C9orf72 Hexanucleotide Repeat Expansions in Clinical Alzheimer Disease

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**Importance:** Hexanucleotide repeat expansions in the chromosome 9 open reading frame 72 (C9orf72) gene underlie a significant fraction of frontotemporal dementia and amyotrophic lateral sclerosis.

**Objective:** To investigate the frequency of C9orf72 repeat expansions in clinically diagnosed late-onset Alzheimer disease (AD).

**Design, Setting, and Patients:** This case-control study genotyped the C9orf72 repeat expansion in 872 unrelated familial AD cases and 888 control subjects recruited as part of the National Institute on Aging Late-Onset Alzheimer Disease Family Study cohort, a multisite collaboration studying 1000 families with 2 or more individuals clinically diagnosed as having late-onset AD.

**Main Outcomes and Measures:** We determined the presence or absence of the C9orf72 repeat expansion by repeat-primed polymerase chain reaction, the length of the longest nonexpanded allele, segregation of the genotype with disease, and clinical features of repeat expansion carriers.

**Results:** Three families showed large C9orf72 hexanucleotide repeat expansions. Two additional families carried more than 30 repeats. Segregation with disease could be demonstrated in 3 families. One affected expansion carrier had neuropathology compatible with AD. In the National Institute on Aging Late-Onset Alzheimer Disease Family Study series, the C9orf72 repeat expansions constituted the second most common pathogenic mutation, just behind the PSEN1 A79V mutation, highlighting the heterogeneity of clinical presentations associated with repeat expansions.

**Conclusions and Relevance:** C9orf72 repeat expansions explain a small proportion of patients with a clinical presentation indistinguishable from AD, and they highlight the necessity of screening frontotemporal dementia genes in clinical AD cases with strong family history.


Alzheimer disease (AD) constitutes the most common cause of dementia in clinical practice. Alzheimer disease manifests clinically with progressive cognitive dysfunction with prominent memory loss, while its neuropathology is characterized by the presence of extracellular neuritic plaques and intracellular neurofibrillary tangles. Familial AD can be caused by mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Interestingly, mutations in genes typically associated with frontotemporal dementia (FTD), including microtubule-associated protein tau (MAPT) and granulin (GRN), have also been reported in clinical AD cases, highlighting the overlapping phenotypes of AD and amnestic FTD.

Recently, an intronic hexanucleotide repeat (GGGGCC) in the chromosome 9 open reading frame 72 (C9orf72) gene was identified as a frequent cause of sporadic and familial FTD and amyotrophic lateral sclerosis (ALS). Because some individuals with clinical AD carry mutations in FTD genes, 2 studies investigated the role of C9orf72 expansions in AD, conflicting results. The first report identified C9orf72 repeat expansions in 3 of 342 cases with familial AD and 6 of 711 cases with sporadic AD. Interestingly, reanalysis of autopsy material from 2 expansion carriers showed FTD pathology, suggesting that both patients had amnestic presentations of FTD rather than AD. The second study identified no repeat expansions in 568 patients with probable AD by clinical criteria and concluded that C9orf72 repeats are specific for FTD.

To clarify the role of C9orf72 hexanucleotide repeat expansions in familial late-onset AD, this study screened 872 un-
related AD cases and 888 unrelated control subjects and investigated whether expanded repeats were associated with age at dementia onset. Furthermore, we addressed whether a larger, but nonexpanded, GGGGCC allele was associated with the risk for AD or age at onset.

**METHODS**

**PATIENTS**

Individuals from 872 unrelated families with at least 2 individuals affected by AD and 888 unrelated unaffected control subjects from the National Institute on Aging Late-Onset Alzheimer Disease (NIA-LOAD) Family Study were included. All AD cases had been diagnosed as having dementia of the Alzheimer type using criteria equivalent to the National Institute of Neurological and Communication Disorders and Stroke–Alzheimer Disease and Related Disorders Association for probable AD.\(^{20,21}\) All patients had a family history of AD but not other types of dementia or other neurodegenerative diseases. Probands were required to have a diagnosis of definite or probable late-onset AD (>60 years) and a sibling with definite, probable, or possible late-onset AD with a similar age at onset. A third biologically related family member (first, second, or third degree) was also required, regardless of affected status. If unaffected, this individual had to be 60 years of age or older, but 50 years of age or older if diagnosed as having late-onset AD or mild cognitive impairment.\(^{22}\) Within each pedigree, we selected a single individual to screen by identifying the youngest affected family member with the most definitive diagnosis (ie, individuals with autopsy confirmation were chosen over those with clinical diagnosis only). A summary of the demographics of all subjects is shown in Table 1. Written informed consent was obtained from all participants, and the study was approved by local institutional review board committees.

**GENETIC ANALYSIS**

**Repeat-Primed Polymerase Chain Reaction**

The presence of the expanded hexanucleotide repeat and the number of repeat units in the longest allele were determined using previously reported methods for repeat-primed polymerase chain reaction (PCR) and fluorescence-based fragment size analysis.\(^{14}\) Briefly, repeat-primed PCR was performed in a total reaction volume of 28 µL containing 100 ng genomic DNA, 1x Fast-Start PCR Master Mix (Roche Applied Science), 3.5% dimethyl sulfoxide, 1x Q solution (Qiagen), and 0.18 mM of deaza-dGTP. Products were run on a 2% agarose gel for visual inspection and then analyzed for fragment size determination, as described for repeat-primed PCR. Based on our analysis, cross-repeat PCR can amplify alleles with 35 or fewer GGGGCC repeats but not the 700 to 1600 repeats reported for pathologic expansions.\(^{14}\) To investigate repeat expansion segregation, we also genotyped all family members (n = 491) from every pedigree with 10 or more hexanucleotide repeats.

**Southern Blot**

Southern blot hybridization analysis was conducted using previously described methods and probe sequences\(^{14}\) to estimate the number of repeat units in expansion carriers.

**Risk Haplotype Genotyping**

We also analyzed all repeat expansion carriers for the 24 single nucleotide polymorphism (SNP) at-risk haplotypes that have been associated with pathologically expanded C9orf72 repeats.\(^{23}\) All samples were genotyped with the Illumina Human 610 Beadchip, with direct genotyping of all analyzed SNPs. Stringent quality control criteria were applied to remove low-quality SNPs.\(^{22}\) We used the entire NIA-LOAD genomewide association study data set and the HapMap CEU population as reference populations. Mach software\(^{24}\) was used to phase the 24 SNPs.

**STATISTICAL AND BIOINFORMATIC ANALYSES**

We identified what we call a repeat expansion marker (C9orf72 REPEAT EXPANSION FREQUENCY AND SEGREGATION IN ALZHEIMER DISEASE FAMILIES)

We screened 872 unrelated familial AD cases and 888 unrelated control subjects for expansions of the hexanucleotide repeat in C9orf72. Five white individuals with a clinical diagnosis of AD (0.57%) and 1 normal control subject

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**Table 1. Cohort Demographics**

<table>
<thead>
<tr>
<th></th>
<th>AD Cases</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>75.8 (8.9)</td>
<td>71.4 (6.7)</td>
</tr>
<tr>
<td>Male, %</td>
<td>33.9</td>
<td>39.7</td>
</tr>
<tr>
<td>APOE 4+, %</td>
<td>76.2</td>
<td>30.6</td>
</tr>
<tr>
<td>C9orf72, No. (%)</td>
<td>5 (0.57)</td>
<td>1 (0.11)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; APOE, apolipoprotein E; C9orf72, chromosome 9 open reading frame 72.

\(^a^\) For AD cases, age indicates onset of symptoms but refers to age at last assessment for control subjects.

\(^b^\) APOE 4+ refers to those carrying at least 1 APOE 4 allele.
summarized in mon mutations in all 5 of these patients were negative for the most com-
probable and possible AD, respectively. Communication Disorders and Stroke–Alzheimer Disease and Related Disorders Association criteria, with three-quarters and one-half shading indicating proba-
able and possible AD, respectively. + indicates the presence of repeat expansion genotypes and − indicates their absence. The absence of a genotype symbol indicates that DNA was not available for analysis. An arrow marks the proband of each pedigree. ALV indicates age at last visit; AO, age at onset.

Figure 1. Alzheimer disease (AD) pedigrees carrying abnormal C9orf72 repeat expansions. Fully shaded symbols indicate autopsy-confirmed AD. Clinical diagnoses were made using National Institute of Neurological and Communication Disorders and Stroke–Alzheimer Disease and Related Disorders Association criteria, with three-quarters and one-half shading indicating probable and possible AD, respectively. + indicates the presence of repeat expansion genotypes and − indicates their absence. The absence of a genotype symbol indicates that DNA was not available for analysis. An arrow marks the proband of each pedigree. ALV indicates age at last visit; AO, age at onset.

The proband of family 1 (1200-1300 repeats), an APOE 2/3 carrier, was diagnosed as having dementia, Alzheimer type, at age 73 years. Formal neurocognitive testing was not available, but prominent memory loss with repetitive questioning and wandering behavior had developed by age 78 years. On death 12 years after diagnosis, a brain auto-
topy was carried out by the Brain Bank at McLean Hos-
pital in Belmont, Massachusetts, in 1999. Microscopic examination found extensive plaque and tangle pathology. Neurofilibrillary tangles and neuritic plaques (>40 plaques per 100X field) were present throughout the neocortex, hippocampus, amygdala, and nucleus basalis of Meynert. Scattered neocortical Lewy bodies were seen. Severe neur-
onal loss in the substantia nigra pars compacta was accom-
panied by a few Lewy bodies. This case would be di-
agnosed as having NIA-Reagan high likelihood criteria for AD and coexisting neocortical-predominant Lewy body dementia using current criteria. Tissue was no longer available to carry out additional relevant staining (eg, tau, ubiquitin, TDP-43, or p62), preventing an assessment for possible FTD pathology.

Aside from age at symptom onset and meeting clinical criteria for probable AD, limited clinical information was available for the remaining index cases. The proband of family 2 (1200-1300 repeats) was diagnosed clinically as having probable AD at the age of 71 years, 3 years after disorientation and memory loss began. By the time of study inclusion at age 74 years, the patient was nonverbal and too impaired to participate in cognitive testing. The prob-
and of family 3 (1200-1300 repeats) was diagnosed as having probable AD at the age of 60 years. Three years later, the Clinical Dementia Rating score was 0.5, which pro-
gressed over 3 years to 1.0. Review of limited caregiver re-
nication Disorders and Stroke–Alzheimer Disease and Related Disorders Association criteria. DNA for additional family members was available for all but family 1. Family 2 showed complete segregation of the large repeat expansion and risk haplotype with disease status (Figure 1 and eTable 2). Family 3, in which all the affected individuals were APOE 3/3 homozygous, showed segregation of the expanded repeat and risk haplotype except for a single individual who developed dementia with only 7 repeat units. Additionally, this individual did not carry the risk haplotype and had dementia onset at a later age than relatives with repeat expansions. In families 4 and 5 (repeat expansions between 35 and 100 repeats), the characteristic repeat-primed chromatogram pattern and the risk haplotype segregated perfectly with disease status. Overall, in these 5 families, 10 of 11 affected individuals for whom DNA was available carried abnormal GGGGCC expansions and the risk haplotype. It is im-
portant to note that all the individuals with more than 30 repeats also carried the risk haplotype.

The age at onset for individuals with more than 30 repeats was earlier than cases with normal repeat alleles (mean [SD], 65.6 [5.5] vs 71.4 [6.8] years; P = .04, Figure 2). This association retained statistical significance even after APOE genotypes were included in the model (P = .03).

**CLINICAL CASE AND NEUROPATHOLOGY DESCRIPTIONS**

The proband of family 1 (1200-1300 repeats), an APOE 2/3 carrier, was diagnosed as having dementia, Alzheimer type, at age 73 years. Formal neurocognitive testing was not available, but prominent memory loss with repetitive questioning and wandering behavior had developed by age 78 years. On death 12 years after diagnosis, a brain auto-
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gressed over 3 years to 1.0. Review of limited caregiver re-
ports suggested that difficulties with disinhibition and anxiety were out of proportion to memory impairment. No additional clinical information was available for members of families 4 and 5 (35-100 repeats in each).

ASSOCIATIONS OF \textit{C9orf72} REPEAT LENGTH IN ALZHEIMER DISEASE

Previous studies in ALS and FTD have clearly demonstrated that \textit{C9orf72} repeat expansions are causative for disease.\textsuperscript{14} However, the minimum repeat number required for disease has not been established. Furthermore, it is not known whether higher repeat numbers (but still within the normal range) are associated with the risk for ALS or FTD. To address this question in AD, we compared the longest nonexpanded allele in cases and control subjects. The average longest allele was not statistically different from control subjects (mean [SD], 6.5 [4.1] vs 4.48 [3.7] repeat units; \(P = .10\)), and the distribution of longest allele lengths were similar. Thus within the normal range, higher repeat numbers did not appear to be a risk factor for AD in this population. Furthermore, we found no association between the length of the longest nonexpanded allele and age at onset (\(P = .52\)), nor evidence for an interaction with APOE genotype.

COMPARISON OF THE C9orf72 REPEAT EXPANSION FREQUENCY WITH OTHER PATHOGENIC GENE MUTATIONS

In a previous study, we sequenced \textit{APP}, \textit{PSEN1}, \textit{PSEN2}, \textit{MAPT}, and \textit{GRN} genes in a discovery series comprising 439 cases included in this study.\textsuperscript{6} The most common pathogenic mutation identified by sequencing in the discovery series (\textit{PSEN1} A79V) was then genotyped in the entire cohort (follow-up series). Overall, the A79V mutation was found in 4 of the 872 cases (0.46%)\textsuperscript{c} compared with the 5 pedigrees where abnormal C9orf72 repeat expansions were found. Furthermore, we analyzed the overall frequency of AD gene mutations (\textit{APP}, \textit{PSEN1}, and \textit{PSEN2}) vs FTD gene mutations (\textit{MAPT}, \textit{GRN}, and \textit{C9orf72}) and found that 1.82% of probands carried a pathogenic, or very likely pathogenic, mutation in \textit{APP}, \textit{PSEN1}, and \textit{PSEN2}, while a slightly larger number (1.94%) had mutations in \textit{MAPT}, \textit{GRN}, or \textit{C9orf72}.

COMMENT

This study assessed C9orf72 hexanucleotide expansions in familial late-onset AD cases and normal control subjects, identifying 5 AD families carrying abnormal C9orf72 hexanucleotide repeat expansions. This frequency is very

### Table 2. Segregation Analysis of Pedigrees With Repeat Expansions

<table>
<thead>
<tr>
<th>\textit{C9orf72} Repeat Expansion</th>
<th>Affected With AD</th>
<th>Unaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Age, mean (SD) [range], y\textsuperscript{a}</td>
<td>65.3 (4.9) [60-73]</td>
<td>65</td>
</tr>
<tr>
<td>Family 1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Age, y</td>
<td>73</td>
<td>NA</td>
</tr>
<tr>
<td>Family 2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Age, y</td>
<td>65, 68</td>
<td>NA</td>
</tr>
<tr>
<td>Family 3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Age, y</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Family 4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Age, y</td>
<td>60, 60, 70</td>
<td>NA</td>
</tr>
<tr>
<td>Family 5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Age, y</td>
<td>67, 70</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; \textit{C9orf72}, chromosome 9 open reading frame 72; NA, not applicable.

\textsuperscript{a}For patients with AD, age refers to age at symptom onset; for unaffected individuals, age refers to the age at last assessment.

\textsuperscript{c}For patients with AD, age refers to age at symptom onset; for unaffected individuals, age refers to the age at last assessment.

![Figure 2. C9orf72 repeat expansions correlate with an earlier age at onset.](http://jamanetwork.net/)

Age at onset was analyzed for association with repeat expansion genotypes by the Kaplan-Meier method and tested for significant differences using a proportional hazards model (proc PHREG; SAS Institute Inc). Repeat expansion carriers show an earlier age at onset than noncarriers (mean [SD], 68.25 [5.8] vs 71.4 [6.8] years; \(P = .94\)).
similar to that found in an independent AD series, but significantly lower than in FTD or ALS.

Three families with clinical AD (0.34%) were found to have repeat expansions in the range reported for FTD and ALS (>1000). In a previous report documenting expansions in clinically diagnosed AD, reevaluation of autopsy material demonstrated FTD pathology and suggested that AD cases with C9orf72 repeat expansions represent amnestic variants of FTD. We were unable to perform an equivalent analysis because autopsies had not been performed or tissue was no longer available. Therefore, even in the proband from family 1, where the neuropathology showed coexisting AD and Lewy body dementia pathology, we cannot rule out the possibility that the families identified in this study also represented amnestic presentations of FTD rather than AD. It is notable that of the many C9orf72 FTD cases reported, several showed concurrent AD pathology and have a high enough burden of AD neuropathology that biomarker analysis (cerebrospinal fluid tau or amyloid, and/or Pittsburgh Compound B–positron emission tomography neuroimaging) would also support an AD diagnosis. This hypothesis is supported by 3 recently reported individuals with early-onset AD, cerebrospinal fluid profiles typical of AD, who were found to carry C9orf72 repeat expansions. In this setting, the correct diagnosis (amnestic FTD) would presumably only be reached by neuropathologic studies or genetic testing. Our cases and previous studies reinforce the heterogeneous clinical and neuropathologic presentations of C9orf72 repeat expansions (ALS, frontotemporal lobar degeneration, frontotemporal lobar degeneration–ALS, and clinical AD).

We also identified 2 families carrying smaller, but abnormal repeats (>35, but <100 units). Despite segregating with disease status, it remains unclear whether these smaller repeat expansions cause disease, increase the risk for dementia, or are incidental. Future studies correlating quantitative repeat sizes with disease status will be required to answer this question.

Although the frequency of large C9orf72 repeat expansions was low in our cohort, it was the second most common pathogenic mutation (3 of 872), just behind PSEN1 A79V (4 of 872). In addition, mutations in FTD genes were as common as mutations in AD genes (1.94% vs 1.87%). Our results confirm that the clinical phenotype of mutations in FTD genes, including GRN, MAPT, and C9orf72, can be clinically indistinguishable from typical AD. This fact has important implications for clinicians, who should consider both FTD and AD genes when evaluating families with strong histories of AD.

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Author Contributions: Drs Harms and Cruchaga contributed equally to this work. Study concept and design: Harms, Mayeux, Goate, and Cruchaga. Acquisition of data: Harms, Cairns, B. Cooper, P. Cooper, Mayo, Carrell, Faber, Williamson, Bird, Diaz-Arrastia, Foroud, Graff-Radford, Mayeux, and Chakraverty. Analysis and interpretation of data: Harms, Benitez, Cairns, P. Cooper, Boeve, and Cruchaga. Drafting of the manuscript: Harms, Benitez, and Cruchaga. Critical revision of the manuscript for important intellectual content: Harms, Cairns, B. Cooper, P. Cooper, Mayo, Carrell, Faber, Williamson, Bird, Diaz-Arrastia, Foroud, Graff-Radford, Mayeux, Chakraverty, and Cruchaga. Statistical analysis: Cruchaga. Obtained funding: Mayeux, Goate, and Cruchaga. Administrative, technical, and material support: Harms, Cairns, B. Cooper, P. Cooper, Mayo, Carrell, Faber, Williamson, Diaz-Arrastia, Boeve, Mayeux, and Chakraverty. Study supervision: Williamson, Diaz-Arrastia, and Foroud.

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work possible.

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Online-Only Material:

tional Cell Repository for Alzheimer's Disease, which receivest government support under cooperative agreement

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