Supplementary Information

Supplementary note:

Sample collections for Stage 1

Singapore: Cases of primary angle closure glaucoma (PACG) included patients with chronic PACG or those with acute PACG. Chronic PACG was defined as the presence of appositional angle closure for > 180 degrees with (a) peripheral anterior synechiae and/ or (b) raised intraocular pressure associated with glaucomatous optic neuropathy (defined as loss of neuroretinal rim with a vertical cup: disc ratio of > 0.7 or an inter-eye asymmetry of > 0.2, and/or notching attributable to glaucoma). Patients with acute PACG had a previous symptomatic episode defined as the presence of at least two of the following symptoms: ocular or periocular pain, nausea or vomiting or both, and an antecedent history of intermittent blurring of vision with haloes; a presenting intraocular pressure of more than 30 mmHg on Goldmann applanation tonometry; and the presence of at least three of the following signs: conjunctival injection, corneal epithelial edema, mid-dilated unreactive pupil, and shallow anterior chamber. Patients diagnosed with secondary angle closure (such as neovascular or uveitic glaucoma) were excluded. All Singapore PACG cases for Stage 1 were recruited between years 2005 – 2010. Controls were ascertained from an on-going population based study of Chinese persons aged 40 years and older (the Singapore Chinese Eye Study [SCES]). The SCES is a population-based, cross-sectional study of Chinese adults residing in the south- western part of Singapore. The Ministry of Home Affairs of Singapore provided an initial computer-generated list ethnic Chinese names of adults aged 40-80+ years of age. A final sampling frame of 6,350 ethnic Chinese residents was derived from this list using an age-stratified random sampling strategy. A control was defined as IOP $\leq$ 21 mm Hg with open angles, healthy optic nerves and normal visual fields, and no previous intraocular surgery.

Hong Kong: Patients with PACG were defined using the same criteria as that in the Singaporean GWAS collection. All subjects of the Hong Kong study population were recruited from the Prince of Wales Hospital and the Hong Kong Eye Hospital, Hong Kong. A total of 303 PACG patients of Han Chinese ancestry were recruited. The controls comprised of 225 Hong Kong Chinese and 976 Guangdong Chinese of Han ancestry, of which 1,049 were genotyped (73 from Hong Kong and 976 from Guangdong) and 1,044 passed quality checks (73 Hong Kong and 971 from Guangdong). The Hong Kong control subjects were recruited in a hospital-based manner. They were all given complete ocular examinations, and confirmed to have no sign of glaucoma, angle closure or narrow angle, or other major eye diseases except for mild cataract and mild refractive errors. Control subjects were recruited from elderly

people aged ≥ 60 years to ensure they were at least free of early-onset major eye diseases. They had IOP < 21 mmHg, and had no known family history of glaucoma. Additional healthy controls were recruited from local communities in the Guangdong province of Southern China[1].

Vietnam: PACG cases were recruited from the Vietnam National Institute of Ophthalmology in Hanoi, Vietnam. They were defined using the same criteria as that in the Singaporean GWAS collection. The controls comprise 2,018 cord bloods, previously described[2].

Malaysia: PACG cases were recruited from the Department of Ophthalmology, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia. They were defined using the same criteria as that in the Singaporean GWAS collection. The controls were a population-based collection of healthy ethnic Malays recruited from Singapore (N = 3065), previously described[3].

India: 337 PACG cases (as defined above) of South Indian ancestry were recruited from a large population based cross sectional study, the Chennai Glaucoma study, and from the outpatient department of the Medical Research Foundation, Sankara Nethralaya, Chennai, India. All PACG cases had peripheral anterior synechiae on gonioscopy, and were identified prior to laser iridotomy. The Chennai Glaucoma study recruited 7851 persons from rural and urban cohorts in the Southern Indian state of Tamil Nadu[4]. The controls were a population-based collection of healthy ethnic Indians recruited from Singapore (N = 2538), previously described[5].

Sample collections for Stage 2

Beijing: PACG patients were recruited from the Beijing Tongren Hospital, Xingtai Eye Hospital and Anyang Eye Hospital, China. The diagnostic criteria for PACG were as described above. Controls were recruited from the Handan Eye Study (HES), a population-based study of eye disease in rural Chinese aged 30 years and over. The criteria for selecting controls are also as described above.

Singapore: All PACG cases and controls were recruited using the exact same criteria from Stage 1. They were recruited from year 2010 onwards.

India: 80 PACG cases (as defined above for Stage 1) were recruited from the outpatient department of the Medical Research Foundation, Sankara Nethralaya, Chennai, India and 309 unrelated healthy controls were recruited from the Chennai Glaucoma study. A control was defined as IOP ≤ 21 mm Hg with open angles, healthy optic nerves and normal visual fields, and no previous intraocular surgery.

UK: Cases of PACG in the UK were defined using the same criteria as that in the Singaporean GWAS collection. All subjects were of UK European descent and were recruited from Moorfields Eye Hospital, London UK. A total of 132 cases were genotyped and 127 passed quality checks. The controls comprised of 4,703 healthy individuals of UK European descent, recruited and genotyped by the Wellcome Trust Case-Control Consortium 2. Their extensive use for genetics studies (such as ankylosing spondylitis, psoriasis, ulcerative colitis, ischaemic stroke, Meningococcal sepsis, and Kawasaki disease) has been well-described[6-11].

Saudi Arabia: PACG cases and controls were collected at the glaucoma clinic at King Abdulaziz University Hospital (KAUH), Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia. They were defined using the same criteria as that in the Singaporean GWAS collection. All patients and controls were unrelated Saudi Arabs, all whose known ancestors were of Saudi Arabian origin. As judged by the family names, PACG patients and controls were representative of the five provinces of the Kingdom of Saudi Arabia.

Shantou: PACG cases and controls were collected at the glaucoma clinic of the Chinese University of Hong Kong Joint Shantou International Eye Centre, Shantou, China. They were defined using the same criteria as that in the Singaporean GWAS collection, and were of Chinese descent.

Distinction between acute angle closure glaucoma and chronic angle closure glaucoma

Approximately 40% of patients in this study were acute angle closure glaucoma (ACG) whilst the remaining patients had chronic ACG.

The unifying characteristic of all these patients is that the cause of their angle closure is not secondary to any other pathology (hence classified as primary) and that all patients have gonioscopic angle closure with significant disease severity.

The clinical classification of acute and chronic ACG, which is based on reported symptoms in patients, is subjective and likely to be affected by recall bias. Further scenarios may blur the distinctions; patients with chronic ACG may have had intermittent angle closure or subclinical episodes before; acute attacks may occur on a background of chronic ACG, and patients with acute ACG may proceed to develop chronic ACG as a result of persistently raised intraocular pressure (IOP).

The International Society of Geographical and Epidemiological Ophthalmology (ISGEO)[12] recommended a revised approach to classification of ACG which does not include symptoms, i.e. does not differentiate between acute and chronic ACG. This

approach was supported by a subsequent report which reported a high rate of symptoms traditionally associated with acute ACG in an unaffected normal population[13]. The ISGEO approach to classification is now the standard approach to classification of ACG, and centers on the concept that:

- Primary angle-closure disease is contact between iris and trabecular meshwork outflow channels occurring in the absence of any other ocular pathology
- This contact is sufficient to significantly obstruct aqueous fluid outflow, causing elevated IOP
- Symptoms are a poor indicator of the presence or absence of disease, and unrelated to the natural history of the disease

We therefore grouped acute and chronic ACG cases together in this analysis as the thrust of our study was to study the molecular biology of development of PACG.

Supplementary Table 1

GWAS (Stage 1) and Replication (Stage 2) results for the 15 SNPs from Stage 1 brought forward for further assessment in Stage 2. Dashes indicate failed genotyping in Stage 2.

			GWAS (Stage 1)		Replication (Stage 2)		All data (Stages 1 + 2)			
Chr	**SNP**	**A1**	**OR**	***P***	**OR**	***P***	**OR**	***P***	***P*het**	**I^2**
11	rs11024102	G	1.27	1.43×10^{-8}	1.18	3.72×10^{-5}	1.22	5.33×10^{-12}	0.64	0%
1	rs3753841	G	1.22	2.82×10^{-6}	1.18	6.62×10^{-5}	1.2	9.22×10^{-10}	0.59	0%
8	rs1015213	A	1.56	3.90×10^{-6}	1.44	1.77×10^{-4}	1.5	3.29×10^{-9}	0.19	19.00%
22	rs3788317	A	0.76	2.27×10^{-7}	0.89	0.028	0.82	1.73×10^{-7}	0.41	3.17%
5	rs2114950	G	1.31	1.31×10^{-6}	1.01	0.89	1.16	3.38×10^{-4}	0.059	45.14%
5	rs3149	C	1.33	2.04×10^{-7}	-	-	-	-	-	-
7	rs3816415	A	1.30	9.13×10^{-6}	-	-	-	-	-	-
11	rs2729389	A	1.39	1.97×10^{-7}	0.96	0.49	1.14	0.00226	0.0025	63.14%
1	rs10881542	A	0.81	6.38×10^{-7}	0.93	0.21	0.85	1.76×10^{-6}	0.35	10.43%
1	rs12035919	A	0.81	4.79×10^{-7}	1.00	0.95	0.90	3.86×10^{-4}	0.0081	59.56%
4	rs1037644	A	0.69	5.02×10^{-6}	1.00	0.95	0.86	0.00379	0.020	54.19%
4	rs13129984	A	0.69	9.32×10^{-6}	0.99	0.93	0.85	0.00317	0.0082	59.49%
6	rs675497	G	1.24	9.64×10^{-7}	-	-	-	-	-	-
4	rs224463	A	1.22	4.39×10^{-6}	1.00	0.95	1.11	8.65×10^{-4}	0.064	44.31%
22	rs1052978	G	0.65	7.63×10^{-6}	-	-	-	-	-	-

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Supplementary Table 2

Per-collection details of the three sequence variants showing genome-wide significant association with susceptibility to PACG.

SNP	Collection	Geno Case	Geno Cont	MAF Case	MAF Cont	OR	*P*
rs11024102	Singapore	176/464/343	122/431/390	0.415	0.358	1.27	2.79×10^{-4}
	Hong Kong	48/142/107	118/481/445	0.400	0.344	1.24	0.032
	India	42/153/143	256/1024/1255	0.351	0.303	1.25	0.011
	Malaysia	20/39/24	430/1425/1202	0.476	0.374	1.63	0.0013
	Vietnam	24/67/62	231/913/872	0.376	0.341	1.20	0.15
				Stage 1 summary		**1.27**	**1.43×10^{-8} (2.93×10^{-9})**
	China (Beijing)	217/486/289	315/813/543	0.464	0.432	1.14	0.024
	Singapore	54/134/111	197/710/572	0.405	0.373	1.14	0.15
	China (Shantou)	52/112/80	96/274/232	0.443	0.387	1.24	0.035
	India	12/39/28	29/127/153	0.399	0.299	1.55	0.019
	Saudi Arabia	3/23/139	1/18/156	0.088	0.057	1.53	0.14
	United Kingdom	14/56/57	395/1962/2339	0.331	0.293	1.19	0.19
				Stage 2 summary		**1.18**	**3.72×10^{-5}**
				All samples		**1.22**	**5.33×10^{-12} (1.27×10^{-12})**
rs1015213	Singapore	2/41/941	0/18/925	0.023	0.0095	2.37	0.0019
	Hong Kong	0/10/287	1/26/1014	0.017	0.014	1.26	0.54
	India	7/98/233	40/540/1957	0.166	0.122	1.43	0.0041
	Malaysia	1/13/69	7/233/2823	0.09	0.04	2.01	0.018
	Vietnam	0/5/148	0/42/1975	0.016	0.01	1.43	0.48
				Stage 1 summary		**1.56**	**3.90×10^{-6} (1.27×10^{-5})**
	China (Beijing)	0/54/938	5/59/1603	0.027	0.021	1.30	0.14
	Singapore	0/11/293	0/41/1438	0.018	0.014	1.32	0.43
	China (Shantou)	0/9/236	0/20/581	0.018	0.017	1.11	0.8
	India	2/15/63	5/69/234	0.119	0.128	0.92	0.75
	Saudi Arabia	7/51/107	1/31/142	0.197	0.095	2.34	2.72×10^{-4}
	United Kingdom	2/30/95	44/746/3911	0.134	0.089	1.57	0.013
				Stage 2 summary		**1.44**	**1.77×10^{-4}**
				All samples		**1.5**	**3.29×10^{-9} (9.10×10^{-9})**
rs3753841	Singapore	142/413/426	91/415/437	0.355	0.317	1.18	0.014
	Hong Kong	30/154/113	116/466/462	0.361	0.344	1.11	0.31
	India	87/159/92	496/1229/812	0.493	0.438	1.26	0.012
	Malaysia	16/36/31	261/1279/1524	0.41	0.294	1.52	0.0099
	Vietnam	19/74/60	182/861/974	0.366	0.304	1.33	0.027
				Stage 1 summary		**1.22**	**2.82×10^{-6} (4.47×10^{-5})**
	China (Beijing)	107/413/472	142/701/829	0.316	0.295	1.11	0.10
	Singapore	42/120/136	152/622/705	0.342	0.313	1.14	0.16
	China (Shantou)	31/112/102	59/244/296	0.355	0.302	1.26	0.03
	India	19/46/15	61/159/89	0.525	0.455	1.35	0.1
	Saudi Arabia	35/79/51	54/81/40	0.548	0.46	1.40	0.026
	United Kingdom	25/62/40	753/2126/1823	0.441	0.386	1.24	0.077
				Stage 2 summary		**1.18**	**6.62×10^{-5}**
						1.20	**9.22×10^{-10} (1.2×10^{-8})**

Geno Case: Genotype counts in PACG cases

Geno Cont: Genotype counts in controls

For Stage 1 summary, the *P*-values in parenthesis were obtained using joint analysis when the total number of 1,854 cases and 9,608 controls were analyzed together with joint correction for genetic stratification along the top 4 axes of ancestry.

For the summary on all samples, the *P*-values in parenthesis were obtained using the Joint Stage 1 *P*-value (in parenthesis) together with the Stage 2 *P*-value.

Supplementary Table 3

Conditional logistic regression analysis at the *PLEKHA7* locus on Chromosome 11; the conditioning SNP is rs11024102.

			Before conditioning		After conditioning	
SNP	**BP**	**A1**	***P***	**OR**	***P***	**OR**
rs11024102	16965181	G	7.97×10^{-9}	1.28	-	-
rs6486334	16972133	A	9.07×10^{-8}	1.25	0.027	0.84
rs3950680	17095242	A	9.67×10^{-5}	1.18	0.63	0.97
rs12577525	17216692	A	1.04×10^{-4}	1.18	0.73	0.98
rs10832757	17292907	G	2.27×10^{-4}	1.17	0.22	1.06
rs2354867	17327277	A	5.50×10^{-4}	1.16	0.19	1.06
rs10766383	17286374	C	6.39×10^{-4}	1.16	0.33	1.05
rs4756887	17351173	A	8.96×10^{-4}	1.15	0.34	1.05
rs214105	17270097	G	9.10×10^{-4}	1.15	0.96	1.00
rs7127347	17257420	C	0.0011	0.87	0.30	0.95
rs1330	17272605	A	0.0030	1.13	0.87	0.99
rs366590	16829016	A	0.0055	1.14	0.020	1.12
rs1557765	17360215	A	0.021	1.10	0.64	0.98
rs757110	17375053	C	0.035	1.09	0.89	0.99
rs2285676	17364601	A	0.036	1.09	0.95	1.00

Supplementary Table 4

Conditional logistic regression analysis at the *COL11A1* locus on Chromosome 1; the conditioning SNP is rs3753841.

			Before conditioning		After conditioning	
SNP	**BP**	**A1**	***P***	**OR**	***P***	**OR**
rs3753841	103152506	G	3.85×10^{-6}	1.22	-	-
rs1676486	103126726	A	1.09×10^{-5}	1.22	0.11	1.11
rs12138977	103166045	G	2.34×10^{-5}	1.21	0.76	1.03
rs7550513	102994366	A	3.04×10^{-5}	1.21	0.06	1.11
rs2229783	103125039	A	3.50×10^{-5}	1.19	0.95	1.01
rs12074523	103040347	A	4.99×10^{-5}	1.20	0.14	1.08
rs713162	102989469	A	6.89×10^{-5}	1.18	0.52	1.05
rs1020918	103103937	A	1.25×10^{-4}	1.18	0.65	1.03
rs1241163	103128353	A	1.47×10^{-4}	1.18	0.51	1.04
rs1085	103128756	A	1.86×10^{-4}	1.18	0.33	1.07
rs921416	103001167	G	2.76×10^{-4}	1.16	0.76	1.02
rs8179334	103139683	A	4.36×10^{-4}	1.18	0.79	1.02
rs12030173	102949180	C	9.44×10^{-4}	1.17	0.16	1.08
rs9659030	103114980	G	0.0011	1.16	0.59	1.03
rs1241202	103077609	C	0.0012	1.15	0.98	1.00
rs12022173	102874238	G	0.0016	1.17	0.17	1.08
rs11164556	102852775	A	0.0051	1.14	0.47	1.04
rs10874639	102906497	G	0.0083	1.13	0.43	1.04
rs11164585	102944531	A	0.010	1.13	0.34	1.05
rs1376359	102975695	A	0.012	1.11	0.88	1.01
rs4907975	102802807	G	0.021	1.10	0.99	1.00
rs7539441	102793412	G	0.033	1.09	0.92	1.00
rs2222748	103530366	G	0.036	1.16	0.22	1.09
rs967554	102836762	G	0.039	1.09	0.69	0.98
rs11164544	102785098	G	0.041	0.92	0.77	0.99
rs7517663	102781216	G	0.044	0.92	0.78	0.99

Supplementary Table 5

Conditional logistic regression analysis at the *PCMTD1-ST18* locus on Chromosome 8; the conditioning SNP is rs1015213.

			Before conditioning		After conditioning	
SNP	**BP**	**A1**	***P***	**OR**	***P***	**OR**
rs1015213	53050094	A	9.38×10^{-6}	1.53	-	-
rs7846408	52523096	A	3.80×10^{-4}	0.84	0.0013	0.85
rs9792278	52593356	G	0.0016	0.88	0.0023	0.88
rs13271514	52561732	G	0.0040	0.88	0.0094	0.89
rs2017341	52516457	A	0.0040	1.23	0.0041	1.23
rs10111115	52778748	G	0.0054	1.15	0.13	1.08
rs16916394	52555316	A	0.0074	0.87	0.013	0.88
rs16916425	52582435	G	0.010	0.75	0.013	0.76
rs2304365	53292766	A	0.013	0.85	0.013	0.85
rs12155844	53292222	G	0.015	0.85	0.013	0.85
rs7830945	53295719	G	0.027	0.85	0.045	0.86
rs11786371	52598500	G	0.029	0.90	0.047	0.90
rs7000275	52602042	A	0.047	0.90	0.072	0.91

Supplementary Table 6

Stage 1 association tests (1,854 PACG cases vs 9,608 controls) looking up previously reported susceptibility loci in Primary Open Angle Glaucoma (POAG).

Chr.	SNP	Gene	A1	Collection	*P*	OR	P_{het}	I^2
7	rs4236601	***CAV1-CAV2***	A	Singapore	0.088	1.70		
				Hong Kong	0.31	0.60		
				India	0.16	1.16		
				Vietnam	0.63	0.77		
				Malays	0.73	0.87		
				All Stage 1	0.26	1.13	0.37	6.14%
7	rs1052990	***CAV1-CAV2***	C	Singapore	0.63	0.96		
				Hong Kong	0.56	0.92		
				India	0.26	1.11		
				Vietnam	0.090	1.31		
				Malays	0.79	1.07		
				All Stage 1	0.42	1.05	0.3875	3.37%
9	rs4977756	***CDKN2BAS***	G	Singapore	0.079	0.87		
				Hong Kong	0.20	0.86		
				India	0.013	1.26		
				Vietnam	0.77	0.96		
				Malays	0.65	1.09		
				All Stage 1	0.93	0.99	0.0253	64.03%
9	rs10120688	***CDKN2BAS***	G	Singapore	0.30	0.93		
				Hong Kong	0.33	0.90		
				India	0.052	1.18		
				Vietnam	0.40	1.14		
				Malays	0.77	0.95		
				All Stage 1	0.86	1.01	0.1624	38.82%
1	rs10800150	***TMCO1***	A	Singapore	0.53	0.96		
				Hong Kong	0.017	1.26		
				India	0.19	1.18		
				Vietnam	0.017	1.35		
				Malays	0.11	1.31		
				All Stage 1	0.039	1.17	0.0385	60.46%
1	rs2790051	***TMCO1***	A	Singapore	0.41	0.93		
				Hong Kong	0.12	1.20		

				India	0.12	1.14		
				Vietnam	0.0011	1.56		
				Malays	0.97	1.01		
				All Stage 1	0.12	1.14	0.0225	64.87%
14	rs10483727	***SIX1***	G	Singapore	0.12	1.13		
				Hong Kong	0.076	1.23		
				India	0.042	0.84		
				Vietnam	0.034	0.72		
				Malays	0.36	0.82		
				All Stage 1	0.62	0.95	0.0047	73.34%

P: *P*-value for association with PACG.

OR: per-allele odds ratio for the effect allele (A1).

P_{het}: *P*-value for heterogeneity in Stage 1 meta-analysis.

I^2: I-squared index for heterogeneity.

Supplementary Table 7

Stage 1 association results for SNPs at the 3 previously reported nanophthalmos loci. SNPs with Stage 1 $P < 0.01$ are shown here. Overall, a total of 9,301 SNPs from *NNO1*, 13 SNPs from *NNO2*, and 4,606 SNPs from *NNO3* were present in our Stage 1 GWAS data.

SNP	CHR	BP	A1	OR	*P*	P_{het}	I^2	Locus
rs11024102	11	16965181	G	1.27	1.43×10^{-8}	0.47	0	*NNO1*
rs6486334	11	16972133	A	1.25	9.07×10^{-8}	0.91	0	*NNO1*
rs3950680	11	17095242	A	1.18	9.67×10^{-5}	0.96	0	*NNO1*
rs12577525	11	17216692	A	1.18	0.00010	0.88	0	*NNO1*
rs353630	11	35144767	A	0.72	0.00013	0.82	0	*NNO1*
rs10832757	11	17292907	G	1.17	0.00023	0.82	0	*NNO1*
rs2354867	11	17327277	A	1.16	0.00055	0.49	0	*NNO1*
rs10766383	11	17286374	C	1.16	0.00064	0.73	0	*NNO1*
rs11022262	11	12216931	A	0.78	0.00067	0.87	0	*NNO1*
rs214105	11	17270097	G	1.15	0.00091	0.72	0	*NNO1*
rs2745879	11	32029355	G	0.81	0.00121	0.68	0	*NNO1*
rs879346	11	45037021	A	0.76	0.00124	0.69	0	*NNO1*
rs4752926	11	46649446	A	0.87	0.00136	0.81	0	*NNO1*
rs11602755	11	45034487	G	0.77	0.00164	0.75	0	*NNO1*
rs4756887	11	17351173	A	1.16	0.00176	0.32	14.87	*NNO1*
rs7106548	11	17550285	G	0.88	0.00266	0.79	0	*NNO1*
rs901555	11	11311920	A	1.22	0.00278	0.56	0	*NNO1*
rs4910413	11	11701087	C	1.15	0.00283	0.80	0	*NNO1*
rs11025951	11	21139294	G	0.68	0.00295	0.58	0	*NNO1*
rs10838502	11	1636686	A	1.26	0.00332	0.77	0	*NNO1*
rs2361069	11	7865203	G	0.83	0.00348	0.50	0	*NNO1*
rs7950226	11	13274715	G	1.13	0.00351	0.95	0	*NNO1*
rs10833053	11	19045326	C	0.89	0.00367	0.93	0	*NNO1*
rs1231637	11	29486823	A	1.13	0.00386	0.48	0	*NNO1*
rs933930	11	12499458	A	0.86	0.00418	0.29	19.48	*NNO1*
rs7127347	11	17257420	C	0.87	0.00424	0.30	17.75	*NNO1*
rs2361065	11	7857944	G	0.84	0.00432	0.41	0	*NNO1*
rs4237704	11	12198606	A	0.87	0.00452	0.92	0	*NNO1*
rs16911799	11	12907129	A	1.13	0.00474	0.68	0	*NNO1*
rs988189	11	12122809	A	1.14	0.00486	0.88	0	*NNO1*
rs10765931	11	12218676	G	0.80	0.00498	0.51	0	*NNO1*
rs7122659	11	44605698	A	0.85	0.00528	0.46	0	*NNO1*
rs366590	11	16829016	A	1.14	0.00547	0.83	0	*NNO1*
rs1459826	11	7702928	G	1.12	0.00548	0.92	0	*NNO1*
rs4420242	11	12940628	C	1.13	0.00552	0.58	0	*NNO1*

rs11822631	11	2577110	C	1.15	0.00556	0.36	8.94	*NNO1*
rs11038993	11	46767492	A	0.87	0.00557	0.77	0	*NNO1*
rs224612	11	32019805	A	0.84	0.00572	0.80	0	*NNO1*
rs11025878	11	20998335	A	1.22	0.00577	0.85	0	*NNO1*
rs1478762	11	37901485	A	1.12	0.00578	0.93	0	*NNO1*
rs1493955	11	12212874	A	0.81	0.00610	0.84	0	*NNO1*
rs1487721	11	45131106	A	1.13	0.00618	0.96	0	*NNO1*
rs1389455	11	26604761	A	0.85	0.00653	0.90	0	*NNO1*
rs1330	11	17272605	A	1.13	0.00655	0.35	10.47	*NNO1*
rs7481099	11	11460104	A	1.12	0.00675	0.85	0	*NNO1*
rs10833809	11	22741425	A	1.12	0.00689	0.60	0	*NNO1*
rs4469873	11	12925354	A	1.12	0.00699	0.57	0	*NNO1*
rs7937953	11	12935831	A	1.12	0.00716	0.56	0	*NNO1*
rs7932167	11	610599	C	0.89	0.00765	0.51	0	*NNO1*
rs10501045	11	26300143	A	0.87	0.00770	0.53	0	*NNO1*
rs12799959	11	7277111	A	0.85	0.00774	0.93	0	*NNO1*
rs1471014	11	11697651	G	1.13	0.00780	0.69	0	*NNO1*
rs897360	11	11720424	A	1.13	0.00808	0.82	0	*NNO1*
rs11021873	11	11457483	A	1.13	0.00820	0.92	0	*NNO1*
rs12269906	11	10976659	A	1.29	0.00823	0.96	0	*NNO1*
rs890249	11	43156514	G	1.12	0.00836	0.77	0	*NNO1*
rs4758417	11	6416514	G	1.17	0.00848	0.39	2.19	*NNO1*
rs7928025	11	11450195	A	1.12	0.00902	0.45	0	*NNO1*
rs1503502	11	19040053	A	0.90	0.00909	0.95	0	*NNO1*
rs1528133	11	8106329	C	1.24	0.00911	0.34	11.99	*NNO1*
rs1351650	11	7703386	A	1.11	0.00933	0.86	0	*NNO1*
rs11039035	11	46923991	A	0.89	0.00942	0.64	0	*NNO1*
rs12417519	11	47085973	G	0.89	0.00955	0.45	0	*NNO1*
rs193276	11	35140414	G	0.86	0.00966	0.49	0	*NNO1*
rs7950535	11	32504854	G	0.67	0.00973	0.92	0	*NNO1*
rs87603	11	35007815	G	1.22	0.00988	0.48	0	*NNO1*
rs1600970	11	7711535	A	1.11	0.00991	0.77	0	*NNO1*
rs4755794	11	44224233	A	0.87	0.00996	0.91	0	*NNO1*
rs10210418	2	118209547	A	0.87	0.00063	0.82	0	*NNO3*
rs6717729	2	99123373	A	0.83	0.00096	0.43	0	*NNO3*
rs11692699	2	99097089	A	0.83	0.00116	0.50	0	*NNO3*
rs7592778	2	120903533	A	0.87	0.00131	0.99	0	*NNO3*
rs12463880	2	106898427	A	1.14	0.00155	0.49	0	*NNO3*
rs6742683	2	106933795	A	1.14	0.00198	0.87	0	*NNO3*
rs2139399	2	104431743	A	0.87	0.00225	0.90	0	*NNO3*
rs4402763	2	126317380	G	0.70	0.00225	0.36	8.11	*NNO3*
rs2193909	2	125926354	A	0.85	0.00246	0.62	0	*NNO3*
rs12464700	2	121572920	G	0.88	0.00258	0.93	0	*NNO3*

rs10515924	2	118202634	A	1.14	0.00267	0.74	0	*NNO3*
rs6709558	2	121603296	G	0.88	0.00271	0.80	0	*NNO3*
rs779984	2	124844266	A	0.79	0.00276	0.88	0	*NNO3*
rs2059029	2	125901384	A	0.86	0.00334	0.66	0	*NNO3*
rs1436304	2	125883201	A	0.85	0.00339	0.77	0	*NNO3*
rs1562313	2	100953887	A	1.15	0.00344	0.89	0	*NNO3*
rs13033073	2	106925339	A	1.13	0.00378	0.70	0	*NNO3*
rs11124141	2	106939196	G	1.13	0.00384	0.77	0	*NNO3*
rs10202196	2	125898078	G	0.86	0.00386	0.69	0	*NNO3*
rs10171785	2	127406758	G	1.29	0.00405	0.91	0	*NNO3*
rs880713	2	128848084	G	1.13	0.00432	0.90	0	*NNO3*
rs7602423	2	125560858	A	0.86	0.00437	0.57	0	*NNO3*
rs4602234	2	125551151	A	0.86	0.00458	0.62	0	*NNO3*
rs1820556	2	126006846	C	0.86	0.00458	0.61	0	*NNO3*
rs2084869	2	125996477	A	0.86	0.00462	0.61	0	*NNO3*
rs6749443	2	104451572	G	0.89	0.00476	0.93	0	*NNO3*
rs7572049	2	125536864	A	0.86	0.00479	0.61	0	*NNO3*
rs908634	2	121615878	G	0.89	0.00507	0.79	0	*NNO3*
rs6542775	2	108679550	A	1.22	0.00539	0.49	0	*NNO3*
rs10192557	2	125534152	G	0.86	0.00580	0.62	0	*NNO3*
rs9789595	2	106905733	G	1.12	0.00626	0.73	0	*NNO3*
rs7571787	2	121584893	A	0.89	0.00639	0.96	0	*NNO3*
rs17030964	2	105460819	A	1.19	0.00658	0.93	0	*NNO3*
rs6742893	2	118192890	G	1.12	0.00659	0.60	0	*NNO3*
rs840887	2	128775685	A	1.14	0.00675	0.59	0	*NNO3*
rs12477316	2	118201160	A	0.89	0.00677	0.79	0	*NNO3*
rs4491733	2	119434498	A	1.12	0.00738	0.48	0	*NNO3*
rs383993	2	109041343	A	1.15	0.00739	0.83	0	*NNO3*
rs6739515	2	125740708	A	0.85	0.00751	0.92	0	*NNO3*
rs11885558	2	121617596	A	0.89	0.00766	0.66	0	*NNO3*
rs10169502	2	121600216	G	0.89	0.00780	0.79	0	*NNO3*
rs7568838	2	108549026	G	1.21	0.00790	0.48	0	*NNO3*
rs12624214	2	124348173	A	1.25	0.00820	0.34	11.08	*NNO3*
rs9308661	2	125909964	G	0.87	0.00834	0.67	0	*NNO3*
rs2610225	2	125681338	G	0.87	0.00880	0.59	0	*NNO3*
rs2059030	2	125901493	A	0.87	0.00890	0.40	0.75	*NNO3*
rs8179791	2	128773387	A	1.13	0.00891	0.57	0	*NNO3*
rs2193910	2	125933823	A	0.85	0.00926	0.36	7.69	*NNO3*
rs2138814	2	121594078	A	1.12	0.00933	0.71	0	*NNO3*
rs6710520	2	126004530	A	0.86	0.00966	0.60	0	*NNO3*

A1: minor allele. OR: Per-allele odds ratio. *P*: *P*-value for association. P_{het}: Heterogeneity *P*-value across the 5 Stage 1 sample collections. I^2: I^2 index for heterogeneity.

Supplementary Table 8

Study power as a function of disease allele frequency and per-allele odds ratio for

(a) the double staged study at $P < 5 \times 10^{-8}$ and (b) statistical power to detect SNPs at $P < 10^{-5}$ in Stage 1.

(a)

Risk allele frequency	Per-allele odds ratio						
	1.20	1.25	1.30	1.35	1.40	1.50	1.60
0.10	21.0%	62.2%	92.1%	>99.9%	>99.9%	>99.9%	>99.9%
0.15	51.4%	91.0%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%
0.20	74.0%	98.1%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%
0.25	86.3%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%
0.30	92.3%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%
0.35	95.0%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%

These power calculations are based on a GWAS and replication (double staged) study design whereby SNPs showing *P*-values < 10^{-5} in Stage 1 (1,854 cases and 9,608 controls) is brought forward for replication in the 6 independent PACG disease collections comprising Stage 2 (1,917 cases and 8,943 controls). The power calculation is based on final meta-analysis to detect SNPs at genome-wide significance ($P < 5 \times 10^{-8}$), as previously described[14-15]. Shaded areas represent > 90 percent statistical power for detection.

(b)

Risk allele frequency	Per-allele odds ratio						
	1.20	1.25	1.30	1.35	1.40	1.50	1.60
0.10	12.6%	36.1%	66.2%	88.1%	97.3%	>99.9%	>99.9%
0.15	29.0%	64.3%	89.8%	98.4%	99.9%	>99.9%	>99.9%
0.20	45.1%	81.3%	97.0%	99.8%	>99.9%	>99.9%	>99.9%
0.25	57.7%	89.8%	99.0%	>99.9%	>99.9%	>99.9%	>99.9%
0.30	66.4%	93.9%	99.6%	>99.9%	>99.9%	>99.9%	>99.9%
0.35	72.0%	95.8%	99.8%	>99.9%	>99.9%	>99.9%	>99.9%

These power calculations are based on the ability of the Stage 1 study to detect SNPs at *P*-values < 10^{-5}. Shaded areas represent > 90 percent statistical power for detection.

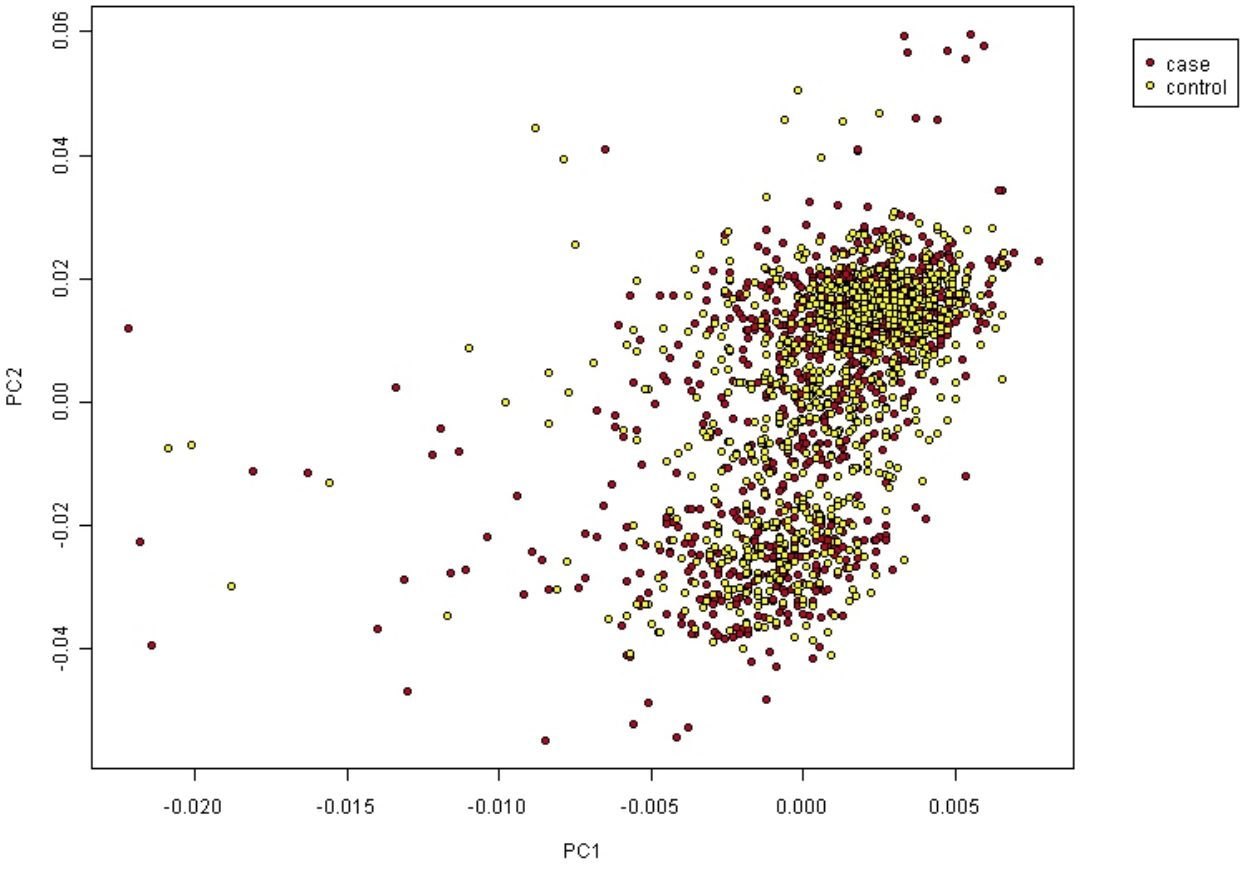
Supplementary Table 9

Gene specific primer sequences for RT-PCR analysis.

Primer ID	Sequences	Amplicon Size (bp)	Annealing Temp (°C)
PLEKHA7-F	5’ TAAAGACAGCCGAGAAGAAG 3’	206	58
PLEKHA7-R	5’ TGTCGGCACTGAAGTAGTAG 3’		
COL11A1-F	5’ GCAGGGAGAGATGGAGTTCAAGG 3’	242	58
COL11A1-R	5’ TGCCCAAACATCCCCTGCTG 3’		
PCMTD1-F	5’ ACACAGATTATGCGAACTGG 3’	166	58
PCMTD1-R	5’ TGTAAATACGAGCCAAGTCC 3’		
ST18-F	5’ AGGGTAGAGAAGGCAGGACGG 3’	223	58
ST18-R	5’ AGGTCTCTTCCACATCGCCCC 3’		
ACTB-F	5’ CCAACCGCGAGAAGATGA 3’	97	58
ACTB-R	5’ CCAGAGGCGTACAGGGATAG 3’		

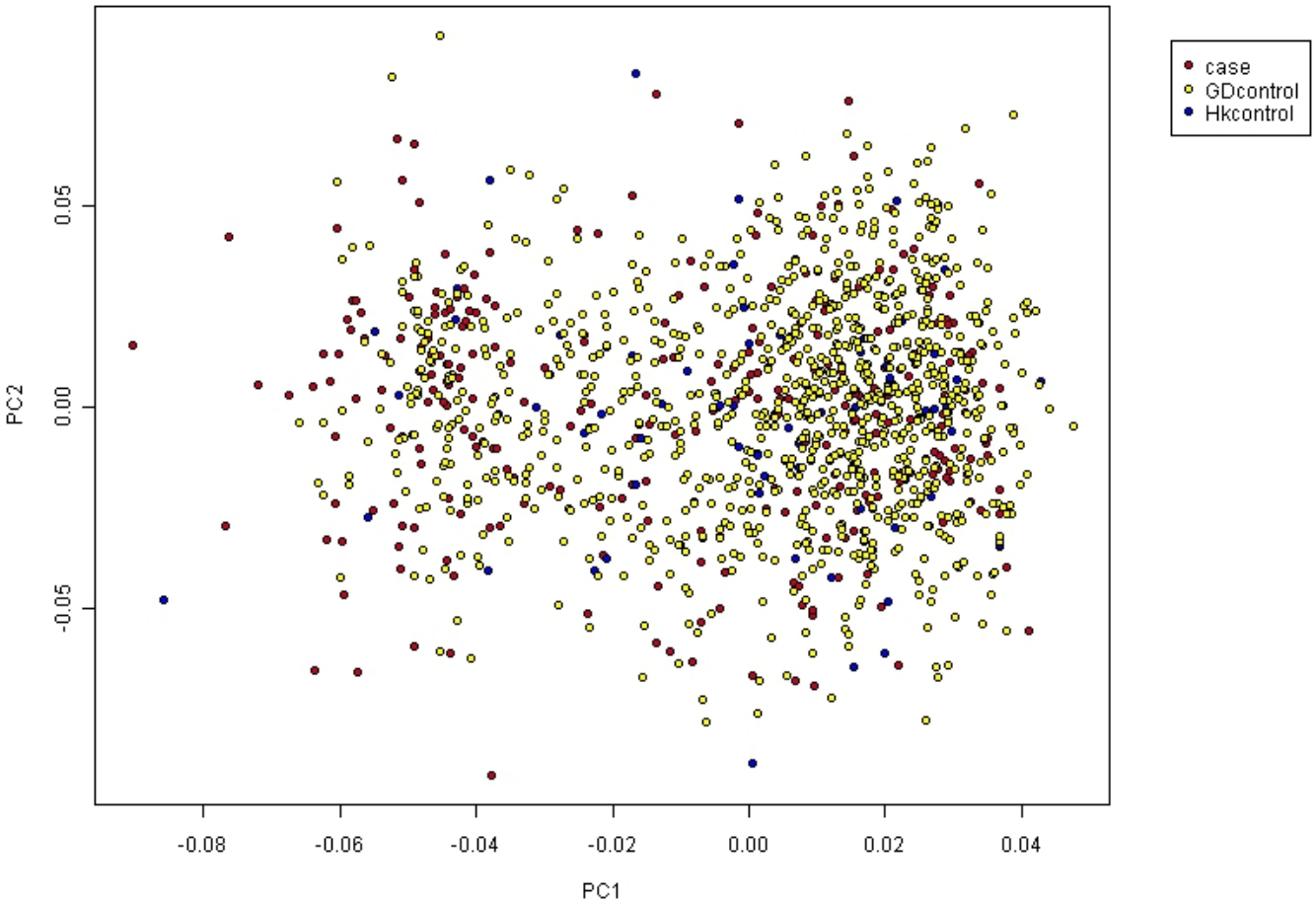
Supplementary Figure 1

(a) Principal component analysis between PACG cases and healthy controls for the Singaporean Chinese PACG collection. The vast majority of cases have genetically matched controls. Additional statistical correction for the top principal components using logistic regression was conducted to minimize residual population stratification.



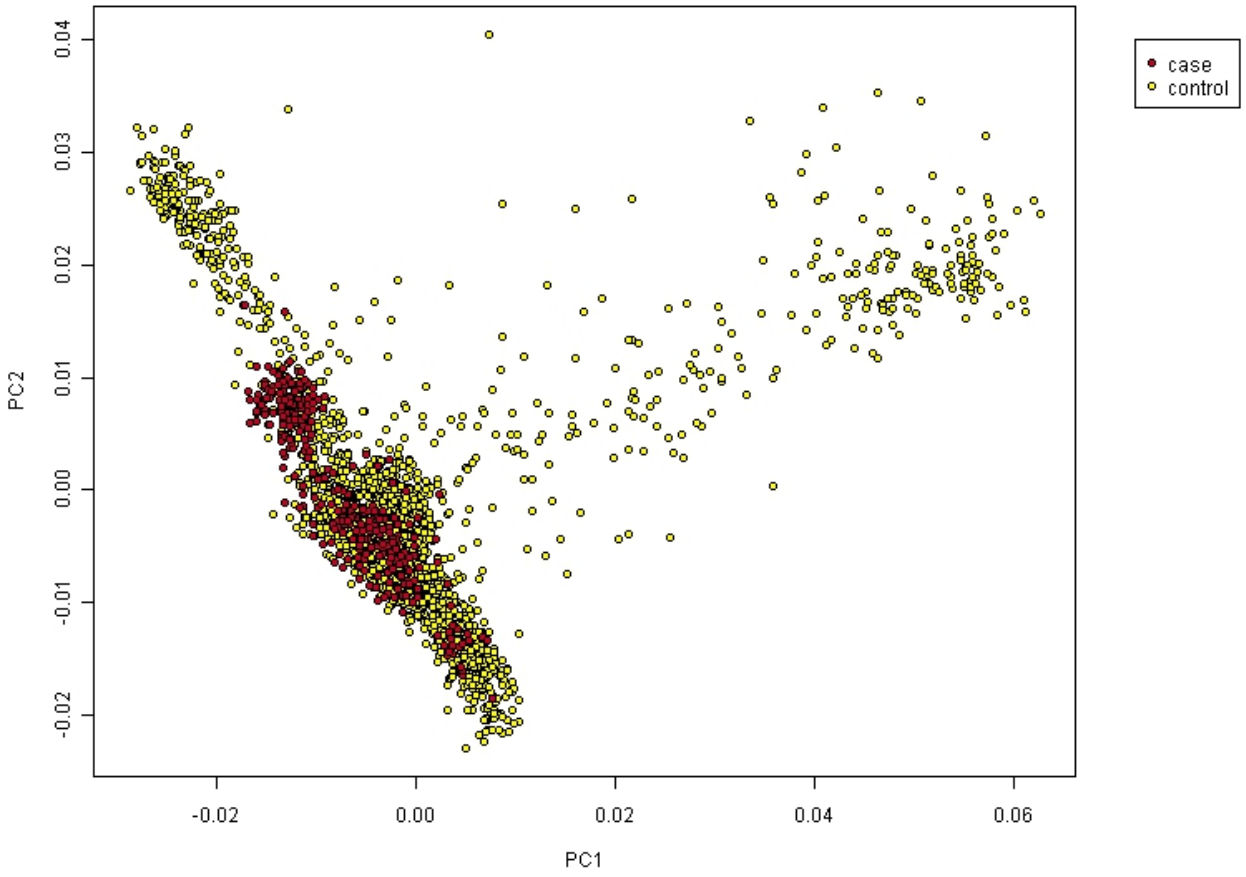
Lambda = 1.04

(b) Principal component analysis between PACG cases and healthy controls for the Hong Kong collection. The vast majority of cases have genetically matched controls. Additional statistical correction for the top principal components using logistic regression was conducted to minimize residual population stratification.



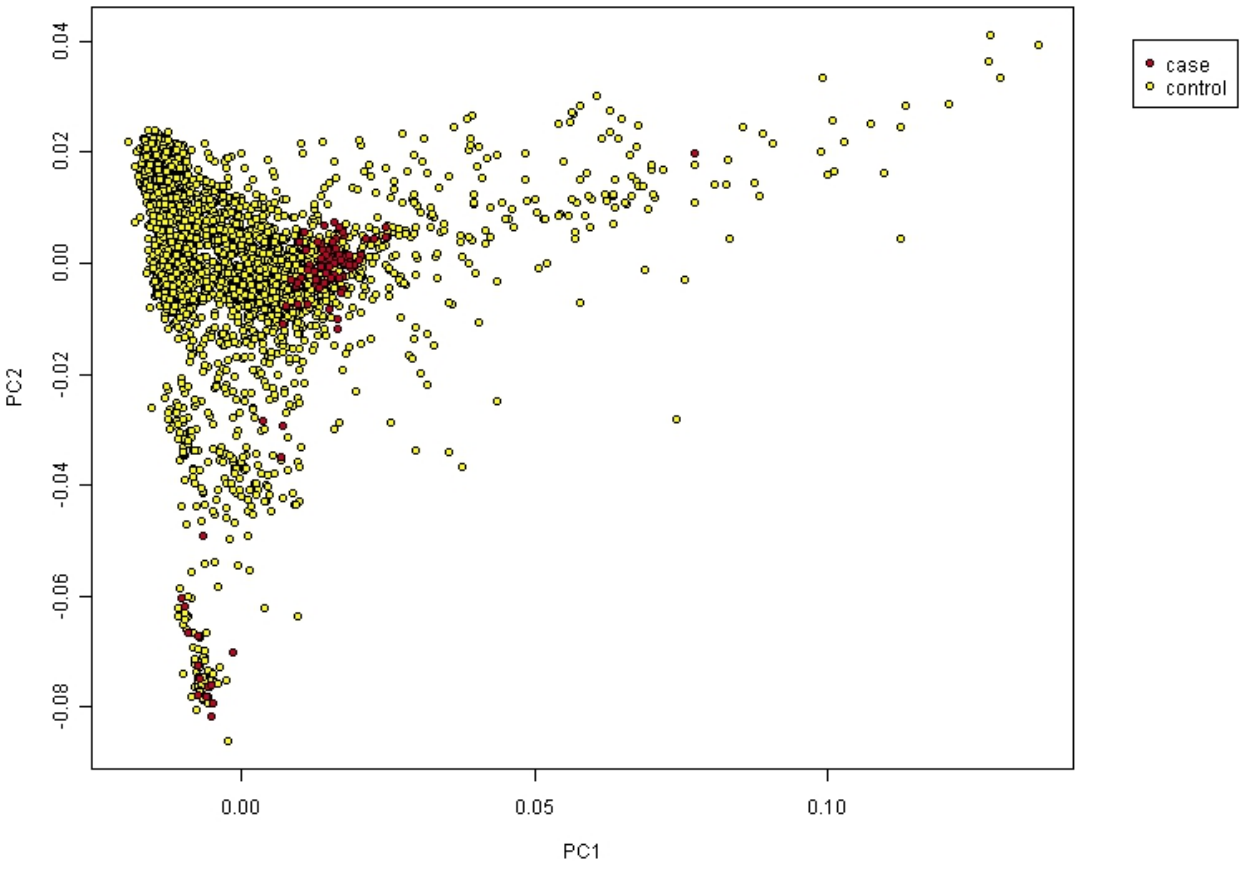
Lambda = 1.01

(c) Principal component analysis between PACG cases and healthy controls for the Indian PACG collection. The vast majority of cases have genetically matched controls. Additional statistical correction for the top principal components using logistic regression was conducted to minimize residual population stratification.



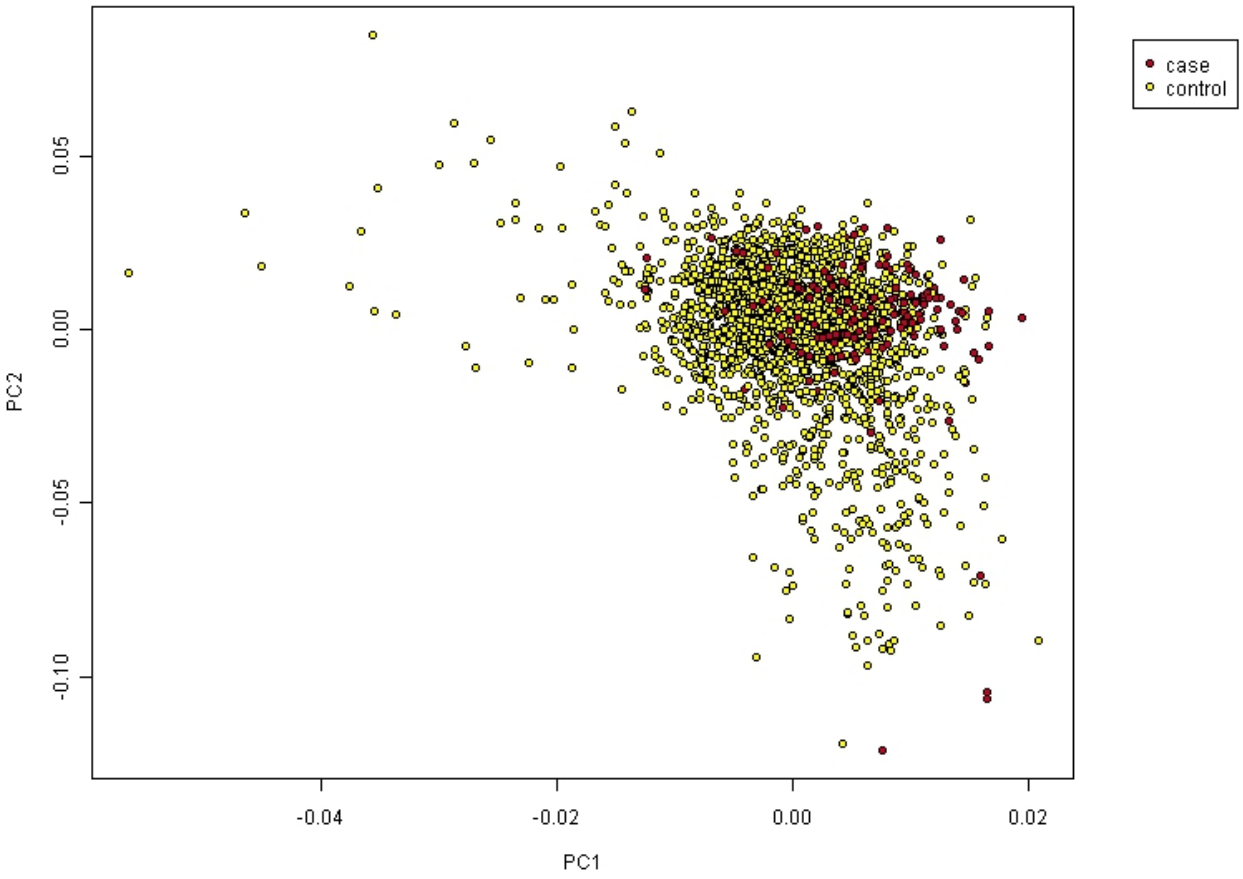
Lambda = 1.13

(d) Principal component analysis between PACG cases and healthy controls for the Malay PACG collection. The vast majority of cases have genetically matched controls. Additional statistical correction for the top principal components using logistic regression was conducted to minimize residual population stratification.



Lambda = 0.90

(e) Principal component analysis between PACG cases and healthy controls for the Vietnamese PACG collection. The vast majority of cases have genetically matched controls. Additional statistical correction for the top principal components using logistic regression was conducted to minimize residual population stratification.

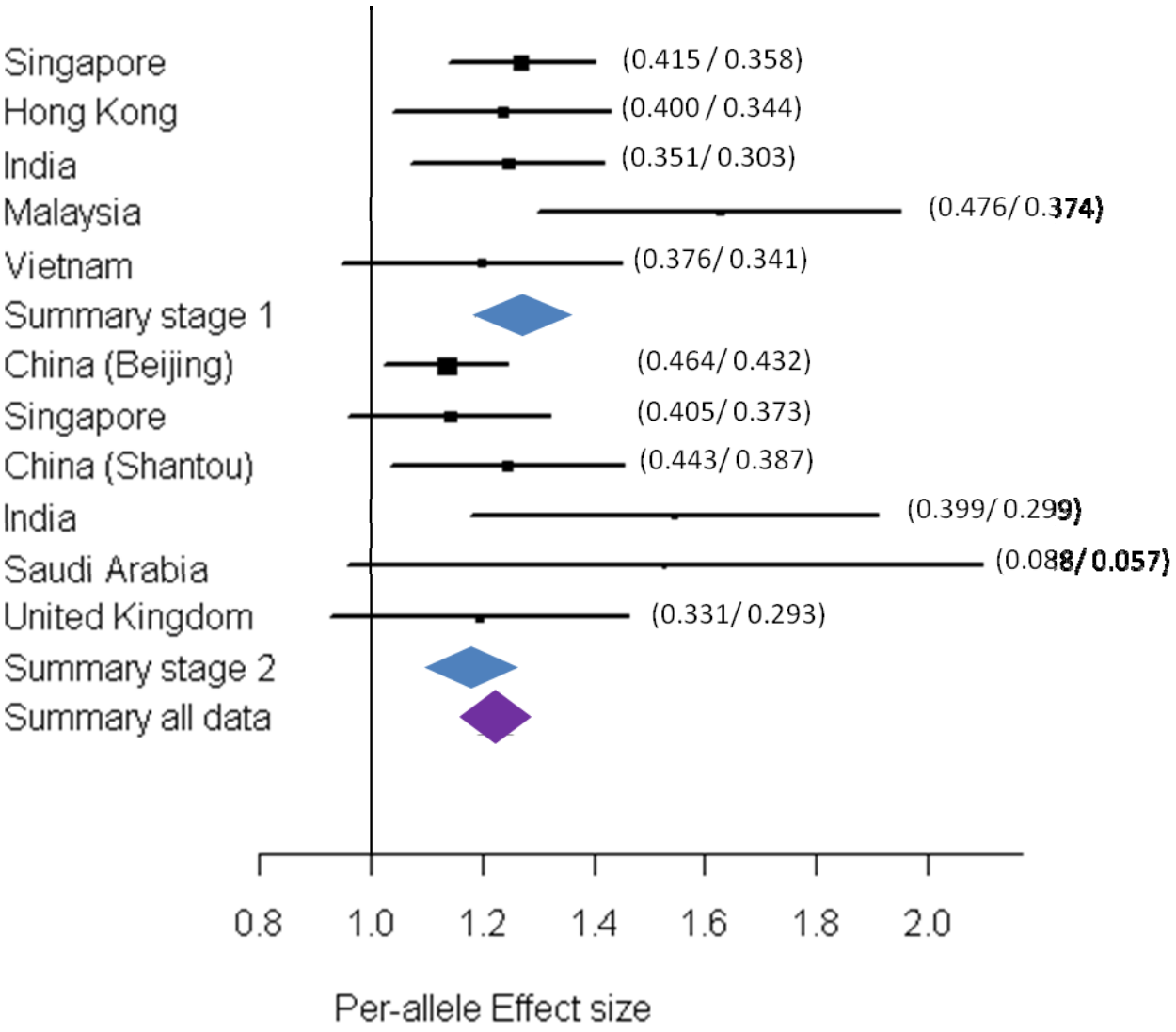


Lambda = 0.95

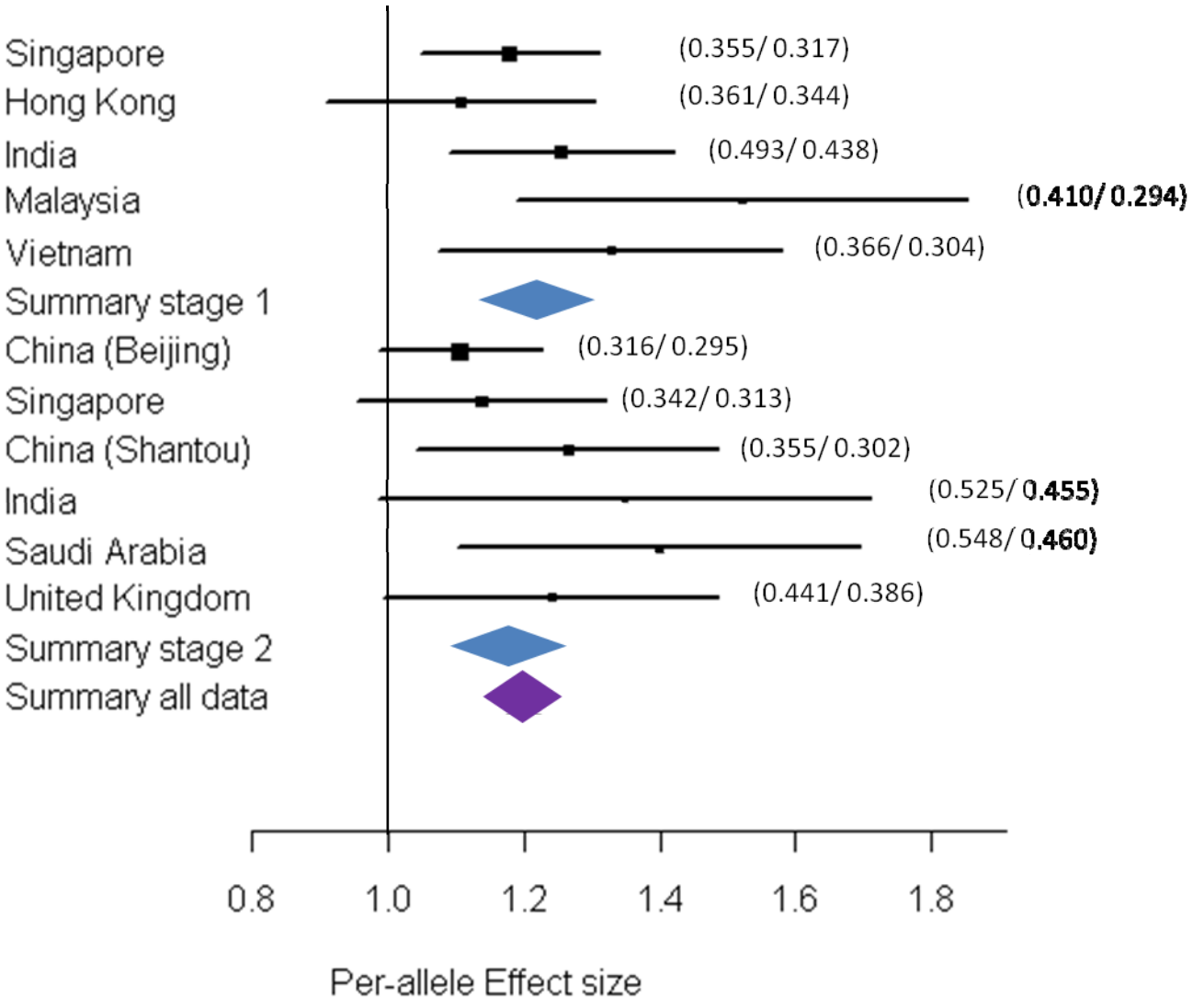
Supplementary Figure 2

Forest plots showing evidence of association between genome-wide significant SNPs; (a) *PLEKHA7* rs11024102, (b) *COL11A1* rs3753841, and (c) *PCMTD1* - *ST18* rs1015213. The vertical line represents a per-allele odds ratio of 1.00. The oblongs represent point estimates (referring to the per-allele odds ratio), with the height of the oblongs inversely proportional to the standard error of the point estimates. Horizontal lines indicate the 95% confidence interval for each point estimate. Meta-analysis of stages 1 and 2 are reflected by blue diamonds, and meta-analysis from all sample collections reflected by purple diamonds. The width of the diamonds indicates their 95% confidence intervals. The number in brackets before each sample collection denotes (minor allele frequency in PACG cases / minor allele frequency in controls).

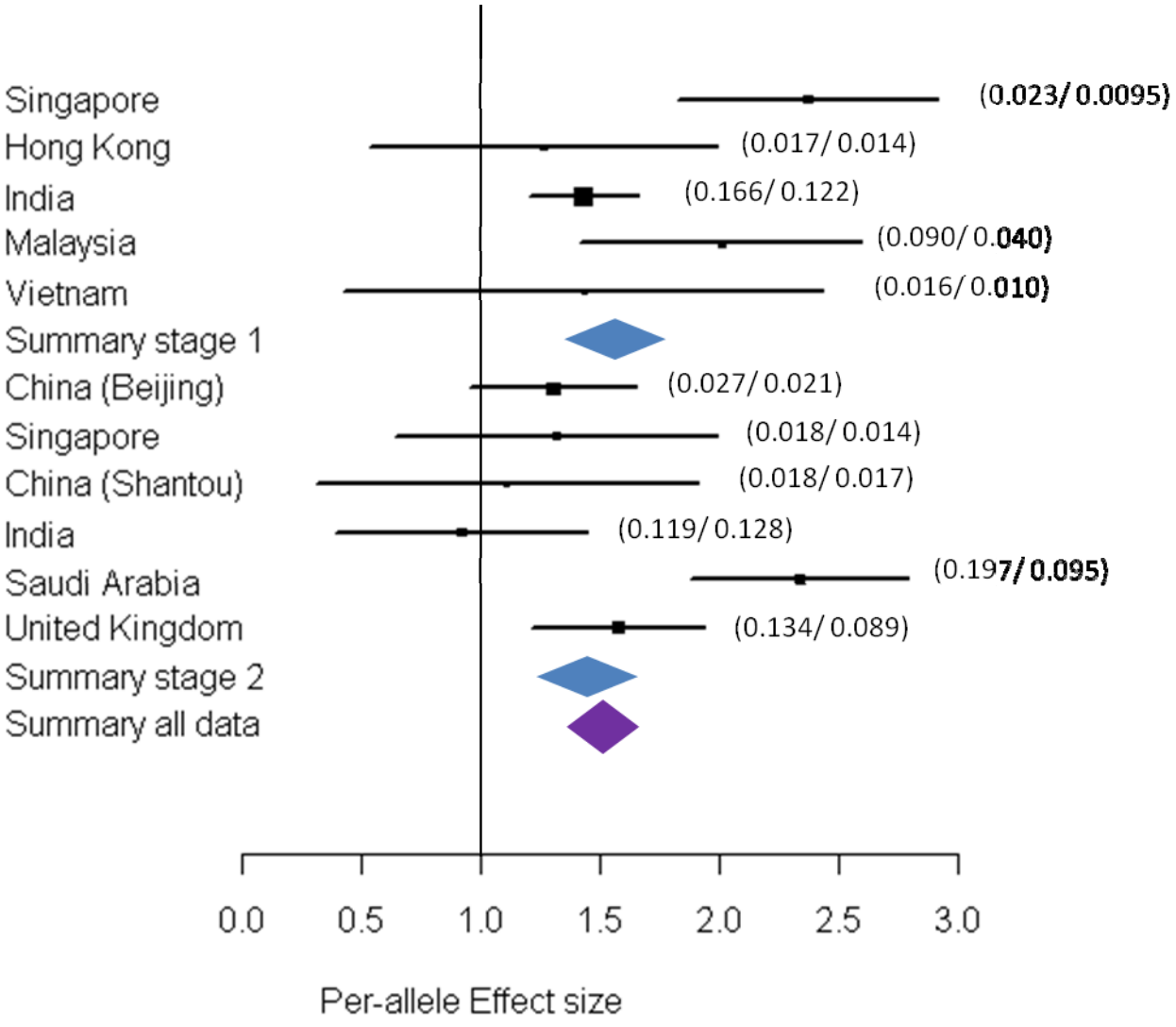
(a)


Singapore
Hong Kong
India
Malaysia
Vietnam
Summary stage 1
China (Beijing)
Singapore
China (Shantou)
India
Saudi Arabia
United Kingdom
Summary stage 2
Summary all data
(0.415 / 0.358)
(0.400 / 0.344)
(0.351/ 0.303)
(0.476/ 0.374)
(0.376/ 0.341)
(0.464/ 0.432)
(0.405/ 0.373)
(0.443/ 0.387)
(0.399/ 0.299)
(0.088/ 0.057)
(0.331/ 0.293)
0.8
1.0
1.2
1.4
1.6
1.8
2.0
Per-allele Effect size

(b)

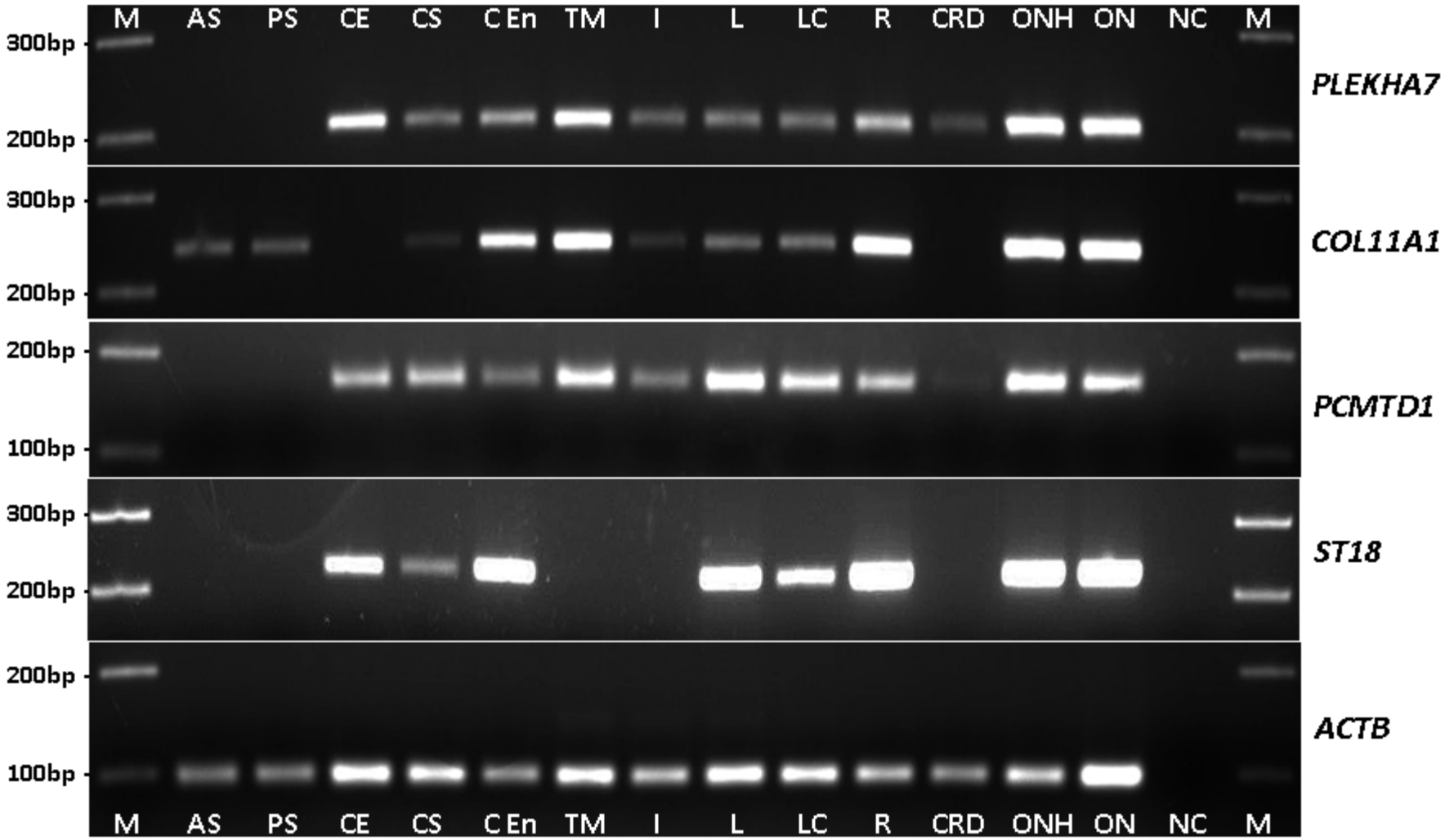

Singapore
Hong Kong
India
Malaysia
Vietnam
Summary stage 1
China (Beijing)
Singapore
China (Shantou)
India
Saudi Arabia
United Kingdom
Summary stage 2
Summary all data
(0.355/ 0.317)
(0.361/ 0.344)
(0.493/ 0.438)
(0.410/ 0.294)
(0.366/ 0.304)
(0.316/ 0.295)
(0.342/ 0.313)
(0.355/ 0.302)
(0.525/ 0.455)
(0.548/ 0.460)
(0.441/ 0.386)
0.8
1.0
1.2
1.4
1.6
1.8
Per-allele Effect size

(c)


Singapore
Hong Kong
India
Malaysia
Vietnam
Summary stage 1
China (Beijing)
Singapore
China (Shantou)
India
Saudi Arabia
United Kingdom
Summary stage 2
Summary all data
(0.023/ 0.0095)
(0.017/ 0.014)
(0.166/ 0.122)
(0.090/ 0.040)
(0.016/ 0.010)
(0.027/ 0.021)
(0.018/ 0.014)
(0.018/ 0.017)
(0.119/ 0.128)
(0.197/ 0.095)
(0.134/ 0.089)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Per-allele Effect size

Supplementary Figure 3

Expression analysis of *PLEKHA7*, *COL11A1*, *PCMTD1* and *ST18* in human ocular tissues. Gene specific RT-PCR products, confirmed to be so through re-sequencing, were observed differentially in anterior sclera (AS), posterior sclera (PS), cornea (corneal epithelium, CE; stroma, CS; and endothelium, CEn), iris (I), trabecular meshwork (TM), lens (L), lens capsule (LC), retina and retinal pigment epithelium (R), choroid (CRD), optic nerve head (ONH) and optic nerve (ON). The ubiquitously expressed gene, *ACTB* was used as the normalizing control. A no template sample acted as the negative control (NC) to ensure non-contamination of the RT-PCR reaction mix. M denotes molecular-weight marker.

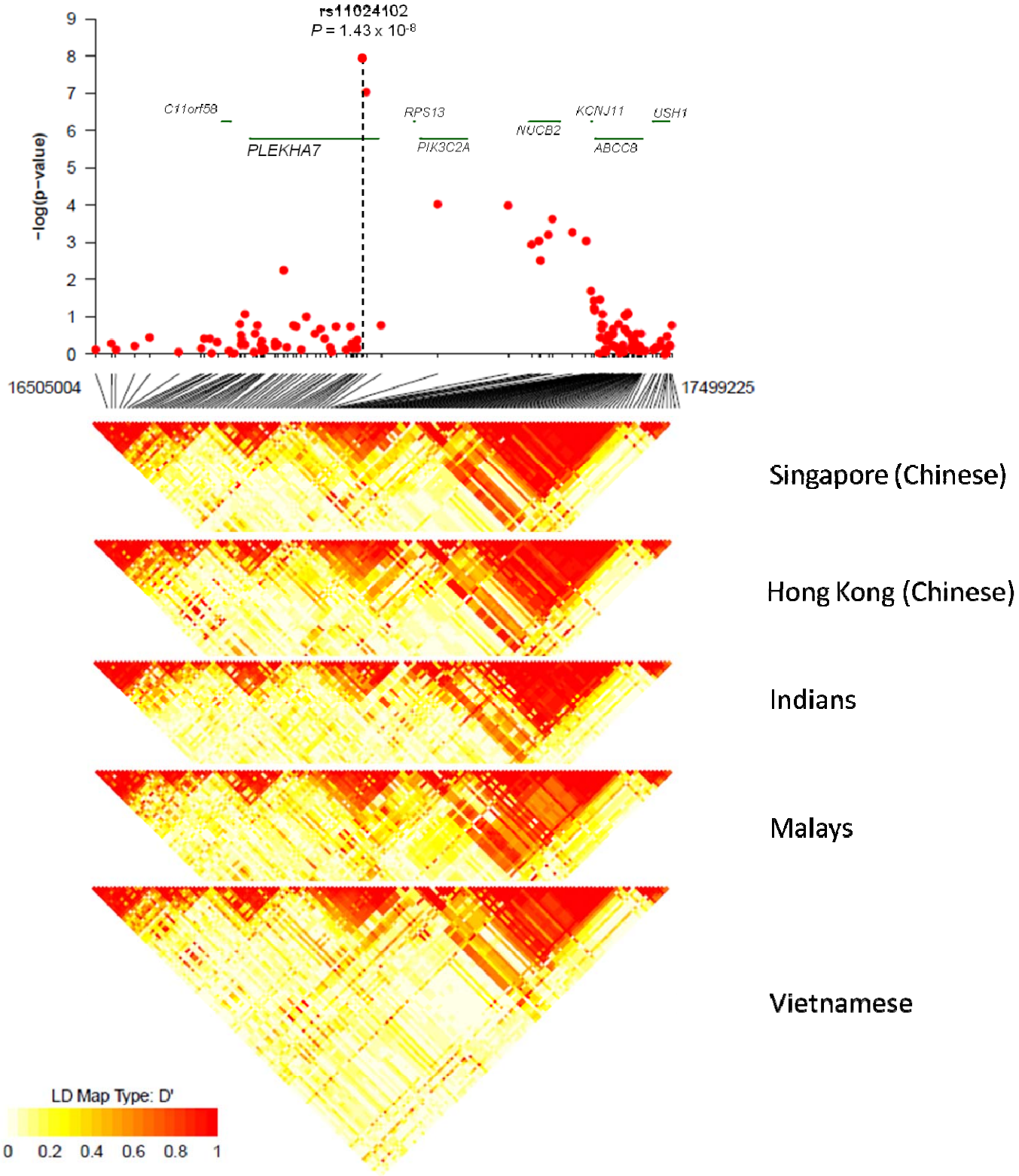


Nature Genetics: doi:10.1038/ng.2390

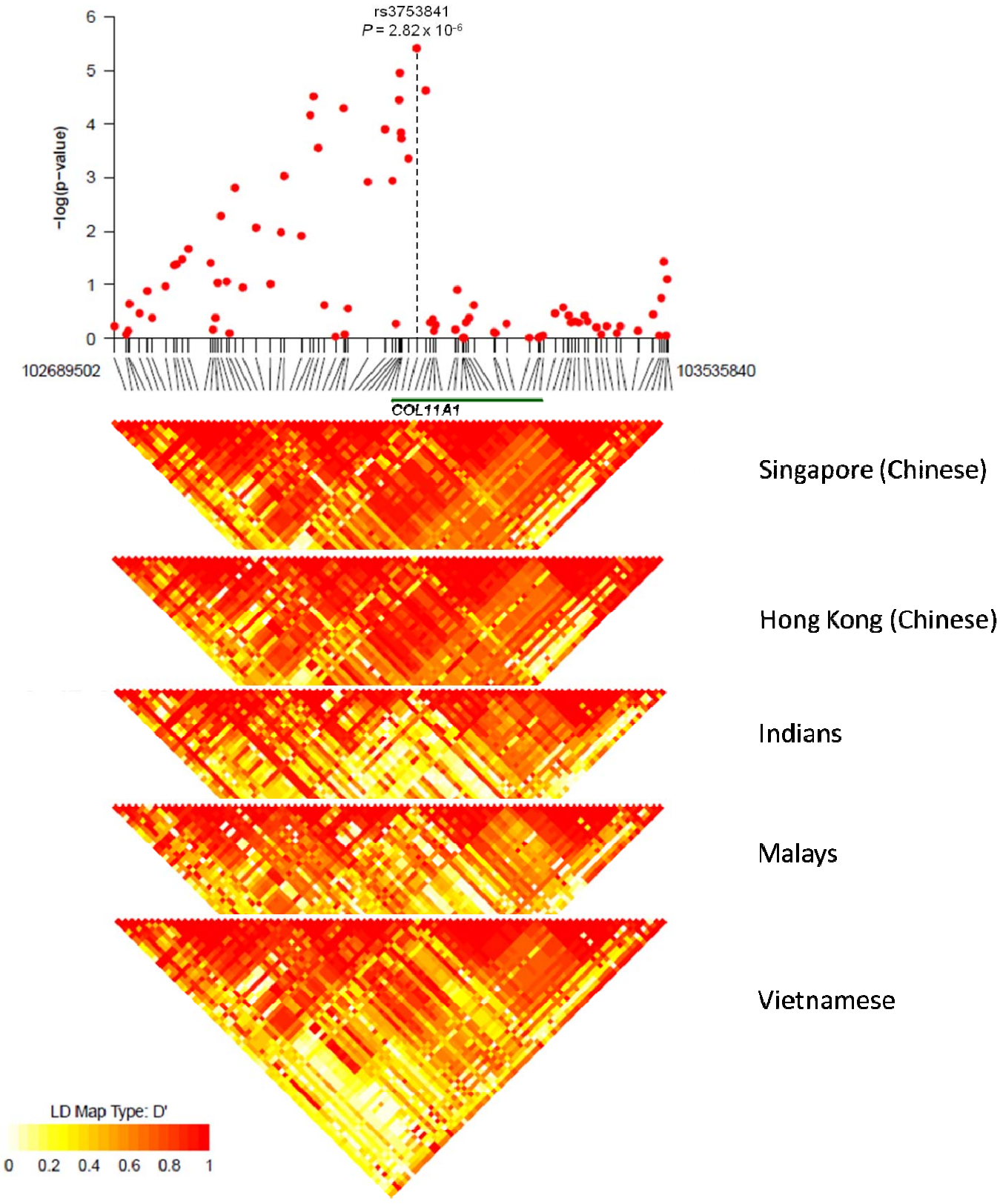
Supplementary Figure 4

Stage 1 data showing regional association (upper panel) and linkage disequilibrium (LD; lower panel) plots of the (a) *PLEKHA7* locus around rs11024102, (b) *COL11A1* locus around rs3753841, and (c) Chromosome 8q locus around rs1015213. Gene annotations are superimposed. The vertical axis represents -Log_{10}*P*-values for association with PACG in Stage 1, and the horizontal axis represents base-pair positions along the chromosome. Pair-wise LD is shown for each Stage 1 sample collection.

(a)

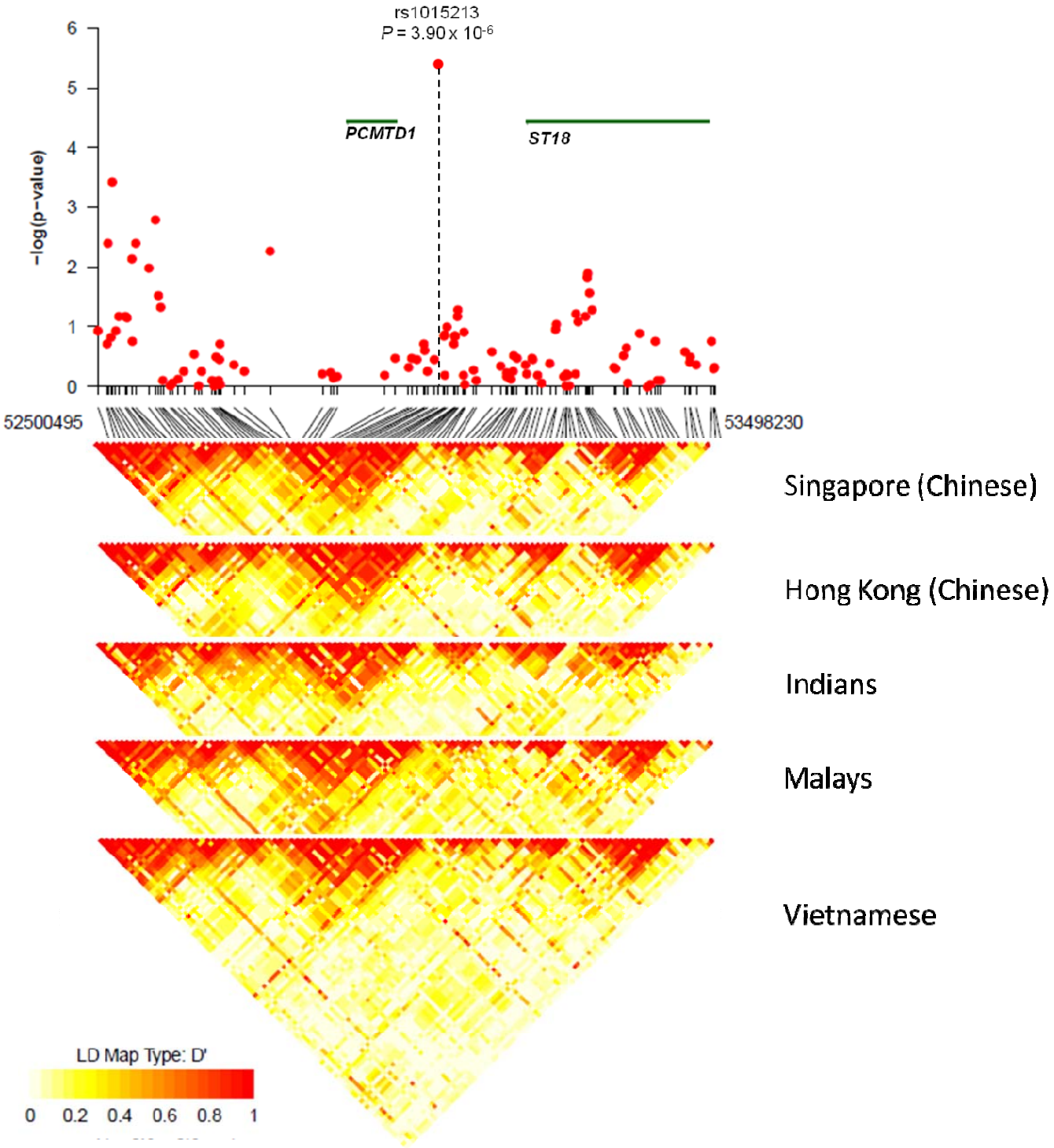

rs11024102
P = 1.43 x 10-8
-log(p-value)
C11orf58
PLEKHA7
RPS13
PIK3C2A
NUCB2
KCNJ11
ABCC8
USH1
16505004
17499225
Singapore (Chinese)
Hong Kong (Chinese)
Indians
Malays
Vietnamese
LD Map Type: D'
0 0.2 0.4 0.6 0.8 1

(b)



Nature Genetics: doi:10.1038/ng.2390

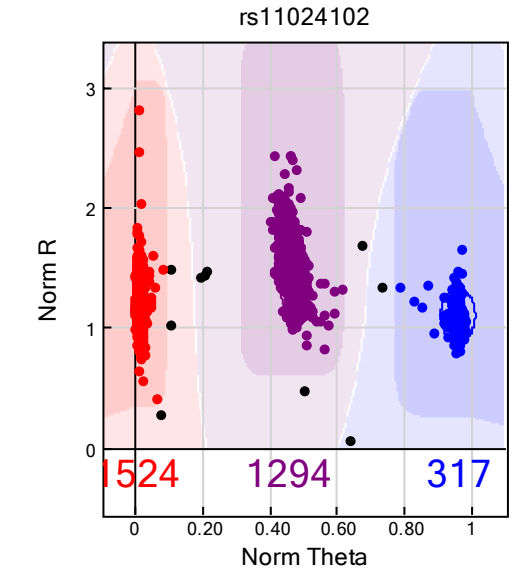
(c)

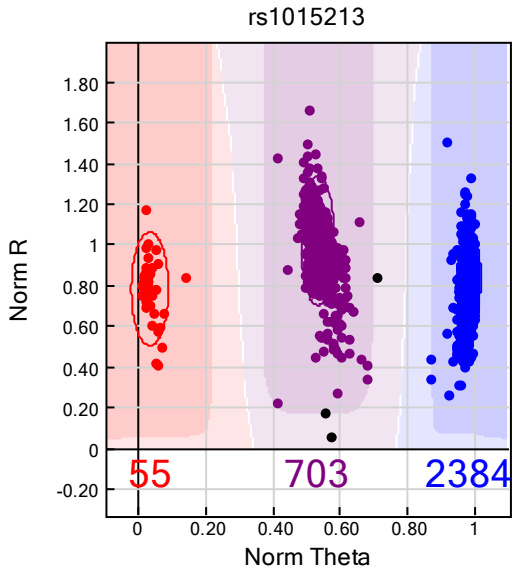


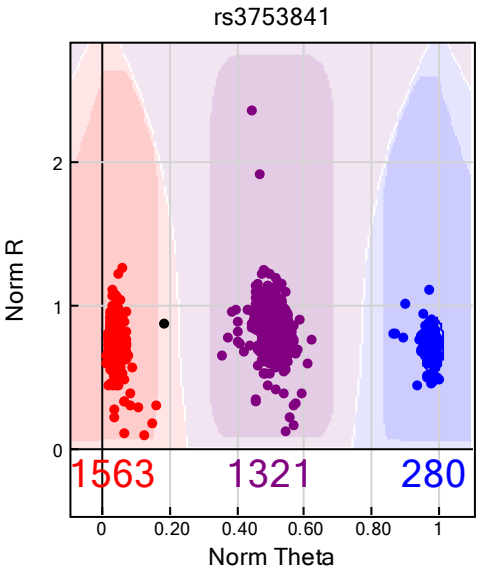
Nature Genetics: doi:10.1038/ng.2390

Supplementary Figure 5a

Illumina genotyping cluster plots for the three genome-wide significant SNPs in Stage 1



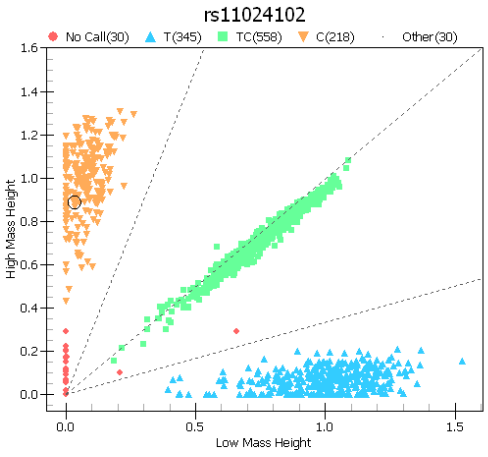


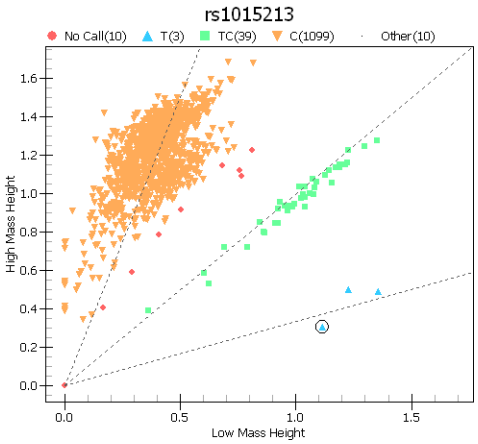


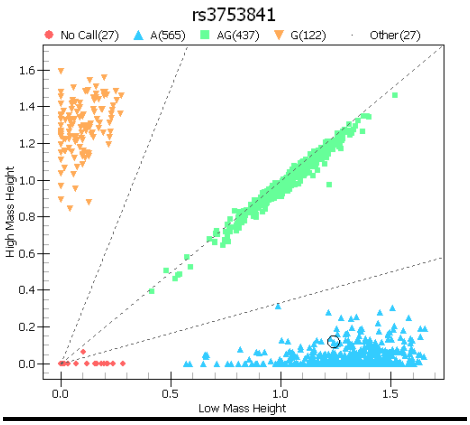
Each of the colors red, purple, and blue denote the different genotypes at the 3 SNPs. Red and blue represent homozygous genotypes, and purple represent the heterozygous genotype (carrier state). For all three SNPs rs11024102, rs1015213, and rs3753841, the three genotypes are clearly distinguishable.

Supplementary Figure 5b

Sequenom genotyping cluster plots for the three genome-wide significant SNPs in Stage 2







Each of the brown, green, and blue denote the different genotypes at the 3 SNPs. Brown and blue represent homozygous genotypes, and green represent the heterozygous genotype (carrier state). For all three SNPs rs11024102, rs1015213, and rs3753841, the three genotypes are clearly distinguishable.

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