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Investigating nucleotide repeat expansions as a cause and modifier of neurodegenerative diseases in Sweden

Anna-Karin Roos

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Faculty opponent:

Professor Åsa Petersén,

Translational Neuroendocrinology Research Unit (TNU)

Department of Experimental Medical Science

Lund University

Department of Clinical Sciences, Neurosciences

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Anna-Karin Roos

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Abstract

Background: Nucleotide repeat expansions are associated with an increased risk of various symptoms and disorders, but their pleiotropic effects are not yet fully understood. Huntington's disease (HD), spinobulbar muscular atrophy (SBMA), and *C9ORF72* hexanucleotide repeat expansion (HRE)-associated amyotrophic lateral sclerosis (ALS) share underlying nucleotide repeat expansions that disrupt gene function and lead to neurodegeneration. Northern Sweden is suggested to harbor high frequencies of such disorders, but regional prevalence and phenotypic characteristics remain insufficiently defined. The aim of this thesis was to investigate nucleotide repeat expansion-related disorders in northern Sweden with focus on prevalence, genotype-phenotype interactions and pathology in HD, SBMA and ALS.

Method: Individuals with HD were identified through electronic medical records in two Swedish counties and comparisons made with national registry data. ALS and SBMA cases were retrieved from the Neurodatabase registry at the Department of Clinical Sciences/Neurosciences, Umeå University and the Department of Neurology, Umeå University Hospital. From the adhering biobank, blood samples were collected for analyses of biomarkers as well as genetic analyses of repeat sizes in the *HTT*, *AR*, and *C9ORF72* genes. Clinical phenotypes were evaluated using medical records. Neuropathological assessment was performed on brain samples from selected autopsies of motor neuron disease (MND) individuals with *HTT* gene expansions and SBMA with atypical clinical progression.

Results: The prevalence of HD in the region of Jämtland was found to be high (22.1/100,000). *HTT* gene expansions within intermediate range were not enriched among ALS patients and did not modify ALS phenotype. However, neuropathological examinations revealed huntingtin inclusions in ALS patients with intermediate and reduced penetrance *HTT* gene expansions. Both HD and SBMA cases carried CAG repeat expansions in the lower pathogenic range (mean 41.1 and 43.1 respectively). SBMA patients frequently exhibited non-motor symptoms and cardiovascular comorbidities, and elevated plasma neurofilament light chain levels indicated atypical disease or cerebrovascular involvement. Evidence of concomitant ALS pathology was found in two SBMA cases. *C9ORF72* HRE-associated ALS had a five year earlier onset ($p < 0.001$), a nine-month shorter disease duration ($p = 0.044$), and a higher incidence of cognitive symptoms ($p = 0.013$) compared to sporadic ALS. Beyond MND and FTD (frontotemporal dementia), families of *C9ORF72* HRE patients showed increased frequencies of other forms of dementia ($p = 0.046$) and psychotic disorders ($p = 0.013$) compared to families of sporadic ALS.

Conclusion: This thesis highlights the role of gene repeat expansions in the neurodegenerative disorders HD, SBMA, and *C9ORF72* HRE-associated ALS. The prevalence of HD in northern Sweden was fourfold higher than the European average. In the investigated ALS cohort, no association was observed between intermediate-range *HTT* expansions and ALS phenotype. SBMA patients harboring lower-range *AR* expansions exhibited a heterogeneous clinical spectrum, including frequent sensory and cardiovascular manifestations. In *C9ORF72* HRE-associated ALS, distinct cognitive and psychiatric features were found further emphasizing the pleiotropic effects of the *C9ORF72* HRE mutation. Collectively, these findings underscore the importance of heightened clinical vigilance in the assessment of patients suffering from MND, particularly those harboring repeat expansions.

Keywords: Huntington's disease, Amyotrophic lateral sclerosis, Spinobulbar muscular atrophy, Nucleotide repeat expansions, Prevalence, Genotype, Phenotype, Pleiotropy.

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