

Characterization of Structural Variants Associated Cognition in the Midwestern U.S. Amish

Yining Liu¹, Yeunjoo E. Song¹, Audrey Lynn^{1,2}, Weihuan Wang¹, Kristy Miskimen¹, Sarada L. Fuzzell¹, Sherri D. Hochstetler¹, Renee A. Laux¹, Dawn R. Miller¹, Laura J. Caywood³, Jason E. Clouse³, Sharlene D. Herington³, Ping Wang¹, Alex Gulyayev³, Daniel A. Dorfsman^{3,4}, Noel C. Moore¹, Dana Z. Jian¹, Michael B. Prough³, Andrew F. Zaman³, Larry D. Adams³, Patrice Whitehead³, Paula Ogrocki^{5,6}, Alan J. Lerner^{5,6}, Jeffery M. Vance^{3,4}, Michael L. Cuccaro^{3,4}, William K. Scott^{3,4}, Margaret A. Pericak-Vance^{3,4}, Jonathan L. Haines^{1,2}

¹Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine;²Cleveland Institute for Computational Biology, Case Western Reserve University School of Medicine; ³John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine;⁴The Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine; ⁵Department of Neurology, University Hospitals Cleveland Medical Center; ⁶Department of Neurology, Case Western Reserve University School of Medicine

Introduction

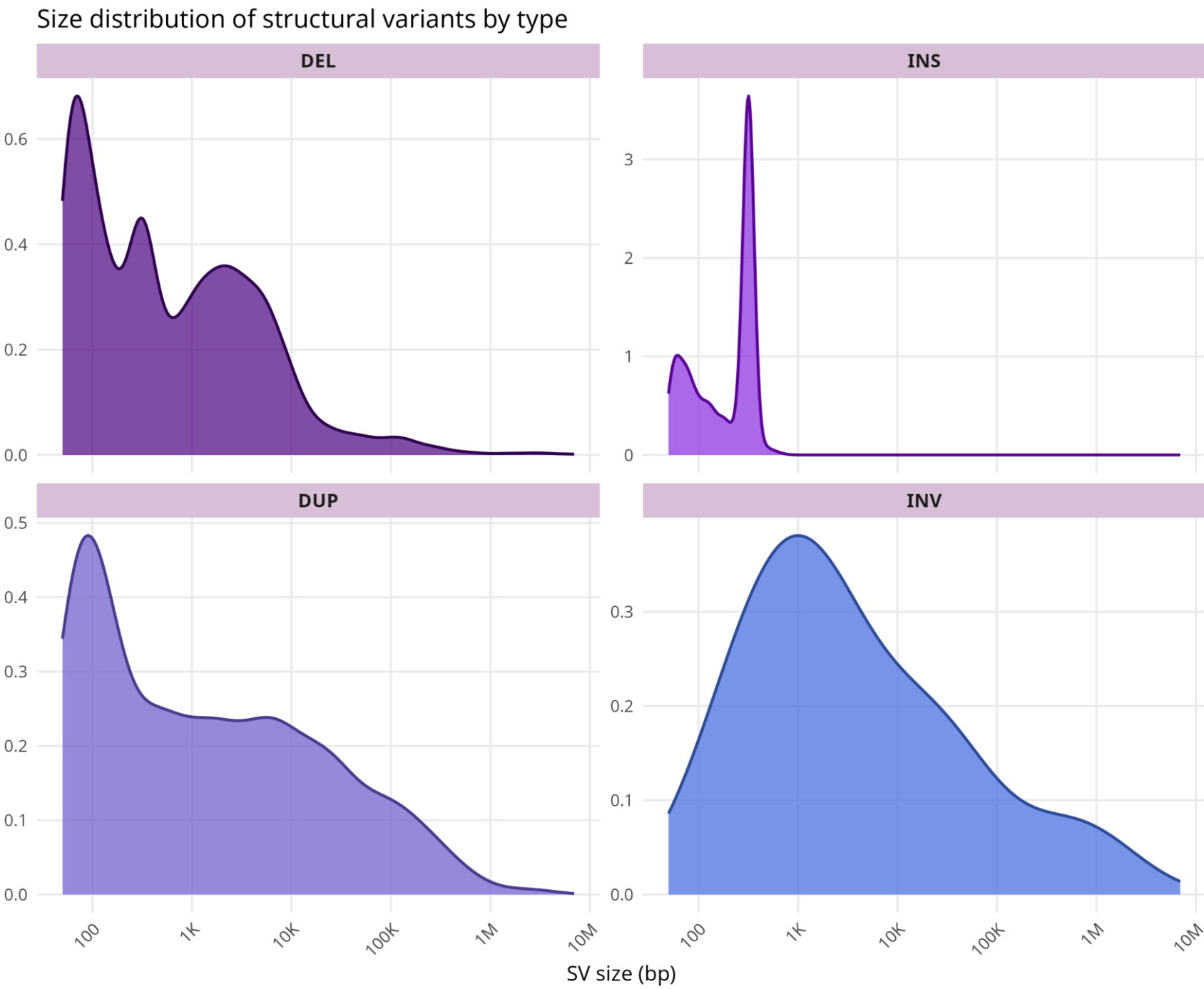
Structural variants (SVs) represent a significant source of genetic variation that might provide novel insights into the genetic architecture of Alzheimer disease (AD) beyond what has been captured by single nucleotide polymorphisms (SNPs). We characterized SVs from whole-genome sequences (WGS) from the Midwestern U.S. Amish, a genetically homogenous population, to identify SVs associated with a cognitive preservation phenotype observed in older Amish individuals who remain cognitively intact despite presumed elevated genetic risk.

Methods

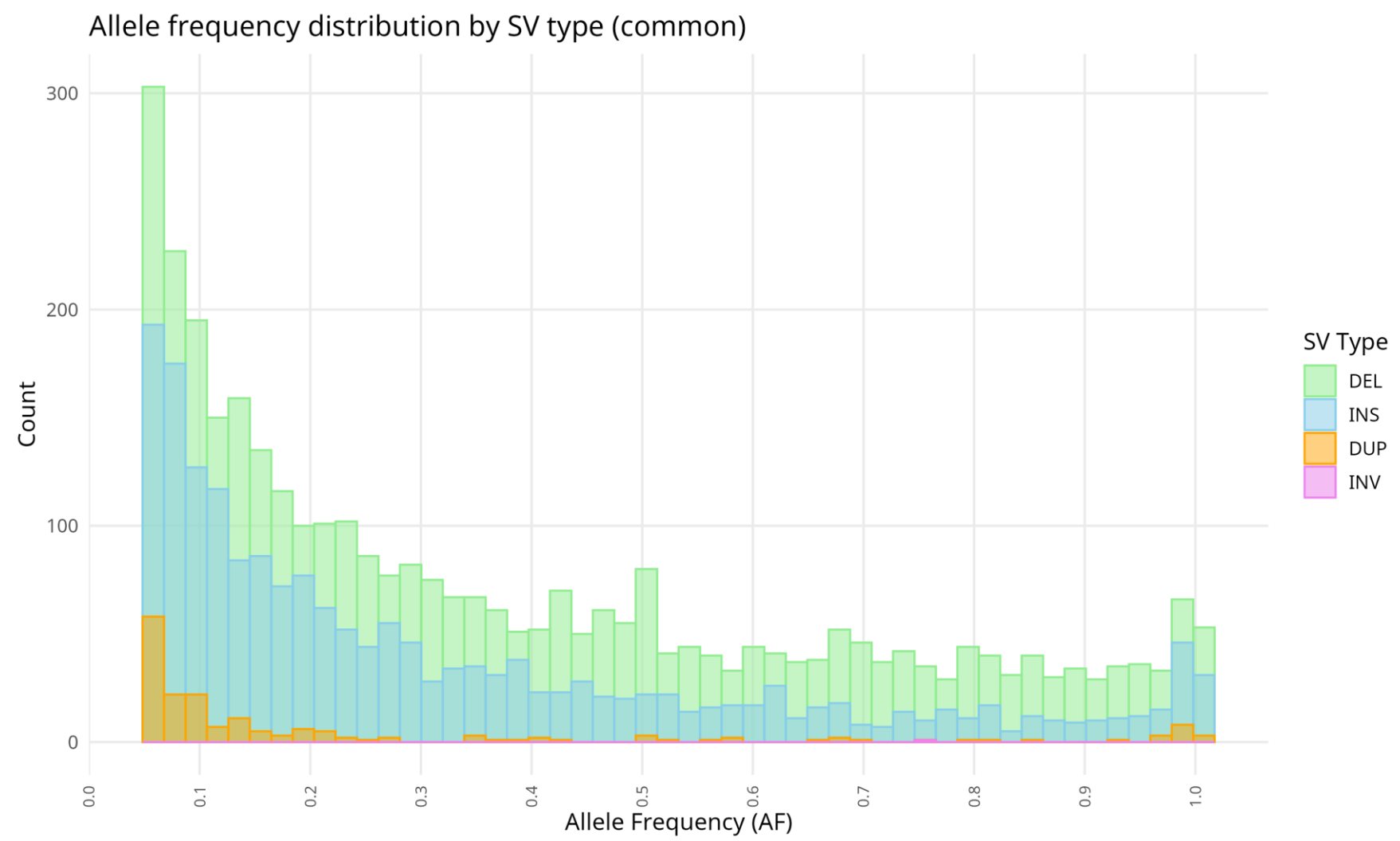
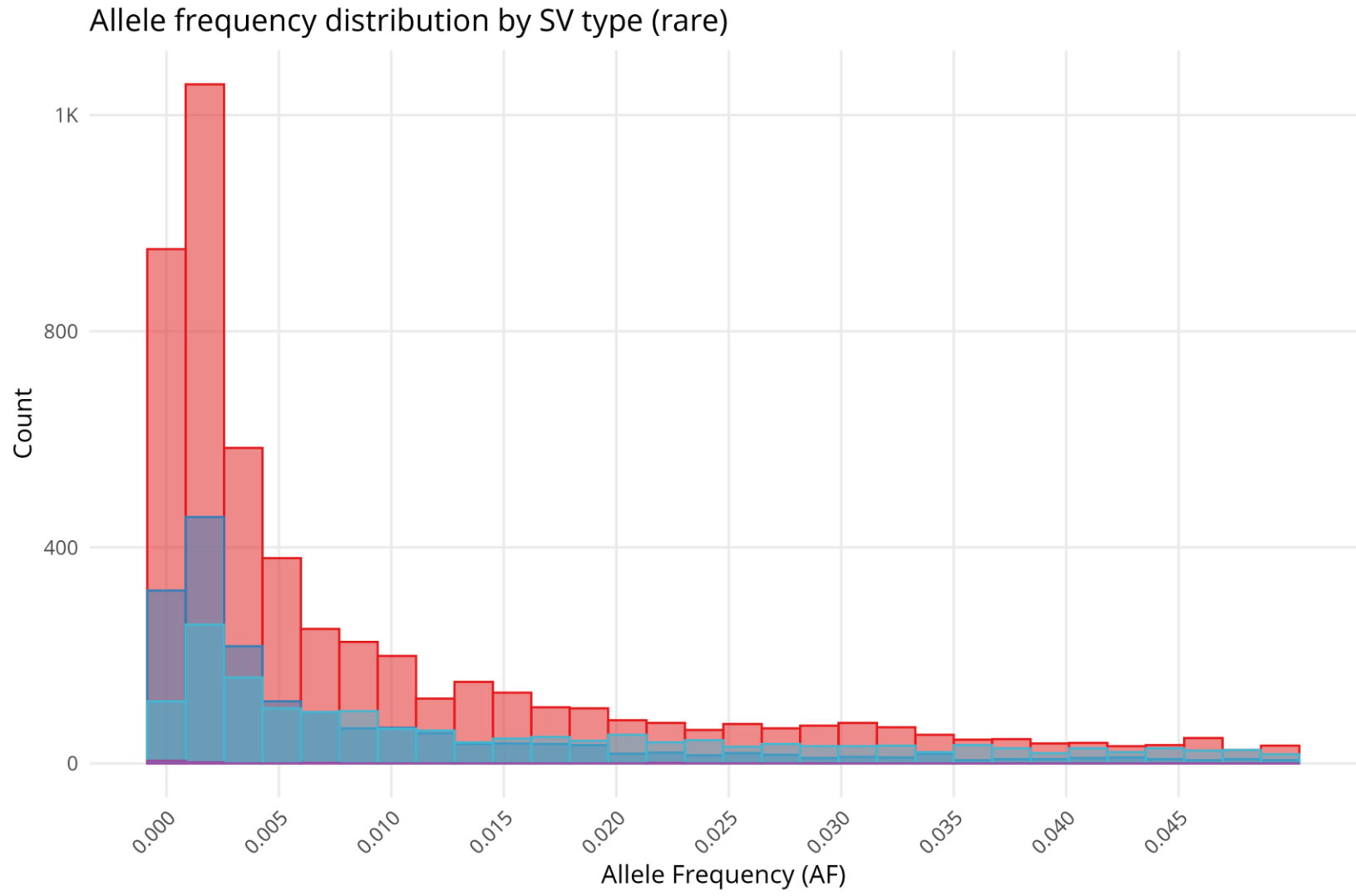
This study included 920 individuals (mean age= 83.1, range: 62.7-101.8) whose cognitive status was determined by clinical experts through adjudication of neurocognitive and physical exams. 526 were cognitively unimpaired (CU) and 394 were cognitively impaired (CI). CIs included 162 mildly cognitively impaired, 177 AD and 55 CI but not AD. SVs were called from WGS using Smoove and Manta, merged with Svimmer, and joint genotyped using GraphTyper2 (ADSP-SV pipeline). SVs were annotated by AnnotSV and VEP. Association analyses were conducted using linear mixed models adjusting for sex, age, study center, and relatedness.

Results

• **Characterization of srWGS-based SVs in the Amish**



SV Type	n	mean size (bp)	Median size (bp)	Q1 size (bp)	Q3 size (bp)
DEL	8,961	14,968	376	100	2,546
INS	3,563	221	295	87	320
DUP	1,925	36,745	926	121	9768
INV	10	74,647	1,543	851	20,175



• **Common SVs in LD with known AD genes**

GENE	CHR	POS	SV	SIZE	AF	pval	beta
PLCG2	16	81765053	DUP	543	0.75	0.036	0.19
	16	81776081	INS	92	0.84	0.76	-0.04

• **Rare SVs in LD with known AD genes**

GENE	CHR	POS	SV	SIZE	AF
SPI1	11	47384111	DEL	757	0.036
	11	47395007	DEL	50	0.0009
PSEN2	1	221964517	DEL	5310722	0.0004
CR1	1	207496847	DEL	173142	0.0004
APP	21	25902439	DEL	198	0.0017
ABCA7	19	1050413	INS	346	0.014

• **Selected SVs (p < 0.05) in LD with AD GWAS loci**

SV POS	Type	Length	P val	Beta	Source
chr16:81765053	DUP	543	0.03641752 (CI)	0.19489881	Bellenguez
chr8:102982543	DEL	1824	0.01801336 (AD)	0.56114543	Bellenguez & Amish
chr9:105794907	INS	78	0.04678768 (AD)	0.4608468	Bellenguez & Amish

Conclusion & Future Directions

In this study, we characterized the structural variants called from short-read WGS in the U.S. Midwestern Amish. We identified two common SVs and five rare SVs in the Amish that are in LD with known AD genes (ADSP Top 20 AD genes). We also detected three SVs that are in LD with previously published AD GWAS loci with p-values smaller than 0.5 when comparing CU vs CI and CU vs AD groups. We also identified an intronic insertion in CTNNA2 and an intronic deletion in NBEAL1 (in LD with WDR12), genes previously nominated as protective in the Amish.

These results highlight that SVs may contribute to AD genetic architecture beyond common and rare SNPs, warranting inclusion in future genetic studies.

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Contact

 yxl3272@case.edu

 www.linkedin.com/in/yining-elaine-liu