

INVESTIGATING COPY NUMBER VARIATIONS IN ALS-CAUSING GENES AS A RARE CAUSE OF DISEASE

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Abstract

Amyotrophic lateral sclerosis (ALS) is a predominantly adult-onset motor neuron disease characterized by progressive loss of motor function leading to paralysis and death by respiratory failure within 3–5 years of disease onset. Approximately 10% of ALS cases have a familial origin (FALS) with the remainder of cases being sporadic (SALS). Many of the genetic defects in familial ALS cases remain unknown. Given that FALS and SALS cases are clinically indistinguishable, scientists believe that by discovering the mechanism of pathology of familial cases treatment can be applied for both familial and sporadic. In order to gain a more thorough understanding of the disease and the genetic underpinnings of FALS cases, we studied copy number variations (CNVs). CNVs are defined as quantitative variations in a DNA segment, that show a variable copy number compared with a reference genome. They can account for population diversity as well as human genetic disease. It is unknown whether rare CNVs in known familial ALS-causing genes can cause disease. We *hypothesized* that duplications or deletions of known ALS-causative genes may be pathogenic and account for a subset of cases with unknown etiology. We performed multiplex ligation-dependent probe amplification, a semi-quantitative technique used to determine relative copy number of up to 10 genes in a single multiplex PCR-based reaction (Schouten et al. 2002). An amount of 277 FALS cases were screened for copy number variations (CNVs) in 10 ALS-causative genes (ALS, SQSTM1, TARDBP, SOD1, FUS, C9ORF72, PFN1, UBQLN2, SPG11 and VCP). We found potential

duplications and deletions that may explain a subset of familial ALS cases. Moreover, healthy control samples will be screened in order to confirm duplications and deletions (CNVs) are only present in mutated genes not wild type genes. Also, targeted approaches using next-generation sequencing will be used to validate our data, such as, region specific sequencing. This data provides new genetic insights and shows how relevant gene modifications may play a role in familial ALS. Overall, the identification of novel CNVs in known ALS-causing genes may provide new genetic insights into the disease.