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Expression-associated polymorphisms of *CAV1-CAV2* affect intraocular pressure and high-tension glaucoma risk

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Purpose: The human *CAV1-CAV2* locus has been associated with susceptibility to primary open-angle glaucoma in four studies of Caucasian, Chinese, and Pakistani populations, although not in several other studies of non-Korean populations. In this study with Korean participants, the *CAV1-CAV2* locus was investigated for associations with susceptibility to primary open-angle glaucoma accompanied by elevated intraocular pressure (IOP), namely, high-tension glaucoma (HTG), as well as with IOP elevation, which is a strong risk factor for glaucoma.
Methods: Two single nucleotide polymorphisms (SNPs) were genotyped in 1,161 Korean participants including 229 patients with HTG and 932 healthy controls and statistically examined for association with HTG susceptibility and IOP. One SNP was rs4236601 G>A, which had been reported in the original study, and the other SNP was rs17588172 T>G, which was perfectly correlated (r^2=1) with another reported SNP rs1052990. Expression quantitative trait loci (eQTL) analysis was performed using GENe Expression VARiation (Genevar) data.
Results: Both SNPs were associated with HTG susceptibility, but the rs4236601 association disappeared when adjusted for the rs17588172 genotype and not vice versa. The minor allele G of rs17588172 was associated significantly with 1.5-fold increased susceptibility to HTG (p=0.0069) and marginally with IOP elevation (p=0.043) versus the major allele T. This minor allele was also associated with decreased *CAV1* and *CAV2* mRNA in skin and adipose according to the Genevar eQTL analysis.
Conclusions: The minor allele G of rs17588172 in the *CAV1-CAV2* locus is associated with decreased expression of *CAV1* and *CAV2* in some tissues, marginally with IOP elevation, and consequently with increased susceptibility to HTG.

Glaucoma, a major eye disease that causes visual blindness, is characterized by optic nerve degeneration and visual defects. Primary open-angle glaucoma (POAG), the most common type of glaucoma, is accompanied by elevated intraocular pressure (IOP >21 mmHg) in high-tension glaucoma (HTG) or by normal IOP (≤21 mmHg) in normal-tension glaucoma (NTG). Although elevated IOP is a major risk factor for glaucoma, increased IOP is neither necessary nor sufficient to develop POAG [1-3]. Several years ago, an intergenic single nucleotide polymorphism (SNP), rs4236601, located between *CAV2* (gene ID: 858; OMIM 601048; upstream) and *CAV1* (gene ID: 857; OMIM 601047; downstream) on human chromosome 7q31.2 was identified as associated with susceptibility to POAG in a genome-wide association study (GWAS); the association was discovered in an Icelandic Caucasian population and replicated in additional European Caucasian, Australian Caucasian, and Chinese Asian populations [4].

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Among eight subsequent replication studies using Iowa U.S. Caucasian [5], Afro-Caribbean [6], Saudi Arabian [7], U.S. Caucasian [8], Japanese Asian [9], African [10], U.S. Caucasian [11], and Pakistani [12] populations, only three studies using U.S. Caucasian and Pakistani populations successfully replicated the POAG association [8,11,12], as well as an additional meta-analysis [13]. In addition, the original study [4] and the first positive replication study [8] reported preferential association with susceptibility to NTG rather than to HTG.

Interestingly, the POAG risk-associated SNP alleles in the *CAV1-CAV2* locus were also associated with IOP elevation [14-17]. Furthermore, the HTG risk association was observed in the Chinese [4] and Pakistani [12] populations. Because it seemed odd that the alleles associated with IOP elevation were preferentially associated with increased susceptibility to NTG with normal IOP rather than HTG with high IOP [4,8], these variants were examined to replicate the associations with HTG susceptibility, as well as with IOP, and *CAV1* and *CAV2* expression.

METHODS

Study samples: Adhering to the ARVO statement on human subjects, this study followed the tenets of the Declaration of Helsinki. A total of 1,161 unrelated Korean participants including 229 patients with HTG (men 68.6%; mean age 56.1±15.9 years) and 932 healthy controls (men 50.1%; mean age: 57.6±13.2 years) were recruited at Chungnam National University Hospital and Seoul St. Mary's Hospital under approval from the Institutional Review Board of each hospital, and each participant provided written informed consent.

In the case group, only patients diagnosed with POAG with high IOP or HTG by two glaucoma specialists (C.-S.K. and C.K.P.) at the glaucoma clinic of the two tertiary referral hospitals as previously described were included [18,19]. Among POAG patients with (1) characteristic glaucomatous optic nerve head defect, (2) visual field defect corresponding to the optic nerve head defect, (3) retinal nerve fiber layer defect and (4) normal open angle or deep anterior chamber angle, only those with IOP of >21 mmHg were included in this HTG case group.

All 932 controls were free of glaucoma and other eye diseases. Participants who were free of glaucoma but had a family history of glaucoma and a history of steroid treatment were excluded in the control group. Intraocular pressure was measured with a Goldman applanation tonometer for each visit, and the average of two measurements was recorded.

SNP genotyping and association tests: Under the approval of the KAIST Institutional Review Board, genomic DNA was extracted from peripheral venous blood collected in Vacutainer tubes using the Gentra Puregene blood kit (Qiagen, Valencia, CA) and stored at -80°C deep freezer until genotyped using the MassARRAY hME assay (Sequenom, San Diego, CA). The call rate was 99.9% for rs4236601 and 98.7% for rs17588172, and the genotype data were under Hardy–Weinberg equilibrium (p=1.00 for rs4236601 and p=0.54 for rs17588172).

SNP association with HTG susceptibility was assessed in a comparison of 229 patients with HTG and 932 controls using logistic regression analysis, with adjustment for age, gender, and recruitment site, unless described otherwise. Association was considered statistically significant when $p \le \alpha$ and marginal when $\alpha < p \le 0.05$, with a significance level of Bonferroni correction for multiple testing of $\alpha = 0.05/2 = 0.025$, as two SNPs were tested.

SNP association of IOP levels was additionally tested among 1,095 participants using nonparametric tests suitable for the non-normal distribution of IOP shown in Appendix 1. There were no pretreatment IOP measurement records for 66 patients with HTG, although their IOP levels were still high after treatment; therefore, these samples were excluded from the IOP association tests. The Jonckheere trend and Mann–Whitney U tests were used for rs17588172 of three genotypes and rs4236601 of two genotypes (with no minor-allele homozygotes), respectively.

All statistical tests were performed using PLINK v.1.07 or IBM SPSS Statistics v.18 (IBM Corporation, Chicago, IL). Statistical power was calculated using the CaTS interface.

Expression quantitative trait loci analysis: Two data sets from the GENe Expression VARiation (Genevar) database [20] were used for the cis-expression quantitative trait loci (eQTL) analysis. The *CAV1* and *CAV2* mRNA levels in adipose, skin, and the lymphoblastoid cell line (LCL) were retrieved from a data set of tissue-dependent mRNA level measurements from 856 British Caucasians by Grundberg et al. [21] and used to calculate standardized regression coefficient β values. To obtain Asian data, the *CAV1* and *CAV2* mRNA levels of 82 Japanese and 80 Chinese participants in the International HapMap Project were retrieved from another data set of population-dependent mRNA level measurements in LCLs from Stranger et al. [22] and used to calculate Spearman's rank-order correlation coefficient ρ values.

RESULTS

HTG susceptibility association of CAV1-CAV2 SNPs: A total of 1,161 case-control subjects of Korean ancestry, whose demographic characteristics are shown in Table 1, were recruited to this HTG association study. The rs4236601 (G>A) SNP had been reported in the original association study [4] and was the first SNP genotyped for replication in this study. Another SNP rs1052990 had been reported in the second positive-association study [8], but the SNP's perfectly correlated (r^2=1) rs17588172 (T>G) was the second SNP genotyped in this study. These two SNPs were tested for HTG susceptibility by comparing genotype distributions in 229 patients with HTG and 932 healthy controls (Table 2).

HTG susceptibility was significantly associated with the second SNP rs17588172 (odds ratio [OR]=1.5, p=0.0069) after Bonferroni correction for multiple testing of two SNPs (α=0.025). This association was maintained after adjusted for the genotype of the other, first SNP rs4236601 (p_{con}=0.010). However, the marginal HTG susceptibility association of the first SNP rs4236601 (p=0.026) disappeared when adjusted for the genotype of the second SNP rs17588172 (p_{con}=0.15). Thus, HTG susceptibility association of the *CAV1-CAV2* locus was found with rs17588172 in this Korean population.

Table 1. Characteristics of study subjects.

Characteristics	Controls	HTG patients	p
Demographic characteristics			
Number of subjects, n	932	229	
Male/female, n	467/465	157/72	<0.001
Age (year)	57.6±13.2	56.1±15.9	<0.001
Body mass index (kg/m^2)	23.9 (4.0)	23.4 (4.1)	0.29
Systolic pressure (mmHg)	109.0 (11.0)	130.0 (20.0)	0.23
Diastolic pressure (mmHg)	64.0 (6.0)	80.0 (10.0)	0.003
Clinical characteristics			
Intraocular pressure (mmHg)	11.5 (1.0)	27.0 (8.5)	<0.001
Cup-to-disc ratio	0.40 (0.0)	0.80 (0.20)	<0.001
Visual field mean deviation (dB)	-	−7.5 (12.3)	
Visual field pattern SD (dB)	-	5.4 (5.5)	

Data are expressed as median (interquartile range) or average ± standard deviation (SD). p Values were calculated using Mann–Whitney U test, except chi-square test for gender and Student *t* test for age. Abbreviation: HTG, high-tension glaucoma.

IOP association of CAV1-CAV2 SNPs: Next, the two SNPs were examined for association with IOP. All 932 healthy controls had IOP measurements, and only 163 patients with HTG had pretreatment IOP measurements. The other 66 patients with HTG had only post-treatment IOP measurements and therefore were excluded from this analysis to exclude the confounding treatment effect on IOP.

In a total of 1,095 samples, IOP was not normally distributed (Appendix 1), and nonparametric tests were used for this analysis. IOP was associated significantly with rs4236601 (p=0.010) but marginally with rs17588172 (p=0.043), while the HTG risk-associated alleles in both SNPs were associated with IOP elevation.

Because IOP elevation is a strong risk factor for glaucoma, we next examined whether the increased HTG susceptibility was derived from the increase in IOP (Table 2). After the adjustment for the IOP, the HTG association of rs17588172 disappeared (p_{adj}=0.40). Accordingly, the HTG risk-associated allele appeared to affect the IOP, which could mostly account for its effect on susceptibility to HTG.

Gene expression association of CAV1 and *CAV2* SNPs: The HTG risk-associated SNP rs17588172 was highly correlated with 15 SNPs (r^2≥0.8) in the Korean HapMap population, suggesting their possible association with HTG susceptibility. Because these SNPs from rs1018859 in chromosome position 116,067,347 to rs7801950 in position 116,154,783 spanned an

Table 2. SNP association of HTG susceptibility.

Association tests	rs17588172	rs4236601
Controls (BB/Bb/bb), n	586/302/31	920/11/0
Cases (BB/Bb/bb), n	129/82/17	221/8/0
Odds ratio (95% CI)	1.5 (1.1, 2.2)	2.9 (1.1, 7.4)
p	0.0069	0.026
Conditional test p_{con} [a]	0.010	0.15
IOP-adjusted test p_{adj} [b]	0.40	0.42

Risk association was tested using an additive genetic model for rs17588172 T>G but using a dominant genetic model for rs4236601 G>A due to the absence of minor-allele homozygote AA. The p values were calculated with adjustment for age, gender, and recruitment site. [a]Conditional test p_{con} values were calculated with adjustment for rs4236601 or rs17588172 genotype as well as age, gender, and recruitment site. [b]IOP-adjusted test p_{adj} values were calculated with adjustment for IOP as well as age, gender, and recruitment site. Abbreviations: HTG, high-tension glaucoma; SNP, single nucleotide polymorphism; B, major allele; b, minor allele; CI, confidence interval; IOP, intraocular pressure.

87 kb region encompassing *CAV1* and *CAV2*, the possible effects on the two gene expression levels were examined using cis-eQTL analysis with two data sets from the Genevar database [20].

The *CAV1* and *CAV2* mRNA levels were associated with the two SNPs, but more strongly with the second SNP rs17588172 than the first SNP rs4236601 (Table 3). These eQTL results were unlikely to be derived from perturbed probe binding because no SNPs in the probe binding sites were in high linkage disequilibrium (LD) with either SNP. The risk allele G of rs1758872 was significantly correlated with decreased *CAV1* mRNA in adipose ($\beta=-0.32$, $p=3.9\times10^{-23}$) and skin ($\beta=-0.22$, $p=3.0\times10^{-18}$) from the Caucasian subjects, although the effect was minimal in the LCLs derived from the Caucasian subjects ($\beta=-0.027$, $p=0.00013$), and no association was found in the LCLs from the Chinese ($p=0.33$) and Japanese ($p=0.92$) subjects.

The same risk allele was also correlated with the *CAV2* mRNA level, but the direction of the effect was opposite depending on the tissue or cell line (Table 3). The risk allele was associated with increased *CAV2* mRNA in the LCLs derived from the Japanese ($\rho=0.82$, $p=9.5\times10^{-21}$), Chinese ($\rho=0.68$, $p=2.8\times10^{-12}$), and Caucasian ($\beta=0.045$, $p=4.9\times10^{-8}$) subjects but decreased mRNA in adipose ($\beta=-0.11$, $p=0.00027$) and skin ($\beta=-0.11$, $p=0.00014$) from the Caucasian subjects. Accordingly, the risk-associated minor alleles, G for rs17518872 and A for rs4236601, decrease *CAV1* and *CAV2* mRNA in adipose and skin, although in the LCLs the alleles increase *CAV2* mRNA but tend to decrease *CAV1* mRNA.

DISCUSSION

This report describes an SNP allele in the human *CAV1-CAV2* locus associated with not only increased susceptibility to HTG but also increased IOP. The HTG risk-associated, minor allele G of rs17588172 was also associated with decreased *CAV1* and *CAV2* mRNA in skin and adipose. Thus, the rs17588172 minor allele appears to increase IOP and consequently increase HTG susceptibility possibly by decreasing the expression of *CAV1*, *CAV2*, or both.

The *CAV1* and *CAV2* genes are expressed in glaucoma- and IOP-related tissues [5], and the respective gene products, caveolin 1 and 2, involved in the formation of caveolae, are known to negatively regulate transforming growth factor beta (TGF-β) signaling [23,24], which has been implicated to cause IOP elevation and optic nerve degeneration [25]. If so, decreased expression of *CAV1* or *CAV2* would be associated with increased IOP and HTG risk. This hypothesis is consistent with our findings that the HTG risk-associated allele of rs17588172 confers decreased expression of *CAV1* and *CAV2* in adipose and skin, although not in LCLs, according to our eQTL analyses using the Genevar data for the mRNA levels.

Recently, *Cav1*-knockout mice were found to have higher IOPs than age- and sex-matched control mice [26]. In perfusion culture of human and porcine anterior segments, however, *CAV2* knockdown rather than *CAV1* knockdown

Table 3. SNP association of *CAV1* and *CAV2* expression.

Cell type (ethnicity)	*n*	*CAV1*		*CAV2*	
		β or ρ[a]	p	β or ρ[a]	p
rs17588172 **G**					
Adipose (CEU)	856	−0.32	3.9×10^{-23}	−0.11	0.00027
Skin (CEU)	856	−0.22	3.0×10^{-18}	−0.11	0.00014
LCL (CEU)	856	−0.027	0.00013	0.045	4.9×10^{-8}
LCL (CHB)[a]	80	−0.11	0.33	0.68	2.8×10^{-12}
LCL (JPT)[a]	82	0.11	0.92	0.82	9.5×10^{-21}
rs4236601 **A**[b]					
Adipose (CEU)	856	−0.28	5.8×10^{-16}	−0.067	0.031
Skin (CEU)	856	−0.20	4.0×10^{-13}	−0.11	0.00041
LCL (CEU)	856	−0.030	0.000085	0.0098	0.27

Standardized regression coefficient β values were calculated using the data from Grundberg et al. [21]. [a]For Asian samples, Spearman's rank-order correlation coefficient ρ values rather than the β values were calculated using the data from Stranger et al. [22]. [b]The β values for rs4236601 are consistent with those recently reported by Hysi et al. [16] but direction of the risk allele effect is additionally shown here. Abbreviations: eQTL, expression quantitative trait loci; CAV, caveolin; LCL, lymphoblastoid cell line; CEU, Caucasians in Europe; CHB, Chinese in Beijing; JPT, Japanese in Tokyo.

decreased the outflow rate possibly leading to IOP elevation [27]. Thus, downregulation of caveolin 1 or 2 in the eye's aqueous outflow pathway could enhance TGF-β signaling to increase IOP and consequently increase HTG susceptibility.

The HTG association was more evident with rs17588172 than rs4236601, as association of rs4236601 with HTG susceptibility disappeared after adjusting for rs17588172, possibly because the minor allele of rs4236601 was too rare in this Korean population to provide sufficient statistical power. This hierarchy of SNP association significance was not consistent with the original GWAS results in which rs1052990 ($p=1.1\times10^{-9}$), which was perfectly correlated with rs17588172, showed a less significant POAG association than rs4236601 ($p=5.0\times10^{-10}$) in a Caucasian population [4].

However, this hierarchy was consistent with a later finding that rs1052990 ($p=3.0\times10^{-4}$) showed a more significant POAG association than rs4236601 ($p=1.4\times10^{-3}$) in another U.S. Caucasian population [8]. Interestingly in a recent study, rs4236601 was the top SNP in association with susceptibility to all POAG, but rs17588172 was the top in association with susceptibility to POAG with early paracentral visual field loss [11].

The statistical power of this study to detect the originally reported association of rs1052990 (OR=1.32) or the perfectly correlated, second SNP rs17588172 was 61% with a minor allele frequency of 21% in our samples. In contrast, the power to detect the original Caucasian association of the first SNP rs4236601 (OR=1.36) was too low (6%), possibly because the minor allele was too rare (0.8%) in Koreans compared with 28% in Caucasians. Therefore, the marginal association of rs4236601 could have been caused by insufficient statistical power.

In summary, in a Korean population, HTG susceptibility and IOP were associated with SNP rs17588172 (and presumably its perfectly correlated SNP rs1052990 as well) in the human *CAV1-CAV2* locus, which appeared to affect *CAV1* and *CAV2* expression. These findings suggest that changes in the expression of *CAV1*, *CAV2*, or both could affect IOP and consequently susceptibility to HTG or POAG with elevated IOP.

APPENDIX 1. DISTRIBUTION OF INTRAOCULAR PRESSURE (IOP).

To access the data, click or select the words "Appendix 1."

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