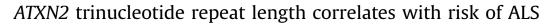
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1. Introduction

Spinocerebellar ataxia type 2 is a trinucleotide repeat disease in which neurodegeneration is a consequence of expansion of a repeated CAG sequence in the *ATXN2* gene. All trinucleotide repeat diseases show neurological features and include Huntington's disease (Paulsen et al., 2014), the spinocerebellar ataxias (Tezenas du Montcel et al., 2014), Friedreich's ataxia (Koeppen, 2011), fragile X syndrome (Jin and Warren, 2000), myotonic dystrophy (Khoshbakht et al., 2014), and Kennedy's disease (Yang and Yamamoto, 2014) among others. The mechanism by which the repeated sequence causes disease remains unknown, but a frequently observed feature is a relationship between age of symptom onset, severity of phenotype, and repeat size, with larger repeats associated with younger onset and more severe disease (Nestor and Monckton, 2011).

Intriguingly, trinucleotide repeat expansion in the *ATXN2* gene is also a risk factor for amyotrophic lateral sclerosis (ALS), a neurodegenerative disease of upper and lower motor neurons, but this association is only seen for repeats of intermediate size, below the range usually associated with spinocerebellar ataxia (34 repeats or more) but above the normal range (Elden et al., 2010). Such pleiotropy is not seen in other trinucleotide repeat diseases and means that the usually observed relationship between repeat size, age of onset, and severity, might not be straightforward. Here, we investigate the size range defining ALS risk and test the relationship of phenotype with repeat size.

2. Methods

2.1. Unpublished case-control studies

A total of 1474 UK DNA samples of unrelated ALS patients (29 with an affected first degree relative) were collected from a consecutive clinical case series obtained from King's College Hospital (n = 116), from the Motor Neurone Disease Association DNA Biobank (n = 1051), and from Queen Mary University of London and UCL Institute of Neurology (n = 307). All patients were diagnosed as having definite or probable ALS according to the El Escorial criteria. The DNA samples of 567 neurologically normal controls, matched to patients for gender, age, and geographical region, were obtained from the MRC London Neurodegenerative Diseases Brain Bank, the Institute of Psychiatry, Psychology and Neuroscience (n = 68), from

ABSTRACT

We investigated a CAG trinucleotide repeat expansion in the *ATXN2* gene in amyotrophic lateral sclerosis (ALS). Two new case-control studies, a British dataset of 1474 ALS cases and 567 controls, and a Dutch dataset of 1328 ALS cases and 691 controls were analyzed. In addition, to increase power, we systematically searched PubMed for case-control studies published after 1 August 2010 that investigated the association between *ATXN2* intermediate repeats and ALS. We conducted a meta-analysis of the new and existing studies for the relative risks of *ATXN2* intermediate repeat alleles of between 24 and 34 CAG trinucleotide repeat alleles (odds ratio 3.06 [95% confidence interval 2.37–3.94]; $p = 6 \times 10^{-18}$), with an exponential relationship between repeat length and ALS risk for alleles of 29–32 repeats (R² = 0.91, p = 0.0002). No relationship was seen for repeat length and age of onset or survival. In contrast to trinucleotide repeat diseases, intermediate *ATXN2* trinucleotide repeat expansion in ALS does not predict age of onset but does predict disease risk.

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> the National Institute for Health Research Mental Health Biomedical Research Centre and the Dementia Unit at South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry, King's College London (n = 306), and from the Motor Neurone Disease Association (n = 193).

> A second case-control population-based set was obtained in collaboration with the University Medical Center Utrecht, the Netherlands, with a total of 1328 unrelated ALS cases (23 with a family history in a first degree relative) and 691 neurologically normal controls, matched to patients for gender, age, and geographical region (Liberati et al., 2009). Samples used did not overlap with previous studies of *ATXN2* repeat size.

2.2. Standard protocol approvals, registrations, and patient consents

Informed consent was obtained from all included in the study. The study was approved by the Trent Research Ethics Committee 08/HO405/60 and by the Medical Ethics Review Board at the University Medical Center Utrecht 05_067/E.

2.3. Genetic analysis

The DNA samples of 1167 ALS cases and 567 controls were analyzed at the Institute of Psychiatry, Psychology and Neuroscience, King's College London, and DNA samples of 307 ALS cases underwent analysis at the Institute of Neurology, UCL. The ATXN2 CAG trinucleotide repeat region was amplified according to a previously published PCR protocol (Pulst et al., 1996). PCR products at King's College London were run on an Applied Biosystems 3130xl Genetic Analyzer, and those at UCL on an Applied Biosystems 3730xl Genetic Analyzer. PCR fragments were analyzed using GeneMapper V 4.0 software (Applied Biosystems) to determine CAG trinucleotide repeat size. Electropherogram peaks were sized using GeneScanTM 500 LIZ as reference dye labeled standard. Sequenced samples of known CAG trinucleotide repeat size were used as internal controls for both PCR and GeneScan analysis. PCR products of cases and controls with more than 26 repeats were regenotyped to validate the obtained results.

The DNA samples of 1328 Dutch ALS cases and 691 controls underwent *ATXN2* CAG trinucleotide repeat amplification according to a previously reported PCR protocol (Van Damme et al., 2011). PCR products were analyzed using an Applied Biosystems 3130xl Download English Version:

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