Supplementary Material: Genetic risk factor clustering within and across neurodegenerative diseases

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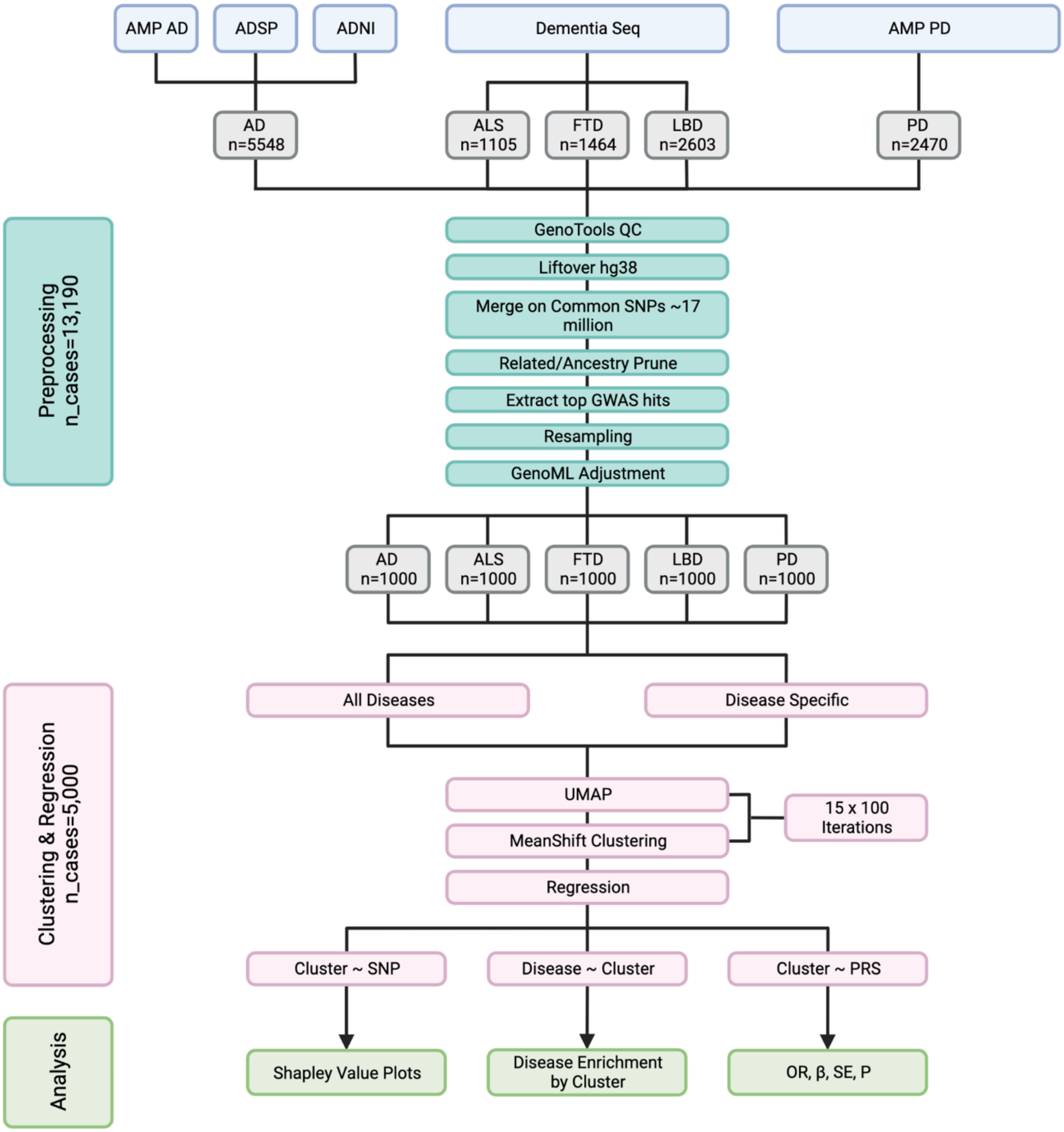
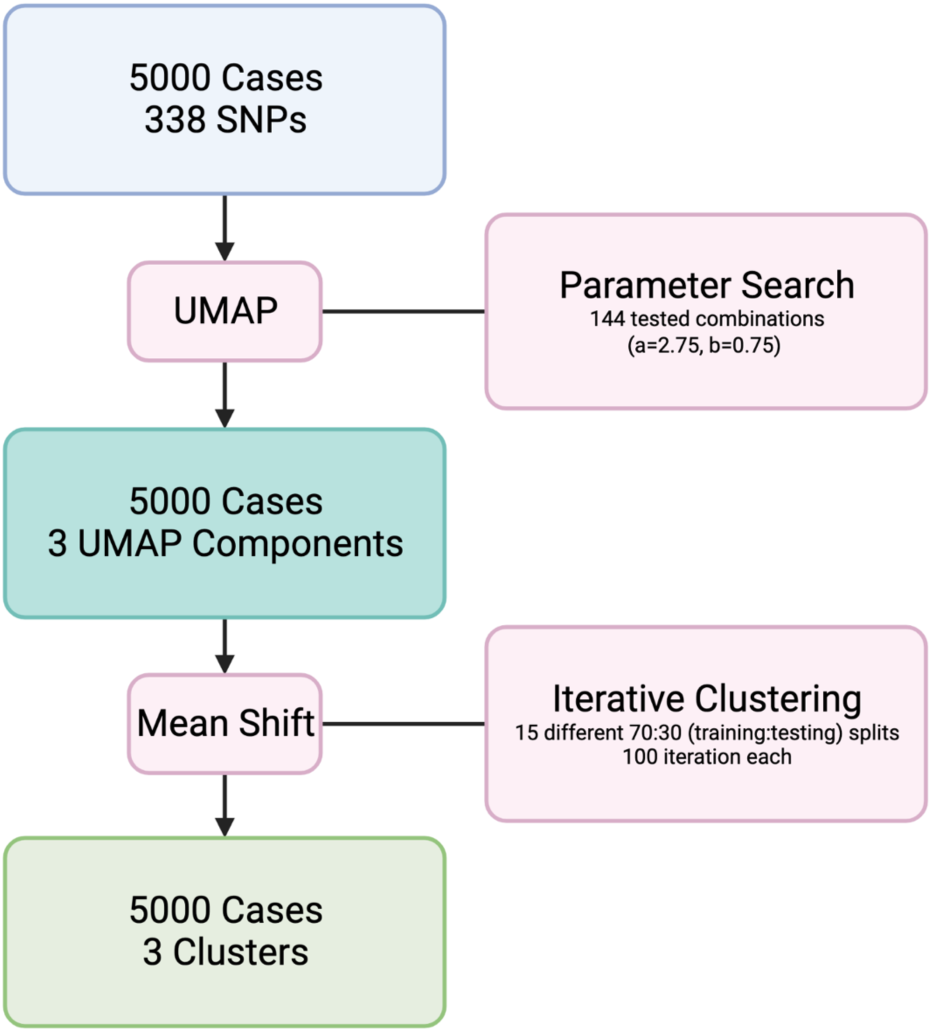
- Supplementary Figures 1-9
- Supplementary Tables 1-18
- Supplementary Methods

Supplementary Figure 1



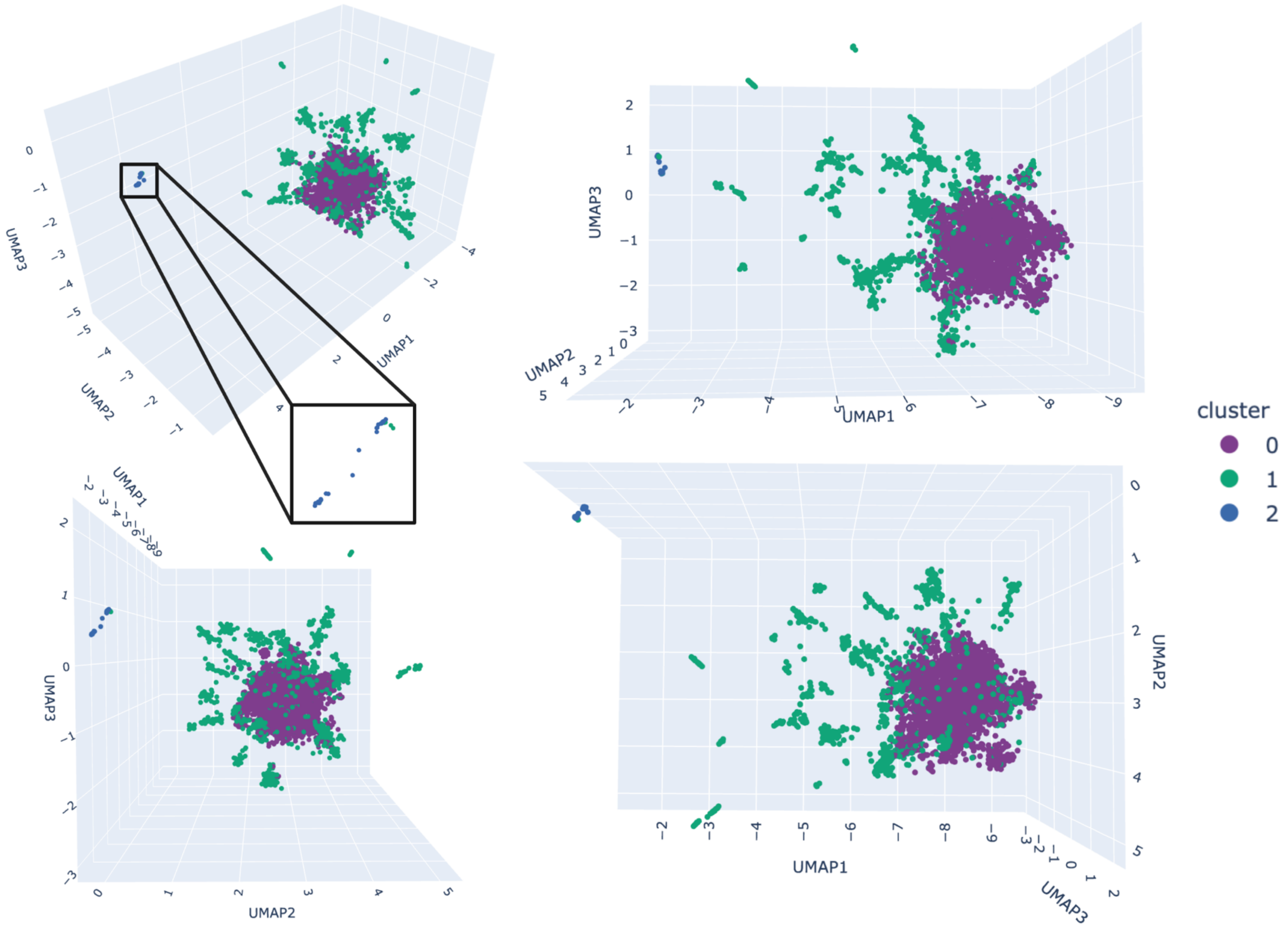
Workflow diagram summarizing cohort information, preprocessing and statistical analysis performed.

Supplementary Figure 2



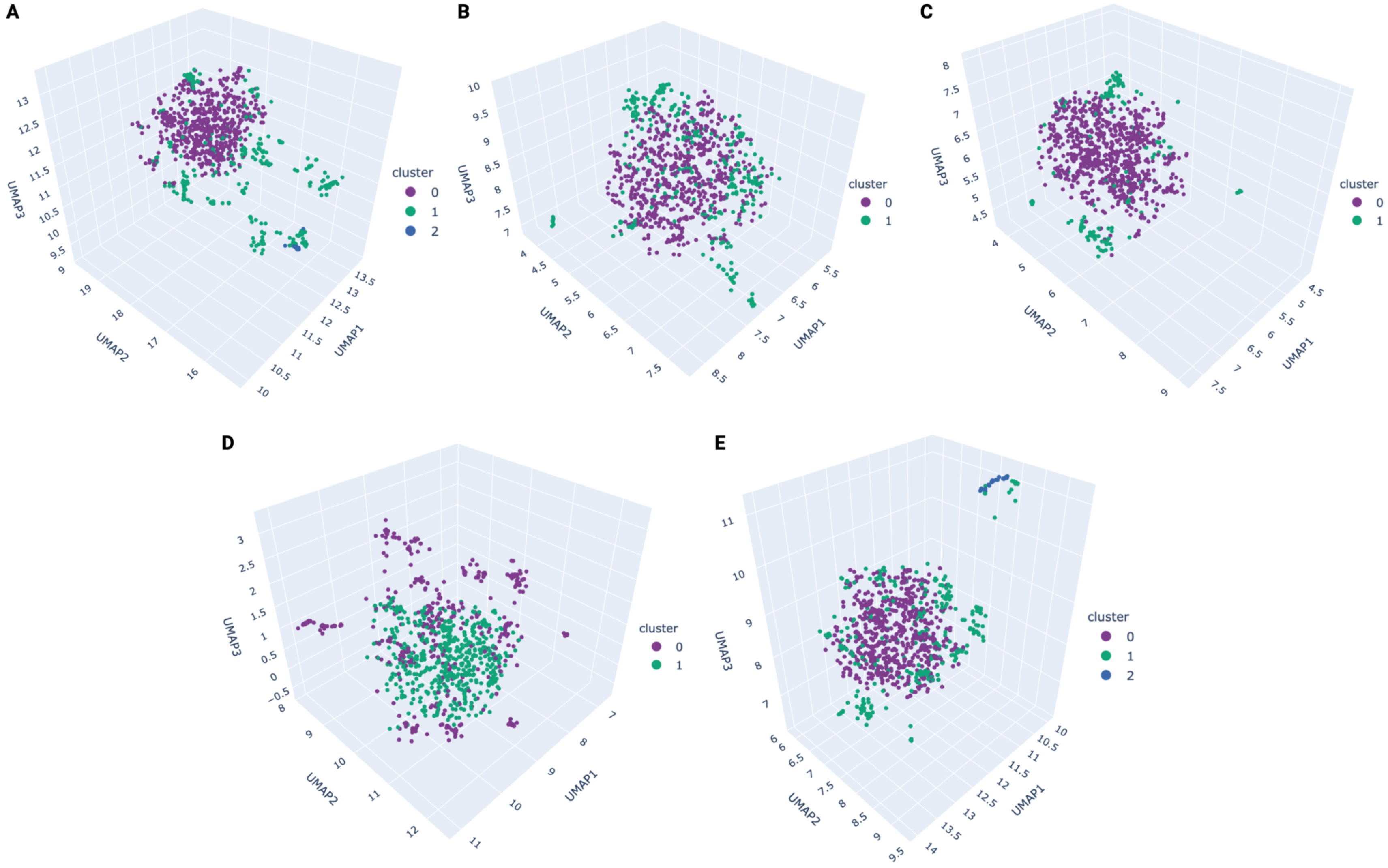
Workflow diagram summarizing the dimensionality reduction and clustering analyses performed.

Supplementary Figure 3



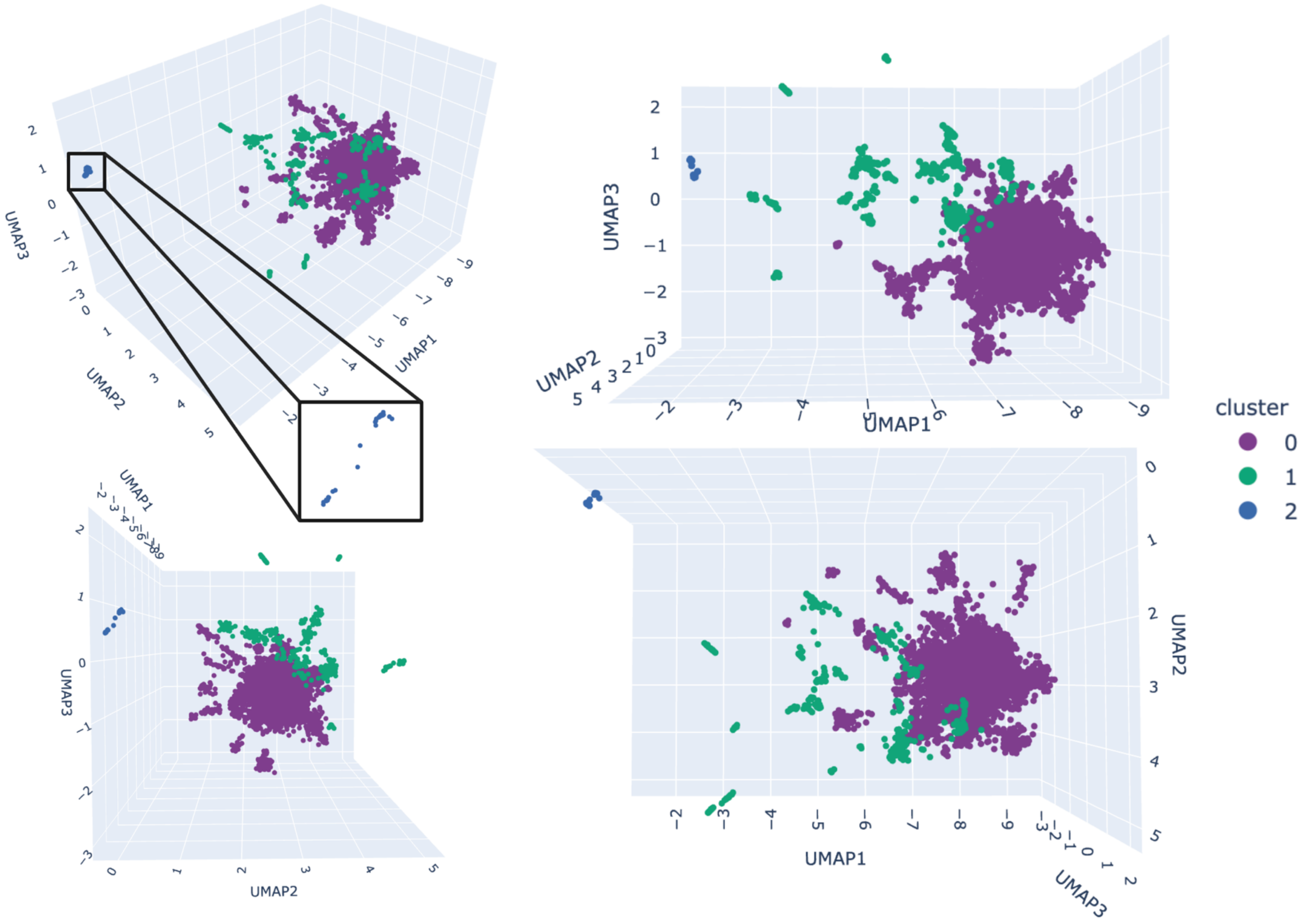
Multi-disease clusters resulting from the iterative clustering approach.

Supplementary Figure 4



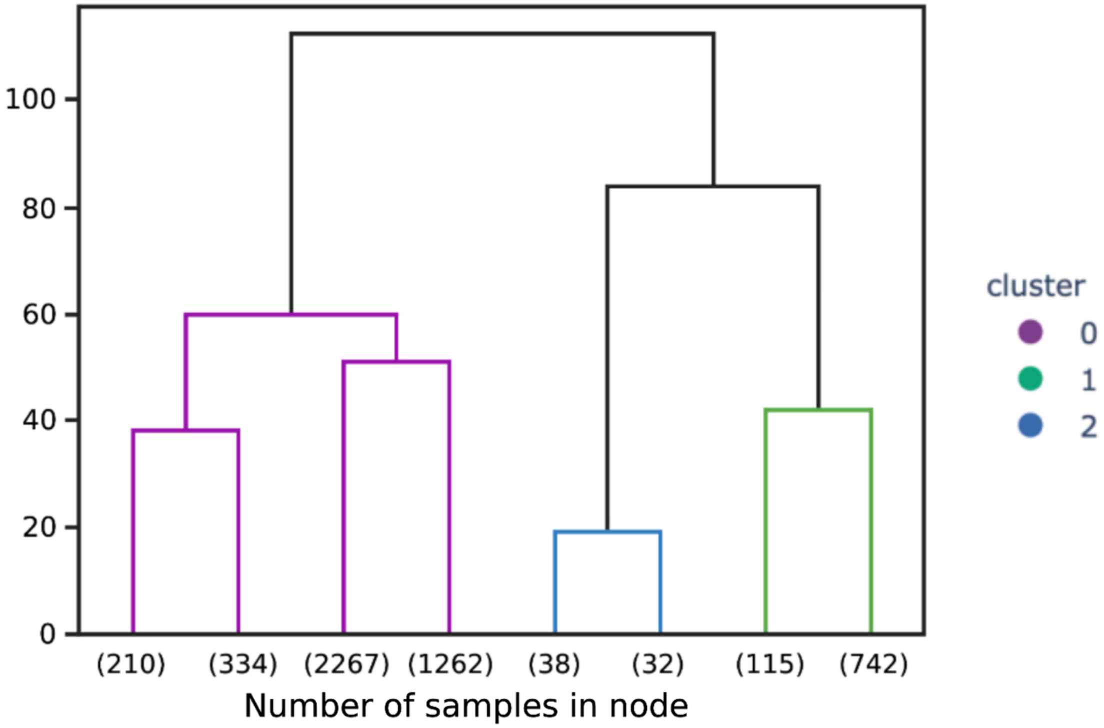
Disease-specific cluster memberships. (A) Alzheimer's disease (AD). **(B)** Parkinson's disease (PD). **(C)** Amyotrophic lateral sclerosis (ALS). **(D)** Lewy body dementia (LBD). **(E)** Frontotemporal dementia (FTD).

Supplementary Figure 5



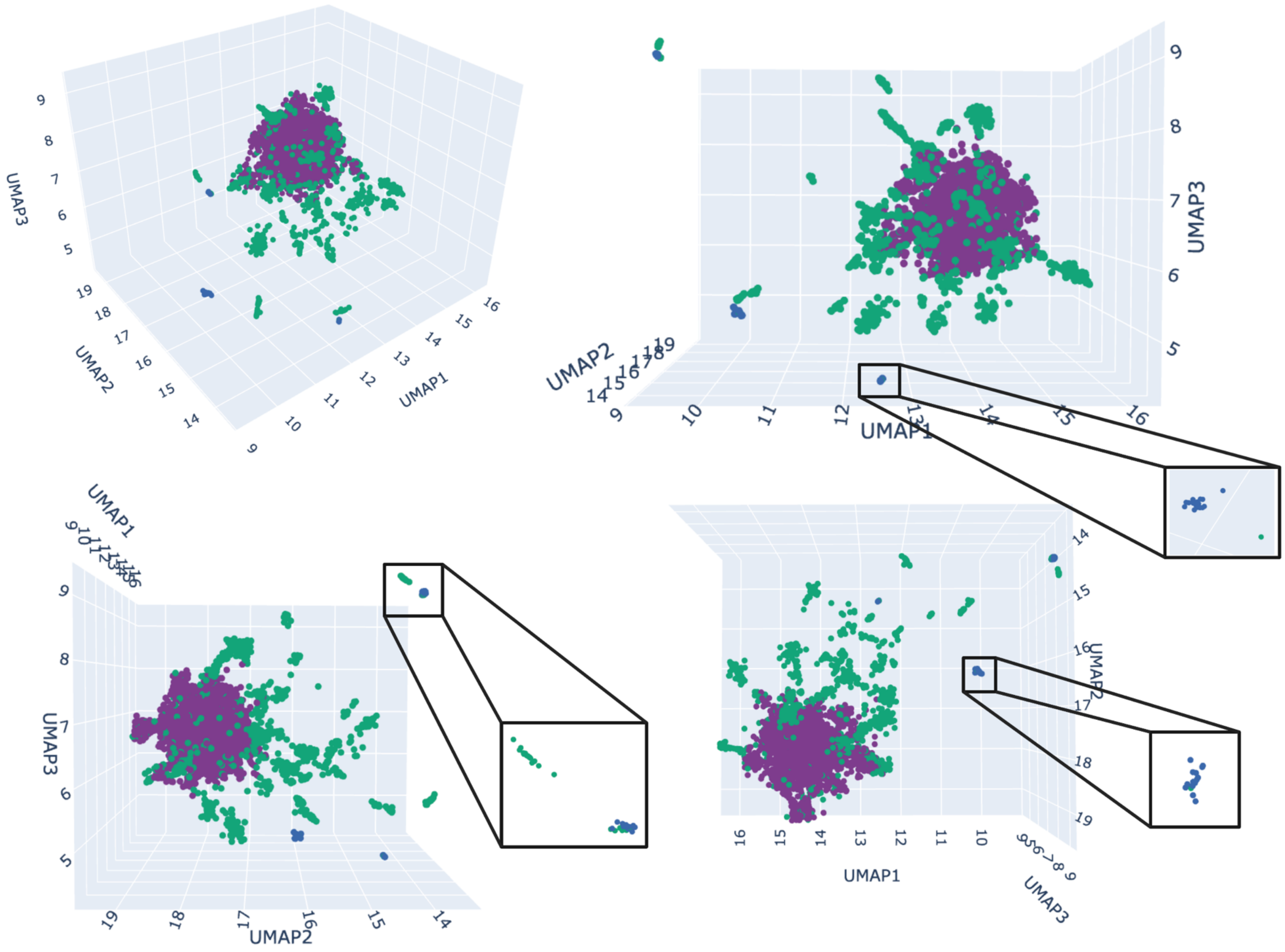
Multi-disease clusters resulting from hierarchical clustering.

Supplementary Figure 6



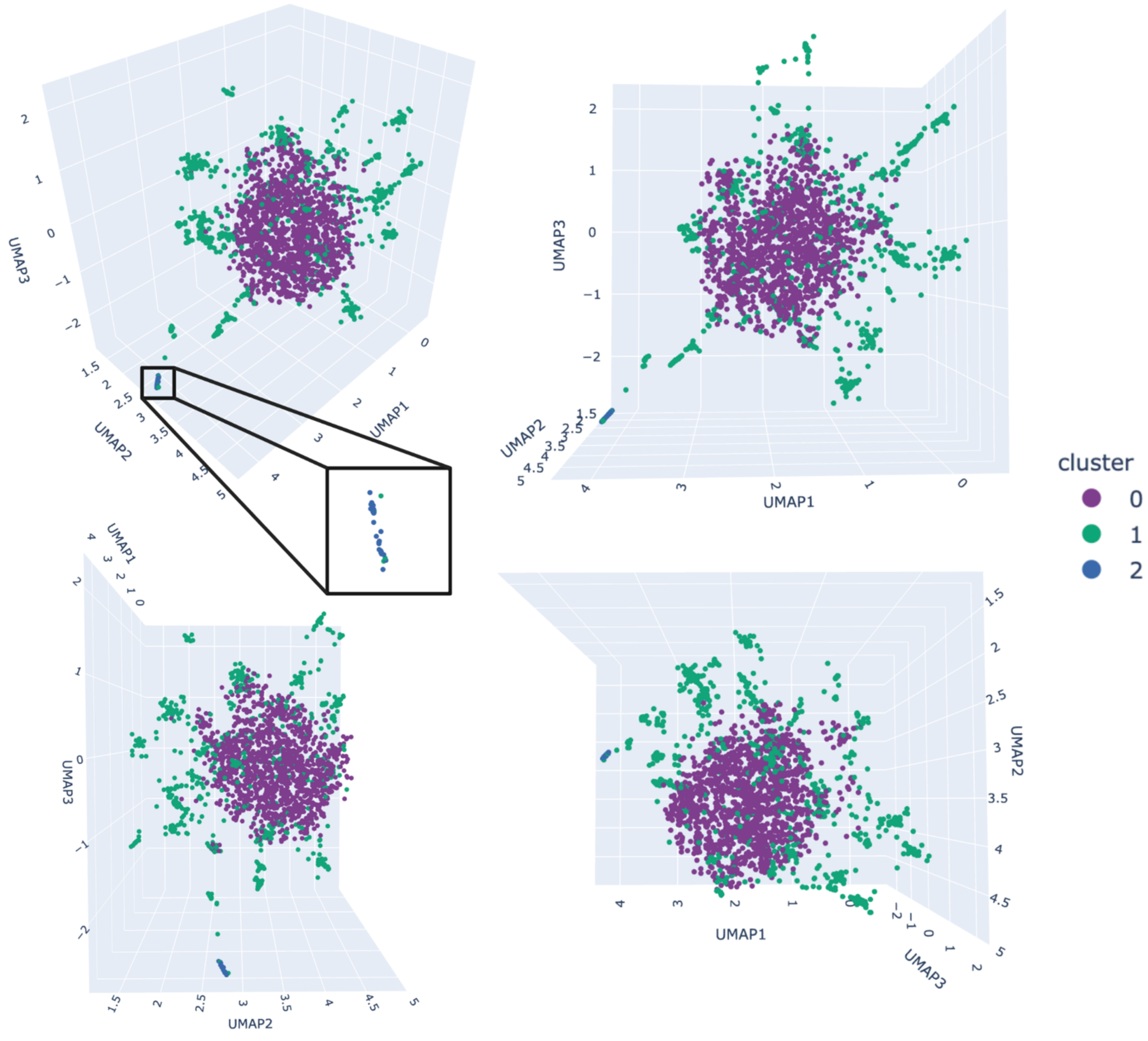
Hierarchical clustering dendrogram.

Supplementary Figure 7



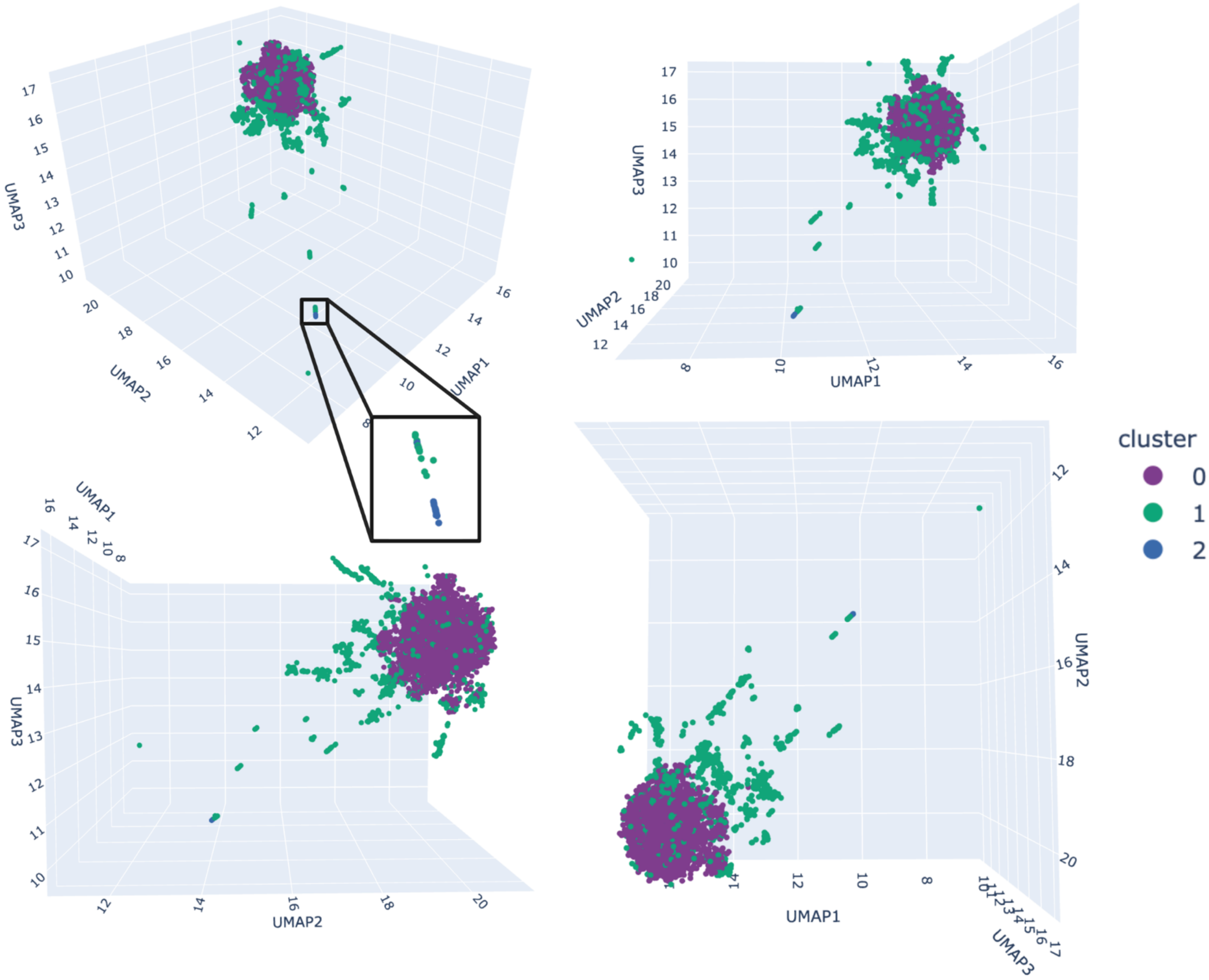
Multi-disease clusters resulting from the iterative clustering approach with the *APOE* locus removed.

Supplementary Figure 8



Multi-disease clusters resulting from the iterative clustering approach with downsampled data (500 cases per disease).

Supplementary Figure 9



Multi-disease clusters resulting from the iterative clustering approach with 1000 controls included as a negative control.

Supplementary Table 1 Cohort information

Cohort	Disease	Full	Downsampled	% Female
ADSP	AD	4697 Cases	955 Cases	60.31
		4317 Controls		
ADNI	AD	45 Cases	13 Cases	38.46
		254 Controls		
Joint Genotyping[a]	AD	806 Cases	32 Cases	40.63
		908 Controls		
AMP-PD	PD	2470 Cases	1000 Cases	39.90
		2023 Controls		
DementiaSeq	ALS	1105 Cases	1000 Cases	45.10
	LBD	2603 Cases	1000 Cases	34.10
	FTD	1464 Cases	1000 Cases	46.30
		3193 Controls[b]		

[a] Joint genotyping is made up of MayoRNAseq, MSBB, and ROSMAP.

[b] Controls were shared across diseases (ALS. LBD, and FTD) in the DementiaSeq cohort.

Supplementary Table 2 Quality control metrics by cohort

	ADSP	**ADNI**	**MayoRNAseq/ROSMAP /MSBB**	**AMP-PD**	**DementiaSeq**
Individual QC Step	**Number of Individuals**				
Genotype Missingness Prune	442	0	0	0	0
Genetic Sex Confirmation	NA	0	12	0	NA
Related Prune	2923	15	58	41	0
Total Pruned	3365	15	70	41	0
Total Remaining	9014	299	1714	4493	8365
Variant QC Step	**Number of SNPs**				
Callrate Prune	14,054,936	2,969,411	683,372	2,931,688	0
Case/Control Missingness Prune	386,306	47	159	300,496	0
Haplotype Prune	1,426,302	138,303	130,016	235,843	0
Hardy-Weinberg Equilibrium Prune	578,638	28,701	480,144	698,633	3824
Total Pruned	16,446,182	3,136,462	1,293,691	4,166,660	3824
Total Remaining	206,582,127	41,331,241	58,359,334	168,929,789	215,514,196

More detailed information on each QC step can be found in the GP2 pipeline descriptions (https://github.com/GP2code/).

Supplementary Table 3 Quality control metrics for merged data

QC Step	Number of Individuals
Related Prune	3929
Ancestry Prune	4325
Total Remaining	16,030

More detailed information on each QC step can be found in the GP2 pipeline descriptions (https://github.com/GP2code/).

Supplementary Table 4 Average number of samples in cluster 0 across the different 70:30 (training:testing) splits in the multi-disease iterative clustering analysis

Training:Testing Split	Average number of samples in Cluster 0
1	4571.46
2	4329.87
3	4344.95
4	4382.14
5	4430.58
6	4360.83
7	4322.33
8	4509.59
9	4307.75
10	4090.93
11	4419.70
12	4645.17
13	4305.07
14	4603.89
15	4412.52

Supplementary Table 5 PheWAS for specified variants important in determining multi-disease cluster membership

Variant	Train	Beta	P-value
rs72654445_AD_APOC1	Low density lipoprotein cholesterol levels	0.082	3.90E-22
	AD or family history of AD	-0.272	5.80E-09
	Lymphocyte counts	-0.039	1.20E-05
	Liver enzyme levels (alanine transaminase)	7.20E-03	2.10E-05
	Monocyte count	-0.030	1.20E-04
rs112952132_AD_CEACAM16_AS1	Low density lipoprotein cholesterol levels	-0.268	3.30E-168
	AD or family history of AD	-0.404	2.10E-15
	High cholesterol	-0.240	6.20E-11
	Red cell distribution width	0.058	5.20E-09
	Mean spheric corpuscular volume	0.052	1.50E-06
rs111278137_AD_CEACAM16_AS1	Low density lipoprotein cholesterol levels	-0.113	1.00E-65
	AD or family history of AD	-0.299	4.50E-15
	High cholesterol	-0.014	8.40E-09
	Red cell distribution width	-0.116	5.90E-05
	Glycine levels	0.125	2.10E-04
rs41290102_AD_NECTIN2	Triglyceride levels	-8.60E-02	5.20E-25
	C-reactive protein levels	0.072	4.00E-19
	Mean platelet volume	0.0548	3.50E-16
	AD or family history of AD	-0.277	7.00E-13
	Serum alkaline phosphatase levels	0.040	4.70E-07
rs79701229_AD_NECTIN2	Low density lipoprotein cholesterol levels	0.188	1.90E-118
	AD or family history of AD	1.070	2.50E-109
	High cholesterol	0.020	6.70E-12
	Cholesterol lowering medication	0.235	1.10E-08
	Platelet distribution width	0.049	1.30E-07

Supplementary Table 6 Top variants in determining multi-disease cluster memberships that are consistent across clustering iterations

Cluster 0	Cluster 1	Cluster 2
rs72654445_AD_APOC1	rs72654445_AD_APOC1	rs112952132_AD_CEACAM16_AS1
rs41290102_AD_NECTIN2	rs41290102_AD_NECTIN2	rs200046586_AD_GEMIN7
rs117261169_AD_CLPTM1	rs117261169_AD_CLPTM1	rs111278137_AD_CEACAM16_AS1
rs114088559_PD_LOC105377329	rs114088559_PD_LOC105377329	rs2965163_AD_GEMIN7
rs112450640_AD_CBLC	rs8102895_AD_CLPTM1	rs80307900_AD_GEMIN7
rs8102895_AD_CLPTM1	rs12983572_AD_CLPTM1	rs713522_PD_MAPT
rs79701229_AD_NECTIN2	rs79701229_AD_NECTIN2	rs2965109_AD_CEACAM16_AS1
rs12983572_AD_CLPTM1	rs183442275_AD_MARK4	rs35385129_AD_ZNF233
rs183442275_AD_MARK4	rs6599388_PD_LBD_TMEM175	rs11767557_AD_EPHA1_AS1
rs75627662_AD_MARK4	rs75627662_AD_MARK4	
rs112952132_AD_CEACAM16_AS1	rs148933445_AD_CBLC	
rs139185008_ALS_MOB3B	rs139185008_ALS_MOB3B	
rs12691088_AD_LBD_APOC1	rs41290102_AD_NECTIN2	

Supplementary Table 7 SNP association summary statistic per multi-disease cluster for variants associated with loci with previously establish pleiotropic associations (*GBA, GRN, LRRK2, MAPT, APOE, C9orf72)*

Cluster	SNP	BETA	SE	OR	P
Cluster 0	rs17696570_ALS_C9orf72	-0.222	0.035	0.801	2.74E-10
	rs537741299_LBD_APOE	-5.346	1.216	0.005	1.10E-05
	rs28903073_PD_LRRK2	-0.397	0.111	0.672	3.60E-04
	rs769446_AD_APOE	0.193	0.079	1.213	0.015
	rs713522_PD_MAPT	0.075	0.034	1.078	0.029
	rs76763715_PD_GBA	-1.618	0.777	0.198	0.037
	rs10812619_ALS_C9orf72	0.069	0.035	1.072	0.045
Cluster 1	rs17696570_ALS_C9orf72	0.229	0.035	1.257	6.07E-11
	rs28903073_PD_LRRK2	0.272	0.061	1.312	7.88E-06
	rs537741299_LBD_APOE	4.670	1.220	106.751	1.29E-04
	rs76763715_PD_GBA	2.082	0.782	8.020	0.008
	rs713522_PD_MAPT	-0.089	0.035	0.914	0.010
	rs769446_AD_APOE	-0.191	0.076	0.826	0.012
Cluster 2	rs537741299_LBD_APOE	11.713	4.907	122210.47	0.017
	rs76763715_PD_GBA	-7.091	3.110	8.33E-04	0.023
	rs28903073_PD_LRRK2	0.138	0.072	1.148	0.054

Supplementary Table 8 *APOE* rs7412 association summary statistic per multi-disease cluster

Cluster	BETA	SE	OR	P
Cluster 0	0.045	0.044	1.047	0.296
Cluster 1	-0.047	0.043	0.954	0.275
Cluster 2	0.065	0.360	1.067	0.857

Supplementary Table 9 PRS mean and standard deviation summary statistics per disease-specific cluster and counts for disease-specific cluster membership

Disease	Cluster	AD PRS	PD PRS	ALS PRS	LBD PRS	FTD PRS	# samples in cluster
AD	Cluster 0	8.00e-03 (0.951)	-0.019 (0.957)	-0.084 (0.895)*	-0.058 (0.979)	-0.035 (1.021)	622
	Cluster 1	0.145 (1.037)*	-0.048 (1.058)	0.231 (1.165)*	0.213 (1.010)*	0.061 (0.971)	364
	Cluster 2	-0.397 (0.771)	0.165 (0.761)	0.107 (1.345)	-0.418 (0.757)	-0.292 (0.904)	12
PD	Cluster 0	0.095 (0.986)*	-0.036 (1.008)	-0.034 (0.925)	-0.031 (1.076)	0.017 (1.004)	643
	Cluster 1	-0.059 (1.094)	0.096 (1.115)	0.024 (1.090)	0.137 (0.975)*	5.01e-03 (1.010)	357
ALS	Cluster 0	0.055 (0.999)	-0.057 (0.948)	-0.123 (0.901)*	-0.033 (0.990)	-0.006 (1.021)	818
	Cluster 1	-0.150 (0.981)*	0.172 (1.087)*	0.422 (1.246)*	0.134 (1.001)	0.073 (0.969)	182
LBD	Cluster 0	-0.159 (0.867)*	-0.041 (0.931)	-0.034 (0.945)	-0.226 (0.927)*	-0.081 (1.032)	534
	Cluster 1	0.113 (1.099)*	0.044 (1.045)	0.079 (1.116)	0.250 (1.021)*	0.070 (0.958)	466
FTD	Cluster 0	-0.039 (0.868)	-0.113 (0.915)*	-0.114 (0.826)*	-0.129 (0.971)*	0.013 (0.974)	611
	Cluster 1	0.130 (1.151)*	0.159 (1.114)*	0.182 (1.149)*	0.174 (1.086)*	0.013 (0.986)	364
	Cluster 2	-1.105 (0.789)*	0.028 (0.904)	0.009 (1.235)	-0.234 (0.949)	-0.081 (1.266)	25

Format: mean (standard deviation).
*denotes a p-value < 0.05 for the deviation of PRS from the normal distribution (mean=0, standard deviation=1) within a cluster.

Supplementary Table 10 Multi-disease cluster counts for different approaches

Cluster	Iterative Clustering	Hierarchical Clustering	Downsampled	Controls
Cluster 0	2863	4073	1464	3743
Cluster 1	2074	857	1006	2222
Cluster 2	63	70	30	35
Total	5000	5000	2500	6000

Supplementary Table 11 Disease enrichments per multi-disease hierarchical cluster

Disease	Multi-disease cluster membership	% samples with disease
AD	Cluster 0	0.177*
	Cluster 1	0.320*
	Cluster 2	0.071*
PD	Cluster 0	0.205
	Cluster 1	0.174*
	Cluster 2	0.228*
ALS	Cluster 0	0.213
	Cluster 1	0.146*
	Cluster 2	0.114*
LBD	Cluster 0	0.198
	Cluster 1	0.210
	Cluster 2	0.200
FTD	Cluster 0	0.207
	Cluster 1	0.150*
	Cluster 2	0.386*

Supplementary Table 12 Disease association summary statistics and frequency per multi-disease cluster with the *APOE* locus removed

Disease	Multi-disease cluster membership	OR	BETA	SE	P	% samples with disease
AD	Cluster 0	0.619	-0.479	0.086	2.31E-08	0.163*
	Cluster 1	1.701	0.531	0.086	6.12E-10	0.254*
	Cluster 2	0.415	-0.879	0.431	0.041	0.090*
PD	Cluster 0	1.117	0.111	0.086	0.196	0.208
	Cluster 1	0.907	-0.098	0.086	0.258	0.191
	Cluster 2	0.813	-0.207	0.334	0.536	0.157*
ALS	Cluster 0	1.752	0.561	0.090	4.76E-10	0.229*
	Cluster 1	0.587	-0.533	0.091	4.48E-09	0.160*
	Cluster 2	0.574	-0.553	0.380	0.145	0.202
LBD	Cluster 0	0.838	-0.177	0.084	0.035	0.191
	Cluster 1	1.132	0.125	0.084	0.139	0.210
	Cluster 2	1.631	0.489	0.276	0.076	0.270*
FTD	Cluster 0	1.016	0.016	0.085	0.851	0.209
	Cluster 1	0.943	-0.058	0.085	0.497	0.184*
	Cluster 2	1.855	0.618	0.269	0.021	0.281*

*denotes a p-value < 0.05 for the frequency increase or decrease in a certain disease status per cluster compared to the null estimate of 20%.

Supplementary Table 13 PRS association summary statistics per multi-disease cluster with the *APOE* locus removed

Disease	Cluster	OR	BETA	SE	P
AD	Cluster 0	0.771	-0.260	0.045	8.37E-09
	Cluster 1	1.330	0.284	0.045	4.00E-10
	Cluster 2	0.743	-0.296	0.180	0.101
PD	Cluster 0	0.819	-0.199	0.045	1.20E-05
	Cluster 1	1.229	0.206	0.046	7.00E-06
	Cluster 2	0.948	-0.053	0.161	0.743
ALS	Cluster 0	0.852	-0.160	0.045	3.25E-04
	Cluster 1	0.178	0.163	0.045	2.61E-04
	Cluster 2	0.984	-0.016	0.161	0.918
LBD	Cluster 0	0.643	-0.442	0.047	4.94E-21
	Cluster 1	1.586	0.461	0.047	1.47E-22
	Cluster 2	0.816	-2.03E-01	0.177	0.251
FTD	Cluster 0	1.009	0.01	0.045	0.827
	Cluster 1	0.989	-0.011	0.045	0.814
	Cluster 2	1.008	0.009	0.16	0.956

Supplementary Table 14 Disease association summary statistics and frequency per downsampled multi-disease cluster (500 cases per disease)

Disease	Multi-disease cluster membership	OR	BETA	SE	P	% samples with disease
AD	Cluster 0	0.594	-0.521	0.121	1.80E-05	0.162*
	Cluster 1	1.735	0.551	0.121	6.00E-06	0.258*
	Cluster 2	0.557	-0.584	0.618	0.345	0.100*
PD	Cluster 0	1.129	0.121	0.121	0.316	0.204
	Cluster 1	0.886	-0.121	0.122	0.320	0.194
	Cluster 2	0.972	-0.029	0.504	0.954	0.233*
ALS	Cluster 0	1.731	0.549	0.127	1.50E-05	0.232*
	Cluster 1	0.592	-0.525	0.128	3.90E-05	0.157*
	Cluster 2	0.541	-0.613	0.618	0.321	0.100*
LBD	Cluster 0	0.846	-0.167	0.119	0.162	0.193
	Cluster 1	1.185	0.170	0.120	0.156	0.210
	Cluster 2	0.972	-0.029	0.504	0.954	0.200
FTD	Cluster 0	1.040	0.039	0.122	0.747	0.210
	Cluster 1	0.903	-0.103	0.124	0.407	0.181
	Cluster 2	2.351	0.855	0.421	0.042	0.367*

*denotes a p-value < 0.05 for the frequency increase or decrease in a certain disease status per cluster compared to the null estimate of 20%.

Supplementary Table 15 PRS association summary statistics per downsampled multi-disease cluster

Disease	Cluster	OR	BETA	SE	P
AD	Cluster 0	0.804	-0.218	0.064	6.78E-04
	Cluster 1	1.317	0.275	0.065	2.10E-05
	Cluster 2	0.149	-1.902	0.505	1.66E-04
PD	Cluster 0	0.867	-0.143	0.065	0.027
	Cluster 1	1.164	0.152	0.065	0.019
	Cluster 2	0.867	-0.142	0.286	0.619
ALS	Cluster 0	0.824	-0.193	0.064	2.50E-03
	Cluster 1	1.229	-0.206	0.064	1.33E-03
	Cluster 2	0.793	-0.232	0.314	0.459
LBD	Cluster 0	0.678	-0.389	0.066	3.63E-09
	Cluster 1	1.484	0.395	0.066	2.39E-09
	Cluster 2	0.955	-0.046	0.286	0.872
FTD	Cluster 0	0.952	-0.048	0.065	0.456
	Cluster 1	1.037	0.036	0.065	0.578
	Cluster 2	1.323	0.280	0.335	0.404

Supplementary Table 16 Disease association summary statistics and frequency per multi-disease cluster with controls included

Disease	Multi-disease cluster membership	OR	BETA	SE	P	% samples with disease
Control	Cluster 0	108.69	4.688	0.450	2.10E-25	0.265*
	Cluster 1	9.47E-03	-4.660	0.450	4.12E-25	4.05E-03*
	Cluster 2	1.08E-08	-18.340	4353.967	0.997	0*
AD	Cluster 0	0.485	-0.723	0.084	8.76E-18	0.123*
	Cluster 1	2.097	0.740	0.084	1.49E-18	0.241*
	Cluster 2	0.442	-0.816	0.738	0.269	0.114*
PD	Cluster 0	0.748	-0.29	0.084	5.85E-04	0.151*
	Cluster 1	1.302	0.264	0.085	1.82E-03	0.191*
	Cluster 2	2.398	0.874	0.431	0.042	0.286*
ALS	Cluster 0	1.097	0.092	0.085	0.278	0.170
	Cluster 1	0.927	-0.076	0.085	0.372	0.162
	Cluster 2	0.415	-0.879	0.738	0.234	0.086*
LBD	Cluster 0	0.591	-0.525	0.082	1.79E-10	0.139*
	Cluster 1	1.710	0.537	0.082	7.62E-11	0.214*
	Cluster 2	0.652	-0.427	0.617	0.488	0.143*
FTD	Cluster 0	0.719	-0.331	0.084	8.99E-05	0.152*
	Cluster 1	1.336	0.290	0.085	6.19E-04	0.188*
	Cluster 2	3.432	1.233	0.410	2.65E-03	0.371*

*denotes a p-value < 0.05 for the frequency increase or decrease in a certain disease status per cluster compared to the null estimate of 20%.

Supplementary Table 17 PRS association summary statistics per multi-disease cluster with controls included

Disease	Cluster	OR	BETA	SE	P
AD	Cluster 0	0.740	-0.301	0.040	9.85E-14
	Cluster 1	1.393	0.331	0.041	4.03E-16
	Cluster 2	0.144	-1.935	0.426	5.45E-06
PD	Cluster 0	0.813	-0.206	0.041	5.16E-07
	Cluster 1	1.233	0.209	0.041	4.11E-07
	Cluster 2	0.968	-0.032	0.253	0.898
ALS	Cluster 0	0.850	-0.163	0.040	4.70E-05
	Cluster 1	1.191	0.175	0.040	1.4E-05
	Cluster 2	0.592	-0.524	0.327	0.108
LBD	Cluster 0	0.601	-0.508	0.042	6.51E-34
	Cluster 1	1.669	0.512	0.042	3.36E-34
	Cluster 2	0.993	-6.50E-03	0.252	0.979
FTD	Cluster 0	0.981	-0.019	0.041	0.636
	Cluster 1	1.031	0.030	0.041	0.466
	Cluster 2	0.722	-0.326	0.213	0.125

Supplementary Table 18 LDSC genetic correlation results between diseases

Disease	AD	PD	ALS	LBD	FTD
AD	x	0.197 (0.084)*	0.154 (0.120)	0.385 (0.188)*	0.311 (0.271)
PD	0.197 (0.084)*	x	0.057 (0.087)	0.599 (0.166)*	0.464 (0.275)
ALS	0.154 (0.120)	0.057 (0.087)	x	0.121 (0.220)	0.168 (0.324)
LBD	0.385 (0.188)*	0.599 (0.166)*	0.121 (0.220)	x	0.290 (0.515)
FTD	0.311 (0.271)	0.464 (0.275)	0.168 (0.324)	0.290 (0.515)	x

Format: genetic correlation (standard error).
*denotes a significant correlation between diseases (p-value < 0.05).

Supplementary Methods

Iterative Clustering Approach

Tracking samples across iterations allows for the variable number of clusters formed outside of the main cluster (i.e., Cluster 0) to be collapsed into Clusters 1 and 2. The variable number of clusters identified by Mean Shift is due to the stochasticity of UMAP. The iterative clustering approach is necessary to capture information provided by Mean Shift over these varying UMAP representations.

When performing the iterative clustering approach for the disease-specific analyses, the sample size was reduced from 5000 samples to 1000 samples for each NDD respectively. This reduction in sample size leads to a large increase in variability between iterations. This led to the decision to group samples into Cluster 0 or Cluster 2 (Cluster 1 if only 2 clusters were identified in a disease subset) if they were consistently inside or outside the main cluster for at least 12 of the 15 training:testing splits, instead of all 15 training:testing splits which was the approach used in the multi-disease analysis. It was necessary to reduce this threshold to account for the increased variability that occurs when performing the analysis on a significantly smaller sample size.