Familial frontotemporal dementia and amyotrophic lateral sclerosis associated with the C9ORF72 hexanucleotide repeat

The discovery of the C9ORF72 gene mutation as a cause of familial frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) represents a clear victory in the war against neurodegenerative disorders although the scale of the discovery is, at present, hard to judge. Is it a skirmish or a battle won; or even the collapse of a vital salient in the enemy’s defense system that will lead to capitulation and final collapse? Time will tell. The great hope shared by clinicians and researchers is that unraveling the molecular pathology will lead to a cure for these devastating diseases. It is now 14 years since the discovery of the first major familial frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) mutations associated with FTD involving the microtubule associated protein tau (MAPT) gene (Hutton et al., 1998; Spillantini et al., 1998). Yet we still lack a disease modifying therapy. The recent discoveries open a new avenue for understanding the pathogenesis and broaden the scope of genetic screening. They also emphasize the close relationship between FTD and ALS at a clinical, pathological and genetic level. It may be that the last of the major autosomal dominant mutations causing familial FTD has now been found and hopefully the new discoveries will propel us further down the road to cure.

This issue of Brain contains no fewer than eight papers describing the clinical, radiological and pathological characteristics of the C9ORF72 syndrome. Rather than itemize the findings, this commentary attempts a synthesis highlighting particularly areas of consensus and controversy. Things have moved with remarkable speed. Less than 6 months ago, two groups working in collaboration described a GGGGCC hexanucleotide repeat in the non-coding intronic region of the chromosome 9 open reading frame 72 gene (C9ORF72) in familial FTD and ALS mutation, publishing back-to-back papers in Neuron (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Linkage to a region of chromosome 9 in families with FTD and/or ALS had been established a few years ago (Morita et al., 2006; Vance et al., 2006; Luty et al., 2008) with hints that this missing FTD–ALS gene may be an important cause of familial FTD–ALS. Tracking down the gene abnormality proved difficult but was eventually shown to be a substantial expansion in the non-coding region of a gene with as yet unknown function. At a basic science level it is fascinating and puzzling that such diverse gene defects can result in the same clinicopathological syndromes.

Groups from The Netherlands (Simon-Sanchez et al., 2012), Manchester (Snowden et al., 2012), London (Mahoney et al., 2012) and Mayo clinics in the USA (Boeve et al., 2012) report the results of screening large cohorts of patients with FTD totalling almost 1200 cases distributed fairly evenly between the centres. Overall, between 7% and 12% of the cohorts were found to have the mutation: a remarkably consistent finding which speaks to the uniformity of clinical diagnosis now achieved in research centres, and the distribution of the defect across largely white populations. These four studies are complemented by one from Vancouver that concentrates on the clinical and pathological findings in 30 patients from 16 unrelated families (Hsiung et al., 2012) including one of the large index families that was critical in the hunt for the gene mutation (DeJesus-Hernandez et al., 2011). The final FTD related paper, also from the Mayo group, contrasts the structural MRI findings in groups of patients with the various subforms of familial FTD compared with non-inherited FTD (Whitwell et al., 2012). Two papers report the findings in large cohorts of sporadic and familial ALS from England and from mainland Europe (Chio et al., 2012; Cooper-Knock et al., 2012).

For the non-FTD expert, one of the most important questions is perhaps: ‘how likely is my patient to have a C9ORF72 mutation… and can I predict the likelihood based upon the family history and the clinical features?’ The current papers go some way to answering these key questions. In terms of the relationship between strength of family history and presence of mutation, the most accurate data are presented by the London group who have adopted the Goldman score as a method for quantifying the strength of family history (Mahoney et al., 2012), which has already been extremely useful in clinical practice. According to this scale, a score of 1 represents an autosomal dominant family history of FTLD or ALS; 2 is a familial aggregation of three or more family members with dementia/ALS; 3 is one other first degree relative with dementia of young onset (<65 years); 3.5 is one other first degree relative with dementia of onset over 65 years of age; and 4 is no or unknown family history. Of patients with a
score of 1, >80% were found to harbour a mutation of one of the three major genes. Interestingly, the numbers with the new C9ORF72, MAPT and the progranulin (GRN) mutation, were roughly equal in their sample. Mutations in those with scores of 3.5 or 4 are rare (<5%), and with scores of 2 or 3 having an intermediate risk. Parallel data from the Mayo clinic samples (Boeve et al., 2012) suggest that the C9ORF72 mutation is the most common of the FTD mutations being present in one-third of people with a family history—followed closely in frequency by MAPT—with GRN mutations being the least common of the three. In the Dutch study, one-third of familial cases were found to have the new mutation (Simon-Sanchez et al., 2012): C9ORF72 and MAPT mutations were of equal prevalence and more common than MAPT mutations, although the numbers of MAPT and GRN cases were inflated by the inclusion of multiple members of certain kindreds. These figures do not, however, take account of the clinical phenotype. In all cohorts, the prevalence was highest in those with FTD/ALS (20–40%) and, among FTD/ALS cases with a positive family history, the frequency approached 50%. Turning to apparently sporadic FTD, the rate of C9ORF72 mutations appears to be between 2% and 5% but as discussed below, there may be clinical or radiological indicators that help to identify this small but important group.

The bottom line is that there are now three important genes known to cause autosomal dominantly inherited FTD (C9ORF72, GRN and MAPT). The new hexanucleotide expansion is perhaps the most common and is particularly likely to be found in families in which members have suffered FTD and ALS, or both. Collectively, they account for three-quarters of cases with an autosomal dominant pattern of inheritance. As with the other mutations, the C9ORF72 expansion is rare in patients with absolutely no family history, although evidence from the ALS studies points to a degree of anticipation; parents of patients presenting in later life may have died of other causes before manifesting features of either disease.

What then is the clinical phenotype associated with the expansion? All five clinical papers under discussion (Boeve et al., 2012; Hsiung et al., 2012; Simon-Sanchez et al., 2012; Snowden et al., 2012) agree that the most common presentation is with behavioural variant FTD, which is frequently accompanied by features of ALS as the disease progresses. There are, however, some interesting variations on the theme. Whereas the Mayo group screened 141 cases with one of the language variants (non-fluent aphasia or semantic dementia) and found none with the C9ORF72 mutation (Boeve et al., 2012), in the Manchester series, four of their 32 patients presented with a progressive non-fluent aphasia. In the Canadian and Dutch series, an even higher proportion (20 and 28%, respectively) had an aphasie presentation which was described as non-fluent (Hsiung et al., 2012; Simon-Sanchez et al., 2012). It appears, therefore, that the majority of patients have the behavioural variant of FTD, although a pattern of progressive non-fluent aphasia should not mitigate against screening for the mutation in patients with a strong family history or concurrent features of ALS. Semantic dementia is rarely, if ever, associated with the C9ORF72 mutation, despite the fact that the underlying pathology in this syndrome is characterized by deposition of TAR DNA-binding protein 43 (TDP-43) positive inclusions (Hodges et al., 2010).

The study from Manchester draws attention to the very high rate of psychosis found in those with the C9ORF72 mutation (Snowden et al., 2012). Of their 32 patients, 12 (38%) presented with florid psychotic symptoms, resulting in initial diagnoses of delusional psychosis, somatofore psychosis or paranoid schizophrenia. The clinical descriptions provided are striking. One patient presented complaining of pieces of plastic emanating from his head. He had been noted in preceding months to be increasingly suspicious and to pluck repetitively at his skull. Another patient described visions of the devil and had developed behavioural strategies for keeping ‘him’ at bay. The rate of psychosis in patients without the mutation was low (<5%) making the presence of delusions a powerful potential predictor. In their discussion, Snowden and colleagues draw attention to the previously high rate of delusions reported in patients with behavioural variant FTD who later develop ALS; and they speculate that many such patients may be harbouring the mutation (Lillo et al., 2010). It is strange, however, that the other studies reviewed here do not report this striking association. It seems unlikely that such florid features would have been overlooked or that the features vary so much across and within countries. Further studies are eagerly awaited.

The basic demographic features of FTD patients with the C9ORF72 mutation appear quite similar to patients with behavioural variant FTD with an average age of presentation in their fifties but a very wide range reported in all five studies, the youngest patient being 32 at the onset and the oldest 76. Survival is also highly variable with occasional patients living for 15 (Boeve et al., 2012; Hsiung et al., 2012) or even 22 years (Mahoney et al., 2012), which is exceptional for a patient with pathologically confirmed FTD (Garcin et al., 2009). This long survival is particularly relevant in the context of the psychiatric presentations described above since the onset of dementia in these cases may be insidious and easily missed. It is also somewhat paradoxical given the association with ALS. Some patients in families with the mutation present with FTD, others with ALS and some with both (Hsiung et al., 2012). The London group report that almost two-thirds of their cohort developed features of ALS (Mahoney et al., 2012). This raises the interesting possibility that subclinical motor dysfunction could be a biomarker for the C9ORF72 mutation. It has recently been shown that a very high proportion of patients with FTD have abnormalities of central motor conduction with cortical hyperexcitability, although the rate of these changes was much higher than the reported rates of mutation in the present cohort studies under review, suggesting that the motor changes shown using repetitive transcranial magnetic stimulation are less specific (Burrell et al., 2011).

The group from the Mayo Clinic compared structural MRI changes using voxel-based morphometry in groups of patients with the ‘big three’ mutations to those of sporadic cases (Whitwell et al., 2012). The most striking grey matter loss in the C9ORF72 group involved orbitofrontal, medial and dorsolateral regions, followed by temporal lobes. But interestingly there was also loss in parietal and occipital lobes and in the cerebellum, a finding that echoes the pathological observations...
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group was not associated with prominent frontal or temporal lobe asymmetry. The same observation in
terms of symmetry of atrophy and the prominence of cerebellar changes was made by the London group (Mahoney et al., 2012).
In summary, asymmetry of atrophy and marked anterior temporal lobe atrophy are more suggestive of a
C9ORF72
mutation in the context of a positive family history or a low serum progranulin level that can be used as a surrogate marker (Schofield et al., 2010). In contrast, symmetrical frontal atrophy with additional cerebellar atrophy in the context of prominent psychiatric symptoms should point to a
C9ORF72
mutation.

Five of the current batch of papers include descriptions of the pathological findings in a total of 64 patients with the mutation (Boeve et al., 2012; Hsiung et al., 2012; Mahoney et al., 2012; Simon-Sanchez et al., 2012; Snowden et al., 2012). Virtually all had intraneuronal deposition of TAR-43 which was most commonly, but not exclusively, the so-called type A pattern. One fascinating, and unexplained, aspect is the finding of neuronal inclusions in the cerebellar cortex that were ubiquitin/p62-positive but TDP-43-negative; this appears to be a specific pathological marker observed in all of the studies. The Vancouver group with the largest pathological experience also found motor system degeneration in virtually all of their 20 patients including those without ante-mortem clinical signs of motor neuron disease (Hsiung et al., 2012) suggesting that patients with the mutation should be examined more carefully in the later stages of life for signs of ALS. The Dutch group included an attempt to identify specific inclusions using fluoresence in situ hybridization. Analysis of brain material from patients with the repeat expansion, MAPT and GRN mutations did not show RNA-positive inclusions specific for brains with the repeat expansion (Simon-Sanchez et al., 2012).

Two of the papers in the current issue describe the clinical and pathological aspects of patients with ALS with the C9ORF72 mutation. Shaw and colleagues screened 563 cases from Northern England, including 63 with a family history of ALS. Overall, the C9ORF72 expansion was found in 11% but with the expected striking difference between the familial and sporadic cases: 43% versus 7%, respectively. Disease duration was significantly shorter in C9ORF72-related ALS cases, but clinical features were otherwise similar to those without the mutation. Dementia was present in the patient or a close family member in a third of cases with the C9ORF72 mutation, although this estimate was based on a retrospective clinical case note review that almost certainly under-estimated the rate of cognitive dysfunction. All patients with the C9ORF72 mutation coming to autopsy showed classical ALS pathology with TDP-43 inclusions in spinal motor neurons; but, unlike those without the mutation, neuronal cytoplasmic inclusions and glial inclusions positive for p62 immunostaining were far more prominent in the hippocampus and frontal regions in keeping with the cognitive findings.

Chio and colleagues report their experience of screening 182 patients with familial ALS comprising 141 Italian and 41 German cases. Pathogenic repeat expansions were detected in a high proportion, but with an interesting geographical gradient: in the German cohort, 22% had the mutation compared with 37.5% of patients from mainland Italy and 57% patients of Sardinian ancestry. When compared with patients carrying mutations of other ALS-related genes, those with C9ORF72 expansion more commonly had a bulbar onset and their mean survival from symptom onset was 3.2 years lower. On average, children developed the disease 7.0 years earlier than their parents, providing clear evidence for anticipation as might be expected in a gene expansion disorder. All of their patients underwent a neuropsychological examination using a standard battery that revealed cognitive impairment in almost half of C9ORF72 cases compared to 30% with TARDBP and only 2% with SOD1 mutations. Taken together, mutations of SOD1, TARDBP, FUS and C9ORF72 account for about 60% of familial ALS in Italy. As well as screening two large cohorts of FTD patients, Boeve and colleagues included a group of 229 ALS patients, 34 of whom had familial ALS. The C9ORF72 mutation was detected in 7% of the sample but, as in other studies, this rose to 25% in those having a family history of ALS.

Summarizing the findings in ALS, the C9ORF72 mutation is one of the most common causes of familial ALS and is found in between 22 and 50% of cases depending on the geographical origins of the population. The pathological findings suggest that non-motor features are likely to be extremely common if not universal. The clinical onset is typically bulbar and the prognosis grim. There is evidence for anticipation. In attempting to synthesize the FTD and ALS data, one would speculate that cognitive defects of the type seen in behavioural variant FTD are likely to be the rule and that major psychiatric symptoms are also very common, but these aspects have not been explored in any detail. Studies of FTD have come a long way since the original descriptions of Arnold Pick (1901, 1904), via the redefining clinical studies in the 1970s and 1980s to the identification of causative gene defects over the past decade. The link with ALS has extended concepts of the clinical phenotype and pathological basis for neurodegeneration and the emerging story of C9ORF72 mutation to which papers in the present issue make a substantial contribution is but one chapter, albeit a very dramatic episode, in this evolving saga.

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Funding

Professor John Hodges is currently supported by an Australian Research Council Federation Fellowship number FF0776229 and NHMRC Progress Grant Project number 630489.

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