

Supplementary Information

Exploring the Novel Susceptibility Gene Variants for Primary Open-Angle Glaucoma in East Asian Cohorts: The GLAU-GENDISK Study

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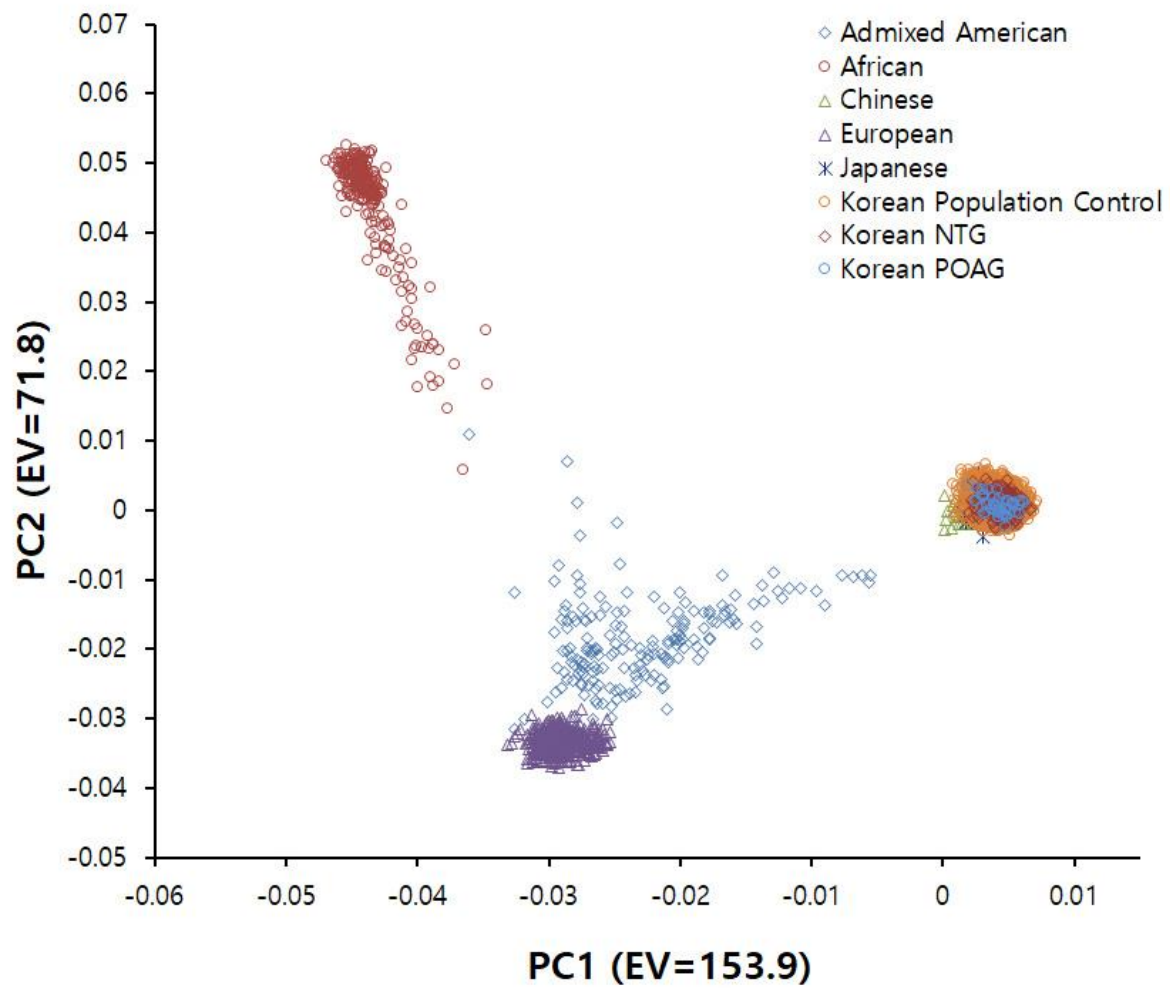
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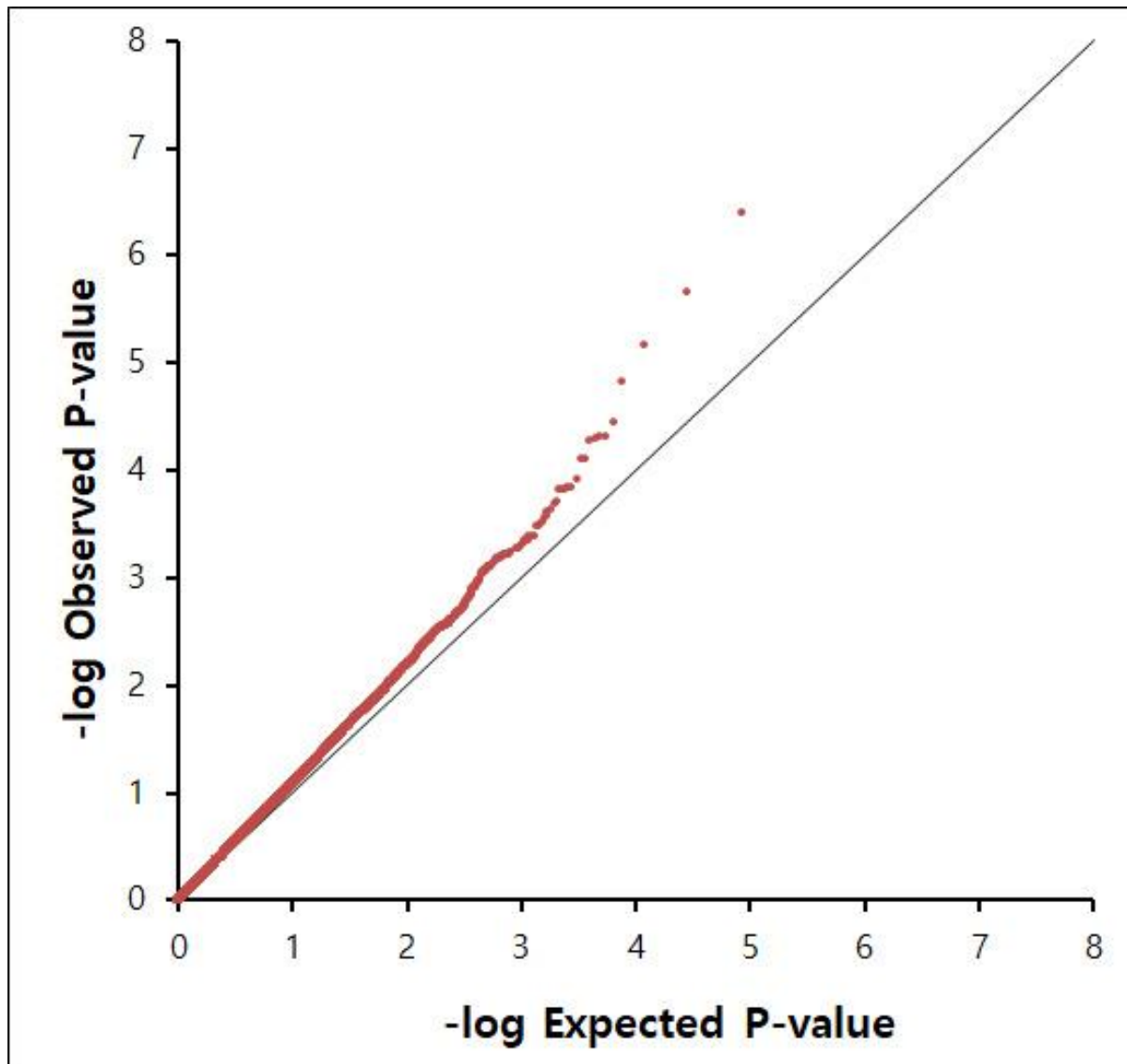
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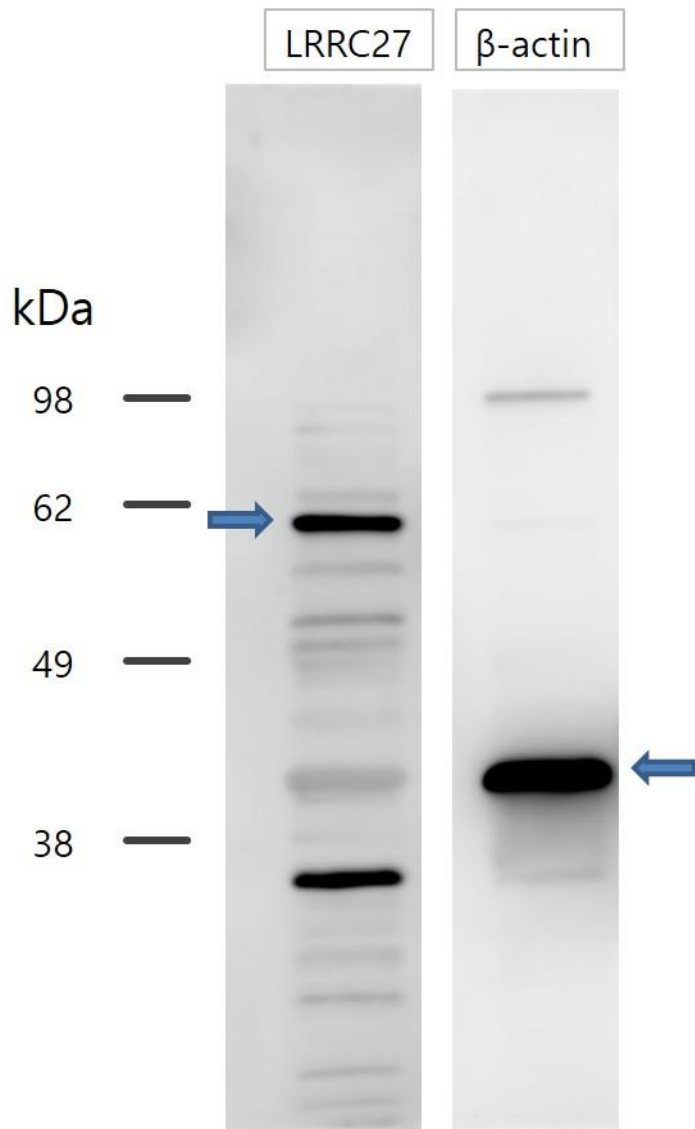
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Supplementary Figure S1. Principal component analysis of study participants. First and second principal components of our study samples and 1000 genomes project samples.



Supplementary Figure S2. Quantile-quantile plots of P values in the association results of the exome chip analysis on the Korean population. Under the null hypothesis, the plots would be expected to follow the red line ($y = x$). The genomic inflation factor (λ) was 1.08, showing no significant dispersion of test statistics from the expected distribution.



Supplementary Figure S3. Full-length gels and blots for LRRC27 and β -actin.

Supplementary Table S1. Candidate Low-Frequency Variants Associated with Primary Open-Angle Glaucoma at $P < 10^{-4}$

rsID	Gene	Chr	Position	AA change	Alleles	Stage	MAF Case	MAF Control	OR (95% CI)	P-value
rs138980799	IVL	1	152882758	H162R	A>G	Primary (KOR)	0.00971	0.00009	83.24 (9.74–711.44)	4.0E-07
						Replication#1 (KOR)	0.00000	0.00018	NA	NA
						Replication#2 (JPN)	0.00000	0.00000	NA	NA
						Combined (KOR)	0.00485	0.00014	27.40 (6.70–111.97)	1.6E-05*
						Meta-analysis (KOR+JPN)			NA	NA
rs191590289	METTL20	12	31820716	D194V	A>T	Primary (KOR)	0.03560	0.01048	3.42 (2.13–5.48)	6.9E-06
						Replication#1 (KOR)	0.00485	0.01186	0.41 (0.13–1.31)	0.08
						Replication#2 (JPN)	0.00000	0.00000	NA	NA
						Combined (KOR)	0.02023	0.01119	1.83(1.21–2.78)	0.012*
						Meta-analysis (KOR+JPN)			NA	NA
rs140732889	ZNF677	19	53741442	G180R	C>T	Primary (KOR)	0.00809	0.00037	20.72 (5.42–79.27)	5.1E-05
						Replication#1 (KOR)	0.00000	0.00053	NA	NA
						Replication#2 (JPN)	0.00000	0.00000	NA	NA
						Combined (KOR)	0.00406	0.00045	9.60 (3.22–28.60)	0.001*
						Meta-analysis (KOR+JPN)			NA	NA
rs4889261	PKD1L2	16	81213378	L711P	G>A	Primary (KOR)	0.01618	0.04630	0.33 (0.18–0.63)	5.4E-05
						Replication#1 (KOR)	0.05519	0.04840	1.13 (0.79–1.61)	0.51
						Replication#2 (JPN)	0.03680	0.02959	1.24 (0.83–1.85)	0.29
						Combined (KOR)	0.03566	0.04736	0.73(0.54–1.00)	0.048*
						Meta-analysis (KOR+JPN)			0.89	0.45*
rs13339342	PKD1L2	16	81219187	R636H	C>T	Primary (KOR)	0.01618	0.04574	0.34 (0.18–0.64)	7.8E-05
						Replication#1 (KOR)	0.05663	0.04758	1.18 (0.83–1.68)	0.36
						Replication#2 (JPN)	0.03680	0.02959	1.24 (0.83–1.85)	0.29
						Combined (KOR)	0.03641	0.04667	0.76(0.56–1.03)	0.07*
						Meta-analysis (KOR+JPN)			0.91	0.45*

Chr: chromosome, AA: amino acid, MAF: minor allele frequency, OR: odds ratio, KOR: Korea, JPN: Japan, NA: not applicable.

*P-values adjusted by Benjamini-Hochberg method to compensate for multiple comparison.

Supplementary Table S2. Comparison of Associations between Normal-Tension Glaucoma (NTG) and High-Tension Glaucoma (HTG) for Candidate SNPs.

rsID	Gene (near gene)	Stage	MAF Control	NTG			HTG		
				MAF Case	OR (95% CI)	P-value	MAF Case	OR (95% CI)	P-value
rs138980799	IVL	Primary	0.00009	0.01181	101.74 (11.78–878.74)	1.5E-07	0.00000	NA	NA
		Rep#1	0.00018	0.00000	NA	NA	0.00000	NA	NA
		Rep#2	0.00000	0.00000	NA	NA	0.00000	NA	NA
		Combined (KOR)	0.00014	0.00598	33.78 (8.24–138.51)	1.0E-05*	0.00000	NA	NA
rs191590289	METTL20	Primary	0.01048	0.03346	3.16 (1.87–5.37)	0.0002	0.04545	4.85 (1.89–12.45)	0.007
		Rep#1	0.01186	0.00605	0.51 (0.16–1.63)	0.21	0.00000	NA	NA
		Rep#2	0.00000	0.00000	NA	NA	0.00000	NA	NA
		Combined (KOR)	0.01119	0.01992	1.81 (1.13–2.88)	0.04*	0.02155	2.02 (0.81–4.99)	0.17*
rs140732889	ZNF677	Primary	0.00037	0.00197	4.50 (0.48–41.98)	0.26	0.03636	89.07 (21.43–370.22)	7.2E-07
		Rep#1	0.00053	0.00000	NA	NA	0.00000	NA	NA
		Rep#2	0.00000	0.00000	NA	NA	0.00000	NA	NA
		Combined (KOR)	0.00045	0.00100	2.41 (0.30–19.15)	0.46	0.01724	39.93 (12.10–131.73)	3.8E-05*
rs4889261	PKD1L2	Primary	0.04630	0.01969	0.41 (0.22–0.77)	0.002*	0.00000	NA	NA
		Rep#1	0.04840	0.06073	1.25 (0.85–1.83)	0.27	0.03279	0.66 (0.24–1.79)	0.38
		Rep#2	0.02960	0.03514	1.16 (0.72–1.87)	0.54	0.04011	1.37 (0.76–2.49)	0.30
		Combined (KOR)	0.04736	0.03992	0.82 (0.60–1.14)	0.35*	0.01724	0.35 (0.13–0.95)	0.013*
rs13339342	PKD1L2	Primary	0.04574	0.01969	0.42 (0.22–0.79)	0.002	0.00000	NA	NA
		Rep#1	0.04758	0.06250	1.31 (0.90–1.91)	0.17	0.03279	0.67 (0.25–1.82)	0.40
		Rep#2	0.02960	0.03514	1.16 (0.72–1.87)	0.54	0.04011	1.37 (0.76–2.48)	0.3008
		Combined (KOR)	0.04667	0.04083	0.86 (0.62–1.18)	0.41*	0.01724	0.36 (0.13–0.96)	0.013*

MAF: minor allele frequency, NTG: normal-tension glaucoma, HTG: high-tension glaucoma, OR: odds ratio, Rep: replication.

*P-values adjusted by Benjamini-Hochberg method to compensate for multiple comparison.

Supplementary Table S3. Gene-based rare variant association analysis using SKAT-O method.

Diagnosis	Gene Name	SNPs	Stage	Glaucoma	Control	P-value
POAG	METTL20	N172S, D188N, D194V	Primary	8.41%	2.93%	0.006*
			Replication#1	2.26%	3.33%	0.38
			Combined	5.49%	3.13%	0.002
NTG	METTL20	N172S, D188N, D194V	Primary	7.48%	2.93%	0.69*
			Replication#1	2.41%	3.33%	0.70
			Combined	5.17%	3.13%	0.02
HTG	ZNF677	G180R, Y347T	Primary	7.3%	0.1%	3.6E-05*
			Replication#1	0.00%	0.12%	0.67
			Combined	0.81%	0.12%	1.5E-06

POAG: primary open-angle glaucoma, NTG: normal-tension glaucoma, HTG: high-tension glaucoma, SNP: single nucleotide polymorphism. *P-value adjusted by Bonferroni correction.

Supplementary Table 4. Gender Difference of Minor Allele Frequency for rs116121322 in *LRRC27* in Korean Population

rsID	Gene	Chr	AA change	Alleles	Diagnosis	Gender	Stage	MAF Case	MAF Control	OR (95% CI)	P-value
rs116121322	<i>LRRC27</i>	10	V189I	G>A	POAG	Male	Primary	0.00649	0.00000	-	-
							Replication#1	0.00588	0.00095	5.69 (1.07–30.32)	0.08
							Combined (KOR)	0.00620	0.00049	13.43 (3.50–51.48)	9.0E–04
						Female	Primary	0.01290	0.00069	15.16 (3.54–64.88_	9.1E–04
							Replication #1	0.00719	0.00017	39.77 (3.46–456.60)	0.004
							Combined (KOR)	0.01020	0.00043	20.59 (6.05–70.10)	1.0E–05

Chr: chromosome, AA: amino acid, MAF: minor allele frequency, OR: odds ratio, POAG: primary open-angle glaucoma, KOR: Korea