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Abstract Topic: - Clinical Genetics

Abstract Title: - Clinical and genetic determinants of Amyotrophic lateral sclerosis

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Aims: - Identification of genetic variants associated with disease course and survival in Amyotrophic lateral sclerosis patients

Methods: - Clinical assessment of the patients was done on the basis of El Escorial-revised criteria. Exome-sequencing of patients (n=165) and healthy individuals (n=65) was carried out using Illumina Hi-Seq-platform. Analysis of exome sequencing data was done to identify variants associated with ALS (ALSoD, https://alsod.ac.uk/). For identification of rare damaging variants, whole exome sequencing data was analyzed for presence of non-synonymous, frameshift, stop-gained and stop lost mutations with genotype quality score of ≥ 25; minor allele frequency (MAF) cutoff of <0.1% in gnomAD and having predicted damaging impact on the protein structure and function based on the assessment of prediction algorithms such as CADD score (≥20), SIFT (≤ 0.15), PolyPhen2 (≥0.5), Mutation taster (≤ 1.0), FATHMM and PROVEAN score. Correlation of genetic variants was performed with survival. Kaplan-meier survival analysis was done with various clinical parameters.

Results: - Mean age of onset was 54.8 years and the peak age of onset was 45–65 years, which accounts for up to 80% of all patients. Male to female ratio was 2:1 and site of onset was limbs in 87% patients and bulbar onset in 13% of patients. 34.7% of the ALS patients carried a confirmed pathogenic or likely pathogenic variation while 65.3% of patients carried a variation of uncertain significance (VUS) in ALS-associated genes. Overall, 9.3% of the patients had variations in more than one ALS gene. Further, according to ALSoD classification, 17% variations were identified in definitive ALS genes, 4% variations each in clinical modifier and strong evidence genes, 24% variations in moderate evidence genes and rest 51% variations were present in tenuous genes. Patients with ALS carrying ≥2 variants (n=17) developed disease at a significantly later age. Estimated median survival time was 36 months (95%CI: 28.620 – 43.380). Patients with bulbar onset developed disease at significantly older age (0.005) as compared to limb onset patients. Similar trend was observed for both males (p value 0.2) and females (p value 0.0127). Similarly, Patients with bulbar onset had shorter survival duration as compared to patients with limb onset

(p value 0.2). Males developed the disease at a younger age as compared to females. Males had a longer survival duration. Patients with 45-65 years of age had a longer disease duration.

Conclusions: - Several clinical phenotypes including site of onset, age at symptom onset and respiratory involvement have been suggested to predict the disease course. However, there is considerable heterogeneity in the disease progression rate, disease severity as well as the length of time from onset of symptoms to death or tracheostomy or last follow up (and survival). Understanding both genetic and phenotypic heterogeneity is necessary for to better understand the underlying mechanisms of ALS.

Keywords: - Mean age of onset was 54.8 years and the peak age of onset was 45–65 years, which accounts for up to 80% of all patients. Male to female ratio was 2:1 and site of onset was limbs in 87% patients and bulbar onset in 13% of patients. 34.7% of the ALS patients carried a confirmed pathogenic or likely pathogenic variation while 65.3% of patients carried a variation of uncertain significance (VUS) in ALS-associated genes. Overall, 9.3% of the patients had variations in more than one ALS gene. Further, according to ALSoD classification, 17% variations were identified in definitive ALS genes, 4% variations each in clinical modifier and strong evidence genes, 24% variations in moderate evidence genes and rest 51% variations were present in tenuous genes. Patients with ALS carrying ≥2 variants (n=17) developed disease at a significantly later age. Estimated median survival time was 36 months (95%CI: 28.620 – 43.380). Patients with bulbar onset developed disease at significantly older age (0.005) as compared to limb onset patients. Similar trend was observed for both males (p value 0.2) and females (p value 0.0127). Similarly, Patients with bulbar onset had shorter survival duration as compared to patients with limb onset (p value 0.2). Males developed the disease at a younger age as compared to females. Males had a longer survival duration. Patients with 45-65 years of age had a longer disease duration.