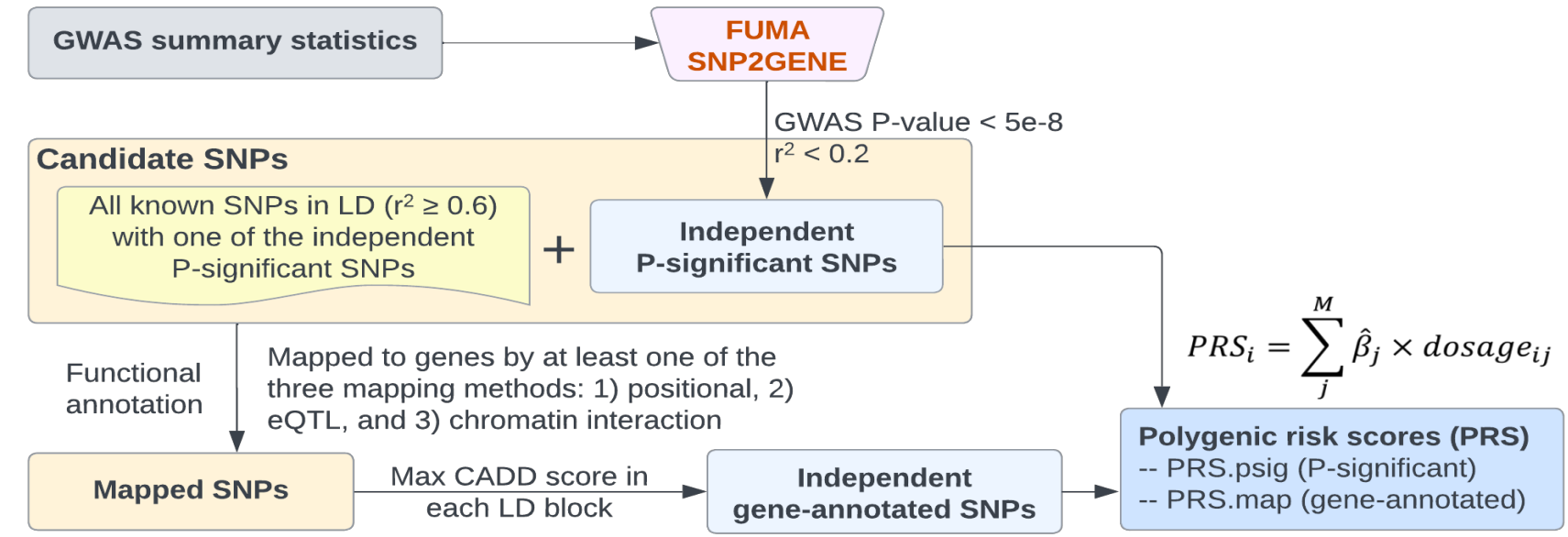
Supplementary Table 1. GWAS information and summary results of FUMA by phenotype

GWAS information				# SNPs (overlapped with UCLA and AOU data[b])		
Phenotype	**Summary statistics**	**1000G reference[a]**	**N case/control**	**Candidate**	**Independent P-significant**	**Independent gene-annotated**
Alzheimer's Disease	Kunkle et al. (2019)	EUR	21,982/41,944	1744	76	75
	Kunkle et al. (2021)	AFR	2,784/5,222	80	11	11
	Jun et al. (2017)	ALL	15,579/17,690	760	54	54
Parkinson's Disease	Nalls et al. (2019)	EUR	Meta-analysis	2640	27	27
Progressive Supranuclear Palsy	Chen et al. (2018)	EUR	1,646/10,662	732	21	21
Lewy Body Dementia	Chia et al. (2021)	EUR	2,981/4,391	356	9	9
Stroke	Malik et al. (2018)	ALL	67,162/454,450	903	21	20

Abbreviations: AFR, African American; EUR, European; GWAS, genome-wide association study; SNP, Single-Nucleotide Polymorphism.

Notes: [a] Reference panel population used for regional linkage disequilibrium patterns in identifying independent SNPs and lead P-significant SNPs. [b] Numbers of features used in PRSs building, feature selection for modeling, and phenotype prediction in the following steps.



Supplementary Figure 1. Workflow of candidate SNP selection. Functional annotation and prioritization of SNPs using FUMA. Two distinct sets of SNPs (independent genome-wide-significant SNPs and independent gene-annotated SNPs) were identified by FUMA and subsequently used in our polygenic risk scores building and modeling steps. *Abbreviations: CADD, Combined Annotation Dependent Depletion; GWAS, genome-wide association study; LD, linkage disequilibrium; PRS, polygenic risk score; SNP, Single-Nucleotide Polymorphism.*

Supplementary Table 2. ICD-10 codes used for dementia phenotype definiiton

ICD-10 code	Description
F01	**Vascular dementia**
F01.5	Multi-infarct dementia
F01.50	Multi-infarct dementia, unspecified
F01.51	Multi-infarct dementia with delirium
F01.511	Multi-infarct dementia with delirium in Alzheimer's disease
F01.518	Multi-infarct dementia with delirium, not elsewhere classified
F02.8*	**Dementia in other diseases classified elsewhere**
F02.80	Dementia in other diseases classified elsewhere, without behavioral disturbance
F02.81	Dementia in other diseases classified elsewhere, with behavioral disturbance
F02.811	Dementia in other diseases classified elsewhere, with behavioral disturbance in Alzheimer's disease
F02.818	Dementia in other diseases classified elsewhere, with behavioral disturbance, not elsewhere classified
F03	**Unspecified dementia**
F03.9	Unspecified dementia without behavioral disturbance
F03.90	Unspecified dementia with delirium
F03.91	Unspecified dementia with delirium in Alzheimer's disease
F03.911	Unspecified dementia with delirium in Alzheimer's disease, with behavioral disturbance
F03.918	Unspecified dementia with delirium in Alzheimer's disease, not elsewhere classified
G30	**Alzheimer's disease**
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset
G30.8	Other Alzheimer's disease
G30.9	Alzheimer's disease, unspecified
G31	**Other degenerative diseases of nervous system, not elsewhere classified**
G31.0	Pick's disease
G31.01	Pick's disease with early onset
G31.09	Pick's disease with late onset
G31.1	Frontotemporal dementia
G31.83	Dementia with Lewy bodies
G31.85	Corticobasal degeneration
G23.1	Parkinson's disease with dementia

Supplementary Table 3. Model performance of *APOE-e4* count, polygenic risk score, and Elastic Net SNP models in dementia genetic prediction, UCLA ATLAS sample, stratified by genetic inferred ancestry[a]

		AUPRC	AUROC	F1 score	Accuracy	Precision	Recall	Specificity
Hispanic Latino Americans (N = 610)								
APOE	e4 count	0.373 (0.347, 0.402)	0.652 (0.634, 0.67)	0.454 (0.421, 0.478)	0.673 (0.595, 0.714)	0.394 (0.346, 0.432)	0.547 (0.428, 0.706)	0.714 (0.558, 0.802)
AD-PRS models								
AD EUR PRS	P-significant	0.359 (0.334, 0.389)	0.618 (0.598, 0.641)	0.352 (0.181, 0.457)	0.659 (0.421, 0.764)	0.436 (0.292, 0.684)	0.429 (0.103, 0.929)	0.735 (0.254, 0.984)
	Gene-annotated	0.349 (0.325, 0.382)	0.609 (0.585, 0.633)	0.322 (0.118, 0.45)	0.682 (0.437, 0.764)	0.457 (0.293, 0.818)	0.355 (0.063, 0.889)	**0.791 (0.288, 0.995)**
AD AFR PRS	P-significant	0.374 (0.35, 0.403)	0.645 (0.63, 0.663)	0.438 (0.232, 0.473)	0.658 (0.538, 0.766)	0.39 (0.324, 0.652)	0.548 (0.143, 0.77)	0.694 (0.468, 0.974)
	Gene-annotated	0.371 (0.345, 0.4)	0.648 (0.631, 0.666)	0.459 (0.433, 0.481)	0.667 (0.597, 0.71)	0.39 (0.347, 0.428)	0.565 (0.46, 0.706)	0.701 (0.561, 0.788)
AD multi-ancestry PRS	P-significant	0.361 (0.336, 0.392)	0.628 (0.609, 0.648)	0.373 (0.132, 0.461)	0.616 (0.425, 0.766)	0.419 (0.293, 0.818)	0.535 (0.071, 0.929)	0.643 (0.264, 0.995)
	Gene-annotated	0.363 (0.338, 0.394)	0.641 (0.624, 0.66)	0.444 (0.207, 0.473)	0.521 (0.423, 0.764)	0.338 (0.294, 0.667)	**0.792 (0.119, 0.944)**	0.431 (0.246, 0.979)
Multi-PRS models								
PRSs using AD GWASs only[b]	P-significant	0.367 (0.34, 0.398)	0.634 (0.612, 0.656)	0.427 (0.212, 0.471)	0.659 (0.559, 0.762)	0.389 (0.327, 0.633)	0.525 (0.127, 0.722)	0.703 (0.51, 0.974)
	Gene-annotated	0.364 (0.335, 0.395)	0.637 (0.613, 0.658)	0.42 (0.168, 0.467)	0.648 (0.446, 0.766)	0.396 (0.301, 0.769)	0.537 (0.095, 0.913)	0.685 (0.291, 0.992)
PRSs using AD + Neuro GWASs[c]	P-significant	0.344 (0.31, 0.38)	0.608 (0.575, 0.637)	0.39 (0.144, 0.456)	0.659 (0.532, 0.76)	0.387 (0.31, 0.636)	0.463 (0.079, 0.762)	0.724 (0.46, 0.984)
	Gene-annotated	0.357 (0.324, 0.393)	0.607 (0.578, 0.634)	0.379 (0.119, 0.462)	0.67 (0.557, 0.766)	0.431 (0.32, 0.889)	0.447 (0.063, 0.699)	0.744 (0.518, 0.997)
Elastic Net SNPs models								
SNPs from AD GWASs only	P-significant	0.398 (0.364, 0.441)	0.68 (0.649, 0.709)	0.476 (0.406, 0.513)	0.617 (0.49, 0.734)	0.374 (0.316, 0.46)	0.706 (0.373, 0.921)	0.587 (0.354, 0.854)
	Gene-annotated	0.41 (0.378, 0.449)	0.681 (0.651, 0.702)	0.45 (0.296, 0.5)	0.675 (0.53, 0.772)	0.426 (0.329, 0.645)	0.555 (0.19, 0.849)	0.715 (0.423, 0.963)
SNPs from AD + Neuro GWASs	P-significant	0.415 (0.376, 0.46)	0.699 (0.664, 0.727)	0.492 (0.437, 0.527)	0.635 (0.508, 0.74)	0.388 (0.323, 0.477)	0.712 (0.412, 0.913)	0.609 (0.378, 0.841)
	Gene-annotated	**0.451 (0.402, 0.495)**	**0.715 (0.662, 0.739)**	**0.498 (0.383, 0.541)**	**0.701 (0.597, 0.776)**	**0.447 (0.363, 0.604)**	0.604 (0.286, 0.833)	0.733 (0.521, 0.934)
African Americans (N = 440)								
APOE	e4 count	0.307 (0.282, 0.343)	0.596 (0.569, 0.623)	0.441 (0.398, 0.474)	0.589 (0.476, 0.679)	0.346 (0.301, 0.374)	0.66 (0.428, 0.857)	0.566 (0.353, 0.762)
AD-PRS models								
AD EUR PRS	P-significant	0.272 (0.249, 0.302)	0.561 (0.525, 0.595)	0.411 (0.367, 0.441)	0.552 (0.327, 0.643)	0.316 (0.266, 0.347)	0.636 (0.428, 0.976)	0.524 (0.111, 0.722)
	Gene-annotated	0.273 (0.243, 0.314)	0.548 (0.505, 0.584)	0.393 (0.069, 0.44)	0.494 (0.354, 0.753)	0.311 (0.214, 0.6)	0.7 (0.048, 0.917)	0.426 (0.162, 0.988)
AD AFR PRS	P-significant	0.277 (0.25, 0.31)	0.566 (0.527, 0.599)	0.402 (0.019, 0.444)	0.492 (0.241, 0.696)	0.293 (0.053, 0.373)	0.715 (0.012, 0.964)	0.418 (0, 0.917)
	Gene-annotated	0.274 (0.25, 0.306)	0.562 (0.527, 0.595)	0.413 (0.381, 0.444)	0.47 (0.238, 0.631)	0.295 (0.239, 0.341)	0.74 (0.488, 0.964)	0.38 (0, 0.671)
AD multi-ancestry PRS	P-significant	0.281 (0.255, 0.314)	0.574 (0.542, 0.604)	0.434 (0.391, 0.453)	0.482 (0.399, 0.661)	0.304 (0.282, 0.356)	0.799 (0.44, 0.929)	0.376 (0.222, 0.738)
	Gene-annotated	0.282 (0.258, 0.313)	0.581 (0.549, 0.61)	0.44 (0.421, 0.458)	0.477 (0.363, 0.595)	0.302 (0.277, 0.327)	**0.823 (0.607, 0.964)**	0.362 (0.171, 0.591)
Multi-PRS models								
PRSs using AD GWASs only[b]	P-significant	0.263 (0.235, 0.292)	0.549 (0.502, 0.591)	0.381 (0.02, 0.449)	0.525 (0.39, 0.697)	0.282 (0.062, 0.342)	0.648 (0.012, 0.893)	0.484 (0.226, 0.925)
	Gene-annotated	0.267 (0.24, 0.298)	0.551 (0.509, 0.589)	0.418 (0.108, 0.453)	0.482 (0.363, 0.634)	0.299 (0.248, 0.324)	0.767 (0.095, 0.941)	0.387 (0.175, 0.81)
PRSs using AD + Neuro GWASs[c]	P-significant	0.234 (0.209, 0.262)	0.486 (0.428, 0.54)	0.177 (0.018, 0.416)	0.558 (0.244, 0.711)	0.17 (0.04, 0.325)	0.305 (0.012, 1)	0.642 (0.012, 0.944)
	Gene-annotated	0.252 (0.225, 0.287)	0.508 (0.463, 0.554)	0.291 (0.02, 0.42)	0.454 (0.244, 0.756)	0.288 (0.071, 1)	0.596 (0.012, 0.988)	0.407 (0, 1)
Elastic Net SNPs models								
SNPs from AD GWASs only	P-significant	0.395 (0.348, 0.445)	0.655 (0.625, 0.685)	0.424 (0.191, 0.493)	0.677 (0.491, 0.774)	0.442 (0.314, 0.819)	0.509 (0.107, 0.881)	0.733 (0.365, 0.992)
	Gene-annotated	0.42 (0.369, 0.473)	0.663 (0.632, 0.694)	0.382 (0.154, 0.495)	0.718 (0.5, 0.783)	**0.548 (0.319, 1)**	0.395 (0.083, 0.893)	**0.826 (0.373, 1)**
SNPs from AD + Neuro GWASs	P-significant	0.445 (0.389, 0.507)	0.689 (0.655, 0.724)	0.416 (0.252, 0.52)	**0.721 (0.503, 0.789)**	0.54 (0.324, 0.867)	0.436 (0.154, 0.917)	0.816 (0.365, 0.992)
	Gene-annotated	**0.451 (0.397, 0.506)**	**0.698 (0.665, 0.73)**	**0.459 (0.28, 0.532)**	0.72 (0.562, 0.789)	0.5 (0.346, 0.827)	0.499 (0.167, 0.845)	0.794 (0.464, 0.988)

Abbreviations: AD, Alzheimer's Disease; APOE, apolipoprotein E; AUROC, Area Under the ROC Curve; AUPRC, Area Under the Precision-Recall Curve; EUR, European; GWAS, Genome-Wide Association Study; PRS, Polygenic Risk Score; SNP, Single-Nucleotide Polymorphism.

Notes:

[a] All models (if not other specified) have regressed out age, sex, and ancestry-specific principal components. Thresholds were determined by maximizing absolute Matthews correlation coefficient.

[b] All AD PRSs built with EUR, AFR, and multi-ancestry GWASs using P-significant/gene-annotated SNPs were included in the model at the same time.

[c] All AD PRSs built with EUR, AFR, and multi-ancestry GWASs, and neurodegenerative disease PRS (Parkinson's disease, progressive supranuclear palsy, Lewy body dementia, and stroke) using P-significant/gene-annotated SNPs were included in the model at the same time.

Supplementary Table 4. Performance of models using lead SNPs (r^2 cut-off <0.1 for defining independent genome-wide-significant SNPs) in dementia genetic prediction, UCLA ATLAS sample, stratified by genetic inferred ancestry[a]

	Overall performace		Threshold maximize absolute MCC				
Hispanic Latino American ancestry sample (N = 610)							
	AUPRC	**AUROC**	**F1 score**	**Accuracy**	**Precision**	**Recall**	**Specificity**
AD EUR PRS	0.343 (0.316, 0.372)	0.598 (0.57, 0.624)	0.289 (0.103, 0.444)	0.702 (0.456, 0.766)	**0.497 (0.295, 0.875)**	0.29 (0.056, 0.841)	0.84 (0.323, 0.997)
AD AFR PRS	0.377 (0.35, 0.407)	0.649 (0.631, 0.666)	0.453 (0.414, 0.48)	0.675 (0.567, 0.718)	0.397 (0.337, 0.439)	0.542 (0.413, 0.754)	0.719 (0.51, 0.812)
AD multi-ancestry PRS	0.369 (0.346, 0.398)	0.624 (0.607, 0.643)	0.342 (0.144, 0.446)	**0.71 (0.551, 0.768)**	0.484 (0.325, 0.819)	0.337 (0.079, 0.738)	**0.835 (0.494, 0.995)**
PRSs using AD GWASs only[b]	0.363 (0.331, 0.396)	0.623 (0.596, 0.65)	0.436 (0.391, 0.467)	0.682 (0.617, 0.724)	0.399 (0.351, 0.443)	0.497 (0.373, 0.643)	0.743 (0.611, 0.844)
PRSs using AD + Neuro GWASs[c]	0.346 (0.31, 0.384)	0.603 (0.569, 0.635)	0.385 (0.2, 0.446)	0.693 (0.589, 0.762)	0.409 (0.332, 0.632)	0.399 (0.119, 0.651)	0.791 (0.577, 0.976)
SNPs from AD GWASs only	0.406 (0.371, 0.438)	0.683 (0.648, 0.705)	0.472 (0.387, 0.504)	0.622 (0.486, 0.74)	0.382 (0.316, 0.475)	**0.687 (0.341, 0.929)**	0.6 (0.341, 0.868)
SNPs from AD + Neuro GWASs	**0.411 (0.373, 0.446)**	**0.689 (0.651, 0.712)**	**0.475 (0.398, 0.509)**	0.628 (0.494, 0.75)	0.386 (0.321, 0.5)	0.683 (0.341, 0.929)	0.61 (0.352, 0.881)
African American ancestry sample (N = 440)							
	AUPRC	**AUROC**	**F1 score**	**Accuracy**	**Precision**	**Recall**	**Specificity**
AD EUR PRS	0.251 (0.214, 0.303)	0.491 (0.428, 0.549)	0.268 (0.02, 0.415)	0.475 (0.241, 0.759)	0.347 (0.067, 1)	0.519 (0.012, 0.976)	0.461 (0, 1)
AD AFR PRS	0.3 (0.271, 0.34)	0.578 (0.552, 0.606)	0.393 (0.286, 0.433)	0.611 (0.333, 0.741)	0.347 (0.269, 0.455)	0.521 (0.214, 0.976)	0.641 (0.119, 0.917)
AD multi-ancestry PRS	0.305 (0.277, 0.34)	0.595 (0.57, 0.62)	0.438 (0.421, 0.459)	0.508 (0.408, 0.595)	0.315 (0.285, 0.337)	**0.776 (0.619, 0.929)**	0.418 (0.234, 0.583)
PRSs using AD GWASs only[b]	0.315 (0.283, 0.355)	0.582 (0.551, 0.613)	0.367 (0.145, 0.45)	0.576 (0.396, 0.759)	0.373 (0.279, 0.751)	0.568 (0.083, 0.917)	0.578 (0.226, 0.992)
PRSs using AD + Neuro GWASs[c]	0.3 (0.267, 0.34)	0.575 (0.539, 0.61)	0.404 (0.11, 0.448)	0.508 (0.351, 0.759)	0.333 (0.27, 0.801)	0.713 (0.06, 0.964)	0.439 (0.151, 0.996)
SNPs from AD GWASs only	0.337 (0.295, 0.382)	0.627 (0.589, 0.662)	0.451 (0.376, 0.49)	0.61 (0.488, 0.729)	0.359 (0.306, 0.456)	0.649 (0.333, 0.845)	0.597 (0.373, 0.857)
SNPs from AD + Neuro GWASs	**0.379 (0.332, 0.429)**	**0.666 (0.634, 0.696)**	**0.476 (0.405, 0.52)**	**0.67 (0.554, 0.762)**	**0.41 (0.335, 0.533)**	0.606 (0.345, 0.833)	**0.691 (0.464, 0.901)**

Abbreviations: AD, Alzheimer's Disease; AFR, African American; AUROC, Area Under the ROC Curve; AUPRC, Area Under the Precision-Recall Curve; EUR, European; GWAS, Genome-Wide Association Study; MCC, Matthews Correlation Coefficient; PRS, Polygenic Risk Score; SNP, Single-Nucleotide Polymorphism.

Notes:

[a] All models (if not other specified) adjusted for age, sex, and first four ancestry-specific principal components.

[b] All AD PRSs built with EUR, AFR, and multi-ancestry GWASs using P-significant/gene-annotated SNPs were included in the model at the same time.

[c] All AD PRSs built with EUR, AFR, and multi-ancestry GWASs, and neurodegenerative disease PRS (Parkinson's disease, progressive supranuclear palsy, Lewy body dementia, and stroke) using P-significant/gene-annotated SNPs were included in the model at the same time.

Supplementary Table 5. Mapped genes of selected risk SNPs from the best-performing Elastic Net SNP model, UCLA ATLAS sample, by genetic inferred ancestry

Hispanic Latino Americans (HLA)									
No	**Gene**	**Symbol**	**CHR**	**Start**	**End**	**Type**	**posMap**	**eqtlMap (Direction)**	**ciMap**
1	ENSG00000144659	*SLC25A38*	3	39424839	39438842	protein_coding	No	Yes (+)	No
2	ENSG00000168028	*RPSA*	3	39448180	39454033	protein_coding	Yes	Yes (+)	No
3	ENSG00000185619	*PCGF3*	4	699537	764428	protein_coding	Yes	Yes (-)	No
4	ENSG00000249519	*RP11-777N19.1*	4	111715559	111718500	lincRNA	Yes	No	No
5	ENSG00000137642	*SORL1*	11	121322912	121504402	protein_coding	Yes	No	No
6	ENSG00000266903	*CTB-171A8.1*	19	45135500	45222031	antisense	Yes	No	No
7	ENSG00000252200	*snoZ6*	19	45229248	45229322	snoRNA	Yes	No	No
8	ENSG00000187244	*BCAM*	19	45312328	45324673	protein_coding	Yes	No	No
9	ENSG00000130202	*PVRL2*	19	45349432	45392485	protein_coding	Yes	No	No
10	ENSG00000130204	*TOMM40*	19	45393826	45406946	protein_coding	Yes	No	No
11	ENSG00000130203	*APOE*	19	45409011	45412650	protein_coding	Yes	No	No
12	ENSG00000130208	*APOC1*	19	45417504	45422606	protein_coding	Yes	No	No
13	ENSG00000214855	*APOC1P1*	19	45430061	45434643	pseudogene	No	No	Yes
14	ENSG00000104859	*CLASRP*	19	45542298	45574214	protein_coding	No	No	Yes
African Americans (AA)									
No	**Gene**	**Symbol**	**CHR**	**Start**	**End**	**Type**	**posMap**	**eqtlMap (Direction)**	**ciMap**
1	ENSG00000136717	*BIN1*	2	127805603	127864931	protein_coding	Yes	No	No
2	ENSG00000159840	*ZYX*	7	143078173	143088204	protein_coding	Yes	No	No
3	ENSG00000050327	*ARHGEF5*	7	144052381	144077725	protein_coding	No	Yes (+)	No
4	ENSG00000080854	*IGSF9B*	11	133778459	133826880	protein_coding	Yes	No	No
5	ENSG00000255406	*RP11-713P17.5*	11	133896882	133898013	lincRNA	No	No	Yes
6	ENSG00000166086	*JAM3*	11	133938820	134021896	protein_coding	No	No	Yes
7	ENSG00000254481	*PTP4A2P2*	11	133993723	133994224	pseudogene	No	No	Yes
8	ENSG00000180329	*CCDC43*	17	42750437	42767147	protein_coding	No	No	Yes
9	ENSG00000161692	*DBF4B*	17	42785976	42829632	protein_coding	No	Yes (-)	No
10	ENSG00000073670	*ADAM11*	17	42836399	42859214	protein_coding	No	No	Yes
11	ENSG00000131095	*GFAP*	17	42982376	42994305	protein_coding	No	No	Yes
12	ENSG00000131094	*C1QL1*	17	43037061	43045439	protein_coding	Yes	Yes (+)	No
13	ENSG00000267788	*CTD-2534I21.9*	17	43059882	43060140	lincRNA	No	No	Yes
14	ENSG00000267282	*CTB-129P6.4*	19	45385284	45394133	antisense	Yes	No	No
15	ENSG00000130204	*TOMM40*	19	45393826	45406946	protein_coding	Yes	No	No
16	ENSG00000130203	*APOE*	19	45409011	45412650	protein_coding	Yes	Yes (-)	No
17	ENSG00000214855	*APOC1P1*	19	45430061	45434643	pseudogene	Yes	Yes (+)	Yes
18	ENSG00000104859	*CLASRP*	19	45542298	45574214	protein_coding	No	No	Yes

Supplementary Table 6A. Descriptive statistics of demographic and electronic health record features by case/control groups, UCLA ATLAS sample (East Asian American ancestry group, N = 673)

	Cases	Controls	P value
N	75	598	-
Age	80.1 (73.2, 83.5)	76.3 (72.9, 80.7)	0.04*
Sex (Female)	48 (64%)	325 (54%)	0.11
Span of records (in yrs)	5.3 (2.7, 7.8)	9.8 (8.0, 12.0)	<0.001*
Encounters per year	17 (9, 28)	12 (7, 18)	0.002*
Number of encounters	73 (23, 137)	121 (68, 185)	<0.001*
Number of unique diagnosis	64 (35, 92)	60 (38, 90)	0.80

Abbreviations: EHR, electronic health record.

Notes: Continuous variables were reported as median (IQR), and categorical variables were reported as n (%). P-values were calcualted based on Wilcoxon rank sum test or Pearson's Chi-squared test as appropriate. * Statistical siginificant at level 0.05.

Supplementary Table 6B. Model performance of *APOE-e4* count, polygenic risk score, and Elastic Net SNP models in dementia genetic prediction, UCLA ATLAS sample (East Asian American ancestry group, N = 673)[a]

		AUPRC	AUROC	F1 score	Accuracy	Precision	Recall	Specificity
APOE	e4 count	0.463 (0.409, 0.516)	0.708 (0.678, 0.733)	0.476 (0.28, 0.539)	0.725 (0.593, 0.793)	0.502 (0.361, 0.818)	0.523 (0.173, 0.827)	0.792 (0.52, 0.987)
				AD-PRS models				
AD EUR PRS	P-significant	0.442 (0.396, 0.493)	0.688 (0.658, 0.715)	0.425 (0.23, 0.516)	0.712 (0.513, 0.787)	0.524 (0.328, 0.9)	0.468 (0.133, 0.907)	0.793 (0.382, 0.996)
	Gene-annotated	0.434 (0.392, 0.482)	0.684 (0.651, 0.714)	0.416 (0.212, 0.513)	0.703 (0.493, 0.787)	0.523 (0.32, 0.909)	0.473 (0.12, 0.92)	0.78 (0.355, 0.996)
AD AFR PRS	P-significant	0.457 (0.408, 0.51)	0.703 (0.673, 0.728)	0.469 (0.28, 0.532)	0.723 (0.573, 0.79)	0.503 (0.352, 0.833)	0.512 (0.173, 0.84)	0.794 (0.484, 0.991)
	Gene-annotated	0.452 (0.404, 0.501)	0.698 (0.669, 0.722)	0.462 (0.264, 0.529)	0.72 (0.583, 0.787)	0.5 (0.355, 0.834)	0.507 (0.16, 0.827)	0.791 (0.502, 0.991)
AD multi-ancestry PRS	P-significant	0.459 (0.407, 0.511)	0.702 (0.671, 0.727)	0.46 (0.27, 0.533)	0.729 (0.587, 0.79)	**0.519 (0.358, 0.857)**	0.49 (0.16, 0.813)	0.808 (0.507, 0.991)
	Gene-annotated	0.454 (0.406, 0.506)	0.697 (0.666, 0.722)	0.457 (0.264, 0.53)	0.727 (0.6, 0.79)	0.514 (0.36, 0.857)	0.487 (0.16, 0.787)	0.807 (0.533, 0.991)
				Multi-PRS models				
PRSs using AD GWASs only[b]	P-significant	0.454 (0.401, 0.507)	0.697 (0.667, 0.723)	0.461 (0.267, 0.529)	0.727 (0.6, 0.79)	0.511 (0.358, 0.842)	0.492 (0.16, 0.787)	**0.805 (0.542, 0.991)**
	Gene-annotated	0.45 (0.4, 0.501)	0.698 (0.665, 0.726)	0.461 (0.253, 0.527)	0.721 (0.563, 0.787)	0.499 (0.346, 0.833)	0.501 (0.147, 0.84)	0.795 (0.471, 0.991)
PRSs using AD + Neuro GWASs[c]	P-significant	0.453 (0.402, 0.51)	0.699 (0.666, 0.728)	0.459 (0.253, 0.532)	0.722 (0.553, 0.79)	0.508 (0.342, 0.846)	0.5 (0.147, 0.867)	0.796 (0.458, 0.991)
	Gene-annotated	0.455 (0.404, 0.513)	0.712 (0.676, 0.743)	0.489 (0.323, 0.549)	0.708 (0.57, 0.787)	0.471 (0.35, 0.739)	0.577 (0.213, 0.853)	0.751 (0.48, 0.973)
				Elastic Net SNPs models				
SNPs from AD GWASs only	P-significant	0.474 (0.403, 0.542)	0.721 (0.674, 0.764)	0.489 (0.308, 0.562)	0.712 (0.553, 0.793)	0.491 (0.349, 0.8)	0.576 (0.187, 0.92)	0.758 (0.435, 0.982)
	Gene-annotated	0.481 (0.406, 0.553)	0.73 (0.674, 0.776)	0.505 (0.312, 0.575)	0.711 (0.58, 0.79)	0.481 (0.358, 0.786)	0.615 (0.2, 0.88)	0.743 (0.476, 0.982)
SNPs from AD + Neuro GWASs	P-significant	0.499 (0.406, 0.582)	0.743 (0.674, 0.795)	0.521 (0.33, 0.599)	0.729 (0.603, 0.8)	0.503 (0.368, 0.734)	0.608 (0.213, 0.88)	0.77 (0.52, 0.973)
	Gene-annotated	**0.511 (0.405, 0.602)**	**0.754 (0.675, 0.808)**	**0.535 (0.343, 0.613)**	**0.734 (0.61, 0.803)**	0.505 (0.373, 0.727)	**0.627 (0.227, 0.88)**	0.77 (0.533, 0.969)

Abbreviations: AD, Alzheimer's Disease; APOE, apolipoprotein E; AUROC, Area Under the ROC Curve; AUPRC, Area Under the Precision-Recall Curve; EUR, European; GWAS, Genome-Wide Association Study; PRS, Polygenic Risk Score; SNP, Single-Nucleotide Polymorphism.

Notes:

[a] All models (if not other specified) have regressed out age, sex, and ancestry-specific principal components. Thresholds were determined by maximizing absolute Matthews correlation coefficient.

[b] All AD PRSs built with EUR, AFR, and multi-ancestry GWASs using P-significant/gene-annotated SNPs were included in the model at the same time.

[c] All AD PRSs built with EUR, AFR, and multi-ancestry GWASs, and neurodegenerative disease PRS (Parkinson's disease, progressive supranuclear palsy, Lewy body dementia, and stroke) using P-significant/gene-annotated SNPs were included in the model at the same time.

Supplementary Table 6C. Selected risk SNPs from the best-performing Elastic Net SNP model, UCLA ATLAS sample (East Asian American ancestry group, N = 673)

rsID	CHR	POS	Variable Importance (percentage, 95% CI)	Nearest Gene	AD EUR	AD AFR	AD multi	LBD	PD	PSP	Stroke
rs429358	19	44908684	0.127 (0.036, 0.26)	*APOE*		x					
rs35106910	19	44781009	0.114 (0.021, 0.298)	*CBLC*	x						
rs66626994	19	44924977	0.076 (0.009, 0.176)	*APOC1P1*			x	x			
rs483082	19	44912921	0.067 (0.007, 0.154)	*APOC1*		x	x				
rs59193782	17	45357199	0.053 (0.003, 0.136)	*CTB-39G8.2*						x	
chr1:207368589:D	1	207195244	0.053 (0.003, 0.138)	*RP11-164O23.7*	x						
rs34096562	8	16843772	0.053 (0.003, 0.137)	*RP11-13N12.1*					x		
rs11724804	4	971991	0.051 (0.003, 0.14)	*DGKQ*				x	x		
rs6857	19	44888997	0.05 (0.004, 0.126)	*PVRL2*		x					
rs7613	17	45394115	0.047 (0.003, 0.122)	*ARHGAP27*						x	
rs2075650	19	44892362	0.045 (0.003, 0.111)	*TOMM40*		x	x	x			
rs10769263	11	47395632	0.042 (0.003, 0.108)	*RP11-750H9.5*	x						
rs117421612	17	45345796	0.029 (0.003, 0.056)	*RNA5SP443*						x	

Abbreviations: AD, Alzheimer's Disease; AFR, African American; CI, confidence interval; EUR, European; LBD, Lewy body dementia; PD, Parkinson's disease; PRS, Polygenic Risk Score; PSP, progressive supranuclear palsy;SNP, Single-Nucleotide Polymorphism.

Supplementary Table 6D. Mapped genes of selected risk SNPs from the best-performing Elastic Net SNP model, UCLA ATLAS sample (East Asian American ancestry group, N = 673)

No	Gene	Symbol	CHR	Start	End	Type	posMap	eqtlMap (Direction)	ciMap
1	ENSG00000203710	CR1	1	207669492	207813992	protein_coding	No	Yes (+)	No
2	ENSG00000127419	TMEM175	4	926175	952444	protein_coding	No	Yes (-)	No
3	ENSG00000145214	DGKQ	4	952675	980683	protein_coding	Yes	Yes (-)	No
4	ENSG00000145217	SLC26A1	4	972861	987228	protein_coding	No	Yes (+)	No
5	ENSG00000253496	RP11-13N12.1	8	16534414	16772553	lincRNA	Yes	No	No
6	ENSG00000175220	ARHGAP1	11	46698630	46722165	protein_coding	No	Yes (+)	No
7	ENSG00000255197	RP11-750H9.5	11	47404699	47430741	antisense	Yes	Yes (-)	No
8	ENSG00000165915	SLC39A13	11	47428683	47438047	protein_coding	No	Yes (-)	No
9	ENSG00000213619	NDUFS3	11	47586888	47606114	protein_coding	No	Yes (-)	No
10	ENSG00000196666	FAM180B	11	47608198	47610746	protein_coding	No	Yes (-)	No
11	ENSG00000184922	FMNL1	17	43298811	43324687	protein_coding	No	Yes (+)	No
12	ENSG00000233175	CTD-2020K17.3	17	43315395	43319101	antisense	No	Yes (+)	No
13	ENSG00000006062	MAP3K14	17	43340488	43394414	processed_transcript	No	No	Yes
14	ENSG00000199953	RNA5SP443	17	43404732	43404863	rRNA	Yes	No	No
15	ENSG00000267446	CTB-39G8.2	17	43448768	43449423	lincRNA	Yes	No	No
16	ENSG00000159314	ARHGAP27	17	43471275	43511787	protein_coding	Yes	Yes (-)	No
17	ENSG00000214425	LRRC37A4P	17	43578685	43627701	pseudogene	No	Yes (+)	No
18	ENSG00000263503	RP11-707O23.5	17	43678235	43679706	pseudogene	No	Yes (-)	No
19	ENSG00000204650	CRHR1-IT1	17	43697694	43725582	pseudogene	No	Yes (-)	No
20	ENSG00000185294	SPPL2C	17	43922256	43924438	protein_coding	No	Yes (-)	No
21	ENSG00000262500	RP11-259G18.2	17	44320972	44322410	pseudogene	No	Yes (-)	No
22	ENSG00000261575	RP11-259G18.1	17	44344403	44346060	pseudogene	No	Yes (-)	No
23	ENSG00000142273	CBLC	19	45281126	45303891	protein_coding	Yes	No	No
24	ENSG00000130204	TOMM40	19	45393826	45406946	protein_coding	Yes	No	No
25	ENSG00000130203	APOE	19	45409011	45412650	protein_coding	Yes	No	No
26	ENSG00000130208	APOC1	19	45417504	45422606	protein_coding	Yes	No	No
27	ENSG00000214855	APOC1P1	19	45430061	45434643	pseudogene	Yes	No	Yes
28	ENSG00000104859	CLASRP	19	45542298	45574214	protein_coding	No	No	Yes

Supplementary Table 7. Descriptive statistics of demographic and electronic health record features, by data sources (All of Us vs. UCLA ATLAS, stratified by the genetic inferred group)

	Hispanic Latino Americans			African Americans		
Characteristic	**All of Us**	**UCLA ATLAS**	**p-value**	**All of Us**	**UCLA ATLAS**	**p-value**
N	526	610	-	2,644	440	-
Age	74.0 (71.9, 78.2)	75.8 (72.5, 80.5)	<0.001*	70.6 (67.6, 74.9)	75.8 (72.5, 80.5)	<0.001*
Sex (Female)	331 (63%)	372 (61%)	0.5	1,735 (66%)	264 (60%)	0.02*
Span of records (in yrs)	6.5 (5.7, 7.6)	9.1 (6.8, 10.2)	<0.001*	6.56 (6.08, 7.13)	9.77 (7.27, 11.02)	<0.001*
Encounters per year	9 (5, 14)	14 (8, 22)	<0.001*	9 (5, 15)	13 (8, 22)	<0.001*
Number of encounters	59 (32, 104)	117 (64, 198)	<0.001*	62 (34, 107)	129 (71, 209)	<0.001*
Number of unique diagnosis	46 (28, 69)	71 (45, 109)	<0.001*	44 (27, 66)	71 (45, 103)	<0.001*
Dementia (Yes)	81 (15%)	126 (21%)	0.02*	181 (6.8%)	84 (19%)	<0.001*
APOE-e4 count			<0.001*			<0.001*
0	486 (92%)	491 (80%)		2,127 (80%)	284 (65%)	
1	38 (7.2%)	117 (19%)		482 (18%)	137 (31%)	
2	2 (0.4%)	2 (0.3%)		35 (1.3%)	19 (4.3%)	

Notes: Continuous variables were reported as median (IQR), and categorical variables were reported as n (%). P-values were calcualted based on Wilcoxon rank sum test or Pearson's Chi-squared test as appropriate. * Statistical siginificant at level 0.05.

Supplementary Table 8. Descriptive statistics of demographic and electronic health record features by case/control groups, All of Us sample, stratified by genetic ancestry

	Hispanic Latino Americans (N = 610)			African Americans (N = 2,644)		
	Cases	**Controls**	**P value**	**Cases**	**Controls**	**P value**
N	81	445	-	181	2,463	-
Age	73.1 (68.4, 80.1)	74.0 (72.0, 78.0)	0.03*	70.7 (65.7, 77.8)	70.5 (67.7, 74.8)	0.4
Sex (Female)	50 (62%)	281 (63%)	0.80	113 (62%)	1,622 (66%)	0.30
Span of records (in yrs)	4.4 (2.6, 6.1)	6.6 (6.0, 7.9)	<0.001*	4.25 (2.12, 6.14)	6.58 (6.18, 7.25)	<0.001*
Encounters per year	10 (5, 18)	8 (5, 14)	0.14	14 (7, 23)	9 (5, 15)	<0.001*
Number of encounters	36 (15, 76)	62 (35, 107)	<0.001*	52 (20, 96)	63 (34, 108)	<0.001*
Number of unique diagnosis	47 (25, 68)	45 (28, 69)	0.80	51 (31, 76)	43 (27, 66)	0.01*

Notes: Continuous variables were reported as median (IQR), and categorical variables were reported as n (%). P-values were calcualted based on Wilcoxon rank sum test or Pearson's Chi-squared test as appropriate. * Statistical siginificant at level 0.05.

Supplementary Table 9. Pearson's correlation of polygenic risk scores that built with genome-wide-significant or gene-annotated SNPs, UCLA ATLAS sample, stratified by genetic inferred ancestry

	Pearson's Correlation	
Polygenic risk score GWAS	**Hispanic Latino American**	**African American**
Alzheimer's Disease (European ancestry)	0.885	0.837
Alzheimer's Disease (African ancestry)	0.953	0.963
Alzheimer's Disease (multi-ancestry)	0.953	0.919
Lewy Body Dementia	0.714	0.698
Parkinson's Disease	0.561	0.29
Progressive Supranuclear Palsy	0.813	0.657
Stroke	0.737	0.669

Abbreviations: GWAS, genome-wide association study, SNP, Single-Nucleotide Polymorphism.

AA	African American
AD	Alzheimer's disease
APOE	Apolipoprotein E
AUPRC	Area Under the Precision-Recall Curve
AUROC	area under the receiver operating characteristic
CADD	Combined Annotation-Dependent Depletion
CI	confidence intervals
EA	European American
EAA	East Asian American
EHR	Electronic Health Records
FTD	Frontotemporal dementia
FUMA	Functional Mapping and Annotation of Genome-Wide Association Studies
GIA	Genetic Inferred Ancestry
GO	Gene Ontology
GWAS	Genome-Wide Association Studies
HLA	Hispanic Latino American
LBD	Lewy body dementia
LD	Linkage disequilibrium
MCC	Matthews Correlation Coefficient
PC	principal components
PDD	Parkinson’s disease dementia
PRS	Polygenic risk scores
SAA	South Asian American
SNP	Single-Nucleotide Polymorphisms