215 AMYOTROPHIC LATERAL SCLEROSIS ASSOCIATED WITH AN INTERMEDIATE LENGTH GGGGCC REPEAT EXPANSION HAS DISTINCT NEUROPATHOLOGY COMPARED TO PATIENTS WITH LARGER EXPANSIONS

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Background An intronic GGGGCC hexanucleotide repeat expansion in C9orf72 is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Thirty repeats is the suggested pathogenic cut-off. However, the 9p21 risk haplotype has been associated with C9orf72 expansions >7 repeats, leading to the description of 7–24 repeats as intermediate. The pathogenicity of intermediate repeat lengths is unknown. Studies have suggested phenotypic similarities between patients with intermediate length expansions and those with larger repeat lengths, although given the broad phenotypic spectrum of ALS this is not conclusive. Previously, there has been no pathological characterisation of an intermediate expansion patient.

Materials and Methods Pathological material was obtained from the Sheffield Brain Tissue Bank. Genomic DNA was extracted from cerebellar material and reverse primed PCR and Southern hybridisation was conducted to size the expansion. Immunohistochemistry and RNA fluorescence in-situ hybridisation (FISH) was used to screen for pathology typical of C9orf72-ALS.

Results Repeat-primed PCR and Southern hybridisation revealed a repeat expansion size of 16 repeats in a sporadic ALS (SALS) patient. Neuropathological analysis demonstrated loss of motor neurons and immunohistochemistry revealed coarse neuronal skein-like inclusions identified by ubiquitin and P62 immunostaining. Pathology characteristic of C9orf72-disease, including extramotor neuronal inclusions, RNA foci and neuronal inclusions containing poly-(Gly-Ala)- dipeptide repeat protein, were absent in this patient.

Conclusion A patient with an intermediate C9orf72 expansion of 16 repeats did not show the characteristic C9orf72 pathology suggesting that, in this case, the disease process was distinct from C9orf72-ALS, and the intermediate expansion is an incidental finding. This is consistent with current toxic gain-of-function theories of C9orf72-ALS. The 9p21 risk haplotype may predispose to expansion of the GGGGCC repeat locus, but we suggest that this must occur to some length larger than 16 repeats to cause the pathology characteristic of the C9orf72 subtype of ALS.