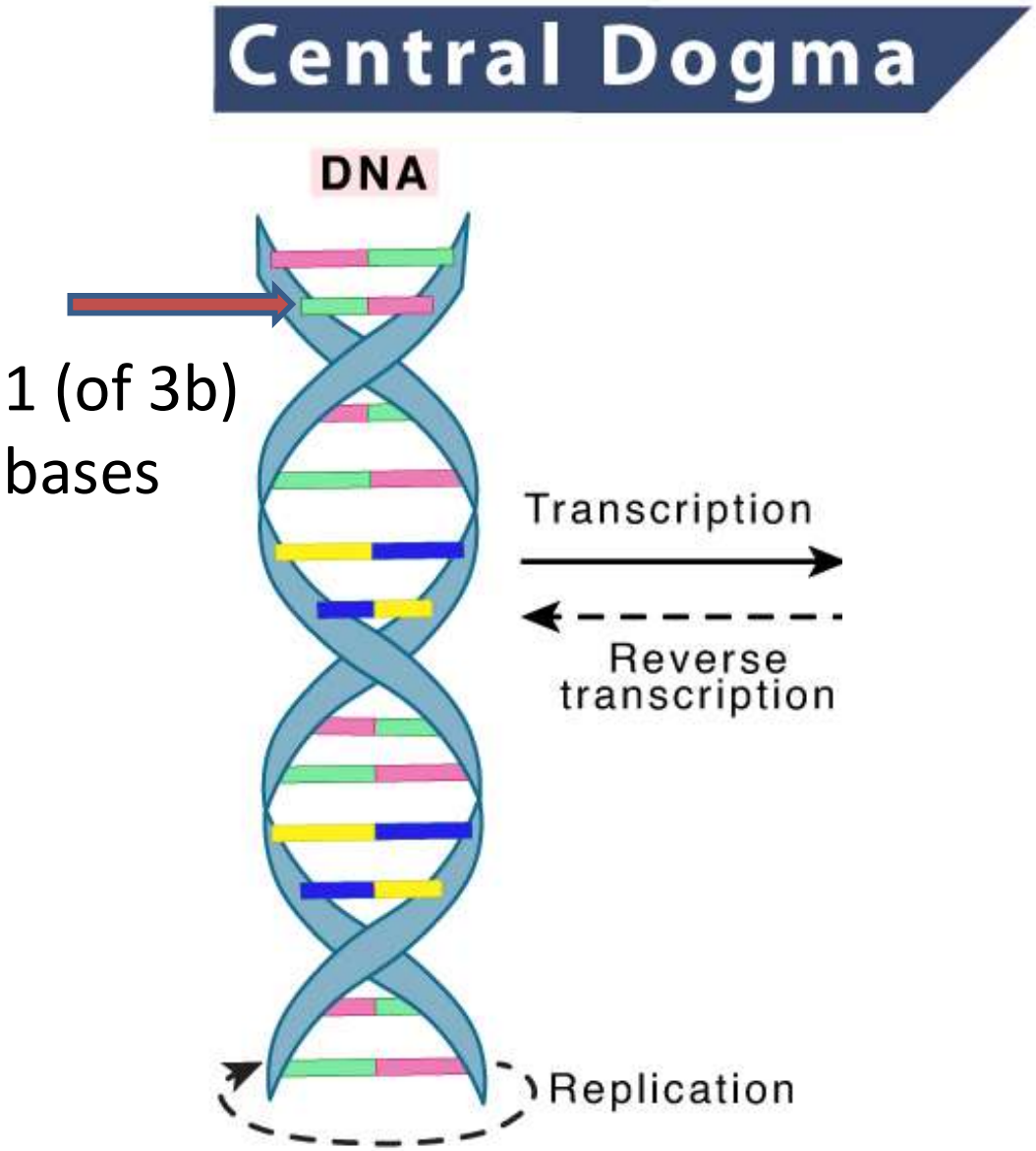
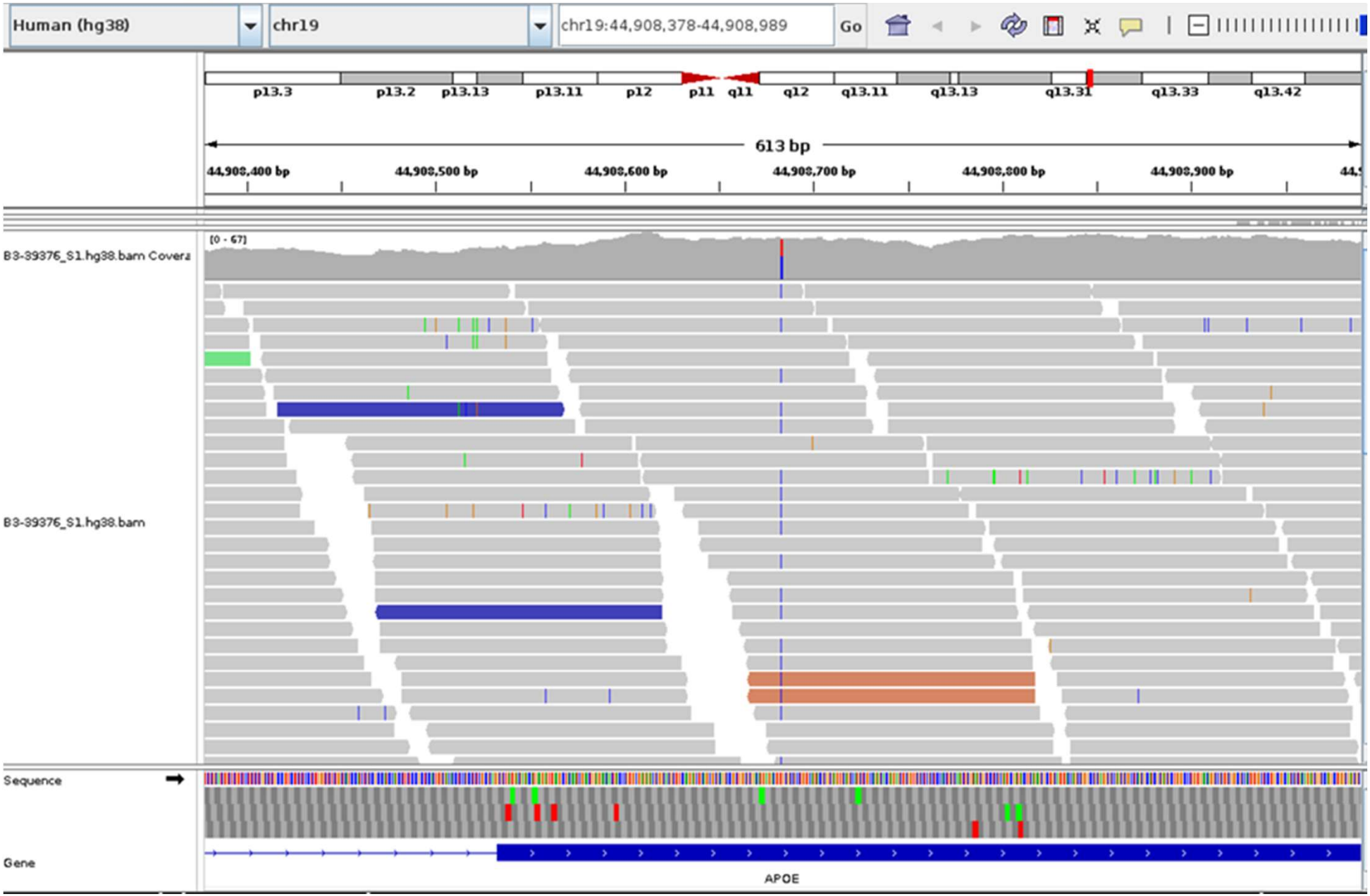
Your Genomes at Work in Alzheimer's Disease and Related Disorders

Mike Greicius, MD
Iqbal Farrukh and Asad Jamal Professor
Department of Neurology and Neurological Sciences
Stanford University

The Central Dogma



Types of Genetic Studies:
Short-Read Whole-Genome Sequencing



Structural Variants

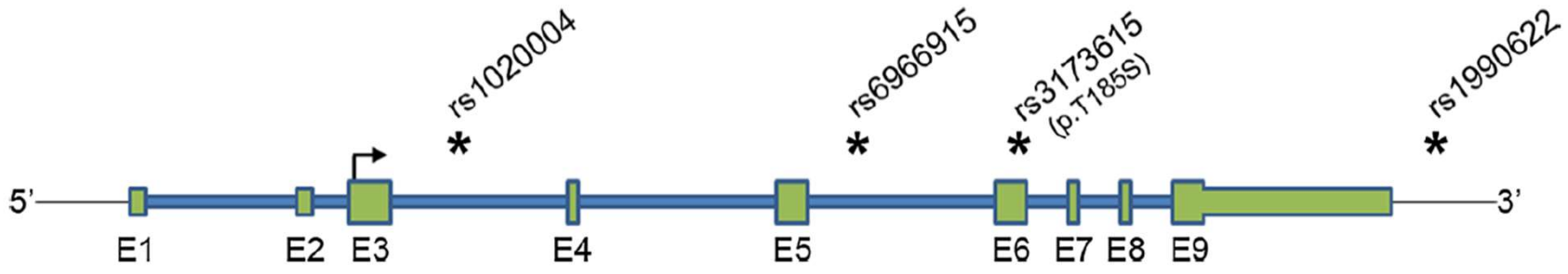
- Single nucleotide variant: Single base change
- Structural variant: Insertion or deletion of more than 50 bases
- Each of us has ~15,000 of these across genome
- Very hard to identify with short-read sequencing (particularly the larger ones)
- More likely than SNVs to disrupt protein function

Types of Genetic Studies:
Long-Read Whole-Genome Sequencing

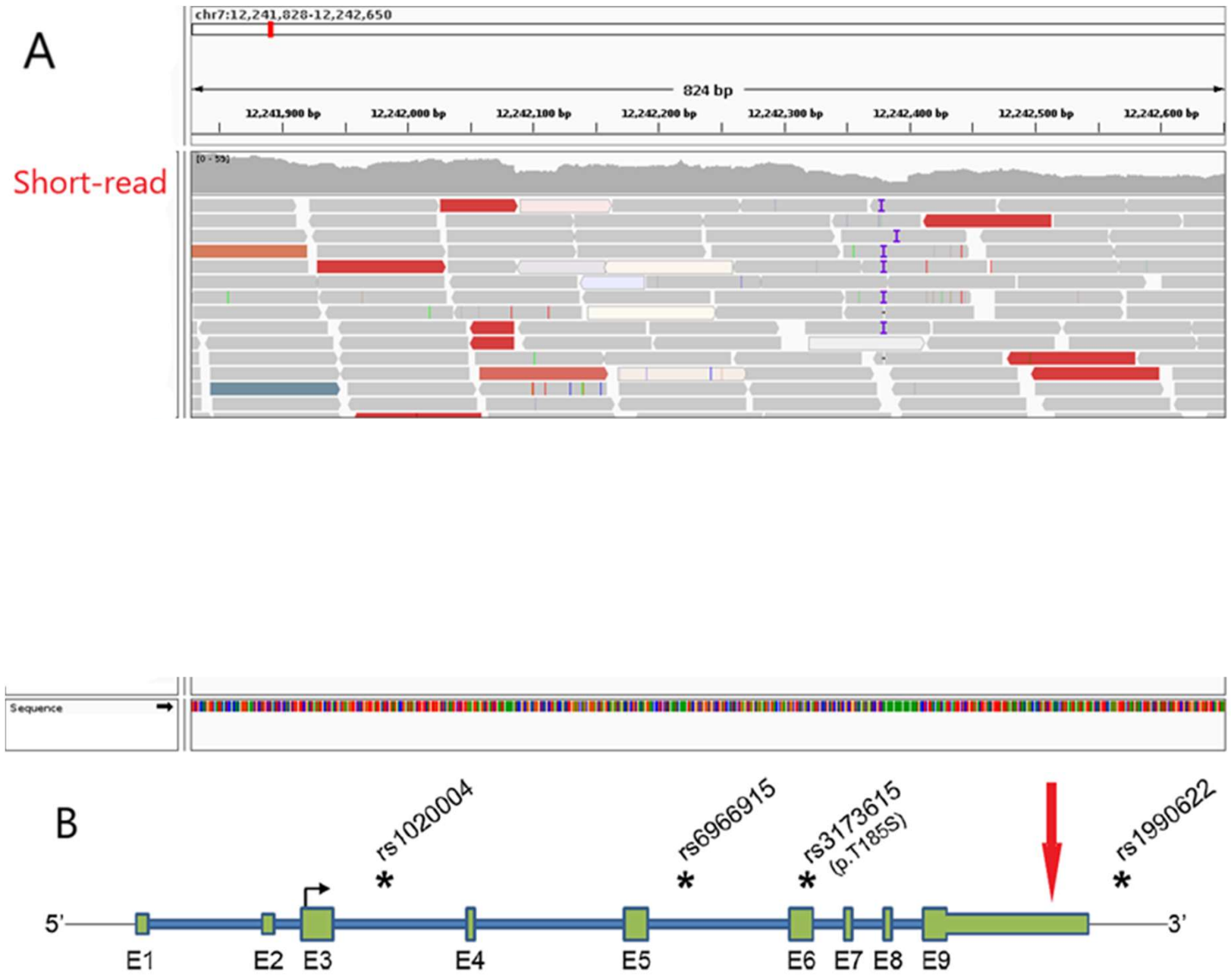
TMEM106B Variant Reduces Risk of Frontotemporal Dementia and Alzheimer's

Table 1 *TMEM106B* risk association studies in *GRN* or *C9orf72* mutation carriers

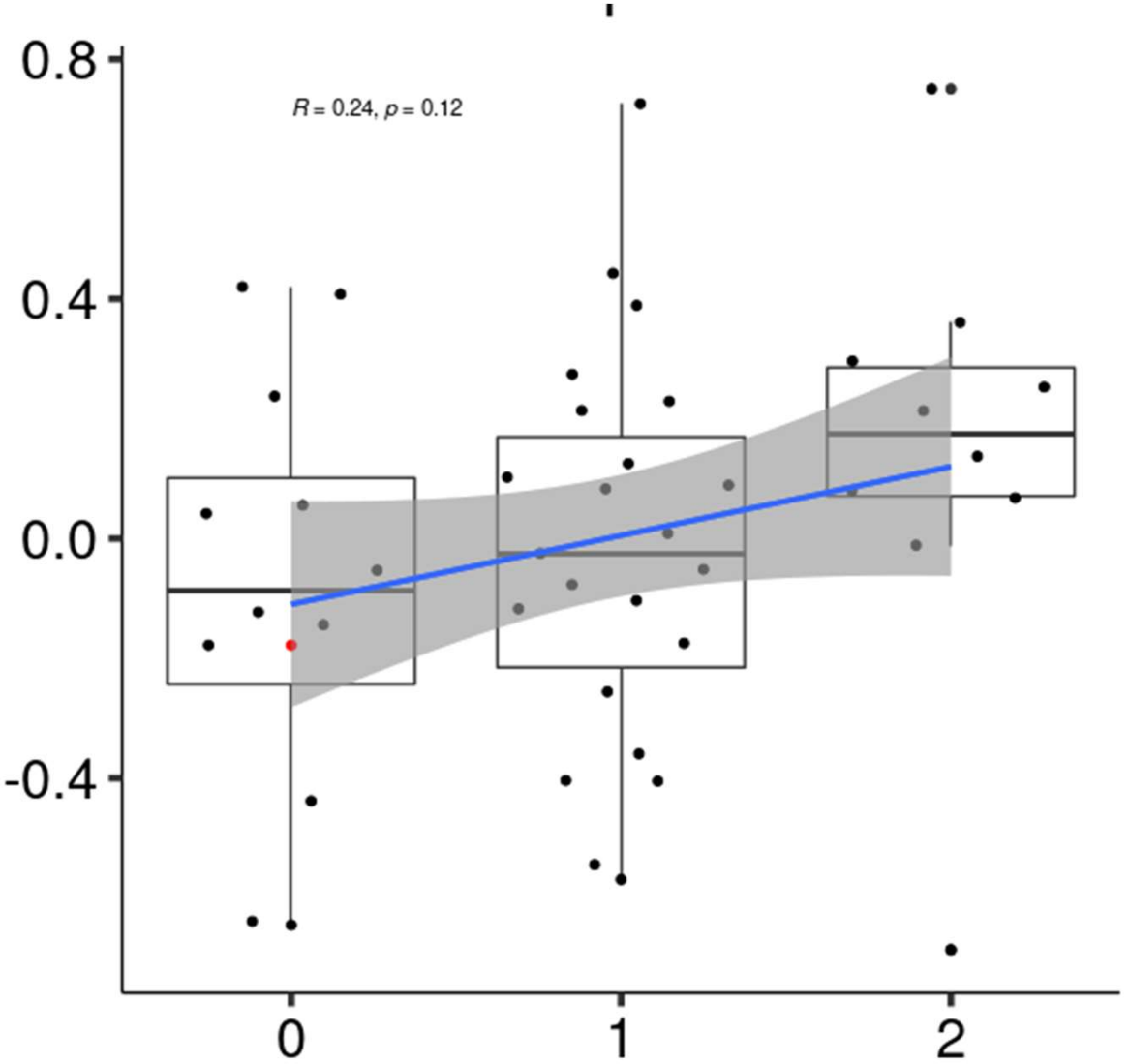
Mutation group	References	Group 1 (*N*)	Group 2 (*N*)	Model	SNP	Minor allele	*p* value[a]	Odds Ratio[b]
GRN	Van Deerlin et al. [76]	CON (2509)	*GRN* (89)	Allelic	rs1990622	C	1.34×10^{-9}	0.34
	Finch et al. [19]	CON (822)	*GRN* (78)	Allelic	rs1990622	C	0.0003	0.51
	Finch et al. [19]	CON (822)	*GRN* (78)	Additive	rs1990622	C	0.003	0.57
	Finch et al. [19]	CON (822)	*GRN* (78)	Dominant	rs1990622	C	0.088	0.65
	Finch et al. [19]	CON (822)	*GRN* (78)	Recessive	rs1990622	C	0.003	0.12
	Nicholson et al. [52]	CON (822)	*GRN* (29)	Recessive	rs1990622	C	0.03	0.15
	Gallagher et al. [21]	CON (2509)	*GRN* (116)	Allelic	rs1990622	C	<0.0001	0.37
	Lattante et al. [38]	CON (552)	*GRN* (76)	Allelic	rs1990622	C	0.0041	0.58
	Lattante et al. [38]	CON (552)	*GRN* (76)	Recessive	rs1990622	C	9.54×10^{-6}	0



TMEM106B


A
chr7:12,241,828-12,242,650
824 bp
12,241,900 bp
12,242,000 bp
12,242,100 bp
12,242,200 bp
12,242,300 bp
12,242,400 bp
12,242,500 bp
12,242,600 bp
Short-read
Sequence
B
rs1020004
rs6966915
rs3173615
(p.T185S)
rs1990622
5'
3'
E1
E2
E3
E4
E5
E6
E7
E8
E9

Measuring Proteins in Your Plasma



Conclusions

- Long-read sequencing (LRS) should help us identify new variants that increase (or decrease!) risk for AD and related disorders
- Having plasma protein measures in subjects with LRS helps us understand how gene changes impact protein levels/function
- So thanks for all your help!

Acknowledgments

Greicius Lab

Michael Belloy
Yann Le Guen
Lia Talozzi
Seth Talyansky
Augustine Chemparathy
Nandita Kasireddy
Ilaria Stewart
Maddie Dailey

Stanford

Aaron Gitler
Zihuai He
Tanner Jensen
Beth Mormino
Euan Ashley
John Gorzynski
Victor Henderson

Funding

NIH: RO1 AG060747; R35 AG072290P30; AG066515 (ADRC)