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Repeat Expansion in C9ORF72 in Alzheimer's Disease

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Alzheimer's disease is the most common progressive neurodegenerative disorder[1] and a leading cause of dementia in the elderly. The genetic causes of Alzheimer's disease are complex, and only four Mendelian genes have indisputably been associated with the disease.[2] Mutations in genes encoding the amyloid precursor protein and presenilin 1 and 2 underlie rare, early-onset Mendelian forms of the disorder. In sporadic Alzheimer's disease, a common genetic variant (APOE4) encoding apolipoprotein E is associated with a high risk of the disease. In contrast, the APOE2 allele is thought to lower the risk.

We recently found that a large hexanucleotide repeat expansion (GGGGCC) within C9ORF72 on chromosome 9p21 accounts for approximately 40% of cases of familial amyotrophic lateral sclerosis (ALS) and 30% of cases of familial frontotemporal dementia.[3] In contrast, the repeat expansion was not detected in 709 unaffected persons of European, African, or Asian ancestry (of these persons, 409 were of European descent). Given the clinical and pathologic overlap between familial frontotemporal dementia and Alzheimer's disease, we tested the hypothesis that the C9ORF72 hexanucleotide expansion may also be associated with susceptibility to Alzheimer's disease.

Using samples obtained from the National Institute of Mental Health Alzheimer's Disease Genetics Consortium, we screened samples from 342 families with members affected by late-onset Alzheimer's disease for the presence of the pathogenic expansion by means of a repeat-primed polymerase-chain-reaction method.[3] The series included 771 subjects who had received a probable diagnosis of Alzheimer's disease (on the basis of criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) and 223 siblings who were assessed as being unaffected at the time of collection.[4] The subjects with Alzheimer's disease, mainly sibling pairs, had a mean age at onset of 74 years (range, 60 to 97).

We found that C9ORF72 large repeat expansions were present in 3 of 342 families (<1%) apparently affected with Alzheimer's disease. The hexanucleotide expansion was seen in 6 of 771 subjects (<1%) in whom probable Alzheimer's disease was diagnosed and in 2 of 223

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unaffected siblings (<1%). The 2 unaffected carriers were siblings of carriers with probable Alzheimer's disease and were the youngest members of their respective family units. It is therefore possible that Alzheimer's disease developed in these subjects after recruitment to the series.

The three families whose members carried the C9ORF72 repeat expansion were of European descent. The first family was composed of four sisters, each of whom carried the expansion. The three oldest sisters had received an initial diagnosis of probable Alzheimer's disease on the basis of their clinical symptoms (with ages at onset ranging from 61 to 63 years). Postmortem analyses of two of the affected sisters showed neuropathological findings consistent with a primary diagnosis of frontotemporal dementia with ubiquitin-positive, tau-negative neuronal inclusions. One sister (with an APOE2/3 genotype) had no lesions that were typical of Alzheimer's disease; the other (with an APOE3/3 genotype) had moderate numbers of neuritic plaques and neurofibrillary tangles. The second family was a sibling pair of brothers in whom probable Alzheimer's disease had been diagnosed at the ages of 65 and 71 years. The third family consisted of four siblings, two of whom had symptom onset at 67 and 68 years of age. One of the two affected siblings carried the pathogenic hexanucleotide expansion; the other did not. All members of this family were heterozygotes for APOE4 and therefore had a comparatively high risk of Alzheimer's disease.[2]

There are two possible explanations for our data. The first possibility is that the hexanucleotide repeat expansion gives rise to Alzheimer's disease. The second and more likely possibility, which is supported by the autopsy findings, is that these subjects had amnestic frontotemporal dementia that was misdiagnosed as probable Alzheimer's disease. If the second possibility holds true, then it is likely to be a consistent feature across cohorts of patients with Alzheimer's disease, especially since postmortem studies show the diagnostic accuracy of clinically probable Alzheimer's disease to be 83%.[5] However, the prevalence of the repeat expansion in persons with symptoms of Alzheimer's disease and without a family history of the disease is probably less than the prevalence we report here. Regardless, the availability of a test for this genetic mutation may provide an opportunity to correct the misclassification of frontotemporal dementia as Alzheimer's disease in current and future patients.

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