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Association of body mass index and *PXDNL* gene variants with acute primary angle closure in southern Chinese population

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ABSTRACT

This study aimed to evaluate the association of body mass index (BMI) and the weight-related gene, peroxidasin-like (*PXDNL*), with acute primary angle closure (APAC) and primary angle-closure glaucoma (PACG) in southern Chinese population. Total 4700 study subjects (1024 APAC, 781 PACG, and 2895 control subjects) with complete ophthalmic examinations were enrolled into this study. The association of BMI with APAC, PACG and ocular biometric parameters was evaluated. Three *PXDNL* missense variants were genotyped by TaqMan assay, and their association with APAC and PACG was also investigated. Multivariable logistic regression analysis showed that BMI and body weight were significantly associated with both APAC and PACG ($P < 0.01$). Multiple linear regression analysis demonstrated that each 1 kg/m^2 increased in BMI was associated with 0.038 mm increase in axial length, 0.018 mm increase in central anterior chamber depth, 0.002 mm increase in lens position, 0.012 mm increase in corneal diameter and 0.014 mm decrease in lens thickness among the APAC subjects ($P < 0.001$), but not with PACG. Genetic association analysis identified that *PXDNL* rs11985241–rs16916207 CT haplotype conferred a higher risk to APAC (OR = 1.25, $P = 0.004$) than the TG haplotype, but not with PACG. The APAC subjects carrying the rs11985241 C or rs16916207 T alleles showed significantly lower weight than those carrying the corresponding protective alleles. In summary, this study revealed that lower BMI could be associated with higher risk of APAC. *PXDNL* could be a new associated gene for APAC.

1. Introduction

Glaucoma is a leading cause of irreversible visual impairment and blindness, affecting 79.6 million people worldwide [1]. It will rise to over 110 million by 2040 [2]. In Asia, primary angle-closure glaucoma (PACG) is the major subtype of glaucoma, accounting for 76.7 % PACG cases in the world [2]. PACG is characterized by the intraocular pressure (IOP) elevation resulted from the blockage of aqueous humor outflow by the close contact of iris to the trabecular meshwork [3]. According to the disease onset and duration, angle

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closure could be sub-divided into acute primary angle closure (APAC) and chronic PACG. Significant ocular biometric parameter differences between APAC and chronic PACG indicates potentially different mechanisms for the angle closure [4]. The APAC and PACG subjects have typical anatomical features of shorter axial length (AL), shallower anterior chamber depth (ACD), and thicker lens

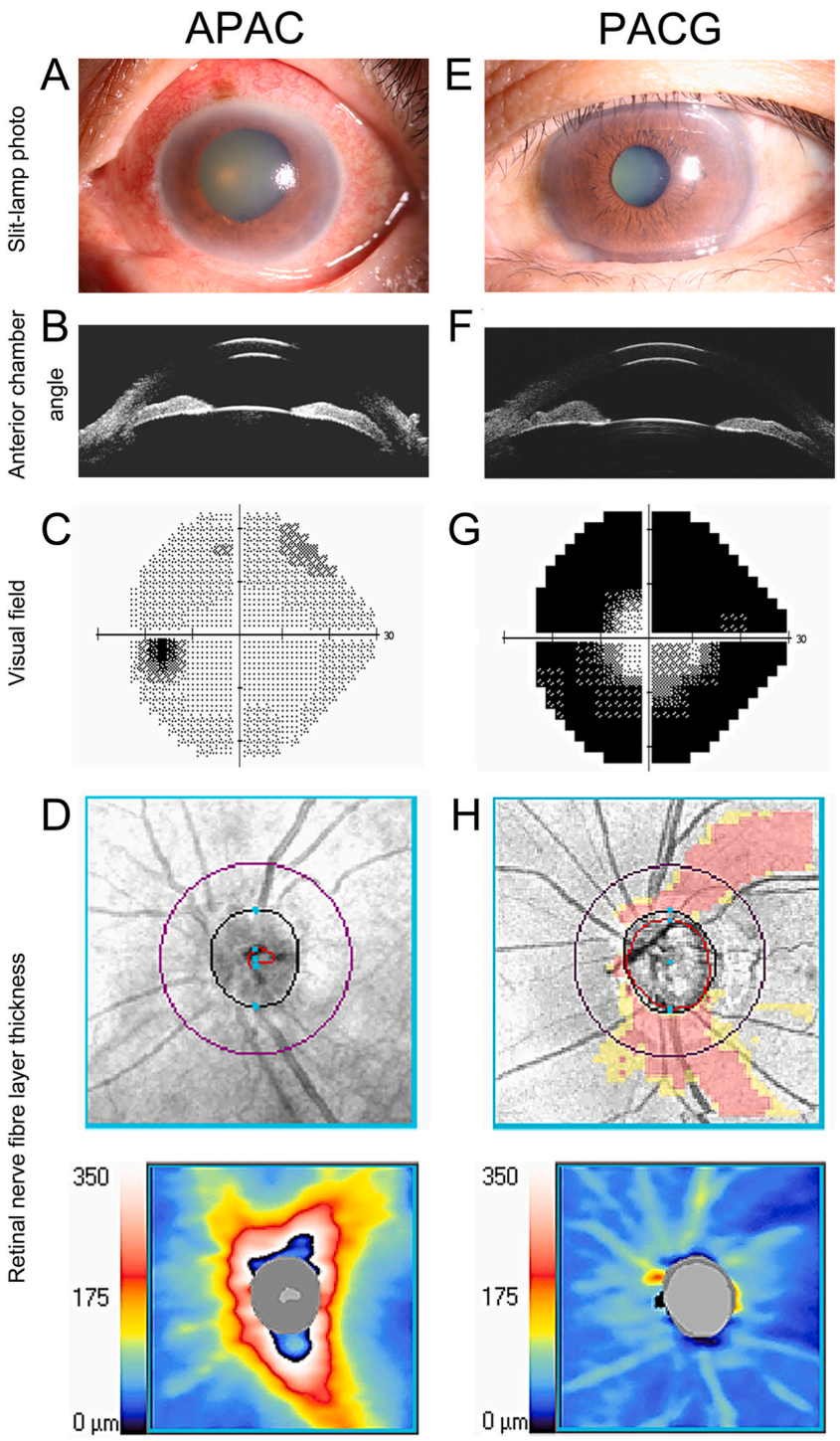


Fig. 1. Ophthalmic examinations on the acute primary angle closure and primary angle-closure glaucoma patients.
(**A**–**D**) The acute primary angle closure (APAC) patients showed (**A**) corneal epithelial edema, (**B**) closed angle, but (**C**) normal visual field and (**D**) retinal nerve fibre layer (RNFL) thickness. (**E**–**H**) The primary angle-closure glaucoma (PACG) patients showed (**E**) clear cornea, but (**F**) closed angle with (**G**) visual field defect and (**H**) reduction in RNFL thickness.

thickness (LT) [5]. Although the PAC suspects show similar crowded anterior segment structures, the incidence of PAC among the PAC suspects is very low (less than 1 % per year) [6]. The benefit of performing prophylactic laser iridotomy in all PAC suspects is limited. To identify the individuals with similar ocular anatomical features for early stage interventions, general risk factors should better be considered.

Previous studies have shown that the elderly, female, hyperopia, and Asian ethnicity are the risk factors for PACG [5]. Body mass index (BMI) has also been reported to be associated with glaucoma [7,8], age-related cataract [9], ACD, narrow angle [10], and neuroretinal rim area [11]. Previous studies suggested that persons with lower body mass index have smaller neuroretinal rim area and larger optic cup-to-disc area ratio [11,12]. However, only limited studies explored the correlation between BMI and PACG, and inconsistent results were reported [8,13]. Herein we aimed to evaluate the association of BMI with APAC, PACG, and ocular biometric parameters in a southern Chinese cohort. In addition, the association of the weight-related gene, peroxidasin-like (*PXDNL*) [14], with APAC, PACG, and blood biochemical and ocular biometric parameters was also determined.

2. Materials and methods

2.1. Study subjects

This study has been approved by the Ethics Committee for Human Medical Research at the Joint Shantou International Eye Center of Shantou University and the Chinese University of Hong Kong (approval number: EC20200120(1)-P02), which is in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study subjects after explaining the nature and possible consequences of the study.

In total, 1024 APAC, 781 chronic PACG, and 2895 control subjects were recruited at the Joint Shantou International Eye Center of Shantou University and the Chinese University of Hong Kong. APAC was diagnosed based on the following criteria [15]: (1) at least two of the following symptoms: ophthalmalgia, headache, nausea, and/or vomiting; (2) acute IOP increase ($\geq$30 mmHg); (3) at least three of the following signs: ciliary or mixed injection, corneal edema, fixed mild-dilated pupil, closed/narrow angle, shallow anterior chamber, and glaucomatous flecks (Fig. 1A – **D**). PACG was diagnosed according to the following criteria [16]: (1) narrow synechiae angle with IOP $\geq$22 mmHg; (2) lack of acute ocular hypertension-induced symptoms and signs in the anterior segment; (3) glaucomatous optic disc and retinal nerve fiber layer (RNFL) damage with corresponding visual field loss (Fig. 1E – **H**). The control group was recruited from subjects: (1) aged above 60 years; (2) no history of glaucoma or ocular surgery that would influence anterior segment construction; (3) open angle in gonioscopy with IOP $\leq$21 mmHg without medications; (4) absent of glaucomatous optic nerve damage or visual field damage; (5) no history of any systemic diseases or complications affecting BMI, including malignant tumors, severe heart failure, cerebral infarction, severe gastrointestinal diseases, hyperthyroidism, hypothyroidism, and depression.

Demographic data, including age, sex, previous medical histories, and blood biochemical test results (fasting blood glucose, cholesterols, triglyceride and hemoglobin levels) of all study subjects at the time of recruitment were retrieved from the electronic medical records.

2.2. Ophthalmic examinations and body mass index measurement

Height and weight were measured at the time of recruitment with the standard scales (HGM-600, Henan, China) when the patients stand up without shoes and coats. BMI was calculated as the weight in kilograms divided by the square of the height in meter (kg/m^2). BMI was sub-classified into underweight ($<$18.5 kg/m^2), normal body weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity ($\geq$30 kg/m^2) according to the BMI classification system from the World Health Organization [17].

All study subjects underwent complete ophthalmic examinations, including best-corrected visual acuity measurement (at a distance of 5 m after refractive correction; the Standard Logarithm Visual Acuity chart, Wehen Vision, Guangzhou, Guangdong, China), IOP measurement (Goldmann applanation tonometry; AT900 BQ, Haag Streit, Koeniz, Switzerland), slit-lamp examination (Model BQ 900; Haag Streit), gonioscopy (Ocular O2M; Ocular Instruments, Bellevue, WA), visual field test (Carl Zeiss Humphrey 750i; Jena, Germany), ultrasound bio-microscope measurement (UBM MD-300 L; Meda Co. Ltd., Tianjin, Chinese), optical coherence tomography (OCT) measurement (Topcon 3D OCT-2000; Tokyo, Japan), and Optical Biometry measurement (TOMEY, OA-2000; Nagoya, Aichi, Japan). If IOP was higher than 30 mmHg, the examinations were conducted after IOP lowering by anti-glaucoma drugs, including beta-blockers, alpha-2 antagonists, topical/systemic carbonic anhydrase inhibitors, miotics, and mannitol. Hyperopia was defined as a spherical equivalence higher than +0.50 diopters. The ocular biometric parameters included flat keratometry, steep keratometry, AL, central ACD, LT, central corneal thickness (CCT), and corneal diameter.

2.3. Genotyping analysis

Peripheral venous blood was collected from 627 APAC, 554 chronic PACG and 1415 control subjects. Genomic DNA was extracted from the whole blood by the QIAamp DNA kit (Qiagen, Hiden, Germany) according to our previously established protocol [18]. Three *PXDNL* missense variants (rs79394014 (p.R367Q), rs16916207 (p.D592A), and rs11985241 (p.S809I)), selected based on our preliminary Sanger sequencing analysis with minor allele frequency (East Asian) $>$ 5 %, were genotyped by the TaqMan assay (Applied Biosystems, Foster City, CA) in a real-time PCR machine (LightCycler 480; Roche Diagnostics, Basel, Switzerland).

2.4. Statistical analysis

Only one eye of each bilaterally affected subject was randomly selected for the data analysis. The normality of data was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) and compared by the independent T-test, whereas the categorical data was compared by the χ^2 test. Multivariable logistic analysis was applied to assess the associated factors with APAC and PACG. The correlation between BMI and ocular biometric parameters were determined using Pearson's correlation and linear regression analyses. Statistical significance was defined as $P < 0.05$.

For the genetic association analysis, Hardy-Weinberg equilibrium (HWE) in the control subjects and the haplotype association analysis were evaluated by χ^2 test using the Haploview (https://www.broadinstitute.org/haploview). Genetic association of *PXDNL* variants with APAC and PACG were evaluated by χ^2 test in six genetic models (genotypic, allelic, dominant, recessive, heterozygous, and homozygous). Odds ratio (OR) and the corresponding 95 % confidence interval (C.I.) were estimated with the reference allele/genotype. Statistical significance was defined as $P < 0.05/3$ variants $= 0.0167$ after Bonferroni's correction. All statistical analyses, except HWE, were conducted using a commercially available software (IBM SPSS STATISTICS 26, SPSS Inc., Chicago, IL).

3. Results

3.1. Association of body mass index and blood biochemical parameters with acute primary angle closure and chronic primary angle closure glaucoma

In total, 447 APAC, 295 PACG, and 1585 control subjects were included in the clinical analysis. There was no significant difference in the age of the PACG subjects (66.0 ± 7.6 years) as compared to the control subjects (67.1 ± 8.9 years, $P = 0.076$), but the age of the APAC subjects was significant lower (66.0 ± 8.1 years) than that of the control subjects ($P < 0.05$; Table 1). More female was found in the APAC group (72.3 %, $P < 0.01$) than the control group (58.5 %), but less female in the PACG group (54.2 %, $P < 0.01$). Both APAC and PACG subjects showed significantly shorter AL, shallower central ACD, thicker LT, lens position and relative lens position closer to the anterior, and smaller corneal diameter than the control subjects ($P < 0.01$). In addition, the APAC subjects also had higher flat keratometry (K)-value (44.11 ± 1.65 D, $P < 0.05$), higher steep K-value (45.26 ± 1.63 D, $P < 0.01$), and thicker CCT (559.69 ± 58.68 μm, $P < 0.01$) than the control subjects (flat K: 43.82 ± 1.57 D; steep K: 44.79 ± 1.54 D; CCT: 531.02 ± 32.10 μm).

Higher proportion in hyperopia was found in both APAC (32.9 %, $P < 0.01$) and PACG subjects (38.6 %, $P < 0.01$) as compared to the control subjects (20.2 %; Table 1). Moreover, both APAC (22.81 ± 3.49 kg/m^2, $P < 0.01$) and PACG subjects (23.40 ± 3.70 kg/m^2, $P < 0.05$) had significant lower BMI than the control subjects (23.93 ± 3.45 kg/m^2). The APAC subjects also showed significant lower body height (154.61 ± 7.97 cm, $P < 0.01$) and body weight (54.70 ± 10.29 kg, $P < 0.01$) as compared to the control subjects (height: 156.94 ± 7.90 cm; weight: 59.04 ± 10.05 kg). In addition, the APAC subjects has significantly higher proportions of underweight (9.0

Table 1
Demographics and clinical data of the study subjects.

	Control ($n = 1585$)	APAC ($n = 447$)	Chronic PACG ($n = 295$)
Age (years)	67.08 ± 8.90	65.97 ± 8.12*	66.00 ± 7.63
Sex (male/female)	657/928	124/323**	135/160**
Height (cm)	156.94 ± 7.90	154.61 ± 7.97**	157.11 ± 8.10
Weight (kg)	59.04 ± 10.05	54.70 ± 10.29**	57.82 ± 10.36
BMI (kg/m^2)	23.93 ± 3.45	22.81 ± 3.49**	23.40 ± 3.70*
#BMI group (G1/G2/G3/G4)	87/921/510/63	40/293/100/12**	25/179/77/14
Hypertension (no/yes)	989/596	297/150	199/96
Hyperopia (no/yes)	1265/320	300/147**	181/114**
BCVA (logMAR)	0.61 ± 0.39	0.46 ± 0.43**	0.40 ± 0.39**
IOP (mmHg)	13.92 ± 3.56	26.17 ± 14.17**	26.19 ± 11.68**
Flat K (diopters)	43.82 ± 1.57	44.11 ± 1.65*	43.77 ± 1.67
Steep K (diopters)	44.79 ± 1.54	45.26 ± 1.63**	44.84 ± 1.67
Axial length (mm)	23.40 ± 1.01	22.35 ± 0.83**	22.80 ± 0.79**
Central anterior chamber depth (mm)	3.16 ± 0.40	2.25 ± 0.26**	2.46 ± 0.28**
Len thickness (mm)	4.42 ± 0.48	5.04 ± 0.35**	4.99 ± 0.33**
Lens position (mm)	5.37 ± 0.30	4.77 ± 0.25**	4.95 ± 0.25**
Relative lens position	0.23 ± 0.01	0.21 ± 0.01**	0.22 ± 0.01**
Central corneal thickness (μm)	531.02 ± 32.10	559.69 ± 58.68**	535.49 ± 39.64
Corneal diameter (mm)	11.67 ± 0.48	11.34 ± 0.47**	11.48 ± 0.46**
Hemoglobin (g/L)	135.68 ± 17.42	137.90 ± 14.66*	139.30 ± 14.68*
Blood glucose (mmol/L)	6.74 ± 2.16	7.07 ± 1.81*	6.64 ± 1.96
Triglyceride (mmol/L)	2.16 ± 1.68	1.82 ± 1.17**	2.00 ± 1.56
Total cholesterol (mmol/L)	5.42 ± 1.11	5.40 ± 1.04	5.39 ± 1.07
LDL-cholesterol (mmol/L)	3.69 ± 1.03	3.56 ± 0.97	3.26 ± 0.91*
HDL-cholesterol (mmol/L)	1.70 ± 0.47	1.72 ± 0.49	1.82 ± 0.69

#G1: underweight (18.5 kg/m^2 or lower); G2: normal body weight (18.5–24.9 kg/m^2); G3: overweight (25–29.9 kg/m^2); G4: obesity (30 kg/m^2 or greater). APAC: acute primary angle closure; HDL: high density lipoprotein; K: keratometry; LDL: low density lipoprotein; PACG: primary angle closure glaucoma. *$P < 0.05$; **$P < 0.01$.

%) and normal weight (65.8 %) than the control subjects (underweight: 5.5 %, normal weight: 58.3 %; $P < 0.01$). The APAC subjects also had higher blood glucose (7.07 ± 1.81 mmol/L, $P < 0.05$) but lower triglyceride (1.82 ± 1.17 mmol/L, $P < 0.01$) levels than the control subjects (glucose: 6.74 ± 2.16 mmol/L; triglyceride: 2.16 ± 1.68 mmol/L). Furthermore, both APAC (137.90 ± 14.66 g/L, $P < 0.05$) and PACG subjects (139.30 ± 14.68 g/L, $P < 0.05$) had significantly higher hemoglobin level than the control subjects (135.68 ± 17.42 g/L).

In the multivariable logistic analysis, female (OR = 2.57, 95 % C.I.: 1.97–3.37, $P < 0.001$), hyperopia (OR = 1.96, 95 % C.I.: 1.54–2.51, $P < 0.001$), hemoglobin level (OR = 1.02, 95 % C.I.: 1.01–1.03, $P < 0.001$), blood glucose level (OR = 1.20, 95 % C.I.: 1.13–1.27, $P < 0.001$), triglyceride level (OR = 0.85, 95 % C.I.: 0.78–0.94, $P = 0.001$), and BMI (OR = 0.89, 95 % C.I.: 0.86–0.92, $P < 0.001$) were found to be significantly associated with APAC (Table 2). In contrast, only sex (OR = 0.95, 95 % C.I.: 0.91–1.00, $P = 0.008$), blood glucose level (OR = 2.60, 95 % C.I.: 1.99–3.40, $P < 0.001$), and BMI (OR = 1.02, 95 % C.I.: 1.01–1.02, $P = 0.001$) were found to be significantly associated with PACG. Substituting the body height and weight for BMI revealed that age (OR = 0.98, 95 % C.I.: 0.97–1.00, $P = 0.017$), female (OR = 1.83, 95 % C.I.: 1.30–2.58, $P = 0.001$), hyperopia (OR = 2.23, 95 % C.I.: 1.82–2.73, $P < 0.001$), hemoglobin level (OR = 1.02, 95 % C.I.: 1.01–1.03, $P < 0.001$), blood glucose level (OR = 1.12, 95 % C.I.: 1.07–1.18, $P < 0.001$), triglyceride level (OR = 0.90, 95 % C.I.: 0.83–0.96, $P = 0.002$), and body weight (OR = 0.95, 95 % C.I.: 0.94–0.97, $P < 0.001$) were significantly associated with APAC (Table 2). Yet, only hyperopia (OR = 2.62, 95 % C.I.: 2.00–3.43, $P < 0.001$), hemoglobin level (OR = 1.02, 95 % C.I.: 1.01–1.03, $P = 0.001$), and body weight (OR = 0.98, 95 % C.I.: 0.96–0.99, $P = 0.006$) were found to be significantly associated with PACG.

3.2. Correlation of body mass index with ocular biometric parameters

Pearson correlation analysis showed that BMI was significantly and positively correlated with AL (r = 0.095, $P = 0.046$) and corneal diameter (r = 0.107, $P = 0.023$) among the APAC subjects (Supplementary Table 1). For the PACG subjects, BMI was significantly and positively correlated with flat (r = 0.123, $P = 0.035$) and steep keratometry (r = 0.116, $P = 0.046$) but negatively correlated with CCT (r = −0.126, $P = 0.031$). Multiple linear regression analysis indicated that every 1 kg/m^2 increase in BMI was associated with 0.058 ± 0.046 mm decrease in flat keratometry ($P = 0.015$), 0.038 ± 0.024 mm increase in AL ($P = 0.001$), 0.008 ± 0.008 mm increase in central ACD ($P = 0.042$), and 0.016 ± 0.014 mm increase in corneal diameter ($P = 0.024$) among the APAC subjects (Table 3), but not significant among the PACG subjects.

3.3. Genetic association of PXDNL variants with primary angle closure glaucoma

In total, 628 APAC, 554 chronic PACG, and 1415 control subjects were included in the genetic association analysis. All 3 *PXDNL* variants followed HWE in the control subjects (Supplementary Table 2). Although *PXDNL* variants showed no significant association with PACG in all six genetic models after Bonferroni's correction, *PXDNL* rs11985241 and rs16916207 variants were significantly associated with APAC in the allelic (rs11985241: OR = 0.81, 95 % C.I.: 0.69–0.93, $P = 0.004$; rs16916207: OR = 0.81, 95 % C.I.: 0.69–0.96, $P = 0.004$) and homozygous (rs11985241: OR = 0.63, 95 % C.I.: 0.44–0.90, $P = 0.011$; rs16916207: OR = 0.63, 95 % C.I.:

Table 2
Multivariable logistic analysis of body mass index, height, weight and blood biochemical parameters with acute primary angle closure and chronic primary angle closure glaucoma.

	APAC ($n = 447$)			Chronic PACG ($n = 295$)		
	OR	95 % C.I.	*P*	OR	95 % C.I.	*P*
Based on BMI						
Age (years)	0.99	0.97–1.00	0.077	0.99	0.97–1.00	0.173
Sex (female)	2.57	1.97–3.37	<0.001	0.95	0.91–0.99	0.008
BMI (kg/m^2)	0.89	0.86–0.92	<0.001	1.02	1.01–1.02	0.001
Hyperopia (yes)	1.96	1.54–2.51	<0.001	1.02	0.94–1.09	0.679
Hypertension (yes)	1.09	0.85–1.39	0.491	0.94	0.86–1.03	0.206
Hemoglobin (g/L)	1.02	1.01–1.03	<0.001	1.00	0.75–1.34	0.975
Blood glucose (mmol/L)	1.20	1.13–1.27	<0.001	2.60	1.99–3.40	<0.001
Total cholesterol (mmol/L)	0.92	0.82–1.02	0.126	0.70	0.47–1.03	0.074
Triglyceride (mmol/L)	0.85	0.78–0.94	0.001	0.91	0.69–1.21	0.526
Based on body height and weight						
Age (years)	0.98	0.97–1.00	0.017	0.99	0.97–1.00	0.096
Sex (female)	1.83	1.30–2.58	0.001	0.83	0.57–1.22	0.350
Height (cm)	1.00	0.98–1.03	0.711	1.00	0.98–1.03	0.979
Weight (kg)	0.95	0.94–0.97	<0.001	0.98	0.96–0.99	0.006
Hyperopia (yes)	1.98	1.55–2.53	<0.001	2.62	2.00–3.43	<0.001
Hypertension (yes)	1.09	0.85–1.40	0.489	0.92	0.69–1.22	0.560
Hemoglobin (g/L)	1.02	1.01–1.03	<0.001	1.02	1.01–1.03	0.001
Blood glucose (mmol/L)	1.20	1.13–1.27	<0.001	1.01	0.94–1.09	0.713
Total cholesterol (mmol/L)	0.91	0.82–1.02	0.104	0.96	0.85–1.09	0.558
Triglyceride (mmol/L)	0.85	0.78–0.94	0.001	0.94	0.86–1.03	0.216

APAC: acute primary angle closure; C.I.: confidence interval; OR: odds ratio; PACG: primary angle closure glaucoma.

Table 3
Multiple linear regression models of body mass index with ocular biometric parameters in acute primary angle closure and chronic primary angle closure glaucoma subjects.

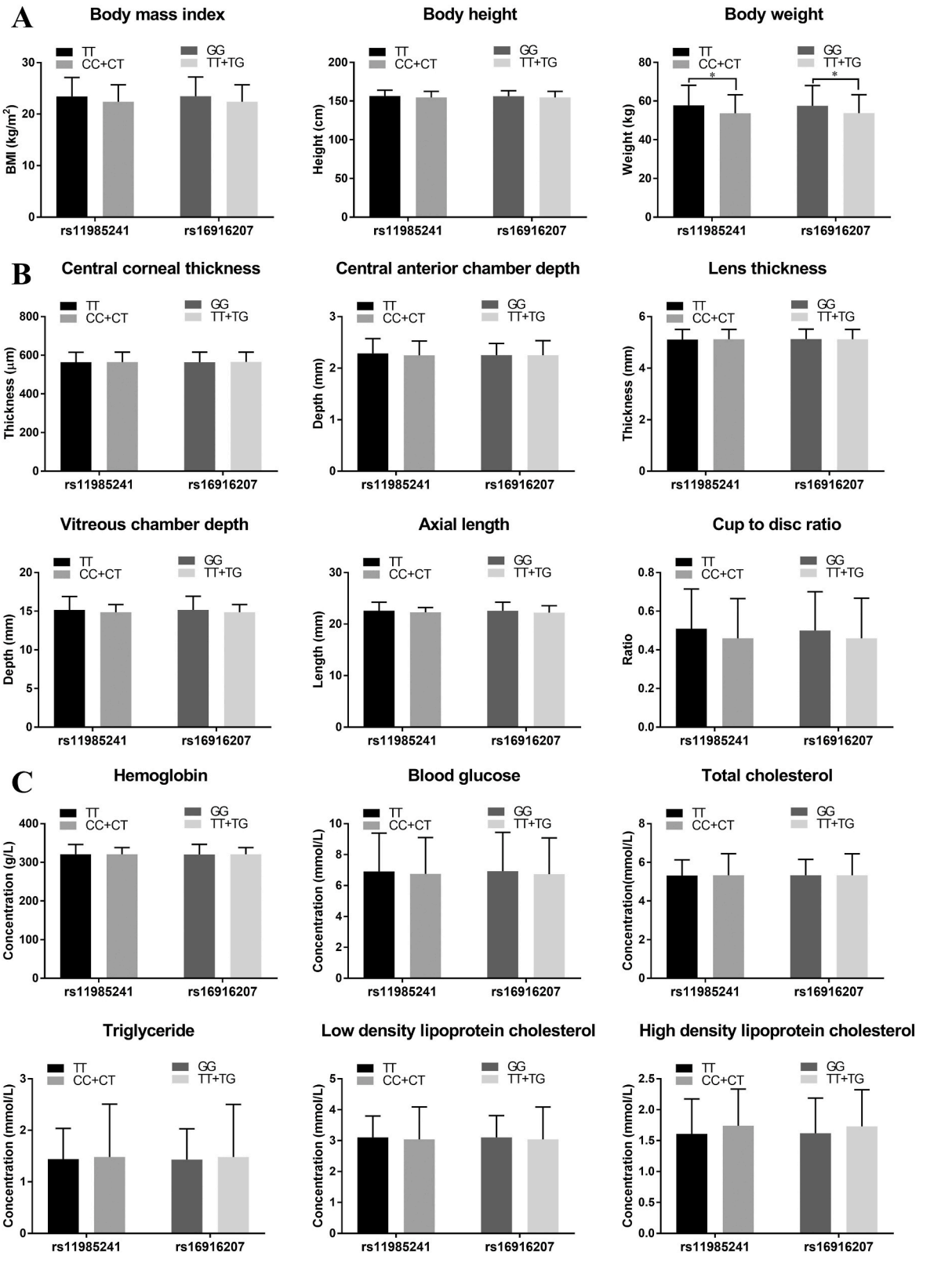
	Flat keratometry			Axial length			Central ACD			Lens position			Lens thickness			Corneal diameter		
	β	SD	*P*	β	SD	*P*	β	SD	*P*	β	SD	*P*	β	SD	*P*	β	SD	*P*
APAC																		
Age, years	−0.034	0.020	0.001	0.022	0.010	<0.001	−0.002	0.004	0.252	0.003	0.004	0.039	0.010	0.004	<0.001	0.002	0.006	0.519
Sex (female)	0.656	0.376	0.001	−0.408	0.188	<0.001	0.003	0.062	0.914	−0.022	0.060	0.462	−0.051	0.080	0.202	−0.170	0.110	0.002
BMI, kg/m^2	−0.058	0.046	0.015	0.038	0.024	0.001	0.008	0.008	0.042	0.006	0.008	0.103	−0.003	0.010	0.484	0.016	0.014	0.024
Hyperopia (yes)	−0.372	0.322	0.021	−0.083	0.162	0.305	0.048	0.052	0.067	0.063	0.052	0.014	0.030	0.068	0.376	0.075	0.094	0.113
Hypertension (yes)	−0.041	0.344	0.814	−0.173	0.172	0.045	−0.013	0.056	0.636	−0.020	0.054	0.455	−0.014	0.072	0.695	0.018	0.102	0.716
Hemoglobin, g/L	−0.001	0.012	0.895	−0.002	0.006	0.482	−0.002	0.002	0.042	0.000	0.002	0.878	0.004	0.002	0.004	−0.002	0.004	0.384
Blood glucose, mmol/L	0.124	0.084	0.004	−0.035	0.042	0.096	−0.016	0.014	0.021	−0.001	0.014	0.891	0.030	0.018	0.001	−0.007	0.024	0.596
Total cholesterol, mmol/L	−0.005	0.154	0.949	0.000	0.076	0.996	0.008	0.026	0.535	0.000	0.024	0.976	−0.016	0.032	0.315	0.059	0.046	0.009
Triglyceride, mmol/L	0.084	0.134	0.208	−0.017	0.066	0.609	−0.007	0.022	0.498	0.003	0.022	0.777	0.021	0.028	0.140	−0.018	0.040	0.364
Chronic PACG																		
Age, years	−0.021	0.026	0.100	0.014	0.012	0.014	0.000	0.004	0.935	0.003	0.004	0.190	0.006	0.006	0.034	−0.004	0.008	0.324
Sex (female)	0.768	0.454	0.001	−0.515	0.204	0.000	−0.082	0.080	0.044	−0.140	0.070	0.000	−0.117	0.092	0.011	−0.134	0.130	0.041
BMI, kg/m^2	0.044	0.056	0.117	0.000	0.024	0.975	0.006	0.010	0.242	0.002	0.008	0.588	−0.007	0.012	0.214	0.004	0.016	0.609
Hyperopia (yes)	−0.442	0.388	0.023	−0.213	0.174	0.015	−0.044	0.068	0.204	−0.016	0.060	0.591	0.056	0.078	0.155	−0.004	0.112	0.937
Hypertension (yes)	0.027	0.438	0.903	0.039	0.196	0.692	−0.011	0.078	0.781	0.035	0.066	0.292	0.092	0.088	0.038	0.035	0.126	0.583
Hemoglobin, g/L	−0.002	0.014	0.804	0.002	0.006	0.492	0.001	0.002	0.604	0.000	0.002	0.915	−0.002	0.002	0.282	0.002	0.004	0.386
Blood glucose, mmol/L	−0.054	0.096	0.263	0.021	0.044	0.328	−0.009	0.018	0.296	−0.001	0.014	0.850	0.015	0.020	0.121	0.025	0.028	0.072
Total cholesterol, mmol/L	0.201	0.192	0.036	−0.082	0.086	0.058	0.030	0.034	0.077	0.029	0.030	0.048	−0.002	0.038	0.908	0.008	0.056	0.782
Triglyceride, mmol/L	−0.039	0.126	0.537	0.021	0.056	0.461	−0.018	0.022	0.117	−0.019	0.020	0.048	−0.003	0.026	0.819	0.018	0.036	0.321

[a]Lens position = ACD+1/2 lens thickness; ACD: anterior chamber depth; APAC: acute primary angle closure; PACG: primary angle closure glaucoma; SD: standard deviation.

Table 4
Genetic association of *PXDNL* variants with acute primary angle closure and chronic primary angle closure glaucoma.

	PXDNL Variants	Ref > Alt	WT/Hetero/Homo		Genotype	Allele		Dominant		Recessive		Heterozygous		Homozygous	
			Controls (*n*)	Patients (*n*)	*P*	OR (95 % C. I.)	*P*	OR (95 % C. I.)	*P*	OR (95 % C. I.)	*P*	OR (95 % C. I.)	*P*	OR (95 % C. I.)	*P*
APAC	rs11985241	C > T	695/569/148	344/234/46	0.019	0.81 (0.69–0.93)	0.004	0.79 (0.66–0.96)	0.017	0.68 (0.48–0.96)	0.029	0.84 (0.81–1.02)	0.078	0.63 (0.44–0.90)	0.011
	rs16916207	T > G	695/572/144	346/236/45	0.019	0.81 (0.69–0.96)	0.004	0.79 (0.66–0.96)	0.016	0.68 (0.48–0.97)	0.031	0.83 (0.81–1.02)	0.073	0.63 (0.44–0.90)	0.011
	rs79394014	C > T	1231/170/12	544/72/5	0.940	0.95 (0.73–1.24)	0.721	0.95 (0.72–1.26)	0.726	0.94 (0.33–2.68)	0.910	0.95 (0.95–1.28)	0.739	0.94 (0.33–2.67)	0.375
Chronic PACG	rs11985241	C > T	695/569/148	269/233/48	0.440	0.97 (0.83–1.13)	0.659	1.01 (0.83–1.23)	0.901	0.82 (0.58–1.15)	0.244	1.06 (0.97–1.30)	0.594	0.84 (0.59–1.20)	0.328
	rs16916207	T > G	695/572/144	270/236/48	0.500	0.97 (0.84–1.13)	0.729	1.02 (0.84–1.24)	0.865	0.83 (0.59–1.17)	0.295	1.06 (0.97–1.30)	0.592	0.86 (0.60–1.22)	0.387
	rs79394014	C > T	1231/170/12	484/70/0	0.089	0.91 (0.69–1.21)	0.528	0.98 (0.73–1.31)	0.873	0.99 (0.99–1.00)	0.063	1.05 (0.91–1.41)	0.771	0.99 (0.99–1.0)	0.064

n: numbers; Ref: reference allele; Alt: variant allele; Hetero: heterozygous genotype; Homo: homozygous variant genotype; WT: homozygous reference genotype; APAC: acute primary angle closure; PACG: primary angle closure glaucoma.



(caption on next page)

Fig. 2. Genotype-phenotype correlation analysis of *PXDNL* rs11985241 and rs16916207 variants with body mass index, ocular biometric and blood biochemical parameters in acute primary angle closure patients.
The correlation of *PXDNL* rs11985241 and rs16916207 variants with (**A**) body mass index (BMI, height and weight), (**B**) ocular biometric (central corneal thickness, central anterior chamber depth, lens thickness, vitreous chamber depth, axial length and cup to disc ratio), and (**C**) blood biochemical (hemoglobin, blood glucose, total cholesterol, triglyceride, low density lipoprotein-cholesterol and high density lipoprotein-cholesterol) parameters in acute primary angle closure patients. Black bar: rs11985241 TT genotype; Grey bar: rs11985241 CC and CT genotypes; Dark grey bar: rs16916207 GG genotype; Light grey bar: rs16916207 TT and TG genotypes. Data was presented as mean ± standard deviation. *$P < 0.05$.

0.44–0.90, $P = 0.011$) models (Table 4). Haplotype association analysis indicated that rs11985241 T – rs16916207 G haplotype conferred a lower risk to APAC (OR = 0.80, 95 % C.I.: 0.69–0.93, $P = 0.004$) than the reference CT haplotype (Supplementary Table 3 and Supplementary Fig. 1).

3.4. Genotype-phenotype correlation analysis of PXDNL variants in primary angle closure glaucoma patients

To further elucidate the contribution of the *PXDNL* variants, we conducted the correlation of the *PXDNL* variants with BMI and ocular biometric and blood biochemical parameters. The APAC subjects carrying rs11985241 C allele (53.72 ± 9.52 kg) or rs16916207 T allele (53.75 ± 9.52 kg) had significantly lower weight than those carrying rs11985241 TT genotype (57.77 ± 10.44 kg, $P = 0.024$) or rs16916207 GG genotype (57.57 ± 7.93 kg, $P = 0.036$) respectively (Fig. 2A–C); yet, no significant correlation of *PXDNL* rs11985241 and rs16916207 variants with BMI and ocular biometric and blood biochemical parameters was found among the PACG subjects (Supplementary Figs. 2A–C).

4. Discussion

Results from this study showed that: (1) lower BMI and lower weight were significantly associated with higher risk of APAC; (2) Female subjects and those with hyperopia, lower BMI, higher blood glucose level, and lower triglyceride levels had a higher risk of APAC; (3) BMI was positively correlated with AL and corneal diameter among the APAC subjects; (4) *PXDNL* rs16916207 and rs11985241 variants were significantly associated with APAC and lower weight. Collectively, our results demonstrated the association of BMI, body weight, and *PXDNL* variants with APAC.

BMI influenced the risk for both POAG and PACG [13]. Lower BMI has been reported to be associated with an increased risk of primary open-angle glaucoma (POAG) [7,19,20], which might be due to the higher IOP peaks and fluctuation in lower BMI people [21]. However, higher BMI has also been reported to be associated with increased risks of POAG, which might be due to the increased IOP in obese people [22]. For PACG, BMI was suggested to be a risk factor with relative influence of 8 % in a Singapore study [13]. Yet, BMI was reported not to be associated with PACG in an Indian study [8], probably due to only 21 PACG eyes (out of total 8869 eyes; 0.24 %) from 14 PACG subjects (out of 4570 subjects; 0.31 %) included in this study. Besides, the differential association could be due to subjects from different ethnicities and populations. In this study, we found that APAC subjects showed lower BMI as compared to the control subjects (Table 1). Multivariable logistic regression analysis demonstrated that subjects with lower BMI had a greater risk to APAC in southern Chinese population, adjusting for age, sex, and hyperopia (Table 2). Although short body stature is common in PACG with the possibility of smaller ocular dimensions [23,24], we found that, instead of height, lower weight was significantly associated with higher risk of APAC in the multivariable logistic regression analysis, adjusting for age, sex, and hyperopia (Table 2). Collectively, we found that lower BMI and lower weight were the independent risk factor contributing to higher risk of APAC in southern Chinese population. In addition to the age, sex, and hyperopia, BMI and weight could also be the potential parameters to assess the risk levels of PAC with similarly crowded ocular structures.

To delineate the association of BMI with APAC, a possible direction could be exploring the correlations of BMI with different ocular biometric parameters. Shallower ACD, thicker lens, shorter AL, smaller corneal diameter, and steeper corneal curvature have been frequently reported among the PACG patients [15,25–27]. BMI has been reported to be positively correlated with ACD [28] and CCT [29,30]. The association of lower BMI and weight with greater odds of narrow angle was also reported in a Chinese study [10]. In the present study, we demonstrated that lower BMI was significantly associated with shorter AL, shallower central ACD, smaller corneal diameter, and greater flat K-value among the APAC subjects (Table 3), indicating that subjects with lower BMI had more crowded anterior ocular structures, which could explain the higher risk of APAC in lower BMI subjects. In contrast, BMI was not associated with ocular biometric parameters among the PACG subjects in multiple linear regression analysis. This could be consistent with the ocular biometric parameter differences between APAC and PACG [4], indicating potentially different mechanisms for the angle closure between APAC and PACG. Apart from the association with the anterior anatomical structure, lower BMI was reported to be associated with thicker choroid, and it was postulated that choroidal expansion may cause a forward movement of the lens and iris [31]. However, the association of BMI with choroid thickness is still controversial [32,33]. Besides, lower BMI is also associated with smaller neuroretinal rim area [11,12]. Further investigations are warranted to delineate the influences and mechanisms of BMI to the anatomical structure of the eyes.

We previously identified *ABCC5*, *COL11A1*, *PLEKHA7*, *EPDR1*, *CHAT*, *GLIS3*, and *FERMT2* variants associated with PACG [34–36]. As the BMI and weight were found to be associated with APAC in this study, we further explored whether the BMI or weight-related gene would be associated with APAC. We, for the first time, identified significant association of *PXDNL* variants rs16916207 and rs11985241 with APAC (Table 4 and Supplementary Table 3). *PXDNL* is an associated gene between the obese individuals and never-overweight controls [14], and associated with high-density lipoprotein-cholesterol variability [37], suggesting that *PXDNL*

could be related to the weight. Our genotype-phenotype correlation analysis showed that the APAC subjects carrying the risk alleles of rs11985241 and rs16916207 variants had significantly lower weight than those carrying the protective allele (Fig. 2), which is consistent with lower weight associated with higher risk in the APAC subjects (Table 2). *PXDNL* and peroxidasin (*PXDN*) belong to the peroxidase-cyclooxygenase superfamily [38]. Mutations in *PXDNL* would cause congenital malformations in developing human embryo and laterality [39], whereas *PXDN* mutations would cause eye developmental glaucoma, microphthalmia, microcornea, and anterior segment dysgenesis in human and mice [40–43]. PXDNL could contribute to the development of angle closure and APAC through the changes in anatomical structures by forming complex with PXDN and antagonizing the peroxidase activity of PXDN [38]. Nevertheless, further investigations are needed to delineate how *PXDNL* contributes to the development of APAC. Replications in different cohorts and ethnicities could confirm the association of *PXDNL* variants with APAC.

There were several limitations in this study. First, this study did not investigate the relationship between BMI and the disease severity. BMI was shown to be related to the severity of PACG in a Malaysian study [44]. Second, the data was collected at the first visit, which could be different from the data at the onset for the chronic PACG subjects. Third, the analysis on the association with IOP was not included as IOP-lowering treatment has been immediately applied to the patients for their hospital visit, especially the APAC subjects.

In summary, this study revealed the correlation of lower BMI and lower weight with higher risk of APAC, and identified the association of *PXDNL* variants with APAC and lower weight. Individuals with lower BMI and weight, should better seek for medical advices on APAC when feeling ophthalmalgia, headache, and nausea.

Ethics statement

This study has been approved by the Ethics Committee for Human Medical Research at the Joint Shantou International Eye Center of Shantou University and the Chinese University of Hong Kong (approval number: EC20200120(1)-P02), which is in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study subjects after explaining the nature and possible consequences of the study.

Data availability statement

The data associated with your study was not deposited into a publicly available repository. Data will be made available on reasonable request to the corresponding authors.

CRediT authorship contribution statement

Jiawei Chen: Writing – original draft, Investigation, Formal analysis. **Shaowan Chen:** Investigation. **Yuqian Zheng:** Formal analysis. **Yanxuan Xu:** Investigation. **Xin Zhong:** Formal analysis, Data curation. **Yuqiang Huang:** Supervision, Resources, Data curation. **Tsz Kin Ng:** Writing – original draft, Supervision, Funding acquisition, Formal analysis. **Chukai Huang:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22240.

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