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Supporting Information

Chemical signatures delineate heterogeneous amyloid plaque populations across the Alzheimer's disease spectrum

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Content

SI Table 1

SI Figures S1-7

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SI Table S1: Masses of the detected Aβ isoforms.

Peptide	Peptide Sequence	$[M+H]^+$	$[M+H]^{+\ Avg}$
Aβ11pE-40	pEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV	3132.67684	3134
Aβ11pE-42	pEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	3317.79802	3319
Aβ11-42	EVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	3334.79802	3336
Aβ9-40	GYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV	3370.76164	3372
Aβ8-40	SGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV	3457.79366	3459
Aβ7-40	DSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV	3572.82061	3574
Aβ4-40	FRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV	4013.04904	4012.042
Aβ5-42	RHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	4050.10181	4052
Aβ3pE-40	pEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV	4124.09164	4127
Aβ4-42	FRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	4197.17022	4199.5
Aβ3pE-42	pEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	4308.21281	4311
Aβ1-40	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV	4328.15569	4329.5
Aβ2-42	AEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	4397.24993	4400
Aβ1-42	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	4512.27687	4515.5
Aβ1-42ox	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA +oxidation	4528.27687	4531.5

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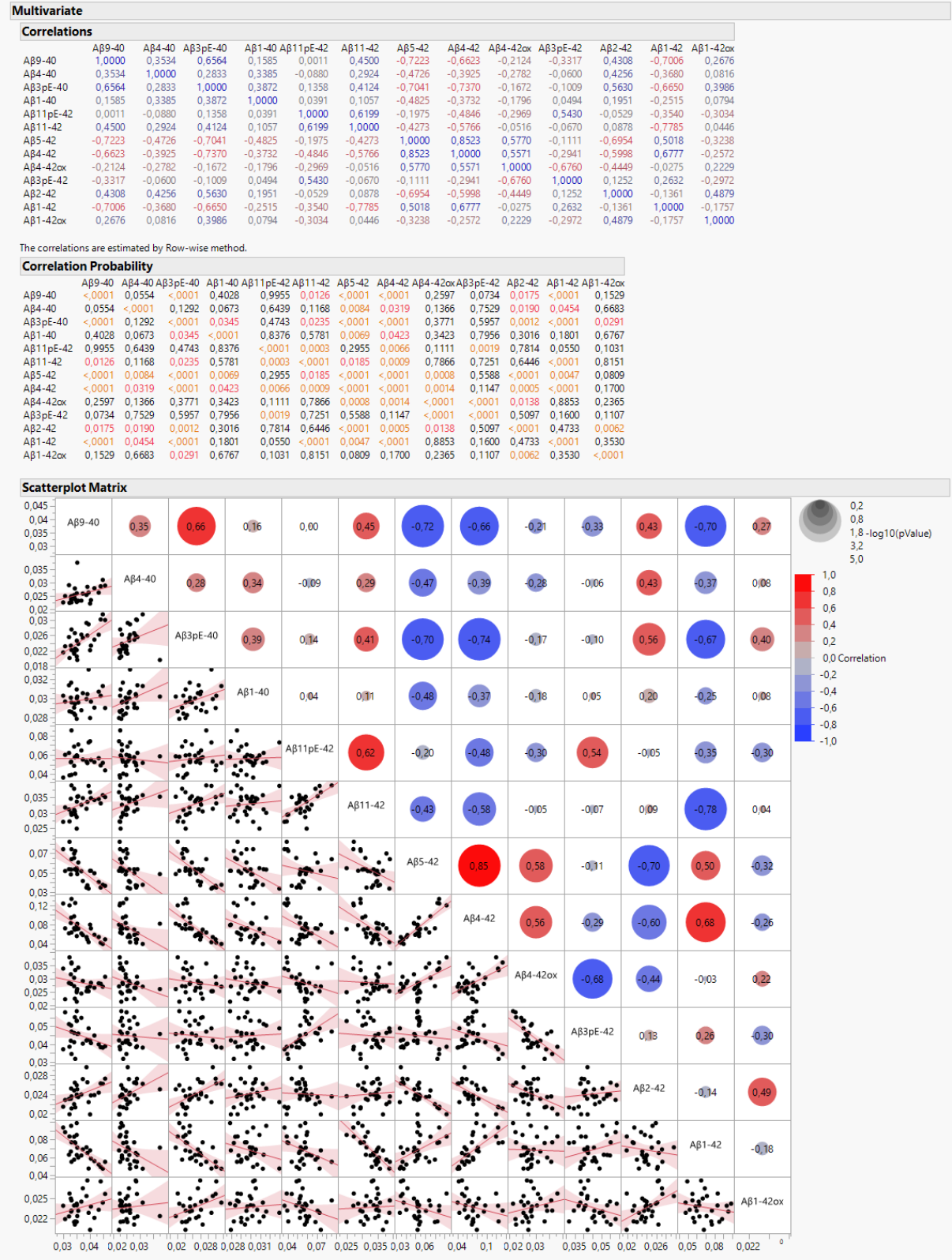

Multivariate

Correlations

	Aβ9-40	Aβ4-40	Aβ3pE-40	Aβ1-40	Aβ11pE-42	Aβ11-42	Aβ5-42	Aβ4-42	Aβ4-42ox	Aβ3pE-42	Aβ2-42	Aβ1-42	Aβ1-42ox
Aβ9-40	1,0000	0,3534	0,6564	0,1585	0,0011	0,4500	-0,7223	-0,6623	-0,2124	-0,3317	0,4308	-0,7006	0,2676
Aβ4-40	0,3534	1,0000	0,2833	0,3385	-0,0880	0,2924	-0,4726	-0,3925	-0,2782	-0,0600	0,4256	-0,3680	0,0816
Aβ3pE-40	0,6564	0,2833	1,0000	0,3872	0,1358	0,4124	-0,7041	-0,7370	-0,1672	-0,1009	0,5630	-0,6650	0,3986
Aβ1-40	0,1585	0,3385	0,3872	1,0000	0,0391	0,1057	-0,4825	-0,3732	-0,1796	0,0494	0,1951	-0,2515	0,0794
Aβ11pE-42	0,0011	-0,0880	0,1358	0,0391	1,0000	0,6199	-0,1975	-0,4846	-0,2969	0,5430	-0,0529	-0,3540	-0,3034
Aβ11-42	0,4500	0,2924	0,4124	0,1057	0,6199	1,0000	-0,4273	-0,5766	-0,0516	-0,0670	0,0878	-0,7785	0,0446
Aβ5-42	-0,7223	-0,4726	-0,7041	-0,4825	-0,1975	-0,4273	1,0000	0,8523	0,5770	-0,1111	-0,6954	0,5018	-0,3238
Aβ4-42	-0,6623	-0,3925	-0,7370	-0,3732	-0,4846	-0,5766	0,8523	1,0000	0,5571	-0,2941	-0,5998	0,6777	-0,2572
Aβ4-42ox	-0,2124	-0,2782	-0,1672	-0,1796	-0,2969	-0,0516	0,5770	0,5571	1,0000	-0,6760	-0,4449	-0,0275	0,2229
Aβ3pE-42	-0,3317	-0,0600	-0,1009	0,0494	0,5430	-0,0670	-0,1111	-0,2941	-0,6760	1,0000	0,1252	0,2632	-0,2972
Aβ2-42	0,4308	0,4256	0,5630	0,1951	-0,0529	0,0878	-0,6954	-0,5998	-0,4449	0,1252	1,0000	-0,1361	0,4879
Aβ1-42	-0,7006	-0,3680	-0,6650	-0,2515	-0,3540	-0,7785	0,5018	0,6777	-0,0275	0,2632	-0,1361	1,0000	-0,1757
Aβ1-42ox	0,2676	0,0816	0,3986	0,0794	-0,3034	0,0446	-0,3238	-0,2572	0,2229	-0,2972	0,4879	-0,1757	1,0000

The correlations are estimated by Row-wise method.

Correlation Probability

	Aβ9-40	Aβ4-40	Aβ3pE-40	Aβ1-40	Aβ11pE-42	Aβ11-42	Aβ5-42	Aβ4-42	Aβ4-42ox	Aβ3pE-42	Aβ2-42	Aβ1-42	Aβ1-42ox
Aβ9-40	<,0001	0,0554	<,0001	0,4028	0,9955	0,0126	<,0001	<,0001	0,2597	0,0734	0,0175	<,0001	0,1529
Aβ4-40	0,0554	<,0001	0,1292	0,0673	0,6439	0,1168	0,0084	0,0319	0,1366	0,7529	0,0190	0,0454	0,6683
Aβ3pE-40	<,0001	0,1292	<,0001	0,0345	0,4743	0,0235	<,0001	<,0001	0,3771	0,5957	0,0012	<,0001	0,0291
Aβ1-40	0,4028	0,0673	0,0345	<,0001	0,8376	0,5781	0,0069	0,0423	0,3423	0,7956	0,3016	0,1801	0,6767
Aβ11pE-42	0,9955	0,6439	0,4743	0,8376	<,0001	0,0003	0,2955	0,0066	0,1111	0,0019	0,7814	0,0550	0,1031
Aβ11-42	0,0126	0,1168	0,0235	0,5781	0,0003	<,0001	0,0185	0,0009	0,7866	0,7251	0,6446	<,0001	0,8151
Aβ5-42	<,0001	0,0084	<,0001	0,0069	0,2955	0,0185	<,0001	<,0001	0,0008	0,5588	<,0001	0,0047	0,0809
Aβ4-42	<,0001	0,0319	<,0001	0,0423	0,0066	0,0009	<,0001	<,0001	0,0014	0,1147	0,0005	<,0001	0,1700
Aβ4-42ox	0,2597	0,1366	0,3771	0,3423	0,1111	0,7866	0,0008	0,0014	<,0001	<,0001	0,0138	0,8853	0,2365
Aβ3pE-42	0,0734	0,7529	0,5957	0,7956	0,0019	0,7251	0,5588	0,1147	<,0001	<,0001	0,5097	0,1600	0,1107
Aβ2-42	0,0175	0,0190	0,0012	0,3016	0,7814	0,6446	<,0001	0,0005	0,0138	0,5097	<,0001	0,4733	0,0062
Aβ1-42	<,0001	0,0454	<,0001	0,1801	0,0550	<,0001	0,0047	<,0001	0,8853	0,1600	0,4733	<,0001	0,3530
Aβ1-42ox	0,1529	0,6683	0,0291	0,6767	0,1031	0,8151	0,0809	0,1700	0,2365	0,1107	0,0062	0,3530	<,0001

Scatterplot Matrix

Figure S1. Correlation analysis of amyloid peptides in sAD-Core Plaque

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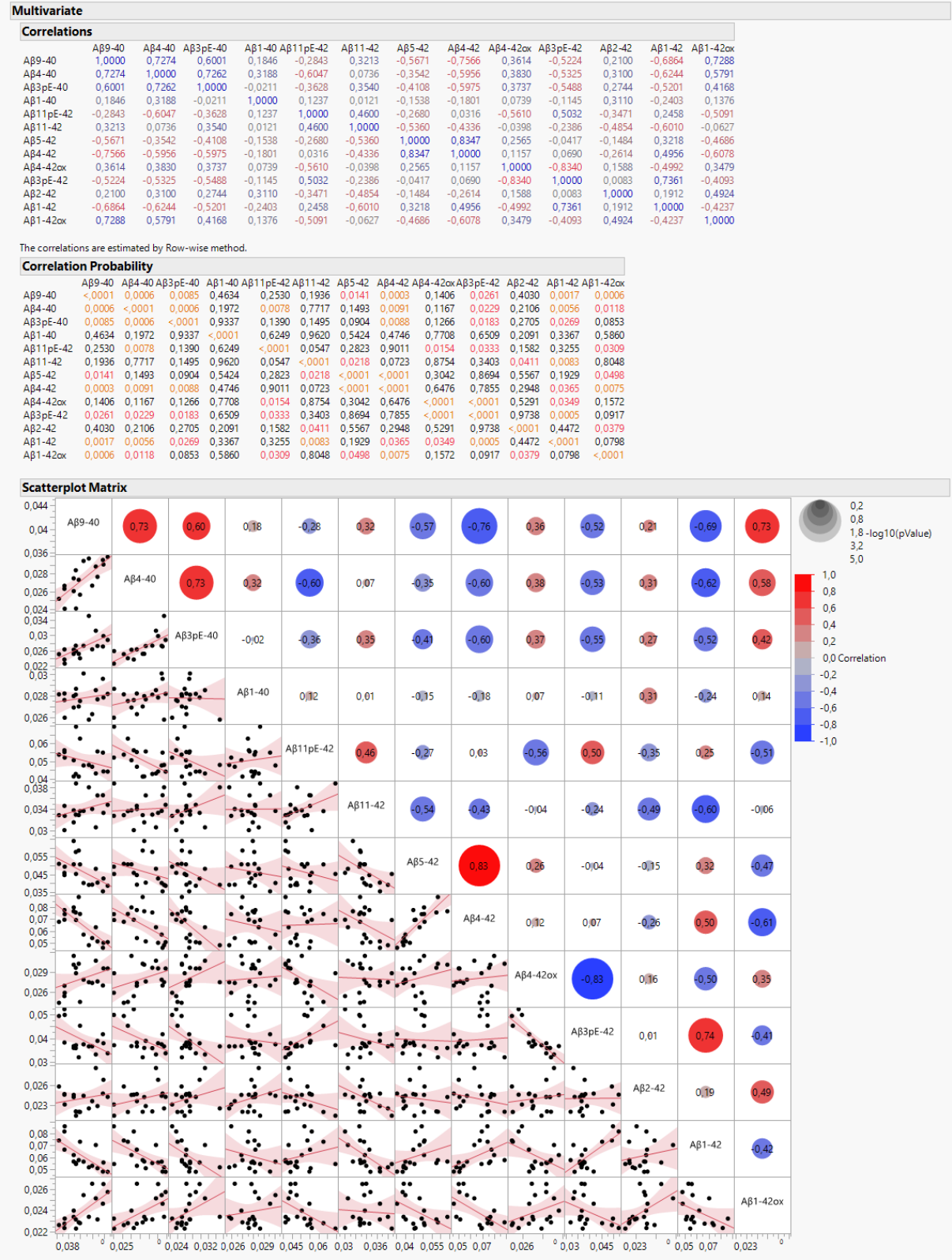

Multivariate

Correlations

	Aβ9-40	Aβ4-40	Aβ3pE-40	Aβ1-40	Aβ11pE-42	Aβ11-42	Aβ5-42	Aβ4-42	Aβ4-42ox	Aβ3pE-42	Aβ2-42	Aβ1-42	Aβ1-42ox
Aβ9-40	1,0000	0,7274	0,6001	0,1846	-0,2843	0,3213	-0,5671	-0,7566	0,3614	-0,5224	0,2100	-0,6864	0,7288
Aβ4-40	0,7274	1,0000	0,7262	0,3188	-0,6047	0,0736	-0,3542	-0,5956	0,3830	-0,5325	0,3100	-0,6244	0,5791
Aβ3pE-40	0,6001	0,7262	1,0000	-0,0211	-0,3628	0,3540	-0,4108	-0,5975	0,3737	-0,5488	0,2744	-0,5201	0,4168
Aβ1-40	0,1846	0,3188	-0,0211	1,0000	0,1237	0,0121	-0,1538	-0,1801	0,0739	-0,1145	0,3110	-0,2403	0,1376
Aβ11pE-42	-0,2843	-0,6047	-0,3628	0,1237	1,0000	0,4600	-0,2680	0,0316	-0,5610	0,5032	-0,3471	0,2458	-0,5091
Aβ11-42	0,3213	0,0736	0,3540	0,0121	0,4600	1,0000	-0,5360	-0,4336	-0,0398	-0,2386	-0,4854	-0,6010	-0,0627
Aβ5-42	-0,5671	-0,3542	-0,4108	-0,1538	-0,2680	-0,5360	1,0000	0,8347	0,2565	-0,0417	-0,1484	0,3218	-0,4686
Aβ4-42	-0,7566	-0,5956	-0,5975	-0,1801	0,0316	-0,4336	0,8347	1,0000	0,1157	0,0690	-0,2614	0,4956	-0,6078
Aβ4-42ox	0,3614	0,3830	0,3737	0,0739	-0,5610	-0,0398	0,2565	0,1157	1,0000	-0,8340	0,1588	-0,4992	0,3479
Aβ3pE-42	-0,5224	-0,5325	-0,5488	-0,1145	0,5032	-0,2386	-0,0417	0,0690	-0,8340	1,0000	0,0083	0,7361	-0,4093
Aβ2-42	0,2100	0,3100	0,2744	0,3110	-0,3471	-0,4854	-0,1484	-0,2614	0,1588	0,0083	1,0000	0,1912	0,4924
Aβ1-42	-0,6864	-0,6244	-0,5201	-0,2403	0,2458	-0,6010	0,3218	0,4956	-0,4992	0,7361	0,1912	1,0000	-0,4237
Aβ1-42ox	0,7288	0,5791	0,4168	0,1376	-0,5091	-0,0627	-0,4686	-0,6078	0,3479	-0,4093	0,4924	-0,4237	1,0000

The correlations are estimated by Row-wise method.

Correlation Probability

	Aβ9-40	Aβ4-40	Aβ3pE-40	Aβ1-40	Aβ11pE-42	Aβ11-42	Aβ5-42	Aβ4-42	Aβ4-42ox	Aβ3pE-42	Aβ2-42	Aβ1-42	Aβ1-42ox
Aβ9-40	<,0001	0,0006	0,0085	0,4634	0,2530	0,1936	0,0141	0,0003	0,1406	0,0261	0,4030	0,0017	0,0006
Aβ4-40	0,0006	<,0001	0,0006	0,1972	0,0078	0,7717	0,1493	0,0091	0,1167	0,0229	0,2106	0,0056	0,0118
Aβ3pE-40	0,0085	0,0006	<,0001	0,9337	0,1390	0,1495	0,0904	0,0088	0,1266	0,0183	0,2705	0,0269	0,0853
Aβ1-40	0,4634	0,1972	0,9337	<,0001	0,6249	0,9620	0,5424	0,4746	0,7708	0,6509	0,2091	0,3367	0,5860
Aβ11pE-42	0,2530	0,0078	0,1390	0,6249	<,0001	0,0547	0,2823	0,9011	0,0154	0,0333	0,1582	0,3255	0,0309
Aβ11-42	0,1936	0,7717	0,1495	0,9620	0,0547	<,0001	0,0218	0,0723	0,8754	0,3403	0,0411	0,0083	0,8048
Aβ5-42	0,0141	0,1493	0,0904	0,5424	0,2823	0,0218	<,0001	<,0001	0,3042	0,8694	0,5567	0,1929	0,0498
Aβ4-42	0,0003	0,0091	0,0088	0,4746	0,9011	0,0723	<,0001	<,0001	0,6476	0,7855	0,2948	0,0365	0,0075
Aβ4-42ox	0,1406	0,1167	0,1266	0,7708	0,0154	0,8754	0,3042	0,6476	<,0001	<,0001	0,5291	0,0349	0,1572
Aβ3pE-42	0,0261	0,0229	0,0183	0,6509	0,0333	0,3403	0,8694	0,7855	<,0001	<,0001	0,9738	0,0005	0,0917
Aβ2-42	0,4030	0,2106	0,2705	0,2091	0,1582	0,0411	0,5567	0,2948	0,5291	0,9738	<,0001	0,4472	0,0379
Aβ1-42	0,0017	0,0056	0,0269	0,3367	0,3255	0,0083	0,1929	0,0365	0,0349	0,0005	0,4472	<,0001	0,0798
Aβ1-42ox	0,0006	0,0118	0,0853	0,5860	0,0309	0,8048	0,0498	0,0075	0,1572	0,0917	0,0379	0,0798	<,0001

Scatterplot Matrix

Figure S2. Correlation analysis of amyloid peptides in sAD-Diffused Plaque

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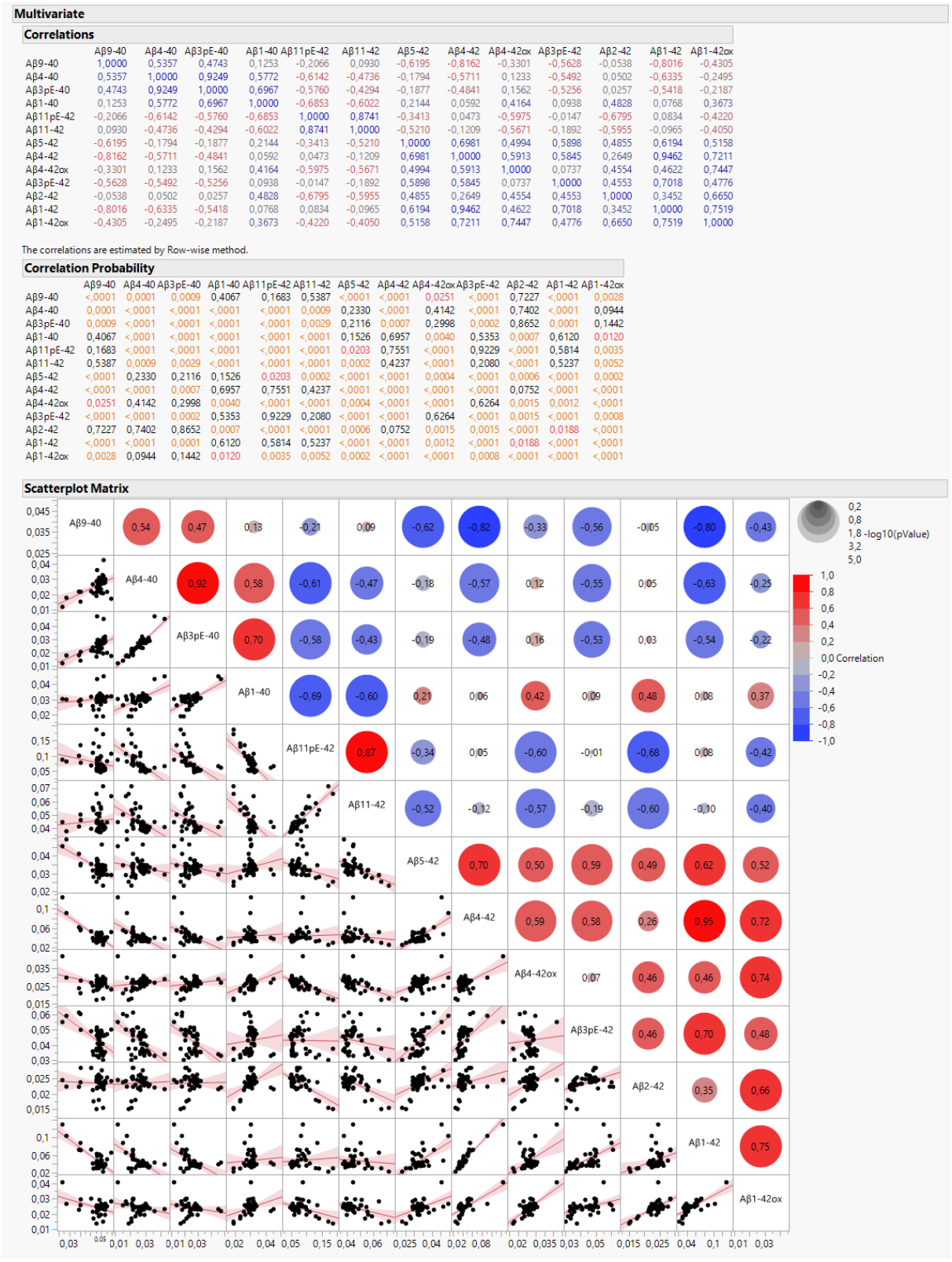

Figure S3. Correlation analysis of Aβ peptides in fAD-Core Plaque

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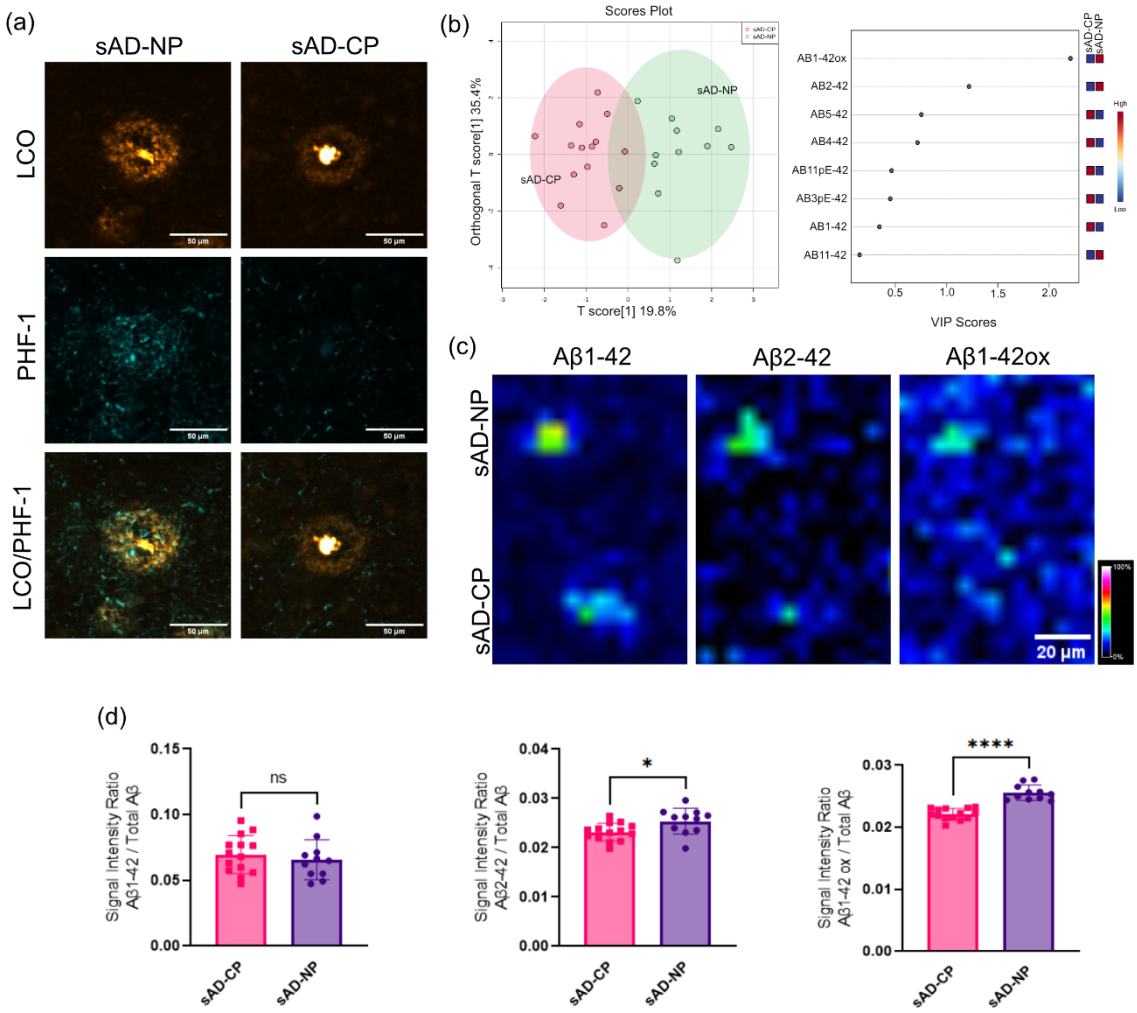

Figure S4. MALDI signatures of neuritic plaques. (a) Delineating plaque types by means of fluorescent microscopy using LCO amyloid probes (q and h FTAA) along with PHF-1 IHC. Neuritic plaques show higher levels of PHF-1 Tau positive neurites. (b) OPLS DA of MALDI signatures(OPLS model characteristics: R2X-0.256; R2Y-0.558; Q2-0.486). Here the VIP reveal elevated levels of Aβ2-42 and Aβ1-42ox in neuritic plaques as compared to cored plaques. (c, d) Bar graphs and single ion images. Scale bar: 30um. Intensity scale: rel. intensity in %.

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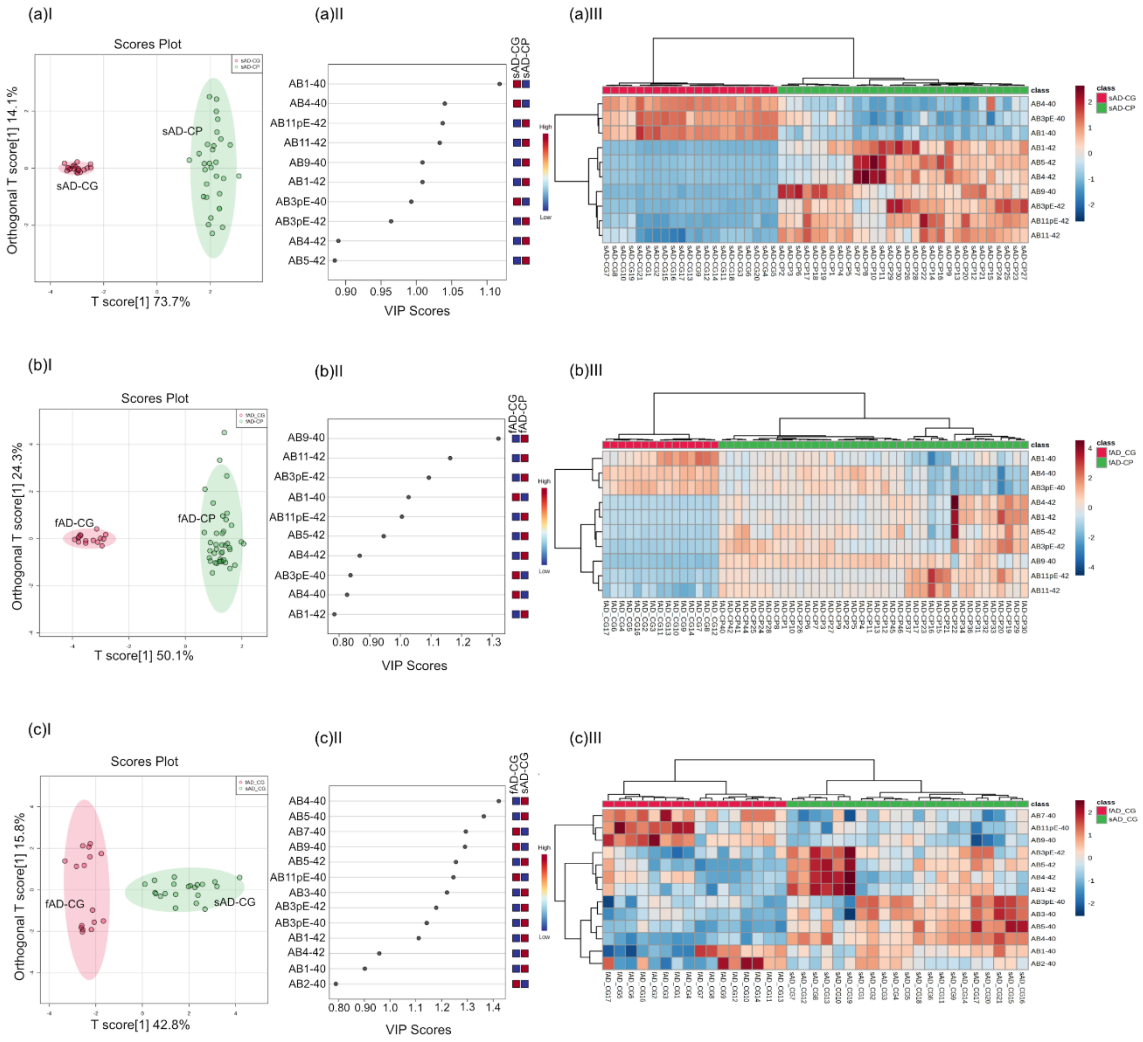

Figure S5. Comparative analysis of Aβ patterns in cored and coarse grain plaques. (a) sAD cored plaques vs coarse grain plaques (OPLS model characteristics: R2X-0.737; R2Y-0.948; Q2-0.947)(b) fAD cored plaques vs coarse grain plaques (OPLS model characteristics: R2X-0.501; R2Y-0.813; Q2-0.81) (c) sAD coarse grain plaques vs fAD coarse grain plaques (OPLS model characteristics: R2X-0.428; R2Y-0.852; Q2-0.835) (a-cI) OPLS-DA score plot. (a-cII) VIP scores. (a-cIII) HCA heatmap.

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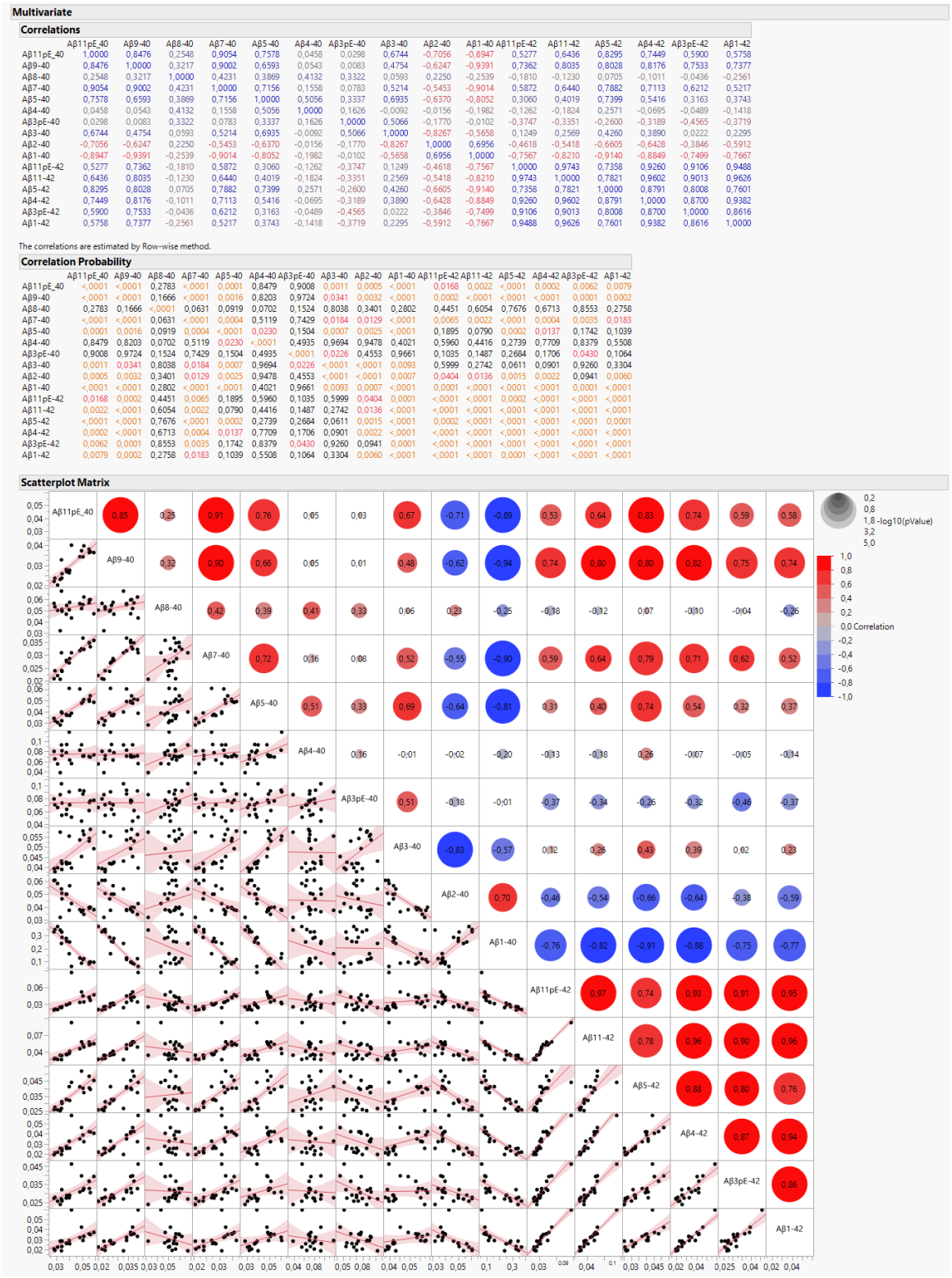

Figure S6. Correlation analysis of amyloid peptides in fAD-Coarse Grain

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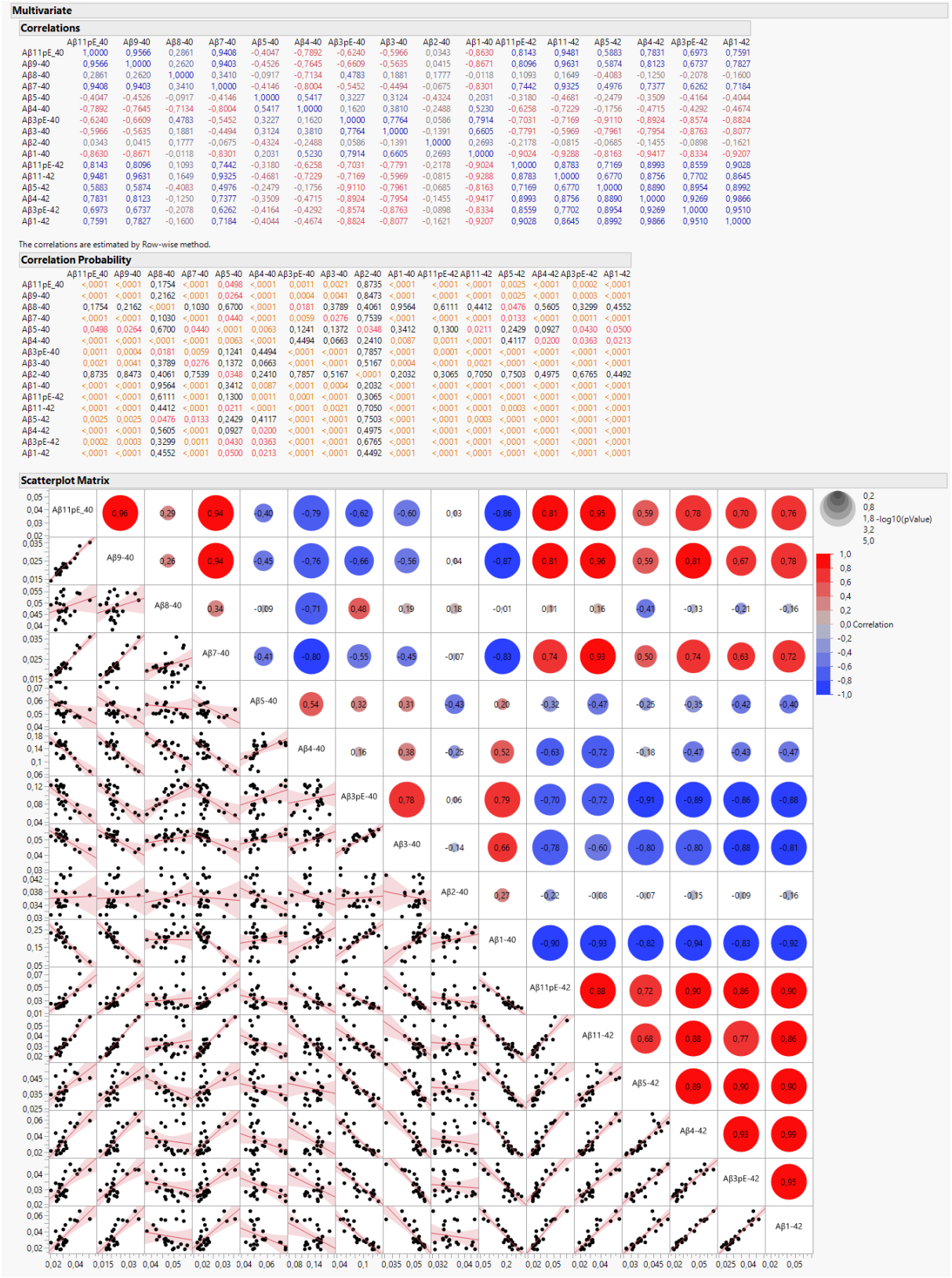

Figure S7. Correlation analysis of amyloid peptides in sAD-Coarse Grain