

Identification of potentially pathogenic AD rare variants in native African population: Insight from the DAWN study

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INTRODUCTION

Alzheimer’s disease (AD) genetics is largely unexplored in native African populations. The DAWN study is a global initiative focused on AD genetics in African ancestry and US Hispanic populations. Here for the first time, we examined rare potentially disease-causing variants in a set of known AD genes using whole genome sequencing (WGS) analysis of individuals from Nigeria, Ghana, Cameroon, Kenya, Ethiopia, Mozambique, Uganda, and Tanzania.

METHODS

- ❑ We analyzed WGS of 2159 individuals; AD cases (35.9%), cognitively unimpaired (46.1%), mild cognitive impairment (MCI) (13.1%), and dementia others (3.2%).
- ❑ We applied the Alzheimer’s Disease Sequencing Project developed bioinformatic pipeline and QC procedure.
- ❑ Genome regions corresponding to *PSEN1*, *PSEN2*, *APP*, *APOE*, *SORL1*, *TREM2*, *MAPT*, and *GRN* were extracted for rare variants identification.
- ❑ Coding and splice variants were prioritized based on their population frequency in Africans, prediction to be damaging, previous reports to be pathogenic, and gene–phenotype correlation.

RESULTS

- ❑ In our study of 2159 case controls; the mean age at examination was 74.3 (+/- 9.2) years, with slight female predominance (57.8%). We detected a total of 394 variants that alter protein structure within the set of genes. After further filtering, we identified 6 variants in six unrelated individuals with AD dementia. Two of the variants were novel: *SORL1* p.E1268X and *MAPT* c.1733-1G>T and four were rare (*PSEN1* p.A431T, *SORL1* p.R985X, *PSEN2* p.R134C, and *GRN* p.W49X).
- ❑ *PSEN1* p.A431T is a missense variant observed in a male subject from Lagos, Nigeria, diagnosed with AD at the age of 52 with positive family history of dementia (PFH) (Fig.1). *PSEN2* p.R134C variant is observed in a 75-year-old Kenyan woman with AD with symptom onset at age 65. We also detected two stopgain variants in *SORL1* gene (p.R985X and p.E1268X) in two females from Nigeria with early onset AD. We also identified a stop gain variant in *GRN* gene (p.W49X) in a 75-year-old Cameroonian women with AD. The sixth marker is a splice acceptor variant in *MAPT* gene (c.1733-1G>T) in a 70-year-old Nigerian man with dementia and PFH (Fig.2).

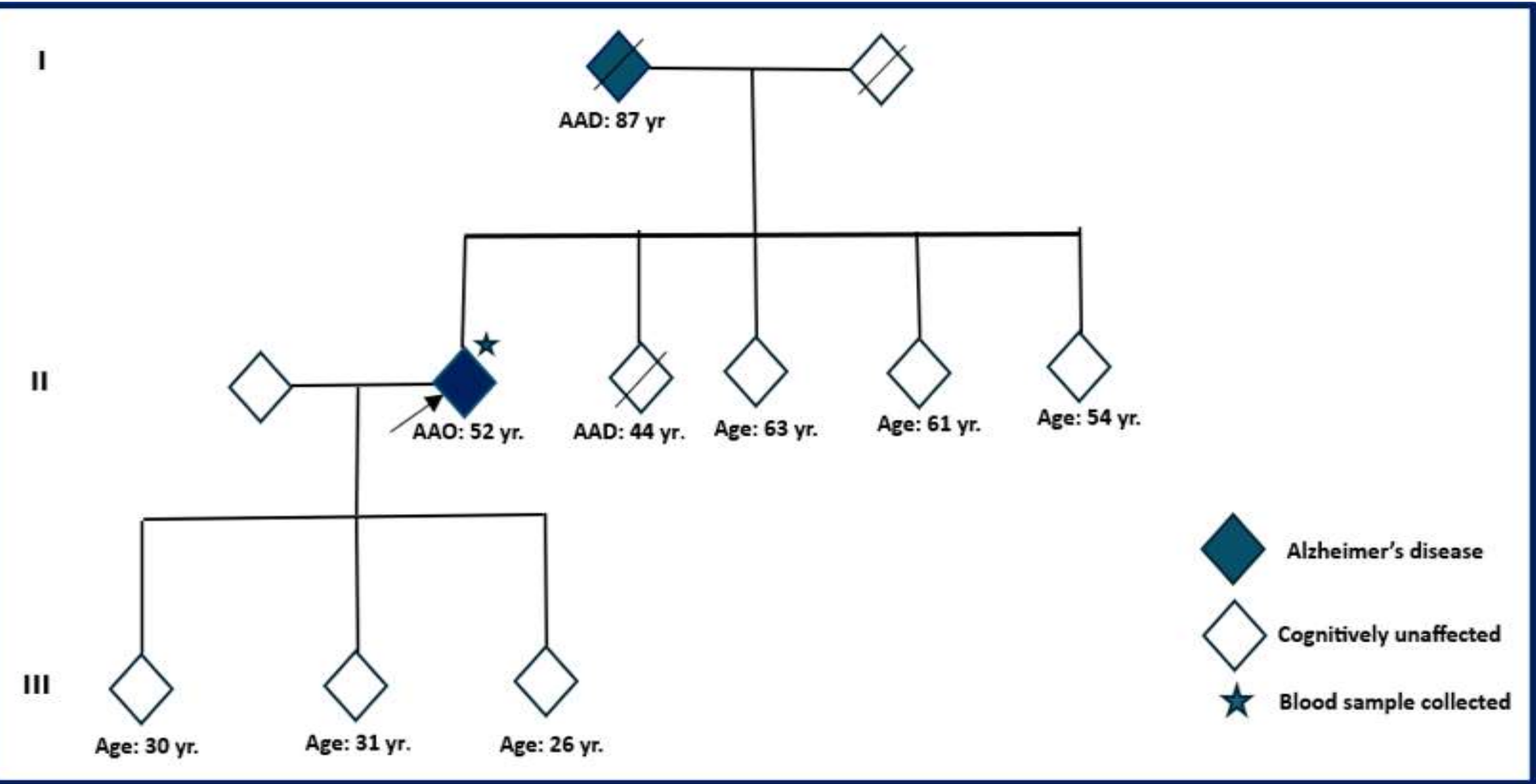


Fig.1: Family pedigree of PSEN1 p.A431T variant carrier

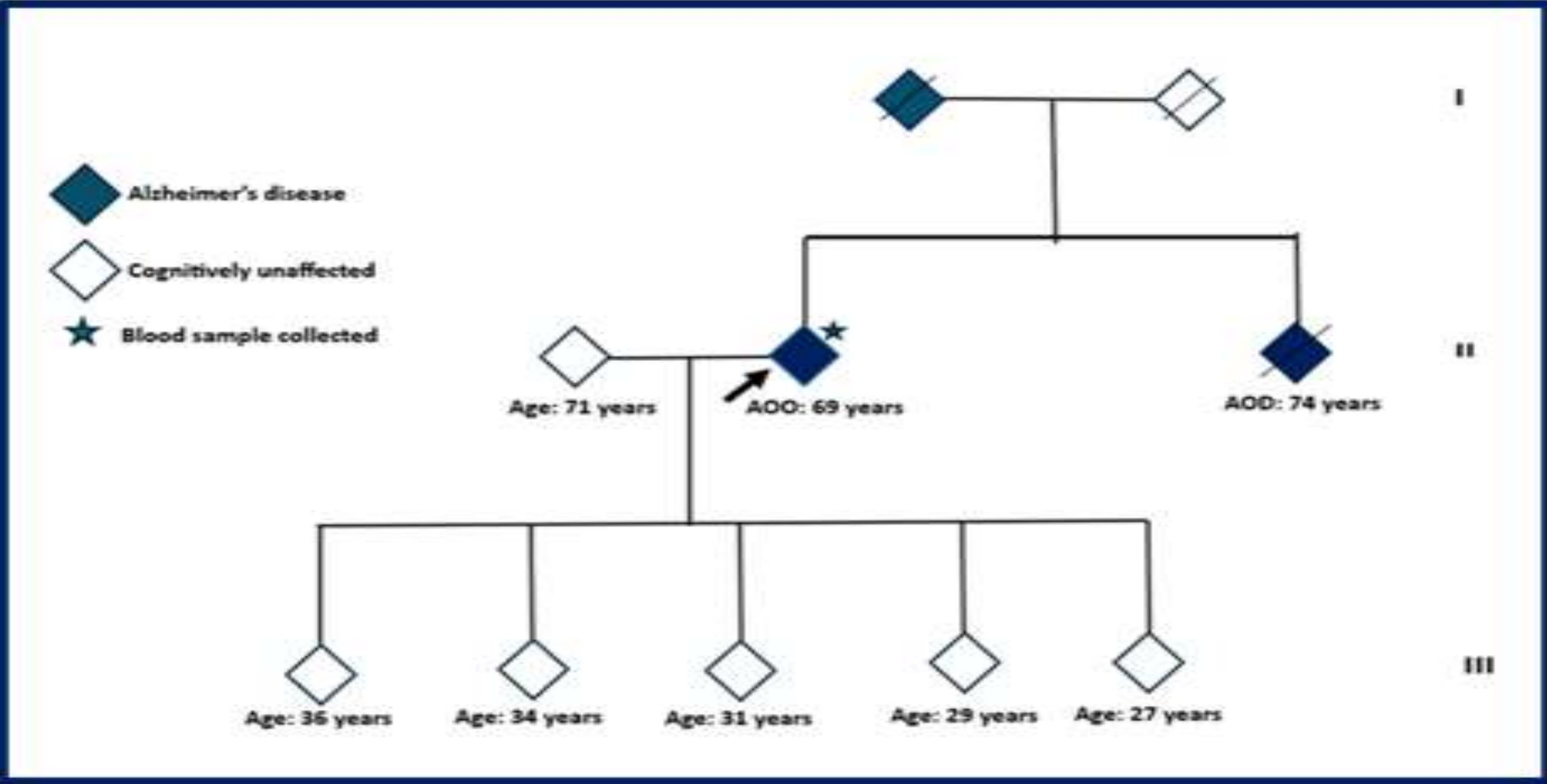


Fig.1: Family pedigree of MAPT c.1733-1G>T variant carrier

Table 1: Characteristics of study participants (n=2159)

	Nigeria (N=1002)	Ghana (N=211)	Kenya (N=372)	Ethiopia (N=29)	Mozambique (N=63)	Cameroon (N=111)	Uganda (N=210)	Tanzania (N=161)
AAE (+/-SD)	72.9(8.6)	72.1(8.4)	78.4(9.3)	65.3(9.3)	67.9(6.4)	70.3 (7.6)	80.8(8.6)	73.9(8.0)
Female (%)	498(49.7%)	146(69.2%)	244(65.6%)	6(20.7%)	33(54.4%)	74 (66.7%)	155(73.8%)	93(57.8%)
Diagnosis ^a								
▪ CU	479(47.8%)	104(49.3%)	160(43.0%)	10(34.5%)	35(55.6%)	48(43.2%)	89(42.4%)	71(44.1%)
▪ AD	369(36.8%)	85(40.3%)	155(41.7%)	10(34.5%)	19(30.2%)	32(28.8%)	41(19.5%)	64(39.8%)
▪ MCI	111(11.1%)	20(9.5%)	52(13.9%)	7(24.1%)	4(6.4%)	15(13.5%)	55(26.2%)	19(11.8%)
Recruitment								
▪ Clinics	644(64.3%)	139(65.9%)	35(9.4%)	27(93.1%)	11(17.5%)	33(29.7%)	0(0)	48(29.8%)
▪ Community	326(32.5%)	72(34.1%)	337(90.6%)	2(6.9%)	51(80.9%)	78(70.3%)	210(100%)	113(70.2%)

AAE= Age at examination; AD = Alzheimer’s disease; CU = Cognitive unaffected; MCI = Mild cognitive impairment; Diagnosis^a = Consensus diagnosis

CONCLUSIONS

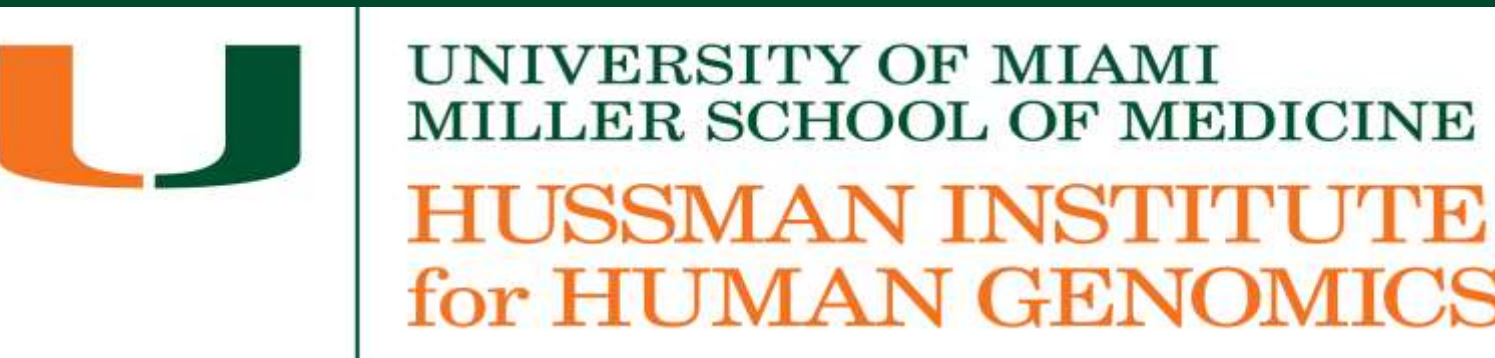
- ❑ We identified six potentially disease-causing variants within *PSEN1*, *PSEN2*, *SORL1*, *MAPT*, and *GRN* genes in native African population supporting the importance of a global approach to identify new and recurrent AD causative/risk markers to support the global effort to identify potential therapeutic targets in AD.

Table 2: Clinical features of individuals with rare pathogenic variants

Patient ID	Sex	CDx	AOO	Gene	Chr	Position	Variant type	Protein	dbSNP ID ^a	APOE	PFH
P01	M	AD	52	<i>PSEN1</i>	14	73219176	Missense	p.A431T	Novel	3/4	Yes
P02	F	AD	57	<i>SORL1</i>	11	121559561	Stop gain	p.R985X	rs372188860	4/4	Yes
P03	M	Dementia ^b	69	<i>MAPT</i>	17	45996398	Splice acceptor	c.1733-1G>T	Novel	2/4	Yes
P04	F	AD	63	<i>SORL1</i>	11	121586317	Stop gain	p.E1268X	Novel	3/4	No
P05	F	AD	65	<i>PSEN2</i>	1	226885581	Missense	p.R134C	Rare	3/3	No
P06	F	AD	75.4	<i>GRN</i>	17	44349434	Stop gain	p.W49X	Rare	3/4	No

CDx = Consensus diagnosis; AD = Alzheimer’s disease; AOO = Age of onset; SNP = Single nucleotide polymorphism; PFH: Positive family history of dementia.

^aMinor allele frequency (MAF): rs372188860 MAF (no-Finish European) = 1.47E-05; ^bDementia = Underlying dementia etiology undetermined.



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