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Length of normal alleles of *C9ORF72* GGGGCC repeat do not influence disease phenotype

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Abstract

Expansions of the non-coding GGGGCC hexanucleotide repeat in the *chromosome 9 open reading frame 72* (*C9ORF72*) gene were recently identified as the long sought-after cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) on chromosome 9p. In this study we aimed to determine whether the length of the normal - unexpanded - allele of the GGGGCC repeat in *C9ORF72* plays a role in the presentation of disease or affects age at onset in *C9ORF72* mutation carriers. We also studied whether the GGGGCC repeat length confers risk or affects age at onset in FTD and ALS patients without *C9ORF72* repeat expansions. *C9ORF72* genotyping was performed in 580 FTD, 995 ALS and 160 FTD-ALS patients and 1444 controls, leading to the identification of 211 patients with pathogenic *C9ORF72* repeat expansions and an accurate quantification of the length of the normal alleles in all patients and controls. No meaningful association between the repeat length of the normal alleles of the GGGGCC repeat in *C9ORF72* and disease phenotype or age at onset was observed in *C9ORF72* mutation carriers or non-mutation carriers.

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Keywords

Amyotrophic lateral sclerosis; Frontotemporal Dementia; *C9ORF72*; Repeat-expansion disease; Association study

1. Introduction

Expansions of the non-coding GGGGCC hexanucleotide repeat located in the *chromosome 9 open reading frame 72* gene (*C9ORF72*) were recently identified as a major cause of both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (DeJesus-Hernandez et al. 2011; Renton et al. 2011). The long-awaited identification of this genetic lesion arose following linkage of a number of families, with members suffering from ALS, FTD or a combination of the 2 diseases (FTD-ALS), to a locus on chromosome 9p21 (Morita et al. 2006; Vance et al. 2006; Valdmanis et al. 2007; Luty et al. 2008; Le Ber et al. 2009; Gijselinck et al. 2010; Boxer et al. 2011; Pearson et al. 2011).

ALS is the most frequent motor neuron disease resulting from the progressive degeneration of both the upper and lower motor neurons, leading to spasticity, muscle weakness and death, commonly within 2-5 years from symptom onset (Boillee et al. 2006). FTD is the second most common form of presenile dementia and is characterized by behavioral and personality changes, and language and cognitive difficulties resulting from the atrophy of the frontal and temporal lobes (Graff-Radford and Woodruff 2007). FTD and ALS often co-occur in a family and sometimes present in the same patient (FTD-ALS), leading to the recognition that ALS and FTD may be part of a disease spectrum with a common underlying pathogenesis; a notion which was reinforced by the discovery of *C9ORF72* repeat expansions in both disorders (Mackenzie et al. 2010).

The length of a number of coding repeats have previously been implicated in ALS susceptibility; the most recent being expansions of the polyalanine repeat (GCG) in *NIPA1* (Blauw et al. 2012), and intermediate expansions of the polyglutamine repeat (CAG) in *ATXN2* (Elden et al. 2010). Association of age at disease onset with the length of the normal allele has been reported in Huntington's disease, in which the unexpanded polyglutamine repeat (CAG) in the *HTT* gene interacts with the expanded allele to influence age at disease onset (Djousse et al. 2003).

The *C9ORF72* GGGGCC hexanucleotide repeat expansion is the first non-coding repeat expansion published to be causal of ALS. So far, patients with an expanded allele appear to have between 700 and 1600 repeats (DeJesus-Hernandez et al. 2011); however, the minimal repeat size associated with disease may be considerably smaller, and it is unknown whether longer repeat lengths within the normal range could increase the risk for ALS or FTD (Rademakers 2012).

In this study, we focus on the length of the normal alleles of the *C9ORF72* repeat in patients with or without repeat expansions, to determine whether the length of this "wild-type" allele has any effect on the disease phenotype or age of disease onset in our patient populations. We hypothesize that longer GGGGCC repeats within the normal range, suggested to be <30 repeats (Cerami et al. 2012), in *C9ORF72* may lead to an increase in disease risk or an earlier age at disease onset.

2. Materials and methods

Our study cohort consisted of 3179 individuals, 1735 patients (580 FTD, 995 ALS and 160 FTD-ALS) and 1444 controls. The demographic information on these individuals is summarized in Table S1. Study participants were obtained from Mayo Clinic Jacksonville (n=1907), the Coriell Institute for Medical Research (n=564), ALS Clinic of Vancouver Coastal Health (n=171), University of California, San Francisco (n=162), Mayo Clinic Rochester (n=135), London Motor Neuron Disease (MND) Clinic (n=79), Northwestern University Feinberg School of Medicine (n=39), Drexel University College of Medicine (n=34), University of Western Ontario (n=31), University of British Columbia (n=30), Mayo Clinic Scottsdale (n=11), University of Texas Southwestern Medical Center (n=11) and Ludwig-Maximilians University (n=5). All subjects and/or their proxies gave informed consent to take part in this study. FTD patients were diagnosed according to Neary criteria (Neary et al. 1998) and a diagnosis of ALS was assigned if El Escorial criteria were fulfilled. If a clinical patient deceased and autopsy was performed, the pathological diagnosis was used. Patients with mutations in known disease genes (*PGRN* and *MAPT* for FTD patients and *SOD1, TARDBP* and *FUS* for ALS patients) were excluded from this study.

All patient and control subjects were genotyped for the *C9ORF72* GGGGCC repeat using our previously published two-step protocol (DeJesus-Hernandez et al. 2011). First, DNA of all subjects was PCR amplified with one fluorescently labeled primer, followed by fragment-length analysis on an ABI 3730 DNA Analyzer. Subjects that appeared to be homozygous in this first assay were further analyzed using the repeat-primed PCR method. A characteristic stutter pattern in this second assay was considered indicative of a pathogenic *C9ORF72* GGGGCC repeat expansion.

To account for the fact that non-mutation carriers have two alleles in the normal range, the number of GGGGCC repeats corresponding to the longest of the two normal alleles was used to evaluate a dominant effect, while we summed the number of repeats on both normal alleles to examine an additive effect. All analyses were performed separately in GGGGCC mutation carriers and non-mutation carriers. For mutation carriers, we considered only the non-expanded ‘normal’ allele. In all analyses, we considered number of GGGGCC repeats as both a continuous variable and also as a categorical variable in order to examine potential non-linear trends. In mutation carriers, associations of number of GGGGCC repeats with disease status (pair-wise comparisons of FTD, ALS, and FTD-ALS) were evaluated using logistic regression models adjusted for gender and age at onset. In non-mutation carriers, associations of number of GGGGCC repeats with disease (FTD, ALS, FTD-ALS, and all diseases vs. controls) were examined using logistic regression models adjusted for age (age at onset in cases and age at blood draw in controls) and gender, with additional adjustment for disease status when all diseases were analyzed together. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. When combining all disease groups, the association of number of GGGGCC repeats with age of onset was examined using linear regression models adjusted for gender and disease group; regression coefficients and 95% CIs were estimated. In order to account for multiple testing, we employed a Bonferroni adjustment for all statistical tests that were performed within the same GGGGCC repeat expansion group (presence or absence) and in relation to the same outcome (disease or age at onset). In analyses including mutation carriers, $p \leq 0.0083$ were considered significant in disease association analysis (6 tests) and $p \leq 0.025$ were considered significant in onset age analysis (2 tests). In analyses including non-mutation $p \leq 0.0031$ were considered significant in disease association analysis (16 tests) and $p \leq 0.0125$ were considered significant in onset age analysis (4 tests). Statistical analyses were performed using R Statistical Software v 2.11.0.

3. Results

In our cohort of 1735 patients and 1444 controls, we identified 211 patients (59 FTD, 94 ALS and 58 FTD-ALS) and 0 controls with a characteristic stutter pattern on the electropherogram following repeat primed PCR, suggesting a pathogenic GGGGCC hexanucleotide repeat expansion. A subset of these patients were already published as part of previous studies (Murray et al. 2011; Boeve et al. 2012; Hsiung et al. 2012; Khan et al. 2012; Stewart et al. 2012; Whitwell et al. 2012). The maximum number of GGGGCC repeats within the normal range that we identified was 25 in a patient and 23 in a control individual. For a complete overview of the allele counts in patients and controls see Tables S2 and S3. A graphical representation of the number of repeats on the normal alleles in non-mutation carriers in each of the disease groups compared to controls is provided in Figure S1.

In *C9ORF72* mutation carriers (Table S4), we observed no statistically significant evidence of an increased risk of developing one disease (FTD, ALS or both) over another as the length of the normal allele increased. The strongest association that we did observe was toward an increased likelihood of FTD in relation to FTD-ALS (OR [3 repeat increase]: 1.35, p=0.089). There was no significant association between increasing allele length and onset age in the overall group of mutation carriers.

For the non-mutation carriers (Table S5) when using an additive model, we did not identify significant evidence of a linear association between repeat length and either disease risk or age at onset (all $p \geq 0.057$). When considering GGGGCC repeat length as a five-level categorical variable based on sample quintiles, we also did not observe a significant association between repeat length and risk of FTD, ALS, FTD-ALS, or any disease after adjusting for multiple testing ($p \leq 0.0031$ considered significant after Bonferroni adjustment for multiple testing). There was a nominally significant difference in risk of FTD-ALS across the 5 repeat length categories (p=0.030), however this finding is of uncertain biological significance given that it was driven by a higher risk of FTD-ALS in individuals with a combined number of GGGGCC repeats between 8 and 10 (OR: 1.75, 95% CI: 1.00 – 3.08) and not observed in any of the lower or higher repeat length groups. Similarly, we observed a significant difference in onset age across the five repeat length categories (p=0.011), however this difference was most apparent by the earlier onset ages in patients carrying 8-10 and 11-13 total GGGGCC repeats but not in patients carrying longer alleles (>13), suggesting this may be a false positive observation.

Using a dominant model in non-mutation carriers (Table S5), we did not identify any significant associations of GGGGCC repeat length with risk of disease or onset age. Linear trends of small magnitude that did not approach significance after multiple testing adjustment ($p \leq 0.0031$ considered significant) were identified toward an increased risk of ALS (OR: 1.09 [3 repeat increase], 95% CI: 1.01 – 1.18, P=0.035) and any disease (OR: 1.07 [3 repeat increase], 95% CI: 1.00 – 1.15, P=0.040) in individuals carrying longer GGGGCC alleles.

4. Discussion

The goal of this study was to examine whether normal - unexpanded - *C9ORF72* GGGGCC hexanucleotide repeat alleles, play a role in disease presentation or affect age at disease onset in patients with or without a pathogenic *C9ORF72* repeat expansion.

C9ORF72 mutation carriers can present with FTD, ALS or a combination of both diseases and the age at which first symptoms appear varies widely, ranging from early 30s to late 70s (Hodges 2012). However, using our large collection of 211 *C9ORF72* mutation carriers, we

did not observe any evidence for a role of the unexpanded GGGGCC allele on disease presentation or onset age, suggesting that other genetic or environmental factors are responsible for the clinical variability. One possibility may be that the length of the pathogenic, expanded, allele plays a role in the disease presentation or penetrance; however, this currently remains a challenging question to study. Accurate sizing of expanded repeats can only be performed by southern blot analyses, which is complicated by somatic instability of the repeat and tissue heterogeneity (DeJesus-Hernandez et al. 2011).

Similar to the mutation carriers, we did not observe any meaningful associations between GGGGCC repeat length and risk of disease (ALS, FTD, FTD-ALS, or any disease) or onset age in the overall disease group when studying our larger cohort of non-mutation carriers. Several trends ($p \leq 0.05$) were observed in non-mutation carriers that did not withstand correction for multiple testing. The only statistically significant finding in our study that did withstand correction for multiple testing was an association of the total number of GGGGCC repeats and age at onset in non-mutation carriers; however this finding was of unclear biological significance and likely resulted from our effort to identify potential non-linear associations by evaluating repeat length as a categorical variable.

In conclusion, this is the first study aimed at determining the role of the normal – unexpanded – GGGGCC repeat in FTD and ALS. Despite our extensive patient and control study cohorts, including more than 3000 individuals, we observed very limited evidence to support the hypothesis that the length of the normal allele of the GGGGCC hexanucleotide repeat in *C9ORF72* has an effect on the disease phenotype or age at disease onset in patients with or without *C9ORF72* repeat expansions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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