Sequence variations in C9orf72 downstream of the hexanucleotide repeat region and its effect on repeat-primed PCR interpretation: a large multinational screening study

Angelica Nordin, Chizuru Akimoto, Anna Wuolikainen, Helena Alstermark, Karin Forsberg, Peter Baumann, Susana Pinto, Mamede De Carvalho, Annemarie Hübers, Frida Nordin, Albert C Ludolph, Jochen H Weishaupt, Thomas Meyer, Torsten Grehl, Kathi Schweikert, Markus Weber, Christian Burkhardt, Christoph Neuwirth, Trygve Holmøy, Mitsuya Morita, Ole-Bjørn Tysnes, Michael Benatar, Joanne Wuu, Dale J Lange, Carsten Bisgård, Nasrin Asgari, Ilkka Tarvainen, Thomas Brännström & Peter M Andersen

A large GGGGCC-repeat expansion mutation (HREM) in C9orf72 is the most common known cause of ALS and FTD in European populations. Sequence variations immediately downstream of the HREM region have previously been observed and have been suggested to be one reason for difficulties in interpreting RP-PCR data. Our objective was to determine the properties of these sequence variations with regard to prevalence, the range of variation, and effect on disease prognosis. We screened a multi-national cohort (n = 6981) for the HREM and samples with deviant RP-PCR curves were identified. The deviant samples were subsequently sequenced to determine sequence alteration. Our results show that in the USA and European cohorts (n = 6508) 10.7% carried the HREM and 3% had a sequence variant, while no HREM or sequence variants were observed in the Japanese cohort (n = 473). Sequence variations were more common on HREM alleles; however, certain population specific variants were associated with a non-expanded allele. In conclusion, we identified 38 different sequence variants, most located within the first 50 bp downstream of the HREM region. Furthermore, the presence of an HREM was found to be coupled to a lower age of onset and a shorter disease survival, while sequence variation did not have any correlation with these parameters.

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