JOURNAL OF CLINICAL AND HEALTH SCIENCES

EDITORIAL

Precision Medicine in Hypertension: Are We There?

Hoh-Boon-Peng[1], Fananta Ibrahim[1], Nur Hasnah Maamor[2, 3]

1 Division of Applied Biomedical Sciences and Biotechnology, School of Health Sciences, IMU University, Kuala Lumpur, Malaysia
2 Faculty of Medicine and Health Sciences, UCSI University, Springhill Campus, Negeri Sembilan, Malaysia
3 Evidence Based Healthcare Sector, National Institute of Health, Ministry of Health, Malaysia

*Corresponding author: B-P. Hoh (hoh.boonpeng@gmail.com; boonpenghoh@imu.edu.my)

INTRODUCTION

Hypertension (HTN), clinically defined as systolic blood pressure (SBP) > 140 mmHg, or diastolic blood pressure (DBP) > 90 mmHg, or both affects approximately 1.28 billion people aged between 30 and 79 years globally [1, 2]. The overall global prevalence of hypertension in 2000 was estimated at 26.4% [3]. In the 2015 estimates, however, the average prevalence had increased to 32.3% in low- and middle-income countries, with prevalence estimates of 39.1% in the Latin American and Caribbean regions [4]. Interestingly, the prevalence of hypertension was also reportedly the highest in populations from the upper middle-income countries (37.8%) and lowest in populations from low-income countries (23.1%) [4]. In addition, prevalence estimates were higher in those aged 65 years and above compared with that in those below 65 years of age. No significant gender-difference in hypertension prevalence was noted, but persons with no formal education (49.0%), or who were overweight/obese (46.4%), and urban settlers (32.7%) were more likely to be hypertensive compared with those who were educated, normal weight, and living in rural areas [4]. In Malaysia, the 2023 National Health and Morbidity Survey (NHMS, 2023) revealed that approximately one in three adults in Malaysia have hypertension [5].

Uncontrolled or untreated HTN is a risk factor for numerous diseases including ischaemic heart disease, heart failure, myocardial infarction, stroke, and kidney disease [6]. Owing to its complex aetiology, and being responsible for a spectrum of consequences, HTN is now recognised more as a syndrome rather than a disease with a known cause and a distinct course [7].

HTN is broadly classified into primary or essential HTN (EHTN) and secondary HTN, of which 95% of the cases fall under EHTN [8]. The underlying causes of EHTN are largely unidentified; whereas secondary HTN is often a result of a known medical condition, for example, renal disease or endocrinopathy, including pheochromocytoma and adrenal adenoma, or single-gene mutations.

EHTN can be further classified into two intermediate phenotypes, i.e., salt-sensitive (SS), which accounts for ~50% of the EHTN, and salt-resistant, based on the BP response to changes in salt intake [9, 10]. Interestingly, salt-sensitivity is not a fixed phenotype, as it increases with age, diabetes, and hypertension where nephron loss increases progressively. SS-HT individuals are also more likely to be women, and those suffering from obesity or kidney disease [11].

HTN has also been subtyped based on the plasma renin activity (PRA) response to upright posture and dietary salt restriction, i.e., high renin, normal renin, and low renin. Based on the inverse relationship between PRA and 24-hour urinary sodium excretion in normotensive subjects, Laragh and colleagues attempted to group hypertensive patients according to their plasma renin activity [12, 13]. They found that

Vol 9(2) (2024) 1-8 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v9i2.27413

30% of patients with hypertension had low PRA, 60% had medium PRA, and 10% had high PRA. Incidentally, patients with low PRA type of hypertension are salt-sensitive and respond well to diuretic therapy. Calcium supplementation has also been found to reduce blood pressure in salt-sensitive, low PRA essential hypertensives [14].

Clinical assessment of HTN based on renin activity is not common, primarily due to its tedious and time-consuming protocol prior to examination. Studies have suggested the intermediate phenotypes of SS EHTN are associated with selected candidate gene variation [8]. Other subtypes of HTN include obesity-related HTN and deoxycorticosterone acetate (DOCA) salt HTN, where the latter exhibits salt-dependent excess mineralocorticoid [15, 16].

The development of essential HTN involves complex interplay between environmental stimuli and multiple candidate genetic variations of an individual; each contributing only modestly, along with gene-gene interactions and pleiotropic effects [17], hence the differential susceptibility. Although genetic variation accounts for 30-50% of the heritability, only ~3% of the variance in BP is explainable [18].

Over the past several decades, it has become apparent that molecular and cellular events in various organs underlie many features of the Mosaic Theory of HTN, which argues that "even the simplest HTN is a mosaic, because factors, including race, environment, adaptive, neural, mechanical, and hormonal perturbations interdigitate to raise blood pressure" [19]. The complexity of the pathogenesis of HTN is well supported by the fact that more than 457 loci that are associated with HTN (or phenotypes related to BP regulation) were identified in genome-wide association studies (GWAS) (genome-wide significance level $p < 10^{-7}$), of which 283 were distinct, corresponding to 245 candidate genes [20]. Yet, there may be more that remain unravelled.

Notably, RAAS is widely accepted as a major system that regulates BP through water and salt homeostasis, as well as vasoconstriction. In brief, renin is released into the circulation in the event of decreased sodium levels, and catalyses the cleavage of the glycoprotein angiotensinogen to form angiotensin I (Ang I). Ang I is further cleaved by ACE producing Ang II, which stimulates the release of aldosterone from the adrenal cortex. Together Ang II and aldosterone promote vasodilation of vascular tissues, sodium reabsorption, water retention and potassium and magnesium loss [21]. In addition, the ACE2/Angiotensin 1 – 7/Mas receptor axis serves to counterbalance the classical RAAS pathway, as characterized by the actions of Ang II and the Ang II type 1 receptor (AT_1R). While the classical pathway promotes vasoconstriction, sodium retention, and inflammation, the ACE2/Ang 1-7/Mas receptor axis opposes these effects, leading to vasodilation, natriuresis, and anti-inflammatory actions [22, 23]. Dysregulation of this axis has been implicated in various cardiovascular diseases, including hypertension, heart failure, and vascular dysfunction [24].

Various anti-hypertensive drugs are available and currently used in the management of hypertension. Essentially, they can be classified into "ABCD" lines of drugs: "A" angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE); "B" Beta-blocker; "C" calcium channel blocker (CCB); "D" thiazide diuretics [22]. In addition, the other class of medication includes the mineralocorticoid receptor (MR) antagonists. It is known that using just a single anti-hypertensive medication is not sufficient in controlling the targeted BP at <140/90 mmHg in most cases, and usage of two or three drugs is, therefore, recommended for a tolerable control [23]. While poor compliance by patients is often claimed to be the underlying factor for the ineffective response to anti-hypertensive medications, inability to identify specific pathophysiologic defect (which then translates to intermediate, or even sub-intermediate phenotypes) of HTN, and inability to match the HTN to specific therapy, is probably another reason for the failure to control the hypertension. In other words, the aim to formulate an effective treatment cannot be achieved without proper consideration of the pathogenesis and pathophysiology of HTN [25], hence the need for precision medicine of HTN. While the holistic concept of precision medicine in HTN seems enticing, achieving its successful implementation at the bedside, however, remains elusive.

Vol 9(2) (2024) 1-8 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v9i2.27413

PRECISION MEDICINE IN HYPERTENSION

Precision medicine is a holistic idea that describes medication or therapeutic strategy customised to an individual or a particular group of patients. Of all approaches available, pharmacogenomics is the lowest hanging fruit to materialising precision medicine. Genetics is the key element to: (i) identify the underlying molecular pathophysiology of the HTN; (ii) associate selected phenotypes of HTN; and (iii) to predict the responsiveness of the patients to selected anti-hypertensive medication. Essentially through such "genotype-guided" approach, clinicians could presumably be able to predict the response of a hypertensive patient to a selected class of medication, with an optimal dose being prescribed.

Some pharmacogenetic trials have been carried out and showed some encouraging results, albeit still at a preliminary stage:

i. A clinical trial to predict the response of diuretics on hypertensive individuals who carried *UMOD* rs13333226-AA genotype had increased *UMOD* excretion, thus greater salt sensitivity [26, 27, 28, 29].
ii. A prospective *UMOD* rs13333226-AA genotype directed trial of a long-acting loop diuretic, torsemide, in uncontrolled HTN was carried out, however the outcome is yet to be unveiled [26, 28].
iii. The Nordic Diltiazem (NORDIL) trial claimed that HTN patients *NEDD4L* rs4149601 G allele exhibited better response to the thiazide/β-blocker treatment compared to those with AA genotype [30, 31].
iv. The Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study revealed that HTN patients who carried the rs4149601-G allele exhibited better response to hydrochlorothiazide but no difference by genotype in response to the β-blocker atenolol [31]. The G allele creates a cryptic splice site in *NEDD4L*, which leads to less ENaC downregulation, thereby increased sodium retention.
v. *ACY3* methylation was associated with bisoprolol, a class of β-blocker, reducing SBP and DBP by 5 and 3 mmHg respectively [32]; but its genetic variation showed an association of BP response to β-blocker [33].
vi. *GNB3* rs5443-T carriers showed a better response to hydrochlorothiazide among the HTN patients of Caucasian and African American ancestries [34].

Nonetheless, majority have either failed outright or struggled to consistently reproduce their results [35].

An alternative approach of precision medicine in HTN is utilising a panel of genetic markers associated with HTN (and possibly together with other HTN risk factors) to generate the genetic risk score (GRS), or polygenic risk score (PRS), to predict individual's risk of developing HTN, and possibly its cardiovascular complications. It was discovered that a predetermined increase in BP could be partially mitigated by lifestyle changes. In individuals with a high genetic risk, a healthy lifestyle acted as a counterbalance, while the opposite was observed for those with a low genetic risk - an unhealthy lifestyle might compromise their inherent protection [36]. However, application of GRS and PRS in the determination of a risk score is still in its early stages, as there is no universal consensus on the best formula to predict an individual's risk score. Besides that, the cost of genetic screening remains a barrier for many lower socioeconomic status communities.

CHALLENGES OF PRECISION MEDICINE IN HYPERTENSION

Despite a handful of successful clinical trials, the use of pharmacogenetic tests to predict the responsiveness of an individual to anti-hypertensive medications have not been available in clinical practice especially to the countries of the global south, because of the following reasons:

Vol 9(2) (2024) 1-8 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v9i2.27413

i. Most if not all, of the studies on gene mapping, pharmacogenetic studies and related clinical trials were carried out on the populations of European ancestry. The applicability of these findings in the other populations, such as those from Southeast Asia is questionable, since the genetic make-up between European and the Southeast Asians are known to be different [37, 38, 39]. Therefore, it remains a challenge to identify which genetic marker(s) best suits the pharmacogenetic approach in HTN of those under-investigated populations.

ii. The genetics of HTN among many marginalised populations (e.g. native or indigenous Malaysians) have not been systematically investigated. Genome-wide association studies have not been conducted before; and only a handful smaller-scale candidate gene-based association studies have been reported, albeit with inconclusive findings, primarily due to the limited power of the studies [40, 41]. For instance, there is no consensus regarding the effects of the variant *AGT* rs699-T on the antihypertensive responses to ACE inhibitors or ARB [8]. The rs699 variant encodes for an amino acid change of Met235Thr, which has been widely accepted to be associated with salt-sensitive hypertension. Leveraging known genetic variants associated with HTN (*AGT*, *ADRB2*, and *CYP11B2*), we conducted a genetic association study on 1,000 samples of Malay ethnicity (normotensive = 500 vs hypertensive = 500) with well characterised clinical phenotypes, and found that our findings contradict those reported in European and East Asian populations. We observed significant variations in the frequencies of the risk alleles, suggesting that a true association might have been obscured (unpublished data). Additionally, two small-scale studies investigating the *ACE* I/D variants in response to enalapril or lisinopril yielded inconsistent outcomes [42, 43]. These contradictions highlight limitations in study design, such as sample size calculation and sample inclusion/exclusion criteria, as well as a lack of comprehensive phenotypic characterizations (e.g., sex, ethnicity, age, intermediate phenotypes, etc.) of the hypertensive individuals recruited.

iii. Although known to be distinguished by respective molecular mechanisms, identifying the intermediate and sub-intermediate phenotypes of HTN has not been systematically documented in many low- and middle-income countries (LMICs), and the prevalence of the intermediate and sub-intermediate phenotypes of HTN remains unclear. Phenotypic characterisation of HTN sub-intermediate phenotypes is not a common practice in many countries. Therefore, most often patients are prescribed anti-hypertensive medications based on “one-drug fits all” concept. In fact, there is no systematic documentation on the responsiveness of the anti-hypertensive medications prescribed on HTN patients from different ethnicities.

iv. Populations that suffer from HTN also include those from the lower socio-economic status, therefore awareness of genetic test and more realistically the affordability to opt for a genetic test is usually not practical.

PRECISION MEDICINE OF HYPERTENSION – ARE WE THERE?

In view of the above stated challenges, precision medicine of HT is still in its infancy stage. Ideally, a pharmacogenetic test should be affordable for the majority of people, user-friendly, specific, easily interpretable, and readily available in most clinical settings. Imagine a patient with HTN presenting at a clinic, where a drop of blood is taken and applied to an affordable "PCR-free genetic rapid test kit." This kit would immediately provide information on the patient's selected genotype(s). The attending physician could then predict which medication to prescribe, saving both time and costs for the patient by avoiding the need for genetic testing. However, before we can reach this stage the following gaps must be addressed:

i. A well-designed genetic association study (candidate gene-based, or GWAS) with

Vol 9(2) (2024) 1-8 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v9i2.27413

sufficient power must be conducted. The putative association signals identified should be replicated in populations of diverse genetic ancestries.

ii. Functional validation of the candidate genetic variants identified must be carried out, ideally both *in vitro* and *in vivo*.

iii. Along with these, comprehensive phenotypic characterisation of HTN patients must be carried out.

iv. Well-designed pharmacogenetic clinical trial(s) should be carried out to confirm the responsiveness of the patients who carried the genetic variants identified to the selected class of anti-hypertensive drugs.

v. Evaluation of cost-effectiveness of the genetic test by public health and health economic experts. This should include how common is the genotype carriers of interest in a given population, economic burden to the healthcare system vs the costs required for the genetic tests in clinical and hospital settings.

vi. Development of a cost-effective rapid genetic test kit.

vii. Accreditation of pipeline for clinical genomics and production of the rapid test kit.

viii. Continuous education and training on genetic counselling to healthcare workers and publics.

ix. Setting regulatory standards, acts and policies to regulate the implementation of precision medicine in the country.

Addressing these gaps require extended coordination and cooperation among various stakeholders and the public.

CONCLUSION

Although precision medicine for hypertension is still in its infancy, with an increased understanding of the underlying mechanisms of hypertension and its pathophysiology, the target of tailored therapy for hypertensive patients is possible. This can be achieved via structured strategies and action plans to close the gaps and overcome the aforementioned challenges. Persistent and substantial investment to research and development to genetics (and "-omics") of HTN is key to success. Continuous education, regulation, monitoring and evaluation involving crossed-disciplines stakeholders is required in making sure the materialisation of precision medicine of HTN.

REFERENCES

1. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nature Reviews Nephrology. 2020; 16(4): 223-37.
2. Ministry of Health Malaysia. Clinical Practice Guideline: Management of Hypertension 5th Edition. 2018. Accessed at www.acadmed.org.my.
3. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. The Lancet. 2005; 365(9455): 217-23. doi: 10.1016/S0140-6736(05)17741-1. PMID: 15652604.
4. Sarki AM, Nduka CU, Stranges S, Kandala NB, Uthman OA. Prevalence of hypertension in low- and middle-income countries: a systematic review and meta-analysis. Medicine. 2015; 94(50): e1959. | Doi: 10.1097/MD.0000000000001959
5. Ministry of Health, Malaysia. National Health and Morbidity Survey (NHMS) 2023 (NMRR-22-00545-XAC) Non-Communicable Diseases and Healthcare Demand. Accessed at https://iku.gov.my/nhms
6. Padmanabhan S, Dominiczak AF. Genomics of hypertension: the road to precision medicine. Nature Reviews Cardiology. 2021; 18(4): 235-50.
7. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Dominiczak AF, Grassi G, Jordan J, Poulter NR, Rodgers A, Whelton PK. Hypertension. Nature reviews. Disease primers, 4, 18014. doi.org/10.1038/nrdp.2018.14.
8. Manosroi W, Williams GH. Genetics of human primary hypertension: focus on hormonal mechanisms. Endocrine reviews. 2019; 40(3): 825-56. doi:10.1210/er.2018-00071

9. Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. Hypertension. 1991; 18(1): 67-71. doi: 10.1161/01.hyp.18.1.67
10. Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension. 1986; 8(6_pt_2): II127–II134. doi: 10.1161/01.hyp.8.6_pt_2.ii127.
11. Elijovich F, Weinberger MH, Anderson CA, Appel LJ, Bursztyn M, Cook NR, Dart RA, Newton-Cheh CH, Sacks FM, Laffer CL. Salt sensitivity of blood pressure: a scientific statement from the American Heart Association. Hypertension. 2016; 68(3): e7-46. doi: 10.1161/HYP.0000000000000047
12. Laragh JH. Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. The American journal of medicine. 1973; 55(3): 261-74. doi: 10.1016/0002-9343(73)90128-9
13. Sealey JE, Blumenfeld JD, Bell GM, Pecker MS, Sommers SC, Laragh JH. On the renal basis for essential hypertension: nephron heterogeneity with discordant renin secretion and sodium excretion causing a hypertensive vasoconstriction-volume relationship. Journal of hypertension. 1988; 6(11): 763-77. doi: 10.1097/00004872-198811000-00001
14. Resnick LM, Laragh JH, Sealey JE, Alderman MH. Divalent cations in essential hypertension: relations between serum ionized calcium, magnesium, and plasma renin activity. New England Journal of Medicine. 1983; 309(15): 888-91.
15. Basting T, Lazartigues E. DOCA-salt hypertension: an update. Current hypertension reports. 2017; 19: 1-8.
16. Coffman TM. Under pressure: the search for the essential mechanisms of hypertension. Nature medicine. 2011; 17(11): 1402-9.
17. Shih PA, O'Connor DT. Hereditary determinants of human hypertension: strategies in the setting of genetic complexity. Hypertension. 2008; 51(6): 1456-64.
18. Ahn SY, Gupta C. Genetic programming of hypertension. Frontiers in pediatrics. 2018; 5: 285 (Vol. 5) doi.org/10.3389/fped.2017.00285.
19. PAGE IH. Pathogenesis of arterial hypertension. Journal of the American Medical Association. 1949; 140(5): 451-8.
20. Hoh BP, Abdul Rahman T, Yusoff K. Natural selection and local adaptation of blood pressure regulation and their perspectives on precision medicine in hypertension. Hereditas. 2019; 156(1): 1. doi.org/10.1186/s41065-019-0080-1.
21. Muñoz-Durango N, Fuentes CA, Castillo AE, González-Gómez LM, Vecchiola A, Fardella CE, Kalergis AM. Role of the renin-angiotensin-aldosterone system beyond blood pressure regulation: molecular and cellular mechanisms involved in end-organ damage during arterial hypertension. International journal of molecular sciences. 2016; 17(7): 797. doi.org/10.3390/ijms17070797.
22. Silva DM, Vianna HR, Cortes SF, Campagnole-Santos MJ, Santos RA, Lemos VS. Evidence for a new angiotensin-(1–7) receptor subtype in the aorta of Sprague–Dawley rats. Peptides. 2007; 28(3): 702-7.
23. Zhang Z, Chen L, Zhong J, Gao P, Oudit GY. ACE2/Ang-(1–7) signaling and vascular remodeling. Science China life sciences. 2014; 57: 802-8.
24. Rabelo LA, Alenina N, Bader M. ACE2–angiotensin-(1–7)–Mas axis and oxidative stress in cardiovascular disease. Hypertension Research. 2011; 34(2): 154-60.
25. Silva IV, de Figueiredo RC, Rios DR. Effect of different classes of antihypertensive drugs on endothelial function and inflammation. International journal of molecular sciences. 2019; 20(14): 3458.
26. Dominiczak A, Delles C, Padmanabhan S. Genomics and precision medicine for clinicians and scientists in hypertension. Hypertension. 2017; 69(4): e10-3.
27. Graham LA, Padmanabhan S, Fraser NJ, Kumar S, Bates JM, Raffi HS, Welsh P, Beattie W, Hao S, Leh S, Hultstrom M, Ferreri NR, Dominiczak

AF, Graham D, McBride MW. Validation of uromodulin as a candidate gene for human essential hypertension. Hypertension. 2014; 63(3): 551-8.
28. Padmanabhan S, Graham L, Ferreri NR, Graham D, McBride M, Dominiczak AF. Uromodulin, an emerging novel pathway for blood pressure regulation and hypertension. Hypertension. 2014; 64(5): 918-23.
29. Trudu M, Janas S, Lanzani C, Debaix H, Schaeffer C, Ikehata M, Citterio L, Demaretz S, Trevisani F, Ristagno G, Glaudemans B, Laghmani K, Dell'Antonio G, the Swiss Kidney Project on Genes in Hypertension (SKIPOGH) team, Loffing J, Rastaldi MP, Manunta P, Devuyst O, Rampoldi L. Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. Nature medicine. 2013; 19(12): 1655-60
30. Cooper-DeHoff RM, Johnson JA. Hypertension pharmacogenomics: in search of personalized treatment approaches. Nature Reviews Nephrology. 2016; 12(2): 110-22.
31. Svensson-Färbom P, Wahlstrand B, Almgren P, Dahlberg J, Fava C, Kjeldsen S, Hedner T, Melander O. A functional variant of the NEDD4L gene is associated with beneficial treatment response with β-blockers and diuretics in hypertensive patients. Journal of hypertension. 2011; 29(2): 388-95.
32. Nuotio ML, Sánez Tähtisalo H, Lahtinen A, Donner K, Fyhrquist F, Perola M, Kontula KK, Hiltunen TP. Pharmacoepigenetics of hypertension: genome-wide methylation analysis of responsiveness to four classes of antihypertensive drugs using a double-blind crossover study design. Epigenetics. 2022; 17(11): 1432-45.
33. Rimpelä JM, Kontula KK, Fyhrquist F, Donner KM, Tuiskula AM, Sarin AP, Mohney RP, Stirdivant SM, Hiltunen TP. Replicated evidence for aminoacylase 3 and nephrin gene variations to predict antihypertensive drug responses. Pharmacogenomics. 2017; 18(5): 445-58.
34. Turner ST, Schwartz GL, Chapman AB, Boerwinkle E. C825T polymorphism of the G protein β3-subunit and antihypertensive response to a thiazide diuretic. Hypertension. 2001; 37(2): 739-43.
35. Oliveira-Paula GH, Pereira SC, Tanus-Santos JE, Lacchini R. Pharmacogenomics and hypertension: current insights. Pharmacogenomics and personalized medicine. 2019: 341-59.
36. Pazoki R, Dehghan A, Evangelou E, Warren H, Gao H, Caulfield M, Elliott P, Tzoulaki I. Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. Circulation. 2018; 137(7): 653-61.
37. Deng L, Hoh BP, Lu D, Fu R, Phipps ME, Li S, Nur-Shafawati AR, Hatin WI, Ismail E, Mokhtar SS, Jin L, Zilfalil BA, Marshall CR, Scherer SW, Al-Mulla F, Xu S. The population genomic landscape of human genetic structure, admixture history and local adaptation in Peninsular Malaysia. Human genetics. 2014; 133: 1169-85.
38. Yew CW, Lu D, Deng L, Wong LP, Ong RT, Lu Y, Wang X, Yunus Y, Aghakhanian F, Mokhtar SS, Hoque MZ, Voo CL, Abdul Rahman T, Bhak J, Phipps ME, Xu S, Teo YY, Kumar SV, Hoh BP. Genomic structure of the native inhabitants of Peninsular Malaysia and North Borneo suggests complex human population history in Southeast Asia. Human genetics. 2018; 137: 161-73.
39. HUGO Pan-Asian SNP Consortium, Abdulla MA, Ahmed I, Assawamakin A, Bhak J, Brahmachari SK, Calacal GC, Chaurasia A, Chen CH, Chen J, Chen YT. Mapping human genetic diversity in Asia. Science. 2009; 326(5959): 1541-5.
40. Say YH, Ling KH, Duraisamy G, Isaac S, Rosli R. Angiotensinogen M235T gene variants and its association with essential hypertension and plasma renin activity in Malaysian subjects: a case control study. BMC cardiovascular disorders. 2005; 5: 1-10.

Vol 9(2) (2024) 1-8 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v9i2.27413

41. Ghazali DM, Rehman A, Rahman AR. Candidate gene polymorphisms and their association with hypertension in Malays. Clinica Chimica Acta. 2008; 388(1-2): 46-50.
42. Heidari F, Vasudevan R, Mohd Ali SZ, Ismail P, Etemad A, Pishva SR, Othman F, Bakar SA. Association of insertion/deletion polymorphism of angiotensin-converting enzyme gene among Malay male hypertensive subjects in response to ACE inhibitors. Journal of the Renin-Angiotensin-Aldosterone System. 2015; 16(4): 872-9.
43. Heidari F, Vasudevan R, Ali SZ, Ismail P, Arkani M. RAS genetic variants in interaction with ACE inhibitors drugs influences essential hypertension control. Archives of medical research. 2017; 48(1): 88-95.

Vol 9(2) (2024) 1-8 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v9i2.27413