Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS

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Several families have been reported with autosomal-dominant frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), genetically linked to chromosome 9p21. Here, we report an expansion of a noncoding GGGGCC hexanucleotide repeat in the gene C9ORF72 that is strongly associated with disease in a large FTD/ALS kindred, previously reported to be conclusively linked to chromosome 9p. This same repeat expansion was identified in the majority of our families with a combined FTD/ALS phenotype and TDP-43-based pathology. Analysis of extended clinical series found the C9ORF72 repeat expansion to be the most common genetic abnormality in both familial FTD (11.7%) and familial ALS (23.5%). The repeat expansion leads to the loss of one alternatively spliced C9ORF72 transcript and to formation of nuclear RNA foci, suggesting multiple disease mechanisms. Our findings indicate that repeat expansion in C9ORF72 is a major cause of both FTD and ALS.

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