Published in final edited form as:

Neurobiol Aging. 2012 August ; 33(8): 1850.e13–1850.e16. doi:10.1016/j.neurobiolaging.2012.02.019.

Familial Lund frontotemporal dementia caused by C9ORF72 hexanucleotide expansion

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Abstract

Frontotemporal dementia (FTD) as an important clinical entity was rediscovered in Lund and Manchester in the early 1990s. Here we show that the large Lund pedigree with behavioral variant of frontotemporal dementia previously described with this disorder has an expansion in the recently described C9ORF72 locus on chromosome 9.

1. Introduction

The modern history of the study of frontotemporal dementia (FTD) began with the identification and description of clusters of cases in Lund and Manchester (Neary et al., 1993, Brun, 1993 and Lund and Manchester Groups, 1994). Cases from the Manchester archive have subsequently been shown to have microtubule-associated protein tau (MAPT) missense mutation (Colombo et al., 2009), progranulin (PGRN) nonsense mutations (Pickering-Brown et al., 2008), and most recently C9ORF72 hexanucleotide expansions (Renton et al., 2011). In contrast, the familial Lund cases have not been extensively characterized and no pathogenic mutations have been reported.

As part of our efforts to clone the chromosome 9 locus (Vance et al., 2006), we assessed the occurrence of a haplotype, first identified in the Finnish population (Laaksovirta et al., 2010), in other populations with both amyotrophic lateral sclerosis (ALS) and FTD (Pearson et al., 2011, Shatunov et al., 2010, Van Deerlin et al., 2010 and van Es et al., 2009), and

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Disclosure statement

The authors disclose no conflicts of interest.

suggested that there was a common Scandinavian founder for this mutation in both family (genetic linkage) and association studies (Mok et al., 2012). We further suggested that this founder effect may, in part, have explained the original Lund focus of FTD.

2. Methods

We sought to assess the occurrence of C9ORF72 expansions in pathological FTD samples from Lund. We analyzed 5 samples from the Lund FTD Brain Bank with Tar DNA-binding protein (TDP)-43 pathology including one from the original autosomal dominant kindred (Passant et al., 1993; see Fig. 1). We screened for the C9ORF72 hexanucleotide repeat using the polymerase chain reaction (PCR) method we have described previously (Renton et al., 2011). The clinical features of affected individuals from this family are consistent with a diagnosis of behavioral variant FTD (Passant et al., 1993 and Rascovsky et al., 2011). Behavioral symptoms included disinhibition, apathy, loss of empathy, perseverative behavior and hyperorality. The development of stereotyped speech with echolalia was prominent in a number of patients. Less common features included hallucinations (visual, auditory or tactile) and paranoid behavior. Details were limited about the extent of cognitive impairment although from history many patients had relatively intact memory and visuospatial abilities early on in the disease process. The pathology has been previously reported (Larsson et al., 2000) but this report predates TDP-43 immunostaining. The cases from this family showed extensive type B TDP-43 pathology (Fig. 2) as has been previously suggested for the majority of chromosome 9-linked disease cases (Mackenzie et al., 2011).

3. Results and discussion

In the sample from the familial case, but not in the sporadic samples, we found the characteristic pathologic hexanucleotide expansion in the C9ORF72 gene on chromosome 9 (DeJesus-Hernandez et al., 2011 and Renton et al., 2011). This sample bore the complete haplotype we had previously shown is associated with the disorder (Mok et al., 2012). These data, therefore, go some way toward explaining the cluster of FTD cases in southern Sweden which prompted the rediscovery of FTD as a clinical entity in the early 1990s and tie the earlier clinical and pathological descriptions from this center to the genetic etiology of the disease. They clearly show that C9ORF72 mutations can lead to the behavioral variant of the disease and are consistent (although not more than that) with the notion that this mutation may have a Scandinavian founder. The fact that the clinical features in this kindred breed true (all cases have the behavioral variant of FTD) suggests that these features may in part be a property of the precise repeat length, although Southern blotting (DeJesus-Hernandez et al., 2011) is necessary to assess this definitively. The pathology is typical of the type described as type B by Mackenzie et al. (2011) as has been previously suggested for this chromosome 9 linked form of the disorder.

Acknowledgements

This work was supported in part by the Intramural Research Programs of the NIH, National Institute on Aging (Z01-AG000949-02), and NINDS and by an MND Association grant to Richard Orrell and J.H. These data are included in an ongoing international survey of the prevalence of C9ORF72 expansions (BJT, JH). The Trolle-Wachtmeister Foundation supported E.E. Research nurse Karin Nilsson, Ph.D., is acknowledged for many years of follow-up and contact with the family members.

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Lund Pedigree with C90RF72 Expansion

Fig. 1.

Pedigree redrawn from Renton et al. (2011). Since the original article, patient 10, third generation, has been diagnosed and this is the sample in which the mutation was found. Patient 11 has died and has had autopsy confirmation of the diagnosis. Ages at onset, in all cases, were between 46 and 60 years.

Fig. 2.
Immunohistochemical Tar DNA-binding protein (TDP)-43 staining from the anterior frontal lobe (site of maximal pathology), type B according to Mackenzie et al. (2011). Scale bar, 100 μ m.