

# Variants of Uncertain Significance in Frontotemporal Dementia: The Need for an Integrated Translational Approach

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## TAKE HOME MESSAGE:

TAKE-HOME MESSAGE    VUS in FTD are not incidental findings: a Translational Medicine Committee converts genetic uncertainty into prioritized, resource-efficient research — and clearer answers for families.

### BACKGROUND

The increasing use of next-generation sequencing has led to a growing identification of variants of uncertain significance (VUS) in frontotemporal dementia (FTD). While pathogenic mutations are well characterized, the clinical relevance and optimal management of VUS remain poorly defined, particularly in real-world cohorts and underrepresented populations. This uncertainty represents a major challenge for diagnosis, genetic counseling, and research prioritization.

### METHODS

Descriptive analysis of FTD patients at a tertiary cognitive neurology center (Fleni, Buenos Aires, Argentina) carrying ≥ 1 VUS (n=18), compared with carriers of pathogenic variants (n=14) and sporadic FTD (n=12). Genetic work-up: C9orf72 testing and whole-exome sequencing (WES); variants screened with in-silico classifiers (Franklin, VarSome) and adjudicated by the Fleni Translational Medicine Committee. Demographic, clinical and family-history data were systematically collected; diagnoses followed current consensus criteria.

### RESULTS

The cohort was predominantly male (56%), mean age 61.4±9.1 y and mean onset 55.8±8.6 y; bvFTD predominated (83%). A family history of neurological/neuropsychiatric disease was present in most cases (78%). Many carriers harbored more than one VUS (44%, up to three), and the same VUS recurred in different patients for several genes.

| Characteristic                   | Pathogenic (n=14) | VUS (n=18) | Sporadic (n=12) | P    |
|----------------------------------|-------------------|------------|-----------------|------|
| <b>Demographics</b>              |                   |            |                 |      |
| Male sex, n (%)                  | 9 (64)            | 10 (56)    | 7 (58)          | 0.88 |
| Age, years                       | 67.0 ± 3.8        | 61.4 ± 9.1 | 62.8 ± 8.7      | 0.30 |
| Education, years                 | 16.4 ± 4.0        | 16.3 ± 2.6 | 15.4 ± 3.1      | 0.32 |
| <b>Clinical phenotype, n (%)</b> |                   |            |                 |      |
| bvFTD                            | 11 (79)           | 15 (83)    | 11 (92)         | —    |
| svPPA                            | 2 (14)            | 3 (17)     | 1 (8)           | —    |
| nfvPPA                           | 1 (7)             | 0 (0)      | 0 (0)           | —    |
| <b>Disease course</b>            |                   |            |                 |      |
| Age at symptom onset, years      | 61.1 ± 3.9        | 55.8 ± 8.6 | 58.4 ± 8.3      | 0.28 |
| Age at diagnosis, years          | 63.4 ± 4.6        | 58.2 ± 9.5 | 60.6 ± 8.7      | 0.26 |
| MMSE, score                      | 28.0 ± 1.4        | 26.0 ± 4.4 | 20.9 ± 7.8      | 0.03 |

Mean ± SD or n (%). p: Kruskal-Wallis /  $\chi^2$ ; exploratory. MMSE available for 2 pathogenic cases.

Table 1. Demographic and clinical characteristics by group.

| Family history            | Pathogenic (N=13) | VUS (N=18)     | Sporadic (N=12) | P           |
|---------------------------|-------------------|----------------|-----------------|-------------|
| <b>Any family history</b> | <b>12 (92)</b>    | <b>14 (78)</b> | <b>9 (75)</b>   | <b>0.47</b> |
| Neurological              | 12 (92)           | 11 (61)        | 7 (58)          | 0.11        |
| Neuropsychiatric          | 6 (46)            | 10 (56)        | 5 (42)          | 0.74        |

n (%). p:  $\chi^2$  across groups; exploratory. Categories not mutually exclusive.

Table 2. Family history by group.

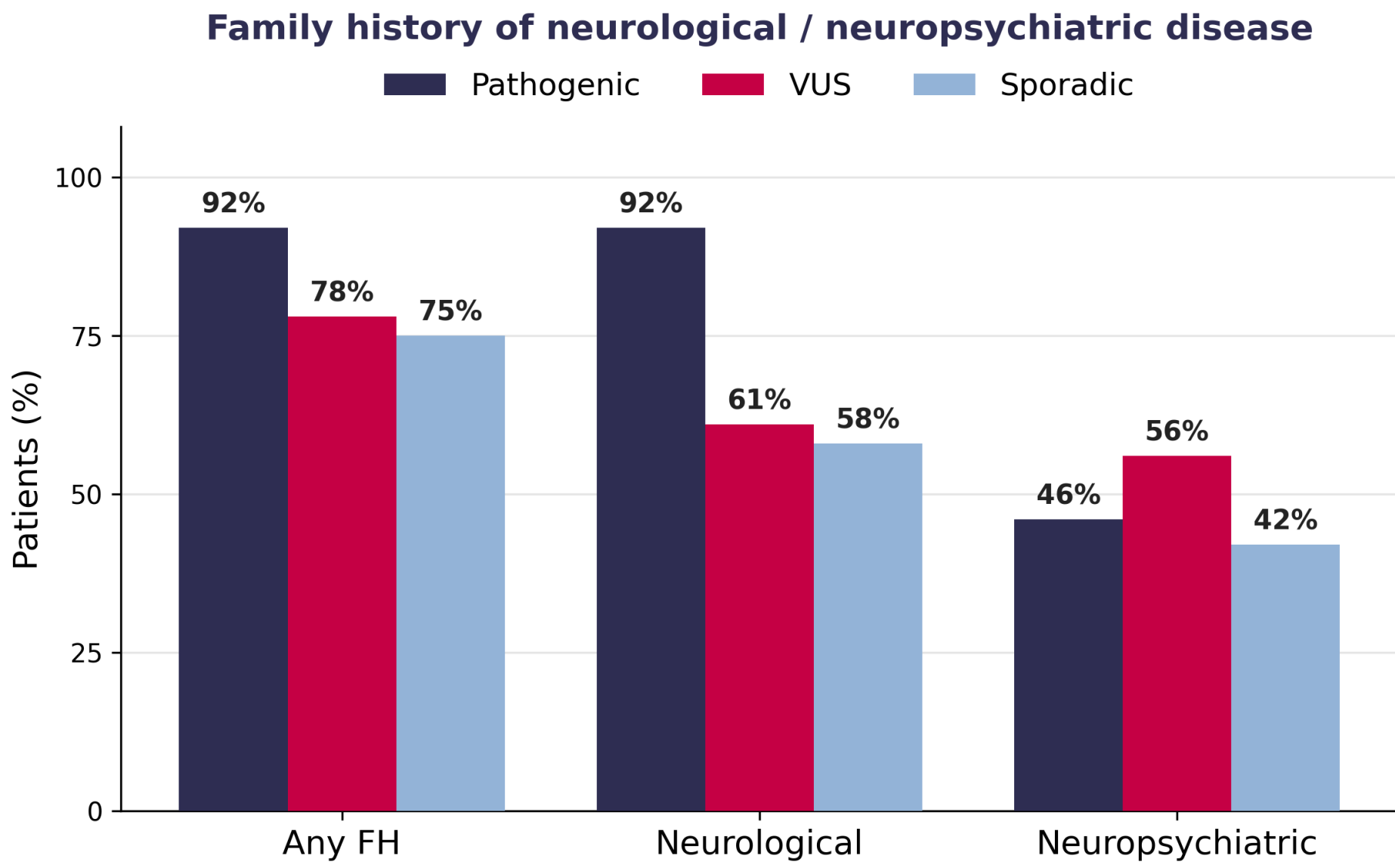


Figure 1. Family history of neurological/neuropsychiatric disease by group.

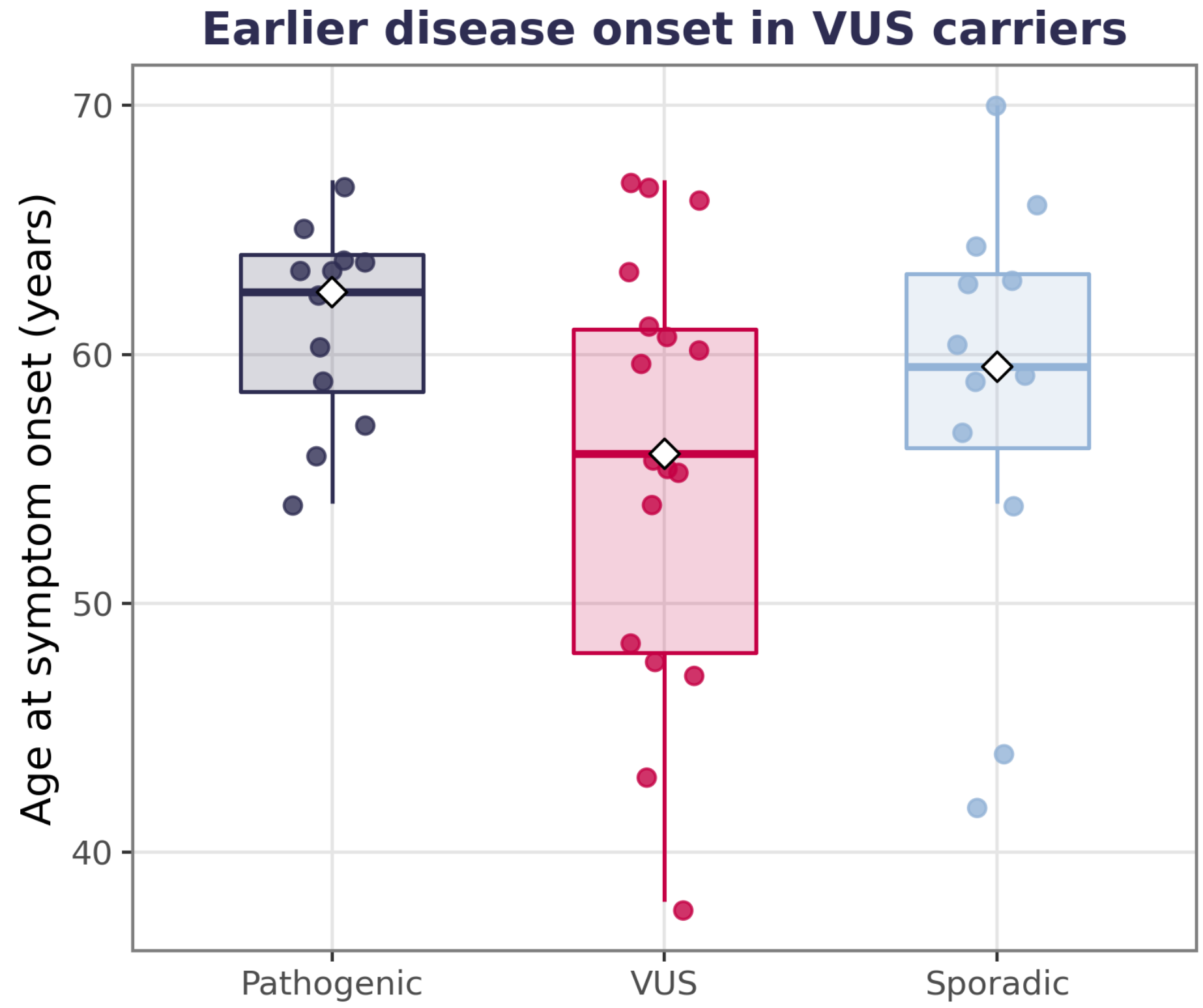


Figure 2. Age at symptom onset by group; VUS carriers debut earliest.

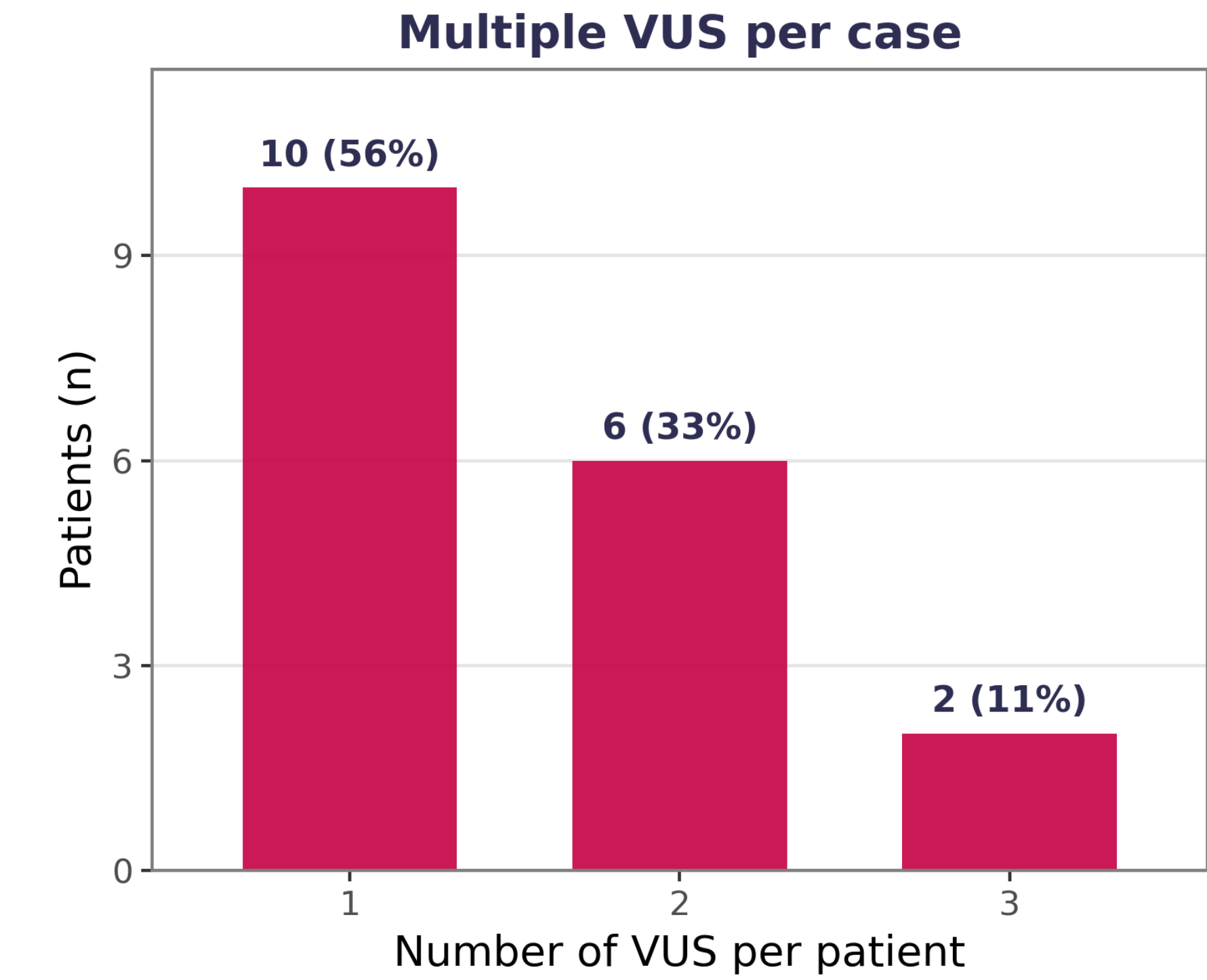


Figure 3. Number of VUS per patient (44% carry ≥2, up to three).

### Marked genetic heterogeneity across VUS carriers

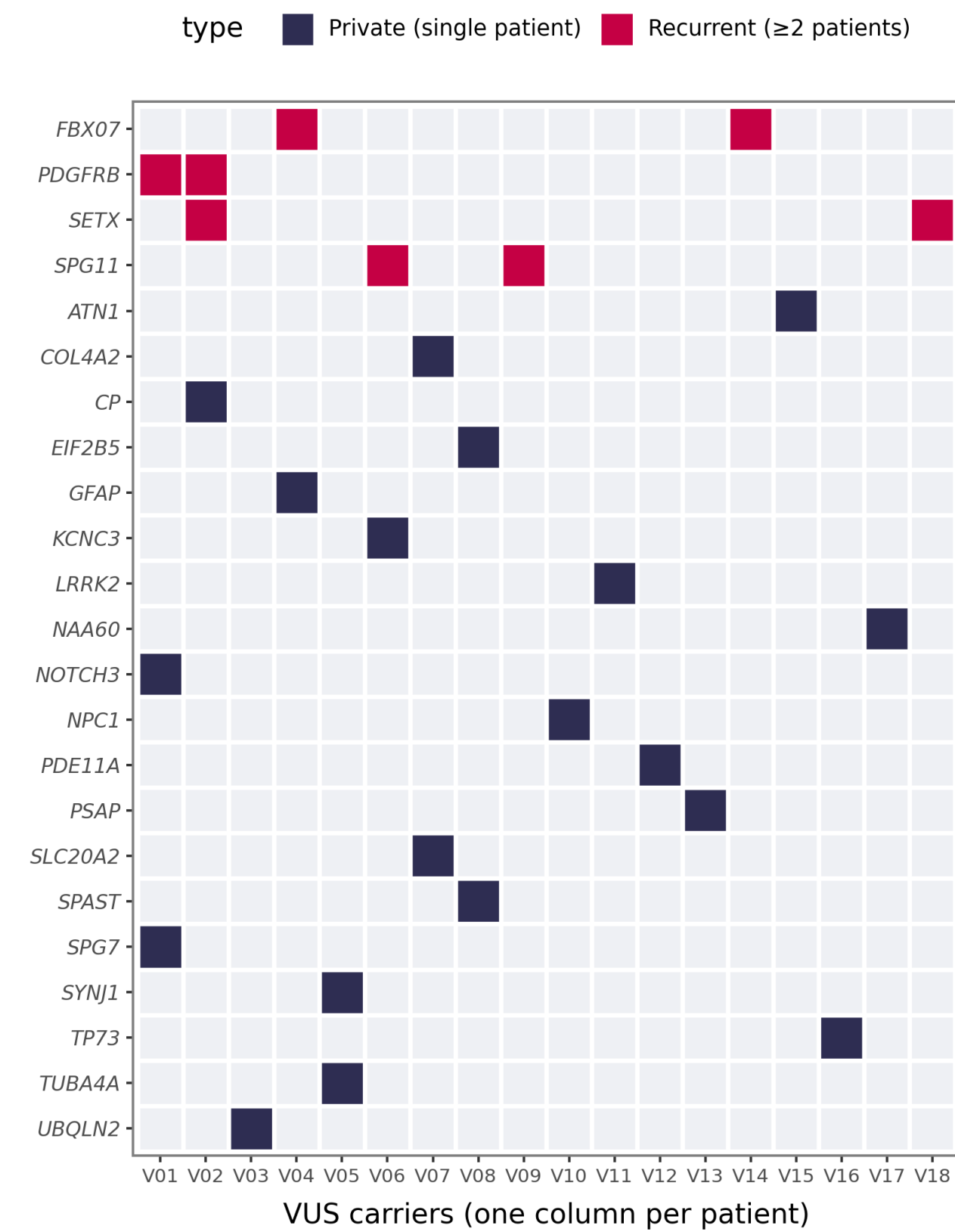


Figure 4. Gene × patient map; recurrent VUS (same gene, different patients) in crimson.

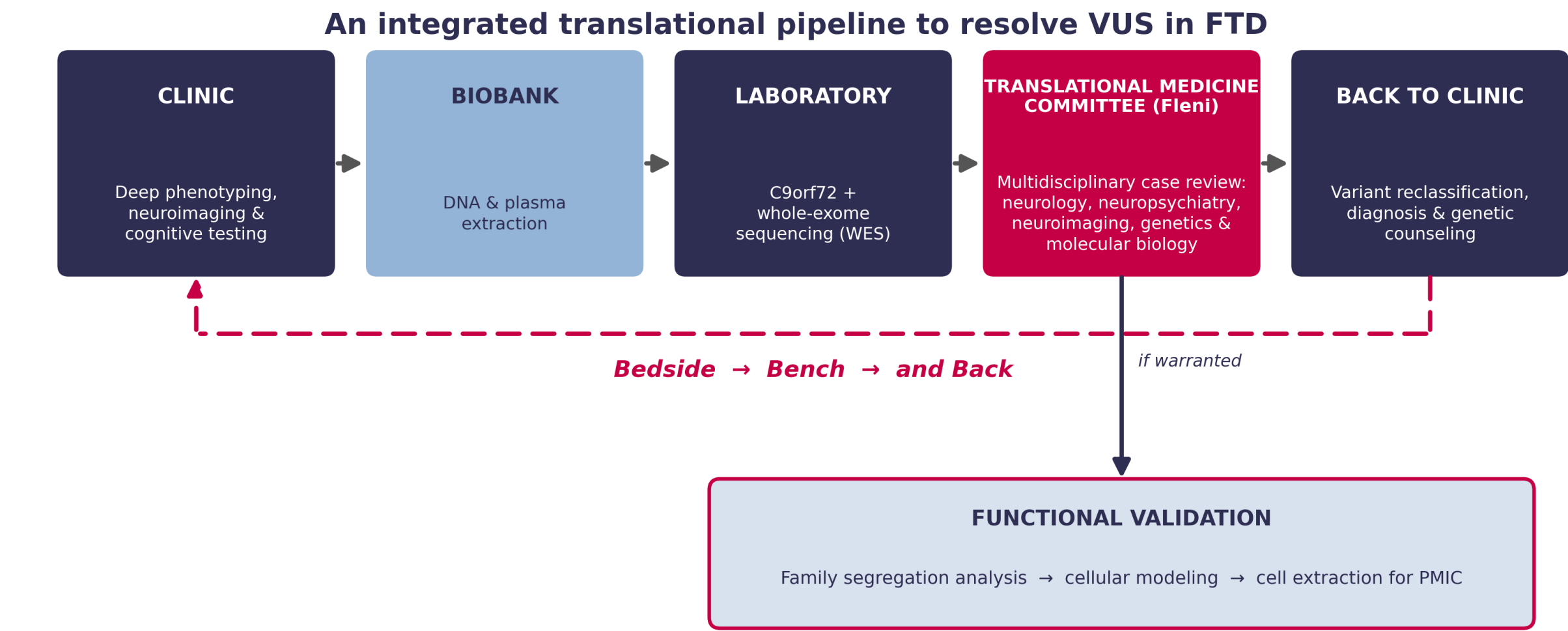


Figure 5. Proposed bedside-to-bench-and-back translational pipeline.

### DISCUSSION & CONCLUSION

- VUS in FTD frequently present with early-onset disease, multiple variants and a complex family history, and should not be hastily dismissed as incidental — each case warrants structured, case-by-case evaluation within an interdisciplinary committee.
- Many patients carried more than one VUS (up to three), and several VUS recurred across different patients. Systematically registering these variants — using broad approaches such as whole-exome or whole-genome sequencing — is essential to document them and record their prevalence.
- In-silico classifiers (Franklin, VarSome) inform but do not resolve a VUS; the final decision rests with the Translational Medicine Committee, which integrates the patient's clinical phenotype and the biological plausibility of the affected gene. Such committees are central to deciding which VUS merit deeper study, given the extensive work of family-segregation analyses and subsequent cellular modeling and cell-line development for pathogenicity validation — particularly relevant in resource-limited settings such as Latin America, where genetic information is also scarce.
- These findings underscore the importance of not dismissing VUS as incidental, particularly with a strong and complex family history, and highlight the critical role of genetic counseling, where such results must be carefully explained and contextualized, including their current interpretative limitations.

### CONTACT

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