Review Article

Hypertension Gene Risk Score in Diagnosis and Prediction of Complications

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ABSTRACT

Hypertension (HT) is a polygenic disease and is the most important risk factor for morbidity and mortality globally due to associated risk of cardiovascular diseases (CVD). The relation between genetic determinants of hypertension and the development of CVD can therefore be important for understanding disease mechanisms. This review aims to highlight the potential of genomic screening to develop and evaluate a gene risk score for cardiovascular risk prediction in hypertension. Gene risk score as a risk prediction tool is a promising area potentially supporting effective prevention of HT and CVD. Generating a gene risk score substantially improves health outcomes by diagnosing the risk of developing a disease, based on the total number of changes related to disease, followed by early and aggressive intervention in patients with high score.

INTRODUCTION

Elevated blood pressure (BP) is a leading risk factor for morbidity and mortality globally.[1] The substantial public health toll arising from hypertension (HT) can be attributed to its high prevalence and associated risk of cardiovascular disease.[2,3] Hypertension has been estimated to account for >45% of all coronary heart disease (CHD) events worldwide.[4] The relation between genetic determinants of hypertension and the development of CVD and CHD can therefore be important for understanding disease mechanisms. The advent of genome wide association studies has initiated elucidation of the genetic architecture of CAD which has brought a positive impact on public health. This review aims to highlight the potential of genomic screening to develop and evaluate a gene risk score for conventional risk prediction in hypertension.

HT is a polygenic disease where one or more genes play a major role in controlling BP. The heritable component of blood pressure documented in familial and twin studies suggests that 30-50% of the variance of blood pressure readings is attributable to genetic heritability and about 50% to environmental factors.[5] The potential of genomics is being explored to gain knowledge about the genetics of hypertension to address its diagnosis, control, and treatment. Tools in molecular diagnostics and biology have revolutionised the identification and analysis of genes and their effects on health of an individual. Focus and goal of genetic studies has been identification of causes and variants underlying diseases like hypertension. Initially this was done through examining associations between a limited number of single nucleotide polymorphisms (SNPs) which can be also referred to as genetic variants and the disease of interest. With the advancements in genomic analysis, research moved to Genome Wide Association Studies (GWAS), where the association between thousands to millions of SNPs and diseases/traits of interest could be investigated simultaneously.

Various terms used to describe scores generated by combining multiple SNPs are as mentioned below: (allelic risk score, genetic/polygenic risk score (PRS), and GRS/GPS are often used interchangeably)[6]

1. Basic/simple/genetic/allelic risk score- Based on combination of a few SNPs.

2. Polygenic/genetic risk score- Larger number of SNPs is included into the PRS calculation than in basic genetic risk scores.

3. Genome-wide polygenic risk score (GRS)- A score developed by incorporation of hundreds of thousands to millions of SNPs across the genome.

GENE RISK SCORES

The individual genetic variants, or single nucleotide polymorphisms (SNPs), that have been identified typically explain a very small fraction of the variation in complex traits and thus have limited predictive capacity for disease risk.[7] Aggregating information about multiple SNPs, each with small effects, into a single genetic risk score (GRS) has become a useful tool for examining the cumulative predictive ability of genetic variation at known loci on cardiovascular disease outcomes and related phenotypes.[8] Polygenic scores, much like other biomarkers, are normally distributed across a population and hence theoretically provide a risk distribution from 0-100%.[6]

A polygenic genotype risk score (GRS) is calculated from GWAS summary statistics by summing the number of risk alleles carried by an individual, weighted by the GWAS effect size.[9] This approach is of advantage as each individual SNP is less important and the influence of imperfect linkages on score is less. The use of polygenic risk scores,[7,10] (PRS, also known as risk profile scoring, genetic scoring, and genetic risk scoring) has become widespread in biomedical and social science disciplines.[11-13] Polygenic risk scores can substantially improve health outcomes as risk of developing a disease, based on the total number of changes related to disease can be known by polygenic risk score. Generating polygenic risk scores can guide healthcare decisions.

There could be multiple applications of GRS in health care, including:[6]

- To identify individuals who have either increased or decreased risk of disease.
- Aiding disease diagnosis
- Informing selection of therapeutic intervention
- Improvement of risk prediction
- Informing disease screening
- Informed life planning.

Generating PRS score has few limitations too. Polygenic scoring studies need to be conducted by strategic collection of large samples from diverse worldwide populations. Correct interpretation of polygenic variation requires correlation and interaction of environmental influences on phenotypes. Methodology used to construct scores should be wisely chosen to create GWAS data.

HYPERTENSION GENOMICS

The Millennium Genome Project for hypertension was started in 2000 to identify genetic variants conferring susceptibility to hypertension, pathogenesis, and to initiate genome-based personalized medical care. Two different approaches were launched, genome-wide association analysis using single-nucleotide polymorphisms (SNPs) and microsatellite markers, and systematic candidate gene analysis, under the hypothesis that common variants have an important role in the etiology of common diseases. [14]

The first GWAS (by the Wellcome Trust Case Control Consortium [WTCCC]) [15] adopted a case-control study design using 3,000 shared controls and 14,000 cases (2,000 for hypertension) of European ancestry to study 7 complex diseases simultaneously. Hypertension was the only disease without any significant results. The first GWAS of quantitative BP phenotypes was conducted in the Framingham Heart Study, which included 1,400 family subjects and found no significant results either.[16] The findings of these studies clearly indicated the complex genetic mechanisms underlying BP regulation. Two large-scale meta-analyses of GWAS from the Global Blood Pressure Genetics (Global BPgen)[17] and Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)[18]consortia identified associations with standing correction for multiple testing (genome-wide significance). Each of the study contained nearly 30,000 subjects at the discovery phase and found 8 genomic loci, among which 3 loci overlapped.

Wang et al, [19] in their study, genotyped 105 simple deletions and SNPs from 64 candidate genes in 3,550 patients and 6,560 control subjects from six case-control association studies conducted in the United States, Europe, and China. Although seven polymorphisms showed a nominal additive association, none remained statistically significant after adjustment for multiple comparisons. In contrast, after stratification for hypertension, two lymphotoxin-alpha polymorphisms, which are in strong linkage disequilibrium, were significantly associated among non-hypertensive individuals.

The International Consortium for Blood Pressure (ICBP)[20]

used a multistage design with 200,000 individuals of European descent, replicated the previous 13 loci effectively and discovered 16 new loci significant at the genome-wide level. A GRS was created from 29 SNPs associated with systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) at $p<5\times10-9$, weighted by the mean effect size for SBP and DBP. The GRS was evaluated in an independent cohort of 23,294 women and showed an increase of 1.65 and 1.10 mmHg per SD of the GRS for SBP and DBP, respectively, as well as a 23% increase in the odds of HTN. Two derived BP phenotypes: mean arterial pressure and pulse pressure (PP)[21] were analyzed by ICBP and this study discovered 4 novel loci for PP and 2 novel loci for mean arterial pressure.

The first large meta-analysis of GWAS on BP traits among East Asians was conducted by the Asian Genetic Epidemiology Network (AGEN) consortium.[22] One of the 8 groups participating in stage 1 meta-analysis, which included 19,608 individuals totally confirmed 7 loci previously identified in the European population reported by Global BPgen and CHARGE, and additionally identified 6 novel loci: ST7L-CAPZA1, FIGNGRB14, ENPEP, NPR3, TBX3, and ALDH2 after de novo genotyping in two stages of replication involving 10,518 and 20,247 East Asian samples.[23] The strongest SNPs associated with different BP traits are in table 1.

Several large-scale genome wide association studies have identified single nucleotide polymorphisms (SNPs) associated with HTN, T2D and obesity.[18,20,24-26] A gene ATP2B1 responsible for hypertension was identified in not only Japanese but also Caucasians. The high blood pressure susceptibility conferred by certain alleles of ATP2B1 has been widely replicated in various populations. Reduced expression of this gene associated with the risk allele may be an underlying mechanism relating the ATP2B1 variant to hypertension.[14] Taal et al[27] in a study, reported that the variance of adult systolic BP explained by GRS, while four- to five-fold greater than single SNPs, is still very small at about <1.2% of the total and very much short of the expected level of inheritability. GRSs consisting of BP-associated SNPs have also been evaluated in non-EA ethnicities. A trans-ethnic GWAS meta-analysis with an African-ancestry discovery sample and a multi-ethnic replication sample identified five SNPs credibly associated with blood pressure that were not previously identified through EA meta-analyses.[28] A GWAS meta-analysis with over 80,000 Han Chinese (including discovery and replication samples) identified several SNPs that met genome-wide significance for association with SBP, DBP, and/or HTN.[29] In a subset of >28,000 subjects, the GRS was significantly associated with HTN (OR=1.66 for the highest versus lowest quintile of GRS) and was also significantly associated with SBP and DBP. This study illustrates a well-powered hybrid approach to GRS SNP selection for use in non-EA ethnic groups.[30] When the same GRS was evaluated in a longitudinal study of >17,000 Swedes, a 1 SD increase in GRS was significantly associated with an increase of 1.0 and 0.6 mmHg in SBP and DBP, respectively, as well as a 61% increase in the odds of hypertension at baseline.[31]

The latest GWAS among UK Biobank participants of European ancestry included 140,000 subjects from a single source at the discovery phase. With dense 1000 Genomes Project and UK10K imputation, they yielded a data set with 9.8 million variants for the meta-analysis. With the help of major international consortia for parallel replication, they included GWAS data from 330,956 individuals in total and reported 107 significant loci, among which 24 were associated with systolic BP (SBP), 41 with diastolic BP (DBP), and 42 with PP.[32] Largest cardiovascular genetic association study to date, with over 1 million participants, demonstrated the total number of genetic signals associated with hypertension surpassing 1000, at 901 genetic loci.[33] Results from the assumption-free surveys across the genome have laid foundations for developing genomic risk scores (GRS) in the estimation of an individual's underlying genomic risk.[38-40] GRS are based on germline DNA, they are quantifiable in early life, at or before birth offering the potential for early risk screening and primary prevention before other conventional risk factors become informative.

Over 500 new gene regions that influence people's blood pressure have been discovered in the largest global genetic study of blood pressure to date, led by Queen Mary University of London and Imperial College London. Involving more than one million participants, the results more than triple the number of blood pressure gene regions to over 1,000 and means that almost a third of the estimated

heritability for blood pressure is now explained.[41] More than 300 single nucleotide polymorphisms (SNPs) with relation to hypertension have been identified in genome-wide association studies (GWAS).[11,42] The relation between these many hypertension associated SNPs and occurrence of CHD has received limited attention.

GENOMICS OF BLOOD PRESSURE AND GENETIC RISK PREDICTION OF CVD

Hypertension being an important risk factor for myocardial infarction, heart failure, and stroke, control of blood pressure in hypertensive patients is of prime importance. Even though many safe and effective

Table 1: Significant genetic loci for blood pressure and hypertension reported in genome-wide association studies in Asians[23]

Chr	Strongest SNP	Position	EA	EAF	OR or BETA	p value	N	Closest gene	Trait
1	rs880315	10736809	C	0.65	0.56	3.05E-10	32,611	CASZ1	DBP
1	rs10745332	112646431	A	0.82	0.96	2.52E-09	46,269	MOV10	SBP
2	rs1344653	19531084	A	0.53	-0.27	7.79E-12	220,853	OSR1	PP
2	rs1275988	26691496	T	0.53	-0.37	4.95E-21	236,311	KCNK3	OH
2	rs7604423	43155602	C	0.66	-0.21	2.40E-08	217,072	NR	DBP
2	rs6736587	81628601	C	0.16	-1.38	5.3E-08	NA	CTNNA2	OH
2	rs16849225	164050310	C	0.61	0.75	3.45E-11	49,511	GRB14, FIGN	SBP
3	rs820430	27507409	A	0.32	0.76	1.36E-12	79,318	SLC4A7	SBP
3	rs9810888	53601568	G	0.39	0.39	4.0E-12	77,555	CACNA1D	DBP
4	rs1902859	80236549	C	0.41	1.34	1.76E-22	45,856	FGF5	SBP
4	rs2014912	85794517	T	0.16	0.62	5.37E-17	242,456	ARHGAP24	SBP
4	rs6825911	110460482	C	0.51	0.39	8.96E-09	49,511	ENPEP	DBP
4	rs13143871	155698052	T	0.80	0.96	5.16E-08	45,737	GUCY1A3	SBP
5	rs1173766	32804422	C	0.60	0.63	1.95E-08	49,970	NPR3	SBP
5	rs13359291	123140763	A	0.31	0.53	8.88E-16	229,584	PRDM6	SBP
5	rs9687065	149011577	A	0.78	0.26	7.36E-11	259,216	ABLIM3, SH3TC2	DBP
6	rs2021783	32077074	C	0.79	0.49	2.18E-12	78,911	CYP21A2	DBP
6	rs1563788	43340625	T	0.31	0.51	2.22E-16	220,757	ZNF318	SBP
6	rs1474698	56199399	T	0.62	-0.20	4.52E-09	274,981	NR	PP
7	rs2107595	19009765	A	0.23	0.31	3.91E-11	209,305	HDAC9	PP
7	rs10260816	45970501	C	0.61	0.31	1.51E-14	207,070	IGFBP3	PP
7	rs17477177	106771412	T	0.77	-0.53	3.69E-12	99,344	PIK3CG	PP
10	rs4919669	102712218	A	0.43	-0.65	2.63E-08	NA	ARL3	SBP
10	rs284844	102794772	A	0.49	-0.75	1.05E-11	NA	WBP1L	SBP
10	rs4409766	102856906	T	0.71	1.24	6.08E-17	46,030	CYP17A1	SBP
10	rs11191548	103086421	T	0.74	1.18	3.94E-17	41,315	CNNM2	SBP
10	rs11191580	103146454	T	0.74	0.97	4.44E-15	NA	NT5C2	SBP
11	rs4757391	16281393	C	0.28	0.88	5.20E-9	46,336	SOX6	SBP
11	rs751984	61510774	T	0.79	0.33	7.66E-12	233,082	LRRC10B, SYT7	MAP
12	rs12579720	20020830	C	0.32	-0.32	2.2E-16	218,606	PDE3A	DBP
12	rs17249754	89666809	G	0.64	1.17	7.72E-20	40,719	ATP2B1	SBP
12	rs3184504	111446804	T	0.46	0.54	2.20E-10	35,342	SH2B3	DBP
12	rs653178	111569952	T	0.50	-0.55	1.20E-08	35,342	ATXN2	DBP
12	rs11066280	112379979	T	0.75	1.01	1.32E-35	46,957	HECTD4	DBP
12	rs35444	115114632	A	0.75	0.52	9.62E-08	29,746	TBX3	DBP
12	rs11067763	115760536	A	0.62	0.51	2E-18	79,651	MED13L	DBP
17	rs2240736	61408032	T	0.66	0.35	2.20E-16	217,197	C17orf82, TBX2	MAP
18	rs403814	6282594	A	NA	1.15	6.13E-09	NA	L3MBTL4	HT
19	rs740406	2232222	A	0.87	-0.55	3.10E-15	193,219	PLEKHJ1, DOT1L	PP
20	rs1887320	10985350	A	0.53	0.78	1.48E-08	46,123	JAG1	SBP

Chr- chromosome; EA-effect allele; EAF- effect allele frequency; SBP- systolic blood pressure; DBP- diastolic blood pressure; PP- pulse pressure; MAP- mean arterial pressure; HT- hypertension; OH- orthostatic hypotension; NA- not available.

therapeutic strategies are available, BP control is not achieved effectively. Therefore, the introduction of new strategies to improve and optimize BP control in hypertensive patients is a need to be met. Most traditional risk factors fail to identify most individuals with high CHD risk and strong efforts are being made to develop and evaluate genomic information for genomic screening in early life to complement conventional risk prediction in daily clinical assessment. To achieve this goal, increased attention has been directed towards the identification of genetic risk markers and quantification of the improvement in risk prediction models that include GRS in general.[43] Study of quantifiable and correct CHD phenotype data sets is necessary to understand the genetic architecture of hypertension.

Franklin et al[44] showed in 6,539 Framingham Heart Study participants, who were not on antihypertensive therapy at baseline, that there was a gradual shift from DBP to SBP and then to PP as predictors of CHD risk with increasing age. The same was concluded in another study.[45]A Korean cohort study, found that GRSs derived from 4 SNPs were independently associated with an increased BP or hypertension and were highly associated with an increased risk of incident hypertension, even after adjusting for traditional risk factors. While adding GRS on the traditional risk factors did not result in improvement of discrimination ability, the reclassification analysis revealed that an addition of GRS produces a statistical significant effect.[46] Inclusion of hypertension GRS of the aggregated risk effects of the associated loci into a cardiovascular risk prediction model could improve both patient risk classification and blood pressure regulation.[47]

The application of a GRS, based on genetic variants associated with coronary heart disease and independent of classical risk factors, in participants from 2 cohort studies, the REGICOR study and the Framingham Heart Study, improved in risk classification, particularly in patients at intermediary coronary risk.[48] The identification of new biomarkers with proven predictive value in estimating cardiovascular risk (CVR), such as genetic variants recently identified in genome-wide association studies, allow better stratification of CVR estimation when formulated as a multi-locus genetic risk score (GRS)[49] even related to subclinical atherosclerosis.[50] Mega et al[51] were able to construct a genetic risk score, based on 27 genetic variants, that in aggregate predicted future coronary heart disease (CHD) risk even after adjusting for traditional risk factors in a community-based cohort study (Malmo Diet and Cancer study) and four randomized controlled trials of statin therapy (JUPITER, ASCOT, CARE, and PROVE IT-TIMI 22).

A 16-week prospective, randomized, single blind cohort study in 2 parallel groups showed that patient knowledge of the impact of genetics on their cardio vascular risk (CVR) improves hypertension control rates defined by ABPM standard cutoffs (24 hour-ABPM <130/80 mmHg), especially in patients at high and very-high CVR.[52] Surendran et al[53] found that blood pressure traits such as SBP, DBP, and PP were positively associated with increased CHD risk. A study was conducted to investigate to which extent increased CHD genetic risk can be offset by a healthy lifestyle. The authors found that individuals in the top quintile of the CHD susceptibility GRS had a substantially lower risk of coronary events if they adhered to a favorable lifestyle.[35] Hoffmann et al[11] investigated the association of SBP, DBP, and PP susceptibility GRSs with MI/CHD and the authors found that a GRS constructed from 70 SNPs were highly significantly associated with MI/CHD with odds of 1.06 (p=1.1x10) per 1 mmHg increase in SNP-based BP. A study showed that individuals which were aware of their personal CHD risk based on CHD susceptibility GRS seemed to show an increased tendency to seek and share disease related information.[54] A single study has indicated a dose-response relationship of increased risk of CHD associated with the number of hypertension associated SNPs.[32] Studies of a relation between hypertension associated SNPs and severity of CHD are scarce. Further understanding of the genetic architecture of hypertension and CHD requires interrogation of datasets where the CHD phenotype is very certain and also quantifiable. Wertwein et al[55] in a study, found that polymorphisms of genes related to CHD (MIA3, MRAS, PCSK9, SMG6, ZC3HC1) were associated with non-dipping SBP and DBP profile and GRS18 was associated with non-dipping status. In addition, this profile was related to a higher risk of revascularization.

A study developed a new genomic risk score for CAD (metaGRS) consisting of 1.7 million genetic variants in a

meta-analytic approach to combine large-scale, genome-wide, and targeted genetic association data. The genomic score developed and evaluated here highlights the potential for genomic screening in early life to complement conventional risk prediction.[56] To evaluate the additive value of a multi-locus GRS to the Framingham risk score (FRS) in coronary artery disease (CAD) risk prediction was evaluated in a study. A total of 2888 individuals (1566 coronary patients and 1322 controls) were divided into three subgroups according to FRS. Multiplicative GRS was determined for 32 genetic variants associated to CAD. The study concluded that GRS provided a better incremental value in intermediate subgroup. In this subgroup, inclusion of genotyping may be considered to better stratify cardiovascular risk.[57] To assess the impact of genetics and exposure to lifestyle factors on blood pressure, a genetic risk score composed of 314 blood pressure loci was assessed together with a healthy lifestyle score (BMI, sedentary hours, alcohol intake, meat intake, urinary sodium excretion, fruit and vegetable intake, fish intake, and smoking status).[58] For all genetic risk score tertiles, a healthier lifestyle score is associated with lower blood pressure and improved outcomes.[59] Krogager et al[60] investigated whether a genetic risk score constructed from identified common genetic variants associated with SBP, DBP, or pulse pressure and the risk of hypertension, CHD and also degree of coronary vessel disease such as multi vessel disease in individuals is associated with burden of coronary heart disease. The study demonstrated a dose-response pattern associated with the genetic burden of hypertension associated SNPs and severity of CHD. The association of hypertension GRS with increased odds of CHD was independent of individuals being diagnosed or receiving treatment for hypertension. PP and SBP GRS seemed to be the strongest determinants of CHD when compared with DBP GRS.

A genetic risk score (GRS) based on 29 single nucleotide polymorphisms (SNPs) associated with high blood pressure (BP) was prospectively associated with development of hypertension, stroke, and cardiovascular events.[61] Genetic loci that overlap with the genetic signals of cardiovascular endpoints should also be considered, although it has limitations due to heterogeneous pathophysiology of cardiovascular endpoints, particularly with heart failure, stroke and chronic renal disease.[62] Signals of association that overlap between BP and coronary artery disease GWAS are given in table 2. Polygenic risk scores for CVD can aid in early stage risk

Table 2: Overlapping signals between blood pressure and cardiovascular endpoint in genome-wide association studies[62]

SNP	Gene (or nearest)	Associated trait	Expression			
			Arteries	Renal cortex	Adrenal	Highest expressing tissues
rs7412 (missense)	APOE (apolipoprotein E)	PP + CAD	Moderate	Very high	Very high	Liver, adrenals
rs78049276/rs6841581* (upstream variant 2KB)	EDNRA (endothelin receptor type A)	PP + CAD	Moderate	Low	Low	Female reproductive organs, arteries
rs360153/rs10840293* (intronic)	SWAP70 (SWAP switching B-cell complex subunit 70)	DBP + CAD	Moderate	Low	Low	Adipose, tibial nerve, spleen
rs9472135 (intergenic)	VEGFA (vascular endothelial growth factor A)	DBP + eGFR	Moderate	Moderate	Moderate	Thyroid
rs1047891 (missense)	CPS1 (carbamoyl-phosphate synthase 1)	SBP + eGFR	Very low	Low	Very low	Liver

SBP-systolic blood pressure; DBP- diastolic blood pressure; PP- pulse pressure; CAD- composite outcome of coronary artery disease including myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, angina or chromic ischemic heart disease;

prediction as genetic contributions to disease risk are defined at birth, and remain stable throughout the life-course. Interventions such as close monitoring and life style modifications, use of appropriate therapeutics can be introduced in individuals identified with risk of disease. Clinical benefits of statin therapy in individuals with different CAD disease risk can be done by PRS. CAD genetic risk scores may improve our ability to identify individuals at high risk who are most likely to respond to therapy.[63] PRS can be added to existing prediction tools such as the Framingham risk score calculator and combined scores shall provide better prediction.

CONCLUSION

Unveiling the complexity of genetic mechanisms underlying BP regulation requires identification of genes associated with HT. No geographic boundaries have been defined to HT thus, a solution to identify risks has a global scope. The global burden of HT can be addressed by incorporating genetic information in addition to lifestyle and environ-mental influences to bring an impact on global cardiovascular health. Usefulness and appropriateness of PRS for HT are being explored. Artificial intelligence can be used in generating predictive models based on PGRS of individuals with HT. Prior to clinical implementation PRS should be tested, validated and assessed for clinical utility. GRS as a risk prediction tool is a promising area potentially supporting effective prevention of HT and CVD. Genomics based personalized prediction and prevention is a necessity in this era.

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