

A09 Whole exome sequencing identifies novel and recurrent variants in Hungarian patients with ALS

Kornélia Tripolszki (1)*, Dóra Nagy (1), Zsófia F. Nagy (1), József I. Engelhardt (2), Péter Klivényi (2), Márta Széll (1)

Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease. Genetic factors play a key role in ALS and uncovering its genetic background may bring us closer to fully understand its pathomechanism. Therefore, the aim was to identify rare damaging variants in major and minor genes involved in pathways annotated to ALS and in genes of other neurogenetic disorders. **Patients and methods:** 21 Hungarian patients with sporadic ALS were enrolled in the study. They all fulfilled the revised El Escorial and the Awaji-shima criteria for ALS. Prior to whole exome sequencing, the patients were prescreened for 7 major ALS genes: C9ORF72 repeat expansion, SOD1, ANG, FUS, SETX, TARDBP and UBQLN2. Exome sequencing was carried out by using Illumina NextSeq sequencer and data analysis was performed according to the best practices to identify single nucleotide variants and small insertions/deletions. Variant filtering was performed to identify damaging variants in ALS "priority" genes (n=32), ALS "candidate" genes (n=98) and other neurogenetic disease genes (n=125). The detected variants were confirmed by Sanger sequencing. **Results:** In ALS "priority" genes, exome sequencing revealed a novel non-synonymous variant (T338I) in the NEFH gene that encodes neurofilament heavy polypeptide; a novel non-synonymous variant (P11S) in the MATR3 gene that is specific to the matrin-3 isoform 1; a previously described pathogenic nonsense mutation (G1177X) in the alsin (ALS2) gene that leads to premature stop codon and may affect endosomal and vesicle transport; a rare variant (R2034Q) in the SPG11 gene with uncertain significance; and finally a known variant (R261H) in the NEK1 gene, encoding NIMA-related kinase-1, that has recently been associated with ALS in the Caucasian population. Further novel and rare recurrent variants have been detected in 10 ALS "candidate" genes and in 7 other neurogenetic disease genes. None of the detected variants were present in healthy Hungarian controls. **Conclusion:** Potentially disease-causing variants in ALS "priority" genes have been detected in 23% (5/21) of this sporadic cohort. While the disease causing role of several mutations identified in this study has been previously well-established, other variants may show reduced penetrance or may be rare benign variants. Our study provides further insight into the genetic etiology of this heterogeneous disease. **Funding:** Hungarian Brain Research Program (Grant No. KTIA_13_NAP-A-II/15)

1) Department of Medical Genetics, University of Szeged, Szeged, Hungary.

2) Department of Neurology, University of Szeged, Szeged, Hungary.

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