag and/or τ+ inclusions*	+	+	+	+	-	-	-	-
white matter gliosis	+	+	+	nm	+	nm	-	nm

DDPAC[47,50] = disinhibition-dementia-parkinsonism-amyotrophy complex
PPND[49,51] = autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration
FMST[58,59] = familial multiple system tauopathy with presenile dementia
PDP[60,61] = familial presenile dementia with psychosis and neurofibrillary tangles
HFTD[62,63] = hereditary fronto-temporal dementia (three Dutch families)
Duke[64] = frontotemporal dementia (Duke university family)
HDD[65,66] = hereditary dysphasic dementia
AusF[67] = autosomal dominant non-Alzheimer dementia (Australian family)

+ = present; - = absent; nm = not mentioned
* = argyrophilic and/or tau positive neuronal inclusions[52]

1.8 PSYCHOLOGICAL AND ETHICAL ISSUES

An increasing number of late-onset neurodegenerative diseases became defined at the molecular level in the last decade, enabling improved diagnosis and presymptomatic testing. Examples are Huntington's disease, hereditary cerebral haemorrhage with amyloid (Dutch type) and some types of familial, early onset Alzheimer's disease.[68] Although gene localization and identification of mutations in a gene may lead to fundamental insight into the functions of this gene, participation in pedigree and linkage studies is a potential burden to patients and family members spanning several generations. Follow-up studies in families with Alzheimer's disease or Huntington's disease showed a variety of psychosocial, legal and ethical problems and dilemmas in individuals at risk.[69-75] Psychosocial effects of predictive DNA-testing have been extensively studied in Huntington's disease, and guidelines for predictive testing have been formulated.[72] However, these guidelines did not address the effects of family studies for establishing linkage and gene identification, which is usually the first confrontation of a family with their genetic problem. Some individuals become aware of the genetic risk for a still incurable disease and only a possible expectation for a future predictive testing program.[69,71,76]

1.9 OBJECTIVES OF THE PRESENT STUDY

The first question addressed in this study was the estimation of familial aggregation in fronto-temporal dementia in the Netherlands.

A review and analysis of part of our family study on FTD were presented to the Dutch medical specialists (chapter 2). This facilitated a nation-wide inventory (updated during more than 3 years) for FTD cases.

All patients with the clinical diagnosis FTD and with an age of onset before the age of 65 years were included in a genetic-epidemiological study, and the occurrence of dementia in first degree relatives was studied (chapter 3). This study will also provide prevalence data on FTD in the Netherlands (population 15 millions), as ascertainment was as complete as possible.

A possible association with Apo E alleles in FTD, as were found as risk factors for Alzheimer's disease, was analyzed in our series (chapter 4).

Gene localization of hereditary FTD by linkage studies in the Dutch material was possible by the extent of the families and their participation. The linkage to chromosome 17q21-q22 allowed comparison with other neurodegenerative disorders in the same region (chapter 5).

Clinical data on the manifestations of FTD in the three Dutch families with linkage to chromosome 17 allowed analysis of inter and intrafamilial differences of the disease phenotype and possible indications for allelic genetic heterogeneity (chapter 6).

Special emphasis was given to the potential psychosocial effects of participation in a genetic family study, like in this study. The psychosocial impact and medical-ethical dilemmas of a family study were also considered to assess the acceptability of future predictive testing (chapter 7 and 8).

APPENDIX

Consensus statement on clinical criteria for fronto-temporal dementia by the Manchester and Lund groups (1994).[8]

1. Core diagnostic features:

Behavioral disorder

- insidious onset and slow progression
- early loss of personal awareness (neglect of personal hygiene and grooming)
- early loss of social awareness (lack of social tact, misdemeanors such as shoplifting)
- early signs of disinhibition (such as unrestrained sexuality, violent behavior, inappropriate jocularity, restless pacing)
- mental rigidity and inflexibility
- hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and alcohol consumption, oral exploration of objects)
- stereotyped and perseverative behavior (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing)
- utilization behavior (unrestrained exploration of objects in the environment)
- distractibility, impulsivity, and impersistence
- early loss of insight into the fact that the altered condition is due to a pathological change of own mental state

Affective symptoms

- depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion (early and evanescent)
- hypochondriasis, bizarre somatic preoccupation (early and evanescent)
- emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy)
- amimia (inertia, aspontaneity)

Speech disorder
- progressive reduction of speech (aspontaneity and economy of utterance)
- stereotypy of speech (repetition of limited repertoire of words, phrases, or themes)
- echolalia and perseveration
- late mutism

Spatial orientation and praxis preserved
- intact abilities to negotiate the environment

Physical signs
- early primitive reflexes
- early incontinence
- late akinesia, rigidity, tremor
- low and labile blood pressure

Investigations
- normal EEG despite clinically evident dementia
- brain imaging (structural or functional, or both): predominant frontal or anterior temporal abnormality, or both
- neuropsychology (profound failure on 'frontal lobe' tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder)

2. Supportive diagnostic features

- onset before 65
- positive family history of similar disorder in a first degree relative
- bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease)

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Chapter 2

Familial forms of Fronto-Temporal Dementia

(Ned Tijdsch Geneeskd 1995;139:871-875)

FAMILIAL FORMS OF FRONTO-TEMPORAL DEMENTIA

INTRODUCTION

The term fronto-temporal dementia (FTD) has been recently introduced for a primary degenerative neuronal disorder of the frontal and temporal cortex.[1-4] Frontal lobe dementia (FLD) is the most frequently occurring type of FTD.[5] Clinical features in frontal lobe dementia, usually presented at presenile age (between 40 and 65 years) are predominantly characterized by changes in personality and behavior, especially in neglect of social and domestic responsibilities, socially disinhibited behavior, excessive eating and drinking, restlessness or apathy, roaming behavior, and stereotyped behavior.[1,2,4,6] Eventually, after a duration of 5-8 years, a state of apathy with incontinence, bradykinesia, rigidity and mutism will develop.[5] Frontal lobe dementia can be distinguished from Alzheimer's disease by the absence of early memory disturbances, and can be distinguished from Huntington's disease by the absence of involuntary movements. Vascular dementia is almost always accompanied by focal neurological abnormalities.

A second, less frequently occurring, form of FTD is frontal lobe dementia in association with clinical features of motor neuron disease (FLD + MND). A third form is progressive aphasia with behavioral changes.

These three clinical variants of FTD have a similar pathological substrate.[3,7,8] Macroscopically, lobar atrophy of frontal and often temporal cortex is present, while at microscopical examination aspecific changes (neuronal loss, gliosis and spongiosis) are found in the cortex and some subcortical areas.[3,5] Senile plaques and neurofibrillary degeneration, characteristic for Alzheimer's disease, are absent.

In this paper we discuss familial occurrence, diagnostic criteria, including imaging techniques, and progress in genetic molecular research concerning FTD.

EPIDEMIOLOGY AND GENETICS

The prevalence of FTD, the number of patients with this disorder within the population, and the incidence, the number of new cases per 100,000 persons per annum, are not known. The ratio of FTD compared to Alzheimer's disease ranges from 1:10, within the group of patients with presenile dementia, to 1:30 within the total group of demented patients.[3,9] A cause for the disorder has not yet been discovered. No environmental factors associated with FTD are known. Apart from a sporadic occurring type of FTD, a familial type with an autosomal dominant pattern of inheritance is known.[10] A Dutch and a Swedish family with a dominant type of inheritance have been described earlier.[11,12] In the Dutch family clinical features, noted in 25 family members in 3 consecutive generations, were presented between the fourth and fifth decade.[11] Results in research concerning the ratio between the sporadic and the familial type are rather contradictory. Until recently familial occurrence was generally estimated to be 20%.[10] However, in recent reports in a fraction of 40-50% of FTD patients, first degree relatives with dementia were found.[1,2,13] However all the reports present series with less than 20 patients and the pattern of inheritance is not mentioned. For further clarification we present a case report from a not earlier published family with the hereditary type of FTD.

CASE REPORT

During the three years before diagnosis was made, a 57 year old woman developed slowly progressive behavioral changes. Previously punctual and tactful, she made increasingly more socially inappropriate remarks and used abusive language in public. The patient showed lack of initiative and apathy, she neglected her domestic responsibilities and spontaneous speech gradually occurred less often. She appeared only to be interested in watching television. She was unaware of her ill-health. Eating and drinking habits became disinhibited and she exhibited a bland affect. The father of the patient had previously developed identical features and died aged 65. Confirmation of the diagnosis of frontal lobe

dementia with similar features was also established by pathological examination in an aunt and two uncles. Substantial neuronal loss was found in the frontal and temporal cortex with some inflated cells ('ballooned' cells), but without Pick inclusion bodies.

During neurological examination orientation in time and place, memory, and visual-spatial functions were intact.
Neuropsychological studies revealed severe deficiencies in tasks testing planning, organizing abilities and executive functions like category restricted naming, sequencing pictures, and Wisconsin Card Sorting test. No word finding difficulties were present. The patient displayed perseveration and echolalia. Proverbs were explained literally, but not figuratively. In complex drawings all the elements were named, but relationships between these elements were not understood. The electro-encephalogram (EEG) showed no abnormalities. Single Photon Emission Computed Tomography (SPECT) showed severe hypoperfusion in the frontal cortex and mild hypoperfusion in parietal and temporal cortex (Figure 1). In MRI studies, transversal T2 weighed Spin-Echo, and transversal and coronal 'Inversion Recovery' scans showed marked atrophy of frontal cortex and caudate nucleus with slight dilated ventricles (Figure 2).

The fact that this patient had the disease had a strong impact on other relatives, particularly a son and a brother of the patient. The son had been aware that the disease ran in his mother's family since he was an adolescent. Before starting a relationship he decided to undergo sterilization. Since quite some time the patient's spouse had suspected his wife's disease to be identical to the one from which her father had died, and he was thus worried about the consequences for his children from that moment on. When his wife was diagnosed as having FTD, the risk for his children of developing the disease was estimated to be 50%. The son assumed that he would develop the disease, but had already decided to refrain from using possible presymptomatic testing in future. He had arranged with his wife if he should become 'unmanageable' she would admit him into a nursing home. The brother of the patient had become increasingly anxious after his sister was diagnosed, even though he had been aware of hereditary dementia running in the family for more than twenty years.

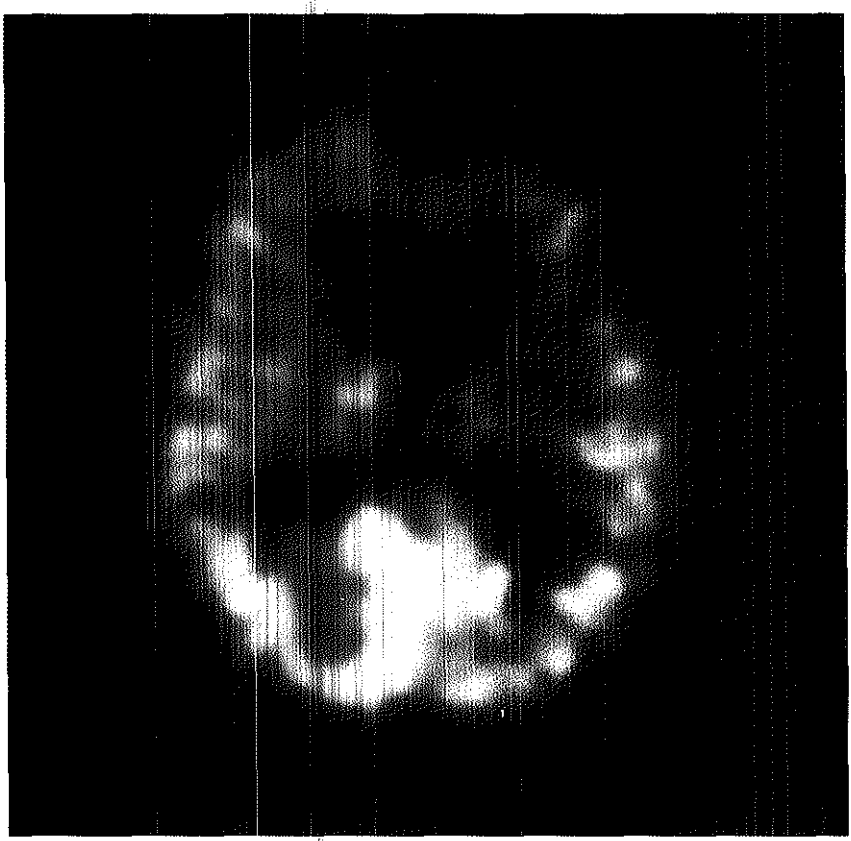

Figure 1.

Severe perfusion deficit of ^{99m}Tc-hexamethylpropyleenamine-oxime (HMPAO) in the frontal lobes (upper position in the figure) and in less extent in the parietal lobes on a 'single-photon emission computed tomography' (SPECT)-scan in patient A.

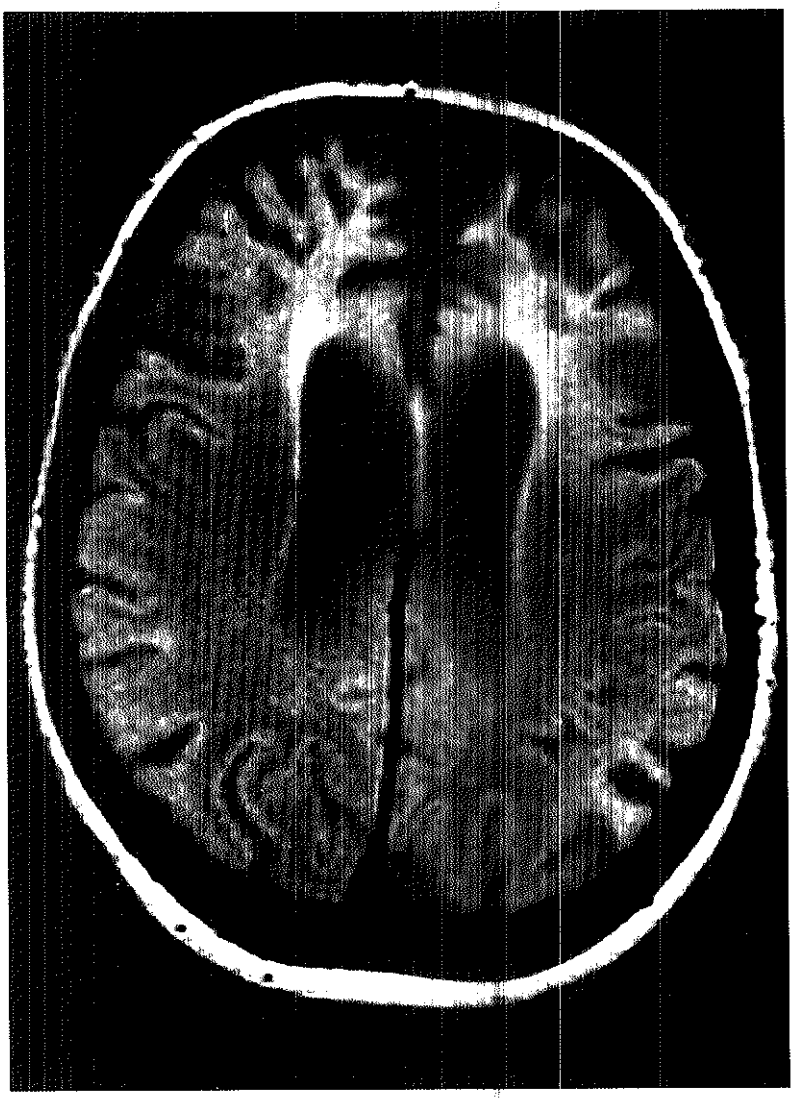

Figure 2.

Marked atrophy of the frontal gyri (upper position of the figure) on a T2-weighed spinresonance-tomogram (spin-echorelaxation time (TRSE): 2222ms; echotime (TE): 30ms) in patient A, with local hyperintensity in the subcortical and periventricular white matter.

His expectation was that he should eventually develop the disease as well. He had two adult daughters and a son and had since undergone sterilization. In these children we observed, because of a 25% risk for developing frontal lobe dementia, a retarded individual personality development. The daughters, in their twenties, did not want to start a steady relationship. One daughter has already considered sterilization. The son was eager to get a job as soon as possible and wanted to waste no time in studying. Reaching the possible age at which the disease could begin to develop, the brother of the patient was increasingly pre-occupied with possible symptoms, especially forgetfulness, although this is not an initial characteristic in FTD. His wife was constantly watching for possible changes in her husband's conduct (symptom-search). Although the threat of the disease was experienced by every family member, there was no communication between them over this topic. The patient's brother was hoping that presymptomatic testing would be possible in the future. He would participate in such testing if his children wanted counselling concerning their risk of developing the disease. He was particularly concerned about his oldest son. In previous years, spanning several generations, intrafamilial relations had been dramatically disturbed because of the disease of the patient's father. Interviewing risk-carriers from various branches of the family often revealed the reproach that closely related family members of a patient were let down by other relatives during the course of the disease. Our request for participation in a research project investigating the cause of the disease evoked very emotional responses in some family members. The sudden confrontation with frontal lobe dementia broke through the psychological blockade (predominantly consisting of denial and avoidance behavior) which was used as a shield against the threat of the disease.

DISCUSSION

Frontal lobe dementia

The described patient is related to a large family with frontal lobe dementia. Data on history given by healthy family members reveal the occurrence of dementia in 28 family members in 5 successive generations.

Retrospectively, diagnosis of probable frontal lobe dementia was made on the basis of contemporary clinical criteria in 18 out of 28 demented family members. The diagnosis was confirmed pathologically in 10 family members. Clinical features, the age at which initial symptoms appeared, and the duration of the disease are remarkably similar in the affected family members. Apart from behavioral changes, decreased spontaneous speech, stereotypical remarks and verbal perseveration are the most characterizing features.[2,10,14]

In a later phase of the disease imaging studies of the brain often support the clinical diagnosis. The CT-scan shows atrophy of the frontal lobe, and in some patients atrophy of the anterior pole of the temporal lobe and atrophy of the caudate nucleus is demonstrated.[3,15,16] In SPECT imaging decreased uptake of the radioactive pharmacon is noticed in the mentioned cortical areas, even before atrophy on CT is detected.[2] Both atrophy and hypoperfusion can be asymmetric. Pathological abnormalities are most prominent in the frontal cortex, whereas the severity in degeneration of temporal cortex and subcortical structures is variable.[3,7,17] The diagnosis Pick's disease is appropriate if Pick inclusions (round intraneuronal argentophilic structures) and ballooned neurons are present in the cortex. Pick's disease, which is the most known type of frontal lobe dementia, is however only responsible for a small part (about 20%) of the total group of patients with frontal lobe dementia, and is clinically not differentiable from frontal lobe dementia without Pick inclusions.[10]

Frontal lobe dementia with motor neuron disease

Dementia of the frontal type is in some cases accompanied by features of motor neuron disease (FLD + MND).[18,19] Patients with this combined disorder develop slurred speech, difficulties in swallowing and muscular weakness in the upper limbs within from a few months up to even more than one year after the start of the behavioral changes. In contrast with amyotrophic lateral sclerosis, motor features in FTD+MND (dysarthria, muscular weakness, fasciculations) are often limited to the tongue and upper extremities.[20] Brisk tendon reflexes and extensor plantar responses can be found in few patients. Generally this disorder is fatal within a few years. Electromyographic investigations reveal loss of anterior horn cells (fasciculations, fibrillations, giant potentials).

As in frontal lobe dementia, in FLD + MND EEG is normal and changes in CT, MRI and SPECT are identical as described above.[19] A familial type of FLD + MND with an autosomal dominant pattern of inheritance has been described.[20] Apart from abnormalities in the frontal cortex, nucleus hypoglossus and anterior horn cells in the cervical and thoracal region are degenerated.[13,19,20]

Progressive aphasia

Progressive aphasia is a slowly developing disorder with wordfinding difficulties, gradually decreased speech and finally mutism.[21,22] In some patients stereotyped and/or disinhibited behavior develops, often a few years but sometimes several years after onset of the aphasia. CT scanning shows uni- or bilateral atrophy of the anterior part of the temporal lobe, accompanied by widening of fissura cerebri lateralis (Sylvii), whereas the frontal lobe is less severely affected.[16,21,23,24] Within one family this disorder can develop in slightly different ways. Two brothers are described both developing progressive aphasia at the age of 60; in one brother the clinical picture with alternating apathy and aggressive conduct was present within a few months, whereas in the other brother the same features developed only after 7 years.[25] In progressive aphasia pathological studies reveal the same changes as in FTD, however these are most prominently present in the temporal lobes.[16,21,23,24] Although aphasia in Alzheimer's disease is usually accompanied by memory disturbances, this entity can only be excluded by pathological examination.

Coherence between different types of fronto-temporal dementia

Up until now it is unclear whether the different variants of fronto-temporal dementia are distinct in regard to etiology. They are all designated, in neutral terminology, as 'lobar atrophies'.[8] The different clinical entities show a partial overlap in symptomatology, pathological abnormalities and familial occurrence. The three types are pathologically distinguishable by their variable severity and localization of abnormalities in the frontal and temporal cortex, and the involvement of subcortical structures, such as corpus striatum, amygdala and hippocampus.[7] Moreover, in both clinical and pathological respect FTD has much in

common with other closely related syndromes, such as hereditary dysphasic dementia and aphasic dementia with motor neuron disease.[26,27]

Etiology

As far as etiology is concerned the different types of fronto-temporal dementia are possibly one disease expressed in different ways. It should not be ruled out that clinical heterogeneity may be caused by variability in one gene defect or by the presence of several gene defects at the same chromosomal locus or even different loci.

Fronto-temporal dementia as a familial disease

The presence of a hereditary disease, already known to family members for several generations, often causes uncertainty and anxiety. Family life is overshadowed by the continuous threat of an untreatable atrocious disease. We often observe preoccupation with early symptoms and symptom-search in a patients' children and other family members at risk to be characteristic features, but also denial and avoidance of the confrontation with the disease ('as long as nobody talks about the disease it does not exist'). Symptom-search in families with fronto-temporal dementia particularly involves behavioral changes like loss of decorum, disinhibition, roaming, and neglect of social activities and personal hygiene. The phenomenon 'preselection', the 'prophesy' by the family members themselves who will and who will not develop the disease, which was earlier observed in families with Huntington's disease, was also seen in families with hereditary FTD.[28] Similarities in personality and physical features with the affected relative are mistakenly connected with preselection and symptom-search. These psychological mechanisms can be regarded as defensive reactions, aimed at the anxiety for the future; thus anxiety is allayed and manageable. These mechanisms can be seen as a kind of 'mental rehearsal': one gradually gets familiar with the 'worst case' scenario concerning this threatening and frightening disease.

Genetic research can have significant impact on the intrafamilial relations.[29,30] This can often be traced back to the effects that the disease had on intrafamilial relations in the past. Conflict may lead to several family members refraining from the essential approval in participation in DNA linkage research. The request for participation can evoke feelings of

guilt and shame. If latent family conflict is encountered during medical interference, psychological support should of course be offered. If presymptomatic testing should be available in the future, it will have far-reaching consequences for the rest of the lives, including family planning, of the family members availing themselves of it.[31]

Molecular-genetic research

Up until now no gene defect has been found to be responsible for the hereditary type of fronto-temporal dementia. Research is hampered because only few families with the hereditary type, with sufficient still-living family members (or availability of tissues from deceased affected family members) have been identified. It is not excluded that, similar to Alzheimer's disease, fronto-temporal dementia is clinically heterogeneous. Recent molecular biological investigations have already traced gene defects, which cause other hereditary brain diseases with an onset in later life, such as cerebral amyloidosis, Alzheimer's disease, Creutzfeldt-Jakob disease and Huntington's disease. Apparently, the familial form of fronto-temporal dementia is not linked to genes involved in the afore mentioned cerebral disorders.[32,33] As far as the amyloid-precursor-protein (APP)-gene is concerned this was not to be expected, because in FTD no or very few senile plaques or amyloid deposits in the blood vessel walls are encountered. Patients with familial FTD do not have a mutation in the prionprotein (PrP)-gene, as described in spongiform encephalopathies which bears some resemblance both clinically and pathologically to FTD.[34,35] Thus, FTD can not be regarded as a variant of spongiform encephalopathy or Alzheimer's disease. Very recently a strong indication for linkage with chromosome 17q21-23 (maximum LOD-score = 3.28 for marker GP3A, and recombination fraction $(\Theta)=0$) was found in the mentioned disinhibition-dementia-parkinsonism-amyotrophy complex, which also closely resembles FTD clinically and pathologically.[36] For the time being it is not clear if linkage to this chromosome is present in families with FTD (and if so, in how many families).

Research

FTD is an important cause of presenile dementia, but as yet no treatment is available. Recently in Rotterdam research involving fronto-

temporal dementia, subsidized by the Dutch Organization for Scientific Research (NWO), has been started. This research is aiming at answering questions like the prevalence of FTD in the population, and the ratio of the familial and sporadic form. In addition, molecular-genetic techniques will be used to try to find the gene defect responsible for the hereditary form. In such a research participation of patients and their relatives is necessary, as well as corporation between several clinicians, geneticists and pathologists. If there is an indication for hereditary transmission of FTD in a family, this family will be requested to participate in this molecular-genetic research. Aspects concerning support, reactions of at risk carriers and medical-ethical problems concerning participation to scientific research and, one day, probably predictive diagnostic investigations, will be subject to research as well. By means of molecular-genetic research more insight will probably be gained in both etiology and the mechanisms causing the clinical heterogeneity of this disease.

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Chapter 3

Familial aggregation in Fronto-Temporal Dementia

(Neurology 1998, in press)

FAMILIAL AGGREGATION IN FRONTO-TEMPORAL DEMENTIA

INTRODUCTION

There is an increasing recognition of non-Alzheimer's dementia affecting predominantly the frontal and temporal cortex.[1-3] Pick's disease characterized by Pick bodies is found in only a minority of these patients.[3] For the large group of frontotemporal degeneration without Pick bodies, various names have come into use: frontal lobe degeneration of non-Alzheimer type, dementia lacking distinctive histology, frontal lobe dementia, and asymmetric cortical syndrome.[1-6] The recently introduced term fronto-temporal dementia (FTD) includes most of these conditions, and is characterized by specific behavioral changes, frontotemporal atrophy on CT or MRI, and the absence of senile plaques and neurofibrillary tangles at postmortem examination.[7]

In families from several countries with an autosomal dominant FTD, linkage was found to a 2 cM region of chromosome 17q21-22.[8-16] Because FTD overlaps with other dementias showing neurofibrillary tangles, amyotrophic lateral sclerosis and Parkinson's disease, delineation of the gene defect of FTD will become crucial in the further diagnostic classification and research of these conditions.

Here, a population-based study of FTD in the Dutch population of 15 million people is presented. Earlier smaller studies in FTD found a positive family history for dementia in 40 to 60% of participants.[1,2,4] We analyzed the familial aggregation in FTD in the Netherlands and its association with other neurodegenerative and cardiovascular diseases, and calculated the lifetime risk for dementia among first-degree relatives of FTD patients. In view of the association of apolipoprotein E4 (ApoE4) genotype with Alzheimer's disease,[17] ApoE genotypes were studied in FTD patients with and without a family history of dementia.

METHODS

Design and diagnosis

A complete ascertainment of patients with FTD in the Netherlands was attempted between January 1, 1994 and March 1, 1997. All hospital-based neurologic and psychiatric practices (n=164) and physicians in psychogeriatric hospitals or nursing homes (n=251) received a yearly postal or telephone enquiry about all suspected FTD cases with onset before the age of 65, irrespective of their family history.

Spouses and first-degree relatives participated in acquiring a detailed clinical history on the evolution of the disease using a checklist of frontal symptoms, speech and spatial functions as well as memory problems. All patients were investigated by one of the two neurologists and, if possible, by a neuropsychologist. Neuroimaging (CT, MRI or single photon emission computed tomography [SPECT]), EEG and laboratory tests were obtained to support the clinical diagnosis of FTD and to exclude other causes of dementia. The severity of dementia varied from mild to severe. In patients with severe dementia, clinical, neuroimaging (including hard copies of CT, MRI or SPECT) and neuropsychological data, already available, were reviewed.

A diagnosis of FTD was based on the criteria of Lund and Manchester groups,[7] which include (1) a progressive behavioral disorder with insidious onset, (2) affective symptoms, (3) speech disorder, (4) preserved spatial orientation and praxis, and (5) selective frontotemporal atrophy (CT,MRI) or selective frontotemporal hypoperfusion (SPECT) on neuroimaging. All patients had at least one year progression of their clinical symptoms. Probable FTD was defined (in the absence of international criteria) when clinical symptoms according to the criteria of the Lund and Manchester groups (1-4) were supported by characteristic neuropsychological findings and frontotemporal atrophy (CT, MRI) or hypoperfusion (SPECT) on neuroimaging. The diagnosis FTD was definite when postmortem examination in patients who died during follow-up confirmed the clinical diagnosis. Patients with possible FTD had symptoms compatible with FTD without supportive neuroimaging (no or normal CT, MRI). All patients with probable FTD had follow-up.

Two independent neurologists (WAvG, PS) not involved in clinical

data collection validated the clinical diagnosis of FTD by reviewing the clinical and neuropsychological data. They had no information about family history. In case of disagreement, the diagnosis was established as possible FTD. Separate brain imaging evaluation (CT, MRI) was done by a neuroradiologist with no knowledge of the patient's history. The frontal and temporal atrophy was scored as mild, moderate or severe.

The study was approved by the Medical Ethical Committee of the University Hospital Rotterdam. Informed consent for participation (including DNA studies) was obtained from the spouse or a first-degree relative of each patient.

FTD patients and control subjects

Of 126 patients brought to our attention, 74 patients had FTD and were included as probands in this study. Fifteen patients with possible FTD and 37 patients with other types of dementia (Alzheimer's disease, vascular dementia, and undetermined) were excluded. We also excluded secondary cases of FTD mentioned in family history to avoid referral bias due to familial clustering. Of the 74 patients entering the study, 36 were seen to confirm the diagnosis at the outpatient department in our hospital. For the other 38 participants, earlier neuropsychological and neuroimaging data were available.

Control subjects (n=561) matched for age and gender were obtained randomly from a population-based study in the elderly in Rotterdam.[18] These control subjects did not show symptoms of dementia at the time of the study nor did they score lower than 26 on the Mini-Mental State Examination.[19] The education level according to three categories in FTD probands (33% primary education, 25% medium level, 42% higher education) was similar to that in control subjects.[18] Blood for DNA isolation was obtained from 71 patients and 561 control subjects. ApoE genotyping was performed according to Reymer et al[20] in patients and control subjects as described earlier.[17,21]

Family questionnaire

The family history of dementia was collected for all probands (patients and control subjects) using a questionnaire, adapted from the Rotterdam Study.[17] Data were obtained on all first-degree relatives:

gender, current age or age at death, cause of death, occurrence and age at onset of dementia or other neurodegenerative disorders (Parkinson's disease, ALS), history of thyroid disease, hypertension, diabetes mellitus, and cardiovascular disorders. The spouse or a first-degree relative (usually offspring) provided this information, which was checked in a telephone interview with a second informant, usually a sibling of the patient. After consent, medical records and CT and/or MRI of affected relatives, if available, were obtained.

Statistical analysis

Risks of developing dementia before age 80 and its age at onset in first-degree relatives (siblings and parents) of the FTD-patients (definite and probable) were compared with that of control subjects. Children of probands and control subjects were excluded because they had neither yet reached the at-risk age for FTD nor were there cases of dementia among them. Survival analysis of first-degree relatives was used to establish the probability of developing dementia before the age of 80 years. The censoring age in this analysis was the age at onset of dementia in the affected relative and the current age or the age of death of the unaffected relatives. Cox proportional hazard analysis was used to estimate the hazard ratio (HR), which may be interpreted as a relative risk; that is, the risk of developing dementia in one group divided by the risk of dementia in another group.[22] Student's t-test was used when appropriate.

RESULTS

FTD patients and control subjects

Ascertainment was made as complete as possible by repeat communication with the various medical specialists. The patients notified were distributed proportionally to the population density of different areas of the country, except for a probable underreporting from an eastern region of the country (population of 200.000 habitants). The estimated prevalence of FTD is 1.2 of 10^6 in age 30 to 40 years, 3.4 of 10^6 in age 40 to 50 years, 10.7 of 10^6 in age 50 to 60 years, and 28.0 of 10^6 in age 60 to 70 years.

The mean age at ascertainment of the 74 probands was 59.4±9.1 years (range 37-73 years) and of control subjects was 59.9±2.8 years (range 55-64 years). The men-women ratio was 3:5 in the FTD group, and 7:10 in the control group. The mean age at onset of dementia in probands was 54.8±8.5 years with a mean duration of 5.9±2.9 years. All patients showed frontotemporal atrophy (CT, MRI) or frontotemporal hypoperfusion (SPECT). Frontotemporal atrophy was moderate or severe in 55 probands and mild in 19 patients. The clinical diagnosis in patients with mild atrophy was supported by linkage to chromosome 17 in 4 patients, by pathological verification in 3 patients, and by frontotemporal hypoperfusion on SPECT in the remaining 12 patients. Definite FTD was established in 11 patients by neuropathological findings (4 patients had Pick bodies).

Familial aggregation

A history of dementia before age 80 in first-degree relatives (parents and siblings) was found in 38% (28 of 74) of patients and in 15% (84 of 561) of control subjects (Table 1). Seven (10%) FTD probands had two or more first-degree relatives with dementia (see Table 1), but only 5 (0.9%) of the control subjects had two or more affected first-degree relatives. Extensive pedigree research and linkage analysis showed that 9 FTD probands coming from nuclear families originated from three large families (patients related in fourth to the seventh degree), and showed linkage to chromosome 17 (FTD-17 probands).[12] The age at onset in FTD probands with positive family history (56.5±7.6 years) was similar to those with a negative family history of dementia (53.7±8.9 years).

ApoE genotype

The ApoE genotype distribution was compared between the total group of FTD patients and the control subjects. The frequency of ApoE4E4 genotype in the total FTD group was 7.0% versus 2.3% in the control group (odds ratio [OR] adjusted for age and gender, 2.2; 95% CI, 0.6 to 8.9). The ApoE4E4 genotype in FTD patients with a negative family history was 8.9%, and 1.5% in similar control subjects (adjusted OR, 5.2; 95% CI, 0.9 to 30.8).

Table 1.

History of dementia in first-degree relatives (parents and siblings) of patients with FTD and in control subjects.

Dementia in first-degree relatives		Cases n = 74	Controls n = 561
Total group			
Family history	positive	28 (38%)	84 (15%)
	negative	46	477
Women			
Family history	positive	17 (36%)	48 (15%)
	negative	30	271
Men			
Family history	positive	11 (41%)	36 (15%)
	negative	16	206
Number of first-degree relatives with dementia			
0		46	477
1		21 (28%)	79 (14%)
2 or more		7 (10%)	5 (0.9%)
FTD patients with unknown linkage			
Family history	positive	19 (29%)	84 (15%)
	negative	46	477

Dementia in first-degree relatives

The age and male-female ratio of first-degree relatives was similar in the FTD and the control groups (Table 2). A total of 127 patients with dementia were identified among 3,345 first-degree relatives of FTD patients and control subjects. Two affected parents of control subjects were excluded by lack of information about age at onset. Dementia before age 80 was reported in 38 of 411 first-degree relatives of FTD probands and in 87 of 2,934 first-degree relatives of control subjects. The age at onset in affected relatives of FTD probands was significantly younger than in relatives of controls subjects (60.9 ± 10.6 years versus 72.3 ± 8.5 years).

Table 2.

Dementia before the age of 80 in 411 first-degree relatives (parents/siblings) of FTD patients and 2,934 first-degree relatives of control subjects.

	first-degree relatives of FTD patients	first-degree relatives of control subjects
	n = 411	n = 2934
Mean age in years (SD)	61.3 ± 17.7	63.2 ± 17.0
Gender		
Women	213	1475
Men	198	1459
Relationship		
Parent	147	1082
Sibling	264	1852
Dementia in affected relatives (%)	38 (9%)	87 (3%)
Mean age of onset in years (SD)	60.9 (±10.6)	72.3 (±8.5)*
Women	20 (53%)	57 (66%)
Men	18	30
Parent	25 (66%)	77 (89%)
Sibling	13	10
Type of dementia		
FTD linked to chr. 17	15	NA
Probable FTD	9	NA
Alzheimer's / unknown	14	NA

* difference statistically significant, $p<0.001$ T-test
NA = information about type of dementia not available

Dementia among FTD-relatives could be divided into three types: familial FTD linked to chromosome 17 in 15 patients (affected FTD-17 relatives), probable FTD in 9 patients and dementia of Alzheimer's or unknown type

in 14 patients. The dementia in affected relatives of controls could not be specified (Table 2).

The cumulative incidence of dementia before age 80 among first-degree relatives of FTD patients was 22% compared with 11% among relatives of control subjects (Table 3, Figure 1). The occurrence of dementia in the FTD group was also studied after the exclusion of the relatives (n=50) of 9 FTD-17 patients, showing a cumulative incidence of 18% in this group (see Figure 1), whereas it was 47% for the FTD-17 group.

Table 3.

Hazard ratio of dementia in first-degree relatives (parents/siblings) of FTD patients and of control subjects.

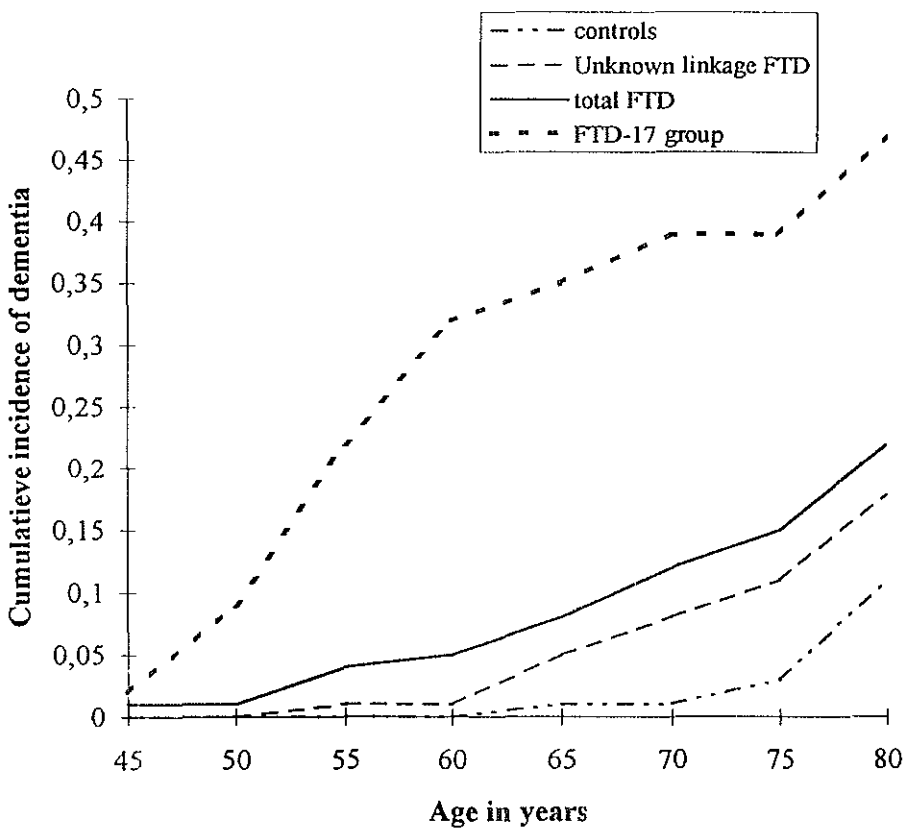
First-degree relatives	Total number	Affected	HR (95% CI)
of FTD patients	411	38	3.5 (2.4-5.2)
of control subjects	2934	87	
female	1688	77	1.3 (0.9-1.8)
male	1657	48	
parent*	1129	102	1.8 (1.1-3.0)
sibling	2116	23	
FTD with unknown linkage			
of FTD patients	361	23	2.4 (1.5-3.7)
of control subjects	2934	87	

* unaffected parents without information about current age or age of death were excluded from this analysis.

Proportional hazard analysis for dementia showed an HR of 3.5 (95% CI, 2.4 to 5.2, Table 3). There was no difference in risk of dementia between men and women (HR, 1.3; 95% CI, 0.9 to 1.8). Parents were

more likely to develop dementia than siblings (HR, 1.8; 95% CI, 1.1 to 3.0). The analysis was repeated for FTD cases with unknown linkage to chromosome 17, showing an HR of 2.4 (95% CI, 1.5 to 3.7; Table 3).

Figure 1.



Estimated incidence of dementia in first-degree relatives of control subjects, of FTD patients with unknown linkage, of all FTD patients, and of patients with FTD linked to chromosome 17 (FTD-17).

DISCUSSION

This is the first population-based study of familial occurrence of dementia in FTD. The approximate prevalence of FTD varies between 1.2 of 10^6 in the age group 30 to 40 years and 28.0 of 10^6 in the age group of 60 to 70 years, considering that our ascertainment is as complete as possible using the design described. The occurrence of FTD seems less uncommon than previously considered. The family history was positive for dementia in 38% of FTD patients. ApoE4 homozygosity is more common, although not significantly, in FTD patients with a negative family history than in similar control subjects. First-degree relatives of FTD patients are at a 3.5 times higher risk of developing dementia before the age of 80 than relatives of control subjects. The higher risk for FTD relatives remains 2.4 after the exclusion of relatives of chromosome 17-linked patients. The onset of dementia was significantly earlier (11 years) in relatives of FTD patients.

The strength of our study lies in the epidemiological design for ascertaining prevalent patients, the stringent criteria for the diagnosis of FTD, a structured family history questionnaire (including the use of a second informant), and evaluation of the diagnosis by two independent neurologists blinded to neuroimaging and family history. However, a few possible sources of bias may remain. Firstly, the accuracy of the diagnosis of FTD in probands is important. FTD is still a relatively uncommon type of dementia, and it shares some of its characteristic behavioral changes with Alzheimer's disease. For probable FTD we therefore required neuroimaging evidence for selective frontotemporal atrophy or hypoperfusion on SPECT, which has a high correlation with a pathological diagnosis of FTD.[23] Moreover, the diagnosis of FTD was definite by neuropathologic confirmation in 11 patients (including three FTD-17 patients), and by linkage to chromosome 17 in another six cases.

Familial clustering in the selection of patients may be another source of bias that was largely prevented by excluding from our study the secondary patients from the families notified. All familial probands were identified independently from each other and all met the criteria for probable FTD in this study. Patients with sporadic FTD might be less likely to be referred for neurological examination. However, all cases of

presenile dementia notified by our study had been thoroughly studied (CT and MRI or SPECT), irrespective of their family history. This might probably be explained by the large impact of the disease on everyday life.

The frequency of positive family history in FTD probands was similar to that found in Alzheimer's disease,[24-26] but lower than the 50% observed in small series of patients with FTD.[2,4]

The controls showed a positive family history in 15%, which was comparable with other studies.[27] The cumulative incidence of dementia in the first-degree relatives of FTD probands linked to chromosome 17q21-22 was 47%, which supports the autosomal dominant inheritance of this familial condition. The cumulative incidence curve (Figure 1) shows a 22% risk for first-degree FTD relatives, who became affected with dementia at a significantly younger age (60.9 ± 10.6 years) than relatives of control subjects (72.3 ± 8.5 years). The age in controls seems identical to the increasing risk of Alzheimer's disease with age.

The influence of the probable heterogenous genetic background of FTD was addressed in this study by comparing three families with FTD linked to chromosome 17, and familial cases without linkage information. The first-degree relatives from the latter group still are 2.4 times more at risk for dementia compared with relatives of control subjects. The future gene identification may help to estimate the real proportion of FTD linked to chromosome 17q21-22. Other genetic or environmental mechanisms may be involved for a proportion of FTD patients.

The association of ApoE4 homozygosity with FTD confirms our earlier results based on a smaller population, and the results of another study of autopsy-proved patients with Pick's disease.[21,28] This association is less pronounced in the subgroup with a positive family history, which might be explained by the fact that familial patients are possibly caused by gene mutations with autosomal dominant expression. However, ApoE4 allelic frequency needs to be investigated in larger samples of FTD patients, because the association between ApoE allelic frequency and FTD has not been found in two other studies.[29,30] Also, a faster progression of the disease in FTD patients with the ApoE4 allele as recently found in Alzheimer's disease,[31,32] has to be studied in our patients at follow-up.

In conclusion, this study shows an evident familial aggregation in FTD that is contributed not only to FTD linked to chromosome 17q21-22.

The eventual solution of the suggested heterogeneity will be helped by identifying the genetic defects associated with FTD on chromosome 17q21-22 and other possible locations.

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Chapter 4

Apolipoprotein E gene and sporadic Fronto-Temporal Dementia

(Neurology 1997;48:1526-1529)

APOLIPOPROTEIN E GENE AND SPORADIC FRONTO-TEMPORAL DEMENTIA

INTRODUCTION

Fronto-temporal dementia (FTD) is a predominantly presenile type of dementia. Although there are a number of families in which the disease segregates as an autosomal dominant disorder, in most cases the disease is sporadic. FTD is characterized by a progressive change in personality and behavior (disinhibition, stereotyped and perseverative behavior), loss of initiative, social awareness and insight, and reduced verbal output. The E4 allele of the apolipoprotein E gene (APOE) is one of the most important risk factors for early- and late-onset Alzheimer's disease (AD) and cognitive decline.[1-6] Although findings have not been as consistent as in AD, also other forms of dementia including vascular dementia,[7-10] Lewy body disease[11-15] and Creutzfeldt-Jacob disease[16,17] have been associated with the E4 allele of APOE-gene (APOE*4). The relationship of apoE with FTD is less clear. Two studies failed to show an association between APOE*4 and FTD,[18,19] one study showed a non-significant increase in APOE*4 allele frequency among patients with Pick's disease (n=6),[20] while one other study reported an earlier onset of FTD in APOE*4 allele carriers.[21] However, the statistical power of previous studies has been limited due to the small number of patients studied (n=8-27, if restricted to FTD patients without other neurological disorders). We examined 34 patients with clinically diagnosed FTD derived from a population-based study in the Netherlands. The relation of apoE to the risk and onset of the disease was investigated.

METHODS

FTD patients were recruited from the Dutch population. The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. To obtain a full ascertainment of FTD patients, all neurologic, psychiatric, geriatric centers and nursing homes

were addressed to report their patients twice a year. The study aimed at a complete ascertainment of FTD patients diagnosed in the period of January 1, 1994 and January 1, 1996. The study was limited to patients in whom the onset was at or before the age of 65 years, as all of these patients are likely to be sent in for diagnosis by relatives and/or their general practitioner, and therefore can be ascertained population-based by addressing the centers as specified above. We did not attempt to ascertain late-onset patients, because the possibility of complete ascertainment was improbable due to the fact that elderly FTD-patients are often not referred to specialized clinics for differential diagnosis. For this study, the clinical diagnosis of FTD was independently confirmed by 3 neurologists using a standardized protocol according to the criteria of the Lund and Manchester study groups.[22] Moreover, imaging studies (CT, MRI or SPECT) and neuropsychological testing should support the diagnosis of FTD. A total of 34 patients fulfilled our inclusion criteria. Data were collected by interviewing at least one next of kin and by reviewing all available medical records. If insufficient data were available, additional clinical investigations were performed. Age at onset was defined as the age at which retrospectively profound personality and behavioral changes were first noted. In this study, we only included patients from families in which there was no evidence for autosomal dominant transmittance of FTD. Autosomal dominant FTD was defined as FTD occurring in at least 2 generations. In our study we ascertained only 3 patients with a positive family history of FTD. The disease occurred in more than 3 generations in all three cases. These patients were therefore excluded from the current analysis. Subjects with one or more (first-degree) relatives with other types of dementia, were considered to have a positive family history of other types of dementia. After a written consent, blood was drawn for DNA extraction. A sample of control subjects (n=561) was drawn randomly from another population-based study conducted in Rotterdam, the Rotterdam Study.[23] These controls were screened for dementia using the Mini Mental State Examination.[24] None of the selected controls had a score lower than 26 or showed symptoms of dementia at the time of the study.

In cases, apoE genotyping was performed according to Reymer et al.[25] ApoE in controls was genotyped as described earlier.[26] Allele

frequencies for patients and controls were assessed by counting alleles and calculating sample proportions. The strength of association between apoE and FTD was estimated as the odds ratio. Odds ratios are presented with a 95% confidence interval (CI).[27] We used multiple logistic regression analysis to take the possible confounding by age, sex and family history of dementia into account. The association between apoE and age of onset and duration of disease was assessed using multiple linear regression analysis.[27]

RESULTS

In table 1, baseline characteristics of the study population are given. The mean age at onset of our patients was 52.1 years. The mean duration of the disease at ascertainment of the patients was 6.6 years. There was no statistically significant difference between the patients and controls in age or sex distribution. When comparing the APOE allele frequencies, the frequency of the APOE*4 allele was significantly higher in patients (25%) than in controls (15%). The odds ratio of FTD was 1.8 (95% CI 1.0-3.26) when comparing APOE*4 carriers to non carriers.

Table 2 shows the apoE genotype distribution in patients and controls. Taking the most frequent genotype apoE3E3 as the reference, a significant increased odds ratio was found for the apoE4E4 genotype when adjusting for age, sex, and family history of other types of dementia. To exclude that the association between apoE4E4 and FTD was related to a family history of dementia other than FTD in FTD patients, we performed an analysis in which patients with such a family history were excluded (n=6). The odds ratio remained significantly increased (odds ratio 8.0; 95% CI 1.6-40.4; p=0.001; not in table), suggesting that the association is independent of the family history of other types of dementia. A non-significant increase in odds ratio was found for the apoE3E4 and apoE2E3 genotypes. The age at onset tended to be lower in patients with the APOE*4 allele (p-value trend test = 0.04). The effect was most pronounced for subjects homozygote for the APOE*4 allele. There was no consistent relationship between the presence of APOE*4 allele and the duration of the disease at the time of the study.

Table 1.

Baseline characteristics and APOE allele frequencies in FTD patients and controls.

	Patients n=34	Controls n=561
Mean age at onset in years (SD)	52.1 (9.2)	-
Range	35-64	
Duration disease ascertainment in years (SD)	6.6 (3.7)	-
Range	1-13	
Age ascertainment in years (SD)	58.7 (10.3)	59.9 (2.8)
Range	37-75	55-65
Number of men (%)	12 (35)	242 (43)
APOE allele frequency (number of alleles)		
APOE*2	0.09 (n=6)	0.09 (n=106)
APOE*3	0.66 (n=45)	0.75 (n=844)
APOE*4	0.25 (n=17)	0.15 (n=172)*

*$p < 0.05$

Table 2.

ApoE genotypes in FTD patients and controls.

ApoE genotype	Patients n=34	Controls n=561	Odds ratio (95% CI) Crude	Adjusted*
ApoE4E4	3 (8.8 %)	13 (2.3 %)	5.2 [1.3-20.3]	4.9 [1.1-20.1]
ApoE3E4	11 (32.4 %)	134 (23.9 %)	1.8 [0.8-4.2]	1.7 [0.7-3.8]
ApoE2E4	0 (0 %)	12 (2.1 %)	- -	-+ -
ApoE3E3	14 (42.1 %)	315 (56.2 %)	1 reference	1 reference
ApoE2E3	6 (18.9 %)	80 (14.3 %)	1.7 [0.6-4.5]	1.5 [0.5-3.9]
ApoE2E2	0 (0 %)	7 (1.2 %)	- -	-+ -

*Adjusted for age, sex, family history of dementia
+No estimation because of division by 0

Table 3.

APOE*4 allele and the age of onset and duration of disease at ascertainment in FTD patients.

	Number of APOE*4 alleles 0	1	2	p value trend*
Age at onset in years	53.7	51.8	43.0	p=0.04
(SD)	(8.5)	(9.6)	(9.6)	
Duration at ascertainment in years	6.4	7.6	3.7	p=0.35
(SD)	(3.7)	(3.8)	(2.5)	

* One-sided p value

DISCUSSION

Our population-based study suggests that subjects homozygous for the APOE*4 allele are at increased risk of FTD. A problem in the interpretation of our findings might be that our study was based on clinically diagnosed patients, in whom the disease was not pathologically confirmed. Misdiagnosis is unlikely, since the diagnosis in the patients was based on very rigid criteria; the clinical diagnosis of FTD was supported by neuropsychological confirmation of frontal lobe dysfunction, and frontal atrophy on CT or MRI, or hypoperfusion on SPECT scan. To have distorted the results of our study, diagnostic misclassification must occurred differentially in APOE*4 allele carriers and non-carriers, and this was improbable.

Our findings are compatible with those of one earlier study of pathologically confirmed patients with FTD, which showed a significantly earlier onset of the disease in APOE*4 allele carriers and an APOE*4 allele frequency in patients of 23%,[21] and one study showing an increased frequency of APOE*4 in patients with Pick's disease.[20] In contrast, two studies failed to show evidence for a relationship between apoE and FTD.[18,19] The largest of these studies was based on a mixture of clinically diagnosed (46%) and pathologically (54%) confirmed patients.[19] A problem in interpreting our study and earlier ones is the small number of patients studied in the individual investigations. Studies had an a priori sufficient statistical power to determine the effect of the APOE*4 allele, but not for studying the relatively rare apoE4E4 genotype. Yet, our study shows a strong relationship between the apoE4E4 genotype and FTD. The association remained significant when including only patients without a family history of other types of dementia in the analysis, suggesting that the association cannot be explained by familial aggregation of FTD and other types of familial dementia.

ApoE has been associated with various types of dementia.[7-16] The APOE*4 allele frequency in our FTD patients was similar to the allele frequency found in sporadic early-onset AD (28%),[28] vascular dementia (21% to 46%),[7,8] Lewy body disease (35%),[12] and Creutzfeldt-Jacob disease (33%).[16] These findings suggest that apoE4 influences the risk of dementias that have a very different pathogenesis and clinical expression.

Also, motor neuron disease with bulbar-onset has been associated with FTD as well as APOE*4 (frequency in patients 24.2%).[29] Uncovering the role of apoE in FTD may lead to new insights in the role of apoE in dementia and related neurological disorders. Further, our findings may have important implications with regard to the use of apoE in the diagnosis of AD. Despite the consensus of the working group of the American College of Medical Genetics and the American Society of Human Genetics stating that apoE testing is not recommended for the use as a predictive genetic test,[30] Roses suggested that testing for homozygosity of APOE*4 may be of use for the differential diagnosis of Alzheimer's disease.[31] If our finding of a strong association between apoE4E4 genotype and FTD is confirmed, the feasibility of diagnosing AD based on apoE testing is reduced considerably.

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Chapter 5

Hereditary Fronto-Temporal Dementia is linked to chromosome 17q21-q22: a genetic and clinicopathological study of three Dutch families

(Ann Neurol 1997;41:150-159)

HEREDITARY FRONTO-TEMPORAL DEMENTIA IS LINKED TO CHROMOSOME 17q21-q22: A GENETIC AND CLINICOPATHOLOGICAL STUDY OF THREE DUTCH FAMILIES

INTRODUCTION

Hereditary fronto-temporal dementia (HFTD) is the familial form of fronto-temporal dementia (FTD), a rare, mostly sporadically occurring and predominantly presenile dementia.[1-4] The characteristic frontal and temporal lobar atrophy was originally described by Arnold Pick in 1892.[5] Gans[6] in 1923, and later others, reported families with an autosomal dominant inheritance pattern.[7-10] The diagnosis of Pick's disease, the best known type of FTD, is now set aside for cases with so-called Pick bodies,[11,12] and several authors introduced diagnostic descriptions for new entities of frontal atrophy without Pick bodies.[15-17] The main clinical features of FTD are personality changes, a disinhibited and inappropriate behavior, hyperorality, stereotyped and perseverative behavior, emotional and social indifference, aspontaneity, loss of judgement and insight, and speech reduction.[1,13]

Molecular genetic studies of HFTD failed to find mutations in the genes implicated in Alzheimer's disease or the mutation in the prion protein gene involved in Creutzfeldt-Jacob disease.[18-20] More recently, linkage to chromosome 17 has been reported in a family with disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), 2 families with progressive subcortical gliosis (PSG) and a family with pallido-ponto-nigral degeneration (PPND).[21-23] The disease in these families shows a strong clinical and pathological resemblance to HFTD, as reported in this study.[24-26]

To investigate whether HFTD could also be linked to the same region on chromosome 17q21-q22, we performed a linkage study with 3 large families with HFTD that were ascertained in the Netherlands. Here, we report evidence for linkage of HFTD to chromosome 17q21-q22, the same chromosomal region were DDPAC, PPND and PSG have previously been localized.

MATERIAL AND METHODS

Family studies

In a genetic-epidemiologic study of FTD in the Netherlands, we aimed to obtain a full ascertainment of FTD patients by addressing all neurologic, psychiatric, geriatric, and nursing homes to report their patients twice a year. In this study, 2 large families (Families I and III) with dementia were identified, whereas a third one (Family II) was reexamined. These families were selected for linkage analysis because of their strong clinical and pathological similarities. The second family has been described before as hereditary Pick's disease, despite the absence of Pick bodies.[2-4] Dementia is transmitted as an autosomal dominant disorder in all 3 families[4] (Figure 1a and b). The clinical picture in affected individuals meets the criteria for FTD.[1] The age at which behavioral changes were reported by more than 1 relative was considered as age of onset. Diagnosis of living patients was established using extensive neuropsychological testing and brain computed tomographic (CT) scanning and/or magnetic resonance imaging (MRI); diagnosis of deceased patients was established either on pathology findings or on available medical records and family interviews.

Family I

The first family consists of 2 sisters with dementia in the first generation and 49 of 160 offspring (28 men and 21 women) of these 2 sisters in the subsequent five generations (see Figure 1a). The diagnosis of FTD was established in 8 living patients. Sufficient clinical information and family history were available on 18 affected relatives to allow establishing age of onset and diagnosis of HFTD, whereas the type of dementia could not be specified by lack of detailed information in the remaining affected family members. A neuropsychological assessment was performed in 15 of 18 patients. Ten patients had CT scanning; 3 cases had a single-photon emission computed tomographic (SPECT) scan and 3 an MRI scan. Neuropathological examination in all 14 autopsied cases confirmed HFTD.

Family II

This family with HFTD was previously documented by Schenk and others.[2-4] There are seven generations with 34 affected relatives (14 men and 20 women). CT scans were performed in 6 patients and SPECT scanning in 1 patient. Neuropathological examination in 15 patients confirmed the clinical diagnosis of HFTD. After the last report another 2 affected cases were identified (V14 and V21).[4]

Family III

Dementia was first recognized in 1 male, and subsequently another 29 affected relatives were identified (see Figure 1b). Relevant clinical data are available on 10 patients, CT scanning and neuropsychological assessment in 7 patients, and SPECT scanning in 2 patients. Neuropathological studies in 1 patient confirmed the diagnosis of HFTD.

After written consent, DNA was isolated from peripheral blood leukocytes as described by Miller and colleagues.[27] Blood was taken from 5 patients from Family I, 2 patients from Family II, and 5 patients from Family III. DNA samples were also obtained from 62 healthy relatives with 50% risk for developing dementia (31, 15 and 16 individuals respectively).

This study was approved by the Medical Ethics Committee of the University Hospital Rotterdam.

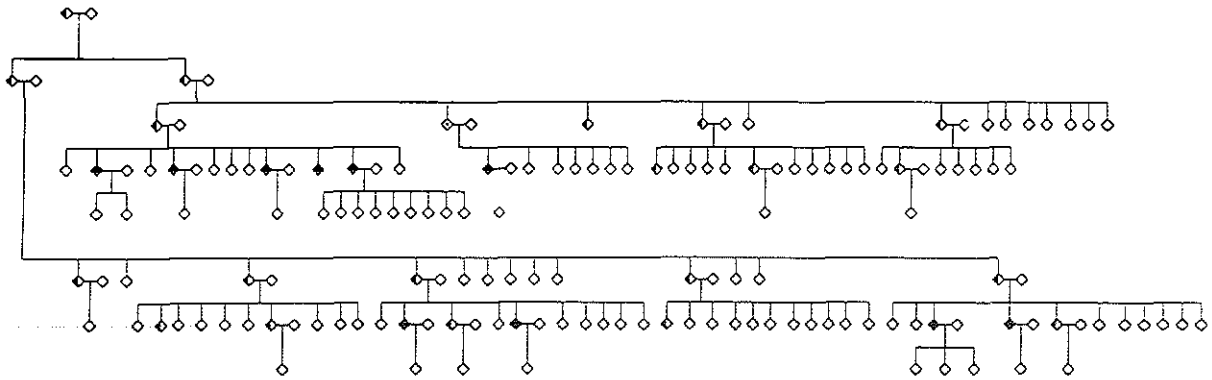
Pathology

Brain specimens of different cortical regions, basal ganglia, and pons from 11 cases (5 from Families I and II each, and 1 from Family III), were reexamined for Pick bodies, ballooned cells, and immunohistochemical features. Immunohistochemistry included the following antibodies: ubiquitin (1:125; Novocastra), tau (1:400; Dako, no. A 024), an antibody against paired helical filaments (PFHs)(1:100; ICN), an antibody against somatodentritic microtubule-associated protein (MAP-2)(1:170; Zymed), and ß-amyloid antibody (1:600; Novocastra). Staining with a conventional peroxidase anti-peroxidase method was done. Age- and sex-matched controls (normal and with Alzheimer's disease) were used for comparison.

Figure 1a.

Pedigree of family I. As the disorder shows clear autosomal dominant inheritance, sex designation of family members has been omitted for privacy reasons. ◇ = unaffected; ◇* = two different spouses; ◈ = possibly affected; ◈ = affected (dementia); clinical information insufficient to establish diagnosis FTD; ◆ = affected (fronto-temporal dementia); sufficient clinical information and/or pathologically confirmed.

Figure 1b.



Pedigree of family III. As the disorder shows clear autosomal dominant inheritance, sex designation of family members has been omitted for privacy reasons. ◇ = unaffected; ◇* = two different spouses; ⊙ = possibly affected; ◐ = affected (dementia); clinical information insufficient to establish diagnosis FTD; ◆ = affected (fronto-temporal dementia); sufficient clinical information and/or pathologically confirmed.

DNA studies

Simple sequence length polymorphisms (SSLPs) from chromosome 17q21-q22 were amplified from 50ng of genomic DNA. One primer from each pair was end labeled with gamma ^{32}P-ATP using T4 polynucleotide kinase. The amplification was performed essentially as described[28] except for markers D17S946 and D17S932 for which 7.5% dimethyl sulfoxide was added to the reaction mix. Analysis of SSLPs was performed on a denaturing 6% acrylamide gel.

Chromosome 17 markers were obtained from the CEPH/Genethon linkage map.[29] Marker order was obtained by combining data from the CEPH/Genethon linkage map and the Whitehead physical map[30] and is shown in Figure 2.

Linkage analysis

Pairwise lod scores were calculated for each family by using the MLINK program of the LINKAGE programs package (version 5.1),[31] assuming HFTD to be an autosomal dominant disease with a gene frequency of 0.0001. The mean age of onset in the available families was 51 years (range 43-75 years). The late age of onset was accounted for by defining 4 liability classes with different penetrance values (Table 1). Phenocopy rate was estimated to be 0.1% for individuals older than 50 years of age and 0.01% for individuals younger than 50 years of age. Mutation rate was set at zero and equal recombination rates for males and females were assumed because of the variable recombination ratio between males and females in this region.[29,30] Marker allele frequencies were kept equal because allele frequencies from the Dutch population were not available. Calculation of pair-wise lod scores with allele frequencies calculated from individuals marrying in into the HFTD kindreds did not substantially alter results ($<10\%$).

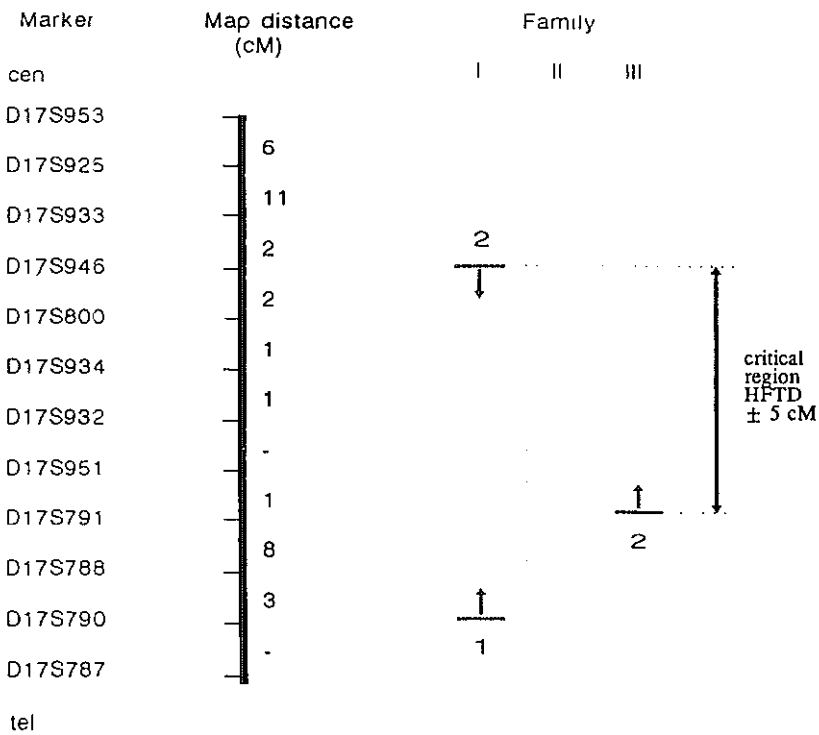


Figure 2.

Schematic map of the hereditary fronto-temporal dementia (HFTD-linked region on chromosome 17q21-q22 with sex-averaged distances based on the CEPH/Geneton linkage map.[29] For each family, the number of recombinational events in affected individuals is indicated with an arrow accompanied by the number of recombinations observed. The double-sided arrow indicates the minimal critical region for HFTD.

Table 1.

Liability classes used in the linkage analysis.

Liability class	Penetrance
Class 1	1.00 < married in or affected
Class 2	0.95 < unaffected, at risk > 50 yr
Class 3	0.75 < unaffected, at risk, between 40 and 50 yr
Class 4	0.10 < unaffected, at risk < 40 yr

RESULTS

Demographic data and clinical features

The age of onset was comparable in Families I and II (mean 50.4 and 46.5 years respectively); all but one patient developed symptoms before the age of fifty-seven. In Family III the mean age of onset was 63.4 years (range from 57 to 75), which is significantly different ($p<0.001$). The mean duration of illness was similar for the three families (8.2-8.7 years)(range between 4 and 16 years). The mean age of death in Family III (71.9, range 63-81 years) again differed significantly ($p<0.001$) from that in Family I and II (58.6 and 54.7 years respectively). The mean age of onset and of death was constant over consecutive generations. The male to female ratio of patients in Family II was 2 to 5, but equal to 1 in Families I and III. There was a remarkable uniformity in clinical symptoms and progression of the disease within each family.

Disinhibition, including aggressive behavior, stealing, jocularity and/or obsessional behavior, was the presenting symptom in all patients of Family I and Family II. Loss of initiative was the prominent presenting feature in Family III, and developed later in Families I and II. Hyperorality, roaming behavior, restlessness and stereotyped behavior developed often during the course of the illness. Spontaneous speech became gradually reduced in all, resulting in a state of mutism. Mild memory problems were common.

Neurological examination was always normal in the early phase of the disease, except sometimes for frontal release reflexes. The progression of the disease was quite similar in these families. Pyramidal and extrapyramidal signs occurred in several patients in the late phase of the disease (see Table 2). Neuropsychological assessment showed frontal dysfunction in all patients of the three families. Perseveration, impaired attention, decreased mental shifting, impaired executive skills and speech reduction reflecting frontal lobe dysfunction were found in combination with intact orientation and memory functions at neuropsychological assessment.

EEG, serum levels of vitamins, lues reactions, and/or thyroid functions tests, performed in most patients, were always normal. CT scanning after a mean duration of illness of 2.5 years (range 1 to 5 years) showed frontal atrophy (mild in 6, moderate to severe in 9 patients) in 15 cases from the three families, whereas CT scan was normal in 4 patients. Increased signal intensities in the subcortical white matter of the frontal lobe on T2-weighted MRI images were found in two patients of Family I. Frontotemporal hypoperfusion on SPECT was found in all six investigated patients.

The brain weights at autopsy from Families I and II were strongly reduced (mean 1035 and 920 g respectively); one case of Family III was 1170 g. Moderate to severe atrophy of the frontal lobe was present in all cases of Families I to III, as well as atrophy of the anterior part of the temporal lobe. The caudate nucleus was atrophied in 9 cases of Family I and II each, and in one patient of Family III. Neuronal loss, gliosis and spongiosis were found in the frontal and temporal cortex, in the absence of senile plaques and neurofibrillary tangles. The substantia nigra was degenerated in 4 brains of Family I and II each, and in one patient of Family III. Neuronal loss in the olivary nuclei was found in 3 brains. Some cases of Families I and II showed white matter changes (demyelination and/or gliosis). Ballooned cells in the cortex and/or basal ganglia were found in a number of cases of the Families I and II, whereas these cells were absent in one case of Family III. Pick bodies were lacking in brains of the three families, except sporadically in one brain from Family II. At re-examination of 10 available brain specimens no Pick bodies were found at all.

Table 2.

Comparison of clinical and pathological features between three chromosome-17 linked neurological disorders and three families with HFTD.

	PPND	DDPAC	PSG	HFTD
Number of patients	26	12	8	49
Mean age of onset (yr)	43	45	46	51
Presenting symptoms				
Personality and behavioral changes	10	12	6	49
Dementia	5	-	-	-
Parkinsonism	14	1	-	-
Subsequent manifestations				
Dementia	26	12	8	49
Supranuclear palsy	15	-	-	-
Extrapyramidal signs	25	11	7	10
Pyramidal signs	16	3	1	7
Amyotrophy	-	1	-	-
Neuropathology	n = 4	n = 6	n = 7	n = 30
Macroscopy				
Frontal atrophy	4*	6	7	30
Microscopical involvement				
Frontal cortex	+/-	++	++	++
Temporal cortex	+/-	++	++	++
Caudate nucleus	+	nm	+/-	+
Substantia nigra	4	6	4	9
Hippocampus	+/-	+/-	+	-
Amygdala	+/-	++	nm	+/-
Thalamus	+/-	nm	+/-	+/-
Spinal cord	nm	+/-	+/-	-
Ballooned cells	nm	+	-	+
Pick bodies	nm	nm	-	-

nm = not mentioned; - = not affected; +/- = not generally affected; + = generally affected; ++ = prominently affected; * = mild generalized atrophy described. PPND = pallido-ponto-nigral degeneration; DDPAC = disinhibition-dementia-parkinsonism amyotrophy complex; PSG = progressive subcortical gliosis; HFTD = hereditary fronto-temporal dementia.

Immunohistochemical studies were negative for tau or ubiquitin. In two patients scattered mild diffuse and granular staining for MAP-2 was visible in both neurons and glia.

Linkage

Three linkage reports[21-23] of variable forms of frontal lobe dementia prompted us to investigate whether the families with HFTD described in this study were linked to the same region on chromosome 17q21-q22. We selected twelve SSLPs from the CEPH/Genethon linkage map. There was a discrepancy in marker order between the CEPH/Genethon linkage map and the Whitehead physical map for markers D17S932 and D17S934.[29,30] In our study we used the marker order obtained by physical mapping data from the Whitehead map.

Positive lod scores were obtained for a number of markers in the region for all three families. Table 3a/b summarizes the pairwise lod scores between HFTD and the twelve chromosome 17q markers. None of the individual families was powerful enough to provide significant evidence for linkage by itself, but with the combined data of the three families significant lod scores were obtained for the marker D17S932 ($Z=4.70$ at $\Theta=0.05$) and D17S934 ($Z=4.28$ at $\Theta=0.00$).

A substantial part of the information that contributed to these lod scores in these families comes from unaffected individuals that are at risk for the disease. We therefore re-analyzed D17S932 and D17S934 giving all the unaffected individuals a diagnosis unknown. The maximum lod score obtained with this analysis for marker D17S932 was 2.99 at $\Theta=0.00$. For marker D17S934 the maximum lod score obtained was 3.46 at $\Theta=0.00$.

The marker order and inter-marker distances of the available genetic and physical maps do not always concur. Therefore multi-point linkage analysis can generate a confidence interval that later would prove to be inaccurate. To strengthen our findings we performed haplotype analysis for all 12 markers positioned according to the physical map. In a number of cases the haplotype of the markers for the affected individuals could not be determined because of the unavailability of first degree relatives (data not shown). As a result it could not be determined whether marker

Table 3a.

Two-point lod scores for chromosome 17 markers and hereditary fronto-temporal dementia.

		Recombination fraction (Θ)						
Marker	Family	0.000	0.010	0.050	0.100	0.200	0.300	0.400
D17S953	I	-3.96	-1.31	-0.59	-0.29	-0.04	0.02	0.08
	II	-1.29	-1.14	-0.77	-0.52	-0.25	-0.10	-0.02
	III	-2.18	-1.96	-1.35	-0.87	-0.36	-0.12	-0.02
	Total	-7.43	-4.41	-2.71	-1.68	-0.65	-0.20	-0.04
D17S925	I	-0.43	-0.37	-0.19	-0.05	0.07	0.08	0.05
	II	-8.16	-1.21	-0.54	-0.29	-0.10	-0.03	-0.01
	III	-1.89	-1.70	-1.17	-0.76	-0.30	-0.08	0.01
	Total	-10.48	-3.28	-1.90	-1.10	-0.33	-0.03	0.05
D17S933	I	-3.55	-1.33	-0.63	-0.34	-0.14	-0.06	-0.01
	II	-8.14	-0.63	-0.02	0.16	0.20	0.11	0.03
	III	-0.96	-0.83	-0.46	-0.21	0.00	0.04	0.01
	Total	-12.65	-2.79	-1.11	-0.41	0.06	0.09	0.03
D17S946	I	1.88	1.84	1.67	1.43	0.95	0.48	0.12
	II	0.34	0.33	0.29	0.24	0.17	0.10	0.04
	III	-2.30	-1.96	-1.20	-0.71	-0.24	-0.06	-0.01
	Total	-0.08	0.21	0.76	0.96	0.88	0.52	0.15
D17S800	I	-0.35	-0.32	-0.23	0.14	-0.04	0.00	0.01
	II	-0.18	-0.18	-0.15	-0.12	-0.07	-0.03	-0.01
	III	0.92	0.94	0.98	0.96	0.77	0.47	0.15
	Total	0.39	0.52	0.60	0.70	0.66	0.44	0.15
D17S934	I	2.76	2.71	2.50	2.22	1.58	0.91	0.32
	II	1.35	1.33	1.23	1.10	0.82	0.49	0.16
	III	0.17	0.20	0.27	0.26	0.16	0.05	-0.02
	Total	4.28	4.24	4.00	3.58	2.56	1.45	0.46

Table 3b.

Two-point lod scores for chromosome 17 markers and hereditary fronto-temporal dementia.

		Recombination fraction (Θ)						
Marker	Family	0.000	0.010	0.050	0.100	0.200	0.300	0.400
D17S932	I	2.64	2.59	2.38	2.10	1.49	0.86	0.29
	II	1.61	1.57	1.44	1.27	0.90	0.50	0.14
	III	-3.98	0.36	0.89	0.96	0.79	0.47	0.14
	Total	0.27	4.52	4.71	4.33	3.18	1.83	0.57
D17S951	I	2.07	2.05	1.93	1.74	1.26	0.71	0.21
	II	0.68	0.67	0.61	0.53	0.37	0.21	0.07
	III	-0.45	-0.29	0.08	0.27	0.34	0.22	0.07
	Total	2.30	2.43	2.62	2.54	1.97	1.14	0.35
D17S791	I	1.55	1.54	1.42	1.25	0.85	0.46	0.16
	II	0.80	0.77	0.68	0.57	0.38	0.21	0.07
	III	-5.12	-0.70	0.05	0.31	0.38	0.25	0.08
	Total	-2.77	1.61	2.15	2.13	1.61	0.91	0.31
D17S788	I	-2.81	-0.79	-0.17	0.03	0.12	0.08	0.02
	II	- ∞	-0.42	0.17	0.34	0.36	0.23	0.07
	III	-13.03	-2.86	-1.35	-0.72	-0.19	-0.02	0.01
	Total	- ∞	-3.27	-1.35	-0.35	0.29	0.29	0.10
D17S790	I	-1.82	-0.02	0.60	0.77	0.73	0.48	0.18
	II	- ∞	-0.20	0.38	0.53	0.50	0.33	0.12
	III	-5.62	-1.43	-0.74	-0.45	-0.19	-0.09	-0.03
	Total	- ∞	-1.65	0.24	0.85	1.04	0.72	0.27
D17S787	I	2.60	2.57	2.43	2.20	1.65	1.02	0.39
	II	- ∞	-0.41	0.18	0.35	0.37	0.24	0.08
	III	-8.40	-2.46	-1.47	-0.92	-0.35	-0.11	-0.03
	Total	- ∞	-0.30	1.14	1.63	1.67	1.15	0.44

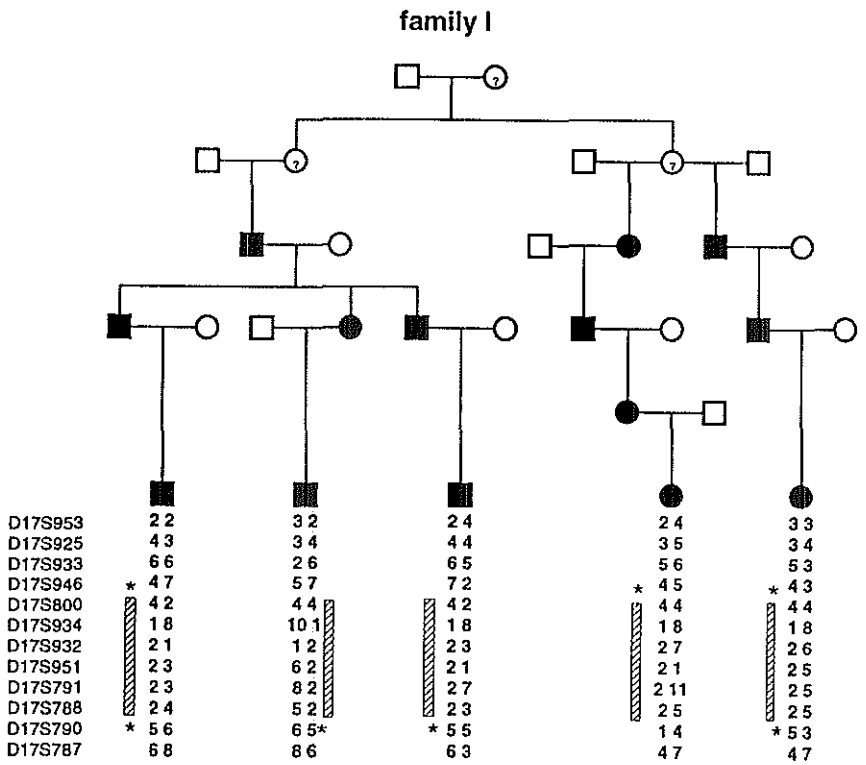


Figure 3a.

Marker data for chromosome 17q21-q22 markers for all available patients in the three families with hereditary fronto-temporal dementia. Markers are oriented from the centromeric side to the telomeric side. The hatched boxes indicate the maximum region of allele sharing between patients. *Alleles that are shared only by some patients in the family. Only relatives leading to a common ancestor are indicated. Family I.
Filled symbols represent affected individuals, question marks in symbols indicate that insufficient data were available to determine diagnosis, open symbols indicate unaffected individuals.

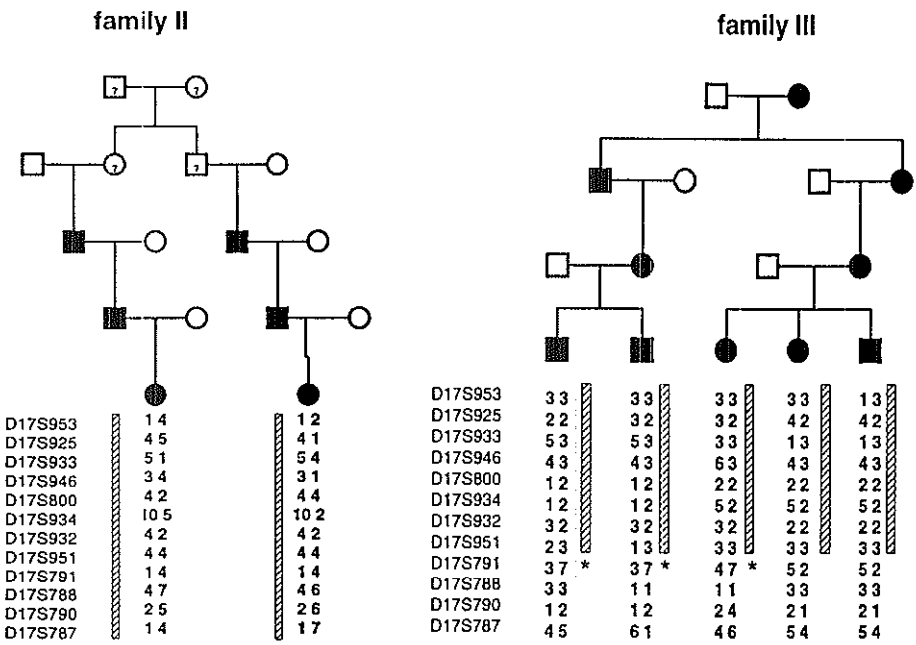


Figure 3b.

Marker data for chromosome 17q21-q22 markers for all available patients in the three families with hereditary fronto-temporal dementia. Markers are oriented from the centromeric side to the telomeric side. The hatched boxes indicate the maximum region of allele sharing between patients. *Alleles that are shared only by some patients in the family. Only relatives leading to a common ancestor are indicated. Family II and Family III.
Filled symbols represent affected individuals, question marks in symbols indicate that insufficient data were available to determine diagnosis, open symbols indicate unaffected individuals.

alleles were identical by descent (IBD) or just identical by state (IBS). In order to determine the size of the critical region for the gene responsible for HFTD we therefore compared marker data for affected individuals only (Figure 3 a/b).

The 5 patients from Family I share a common allele for 6 of the markers tested (Figure 3a). On the centromeric side no sharing was found for D17S953, D17S925, D17S933 and D17S946. On the telomeric side no sharing was obtained for D17S790 and D17S787. The two patients in Family II (Figure 3b) share a common allele for all 12 markers that were tested and no recombination event could be detected by comparing inherited alleles. The linkage analysis, however, revealed recombination events in this family for markers D17S788, D17S790 and D17S787 (Table 3). In Family III (Figure 3b) the patients share at least one allele for almost all markers except for markers D17S791, D17S788, and D17S787. At least two recombination events must have taken place in this family since only 3 out of 5 patients share a common allele for D17S791.

These data places the HFTD locus telomeric from D17S946 and centromeric from D17S791. The distance between both markers is 5 cM on the sex average linkage map (Figure 2).[29]

A common ancestor for the three families could not be traced genealogically. The patients from the three families do not share a common disease haplotype. This indicates that HFTD in the three families is caused by independent mutational events.

DISCUSSION

The three families with HFTD described in this study show strong clinical and pathological similarities. All patients presented with behavioral changes followed by mutism, and sometimes by pyramidal and/or extrapyramidal signs in the final phase. Selective atrophy of the frontal and temporal lobe is the characteristic feature on CT/MRI and at neuropathological examination in all three families. Anterior hypoperfusion on SPECT was a common finding. The unifying pathological feature in all three families was the selective frontotemporal atrophy with aspecific features. Although ballooned cells were present in

some cases, Pick bodies were lacking in all.

There are also some clinical differences between the three families. The mean age of onset in Family III was significantly higher than in the other two families. Disinhibition was the presenting clinical symptom in Families I and II, but loss of initiative in patients of Family III. Caudate atrophy, degeneration of the substantia nigra and white matter involvement found in some brains of the three families might reflect intra-familial phenotypical variation. Similar observations are reported in hereditary dysphasic dementia and other conditions with a descriptive diagnosis.[16,24,26] Ballooned cells were present in some brains of Families I and II. The fact that they were lacking in the only autopsied case of Family III does not indicate a pathological distinction from Families I and II, since ballooned cells were not found in several brains from these families either.

Family II has been cited as hereditary Pick's disease (HPD) in McKusick Mendelian Inheritance of Man.[32] However, if Pick bodies are essential for diagnosis Pick's disease then, according to the criteria, this family should not be considered as having Pick's disease, since Pick bodies were lacking in all cases. It is even doubtful if other earlier reported families did have HPD, since most of these families did not show Pick bodies.[7-10] Taking into account the contribution of Arnold Pick to the recognition of this type of dementia,[5] one might also re-define and re-introduce the diagnosis Pick's disease for all cases with frontotemporal atrophy. In that case, frontal atrophy with Pick bodies should be considered as a subtype.

We report linkage of HFTD in three Dutch families to chromosome 17q21-q22. All families generated positive lod scores with several markers from this chromosomal region. None of the families is informative enough to generate a significant lod score by itself but combining the data from all families gives significant evidence for linkage. The clinical heterogeneity of Family III compared with Families I and II is not reflected in the linkage results. Family III also generated positive lod scores for a number of markers (Table 3). Two unaffected individuals in this family share part of the haplotype that is found in patients (data not shown). These individuals are 70 and 75 years of age respectively and in the linkage analysis we assumed 95% penetrance of

the disease phenotype at that age. For this reason these individuals are regarded by the linkage program as likely recombinant cases, resulting in low lod scores curves that had their peak at a considerable recombination value from markers. Considering the later onset of the disease in this family, the linkage parameters that were used are probably to conservative for this specific family. It is still unclear whether these individuals will still develop the disease phenotype. Further support that Family III is indeed linked to chromosome 17q21 comes from the fact that all five patients share a common allele for more then 20 cM on chromosome 17q21-q22 (Figure 2 and 3b).

Comparison of marker alleles revealed recombination events in affected individuals with a number of markers. Recombination events with the markers D17S946 and D17S791 define the boundaries of the critical region. According to the CEPH/Genethon linkage map these markers are separated by a genetic distance of approximately 5 cM. The three families do not share a common "disease" haplotype suggesting that independent mutations are responsible for the onset of the disease in these families.

For a number of markers it could not be determined whether the shared alleles were IBD or IBS. We are currently constructing hybrid cell lines of all available patients in order to separate the "disease" chromosome and the "healthy" chromosome. This will enable us to determine whether shared alleles are IBD or IBS. These data could reduce the critical region further.

A large number of genes have been localized on chromosome 17q. Several of them are involved in neurological functions or diseases and could be regarded as candidate genes for HFTD. Glial fibrillary acidic protein (GFAP) is an intermediate-filament protein that is highly specific for cells of astroglial lineage (glial fibrillary tangles). The level of protein expression is elevated in patients with Alzheimer disease, Down syndrome and scrapie infection.[33-35] The exact localization of this gene on chromosome 17q is unclear.[36] The nerve growth factor receptor (NGFR) is able to bind nerve growth factors and is an essential component in the survival and maintenance of sympathetic and sensory neurons.[37,38] NGFR was located on a single restriction fragment of 500 kb with the HOX2B gene.[39] According to the mapping data in the Human Genome Database[40] the HOX2B gene is localized within the critical region for HFTD.

The microtubule associated protein tau that was localized on the long arm of chromosome 17 appears to be involved in the maintenance of axonal cytoskeletal structure. The gene is expressed in neurons and its transcript is subject to alternative splicing and post-transcriptional modifications. These modifications can lead to the formation of the paired helical filament, which is a major component of neurofibrillary tangles. Neurofibrillary tangles in Alzheimer disease[41,42] and neurofilaments in Pick bodies, as observed in sporadic patients with Pick's disease, stain intensively with antibodies against phosphorylated tau.[43] However, in brain tissue of cases of HFTD from this study no Pick bodies were found; ballooned cells were observed but they did not stain with antibodies against tau.

Genetic mapping on radiation hybrids places tau between markers D17S190 and D17S409.[44] These markers are not part of the CEPH/Genethon map that was used for this study and it is difficult to determine whether tau or one of the other genes mentioned above are localized within the critical region. We are currently in the process of mapping these genes into the CEPH/Genethon linkage map by using the GeneBridge 4 radiation hybrid mapping panel.[45]

This study demonstrates linkage in three families with HFTD to chromosome 17q21-q22. Recently, linkage was reported to the same region of three hereditary neurological disorders with a very strong clinical and pathological resemblance: disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC),[21] familial progressive subcortical gliosis (PSG)[22] and autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration (PPND).[23] Now an important question is whether these chromosome 17q21-q22 disorders are caused by mutations in the same gene, or whether there are different genes in this region that are responsible for these disorders.

The three conditions show considerable clinical and pathological overlap with HFTD in age of onset, presenting and subsequent symptoms, and most affected brain regions[24-26] (Table 2). All four conditions share a presenile age at onset and most patients show personality and behavioral changes as an initial manifestation. The mean age of onset between families varies, but this difference is smaller than the intra-familiar differences in age of onset. Brain tissue reveals only general features of

degeneration like neuronal cell loss and gliosis. Pick inclusion bodies are absent in all cases. Varying degrees of frontal lobe atrophy was present in all cases of DDPAC, PSG, and HFTD. In the PPND-family mild generalized atrophy with mild neuronal loss and gliosis was found. Degeneration of subcortical structures (caudate nucleus, hippocampus and substantia nigra) showed a rather similar pattern in all families.

There are, however, also some differences within the 'chromosome 17-families'. Firstly, parkinsonism was the only presenting symptom in 14 out of 26 affected family members of the PPND-family, but only in one out of 69 patients of the other families. During the course of the disease parkinsonism is also observed in the majority of the patients with DDPAC and PSG and in 10 out of 49 patients with HFTD. The absence of parkinsonism in the majority of HFTD patients must be interpreted with caution because most patients had their neurological examination in an early phase of the illness. The actual frequency of parkinsonism might have been higher in later phase of the illness.

Secondly, 5 patients from the PPND-family had dementia as the presenting symptom whereas in the other families these were personality and behavioral changes. To determine if these manifestations show overlap requires a detailed comparison of clinical data. Finally, there was a significant difference in age of onset between the first two families and third family of the present study. Even if there are some clinical and pathological differences between the phenotypes of HFTD, DDPAC and PSG these are no basis for a sharp differentiation into separate entities. Also the presentation of parkinsonism in PPND seems different from the other families, but it needs additional study to establish if this is phenotypic variation or locus heterogeneity.

At this moment it is unknown if these four conditions are genetically related. The published data do not allow definition of an overlapping critical region for the four disorders. The critical region for the responsible gene(s) for PSG and DDPAC has not yet been determined; multi-point linkage analysis for DDPAC suggested a localization between D17S800 and D17S787 but these borders are based on healthy "at risk" individuals and must be interpreted cautiously. The critical region for PPND was determined based on recombination events in affected individuals. This region, between markers D17S250 and D17S943 partly

overlaps with the critical region for HFTD reported in this paper.

The currently available data suggest that all four disorders might very well be caused by different mutations in the same gene or even by variant expressions of a single mutation. Another explanation might be different genes, localized in close proximity of each other, being responsible for the four linked neurological diseases. The answer to this question requires further dissection of this region and the identification of its genes.

In conclusion HFTD is part of a group of neurodegenerative diseases with striking clinical and pathological similarities. The critical regions for all four disorders show considerable overlap on chromosome 17q21. The available clinical and genetical data suggest that this group of disorders might be considered as phenotypic variants of the same disorder. The discussion whether the group of "chromosome 17 linked neurological diseases" should be considered as separate entities, as subtypes of HFTD, or even hereditary Pick's disease, will only be resolved after the identification of the responsible genedefect for these disorders.

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Chapter 6

Clinical heterogeneity in Fronto-Temporal Dementia linked to chromosome 17

(submitted for publication)

CLINICAL HETEROGENEITY IN FRONTO-TEMPORAL DEMENTIA LINKED TO CHROMOSOME 17

INTRODUCTION

Fronto-temporal dementia (FTD) is a common non-Alzheimer type of presenile dementia with frontal and temporal involvement, and behavioral rather than memory problems.[1-4] Among FTD cases a familial or genetic form is suggested by the family history in 20-50% of cases.[5-8] An autosomal dominant inheritance is documented in Northern European families and different designations are known, such as hereditary Pick's disease.[9-14]

Genetic and clinical heterogeneity among the familial fronto-temporal dementias became recently documented. Disinhibition-dementia-parkinsonism-amyotrophy complex linked to chromosome 17q21-q22 was the first disorder localized to this chromosomal area.[15] It was followed by about 10 families with hereditary FTD, including three from The Netherlands.[16] The descriptive diagnoses included familial progressive subcortical gliosis, presenile dementia with psychosis and dementia with pallido-ponto-nigral degeneration.[17-22]

This study reports three Dutch FTD families, genetically linked to chromosome 17q2-q22; the intra- and inter-familial differences in presenting symptomatology and age of onset and their ApoE genotype as a possible approach to risk differentiation.

METHODS

A nation-wide, three years (1994-1997) genetic-epidemiological study of fronto-temporal dementia in the Netherlands identified three large families in the Netherlands. These families were apparently unlinked, as demonstrated by genealogical studies up to 1800, showing no interfamilial connections. Dementia was transmitted as an autosomal dominant disorder in all three families.

Clinical information on affected cases was obtained by proxy interviews with first degree relatives and spouses, and information from clinicians and medical records. The age of onset was established from the ages at which behavioral changes developed as remembered by more than one relative. Early (first two years) and subsequent (from 2 years after onset) symptoms were obtained using a checklist of frontal features.

Complete clinical information was available on 18 cases (8 alive) in family I, and 21 cases (2 alive) in family II and 10 cases (3 alive) in family III.[9,10] Partial neuropsychological data were available on 12 cases in family I, 16 cases from family II and 5 cases from family III. Complete data were present on 3, 1 and 1 cases respectively.

CT scans were available in 23 cases (10 in family I, 6 in family II, and 7 in family III). 15/23 CT scans were reviewed by HT. MRI was available on three patients in family I. Six SPECT analyses were performed (3 in family I, 1 in family II and 2 in family III).

DNA studies were done on peripheral leukocytes after informed consent by proxy. ApoE genotyping was performed according to Reymer et al.[23]

A neuropathological diagnosis of FTD was available in 14 cases in family I (6 of these with a documented clinical history), in 15 cases from family II (11 of these fully clinically documented) and one case in family III. Neuropathological review of brain tissues (JMK, WK) was done on 5 cases (family I), 5 cases (family II) and 1 case (family III). Sections of different cortical regions, basal ganglia and pons were re-stained (hematoxylin-eosin and Bodian) and analyzed for Pick bodies and ballooned cells. Immunohistochemistry was done using antibodies against ubiquitin (1:125; Novocastra), τ (1:400; Dako, no. A 024), paired helical filaments (PHF)(1:100; ICN), somatodendritic microtubules associated protein (MAP-2)(1:170; Zymed), and ß-amyloid (1:600; Novocastra). A conventional peroxidase- anti-peroxidase method was used for staining. Age and sex matched controls (normal and with Alzheimer's disease) were used for comparison.

RESULTS

Clinical features

A relative early (Table 1) mean age of onset (50.4 years, family I and 46.5 years, family II) was seen in family I and II. The majority of affected cases manifested before 57 years. A significantly later onset (mean 63.4 years) was found in family III ($p < 0.001$) (Figure 1). However, the mean duration of illness was similar in the three families (8.2-8.7 years, range 4 to 16 years). The mean age of death differed from early (58.6 and 54.7 years) in families I and II to 71.9 years in family III ($p < 0.001$). The clinical evolution, the mean age of onset and of death remained stable over consecutive generations in the different families. The sex ratio of affected men and women was 2 to 5 in family II, and 1 to 1 in families I and III.

Progressive behavioural changes and speech reduction during the disease were found in all cases (Table 1). Disinhibition was the presenting symptom in 17 (94%) of family I-cases and 18 (86%) of family II-cases. However, loss of initiative was the major presenting symptom in family III (80%), with disinhibition developing only later. Hyperorality (76-90%), restlessness (60-83%) and stereotypic behavior (89-95%) occurred as an early or late symptom in all patients, similarly as a reduction of spontaneous speech (100%), and word finding difficulties (10-28%). Delusions (10-22%) were less frequent. Neurological evaluation early in the disease was normal, except for frontal release reflexes in some cases. Later, pyramidal (10-19%) and extrapyramidal signs (14-28%) occurred.

The neuropsychological profile, based on 5 cases with complete evaluation, showed associative and perseverative conduct, and decreased attention, concentration and initiative, and impaired abstraction, planning, and mental shifting. Visuoconstruction, orientation and praxis remained normal. In the remaining cases with partial data perseveration (88%), impaired executive skills (38%), decreased verbal fluency and speech reduction (54%) were frequently found. Orientation and memory functions were usually normal or only mildly impaired.

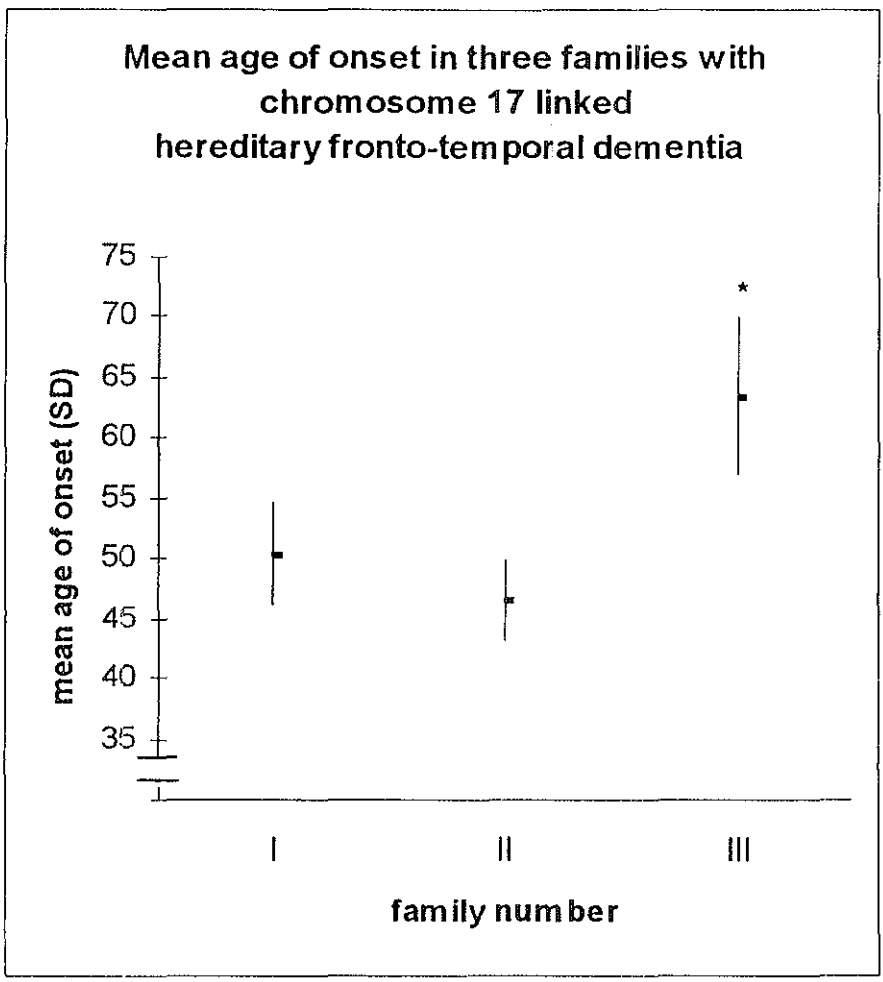
Table 1.

Demographic and clinical characteristics in three families with chromosome 17 linked hereditary fronto-temporal dementia.

	Family I		Family II		Family III	
	n = 18		n = 21		n = 10	
Age of onset (range)	50.4 (44-65)		46.5 (40-53)		63.4 (57-75)*	
Duration (range)	8.2 (4-15)		8.3 (5-15)		8.7 (6-16)	
Age of death (range)	58.6 (53-67)		54.7 (49-62)		71.9 (63-81)**	
	early# (%)	late## (%)	early (%)	late (%)	early (%)	late (%)
Restlessness	44	83	43	67	40	60
Disinhibition	94	100	86	95	30	100
Hyperorality	39	89	48	76	20	90
Stereotyped behavior	33	89	67	95	10	90
Loss of initiative	61	100	62	86	80	100
Delusions	28	39	10	19	20	30
Decreased speech	22	100	19	100	10	100
Imaging (CT)	n = 10		n = 6		n = 7	
Atrophy:						
frontal ≥ temporal	8		6		5	
temporal > frontal	1		0		1	
no abnormalities	1		0		1	
asymmetry	2		0		2	

* Mean age of onset in patients from family III significantly higher ($p<0.001$).
** Mean age of death in patients from family III significantly higher ($p<0.001$).
\# Early: manifesting during first two years after disease onset.
\## Late: manifesting ≥ 2 years after disease onset.

Figure 1.



* = Mean age of onset in family III (63.4 years) is significantly higher than in family I (50.4 years) and family II (46.5 years).

Imaging studies

On brain CT, 1 to 5 years after onset of the disease (Table 1) frontotemporal atrophy was seen in 21/23 cases. Temporal involvement was usually limited to the anterior pole. Two CT scans were normal. The severity of frontal atrophy usually (19/21) exceeded or was similar to temporal atrophy; temporal atrophy was predominant in 2/21 cases. The frontotemporal atrophy was symmetrical in 19/21 cases. Mild asymmetric ventricular dilatation was seen in 4 cases. The atrophy in families I-III was similar in degree and distribution. Increased signal intensities in the frontal subcortical white matter were seen on T2-weighted MRI images in two of three cases (see Figure 2). Frontotemporal hypoperfusion was found on 6/6 cases analyzed by SPECT (Figure 3); two of these had a normal CT scan. Anterior cerebral hypoperfusion increased during yearly, serial SPECT observations in one patient.

ApoE genotypes

ApoE genotyping was obtained in 7 cases (family I), 2 cases (family II), and 5 cases (family III)(Table 3). The frequency of ApoE2E2 was 7%, of ApoE2E3 36%, and of ApoE3E3 57%, and the ApoE4 allele was absent in all cases.

Pathology

The mean brain weight was 1035 g (n=14; range 855-1230 g) in family I, 920 g (n=15; range 730-1250 g) in family II, and 1170 g in the case from family III. Frontal atrophy was a consistent feature and anterior temporal atrophy was nearly constant (Table 2). Asymmetrical, predominant left frontotemporal, atrophy was found in 3 brains from family I. Degeneration of the caudate nucleus was found in 19 cases (in family I 9/14, in family II 9/15, and in family III 1/1). Neuronal loss, gliosis and spongiosis in the frontal and temporal cortex were constant findings. Substantia nigra degeneration was seen in 4/14 brains from family I and 4/15 in family II, and in the single case of family III. White matter demyelination and gliosis were found in 6/14 cases (family I), 5/15 cases (family II) and 1/1 case (family III). Sporadic neurofibrillary tangles were seen in the hippocampus in one case from family I and vague senile plaques were seen in the temporal lobe in another case from family I.

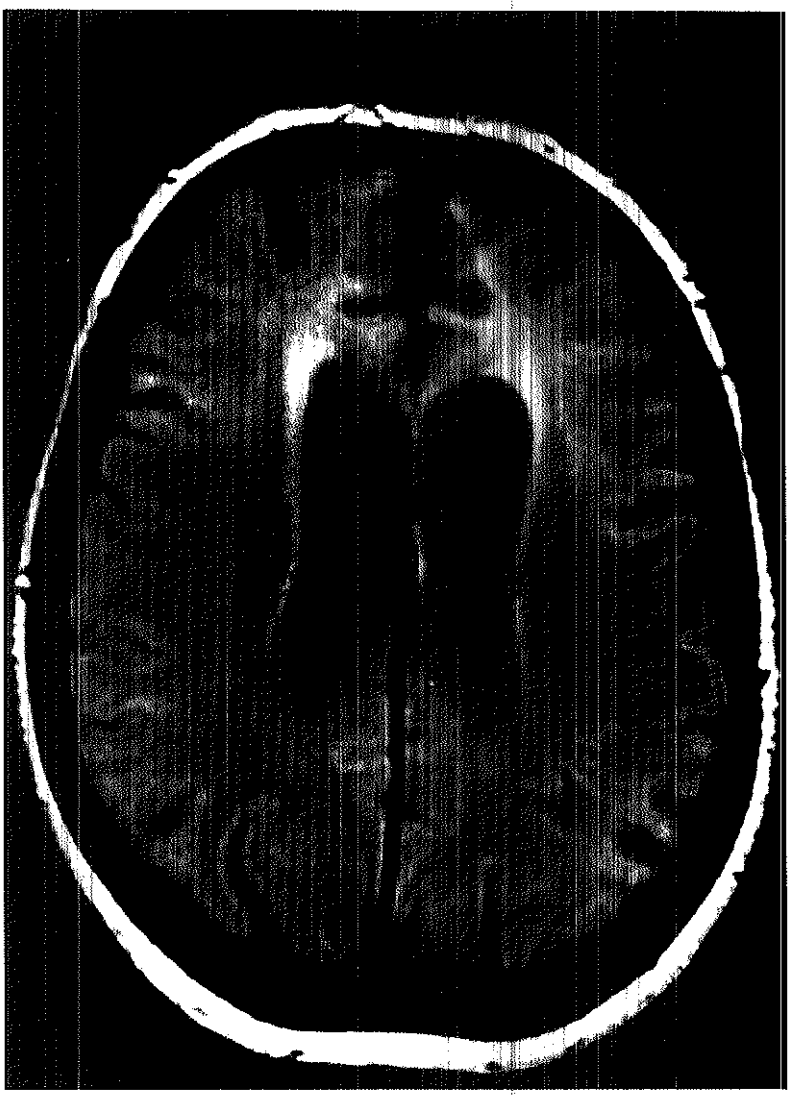


Figure 2. MRI scan of a patient from family I showing increased signal intensities in the subcortical white matter of the frontal lobe on T2-weighted images.

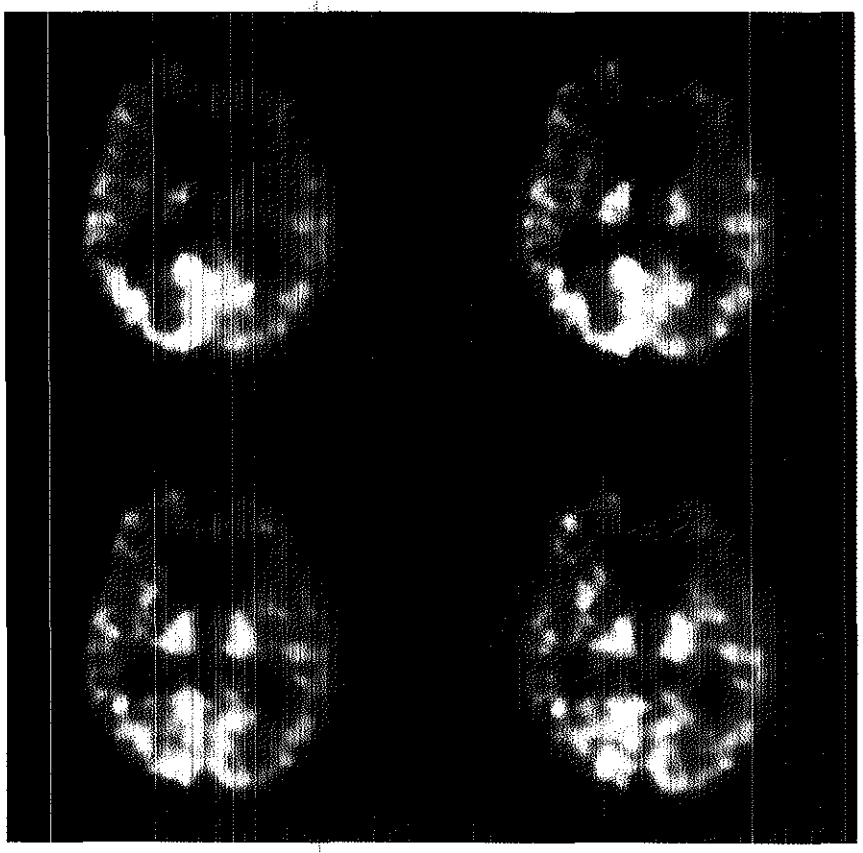


Figure 3. SPECT scans of a patient from family I showing marked frontotemporal hypoperfusion.

Table 2.

Pathology in three families with chromosome 17 linked hereditary fronto-temporal dementia.

	Family I	Family II	Family III
	n = 14	n = 15	n = 1
Macroscopical atrophy			
- frontal	14	15	1
- temporal	10	14	1
- caudate nucleus	9	9	1
Microscopical changes			
- white matter	6	5	1
- nigral degeneration	4	4	1
- ballooned cells	7	5	0
- Pick bodies	0	0	0

Table 3.

ApoE genotypes in three families with chromosome 17 linked hereditary fronto-temporal dementia.

Family	Patient	ApoE genotype	Age of onset	Duration (at death)
I	1	E2E2	65	-
I	2	E2E3	45	8
I	3	E2E3	44	-
I	4	E2E3	53	-
I	5	E3E3	54	-
I	6	E3E3	56	11
I	7	E3E3	57	-
II	1	E3E3	50	-
II	2	E3E3	44	-
III	1	E2E3	75	-
III	2	E2E3	57	-
III	3	E3E3	70	-
III	4	E3E3	57	10
III	5	E3E3	64	-

Pick bodies were observed neither initially nor on revision but for one case in family II. Ballooned neurons in cortex and/or basal ganglia were present in 7/14 cases (family I), 5/15 cases (family II), and 0/1 case (family III). No paired helical filaments, ß-amyloid, τ or ubiquitin were observed by immunohistochemistry (see Methods for antibodies used). Scattered and granular staining for MAP-2 was seen in neurons and glia in two cases.

DISCUSSION

Clinical heterogeneity for age of onset and presenting symptoms is observed in three Dutch families with FTD linked to chromosome 17. Brain atrophy is generally symmetrical as is shown by imaging and pathological studies. The ApoE4 allele was absent among cases tested and this suggests that ApoE4 does not influence the phenotype in familial cases with FTD as also recently reported by us.[24,25]

The age at onset in families I and II is quite constant over the generations (between 45 and 57 years); anticipation through an expanding trinucleotide repeat mechanism is thus very unlikely. The relatives at risk consider reaching the age of 55 as coming into the safety zone for developing dementia. A significantly higher mean age of onset (63.4 years; range 57-75 years) is present in family III. Other families with fronto-temporal dementia linked to chromosome 17 (FTD-17) show even a wider range between 27 and 74 years.[12,26] The mean duration of illness in the present families (8.2-8.7 years) is similar as seen in most other FTD-17 families; however, shorter duration and a few longer disease courses up to 26 years were reported.[22,26,27] The variation in age of onset within the Dutch families could not be explained by the distribution of the ApoE genotype, as has also been shown in presenilin families.[28]

Further clinical variability in FTD-17 is shown by the frequent disinhibition in families I and II, and other reported families[12,18,19,26,27,29], while loss of initiative as prominent feature in family III might lead to an erroneous clinical diagnosis of Alzheimer's disease. Speech impairments developed gradually in all cases in this study. The early occurrence of dysphasia (reduction of spontaneous speech and of fluency), dysnomia and

impaired comprehension is characteristic for hereditary dysphasic dementia, in which linkage to chromosome 17 also was established.[12,30] In that family, the temporal area might be affected early on in the disease as an enlarged temporal horn on CT has been found in one case.[12] Psychiatric symptoms, as delusions and paranoid ideas, were rarely seen in our study, but were frequent in familial presenile dementia with psychosis[27], and an initial diagnosis of schizophrenia was often made as in a few other patients from other FTD-17 families.[26,27]

Parkinsonism is another variable feature of FTD-17. It was seen during the course of FTD in some cases in this study, but is the presenting sign in more than half of cases with pallido-ponto-nigral degeneration with parkinsonian signs.[18] Reduced striatal tracer uptake was seen in 4 patients with this disorder.[18] The nigrostriatal dopaminergic pathway needs to be analysed in other FTD-17 families as well. Degeneration of substantia nigra, a rather constant feature of FTD-17, was clearly present in 9/30 cases in our study; however detailed neuropathological reports did not routinely mention the aspect of the substantia nigra.

A symmetrical frontotemporal atrophy on CT was found in all but four Dutch cases, the latter having asymmetric ventricular enlargement. Such an asymmetric pattern is also found in hereditary dysphasic dementia and the Swedish FTD-17 family.[12,22] Frontal atrophy on CT was absent in two early FTD-17 cases, but frontal hypoperfusion was shown by SPECT in these cases. Absence of frontal atrophy has been found in other (familial) FTD cases.[4,19,31] The frontotemporal atrophy was severe in all cases in our families, as contrasting to mild in disinhibition-dementia-parkinsonism-amyotrophy complex and pallido-ponto-nigral degeneration.[18,19] White matter gliosis induces increased signal intensity on T2-weighted MRI images as seen in 2 patients (Figure 2), which is also documented in neuropathological studies, and shows similarities to familial subcortical gliosis.[19]

Tau abnormalities were absent as studied by conventional immunocytochemistry in our families. Abnormal tau positive neuronal and glial inclusions (hyperphosphorylated sites) have been described in some FTD-17 families, using anti-tau antibodies (AT 8, AT 270, AT 100, AT 180, PHF1).[27,32-35] Studies with identical antibodies in the Dutch and other

families may be helpful to see if there is an FTD subgroup with a 'tau-o-pathy'; and whatever role tau has as a primary or secondary phenomenon in the disease.

Interfamilial phenotypical variation might be caused by different mutations in the same gene or in different genes. The patients from the three families do not have a common haplotype for the locus of the disease-gene. The disorder in these three families may be caused by independent mutational events.[16] The identification of an FTD gene and its mutational heterogeneity may give further insight into the causes of the clinical variability in these families.

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Chapter 7

Once revealed, no more to be concealed: pitfalls in genetic research on neurodegenerative disease: the case of Fronto-Temporal Dementia

(submitted for publication)

ONCE REVEALED, NO MORE TO BE CONCEALED: PITFALLS IN GENETIC RESEARCH ON NEURODEGENERATIVE DISEASE: THE CASE OF FRONTO-TEMPORAL DEMENTIA

INTRODUCTION

General introduction

An increasing number of neurodegenerative diseases is becoming defined at the molecular level since the last decade, enabling improved diagnosis and presymptomatic testing in late-onset disorders. Examples are Huntington disease, hereditary cerebral hemorrhage with amyloid-Dutch type, inherited cerebral ataxia, myotonic dystrophy, Alzheimer disease and many others.[1-6] The rate of detection of defects is increasing, especially in dominant disorders. Finding mutations in a gene often leads to fundamental insight into the normal and pathological functions of this gene. However translation of this knowledge into effective pharmacological or gene therapy for late onset neurodegenerative disorders is not expected in the immediate future.

Although gene localization and identification are obviously necessary steps to understand the etiology and molecular-genetic aspects of early and late-onset dementias, pedigree and linkage studies may be an underestimated burden for participants in families with a hereditary disease. Relatives may learn about their own risk for the first time through participation.[7] Facing the threat of an appalling disease can cause a variety of psychological, legal, and ethical problems for individuals at risk, which problems are often unfamiliar to clinicians and scientists.[8-13] Psychosocial effects of predictive DNA-testing have been extensively studied in Huntington families.[8,12,14-16] Little attention has been given to the effects of conducting family studies for establishing linkage and gene identification.

In a neurogenetic study on early-onset fronto-temporal dementia,[17,18] a careful study design attempted to prevent psychological distress when participants might become aware of their personal risks. The present paper describes several medical-ethical dilemmas not foreseen in the study

protocol, which required ad hoc decisions. This experience may contribute to improvement of genetic research protocols.

Fronto-temporal dementia

Fronto-temporal dementia (FTD), including Pick's disease, is a degenerative type of dementia, with onset usually in the fourth to sixth decade and with a duration of illness of 5-10 years. FTD is often sporadic, but a familial type is present in 20-40%.[19-22] The personality and behavioral changes (especially disinhibition), restlessness, stereotyped and perseverative behavior, emotional insensitivity with loss of insight and impaired judgement have a great impact on care givers and relatives. No specific treatment is available, but palliative interventions for behavioral disturbances are now being explored. Most patients are admitted in a nursing home when they become mute and severely demented.

METHODS

The Research Program

In a collaborative program on neurogenetics, patients with FTD (either sporadic or familial) were recruited from the Dutch population. This study included clinical, genetic-epidemiological and pathological aspects. Participation was asked from all neurological, psychiatric and geriatric centers to report data on patients with FTD, with the consent of the patient or his/her legal representative. Three large families were identified, showing an autosomal dominant transmission of FTD over 5 to 7 generations, and genetic linkage study allowed gene localization to chromosome 17 q21-q22.[17,18]

A family study implies that the investigators bear legal and ethical responsibilities to inform their subjects adequately.[23] All referred patients and their spouses or close relatives were requested to participate in the study through a letter handed out by the referring clinician.

At the interview (often held at the homes of patients/relatives) patients and their representatives were informed about the disease, its genetics, and the aims of the genetic study. A clear distinction was made between the research phase of the study: no information on the personal genetic

status would be disclosed. Later on, those wishing personal information, when linkage or a mutation would be established, could make an individual request at that time, for personal risk assessment and counseling after taking another blood sample. We did not want to harm individuals who only wanted to participate for scientific research. When the family history suggested more FTD cases, we asked the first participant to inform his/her relatives of this study and request, by means of an information letter, for participation as well.[24]

After giving adequate information, and establishing that this was understood, written consent was obtained.

The patient's medical records were reviewed, and the medical history was completed with information from the patient, the spouse or close relatives. The family history was obtained and checked for similar or related diseases in the first and other degree relatives. Genealogical searches using population registration data from 1800 onwards allowed linkage of pedigrees.

Clinical data on patients, obtained in our or other hospitals, included a general medical examination, neurological examination, neuropsychological testing, brain imaging (Computerized tomography (CT)/Magnetic Resonance Imaging (MRI) or Single Photon Emission Computerized Tomography (SPECT)). A blood sample was taken for DNA isolation.

Participating relatives at risk contributed a DNA sample. To prevent dissemination of unwanted information, doctors seeing the families were kept unaware of the distribution of the 'disease' haplotype in the pedigree. It was mentioned that localization or identification of the gene might enable predictive testing. Participants who asked for defining their personal risk status were referred to the clinical genetics department for genetic counseling and psychological support.[25]

The study protocol was approved by the Medical Ethics Committee of the University Hospital Dijkzigt, Rotterdam.

The ethical background of the research protocol

The protocol was based upon two moral key principles for involving individuals as subjects of research: respect for autonomy, and beneficence. Respect for autonomy implies that the informed consent of

the potential research participant must precede involvement in the research.[26] The information must be adequate and allow comprehension and 'informed decisions' by the research subject. Subjects should be told, amongst others, about the purpose, limitations, and possible outcomes of the study. Possible benefits and risks should be communicated in a balanced way. The consent component of informed consent refers to a voluntary decision on the part of a competent person. In case of incompetence of a candidate research subject, proxy consent of a representative should be obtained. The principle of beneficence c.q. 'do not harm' obliges the researcher to protect the best interests of research subjects. The relationship of risks to benefits should be assessed independently, and based on available data.

It was decided that personal results from the linkage or mutation research would not be communicated without an independent request for personal risk assessment and genetic counseling. Reasons for this approach are: (1) consent for a family study should not imply automatic identification of the at risk status for a late onset disorder, (2) there is often a long delay (> 2 years) before practical linkage or mutation analysis becomes possible, (3) an independent blood sample handled in a diagnostic laboratory is always needed to obtain a reliable personal risk assessment.

CASE-REPORTS

Case 1: the issue of beneficence: clinical versus research roles

The medical specialist who is also involved in research programs has the potential conflict of approaching the patient as a doctor (what is good medical practice?) or as a researcher (how will research benefit from this patient?).[25,27] It can be a dilemma to balance between on the one hand the importance of participation of a patient for the ongoing research in FTD, and on the other hand the necessity to avoid possible harm to patient and family. Another dilemma concerns the timing of asking consent. In the next case the dilemmas regarding the issue of beneficence, and balancing between clinical care and research interests are discussed.

Clinical course

A 47 year-old woman (married, three adolescent children) was referred to our clinic with a two year history of progressive changes in her behavior. Previously an efficient, serious and hard-working person she became slowly and progressively absent-minded, and neglected her domestic responsibilities. Her conduct became impulsive and restless. She was easily irritated and exhibited a rigid inflexibility in thinking. She walked an identical route every day regardless the weather. She lost emotional concern for her family. Obsessive economizing developed as she stopped buying groceries and new clothes. She nearly lacked any insight in her altered behavior and relations.

Neuropsychological and neurological examination, and imaging studies confirmed the clinical diagnosis FTD. Her mother died in a nursing home at the age of 62 with a dementing illness. Mother's father died in psychiatric hospital at the age of 70. Despite this family history the spouse and children were not aware that a dementing illness could be running in the family.

The clinician, who was member of the research team, recognized the name of the patient's grandfather as potentially belonging to a large kindred already known with hereditary FTD. Genealogical research, performed with the family's consent - as part of the diagnostic process - showed that this family was indeed related to the large FTD kindred.

Outcome of this case

The outcome of the genealogical research was not immediately communicated as the spouse and children were very upset about the diagnosis and perspectives of the patient, and needed time to cope with the situation. After one month, the clinician estimated that the spouse could be informed on the heredity of his wife's disease and the consequences for the children. The spouse had great difficulties in grasping the far-reaching impact of the genetic aspects of his wife's disease for his children. He discussed his confusion and anxieties about the burdening information with the psychologist of the team. Later another member of the research team informed the spouse and children on the study on FTD. After weighing the pros and cons they consented for participation, and expressed interests in further genetic counseling.

Case 2: the dilemma of the unexpected finding

Results from an autopsy are generally communicated to the spouse or children to confirm or refute a diagnosis. In this study, non-disclosure of personal results of the linkage study was agreed upon.[25] However, does this exclude the need to inform a family on the unexpected post-mortem change of a diagnosis in the deceased index patient?

Clinical course

A 55-year-old man was referred with a four year history of progressive changes in behavior. He had been admitted to a nursing home since a year.

Problems started at age 51, after the death of his wife. He left his work too early, he quarreled about irrelevant matters, showed inappropriate behavior and lack of emotional concern for his children. He was unaware of these problems. The family physician observed impulsive, disinhibited, and stereotyped behavior, hyperorality, and memory problems. He first diagnosed the problems as belonging to a severe mourning process. Six months later he referred the patient to an out-patient neurologic clinic. He had a weight gain of more than 20 kg. Speech, judgement and anticipation were severely reduced. Neurological examination and routine laboratory tests were normal. Neuropsychological tests indicated organic frontal dysfunction and CT-scanning demonstrated frontotemporal atrophy. The family history was negative.

A possible diagnosis of sporadic FTD was made. The children consented to participate in the study and a blood sample of the index patient for DNA analysis was obtained.

The patient died at age 57 after a progressive course into akinesia and near mutism. The autopsy showed macroscopically severe frontal atrophy and a degenerated caudate nucleus. Microscopically neuronal cell loss was noticed in the caudate nucleus, putamen and nigral substance. The neuropathological results could not confirm the clinical diagnosis FTD but provided strong indications for the autosomal dominant Huntington's disease, with the consequence of a 50% risk for the children to develop the disease. DNA-testing for confirmation of diagnosis or prediction in individuals at 50% risk is possible since 1987.[1]

Outcome of this case

The children were informed on the possible diagnosis of HD and briefly on the heredity of the disease by a member of the research team. They were referred to the department of clinical genetics for counseling and discussing the option of confirming diagnosis of HD in their father. In individual sessions the consequences were considered. All children and their partners wished to have diagnosis of HD in their father confirmed by the DNA-test. After confirmation of diagnosis they were counseled on the presymptomatic test for themselves. Initially, they all wished to have certainty, but after follow-up counseling (by the psychologist) they fully realized the implications of becoming identified as a gene carrier and reacted with shock and fear. All children expressed that they thought that they could not deal with a future that will inevitably be overshadowed by HD. One of them became pregnant and decided not to have the pregnancy tested on HD. The availability for additional support and/or counseling when needed was offered. They were informed on the Dutch patient organization. Only one (a year later) opted for presymptomatic testing.

Although the confirmation had also consequences for the siblings of the patient, and for their offspring, the children decided not to inform these relatives. They argued that they had underestimated the appalling impact for themselves and wished not to burden their relatives.

Case 3. The dilemma of safeguarding autonomy: individual versus joint sessions

In genetic research families are usually approached through a key relative who is willing to inform the other family members. Such information may have a far-reaching psychological influence in the family communication patterns. Therefore, as a rule, potential participants are individually approached, informed on the study, and asked for consent by the research team. This is done to protect the individual privacy and enable answering individual questions and needs. However, for reasons of convenience, researchers or families may ask for joint sessions to inform an entire family, ask their consent and sample the blood. In the next case the need and value of individual sessions are demonstrated.

Clinical course

A 57 years old man became progressively restless and aggressive after showing declining initiative in the previous years. He had difficulties in doing his work and gave up leisure activities. He wandered in town and drove around aimlessly without losing his way. He had no insight into his illness. His spontaneous speech diminished, he became completely apathic, mute and incontinent for urine. He died in a nursing-home at the age of 67. Neuropathological results revealed strong evidence for FTD.

The spouse and children knew that a form of early onset dementia was segregating for many generations in the family. Some children had been aware of their personal risks for developing the disease without knowing the precise magnitude of their risk. There was little communication about their father's disease and its possible genetic nature. After referral by the physician of the psycho geriatric hospital the spouse and one of her twelve children (age ranged from 20 to 45 years) allowed the research team to inform the other children about the study. They indicated that a joint information session at the mother's house would be the only option to obtain participation of all children.

Outcome of the case

The investigators insisted to have separate sessions with all individuals and four children decided to refrain from participation. The spouse was eager to learn more about her husbands diagnosis, but was also reluctant because of the possible consequences for her children. Of the 12 children at risk, some of the older had completed their families and approached the age of onset, which increased their uncertainty. Moreover, they had to face the problem how and when to communicate this knowledge to their children. The younger children were in the process of forming relationships and starting a family, and the sudden genetic information confronted them with their risks to pass the gene on to their future offspring.

Different problems were experienced. Some children at risk had supportive partners, others felt abandoned by their partners. Two daughters had greater experience with the disease through their years of involvement in care giving to their father, but that caused reactivation of those painful early memories. Lack of support by other siblings was

resented by them. The disease of the father and the different degree of involvement in care giving had caused anguish and family secrets influencing the inter-sibling relationships. The investigators were initially unaware of these perspectives when the children asked different questions. Some children said that certain questions could not have been asked in presence of their siblings or mother. Guilt feelings and resentments played an important role in their mutual communication. A son stated for example that it had been better when his father was admitted to a nursing home in an earlier stage.

DISCUSSION

The role antagonism of clinician - investigator, the problem of unexpected findings, and the impossibility of giving adequate pre-consent information during a family session are recurring themes in genetic family studies. Their frequency is only to increase as the power and speed of positional cloning of disease related genes through family studies increases, and clinicians and geneticists adapt more readily to the requirements of that 'trade'. However, every separate family and their individuals members will have a similar set of problems to be expected when confronted with an usually interested and eager clinician who wants to catch the familial disease in the network of modern genetics.

In the present study, the 'clinician - investigator' dilemma, the 'unexpected finding', and the 'personal versus group' concept of information of research subjects in a family study are addressed.

The 'clinician - investigator' dilemma

The 'Aha-Erlebnis' to hear a name of one of the ancestors in a kindred known to a clinician because of an inherited disease, is a classical 'clinical instrument', but not to be applied without great discretion and prudence. The clinician has the eventual responsibility to explain a diagnosis, and - if present - its heredity, as part of the diagnostic process. However, timing of information, and utilization of family and pedigree data for the diagnosis might consider the family's ability to comply with the speed and consequences of clinical thinking and wisdom. When the

family is entangled in a domestic crisis because of the diagnosis of the disease, the research involved clinician must use restraint before asking consent to proceed with agenetic study and to involve at risk individuals in research leading to future predictive testing. Asking participation and consent at a stage when shock and emotional imbalance predominate is inappropriate as the family members can not oversee all the ramifications of participation. The competence to consent is a necessary condition of informed consent. The notion of competence refers to a precondition of acting voluntarily and understanding information. Psychological conditions like shock and emotional disturbance may temporarily limit competence, rendering a possible consent invalid.

A second dilemma is the interaction of a clinical and research role of the doctor involved. It could be argued that a physician, who has also research interests, can not adequately safeguard the patient's process of making an independent decision. The researcher - clinician might be tempted to talk the family 'into' participating to research. However, if the family is interested in knowing about the disease and its heredity, they may be referred to a clinician not involved in the research team, or a clinical geneticist to secure the independent information about the clinical responsibility and research interests.[12]

Unexpected findings during clinical work-up or as a sequela of research interests

The post-mortem diagnosis in the second case was an unexpected finding which gave rise to a series of dilemmas. The suggestion of Huntington's disease could be confirmed with the use of DNA-mutation analysis. The first question is whether the team could ignore the unexpected finding, because information on this issue could possibly burden the children and secondly was beyond the purpose of the study on FTD. Given the relevance of excluding or confirming the diagnosis for the children the team considered this option to be unjustified.

The second question, thus, was when should children be informed? A first option is to test the paternal blood on HD by means of the patient's DNA without discussing this issue with the family. If HD is excluded the problem regarding HD is solved, confirmation of HD leads to informing the family. However, the golden rule - that nothing shall be done without

permission and consent of the participants - should not be violated. This leaves the second option to first inform the children about the hypothesis of HD and discuss with them to have it confirmed/excluded or not.[25,28]

The third question is who should inform the children? Should this be the research team, the general practitioner or referring medical specialist? In our opinion, the researcher should be cautious in taking this role. He has a professional responsibility that the consequences of his research efforts are adequately dealt with in the interests of the participants. However, with full awareness of the pitfalls the researcher may be the most appropriate person to inform and provide support, not in the least due to his professional relationship with the family. In addition, providing good medical care implies also a profound exchange and discussion with the participants' physicians.[25,27]

The fourth question is what should be told and how comprehensive should the provided information be? One alternative is to proceed with the paternal DNA testing for the specific disorder as part of the post-mortem diagnosis. The focus of the information at that stage is the relevance of the diagnosis and not the consequences for the children. If, in this case, HD is confirmed, the implications may be discussed with the children individually, including the option of predictive testing. Alternatively, information on the disease may be given in individual sessions with the emphasis on the risks for children of affected persons. However, discussing personal risks might cause uncertainties and preoccupation with early symptoms ('symptom search') which may prove unnecessary when HD is excluded. In our view this last alternative however does informed consent justice most adequately.

The subject of unexpected findings, with unexpected consequences for relatives of a research subject to be at risk for a different disorder as from one originally tested for, underscores the importance of 'preventive ethics', i.e. clinical ethics which is anticipatory and proactive, rather than only reactive, which has been advocated in this case. Preventive ethics, ideally, allows physicians and researchers to avert ethical dilemmas or at least identify potential moral conflicts earlier, when management may be simpler and more effective.[29] To prevent dilemmas in the second case, the possibility of unexpected findings should be discussed during the consent process.[30] It should be documented under which circumstances research subjects wish to be informed of such unexpected findings in the future.

Personal versus group setting

Concerning the dilemma raised in the third case, lessons from previous experience with Huntington disease have learned how the burden of a genetic disease can overshadow the entire family.[7,16,31,32] Collective denial and myths can accompany the segregation of the disease over more than two generations. Familial bonds can be severed due to the appalling disease, and marital discord is not seldom the result of the incapacity to adequately cope with the distress as a result of the disease.[33] These psychological effects may have profound influence on the current family communication and interaction patterns. An important reason for an individual approach in family studies is that the individual's participation must be based on free choice (the issue of autonomy), unimpeded by family pressure and divergent expectations. Also, there are individual differences in the need and capacity to receive information. The dosage of information might be tailored to the individual ability to work through the threatening perspective, and on the availability of emotional support by spouses.[34] The differences in age and the structure of the family (having or not having children) may result in different agendas that must be addressed.[10] Moreover, some individuals may wish to become extensively informed about the disease and personal risks (the novelty seekers), whereas others wish to remain ignorant (the deniers-avoiders). All these aspects of privacy of individual relatives cannot be safeguarded in joint sessions. Also, in the group setting individual questions and answers may induce adverse reactions in relatives such as rejection of thoughts about prenatal testing or suicide.

The investment of any research team or genetic counselor to provide information on a per-person/couple basis will be widely reimbursed by better understanding of individuals. The individual approach is most fit for implementing the subjective standard for disclosure of information, which takes account of the individual informational needs of persons in the process of making difficult decisions. It is this standard alone that can assure that persons are receiving the sort of information needed for valid informed consent.[35] Furthermore, the individual approach allows for a better ability of relatives to share or not share emotions or decisions. In conclusion, an individual/couple approach in genetic studies is a fundamental prerequisite.

Conclusions and ethical evaluation

What are the lessons from the cases described in this article? First, the clinician/researcher must be aware of the temptations of role reversal and act according to good medical practice. His first interest is the care for the patient; the scientific excitement ought not to interfere with good patient care. Requests for participation in research should be discussed at an appropriate moment. Second, informed consent, which is obviously a prerequisite for conducting genetic research, should account for unexpected findings in general. Even though it is an illusion that adequate informed consent can cover all specific unexpected findings or psychological ramifications, at least some of the dilemmas concerning unexpected findings can be prevented or more adequately dealt with. Third, the individual approach of participants safeguards all individual interests. Pragmatic reasons (practical availability of time and manpower) and the risk of loosing participants should be considered as subordinate to the individual interests.

Genetic research may result in predictive testing programs with the inclusion of psychological evaluation.[1,36] We emphasize that full and continuous attention should also be given in the stage of genetic research. This requires that members of the research team who have contacts with families must be knowledgeable about the psychosocial aspects. Although researchers may be optimal sensitive for the psychosocial impact of their research efforts on participants, there may be moments that they become blinded for the effects of their acting. Therefore, genetic research would ideally include systematic psychological and ethical evaluation in order to safeguard the needs of participants.[7]

We have observed that many participants have not made use of the availability of additional genetic counseling and psychological support while the research has raised many questions and uncertainties in them.[37] We need more insight into their coping strategies, i.e. how they come to terms with the burden of their personal risks. Also, observations in this group may increase the knowledge of how genetic research affects the communication within extended families.

Our presentation of three cases may contribute to the development of sound research protocols. In the final section of our paper we want to focus on what we consider to be a primary moral issue with regard to

genetic research, both chronologically and materially: the recruitment of participants among relatives of the index person. This issue is especially relevant in the context of genetic research on late onset, untreatable, disorders.

A key principle of research involving human subjects, namely that concern for the interests of participants must always prevail over the interests of science and society, should, of course, also apply to relatives who are approached for participation in genetic research. Can the recruitment of relatives be justified in view of this principle? An affirmative answer can only be given if the (possible) benefits of participation outweigh the (possible) risks.

During the study we gradually discovered that a larger than expected number of relatives did not suspect that the condition of the index person may be genetic, and that they themselves carry an increased risk of getting the disease.[7] If they do suspect this, they may underestimate the magnitude of their risk. In view of this, asking relatives to participate in genetic research may imply an unsolicited message that they (and their children) are at high risk of carrying harmful genes. This message is particularly burdensome if the condition under study is untreatable, and effective preventive measures are absent. The ethics of genetic research primarily focusses on possible risks of participation in research. The psychological risks involved in the recruitment of possible participants among relatives should, we think, be given due attention in the 'risk-benefit' analysis.

The latter risk can be considered acceptable from a moral point of view if they are being outweighed by possible benefits for participants in genetic research. One should, however, not take for granted that this is the case. Benefits often mentioned in the literature include that such research will provide options for predictive testing, that it will allow for better preparation on the future (especially planning career and family), and that research will ultimately give an outlook on prevention and (better) treatment of the disease under study. One should, however, acknowledge that these benefits are uncertain, if not speculative, and probably not eminent. Indeed, the time scale for the development of preventive or therapeutic treatment for dementia will probably be measured in decades, rather than years.[38] Furthermore, in many cases the

information that relatives are (or may be) at high risk will not contribute to their informed reproductive decision making. After all, some of the candidate participants will have completed their families, and if not, it is uncertain whether they will consider the information relevant for future reproductive choices. Finally, from the experience with presymptomatic testing for Huntington's disease it can be extrapolated that only a minority of the persons at risk will ultimately ask for presymptomatic diagnosis (if available) of late onset, untreatable, disorders when preventive options are absent.

In view of this, we suggest that recruiting relatives, who may not suspect that they are 'at risk', for participation in genetic research on late onset, untreatable disorders, may be more difficult to justify than is often assumed. In any case, this preliminary issue deserves a prominent place on the agenda for the ethics of genetic research.

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Chapter 8

Preparing for presymptomatic DNA testing for early onset Alzheimer's Disease / Cerebral Haemorrhage and Hereditary Fronto-Temporal Dementia

(J Med Genet 1997;34:63-72)

PREPARING FOR PRESYMPTOMATIC DNA TESTING FOR EARLY ONSET ALZHEIMER'S DISEASE/ CEREBRAL HAEMORRHAGE AND HEREDITARY FRONTO-TEMPORAL DEMENTIA

INTRODUCTION

An increasing number of neurodegenerative diseases have been defined at the molecular level in recent years, making it possible to determine the genotype precisely before the onset of symptoms. Presymptomatic testing programs are available for Huntington's disease (HD), hereditary cerebral haemorrhage with amyloid-Dutch type, inherited cerebral ataxia, myotonic dystrophy, and Alzheimer's disease.[1-6] For other autosomal dominant disorders, the genetic cause will be detected in the near, foreseeable future. Significant progress has been made in unravelling the dynamics of genes and their products.[7] However, effective pharmacological or gene therapy for late onset neurodegenerative disorders is not expected to be available in the immediate future.

In a collaborative programme on neurogenetics in Rotterdam, two studies on early onset dementia are currently being carried out. The first study concerns a family with presenile Alzheimer's dementia and cerebral haemorrhage (FAD-CH). FAD-CH is caused by a mutation in codon 692 of the gene for ß-amyloid precursor protein (ßAPP) on chromosome 21.[8] Extracellular amyloid plaques, intra-neuronal neurofibrillar tangles, and amyloid angiopathy were found in the brains of two FAD-CH patients. Mutations in the ßAPP-gene account for less than 3% of disease onset before 65 years of age.[8]

In a second study, early onset fronto-temporal dementia was found in three Dutch families with an autosomal dominant transmission pattern over 5 to 7 generations. The typical clinical features in the patients with hereditary fronto-temporal dementia (HFTD) were disinhibition, stereotyped behavior, roaming, and hyperorality. Frontal and temporal atrophy on CT scan supported the clinical diagnosis in eight, two, and five living patients in the three families, respectively. The diagnosis of HFTD was confirmed in each family by pathological examination of the

brain in one, 14, and 15 patients, respectively. Macroscopic examinations showed selective atrophy of the frontal cortex, non-specific changes (neuronal loss, spongiosis, gliosis), and ballooned cells. Evidence was found in these three families for linkage of HFTD to chromosome 17.[27]

HFTD and FAD-CH are primary degenerative diseases of the brain, with onset usually in the fourth to sixth decades of life.[9-12] Both conditions have an average age of onset between 40 and 60 years of age. The course in both disorders is variable, with the development of profound dementia ranging from two to 10 years after diagnosis. No specific treatment is available, but the use of palliative treatments is now being explored.

Misdiagnosis of HFTD or FAD-CH, such as depression (FAD-CH) or manic states (HFTD), may occur in the early stages of the disease and has often led to unsuccessful psychotherapy of couples. The diagnosis of FAD-CH and HFTD is psychologically devastating to the partner and his/her offspring, who have seen the patient's parent, sib, or another close relative become progressively disabled. People sometimes incorrectly believe themselves to be at risk because of symptom searching or preoccupation with early signs. Often, "soft" signs, which are not specific for FAD-CH or HFTD, are perceived as a precursor of the disease.

Genetic mutational or linkage analysis may confirm the diagnosis in patients with HFTD or FAD-CH and could provide presymptomatic testing for at risk subjects. Presymptomatic testing for Huntington's disease is considered as the paradigm for prediction programmes for other late onset neurodegenerative diseases and cancers[13] and should provide the experience necessary to improve pretest and post-test counselling. Before the introduction of the predictive test, attitudinal studies among those at risk for Huntington's disease have shown that the commonly cited reasons to take the predictive test were the unbearable uncertainty, anticipating the future, and planning a family, but that an unfavorable result might also lead to depressive feelings and suicidal behavior.[14-16] These surveys indicated that the majority would make use of a predictive test if it were available. With careful consideration of the ethical, clinical, and legal implications of presymptomatic testing for an incurable late onset disease,[13,17-19] guidelines were carefully developed and testing was carried out cautiously in research settings.[20] To date, requests for the test have been far below the expected rate, although in The Netherlands 150 people

apply for it yearly, and about 15% of the estimated cohort at 50% risk has received test results.[21,22] Only a small amount of experience has been reported on testing for presenile dementia. In Sweden, one out of three people tested at 50% risk for the APP 670/671 mutation was identified as a mutation carrier. After a one year period with depressive feelings and suicidal thoughts, this subject could eventually handle his situation. Intensive attention and care at the genetics clinic was needed. The non-carriers had expressed their relief.[23] Although the potential benefits of predictive testing may include relieving uncertainty and planning the future, the acceptability of, and need for, presymptomatic testing for early onset dementia has not yet been established.[4,25]

This study addresses the impact of approaching families with a hereditary presenile dementia for genetic research with the aim of establishing a predictive testing programme, as was done for Huntington's disease. We studied the ability to cope with being at risk for HFTD or FAD-CH, the influence of the disease upon a variety of areas of life, and the attitude towards presymptomatic testing. Guided by our clinical experience with these neurodegenerative disorders, we expected similar attitudes as were found in people at risk for Huntington's disease in the Dutch presymptomatic testing programme.[26] The results could be helpful for the medical-ethical evaluation of this and other genetic research programmes, to establish a suitable, disease specific testing protocol, and to develop support strategies when testing does become available.

SUBJECTS AND METHODS

Clinical, genetic-epidemiological, and pathological research was conducted on FAD-CH and HFTD in a collaborative programme in Rotterdam, The Netherlands. DNA linkage and mutation studies were done in one family with familial early onset FAD-CH[8] and three families with HFTD.[27,28] Participants were at 50% risk for HFTD (n=43) or FAD-CH (n=21) and cooperated after fully informed consent. Participants had a general medical examination, neurological examination, neuropsychological testing, brain imaging (MRI-scan), blood sampling, and were asked to participate in a clinical psychological assessment and

an attitudinal survey. The Medical Ethics Committee of the University Hospital Dijkzigt, Rotterdam, approved the protocols. Participants were informed about the disease (MS, CMvD, JCvS), and received information about the genetic pattern of the familial FAD-CH or HFTD. They were referred, when needed, to the Clinical Genetics Department for further genetic counselling (MFN) or psychological support (AT).

Forty-three out of 50 people at risk for HFTD (86%) and 21 out of 26 people at risk for FAD-CH (81%) gave consent for the clinical psychological study which consisted of an in depth interview and administering psychological questionnaires that were completed at home. Questionnaires were returned within a week after the interview. Demographic data (gender, age, marital status, employment status, number of children, number of sibs, and level of education) were collected. An Attitude Questionnaire (AQ) was administered that consisted of questions on the following areas: experience with the disorder, the age at which the person learned about the heredity of HFTD or FAD-CH, the subject's attitudes towards taking the presymptomatic test, the expected outcome of the test, attitudes toward prenatal testing and terminating a pregnancy in different circumstances. Most questions had the response categories yes/agree, don't know, no/not agree. Questions on experience with the disease, impact on personal life, and reasons for and against predictive testing were open ended, for which response categories were compiled to suit the common themes emerging from the answers. The estimated risk of inheriting the gene or developing the disease was assessed using a visual analogue scale. People who considered taking a future predictive test when it became clinically available answered questions about the anticipated impact of either test results. The AQ was adapted from the Dutch Huntington Presymptomatic Programme.[26]

The data were analyzed with version 6.0 of SPSS for Windows and the software Confidence Interval Analysis (CIA).[29] The data are presented as the 95% confidence intervals (95% CI) of proportions. For comparisons between groups, 95% confidence intervals for differences of proportions were used; a confidence interval that did not include zero indicated statistical significance. Chi-square analyses (for categorical variables) and t tests (for continuous variables) were used to determine whether there were any differences in demographic variables between groups.

RESULTS

Demographic information

The demographic information on the participants is given in table 1.

Table 1.

Characteristics of people at risk for hereditary fronto-temporal dementia (HFTD) and familial Alzheimer's disease/cerebral haemorrhage (FAD-CH).

	HFTD (n = 43)	FAD-CH (n = 21)
Mean age		
Years	38.7 (21-61)	38.1 (22-60)
SD	9.7	10.4
Time lag*		
Years	5.4 (0-37)	6.6 (0-40)
SD	8.9	6.9
No of affected relatives**		
Range	3.0 (1-7)	1.0
Male/female ratio	21/22	12/9
	No (%)	No (%)
Marital status		
Single	10 (23)	2 (10)
Married	26 (61)	14 (67)
Common law	6 (14)	2 (10)
Widow	1 (2)	-
Divorced	-	3 (14)
Children		
0 Children	17 (40)	9 (43)
1 Child	4 (9)	3 (14)
≥ 2 Children	22 (51)	9 (43)
Highest level of education		
Elementary/lower vocational school	14 (33)	9 (43)
≥ High school	29 (67)	12 (57)

* Period that elapsed since participant learned about personal risk for FAD-CH/HFTD.
** First or second degree.

Thirty-four subjects at 50% risk for HFTD and 21 for FAD-CH participated in the study on gene localization, and all except three from the HFTD group completed the psychological questionnaires. The latter three individuals withdrew from the study because they felt too anxious about their risk after having undergone the entire procedure. No significant differences were found between the HFTD and FAD-CH groups. The majority had a stable relationship and fewer than half had no children. Participants with children (60%) had a mean of two children.

Learning about HFTD or FAD-CH and personal risk

The average period that had elapsed (time lag) since participants first learned about their personal risks was about six years in both groups (Table 1). However, 24% of the group at risk for FAD-CH and 45% of the HFTD group first heard about their personal risks during this study. Eighty percent of both groups at risk learned about their own risk after the age of 18 years, at a mean age of 25.9 years (SD 8.6) and 26.5 years (SD 11.3). In the interviews, some people reported severe reactions, such as depressive feelings, guilt towards spouse and children, sleeping disturbances, phobic reactions, and marital problems. For others, participation in the genetic study meant relief because the scientific attention had given them some hope for the future.

Uptake of presymptomatic testing

Twenty-seven people at risk for HFTD (68%) and 12 at risk for FAD-CH (57%) would take the presymptomatic test when it became clinically available, whereas five (13%) and three (14%) people in either group were still uncertain about it. Nineteen (49%) out of the total group of 39 individuals who would take the test indicated that they would use it as soon as it became available. The others did not feel prepared to learn about precise risks at this stage. Eight people at risk for HFTD (20%) and six at risk for FAD-CH (26%) would not take the test.

Those who would not take the presymptomatic test were also against testing minors (<18 years). Half of the group that considered predictive testing had the opinion that children under 18 should be allowed to have the test. No differences were found between the HFTD and the FAD-CH groups.

Reasons for or against presymptomatic testing

For people who would take or consider taking a future presymptomatic test, the major reasons for uptake are presented in table 2. Generally, those at risk for either FAD-CH or HFTD cited similar reasons. Almost half of the participants declared their reasons as: helping research, informing their children, general planning for the future, and relieving uncertainty. Planning a family was only a minor reason for uptake. Two people would take the test for reasons of insurance. Considerations against presymptomatic testing were expressed by 28 people out of the group that considered predictive testing (60%). Fear of adverse effects such as anxiety and depression after an unfavorable result was mentioned by 24 of them (51%). Seven (15%) emphasized that an unfavorable result would overshadow their life entirely. One person feared that an unfavorable test result might lead to being refused insurance.

Table 2.

Reasons* for taking the presymptomatic DNA test for hereditary fronto-temporal dementia (HFTD) or familial Alzheimer's disease/cerebral haemorrhage (FAD-CH).

		HFTD[5] (n = 32)	FAD-CH[5] (n = 15)	
		No (%)	No (%)	95% CI for differences
(1)	For the sake of the children/ clarify risk to children	16 (50)	7 (47)	(-27; 34)
(2)	To help research/ to stop the disease	13 (42)	7 (47)	(-37; 24)
(3)	General planning for the future	9 (29)	7 (47)	(-48; 11)
(4)	To relieve uncertainty	15 (46)	4 (27)	(-08; 49)
(5)	To plan a family	3 (8)	3 (20)	(-33; 12)
(6)	To prepare for the future (anticipating the disease)	4 (13)	3 (20)	(-31; 16)
(7)	Insurance	-	2 (13)	(-31; 04)

* This was an open ended question; more than one reason could be given.

[5] Answered by those who would consider taking the presymptomatic test.

Fourteen subjects who would not take the test (eight at risk for HFTD (20%) and six at risk for FAD-CH (26%)) cited as the main reasons against testing the fear of unfavorable test results and the inability to cope with such an outcome, preoccupation with signs of the onset of the disease, and expected distortion of the current course of life. One person feared possible misuse by insurance companies. In this group only few reasons for testing were given: the responsibility to inform children (n=2), family planning (n=2), and to help research (n=2). No differences were found between the HFTD group and the FAD-CH group.

Impact of HFTD/FAD-CH on personal life

The impact of the disease on personal life is presented in table 3. Subjects at risk for HFTD reported significantly more preoccupation with symptoms than the FAD-CH-group. More than half (60%) of the HFTD-group said that the disease in their relatives had affected their mood (anxiety, depression) and had led to feelings of uncertainty.

Table 3.

Impact of hereditary fronto-temporal dementia (HFTD) or familial Alzheimer's disease/cerebral haemorrhage (FAD-CH) on life of people at 50% risk.

		HFTD (n = 40)	FAD-CH (n = 21)	
		No (%)	No (%)	95% CI for differences
(1)	Preoccupation with symptoms	24 (60)	3 (14)	(24; 67)
(2)	Restriction in planning the future	21 (53)	7 (33)	(-06; 45)
(3)	Anxiety, depression, uncertainty	24 (60)	6 (29)	(07; 56)
(4)	Disturbances of family life	5 (13)	2 (10)	(-13; 19)
(5)	Positive influence	-	4 (20)	(-36;-02)
(6)	No influence	8 (20)	11 (52)	(-57;-08)

More than half (53%) of the HFTD group felt restricted in making plans for the future. Four had previously undergone sterilization to prevent

transmission of the gene to their offspring. For FAD-CH, more than half of those at risk (52%) said that the disease had not influenced their personal life.

Comparison of the most significant symptoms of HFTD/FAD-CH in affected relatives as perceived by the participants (Table 4) showed that more than two-thirds (70%) of the HFTD group mentioned the disinhibition and restlessness as the most significant symptoms. In some cases, specific changes in oral/dietary behavior and sexual disinhibition was mentioned. In the FAD-CH group at risk, the most significant symptoms were dysmnesia and personality changes.

Table 4.

Most significant symptoms* of hereditary fronto-temporal dementia (HFTD) or familial Alzheimer's disease/cerebral haemorrhage (FAD-CH) as perceived and experienced by people at risk.

		HFTD (n = 40)	FAD-CH (n = 21)	
		No (%)	No (%)	95% CI for differences
(1)	Change of personality	12 (30)	6 (29)	(-23; 25)
	Disinhibition/restlessness	28 (70)	1 (5)	(48; 82)
	Loss of insight and judgement	12 (30)	4 (19)	(-11; 33)
	Emotional lability/euphoria	-	2 (10)	(-22; 03)
	Lack of spontaneity/ emotional unconcern	9 (23)	1 (5)	(02; 34)
	Depressive episodes	4 (10)	3 (14)	(-22; 13)
	Aggression	9 (23)	1 (5)	(02; 34)
(2)	Stereotyped behavior	4 (10)	2 (10)	(-15; 16)
(3)	Cognitive deterioration			
	Dysmnesia	17 (40)	7 (33)	(-19; 32)
	Disorientation	4 (10)	6 (29)	(-40; 03)
	Dysphasia	3 (7)	1 (5)	(-09; 15)
	Dyspraxia	12 (30)	2 (10)	(02; 39)

* In first or second degree affected relatives.

Expected effects of risk for HFTD/FAD-CH

Previous feelings about getting the disease or not were assessed with a visual analogue scale. Twenty-seven people at risk for HFTD (68%) and 15 at risk for FAD-CH (71%) thought that their personal risk was equal to or less than 50%. Eighteen percent in the HFTD group and 10% in the FAD-CH group estimated their risk as higher than 70%. Anticipation of the effects of being identified as a gene carrier did not differ between the groups and showed a high awareness of the increased burden for the spouse (Table 5).

Table 5.

The expected influence after receiving an increased risk of presymptomatic testing for hereditary fronto-temporal dementia (HFTD) or familial Alzheimer's disease/cerebral haemorrhage (FAD-CH).

An increased risk	HFTD (n = 40*)	FAD-CH (n = 21)	
	No (%)	No (%)	95% CI for differences
Will increase the problems of my partner	22 (55)	16 (76)	(-45; 03)
Will increase the problems of my children	17 (43)	12 (57)	(-41; 12)
Will allow me to plan my own future better	16 (40)	11 (52)	(-39; 14)
Will allow me to plan the future of my family better	14 (35)	11 (52)	(-44; 09)
Will increase my problems	16 (40)	7 (33)	(-19; 32)
Will cause me to become depressed	9 (23)	3 (14)	(-12; 28)
Will adversely affect my marriage/ relationship	4 (10)	5 (24)	(-34; 07)
Will decrease the quality of my life	7 (18)	2 (10)	(-09; 25)

* Participants who considered uptake of presymptomatic testing.

Participants vividly commented on how their affected parent was not aware of the deterioration in the later stages of the disease, but that the healthy parent became extremely burdened by the devastation caused by the disease and the difficult decisions to be made regarding the patient.

Twenty-three percent of the HFTD/FAD-CH group were afraid of becoming depressed. Forty-nine percent of the HFTD/FAD-CH groups had confidence that they could cope with an unfavorable test outcome, whereas 12% stated that such a result would ruin their life.

Two out of 39 subjects at risk for HFTD/FAD-CH (5%), who would undergo presymptomatic testing, indicated in the questionnaire that they might commit suicide after an unfavorable result and nine (23%) stated that they had not resolved this question. All but two indicated that they would seek professional help after an unfavorable test result.

The most commonly cited effect of receiving a decreased risk was a reduction in problems for spouses (70%) and children (54%) and improved planning for their personal future (51%) and the family's future (49%). Only 13% agreed that a decreased risk would improve the marriage/relationship.

Expected impact on family planning

Among the 26 childless people (41%), six persons wished to have children, another seven were uncertain. Three people with offspring would have more children. Six of the nine who wished to have (more) children would take the presymptomatic test. In case of an unfavorable result, one of them would refrain from having children, three were uncertain about prenatal diagnosis, one would opt for pregnancy termination of a fetus with an increased risk for the disease, and one would not use prenatal testing. Two people were uncertain about taking the presymptomatic test and did not agree with prenatal diagnosis. One did not wish to learn of his or her personal status, but would opt for exclusion testing, that is, excluding whether or not a fetus has received a chromosome from the affected grandparent.

Some participants would encourage their offspring to take the test before starting a relationship (35%), or before planning a family (42%). If an increased risk was found in their adult child, 31% of the respondents would encourage this child to opt for prenatal diagnosis.

The majority of respondents (59%) were against the availability of prenatal testing for HFTD or FAD-CH. When asked whether pregnancy termination was acceptable in a variety of situations (Table 6), a minority of all respondents found abortion acceptable in the case of prenatal

detection of an increased risk for HFTD or FAD-CH (20% and 29%, respectively). Among those who found the availability of prenatal testing acceptable as a clinical service (n=25, 41%), 19 would actually use it in the event of a pregnancy in their own family, whereas nine of this subgroup would terminate the pregnancy if the fetus showed an increased risk for HFTD of FAD-CH.

Table 6.

Attitudes of people at risk for hereditary fronto-temporal dementia (HFTD) or familial Alzheimer's disease/cerebral haemorrhage (FAD-CH) towards abortion in different circumstances.

I think abortion is acceptable if	HFTD (n = 40)	FAD-CH (n = 21)	
	No (%)	No (%)	95% CI for differences
Health of mother is in danger because of pregnancy	31 (78)	20 (95)	(-34;-02)
Prenatal diagnosis shows a serious disease	25 (63)	16 (76)	(-37; 10)
Prenatal diagnosis shows Down syndrome	18 (45)	10 (48)	(-29; 24)
Prenatal diagnosis shows increased risk for HFTD/FAD-CH	8 (20)	6 (29)	(-32; 14)
The baby is unwanted (for other than medical reasons)	12 (30)	6 (29)	(-23; 25)

Presymptomatic testing and additional support

Almost all participants (90%) emphasized that extensive pretest genetic counselling is a necessity when presymptomatic testing becomes available. Counselling should include exploration of all pros and cons of testing, with the inclusion of the emotional ramifications and the impact on marital and family interactions. In addition, 82% found that psychological assessment is necessary to assess whether test candidates can cope with the test outcome. Half of the participants (49%) held the opinion that the test should not be offered if the test candidate intends to commit suicide after an unfavorable result. Thirty-one percent stated that the test should not be offered unless the disease can be cured. Twenty-one

percent felt that the test results should not be added to the medical records.

DISCUSSION

Participation in pedigree linkage studies

Gene localization and identification are obviously necessary for obtaining information about the aetiology and molecular genetic aspects of early and late onset dementia. Common interests in the insight into the hereditary nature of dementia may contribute to future therapeutic interventions. Half of those at risk in this study mentioned "to help research" as an important motive for participation. Yet the potential burden of participation in pedigree and linkage studies is often underestimated by researchers and medical specialists. Facing the threat of an appalling disease can cause a variety of psychological, legal, and ethical problems for people at risk. In addition, family members may learn about their own risk for the first time through participation. This problem was often the case for the groups at risk for HFTD or FAD-CH. In the information sessions, many people did not fully understand all the ramifications of being at risk. Ideas about the heredity were only vague and information previously obtained from professionals (neurologist, general practitioner) were often similarly unclear. Most of the participants were accordingly shocked by the information about their own risks. Is it acceptable to recruit relatives for participation in research who may not even suspect that the disease under investigation is genetic, and that they may carry genes potentially harmful to them or their offspring? For some relatives the request for participation was not ominous news because they suspected that the disease was hereditary. Other relatives may have a positive attitude towards research because genetic information may be relevant, for example, for reproductive decisions or informing their children. Refraining from conducting family studies leaves a family ignorant and might prevent members from knowing the potential threat of personal risks. The moral price of such a policy is that family members are denied the possibility of anticipating their future and making general decisions. Obtaining consent, protecting privacy and confidentiality, and

safeguarding divergent and conflicting intrafamilial and intergenerational interests present moral challenges to the conduct of sound research.[30] Our experience emphasizes that strong collaboration of all disciplines (molecular and clinical geneticist, neurologist, psychologist, medical ethicist, general practitioner) involved is a requirement for conducting genetic studies.

Many people at risk for HFTD were preoccupied with early symptoms in themselves which reflected anxiety and great concern about their future, which was different for the FAD-CH group. The disinhibition/restlessness in the affected parent and other affected relatives was often experienced as frightening and overshadowed the lives of many of those at risk for HFTD. This fear affected their self-esteem, future prospects, and their relationship with spouses and relatives. Therefore, in the programming and institutional ethical review of pedigree and linkage studies, attention must be paid to the provision of genetic and psychological counselling. Also, familiarity with genetic concepts in all medical disciplines becomes essential and medical curricula must meet such requirements.

Localization or finding of the gene often results in the clinical application of predictive testing programmes, given the experience with Huntington's disease, polyposis coli, and breast and ovarian cancer. The predictive programme for Huntington's disease was embedded in careful genetic counselling following the international guidelines, and psychological follow-up.[20,31,32] Although the medical-ethical issues and benefits of predictive testing are still under debate, the widespread application of such testing as a clinical service proceeds for untreatable genetic disorders. It is not known whether alternatives for solving the emotional and decision problems in people at risk are offered and can be sufficiently met in health care. Predictive programmes may be too easily established as a result of finding a linkage or mutation, without proper ethical reflection or containment in a follow up research experimental condition.

Although genetic counselling often implies being the devil's advocate by discouraging people at risk from undergoing the test for diseases that have no outlook on treatment, the Huntington experience shows that applicants for the test are very determined to have test results, even in

those cases where other options of dealing with the threat might be preferable. Weighing the pros and cons of testing is eventually a personal responsibility.

Acceptance of presymptomatic testing programmes

Both FAD-CH and HFTD are rare, devastating diseases, yet the majority of participants in this study would take a presymptomatic test if it became available. As with results found in those at risk for Huntington's disease, many denied the potential untoward effects of becoming identified as a gene carrier.[26,33,34] Preparation for the future and worry about the spouse were the main reasons for taking the test, in contrast to the HD group, where family planning was paramount.[26] Because for the HFTD/FAD-CH groups the age of onset is usually much later and the risk increases dramatically as age advances, people at risk for HFTD/FAD-CH might consider testing for general planning such as retirement, medical directives, and early diagnosis and appropriate treatment.[24]

The purpose of counselling is to safeguard considerable deliberation. Half of the group that considered predictive testing found that testing should also be accessible for minors under 18 years, which is similar to the opinions of test candidates for Huntington's disease.[26] Yet the request of parents to test their children who are minors should be rejected as this would violate the child's right "not to know". It should be safeguarded that the child can make an autonomous decision when he/she reaches the age of majority.[35]

Twenty-eight percent of those who considered predictive testing would either commit or consider committing suicide after becoming identified as a gene carrier, although they would seek professional support. This is similar to attitudinal studies in HD.[16] Half of the participants thought that those who considered committing suicide after an unfavorable result should not be given the test. This raises the question of what is good clinical practice. Applicants for the predictive test who are in a shock or who are depressive, and who are consequently not able to make a well considered, autonomous choice, should not be given access to the test or testing should be postponed. In all cases, extensive pretest counselling is a prerequisite, in which the pros and cons of testing are

explored and weighed. It should be investigated whether the suicidal intention is an indication of either a depressive state of mind or of rational considerations. In addition, the counsellor can actively raise the issue of possible adverse reactions to unfavorable test results, with the inclusion of suicide intentions. It should be noted that the experience with testing for Huntington's disease has shown that people at risk who are not able to cope with unfavorable test results exclude themselves from testing (self-exclusion). What if a competent applicant expresses his intentions to commit suicide after unfavorable results? Should access to the test be refused in such cases? Such a policy has certain objections. First, prohibition of testing those considering suicide would lead to the concealment of suicidal intentions, as was experienced in the HD presymptomatic testing programme. Second, unconditional refusal of access to testing would be a violation of the principle of autonomy. This principle implies the professional respect for the applicant's considerations regarding the consequences of either test result. Moreover, refusal of access to the test has its moral price because this would force test candidates to remain uncertain about their genetic status. Suicide is not immoral and the intention to commit suicide in certain circumstances not unreasonable. Hence, suicide in case of an unfavorable test result is not a priori irrational. Consequently, it is, in our opinion, a priori morally tenable to allow access to a future predictive test if an applicant expresses his intention to commit suicide after unfavorable test results. In conclusion, we recommend that anxieties and expectancies regarding one's fate be openly discussed. Testing may be postponed and additional support offered when needed. It should also be noted that, as clinical experience with Huntington's disease has shown, suicide may become an option in the final stages of the disease, and not as a reaction to an increased risk test result or after onset of the first signs of the disorder.

People who are the first in a family to participate in genetic studies and presymptomatic testing programmmes may assume the responsibility for informing their offspring and relatives about the new information. In the families studied, the key person was often the patient's spouse with whom the heredity of the disease was first discussed and who consented by proxy to testing the affected patient. Such proxy consent is acceptable given the potential interests of children and other relatives with regard to

certainty about personal risks, or the relevance of differential diagnosis. In addition, confirmation of diagnosis using DNA testing does not conflict with the demented patient's interests. It may be objected, however, that the potential interests of children and other relatives disqualify them as proxy. Therefore, good medical and ethical practice requires close consideration and discussion whether personal interests interfere with being a proxy.

Information on genetic studies may cause emotional upheaval in relatives who are informed and resentment against the informants. Informing and supporting people with this specific mission about these family issues, which are usually unexpected, may stimulate other relatives to appreciate the value of family studies.

The intended uptake of testing among the HFTD/FAD-CH groups is similar to the intended uptake in the HD groups at risk. The actual uptake may be much lower given the HD experience,[36] which is illustrated by the finding that only a minority wishes testing immediately upon availability. As in the HD studies, participants at risk for HFTD/FAD-CH emphasized the need for extensive pretest counselling and psychological assessment. Again, the group that requires predictive testing should also be informed about alternative ways of dealing with the issues that led to uptake of the test. Psychotherapy or behavioral therapy might help people to cope better with their anxieties. Couples could be supported in exploring other ways of dealing with their wish to have children. Predictive testing programmes seem to be subject to the "technological imperative". Therefore, the counsellor should approach applicants with full respect for their opinions but must also play the role of the devil's advocate when trying to discuss the pros and cons of testing and consideration of alternative coping strategies. However, this requires a closer collaboration of clinical genetics services and institutions of mental health.

Predictive testing for presenile dementia, such as Alzheimer's disease, should be undertaken only in the context of research protocols, using careful neurological and psychological assessments.[24] Testing should not run unnoticed in a widespread clinical application without proper previous evaluation of such a service. However, predictive testing is generally considered, by both professionals and potential users, as a clinical service and not as a research protocol, with the consequence of a lack of follow

up data, which hampers a thorough medical-ethical evaluation. Obviously, the relevance of mandatory research assessments for the evaluation of predictive testing should be clarified. Consequently, the contribution to the improvement of the clinical service must be convincing. If these requirements are met, people should be encouraged to participate in research assessments, and to adhere to the provisions of a research protocol. This may be an appropriate expectation by those offering presymptomatic testing for HFTD or FAD-CH and HFTD.

One special issue that was not addressed by the Alzheimer's study group,[24] but which needs attention, concerns those at 25% risk, who are asymptomatic grandchildren of affected subjects. Identification of a person at 25% risk as a gene carrier identifies the unaffected, intervening, parent as a carrier of the disease mutation. Moreover, sibs would see their risks increase to 50%. After the identification of the HD gene, recommendations for presymptomatic testing included a statement regarding those at 25% risk. These recommendations stated that extreme care should be exercised when testing a person at risk would inadvertently provide information about another person who has not requested the test. In such cases, every effort should be made by the counsellors and the subjects concerned to provide a satisfactory resolution of this conflict.[20] The majority of representatives from lay organizations favored the opinion that if no consensus could be reached, the right of the person at 25% risk should have priority over the right of the parent not to know. An important argument is that planning a family may be the main reason for young adults to take the test, whereas their unaffected parents see their chances of ever developing HD dramatically decrease after the age of 50. Those at risk for presenile dementia are approaching the mean age of onset after 50 years of age, at a time when their children may start a family (three-quarters of the grandchildren in the study group are older than 18 years). Thus, we expect more conflict of interests compared with HD and, in line with the HD guidelines, every effort must be made to solve such controversies both at an individual and a family level. The serious dilemma for the counsellor is whose rights and interests should prevail. Should the counsellor give priority to the applicant's right to know or should he deny testing in order to protect an invasion of the relatives' right not to know? Exclusion testing in a person at 25% risk

may be a solution, that is, excluding whether or not one has received a chromosome of the affected grandparent. Such an outcome does not change the risk of the parent at 50% risk. However, the initial conflict arises again if the applicant's risk has increased to 50% and he/she wishes full certainty. Obviously, an unequivocal guideline is not compatible with the individual interests of all parties involved. The counsellor's responsibility is to safeguard that all advantages and disadvantages are discussed and weighed, with the inclusion of the impact of testing for relatives. Eventually, the test candidate should decide and have the responsibility for his decisions. It is obvious that inherited late onset disorders should be considered as a problem that may have affected the whole family for more than two generations. The family is therefore a relevant clinical frame of reference for the genetic counsellor and other health care professionals.[18,37,38]

Prenatal testing

When using the Dutch HD testing programmme, one of the main aims was to obtain information useful for family planning.[26] Family planning was found to be less important in the present survey of people at risk for HFTD/FAD-CH. The majority were against the availability of prenatal diagnosis as a clinical service. Little more than half of those who supported such provision would use it personally and even in this group half of the respondents rejected pregnancy termination if an increased risk in the fetus was found. The eventual demand for HD prenatal testing was lower than was expected from pretest attitudes, but was constant over time (unpublished data presented at the 16th International Meeting of the World Federation of Neurology Research Group on Huntington's Disease, 1995). The expected use of prenatal diagnosis in HFTD/FAD-CH might be even lower. This expected uptake might reflect feelings in the latter group that onset of the disease is generally later.[9,39] These attitudes reflect the painful and thoughtful handling of options by those at risk and make clear the need for human compassion for people who have experienced the tragedy of the disease in their families. Hence, the individual request for prenatal diagnosis ought to be appreciated. However, access to prenatal diagnosis for untreatable late onset disorders should be denied to couples who would consider a selective pregnancy termination, in order to

prevent the violation of the future child's right not to know. In the present study, 10 out of 19 couples would opt for prenatal testing but not for selective abortion. This requires prudent counselling of couples before conception, if possible. This may be a task for the general practitioner followed by referral to a clinical genetics department.

Preimplantation genetic diagnosis may become an alternative in the near future. Recently, it has been suggested that preimplantation genetic diagnosis could be used as a method to achieve prevention of untreatable, autosomal dominant late onset disorders in offspring without disclosure of parental genotype.[40] The couple would be told only that their embryos were tested, and that only apparently disease free embryos were replaced. No information would be given which might provide a basis for inferring whether or not any embryos with the mutation were identified. Hence, parents would derive no direct or indirect information about their own genetic risk, while preimplantation diagnosis could reduce the fetal risk to zero. This option could be valuable for parents at risk who prefer not to know their genetic status. It remains to be seen, however, whether this is a realistic alternative. First, the burdens and risks of in vitro fertilization should not be underestimated. Furthermore, a condition would be to separate those involved in the testing procedure and the counsellor, otherwise it may become impossible to protect the parent's right not to know adequately.

Genetics and discrimination

Both employers and the health, life, pension or disability insurance companies may discriminate against people known to have an increased risk for cancer or neurodegenerative diseases.[41] The Dutch debate on the person's duty to reveal genetic information to insurance companies, and on exclusion from life insurance of those at risk for HD and myotonic dystrophy, leads us to emphasize the potential harm to carriers of genes for untreatable genetic disorders with delayed onset. Our clinical experience has taught us that most people at risk for a variety of inherited late onset disorders are not aware of the risk of insurance and employment discrimination or tend to underestimate these issues. Some people have requested predictive testing in order to get access to life insurance. This experience underlines the need for further discussion

regarding the use of genetic information by insurance companies and employers. We advocate that participants in genetic studies must be extensively informed of the potential hazards, which may lead to withdrawal from the protocol, or to delay testing until arrangements have been made. At the time of our study, much media attention was paid to the discrimination based on genetic risks, which might explain that 20% of the participants held the opinion that test results should not be added to the medical records. Local legislation should protect people with a genetic susceptibility so that those at risk feel free to use the options of genetic testing, and scientists can proceed with research.[41] Although legal, ethical, biomedical, and psychosocial issues must be extensively addressed in pre- and post-test counselling sessions, we are aware that the informed consent remains unsatisfactory and has much limitations with regard to these issues.

Genetic research and health care

The increasing number of diseases that can be predicted by genetic testing (with far reaching consequences) raises the question of how genetics services and other medical disciplines can meet the need for careful pre and post-test counselling and additional support. Although the need is acknowledged and emphasized in every study, the planning and resources required are rarely considered in most countries. This leaves the human aspect of genetics, such as psychological support and evaluation studies, dependent upon external, temporary financial support. Such lack of continuity in patient care and research and dissemination of clinical research findings may greatly endanger the quality of genetic medicine in the future.

Follow up care must provide proper and consistent information and support about the effects of test results on partner relationships and families. General practitioners must be properly informed about the impact of being at high risk on psychological well being. Health care providers must consider the complex psychological, ethical and social issues in the application of presymptomatic testing. They should be aware of their own feelings of helplessness,[42-44] and be careful not to consider the test as the only option. They must be educated on these issues in order to establish adequate support provisions.

Conclusions

The major limitation of this study was the relatively small number of participants. Another bias may be caused by a number of sibs in the study as four different families were involved. Therefore, the results must be considered with caution. The group studied may not be representative of the entire population at risk for presenile dementia. Moreover, the results, with the inclusion of the intention to have predictive testing when available, may have been biased by the extensive psychological attention of the researchers that the participants received. An important limitation is that the data were obtained by means of self-report. The disadvantages of self-report data are well known and include possible social desirability bias. Therefore, qualitative studies using observation and interview techniques and case studies conducted by people who are able to observe people at risk and their families objectively can improve the understanding of the observations which will consequently increase the clinical significance.

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Chapter 9

General discussion and conclusions

GENERAL DISCUSSION AND CONCLUSIONS

9.1 INTRODUCTION

The familial and genetic aspects of fronto-temporal dementia (FTD) are the central theme in this study. The update and extension of earlier work on familial FTD in our country[1,2] allowed, also through a nation-wide inventory, the analysis of family material that enabled localization of the gene (see chapter 5).

Simultaneously, the first, three-years prospective case-finding study in this country, allowed an estimation of the prevalence of this disease (see chapter 3).

The genetic-epidemiological comparison of familial and non-familial FTD was addressed, and the differentiation of the disease from Alzheimer's disease: in familial FTD no association for disease risk or other parameter was found for apolipoprotein E4 (ApoE4)(see chapter 3 and 4).

The psychological burden and ethical implications for relatives to become involved in a genetic study of an untreatable disease in their family may reinforce the genetic threat of that disease and bring people closer to the fear of losing their own personality, strength and characteristics. These aspects are rarely addressed in family studies in late onset genetic disease (see chapter 7 and 8).

9.2 METHODOLOGICAL CONSIDERATIONS

The studies on familial aggregation of dementia in FTD (chapter 3) and the association with the apolipoprotein E 4 allele in FTD (chapter 3 and 4) were the first population based studies, allowing ascertainment of cases as complete as possible. Misdiagnosis and selection bias of cases could still have influenced the data on prevalence and familial aggregation. Diagnostic accuracy might be impaired in two ways. Firstly, FTD might eventually (at autopsy) be proven as Alzheimer's disease (AD) or another non-FTD disorder. In our study (n=74) the diagnosis FTD was probable in 55 cases and definite in 19 cases using autopsy and/or

linkage to chromosome 17 as criteria. In 43 out of these 55 cases the clinical diagnosis was supported by severe frontotemporal atrophy on CT, which correlates strongly with the pathological diagnosis[3-7], and by frontotemporal hypoperfusion on SPECT in the remaining 12 cases with mild atrophy on CT. It seems very unlikely that the probable diagnosis in our patients will proven to be wrong, due to the strict supportive neuroimaging criteria. Many spouses and first degree relatives of living FTD patients are willing to give informed consent for post-mortem studies, which will enable us to verify the diagnosis in the near future. This will increase retrospective diagnostic accuracy in the future.

Also, an erroneous diagnosis of AD might, in fact, be FTD. Early FTD cases may easily become mislabelled as AD when FTD still shows normal findings on CT or MRI.[8] The distinct nature of FTD usually becomes evident soon by the its prominent frontal symptomatology, selective frontotemporal atrophy, and by the relative preservation of spatial orientation, praxis and memory functions.

9.3 GENETIC-EPIDEMIOLOGICAL DATA

The genetic-epidemiological study (chapter 3), the first nation-wide study of this disease, shows a prevalence of FTD in the Netherlands ranging from $1.2/10^6$ (age group 30-40 years), $3.4/10^6$ (age group 40-50 years), $10.7/10^6$ (age group 50-6- years) to $28.0/10^6$ (age group 60-70 years). These data are comparable to other observations.[9] Familial aggregation of dementia as evidenced by a positive family history for dementia in first degree relatives was found in 38% of FTD in our series.

If one takes the total of FTD cases (n=74) in our epidemiological survey, their first degree relatives have a 3.5 fold elevated risk for developing dementia as gender and age matched controls. Even after excluding the FTD cases with known linkage to chromosome 17, the hazard ratio of dementia in first degree relatives of FTD patients with unknown linkage remains significantly elevated (HR=2.4; 95% CI: 1.5-3.7)(chapter 3).

The families with FTD in the Netherlands allowed gene localization of a gene for FTD to the chromosome 17q21-q22 area (chapter 5); this result was possible by extensive analysis of the original family from the

Netherlands,[1,2,10] and two newly identified families. Haplotype studies (chapter 5) on the chromosomal area containing the mutation gave evidence for independent mutations in these families as no shared haplotypes were found, indicating possible allelic heterogeneity; the age of onset (earlier in families I and II, later in family III) supports this evidence for genetic heterogeneity (chapter 6).

Recent gene localization studies on the various forms of FTD have given an expanding spectrum of clinical designations and eponyms (see Table 1 in chapter 1) of diseases linked to an apparently identical area on chromosome 17q21-q22, resulting in the questions:

- are there so many genes in this rather narrow chromosomal region?
- are there so many different mutations in a single gene in that area, and is the τ-gene a possible candidate? The absence of haplotype sharing among the three Dutch FTD families suggests rather heterogeneous mutations in this area.
- which molecular mechanism will eventually be found as a unifying concept for FTD-17 diseases, that broadly share important clinical characteristics?

As $\pm$ 60% of Dutch FTD cases had a negative family history for dementia, it remains to be clarified if the disease mechanism is similar as in the genetic forms, or if other errors-like somatic mutations, transcriptional or translational errors occurred. The similarity arises with the debate on the different causes of 'sporadic' Alzheimer's disease (possible transcriptional error)[11] and early onset familial Alzheimer's disease (mutations in genes located on chromosomes 1, 14 and 21).

9.4 APO E4 GENOTYPE IN FTD

The occurrence of the apolipoprotein E4 allele in homozygous and heterozygous state was found to be a risk indicator especially for non-familial Alzheimer's disease.[12-14] The ApoE4 genotype in FTD was analyzed in our population based study in a subgroup of 34 FTD cases without clear evidence of autosomal dominant inheritance (chapter 4) and showed a significant association with FTD (OR=4.9; 95% CI: 1.1-20.1). A decreased age of onset was found as the number of ApoE4 alleles

increased, suggesting a similar mechanism as the ApoE effect in Alzheimer's disease.[13,15-17] A re-analysis of ApoE4 in a larger set of FTD patients also showed (see chapter 3) a higher frequency of the ApoE4E4 genotype in cases, most pronounced in those without a family history of dementia, compared to controls.

The predictive value of ApoE4 status for risk identification is clearly absent in familial FTD (none of the tested patients with linkage to chromosome 17 had an ApoE4 allele), and only contributory in sporadic FTD. These results also imply that ApoE4 status is probably useless in the differential diagnosis between AD and FTD. Since the different Apo E alleles may be related to the formation of hyperphosphorylated τ, τ-pathology has to be further investigated in FTD.[18,19]

The analysis of families at the level of clinical phenotype, ApoE4 association and chromosomal linkage has greatly contributed to our understanding of the complexities of fronto-temporal dementias, in their course to become identified at the molecular level. The clinical diversity of disorders mapped to the candidate area will give a further insight into the tremendous variability between a gene mutation and the phenotype in major brain disease.

9.5 PSYCHOSOCIAL AND ETHICAL ASPECTS OF GENETIC FAMILY STUDIES ON NEURODEGENERATIVE DISEASE

The participation of families is inevitable in molecular-genetic studies. Neurologists and scientists working with them have a long tradition of taking family participation, also of healthy but at risk relatives, for granted: are not the researcher's endeavors for the benefit of the family? However, in disorders associated with early onset dementia (other than in the better studied and better informed Huntington's chorea families) there is a lack of information, and also fear, suppression and denial of obvious autosomal dominant transmission. This renders these families quite unprepared for the confrontation with potentially high genetic risk of the disease, when they are asked (as healthy sib or offspring of a FTD patient) to donate blood for a DNA-linkage study, or to participate in a family, genetic or psychological study, where questionnaires or interview questions may inform them about their own, often unexpected risk for

dementia.

Another specific aspect in familial FTD is the threatening impact of the personality changes during an extended period in the index patients. It is generally experienced as worse than in Alzheimer's disease (where personality and mood changes are less threatening) and in Huntington's disease (where changes in character and mood may extend for a longer period, but the contact with the patient may be preserved) where these aspects are generally better recognized by the family, also because there is easily available information.

This study gives the first observations and problems perceived by FTD relatives in participating in and consenting to a family study (see chapter 7 and 8).

We address a well known but generally under-reported problem of role-interchange of the clinician and the researcher, and the potential sources of conflict, even if 'written informed consent after full information' was obtained. The purpose of including these observations on the psychological and ethical implications of family studies is three-fold:

(1) Family studies on late-onset diseases are 'classical tools of the trade' in neurology and their ramifications became only recently recognized, with the introduction of presymptomatic testing for Huntington's disease.

(2) Clinical specialists in university hospital practices have often multiple roles subsequent or simultaneously to patients, relatives and others. Reflection on the different status of each role remains essential.

(3) Perceptions and acceptance of emotions and reactions of individual relatives in a family study are necessary to remain aware of the relatives' grief, concern about the index cases and their own anxiety and despair about the future.

Also the group approach for counseling or informing relatives gives problems. Different relatives have different needs and capacities to learn about their personal risk for a dementing disease without treatment or prevention. Individual sessions are better suitable to give information and obtain consent.

Also, the need for additional support may be established. The

potential outcome, including unexpected findings, may become explored.

9.6 ATTITUDES TOWARDS FUTURE PRESYMPTOMATIC TESTING

As expected from other attitudinal studies on late onset genetic diseases, two-third of relatives at risk generally expect to utilize a future presymptomatic test (see chapter 8), but if this possibility becomes real, the experience with Huntington's disease learns that only 10-15% of risk carriers will actually apply for it during its first years.[20,21] The previous data fully explain how painful this process is of handling anticipation, expectation, hope, fear and uncertainty.

9.7 FUTURE STUDIES

The next years will probably bring answers to the question of the 'dementia burdened locus on chromosome 17q21-q22' with more than ten clinically and pathologically generally similar disorders (FTD-17), but with widely different names, clinical presentations and age of onset (see also chapter 1).[22]

Tau pathology has to be investigated more closely with phosphorylation-dependent antibodies like PHF1, AT8, AT100, AT180 and AT270. Tau-positive lesions in neurons and glial cells will be studied in Dutch FTD-17 cases in the next months and immunoblotting of τ protein enables comparison with other FTD-17 families and Alzheimer's disease.[23,24]

After gene identification the prevalence of familial FTD linked to chromosome 17q21-22 may be estimated and a presymptomatic testing programme enabling genetic counseling in people at risk may be developed.

The eventual question will become the disease mechanism, reliable family information, and understanding the possible interventions in the molecular wrong doings.

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Chapter 10

Summary

10.1

10.1 SUMMARY

INTRODUCTION

Fronto-temporal dementia (FTD), its clinical, genetic and epidemiological aspects were assessed in a study aiming at complete ascertainment of FTD in the Netherlands. We analysed in depth since 1994 more than hundred patients, their spouses and families, including 28 families with two or more relatives with dementia and three large multi generation kindreds.

Fronto-temporal dementia and Pick's disease have a long history, reviewed briefly in **chapter 1**. FTD, as it became recently defined by the Lund and Manchester groups may be differentiated from Pick's disease by the absence of specific neuropathological findings like Pick cells and Pick bodies. FTD is a primary degenerative disease of the brain. It starts usually from age 40-60 years. Progressive behavioral changes occur early in the disease. Three forms of FTD are known (**chapter 2**): frontal lobe dementia, frontal lobe dementia with motor neuron disease, and progressive aphasia with behavioral disorders. Lobar atrophy of the frontal and temporal cortex is seen by imaging and at autopsy. Microscopically, there are aspecific neuronal loss, gliosis and spongiosis in several cortical layers. FTD is a rare disease, but epidemiological data are lacking. A few families show an autosomal dominant inheritance. The autosomal dominant form of FTD in the Netherlands is studied including a family previously studied by Schenk. This review (**chapter 2**) of the clinical, pathological and imaging aspects formed the starting point of an over three years nation wide case finding study.

EPIDEMIOLOGIC AND GENETIC ASPECTS

Our study is the first prospective population based study (15 million inhabitants) of FTD (**chapter 3**) showing a prevalence ranging from $1.2/10^6$ (age group 30-40 years), $3.4/10^6$ (age group 40-50 years), $10.7/10^6$ (age group 50-60 years) to $28.0/10^6$ (age group 60-70 years).

The family history of dementia was analysed in 74 FTD patients and 561 age- and gender-matched control subjects. Dementia before the age of 80 years in at least one relative was found in 38% (28/74) of cases but only in 15% (84/561) of controls. Also, dementia in at least two first-degree relatives was significantly more common among FTD patients (10%) than in the controls (0.9%). The first-degree relatives of FTD had a risk of 22% for dementia before 80 years, as compared with 11% in relatives of controls. The age of onset of dementia in affected first-degree relatives of FTD cases (60.9±10.6 yrs) was significantly lower than among affected relatives of controls (72.3±8.5 yrs). The risk of dementia among first-degree relatives of FTD patients was 3.5 times (95% CI 2.4-5.2) higher than among relatives of controls. The hazard ratio in the subgroup with unknown linkage to chromosome 17 was 2.4 (95% CI 1.5-3.7).

The risk for dementia in first-degree relatives shows suggestive evidence for genetic heterogeneity. In first-degree relatives of FTD cases linked to chromosome 17, this is 47% (suggestive for autosomal dominant inheritance). It is 18% in relatives of FTD cases with unknown linkage and 11% in relatives of controls.

LINKAGE ANALYSIS

Three multi-generation Dutch kindreds with FTD (**chapter 5**) were investigated for clinico-pathological comparison and linkage analysis. We found linkage to chromosome 17q21-q22 with a maximum lod score of 4.70 at $\Theta=0.05$ with the marker D17S932. The gene for hereditary FTD (HFTD) is in a region of approximately 5 cM between markers D17S946 and D17S791. The patients from the three families did not share a common haplotype for the region of this disease gene. This may indicate that HFTD in the three families is caused by independent mutational events. Three other neurodegenerative disorders with a strong clinical and pathological resemblance have recently been mapped to the same chromosomal region, suggesting that a group of clinically related neurodegenerative disorders may originate from mutations in the same gene (or genes).

CLINICAL HETEROGENEITY IN HFTD

To analyze phenotypic heterogeneity, we further (**chapter 5 and 6**) compared age of onset, and clinical symptoms, neuroradiological and neuropathological changes in the three Dutch HFTD families. Frontotemporal atrophy on CT and/or MRI was usually present (91% of cases). Single photon emission computerized tomography (SPECT) showed anterior hypoperfusion in the early phase of the disease. Moderate to severe atrophy of frontal and temporal cortex was seen with neuronal loss, gliosis and spongiosis, but no Pick bodies were seen in all autopsied cases of the three families. No immunohistochemical evidence for accumulation was found for ubiquitin, tau, ß-amyloid or paired helical filaments.

The mean age of onset showed interfamilial differences: in family I and II these were 50.4 and 46.5 years respectively, significantly lower than in family III (63.4 years) ($p < 0.001$). Progressive behavioral changes and speech reduction were the dominant symptoms in all cases. Intra-familial similarity and inter-familial differences were found as disinhibition was the presenting symptom in family I and II, and loss of initiative predominated early in affected cases in family III.

APOLIPOPROTEIN E

The ApoE4 genotype in FTD was analyzed in our population based study in a subgroup of 34 FTD cases without clear evidence of autosomal dominant inheritance (**chapter 4**) and showed a significant association with FTD (OR=4.9; 95% CI: 1.1-20.1). A decreased age of onset was found as the number of ApoE4 alleles increased, suggesting a similar mechanism as the ApoE effect in Alzheimer's disease (AD). A re-analysis of ApoE4 in a larger set of FTD patients also showed (**chapter 3**) a higher frequency of the ApoE4E4 genotype in cases, most pronounced in those without a family history of dementia, compared to controls.

The predictive value of ApoE4 status for risk identification is clearly absent in familial FTD (none of the tested patients with linkage to chromosome 17 had an ApoE4 allele), and only contributory in sporadic FTD. These results also imply that ApoE4 status is probably useless in

the differential diagnosis between AD and FTD. Since the different Apo E alleles may be related to the formation of hyperphosphorylated τ, τ-pathology has to be further investigated in FTD.

PSYCHOLOGICAL AND ETHICAL ASPECTS

Genetic studies often require the cooperation of many relatives. The ethical and psychological effects of family studies for untreatable disorders preparing for later predictive testing are rarely addressed. In our Dutch study on FTD three types of medical-ethical dilemmas were encountered (**chapter 7**). The first is the controversy of the role of clinician versus researcher: scientific excitement ought to be secondary to good medical care. The emotional impact of information on the genetic nature of a disease may necessitate postponement of the request for participation. The second problem is unexpected outcomes like change of diagnosis: Huntington's disease became an alternative diagnosis in a patient, with far-reaching consequences for relatives. Discussing all possible unforeseeable findings during the information process is difficult. Reasons for disclosure of such unexpected information must be ideally given in a protocol. The third problem is the group approach to provide information on the disease and the study. This is often asked by a family and attractive to the researcher, but often fraught with risks for free informed consent and for safeguarding the individual interests.

Genetic family studies may be supported by psychological evaluation and so contribute to adequate information of families and insight of researchers into relevant psychological factors to be addressed in family studies.

The acceptability of presymptomatic testing in 21 Dutch individuals at 50% risk for the APP-692 mutation causing presenile Alzheimer's disease and/or cerebral haemorrhage resulting from cerebral amyloid angiopathy (FAD-CH), and in 43 people at 50% risk for HFTD was assessed (**chapter 8**). Both groups had similar demographic variables. Of the total group 64% intended to request presymptomatic testing when it became clinically available, although two-thirds did not yet feel ready to take it. The most important reasons in the HFTD and FAD-CH group for taking

the test were: to promote basic research (42% and 47% resp.), informing the children (47% and 50% resp.), planning of the future (29% and 47% resp.) and relieving uncertainty (46% and 27% resp). An unfavorable test outcome was expected to increase problems for spouses (75% and 76% resp.) and children (61% and 57% resp.). Such an unfavorable result was not expected to have adverse effects on personal mood or relationship. Prenatal testing would be considered by one third of the couples in case of an increased risk for HFTD or FAD-CH. Participants would encourage their offspring to have the test before starting a relationship (35%), and before family planning (44%) and would encourage (37%) their children to opt for prenatal diagnosis. People at risk for HFTD were significantly more pre-occupied with the occurrence of potential symptoms in themselves, compared with those at risk for FAD-CH, reflecting the devastating impact that disinhibition in the affected patient has on the family. Our findings underline the need for adequate counselling and the availability of professional and community resources to deal with the impact of test results in subjects and their relatives.

CONCLUSION

In conclusion, hereditary FTD and other neurological disorders mapped to the chromosomal region of 17q21-q22 show an increasing and intriguing variability, and have great impact on the patient and the family. Further gene- and mutation detection will become a next step to unravel the disease mechanism. That knowledge will be essential for the development of any future therapy.

Samenvatting

10.2

10.2 SAMENVATTING

INLEIDING

De klinische, genetische en epidemiologische aspecten van fronto-temporale dementie (FTD) zijn onderzocht in een groep van meer dan honderd patiënten met FTD in Nederland.

De dementie met achteruitgang (atrofie) van de voorste en zij (slaap) kwabben van de hersenen werd door Arnold Pick in 1892 als eerste beschreven. Sindsdien (hoofdstuk 1) hebben o.a. de uit Manchester en Lund komende onderzoeksgroepen in 1994 aan de aandoening de naam gegeven van fronto-temporale dementie. Ook werden klinische, radiologische en pathologische criteria voor de diagnose opgesteld. De ziekte van Pick is een bijzondere vorm van FTD en gaat gepaard met ronde insluitlichaampjes in de zenuwcellen van de hersenen, de zogenaamde Pick bodies.

FTD is een degeneratie van de hersenen, met verschijnselen vanaf het 40e-60e jaar. Er zijn vanaf het begin toenemende gedragsveranderingen, zoals ontremd en stereotiep gedrag en verlies van initiatief. Later gaan de intellectuele functies achteruit. Er zijn drie types van FTD (hoofdstuk 2): geïsoleerde FTD, FTD met afwijkingen van de motorische voorhoorn cellen, en progressieve afasie met gedragsveranderingen. Een verschrompeling van de voorkwab en/of de slaapkwab kan zowel bij beeldvormend onderzoek (CT of MRI scan) als bij obductie worden gevonden. Microscopisch ziet men een verlies van zenuwcellen in de hersenschors, evenals verlittekening (gliose) en verweking (spongiose).

FTD is zeldzaam, maar vóórkomen en overerving waren onvolledig bekend. Een Nederlandse familie met FTD in opeenvolgende generaties, beschreven door Schenk, Sanders en Groen, vormde het startpunt om autosomaal dominante vormen van FTD te onderzoeken in drie families in Nederland (hoofdstuk 2). Tegelijkertijd werd gedurende 1994-1997 een ruim drie jaar durend genetisch en epidemiologisch onderzoek gedaan om zo volledig mogelijk het vóórkomen van FTD vast te stellen.

EPIDEMIOLOGISCHE EN GENETISCHE GEGEVENS

Het eerste prospectieve onderzoek naar FTD in Nederland (hoofdstuk 3) toont dat het vóórkomen toeneemt tussen het 30e en 70e jaar: van de 4e tot 8e decade zijn er respectievelijk 1,2, 3,4, 10,7, 28,0 patiënten per miljoen Nederlanders. Deze gegevens werden verkregen door gedurende 3 jaar zo nauwkeurig mogelijk alle patiënten met deze diagnose, bekend bij neurologen en centra met specialisten betrokken bij deze groep van patiënten, vast te leggen.

Het vóórkomen van dementie in de familie, onderzocht bij 74 patiënten met FTD en 561 controles (vergelijkbaar in leeftijd en geslacht) toonde een duidelijke rol van erfelijke factoren. 38% van de FTD patiënten had tenminste één eerste graads familielid met dementie voor het 80e jaar (en slechts 15% van de controles). Dementie bij twee of meer eerste graads familieleden kwam voor bij 10% van de FTD patiënten, significant vaker dan bij controles (0,9%). Eerste graads familieleden van patiënten met FTD hebben 22% kans op dementie voor het 80e levensjaar (en bij controles is dit 11%). Deze dementie treedt vroeger op bij verwanten van FTD patiënten (60,9 $\pm$ 10,6 jaar) dan bij verwanten van controles (72,3 $\pm$ 8,5 jaar). Globaal hebben eerste graads familieleden van FTD patiënten 3,5 keer hoger (95% betrouwbaarheidsinterval 2,4-5,2) risico op dementie dan verwanten van controles. Sluiten we in die analyse mensen uit bekende FTD families uit, dan houden eerste graads familieleden van FTD patiënten een 2,4 keer groter (95% betrouwbaarheidsinterval 1,5-3,7) risico op dementie dan familieleden van controles. Naast dominant erfelijke factoren zijn er dus waarschijnlijk verschillende andere genetische factoren betrokken bij het ontstaan van deze vorm van dementie.

Het risico op dementie voor eerste graads familieleden is 47% in de drie beschreven families met dominante overerving, hetgeen past bij dat model. Bij FTD niet gekoppeld aan het chromosoom 17 locus hebben 18% (versus 11% in controles) eerste graads verwanten dementie.

KOPPELINGSONDERZOEK:
plaatsbepaling van familiaire FTD op de chromosoomkaart.

In drie Nederlandse families met dominant erfelijke FTD (hoofdstuk 5) werden klinische en pathologische aspecten ondezocht. Tevens werd de plaats van de ziekte-eigenschap op de chromosoomkaart bepaald bij een zogenoemd koppelingsonderzoek. De eigenschap voor FTD ligt in een kleine regio op de lange arm van chromosoom 17 (q21-22). Dit gebied is ongeveer 5 centiMorgan groot, en wordt afgebakend door de markers D17S946 en D17S791. De series DNA-kenmerken die dit gebied in de betrokken families markeren (het haplotype) zijn verschillend, wat één gemeenschappelijke voorouder onwaarschijnlijk maakt. Dit zou kunnen betekenen dat de erfelijke vorm van FTD in deze drie families veroorzaakt is door onafhankelijke mutaties.

Drie andere neurodegeneratieve aandoeningen die klinisch en pathologisch lijken op FTD, zijn recent eveneens gelokaliseerd in dezelfde chromosomale regio, hetgeen erop duidt dat een groep van klinisch verwante neurodegeneratieve aandoeningen zijn genetische oorzaak heeft in mutaties in hetzelfde gen of genen in hetzelfde gebied.

KLINISCHE VARIABILITEIT IN ERFELIJKE FTD

De beginleeftijd van dementie en de klinische, neuroradiologische en neuropathologische kenmerken bij de drie Nederlandse families met erfelijke FTD zijn beschreven in hoofdstuk 5 en 6.

De beginleeftijd waarop de dementie ontstond verschilt: in familie I en II bij 50,4 en 46,5 jaar, hetgeen significant eerder is dan in familie III (63,4 jaar)(p-waarde $< 0{,}001$). Progressieve veranderingen in gedrag, en een verminderde spraakproductie zijn het meest opvallend. Er werd een sterke overeenkomst binnen de familie, en verschillen tussen de families gevonden. Ontremd gedrag blijkt het vroegste symptoom te zijn in familie I en II, terwijl initiatiefverlies het meest op de voorgrond staat in het begin van de ziekte bij demente familieleden uit familie III. Frontotemporale atrofie is nagenoeg altijd (91%) aanwezig bij beeldvormend onderzoek (CT scans en/of MRI scans). Een verminderde

doorbloeding van de frontotemporale regio wordt in de beginfase op SPECT-scans (=single photon emission computed tomography) gevonden. De hersenen vertonen (na overlijden) een matige tot ernstige atrofie van de frontale en temporale hersenschors. Microscopisch ziet men een verlies van zenuwcellen in meerdere schorslagen met gliose en spongiose, zonder Pick insluitsels. Immunohistochemisch onderzoek met conventionele antilichamen heeft geen positieve reactie op eiwitten als ubiquitine, tau, beta-amyloid en paired helical filaments laten zien.

APOLIPOPROTEINE E

Apolipoproteine E is een polymorf eiwit dat in de hersenen een rol speelt bij de groei en regeneratie van zenuwcellen. De E4 isovorm van het apolipoproteine E (ApoE4) is geassocieerd met een verhoogde kans op de ziekte van Alzheimer. De frequentie van het ApoE4 allel en ApoE4E4 genotype is allereerst onderzocht in een subgroep van 34 patiënten met de niet erfelijke vorm van FTD (hoofdstuk 4). Dit onderzoek liet een statistisch significant verband zien tussen het ApoE4 en FTD. De beginleeftijd van de aandoening was lager naarmate het aantal E4 allelen toenam, hetgeen een aanwijzing is voor aanwezigheid van een ApoE4-effect net als bij de ziekte van Alzheimer. Een heranalyse van ApoE4 bij een grotere groep van FTD patiënten heeft eveneens een hogere frequentie van het ApoE4 genotype bij patiënten t.o.v. controles laten zien. Dit verband tussen ApoE4 en FTD is het meest uitgesproken bij FTD patiënten met een negatieve familie anamnese voor dementie (hoofdstuk 3).

De voorspellende waarde van de ApoE4 status om het risico voor dementie in kaart te brengen is duidelijk afwezig bij de erfelijke vorm van FTD (ApoE4 kwam namelijk bij deze patiënten niet voor), en slechts van aanvullende waarde bij de sporadische vorm van FTD.

Het bepalen van de ApoE4 status is dus niet bruikbaar bij de diffentiële diagnose van de ziekte van Alzheimer en FTD. Daar de verschillende ApoE4 allelen mogelijk gerelateerd zijn aan de vorming van de gehyperfosforyleerde vorm van het tau-eiwit, moet de rol van deze afwijkende tau-eiwitten bij FTD nader onderzocht worden.

PSYCHOLOGISCHE EN ETHISCHE ASPECTEN

Genetisch onderzoek binnen een familie vraagt vaak de medewerking van gezonde en aangedane familieleden. Deelname kan zeer belastend zijn vanwege de confrontatie met de ziekte en de persoonlijke risico's. De ethische en psychologische effecten van dergelijk onderzoek zijn echter zelden bestudeerd. In de huidige studie zijn wij drie medisch-ethische dilemma's tegengekomen (hoofdstuk 7).

Ten eerste was er de tegenstelling tussen de rol van clinicus en onderzoeker: het wetenschappelijk enthousiasme dient ondergeschikt te zijn aan goede medische zorg en begeleiding. De emotionele betekenis van de erfelijke achtergrond van een ziekte maakt het soms nodig om het verzoek tot deelname aan het wetenschappelijk onderzoek uit te stellen.

Het tweede probleem betrof onverwachte bevindingen die van grote klinische betekenis zijn voor deelnemers of hun verwanten en nageslacht. Zo werden bij een patiënt aanwijzingen gevonden voor de ziekte van Huntington, een autosomaal dominante erfelijke aandoening met - indien bevestigd - grote gevolgen voor de kinderen en overige verwanten. Niet alle mogelijke onverwachte uitkomsten kunnen tijdens het proces van informatieverstrekking worden besproken. Toch moeten in het onderzoeksprotocol algemene richtlijnen worden opgenomen over hoe gehandeld moet worden bij onverwachte bevindingen.

Het derde probleem betrof het groepsgewijs informeren over de aandoening en het onderzoek. Deze benadering wordt vaak door de familie gevraagd en lijkt aantrekkelijk en efficient voor de onderzoeker. Bij groepsgewijze informatie kunnen individuele vragen onvoldoende besproken worden. Ook de psychologische effecten voor de individuele deelnemers zijn niet zorgvuldig in te schatten. Genetisch familieonderzoek dient gepaard te gaan met psychologisch onderzoek om een evaluatie mogelijk te maken.

De aanvaardbaarheid van toekomstig voorspellend onderzoek werd onderzocht bij 21 mensen met een 50% risico op de aanwezigheid van een mutatie (APP-692) die leidt tot de ziekte van Alzheimer op jonge leeftijd en/of hersenbloedingen (FAD-CH), en bij 43 mensen met 50% risico op het krijgen van FTD (hoofdstuk 8). Beide groepen hadden overeenkomstige demografische kenmerken. 64% wenste voorspellend

onderzoek als dat mogelijk wordt, echter tweederde was daar op dit moment nog niet aan toe. De belangrijkste redenen voor het laten verrichten van een voorspellende test waren: hulp aan wetenschappelijk onderzoek, informeren van kinderen, toekomstplanning en bevrijding van de ondragelijke onzekerheid. Als een testuitslag ongunstig zou blijken, dan werd verwacht dat vooral de partner en de kinderen meer problemen krijgen. Men verwachtte van een ongunstige uitslag geen nadelig effect op de eigen stemming of op de huwelijksrelatie. Het verrichten van prenataal onderzoek werd overwogen bij eenderde van de paren in geval één van de ouders drager blijkt van de erfelijke eigenschap. 35% zou hun kinderen aanmoedigen voorspellend onderzoek te ondergaan voordat zij een relatie aangaan, en 44% voordat kinderen een eigen gezin stichten. Risicodragers voor FTD waren angstiger en meer gepreoccupeerd met ziekteverschijnselen bij zichzelf dan risicodragers voor FAD-CH. Onze bevindingen benadrukken het belang van goede voorlichting en professionele begeleiding bij genetisch familieonderzoeken en - in de toekomst - voorspellend onderzoek.

CONCLUSIE

De erfelijke vorm van FTD en andere neurologische aandoeningen die gekoppeld zijn aan chromosoom 17, laten een toenemende en intrigerende variabiliteit zien, en hebben een niet te onderschatten uitwerking op patiënt en familie. Verder onderzoek naar de identificatie van gen en mutaties zullen de volgende stap zijn in het begrijpen van het ziekte mechanisme. Deze kennis is belangrijk voor de ontwikkeling van behandeling van FTD.

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CURRICULUM VITAE

Martijn Stevens was born in Meppel on January 23, 1966. He attended grammar school at the Rijksscholengemeenschap Schoonoord, Zeist, and passed his exams (Gymnasium ß) in 1985. He studied at the University of Utrecht and obtained his candidate degree in Biology in 1986 (cum laude), and his candidate degree in Medicine in 1987 (cum laude).
During his studies in Medicine at Utrecht, he did research electives in neuropharmacology at the Rudolf Magnus Institute at Utrecht (Department of Medical Pharmacology; Prof.dr T.B. van Wimersma Greidanus) and in Neurology at the Academic Hospital Utrecht (Department of Neurology; Prof.dr J. van Gijn), where he was involved in studies on vascular and metabolic risk factors in patients with septic encephalopathy following surgical procedures, effects of carbaspirin calcium and aspirin on thromboxane B_2 production in healthy subjects, and the role of neurohypophyseal hormones on grooming behavior of the rat. In 1992 he did an internship at the Royal Hallemshire Hospital at Sheffield (Department of Neurology; Dr G.S. Venables). During his studies he was a student-teacher in anatomy, family medicine and prehospital emergency care.
After graduation from medical school in 1993 he became a research fellow in Neurology at the Erasmus University and University Hospital Dijkzigt at Rotterdam (under supervision of Dr J.C. van Swieten) studying on fronto-temporal dementia.
On March 1, 1997, he started his residency in Neurology at the University Hospital Dijkzigt at Rotterdam (Prof.dr F.G.A. van der Meché).

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