

Supplementary Information

Proteo-genomic analyses in relatively lean Chinese adults identify proteins and pathways that affect general and central adiposity levels

Contents

Members of the China Kadoorie Biobank collaborative group.....	3
Supplementary Table 1. Baseline characteristics of participants by quintiles of measured WC	4
Supplementary Table 2. Baseline characteristics of participants with proteomic assays in CKB	5
Supplementary Table 3. Number of proteins significantly associated at FDR<0.05 with general and central adiposity in conventional and genetic analyses	6
Supplementary Table 4. Number of proteins associated with general and central adiposity in conventional and genetic analyses after Bonferroni correction	7
Supplementary Table 5. Number of proteins significantly associated at FDR<0.05 with general and central adiposity in conventional analyses after adjustments	8
Supplementary Table 6. List of significantly enriched biological process terms of adiposity-related proteins after accounting for the potential pre-enrichment of proteins included in Olink.....	9
Supplementary Table 7. Genetic effect estimates, PheWAS results, tissue expression, and relevant drug targets of 31 proteins showing genetic effects on BMI and WC	10
Supplementary Table 8. Colocalisation analyses between adiposity traits and selected proteins	12
Supplementary Table 9. PheWAS results of 31 proteins showing genetic effects on levels of BMI and WC.....	13
Supplementary Table 10. Number of proteins with QC warnings	14
Supplementary Table 11. Variance explained by adiposity genetic scores in CKB and UKB.....	15
Supplementary Table 12. Associations of potential confounders with BMI and WC GS	16
Supplementary Figure 1. Correlation between adiposity measures and genetic scores	17
Supplementary Figure 2. Number of proteins significantly associated with adiposity in conventional and genetic analyses	18
Supplementary Figure 3. Global comparison of associations of protein biomarkers with 1-SD higher BMI, BF%, WC and WHR in conventional and genetic analyses in OLINK batch 1 (black dots) and 2 (red dots).....	19
Supplementary Figure 4. Number of proteins significantly associated with adiposity in conventional and genetic analyses after mutual adjustments	20

Supplementary Figure 5. Global comparison of associations of protein biomarkers with 1-SD higher BMI, BF%, WC and WHR in conventional and genetic analyses in OLINK batch 1 (black dots) and 2 (red dots), by sex	21
Supplementary Figure 6. Volcano plot of associations of proteins with 1-SD higher BMI, BF%, WC and WHR in conventional and genetic analyses in OLINK batch 1 (solid dots) and 2 (open dots) in the subcohort.....	22
Supplementary Figure 7. Comparison of associations of protein biomarkers with 1-SD higher BMI in genetic analyses in CKB and CKB vs. UKB using different CKB BMI GS23	
Supplementary Figure 8. Comparison of associations of protein biomarkers with 1-SD higher BMI, BF%, WC and WHR in conventional and genetic analyses in CKB vs. UKB, with black dots indicating OLINK batch 1 and red dots indicating OLINK batch 2	24
Supplementary Figure 9. Correlation matrix between the 31 proteins showing causal relationships with adiposity.....	25
Supplementary Figure 10. Locus-zoom plots of colocalisation analyses.....	26
Supplementary Figure 11. Human tissux10-specific gene expression for the 31 proteins showing causal relationships with adiposity	36
Supplementary Figure 12. Flow diagram of study design and participant selection in CKB.....	37
Supplementary Figure 13. Distribution of proteins	38

Members of the China Kadoorie Biobank collaborative group

International Steering Committee: Junshi Chen, Zhengming Chen (PI), Robert Clarke, Rory Collins, Liming Li (PI), Jun Lv, Richard Peto, Robin Walters.

International Co-ordinating Centre, Oxford: Daniel Avery, Maxim Barnard, Derrick Bennett, Lazaros Belbasis, Ruth Boxall, Ka Hung Chan, Yiping Chen, Zhengming Chen, Charlotte Clarke, Johnathan Clarke; Robert Clarke, Huaidong Du, Ahmed Edris Mohamed, Hannah Fry, Simon Gilbert, Pek Kei Im, Andri Iona, Maria Kakkoura, Christiana Kartsonaki, Hubert Lam, Kuang Lin, James Liu, Mohsen Mazidi, Iona Millwood, Sam Morris, Qunhua Nie, Alfred Pozarickij, Maryanm Rahmati, Paul Ryder, Saredo Said, Dan Schmidt, Becky Stevens, Iain Turnbull, Robin Walters, Baihan Wang, Lin Wang, Neil Wright, Ling Yang, Xiaoming Yang, Pang Yao.

National Co-ordinating Centre, Beijing: Xiao Han, Can Hou, Qingmei Xia, Chao Liu, Jun Lv, Pei Pei, Dianjianyi Sun, Canqing Yu

10 Regional Co-ordinating Centres:

Guangxi Provincial CDC: Naying Chen, Duo Liu, Zhenzhu Tang. **Liuzhou** CDC: Ningyu Chen, Qilian Jiang, Jian Lan, Mingqiang Li, Yun Liu, Fanwen Meng, Jinhui Meng, Rong Pan, Yulu Qin, Ping Wang, Sisi Wang, Liuping Wei, Liyuan Zhou. **Gansu** Provincial CDC: Caixia Dong, Pengfei Ge, Xiaolan Ren. **Maiji** CDC: Zhongxiao Li, Enke Mao, Tao Wang, Hui Zhang, Xi Zhang. **Hainan** Provincial CDC: Jinyan Chen, Ximin Hu, Xiaohuan Wang. **Meilan** CDC: Zhendong Guo, Huimei Li, Yilei Li, Min Weng, Shukuan Wu. **Heilongjiang** Provincial CDC: Shichun Yan, Mingyuan Zou, Xue Zhou. **Nangang** CDC: Ziyang Guo, Quan Kang, Yanjie Li, Bo Yu, Qinai Xu. **Henan** Provincial CDC: Liang Chang, Lei Fan, Shixian Feng, Ding Zhang, Gang Zhou. **Huixian** CDC: Yulian Gao, Tianyou He, Pan He, Chen Hu, Huarong Sun, Xukui Zhang. **Hunan** Provincial CDC: Biyun Chen, Zhongxi Fu, Yuelong Huang, Huilin Liu, Qiaohua Xu, Li Yin. **Liuyang** CDC: Huajun Long, Xin Xu, Hao Zhang, Libo Zhang. **Jiangsu** Provincial CDC: Jian Su, Ran Tao, Ming Wu, Jie Yang, Jinyi Zhou, Yonglin Zhou. **Suzhou** CDC: Yihe Hu, Yujie Hua, Jianrong Jin, Fang Liu, Jingchao Liu, Yan Lu, Liangcai Ma, Aiyu Tang, Jun Zhang. **Qingdao** CDC: Liang Cheng, Ranran Du, Ruqin Gao, Feifei Li, Shanpeng Li, Yongmei Liu, Feng Ning, Zengchang Pang, Xiaohui Sun, Xiaocao Tian, Shaojie Wang, Yaoming Zhai, Hua Zhang, Licang CDC: Wei Hou, Silu Lv, Junzheng Wang. **Sichuan** Provincial CDC: Xiaofang Chen, Xianping Wu, Ningmei Zhang, Xiaoyu Chang. **Pengzhou** CDC: Xiaofang Chen, Jianguo Li, Jiaqiu Liu, Guojin Luo, Qiang Sun, Xunfu Zhong. **Zhejiang** Provincial CDC: Weiwei Gong, Ruying Hu, Hao Wang, Meng Wang, Min Yu. **Tongxiang** CDC: Lingli Chen, Qijun Gu, Dongxia Pan, Chunmei Wang, Kaixu Xie, Xiaoyi Zhang.

Supplementary Table 1. Baseline characteristics of participants by quintiles of measured WC

Characteristics ^a	Sex-specific quintiles of WC, kg/m ²					All (n=3977)
	Q1 (n=798)	Q2 (n=788)	Q3 (n=797)	Q4 (n=807)	Q5 (n=787)	
Age and socioeconomic factors						
Age, years (SD)	55.9 (14.5)	55.1 (12.9)	56.5 (11.8)	58.2 (12.1)	58.4 (12.6)	57.3 (11.6)
Women, %	53.4	53.6	52.1	54.8	55.9	53.7
Urban, %	29.9	38.5	52.0	56.9	61.7	48.8
≥6 years of education, %	46.4	43.8	45.2	45.7	41.7	45.1
Anthropometry, blood pressure and fasting time, mean (SD)						
BMI, kg/m ²	19.9 (2.1)	22.0 (1.8)	23.8 (2.0)	25.4 (2.0)	28.5 (3.0)	23.9 (3.3)
Body fat percentage	20.3 (4.2)	24.6 (4.1)	28.1 (4.9)	30.8 (4.6)	35.1 (5.9)	25.4 (6.3)
Waist circumference, cm	68.4 (3.5)	75.9 (1.8)	81.5 (1.6)	87.0 (1.9)	96.5 (6.4)	81.9 (9.1)
Waist-to-hip ratio	0.81 (0.042)	0.86 (0.038)	0.90 (0.039)	0.93 (0.044)	0.97 (0.064)	0.89 (0.001)
SBP, mmHg	129.5 (22.9)	134.8 (21.7)	139.2 (22.0)	141.1 (22.1)	147.7 (25.3)	138.3 (22.0)
Fasting time, hour	4.6 (4.3)	4.9 (4.3)	4.7 (4.3)	4.5 (3.6)	4.5 (3.5)	4.7 (4.1)
Lifestyle factors						
Ever regular smoker, %						
Men	83.2	70.1	75.7	69.7	77.9	75.0
Women	4.3	6.3	4.4	6.7	5.1	5.8
Regular alcohol drinker, %						
Men	31.8	31.1	40.2	36.2	28.5	34.6
Women	2.5	1.8	2.5	4.3	4.3	3.0
Physical activity, MET-h/day (SD)	17.7 (12.1)	17.7 (12.3)	17.2 (10.7)	17.0 (10.5)	15.6 (10.5)	17.3 (10.7)
Medical history and health status,^b %						
Self-rated poor health	16.2	10.6	8.0	9.0	12.7	16.6
Diabetes	4.7	7.7	9.5	12.5	19.4	11.2
Chronic kidney disease	1.4	1.7	2.1	0.7	1.7	1.4
Cancer	1.1	0.3	0.5	0.4	0.5	0.6

^a Adjusted for age, sex and study area, as appropriate.

^b Based on self-report, while for diabetes, screen-detected diabetes at baseline was also included.

Abbreviations: SD=standard deviation; BMI= body mass index; SBP=systolic blood pressure; MET= metabolic equivalent of task.

Supplementary Table 2. Baseline characteristics of participants with proteomic assays in CKB

Characteristics ^a	All (n=3977)	Subcohort (n=2026)	IHD Cases (n=1951)
Age and socioeconomic factors			
Age, years (SD)	57.3 (11.6)	51.3 (10.4)	52.2 (10.6)
Women, %	53.7	62.1	45.1
Urban, %	48.8	50.6	47.0
≥6 years of education, %	45.1	52.1	37.7
Anthropometry, blood pressure and fasting time, mean (SD)			
BMI, kg/m ²	23.9 (3.3)	23.9 (3.2)	24.0 (3.4)
Body fat percentage	25.4 (6.3)	28.6 (6.3)	27.0 (6.7)
Waist circumference, cm	81.9 (9.1)	80.3 (8.7)	83.6 (9.4)
Waist-to-hip ratio	0.89 (0.001)	0.88 (0.062)	0.91 (0.067)
SBP, mmHg	138.3 (22.0)	130.6 (19.7)	146.3 (23.5)
Fasting time, hour	4.7 (4.1)	5.1 (4.3)	4.3 (4.0)
Lifestyle factors			
Ever regular smoker, %			
Men	75.0	74.9	75.1
Women	5.8	3.3	9.3
Regular alcohol drinker, %			
Men	34.6	40.1	30.6
Women	3.0	2.7	3.4
Physical activity, MET-h/day (SD)	17.3 (10.7)	21.3 (12.3)	13.0 (8.7)
Medical history and health status, ^b %			
Self-rated poor health	16.6	13.4	19.8
Diabetes	11.2	16.1	6.4
Chronic kidney disease	1.4	1.4	1.3
Cancer	0.6	0.6	0.6

^a Adjusted for age, sex and study area, as appropriate.

^b Based on self-report, while for diabetes, screen-detected diabetes at baseline was also included.

Abbreviations: SD=standard deviation; BMI= body mass index; IHD=ischemic heart disease; SBP=systolic blood pressure; MET= metabolic equivalent of task.

Supplementary Table 3. Number of proteins significantly associated at FDR<0.05 with general and central adiposity in conventional and genetic analyses

Adiposity	Batch 1 (n=1463)	Batch 2 (n=1463)	Total (n=2926)
Conventional analyses			
BMI	1088 (73.9)	721 (49.0)	1809 (61.8)
BF%	1115 (75.7)	723 (49.1)	1838 (62.8)
WC	1099 (74.7)	709 (48.2)	1808 (61.8)
WHR	1055 (71.7)	681 (46.3)	1736 (59.3)
Any	1237 (84.0)	859 (58.4)	2096 (71.6)
All	937 (63.7)	576 (39.1)	1513 (51.7)
Genetic analyses			
BMI	304 (20.7)	95 (6.5)	399 (13.6)
BF%	212 (14.4)	27 (1.8)	239 (8.2)
WC	365 (24.8)	71 (4.8)	436 (14.9)
WHR	261 (17.7)	25 (1.7)	286 (9.8)
Any	542 (36.8)	120 (8.2)	662 (22.6)
All	75 (5.1)	5 (0.3)	80 (2.7)

Abbreviations: BF%=body fat percentage; BMI=body mass index; WC= waist circumference; WHR=waist-to-hip ratio

Supplementary Table 4. Number of proteins associated with general and central adiposity in conventional and genetic analyses after Bonferroni correction

Adiposity	Batch 1 (n=1463)	Batch 2 (n=1463)	Total (n=2926)
Conventional analyses			
BMI	798 (54.2)	461 (31.4)	1259 (42.8)
BF%	836 (56.8)	476 (32.4)	1312 (44.6)
WC	824 (56.0)	479 (32.7)	1303 (44.3)
WHR	782 (53.1)	460 (31.4)	1242 (42.3)
Any	925 (62.8)	541 (36.9)	1466 (49.9)
All	691 (46.9)	398 (27.1)	1089 (37.1)
Genetic analyses			
BMI	58 (3.8)	28 (1.8)	86 (2.8)
BF%	34 (2.3)	5 (0.3)	39 (1.3)
WC	98 (6.7)	25 (1.7)	123 (4.2)
WHR	45 (3.1)	8 (0.5)	53 (1.8)
Any	151 (10.3)	42 (2.9)	193 (6.6)
All	3 (0.2)	1 (0.1)	4 (0.1)

Abbreviations: BF%=body fat percentage; BMI=body mass index; WC= waist circumference; WHR=waist-to-hip ratio

Supplementary Table 5. Number of proteins significantly associated at FDR<0.05 with general and central adiposity in conventional analyses after adjustments

Adiposity	Batch 1 (n=1463)	Batch 2 (n=1463)	Total (n=2926)
Usual adjustments*			
BMI	1088 (73.9)	721 (49.0)	1809 (61.8)
BF%	1115 (75.7)	723 (49.1)	1838 (62.8)
WC	1099 (74.7)	709 (48.2)	1808 (61.8)
WHR	1055 (71.7)	681 (46.3)	1736 (59.3)
Any	1237 (84.0)	859 (58.4)	2096 (71.6)
All	937 (63.7)	576 (39.1)	1513 (51.7)
Usual adjustments* + physical activity			
BMI	1088 (74.4)	720 (49.4)	1808 (61.8)
BF%	1116 (76.3)	721 (49.5)	1837 (62.8)
WC	1099 (75.1)	708 (48.6)	1807 (61.8)
WHR	1055 (72.1)	681 (46.7)	1736 (59.4)
Any	1238 (84.0)	857 (58.4)	2095 (71.6)
All	937 (64.0)	576 (39.5)	1513 (51.7)
Usual adjustments* + smoking			
BMI	1078 (73.7)	722 (49.5)	1800 (61.6)
BF%	1125 (75.7)	723 (49.6)	1848 (63.3)
WC	1097 (75.0)	707 (48.5)	1804 (61.8)
WHR	1058 (72.3)	682 (46.8)	1740 (59.6)
Any	1239 (84.0)	852 (58.3)	2091 (71.6)
All	944 (64.4)	582 (39.9)	1526 (52.2)
Usual adjustments* + alcohol			
BMI	1090 (74.5)	721 (49.5)	1811 (61.9)
BF%	1120 (76.6)	723 (49.6)	1843 (63.1)
WC	1104 (75.5)	708 (48.6)	1812 (62.0)
WHR	1064 (72.7)	680 (46.6)	1744 (59.7)
Any	1205 (82.4)	858 (58.9)	2099 (71.8)
All	941 (63.3)	580 (39.8)	1521 (52.1)
Usual adjustments* + physical activity + smoking + alcohol			
BMI	1078 (73.7)	726 (49.8)	1804 (61.7)
BF%	1116 (76.3)	722 (49.5)	1838 (62.9)
WC	1099 (75.1)	705 (48.4)	1804 (61.8)
WHR	1070 (73.1)	679 (46.6)	1749 (59.9)
Any	1239 (84.6)	855 (58.6)	2094 (71.6)
All	949 (63.7)	583 (39.9)	1532 (52.3)

*Usual adjustments: age, age squared, sex, study area, fasting time, ambient temperature, ascertainment status

Supplementary Table 6. List of significantly enriched biological process terms of adiposity-related proteins after accounting for the potential pre-enrichment of proteins included in Olink

Adiposity	ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	geneID	Count
BF%	GO:0051241	negative regulation of multicellular organismal process	15/39	328/2759	1.68E-05	0.026393	0.02491	LEP/ADM/VSIG4/LBP/RTN4R/CALCA/CST3/FSTL3/TNFRSF1A/NTRK3/LGALS9/OXT/FURIN/PLAT/ACVRL1	15
WC	GO:0009628	response to abiotic stimulus	31/121	311/2759	5.01E-06	0.011967	0.011026	PRAP1/LEP/PGF/ADM/CALCA/NOS3/DAG1/PLAT/TNFRSF10B/CTSS/OXT/PLIN1/TNFRSF1A/SCARA5/CDH2/YAP1/HNMT/FAS/TNFRSF10A/IGFBP2/STC1/LPL/TNFRSF11A/TGFB/ACVRL1/CXCL10/IGFBP7/VEGFB/F7/KRT8/SERPINF1	31
WHR	GO:0042632	cholesterol homeostasis	6/50	28/2759	7.25E-06	0.005313	0.005116	LDLR/LCAT/CES1/LPL/FGFR4/FABP4	6
WHR	GO:0055092	sterol homeostasis	6/50	28/2759	7.25E-06	0.005313	0.005116	LDLR/LCAT/CES1/LPL/FGFR4/FABP4	6
WHR	GO:0010876	lipid localization	9/50	103/2759	6.93E-05	0.025396	0.024452	LDLR/FURIN/ADIPOQ/LCAT/CES1/LPL/PRAP1/FABP4/OXT	9

Supplementary Table 7. Genetic effect estimates, PheWAS results, tissue expression, and relevant drug targets of 31 proteins showing genetic effects on BMI and WC

Adipo sity	Protein ^a	SNP information		CKB cis-pQTL		Two-sample MR ^c		UKB replic ation ^e	PheWAS associations ^f	Levels of expression ^g					Drug Target		
		rsID	EA b	Beta (SE)	P	Beta (SE) ^d	P			Adip ose	Brain	Liver	Panc reas	Inte stine	Disease	Max Phas	Status
BMI	ADH1B	rs1229984	C	0.204 (0.024)	5.9x10 ⁻¹⁷	0.127 (0.028)	9.6x10 ⁻⁰⁶	-	Fat % of leg/whole body	+++	+	+++	++	++	Alcohol dehydrogenase class I	IV	Approved
	ALDH5A1	rs2235502	C	0.314 (0.043)	2.6x10 ⁻¹³	-0.056 (0.019)	3.8x10 ⁻⁰³	-	-	++	+++	+++	++	++	Bipolar disorder, Epilepsy, Generalised not-motor seizure,	IV	Approved
	APOBR	rs180743	C	1.199 (0.036)	1.2x10 ⁻²⁴⁶	-0.057 (0.011)	1.4x10 ⁻⁰⁷	-	BMI, Body fat%, Fat mass leg/arm	+	+	+	+	++	-	-	-
	APOE	rs429358	T	1.030 (0.038)	4.9x10 ⁻¹⁵⁸	0.028 (0.006)	1.5x10 ⁻⁰⁵	-	BMI, Body fat%, Fat mass leg/arm/ body, Weight change	+++	+++	+++	++	++	Glioblastoma multiform, Brain neoplasm	II	Completed
	ASAH1	rs2299604	C	0.461 (0.023)	5.0x10 ⁻⁸⁶	-0.024 (0.008)	2.5x10 ⁻⁰³	X	-	++	++	+	++	++	-	-	-
	BMPER	rs6951634	C	0.357 (0.039)	2.4x10 ⁻²⁰	0.043 (0.013)	1.3x10 ⁻⁰³	-	-	+	+	+	+	+	-	-	-
	CACYBP	rs12563930	G	0.174 (0.027)	6.8x10 ⁻¹¹	-0.122 (0.031)	1.0x10 ⁻⁰⁴	-	BMI, Impedance of arm/whole body, Fat mass/% of leg	++	++	+	+	++	-	-	-
	CD164L2	rs79775449	T	0.178 (0.025)	1.1x10 ⁻¹²	-0.117 (0.030)	8.6x10 ⁻⁰⁵	-	BMI	+	+	+	+	+	-	-	-
	CFB	rs1265888	G	0.820 (0.048)	1.5x10 ⁻⁶⁵	0.036 (0.008)	2.8x10 ⁻⁰⁶	√	Impedance of arm/leg/whole body, Fat-free mass of trunk/leg	++	+	+++	+	++	Paroxysmal nocturnal hemoglobinuria, Glomerulonephritis, Atypical haemolytic-uremic syndrome	III	Completed/ Recruiting
	CFHR2	rs4085749	C	1.035 (0.024)	2.1x10 ⁻²⁹⁹	0.013 (0.004)	6.80x10 ⁻⁰⁴	X	-	+	+	++	+	+	-	-	-
	EFEMP1	rs58680090	A	0.166 (0.028)	4.30x10 ⁻⁰⁹	0.110 (0.031)	4.70x10 ⁻⁰⁴	√	Impedance of whole body, Fat-free mass arm/leg/trunk, Fat and fat-free mass of trunk, Height	++	++	+	++	++	-	-	-
	F13B	rs12134960	G	0.505 (0.024)	1.8x10 ⁻⁹⁷	0.026 (0.008)	8.2x10 ⁻⁰⁴	X	-	+	+	++	+	+	-	-	-
	FGL1	rs3739404	A	0.546 (0.023)	1.1x10 ⁻¹²⁴	0.020 (0.006)	1.2x10 ⁻⁰³	-	-	+	+	+++	++	+	-	-	-
	FN1	rs1437787	C	0.297 (0.041)	3.0x10 ⁻¹³	-0.084 (0.028)	2.5x10 ⁻⁰³	√	-	++	++	++	+	++	Eye disease	IV	Approved
	ITIH3	rs2286797	G	0.730 (0.033)	7.9x10 ⁻¹⁰⁷	-0.26 (0.006)	9.9x10 ⁻⁰⁶	√	BMI	+	+	+++	+	+	-	-	-
	ITIH4	rs6803519	T	0.282 (0.024)	4.5x10 ⁻³¹	0.070 (0.014)	1.7x10 ⁻⁰⁶	-	Height	++	+	+++	++	+	-	-	-
	LRP11	rs9688902	T	0.662 (0.030)	4.7x10 ⁻¹¹³	0.030 (0.007)	8.5x10 ⁻⁰⁶	X	BMI	++	++	+	+	+	-	-	-
	NCR3LG1	rs2051772	A	0.356 (0.024)	4.6x10 ⁻⁵¹	-0.042 (0.011)	1.4x10 ⁻⁰⁴	-	BMI, Impedance of arm/leg/whole body, Height	+	+	+	+	+	-	-	-
	NUDT5	rs7100710	A	0.154 (0.023)	2.4x10 ⁻¹¹	-0.122 (0.029)	3.8x10 ⁻⁰⁵	X	BMI	++	+	++	+	++	-	-	-
	OGN	rs7023004	G	0.598 (0.031)	1.5x10 ⁻⁸⁰	0.033 (0.009)	3.2x10 ⁻⁰⁴	√	Impedance of arm/leg/whole body, Height	++	+	+	+	++	-	-	-
	PRDX6	rs61826753	A	0.370 (0.025)	1.8x10 ⁻⁵¹	0.036 (0.011)	6.8x10 ⁻⁰⁴	-	-	+++	++	++	++	++	-	-	-
	PRSS53	rs11150606	C	0.861 (0.028)	2.2x10 ⁻²⁰¹	0.013 (0.004)	1.5x10 ⁻⁰³	-	-	+	+	++	+	+	-	-	-
	PTPRB	rs2465811	T	0.239 (0.024)	1.6x10 ⁻²²	-0.050 (0.016)	2.3x10 ⁻⁰³	X	-	++	+	+	+	++	-	-	-
	PTPRZ1	rs28379507	C	0.171 (0.025)	3.4x10 ⁻¹²	-0.079 (0.026)	2.4x10 ⁻⁰³	X	-	+	++	+	+	+	-	-	-
	SCAMP3	rs4971072	A	0.185 (0.026)	1.0x10 ⁻¹²	0.115 (0.027)	2.7x10 ⁻⁰⁵	X	-	++	++	+	+	++	-	-	-
	SERPINF2	rs8077638	C	0.240 (0.032)	3.7x10 ⁻¹⁴	0.101 (0.023)	2.0x10 ⁻⁰⁵	√	-	++	+	+++	+	++	-	-	-
	SLURP1	rs1036385	T	0.353 (0.024)	3.0x10 ⁻⁵⁰	-0.043 (0.014)	2.7x10 ⁻⁰³	-	-	+	+	+	+	+	-	-	-
	SUSD5	rs6764459	T	0.567 (0.024)	1.5x10 ⁻¹²⁷	-0.023 (0.008)	3.7x10 ⁻⁰³	-	-	+	+	+	+	+	-	-	-
	TSPAN8	rs9683252	G	0.700 (0.025)	7.5x10 ⁻¹⁶⁶	-0.022 (0.005)	5.4x10 ⁻⁰⁵	-	-	+	+	+	++	+++	-	-	-
	TXNDC15	rs3733897	G	1.045 (0.025)	2.0x10 ⁻³¹⁷	0.012 (0.004)	4.5x10 ⁻⁰⁴	√	Height	++	+	+	+	++	-	-	-

WC	<u>ALDH2</u>	rs4646776	G	0.371 (0.028)	6.3x10 ⁻⁴¹	0.183 (0.027)	<u>2.0X10⁻¹¹</u>	-	-	++	++	++	++	++	Alcohol dependence, parasitic infection	IV	Approved
	<u>ITI4</u>	rs6803519	T	0.282 (0.024)	4.5x10 ⁻³¹	0.081 (0.019)	<u>1.7X10⁻⁰⁵</u>	-	Height	++	+	+++	++	+	-	-	-

^aEvidence of colocalization (PH4>0.6): bold; Strong evidence of colocalization (PH4>0.8): bold and underline; ^bEA referred to allele associated with increased protein levels in CKB, and EAF affect allele was obtained from Biobank Japan; ^c2SMR: cis-pQTL obtained from CKB, with lookups in Biobank Japan for GWAS and Korean Biobank Project summary statistics; ^dBeta and SE were calculated using Wald ratio method; ^e2SMR: cis-pQTL obtained from UKB, with lookups in GIANT for GWAS summary statistic; ^fTraits or diseases in bold: P<5 × 10⁻⁸, other were P<5x10⁻⁶; ^gLevels of expression was estimated using GTEx and categorized into three groups as denoted: +(low); ++ (moderate) and +++ (high)

Supplementary Table 8. Colocalisation analyses between adiposity traits and selected proteins

Adiposity	Protein	No. SNPs	PP0	PP1	PP2	PP3	PP4
BMI	ADH1B	2567	6.3x10 ⁻¹³	8.2x10 ⁻⁰⁶	2.0x10 ⁻¹⁰	5.4x10 ⁻⁰⁴	1.0x10 ⁺⁰⁰
	ALDH5A1	947	3.0x10 ⁻⁰⁸	4.9x10 ⁻⁰¹	3.1x10 ⁻⁰⁸	5.0x10 ⁻⁰¹	1.3x10 ⁻⁰²
	APOBR	-	-	-	-	-	-
	APOE	803	1.4x10 ⁻¹³²	1.8x10 ⁻⁰³	2.6x10 ⁻¹³⁰	3.4x10 ⁻⁰¹	6.6x10 ⁻⁰¹
	ASAH1	-	-	-	-	-	-
	BMPER	-	-	-	-	-	-
	CACYBP	3390	2.5x10 ⁻¹⁰	1.5x10 ⁻⁰⁴	1.4x10 ⁻⁰⁶	7.8x10 ⁻⁰¹	2.2x10 ⁻⁰¹
	CD164L2	686	8.2x10 ⁻⁰⁹	1.7x10 ⁻⁰¹	3.6x10 ⁻⁰⁸	7.5x10 ⁻⁰¹	8.4x10 ⁻⁰²
	CFB	-	-	-	-	-	-
	CFHR2	-	-	-	-	-	-
	EFEMP1	-	-	-	-	-	-
	F13B	-	-	-	-	-	-
	FGL1	-	-	-	-	-	-
	FN1	457	1.6x10 ⁻⁰⁷	2.3x10 ⁻⁰¹	7.6x10 ⁻⁰⁸	1.1x10 ⁻⁰¹	6.6x10 ⁻⁰¹
	ITIH3	7096	2.9x10 ⁻⁶¹	2.3x10 ⁻¹⁰	1.3x10 ⁻⁵¹	1.0x10 ⁺⁰⁰	9.4x10 ⁻⁰⁴
	ITIH4	7568	7.4x10 ⁻³⁴	1.1x10 ⁻¹⁰	6.5x10 ⁻²⁴	1.0x10 ⁺⁰⁰	1.7x10 ⁻⁰⁴
	LRP11	4186	1.xX10 ⁻¹¹⁷	6.1x10 ⁻⁰⁴	6.7x10 ⁻¹¹⁵	3.1x10 ⁻⁰¹	6.9x10 ⁻⁰¹
	NCR3LG1	1116	1.4x10 ⁻⁴³	8.0x10 ⁻⁰³	4.9x10 ⁻⁴²	2.8x10 ⁻⁰¹	7.1x10 ⁻⁰¹
	NUDT5	973	6.8x10 ⁻⁰⁸	1.9x10 ⁻⁰⁴	3.6x10 ⁻⁰⁴	9.9x10 ⁻⁰¹	8.0x10 ⁻⁰³
	OGN	4061	4.4x10 ⁻¹²	2.3x10 ⁻⁰³	3.5x10 ⁻¹⁰	1.8x10 ⁻⁰¹	8.2x10 ⁻⁰¹
	PRDX6	3430	9.1x10 ⁻⁴⁷	1.8x10 ⁻⁰⁴	4.9x10 ⁻⁴³	1.0x10 ⁺⁰⁰	3.4x10 ⁻⁰³
	PRSS53	3166	7.0x10 ⁻³¹⁷	3.9x10 ⁻⁰²	1.7x10 ⁻³¹⁵	9.6x10 ⁻⁰¹	3.6x10 ⁻⁰³
	PTPRB	-	-	-	-	-	-
	PTPRZ1	-	-	-	-	-	-
	SCAMP3	998	3.0x10 ⁻¹²	1.5x10 ⁻⁰⁶	2.0x10 ⁻⁰⁶	9.7x10 ⁻⁰¹	2.9x10 ⁻⁰²
	SERPINF2	144	8.0x10 ⁻¹⁹	5.3x10 ⁻⁰⁴	7.1x10 ⁻¹⁷	4.6x10 ⁻⁰²	9.5x10 ⁻⁰¹
	SLURP1	1902	0.0x10 ⁺⁰⁰	0.0x10 ⁺⁰⁰	4.7x10 ⁻⁰⁴	1.0x10 ⁺⁰⁰	3.4x10 ⁻⁰³
	SUSD5	-	-	-	-	-	-
	TSPAN8	1577	4.0x10 ⁻⁸⁴	6.8x10 ⁻⁰³	2.1x10 ⁻⁸²	3.4x10 ⁻⁰¹	6.5x10 ⁻⁰¹
	TXNDC15	2821	0.0x10 ⁺⁰⁰	3.7x10 ⁻⁰³	0.0x10 ⁺⁰⁰	1.0x10 ⁺⁰⁰	2.2x10 ⁻⁰⁴
WC	ALDH2	6258	3.8 x10 ⁻⁶³	9.4 x10 ⁻³¹	8.3 x10 ⁻³⁵	1.8 x10 ⁻⁰²	9.8 x10 ⁻⁰¹
	ITIH4	6640	2.1 x10 ⁻²⁶	3.3 x10 ⁻⁰³	1.1 x10 ⁻²⁴	1.6 x10 ⁻⁰¹	8.3 x10 ⁻⁰¹

Abbreviations: BMI=body mass index; PP=Posterior probabilities; WC=waist circumference

Supplementary Table 9. PheWAS results of 31 proteins showing genetic effects on levels of BMI and WC

Adiposity	Protein	rsID	Proxy	PheWAS associations ^a	
				Traits	Disease
BMI	ADH1B	rs1229984	None	Alcohol, SBP, Whole body fat, Leg fat percentage mass	Esophageal, head and neck and
WC	ALDH2	rs4646776	None	Alcohol	Esophageal cancer
BMI	ALDH5A1	rs2235502	AFR/AMR/EAS/EUR/SAS	-	Allergy, Cause of death: cerebrum,
BMI	APOBR	rs180743	None	Alcohol, BMI, Body fat percentage, Weight, Whole body fat, WC, HC, Leg and arm fat mass, Education	Inflammatory bowel disease
BMI	APOE	rs429358	None	BMI, Body fat percentage, Blood pressure, Cholesterol, C-reactive protein, Leg and arm fat mass, Pulse rate, Physical activity, WC, Weight	Alzheimer disease, Coronary artery disease, Dementia, Diabetes
BMI	ASAH1	rs2299604	-	-	-
BMI	BMPER	rs6951634	AMR/EAS/EUR/SAS	-	Alzheimer disease
BMI	CACYBP	rs12563930	None	BMI, Impedance of whole body and arm, Leg fat mass and percentage	-
BMI	CD164L2	rs79775449	None	BMI	-
BMI	CFB	rs1265888	None	Impedance of whole body, arm and leg, Trunk and leg fat-free mass, Whole body water mass, Cholesterol, Blood pressure	Rheumatoid arthritis, Schizophrenia, Diabetes
BMI	CFHR2	rs4085749	None	-	Neovascularization, Agx10-related
BMI	EFEMP1	rs58680090	None	Basal metabolic rate, Height, Trunk fat-free mass, Weigh, Whole body, arm and leg fat-free mass, Whole body water mass, Trunk fat mass, Impedance of whole body, Forced vital capacity	Inguinal hernia
BMI	F13B	rs12134960	None	SBP	Neovascularization, Agx10-related
BMI	FGL1	rs3739404	-	-	-
BMI	FN1	rs1437787	EAS	-	Coronary artery disease
BMI	ITIH3	rs2286797	None	BMI	Myocardial infraction
BMI, WC	ITIH4	rs6803519	None	Height, Anxiety	Schizophrenia
BMI	LRP11	rs9688902	None	BMI, Hand grip strength	Hip pain
BMI	NCR3LG1	rs2051772	None	BMI, Height, Impedance of whole body, arm and leg	Diabetes
BMI	NUDT5	rs7100710	None	BMI, Peak expiratory flow, Forced expiratory volume	Diabetes
BMI	OGN	rs7023004	None	Height, Impedance of whole body, arm and leg	-
BMI	PRDX6	rs61826753	-	-	-
BMI	PRSS53	rs11150606	-	-	-
BMI	PTPRB	rs2465811	-	-	-
BMI	PTPRZ1	rs28379507	EAS/EUR	Heel bone mineral density	-
BMI	SCAMP3	rs4971072	None	Serum magnesium, Monocytes	Crohn's disease
BMI	SERPINF2	rs8077638	EAS	Serum albumin	-
BMI	SLURP1	rs1036385	None	Duodenal ulcer	-
BMI	SUSD5	rs6764459	None	Forced vital capacity	-
BMI	TSPAN8	rs9683252	AFR/EAS/EUR/SAS	-	Asthma
BMI	TXNDC15	rs3733897	None	Height	-

^aTraits or diseases in bold: $P < 5 \times 10^{-8}$, others were $P < 5 \times 10^{-6}$; BMI: body mass index; HC: hip circumference; SBP: systolic blood pressure; WC: waist circumference

Supplementary Table 10. Number of proteins with QC warnings

Number of QC warnings per protein, n (%)¹	Number of proteins, n (%)²
9 (0.2%)	108 (3.7%)
10 (0.3%)	51 (1.7%)
13 (0.3%)	148 (5.1%)
15 (0.4%)	145 (5.0%)
20 (0.5%)	62 (2.1%)
22 (0.6%)	93 (3.2%)
23 (0.6%)	62 (2.1%)
25 (0.6%)	115 (3.9%)
31 (0.8%)	85 (2.9%)
32 (0.8%)	76 (2.6%)
34 (0.9%)	62 (2.1%)
36 (0.9%)	89 (3.0%)
37 (0.9%)	92 (3.1%)
45 (1.1%)	181 (6.2%)
46 (1.2%)	98 (3.4%)
53 (1.3%)	109 (3.7%)
58 (1.5%)	113 (3.9%)
79 (2.0%)	93 (3.2%)
90 (2.3%)	109 (3.7%)
105 (2.6%)	96 (3.3%)
113 (2.8%)	144 (4.9%)
115 (2.9%)	103 (3.5%)
121 (3.0%)	143 (4.9%)
123 (3.1%)	92 (3.1%)
127 (3.2%)	88 (3.0%)
139 (3.5%)	79 (2.7%)
141 (3.5%)	69 (2.4%)
148 (3.7%)	109 (3.7%)
158 (4.0%)	105 (3.6%)

¹ A total of 3977 samples² A total of 2923 proteins

Supplementary Table 11. Variance explained by adiposity genetic scores in CKB and UKB

Adiposity measures	CKB			UKB		
	Men (n=1840)	Women (n=2137)	All (n=3977)	Men (n=15,353)	Women (n=19,094)	All (n=34,447)
BMI	2.4	4.8	3.7	8.5	8.0	8.1
BF%*	2.7	3.9	1.9	7.3	6.4	3.5
WC	1.6	3.6	2.5	5.9	5.6	4.7
WHR	1.0	2.4	1.5	2.7	6.9	3.0

* In CKB, for BF% the analyses were performed for 3973 participants (1838 men and 2135 women)

Abbreviations: BF%=body fat percentage; BMI=body mass index; CKB=China Kadoorie Biobank; UKB=UK Biobank; WC=waist circumference; WHR=waist-to-hip ratio

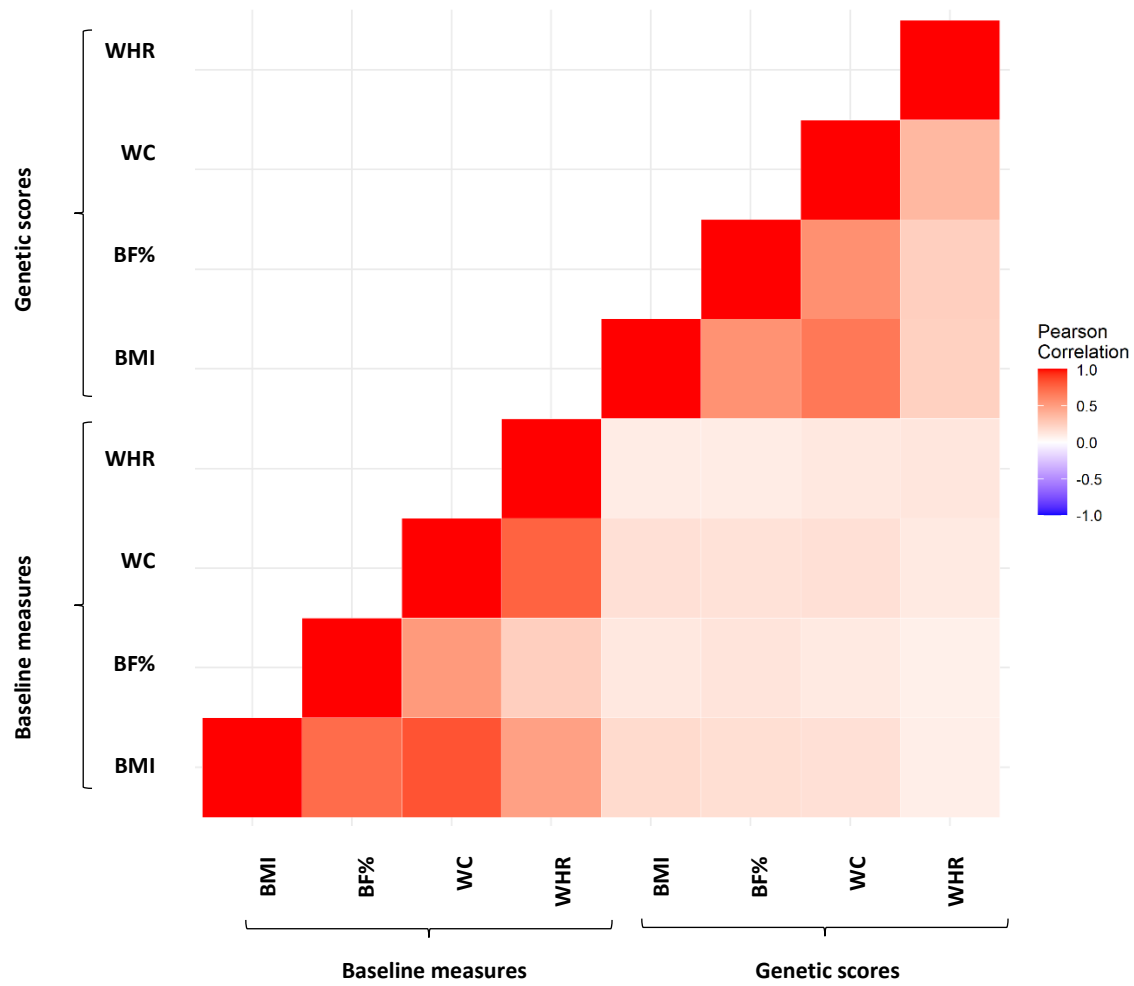
Supplementary Table 12. Associations of potential confounders with BMI and WC GS

Confounder	OR or β (95% CI) per 1-SD higher genetically-instrumented	
	BMI	WC
Ever-regular smoker	1.08 (0.97, 1.20)	1.09 (0.98, 1.22)
Ever-regular alcohol drinker	0.96 (0.86, 1.06)	0.99 (0.90, 1.10)
Physical activity	0.94 (0.85, 1.03)	0.97 (0.88, 1.06)
Education	1.01 (0.92, 1.10)	1.02 (0.94, 1.10)
Income	1.02 (0.95, 1.10)	1.01 (0.94, 1.08)
Standing height, cm	0.02 (-0.17, 0.17)	0.22 (0.04, 0.39)
RPG, mmol/L	0.21 (0.11, 0.31)	0.23 (0.14, 0.33)
SBP, mmHg	1.23 (0.55, 1.92)	0.42 (-0.27, 1.12)
BMI, kg/m ²	-	0.57 (0.46, 0.67)
Waist circumference, cm	1.57 (1.28, 1.86)	-

The model was adjusted for age at baseline, age squared, sex, 10 regions, and 11 PCs. Potential confounders were dichotomised: ever-regular smoker (yes vs no), ever-regular alcohol drinker (yes vs no), total PA (≥ 30 vs < 30 MET-h/day), education (≥ 9 vs < 9 years), and household income ($\geq 10,000$ vs $< 10,000$ RMB/year). The analyses of smoking and alcohol were conducted in men due to the small number of women who smoked (4%) or drank (2%).

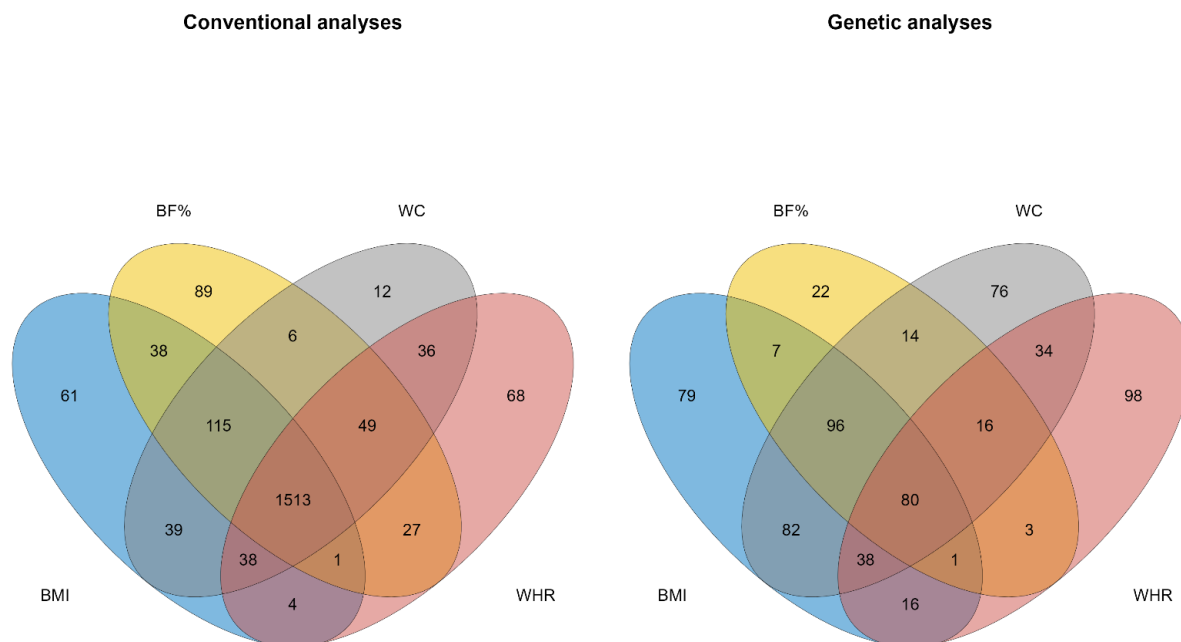
Abbreviations: BMI=body mass index; OR=odds ratio; RPG=random plasma glucose; SBP=systolic blood pressure; WC=waist circumference

Supplementary Figure 1. Correlation between adiposity measures and genetic scores

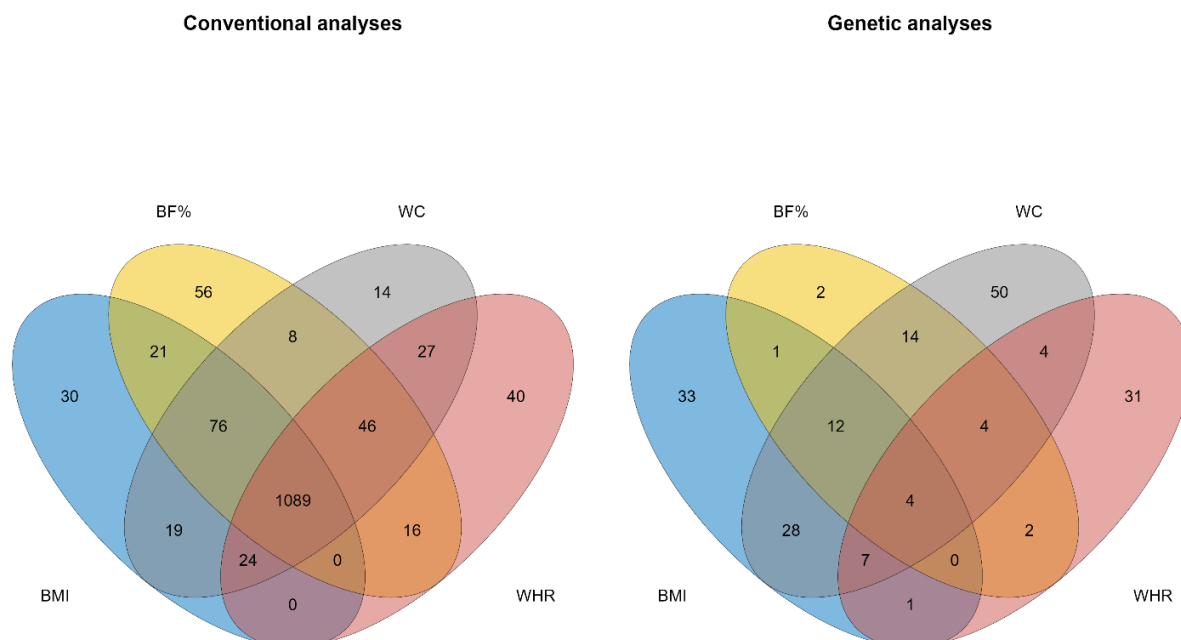


Supplementary Figure 2. Number of proteins significantly associated with adiposity in conventional and genetic analyses

a) FDR<0.05



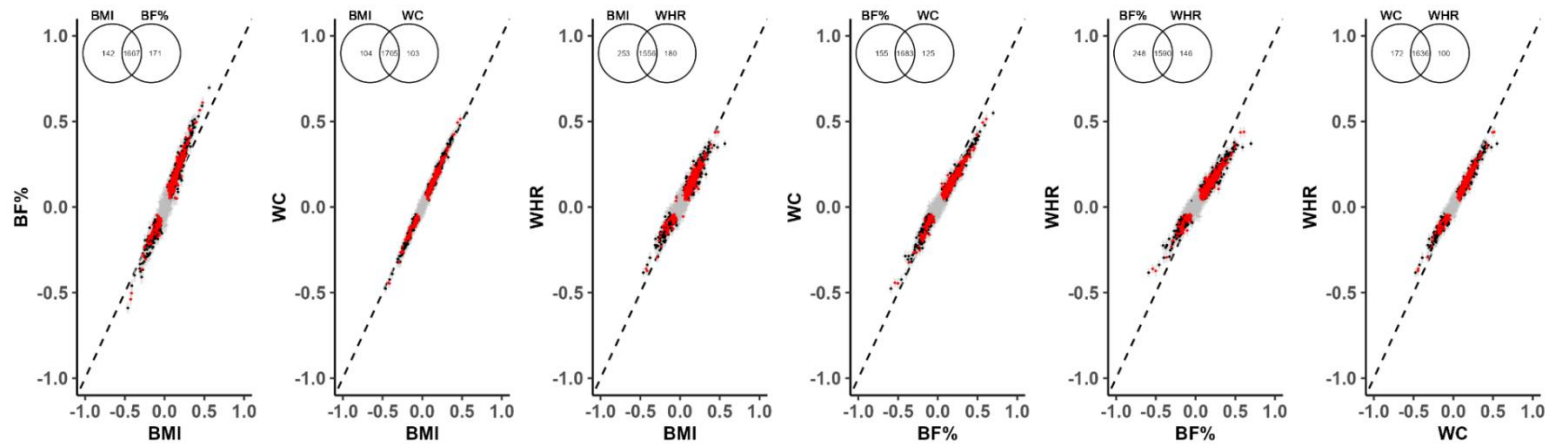
b) Bonferroni<0.05



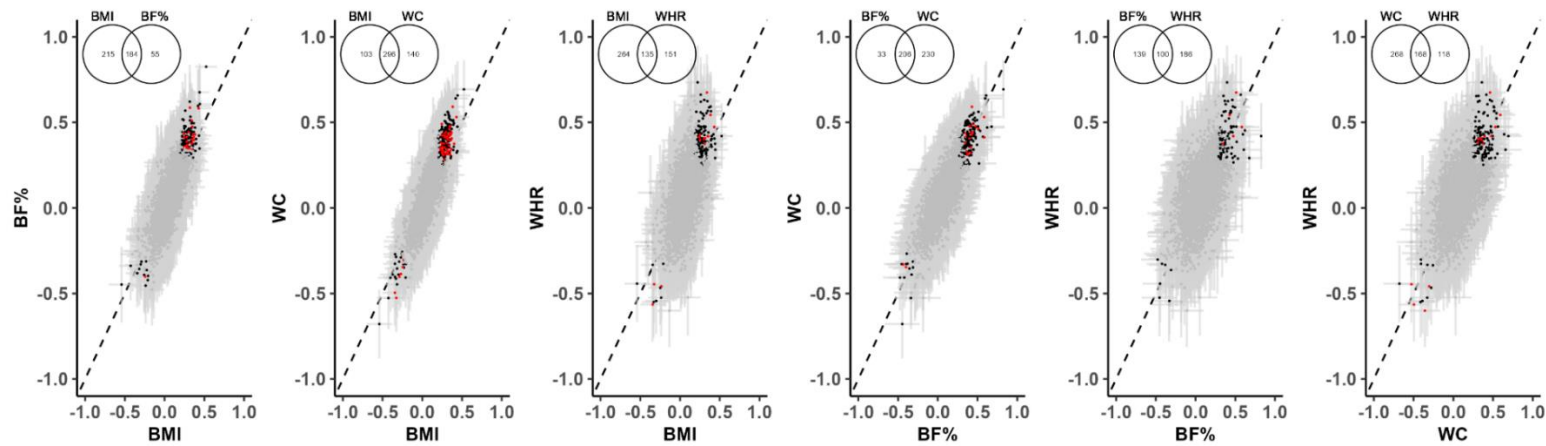
Supplementary Figure 3. Global comparison of associations of protein biomarkers with 1-SD higher BMI, BF%, WC and WHR in conventional and genetic analyses in OLINK batch 1 and 2

Black dots denote Olink batch 1, while red dots denote batch 2 and grey lines denote the 95% confidence intervals. Analyses were adjusted for age, age², sex, study area, fasting time, ambient temperature, ascertainment status, and the first 11 PCs (for genetic analyses only).

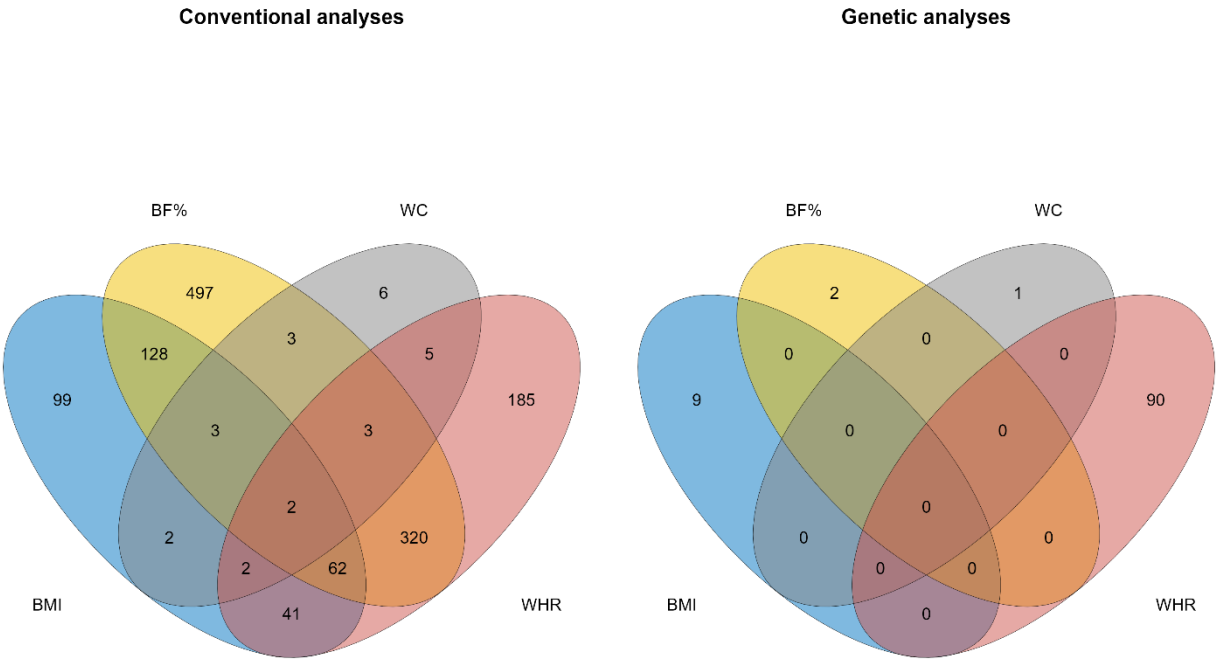
Conventional analyses



Genetic analyses



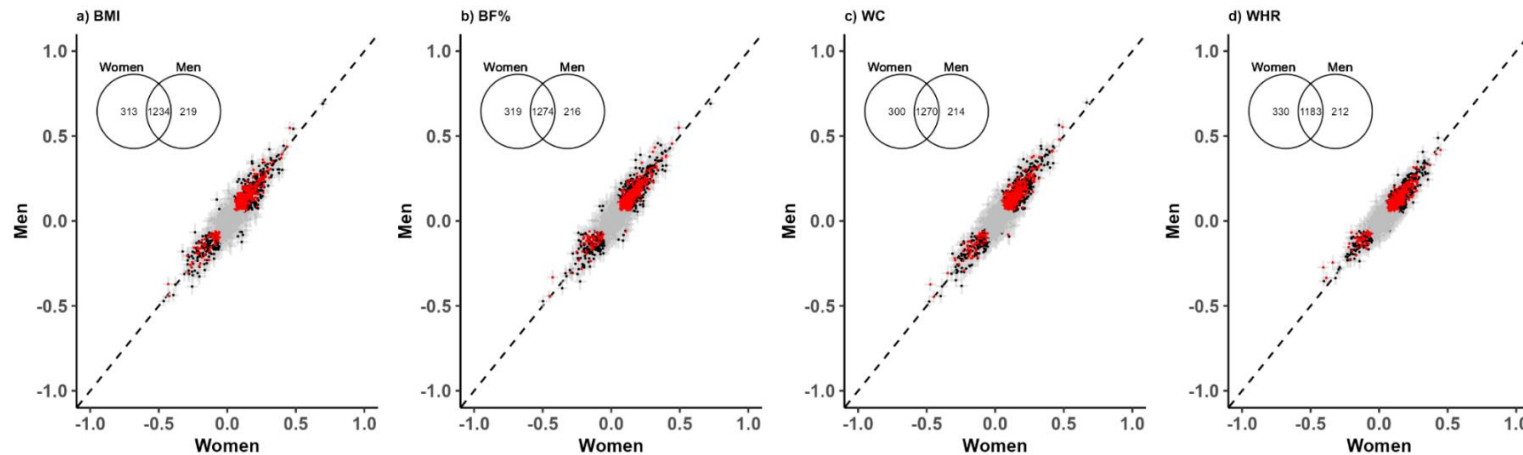
Supplementary Figure 4. Number of proteins significantly associated with adiposity in conventional and genetic analyses after mutual adjustments



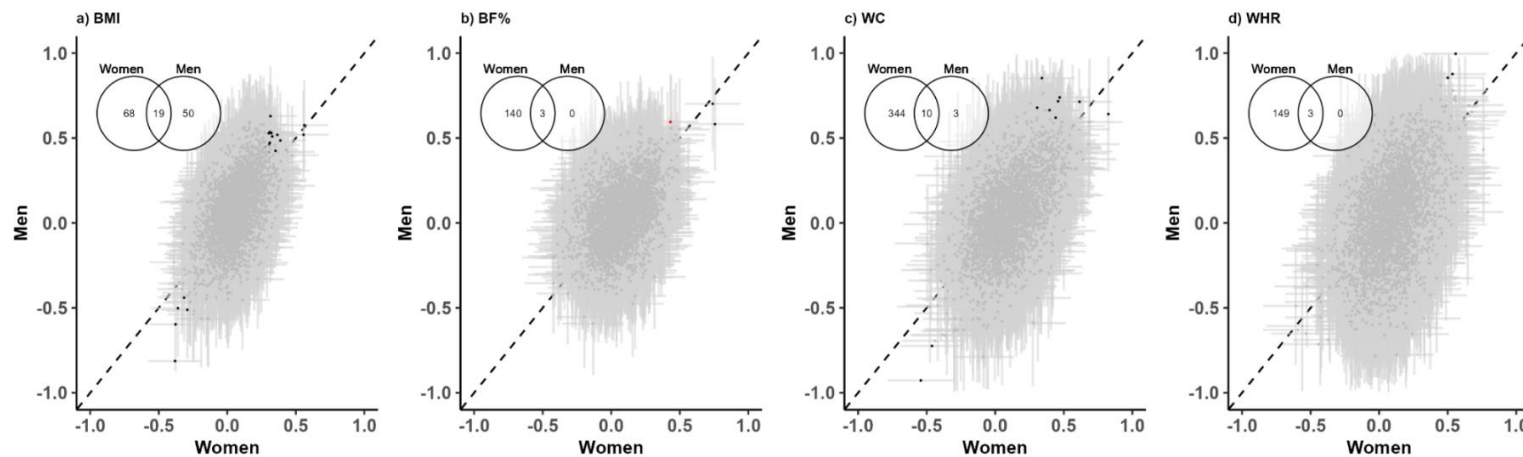
Supplementary Figure 5. Global comparison of associations of protein biomarkers with 1-SD higher BMI, BF%, WC and WHR in conventional and genetic analyses in OLINK batch 1 and 2, by sex

Black dots denote Olink batch 1, while red dots denote batch 2 and grey lines denote the 95% confidence intervals. Analyses were adjusted for age, age², study area, fasting time, ambient temperature, ascertainment status, and the first 11 PCs (for genetic analyses only).

Conventional analyses



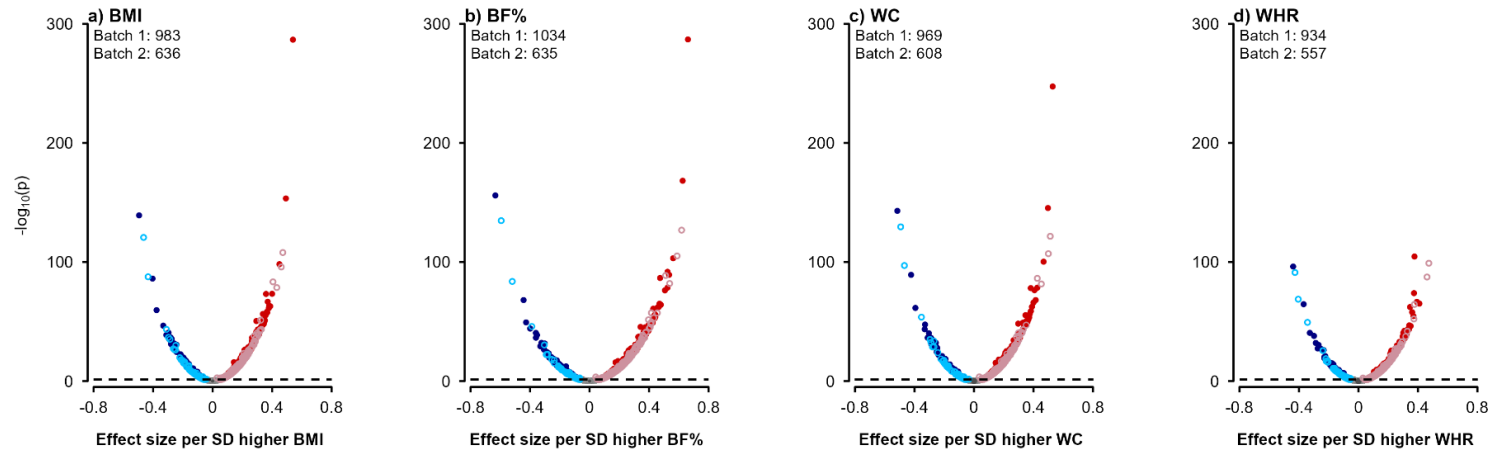
Genetic analyses



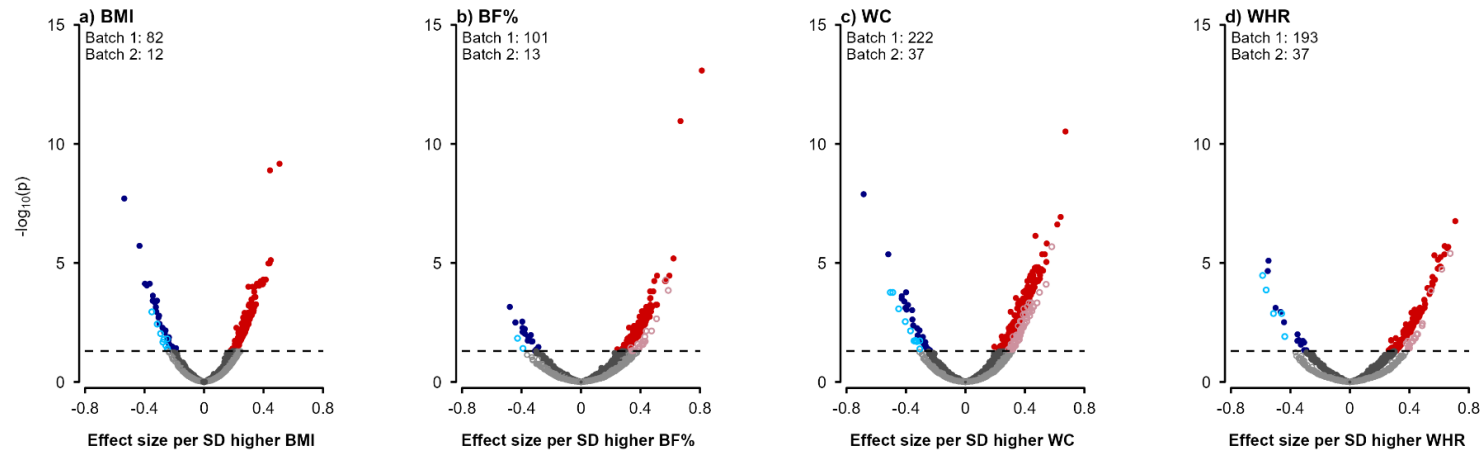
Supplementary Figure 6. Volcano plot of associations of proteins with 1-SD higher BMI, BF%, WC and WHR in conventional and genetic analyses in OLINK batch 1 and 2 in the subcohort

Solid dots denote Olink batch 1, while open dots denote batch 2. Analyses were adjusted for age, age², sex, study area, fasting time, ambient temperature, plate ID, ascertainment status, and the first 11 PCs (for genetic analyses only).

Conventional analyses



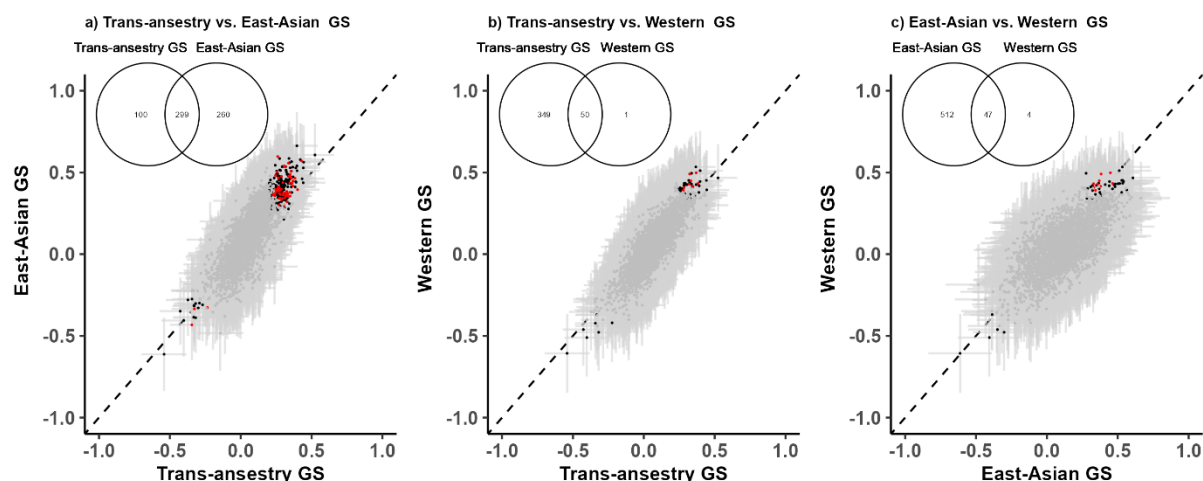
Genetic analyses



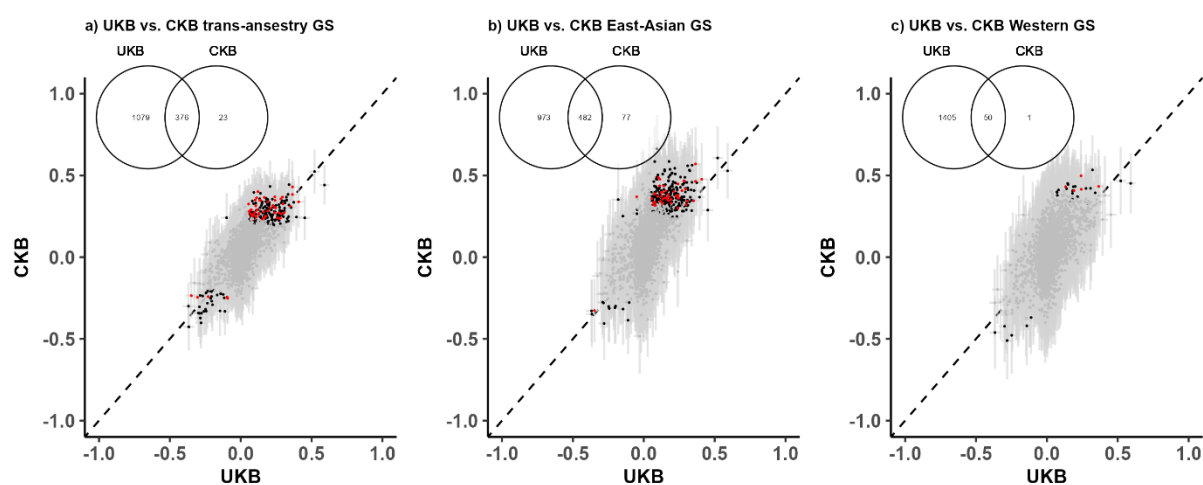
Supplementary Figure 7. Comparison of associations of protein biomarkers with 1-SD higher BMI in genetic analyses in CKB and CKB vs. UKB using different CKB BMI GS

Black dots denote Olink batch 1, while red dots denote batch 2 and grey lines denote the 95% confidence intervals. In CKB, analyses were adjusted for age, age², sex, study area, fasting time, ambient temperature, ascertainment status, and the first 11 PCs. In UKB, analyses were adjusted for age, age², sex, assessment centre, fasting time, plate ID, and the first 40 PCs.

Comparison of CKB GSs

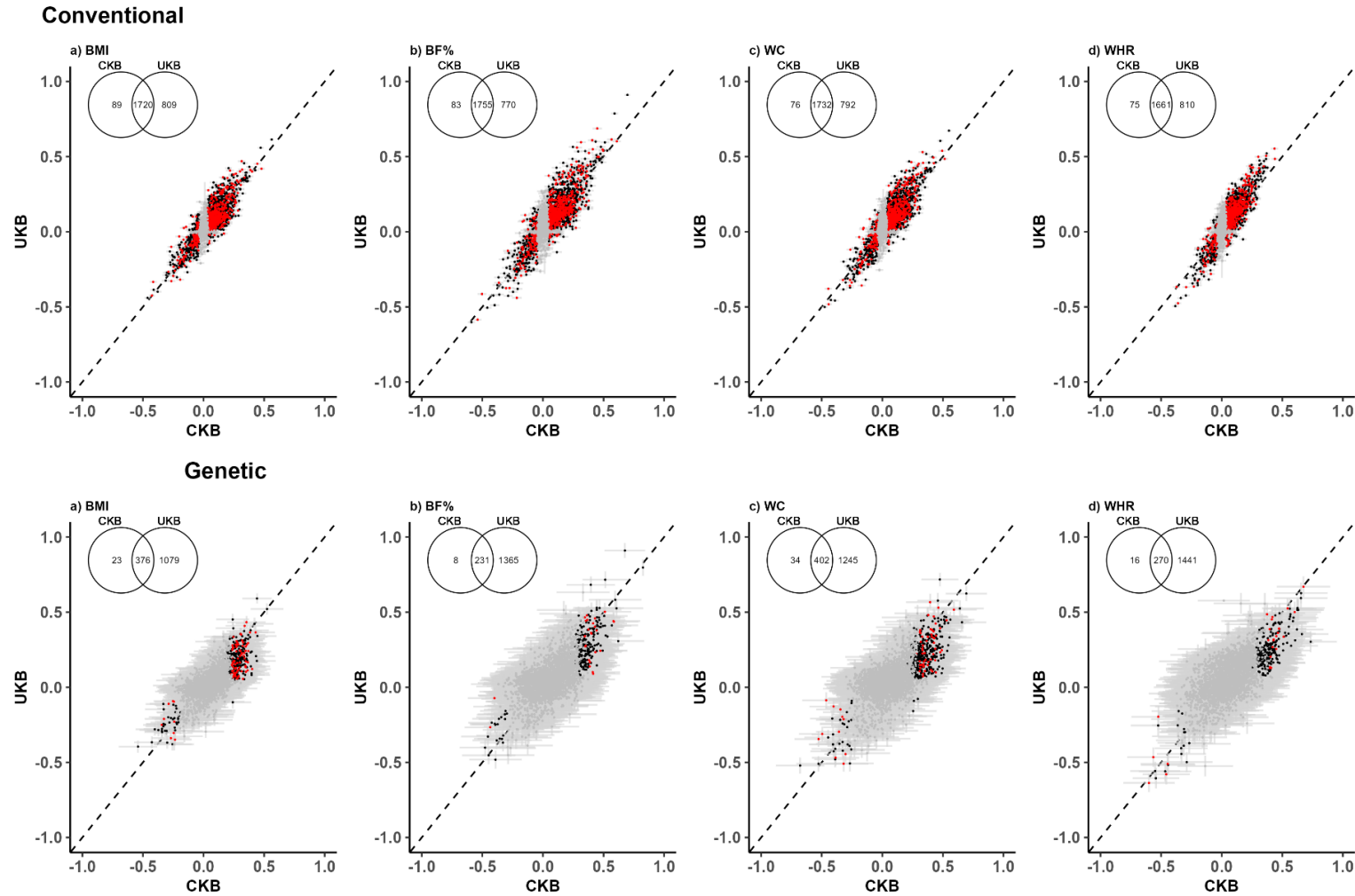


UKB vs. CKB GS

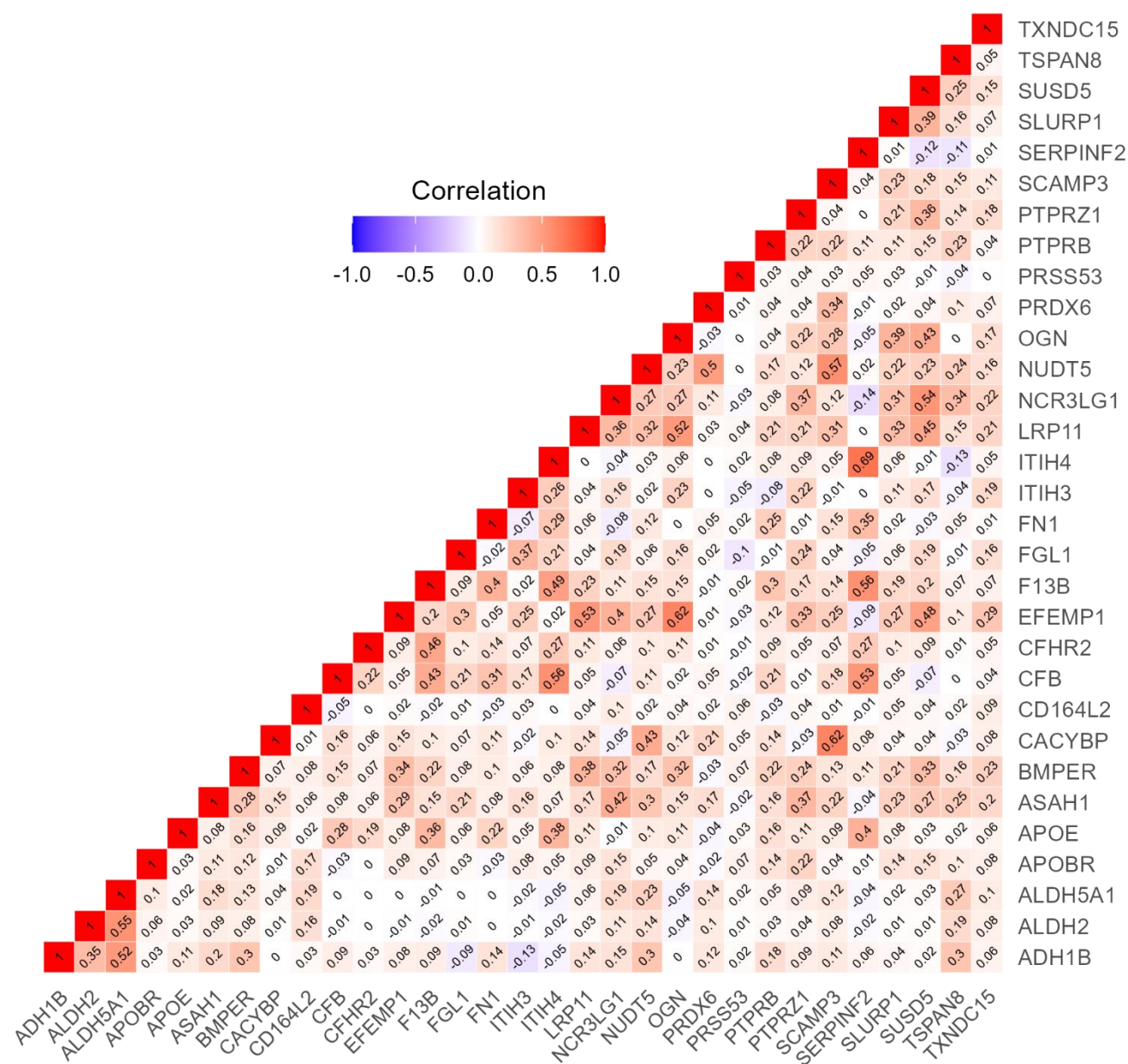


Supplementary Figure 8. Comparison of associations of protein biomarkers with 1-SD higher BMI, BF%, WC and WHR in conventional and genetic analyses in CKB vs. UKB, in OLINK batch 1 and 2

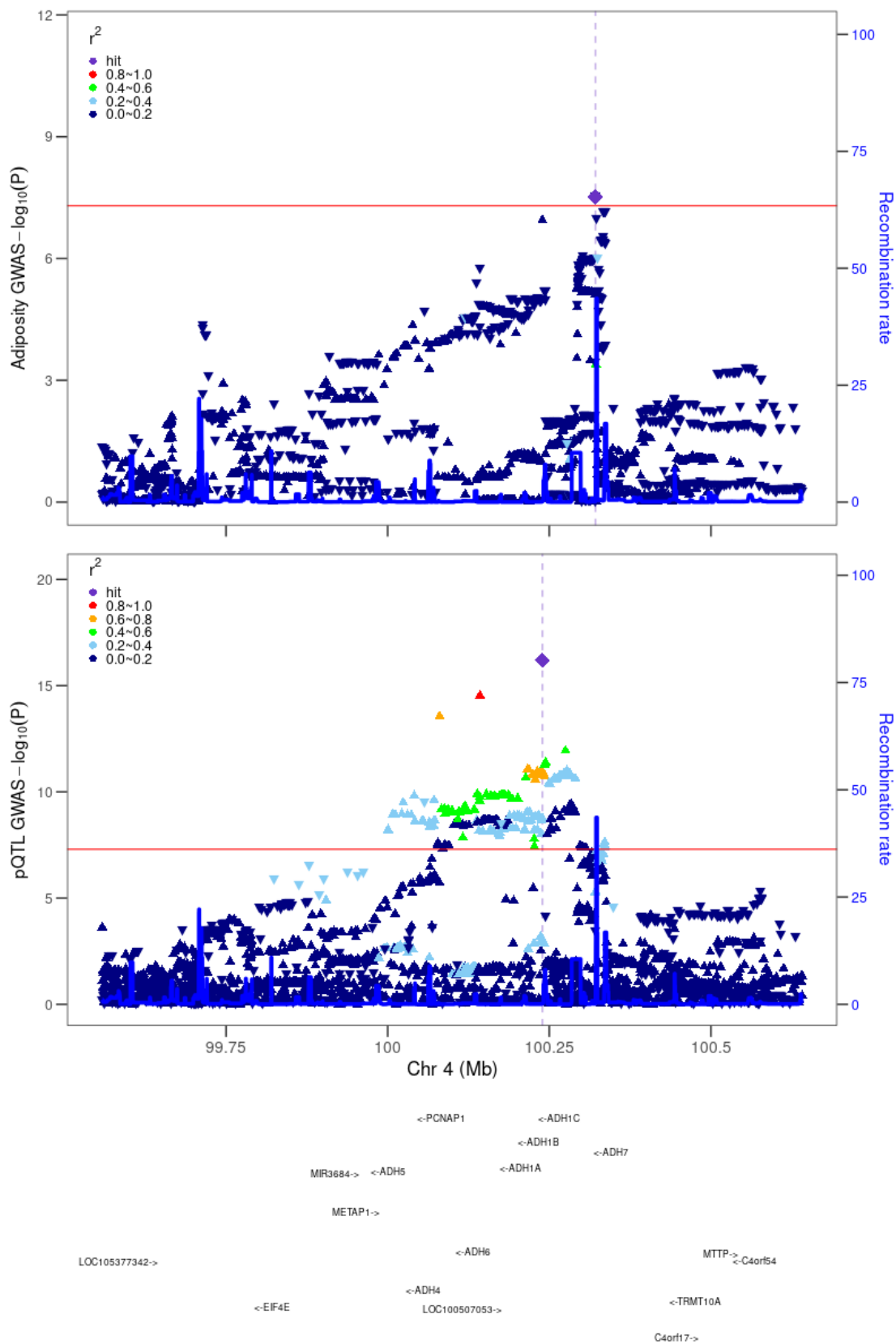
Black dots denote Olink batch 1, while red dots denote batch 2 and grey lines denote the 95% confidence intervals. In CKB, analyses were adjusted for age, age², sex, study area, fasting time, ambient temperature, ascertainment status, and the first 11 PCs (for genetic analyses only). In UKB, analyses were adjusted for age, age², sex, assessment centre, fasting time, plate ID, and the first 40 PCs (for genetic analyses only).



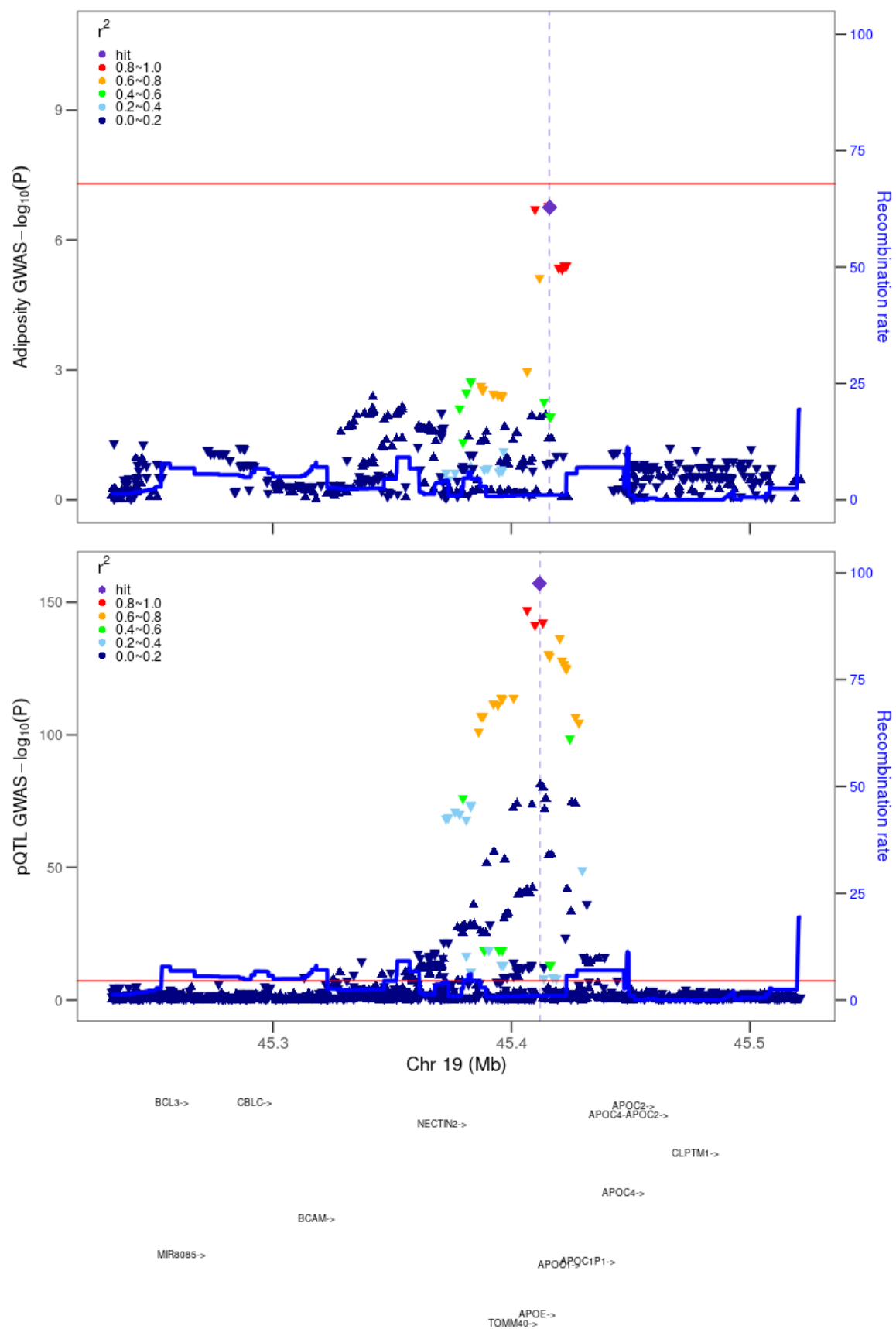
Supplementary Figure 9. Correlation matrix between the 31 proteins showing causal relationships with adiposity



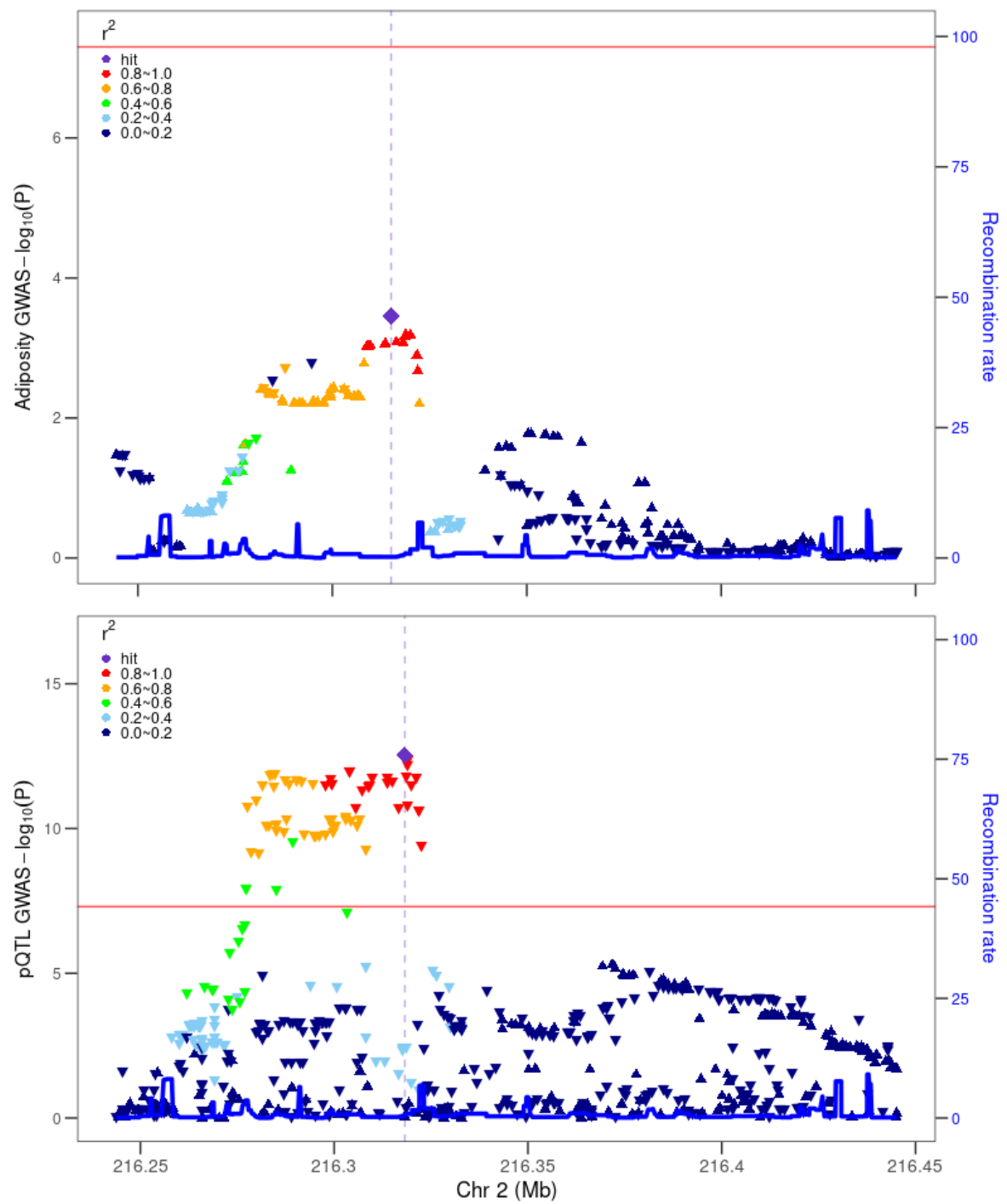
Supplementary Figure 10. Locus-zoom plots of colocalisation analyses
a) BMI and ADH1B



b) BMI and APOE

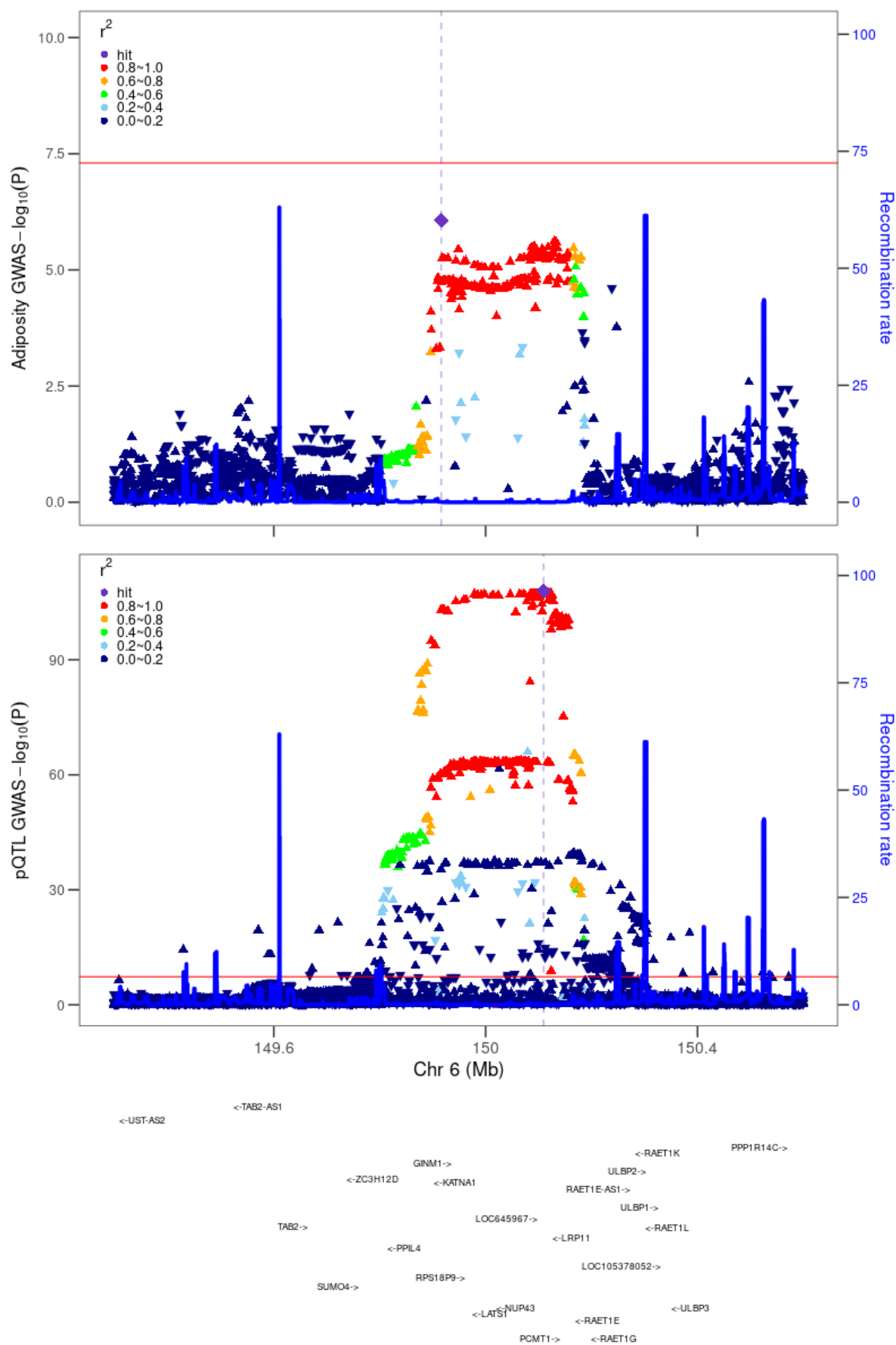


c) BMI and FN1

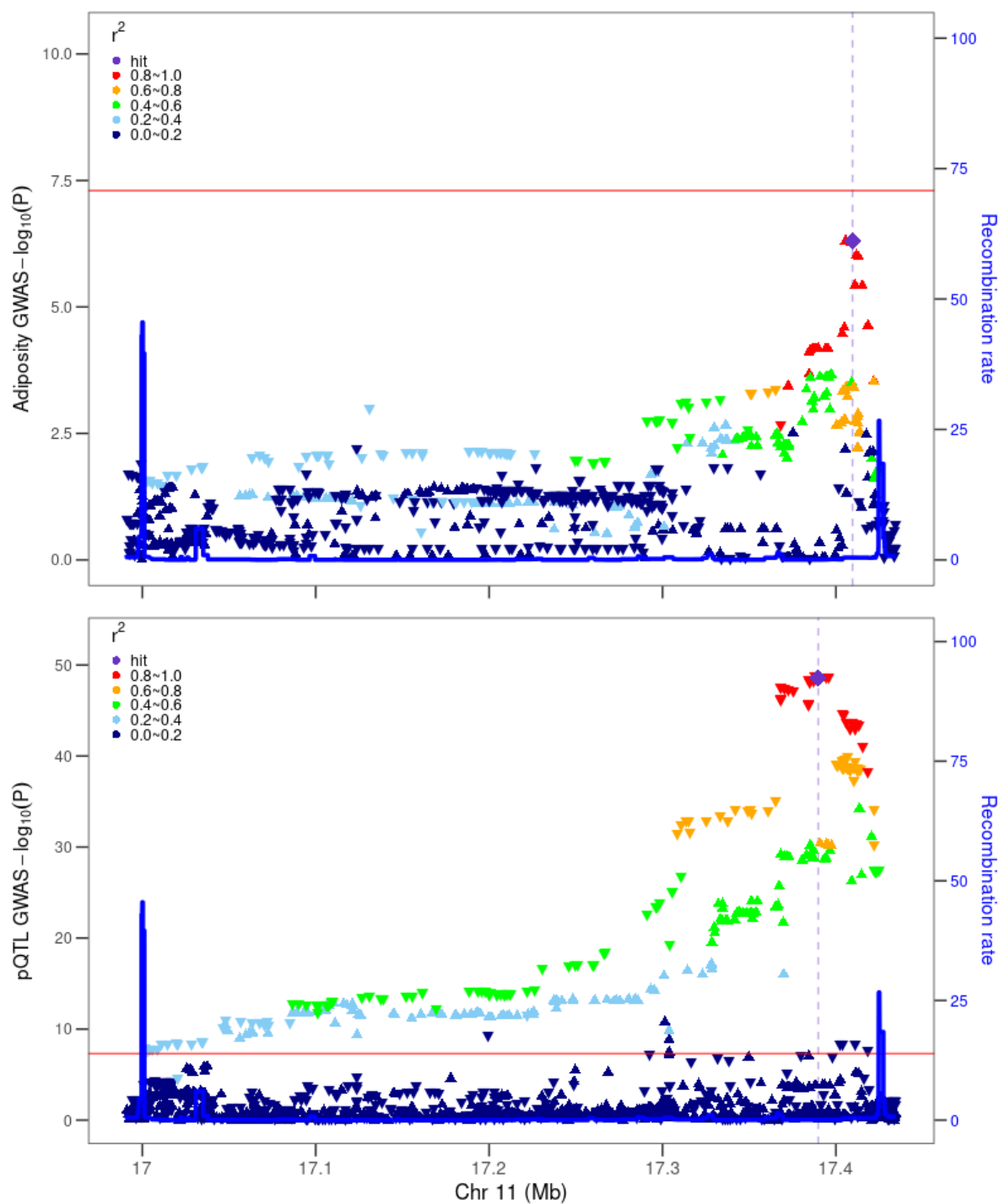


LOC102724849->

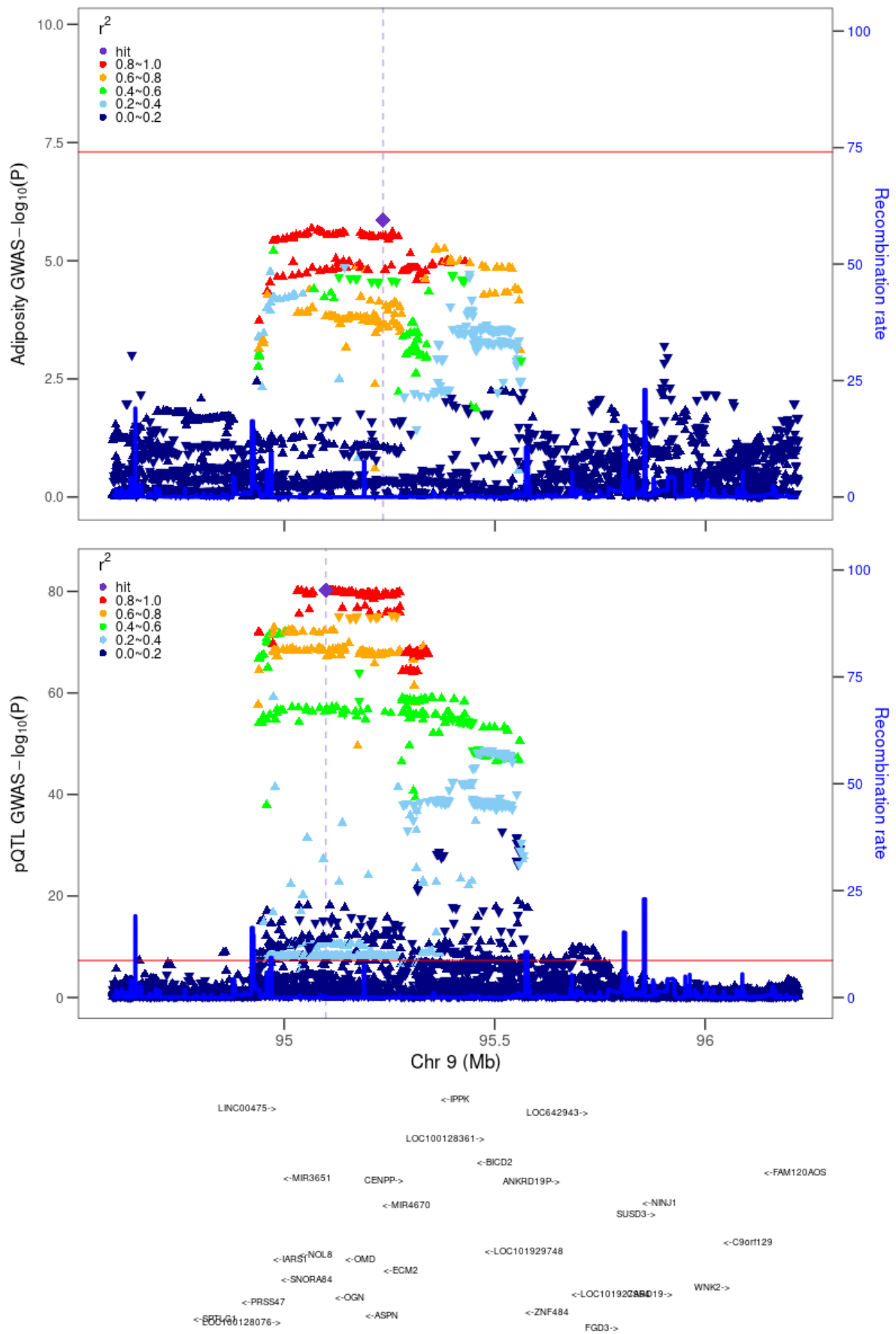
d) BMI and LRP11



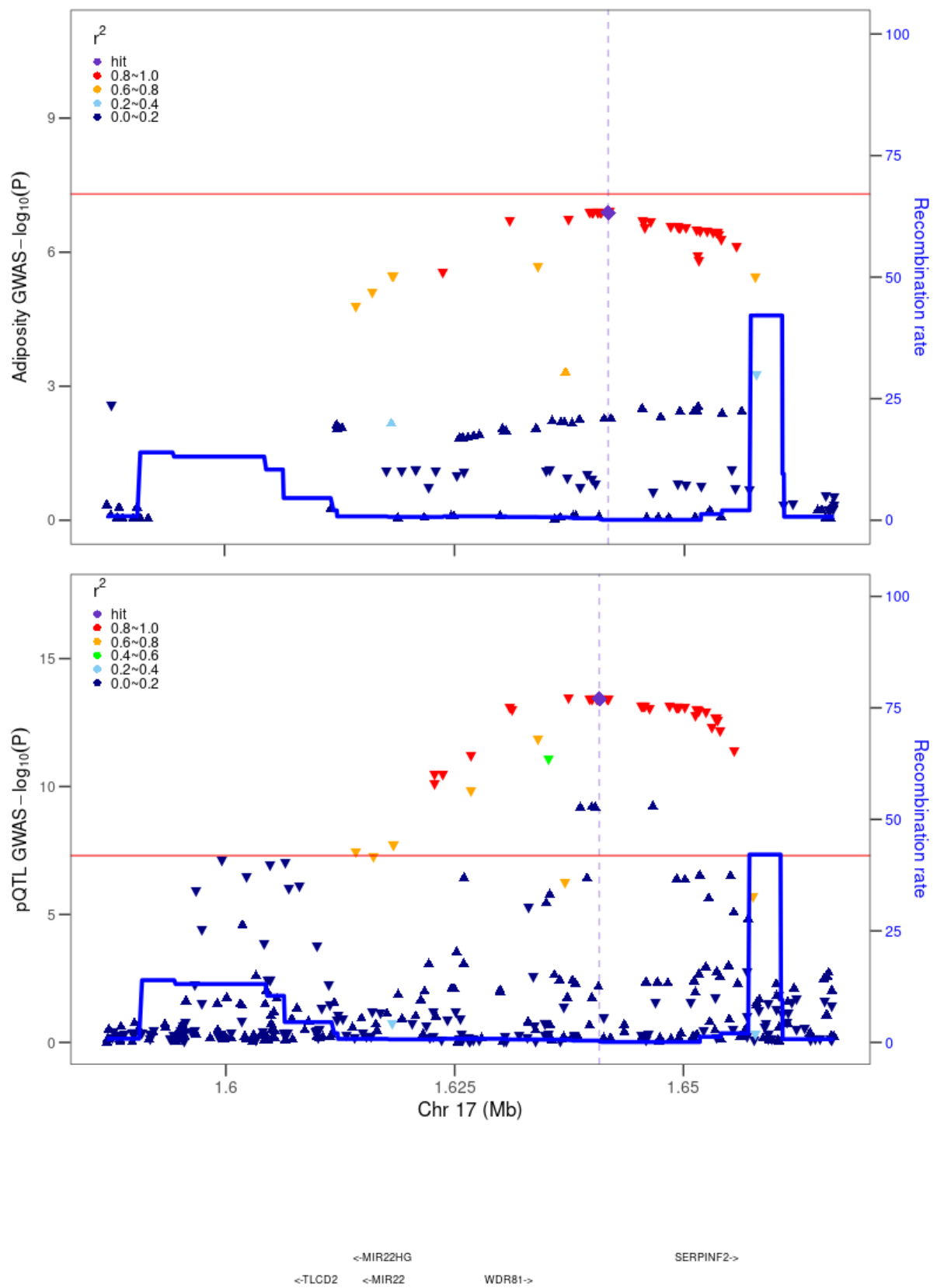
e) BMI and NCR3LG1



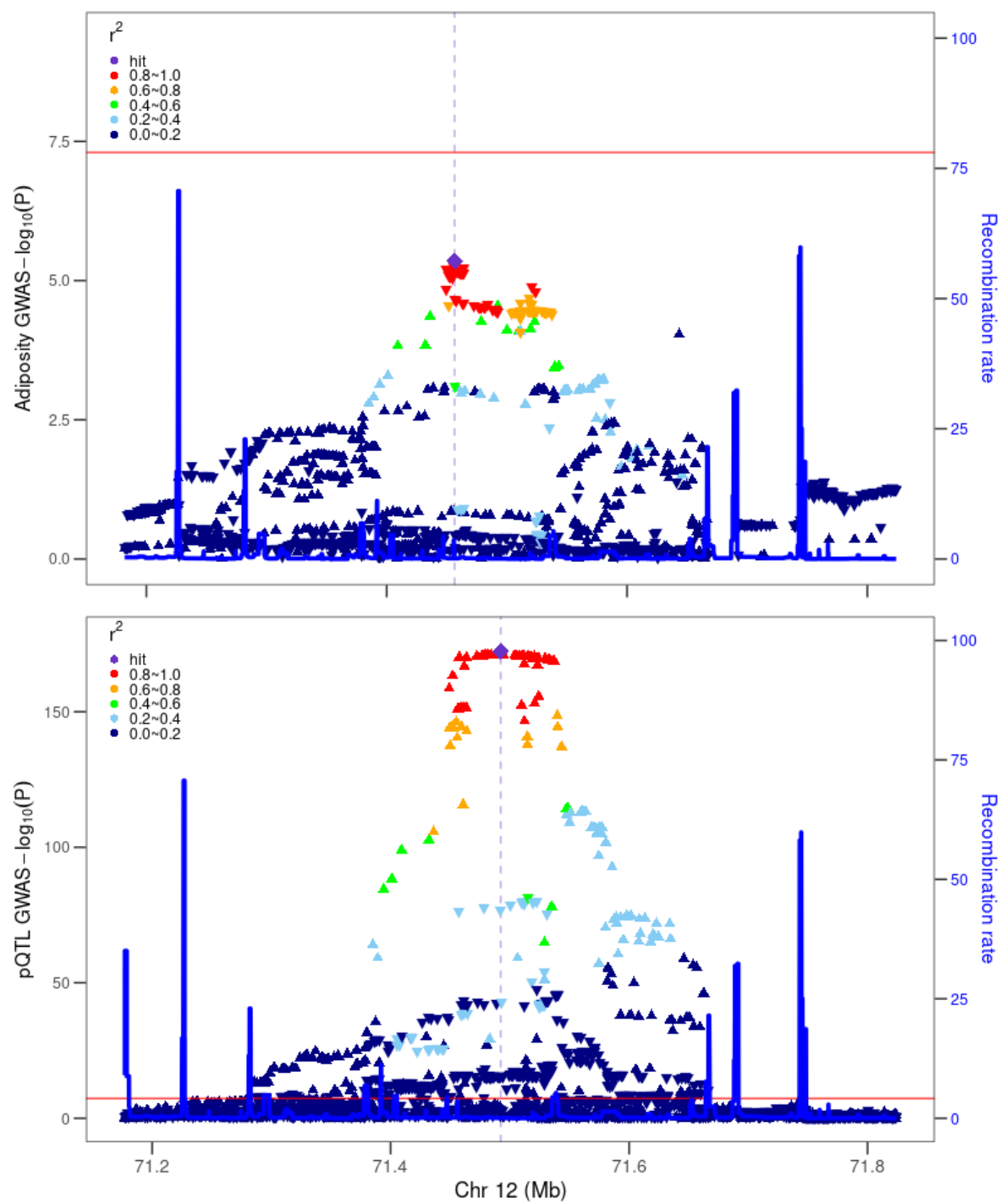
f) BMI and OGN



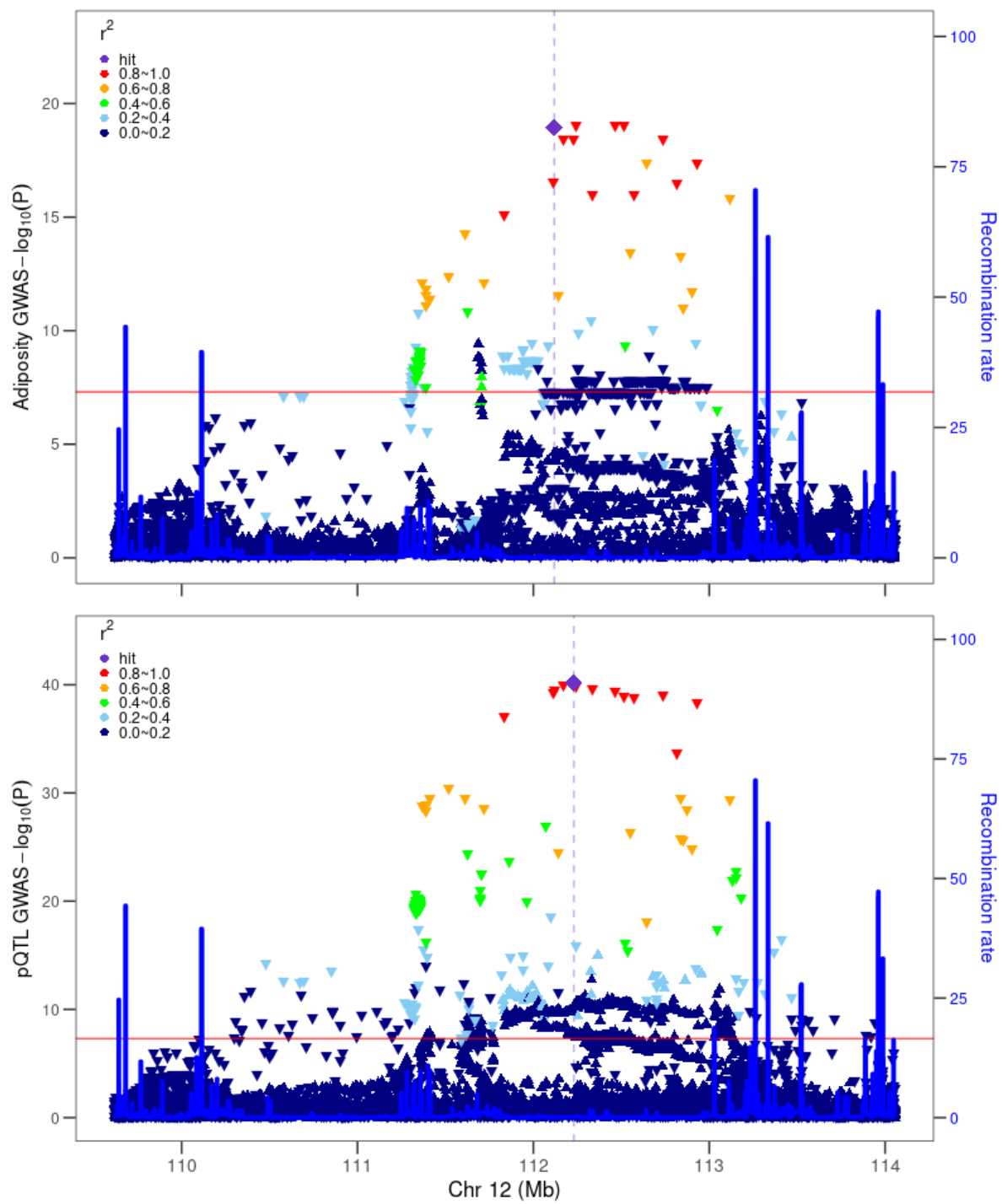
g) BMI and SERPINF2



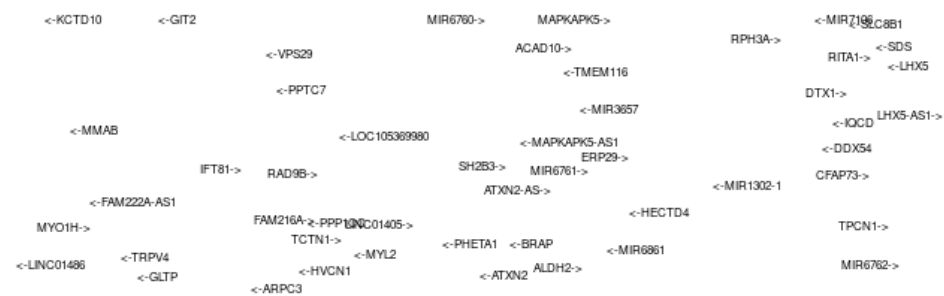
h) BMI and TSPAN8



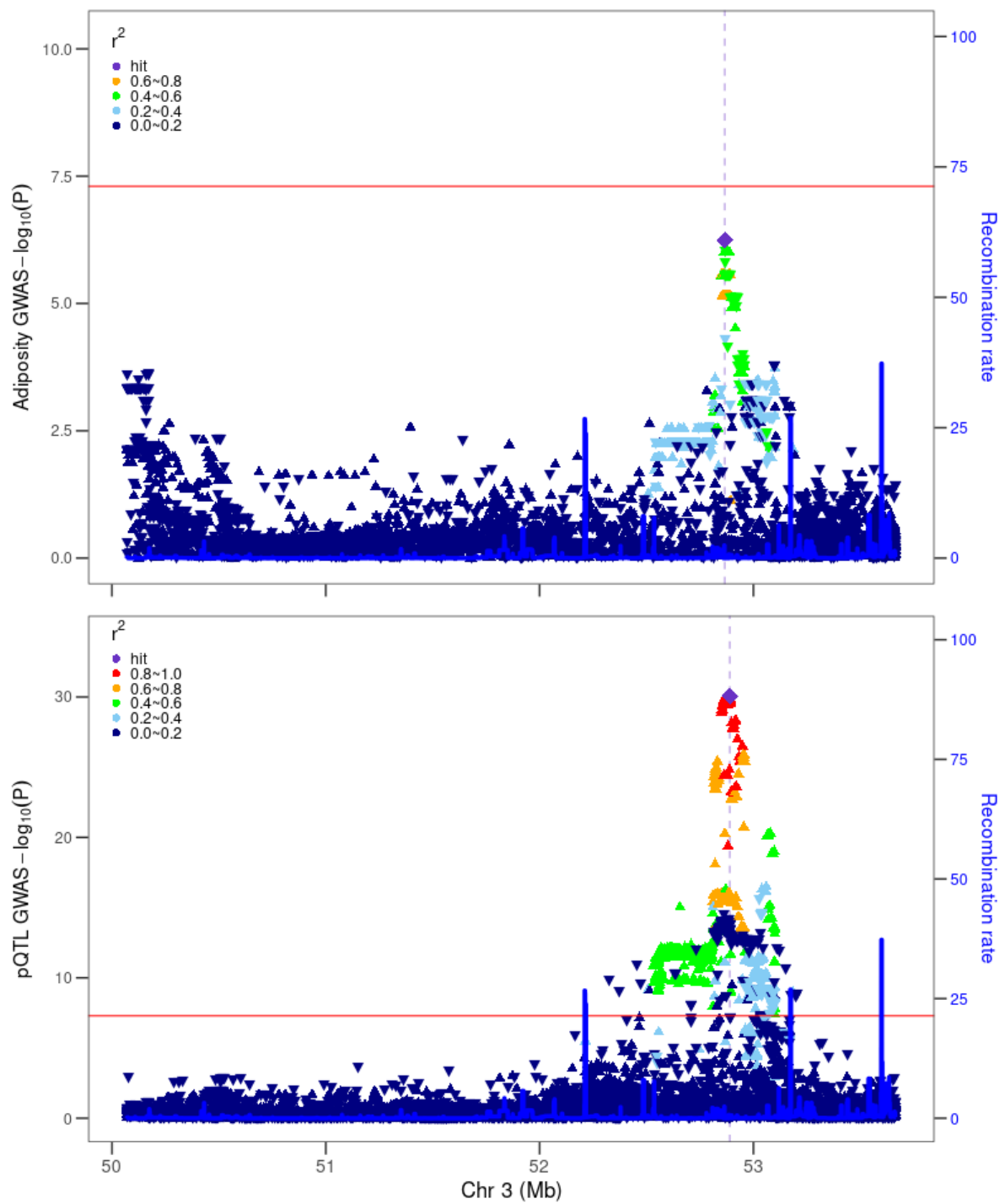
i) WC and ALDH2



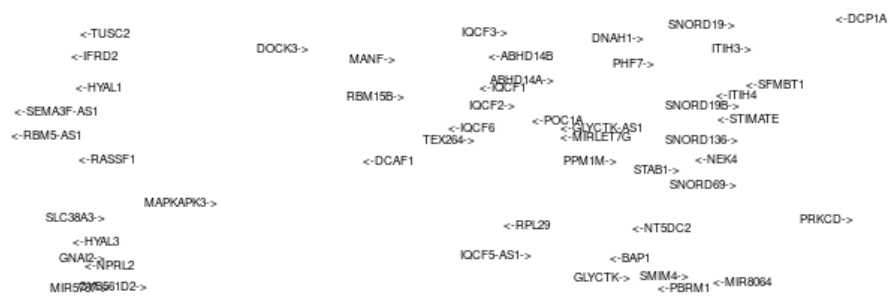
plotting 50 genes



j) WC and ITIH4

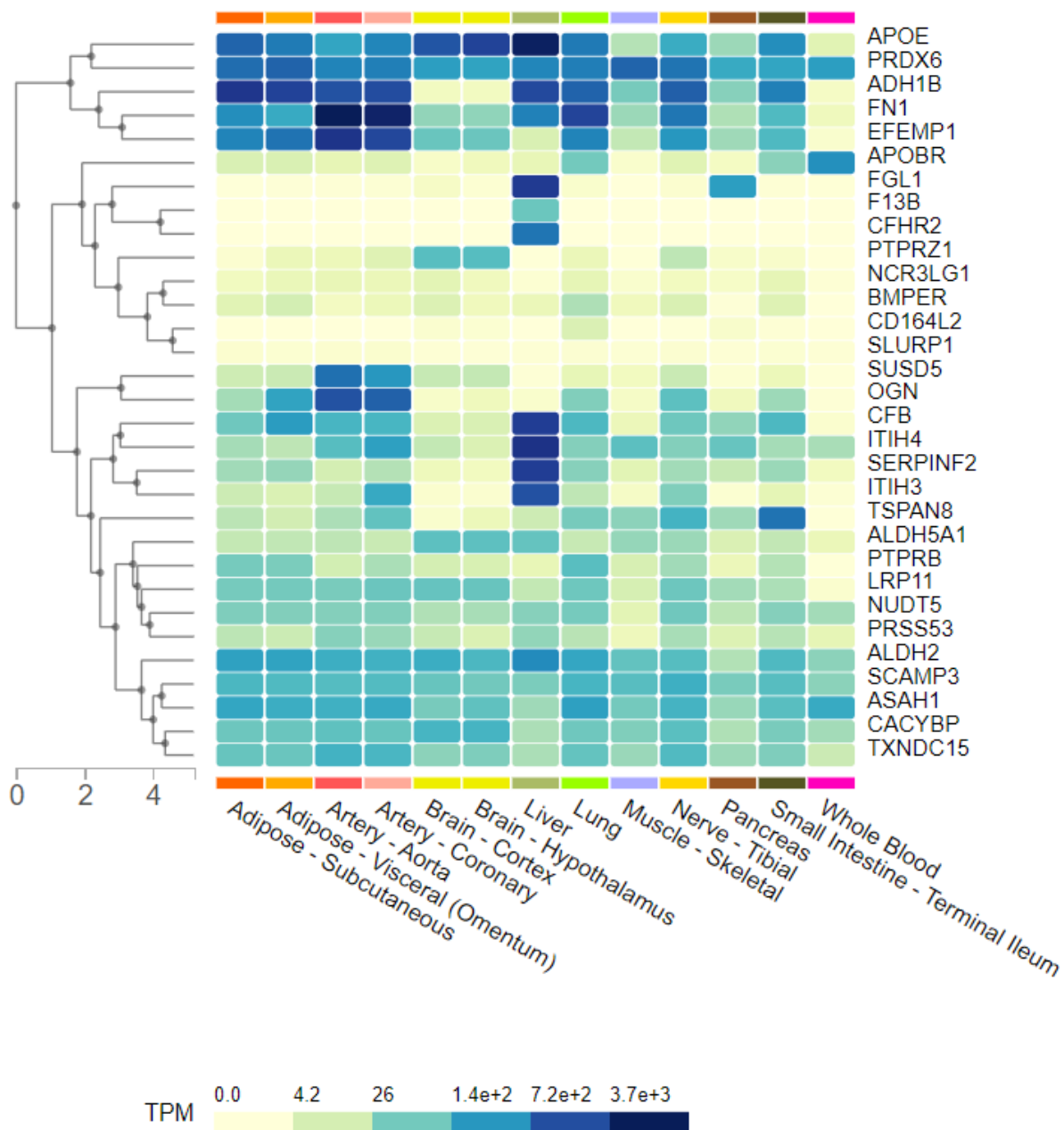


plotting 50 genes



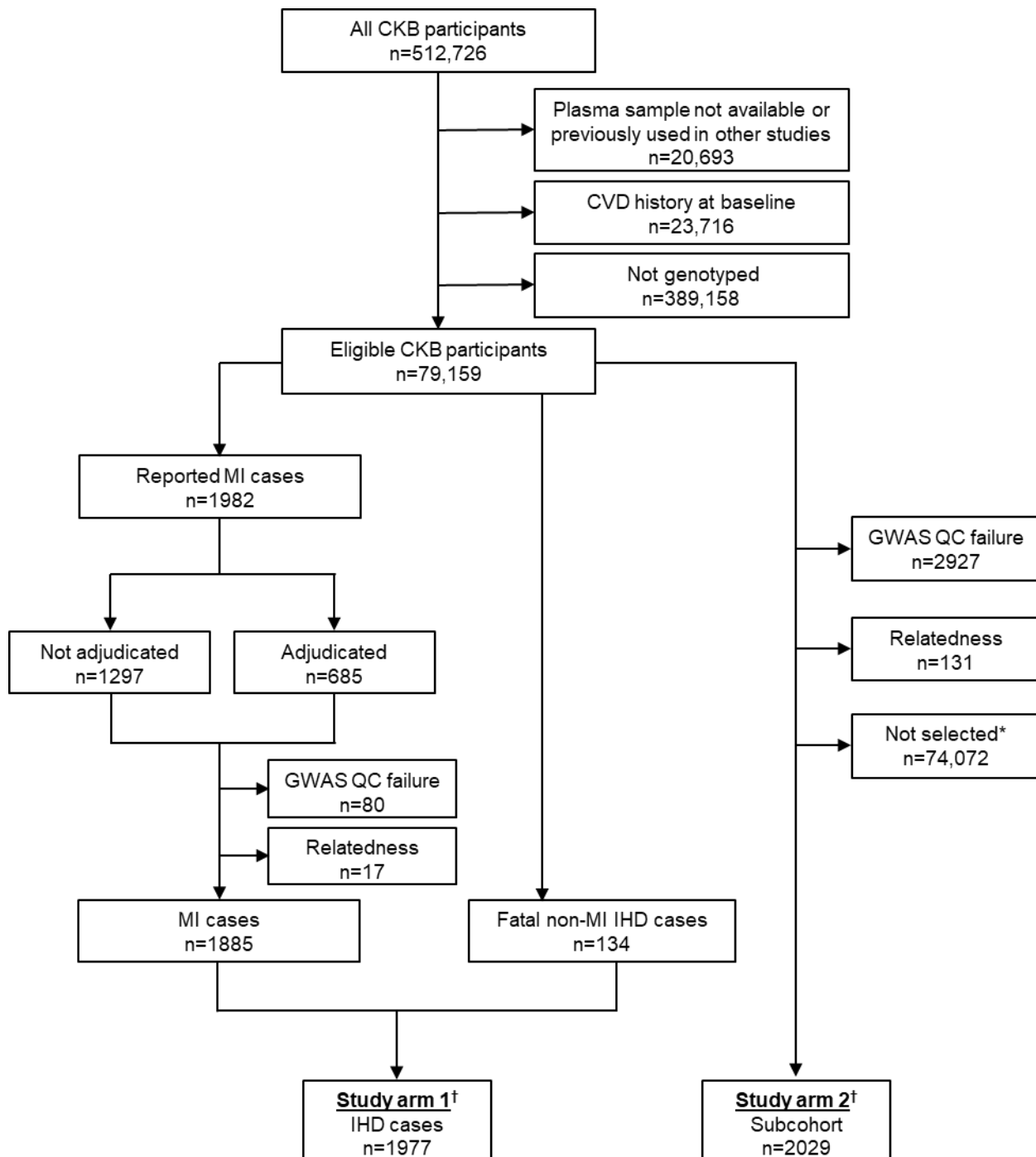
Supplementary Figure 11. Human tissue-specific gene expression for the 31 proteins showing causal relationships with adiposity

Human RNA-seq data from GTEx showing the transcript per million (TPM) expression values for the genes encoding the proteins



Supplementary Figure 12. Flow diagram of study design and participant selection in CKB

*Selection for the subcohort used simple random sampling; †Individuals may be included in more than one study arm



Supplementary Figure 13. Distribution of proteins

