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Systematic Review

AGT, CYP11B2 & *ADRB2* gene polymorphism & essential hypertension (HT): A meta-analysis

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***Background & objectives*: The results of the genetic association studies between the selected candidate genes and hypertension (HT) contradicted across different populations. Majority of the meta-analyses carried out did not consider population genetic ancestry as a confounding factor. Therefore, this meta-analysis attempted to consolidate and re-evaluate the findings of the association between the selected candidate variants (*AGT*-rs699, *CYP11B2*-rs1799998, *ADRB2*-rs1042713 and rs1042714) and HT, by categorizing the genotyping data based on known genetic ancestry, and/or major geographical populations.**

***Methods*: Publications were retrieved from PubMed, Cochrane and World of Science. The included articles were further divided into different populations based on their known genetic and/or geographical ancestry.**

***Results*: *AGT*rs699-G was significantly associated with HT among Indians for *(i)* allele [*P*=0.03, Odds ratio (OR): 1.37, 95% Confidence Interval (CI): 1.03–1.82], and *(ii)* dominant mode of inheritance (*P*=0.009, OR:1.45, 95% CI: 1.09–1.91). *CYP11B2*rs1799998-G was significantly associated with HT in Europeans for *(i)* allele (*P*=6.9 × 10^{-5}, OR: 0.82, 95% CI: 0.74–0.9), *(ii)* recessive (*P*=6.38 × 10^{-5}, OR: 0.7, 95% CI: 0.59–0.83) and *(iii)* dominant mode of inheritance (*P*=0.008, OR: 0.81, 95% CI: 0.7–0.94). *ADRB2*-rs1042713-G was significantly associated with HT in east Asians for *(i)* allele (*P*=0.01, OR: 1.26, 95% CI: 1.05–1.51), and *(ii)* recessive mode of inheritance (*P*=0.04, OR: 1.36, 95% CI: 1.01–1.83).**

***Interpretation & conclusions*: Different genotype and allele frequencies in diverse populations result in different genetic associations with HT across populations. This meta-analysis finding provides an update and summary of the genetic association between the selected simple nucleotide polymorphism (SNPs) and HT across different populations and essential insights into selecting appropriate pharmacogenetic marker(s) for effective HT management in populations of different ancestries.**

Key words *ADRB2-AGT* - *CYP11B2* - essential hypertension - meta-analysis - populations

Hypertension (HT) is an escalating problem in modern society, affecting nearly a third of the adult

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population globally. It is a major risk factor for cardiovascular complications, including stroke and left ventricular hypertrophy, among others[1]. HT is caused by the interplays between individual susceptible genetic variants and environmental factors[2]. Studies have shown that genetics accounts for 30–60 per cent of the blood pressure (BP) variability[3,4,5], yet the molecular pathophysiology of HT is inconclusive, as evidenced by the discovery of over 1000 genetic loci associated with BP regulation[6].

Essential HT (ESH), which accounts for ~95 per cent of all HT cases[7], is primarily considered a salt-sensitive (SS) phenomenon[8]. Salt-sensitive HT (SS-HT) is classified into two sub-intermediate phenotypes based on the plasma renin activity, normal and low renin, in response to upright posture and dietary salt restriction[8]. Notably, angiotensinogen (*AGT)* has been associated with normal renin SS-HT, while beta-2 adrenergic receptor (*ADRB2*) and aldosterone synthase (*CYP11B2*) are associated with low renin SS-HT[8].

AGT and *CYP11B2* are two important components in the renin-angiotensin-aldosterone system that are responsible for water and sodium homeostasis, hence BP regulation. *AGT*-rs699G allele is attributed to elevated plasma angiotensinogen[9,10,11]. *CYP11B2* is involved in the terminal steps of the aldosterone biosynthesis[12].The variant rs1799998 has been reported to alter its transcription binding site of putative steroidogenic factor-1, leading to downregulation of *CYP11B2* promoter activity thence altered expression of *CYP11B2*[13,14,15]. *ADRB2* mediates effects on vascular tone and cardiac contractility *via* the sympathetic nervous system[16,17]. It attenuates vasodilation that leads to the elevation of vascular resistance[17], hence salt excretion and HT[18]. *ADRB2*-46AA/79CC (rs1042713-AA/rs1042714-CC) was associated with a disproportionate elevation of aldosterone levels during liberal salt intake[19].

Despite promising evidence on the functionality of these candidate genetic variants, their associations with HT have been contradicting[20-24]. Besides potentially unclear intermediate phenotyping, we postulated that the variability of minor allele frequencies across different populations could potentially be a reason for this equivocal conclusion.

Although meta-analysis offers an alternative to solve a problem associated with genetic association studies, most of the meta-analyses on the candidate gene have not considered the genetic ancestry of the studied populations as a potential confounding factor to the statistical analysis. Different genetic ancestries often result in variability of selected allele frequencies owing to evolutionary processes, for example, migration, admixture and natural selection[25]. Therefore, this meta-analysis attempted to consolidate and re-evaluate the findings of the association between the selected candidate variants (*AGT*-rs699, *CYP11B2*-rs1799998, and *ADRB2*-rs1042713 and rs1042714) and HT, by categorizing the genotyping data retrieved from the publications included based on known genetic ancestry, and/or major geographical populations.

Methods

Search Strategy: A comprehensive systematic literature search was conducted in several databases: PubMed, Cochrane and Web of Science (WOS). Publications related to a case-control genetic association study for *AGT* (rs699), *CYP11B2* (rs1799998), *ADRB2* (rs1042713 and rs1042714) and HT were retrieved. The terms and keywords used when performing the search were tabulated in Supplementary Table I.

The search was conducted independently by one author (NHM) and the full text was retrieved for possible relevant studies. The search was conducted until January 2023.

The following criteria were used during articles search: *(i)* article written in English; *(ii)* full-text article; *(iii)* case-control study; *(iv)* aged 18 yr and above; *(v)* ESH; *(vi)* available candidate single nucleotide polymorphisms (SNPs) genotype profile for HT and normotensive (NT) for *AGT*-rs699, *ADRB2*-rs1042713 and rs1042714 and *CYP11B2*-rs1799998; *(vii)* HT defined as BP ≥140 in systolic blood pressure or ≥90 diastolic blood pressure mmHg and both or on anti-hypertensive medication; *(viii)* NT defined as BP <140/90mmHg.

Articles were excluded based on following criteria: *(i)* samples with secondary HT, or with any known systemic diseases; *(ii)* publication from letters, review articles, meta-analysis, abstracts, and meeting reports; *(iii)* duplicating first and corresponding authors; *(iv)* suspected genotyping error (reported frequencies significantly deviated from expected or potential in genotyping error potentially due to flipping strand issue).

Study selection: Publications that fulfilled the inclusion and exclusion criteria were further divided into different

populations based on geographical continents/known to share the same genetic ancestry: *(i)* European, *(ii)* Southern Chinese, *(iii)* East Asian: Northern Chinese and Japanese, *(iv)* Southern Indian, *(v)* Northern Indian, *(vi)* Latin American, *(vii)* African and *(viii)* the Middle East.

Data extraction: The data from eligible publications was extracted independently by three reviewers (NHM, IJR and KAM). Any discrete publication results were referred to the fourth reviewers (HBP). A standardized data collection form was piloted, containing information on the name of the first author, year of publications, ethnicities, number of cases and control. The genotype of *AGT* (rs699), *CYP11B2* (rs1799998) and *ADRB2* (rs1042713 and rs1042814) genotypes were extracted and categorized based on populations. The eligible articles included in this study are listed in Supplementary Table II.

Quality assessment of included studies: Two reviewers (IJR and KAM) independently assessed the quality of the included studies. An adapted version of the modified Newcastle-Ottawa Quality Assessment Scale Form was used to perform a quality assessment of case-control studies for this systematic review (Supplementary Table III).

Statistical analysis: Meta-analysis was performed using MetaGenyo, an online tool for meta-analysis of genetic association study (*https://metagenyo.genyo.es/*). Association between the candidate variants and HT was assessed using odds ratio (OR) with 95% confidence interval (Cl). In this study, either fixed or random-effect models were acquired based on the significance of inter-study heterogeneity ($P< 0.05$).

To assess possible publication bias, a funnel plot was generated (Supplementary Fig. 1) and evaluated using Egger's test. A sensitivity test was also performed to examine the robustness of the meta-analysis. MetaGenyo requires a minimum of three publications for a meta-analysis to be carried out. Therefore, populations with less than three publications were excluded from the analysis.

Results

AGT-rs699:

Characteristics of the included studies: Overall, 947 publications were retrieved: PubMed (n=772 publications), Cochrane (n=22 publications) and WOS (n=153 publications). After applying pre-determined stringent filtering criteria, 48 publications remained. Overall, 12,336 HT and 10,784 NT individuals were involved in this analysis: *(i)* East Asian (Northern Han Chinese and Japanese), involving 4313 HT and 3565 NT: *(a)* Southern Han Chinese consisted of 1063 HT and 959 NT; *(b)* Southern Indian consisted of 1196 HT and 1131 NT; *(c)* North Indian consisted of 1244 HT and 1009NT; and *(d)* West Asia consisted of 359 HT and 281 NT. *(ii)* Europe consisted of 3601 HT and 3269 NT; *(iii)* Latin America consisted of 401 HT and 371 NT. Figure summarizes the flow search process for *AGT-rs699*. A similar flow search applies to other variants.

Meta-analysis result: Eight subgroup analyses revealed significant association between rs699-G and HT among the South Asian population (Southern India + Northern India) in allele [P=0.03, OR: 1.37, 95% CI: 1.03–1.82, $P_{heterogeneity}$= 0.0001]and dominant mode of inheritance (GG + GA *vs.* AA) (P=0.009, OR: 1.45, 95% CI: 1.09–1.91, $P_{heterogeneity}$= 0.0086) under random model effect.

Publication bias: With an exception in the allelic model of the West Asian (P=0.0008), Egger's test revealed no publication bias in other populations. The funnel plot result is shown in Supplementary Figure 2.

Sensitivity test: The sensitivity test revealed no significant change observed between the overall OR value and in each omitted publication OR value, as the percentage between the two ORs is less than 20 per cent, indicating the meta-analysis results were reliable. A similar finding was observed for other included variants in this study. The summary of the *AGT*-rs699 finding is shown in Supplementary Table IV and Supplementary Figure 3.

CYP11B2-rs1799998:

Characteristics of the included studies: A total of 589 publications were retrieved for *CYP11B2*-rs1799998: PubMed (n=180), Cochrane (n=49) and WOS (n=360). Twenty-two publications remained in subsequent analysis: Japanese (4), European (5), Indian (5) and Northern Chinese (8). Overall, 11,745 HT and 11,014 NT individuals were included: *(i)* European (3037 HT and 2018 NT), *(ii)* Northern Han Chinese (4603 HT and 4113 NT), *(iii)* Japanese (2666 HT and 3502 NT), *(iv)* Indian (1439 HT and 1381 NT).

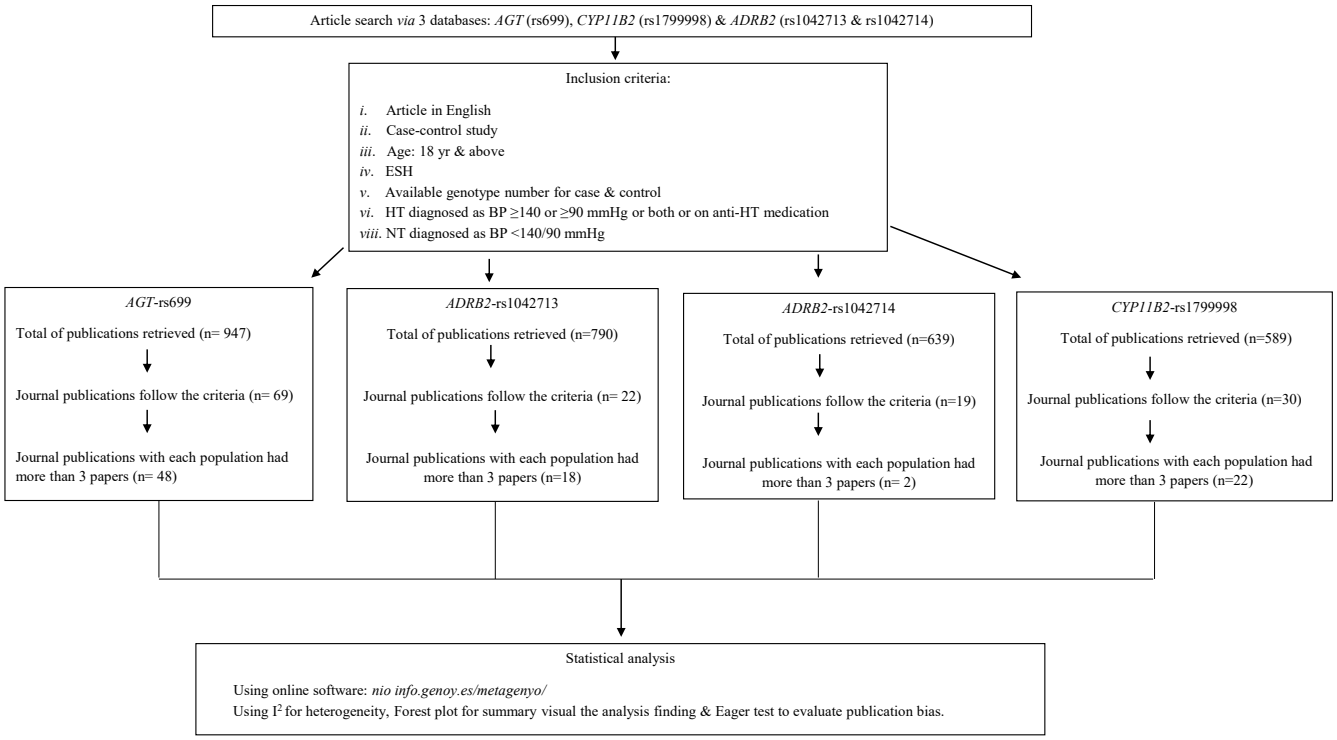

Figure. Summary of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow search process for *AGT-rs699*, *CYP11B2* (rs1799998) and *ADRB2* (rs1042713 and rs1042714). ESH, established hypertension; HT, hypertension; BP, blood pressure; NT, normotensive.

Meta-analysis results: Meta-analysis revealed significant association between *rs1799998-G* and HT among the European population (P=0.00012, OR: 1.21, 95% CI: 1.1–1.33, $P_{heterogeneity}$ = 0.55), in both recessive (GG + GA *vs*. AA) (P=0.008, OR: 1.22, 95% CI: 1.05–1.42, $P_{heterogeneity}$ = 0.97), and dominant mode of inheritance (GG *vs*. GA + AA) (P=0.00019, OR: 1.38, 95% CI: 1.16–1.62, $P_{heterogeneity}$ = 0.18), under the fixed-effect model. The association effect was stronger when the article by Bengra *et al*[26] was excluded. This is possibly due to the difference in G and A allele frequencies reported in the publication as compared to other included articles. Analysis showed a significant association between HT and the allele G (P=6.9×10^{-5}, OR: 1.22, 95% CI: 1.1–1.34, $P_{heterogeneity}$ = 0.69), in recessive (GG + GA *vs.* AA) (P=0.008, OR: 1.22, 95% CI: 1.05–1.42, $P_{heterogeneity}$ = 0.97) and dominant mode of inheritance (GG *vs.* GA + AA) (P=6.8×10^{-5}, OR: 1.42, 95% CI: 1.19–1.68, $P_{heterogeneity}$ = 0.3) under the fixed effect model.

Publication bias: Egger's test suggested no publication bias was detected in the included articles (Supplementary Fig. 3). The summary of the *CYP11B2*-rs1799998 finding is shown in Supplementary Table IV and Supplementary Figure 2.

ADRB2-rs1042713:

Characteristics of the included studies: A total of 790 publications were retrieved: PubMed (n=607), Cochrane (n=2) and WOS (n=159), of which 18 publications remained in meta-analysis representing three populations: European (11), African American (3) and East Asian (4; covering 2 for Northern Han Chinese and 2 for Japanese). Overall, 5739 HT and 3681 NT subjects were included: *(i)* European: 2922 HT and 1844 NT; *(ii)* African American: 329 HT and 336 NT; and *(iii)* East Asian: 2128 HT and 1501 NT.

Meta-analysis results: Meta-analysis results revealed a significant association between HT among the East Asian (Northern Han and Japan) in rs1042713-G allele (P=0.01, OR: 1.26, 95% CI: 1.05–1.51, $P_{heterogeneity}$ = 0.05), and recessive mode of inheritance (GG + GA *vs.* AA) (P=0.04, OR: 1.36, 95% CI: 1.01–1.83, $P_{heterogeneity}$ = 0.07), under the random model effect. A similar finding was also observed in the African-American

population in the dominant mode of inheritance (GG *vs.* GA + AA) (P=0.03, OR: 0.68, 95% CI: 0.48–0.97, $P_{heterogeneity}$ = 0.84) under the fix model effect.

Publication bias: Egger's test suggested publication bias in studies involving African-American population (*P*=0.02) but not in others. The summary of the *ADRB2*-rs1042713 finding is listed in Supplementary Table IV and Supplementary Figure 2 and 3.

ADRB2-rs1042714:

Characteristics of the included studies: Overall, 639 publications were retrieved: PubMed (n=508), Cochrane (n=22) and WOS (n=158), of which 12 publications were included: European (7); and East Asian (5; covering two from Southern Chinese and Japanese), comprising 4953 HT and 3359 NT individuals: *(i)* European: 2250 HT and 1435 NT, *(ii)* Northern Han Chinese (1298 HT and 936 NT), *(iii)* East Asian consisting of 2706 HT and 1924 NT: (*a*) Northern Han Chinese (1298 HT and 936 NT); *(b)* Southern Han Chinese (288 HT and 149 NT) and *(c*) Japanese (1120 HT and 839 NT).The summary of the flow search process for *ADRB2*-rs1042714 is shown in Figure.

Meta-analysis results: No appreciative association between *ADRB2*-rs1042714 and HT was observed as shown in Supplementary Table IV.

Publication bias: The Egger's test suggested no publication bias was detected.

Discussion

In this review, we categorized the data based on geographical populations. Significant genetic association was observed between HT and *(i) AGT*-rs699 G risk allele among the South Asian (Southern + Northern Indian); *(ii) CYP11B2*-rs1799998 G risk allele among the European; and *(iii) ADRB2*-rs1042713 G risk allele observed among the east Asian (Northern Han Chinese and Japanese).

AGT-rs699 G allele was associated with elevated AGT plasma levels, leading to elevated BP[27]. However, its association with HT across different populations was not universal, as evident by the inconsistency of the meta-analysis performed in this study. This is not surprising as studies have revealed that the *AGT*-rs699 diversity is correlated to the geographical latitude of the studied populations[28,29] whilst the derived allele frequency increases moving away from the equator, nearly all populations close to the equator were homozygous or heterozygous for the ancestral allele, for what other studies have identified as being the *AGT* risk allele. However, our results contradict the study performed on the African population[30]. The *AGT*-rs699 surprisingly was not associated with HT in the European population, even though Europeans contributed more HT samples than the South Asians in this study. The recruitment of a small sample size in the European population partly could be a reason leading to sampling error[31], hence a non-significant finding. When the sample size is large, the sampling variance of the effect size can be assumed to be approximately known and normal[32].At least 500 HT individuals should be acquired in each publication to increase the power of meta-analyses[20], as a small number could result in insufficient statistical power to estimate the effect of the variant on the disease[33]. In addition, the allele frequencies may appear heterogenous solely due to the nature of sampling variability when the trial sizes are small[21]. However, because the sample size per publication was not restricted in this study, the effect of heterogeneity may have been compromised.

ADRB2-rs1042713A allele carriers exhibited significantly lower basal blood flow and attenuated elevation in forearm blood flow as opposed to the G allele[34], perhaps due to the variability in vascular responsiveness to isoproterenol in the vascular bed associated with *ADRB2*-rs1042713[35]. In contrast, it remains unclear whether the *ADRB2*-rs1042713 influences the β2-mediated vasodilation that affects the blood flow[36], BP control and new onset of HT[37]. Our finding is similar to Yan *et al*[17] in 2020. Although previous meta-analyses reported a significant association between the *ADRB2*-rs1042713-G allele and HT in Africa[20], we did not observe similar results. We speculated the contradiction may be due to unclassified intermediate phenotypes, resulting in the dilution of detection power.

The *CYP11B2*-rs1799998T allele leads to downregulation of *CYP11B2* promoter[13] hence influencing the level of aldosterone synthesis[38]. In contrast to this review, a previous publication reported a significant association between *CYP11B2*-rs1799998 and HT in the Northern and Southern Chinese[13].

On a separate note, whether the rs1799998 G or T allele is more prevalent in HT is conflicting–some argued that the G allele carrier had a lower risk of

HT[39,40]; while others claimed the opposite[41]. We speculate that, first, heterogeneity of the population studied. Most of the studies were based on the population genetic ancestry not controlled. Second, the phenotype of the genes involved in sodium/volume homeostasis, in this case, *CYP11B2*, low renin and BP levels are likely dependent on the environmental factors[15]. Third, different minor allele between different populations may have complicated the association signal[42]. Finally, genetic association analysis between *CYP11B2*-rs1799998 and BP by gender was observed[43], thus conceivably confounded sampling neutrality, as aldosterone level can be influenced by gender bias[44].

In this meta-analysis, we focused on ESH without co-existing other diseases, such as diabetes and heart disease, thus reducing potential analysis bias. Further, this study categorized the publication genotyping data according to known major geographical populations and hence mitigates the influence introduced by the variability of allele frequencies among different populations. Findings of this review summarised that different genotypes and allele frequencies in diverse populations with different ancestries result in different genetic associations with HT across the population and, therefore, the treatment may be different across populations.

The study has some limitations. First, the phenotypic characterization of HT for some of the publications was not documented as most of the studies defined HT by elevated BP measurements, but whether they were SS was not diagnosed. Knowing that different intermediate phenotypes of HT are associated with selected genetic variations[8], unclassified intermediate phenotypes could have diluted the statistical power to detect a true genetic association. Second, the sample size included in meta-analyses for some publications in this study was small (n=30). This may have led to insufficient statistical power to detect fluctuated risk estimate[45]. Owing to the small effect size (OR: 1–1.61) of the variants of interest, the statistical power of this study may have been too weak to detect statistical association[46]. Third, our findings only included the articles published in the English language, which may not be generalizable to all countries and settings.

Overall, this review provides an update and summary of the genetic association between the selected SNPs and HT across populations with different genetic ancestries. Owing to different genetic susceptibility across different populations, levels of genetic variation in populations of different genetic ancestries should be considered if the pharmacogenetic approach is applied to the management of HT. Further meta-analyses are required to warrant the findings of this study.

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