Pathogenicity of Indel variants in the fused in sarcoma (FUS) gene in amyotrophic lateral sclerosis

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Introduction

In the past year, numerous pathogenic missense mutations have been reported in the fused in sarcoma (FUS) gene as a novel cause of amyotrophic lateral sclerosis (ALS). Small insertion/deletion variants (indel) in FUS were also reported as being causative of the disease, however a number of indels within glycine-rich regions of the FUS protein were recently identified in controls. In this study, we investigated the pathogenicity of previously published and novel indels in FUS in an extensive cohort of ALS cases and controls.

Methods

We performed PCR amplification of each of the 15 exons of FUS, using one fluorescently labeled primer, in 631 ALS cases and 1063 controls followed by fragment length analysis on an automated ABI3730 DNA-analyzer. To identify the indel variants in FUS, direct sequencing was performed on each sample with abnormal allele sizes. Where available, the effect of FUS exonic indels on the nuclear localization of FUS was investigated in patient lymphoblastoid cell lines.

Results

We detected 29 variants in patients (4.6%) of which 6 were exonic (0.95%), and 38 variants in controls (3.6%) of which 8 were exonic (0.75%). Exonic variants occurred in exons 5, 6, 12 and 14, with 3 occurring within, and 3 outside of glycine stretches. The most common exonic variant was c.521_523+3delGAGgtg, predicted to result in p.Gly174del, which was found in 3 cases and 4 controls. One case was found to have c.1422_1424delTGG, occurring in exon 14, predicted to result in p.Gly475del and is potentially pathogenic. Other interesting indels detected include c.412_429delGGACAGCAGCAAAGCTAT in exon 5, predicted to lead to p.Gly138_Tyr143del, and c.1204_1206delAGT in exon 12, expected to result in p.Ser402del, both of which were detected in controls.

Discussion

Although mutations in FUS have been shown to be pathogenic in ALS, our data suggest that not all genetic variants in FUS cause disease. We identified indels in four FUS exons, with two exons showing variation in both cases and controls. Exonic indels were identified at a slightly higher frequency in patients compared to controls, suggesting that these may confer susceptibility to ALS. Subcellular localization studies of FUS in lymphoblast cell lines derived from FUS indel carriers are currently ongoing.