



Genetic Phenotypes of Alzheimer’s disease Mutations

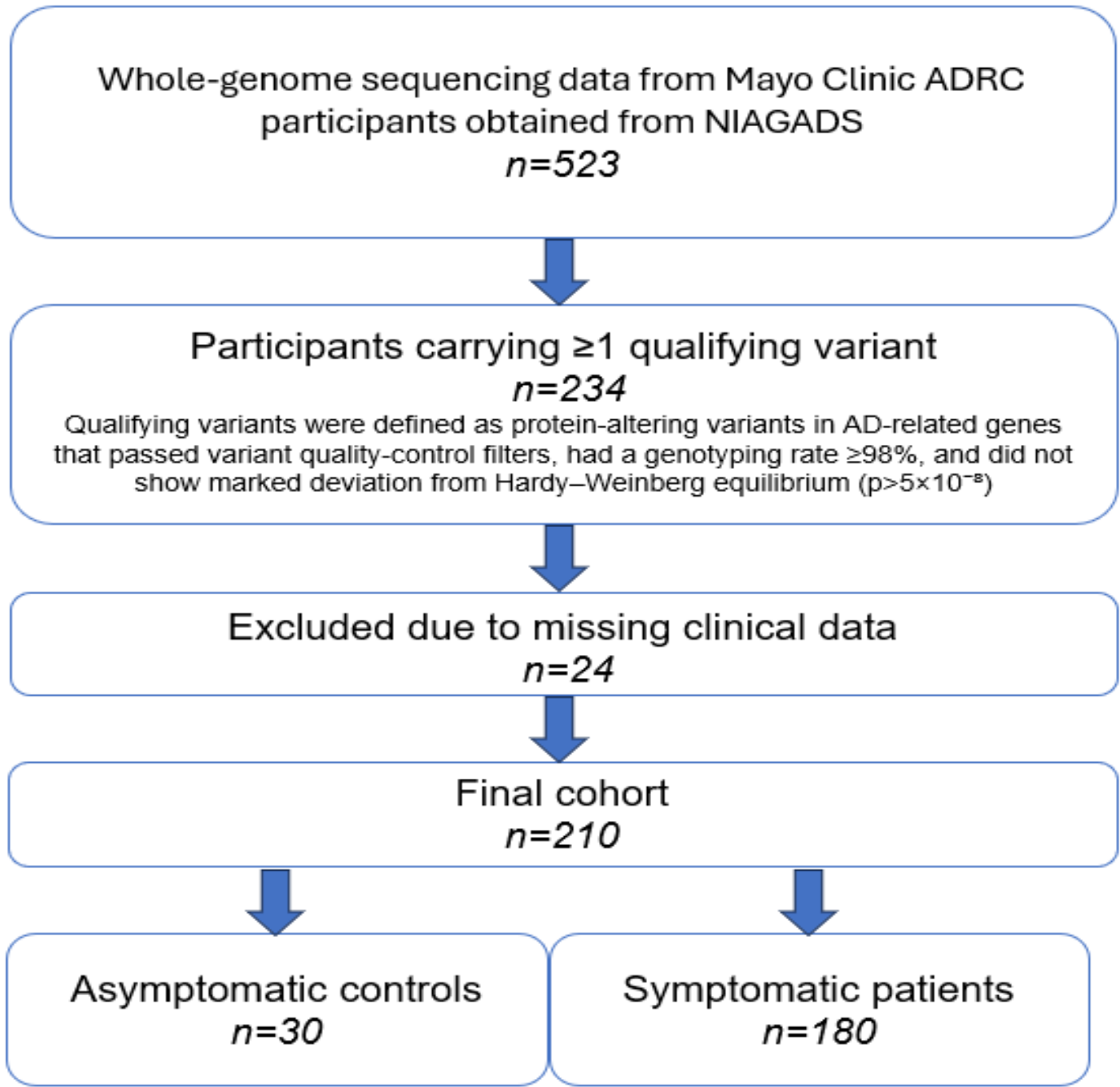
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BACKGROUND

Protein-altering variants in AD-related genes are increasingly identified through genomic sequencing, but most are not clearly pathogenic. The clinical and neuropathologic significance of many genetic variants remains uncertain. We examined whether genetic variant clinical classification is associated with clinical features and phenotype and neuropathology in an ADRC cohort.

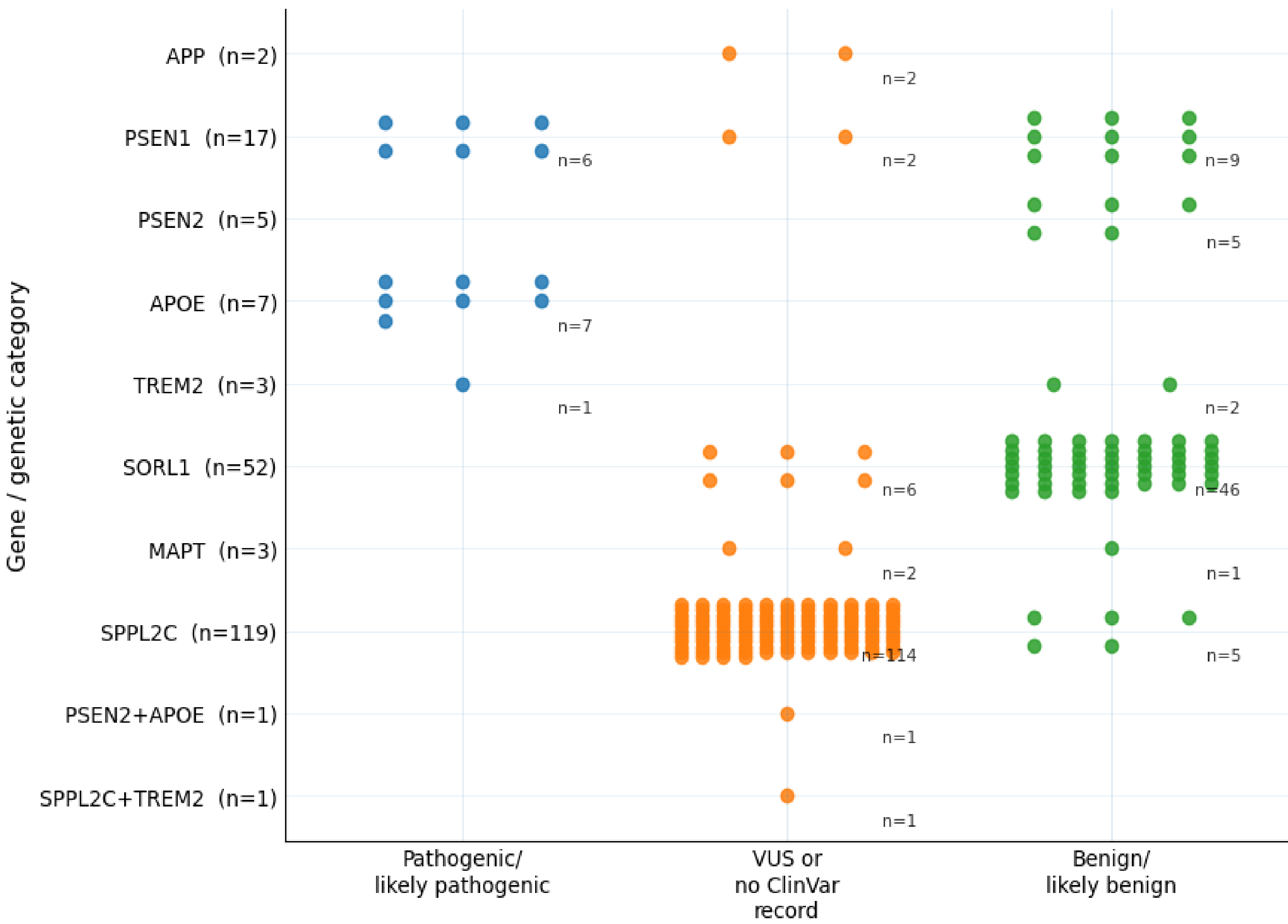
METHODS

Whole-genome (n=523) data from Mayo Clinic ADRC participants was downloaded from the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). Carriers of protein-altering variants in AD-related genes passing VQSR filters, with genotyping rate $\geq 98\%$ and Hardy–Weinberg $p > 5 \times 10^{-8}$ were identified. Electronic health records were reviewed; demographics, longitudinal clinical features and post-mortem neuropathology were abstracted.



RESULTS

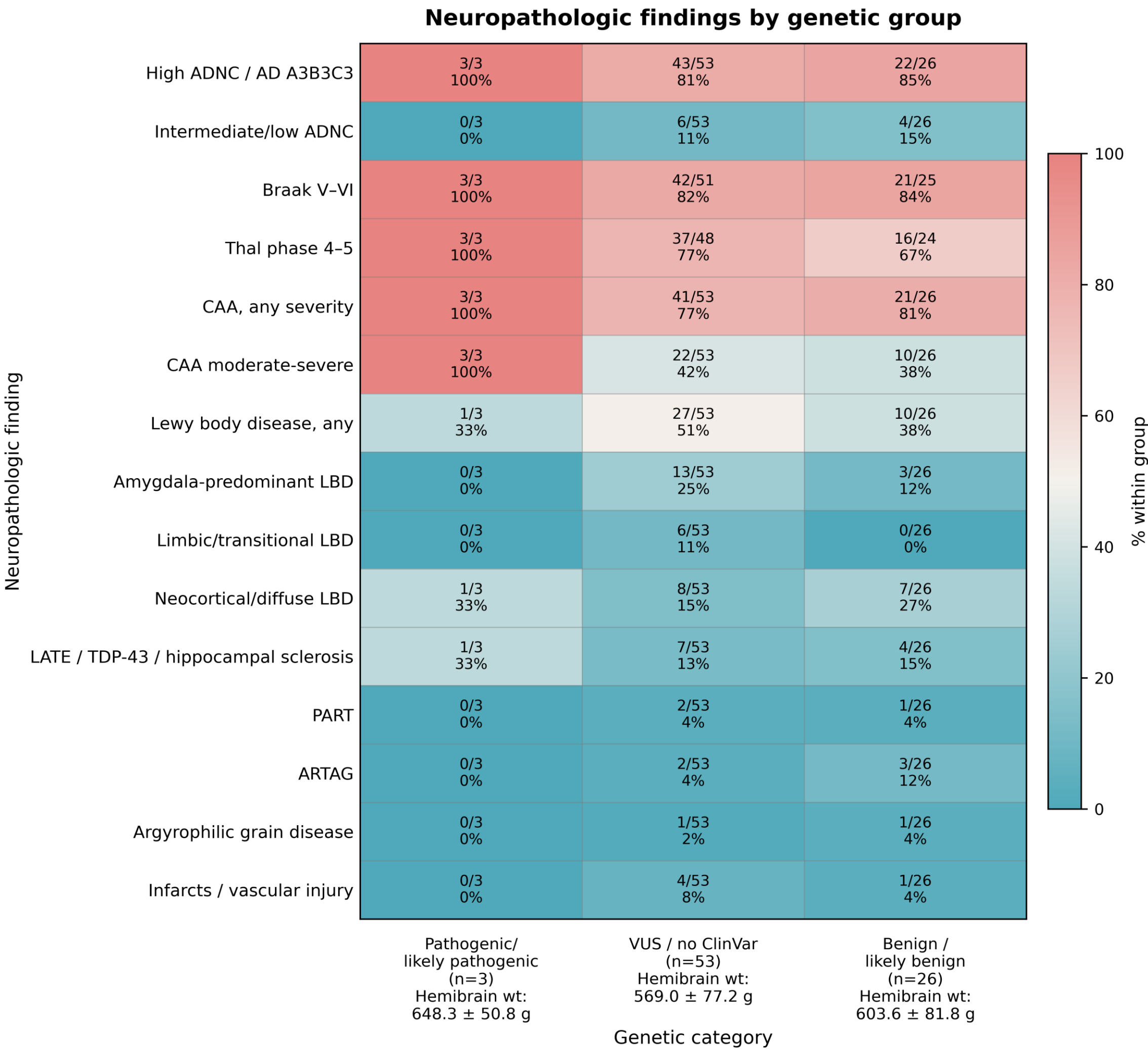
Variable	Full cohort N=210	Pathogenic / likely pathogenic N=14	VUS / no ClinVar N=128	Benign / likely benign N=68	P
Age at onset, y	66 (58-75)	58.5 (48-67)	66 (58-74)	68 (58-76)	0.09
Age at death, y	81 (69-89)	69 (60-82)	80 (70-88)	84 (71-92)	0.04
Baseline STMS	30 (25-33)	31 (25-35)	31 (26-34)	28 (24-32)	0.06
Last follow-up STMS	18 (12–30)	19.0 (11-28.5)	18 (12-28)	19.5 (13-31)	0.79
Follow-up time, y	5 (3-8)	4 (3-9.5)	5 (3-8)	5 (3-7.5)	0.45
1st-degree family history, n (%)	102 (51.8)	8 (66.7)	66 (52.8)	28 (48.7)	0.41
Symptomatic, n (%)	180 (86)	10 (71)	118 (92)	52 (78.5)	0.01
Pyramidal/EPScerebe llar signs, n (%)	46 (22)	1 (7)	32 (25)	13 (19)	0.27
Phenotype at presentation, n (%)					
Amnestic predominant	131 (75.3)	8 (80.0)	88 (77.2)	35 (70.0)	0.59
Atypical phenotype	43 (24.7)	2 (20.0)	28 (22.8)	15 (30.0)	



Distribution of Genetic Variant Significance by Gene. Each dot represents one participant. Variants are grouped by gene and clinically classified according to ClinVar*.

*Landrum et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Research*. 2018;46(D1):D1062–D1067. doi:10.1093/nar/gkx1153.

NEUROPATHOLOGY



Among autopsied participants, high ADNC was common across all genetic categories, including all pathogenic/likely pathogenic carriers and most VUS/no ClinVar and benign/likely benign carriers. CAA was also frequent across groups, with moderate-to-severe CAA present in all pathogenic/likely pathogenic carriers but also observed in VUS/no ClinVar and benign/likely benign groups. Overlapping co-patholigues were common among VUS/no ClinVar carriers.

CONCLUSIONS

In this ADRC cohort, pathogenic/likely pathogenic variants in AD-related genes were uncommon, while VUS/no-ClinVar and benign/likely benign variants accounted for most qualifying variants. Among 210 participants with qualifying variants, only a small minority had pathogenic/likely pathogenic variants, while most carried VUS/no-ClinVar or benign/likely benign variants. **Participants with pathogenic/likely pathogenic variants had younger age at death and more frequent antiseizure treatment.** **Neuropathology findings of cerebral amyloid angiopathy and Lewy body disease also present in a substantial proportion of cases.**