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GENETICS FACTORS BEHIND THE OCCURRENCE OF HYPERTENSION: SYSTEMATIC REVIEW IN LITERATURE

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Abstract:
This review is aiming to discuss the Genetics factors which lead to the occurrence of HTN. The present review was conducted by searching in Medline, Embase, Web of Science, Science Direct, BMJ journal and Google Scholar for, researches, review articles and reports, published over the past years during the period from 3 of August 2018 to 7 October 2018 . Books published on the Genetics factors of HTN. If several studies had similar findings, we randomly selected one or two to avoid repetitive results. On the basis of findings and results this review found The heritability of blood pressure (BP) is estimated to be 30–50%. A great effort was made to find genetic variants affecting BP levels through Genome-Wide Association Studies (GWAS). This approach relies on the "common disease–common variant" hypothesis and led to the identification of multiple genetic variants which explain, in aggregate, only 2–3% of the genetic variance of hypertension.

Keywords: *HTN , Genetics, essential hypertension; blood pressure; genome-wide association studies; next-generation sequencing; rare variants; rare-variants association testing; burden test; sequence kernel association test*

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INTRODUCTION:

Hypertension is a major modifiable risk factor for renal, cardiovascular, and cerebrovascular disease, and a leading underlying cause of global mortality and morbidity [1]. Incremental advances in our understanding of blood pressure have highlighted its complex pathophysiology, whereby genetic and environmental factors combine with a plethora of physiological pathways and mechanisms ultimately to yield the phenotype. While epidemiological studies have improved our understanding of environmental factors in relation to blood pressure, especially with regards to diet and exercise, the exact role of genetics in this setting has been challenging to tease apart from the shared environment often found in families and communities [2].

Systemic hypertension is a consistently elevated systolic or diastolic blood pressure in the systemic arteries. Systolic blood pressure (SBP) is generated by the contraction of the ventricles and represents the highest blood pressure

(BP) level. Diastolic blood pressure (DBP) is the BP remaining during the relaxation of the ventricles and represents the lowest BP level. The term Pulse Pressure (PP) refers to the difference (in mmHg) between the systolic and diastolic pressures, while the Mean Arterial Pressure (MAP) is the average BP during a single cardiac cycle [3]. Clinicians consider 140 mmHg as the maximum normal adult SBP value, and 90 mmHg as the upper limit for normal DBP value, as suggested by the World Health Organization (WHO) [4]. Usually, high SBP is caused by the narrowing of the arterioles. This narrowing raises the peripheral resistance to blood flow, which requires a greater workload for the heart and raises arterial pressure[1]. Elevated BP levels still represent a huge public health issue worldwide, being the major risk factor for cardiovascular disease, including coronary heart disease, stroke, and heart failure. Each year, 17 million people prematurely die because of cardiovascular disease, and, among these, nine million deaths occur because of hypertension-related complications [5].

METHODS:

The present review was conducted October 2018 in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) declaration standards for systematic reviews. We reviewed all the topics on HTN, such as genetics, etiology, epidemiology, and clinical statistics. To achieve this goal, we searched Medline, Embase, Web of Science, Science Direct, and Google Scholar for, researches, review articles and reports, published over the past 15 years. Books published on HTN and on Genetics factors.

Our search was completed without language restrictions. Then we extracted data on study year, study design, and key outcome on HTN. The selected studies were summarized and unreproducible studies were excluded. Selected data is shown in the Table 1.

Data extraction and analysis

Information relating to each of the systematic review elements was extracted from the studies and collated in qualitative tables. Direct analysis of the studies of HTN is made with extreme caution, as different sampling techniques can provide bias as overview of the assemblage.

RESULTS:

Ninety-five percent of hypertensive patients presents a type lacking an obvious identifiable cause (Essential or Primary Hypertension). Investigations of twin and family studies revealed a moderate heritability ranging between 30% and 50% [6].

Results from Next-Generation Sequencing Studies GWAS identified more than 100 genetic variants influencing BP [7]. However, the causal variants underlying the majority of genetic associations remained unknown. In recent years, three different NGS approaches have been proposed to study rare variants in hypertension and BP (Table 1).

The first approach is to check GWAS signals and describe novel associations by performing are sequencing of only a few genes previously indicated by GWAS. This approach, commonly called target re-sequencing, is cheaper and allows one to highlight the variations within the whole frequency spectrum in a precise genomic locus. The CHARGE Consortium adopted the strategy. In the frame of this consortium, the signals identified by precedent GWAS were re-sequenced with the aim of describing novel variations with large effects on several common diseases [8]. Concerning BP, within the CHARGE Targeted Sequencing Study, target re sequencing of 4178 Europeans was performed on six BP genes identified by GWAS (ATP2B1, CACNB2, CYP17A1, JAG1, PLEKHA7, and SH2B3), however, neither common nor rare variants were consistently associated with the trait with large effect sizes, independently of the original GWAS signals [9]. Regarding hypertension, an association with rs3918226 in the eNOS gene

promoter was described in the GWAS from Salvi et al [10]. (OR for minor allele T = 1.34 (95% CI, 1.25–1.44); p = 1.03 _ 10-14). In 2013, a 140 kb genomic area encompassing the eNOS gene was re-sequenced from the same group.

The study identified 338 variants, including 61 novel variants, and rs3918226 still appeared as the SNP most closely associated with hypertension. Moreover, if compared with the C major allele, the T riskallele was associated with lower eNOS transcriptional activity when tested in HeLa cells [11].

A second approach is whole exome sequencing (WES) in which only the coding portions of the genome, (about 2%), estimated to harbor 85% of disease-causing mutations, are sequenced [12]. A WES

Study was performed on DNA samples from 17,956 individuals of European and African ancestries, included in the CHARGE, National Heart, Lung, and Blood Institute GO Exome Sequencing Project, Rotterdam Study, and the Erasmus Rucphen Family cohorts. These findings implicate the effect of the aggregation of 95 rare coding variants in CLCN6 on decreasing BP levels of 3–4 mmHg, independently of the tagging SNP rs17367504 previously reported. The effect size described here was about four- to six-fold larger than previous common BP variants from GWAS [13].

Table (1) Results from Sequencing Studies.

Authors	Sample	Technology	Design	Population	Main Results
Ji et al [14].	1985 unrelated subjects and 1140 relatives	WES	Screening of SLC12A3, SLC12A1 and KCNJ1 genes exons to identify rare variants within FHS offspring cohort	Largely whites of European descent	30 different mutations observed Mean long-term SBP among mutation carriers was 6.3 mmHg lower than the mean of the cohort (p = 0.0009). For DBP, mean effect was 3.4 mmHg (p = 0.003)
Morrison et al [15].	4178	Target-re-sequencing	Case-cohort study design within the CHARGE Targeted Sequencing Study on 6 BP loci	European	None of the common variants reached statistical significance threshold of p = 0.0001 Rare variation was not significantly associated with any of the BP measures
Lin et al [16].	1509 unrelated subjects; 256 individuals in 47 families	WGS and WES	To apply CAPL-burden and CAPL-SKAT tests to the GAW19 data set using the combined family and case–control data for HTN (GAW19)	Mexican American	None of the tests for the top 10 genes passed the multiple testing correction threshold (p= 3.4×10−6)
Tong et al [17].	142	WGS	WGS and gene expression joint analysis in relation to SBP, DBP, and HTN (GAW19)	Mexican American	No gene reached statistical significance after adjusting for multiple testing
Sun et al [18].	1851	WES	To apply W-test on real NGS data set of hypertensive disorder (GAW19)	Mexican American	MACROD1/LRP16 locus was associated with HTN after Bonferroni correction (OR = 3.8; p= 6.1 × 10−7)
Yu et al [19].	Discovery: 14,497 in first stage and 3459 in second stage	WES	To examine the impact of rare variants in CHARGE and ESP studies with meta-analysis of two-stage discovery cohorts	European and African ancestry	95 rare coding variants identified in CLCN6 associated, in aggregate, with decreased BP (3–4 mmHg), independent of the tagging SNP rs17367504 previously identified _ The effect size was about four- to six-fold larger than previous common BP variants from GWAS
Lu and Cantor [20].	275 trios	WGS	To analyse rare variants within ADCY5 and UBE2E2 genes in parent-child trios (GAW18)	Mexican American	ADCY5 and UBE2E2 genes showed marginal association with HTN with p = 3.2 × 10−4 for ADCY5 and p = 0.035 for UBE2E2
Derkach et al [21].	103 unrelated individuals	WGS	To analyse rare variants from Chr. 3 (GAW18)	Mexican American	No significant results in the analysis of real phenotype data (p = 5.6 × 10−5 for coding variants; p = 6.9 × 10−5 for changing variants; p = 1.1 × 10−4 for damaging variants)
Cao et al [22].	783 (GWAS); 506 (WGS)	WGS	To apply USR algorithm to data from GAW18	Mexican American	23 promising genes and 3 significant pathways relevant to HTN identified (p < 5.28 × 10−3)

Sample number (N), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse Pressure (PP), Mean Artery Pressure (MAP), Hypertension (HTN), Single Nucleotide Polymorphism (SNP), Genome-Wide Association Studies (GWAS), Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES), Genetic Analysis Workshop (GAW), Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), Exome Sequencing Project (ESP), Sequence Kernel Association Test (SKAT), Optimal Unified Test (SKAT-O), SKAT-Combined (SKAT-C), Quality-based Multivariate Score Association Test (qMSAT), Combined Multivariate and Collapsing (CMC), Family-based Association Test (FBAT), Genome-wide Complex Trait Analysis (GCTA), Combined Association in the Presence of Linkage (CAPL), support vector machine (SVM), Unified Sparse Regression (USR), Odds Ratio (OR).

DISCUSSION:

The main purpose of this article was to determine the genetics which lead to the occurrence of HTN. Two additional studies exploited WES data to focus on selected genes. Loss-of-function mutations in SLC12A3, SLC12A1, and KCNJ1 genes, essential for normal renal NaCl reabsorption, cause Bartter's and Gitelman's syndromes. Their exons were screened to search for rare heterozygous variants within the Framingham Heart Study offspring cohort. Thirty different mutations were observed. The mean long-term SBP among mutation carriers was 6.3 mmHg lower than the mean of the cohort ($p = 0.0009$).

For DBP, the mean effect was 3.4 mmHg ($p = 0.003$) [62]. Findings from previous GWAS indicated ULK4 and MAP4 genes, encoding, respectively, a Serine/Threonine-Protein Kinase and a non-neuronal microtubule-associated protein, as related to BP and hypertension[23]. Thirty-six rare haplotype blocks were found to be significantly associated with BP in ULK4 gene, and ten in MAP4 gene[24].

The study described above was conducted in the frame of the Genetic AnalysisWorkshops (GAWs).

Since 1982, GAWs were held by a group of multidisciplinary scientists to deal with the role of genetics in complex diseases. For GAW18, GT2D-GENES Consortium and the San Antonio Family Heart Study provided data overall genome, systolic and diastolic BP, and related covariates in two Mexican American samples. In the GAW19, new data were included reaching a collection of WGS, WES, and gene expression data from 20 large families in addition to a set of 1943 unrelated subjects whose exome sequences were available. Simulated phenotypes were also included for each sample on the basis of the real sequence data [25]. Several papers have been published so far, mostly on methodological approaches (see the following paragraph "Statistical analysis of rare variants") to handle rare variations in relation to hypertension

CONCLUSIONS:

Thanks to the introduction of exome arrays technologies, great efforts have been conducted to extend association analyses to rare and coding variants. This finding has potential implications concerning early lifestyle interventions in high-risk individuals. In summary, although several complex networks of interacting pathways controlling BP have been established (e.g., RAAS and ENaC-related pathways), the current efforts on rare variants analysis have not yet provided a clear answer on where the missing heritability lies. The advent of NGS provided the opportunity to detect, in a high-throughput way, the entire spectrum of genomic variation ranging from rare to common variants and from SNVs to insertions, deletions, and copy number variants. Despite the undeniable advantages, few studies have been conducted so far using NGS technologies in relation to hypertension and/or BP WES and, more so, WGS costs are still too high to analyze the large sample size required to identify rare variants. Target re-sequencing allows the cutting of laboratory costs and increases the statistical power by reducing multiple signals testing, therefore, this approach could be useful to detect causative variants underlying the trait by deeply analyzing BP-associated loci described by GWAS. However, the studies reported here failed to identify new rare variants, likely because of the reduced sample size compared to GWAS. The joint effort of large consortia with available sequencing data would be helpful to meet the need of a larger sample size.

Another main limitation of rare variants analysis is the study of gene-gene and gene-environment interactions at a population level, which can be investigated only in terms of burden and collapsing tests, with environmental factors playing, anyway, an important role in systemic hypertension.

Functional in vitro and in vivo models should further support the statistical interactions. Rodent models represent an attractive genetic resource to

functionally evaluate previously.

REFERENCES:

1. Oparil S, Zaman, M.A, Calhoun D.A. Pathogenesis of hypertension. Ann. Intern. Med. **2003**, 139, 761–776. [CrossRef] [PubMed].
2. Dart A.M, Kingwell B.A. Pulse pressure—A review ofmechanisms and clinical relevance. J. Am. Coll. Cardiol. **2001**, 37, 975–984. [CrossRef].
3. Henry J.B, Miller M.C, Kelly K.C, Champney D. Mean arterial pressure (MAP): An alternative and preferable measurement to systolic blood pressure (SBP) in patients for hypotension detection during hemapheresis. J. Clin. Apher. **2002**, 17, 55–64. [CrossRef] [PubMed].
4. Shrout, T, Rudy D.W, Piascik M.T. Hypertension update, JNC8 and beyond. Curr. Opin. Pharmacol. **2017**, 33, 41–46. [CrossRef] [PubMed].
5. Lim S.S , Vos T. Flaxman A.D, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson H.R, Andrews K.G, Aryee M. et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet **2012**, 380, 2224–2260. [CrossRef]
6. Luft F.C. Twins in cardiovascular genetic research. Hypertension **2001**, 37, 350–356. [CrossRef] [PubMed].
7. Seidel E, Scholl, U.I. Genetic mechanisms of human hypertension and their implications for blood pressure physiology. Physiol. Genom. 2017, 49, 630–652. [CrossRef] [PubMed].
8. Lin H, Wang M, Brody J.A, Bis J.C, Dupuis J, Lumley T, McKnight B, Rice K. M, Sitlani C.M, Reid J. G et al. Strategies to design and analyze targeted sequencing data: cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Targeted Sequencing Study. Circ. Cardiovasc. Genet. 2014, 7, 335–343. [CrossRef] [PubMed].
9. Morrison A.C, Bis J.C, Hwang S.J, Ehret G.B, Lumley T., Rice K., Muzny D., Gibbs R.A, Boerwinkle E., Psaty B.M, et al. Sequence analysis of six blood pressure candidate regions in 4178 individuals: the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) targeted sequencing study. PLoS ONE **2014**, 9, e109155. [CrossRef] [PubMed]
10. Salvi E., Kutalik Z., Glorioso N., Benaglio P., Frau F., Kuznetsova T., Arima H., Hoggart C., Tichet J., Nikitin Y.P, et al. Genomewide association study using a high-density single nucleotide polymorphism array and case-control design identifies a novel essential hypertension susceptibility locus in the promoter region of endothelial NO synthase. Hypertension 2012, 59, 248–255. [CrossRef] [PubMed].
11. Salvi E., Kuznetsova T., Thijs L., Lupoli S., Stolarz-Skrzypek K., D'Avila F., Tikhonoff V., De Astis S., Barcella M., Seidlerova J., et al. Target sequencing, cell experiments, and a population study establish endothelial nitric oxide synthase
12. Choi M., Scholl U.I., Ji W., Liu T., Tikhonova I.R, Zumbo P., Nayir A., Bakkaloglu A., Ozen S.,Sanjad S., et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. Proc. .Natl. Acad. Sci. USA **2009**, 106, 19096–19101. [CrossRef] [PubMed].
13. Yu B., Pulit S.L, Hwang S.J, Brody, J.A, Amin N., Auer P.L, Bis J.C, Boerwinkle E., Burke G.L, Chakravarti A., et al. Rare Exome Sequence Variants in CLCN6 Reduce Blood Pressure Levels and Hypertension Risk. Circ. Cardiovasc. Genet. **2016**, 9, 64–70. [CrossRef] [PubMed].
14. Ji W., Foo J.N, O'Roak B.J, Zhao H., Larson M.G, Simon D.B, Newton-Cheh C., State, M.W, Levy D., Lifton R.P. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat. Genet. **2008**, 40, 592–599. [CrossRef] [PubMed].
15. Morrison A.C, Bis J.C, Hwang, S.J, Ehret G.B, Lumley T., Rice K., Muzny D., Gibbs R.A , Boerwinkle E., Psaty B.M, et al. Sequence analysis of six blood pressure candidate regions in 4178 individuals: the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) targeted sequencing study. PLoS ONE 2014, 9, e109155. [CrossRef] [PubMed].
16. Lin P.L, Tsai W.Y, Chung R. H. A combined association test for rare variants using family and case-control data. BMC Proc. **2016**, 10, 215–219. [CrossRef] [PubMed].
17. Tong X., Wei C., Lu, Q. Genome-wide joint analysis of single-nucleotide variant sets and gene expression for hypertension and related phenotypes. BMC Proc. **2016**, 10, 125–129. [CrossRef] [PubMed].
18. Sun R., Weng H.Y, Hu I.C, Guo J.F, Wu W.K, Zee C.Y, Wang M.H. A W-test collapsing method for rare-variant association testing in exome sequencing data. Genet. Epidemiol. **2016**, 40, 591–596. [CrossRef] [PubMed].
19. Yu B., Pulit S.L, Hwang S.J., Brody J.A, Amin N., Auer P.L, Bis J.C, Boerwinkle E., Burke G.L, Chakravarti A. et al. Rare Exome Sequence Variants in CLCN6 Reduce Blood Pressure

Levels and Hypertension Risk. Circ. Cardiovasc. Genet. **2016**, 9, 64–70. [CrossRef] [PubMed].
20. Lu A.T, Cantor R.M. Identifying rare-variant associations in parent-child trios using a Gaussian support vector machine. BMC Proc. **2014**, 8, S98. [CrossRef] [PubMed]
21. Derkach A., Lawless J.F, Merico D., Paterson A.D, Sun L. Evaluation of gene-based association tests for analyzing rare variants using Genetic Analysis Workshop 18 data. BMC Proc. **2014**, 8, S9. [CrossRef] [PubMed].
22. Cao S., Qin H., Deng H.W, Wang, Y.P. A unified sparse representation for sequence variant identification for complex traits. Genet. Epidemiol. **2014**, 38, 671–679. [CrossRef] [PubMed].
23. Wain L.V, Verwoert G.C, O'Reilly P.F, Shi G., Johnson T., Johnson A.D, Bochud M, Rice K.M, Henneman P., Smith A.V, et al. Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. Nat. Genet. 2011, 43, 1005–1012. [CrossRef] [PubMed].
24. Datta A.S, Zhang, Y., Zhang L., Biswas S. Association of rare haplotypes on ULK4 and MAP4 genes with hypertension. BMC Proc. **2016**, 10, 363–369. [CrossRef] [PubMed].
25. Blangerov J., Teslovich T.M., Sim X., Almeida M.A., Jun G., Dyer T.D, Johnson M., Peralta J.M, Manning, A., Wood, A.R., et al. human genomic, transcriptomic and phenotypic data for genetic analysis workshop 19. BMC Proc. **2016**, 10, 71–77. [CrossRef] [PubMed]

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