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Genetic Variants Associated with Adverse Events after Angiotensin-Converting Enzyme Inhibitor Use: Replication after GWAS-Based Discovery

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Purpose: Angiotensin-converting enzyme inhibitors (ACEIs) are medications generally prescribed for patients with high cardiovascular risk; however, they are suboptimally used due to frequent adverse events (AEs). The present study aimed to identify and replicate the genetic variants associated with ACEI-related AEs in the Korean population.

Materials and Methods: A two-stage approach employing genome-wide association study (GWAS)-based discovery and replication through target sequencing was used. In total, 1300 individuals received ACEIs from 2001 to 2007; among these, 228 were selected for GWAS. An additional 336 patients were selected for replication after screening 1186 subjects treated from 2008 to 2018. Candidate genes for target sequencing were selected based on the present GWAS, previous GWASs, and data from the PharmGKB database. Furthermore, association analyses were performed between no AE and AE or cough groups after target sequencing.

Results: Five genes, namely *CRIM1*, *NELL1*, *CACNA1D*, *VOPP1*, and *MYBPC1*, were identified near variants associated with ACEI-related AEs. During target sequencing of 34 candidate genes, six single-nucleotide polymorphisms (SNPs; rs5224, rs8176786, rs10766756, rs561868018, rs4974539, and rs10946364) were replicated for association with all ACEI-related AEs. Four of these SNPs and rs147912715 exhibited associations with ACEI-related cough, whereas four SNPs (rs5224, rs81767786, rs10766756, and rs4974539 near *BDKRB2*, *NELL1*, *NELL1* intron, and *CPN2*, respectively) were significantly associated with both categories of AEs.

Conclusion: Several variants, including novel and known variants, were successfully replicated and found to have associations with ACEI-related AEs. These results provide rare and clinically relevant information for safer use of ACEIs.

Key Words: Pharmacogenomics, safety, drug therapy, antihypertensive agents, heart failure

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INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) are commonly recommended to reduce cardiovascular risk, irrespective of the presence of vascular disease.[1] Agents of this class are also first-line drugs used to control blood pressure.[2,3] ACEIs act on the renin–angiotensin–aldosterone pathway, which exerts potent effects on vascular cells[4] and on the cardiovascular system. Unfortunately, these agents can cause irritating adverse events (AEs), such as cough, particularly in East Asian populations.[5] Due to these AEs, patients may withdraw from the treatment. In practice, prescription and administration of pharmacotherapeutic agents are frequently suboptimal, even in

high-risk patients.[6] Furthermore, medication nonpersistence is associated with increased frequencies of cardiovascular events in individuals with high cardiovascular risk.[7] Therefore, it is crucial to investigate factors influencing ACEI-related AEs.

Before 2010, a targeted approach to identify genetic variants associated with ACEI-related AEs was attempted;[8] however, it had certain limitations. With the introduction of new genetic techniques, many studies have found novel genetic variants in the field of cardiology.[9] Recently, genome-wide association studies (GWASs) have reported several genetic variants associated with AEs: for example, a study by the PREDICTION-ADR consortium on patients of European descent reported AE-associated single-nucleotide polymorphisms (SNPs) in a few novel genes, including *GABRG2*.[10] In addition, several significant SNPs were identified in studies with different designs, such as GWAS discovery, replication, and meta-analysis.[11]

The present study aimed to identify and replicate variants associated with ACEI-related AEs in Korean subjects. Through the study, novel and previously reported variants exhibiting significant association with AEs were identified.

MATERIALS AND METHODS

Study population and study design

This study utilized a two-stage approach comprising GWAS-based discovery and replication using target sequencing in an independent population (Supplementary Fig. 1, only online). Participants included in the discovery set were selected from an early-period database (from March 2001 to December 2007) of the Cardiovascular Genome Center cohort at Yonsei University College of Medicine. Among the patients who visited Severance Hospital for chest symptoms, risk-factor control, or a health checkup, 1300 patients were administered ACEIs and were followed up for more than 6 months. After excluding 1072 patients with insufficient records or late development of AEs (>60 months since the first prescription), 228 patients were selected for GWAS (143 patients with AEs and 85 without AEs).

The replication set for target sequencing comprised participants of the late period (from January 2008 to July 2018). Among 1186 screened cohort subjects, 850 were excluded due to insufficient records or late development of AEs, and 336 patients were selected (212 with AEs and 124 without AEs). No individual was included in both discovery and replication sets. The subjects in the two groups were mutually exclusive. Informed consent was obtained from all participants. The study complied with the latest version (2013) of Declaration of Helsinki. This study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (approval number 4-2017-1225). Clinical data, including age, sex, medical history, laboratory values, and presence of AEs were extracted from the database. AEs were defined as unintended, harmful events attributed to use of the drug. These were evaluated by combining clinical and laboratory AEs.

Discovery of AE-associated genes using GWAS

A CEL file containing raw data of the Axiom Genome-Wide ASI Array chip, which cleared the quality control (QC) test,[12] was used for the GWAS. No patients were excluded from the QC test. After QC of 904333 marker positions, the associations of 668091 marker positions were analyzed. The following criteria were used for marker QC: 1) Hardy-Weinberg equilibrium *p*-value ≥ 1E-07; 2) call rate: case >0.95 and control >0.95; and 3) minor allele frequency: case >0.01 or control >0.01. Using PLINK software,[13] logistic regression analysis based on additive models was conducted to test these associations. This approach was used to identify genes associated with AEs after using ACEIs.

High-throughput sequencing and analyses

Candidate genes included those identified in the present GWAS, genes reported to be associated with AEs in previous GWASs, and genes linked to the biological pathways of ACEIs according to the Pharmacogenomics Knowledge Base (PharmGKB) database. Fine mapping of the coding regions in proximity to the top markers and marker-SNPs was performed for subsequent targeted sequencing.

Target enrichment from blood samples was performed using a Human In-solution Hybrid Capture Kit (Celemics, Seoul, Korea), and paired-end sequencing (2×150 bp) was carried out using an Illumina HiSeq 2500 sequencing platform (Illumina, San Diego, CA, USA). High-throughput data were analyzed using BWA-MEM, Picard (v1.115), SAMtools (v1.1), GATK (v4.0.4.0), and VarScan (v2.4.0) to call single nucleotide variants and insertions/deletions.

Statistical analyses

Continuous variables were tested for normality using the Shapiro-Wilk normality test. Variables with nonnormal distribution are presented as medians (interquartile range). Categorical data are presented as frequencies and percentages. For the case–control study, subjects were classified into case and control subjects, that is, subjects with AEs after ACEI use and subjects without AEs, respectively. To compare clinical characteristics, the chi-square test was performed for categorical variables. Continuous variables with nonnormal distribution were analyzed using the Mann-Whitney test. To test the associations of SNPs and ACEI-related AEs, the chi-square test was used. *P* values <0.05 were considered statistically significant, and all tests were two-sided. Statistical analyses were conducted using commercially available statistical software (R version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

The mean age of the patients in the discovery set for the GWAS (n=228) was 50 years, and 72 patients (31.6%) were female. Clinical characteristics, such as medical history, body mass index, and medications, did not differ between patients with or without AEs (Table 1). The mean age of the patients in the replication set for target sequencing (n=336) was 60 years, and 93 patients (27.7%) were female. Patients with AEs tended to be older than those without AEs (p=0.081). Other clinical characteristics were similar between the two groups (Table 1). Frequent types of AEs were cough (52.4%), hypotension (13.2%), and dizziness (9.6%) (Supplementary Table 1, only online).

GWAS and candidate gene selection for target sequencing

Screening of associated variants using the PLINK software[13] revealed significance in 30 regions ($p<10\times10^{-4}$). Variants in the intergenic region of chromosome 13 ($p=5.21\times10^{-6}$) and intron regions of chromosomes 2 and 11 exhibited the strongest associations. By studying the sections using regional plots of the aforementioned regions, five candidate genes associated with ACEI-related AEs were determined: cysteine rich transmembrane BMP regulator 1 (*CRIM1*), NEL-like protein 1 (*NELL1*), calcium voltage-gated channel subunit alpha1 D (*CACNA1D*), *VOPP1* (VOPP1 WW domain binding protein), and myosin binding protein C1 (*MYBPC1*) (Table 2 and Supplementary Fig. 2, only online). In total, 34 genes, comprising five genes identified in the present GWAS, nine genes reported to be associated with AEs in previous GWAS,[10,14,15] and 20 genes linked to biological pathways of ACEIs were selected for target sequencing (Table 2).

Target sequencing and replication

Next-generation sequencing-based target sequencing was successfully performed, and more than 95% of the captured region showed an average depth of >300× coverage, with a minimum depth of >20× (Supplementary Fig. 3, only online). Among the 405 SNPs analyzed, six (rs5224, rs8176786, rs10766756, rs561868018, rs4974539, and rs10946364) exhibited significant associations with all ACEI-related AEs (Table 3). While analyzing patients with cough and those without AEs, five SNPs (rs5224, rs147912715, rs8176786, rs10766756, and rs4974539) revealed significant associations (Table 3). Four of these (rs5224, rs8176786, rs10766756, and rs4974539) were significant in both categories of AEs; genes containing or located near these SNPs were *BDKRB2*, *NELL1*, *NELL1* intron, and *CPN2*, respectively. Among the SNPs selected from the present and previous GWASs, only the variant in *NELL1* exhibited an association at this stage (Supplementary Table 2, only online).

DISCUSSION

The major findings of this discovery and replication study are as follows: 1) in the discovery stage, five genes in or near variants associated with ACEI-related AEs were found in GWAS (namely *CRIM1*, *NELL1*, *CACNA1D*, *VOPP1*, and *MYBPC1*); 2) among 405 SNPs analyzed via target sequencing, six and five SNPs exhibited associations with all ACEI-related AEs and ACEI-related cough, respectively. Moreover, four SNPs (rs5224, rs8176786, rs10766756, and rs4974539 near *BDKRB2*, *NELL1*, *NELL1* intron, and *CPN2*, respectively) were significantly associated with both categories of AEs. Replication of a known SNP near *BDKRB2* indicated the presence of this variant in diverse ethnicities, whereas that of a new SNP near *NELL1* suggested a novel link to ACEI-related AEs that may be specific to East Asian

Table 1. Clinical Characteristics of the Subjects in the Discovery and Replication Sets according to Experience of AEs after ACEI Use

Characteristics	Discovery set			Replication set		
	No AE (n=85)	AE (n=143)	*p* value	No AE (n=124)	AE (n=212)	*p* value
Age, yr	49 (44–54)	51 (46–56)	0.21	59 (50–67)	61 (53–69)	0.081
Female	22 (25.9)	50 (35.0)	0.15	31 (25.0)	62 (29.2)	0.48
Past history						
Diabetes mellitus	19 (22.4)	28 (19.6)	0.62	32 (25.8)	52 (24.5)	0.79
Hypertension	40 (47.1)	64 (44.8)	0.74	80 (64.5)	132 (62.3)	0.68
Hypercholesterolemia	11 (12.9)	23 (16.1)	0.52	28 (22.6)	34 (16.0)	0.14
Smoking	48 (57.1)*	67 (49.3)*	0.26	77 (62.1)	113 (53.6)	0.13
Body mass index, kg/m^2	24.6 (22.8–26.3)	25.3 (23.2–27.7)	0.12	27.6 (24.7–30.1)	27.2 (23.9–30.5)	0.66
Other medications						
Calcium channel blocker*	21 (24.7)	36 (25.2)	0.94	43 (37.4)†	58 (31.5)†	0.30
Diuretics*	9 (10.6)	17 (11.9)	0.77	26 (22.6)†	53 (28.8)†	0.24
Statin	70 (82.4)	116 (81.1)	0.82	72 (58.1)	136 (64.2)	0.24

ACEI, angiotensin-converting enzyme inhibitor; AE, adverse event.
Data are presented as a median (interquartile range) or number (%).
*Missing data in no AE (n=1) and AE (n=7) groups; †Missing data in no AE (n=9) and AE (n=28) groups.

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Table 2. List of Targeted Sequencing Regions

Gene	Marker SNP	Reference
CRIM1	rs848547	
CACNA1D	rs3774602	
VOPP1	rs1880528	In house GWAS data
NELL1	rs10766756	
MYBPC1	rs11110928	
RBFOX3	rs2061538	
GABRG2	rs77370934	Pharmacogenet Genomics 2017,
SH2B1	rs192613545	PREDICTION-ADR consortium GWAS data
MBOAT1	rs10946364	
KCNIP4	rs1495509)	Pharmacogenomics J 2016, eMERGE network GWAS data
CLASP1	rs62151109	
PDE11A	rs2252726	Pharmacogenomics 2017, Swedish GWAS data
TGFA	rs3771479	
MMP16	rs556450158	
ACE		
AGTR1		
BDKRB1		
BDKRB2		
CPN1		
CPN2		
MME		
TACR2		
XPNPEP1		
NOS1		Knowledge-based candidate genes
PTGER1		
PTGER2		
PTGER3		
PTGER4		
PTGES		
PTGIR		
PTGIS		
SLCO1B1		
ABO		
MCC		

GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.

populations.

A few studies have attempted replication of variants associated with ACEI-related AEs. For example, SNPs in the intron of *KCNIP4* were found to be potential candidates in a study based on the eMERGE network that was conducted mainly in individuals of European descent in the USA.[14] *KCNIP4* is associated with neuronal structures, and variation in this gene may be related to inflammatory pathways in the lung. Meanwhile, a study in a Swedish population reported several related variants, and rs62151109 in *CLASP1* was the most significant variant linked to a biological pathway independent of bradykinin.[15] In this regard, top variants identified previously in studies on non-East Asian patients did not reveal significant associations with AEs in the present study. Although ethnic diversity may have contributed to this difference, the underlying reasons remain unclear.

Genes in or near AE-associated regions identified in the present study included *NELL1*, *BDKRB2*, and *CPN2*. *NELL1* encodes the neural epidermal growth factor-like 1 protein; this gene was studied in bone cells and was found to be upregulated during premature closure of the coronal suture.[16] Subsequently, associations of this gene with Crohn's disease,[17] adipose differentiation,[18] and neural development[19] have been demonstrated in previous studies. Unfortunately, these studies are not sufficient to understand the background of our findings with respect to the correlation of *NELL1* variants and ACEI-related AEs. Interestingly, however, recent studies have reported adverse metabolic responses in triglycerides[20] and QT prolongation[21] after using thiazide diuretics. These results indicate that *NELL1* variants may play a pivotal role in the pharmacogenomic field. In addition, a reported association between *NELL1* and idiopathic pulmonary fibrosis[22] suggests a possible influence of this gene in the lungs where the most common AEs associated with ACEI occur. Further research based on this finding may help in elucidating the effects of *NELL1* variants on lung tissue in the context of ACEI-induced cough.

BDKRB2, another gene associated with ACEI-related AEs in the present study, has been repeatedly reported in previous genotyping studies[23] and systemic reviews.[24] *BDKRB2* encodes receptor of bradykinin, which is known to be major effector of ACEI-induced cough. Notably, a variant in an ACEI-related biological pathway revealed associations in our population similar to those in other reports. *CPN2*, associated with AEs in the present study, encodes a subunit of carboxypeptidase N and is related to kinin levels. Moreover, it regulates peptides, such as complement anaphylatoxins and kinin.[25] Interestingly, a recent study using a nested case–control design and whole exome sequencing on Chinese individuals demonstrated a relationship between *CPN1* and ACEI-induced cough,[26] which is consistent with our results. Although the role of *CPN* in drug metabolism or AEs has not been thoroughly investigated, the present study may provide clinical evidence on the relationship between *CPN* and ACEI-related AEs.

It is difficult to calculate the predictability of AEs based on our results. Estimated risk (odds ratio) in risk allele carriers can be affected by the number of variants or risk alleles in an individual. In further analysis, odds ratios of risk alleles for all AEs ranged up to 2.12, whereas those for cough ranged up to 2.17.

The present study has limitations. Because the subjects of this study were exclusively Korean, generalization of our results to other ethnicities requires caution; however, a variant, such as *BDKRB2*, has been found to exhibit an association with ACEI-related AEs in previous studies on other ethnicities. It would be reasonable to assume that some variants identified in our study may exert similar effects in different populations, whereas others may be population specific. In addition, the study popula-

Table 3. SNPs Significantly Associated with All AEs and Cough after ACEI Use (n=212) in Targeted Sequencing

rs number	Genes in or near associated region	Genomic position	Allele (risk allele)	RAF (control)	RAF (case)	*p* value*	Geno	No AE n (%)	AE n (%)	*p* value†
All AEs										
rs5224	BDKRB2 p.Thr264Thr	chr14:96,707,457	A/G (A)	19.8	15.6	0.170	AA	1 (0.8)	9 (4.3)	**0.003**
							AG	47 (37.9)	48 (22.6)	
							GG	76 (61.3)	155 (73.1)	
rs8176786	NELL1 p.Arg382Trp	chr11:20,959,394	C/T (T)	5.6	10.8	**0.025**	CC	110 (88.7)	167 (78.8)	**0.025**
							CT	14 (11.3)	44 (20.7)	
							TT	0 (0.0)	1 (0.5)	
rs10766756	NELL1 intron	chr11:21,009,736	T/C (C)	18.1	26.2	**0.018**	TT	81 (65.3)	115 (54.2)	**0.018**
							TC	41 (33.1)	83 (39.2)	
							CC	2 (1.6)	14 (6.6)	
rs561868018	TGFA p.Leu9Leu	chr2:70,780,347	G/T (T)	2.0	0.2	**0.028**	GG	119 (96.0)	211 (99.5)	**0.027**
							GT	5 (4.0)	1 (0.5)	
							TT	0 (0.0)	0 (0.0)	
rs4974539	CPN2 p.Gln509Arg	chr3:194,061,906	T/C (T)	13.7	17.0	0.270	TT	2 (1.6)	0 (0.0)	**0.025**
							TC	30 (24.2)	72 (34.0)	
							CC	92 (74.2)	140 (66.0)	
rs10946364	MBOAT1 intron	chr6:20,177,222	T/A (A)	44.4	50.2	0.150	TT	34 (27.4)	54 (25.5)	**0.042**
							TA	70 (56.5)	103 (48.6)	
							AA	20 (16.1)	55 (25.9)	
Cough										
rs5224	BDKRB2 p.Thr264Thr	chr14:96,707,457	A/G (A)	19.8	18.2	0.640	AA	1 (0.8)	7 (6.3)	**0.007**
							AG	47 (37.9)	26 (23.4)	
							GG	76 (61.3)	78 (70.3)	
rs147912715	ACE p.Gln59Gln	chr17:61,554,632	G/A (A)	6.0	0.9	**0.003**	GG	110 (88.7)	109 (98.2)	**0.003**
							GA	13 (10.5)	2 (1.8)	
							AA	1 (0.8)	0 (0.0)	
rs8176786	NELL1 p.Arg382Trp	chr11:20,959,394	C/T (T)	5.6	10.9	**0.043**	CC	110 (88.7)	87 (78.4)	**0.035**
							CT	14 (11.3)	24 (21.6)	
							TT	0 (0.0)	0 (0.0)	
rs10766756	NELL1 intron	chr11:21,009,736	T/C (C)	18.1	28.2	**0.015**	TT	81 (65.3)	55 (49.6)	**0.015**
							TC	41 (33.1)	50 (45.1)	
							CC	2 (1.6)	6 (5.3)	
rs4974539	CPN2 p.Gln509*	chr3:194,061,907	G/A (A)	33.9	40.5	0.180	GG	49 (39.5)	40 (36.0)	**0.040**
							GA	66 (53.2)	53 (47.8)	
							AA	9 (7.3)	18 (16.2)	

ACEI, angiotensin-converting enzyme inhibitor; AE: adverse event; Geno, genotype; RAF, risk allele frequency; SNP, single-nucleotide polymorphism.
Bold values denote statistical significance at $p<0.05$.
*p values were obtained by comparing allele frequencies between no AE and AE or cough groups; †Represents the lowest p value in the association between no AE and AE or cough groups under three gene models (codominant, dominant, recessive).

tion was relatively small. We cannot rule out the potential that more genetic variants could have exhibited significant associations with ACEI-related AEs in a larger scale analysis.

In conclusion, through a two-stage approach using GWAS and target sequencing of candidate genes, genetic variants in or near *BDKRB2*, *NELL1*, and *CPN2* were found to be associated with ACEI-related AEs, such as cough. Replication of known SNPs suggest effects of this variant in diverse ethnicities, whereas that of a new SNP may indicate associations presumably specific to East Asians. The results of the present study provide rare and valuable information for the safer use of ACEIs in clinical practice.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

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