

Background

- Vascular cognitive impairment and dementia (VCID) is the second-leading cause of dementia.
- VCID research is limited by extreme heterogeneity.
- CADASIL is an effective model for highly prevalent sporadic VCID.
- This is the first US cohort to collect genetic, clinical, neuropsychological, functional, neuroimaging, and biofluid biomarkers of CADASIL.

Methods

- The United States CADASIL Consortium (USCC) is a collaboration of 12 academic sites.
- Clinical assessment, biofluid collection, and brain MRI occur every 18 months (three total visits).
- Companions provide external documentation of phenotype changes or functional declines.
- Statistical analysis: P-values were derived from Fisher exact tests for categorical variables and Kruskal-Wallis tests for continuous variables.

Results

- 560 total participants: 459 with confirmed gene-status stratified by *NOTCH3* pathogenicity risk based on EGFr domain (Hack et al., 2023) (Figure 1).
- Participants in analytic cohort are typically middle-aged adults (median age = 47.9 years, Table 1).
- Most cases present with early CADASIL (Table 2).
 - 74.8% (240/321) with mRS ≤1.
 - 38.0% (130/342) with history of stroke.
 - 10.0% (34/342) with mild cognitive impairment.
 - 51.4% (169/329) with ≤1 neurological exam abnormalities.
- Functional impairment, cerebrovascular events, and neurocognitive decline scale progressively with mutation pathogenicity (Table 2).
- 92 unique *NOTCH3* variants were identified, with the the most common variant by unique participant count located in EGFr domain 3 (*n* = 72) (Figure 2).
- Apolipoprotein E (*APOE*) ε4 carrier status was balanced uniformly across all analysis groups (≈ 25%).
- Distinct phenotypic profiles across the mutation tiers.
 - High-pathogenicity cohort was characterized by significantly younger ages at clinical diagnosis and elevated rates of migraine with aura.
 - Medium-pathogenicity group was enriched with secondary neuropsychiatric manifestations, e.g. obsessive-compulsive behaviors.
- Limitations: cross-sectional design; missingness of clinical metadata; demographic diversity.

Conclusion

- Large, genetics-confirmed cohort of CADASIL family members spanning presymptomatic through moderate disease, with a well-defined analysis-ready subset.
- The USCC provides a strong foundation for cross-sectional and longitudinal investigations of VCID in a single-cause, monogenic model.

Disclosures

The authors report no conflicts of interest.

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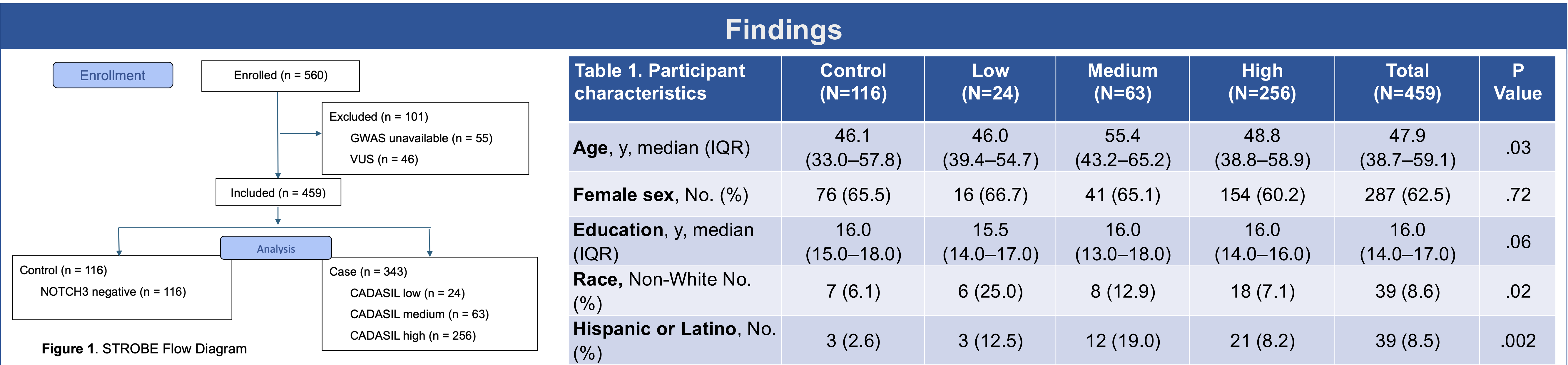


Table 2. Clinical characteristics	Control (N=116)	Low (N=24)	Medium (N=63)	High (N=256)	Total (N=459)	P Value
mRS score, No. (%)						<.001
No symptoms	86 (74.1)	12 (50.0)	23 (36.5)	82 (32.0)	203 (44.2)	
No significant disability	25 (21.6)	7 (29.2)	19 (30.2)	97 (37.9)	148 (32.2)	
Slight disability	2 (1.7)	3 (12.5)	16 (25.4)	40 (15.6)	61 (13.3)	
Moderate disability	0 (0.0)	1 (4.2)	3 (4.8)	21 (8.2)	25 (5.4)	
WHODAS 12-item total score, median (IQR)	1.0 (0.0-4.0)	3.5 (0.0-10.5)	6.0 (1.0-13.0)	4.0 (1.0-11.0)	3.0 (1.0-10.0)	<.001
Age at CADASIL diagnosis, y, median (IQR)	NA	40.0 (36.0-48.0)	52.0 (45.0-56.0)	44.0 (37.0-50.0)	45.0 (37.5-51.0)	.02
Age at first stroke or TIA, y, median (IQR)	48.0 (41.0-53.0)	43.0 (36.0-45.0)	48.0 (35.0-53.0)	43.0 (35.0-50.0)	43.0 (35.0-51.0)	.53
History of stroke, No. (%)	2 (1.7)	5 (20.8)	19 (30.2)	106 (41.6)	132 (28.8)	<.001
History of TIA, No. (%)	5 (4.3)	7 (29.2)	21 (33.3)	95 (37.3)	128 (27.9)	<.001
Migraine with aura, No. (%)	35 (50.7)	7 (58.3)	27 (64.3)	146 (76.0)	215 (68.3)	.002
Mild cognitive impairment diagnosis, No. (%)	0 (0.0)	1 (4.2)	8 (12.7)	25 (9.8)	34 (7.4)	<.001
Number of neurological exam abnormalities, n (%)						<.001
None	53 (45.7%)	13 (56.5%)	14 (23.3%)	72 (29.3%)	152 (34.2%)	
1	31 (26.7%)	2 (8.7%)	16 (26.7%)	52 (21.1%)	101 (22.7%)	
2	24 (20.7%)	3 (13.0%)	12 (20.0%)	43 (17.5%)	82 (18.4%)	
≥3	8 (6.9%)	5 (21.7%)	18 (30.0%)	79 (32.1%)	110 (24.7%)	
Hypertension, No. (%)	30 (25.9)	5 (20.8)	15 (23.8)	51 (20.0)	101 (22.1)	.61
Diabetes, No. (%)	7 (6.0)	3 (12.5)	9 (14.3)	13 (5.1)	32 (7.0)	.047
Dyslipidemia, No. (%)	34 (29.3)	11 (45.8)	34 (54.0)	101 (39.6)	180 (39.3)	.01
MoCA total score, median (IQR)	27.0 (25.0-29.0)	27.0 (25.5-28.0)	27.0 (24.0-28.0)	26.0 (24.0-28.0)	27.0 (25.0-28.0)	.01
MoCA score <26, No. (%)	31 (26.7)	6 (25.0)	26 (41.9)	102 (40.3)	165 (36.3)	.03
SAS total score, median (IQR)	10.0 (6.0-15.0)	11.0 (6.5-15.5)	12.5 (8.5-17.0)	11.0 (6.0-16.0)	11.0 (7.0-16.0)	.17
SAS total score ≥14, No. (%)	31 (28.7)	9 (37.5)	29 (48.3)	87 (35.2)	156 (35.5)	.09
NPI-Q severity score, median (IQR)	1.0 (0.0-3.0)	2.0 (0.5-4.0)	2.0 (0.0-6.0)	3.0 (0.0-7.0)	2.0 (0.0-6.0)	<.001
NPI-Q distress score, median (IQR)	0.0 (0.0-3.0)	1.0 (0.0-4.0)	1.0 (0.0-8.0)	2.0 (0.0-8.0)	2.0 (0.0-6.0)	<.001

Abbreviations: MoCA = Montreal Cognitive Assessment; mRS = modified Rankin Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire; SAS = Starkstein Apathy Scale; TIA = transient ischemic attack; WHODAS = World Health Organization Disability Assessment Schedule.

