TITLE

Large scale genome-wide association study in a Japanese population identified 45 novel susceptibility loci for 22 diseases

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135 **INTRODUCTORY PARAGRAPH**

136 The overwhelming majority of participants in current genetic studies are of European ancestry^{1–3}, limiting our
137 genetic understanding of complex disease in non-European populations. To address this, we aimed to elucidate
138 polygenic disease biology in the East Asian population by conducting a genome-wide association study (GWAS)
139 with 212,453 Japanese individuals across 42 diseases. We detected 383 independent signals in 331 loci for 30
140 diseases, among which 45 loci were novel ($P < 5 \times 10^{-8}$). Compared with known variants, novel variants have lower
141 frequency in European populations but comparable frequency in East Asian populations, suggesting the advantage
142 of this study in discovering these novel variants. Three novel signals were in linkage disequilibrium ($r^2 > 0.6$) with
143 missense variants which are monomorphic in European populations (1000 Genomes Project) including rs11235604
144 (p.R220W of *ATG16L2*, a autophagy-related gene) associated with coronary artery disease. We further
145 investigated enrichment of heritability within 2,868 annotations of genome-wide transcription factor occupancy, and
146 identified 378 significant enrichments across nine diseases (FDR < 0.05) (e.g. NF- κ B for immune-related diseases).
147 This large-scale GWAS in a Japanese population provides insights into the etiology of common complex diseases
148 and highlights the importance of performing GWAS in non-European populations.

149

150 MAIN TEXT

151 We conducted a genome-wide association study (GWAS) of 42 diseases in a Japanese population, comprising
 152 179,660 patients who participated in the BioBank Japan Project (BBJ)^{4,5} and 32,793 population-based controls
 153 (Supplementary Table 1). The 42 diseases encompassed a wide-range of disease categories; 13 neoplastic
 154 diseases, five cardiovascular diseases, four allergic diseases, three infectious diseases, two autoimmune diseases,
 155 one metabolic disease, and 14 uncategorized diseases. By including patients with unrelated diagnoses into control
 156 samples, we maximized the power of our GWAS (Supplementary Table 1 and Supplementary Figure 1). We
 157 employed a generalized linear mixed model in our association analysis using SAIGE⁶. Following imputation with
 158 1000 Genomes Project Phase 3 reference data (1KG Phase3)⁷, we tested 8,712,794 autosomal variants and
 159 207,198 X chromosome variants for association with 42 diseases. We estimated their heritability using linkage
 160 disequilibrium score regression (LDSC) analysis⁸ (Supplementary Table 2). Consistent with a recent finding in the
 161 European population⁹, incorporating the baselineLD model¹⁰ into the LDSC analysis improved heritability estimation
 162 in our GWAS (Methods; Supplementary Figure 2 and Supplementary Table 2). Although we observed high genomic
 163 inflation factors (λ_{GC}) for some diseases (e.g. $\lambda_{GC} = 1.3$ for type 2 diabetes (T2D); Supplementary Table 2), LDSC
 164 analysis indicated that the majority of the inflated chi-squared statistics originated from polygenic effects rather than
 165 confounding biases (e.g. intercept = 1.01 for T2D; Supplementary Table 2). Overall, we detected significant
 166 associations for 30 diseases at 309 autosomal loci (outside of the HLA region) and nine loci on the X chromosome
 167 ($P < 5 \times 10^{-8}$) (Supplementary Table 3 and 4). Associations at the HLA region have been investigated in detail in a
 168 separate article¹¹.

We further performed conditional analyses in these 318 loci to explore disease-associated variants independent of the lead variants. We detected 52 additional independent signals for 11 diseases ($P < 5 \times 10^{-8}$) (Supplementary Table 5). The largest number of independent signals in a single locus was seven, found in the *FAM84B/POU5F1B* locus associated with prostate cancer and in the *KCNQ1* locus associated with T2D.

For 35 diseases for which we have both male and female patients, we conducted male- and female-specific GWAS. We detected 13 additional loci for 10 diseases which were not identified in a sex-combined analysis ($P < 5 \times 10^{-8}$) (Supplementary Table 6). We tested heterogeneity between effect size estimates for males and females using Cochran's Q test. This analysis found seven loci showing significant differences in effect size estimates between sexes (P values of heterogeneity (P_{het}) $< 0.05/13$); two asthma loci, a cataract locus, a cerebral aneurysm locus, and a lung cancer locus were specifically associated with females; and a coronary artery disease (CAD) locus and a T2D locus were specifically associated with males.

In total, we detected 383 independent signals in 331 loci outside of the HLA region for 30 diseases, of which 45 loci were novel (Figure 1a, Table 1, Supplementary Table 3, 4, and 6). Five novel disease-associated variants were rare variants (MAF < 0.01), and four of them had large effect sizes (odds ratio > 2 , Figure 1b). To understand the characteristics of novel and known disease-associated variants, we examined their allele frequencies in East Asian and European populations of 1KG Phase3. Allele frequencies of novel and known variants were of comparable level in East Asian populations ($P = 0.35$, Figure 1c). However, novel variants have lower allele frequencies than known variants in European populations ($P = 0.0030$, Figure 1d). Although both of novel and known variants have lower allele frequencies in European populations than in East Asian populations,

188 novel variants have larger inter-population differences than known variants ($P = 0.0047$, Supplementary Figure 3).

189 To estimate population specificity in our GWAS results, we compared our results with those reported in previous

190 European GWAS. We utilized publicly available GWAS summary statistics of European populations for 10 diseases

191 (Methods), and tested for consistency in direction of effect between populations at 11 novel and 146 known

192 disease-associated variants from our GWAS; 10 out of 11 novel and 141 out of 146 known variants were replicated

193 in the same allelic direction in European GWAS (binomial test P values were 0.011 and 1.1×10^{-35} , respectively;

194 Supplementary Figure 4). In addition, 595 out of 665 disease-associated variants detected in European GWAS

195 were replicated in the same allelic direction in our GWAS (binomial test P values = 1.1×10^{-104} ; Supplementary

196 Figure 4). These findings suggested that genetic etiologies around the disease-associated variants are generally

197 shared across populations, and the higher allele frequencies at novel associated variants in our East Asian cohort

198 increased the efficiency of the variant discovery. This highlights the importance of performing GWAS in non-

199 European populations.

200 We next investigated the potential impact of the disease-associated variants on protein functions

201 (Supplementary Table 7). Nine novel variants were in linkage disequilibrium (LD) with missense variants ($r^2 > 0.6$ in

202 the 1KG Phase3 East Asian populations) (Table 2). Among them, three missense variants are monomorphic in

203 European populations (1KG Phase3); p.R220W of *ATG16L2* associated with CAD; p.V326A of *POT1* associated

204 with lung cancer; and p.E62G of *PHLDA3* associated with keloid (Figure 2 and Supplementary Figure 5). First,

205 *ATG16L2* is an autophagy-related gene. Although p.R220W of *ATG16L2* is not the lead variant at this locus,

206 conditioning on this variant cancelled the signal of the lead variant (Figure 2a). Previous GWAS for CAD in

European populations did not detect significant associations at this locus¹² (Figure 2a). These findings suggested that p.R220W of *ATG16L2* which is absent in Europeans may be the causal variant. p.R220W of *ATG16L2* is also associated with Crohn's disease in a Chinese population¹³, and *ATG16L2* is highly expressed in immune cells. Therefore, dysregulated autophagy in immune cells might have an important role in CAD. Second, *POT1* is a member of the telombin family and this protein binds to telomeres, regulating telomere length. Missense variants of *POT1* have been described to be responsible for several familial cancers^{14–16}. Together with a known association at the *TERT* locus (Supplementary Table 3), we provide additional evidence that telomere dysregulation is pathogenic for lung cancer. Intriguingly, this association was discovered in the female-specific GWAS, and a significant heterogeneity in effect sizes between males and females was observed ($P_{het} = 7.7 \times 10^{-4}$) (Figure 2b; Supplementary Table 6). This finding might help to understand the inter-sex differences in the etiology of lung cancer. Third, p.E62G of *PHLDA3* is predicted to have a deleterious effect to its protein function (SIFT score¹⁷=0; CADD score¹⁸=33), and we detected a large effect size for keloid (odds ratio = 9.56; 95% CI 5.91-15.45). *PHLDA3* is known to be a suppressor of AKT¹⁹, and upregulated AKT signaling pathway is related to increased collagen production from dermal fibroblasts²⁰. Therefore, damaged *PHLDA3* may activate the AKT pathway, promoting the development of keloid. Together, our study successfully identified novel potential causal genes which would be hard to be discovered by GWAS in European populations due to restrictive European allele frequencies.

We also investigated the potential impacts of the disease-associated variants on the mRNA levels using two databases of expression quantitative trait locus (eQTL) analysis^{21,22}. Out of the remaining 36 novel variants whose functions were not explained by missense variants, 11 variants were in LD with at least one eQTL variant (r^2

226 > 0.6), regulating the expression of 17 genes in total (Supplementary Table 8); *P2RY13*, *SIAH2*, and *SIAH2-AS1* for
 227 breast cancer; *ATP2B1*, *BET1L*, *POC1B*, and *ZNF767* for cerebral aneurysm; *CCAT1* and *CD40* for Graves's
 228 disease; *GABPB2* for osteoporosis; *MOV10* and *WNT2B* for pancreatic cancer; *CYP2A6* and *CYP2B7P1* for
 229 peripheral artery disease; *ZMIZ1-AS1* for prostate cancer; and *STIM1* and *TRIM21* for urolithiasis. Intriguingly, the
 230 eQTL signals for *ATP2B1* which are in LD with a novel variant of cerebral aneurysm (rs11105352) is highly specific
 231 to arterial tissues (Figure 3). Since the loss of *ATP2B1* in vascular smooth muscle cells induced blood pressure
 232 elevation in mice²³, decreased expression of *ATP2B1* in arteries might induce hypertension, which leads to
 233 increased risk of cerebral aneurysm.

234 To understand differences in the genetic risks between males and females, we assessed genetic
 235 correlations using LDSC²⁴ between the results of sex-specific GWAS for the 20 diseases (see Methods for
 236 selection of diseases). Although most correlations are close to one, correlation of asthma was significantly smaller
 237 than one ($P = 2.2 \times 10^{-3} < 0.05/20$; Supplementary Figure 6). This finding suggested that genetic risks of asthma is
 238 slightly different between males and females. To explore the biological mechanism underlying this finding, we
 239 estimated the enrichment of the heritability of male or female asthma in the 220 cell-type specific regulatory regions
 240 using stratified LD-score regression (S-LDSC)²⁵. We found significant enrichments for either of male or female
 241 asthma in three annotations; Th0, Th1, and colonic mucosa ($P < 0.05/220$; Supplementary Figure 6). Among them,
 242 the colonic mucosa annotation showed significant heterogeneity in the enrichment of heritability ($P_{het} = 0.006 <$
 243 $0.05/3$). Recent studies suggested that host-microbiome interactions at intestinal mucosa (gut-lung axis) have

important roles in the development of asthma^{26,27}, and our study suggested that the importance of the gut-lung axis in asthma might be different between males and females.

To acquire more insights to disease biology, we estimated the heritability enrichments in the binding sites of a variety of transcription factors (TFs) using S-LDSC. We included TF binding sites defined by 2,868 publicly available chromatin immunoprecipitation sequencing (ChIP-seq) datasets for 410 unique TFs (Supplementary Table 9). To make mutually comparable data, we began our analysis from the raw sequencing data, and defined TF binding sites using a uniform protocol (Methods). Using LD-scores of all TF binding sites, we grouped them into 15 clusters (cluster name was defined by the most dominant TF), and performed uniform manifold approximation and projection (UMAP)²⁸ to project all TF binding sites into a two-dimensional space (Methods; Figure 4a and Supplementary Figure 7). To scale the performance of this analysis, we first analyzed previously reported GWAS for red blood cell-related traits²⁹ where the critical role of *GATA1* was supported by multiple pieces of evidence^{30–34}, and we successfully recapitulated this biology (Figure 4b). We then applied this analysis to our 24 GWAS results (see Methods for selection of diseases), and detected 378 significant enrichments for nine disease (FDR < 0.05) (Figure 4c, Supplementary Figure 8, and Supplementary Table 10). Biologically plausible TFs were highlighted by this analysis; *RELA*, a subunit of NF- κ B, for atopic dermatitis, RA, and Graves' disease; sex hormone receptors (*AR* and *ESR1*) for prostate cancer; and *FOXA2*, which regulates insulin secretion in pancreatic beta-cells³⁵, for T2D (Figure 4c). This analysis also suggested that *NKX3-1*, a prostate-specific homeobox gene, has an important role in the biology of prostate cancer (Figure 4c). In addition to this polygenic analysis, the importance of *NKX3-1* was also suggested by the regional analysis integrating eQTL databases; the risk allele of prostate cancer at

263 *NKX3-1* locus (rs4872174-C) was suggested to decrease the expression of *NKX3-1* (Supplementary Table 8).

264 Consistently, loss of *NKX3.1* expression in human prostate cancers was reported to be correlated with tumor

265 progression³⁶. Together, our results confirmed and expanded our current understanding of complex traits in the

266 context of TF activity.

267 In summary, we conducted a large-scale GWAS of 42 diseases in a non-European population and

268 provided rich public resources for genetic studies. Our study provided multiple insights into the etiology of complex

269 traits by integrating annotations of missense variants, eQTL variants, and transcription factor binding site tracks.

270 Currently, genetic studies are overwhelmed by European-descent samples, and the clinical translation of genetic

271 findings would be far more beneficial to European individuals than other populations¹. Our study contributed to

272 broaden the population diversity in genetic studies and should potentially mitigate the problems originating from this

273 imbalance.

274

275 **TABLE**

276

277 **Table 1. 45 novel loci detected in this GWAS.**

Disease	Variant	Chr.	Position	REF	ALT	Gene	OR	L95	U95	P
Loci detected in sex-combined analysis										
Asthma	rs3835894	2	204576923	C	CA	<i>CD28</i>	1.09	1.06	1.13	3.22E-08
Asthma	rs10797119	9	92202495	T	C	<i>GADD45G</i> <i>SEMA4D</i>	1.11	1.07	1.15	1.45E-08
*Breast cancer	rs146383533	3	150480100	T	TTTTC	<i>SIAH2</i>	0.86	0.83	0.90	1.04E-11
Coronary artery disease	rs332827	1	61743160	G	A	<i>NFIA</i>	1.06	1.04	1.08	3.22E-08
Coronary artery disease	rs9720071	7	155086439	A	C	<i>HTR5A</i> <i>INSIG1</i>	0.94	0.91	0.96	2.03E-08
Coronary artery disease	rs11235571	11	72411843	G	A	<i>ARAP1</i>	0.90	0.87	0.93	2.64E-09
Cataract	rs75812946	14	86192480	G	A	<i>FLRT2</i>	1.35	1.22	1.50	3.41E-09
Cerebral aneurysm	rs12226402	11	215904	G	A	<i>SIRT3</i>	1.34	1.23	1.45	1.57E-12
Cerebral aneurysm	rs78535549	12	20156904	C	T	<i>AEBP2</i> <i>PDE3A</i>	0.85	0.81	0.90	7.97E-09
Cerebral aneurysm	rs11105352	12	90026462	G	A	<i>ATP2B1</i>	0.85	0.81	0.90	1.22E-08
Cervical cancer	rs139337062	6	123096973	AAAAC	A	<i>FABP7</i> <i>PKIB</i>	0.70	0.62	0.80	2.98E-08
Congestive heart failure	rs2129981	4	111704199	G	T	<i>C4orf32</i> <i>PITX2</i>	1.09	1.06	1.12	9.60E-09
Colorectal cancer	rs140989504	11	100439234	C	T	<i>CNTN5</i> <i>TMEM133</i>	1.37	1.22	1.52	2.17E-08
COPD	rs11066008	12	112140669	A	G	<i>ACAD10</i>	1.29	1.21	1.37	4.34E-17
Graves' disease	rs10673095	8	128203024	T	TTC	<i>FAM84B</i> <i>POU5F1B</i>	0.81	0.76	0.87	2.11E-09
Graves' disease	rs11065783	12	111396249	A	G	<i>CUX2</i> <i>MYL2</i>	1.34	1.24	1.44	7.23E-14
Graves' disease	rs1569723	20	44742064	C	A	<i>CD40</i> <i>NCOA5</i>	1.20	1.13	1.28	4.06E-09
Hepatocellular carcinoma	rs8107030	19	39736719	A	G	<i>IFNL2</i> <i>IFNL3</i>	1.44	1.28	1.62	7.96E-10

Interstitial lung disease	rs6477542	9	109507432	C	T	<i>TMEM38B</i> <i>ZNF462</i>	1.34	1.21	1.48	6.90E-09
Keloid	rs192314256	1	201437730	T	C	<i>PHLDA3</i>	9.56	5.91	15.45	3.28E-20
Osteoporosis	rs578031265	2	168857545	C	T	<i>STK39</i>	10.16	4.74	21.74	2.38E-09
Pancreatic cancer	rs60579835	1	113113194	C	T	<i>ST7L</i>	1.48	1.29	1.69	1.00E-08
Prostate cancer	rs11002805	10	80825897	G	A	<i>RPS24</i> <i>ZMIZ1</i>	1.15	1.10	1.20	1.67E-10
Prostate cancer	rs1997577	21	16371102	A	T	<i>NRIP1</i> <i>USP25</i>	0.88	0.84	0.92	1.83E-09
Prostate cancer	rs138426	22	38871891	G	A	<i>KDELR3</i>	1.19	1.13	1.25	2.04E-12
Type 2 diabetes	rs28403309	2	218782540	T	C	<i>CXCR2</i> <i>TNS1</i>	1.06	1.04	1.08	3.76E-08
Type 2 diabetes	rs7721099	5	87936379	T	C	<i>MEF2C</i> <i>TMEM161B</i>	1.05	1.04	1.07	1.41E-09
Type 2 diabetes	rs200525873	5	122652913	GT	G	<i>CEP120</i> <i>PRDM6</i>	0.91	0.88	0.94	4.90E-09
Type 2 diabetes	rs39218	7	89740018	T	C	<i>STEAP1</i> <i>ZNF804B</i>	1.06	1.04	1.08	1.28E-09
Type 2 diabetes	rs2277339	12	57146069	T	G	<i>PRIM1</i>	1.06	1.04	1.08	4.53E-08
Type 2 diabetes	rs17105012	14	77375691	C	A	<i>IRF2BPL</i> <i>LRRC74A</i>	1.05	1.03	1.07	1.54E-08
Urolithiasis	rs4148155	4	89054667	A	G	<i>ABCG2</i>	1.12	1.08	1.16	1.70E-08
Urolithiasis	rs12290747	11	3939650	T	C	<i>STIM1</i>	0.89	0.85	0.92	3.24E-09
Arrhythmia	rs73205368	X	23399501	T	C	<i>PTCHD1</i>	1.08	1.06	1.10	4.25E-15
Gastric cancer	rs1205528	X	108542014	T	C	<i>GUCY2F</i> <i>IRS4</i>	0.92	0.89	0.94	2.80E-10
Loci detected in sex-specific analysis										
Asthma	rs9836823	3	26845523	A	G	<i>LRRC3B</i> <i>NEK10</i>	0.86	0.82	0.91	5.19E-09
Asthma	rs13227841	7	73279482	T	C	<i>WBSR28</i>	0.86	0.81	0.90	2.04E-09
Cataract	rs557090273	22	28942263	G	A	<i>TTC28</i>	2.71	1.89	3.87	4.52E-08
Cerebral aneurysm	rs855917	7	149197364	A	G	<i>ZNF467</i> <i>ZNF746</i>	1.22	1.14	1.31	2.72E-08
Lung cancer	rs75932146	7	124487025	A	G	<i>POT1</i>	2.29	1.71	3.05	2.21E-08
Osteoporosis	rs2864700	1	151028929	C	T	<i>CDC42SE1</i>	1.18	1.11	1.25	2.03E-08

Peripheral artery disease	rs72480748	19	41414481	G	A	<i>CYP2A7</i>	1.21	1.13	1.30	3.64E-08
						<i>CYP2B6</i>				
Type 2 diabetes	rs58202132	8	121764521	C	A	<i>SNTB1</i>	1.08	1.05	1.11	1.28E-08
Type 2 diabetes	rs2526678	11	61623793	G	A	<i>FADS2</i>	0.93	0.91	0.96	2.44E-08
Type 2 diabetes	rs202209118	18	42361423	T	TCC	<i>SETBP1</i>	1.16	1.10	1.22	7.78E-09

Summary data of the novel disease-associated variants are provided. For variants detected in sex-specific GWAS, statistics of sex with significant associations are provided. REF, reference allele; ALT, alternative allele; OR, odds ratio relative to the alternative allele; L95, lower 95% confidence interval; U95, upper 95% confidence interval; COPD, chronic obstructive pulmonary disease. *, SIAH2 locus was also detected in an accompanying GWAS project of breast cancer (Lee et al. in submission).

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Table2. Missense variants in LD with nine novel disease-associated variants.

												Allele freq. in 1KG Phase3		
Disease	Variant	Chr.	Position	Gene	Amino acid change	REF	ALT	OR	L95	U95	P	EAS	EUR	AFR
Loci detected in sex-combined analysis														
Coronary artery disease	rs11235604	11	72533536	ATG16L2	p.R220W	C	T	0.91	0.88	0.94	1.73E-08	0.100	0.000	0.000
Hepatocellular carcinoma*	rs8103142	19	39735106	IFNL3	p.K70R	T	C	1.38	1.23	1.54	1.14E-08	0.083	0.312	0.695
Keloid	rs192314256	1	201437730	PHLDA3	p.E62G	T	C	9.56	5.91	15.45	3.28E-20	0.010	0.000	0.000
Type 2 diabetes	rs2303720	5	122682334	CEP120	p.R921H p.R947H	C	T	0.91	0.89	0.94	1.77E-08	0.084	0.026	0.048
Type 2 diabetes	rs194520	7	89854446	STEAP2	p.F17C	T	G	1.06	1.04	1.08	1.23E-08	0.183	0.512	0.286
Type 2 diabetes	rs194524	7	89861832	STEAP2	p.R456Q	G	A	1.06	1.04	1.08	1.18E-08	0.183	0.512	0.269
Type 2 diabetes	rs2277339	12	57146069	PRIM1	p.D5A	T	G	1.06	1.04	1.08	4.53E-08	0.206	0.111	0.199
Urolithiasis	rs2231142	4	89052323	ABCG2	p.Q141K	G	T	1.12	1.08	1.16	1.74E-08	0.291	0.094	0.013
Loci detected in sex-specific analysis														
Asthma	rs13246460	7	73249165	WBSCR27	p.R216W	T	A	0.89	0.85	0.93	9.23E-07	0.581	0.726	0.463
Asthma	rs13232463	7	73249299	WBSCR27	p.S171W	G	C	0.89	0.85	0.93	9.23E-07	0.581	0.726	0.463
Asthma	rs13241921	7	73254812	WBSCR27	p.Q107R	T	C	0.89	0.85	0.93	9.54E-07	0.581	0.726	0.464
Asthma	rs11770052	7	73275565	WBSCR28	p.I14N	T	A	0.87	0.83	0.92	3.20E-08	0.630	0.726	0.285
Asthma	rs13227841	7	73279482	WBSCR28	p.W78R	T	C	0.86	0.81	0.90	2.04E-09	0.650	0.677	0.334
Lung cancer	rs75932146	7	124487025	POT1	p.V326A	A	G	2.29	1.71	3.05	2.21E-08	0.003	0.000	0.000

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Summary data of the missense variants in LD ($r^2 > 0.6$) with novel disease-associated variants are provided. For variants detected in sex-specific GWAS, statistics of sex with significant associations are provided. Rows highlighted in bold indicate east Asian-specific variants (MAF = 0 in Europeans of 1KG Phase3). REF, reference allele; ALT, alternative allele; Allele freq., allele frequency of alternative allele; OR, odds ratio relative to the alternative allele; L95, lower 95% confidence interval; U95, upper 95% confidence interval; EAS, East Asian populations; EUR, European populations; and AFR, African populations. *, the lead variant at this region (rs8107030) is in LD ($r^2 = 0.880$) with ss469415590 (comprised of rs67272382 and rs74597329). ss469415590 is a frameshift variant of *IFNL4*³⁷ (not listed as a functional gene in GRCh37 coordinates), and it might also explain this association.

296 **FIGURE**

306 When $MAF < 0.001$, MAF was adjusted to 0.001 to fit in log scale. MAF_{EAS} , MAF in East Asian population (1KG
307 Phase3). MAF_{EUR} , MAF in European population (1KG Phase3).

Figure 2. Novel associations which can be explained by East Asian-specific missense variants.

Regional association plots are provided (**a**, coronary artery disease; and **b**, lung cancer). For coronary artery disease (**a**), P values from conditional analysis and those in European GWAS¹² were plotted separately. For lung cancer (**b**), P values from female- and male-specific GWAS were plotted separately.

Figure 3. A novel association of cerebral aneurysm can be explained by artery-specific eQTL signals for *ATP2B1*.

a. Regional association plots of cerebral aneurysm GWAS at *ATP2B1* locus (top) and those of eQTL signals for *ATP2B1* in the tibial artery (bottom) are provided. The lead variant of GWAS (rs11105352; ◆ dot) and the lead variant of eQTL (rs2681492; ■ dot) are indicated by different shapes. Variants in LD with rs11105352 are highlighted by red ($r^2 > 0.6$ both in East Asian and European populations of 1KG Phase3). **b.** Tissue-specificity of eQTL signals for *ATP2B1* at rs2681492 (the lead variant of eQTL in the tibial artery (■ dot in **a**)). P values in eQTL analysis and M values (the posterior probability that an eQTL effect exist in each tissue tested in the cross-tissue meta-analysis) in all tissues in GTEx project³⁹ are provided. Each dot indicates each tissue. All statistics of eQTL analysis were derived from release v7 of GTEx project³⁹.

329 **Figure 4. Transcription factors whose binding sites were enriched for heritability of diseases.**
330 **a**, All of the 2,868 sets of TF binding sites grouped into 15 clusters were plotted in the UMAP space. **b and c**, The
331 results of S-LDSC were plotted on the UMAP space. The significant results ($FDR < 0.05$) are highlighted by cluster-
332 specific colors. The names of the top five most significant TFs are also shown on the plot. **b**, The results of red
333 blood cell-related traits. **c**, The results of diseases in this GWAS which had more than five significant TF binding
334 site tracks (the results of other diseases are provided in Supplementary Figure 8).
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ONLINE METHODS

Subjects

All case samples in this GWAS were collected in the BioBank Japan Project (BBJ)^{4,5}, which is a biobank that collaboratively collects DNA and serum samples from 12 medical institutions in Japan and recruited approximately 200,000 patients with the diagnosis of at least one of 47 diseases. Among them, cases with dyslipidemia were excluded because it was already reported in our previous study²⁹. Amyotrophic lateral sclerosis and febrile seizure were also excluded due to limited sample size. Cases with myocardial infarction, stable angina, and unstable angina were re-classified into a single disease category (coronary artery disease). Thus, we analyzed 42 disease in this study. For control samples, we used samples from the population-based prospective cohorts; the Tohoku University Tohoku Medical Megabank Organization (ToMMo), Iwate Medical University Iwate Tohoku Medical Megabank Organization (IMM)⁴⁰, the Japan Public Health Center-based Prospective Study and the Japan Multi-institutional Collaborative Cohort Study. In addition, we also included samples in BBJ without related diagnoses into control group (Supplementary Figure 1). The sample sizes and the demographic data are provided in Supplementary Table 1. All participating studies obtained informed consent from all participants by following the protocols approved by their institutional ethical committees. We obtained approval from ethics committees of RIKEN Center for Integrative Medical Sciences, and the Institute of Medical Sciences, The University of Tokyo.

Genotyping

We genotyped samples with the Illumina HumanOmniExpressExome BeadChip or a combination of the Illumina HumanOmniExpress and HumanExome BeadChips. For quality control (QC) of samples, we excluded those with (i) sample call rate < 0.98 and (ii) outliers from East Asian clusters identified by principal component analysis using the genotyped samples and the three major reference populations (Africans, Europeans, and East Asians) in the International HapMap Project⁴¹. For QC of genotypes, we excluded variants meeting any of the following criteria: (i) call rate < 99%, (ii) P value for Hardy Weinberg equilibrium (HWE) < 1.0×10^{-6} , and (iii) number of heterozygotes less than five. Using 939 samples whose genotypes were also analyzed by whole genome sequencing (WGS), we added additional QC based on the concordance rate between genotyping array and WGS. Variants with a concordance rate < 99.5% or a non-reference discordance rate $\geq 0.5\%$ were excluded. We note that the allele frequency of rs671 (the East Asian-specific functional missense variant at ALDH2) substantially varies among the domestic regions within Japan due to strong selection pressure⁴² and that genotypes of rs671 did not follow HWE. We thus did not apply the HWE QC for rs671. We had confirmed the 100% concordance of rs671 genotypes between the SNP microarray data used in this study and our internal WGS data ($n = 2,798$; see details in Matoba N. et. al. manuscript in revision).

Imputation

We utilized all samples in the 1000 Genomes Project Phase 3 (version 5)⁷ as a reference for imputation. We first prephased the genotypes with SHAPEIT2 (v2.778) and then imputed dosages with minimac3 (v2.0.1). After imputation, we excluded variants with imputation quality of $R_{sq} < 0.7$. For X chromosome, we performed

prephasing and imputation separately for males and females, and we excluded variants with imputation quality of $Rsq < 0.7$ in either of them.

Genome-wide association analysis

We conducted a GWAS by employing a generalized linear mixed model (GLMM) using SAIGE (v0.29.4.2)⁶. This strategy enabled us to maintain related samples in our GWAS, and the sample sizes were increased by 6% on average compared to removing related samples. Briefly, there are two steps in SAIGE. In step 1, we fit a null logistic mixed model using genotype data, and we added covariates in this step (see below). In step 2, we performed the single-variant association tests using imputed variant dosages. We applied the leave-one-chromosome-out (LOCO) approach. For the X chromosome, we conducted GWAS separately for males and females, and merged their results by inverse-variance fixed-effect meta-analysis. We used only female control samples for GWAS of female-specific diseases; breast cancer, cervical cancer, endometrial cancer, ovarian cancer, endometriosis, and uterine fibroids. Similarly, we used only male control samples for GWAS of prostate cancer. We incorporated age and top 5 principal component (PC) as covariates. We also used sex as covariate for GWAS of diseases which include both of male and female samples. We created regional association plots by LocusZoom (v1.2)⁴³.

We performed stepwise conditional analysis within ± 1 Mb from the lead variant; we repeated the association test by additionally incorporated the dosages of the identified variants as covariates in SAIGE step 1 until we do not detect any significant associations.

We also conducted male-specific and female-specific GWAS using the same pipeline as described above, and estimated heterogeneity in the effect size estimates using Cochran's Q test.

We set a genome-wide significance threshold at $P = 5.0 \times 10^{-8}$. For each disease, we defined a significantly associated locus as a genomic region within ± 1 Mb from the lead variant. When a locus did not include any variants which were previously reported to be significantly associated with the same disease ($P < 5.0 \times 10^{-8}$), we defined it as a novel locus.

Estimation of heritability

We estimated heritability and confounding bias in our GWAS results with LDSC (v1.0.0)⁸ using the baselineLD model (v2.1)¹⁰ which include 86 annotations, including 10 MAF- and 6 LD-related annotations that correct for bias in heritability estimates⁹, and were calculated using 481 East Asian samples in 1KG Phase3. For the analysis using LDSC, we excluded variants in the HLA region (chr6:26 Mb-34 Mb). We also calculated heritability Z-score to assess the reliability of heritability estimation.

Absolute quantification of heritability estimation using GWAS results using GLMM can be biased because effective sample size could be different from the true sample size (relative quantification is not biased, and hence GWAS results using GLMM can be applied for genetic correlation analysis and S-LDSC safely). Therefore, to confirm the robustness of heritability estimation in our analysis, we also performed GWAS using generalized linear regression model (GLM). As simple GLM does not account for the bias caused by genetic relationships, we further

excluded related samples ($\text{Pi-hat} > 0.187$), and we analyzed genotype data with PLINK (v1.90)⁴⁴ using the same covariates as described above. Heritability estimates based on GWAS using two different methods (SAIGE vs PLINK) were comparable level (Supplementary Table 2).

Comparison of GWAS results between populations

To compare the GWAS results of our study with those conducted in European populations, we prepared publicly available GWAS summary statistics for 10 diseases. Summary statistics for eight diseases were downloaded from GWAS Catalog (URL) and their names and their PMID were as follows; atrial fibrillation (30061737), breast cancer (29059683), coronary artery disease (29212778), glaucoma (29891935), ischemic stroke (29531354), prostate cancer (29892016), rheumatoid arthritis (24390342), and type 2 diabetes (30054458). Summary statistics of two diseases were downloaded from UK Biobank GWAS summary statistics at Neale Lab (URL) and their names and their phenotype code were as follows; asthma (22127), and congestive heart failure (I50).

Pleiotropy

We utilized the following variants detected in GWAS for each disease; (i) lead variants in the significantly associated loci, (ii) independent signals detected by conditional analysis, and (iii) lead variants detected in sex-specific GWAS. We defined pleiotropic association when these variants were in LD ($r^2 > 0.6$). We calculated r^2 using East Asian samples in the 1KG Phase3⁷ by PLINK (v1.90)⁴⁴.

Functional annotation of associated variants

We utilized the same disease-associated variants as used in the previous section for this analysis. We calculated r^2 using East Asian samples (r^2_{EAS}) and European samples (r^2_{EUR}) in the 1KG Phase3⁷ by PLINK (v1.90)⁴⁴. We annotated disease-associated variants with eQTLs detected in the Japanese population²¹ in the following conditions; (i) the lead variants in eQTL study is in LD ($r^2_{\text{EAS}} > 0.6$) with GWAS variants and (ii) Q value of the lead variants in eQTL study is less than 0.05. We annotated GWAS variants with eQTL detected in the European population (release v7 of GTEx project)³⁹ in the following conditions; (i) the lead variants of eQTL study is in LD ($r^2_{\text{EAS}} > 0.6$ and $r^2_{\text{EUR}} > 0.6$) with GWAS variants and (ii) Q value of the lead variants in eQTL study is less than 0.05.

For the annotation of exonic nonsynonymous variants, we used ANNOVAR⁴⁵. We annotated GWAS variants with nonsynonymous variants when they are in LD ($r^2_{\text{EAS}} > 0.6$). GRCh37 coordinates were used in this study.

Genetic correlations between sex-specific GWAS

We estimated genetic correlations between our GWAS results by LDSC (v1.0.0)⁸ using East Asian LD scores which we presented in our previous study²⁹. We excluded variants in the HLA region (chr6:26 Mb-34 Mb). We analyzed 20 diseases based on two criteria; (i) heritability was reliably estimated (heritability Z-score > 2 ; Supplementary Table 2); and (ii) both of male and female patients were included.

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Transcription factor binding sites

We obtained 3,158 raw human ChIP-seq data files in SRA format from the GEO database. We converted them to FASTQ format using the fastq-dump function of SRA Toolkit. We performed QC of sequence reads using FastQC. We mapped these reads to the genome assembly GRCh37 using Bowtie2 (v2.2.5) with default parameters. We called peaks using MACS (v2.1) with default parameters ($q < 0.01$) and defined them as TF binding sites. We excluded TF binding site tracks which do not have at least one binding region in every chromosome, and 2,868 genome-wide TF binding site tracks remained (Supplementary Table 9).

Stratified LD score regression

We conducted stratified LD score regression (S-LDSC)²⁵ to partition heritability. For S-LDSC analysis of sex-specific GWAS of asthma, we used 220 cell-type specific annotations used in previous articles^{25,29}. For other S-LDSC analysis, we used TF binding site tracks which were described in the previous paragraph. For all sites of TF binding, we empirically extended sites by 500 bp at the both ends for this analysis. We computed annotation-specific LD scores using the 1000 Genomes Project Phase 3 (version 5) East Asian reference haplotypes⁷. We estimated heritability enrichment of binding sites of each TF, while we controlled for the merged binding sites of all TFs and the 53 categories of the full baseline model available at the authors' website (see URLs). We did not use the baselineLD model (v2.1)¹⁰ in this analysis to avoid false negative findings. We excluded variants in the HLA region (chr6:26 Mb-34 Mb). We analyzed 24 diseases whose heritability was reliably estimated (heritability Z-score > 2 ; Supplementary Table 2). We calculated the P value of the regression coefficient. For each trait, we calculate FDR using the Benjamini-Hochberg method. We set a significance threshold at $FDR < 0.05$ for this analysis.

Visualization of TF binding sites

There is a complex correlation structure among 2,868 TF binding site tracks used for S-LDSC analysis. In S-LDSC, we regress GWAS chi-squared statistics on LD-scores of each TF binding site (TF LD-score), and hence we focused on correlations between TF LD-scores, not correlations between TF binding sites. We first performed PCA using all TF LD-scores. To classify them into mutually correlated TF groups, we performed k-means clustering ($k=15$) using top 15 PCs. We named each cluster by the most dominant TF in each cluster (Figure 4). The list of each TF binding site and its assigned cluster name was provided in Supplementary Table 9. We then performed uniform manifold approximation and projection (UMAP)²⁸ using top 15 PCs to project all TF binding sites into a two-dimensional space. UMAP was conducted using R package umap (v.0.2.0.0). Our workflow was illustrated in Supplementary Figure 7.

Data availability

GWAS summary statistics of the 40 diseases (all except breast cancer and coronary artery disease) are publicly available at our website (JENGER; see URLs) and the National Bioscience Database Center (NBDC) Human Database (Research ID: hum0014) without any access restrictions. For breast cancer and coronary artery disease,

485 we will deposit the results after acceptance to the journal due to accompanying projects. GWAS genotype data for
486 case samples were deposited at the NBDC Human Database (Research ID: hum0014).
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References:

1. Martin, A. R. *et al.* Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat. Genet.* **51**, 584–591 (2019).
2. Popejoy, A. B. & Fullerton, S. M. Genomics is failing on diversity. *Nature* **538**, 161–164 (2016).
3. Morales, J. *et al.* A standardized framework for representation of ancestry data in genomics studies, with application to the NHGRI-EBI GWAS Catalog. *Genome Biol.* **19**, 21 (2018).
4. Nagai, A. *et al.* Overview of the BioBank Japan Project: Study design and profile. *J. Epidemiol.* **27**, S2–S8 (2017).
5. Hirata, M. *et al.* Cross-sectional analysis of BioBank Japan clinical data: A large cohort of 200,000 patients with 47 common diseases. *J. Epidemiol.* **27**, S9–S21 (2017).
6. Zhou, W. *et al.* Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. *Nat. Genet.* **50**, 1335–1341 (2018).
7. Auton, A. *et al.* A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
8. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* **47**, 291–295 (2015).
9. Gazal, S., Marquez-Luna, C., Finucane, H. K. & Price, A. L. Reconciling S-LDSC and LDAK functional enrichment estimates. *Nat. Genet.* **51**, 1202–1204 (2019).
10. Gazal, S. *et al.* Linkage disequilibrium-dependent architecture of human complex traits shows action of negative selection. *Nat. Genet.* **49**, 1421–1427 (2017).
11. Hirata, J. *et al.* Genetic and phenotypic landscape of the major histocompatibility complex region in the Japanese population. *Nat. Genet.* **51**, 470–480 (2019).
12. van der Harst, P. & Verweij, N. The Identification of 64 Novel Genetic Loci Provides an Expanded View on the Genetic Architecture of Coronary Artery Disease. *Circ. Res.* CIRCRESAHA.117.312086 (2017). doi:10.1161/CIRCRESAHA.117.312086
13. Ma, T., Wu, S., Yan, W., Xie, R. & Zhou, C. A functional variant of *ATG16L2* is associated with Crohn's disease in the Chinese population. *Color. Dis.* **18**, O420–O426 (2016).
14. Calvete, O. *et al.* The wide spectrum of POT1 gene variants correlates with multiple cancer types. *Eur. J. Hum. Genet.* **25**, 1278–1281 (2017).
15. Bainbridge, M. N. *et al.* Germline Mutations in Shelterin Complex Genes Are Associated With Familial Glioma. *J Natl Cancer Inst* **107**, 384 (2015).
16. Robles-Espinoza, C. D. *et al.* POT1 loss-of-function variants predispose to familial melanoma. *Nat. Genet.* **46**, 478–481 (2014).
17. Ng, P. C. & Henikoff, S. Predicting deleterious amino acid substitutions. *Genome Res.* **11**, 863–74 (2001).
18. Rentzsch, P., Witten, D., Cooper, G. M., Shendure, J. & Kircher, M. CADD: predicting the deleteriousness of variants throughout the human genome. *Nucleic Acids Res.* **47**, D886–D894 (2019).
19. Kawase, T. *et al.* PH Domain-Only Protein PHLDA3 Is a p53-Regulated Repressor of Akt. *Cell* **136**, 535–550 (2009).

- 525 20. Bujor, A. M. *et al.* Akt Blockade Downregulates Collagen and Upregulates MMP1 in Human Dermal
526 Fibroblasts. *J. Invest. Dermatol.* **128**, 1906–1914 (2008).
- 527 21. Ishigaki, K. *et al.* Polygenic burdens on cell-specific pathways underlie the risk of rheumatoid arthritis. *Nat.*
528 *Genet.* **49**, 1120–1125 (2017).
- 529 22. Aguet, F. *et al.* Genetic effects on gene expression across human tissues. *Nature* **550**, 204–213 (2017).
- 530 23. Kobayashi, Y. *et al.* Mice Lacking Hypertension Candidate Gene ATP2B1 in Vascular Smooth Muscle Cells
531 Show Significant Blood Pressure Elevation. *Hypertension* **59**, 854–860 (2012).
- 532 24. Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**,
533 1236–1241 (2015).
- 534 25. Finucane, H. K. *et al.* Partitioning heritability by functional annotation using genome-wide association
535 summary statistics. *Nat. Genet.* **47**, 1228–1235 (2015).
- 536 26. Frati, F. *et al.* The Role of the Microbiome in Asthma: The Gut–Lung Axis. *Int. J. Mol. Sci.* **20**, 123 (2018).
- 537 27. Stokholm, J. *et al.* Maturation of the gut microbiome and risk of asthma in childhood. *Nat. Commun.* **9**, 141
538 (2018).
- 539 28. McInnes, L., Healy, J. & Melville, J. UMAP: Uniform Manifold Approximation and Projection for Dimension
540 Reduction. (2018).
- 541 29. Kanai, M. *et al.* Genetic analysis of quantitative traits in the Japanese population links cell types to complex
542 human diseases. *Nat. Genet.* **50**, 390–400 (2018).
- 543 30. Matsuda, M., Sakamoto, N. & Fukumaki, Y. Delta-thalassemia caused by disruption of the site for an
544 erythroid-specific transcription factor, GATA-1, in the delta-globin gene promoter. *Blood* **80**, 1347–51 (1992).
- 545 31. De Gobbi, M. *et al.* A regulatory SNP causes a human genetic disease by creating a new transcriptional
546 promoter. *Science* **312**, 1215–7 (2006).
- 547 32. Pevny, L. *et al.* Erythroid differentiation in chimaeric mice blocked by a targeted mutation in the gene for
548 transcription factor GATA-1. *Nature* **349**, 257–260 (1991).
- 549 33. Elhanati, Y., Marcou, Q., Mora, T. & Walczak, A. M. RepgenHMM: A dynamic programming tool to infer the
550 rules of immune receptor generation from sequence data. *Bioinformatics* **32**, 1943–1951 (2016).
- 551 34. Welch, J. J. *et al.* Global regulation of erythroid gene expression by transcription factor GATA-1. *Blood* **104**,
552 3136–3147 (2004).
- 553 35. Lantz, K. A. *et al.* Foxa2 regulates multiple pathways of insulin secretion. *J. Clin. Invest.* **114**, 512–520
554 (2004).
- 555 36. Bowen, C. *et al.* Loss of NKX3.1 expression in human prostate cancers correlates with tumor progression.
556 *Cancer Res.* **60**, 6111–5 (2000).
- 557 37. Prokunina-Olsson, L. *et al.* A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is
558 associated with impaired clearance of hepatitis C virus. *Nat. Genet.* **45**, 164–171 (2013).
- 559 38. Wolfe, D., Dudek, S., Ritchie, M. D. & Pendergrass, S. A. Visualizing genomic information across
560 chromosomes with PhenoGram. *BioData Min.* **6**, 18 (2013).
- 561 39. Aguet, F. *et al.* Genetic effects on gene expression across human tissues. *Nature* **550**, 204–213 (2017).

562 40. Kuriyama, S. *et al.* The Tohoku Medical Megabank Project: Design and Mission. *J. Epidemiol.* **26**, 493–511
563 (2016).
564 41. Altshuler, D. M. *et al.* Integrating common and rare genetic variation in diverse human populations. *Nature*
565 **467**, 52–58 (2010).
566 42. Okada, Y. *et al.* Deep whole-genome sequencing reveals recent selection signatures linked to evolution and
567 disease risk of Japanese. *Nat. Commun.* **9**, 1631 (2018).
568 43. Pruim, R. J. *et al.* LocusZoom: regional visualization of genome-wide association scan results.
569 *Bioinformatics* **26**, 2336–2337 (2010).
570 44. Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets.
571 *Gigascience* **4**, 7 (2015).
572 45. Wang, K., Li, M. & Hakonarson, H. ANNOVAR: functional annotation of genetic variants from high-
573 throughput sequencing data. *Nucleic Acids Res.* **38**, e164 (2010).
574
575

576 **URLs.**

577 BBJ, <https://biobankjp.org/english/index.html>
 578 JENGER, <http://jenger.riken.jp/en/>
 579 PLINK 1.9, <https://www.cog-genomics.org/plink2>
 580 MACH, <http://csg.sph.umich.edu/abecasis/MaCH/>
 581 Minimac, <https://genome.sph.umich.edu/wiki/Minimac>
 582 SAIGE, <https://github.com/weizhouUMICH/SAIGE>
 583 GWAS Catalog, <https://www.ebi.ac.uk/gwas/>
 584 Neale Lab, <http://www.nealelab.is/uk-biobank>
 585 PASCAL, <https://www2.unil.ch/cbg/index.php?title=Pascal>
 586 ldsc, <https://github.com/bulik/ldsc/>
 587 LD score, <https://data.broadinstitute.org/alkesgroup/LDSCORE/>
 588 ANNOVAR, <http://annovar.openbioinformatics.org/en/latest/>
 589 Locuszoom, <http://locuszoom.sph.umich.edu/locuszoom/>
 590 R, <https://www.r-project.org/>
 591 SRA Toolkit, <https://www.ncbi.nlm.nih.gov/sra/docs/toolkitsoft/>
 592 FASTQC, <https://www.bioinformatics.babraham.ac.uk/projects/fastqc/>
 593 Bowtie2, <http://bowtie-bio.sourceforge.net/bowtie2/manual.shtml>
 594 MACS, <https://github.com/taoliu/MACS>
 595 NBDC Human Database, <https://humandbs.biosciencedbc.jp/en/>
 596 1000 Genomes Project, www.1000genomes.org/

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K.Ishigaki wrote the manuscript with critical inputs from S.R and Y.Kamatani. K.Ishigaki conducted all bioinformatics analyses with the help of M.A, M.Kanai, A.T, S.S, N.Matoba, S.K.L, Y.O, C.Terao, T.A, S.G, S.R, and Y.Kamatani. Y.Momozawa and M.Kubo performed genotyping. H.S and E.K. analyzed ChIP-seq data. M. Ikeda and N. I managed GWAS data of psychiatric diseases. S.K.L, Y.Kochi, M.Horikoshi, Ken Suzuki, K.Ito, M.Hirata, K.M, S.I, I.K, T.Tanaka, H.N, A.Suzuki, T.H, M.T, K.C, D.M, M.M, S.N, Y.D, Y.Miki, T.Katagiri, O.O, W.O, H.I, T.Yoshida, I.I, T.Takahashi, C.Tanikawa, T.S, N.Sinozaki, S.Minami, H.Yamaguchi, S.A, Y.T, K.Yamaji, K.T, T.F, R.T, H.Yanai, A.M, Y.Koretsune, H.K, M.H, S.Murayama, K.Yamamoto, Y.Murakami, Y.N, J.I, T.Yamauchi, T.Kadowaki, M.Kubo, and Y.Kamatani contributed to the management of BBJ data. N.Minegishi, Kichiya Suzuki, K.Tanno, A.Shimizu, T.Yamaji, M.Iwasaki, N.Sawada, H.U, K.Tanaka, M.N, M.S, K.W, S.T, and M.Y contributed to the management of cohort control data. S.R, J.I, T.Yamauchi, T.Kadowaki, M.Kubo, and Y.Kamatani jointly supervised this study.

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