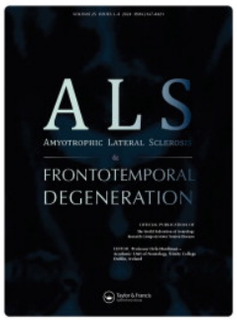

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BRIEF REPORT

Short tandem repeat expansions in *LRP12* are absent in cohorts of familial and sporadic amyotrophic lateral sclerosis patients of European ancestry

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Abstract

In patients of Asian ancestry, a heterozygous CGG repeat expansion of >100 units in *LRP12* is the cause of oculopharyngodistal myopathy type 1 (OPDM1). Repeat lengths of between 61 and 100 units have been associated with rare amyotrophic lateral sclerosis (ALS) cases of Asian ancestry, although with unusually long disease duration and without significant upper motor neuron involvement. This study sought to determine whether *LRP12* CGG repeat expansions were also present in ALS patients of European ancestry. Whole-genome sequencing data from 608 sporadic ALS patients, 35 familial ALS probands, and 4703 neurologically normal controls were screened for *LRP12* CGG expansions using ExpansionHunter v4. All individuals had *LRP12* CGG repeat lengths within the normal range of 3–25 units. To date, *LRP12* CGG repeat expansions have not been reported in ALS patients of European ancestry and may be limited to rare ALS patients of Asian ancestry and atypical clinical presentations.

Keywords: *Amyotrophic lateral sclerosis, short tandem repeat expansions,* LRP12

Introduction

Short tandem repeat (STR) expansions are increasingly being identified in neurodegenerative disorders, in part due to the increasing availability of large whole-genome sequencing datasets and advances in bioinformatic algorithms. A recent publication by Kume et al. (1) implicated *LRP12* repeat expansions in amyotrophic lateral sclerosis (ALS). They described *LRP12* CGG repeat expansions of 61–100 repeats in ALS patients of Asian ancestry from two ALS families, three progressive muscular atrophy families (PMA, a lower-motor neuron form of ALS) (2) and two sporadic ALS individuals and provided detailed clinical data for 10 patients. *LRP12* CGG repeat expansions >100 repeat units had initially been described in patients of Asian ancestry with oculopharyngodistal myopathy type 1 (OPDM1), an autosomal dominant disease characterized by adult-onset ptosis, dysphagia, dysarthria, external ophthalmoplegia, and distal limb muscle weakness and atrophy (3, 4). However, some expansion carriers lacked the distinct oculopharyngeal symptoms and presented as isolated distal myopathies (5).

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The genetic landscape of ALS differs in different population groups. In European populations, a pathogenic GGGGCC repeat expansion in *C9orf72* is the most common genetic cause of both familial (~33%) and sporadic ALS (7%) (6), whereas in Asian populations, pathogenic *C9orf72* repeat expansions account for only 2.3% of familial ALS and 0.3% of sporadic ALS (7). Considering other major ALS genes, European populations have a higher prevalence of *TARDBP* mutations as the cause of familial and sporadic ALS compared to Asian populations; conversely, Asian populations have a higher proportion of familial *SOD1* and *FUS* ALS mutations than European populations (7). Therefore, we sought to establish the prevalence of expanded *LRP12* CGG repeats in an extensive cohort of ALS patients and controls of European ancestry.

Materials and methods

Our study examined *LRP12* CGG repeat expansions in 608 sporadic ALS (sALS) patients, 35 familial ALS (fALS) probands, and 4,703 neurologically normal controls obtained from the NHLBI Trans-Omics for Precision Medicine (TOPMed) studies (dbGaP Study Accessions: phs001368.v3.p2, phs001402.v3.p1, phs001725.v2.p1, phs001024.v5.p1, phs001544.v2.p1 and phs001598.v2.p1). The sporadic ALS and control cohorts were previously described by Henden et al. (8). Samples from all patients and controls in our cohorts underwent short-read whole-genome sequencing and sequence data processing as previously published (8), with *LRP12* CGG repeat sizes detected and quantified using ExpansionHunter v4 (9).

Results

We assessed the prevalence of CGG repeat expansions in *LRP12* in 608 sALS patients, 35 fALS probands, and 4703 neurologically normal controls. Principal component analysis against the HapMap Phase II and III populations confirmed all ALS patients and controls were of European ancestry. The range of *LRP12* CGG repeat allele lengths were between 3 and 25 repeat units across >5000 fALS, sALS, and controls of European ancestry (Table 1), all less than the reported ALS threshold of 61 repeat units by Kume et al. (1).

Discussion

Kume et al. (1) described several Japanese familial and sporadic ALS patients with *LRP12* repeat expansions comprising 61–100 repeat units. However, none of the European fALS cases, sALS cases, or controls analyzed here had an allele larger than 25 repeats. The range of *LRP12* CGG repeat allele sizes in the European control cohort (3–25 repeats) was concordant with non-Finnish Europeans in gnomAD v3.1.2 (10) (range of 1–29 repeats), as well as two Japanese control cohorts analyzed by Kume et al. (1) ($n = 853$, range of 5–48 repeats), and Ishiura et al. (3) ($n = 998$, range of 9–41 repeats). Only one of the 10 patients reported by Kume et al. (1) had typical ALS that progressed to ventilation four years after disease onset. The remaining nine *LRP12* expansion patients were still alive between 9 and 31 years after symptom onset, noting that ALS and PMA have similar probabilities of survival after 8 years (2). This differs substantially from our reported sporadic ALS cohort, where only 10% of patients were alive 9 years after disease onset, with <1.5% alive three decades after onset (8). This suggests that *LRP12*-ALS patients have a very slowly progressive form of ALS. Further supporting atypical disease is that the clinically described *LRP12*-ALS patients had decreased or normal tendon reflexes, inconsistent with significant upper motor neuron disease.

The absence of *LRP12* CGG repeat units larger than 25 repeats in a large ALS and control cohort of European ancestry suggests that ALS-associated CGG expansions in *LRP12* may be limited to ALS patients of Asian ancestry and unusually long disease duration, without significant upper motor neuron involvement. Additional genotyping of large and well-phenotyped cohorts, including additional fALS cases of European ancestry, and different population groups, will be required to better understand the genetic contribution and phenotypic variation associated with *LRP12* in ALS.

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Table 1. Description of the cohorts assessed and the allele size ranges of the *LRP12* CGG repeat.

Cohort of European ancestry	*n* (% female)	*LRP12* CGG repeat allele size range (ExpansionHunter v4)
Sporadic ALS	608 (36.8%)	3–21 repeats
Familial ALS	35 (36.1%)	3–13 repeats
Controls	4703 (50.9%)	3–25 repeats

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Author contribution

L.H.: Conceptualization, Formal Analysis, Data Curation, Writing – Review & Editing; **L.G.F.**: Software, Formal Analysis, Data Curation; Writing – Review & Editing; **D.S.**: Investigation, Writing – Original Draft, Writing – Review & Editing; **A.S.**: Software, Formal Analysis, Data Curation, Writing – Review & Editing; **D.B.R.**: Resources, Writing – Review & Editing; **M.C.K.**: Resources, Investigation, Writing – Review & Editing; **R.P.**: Resources, Writing – Review & Editing; **M.B.**: Supervision, Writing – Review & Editing; **I.P.B.**: Funding acquisition, Resources, Supervision, Writing - Review & Editing; **K.L.W.**: Conceptualization, Investigation, Data Curation, Funding Acquisition, Resources, Supervision, Writing – Original Draft, Writing – Review & Editing

Declaration of interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Data availability statement

The data and code supporting the findings of this study are available in a Zenodo repository (https://doi.org/10.5281/zenodo.10253473).

References

1. Kume K, Kurashige T, Muguruma K, Morino H, Tada Y, Kikumoto M, et al. CGG repeat expansion in LRP12 in amyotrophic lateral sclerosis. Am J Hum Genet. 2023;110: 1086–97.
2. Kim WK, Liu X, Sandner J, Pasmantier M, Andrews J, Rowland LP, et al. Study of 962 patients indicates progressive muscular atrophy is a form of ALS. Neurology 2009;73:1686–92.
3. Ishiura H, Shibata S, Yoshimura J, Suzuki Y, Qu W, Doi K, et al. Noncoding CGG repeat expansions in neuronal intranuclear inclusion disease, oculopharyngodistal myopathy and an overlapping disease. Nat Genet. 2019; 51:1222–32.
4. Kumutpongpanich T, Ogasawara M, Ozaki A, Ishiura H, Tsuji S, Minami N, et al. Clinicopathologic features of oculopharyngodistal myopathy with LRP12 CGG repeat expansions compared with other oculopharyngodistal myopathy subtypes. JAMA Neurol. 2021;78:853–63.
5. Shimizu T, Ishiura H, Hara M, Shibata S, Unuma A, Kubota A, et al. Expanded clinical spectrum of oculopharyngodistal myopathy type 1. Muscle Nerve. 2022;66:679–85.
6. Majounie E, Renton AE, Mok K, Dopper EGP, Waite A, Rollinson S, et al. Frequency of the *C9orf72* hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: A cross-sectional study. Lancet Neurol. 2012;11:323–30.
7. Zou ZY, Zhou ZR, Che CH, Liu CY, He RL, Huang HP. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2017;88:540–9.
8. Henden L, Fearnley LG, Grima N, McCann EP, Dobson-Stone C, Fitzpatrick L, et al. Short tandem repeat expansions in sporadic amyotrophic lateral sclerosis and frontotemporal dementia. Sci Adv. 2023;9: eade2044.
9. Dolzhenko E, Deshpande V, Schlesinger F, Krusche P, Petrovski R, Chen S, et al. ExpansionHunter: A sequence-graph-based tool to analyze variation in short tandem repeat regions. Bioinformatics. 2019;35:4754–6.
10. Chen S, Francioli LC, Goodrich JK, Collins RL, Wang Q, Alfoldi J, et al. A genome-wide mutational constraint map quantified from variation in 76,156 human genomes. bioRxiv. 2022;