NIH National Institute on Aging
Turning Discovery Into Health

FNIH
Foundation for the National Institutes of Health

Integrative Metabolomics: From Target Discovery to Disease Sub-Classification

Alzheimer's Disease Metabolomics Consortium

NIA-AA Symposium
July 19-20, 2018 – Chicago, IL

Matthias Arnold

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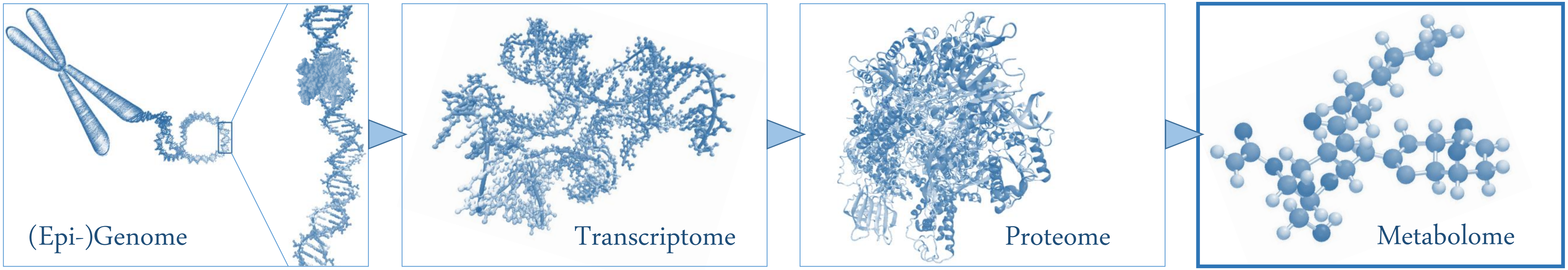
HelmholtzZentrum münchen
German Research Center for Environmental Health
Duke University School of Medicine

Metabolomics:
Readout of the physiological state of a biological system



Metabolism

- captures the combined output of upstream regulatory mechanisms
- tracks external influencers, including diet and environmental exposures
- is the molecular layer most closely linked to a phenotype or disease

Mission of ADMC: Metabolomics for AMP-AD and M²OVE-AD

METABOLOMICS DATA GENERATION

$N_{metabolites}$ ~ 1000

in up to 1600 subjects

ADNI
ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

ROS/MAP

- *Targeted metabolomics*
- *Targeted bile acid profiles*
- *Non-targeted broad metabolomics*
- *Non-targeted broad lipidomics*

DATA PROCESSING AND QC

Raw data

Primary QC
Remove poor quality samples
Remove structured missing data

Univariate QC
Samples: high % missing, non-fasting
Analytes: high CV, low ICC, high % missing

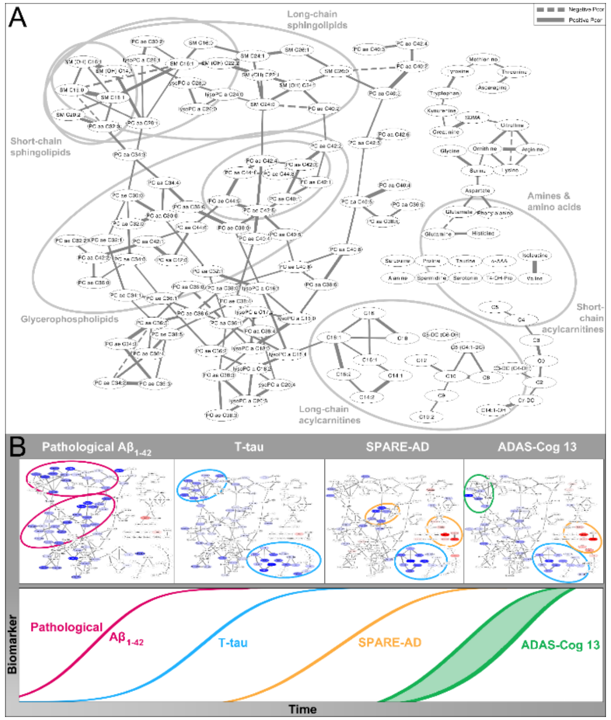
Data imputation

Data normalization

Multivariate outlier removal

Filtered, high quality data

DATA ANALYSIS



Toledo et al., Alz Dement, 2017

OPEN SCIENCE – SHARING DATA / CODE / RESULTS

AMP-AD Knowledge Portal

LONI

SCIENTIFIC DATA

PubMed

Integrative Metabolomics:
Target Discovery and Prioritization

ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE - **Target Discovery and Preclinical Validation Project**

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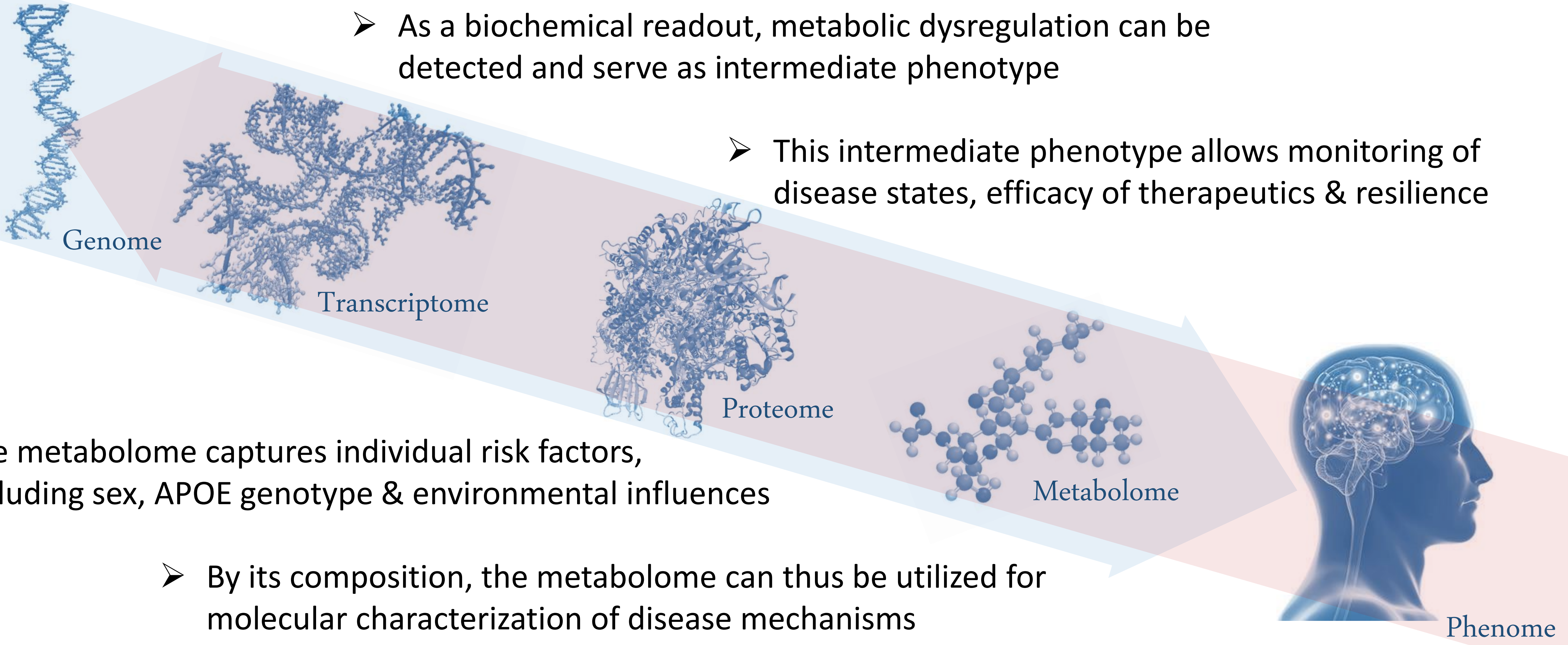
Target discovery:
Metabolite levels as intermediate phenotype of disease

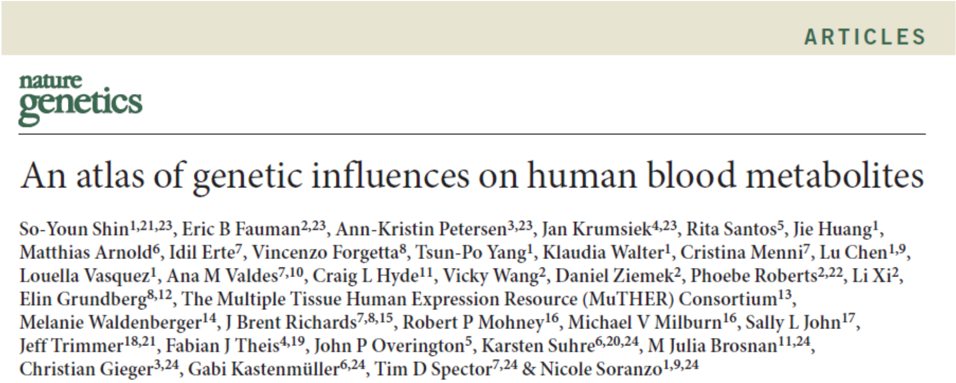
- As a biochemical readout, metabolic dysregulation can be detected and serve as intermediate phenotype
- This intermediate phenotype allows monitoring of disease states, efficacy of therapeutics & resilience



- The metabolome captures individual risk factors, including sex, APOE genotype & environmental influences
- By its composition, the metabolome can thus be utilized for molecular characterization of disease mechanisms

Target discovery: Linking metabolite levels to potential target genes

- Genome-wide association studies (GWAS) with metabolomics data
- Canonical, knowledge-based pathway information (e.g. enzymatic reactions) and data-driven metabolic pathway reconstruction approaches
- Multi-omics – link metabolomics data to proteomics and transcriptomics
- Big data integration from different population-based cohort studies

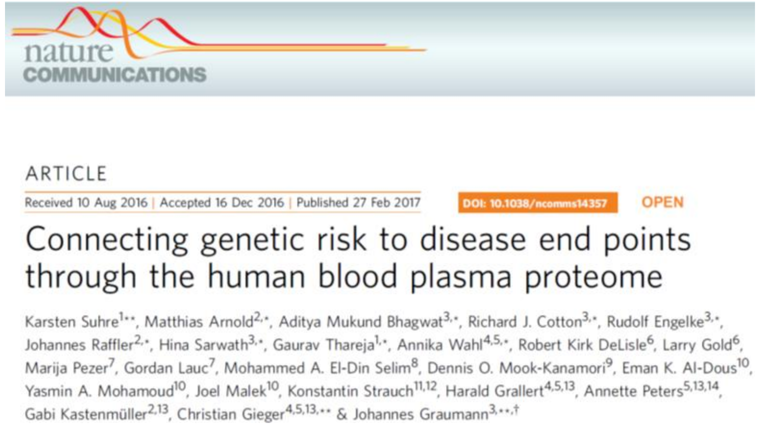


ARTICLES

nature genetics

An atlas of genetic influences on human blood metabolites

So-Youn Shin[1,21,23], Eric B Fauman[2,23], Ann-Kristin Petersen[3,23], Jan Krumsiek[4,23], Rita Santos[5], Jie Huang[1], Matthias Arnold[6], Idil Erte[7], Vincenzo Forgetta[8], Tsun-Po Yang[1], Klaudia Walter[1], Cristina Menni[7], Lu Chen[1,9], Louella Vasquez[1], Ana M Valdes[7,10], Craig L Hyde[11], Vicky Wang[2], Daniel Ziemek[2], Phoebe Roberts[2,22], Li Xi[2], Elin Grundberg[8,12], The Multiple Tissue Human Expression Resource (MuTHER) Consortium[13], Melanie Waldenberger[14], J Brent Richards[7,8,15], Robert P Mohney[16], Michael V Milburn[16], Sally L John[17], Jeff Trimmer[18,21], Fabian J Theis[4,19], John P Overington[5], Karsten Suhre[6,20,24], M Julia Brosnan[11,24], Christian Gieger[3,24], Gabi Kastenmüller[6,24], Tim D Spector[7,24] & Nicole Soranzo[1,9,24]



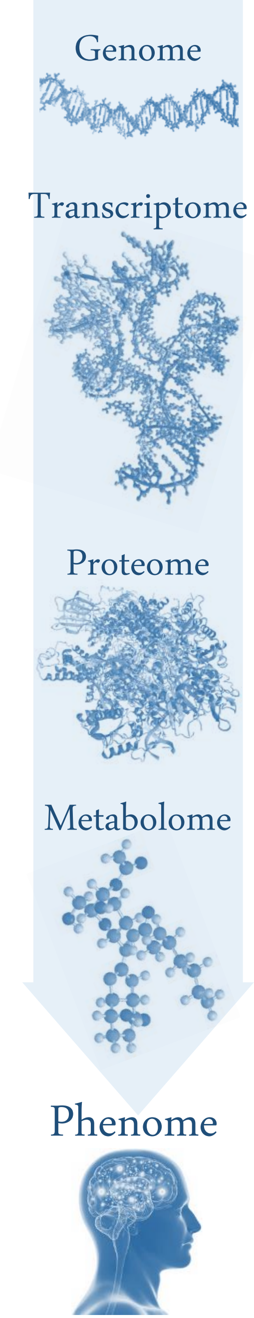
nature COMMUNICATIONS

ARTICLE

Received 10 Aug 2016 | Accepted 16 Dec 2016 | Published 27 Feb 2017 DOI: 10.1038/ncomms14357 OPEN

Connecting genetic risk to disease end points through the human blood plasma proteome

Karsten Suhre[1,**], Matthias Arnold[2,*], Aditya Mukund Bhagwat[3,*], Richard J. Cotton[3,*], Rudolf Engelke[3,*], Johannes Raffler[2,*], Hina Sarwath[3,*], Gaurav Thareja[1,*], Annika Wahl[4,5,*], Robert Kirk DeLisle[6], Larry Gold[6], Marija Pezer[7], Gordan Lauc[7], Mohammed A. El-Din Selim[8], Dennis O. Mook-Kanamori[9], Eman K. Al-Dous[10], Yasmin A. Mohamoud[10], Joel Malek[10], Konstantin Strauch[11,12], Harald Grallert[4,5,13], Annette Peters[5,13,14], Gabi Kastenmüller[2,13], Christian Gieger[4,5,13,**] & Johannes Graumann[3,**,†]



Target discovery & prioritization: Integrated molecular atlas of AD

Population-based data

- ➢ 20 million eQTL associations
- ➢ 20,000 pQTL associations
- ➢ 500,000 mQTL associations

SNiPA.org
single nucleotide polymorphisms annotator

Bioinformatics, 31(8), 2015, 1334–1336
doi: 10.1093/bioinformatics/btu779
Advance Access Publication Date: 26 November 2014
Applications Note
OXFORD

Databases and ontologies

SNiPA: an interactive, genetic variant-centered annotation browser

Matthias Arnold[1,†], Johannes Raffler[1,†], Arne Pfeufer[1], Karsten Suhre[1,2] and Gabi Kastenmüller[1,*]

Genetics of AD & associated markers

- ➢ IGAP / UKB 2018 – AD case/control
- ➢ IGAP 2017 – Age of onset
- ➢ Deming 2016/2017: CSF Aβ, t-/p-tau, CLU
- ➢ Beecham 2014: Neuropathological features

NIAGADS DATA RESOURCES NEWS GENOMICS DB

The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site

ADNI / ADMC data (about 1500 ADNI samples)

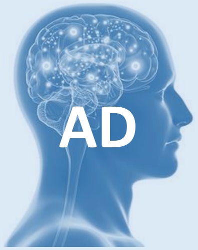
- ➢ Comprehensive coverage of markers for AD
- ➢ 157 metabolic traits and their associations to AD
- ➢ Genetic associations with metabolites & AD
- ➢ Metabolite/metabolite links (GGM)

ADMC

ADNI
Alzheimer's Disease Neuroimaging Initiative

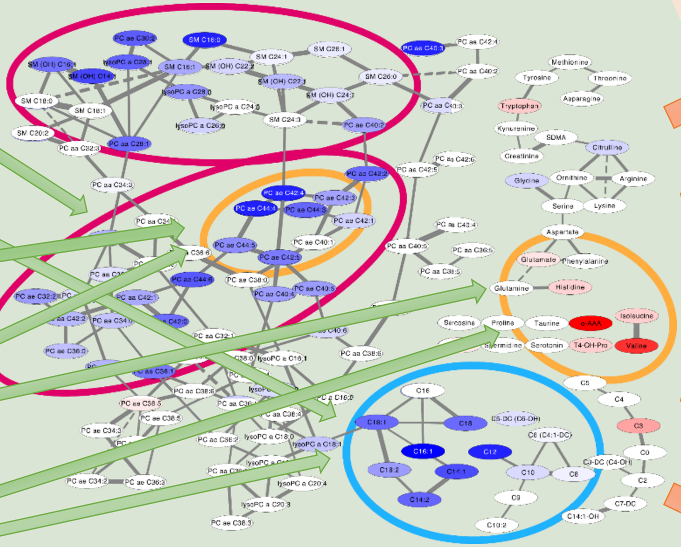
Kwangsik Nho (IU)

AD & Clinical / diagnostic markers

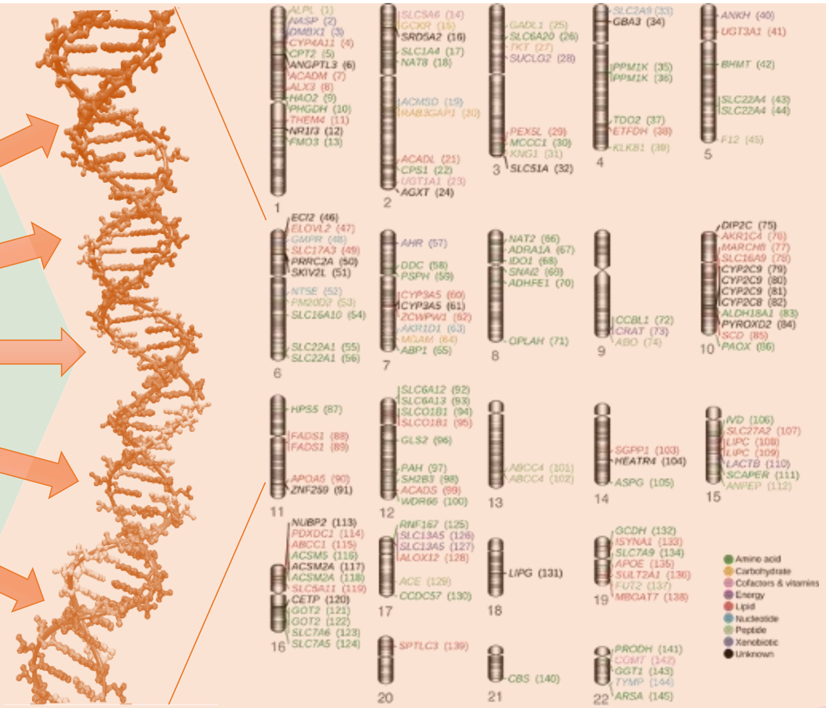


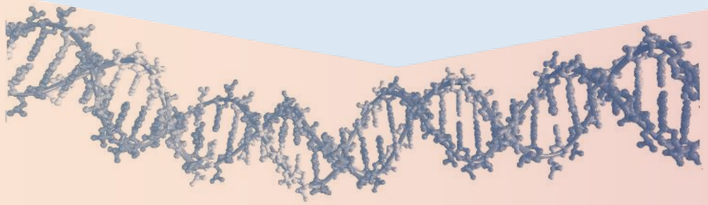
- CSF Aβ
- CSF t-/p-tau
- Functional PET
- MRI / atrophy
- Cognition

Intermediate metabolic phenotype



Metabolite quantitative trait loci



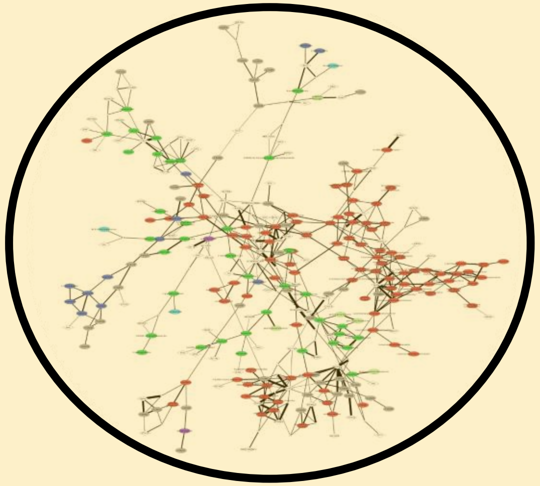


AD GWAS & Clinical marker QTLs

\+

Locus annotation

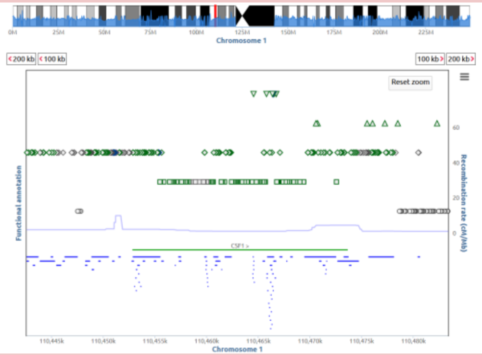
- *gene body*
- *regulatory*
- *eQTL*
- *pQTL*



Integrated molecular atlas

Locus annotation

- *gene body*
- *regulatory*
- *eQTL*
- *pQTL*



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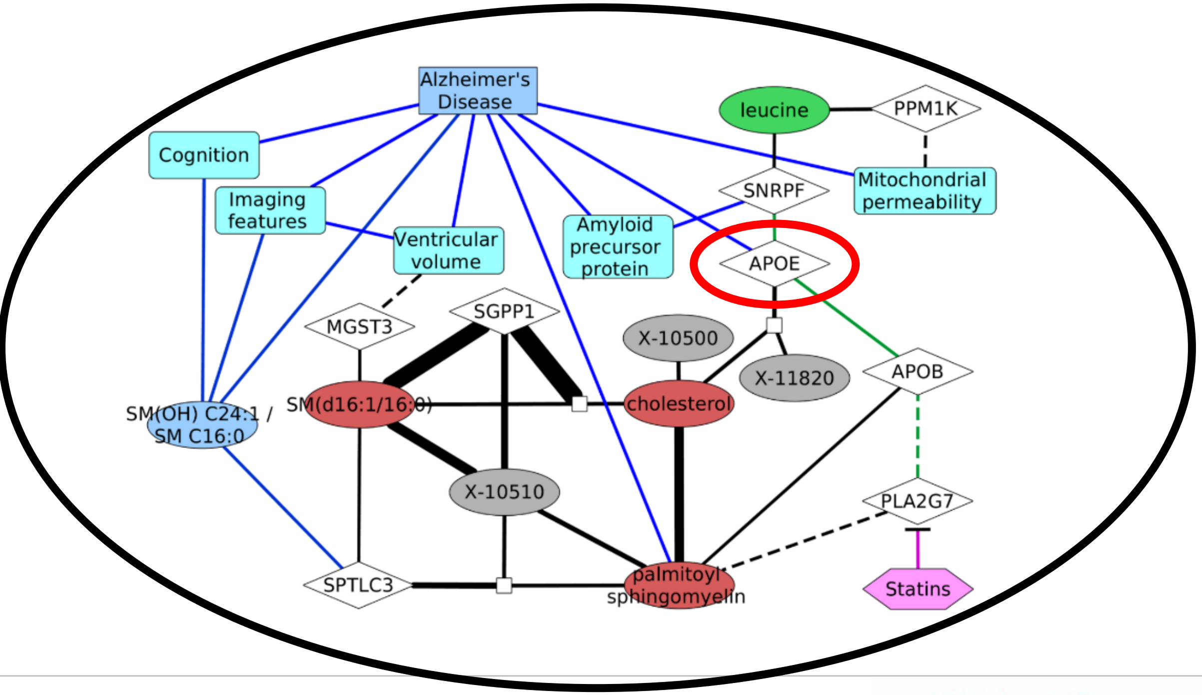
HelmholtzZentrum münchen
German Research Center for Environmental Health

Arnold et al., in preparation

Duke University School of Medicine

Integrated molecular atlas of AD: Genome-wide mapping of metabolic readouts

- ➢ Genetic map to AD / endophenotypes
- ➢ Integrated with metabolite QTLs
- ➢ Replication across large cohort studies
- ➢ All-in-one in the ADNI



SNP	CHR	BP	EA	UKB.AD	ADAS13_woAPOE4	ADNI_EF_woAPOE4	ADNI_MEM_woAPOE4	AV45_PiBROI_WC_woAPOE4	AV45_SUM_WC_woAPOE4	AVTOT_woAPOE4	CSF_ABeta_woAPOE4	CSF_pTauAbeta_woAPOE4	CSF_pTau_woAPOE4	CSF_TauAbeta_woAPOE4	CSF_Tau_woAPOE4	EntCtx_woAPOE4	FDG_AAL_GlCtx_woAPOE4	FDG_FDGROI_woAPOE4	HippVol_woAPOE4
rs2075649	19	45395330	G	-117	-2.73	NA	4.16	-6.3	-5.76	2.93	6.94	-7.81	-3.04	-7.88	-2.4	1.73	NA	NA	3.19
rs157584	19	45396899	C	-71.9	-1.69	1.53	3.09	-3.26	-2.82	2.34	1.98	-2.95	-1.84	-3.05	-1.74	1.45	NA	1.63	2.84
rs77301115	19	45396973	A	207	6.19	-2.69	-5.53	7.03	7.6	-3.77	-16.4	17	5.82	17.2	4.48	-2.65	NA	-1.73	-3.84
rs1160983	19	45397229	A	-32	-3.36	2.83	3.77	-1.79	-1.78	2.74	4.41	-4.95	-2.26	-5.11	-1.98	NA	NA	1.67	1.71
rs112849259	19	45397307	T	205	6.19	-2.69	-5.53	7.03	7.6	-3.77	-16.4	17	5.82	17.2	4.48	-2.65	NA	-1.73	-3.84
rs157585	19	45397512	C	-89.1	-2.59	2.05	4.35	-4.12	-3.54	3.16	2.66	-3.81	-2.23	-3.95	-2.08	2.24	1.36	2.52	4.32
rs116881820	19	45397952	C	205	6.1	-2.59	-5.46	7.03	7.6	-3.77	-16.9	17.5	5.95	17.7	4.56	-2.42	NA	-1.73	-3.7
rs157588	19	45398264	T	-89	-2.59	2.01	4.35	-4.19	-3.62	3.18	2.71	-3.87	-2.24	-4	-2.09	2.21	1.38	2.53	4.33
rs11668327	19	45398633	C	-106	-4.39	4.09	4.49	-3.26	-2.93	2.89	11.6	-12.1	-4.54	-12	-3.41	NA	NA	1.75	1.93
rs157590	19	45398716	C	-94.4	-2.93	2.12	4.88	-4.5	-3.94	3.64	3.05	-4.16	-2.27	-4.31	-2.09	2.34	1.31	2.5	4.55
rs79398853	19	45398785	T	206	6.19	-2.69	-5.53	7.03	7.6	-3.77	-16.4	17	5.82	17.2	4.48	-2.65	NA	-1.73	-3.84
rs2238681	19	45398817	T	-151	-4.35	2.2	6.28	-7.89	-7.37	4.37	8.43	-10.3	-4.49	-10.5	-3.79	3.52	1.3	2.43	5.86
rs75687619	19	45399344	T	206	6.19	-2.69	-5.53	7.03	7.6	-3.77	-16.4	17	5.82	17.2	4.48	-2.65	NA	-1.73	-3.84
rs76366838	19	45399896	A	205	6.19	-2.69	-5.53	7.03	7.6	-3.77	-16.4	17	5.82	17.2	4.48	-2.65	NA	-1.73	-3.84
rs114536010	19	45400725	T	206	6.19	-2.69	-5.53	7.03	7.6	-3.77	-16.4	17	5.82	17.2	4.48	-2.65	NA	-1.73	-3.84
rs61679753	19	45400747	A	-31.7	-3.55	3.27	3.98	-1.79	-1.78	2.98	4.26	-4.73	-2.13	-4.9	-1.89	NA	NA	1.67	1.48
rs8106922	19	45401666	G	-158	-4.39	2.05	6.5	-8.25	-7.7	4.63	9.4	-11.5	-5.05	-11.8	-4.28	3.67	NA	2.26	6.62
rs118170342	19	45401868	C	146	4.7	-2.11	-4.93	6.13	6.21	-3.92	-14.2	15.3	5.62	15.3	4.23	-2.28	NA	NA	-4.25
rs34878901	19	45402477	T	-158	-4.37	2	6.47	-9.02	-8.34	4.48	9.12	-11.4	-5.13	-11.6	-4.32	3.82	NA	2.45	6.76
rs115881343	19	45403216	T	222	5.84	-2.59	-5.62	8.14	8.61	-4.04	-17.2	18.5	6.7	18.7	5.23	-2.6	NA	-1.7	-3.83
rs1160985	19	45403412	T	-210	-6.96	4.18	9.64	-10.9	-10.4	6.78	13.2	-16.3	-7.22	-16.8	-6.16	4.95	2.2	4.06	8.96
rs760136	19	45403858	G	-211	-6.96	4.18	9.64	-10.9	-10.4	6.78	13.2	-16.3	-7.22	-16.8	-6.16	4.95	2.2	4.06	8.96
rs741780	19	45404431	C	-212	-6.96	4.18	9.64	-10.9	-10.4	6.78	13.2	-16.3	-7.22	-16.8	-6.16	4.95	2.2	4.06	8.96
rs405697	19	45404691	A	-97	-3.18	1.52	3.98	-2.85	-3.87	3.51	6.77	-8.55	-4.63	-8.63	-3.94	NA	1.56	1.81	2.06
rs112019714	19	45404857	C	224	5.34	-2.39	-5.31	8.14	8.61	-3.82	-17.2	18.5	6.7	18.7	5.23	-2.42	NA	-1.57	-3.79
rs1038025	19	45404972	C	-212	-6.67	4.05	9.41	-10.9	-10.4	6.61	13.2	-16.3	-7.22	-16.8	-6.16	4.81	2.23	3.94	8.9
rs1038026	19	45405062	G	-211	-6.67	4.05	9.41	-10.9	-10.4	6.61	13.2	-16.3	-7.22	-16.8	-6.16	4.81	2.23	3.94	8.9
rs1305062	19	45405521	C	-159	-4.37	2	6.47	-9.02	-8.34	4.48	9.12	-11.4	-5.13	-11.6	-4.32	3.82	NA	2.45	6.76
rs7259620	19	45407788	A	-213	-6.65	4.15	9.62	-10.5	-10	6.85	13.4	-16.5	-7.23	-17	-6.18	4.71	2.56	4.28	8.68
rs405509	19	45408836	G	-144	-3.2	2.68	4.9	-6.42	-5.79	3.58	4.97	-6.65	-3.47	-6.75	-3	3.07	1.54	3.1	5.69
rs440446	19	45409167	C	-142	-7.06	3.94	7.81	-4.56	-5.51	5.62	13.5	-15.8	-7.27	-16	-6.05	NA	2.45	2.89	3.82

SNP	ADNI.Met.C10.2	ADNI.Met.C3.DC..C4.OH.	ADNI.Met.C3	ADNI.Met.C4	ADNI.Met.C5.DC..C6.OH.	ADNI.Met.C5	ADNI.Met.Creatinine	ADNI.Met.Orn	ADNI.Met.PC.aa.C38.3	ADNI.Met.Glu	ADNI.Met.Ile	ADNI.Met.Kynurenine	ADNI.Met.Ala	ADNI.Met.Phe	ADNI.Met.Pro	ADNI.Met.Val
rs2075649	2.1	1.64	NA	1.95	NA	NA	1.46	NA	NA	NA	1.52	NA	NA	NA	2.42	NA
rs157584	2.37	NA	NA	2.28	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs77301115	NA	NA	NA	NA	NA	NA	NA	-1.32	-2.63	-2.25	-1.92	-1.69	-2.01	-1.79	-1.86	-1.79
rs1160983	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs112849259	NA	NA	NA	NA	NA	NA	NA	-1.32	-2.63	-2.25	-1.92	-1.69	-2.01	-1.79	-1.86	-1.79
rs157585	2.23	NA	NA	1.86	1.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs116881820	NA	NA	NA	NA	NA	NA	NA	NA	-2.78	-2.22	-1.91	-1.65	-1.93	-1.79	-1.78	-1.81
rs157588	2.27	NA	NA	1.91	1.55	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs11668327	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.52	NA	NA	NA	NA
rs157590	2.37	NA	NA	1.8	1.47	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs79398853	NA	NA	NA	NA	NA	NA	NA	-1.32	-2.63	-2.25	-1.92	-1.69	-2.01	-1.79	-1.86	-1.79
rs2238681	2.44	1.63	NA	1.33	NA	NA	NA	NA	NA	NA	1.37	NA	NA	NA	1.56	NA
rs75687619	NA	NA	NA	NA	NA	NA	NA	-1.32	-2.63	-2.25	-1.92	-1.69	-2.01	-1.79	-1.86	-1.79
rs76366838	NA	NA	NA	NA	NA	NA	NA	-1.32	-2.63	-2.25	-1.92	-1.69	-2.01	-1.79	-1.86	-1.79
rs114536010	NA	NA	NA	NA	NA	NA	NA	-1.32	-2.63	-2.25	-1.92	-1.69	-2.01	-1.79	-1.86	-1.79
rs61679753	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs8106922	2.42	1.59	NA	1.34	NA	NA	NA	NA	NA	NA	1.4	NA	NA	NA	1.45	NA
rs118170342	NA	NA	NA	NA	NA	NA	NA	NA	-2.71	-2.13	-2.53	-2.03	-1.5	-1.9	NA	-1.95
rs34878901	2.32	1.74	NA	1.45	NA	NA	1.33	NA	NA	NA	1.48	NA	NA	NA	1.48	NA
rs115881343	NA	NA	NA	NA	NA	NA	NA	-1.45	-2.08	-2.14	-2.11	-1.83	-1.83	-1.73	-1.77	-1.96
rs1160985	2.25	1.88	1.39	2.17	NA	1.44	1.55	NA	NA	NA	2.02	NA	NA	NA	1.62	1.52
rs760136	2.25	1.88	1.39	2.17	NA	1.44	1.55	NA	NA	NA	2.02	NA	NA	NA	1.62	1.52
rs741780	2.25	1.88	1.39	2.17	NA	1.44	1.55	NA	NA	NA	2.02	NA	NA	NA	1.62	1.52
rs405697	-2.38	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs112019714	NA	NA	NA	NA	NA	NA	NA	-1.51	-2.01	-2.12	-2.05	-1.76	-1.92	-1.63	-1.83	-1.8
rs1038025	2.27	1.88	1.38	2.2	NA	1.45	1.57	NA	NA	NA	1.98	NA	NA	NA	1.64	1.44
rs1038026	2.27	1.88	1.38	2.2	NA	1.45	1.57	NA	NA	NA	1.98	NA	NA	NA	1.64	1.44
rs1305062	2.32	1.74	NA	1.45	NA	NA	1.33	NA	NA	NA	1.48	NA	NA	NA	1.48	NA
rs7259620	2.32	1.6	NA	2.09	NA	1.38	2.05	NA	NA	NA	1.83	NA	NA	NA	1.73	NA
rs405509	2.41	NA	NA	1.87	1.67	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs440446	-1.63	NA	NA	NA	NA	NA	NA	NA	2.29	1.39	NA	NA	NA	1.42	NA	NA

AD association (UK biobank study)

ADNI AD endophenotypes

ADNI metabolomics

Integrated molecular atlas of AD: Metabotypes – genetics mirroring AD associations

MS4A2

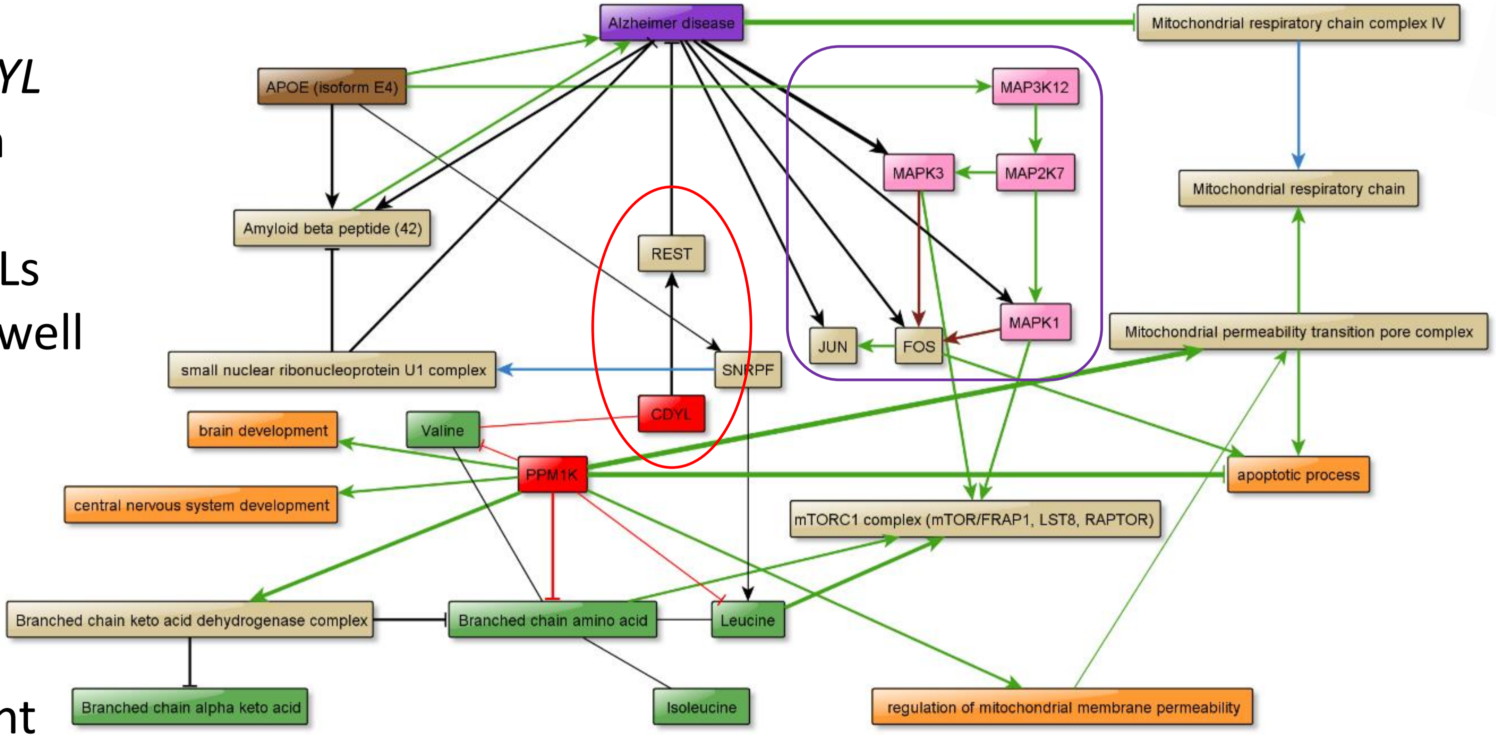
SNP	CHROMOSOME	POSITION	EA.UKB	UKB.AD	EA.ADNI	ADAS-Cog. 13	Entorhinal Cortex	Hippocampus	SM C26:0	SM (OH) C24:1	Histidine	Isoleucine	Valine
rs580064	11	59869119	C	-7.7211012	C	-1.7929	1.84375	1.73447	1.31025	1.82391	1.88207	2.23055	2.68027
rs580817	11	59869090	G	-9.392171	G	-1.72216	1.42366	1.39892	1.53536	1.94962	2.58104	2.30839	2.83327
rs487997	11	59871604	C	-9.5962717	C	-1.72216	1.42366	1.39892	1.53536	1.94962	2.58104	2.30839	2.83327
rs574704	11	59867913	G	-9.416886	G	-1.71153	1.41657	1.39502	1.51513	1.93892	2.54668	2.3934	2.9307
rs521952	11	59870196	C	-9.5387986	C	-1.71153	1.41657	1.39502	1.51513	1.93892	2.54668	2.3934	2.9307
rs516478	11	59870788	A	-9.5150729	A	-1.71153	1.41657	1.39502	1.51513	1.93892	2.54668	2.3934	2.9307
rs1786137	11	59873448	C	-9.5177706	C	-1.71153	1.41657	1.39502	1.51513	1.93892	2.54668	2.3934	2.9307
rs558788	11	59852078	G	-10.146167	G	NA	NA	1.33734	NA	1.45445	NA	1.5447	1.31921
rs1813217	11	59872498	C	-10.606488	C	-1.65956	1.31372	1.53462	1.35704	1.70071	2.72769	2.08066	2.034
rs11230147	11	59877394	T	-10.766301	T	-1.61672	NA	1.51784	1.35704	1.70071	2.72769	2.08066	2.034
rs4939311	11	59877967	T	-10.675478	T	-1.61672	NA	1.51784	1.35704	1.70071	2.72769	2.08066	2.034
rs1125357	11	59885493	C	-10.541011	C	-1.5516	NA	1.34056	1.3919	1.7602	2.80162	2.06722	2.06419
rs2855017	11	59866309	T	-10.540437	T	-1.57757	NA	1.51004	1.37428	1.68888	2.76675	2.1303	2.06982
rs17528859	11	59867379	C	-10.661921	C	-1.57757	NA	1.51004	1.37428	1.68888	2.76675	2.1303	2.06982
rs2583471	11	59861814	A	-10.374859	A	-1.54016	NA	1.55549	1.39469	1.81079	2.78516	2.19484	2.10095
rs2070970	11	59861983	T	-10.419124	T	-1.54016	NA	1.55549	1.39469	1.81079	2.78516	2.19484	2.10095
rs2847664	11	59858497	A	-10.063463	A	-1.5071	NA	1.50906	1.39094	1.803	2.78357	2.19314	2.1053
rs2847668	11	59862261	T	-10.398245	T	-1.54485	NA	1.56655	1.42516	1.81987	2.83803	2.22446	2.10763
rs2847663	11	59858036	G	-10.065236	G	-1.47886	NA	1.47965	1.39469	1.82857	2.77211	2.24154	2.12633
rs2583476	11	59857581	A	-9.8880136	A	-1.4537	NA	1.57594	1.45149	1.87095	2.68256	2.24397	2.12668
rs2847666	11	59859576	G	-9.7916411	G	-1.46674	NA	1.6187	NA	1.68256	3.00432	2.27638	2.15945
rs2847667	11	59859609	T	-9.7900287	T	-1.46674	NA	1.6187	NA	1.68256	3.00432	2.27638	2.15945
rs2847655	11	59865671	C	-10.072354	C	-1.45284	NA	1.60995	NA	1.47057	2.88941	2.31336	2.21042
rs555635	11	59877143	C	-9.4811187	C	-1.67861	1.35813	1.38289	1.53536	1.94962	2.58104	2.30839	2.83327
rs563803	11	59878001	A	-9.6684014	A	-1.67861	1.35813	1.38289	1.53536	1.94962	2.58104	2.30839	2.83327
rs540170	11	59880038	T	-9.6528819	T	-1.67861	1.35813	1.38289	1.53536	1.94962	2.58104	2.30839	2.83327
rs574695	11	59881524	C	-9.436675	C	-1.67861	1.35813	1.38289	1.53536	1.94962	2.58104	2.30839	2.83327
rs1441586	11	59856028	C	-8.5691433	C	-1.44069	NA	NA	1.46483	2.06313	2.40682	2.31731	2.84103
rs502419	11	59866175	A	-9.2976439	A	-1.63884	1.34843	1.37551	1.55284	1.93629	2.61816	2.35952	2.87354
rs581133	11	59882306	G	-9.6012043	G	-1.65777	NA	NA	1.55736	1.99012	2.58104	2.37376	2.92775
rs512495	11	59876036	G	-9.5019367	G	-1.66817	1.35115	1.37914	1.51513	1.93892	2.54668	2.3934	2.9307
rs514266	11	59877697	C	-9.6802426	C	-1.66817	1.35115	1.37914	1.51513	1.93892	2.54668	2.3934	2.9307
rs574798	11	59881561	G	-9.600359	G	-1.66817	1.35115	1.37914	1.51513	1.93892	2.54668	2.3934	2.9307
rs556917	11	59858712	T	-8.9302511	T	-1.57284	1.39686	1.39115	1.57971	2.09464	2.62746	2.47978	2.93704
rs502581	11	59860178	T	-9.3011995	T	-1.57284	1.39686	1.39115	1.57971	2.09464	2.62746	2.47978	2.93704
rs1303615	11	59885120	T	-9.5065769	T	-1.54031	NA	NA	1.62912	2.07381	2.63601	2.43498	3.00749
rs564912	11	59885888	T	-9.5600256	T	-1.54242	1.31939	NA	1.58603	2.0215	2.60119	2.45494	3.01068
rs1303621	11	59890674	C	-9.5622631	C	-1.54242	1.31939	NA	1.58603	2.0215	2.60119	2.45494	3.01068

	ADAS-Cog. 13	Entorhinal Cortex	Hippocampus
SM C26:0	0.200112	**0.002221**	0.203232
SM (OH) C24:1	0.095847	**8.76E-05**	0.074616
Histidine	0.14245	0.106239	**0.010791**
Isoleucine	**0.004752**	**0.008568**	0.05895
Valine	**0.003687**	**0.0197**	**0.004324**

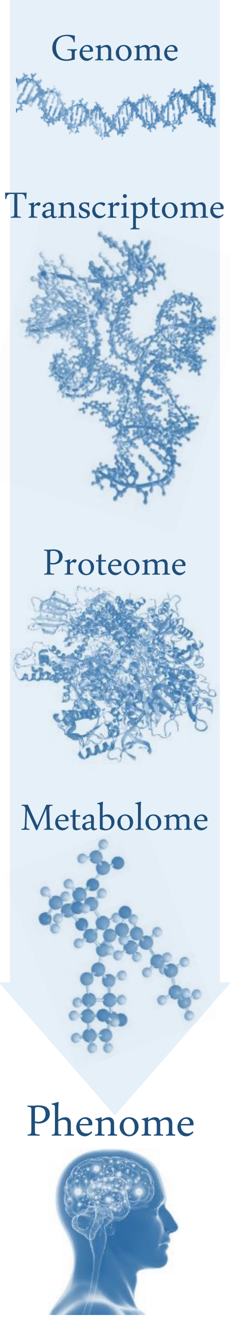
- Genetically influenced metabotype shows the same effect directions as metabotype-trait associations
- Metabolite associations are more significant (> 1 order of magnitude)

Target discovery & prioritization: Unbiased metabolomics leads to discovery of CDYL

- We observed valine levels to be decreased in AD / associated with cognition
- GWAS for valine yielded the *CDYL* locus as top-ranking association
- Our data lists hippocampal eQTLs for *CDYL* for the same locus, as well as additional QTLs
- CDYL is a co-factor of REST
- *REST* and binding partners have been reported to have significant neuroprotective effects (e.g. *Lu et al., Nature, 2014*)

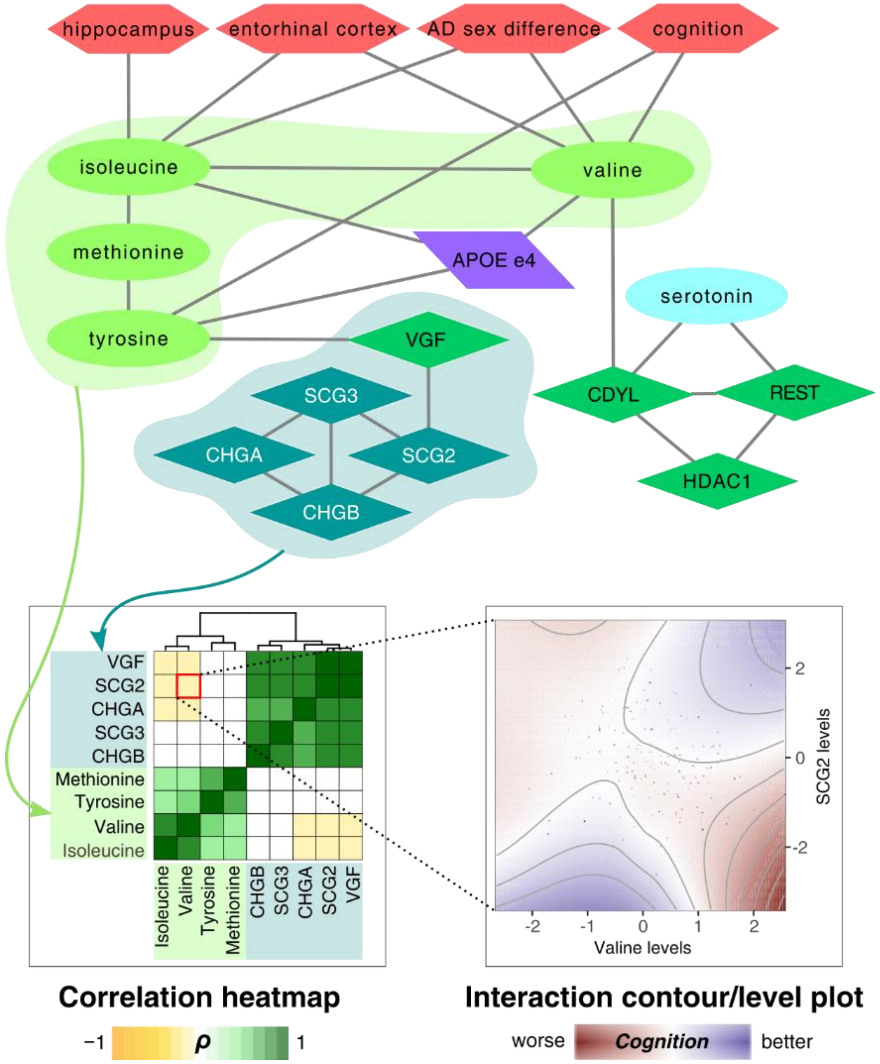


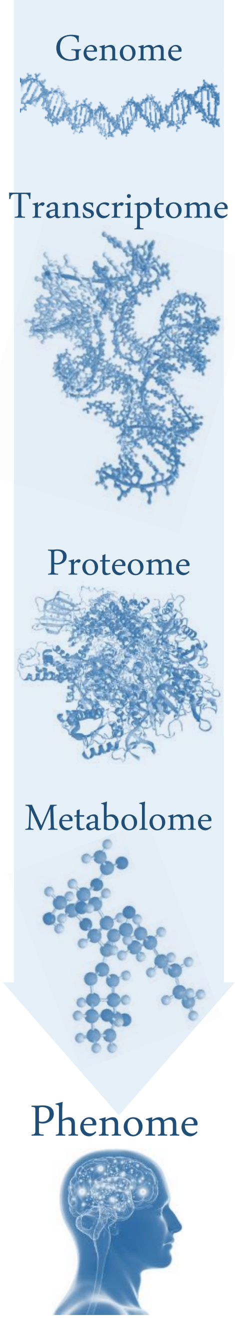
CIDeR – curated disease networks
Lechner et al., Genome Biol, 2012



Target discovery & prioritization: Multi-omics to strengthen confidence in targets

- CDYL regulates enzymes in pathways for valine degradation
- Closely linked amino acids are associated with genetic variants in *VGF*
- *VGF* interacts / is co-regulated with granins, neuroendocrine secretory granule proteins
- Interaction analysis of AA levels and CSF granin/VGF levels revealed significant interaction effects on cognition
- Literature shows that REST regulates some granins → disturbed REST binding specificity



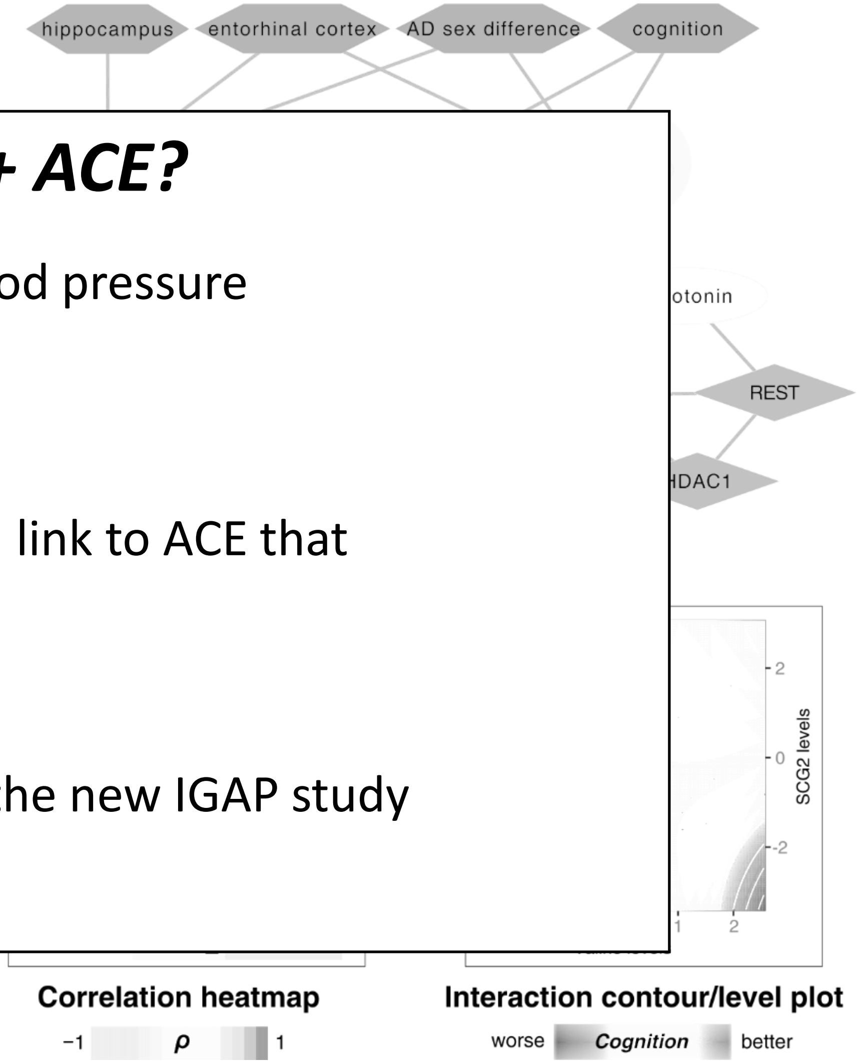


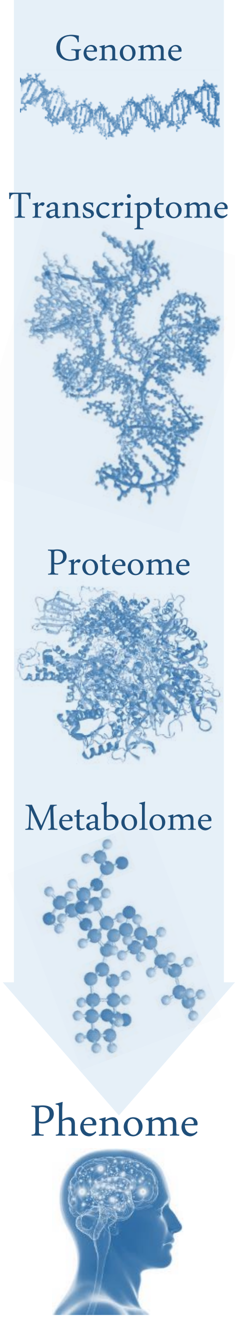
Target discovery & prioritization: Integrated hypotheses for sets of targets

- CDYL regulates enzymes in pathways for valine degrad
- Closely linked with genetic v
- *VGF* interacts neuroendocri
- Interaction an granin/VGF le interaction ef
- Literature sho granins → disturbed REST binding specificity

CDYL – REST – HDAC1 – VGF + ***ACE?***

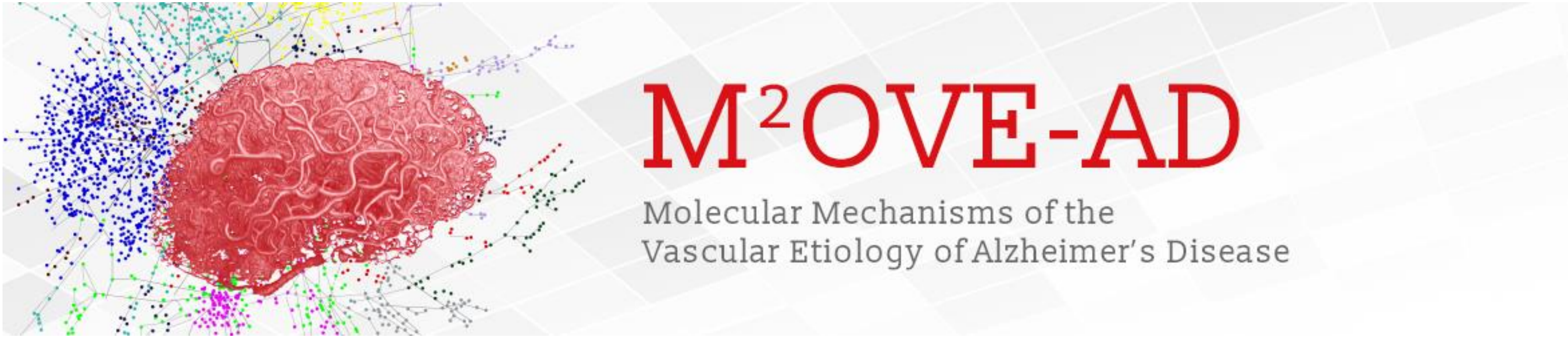
- The CDYL locus is associated with blood pressure
- It is also associated with dipeptides
- We hypothesized that there may be a link to ACE that
  - regulates blood pressure and
  - functions as dipeptidase
- ACE detected as genetic risk gene in the new IGAP study





Arnold et al., in preparation

Integrative Metabolomics:
Disease Sub-Classification for Precision Medicine



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Sex-differences in the blood metabolome

KORA F4 (German population-based cohort)

- Non-targeted metabolomics platform (Metabolon):
  n ~ 1800; 507 metabolites (different pw)
  Krumsiek et al., Metabolomics 2015

  => **180 of 507 metabolites** show significant differences

- Targeted metabolomics platform (Biocrates p150):
  n ~ 3000; 131 metabolites (mostly lipids & amino acids)
  Mittelstrass et al., PloS Genetics, 2011

  => **102 of 131 metabolites** show significant differences

Metabolomics (2015) 11:1815–1833
DOI 10.1007/s11306-015-0829-0

ORIGINAL ARTICLE

Gender-specific pathway differences in the human serum metabolome

Jan Krumsiek[1,2] · Kirstin Mittelstrass[3,4] · Kieu Trinh Do[1] · Ferdinand Stückler[1] · Janina Ried[5] · Jerzy Adamski[2,6,7] · Annette Peters[2,4,8] · Thomas Illig[9] · Florian Kronenberg[10] · Nele Friedrich[11,12] · Matthias Nauck[11,12] · Maik Pietzner[11,12] · Dennis O. Mook-Kanamori[13,14,15] · Karsten Suhre[15,16] · Christian Gieger[3,4] · Harald Grallert[3,4] · Fabian J. Theis[1,17] · Gabi Kastenmüller[2,16]

OPEN ACCESS Freely available online PLoS GENETICS

Discovery of Sexual Dimorphisms in Metabolic and Genetic Biomarkers

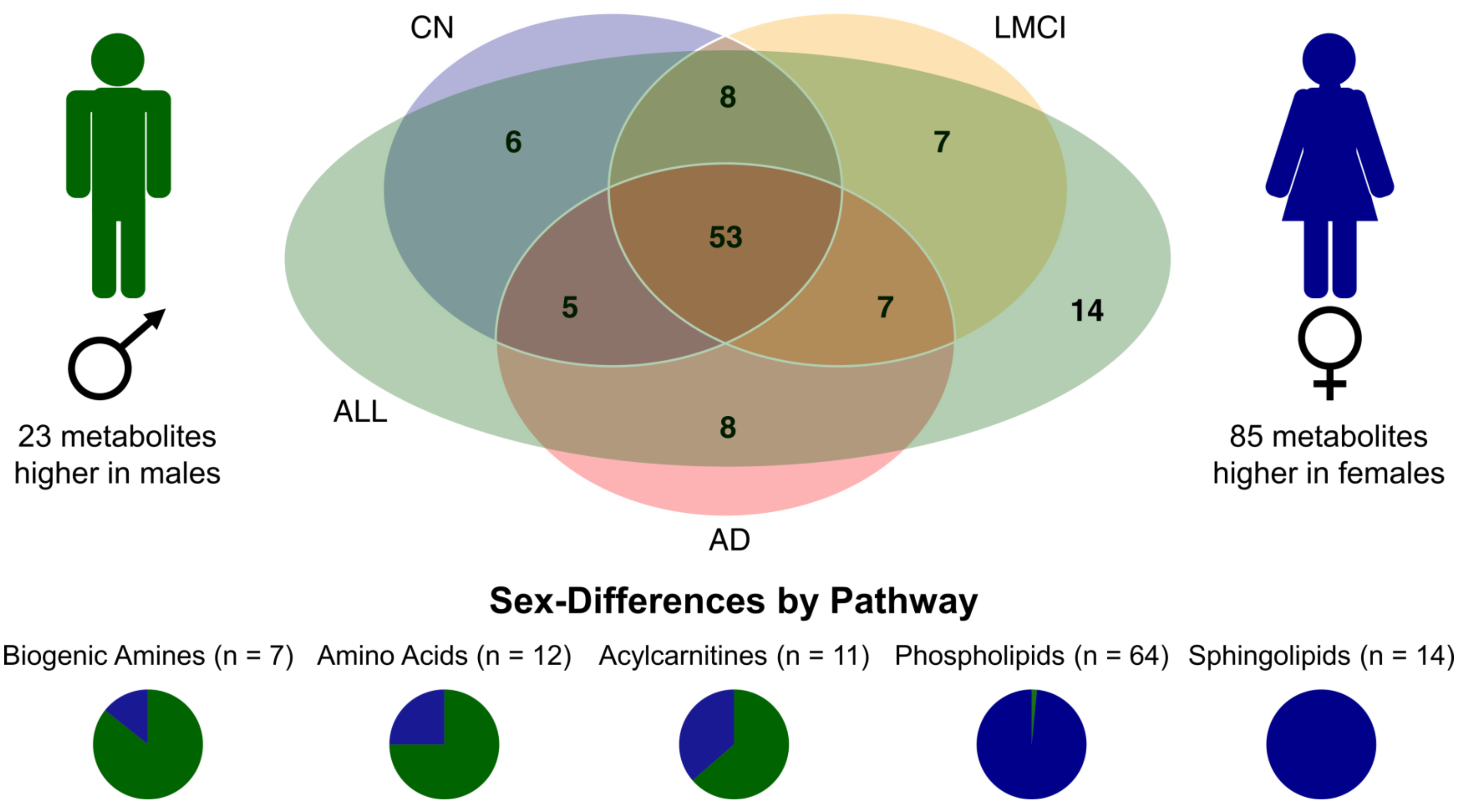
Kirstin Mittelstrass[1,9], Janina S. Ried[2,9], Zhonghao Yu[1,9], Jan Krumsiek[3], Christian Gieger[2], Cornelia Prehn[4], Werner Roemisch-Margl[3], Alexey Polonikov[5], Annette Peters[6], Fabian J. Theis[3], Thomas Meitinger[7,8], Florian Kronenberg[9], Stephan Weidinger[10], Heinz Erich Wichmann[11,12,13], Karsten Suhre[3,14,15], Rui Wang-Sattler[1], Jerzy Adamski[4,16¶*], Thomas Illig[1¶*]

... many other studies showed the same trends

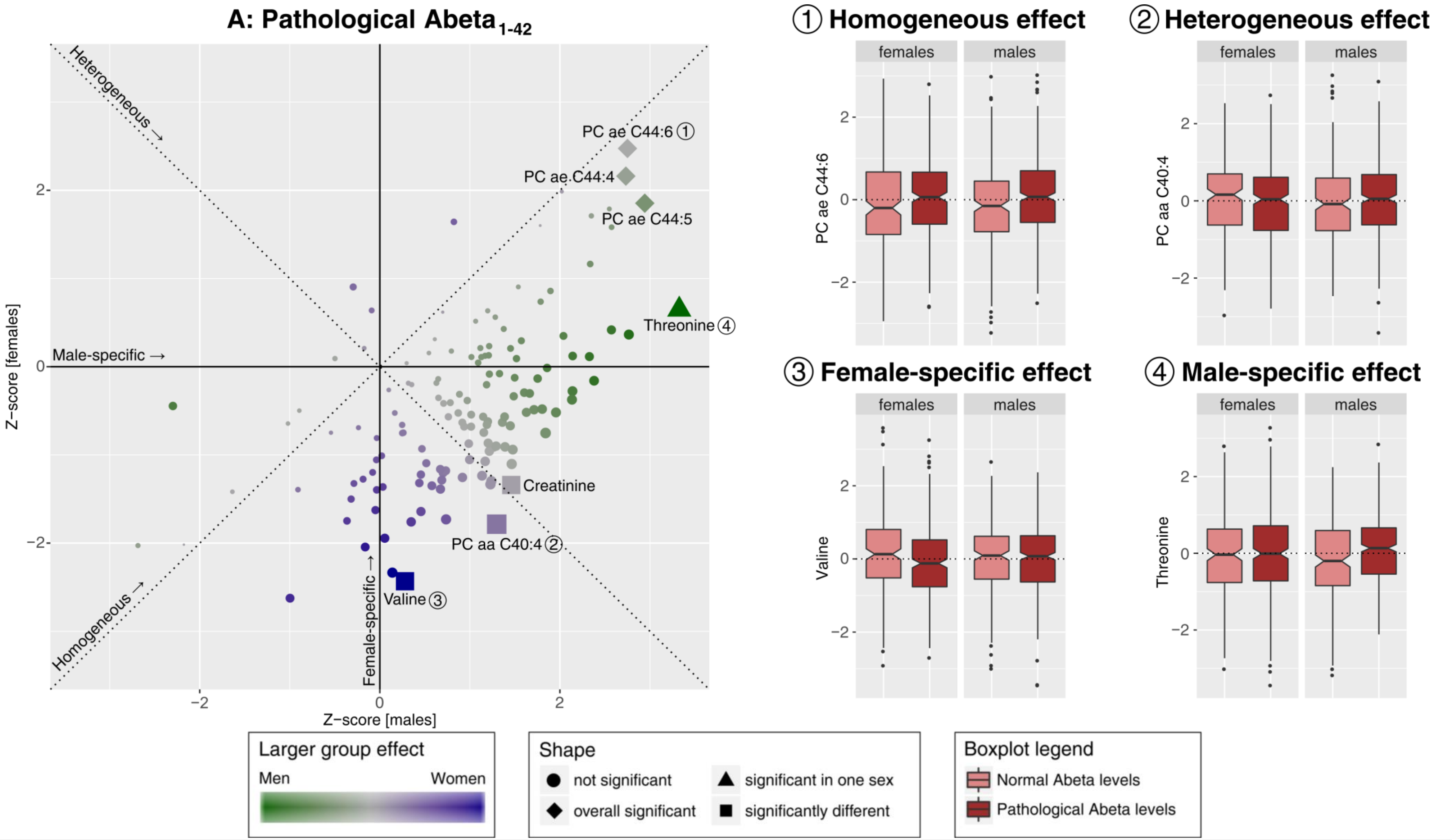
Sex-differences in the blood metabolome in AD

ADNI – 1/GO/2 (n = 1,531)

- In ADNI, we find significant sex-differences for **108 of 140 metabolites**
- Of those, 70 are also significantly different in KORA with **consistent effect directions**
- Metabolic sex-differences **are not changed by AD**



Sex-differences in metabolic effects on CSF Aβ$_{1\text{-}42}$ pathology

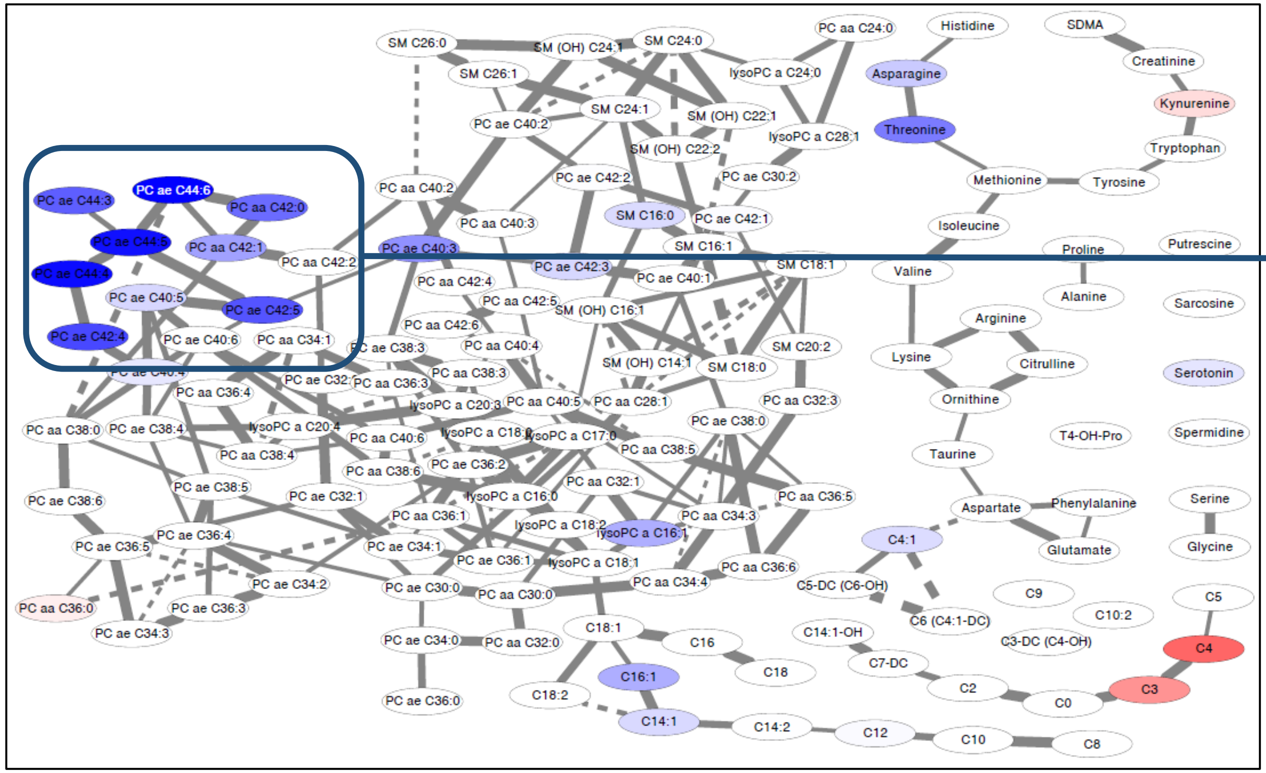


Disease sub-classification: CSF A$\beta_{1\text{-}42}$ pathology

Targeted metabolomics platform (Biocrates AbsoluteIDQ® p180)

ADNI-1/GO/2: 1531 samples

Associations with pathological A$\beta_{1\text{-}42}$ threshold



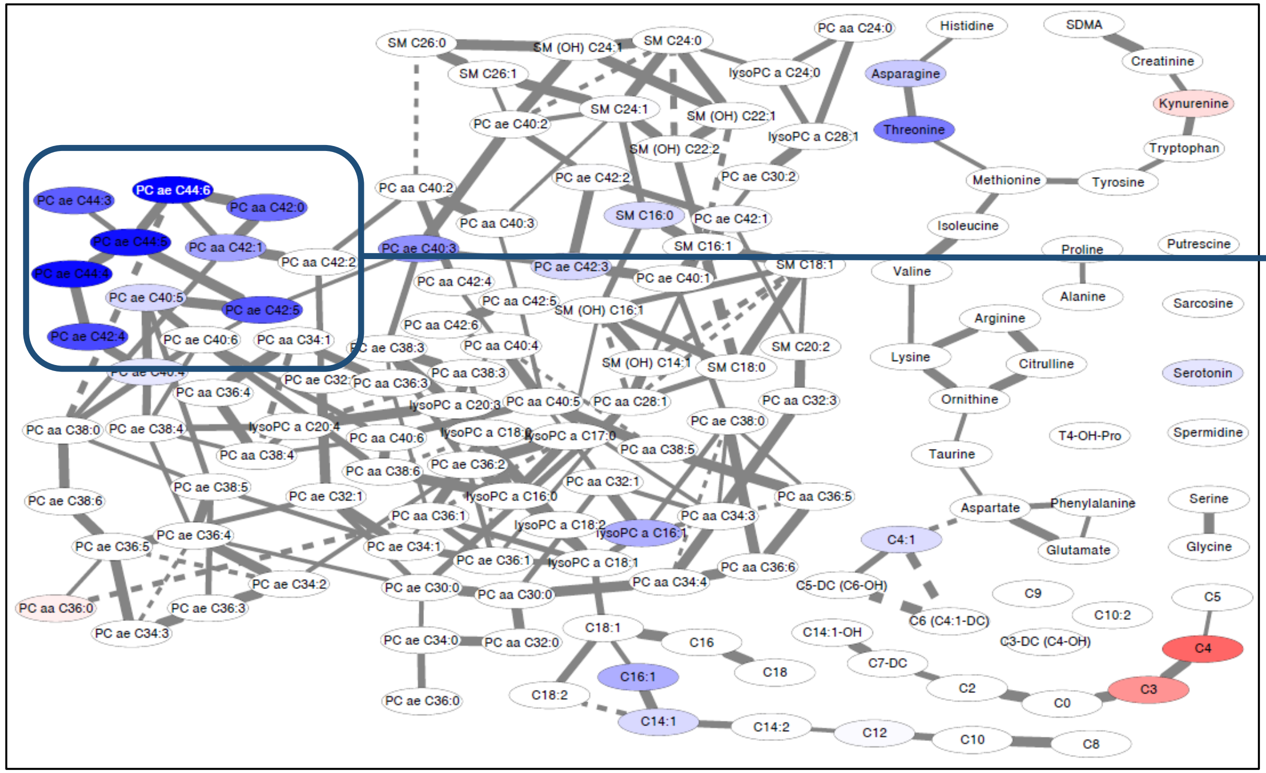
Tightly connected module of related phosphatidylcholines

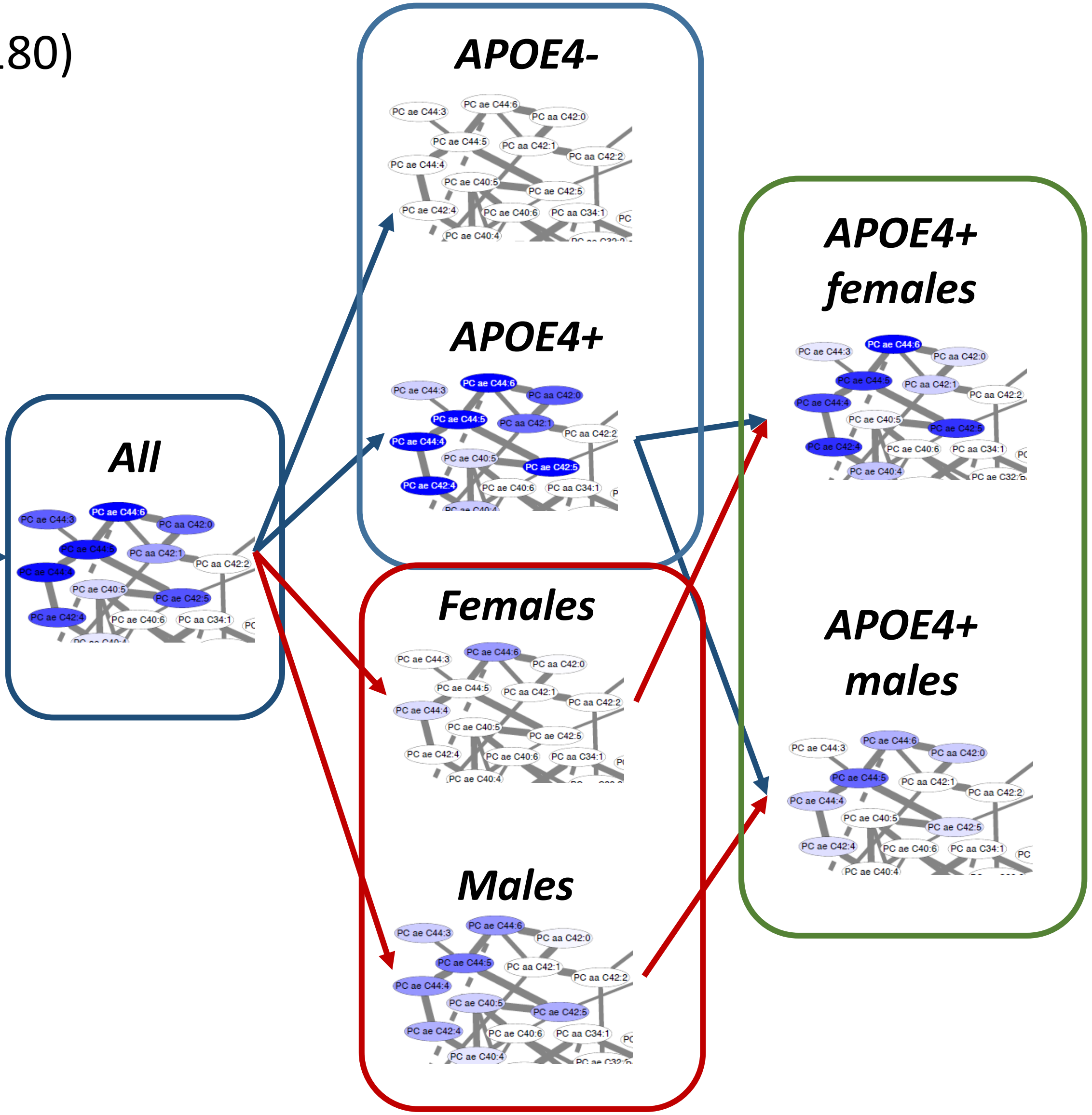
Disease sub-classification: CSF Aβ_{1-42} pathology

Targeted metabolomics platform (Biocrates AbsoluteIDQ® p180)

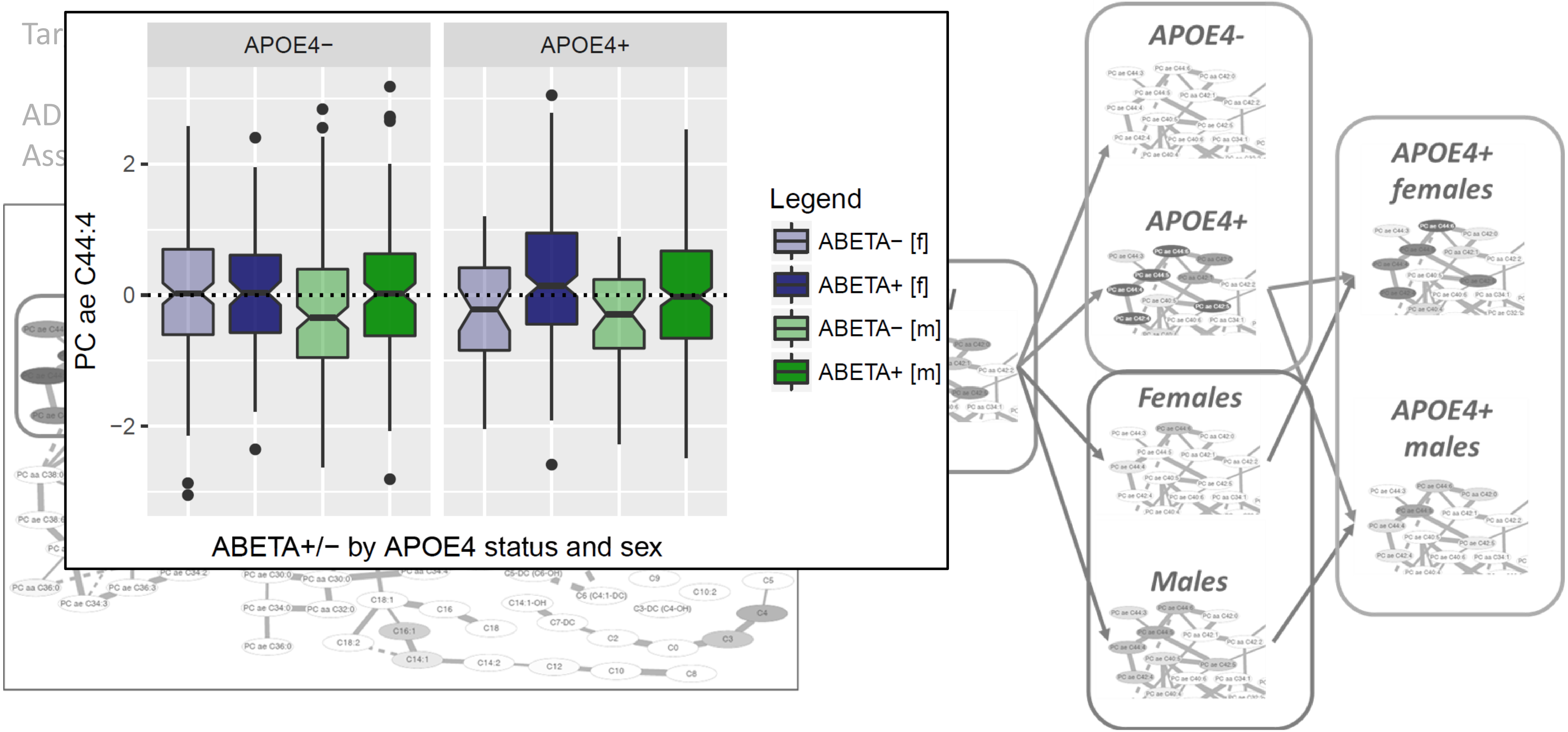
ADNI-1/GO/2: 1531 samples

Associations with pathological Aβ_{1-42} threshold

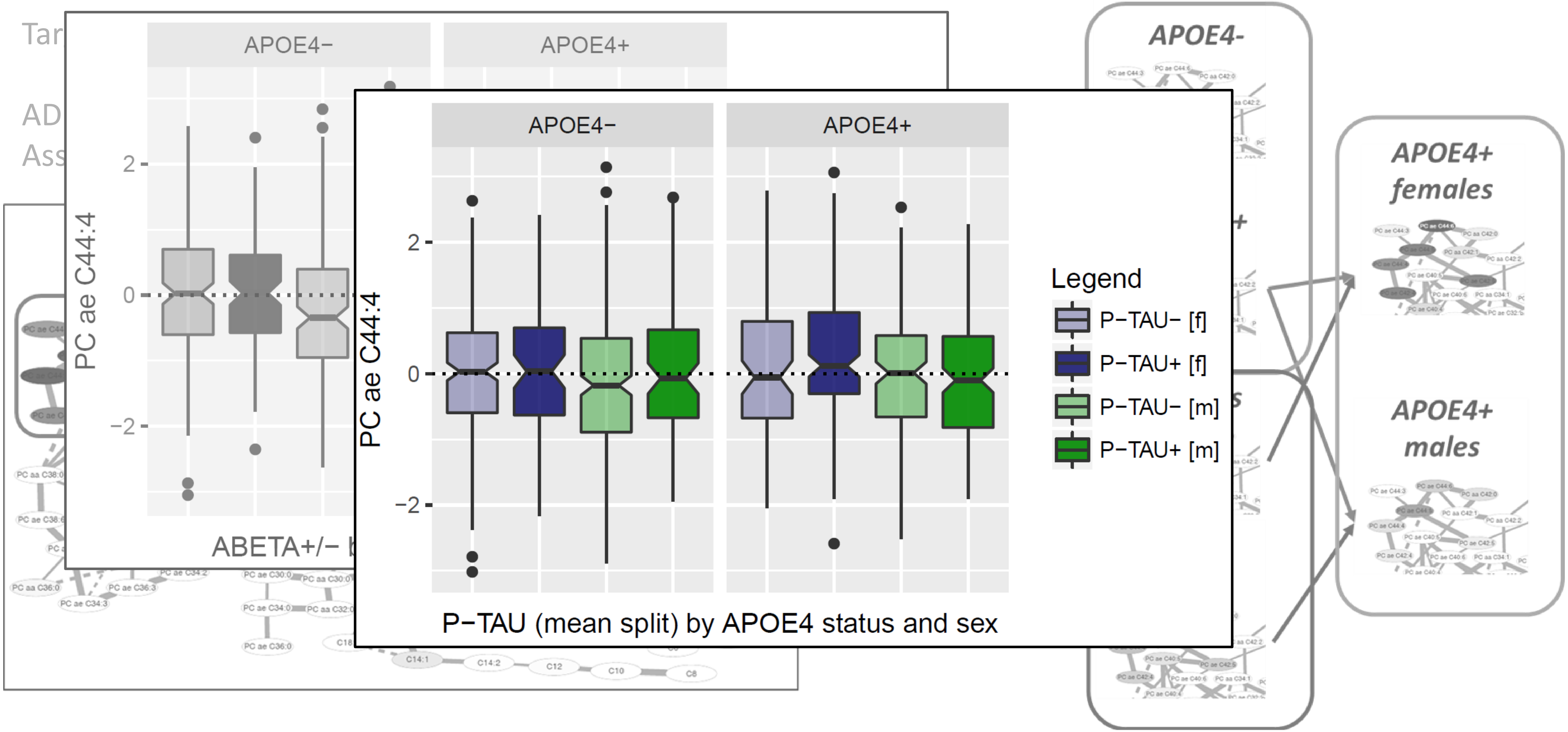




Disease sub-classification: CSF A$\beta_{1\text{-}42}$ pathology

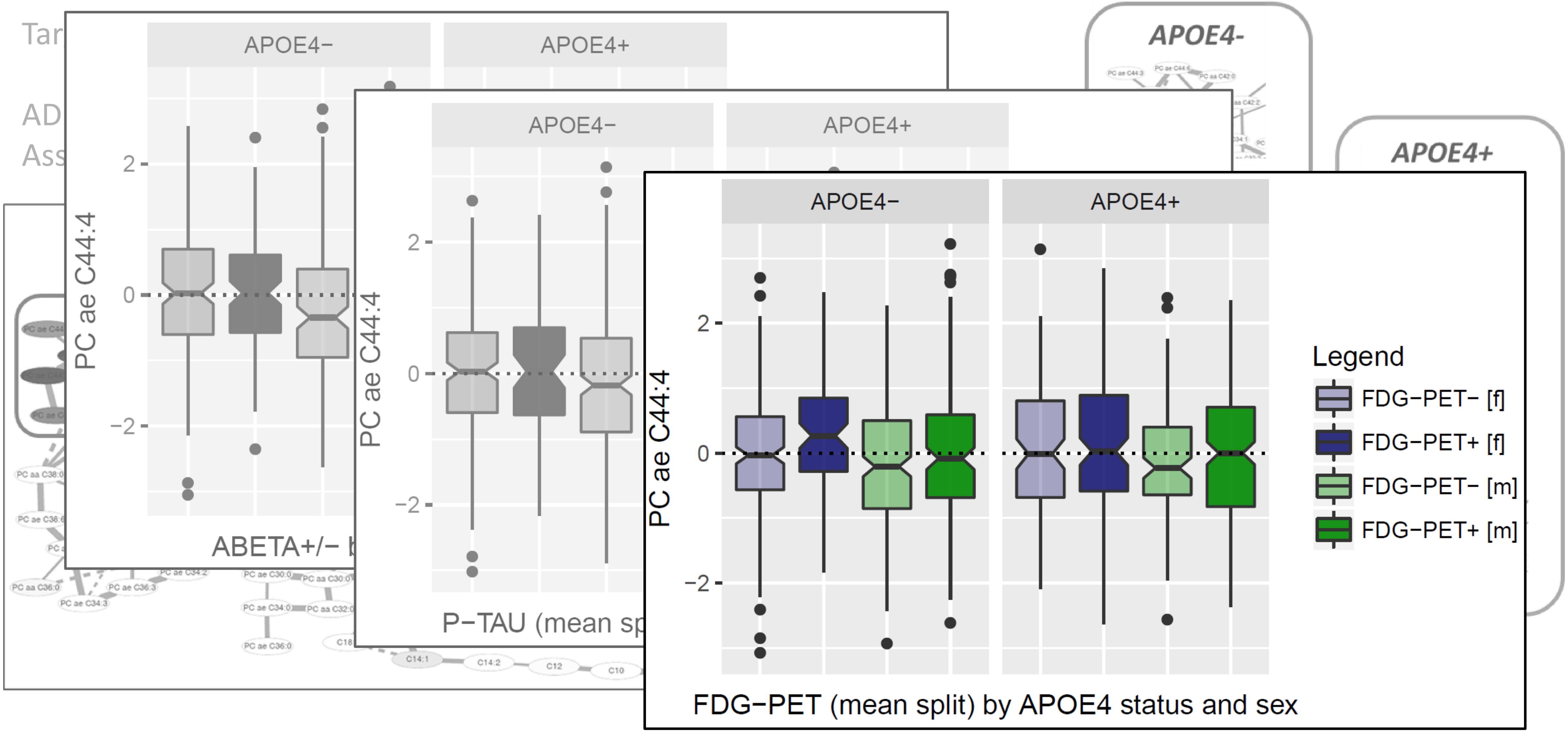


Disease sub-classification: CSF tau pathology



Arnold et al., in preparation

Disease sub-classification: Brain glucose hypometabolism



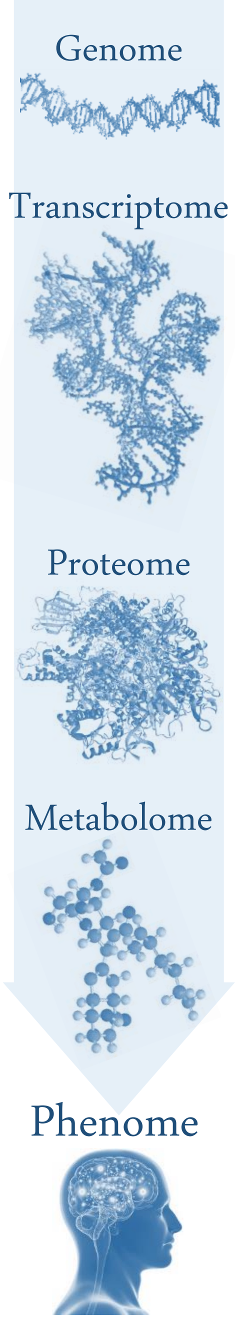
Arnold et al., in preparation

Integrative Metabolomics:
Target Discovery, Prioritization & Sub-Classification

Metabolomics – a molecular readout for functional hypotheses

Ongoing studies and next steps:

- Longitudinal metabolomics profiling across multiple cohorts to capture early changes
- Understand the relationship between the blood and brain metabolome
- Large-scale cross-omics/neuroimaging data integration and use of metabotypes (sets of metabolites) to identify disease subtypes



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Michael Weiner and
leadership of ADNI

NIA - R01 AG057452 - *Metabolic Network Analysis of Biochemical Trajectories in Alzheimer's Disease*
NIA - R01 AG046171 - *Metabolic Networks and Pathways in Alzheimer's Disease*
NIA - R01 AG051550 - *Metabolic Signatures Underlying Vascular Risk Factors for Alzheimer-type Dementias*
FNIH #DAOU16AMPA - *An integrated AMP-AD biomarker discovery study*