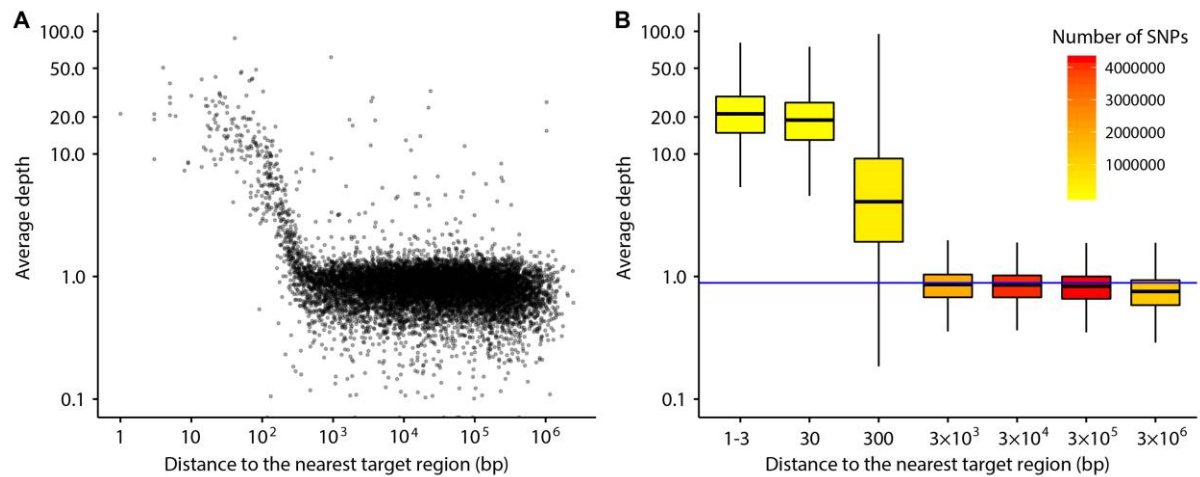
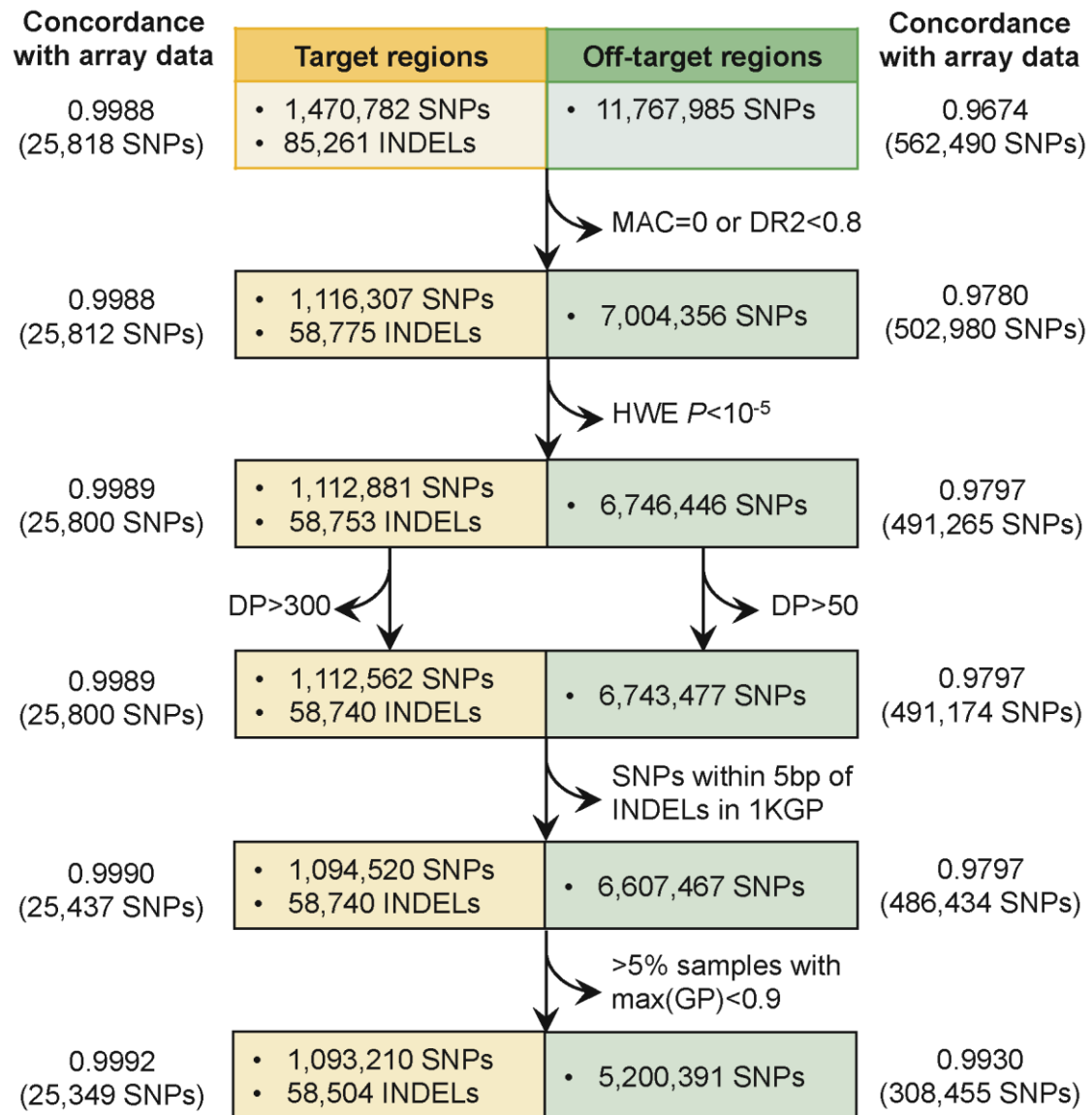


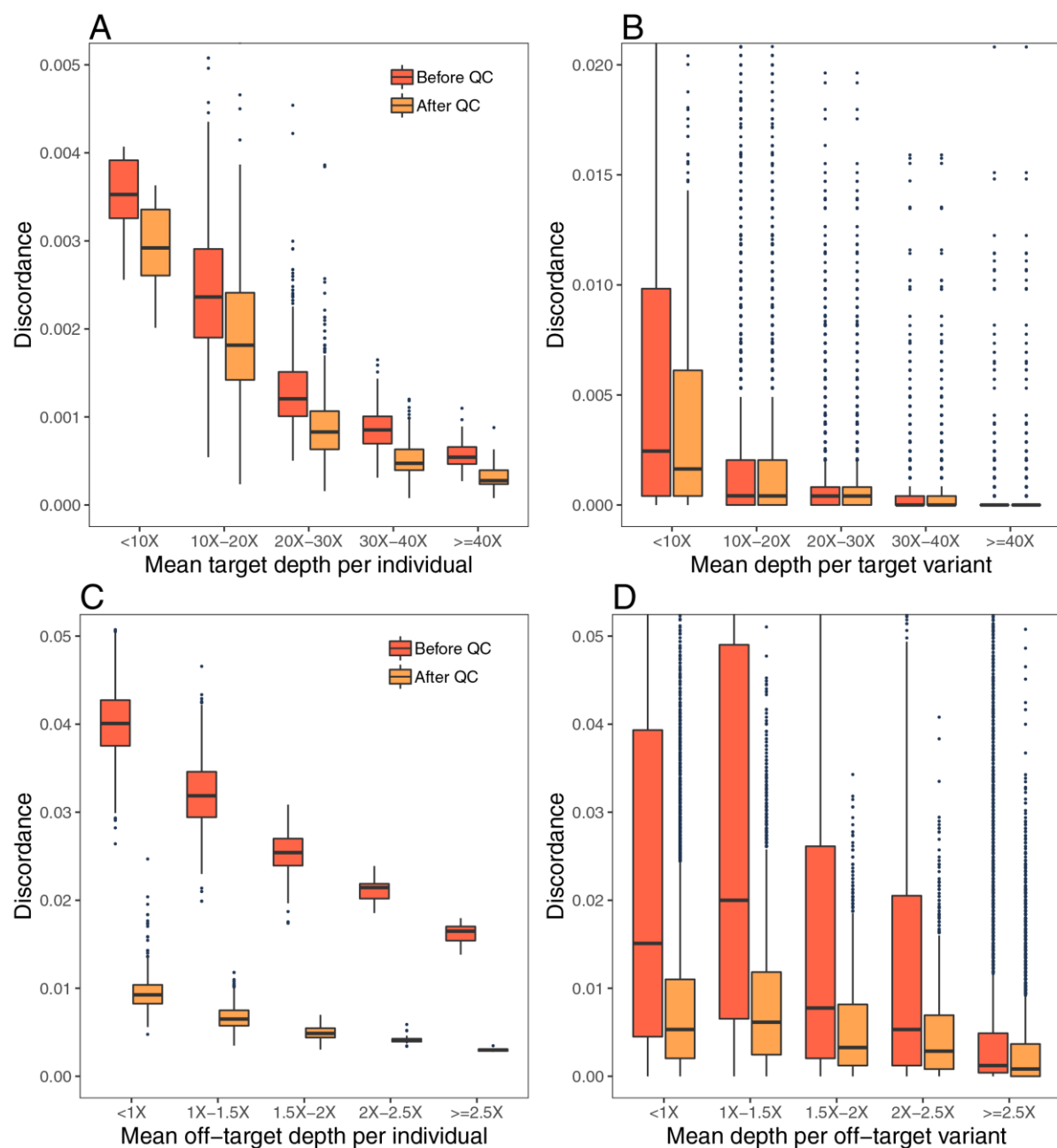
## Supplementary Figures and Tables



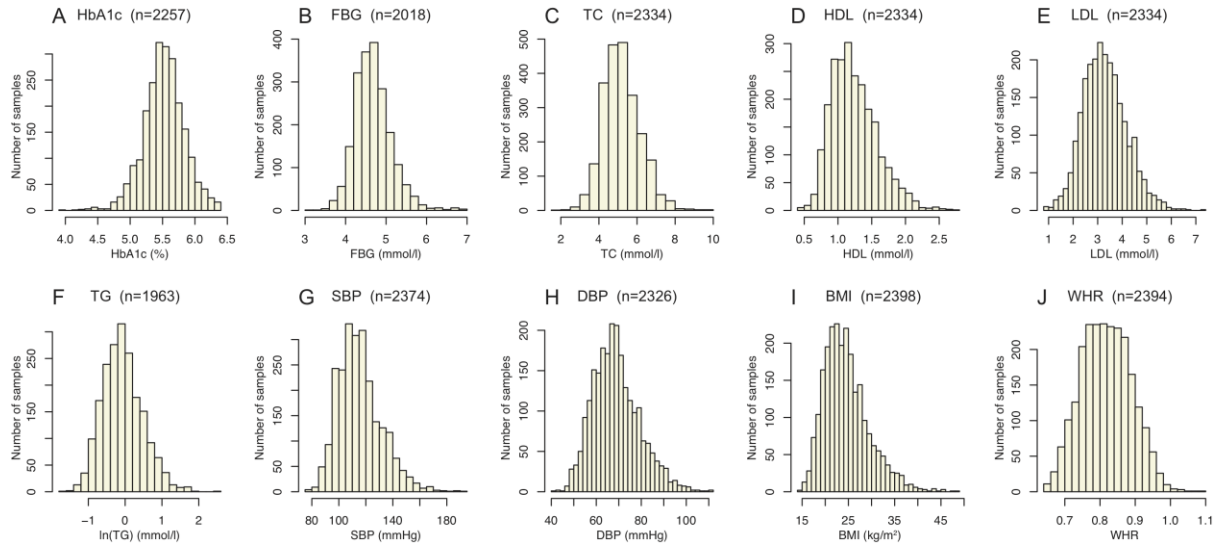
**Figure S1: Off-target sequencing depth as a function of the physical distance to the nearest target region.** We calculated sequencing depth averaged across 2527 individuals in the Living Biobank WES dataset for 12 million off-target SNPs that had MAF $>0.01$  in 1KGP. (A) Results for 10,000 randomly selected off-target SNPs. (B) Boxplots summarizing sequencing depth across all SNPs, grouped by their distance to the nearest target region: 1 to 3 bp; 4 to 30 bp; 31 to 300 bp; 301 to 3,000 bp; 3,001 to 30,000 bp; 30,001 to 300,000 bp; and 300,001 to a maximum of 2,462,123 bp. The blue horizontal line indicates the mean depth of 0.9 $\times$  for SNPs  $>300$  bp away from the nearest target regions. Whiskers indicate 1.5 times of the interquartile range away from the upper and lower quartiles.



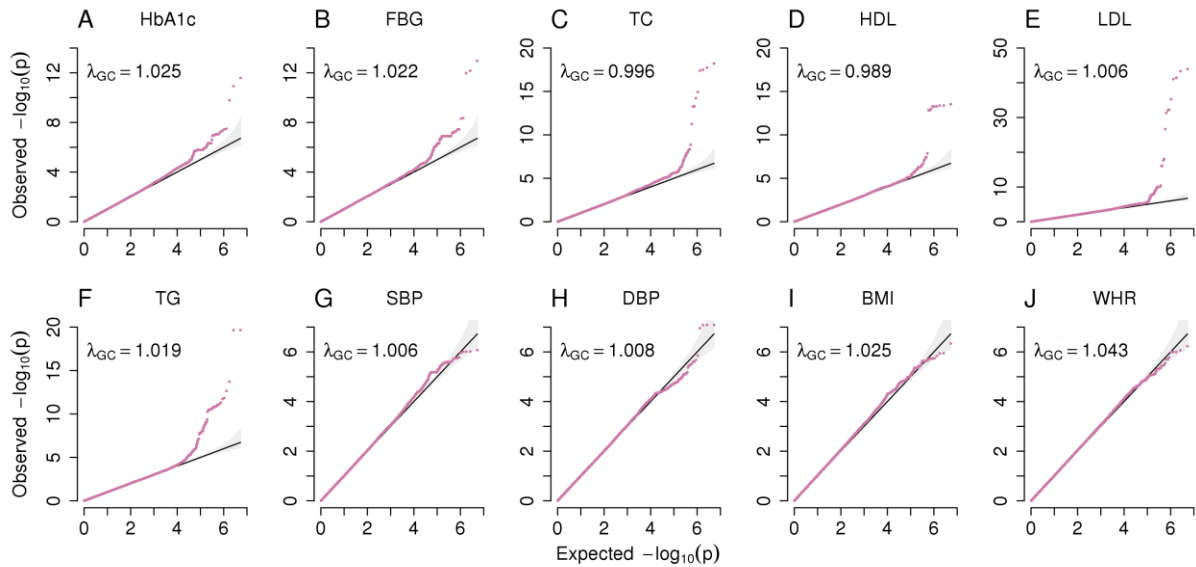
**Figure S2. QC workflow for the genotype call set of the Living Biobank WES samples.** Numbers of SNPs overlapped with the array data in each step were listed in the parentheses.



**Figure S3. Improvement of genotyping accuracy in target and off-target regions by QC** (A) Genotype discordance rate per individual for SNPs in the targeted regions. (B) Genotype discordance rate per SNP in the targeted regions. (C) Genotype discordance rate per individual for SNPs in the off-target regions. (D) Genotype discordance rate per SNP in the off-target regions.



**Figure S4. Distributions of 10 metabolic traits.** The number of samples used for downstream GWAS was labelled on the top of each panel in the parentheses. The values of TG were transformed by natural logarithm to reduce the skewness.



**Figure S5. QQ plots of single-variant association analyses of 10 metabolic traits.** The genomic inflation factor  $\lambda_{GC}$  is indicated in each panel.

**Table S1. Genotype discordance rate as a function of sequencing depth in target regions.**

<b>Individual level</b>	<b>≤10× (n=9)<sup>a</sup></b>	<b>10-20× (n=143)</b>	<b>20-30× (n=1,649)</b>	<b>30-40× (n=537)</b>	<b>&gt;40× (n=113)</b>	<b>All (n=2,451)</b>
Target	0.0084 (1.9×10 <sup>-4</sup> )	0.0056 (3.9×10 <sup>-5</sup> )	0.0027 (8.0×10 <sup>-6</sup> )	0.0017 (1.1×10 <sup>-5</sup> )	0.0010 (1.9×10 <sup>-5</sup> )	0.0026 (6.4×10 <sup>-6</sup> )
Target + 1KGP	0.008 (1.9×10 <sup>-4</sup> )	0.0055 (4.1×10 <sup>-5</sup> )	0.0026 (8.3×10 <sup>-6</sup> )	0.0017 (1.2×10 <sup>-5</sup> )	0.0010 (1.9×10 <sup>-5</sup> )	0.0025 (6.3×10 <sup>-6</sup> )
Target + off-target	0.0083 (1.9×10 <sup>-4</sup> )	0.0061 (3.9×10 <sup>-5</sup> )	0.0029 (7.9×10 <sup>-6</sup> )	0.0019 (1.1×10 <sup>-5</sup> )	0.0011 (1.8×10 <sup>-5</sup> )	0.0028 (6.7×10 <sup>-6</sup> )
Target + off-target + 1KGP	0.0034 (1.2×10 <sup>-4</sup> )	0.0025 (2.6×10 <sup>-5</sup> )	0.0012 (5.4×10 <sup>-6</sup> )	0.0008 (7.6×10 <sup>-6</sup> )	0.0005 (1.3×10 <sup>-5</sup> )	0.0012 (4.4×10 <sup>-6</sup> )
<b>Variant level</b>	<b>≤10× (n=451)<sup>b</sup></b>	<b>10-20× (n=4,533)</b>	<b>20-30× (n=9,937)</b>	<b>30-40× (n=6,720)</b>	<b>&gt;40× (n=3,943)</b>	<b>All (n=25,584)</b>
Target	0.0308 (1.6×10 <sup>-4</sup> )	0.0055 (2.2×10 <sup>-5</sup> )	0.0020 (9.0×10 <sup>-6</sup> )	0.0009 (7.4×10 <sup>-6</sup> )	0.0007 (8.7×10 <sup>-6</sup> )	0.0026 (6.4×10 <sup>-6</sup> )
Target + 1KGP	0.0279 (1.6×10 <sup>-4</sup> )	0.0053 (2.2×10 <sup>-5</sup> )	0.0020 (9.0×10 <sup>-6</sup> )	0.0009 (7.3×10 <sup>-6</sup> )	0.0007 (8.7×10 <sup>-6</sup> )	0.0025 (6.3×10 <sup>-6</sup> )
Target + off-target	0.0349 (1.7×10 <sup>-4</sup> )	0.0059 (2.3×10 <sup>-5</sup> )	0.0021 (9.2×10 <sup>-6</sup> )	0.0009 (7.4×10 <sup>-6</sup> )	0.0007 (8.7×10 <sup>-6</sup> )	0.0028 (6.7×10 <sup>-6</sup> )
Target + off-target + 1KGP	0.0125 (1.1×10 <sup>-4</sup> )	0.0022 (1.4×10 <sup>-5</sup> )	0.0009 (6.1×10 <sup>-6</sup> )	0.0005 (5.4×10 <sup>-6</sup> )	0.0006 (7.7×10 <sup>-6</sup> )	0.0012 (4.4×10 <sup>-6</sup> )

Standard error of each discordance rate estimate is shown in the parentheses.

<sup>a</sup>: number of samples in each bin of sequencing depth.

<sup>b</sup>: number of variants in each bin of sequencing depth.

**Table S2. Genotype discordance rate as a function of sequencing depth in off-target regions.**

<b>Individual level</b>	<b><math>\leq 1.0\times</math> (n=379)<sup>a</sup></b>	<b><math>1.0-1.5\times</math> (n=1,809)</b>	<b><math>1.5-2.0\times</math> (n=234)</b>	<b><math>2.0-2.5\times</math> (n=23)</b>	<b><math>&gt;2.5\times</math> (n=6)</b>	<b>All (n=2,451)</b>
Target + off-target	0.2536 ( $3.0\times 10^{-5}$ )	0.2344 ( $1.3\times 10^{-5}$ )	0.2153 ( $3.6\times 10^{-5}$ )	0.2012 ( $1.1\times 10^{-4}$ )	0.1667 ( $2.0\times 10^{-4}$ )	0.2350 ( $1.1\times 10^{-5}$ )
Target + off-target + 1KGP	0.0408 ( $1.4\times 10^{-5}$ )	0.0321 ( $5.5\times 10^{-6}$ )	0.0253 ( $1.4\times 10^{-5}$ )	0.0212 ( $4.0\times 10^{-5}$ )	0.0162 ( $6.9\times 10^{-5}$ )	0.0326 ( $4.8\times 10^{-6}$ )
<b>Variant level</b>	<b><math>\leq 1.0\times</math> (n=457,341)<sup>b</sup></b>	<b><math>1.0-1.5\times</math> (n=82,605)</b>	<b><math>1.5-2.0\times</math> (n=3,539)</b>	<b><math>2.0-2.5\times</math> (n=1,696)</b>	<b><math>&gt;2.5\times</math> (n=17,309)</b>	<b>All (n=562,490)</b>
Target + off-target	0.2506 ( $1.3\times 10^{-5}$ )	0.2035 ( $2.8\times 10^{-5}$ )	0.1054 ( $1.0\times 10^{-4}$ )	0.0741 ( $1.3\times 10^{-4}$ )	0.0201 ( $2.2\times 10^{-5}$ )	0.2350 ( $1.11\times 10^{-5}$ )
Target + off-target + 1KGP	0.0327 ( $5.3\times 10^{-6}$ )	0.0387 ( $1.4\times 10^{-5}$ )	0.0229 ( $5.1\times 10^{-5}$ )	0.0188 ( $6.7\times 10^{-5}$ )	0.0061 ( $1.2\times 10^{-5}$ )	0.0326 ( $4.8\times 10^{-6}$ )

Standard error of each discordance rate estimate is shown in the parentheses.

<sup>a</sup>: number of samples in each bin of sequencing depth.

<sup>b</sup>: number of variants in each bin of sequencing depth.

**Table S3. Genotype discordance rate in target regions before and after QC.**

Depth		$\leq 10\times$	10-20 $\times$	20-30 $\times$	30-40 $\times$	$>40\times$	All
Individual level	Before QC	0.0035 ( $1.2\times 10^{-4}$ )	0.0025 ( $2.6\times 10^{-5}$ )	0.0013 ( $5.5\times 10^{-6}$ )	0.0009 ( $7.9\times 10^{-6}$ )	0.0006 ( $1.4\times 10^{-5}$ )	0.0012 ( $4.4\times 10^{-6}$ )
	After QC	0.0029 ( $1.1\times 10^{-4}$ )	0.0020 ( $2.4\times 10^{-5}$ )	0.0009 ( $4.6\times 10^{-6}$ )	0.0005 ( $6.1\times 10^{-6}$ )	0.0003 ( $1.0\times 10^{-5}$ )	0.0008 ( $3.6\times 10^{-6}$ )
Variant level	Before QC	0.0125 ( $1.1\times 10^{-4}$ )	0.0022 ( $1.4\times 10^{-5}$ )	0.0009 ( $6.2\times 10^{-6}$ )	0.0005 ( $5.4\times 10^{-6}$ )	0.0006 ( $7.7\times 10^{-6}$ )	0.0012 ( $4.4\times 10^{-6}$ )
	After QC	0.0041 ( $6.5\times 10^{-5}$ )	0.0019 ( $1.3\times 10^{-5}$ )	0.0008 ( $5.7\times 10^{-6}$ )	0.0004 ( $4.7\times 10^{-6}$ )	0.0003 ( $5.6\times 10^{-6}$ )	0.0008 ( $3.6\times 10^{-6}$ )

Standard error of each discordance rate estimate is shown in the parentheses.

**Table S4. Genotype discordance rate in off-target regions before and after QC.**

Depth		$\leq 1.0\times$	1.0-1.5 $\times$	1.5-2.0 $\times$	2.0-2.5 $\times$	$>2.5\times$	All
Individual level	Before QC	0.0408 ( $1.4\times 10^{-5}$ )	0.0321 ( $5.5\times 10^{-6}$ )	0.0253 ( $1.4\times 10^{-5}$ )	0.0212 ( $4.0\times 10^{-5}$ )	0.0162 ( $6.9\times 10^{-5}$ )	0.0326 ( $4.8\times 10^{-6}$ )
	After QC	0.0096 ( $9.0\times 10^{-6}$ )	0.0067 ( $3.4\times 10^{-6}$ )	0.0049 ( $8.2\times 10^{-6}$ )	0.0042 ( $2.4\times 10^{-5}$ )	0.0030 ( $4.0\times 10^{-5}$ )	0.0070 ( $3.0\times 10^{-6}$ )
Variant level	Before QC	0.0327 ( $5.3\times 10^{-6}$ )	0.0387 ( $1.4\times 10^{-5}$ )	0.0229 ( $5.1\times 10^{-5}$ )	0.0188 ( $6.7\times 10^{-5}$ )	0.0061 ( $1.2\times 10^{-5}$ )	0.0326 ( $4.8\times 10^{-6}$ )
	After QC	0.0071 ( $3.4\times 10^{-6}$ )	0.0078 ( $8.9\times 10^{-6}$ )	0.0054 ( $3.0\times 10^{-5}$ )	0.0049 ( $4.0\times 10^{-5}$ )	0.0029 ( $8.7\times 10^{-6}$ )	0.0070 ( $3.0\times 10^{-6}$ )

Standard error of each discordance rate estimate is shown in the parentheses.

**Table S5. Suggestive loci associated with metabolic traits ( $5 \times 10^{-8} < p < 10^{-6}$ ) in the WES samples.**

Trait	Locus	Lead variant	Position	Alleles (Ref/Alt)	AF <sub>Chinese</sub> (Alt)	AF <sub>Malay</sub> (Alt)	Beta (Alt)	SE	<i>p</i>	Known	Target or off-target
HbA1c	<i>LRRC37A4P</i>	rs1743626365	17:43626365	C/A	0.001	0.011	-0.313	0.063	$7.67 \times 10^{-7}$	NO	Target
HbA1c	<i>PKLR</i>	rs374805791	1:155270050	C/T	0.001	0.019	-0.230	0.046	$6.58 \times 10^{-7}$	NO	Target
HbA1c	<i>SERPINB6</i>	rs80103243	6:2966578	T/C	0.027	0.012	-0.156	0.032	$7.98 \times 10^{-7}$	NO	Off-target
HbA1c	<i>C6orf203</i>	rs73761779	6:107348465	G/A	0.001	0.012	0.313	0.062	$4.73 \times 10^{-7}$	NO	Off-target
HbA1c	<i>TMEM243</i>	rs61243578	7:86839167	C/A	0.649	0.687	-0.049	0.010	$4.78 \times 10^{-7}$	NO	Off-target
FBG	<i>TRIM6</i>	rs143334533	11:5632525	C/A	0.002	0.009	0.482	0.089	$6.26 \times 10^{-8}$	NO	Target
FBG	<i>MTNR1B</i>	rs10466351	11:92697981	C/T	0.465	0.457	0.066	0.013	$6.29 \times 10^{-7}$	YES	Off-target
FBG	<i>LOC100419926</i>	rs368576835	9:70654801	T/G	0.005	0.006	0.451	0.090	$5.63 \times 10^{-7}$	NO	Off-target
FBG	<i>TRPM3</i>	rs4615646	9:73537400	T/C	0.001	0.014	0.442	0.083	$1.28 \times 10^{-7}$	NO	Off-target
TC	<i>DPP3</i>	rs146383570	11:66275363	A/C	0.061	0.017	0.363	0.067	$8.10 \times 10^{-8}$	NO	Off-target
TC	<i>PCDH9</i>	rs59484997	13:67734544	T/C	0.005	0.011	-0.755	0.151	$5.49 \times 10^{-7}$	NO	Off-target
TC	<i>HMGCR</i>	rs79225634	5:74619639	C/T	0.323	0.288	0.154	-0.030	$2.36 \times 10^{-7}$	YES	Off-target
HDL	<i>LIPC</i>	rs2070895	15:58723939	G/A	0.412	0.453	0.047	0.009	$2.46 \times 10^{-7}$	YES	Off-target
HDL	<i>INPP5K</i>	rs76568554	17:1477062	C/T	0.104	0.145	0.072	0.014	$1.90 \times 10^{-7}$	NO	Off-target
HDL	<i>GLI3</i>	rs17756258	7:42322229	T/C	0.016	0.018	0.171	0.035	$9.03 \times 10^{-7}$	NO	Off-target
LDL	<i>SUGP1</i>	rs10401969	19:19407718	T/C	0.096	0.113	-0.214	0.040	$1.17 \times 10^{-7}$	YES	Both
LDL	<i>AC009185.1</i>	rs112811239	5:156689921	T/C	0.335	0.378	-0.128	0.026	$9.57 \times 10^{-7}$	NO	Off-target
TG	<i>CASP4</i>	rs949153	11:104853392	C/T	0.024	0.114	0.167	0.033	$7.29 \times 10^{-7}$	NO	Off-target
TG	<i>ZNF268</i>	rs148604037	12:133780459	C/T	0.030	0.005	0.290	0.059	$9.29 \times 10^{-7}$	NO	Off-target
TG	<i>RN7SL366P</i>	rs3799336	6:164298976	A/T	0.138	0.272	-0.099	0.020	$8.51 \times 10^{-7}$	NO	Off-target
TG	<i>CCDC102B</i>	rs116111430	18:66748881	A/G	0.025	0.017	0.283	0.053	$1.16 \times 10^{-7}$	NO	Off-target
TG	<i>ZNF665</i>	rs189318604	19:53668470	T/C	0.017	0.013	0.340	0.069	$9.01 \times 10^{-7}$	NO	Off-target
SBP	<i>ZFYVE9P2</i>	rs10205002	2:17470470	A/G	0.037	0.055	4.910	-0.994	$8.43 \times 10^{-7}$	NO	Off-target
SBP	<i>ABCG2</i>	rs11943824	4:89031519	A/G	0.347	0.385	2.150	-0.438	$9.73 \times 10^{-7}$	NO	Off-target
SBP	<i>NUFIP</i>	rs12202343	6:66760443	A/G	0.094	0.214	2.600	0.528	$9.64 \times 10^{-7}$	NO	Off-target
DBP	<i>ANKS1B</i>	rs145863749	12:99150569	G/A	0.016	0.020	5.480	1.020	$8.25 \times 10^{-8}$	NO	Off-target
BMI	<i>LINC00152</i>	rs370898962	2:87820709	G/T	0.004	0.009	4.107	0.812	$4.59 \times 10^{-7}$	NO	Target
WHR	<i>CES1</i>	rs12373058	16:55502951	C/G	0.023	0.042	-0.024	0.005	$5.91 \times 10^{-7}$	NO	Off-target

Each locus is labelled by the nearest gene, and the lead variant is the one with the smallest *p* value. For each lead variant, we reported genomic position (in the format of chromosome:position), reference allele (Ref) and alternative allele (Alt), frequencies of the alternative allele (AF) in Chinese and Malay, and the effect size (beta) and its standard error (SE) of the alternative allele. We consider a locus as known if its lead variant is within 500 kb of reported genes in the GWAS Catalog for the corresponding trait. The last column indicates where the variants with  $p < 10^{-6}$  in each locus come from.



**Table S6: Number of variants overlapped with GWAS summary statistics for each trait.**

Trait	Living Biobank WES call set			SNPs with $p < 10^{-6}$ in the meta-analysis of UKB and BBJ
	Target	Off-target	Total	
HbA1c	977 (2.9%)	14,395 (42.4%)	15,372 (45.3%)	33,963
FBG	475 (3.7%)	4,990 (38.7%)	5,465 (42.3%)	12,908
TC	1,845 (3.4%)	28,840 (53.3%)	30,685 (56.8%)	54,060
HDL	2,283 (2.9%)	43,574 (55.6%)	45,857 (58.5%)	78,407
LDL	1,517 (3.4%)	23,928 (53.1%)	25,445 (56.5%)	45,046
TG	1,788 (2.9%)	31,159 (51.3%)	32,947 (54.2%)	60,792
SBP	324 (1.8%)	7,579 (43.1%)	7,903 (44.9%)	17,585
DBP	421 (2.5%)	6,850 (40.4%)	7,271 (42.9%)	16,956
BMI	1,062 (2.0%)	28,214 (54.1%)	29,276 (56.1%)	52,156

Numbers in parentheses were the corresponding proportions among all SNPs with  $p < 10^{-6}$  in the meta-analysis of UKB and BBJ.

**Table S7: Sample QC steps for association analyses of 10 metabolic traits.**

QC step	Trait									
	HbA1c	FBG	TC	HDL	LDL	TG	SBP	DBP	BMI	WHR
Number of samples with non-missing phenotype	2,380	2,125	2,526	2,526	2,526	2,126	2,498	2,444	2,527	2,524
Remove trait outliers >5 sd from the mean	39	22	34	34	34	22	34	30	35	36
Remove MZ twins with inconsistent age or sex	9	8	9	9	9	8	9	7	9	9
Remove diabetic samples	75	77	85	85	85	77	81	81	85	85
Remove samples on cholesterol medications from lipid traits	0	0	64	64	64	56	0	0	0	0
Final sample size	2,257	2,018	2,334	2,334	2,334	1,963	2,374	2,326	2,398	2,394