

# C9orf72, age at onset, and ancestry help discriminate behavioral from language variants in FTLD cohorts

Beatrice Costa, BSc, Claudia Manzoni, PhD, Manuel Bernal-Quiros, PhD, et al., for the International FTD-Genetics Consortium

Cite as: *Neurology*® 2020;95:e3288-e3302. doi:10.1212/WNL.000000000010914

## Correspondence

Dr. Ferrari  
r.ferrari@ucl.ac.uk  
or Dr. Manzoni  
c.manzoni@ucl.ac.uk

## Study question

Can *C9orf72* expansions, in combination with genetic ancestry and age at onset (AAO), provide a basis for differentiating behavioral-variant frontotemporal dementia (bvFTD) from primary progressive aphasia (PPA)?

## What is known and what this paper adds

Previous studies of patients with frontotemporal lobar degeneration (FTLD) have suggested that *C9orf72* expansions are more likely to occur in patients of northern European ancestry than in those of southern European ancestry and that *C9orf72* expansions act as genetic modifiers of AAO. This investigation's results provided further evidence for such relationships and showed that *C9orf72* expansions were more common among patients with bvFTD than among those with PPA.

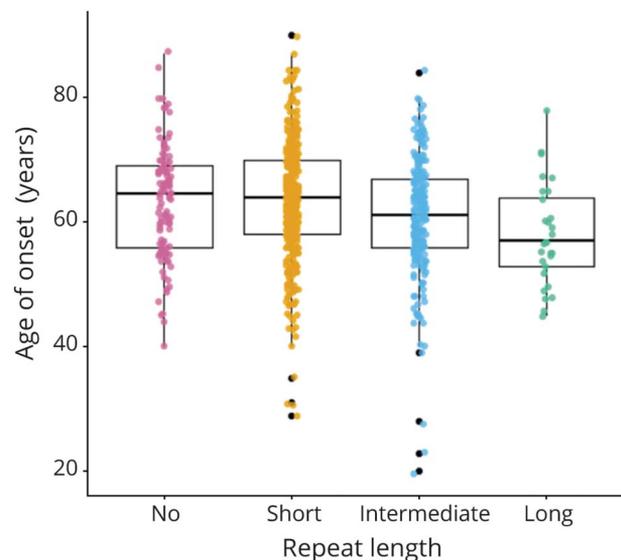
## Methods

For this cross-sectional study, the investigators analyzed data from 800 patients with bvFTD, 495 patients with PPA, and 101 patients with FTLD with motor neuron disease (FTLD-MND). Data collection occurred through clinics in Europe and the US between 2016 and 2018. The investigators used principal component analysis (PCA) to identify ancestry-based patient groups. They used logistic and linear mixed-effects models to test for associations between *C9orf72* expansions and the patients' ancestries and AAOs and to determine whether such associations provided a basis for distinguishing bvFTD from PPA. The primary outcome was the accuracy of the prediction model at differentiating bvFTD from PPA.

## Results and study limitations

Genotyping revealed pathogenic *C9orf72* expansions in 56 patients (4%), including 12 patients with FTLD-MND (11.9%), 40 patients with bvFTD (5%), and 4 patients with PPA (0.8%). PCA separated the patients into groups of central/northern European ancestry (n = 873) and southern European ancestry (n = 523). *C9orf72* expansions were more

**Figure** AAO distributions for patients with differing *C9orf72* repeat lengths



common in patients of central/northern European ancestry, and their presence inversely correlated with AAOs. The prediction model identified cases of bvFTD with 64% accuracy implying to complex genetic risk-architectures differently underpinning the behavioural and language variant syndromes. A limitation of the present study is the possibility of residual confounding related to various environmental risk factors. The reliance on data from people of European ancestry may limit generalizability.

## Study funding and competing interests

This study was funded by various research institutes, foundations, consortia, and professional societies; Grifols; and the Norwegian, Italian, UK, US, Swedish, Slovenian, Spanish, Flemish, and EU governments. Some authors report additional competing interests. Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

# Neurology<sup>®</sup>

## ***C9orf72*, age at onset, and ancestry help discriminate behavioral from language variants in FTL D cohorts**

Beatrice Costa, Claudia Manzoni, Manuel Bernal-Quiros, et al.

*Neurology* 2020;95:e3288-e3302 Published Online before print September 17, 2020

DOI 10.1212/WNL.0000000000010914

### **This information is current as of September 17, 2020**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://n.neurology.org/content/95/24/e3288.full">http://n.neurology.org/content/95/24/e3288.full</a>
<b>References</b>	This article cites 37 articles, 5 of which you can access for free at: <a href="http://n.neurology.org/content/95/24/e3288.full#ref-list-1">http://n.neurology.org/content/95/24/e3288.full#ref-list-1</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>All Genetics</b> <a href="http://n.neurology.org/cgi/collection/all_genetics">http://n.neurology.org/cgi/collection/all_genetics</a> <b>Frontotemporal dementia</b> <a href="http://n.neurology.org/cgi/collection/frontotemporal_dementia">http://n.neurology.org/cgi/collection/frontotemporal_dementia</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a>

*Neurology*® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

