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Chromosome 17-linked dementias

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Abstract. Chromosome 17-linked dementias have been defined by linkage analysis. The most common of these syndromes has been estimated to be the cause of between 2 and 20% of all dementia and has alternately been called frontotemporal dementia, Pick's disease (without Pick bodies) and dementia lacking distinctive features [1–3]. The identification of the mutation responsible for these conditions in a group of clinically and pathologically heterogeneous disorders may allow us to gain broad insight into the processes of neurodegeneration.

Key words. Frontotemporal dementia; pallido-ponto-nigral-degeneration; familial multisystem tauopathy; chromosome 17.

Genetics

Chromosome 17-linked dementias are defined based on the detection of linkage of the neurodegenerative diseases found in families to a segment on chromosome 17q21-22. Until mutations are identified, it will be left to speculation whether these families have mutations in one gene or a cluster of genes. Were it not for the significant clinical and pathological heterogeneity among the linked families, there would be less uncertainty in speculating that allelic mutations were responsible for these conditions.

In autumn of 1996 a consensus meeting including representatives from all of the groups that have identified families with neurodegenerative conditions linked to 17q21-22 was held in Ann Arbor, Michigan, USA [4]. As a group these conditions have been labelled frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). The conference participants concluded, based on linkage studies, that it is possible that all of these conditions are due to mutations in a single gene. They further concluded that although there are common themes among the linked conditions, there is also significant clinical and pathological heterogeneity.

The first condition linked to 17q21-22 was given the name disinhibition-dementia-parkinsonism amyotrophy complex (DDPAC) based on the detection of linkage to chromosome 17q21-22 and a lack of consensus in the nosology of non-Alzheimer's dementia [5]. DDPAC encompasses most of the features identified among other 17q21-22-linked syndromes with the appearance of combinations of the cardinal features that form the name [6]. The key clinical features that distinguish this syndrome from Alzheimer's disease, the most common form of dementia, are its presenile nature, its high heritability and the presence of a prolonged prodromal period of behavioural disturbance that can be accounted for by dysfunction of the executive activities of the frontal lobes. DDPAC shows a striking heterogeneity of the clinical features found among affected family members. This heterogeneity initially led to a concern that, in fact, affected family members had unrelated diseases. To determine whether this was the case, a genomic scan was performed. This scan was done based on an ad hoc criterion for affected status in which affected individuals were required to manifest at least three of four cardinal features of the disease. This approach successfully identified a region on chromosome 17q21-22 consistent with the hypothesis that there was an autosomal dominant trait that caused DDPAC. This work was done prior to the availability of a systematic pathologi-

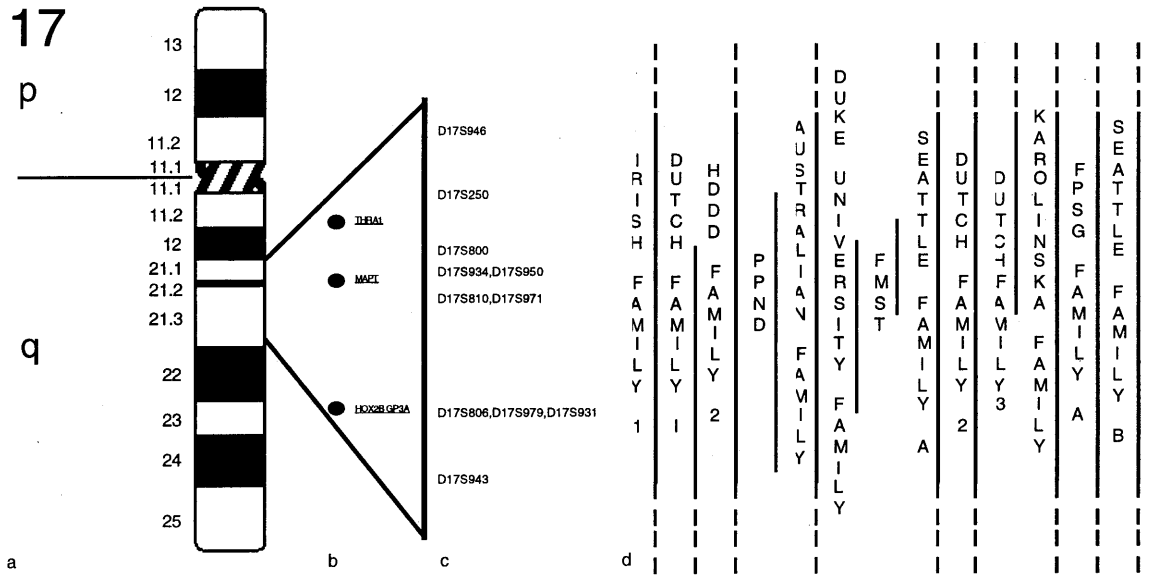

Figure 1. The results of the linkage analyses for frontotemporal dementia and parkinsonism linked to chromosome 17 families. (a) Denotes an ideogram of the chromosome 17 locus; (b) denotes the gene loci; (c) denotes marker loci based on the 1996 Généthon map. The line to the right of each family shown indicates the probable region in which the disease gene lies, with dashed lines representing the possible extension of those regions. Reprinted with permission from: Foster N. L., Wilhelmsen K., Sima A. A. F., Jones M. Z., D'Amato C. J. and Gilman S. (1997) Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Ann. Neurol. **41:** 706–715, © 1998 Lippincott Raven Publishers, Philadelphia, PA, USA.

cal examination which has clarified how DDPAC is related to other previously described non-Alzheimer's dementias. Based on the broad spectrum of disease in DDPAC, other families with atypical neurodegenerative processes were also investigated for linkage to 17q21-22. Surprisingly, there were a large number of families with named conditions that were shown to be linked to the same chromosomal segment [4].

There are three general classes of families that have been identified with linkage to 17q21-22. The largest group of families have been affected with frontotemporal dementia (FTD), DDPAC, Pick's disease and hereditary dysphasic dementia [7–10], and fit into the classification system proposed in the Lund and Manchester Consensus Statement on FTD [11]. In addition there is at least one kindred in which the syndrome is predominantly related to parkinsonism with pallidoponto-nigral degeneration (PPND) [12]. Affected members of families with PPND and familial progressive subcortical gliosis have more subcortical neuronal loss and gliosis than is reported for families with FTD and related disorders [13, 14]. Other families have intensive microtubule-associated protein tau (MAPτ) changes that can be seen with special stains. This includes families said to have familial multisystem tauopathy with presenile dementia, and a family that has been said to have presenile dementia with psychosis [15, 16]. Each of the families with conclusive linkage to 17q21-22 has the support interval containing the region between D17S800 and D17S791 (see fig. 1).

Clinical syndromes

Common to all dementing syndromes that show linkage to 17q21-22 is presenile onset of a mixed neurodegenerative disorder almost always including behavioural changes, dementia characterized by the relative preservation of recent memory and the ability to perform complex overlearned tasks (praxis). These clinical features reflect the frequent involvement of the frontal lobes and relative sparing of the parietal lobes [17]. Characteristically in Alzheimer's disease the parietal lobes are affected and the frontal lobes are spared. At the end of the disease course global impairment usually makes FTDP-17 impossible to distinguish from Alzheimer's disease [18]. Some of the extrapyramidal dysfunction associated with Parkinson's disease is present in most cases, but these can clearly be distinguished from this more common condition. Parkinsonism is the most prominent feature in PPND [13]. The key features of parkinsonism present are muscular rigidity, slowness of movement (bradykinesia) and pos-

tural instability. Although tremor, another cardinal feature of Parkinson's disease, has occasionally been seen, it was not a prominent feature nor did these symptoms respond to pharmacologic therapy that is usually successful in ameliorating the symptoms of idiopathic Parkinson's disease. Motor neuron disease has been associated with both Alzheimer's disease and Parkinson's disease in other clinical syndromes and has been found in FTDP-17, but it is far from common. Eye movement abnormalities and early onset of incontinence have also been seen in the FTDP-17 syndromes [4].

Although in DDPAC there was marked clinical heterogeneity between different family members, other families clearly showed a more homogeneous familial condition. Some of the clinical distinctions that have been made between the named syndromes that make up the FTDP-17 group are due to differences in the methodologies used.

Pathology

A feature common to all of the patients affected with 17q21-22 linked conditions is the presence of nonspecific neuronal loss and gliosis [1]. The focal distribution of neuronal loss is consistent with clinical findings in patients. The behavioural symptoms associated with FTDP-17 are linked to the frontal cortex, where the bulk of the pathology is found [17]. Patients with more social withdrawal and isolation have dorsolateral frontocortical involvement with more disinhibition and tend to have more inferior orbital frontal involvement. Patients with left hemispheric dysfunction characteristically have more language disturbances. Those with right hemispheric dysfunction characteristically present with more problems that can be traced to a level of self-awareness. Loss of cortical neurons is predominantly in the superficial layers. The extrapyramidal features are referable to involvement of the basal ganglia, and the appearance of amyotrophy correlates with motor neuron disease. Among the behavioural disturbances that have been seen in FTDP-17 are a Kluver-Bucy-like picture as well as a semantic dementia that includes the degeneration of the ability to form structured categories for words and images. These syndromes are both attributable to bitemporal lesions.

Epidemiology

It is unknown where the spectrum of clinical and pathological features among the FTDP-17 syndromes will end. The most common presentation of families that are linked to 17q21-22 is frontotemporal dementia, which has also been variously called Pick's disease, or dementia lacking distinguishing features. After Alzheimer's disease frontotemporal dementia is one of the more common causes of dementia and an important cause of presenile dementia. The frequency of frontotemporal dementia among demented patients has been estimated by different investigators to be between 2 and 20%. There have historically been fluctuations in the recognition of this condition, suggesting that it has been underrecognized. A recent autopsy series of subjects with a clinical diagnosis of Alzheimer's disease found that 3–10% of the cases (depending on the criteria used) have pathology consistent with FTDP-17 [19]. There are also differences in referral patterns of subjects that come to autopsy, creating a further obstacle to reliable estimates. As much as 60% of the subjects known to have FTD have a positive family history for other neurodegenerative conditions [20]. It is uncertain what fraction of these are due to mutations on 17q21-22, though it appears that most large multiplex families are due to chromosome 17 mutations. Whether these sporadic cases are aetiologically related is unknown. It will be necessary to identify the mutation rate possible for FTDP-17 before any reasonable assessment can be made.

Candidate genes

If one assumes that the FTDP-17 conditions are allelic, then the locus for this spectrum of diseases maps to between a 2–3 centimorgan region on chromosome 17q21-22, a region which also contains the breast cancer locus (BRCA-1) [21]. This region has been intensively studied, and dense transcription maps have been constructed. Among the transcripts that map to this region, there are several intriguing candidates, including the p-75 nerve growth factor receptor, a homeobox b cluster, glial fibrillary acidic protein and topisomerase 2-α.

Genetic anticipation has not been an observed feature of the neurodegenerative conditions that are linked to 17q21-22, but this does not exclude the possibility of these conditions being due to trinucleotide repeat expansions within, or adjacent to, coding sequences of the gene. It seems entirely possible though that, with the accumulation of evidence, aggregation of proteins that are processed incorrectly may frequently lead to neurodegenerative conditions. Thus any of the genes in the region can be viewed as potential candidates.

MAPτ

One gene that has been extensively studied in this region is that for MAPτ. The occurrence of abnormal forms of MAPτ is a common feature among FTDP-17 syn-

dromes as well as Alzheimer's disease and other neurodegenerative conditions. MAPτ has been extensively investigated for coding sequence mutations in several FTDP-17 syndromes without success ([9] and Lorraine Clark, personal communication). It is certainly possible that some of the FTDP-17 spectrum could be due to mutations in MAPτ, and it would not be surprising if, at some time in the future, families with neurodegenerative conditions caused by mutations in this gene were identified.

MAPτ has also been implicated recently in progressive supranuclear palsy (PSP), a condition that is nearly always sporadic and which has clinical features that overlap with other conditions in the FTDP-17 spectrum. Patients with this condition typically have marked extrapyramidal symptoms with prominent findings of vertical gaze deficits and autonomic dysfunction. In a study by Conrad et al., linkage disequilibrium was detected using an MAPτ intronic microsatellite polymorphism in a case-control designed experiment [22]. The striking findings from the initial observation were that the particular associated allele called the A0 allele increased from approximately 74.6% in the control population to 97.7% in the population of PSP subjects. This dramatic increase may be due to causes unrelated to disease, but if the finding holds up, this would demonstrate an expansion of the spectrum of diseases that are linked to 17q21-22. The associated polymorphism is unlikely to be causal, and it is possible that the association is not due to mutations in MAPτ but a nearby gene. Furthermore, it should not be assumed that PSP and the other FTDP-17 conditions are allelic.

Conclusion

The detection of a locus on 17q21-22 is an exciting development in the understanding of non-Alzheimer's disease dementia. The identification of a spectrum of diseases that appear to be caused by mutations in the same chromosomal region may allow for a broad understanding of the mechanisms by which these various syndromes develop. If the locus or loci for these conditions is within the region that intersects for all of the 17q21-22 linked families it is possible that each of the candidate genes in this region can be systematically tested for causal mutations. Most of the investigators involved in this research are screening candidate genes for causal mutations. If these attempts fail, it should still be possible to systematically screen all of the transcripts in the region. But it is hoped that detection of linkage disequilibrium in isolated populations will allow a more precise localization of the disease gene, allowing the field to progress to biochemical understanding of these conditions.

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