Philippine Journal of Science
149 (1): 35-41, March 2020
ISSN 0031 - 7683
Date Received: 30 Jul 2019

BAG6 Variant rs805303 is Nominally Associated with ACEi-induced Cough Among Filipinos

Paul Ferdinand M. Reganit[1], **Jose B. Nevado Jr.**[2], **Eva Maria C. Cutiongco – de la Paz**[2,3], **Jezreel L. Taquiso**[1], **Aimee Yvonne Criselle L. Aman**[2,3], **Elmer Jasper B. Llanes**[1], **Jose Donato A. Magno**[1], **Deborah Ignacia D. Ona**[1], **Felix Eduardo R. Punzalan**[1], **Lourdes Ella G. Santos**[1], **Richard Henry P. Tiongco II**[1], **Jaime M. Aherrera**[1], **Lauro L. Abrahan IV**[1], **Charlene F. Agustin**[1], **Adrian John P. Bejarin**[2,3], and **Rody G. Sy**[1]*

[1]Department of Medicine, Philippine General Hospital
[2]Institute of Human Genetics, National Institutes of Health
University of the Philippines Manila, Ermita, Manila, Philippines
[3]Philippine Genome Center, University of the Philippines Diliman
Diliman, Quezon City, Philippines

Cough is a common side effect of angiotensin converting enzyme inhibitor (ACEi) therapy. The incidence of ACEi-induced cough has been shown to correlate with genetic variation among different populations. This study aimed to determine the association of candidate genetic polymorphisms with ACEi-induced cough among Filipinos. Two hundred twenty (220) participants on ACEi therapy pressure-lowering in an unmatched case-control study (82 cases with ACEi-induced cough and 138 controls). Genomic DNA samples were extracted and genotyped for selected genetic variants. The association of genetic variants and clinical factors with ACEi-induced cough was determined using regression analyses. Univariate logistic regression showed that the *BAG6* variant rs805303 is nominally associated with ACEi-induced cough among Filipinos, at a per-comparison error rate (PCER) of 0.05 (OR 2.10, $p = 0.016$). The association of the variant with ACEi cough was statistically significant after multiple regression analysis (adjusted OR 2.09, $p = 0.022$) while adjusting for confounding clinical factors (sex, alcohol intake, and diastolic blood pressure). Further studies are needed to validate these findings.

Keywords: angiotensin converting enzyme inhibitor, *BAG6*, cough, Filipino, rs805303

INTRODUCTION

ACEis are among the first-line therapeutic agents used in the management of hypertension. The blood pressure-lowering effect of this class of drugs has been well documented along with risk-reduction and survival benefits extending to heart failure and myocardial infarction patients (Hall *et al.* 1997). These properties of ACEis highlight its importance in the prevention of cardiovascular disease.

*Senior Corresponding Author: rodysymd@gmail.com

Despite proven effectiveness, ACEis have been underutilized due to concerns of adverse effects, the most common of which is persistent dry cough (Khalil *et al.* 2001). The mechanism behind ACEi-induced cough remains uncertain (Yilmaz 2019). However, the most implicated cause is the accumulation of bradykinin and substance P – otherwise degraded by angiotensin-converting enzyme – in the respiratory tracts, which then stimulates vagal afferents that incite the cough reflex. The cessation of the offending agent is found to be the only uniformly effective intervention to resolve cough (Dicpinigaitis 2006).

Regardless of etiology, there has been conflicting data on the incidence of cough. A meta-analysis of 125 studies by Bangalore *et al.* (2010) reported the incidence of ACEi-induced cough to be ranging from 5–15%. Incidences have been known to vary with predisposing conditions such as age, gender, smoking history, and ethnicity (Morimoto *et al.* 2004). Asian populations were reported to have higher incidences compared to Caucasians (Woo *et al.* 1995; Morimoto *et al.* 2004; Ng and Goh 2014). Among Filipinos, the incidence of ACEI-induced cough is 17% (Tumanan-Mendoza *et al.* 2007).

Genotyping may offer a more reliable means of predicting the occurrence of ACEi-induced cough with respect to ethnicity. Bradykinin (B2) receptor (*BDKRB2*) polymorphisms were implicated among Caucasians and Asians (Mukae *et al.* 2000; Mas *et al.* 2011). Specifically, among Caucasians, genetic polymorphisms in the histo-blood group ABO system transferase (*ABO*) (Mas *et al.* 2011) and potassium voltage-gated channel interacting protein 4 (*KCNIP4*) genes (Mosley *et al.* 2016) have been associated with susceptibility to ACEi-induced cough. On the other hand, an insertion/deletion polymorphism in *ACE* was involved in ACEi-induced cough among Asians but not among Caucasians (Nishio *et al.* 2011; Li *et al.* 2012). These findings reinforce the idea that genetic determinants may be good predictors for the development of ACEi-induced cough and provide a basis for genetic studies in different ethnic populations. However, these studies were done predominantly on cohorts without a clear indication of the significant representation of the Filipino population.

Therefore, this study aims to determine the association of candidate genetic variants to ACEI-induced cough among Filipinos. The variants included in this study include those with known association with hypertension, ACE inhibitor response, and ACE inhibitor-induced cough. Findings from this study can potentially add a genetic component to the understanding of ACEi-induced cough pathophysiology.

METHODOLOGY

Study Design and Enrollment of Participants

This is an unmatched case-control study investigating the association of candidate variants with ACEi-induced cough among Filipinos. Volunteer participants were enrolled from the Philippine General Hospital, different communities in Metro Manila, and private clinics from July 2013 to March 2017. All procedures have been reviewed in compliance with ethical standards of the University of the Philippines Manila – Research Ethics Board (Study protocol code UPMREB-2012-0186-NIH) on 04 Oct 2012.

Participants were included if they satisfied the following criteria: a) age 18 or above, b) of Filipino descent up to the 3rd degree of consanguinity, c) have been treated or are undergoing current treatment using ACEi, and d) able to independently provide consent. Participants were excluded if they had any of the following conditions at the time of enrollment: decompensated heart failure, decompensated chronic lung disease, decompensated chronic liver disease, end-stage renal disease, active malignancy, secondary hypertension, secondary dyslipidemia, pregnancy, and related to other enrolled participants up to the 3rd degree of consanguinity.

Cases are those with ACEi-induced cough, defined as one or more of the following: a) dry cough occurring within 6 mo after beginning of treatment with lack of constitutional or infectious signs and symptoms such as fever, rhinorrhea, or myalgia; b) cough diagnosed as ACE inhibitor-induced with the medication discontinued; and c) cough disappearing or had been alleviated with withdrawal of ACEi medication/s. Controls are those who took ACEi for at least 5 mo, with no reports of cough consistent with ACEi-induced cough.

Clinical Data Collection

Demographic data and clinical characteristics of the participants (co-morbidities and diagnostics) were obtained from their patient records and from verbal interviews. Lipid profile and serum creatinine results were obtained and recorded.

Customization of Genotyping Chip

A customized GoldenGate Genotyping (GGGT) beadchip (Illumina, Inc., San Diego, CA, USA) was designed in 2012 using candidate SNPs from both coding and noncoding regions – including SNPs which have shown evidence of association with hypertension, ACEi response, and ACEI-induced cough (Appendix Table I). These were selected after an extensive search was done in the following databases: PharmGKB (Pharmacogenomics Knowledgebase) database, NHGRI GWAS Catalog (National Human Genome Research Institute Genome-wide Association Study), and PubMED and patent databases (*e.g.* Patentscope and Espacenet) where risk and protective ORs were provided. While the microarray platform used is optimally designed to detect bi-allelic SNPs, the study included tri- or quad-allelic SNPs in cases where the variants have been correlated with significant clinical outcomes. The selected SNPs were submitted to Illumina, Inc. for scoring to determine the suitability of the SNPs to discriminate genetic variants, as well as estimate their specificity.

DNA Extraction and Quantification

DNA was extracted using the QiaAmp DNA minikit, following the spin protocol for blood buffy coat specified in the manufacturer's instruction manual. DNA was quantified using a spectrometer at 260 nm and stored at – 20 °C until use. All DNA samples had A-260 nm / A-280 nm value above 1.80.

Genotyping

Customized genotyping of candidate SNPs was performed using a DNA microarray following the GGGT protocol specified in the manufacturer's manual. After microarray processing, the beadchip was imaged on the HiScan System and data from these images were analyzed using GenomeStudio software.

To ensure high-quality data, GenomeStudio 2.0 and PLINK version 2.05.10 were used to identify and remove participants and markers that may lead to false-positive and false-negative associations. Genotype data from participants with call rates > 95% after evaluation with GenomeStudio and with individual missingness < 0.05 (missingness test) in PLINK were included. The following thresholds were used for the genotype data: minor allele frequency of 0.01 (frequency test), genotype missingness of 0.05 (missingness test), and Hardy-Weinberg Equilibrium (HWE) of controls of $p < 0.001$ (HWE test).

Data Analyses

Determination of possible mode of inheritance. Chi-square tests were performed to assess for significant differences among variants of interest, *i.e.* allelic and genotypic association tests (additive, dominant, and recessive models). These models are identified based on the distribution of the case and control genotypes. Tests for allelic and genotypic associations were done setting the cut-off at the PCER of 0.05 to avoid exclusion of SNPs that may be restricted by Bonferroni correction.

Logistic regression analysis. Upon determination of models, the genotypes are recoded according to the significant model for univariate analysis in Stata. Univariate logistic regression analysis was done to determine the association of SNPs with ACEi-induced cough, with the cut-off *p*-value set at 0.05. Multiple logistic regression was performed to include possible confounding clinical factors.

RESULTS

A total of 220 participants were considered in the study. After quality control, two participants were removed due to a < 95% call rate in GenomeStudio. This leaves 218 participants (80 cases, 138 controls) for further analyses (Figure 1A). Quality control was also applied for the 102 candidate SNPs, and 74 SNPs passed the criteria (Appendix Table II). There were no variants noted to be associated with ACE inhibitor-induced cough using the Bonferroni-adjusted α of 0.00068. However, at PCER of 0.05 after the genotypic association analysis of candidate SNPs, one SNP was nominally associated and underwent further analysis (Figure 1B).

Those identified with ACEi-induced cough are compared with controls in terms of clinical characteristics (Table 1) and laboratory profiles (Table 2). There is no observed age difference between the two groups. Cases present with higher diastolic blood pressures and poorer kidney function tests. There is a greater proportion of males and alcoholic beverage drinkers that do not present with cough.

After genotypic association analysis, only rs805303 is found to have a nominally significant association with ACEi cough on $p < 0.05$ under a dominant model with allele A as the risk allele (AA and AG *vs.* GG; crude OR 2.10; CI 1.15, 3.83; *p*-value 0.016).

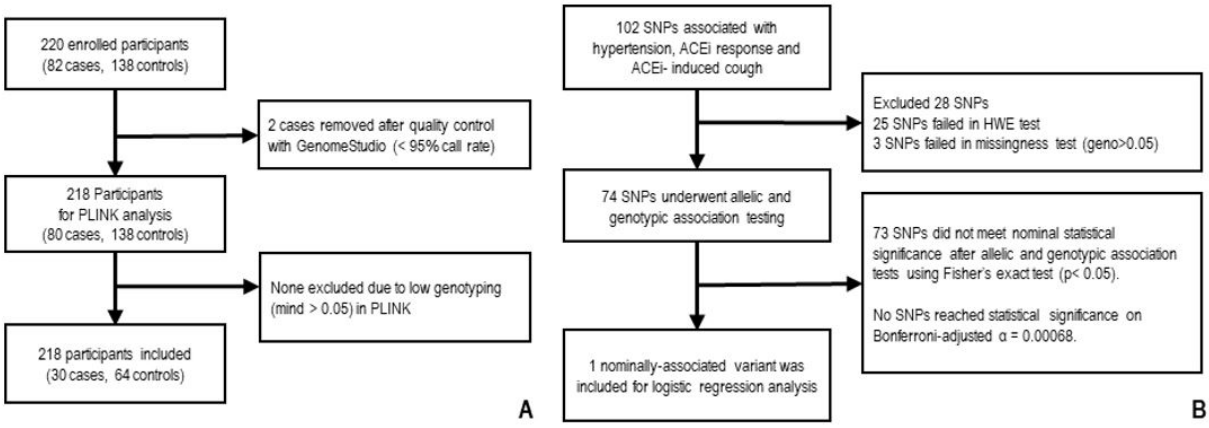

Figure 1. Overview of data processing and analysis. Abbreviations: mind – individual missingness; SNP – single nucleotide polymorphism; HWE – Hardy-Weinberg equilibrium; geno – genotypic missingness.

Table 1. Clinical characteristics of study participants.

Clinical factors	Cases (n = 80)	Controls (n = 138)	*p* -value*
Age, ≥ 60 years old	42.50	39.13	0.625
Sex, male	40.00	60.14	0.004
Co-morbidities, %			
Hypertension	92.50	84.06	0.073
Abnormal BMI, ≥ 25 kg/m^2	55.00	46.09	0.211
Type 2 diabetes mellitus	27.50	40.58	0.052
Ischemic heart disease	70.00	68.12	0.772
Dyslipidemia	98.75	99.28	0.695
Stroke	7.50	13.04	0.208
Blood pressure (SD)**			
Systolic BP	130 (17.48)	126.88 (16.79)	0.195
Diastolic BP	81.38 (11.56)	78.01 (10.77)	0.031
Ever smoked, %	40.00	48.55	0.222
Ever drank alcohol, %	47.50	63.04	0.025

Abbreviations: SD – standard deviation; BMI – body mass index; BP – blood pressure; eGFR – estimated glomerular filtration rate; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol
*Statistical significance set at p = 0.05 using chi-square test
**Statistical significance set at *p* = 0.05 using Student's t-test

Table 2. Laboratory profile of study participants.

Clinical factors	Cases (n = 80)	Controls (n = 138)	*p*-value
Creatinine, mg/dl	0.94 (0.32)	0.93 (0.31)	0.722
eGFR, ml/min*	81.32 (23.94)	88.26 (25.40)	0.049
Total cholesterol, mg/dl	169.44 (42.22)	177.68 (55.41)	0.252
Triglycerides, mg/dl	114.99 (53.88)	128.91 (86.79)	0.197
HDL, mg/dl	48.39 (11.10)	46.23 (14.94)	0.262
LDL, mg/dl	103.15 (36.07)	106.41 (46.42)	0.589

Abbreviations: eGFR – estimated glomerular filtration rate; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol
*Statistical significance set at *p* = 0.05 using Student's t-test

The association of the SNP remained after adjusting for clinical variables that may have confounding effects on the association being tested, *i.e.* clinical variables with a significant difference between the two groups, $p < 0.05$: sex, alcohol use, and diastolic blood pressure. The odds ratio after adjusting for these variables is 2.09 (95% CI 1.11, 3.94; *p*-value 0.022). The full model is shown in Table 3.

Table 3. Association of different factors after multiple regression analysis.

Variable	Adjusted OR (95% CI)	*p*-value
rs805303 (AA and AG *vs.* GG)	2.09 (1.11, 3.94)	0.022
Male sex	0.46 (0.22, 0.98)	0.044
Ever used alcohol	0.79 (0.37, 1.66)	0.516
Diastolic blood pressure	1.03 (1.00, 1.06)	0.039

Abbreviations: OR – odds ratio; CI – confidence interval; eGFR – estimated glomerular filtration rate

DISCUSSION

Cough is a common side effect of ACEi therapy that causes significant discomfort among patients and leads to poor treatment compliance. Studies on genetic polymorphisms can be useful in producing new insight into the mechanism behind this adverse effect and in possibly determining susceptibility. This study investigated candidate variants and their association with ACEi-induced cough among Filipinos on the background of clinical correlates. Logistic regression analysis was used to identify significant factors. The presence of the risk allele (A) for rs805303 confers 2.13 times increased odds of developing ACEi-coughing. The risk allele (A) frequency of the variant among the study population is 40%. Among clinical factors, both male sex and diabetes mellitus type 2 have an inverse association with ACEi-induced cough.

The SNP rs805303 is an intron variant of BCL2-associated athanogene 6 *(BAG6)* gene located on the short arm of chromosome 6. BAG6 protein is involved in several cellular processes – including apoptosis, gene regulation, protein synthesis, protein quality control, and protein degradation (Binici and Koch 2014). It is uncertain whether the variant rs805303 has regulatory or functional implications for *BAG6.* In expression studies, the AA genotype of rs805303 negatively affects the expression of *BAG6* by decreasing it in the coronary and tibial arteries, the aorta, the sigmoid colon, and the esophagus. Aside from *BAG6*, the variant may also be affecting the expression of other nearby genes such as lymphocyte antigen 6 family member G5B and G5C (*LY6G5B*, *LY6G5C*) in 37 tissues and major histocompatibility complex, class II, DR beta 5 (*HLA-DRB5*) in 26 tissues (Lonsdale *et al.* 2013).

Although this variant has not yet been previously associated with ACEi-induced cough, it has been linked in the development of hypertension in GWAS involving European, African-American, Hispanic, and South Asian populations (Surendran *et al.* 2016; Wain *et al.* 2017). The A allele is associated with a 0.23 mmHg decrease in diastolic blood pressure among individuals of European ancestry (Wain *et al.* 2017).

The commonly suspected mechanism behind the ACEi-induced cough is the accumulation of protrusive substances such as bradykinin and substance P that are normally degraded by the enzyme. ACE exhibits most functions in the cell membrane; however, it can also be found in the endoplasmic reticulum where it participates in MHC class I antigen processing (Zhao *et al.* 2017). Interestingly, BAG6 acts as a chaperone protein taking part in MHC class I antigen presentation and regulation of the supply of antigenic peptides (Binici and Koch 2014). Whether the functions of BAG6 can correlate with ACE

activity remains to be investigated. The diverse functions of BAG6 in protein synthesis and degradation may be enough to incite future assumptions.

Based on previous studies, genetic polymorphisms that could potentially be used to predict the occurrence of ACEi-induced cough are the *BDKRB2* variant rs8016905 and *ABO* variant rs495828 (Mas *et al.* 2011). However, this study failed to show a significant association of rs8016905 (allelic association test OR 1.12, CI 0.73, 1.72; $p = 0.611$) and rs495828 (allelic association test OR 1.27, CI 0.81, 1.99; $p = 0.30$). Two SNPs of ACE that are associated with ACEi-induced cough in other studies, rs4459610 and rs4267385, were included in the initial list of SNPs for analysis but were removed during quality control using PLINK. This may be reflective of the differences in genetic profile between ethnic groups, and that findings from studies done predominantly on Caucasian cohorts cannot be readily applied to the Filipino population. However, it is still recommended that a study involving a larger population be done to confirm these results.

This study also showed that male sex is associated with less likelihood of developing cough with ACEi use. This finding is consistent with an early post-marketing surveillance study of 47,000 perindopril users conducted in France (Speirs *et al.* 1998) and a retrospective cohort study done in the United States among patients of diverse ethnicities prescribed with ACE inhibitors (Morimoto *et al.* 2004). The reason behind the gender difference remains obscure as mechanism of ACEi-induced cough also remains unclear. It was previously speculated that sex hormones may influence the effect of ACEi on the sensitivity of the airways. However, there was no difference in cough incidence among women regardless of menopausal status, which implies a lack of sex hormonal influence on ACEi-induced cough – contradicting the previous assumption (Os *et al.* 1994).

Alcohol use and diastolic blood pressure were two possible confounders in this study. It is possible that alcohol use may also be associated with the male sex. Diastolic blood pressure, on the other hand, was included in the analysis because of its possible confounding effect, as the variant is also known to affect diastolic blood pressure among Caucasians (Wain *et al.* 2017). The SNP retained its significance after adjusting for these confounding factors.

LIMITATIONS AND RECOMMENDATIONS

The study suggests an association of the *BAG6* variant rs805303 in the occurrence of ACEi-induced cough. There is a need to validate the results of this study through a replication study, using an independent data set to ensure that the result is not a false-positive association. The predictive value of the variant could not be assessed due to the inherent limitations of a case-control design, as case-control designs are usually done to determine the association of the variant with the phenotype. It is, thus, suggested that future studies – such as a prospective cohort study or a nested case-cohort study – investigate the utility of this genetic component in predicting susceptibility to ACEi- induced cough to complement clinical indicators. The association of the variant to other ACEi adverse effects could also be explored. The functional role of *BAG6* expression to ACE activity or to the development of cough can also be further investigated.

CONCLUSION

Genetics may play a major role in the occurrence of ACEi-induced cough as evidenced in some populations. Among Filipinos, genetic polymorphism of *BAG6* – rs805303 – may be associated with ACEi-induced cough. Further studies are needed to demonstrate the utility of pharmacogenetic approaches in the identification of patients susceptible to ACEi-induced cough.

ACKNOWLEDGMENTS

This study was funded by the Philippine Council for Health Research and Development of the Department of Science and Technology through the GIA Program. We thank Dr. Ivy Melgarejo, Dr. Winston Li, and Dr. Julius Gatmaitan, Virginia dela Cruz, Ralph Duhaylungsod, Romer Guerbo, Michael Hernandez, Hazel Joyohoy, Jessa Lu, Babylyn Pernites, Angela Ramones, Keith Serrano, Jonathan Terante, Ralph Torres, and Pauline Villanueva for recruiting patients. We also thank Chembie Almazar, Jessica Biwang, Reynand Canoy, Marjo Mendoza, Roemel Luna, Jody Melegrito, and Kate Wad-Asen of the Microarray Unit of the Institute of Human Genetics, National Institutes of Health for assistance in genotyping; and Prof. Cynthia Cordero and Prof. Kim Cochon for help with statistical analysis. We also thank Dr. Alvin Lirio, Dr. Jan Cyril Hiwatig, Dr. April Catibog, and Dr. Samantha Llamzon for proofreading and editing this manuscript.

STATEMENT ON CONFLICT OF INTEREST

The authors declare no conflicts of interest.

NOTES ON APPENDICES

The complete appendices section of the study is accessible at http://philjournsci.dost.gov.ph

REFERENCES

BANGALORE S, KUMAR S, MESSERLI FH. 2010. Angiotensin-converting enzyme inhibitor associated cough: deceptive information from the Physicians' Desk Reference. The American Journal of Medicine 123(11): 1016–1030.

BINICI J, KOCH J. 2014. BAG-6, a jack of all trades in health and disease. Cellular and molecular life sciences 71(10): 1829–1837.

DICPINIGAITIS PV. 2006. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest 129(1): 169S–173S.

HALL AS, MURRAY GD, BALL SG, AIREX Study Investigators. 1997. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. The Lancet 349(9064): 1493–1497.

KHALIL ME, BASHER AW, BROWN EJ JR, AL-HADDAD IA. 2001. A remarkable medical story: benefits of angiotensin-converting enzyme inhibitors in cardiac patients. 2001. J Am Coll Cardiol 37(7): 1757–1764.

LI YF, ZHU XM, LIU F, XIAO CS, BIAN YF, LI H, CAI J, …, YANG XC. 2012. Angiotensin-converting enzyme (ACE) gene insertion/deletion polymorphism and ACE inhibitor-related cough: a meta-analysis. PloS one 7(6): e37396.

LONSDALE J, THOMAS J, SALVATORE M, PHILLIPS R, LO E, SHAD S, HASZ R, …, FOSTER B. 2013. The genotype-tissue expression (GTEx) project. Nature Genetics 45(6): 580.

MAS S, GASSÒ P, ÁLVAREZ S, ORTIZ J, SOTOCA JM, FRANCINO A, …, LAFUENTE A. 2011. Pharmacogenetic predictors of angiotensin-converting enzyme inhibitor-induced cough: the role of ACE, ABO, and BDKRB2 genes. Pharmacogenetics and Genomics 21(9): 531–538.

MORIMOTO T, GANDHI TK, FISKIO JM, SEGER AC, SO JW, COOK EF, …, BATES DW. 2004. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. Journal of Evaluation in Clinical Practice 10(4): 499–509.

MOSLEY JD, SHAFFER CM, VAN DRIEST SL, WEEKE PE, WELLS QS, KARNES JH, …, CRAWFORD DC. 2016. A genome-wide association study identifies variants in KCNIP4 associated with ACE inhibitor-induced cough. The Pharmacogenomics Journal 16(3): 231.

MUKAE S, AOKI S, ITOH S, IWATA T, UEDA H, KATAGIRI T. 2000. Bradykinin B2 receptor gene polymorphism is associated with angiotensin-converting enzyme inhibitor-related cough. Hypertension 36(1): 127–131.

NG LP, GOH PS. 2014. Incidence of discontinuation of angiotensin-converting enzyme inhibitors due to cough, in a primary healthcare centre in Singapore. Singapore Medical Journal 55(3): 146.

NISHIO K, KASHIKI S, TACHIBANA H, KOBAYASHI Y. 2011. Angiotensin-converting enzyme and bradykinin gene polymorphisms and cough: a meta-analysis. World Journal of Cardiology 3(10): 329.

OS I, BRATLAND B, DAHLÖF B, GISHOLT K, SYVERTSEN JO, TRETLI S. 1994. Female preponderance for lisinopril-induced cough in hypertension. American Journal of Hypertension 7(11): 1012–1015.

SPEIRS C, WAGNIART F, POGGI L. 1998. Perindopril postmarketing surveillance: a 12 month study in 47 351 hypertensive patients. British Journal of Clinical Pharmacology 46(1): 63–70.

SURENDRAN P, DRENOS F, YOUNG R, WARREN H, COOK JP, MANNING AK, … STALEY JR. 2016. Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. Nature Genetics 48(10): 1151.

TUMANAN-MENDOZA BA, DANS AL, VILLACIN LL, MENDOZA VL, RELLAMA-BLACK S, BARTOLOME M, …, VALDEZ J. 2007. Dechallenge and rechallenge method showed different incidences of cough among four ACE-Is. Journal of Clinical Epidemiology 60(6): 547–553.

WAIN LV, VAEZ A, JANSEN R, JOEHANES R, VAN DER MOST PJ, ERZURUMLUOGLU AM, …, VERWOERT GC. 2017. Novel blood pressure locus and gene discovery using genome-wide association study and expression data sets from blood and the kidney. Hypertension 70(3): e4–e19.

WOO KS, NORRIS RM, NICHOLLS G. 1995. Racial difference in incidence of cough with angiotensin-converting enzyme inhibitors (a tale of two cities). The American Journal of Cardiology 75(14): 967–968.

YILMAZ İ. 2019. Angiotensin-Converting Enzyme Inhibitors Induce Cough. Turkish Thoracic Journal 20(1): 36.

ZHAO T, BERNSTEIN KE, FANG J, SHEN XZ. 2017. Angiotensin-converting enzyme affects the presentation of MHC class II antigens. Laboratory Investigation 97(7): 764