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ORIGINAL ARTICLE

Single Nucleotide Variants in the Angiotensin II Receptor Type 2 and its Association With Arterial Hypertension: A Systematic Review

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Abstract

Background: Arterial hypertension (AH) is a chronic disease distributed worldwide, and the Angiotensin II receptor type 2 (AGTR2) gene variants are potential DNA markers to study in association with this disease.

Objective: This systematic review (SR) aimed to identify single nucleotide variants in the AGTR2 gene as genetic markers associated with AH.

Methods: The electronic databases MEDLINE, Web of Science, SCOPUS, Cochrane Central Register, EMBASE, SciELO, and TripDatabase were searched for research up to September 2023. Case-control studies with DNA variants in the AGTR2 gene associated with AH as the outcome were included in the review. Boolean connectors and keywords were used according to each database.

Results: After diverse rounds of scrutiny, a final number of eight articles were included for 8911 participants, comprising 5451 cases and 3460 controls. A significant proportion of the selected studies were performed in Asian populations and were heterogeneous. Although 238 variants were shown in the gnomAD v2.1.1 database for September 2023, only six variants were identified in all the analyzed studies.

Conclusions: The results obtained were not conclusive that a specific variant located in the AGTR2 gene has a strong association with AH. The study of this gene re-emerged last year as an essential target to investigate due to its participation in the development of agonist therapy to treat mild COVID-19 cases. Future studies with better statistical power are desirable to replicate the primary findings.

Keywords: Genetic Association Studies; Hypertension; Angiotensin II Type 2 Receptor.

Introduction

Arterial hypertension (AH) is a chronic disease distributed worldwide.[1,2] In terms of costs, it was calculated in ten years at close to a billion dollars for 2009.[3] An increase in blood pressure leads to cardiovascular comorbidities in diverse organs, such as the brain, kidney, and heart,[4] which may contribute to the development of metabolic alterations and related traits in later stages of life.[5] This disease is considered multifactorial.[6,7] However, a significant part of the genetic component remains elusive even in European and US populations, which are the most studied.[8] Regarding the renin-angiotensin system (RAS), angiotensin II leads to vasodilation and natriuresis by union with angiotensin II receptor type 2 (*AGTR2*),[9] which is proposed as part of a protective branch in the RAS.

The *AGTR2* protein has been associated with anti-apoptosis and antioxidative stress function.[10] The receptor activation induces vasorelaxation and has opposite effects on vasodilatation compared to the

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Central Illustration: Single Nucleotide Variants in the Angiotensin II Receptor Type 2 and its Association With Arterial Hypertension: A Systematic Review

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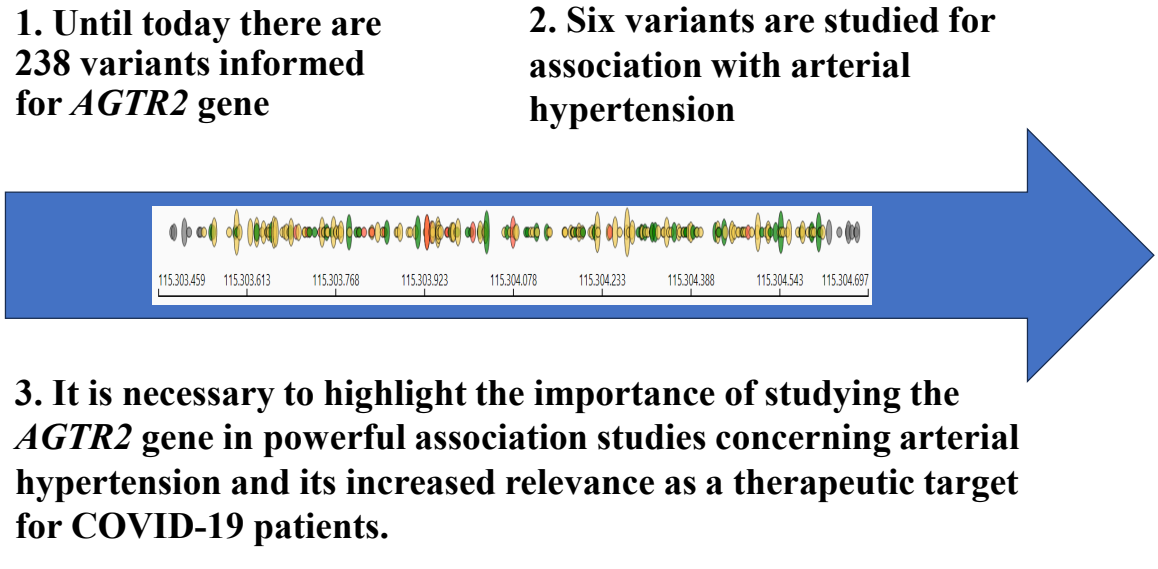

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The importance of studying AGTR2 in relation to AH. AGTR2: Angiotensin II receptor type 2

AGTR1 receptor. *AGTR2* stimulated experimentally increases ACE2 expression; therefore, it also increases Ang-(1-7) and Ang-(1-9) expression (both *AGTR2* agonists), even with a reduction of substrates AngI and AngII in the RAS. Based on these results, *AGTR2* is proposed as a critical negative regulator for blood pressure.[11] Up to September 2023, there were almost 238 variants identified in the genome aggregation database (gnomAD) for *AGTR2*, and a significant proportion of these variants had been published for less than ten years, with many of them as part of a genetic consortium. In 2003, the first association of *AGTR2* with AH was published by a Chinese group.[12] Later, diverse groups, predominantly from Asia, obtained heterogeneous results concerning the association of this gene with AH. In the last three years, this gene has been gaining attention because it was proposed that the receptor could act as an agonist in treating COVID-19 cases[13] and was associated with type 2 diabetes in a pilot study.[14] This systematic review (SR) aims to identify DNA variants in the *AGTR2* gene as genetic markers associated with hypertension.

Methods

The study followed the PRISMA guidelines for SRs. The protocol was included in the PROSPERO Register: CRD42020153420. Two researchers independently performed the literature review. This involved first reviewing the databases, abstracts, and related articles. This was followed by a second round examining the selected articles in full text and discussing the results. When there was no agreement between the two researchers, a third researcher addressed the controversy and contacted the corresponding authors when clarification was required. Additionally, the results were analyzed to assess the risk of bias by implementing the "Risk of bias in non-randomized studies of interventions" and the "Research Triangle Institute item bank for assessment of the risk of bias and precision for observational studies of interventions or exposures" tools.

The information in the database included the identification number of each study, study title, name of the first author, publication year, journal name, the language of publication, country of the population included in the study, sample size, variant identified, Hardy-Weinberg equilibrium (HWE) value for the control group, genotype and allele frequencies, statistical model, the laboratory technique used for genotyping, and characteristics of the study participants.

The searched databases included MEDLINE (https://www.nlm.nih.gov/bsd/medline.html), Web of Science

(www.webofknowledge.com), SCOPUS (https://www.scopus.com), Cochrane Central Register (https://www.cochranelibrary.com), EMBASE (https://www.embase.com), SciELO (https://www.scielo.org) and TripDatabase (https://www.tripdatabase.com). The following keywords were used: (("AH " OR "essential hypertension" OR "hypertension") AND ("AGTR2" OR "Angiotensin II receptor type 2" OR "AGTR2 gene" OR "angiotensin II type 2 receptor") AND ("variant" OR "SNP" OR "single nucleotide polymorphism" OR "polymorphism")) according to each database selected.

The inclusion criteria were based on the "PICOS principle": P (participants), participants with T2D and healthy controls; I (intervention), participants where genotypic and associated clinical data was informed; C (comparison) case-control groups and subgroup analysis; O (outcomes), allelic frequencies and results of association analysis; and S (study design) observational study. This study included articles about single nucleotide variants in the *AGTR2* gene and its association with AH as described above and in the English language.

The following were excluded: case reports, case series, family-based studies, clinical trials (protocols included), narrative reviews, book chapters, conference abstracts, opinion articles, and letters to the editor. Studies without clear information about genotyping and statistical analysis, which were not obtained after direct contact with the authors and editorial, were also excluded.

Results

A flowchart of the selection strategy followed in this SR is shown in **Figure** 1. A total of eight case-control articles were included for analysis. **Table** S1 shows the specific country, ethnic origin, city, and the number of samples per gender included in this SR. A significant proportion of the studies were conducted in Asia; there were four from China, two from Japan, and one each from Tunisia and Serbia. A significant proportion of them was recruited from tertiary health centers. The number of studies selected per year was low between 2002 and 2014. It was divided into two clusters; four articles were published between 2002 and 2007 and four between 2012 and 2014. To date, 8,911 individuals have been studied, divided into 5451 cases and 3460 controls, concentrated in Asian populations. All included articles were published in English and were case-control designs. Although 238 variants were shown in the gnomAD v2.1.1 database

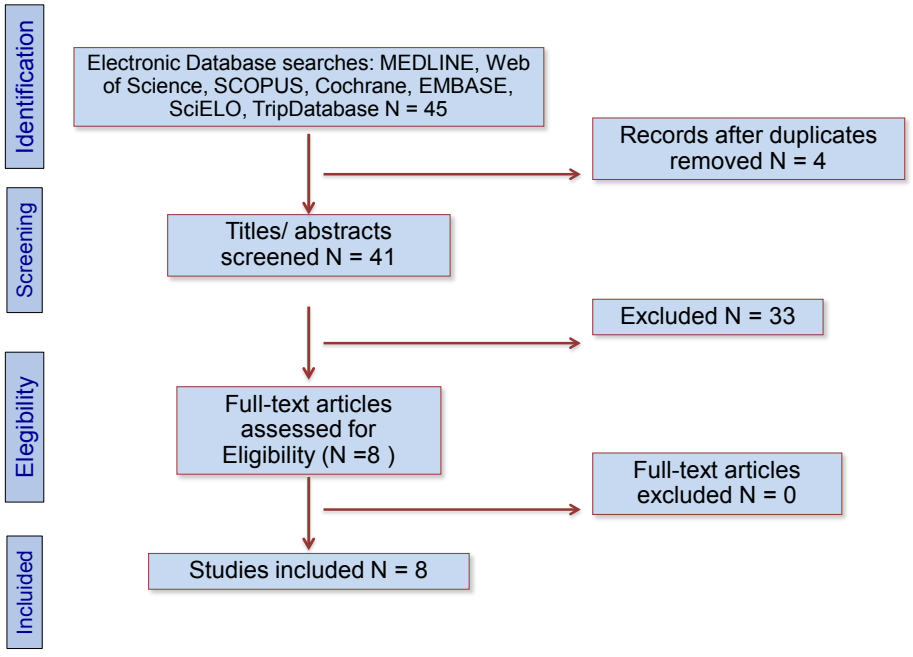

Figure 1 – Flowchart of studies included in this SR.

Table 1 - Description of studies included

Author	Cases with HAS	Controls	Total	Variant as reported in the primary article	Location and reference	HWE	Initial screening	HAT association	Other association or observation
Zivković et al., (2007)[11]	114	190	304	-1332 A/G	Intron 1 NC_000023.11:g.116170939G>A	Not informed	Not performed	Hemizygosity for "G" allele in variant -1332 A/G was susceptible for hypertension in males [OR=1.6; CI 95%=1.0-2.6; P=0.04]	It is suggested a higher association with the variant in older hypertensive Serbians [OR=2.4; CI=1.2-5.0; P=0.02]
Jin et al., (2003)[12]	2262	1007	3269	1.- A1675G 2.- A1818T 3.-G4303A 4.- C4599A	1.- Intron 1 NC_000023.11:g.116170939G>A 2.-Intron 2 NC_000023.11:g.116171082A>T 3.- 3'UTR G4303A (NC_000023.11:g.116173577A>G) 4.- 3'UTR NC_000023.11:g.116173873A>C	Tested	30 unrelated healthy men were included for screening *AGTR2* variant frequencies	C4599A was associated with AH in women. [OR=0.46; CI 95%=0.26-0.81; P-value=0.0058] conferring a protective role of the genotypes AC or CC.	Significant association remained after adjustment to age in women. It is informed that women with the AA genotype in variant C4599A have higher odds of developing AH.
Zhang et al., (2003)[15]	250	250	500	SNP03 (new variant [1334T/C])	Promoter NC_000023.11:g.116170599T>C	Not informed	19 persons, sequencing 2938 kb region	Association of variant 1334T/C in male hypertensive subjects [X2= 5.63;P=<0.05]	Substitution T to C was not found with different distribution in women,
Zhang et al., (2006)[16]	262	75	337	1.- G/T rs5193 2.- G/A rs5194 (G2274A)	1.- 3' UTR NC_000023.11:g.116173571G>T 2.-3' UTR NC_000023.11:g.116173577A>G	Tested	16 persons to amplify the whole length of AGTR2	Negative	T-A haplotype carriers with AH indicated lower levels of left ventricular mass and left ventricular hypertrophy index
Kabadou et al., (2012)[17]	382	403	785	C3123A	3' UTR NC_000023.11:g.116173873A>C	Tested	Not performed	Negative	Based on their results, suppose BMI must be studied for association with the variant
Kotani et al., (2013)[18]	82	79	161	(A/C) 3124	3' UTR NC_000023.11:g.116173873A>C	Tested	Not informed	Negative	"A" allele carriers had lower HDL-C levels among non-hypertensive women

Wang et al., (2014)[19]	1090	700	1790	1.- rs5193 2.- rs5194	1.-3' UTR NC_000023.11:g.116173571G>T 2.-3' UTR NC_000023.11:g.116173577A>G	Tested only in women	Not informed	In women, rs5193 and rs5194 were nearly associated under the allelic model, but the association disappeared under posterior analysis [P-value X^2 test=0.002; P-value logistic regression=0.229; OR=0.729; IC 97%=0.485-1.19]	It was found an association for ADRB3 rs4994 and CYP11B2 rs1799998 with AH
Li et al., (2015)[20]	1009	756	1765	1.- rs1403543 (G1675A) 2.- rs5194 (G2274A)	1.- Intron 1 NC_000023.11:g.116170939G>A 2.-3' UTR NC_000023.11:g.116173577A>G	Tested	Not performed	Variant rs1403543 was associated with AH in males [allelic model; OR=1.72; CI 95%= 1.15-2.58; P=0.008] and females [additive model; OR=1.8; CI 95%=1.4-2.31; P=<0.001]; [dominant model; OR=1.87; CI 95%=1.4-2.51; P=<0.001]; [recessive model; OR= 3.06; CI 95%=1.43-6.53;P=0.004]	Haplotype G-T-G-G-A was over-represented, including other genes in the X chromosome (rs1978124, rs2106809, rs1403543, rs5194, rs 56204867)

AGTR2: Angiotensin II receptor type 2; AH: arterial hypertension; BMI: body mass index; HWE: Hardy-Weinberg equilibrium; CI: confidence interval; UTR: untranslated region; NC: Reference sequence accession number; HDL-C: high-density-lipoprotein cholesterol; AC: Adenine-Citocine; CC: Citocine-Citocine:

for September 2023, only six variants were identified in all the analyzed studies.

Only one article had a sample size (n = 3,269 case-controls) sufficient to detect variants with a medium-sized effect, but it included fewer than 1000 women. The subsequent study with the most samples included 1790 individuals in total, and the rest of the studies were more limited in the number of participants. This primary association includes haplotype analysis, inheritance models, and multivariate analysis adjusted to confounding factors that reduce the risk of bias. A significant portion of the studies recruited via convenience sampling and used qualitative restriction fragment length polymorphisms (RFLPs) for genotyping, which influenced the risk of bias.

Table S2 depicts the main genotyping methods used in the diverse studies included. Direct sequencing was reduced in the selected studies, but the use of RFLPs in four studies had a significant impact, some of them for primary screenings or in combination with other validation techniques. Other techniques included in genotyping were dot blot, real-time PCR, PCR-LDR and Snapshot ddNTPs. However, three groups did not publish the primers used and the HWE was not reported in two studies and was only calculated for women in some specific cases. Regarding the nomenclature of single-nucleotide variants, the publications are heterogeneous, and some of them are new variants obtained from the initial screening by direct sequencing of a significant part of the *AGTR2* gene in a reduced sample size (n = 30). In the SR, seven variants studied for association with T2D were found; however, in the gnomAD v2.1.1 database, 238 variants were identified (**Figure** 2). Moreover, this number is increasing in the present year due to the COVID-19 pandemic and the need to find potential therapeutic targets. In **Figure** 3, the location of the variants described in this SR is shown; a large proportion of them are located in a promotor (1 variant), 3'UTR region (3 variants), and intron 1 and 2 (2 variants).

Table 1 displays descriptive information concerning the variants identified in the eight collected articles. The article with more participant cases included 3269 participants from Japan, and the authors found hypertension association with variant C4599A (NC_000023.11:g.116173873A>C) (OR = 0.46; CI 0.26-0.81; P-value = 0.0058), conferring a protective role of the genotypes AC or CC and an increased odds in AA carriers. Another article that identified a high association included 1,765 participants from China (Qiqihar City).

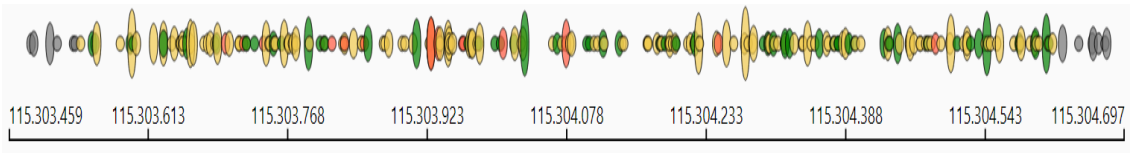

Figure 2 – Distribution of 238 DNA variants located in Chromosomal Region: X-115.303.459- 115.304.697 (AGTR2 gene). Red means Putative loss-of-function; Yellow, Missense/Inframe indel; Green, Synonymous; Grey, Other variants. A complete version of the figure can be consulted at https://gnomad.broadinstitute.org/gene/ENSG00000180772 (gnomAD v2.1.1)

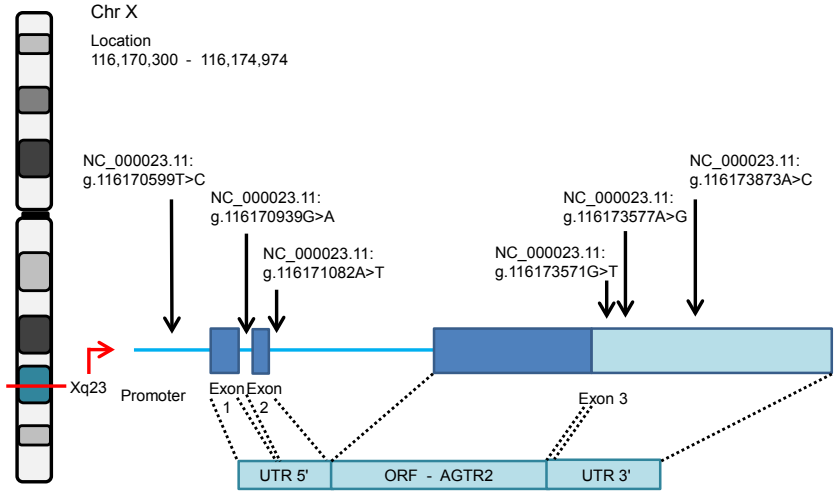

Figure 3 - Location of variants associated with hypertension in the AGTR2 gene (created with BioRender.com).
AGTR2: Angiotensin II receptor type 2; NC: reference sequence accession number; UTR: untranslated region; ORF: open reading frame.

These authors showed that the association with variants rs1403543 (NC_000023.11:g.116170939G > A) was with AH in males (allelic model; OR = 1.72; CI 95% = 1.15-2.58; P = 0.008) and females (additive model; OR = 1.8; CI 95% = 1.4-2.31; P = < 0.001; dominant model; OR = 1.87; CI 95% = 1.4-2.51; P = < 0.001; recessive model; OR = 3.06; CI 95% = 1.43-6.53; P = 0.004). A different article with fewer participants — including a population of 500 participants from China (Han from Shanghai) — found differences in the distribution of genotypes of variant 1334T/C (NC_000023.11:g.116170599T>C) in male hypertensive subjects (X^2 = 5.63; P = < 0.05). Additionally, another positive association with sample limitations in the results includes 304 Serbian participants for variant -1332 A/G (NC_000023.11:g.116170939G>A) in males (OR = 1.6; CI 95% = 1.0-2.6; P = 0.04).

In two studies that did not support an association with AH (four with a negative association), subsequent analysis indicated that the association with related traits, such as the *AGTR2* haplotype, occurred by rs5193 (NC_000023.11:g.116173571G>T) and rs5194 (NC_000023.11:g.116173577A>G). These studies indicated lower levels of left ventricular mass and an index of left ventricular hypertrophy. On the other hand, "A" allele carriers for variant 3124A/C (NC_000023.11:g.116173873A>C) had lower levels of HDL-C among non-hypertensive women.

Discussion

This review is based on information obtained from primary articles related to the association between the

AGTR2 gene and AH. No previous SR of the aim of this manuscript has been identified. The research included eight observational and retrospective case-control studies,[11,12,15-20] with considerable heterogeneity between the identified articles from which the information was extracted. This made a meta-analysis unfeasible. In the first phases of the SR, two articles were not obtained after several attempts to communicate with the editorials or the authors. As a response was not received, they were excluded from the review process. It has been almost 20 years since the first results informed the study of this gene in association with AH in a Japanese population in 2003.[12] The last significant study was performed 12 years later in a Chinese population in 2015.[20] In recent years, scientific articles studying this potential association have not been performed, or articles have not matched the research criteria in this SR.

The *AGTR2* gene is located in Xq23, which makes a specific gender analysis in genetic association analysis complex, and a large proportion of primary studies do not separate this variable in the analysis. Further, the number of cases and controls limits the number of articles that respond to the first significant results of association between AH and *AGTR2*,[12] and in some cases, the information concerning the RFLP technique used is unclear in the methodology sections, which complicates the qualitative information obtained using this technique. None of the posterior articles have been able to recruit or similarly contrast the results obtained due to the smaller sample size, which increases the probability of obtaining a type 2 error. Thus, a strong recommendation cannot be made on the association between AH and variants located in the *AGTR2*. Therefore, it is essential to replicate the results in diverse populations (Asia predominates in this SR) with a greater sample size and include multivariate analysis, adjustment for covariates, power calculation, and information concerning the control of quality in the genotyping process (**Central Illustration**).

AH is a multifactorial disease that affects a significant part of the population around the world and is one of the main causes of death because of comorbidity and metabolic and vascular complications. To date, about 50 candidate genes have been reported in the literature,[21] and the combination of modern techniques has identified nearly 120 loci with moderate or weak effects.[22] The RAS has been highlighted to study candidate genes related to AH due to its importance in regulating vascular homeostasis. However, among the protective branches of the RAS, the *AGTR2* gene has been scarcely studied until today. In the past decades, there have been descriptions of knockout mice models and an increase in vasopressor response when angiotensin II is administered,[23] attenuated exploratory behaviors and a decrease in body temperature.[24]

Initially, it was proposed as a candidate gene and associated with AH by Jin et al. in 2003.[12] In this primary article, the sample size was > 3000 divided into cases and controls, predominating the group of men, claiming association for variant C4599A (NC_000023.11:g.116173873A>C). Since then, small studies have been performed in diverse populations until Li et al.'s study in 2015,[20] which included a Chinese population of 1765 participants and found an association for rs1403543 (NC_000023.11:g.116170939G>A) in both genders and under diverse models of inheritance analyzed. Subsequently, various Asian groups have tried to identify an association with this variant or *AGTR2* gene, but the quality of the chosen design has been more limited in identifying low and medium effects. Only two Asian and Serbian research groups have identified an association in small sampling, but the methodology issues mentioned previously persist in several studies. In recent months, the *AGTR2* gene has been highlighted as a candidate gene to perform association studies with AH because of its importance as an agonist against COVID-19 infection and cardiorespiratory failure.

The product of this gene encodes for a G-coupled protein receptor that is part of the protective branch of RAS, encoded by exon number 3 (three exons) and is highly expressed in fetuses and neonates, and maintains expression in the brain of adults, adrenal medulla, heart, and lungs (due to COVID-19, this relevance has been highlighted), and atretic ovary (https://www.genecards.org/). It has also been associated with X-linked mental retardation [MIM*300034]. In a pilot genome-wide study, it was recently identified as a candidate gene associated with T2D in a Maya population,[14] and it is proposed to deepen this participation due to the prospect of agonist therapy (C21), including *AGTR2*,[13] in a successful phase 2, double-blind, randomized, placebo-controlled trial in an Indian population.[25] The relevance of this gene in the lung has been recently identified through the study of RNAseq, where it is highly expressed in alveolar type 2 cells (https://www.proteinatlas.org). It is also upregulated in the samples of bronchoalveolar lavages of COVID-19 individuals (https://www.ncbi.nlm.nih.gov/gene/186).

Conclusion

This study reviews and analyzes the participation of *AGTR2* variants in AH. Unfortunately, the heterogeneity in the different studies included in this research does not allow us to conclude or rule out an association between this gene and AH. However, it is identified as a potential gene to be studied as a candidate in case-control studies. It is relevant to replicate the study of this gene in a diverse population due to its apparent relevance in the development of therapies, such as C21 agonists, with promising results in a phase 2, double-blind, randomized, placebo-controlled trial.

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Author Contributions

Conception and design of the research: Totomoch-Serra A, Muñoz ML; acquisition of data and statistical analysis: Totomoch-Serra A, Brito-Carreón CA; analysis and interpretation of the data: Totomoch-Serra A, Brito-Carreón CA, Muñoz ML; writing of the manuscript and critical revision of the manuscript for intellectual content: Totomoch-Serra A, Brito-Carreón CA, Muñoz ML, García-Méndez N.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. World Health Organization. Global Health Observatory (GHO) Data [Internet]. Geneva: World Health Organization; 2021 [cited 2021 Jul 5]. Available from: http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence/en/.
2. México. Secretaría de. Secretaría de Salud. Dirección General de Epidemiología. Anuario de Morbilidad 1984-2016. Incidencia. Casos Nuevos de enfermedad por Grupo de Edad [internet]. México: Secretaría de Salud; 2021 [cited 2021 Jul 5]. Available from: http://www.epidemiologia.salud.gob.mx/anuario/2.
3. Gaziano TA, Bitton A, Anand S, Weinstein MC. The Global Cost of Nonoptimal Blood Pressure. J Hypertens. 2009;27(7):1472-7. doi: 10.1097/HJH.0b013e32832a9ba3.
4. Hong YM. Atherosclerotic Cardiovascular Disease Beginning in Childhood. Korean Circ J. 2010;40(1):1-9. doi: 10.4070/kcj.2010.40.1.1.
5. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension Guidelines for the Management of High Blood Pressure in Children and Adolescents. J Hypertens. 2016;34(10):1887-920. doi: 10.1097/HJH.0000000000001039.
6. Miall WE, Oldham PD. The Hereditary Factor in Arterial Blood-Pressure. Br Med J. 1963;1(5323):75-80. doi: 10.1136/bmj.1.5323.75.
7. Hottenga JJ, Boomsma DI, Kupper N, Posthuma D, Snieder H, Willemsen G, et al. Heritability and Stability of Resting Blood Pressure. Twin Res Hum Genet. 2005;8(5):499-508. doi: 10.1375/183242705774310123.
8. Waken RJ, de Las Fuentes L, Rao DC. A Review of the Genetics of Hypertension with a Focus on Gene-Environment Interactions. Curr Hypertens Rep. 2017;19(3):23. doi: 10.1007/s11906-017-0718-1.
9. Yayama K, Okamoto H. Angiotensin II-Induced Vasodilation Via Type 2 Receptor: Role of Bradykinin and Nitric Oxide. Int Immunopharmacol. 2008;8(2):312-8. doi: 10.1016/j.intimp.2007.06.012.
10. Mori H, Nakashima C, Kishi S, Nishiguchi Y, Fujii K, Luo Y, et al. Significance of Intranuclear Angiotensin-II Type 2 Receptor in Oral Squamous Cell Carcinoma. Oncotarget. 2018;9(93):36561-74. doi: 10.18632/oncotarget.26337.
11. Zivković M, Djurić T, Stancić O, Alavantić D, Stanković A. X-Linked Angiotensin II Type 2 Receptor Gene Polymorphism -1332A/G in Male Patients with Essential Hypertension. Clin Chim Acta. 2007;386(1-2):110-3. doi: 10.1016/j.cca.2007.07.014.
12. Jin JJ, Nakura J, Wu Z, Yamamoto M, Abe M, Chen Y, et al. Association of Angiotensin II Type 2 Receptor Gene Variant with Hypertension. Hypertens Res. 2003;26(7):547-52. doi: 10.1291/hypres.26.547.
13. Totomoch-Serra A, Domínguez-Cruz MG, Manterola C, Muñoz ML. Variants in AGTR2 Gene in Maya People with COVID-19. Gene. 2021;795:145794. doi: 10.1016/j.gene.2021.145794.
14. Domínguez-Cruz MG, Muñoz ML, Totomoch-Serra A, García-Escalante MG, Burgueño J, Valadez-González N, et al. Pilot Genome-Wide Association Study Identifying Novel Risk Loci for Type 2 Diabetes in a Maya Population. Gene. 2018;677:324-31. doi: 10.1016/j.gene.2018.08.041.
15. Zhang Y, Zhang KX, Wang GL, Huang W, Zhu DL. Angiotensin II Type 2 Receptor Gene Polymorphisms and Essential Hypertension. Acta Pharmacol Sin. 2003;24(11):1089-93.
16. Zhang M, Ma H, Wang BS, Zhao YZ. Angiotensin II Type 2 Receptor Gene Polymorphisms and Cardioprotective Role in Essential Hypertension. Heart Vessels. 2006;21(2):95-101. doi: 10.1007/s00380-005-0865-1.
17. Kabadou IA, Soualmiaa H, Jemaa R, Feki M, Kallel A, Souheil O, et al. Lack of Association between C3123A Polymorphism of the Angiotensin II Type 2 Receptor Gene and Hypertension in Tunisian Population. Tunis Med. 2012;90(8-9):619-24.

18. Kotani K, Sakane N, Taniguchi N. Association between Angiotensin II Type 2 Receptor Gene A/C3123 Polymorphism and High-Density Lipoprotein Cholesterol with Hypertension in Asymptomatic Women. Med Princ Pract. 2013;22(1):65-9. doi: 10.1159/000339892.

19. Wang L, Zhang B, Li M, Li C, Liu J, Liu Y, et al. Association between Single-Nucleotide Polymorphisms in Six Hypertensive Candidate Genes and Hypertension among Northern Han Chinese Individuals. Hypertens Res. 2014;37(12):1068-74. doi: 10.1038/hr.2014.124.

20. Li J, Feng M, Wang Y, Li Y, Zhang Y, Li L, et al. The Relationship between Three X-Linked Genes and the Risk for Hypertension among Northeastern Han Chinese. J Renin Angiotensin Aldosterone Syst. 2015;16(4):1321-8. doi: 10.1177/1470320314534510.

21. Tanira MO, Al Balushi KA. Genetic Variations Related to Hypertension: a Review. J Hum Hypertens. 2005;19(1):7-19. doi: 10.1038/sj.jhh.1001780.

22. Kraja AT, Cook JP, Warren HR, Surendran P, Liu C, Evangelou E, et al. New Blood Pressure-Associated Loci Identified in Meta-Analyses of 475 000 Individuals. Circ Cardiovasc Genet. 2017;10(5):e001778. doi: 10.1161/CIRCGENETICS.117.001778.

23. Hein L, Barsh GS, Pratt RE, Dzau VJ, Kobilka BK. Behavioural and Cardiovascular Effects of Disrupting the Angiotensin II Type-2 Receptor in Mice. Nature. 1995;377(6551):744-7. doi: 10.1038/377744a0.

24. Ichiki T, Labosky PA, Shiota C, Okuyama S, Imagawa Y, Fogo A, et al. Effects on Blood Pressure and Exploratory Behaviour of Mice Lacking Angiotensin II Type-2 Receptor. Nature. 1995;377(6551):748-50. doi: 10.1038/377748a0.

25. Tornling G, Batta R, Porter JC, Williams B, Bengtsson T, Parmar K, et al. Seven Days Treatment with the Angiotensin Ii Type 2 Receptor Agonist C21 in Hospitalized Covid-19 Patients; A Placebo-Controlled Randomised Multi-Centre Double-Blind Phase 2 Trial. EClinicalMedicine. 2021;41:101152. doi: 10.1016/j.eclinm.2021.101152.

*Supplemental Materials

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