Key Summary of Published Article

Frequency of Frontotemporal Dementia Gene Variants in *C9ORF72*, *MAPT*, and *GRN* in Academic Versus Commercial Laboratory Cohorts

Background

- Frontotemporal lobar degeneration (FTLD) is a common cause of dementia.[1] Understanding the distribution of variants associated with FTLD could improve diagnostic specificity and help develop therapies.
- Most data on variant distribution have been collected from academic centers, which excel at characterizing variants but may be limited by recruitment bias.
- Commercial clinical laboratories may reflect broader populations; thus, variant distributions may be different than those of academic centers.
- **Objective:** This study compared the distributions of *GRN*, *MAPT*, and *C9ORF72* variants identified at an academic center laboratory to those identified at a commercial clinical laboratory.

Methods

- De-identified genetic screening data of FTLD-associated variants of *GRN*, *MAPT*, and *C9ORF72* were obtained from:
  - 2,089 patients recruited at the University of California, San Francisco (UCSF) Memory and Aging Center.
  - 2,082 patients who received genetic testing results from a CLIA-certified, commercial clinical laboratory.
- Variant classification was performed using an algorithm published by Quest Diagnostics,[2] and in accordance with guidelines from the American College of Medical Genetics and Genomics (ACMG).

Results

- A total of 78 patients from the academic center laboratory cohort and 387 patients from the commercial clinical laboratory cohort had FTLD-associated variants.
- Among the 2 cohorts, the variant distributions of *GRN, MAPT,* and *C9ORF72* were similar in frequency order but different in magnitude.
  - Academic center laboratory cohort:
    - *C9ORF72* hexanucleotide expansions: 63% (n=49)
    - *GRN* variants: 26% (n=20)
    - *MAPT* variants: 11% (n=9)
  - Commercial clinical laboratory cohort:
    - *C9ORF72* expansions: 89% (n=344)
    - *GRN* variants: 6% (n=24)
    - *MAPT* variants: 5% (n=19)
- Most *GRN* or *MAPT* variants were rare. While 37 *GRN* or *MAPT* variants were identified in total, only 6 were common to both cohorts.

Conclusions

- The results of this study demonstrate the genetic heterogeneity of FTLD and highlight the importance of developing therapeutic interventions that will be amenable to a broad spectrum of underlying pathogenic causes.
- This study highlights the value of sharing data across academic and commercial laboratories, and the role of commercial laboratories in identifying extremely rare disease-associated alleles.

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