FULL-LENGTH ARTICLE NPub.org/9u358r

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

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Cite as: *Neurology*® 2020;95:e3288-e3302. doi:10.1212/WNL.0000000000010914

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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.

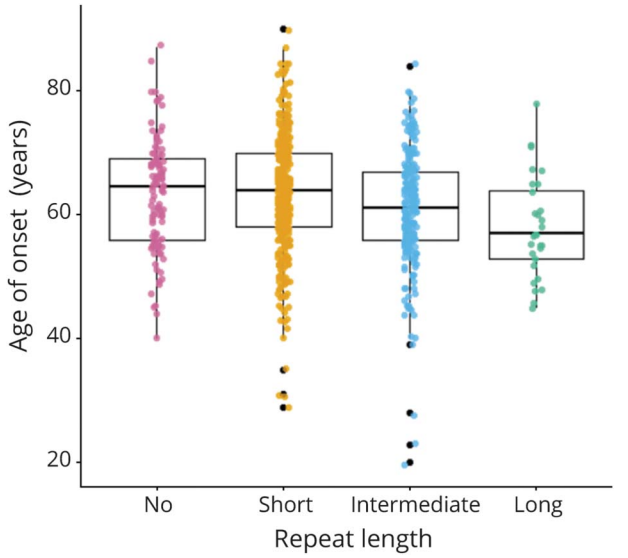
Methods

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 pathogenetic *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 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.

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



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 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.

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Neurology 2020;95;e3288-e3302 Published Online before print September 17, 2020
DOI 10.1212/WNL.0000000000010914