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C9ORF72 Repeat Expansion bioinformatics analysis in a Brazilian cohort of Amyotrophic Lateral Sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a fast progression motor neuron degenerative disease. Genetic mutations are the unique defined risk factors for Familial forms (FALS) of ALS. The risk factors for Sporadic forms (SALS) of the disease are still unknown, despite the presence of specific mutations in those patients. Advances in technology and bioinformatics analyses have contributed to identify mutations and also to understand the relationship among genotypes and phenotypes of ALS patients. The expanded GGGGCC hexanucleotide repeats in *C9ORF72* gene is the most prevalent genetic mutation in FALS in USA and Europe. The aim of this study was to investigate the frequency of *C9ORF72* repeat expansions in a cohort of Brazilian ALS patients and also to evaluate the number of repeats, employing advanced bioinformatics methods. FALS (39) and in SALS (189) patients from the Research Center of the Clinics Hospital of the University of São Paulo School of Medicine, in Brazil, were evaluate. A repeat-primed polymerase chain reaction (PCR) amplification was performed on a genetic analyzer. The electropherograms were interpreted using a semi-automatic informatics analysis, which was accomplished by means of two different sampled panels as reference. In the first analysis, the fluorescence peaks were identified by a specific software based on a built-in digital panel. The second analysis was based on a digital panel that was created using proportional representative samples of all previously genotyped ALS patients. This panel was then composed by 2 patients with *C9ORF72* repeat-expansion (more than 31 repeats), 1 patient with a borderline number of repeats (between 20 and 30 repeats) and 47 with less than 20 repeats. Peaks with a 6-base-pair periodicity were counted in both analyses. A cutoff of >30 repeats combined with a decrementing saw-tooth pattern was considered as pathological repeat-expansion. Patients who have had up to 20 repeats were considered non-pathogenic, while those who presented 21 to 30 repeats were classified as intermediate group. Differences between the two methods were compared using a two-tailed unpaired t-test. *C9ORF72* repeat expansions were identified in 5 FALS (12.8%) and 5 SALS (2.64%). Patients with repeat expansions had more than 54 repeats, 4 patients had 21-30 repeats and 214 patients had less than 21 repeats. There was no difference between the two applied methods. *C9ORF72* repeat expansions were found in FALS and SALS patients. Both bioinformatics analyses seemed suitable for the *C9ORF72* repeat expansion diagnosis. FUNDING: This work was supported by FAPESP and CNPq, Brazil.

Biography

The authors, which have equal contribution to the work, belong to the Neuroregeneration Center of the Department of Neurology of the University of Sao Paulo Medical School, Brazil. The Center was stablished in 2006 and it is composed by students, post doctoral, post doctorates, biologists, molecular biologists, bioinformatics, physiotherapists, speech therapists, psychologists, physicians and clinicians interested to perform translational neurology and clinical neurology research in the field of neurodegenerative disorders. The group is headed by Professor Gerson Chadi, MD. PHD., Full Professor of the Department. The Group has put a great effort on the mechanisms of neuronal degeneration of Amyotrophic Lateral Sclerosis (ALS) by developing Translational Neurology Projects (bench to bed), being responsible for various clinical and laboratory studies. The Group members have published important papers in the most prestigious journals in the field.

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