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The Promises and Challenges of the Use of Genomics in the Prescription of Exercise for Hypertension: The 2013 Update

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Abstract: Hypertension is a major global public health problem, resulting in over 7.6 million deaths per year (13.5% of the total), more than any other cardiovascular disease risk factor. Exercise decreases blood pressure (BP) 5-7 mmHg among those with hypertension. Thus, the American College of Sports Medicine recommends the exercise prescription (ExR_x) of 30 min or more of moderate intensity, aerobic activity on most days of the week to lower BP. Yet, there is considerable individual variability in the BP response to exercise due to genetic and environmental factors that are poorly understood. We and others have shown there is a genetic component to the BP response to exercise accounting for a significant proportion of this variability. However, identification of specific genetic variants accounting for this variability is a significant challenge. This review describes new work on candidate gene and BP association studies. It also describes other important emerging work in genome wide association studies, next generation sequencing, epigenetics, and gene expression regulation, and how this work may have future relevance to ExR_x for hypertension. The ultimate goal of our research is to use genetic information to personalize ExR_x to optimize the effectiveness of exercise as a therapeutic modality for the prevention, treatment, and control of hypertension. Because of the complexities surrounding work in exercise genomics, the future use of genomics in ExR_x for hypertension still remains a vision of the future rather than a reality of the present.

Keywords: Blood pressure, genetics, physical activity, polymorphisms, pre-hypertension.

INTRODUCTION

Hypertension is a significant global public health issue. High blood pressure (BP) {systolic BP (SBP) >115 mmHg} results in 7.6 million deaths (13.5% of total deaths) and 92 million disability adjusted life years (DALYs) (6.0% of total DALYs) worldwide [1]. Much of the global disease burden attributed to high BP occurs in low- and middle-income countries, in middle aged people, and in those with pre-hypertension {SBP 120-139 and/or diastolic BP (DBP) 80-89 mmHg}. Over 58% of adults in the United States have higher than normal BP (SBP $\geq$ 120 and/or DBP $\geq$ 80 mmHg) [2], and nearly all Americans will acquire hypertension (SBP $\geq$ 140 and/or DBP $\geq$ 90 mmHg) if they live long enough [3]. Hypertension is a major risk factor for coronary heart disease, stroke, congestive heart failure, chronic kidney disease, and peripheral arterial disease [2]. It is the most common primary diagnosis in the United States, and the leading cause for medication prescriptions in Americans over 50 yr of age [4]. The total direct medical costs attributable to hypertension and its complications in the United States are projected to triple to $389.9 billion annually by 2030 [5]. Due to its significant public health burden, the prevention, treatment, and control of hypertension is a global health priority [1]. First, this review will briefly overview the antihypertensive effects of exercise and current exercise prescription (ExR_x) recommendations to lower BP. Second, it will describe new work on candidate gene association studies regarding the BP response to exercise. Finally, it will describe other important emerging work in genome wide association studies (GWAS), next generation sequencing, epigenetics, and gene expression regulation, and how this work may have future relevance to ExR_x for hypertension.

THE ANTIHYPERTENSIVE EFFECTS OF EXERCISE

Aerobic exercise is recommended as initial lifestyle therapy for the prevention, treatment, and control of hypertension [3, 6]. Meta-analyses have examined the effect of aerobic exercise training on resting auscultatory and ambulatory BP among individuals with normal and high BP [7-14]. A majority of participants in these meta-analyses were middle-aged, white men. The training programs averaged 16 wk in length and consisted of three weekly, 40 min sessions. Two-thirds of the studies used walking, jogging, and running as the primary exercise modality, and another half of the studies used cycling. The intensity of these exercise training sessions ranged from moderate {40%-<60% peak oxygen consumption (VO_2peak)} to vigorous ($\geq$60% VO_2peak). Whelton *et al.* [11] found resting auscultatory SBP decreased an average of -4.9 {with a

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confidence interval of (-7.2, -2.7)} and DBP -3.7 (-5.7, -1.8) mmHg among participants with hypertension, and -4.0 (-5.3, -2.8) / -2.3 (-3.1, -1.5) mmHg among subjects with normal BP, respectively. Similarly, Cornelissen and Fagard [7] reported BP reductions were greater in adults with hypertension (-6.9 / -4.9 mmHg) than those with normal BP (-2.4 / -1.6 mmHg), as did others [10, 12, 13]. The magnitude of the BP reductions resulting from exercise tended to be less when measured with ambulatory BP monitoring than those assessed with auscultation [14]. Age, sex, or ethnicity did not appear to alter the BP response to aerobic exercise training, although the literature was limited in its ability to explore these important sociodemographic characteristics as most studies were conducted only in middle-aged, men of European descent.

An evidenced based review on exercise and hypertension has been published by the American College of Sports Medicine (ACSM) (Table **1**) [6]. This review of the literature indicated aerobic exercise training lowers BP an average of 5-7 mmHg in the majority of people with hypertension. Nonetheless, 25% of the people with hypertension do not lower their BP with aerobic exercise training [15-17], and the standard deviation often exceeds the mean BP change [18]. The inter- and intra- study variability in the BP response to exercise is considerable, and has been attributed to methodological issues, redundancies in BP regulation, and interactions among environmental and genetic factors that are poorly understood [6, 17].

THE ACSM EXERCISE PRESCRIPTION FOR HYPERTENSION

The exercise prescription (ExR_x) to lower BP consists of the following principles: *F*requency (how often), *I*ntensity (how hard), *T*ime (how long), and *T*ype (what kind) or *FITT*. The BP reductions that result from aerobic exercise training occur rapidly after just three sessions [19-21], and after short amounts of time (durations as short as 10 min) and low levels of physical exertion (intensities that increase heart rate and breathing but still allow conversation) of exercise. Therefore, the ACSM ExR_x for those with high BP (SBP $\geq$ 120 and/or DBP $\geq$ 80 mmHg) is as follows [6]:

Frequency

Aerobic exercise on most, preferably all days of the week; resistance exercise 2 to 3 $d \cdot wk^{-1}$ as a supplement to aerobic exercise.

Intensity

Moderate intensity, aerobic exercise (i.e., 40% to <60% VO_2peak) supplemented by resistance training at 60% to 80% of the one repetition maximum (1-RM).

Time

30 to 60 $min \cdot d^{-1}$ of continuous or intermittent aerobic exercise. If intermittent, perform a minimum of 10 min bouts accumulated to total 30 to 60 $min \cdot d^{-1}$ of exercise. Resistance training should consist of at least one set of eight to 12 repetitions.

Type

The primary emphasis should be placed on aerobic activities such as walking, jogging, cycling, and swimming. Resistance training using either machine weights or free weights may supplement aerobic training. Such training programs should consist of eight to 10 different exercises targeting the major muscle groups of the body.

Despite the generic appearance of the ACSM ExR_x for hypertension, the BP response to exercise is quite variable and should be tailored to the clinical profile of the patient as well as the patient's goals [22-24]. As factors contributing to the variability in the BP response to exercise become better understood, the ExR_x for hypertension will become more personalized. We now turn our focus to new information about genetic predispositions and how they account for some of the variability in the BP response to exercise.

RECENT ADVANCES IN EXERCISE GENOMICS AND THE ANTIHYPERTENSIVE EFFECTS OF ACUTE AND CHRONIC AEROBIC EXERCISE

We utilized a systematic literature search to locate recent studies of candidate genes and the BP response to exercise warranting inclusion in this review that updates our previous review [25]. Thus, this review includes articles published between May 30, 2009 and April 30, 2013. We searched Pubmed for articles using the terms: exercise, aerobic, training, genotype, single nucleotide polymorphism, allele, variant, genome wide association study, BP, and hypertension. Next, we searched for articles cited within reviews from *Exercise Genomics* [26] and the *Journal of Applied Physiology Highlighted Topic Series* [27]. We also reviewed tables of contents from the following relevant journals from 2009-2013: *Medicine and Science in Sport and Exercise*, *Journal of Applied Physiology*, *Physiological Genomics*, *Hypertension*, *Journal of Hypertension*, *American Journal of Hypertension*, and *PLoS One*. We examined the reference lists of all articles we located for additional articles possibly warranting inclusion. We only included studies measuring BP according to standards of the American Heart Association [28]. We did not include studies in which participants lost or gained weight following exercise as weight changes can confound BP outcomes [3].

We located 10 articles warranting inclusion. Five of these articles describe recent findings from our laboratory [29-31] and other laboratories [32, 33] utilizing an acute or short-term aerobic exercise model. The rationale for using this acute exercise model is that there is a rapid onset of the long-term BP reductions that result from aerobic exercise training [20, 21]. Indeed, some if not all of the BP reductions from aerobic exercise training programs are thought to be the result of the acute or immediate BP reductions following a single exercise session [6, 17, 34-44]. The immediate BP lowering effects of exercise are termed *postexercise hypotension* (PEH) [17, 37, 44]. The other five included articles examined the BP response to exercise training among larger samples of men and women with normal BP to Stage 1 hypertension [45-49]. These volunteers performed 3

Table 1. American College of Sports Medicine (ACSM) Exercise and Hypertension Position Stand Evidence Statements [6]

Section Heading	Evidence Statement	Evidence Category *
Exercise BP and the prediction of hypertension and CVD morbidity and mortality	● Exercise BP contributes to the prediction of future hypertension in persons with normal BP.	C
	● The prognostic value of exercise BP regarding CVD complications depends on the underlying clinical status and hemodynamic response and is therefore limited.	D
Exercise BP benefits	● Higher levels of physical activity and greater fitness at baseline are associated with a reduced incidence of hypertension in white men; however, the current paucity of data precludes definitive conclusions regarding the role of gender and ethnicity.	C
	● Dynamic aerobic training reduces resting BP in individuals with normal BP and in those with hypertension.	A
	● The decrease in BP with aerobic training appears to be more pronounced in those with hypertension.	B
	● Aerobic training reduces ambulatory BP and BP measured at a fixed submaximal work load.	B
	● BP response differences among individual studies are incompletely explained by the characteristics of the training programs, that is, the weekly exercise frequency, time per session, exercise intensity and type of exercise.	B
	● Dynamic exercise acutely reduces BP among people with hypertension for a major portion of the daytime hours.	B
	● Resistance training performed according to the ACSM guidelines reduces BP in normotensive and hypertensive adults.	B
	● Limited evidence suggests static exercise reduces BP in adults with elevated BP.	C
	● Limited evidence suggests resistance exercise has little effect on BP for up to 24 h after the exercise session.	C
	● There are currently no studies available to provide a recommendation regarding the acute effects of static exercise on BP in adults.	None
	● Regular endurance exercise reduces BP in older adults as it does in younger persons.	B
	● Limited evidence suggests PEH occurs in older adults.	C
	● Endurance and resistance training do not reduce BP in children and adolescents.	B
	● Endurance exercise training reduces BP similarly in men and women.	B
	● Limited evidence suggests acute endurance exercise reduces BP similarly in white men and women.	C
	● Currently no convincing evidence exists to support the notion ethnic differences exist in the BP response to chronic exercise training.	B
	● Currently no convincing evidence exists to support the notion ethnic differences exist in the BP response to acute exercise.	C
Exercise recommendations	● For persons with high BP, an exercise program that is primarily aerobic-based is recommended.	A
	● Resistance training should serve as an adjunct to an aerobic-based program.	B
	● The evidence is limited regarding frequency, intensity, and duration recommendations; nonetheless, the antihypertensive effects of exercise appear to occur at a relatively low total volume or dosage.	C
	● Limited evidence exists regarding special considerations for those with hypertension.	D
Mechanisms	● Neural and vascular changes contribute to the decreases in BP that result from acute and chronic endurance exercise.	C
	● Emerging data suggest possible genetic links to acute and chronic exercise BP reductions.	D

BP=blood pressure; CVD=cardiovascular disease; PEH=postexercise hypotension.
* Evidence category weighting description, A=highest to D=lowest.
Reprinted with permission by Pescatello LS, Franklin BA, Fagard R, Farquhar W, Kelly GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc 2004; 25: 533-53.

sessions per week of 20-60 min of moderate intensity (40%-70% VO_2peak), aerobic training for 2-6 months with BP measured pre and post training.

In addition, many of the genetic variants examined in these articles were previously studied in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study [50-54]. The primary purpose of the HERITAGE study was to examine the health-related responses to 20 wk of aerobic training in 762 sedentary, healthy subjects without chronic disease or hypertension from approximately 200 families that were approximately

Table 2. Mean (±SEM) Fasting Physical Characteristics of the Total Sample and Among those with and without the Metabolic Syndrome [31]*

Variable	Total Sample (n=50)	Metabolic Syndrome	
		With (n=20)	Without (n=30)
Age (yr)	43.8±1.3	45.8±1.7	42.5±1.9
Peak Oxygen Consumption ($ml \cdot kg^{-1} \cdot min^{-1}$)	31.3±0.9	27.2±0.8	34.0±1.2
Body Mass Index ($kg \cdot m^{-2}$)	29.4±0.7	32.4±1.3	27.5±0.5†
Waist Circumference (cm)	101.8±1.9	111.1±3.5	95.7±1.6‡
Awake Systolic Blood Pressure § (mmHg)	145.3±1.5	147.6±2.0	143.7±2.1
Awake Diastolic Blood Pressure § (mmHg)	85.9±1.5	87.6±1.7	84.8±1.4
Insulin ($pmol \cdot L^{-1}$)	79.4±8.5	117.1±15.7	53.6±6.1†
Glucose($mmol \cdot L^{-1}$)	4.5±0.1	4.7±0.1	4.4±0.1
Homeostasis Model Assessment	2.3±0.3	3.6±0.5	1.4±0.2
Total Cholesterol (TCHOL) ($mmol \cdot L^{-1}$)	4.9±0.2	5.3±0.3	4.6±0.2**
High Density Lipoprotein-Cholesterol ($mmol \cdot L^{-1}$)	1.10±0.03	1.05±0.04	1.14±0.05
Low Density Lipoprotein-Cholesterol ($mmol \cdot L^{-1}$)	3.1±0.2	3.3±0.3	3.0±0.2
Total Cholesterol / High Density Lipoprotein Ratio (U)	4.6±0.2	5.2±0.3	4.2±0.2†
Triglycerides ($mmol \cdot L^{-1}$)	1.6±0.1	2.2±0.2	1.2±0.1†

* National Cholesterol Education metabolic syndrome diagnosis is established when three of five criteria are present [2]. The fasting criteria include: waist circumference > 102 cm; triglycerides ≥ 1.7 $mmol \cdot L^{-1}$; high density lipoprotein-cholesterol <1.2 $mmol \cdot L^{-1}$; blood pressure ≥130 and/or 85 mmHg; and glucose > 6.0 $mmol \cdot L^{-1}$.
**p<0.05, †p<0.01, p<0.001‡ with versus without the Metabolic Syndrome
§ Awake blood pressure= ambulatory blood pressure averaged over the time period when men were awake and ambulating, i.e., day time blood pressure

two-thirds of European descent and one-third African descent [18]. HERITAGE investigators examined the BP response to acute exercise by assessing BP *via* auscultation at fixed workloads during submaximal exercise. HERITAGE investigators also examined the BP response to exercise training by measuring BP pre- and post- training at rest as well as during sub-maximal exercise. Because of the similarities in genetic variants examined, findings from HERITAGE are discussed in comparison to the newer studies located *via* our systematic search.

Acute Exercise Studies

We are one of the few research teams that have conducted candidate gene studies examining the BP response to acute aerobic exercise (i.e., PEH) among individuals with pre- to Stage 1 hypertension. Our PEH candidate gene association studies involved a cohort of 50 middle aged, men of European descent with pre- to Stage 1 hypertension. Their clinical profile matched that of typical Americans with high BP, as they were overweight [55, 56], and had below average cardiorespiratory fitness for their age and sex [57] and borderline dyslipidemia, with 40% classified as having the metabolic syndrome (Table **2**) [23, 29-31, 58-60]. These men completed four randomly assigned experiments on different days: a non-exercise control session of seated rest, and three cycle exercise bouts, one at 40% peak oxygen consumption (VO_2peak) (LIGHT), one at 60% VO_2peak (MODERATE), and a graded maximal exercise stress test (GEST) to exhaustion or 100% VO_2peak (i.e., VIGOROUS) (Fig. **1**) [31]. The men then left the laboratory instrumented to an ambulatory BP monitor for the remainder of the day.

SBP tended to increase 2.8±1.6 mmHg less after LIGHT (p=0.09), and increased 5.4±1.4 mmHg less after MODERATE (p≤0.001) and 11.7±1.5 mmHg less after VIGOROUS than control over 9 h (p≤0.001) (Fig. **2**). DBP tended to decrease 1.5±1.2 mmHg more after LIGHT (p=0.207) and 2.0±1.0 mmHg more after MODERATE (p=0.055), and decreased 4.9±1.3 mmHg more after VIGOROUS versus control over the same time period (p≤0.001) (Fig. **3**) [31]. Thus, the influence of exercise intensity on PEH occurred in dose response fashion such that for each 10% increase in relative VO_2peak, SBP decreased 1.5 mmHg and DBP 0.6 mmHg (Fig. **4**). These findings suggest the current ACSM ExR_x for hypertension should be expanded to include more vigorous levels of physical exertion for individuals willing and able to tolerate more intense levels of exercise.

In this same study, we explored clinical and genetic determinants of the BP response following VIGOROUS. Our findings of clinical and genetic determinants of the BP response following LIGHT and MODERATE have been

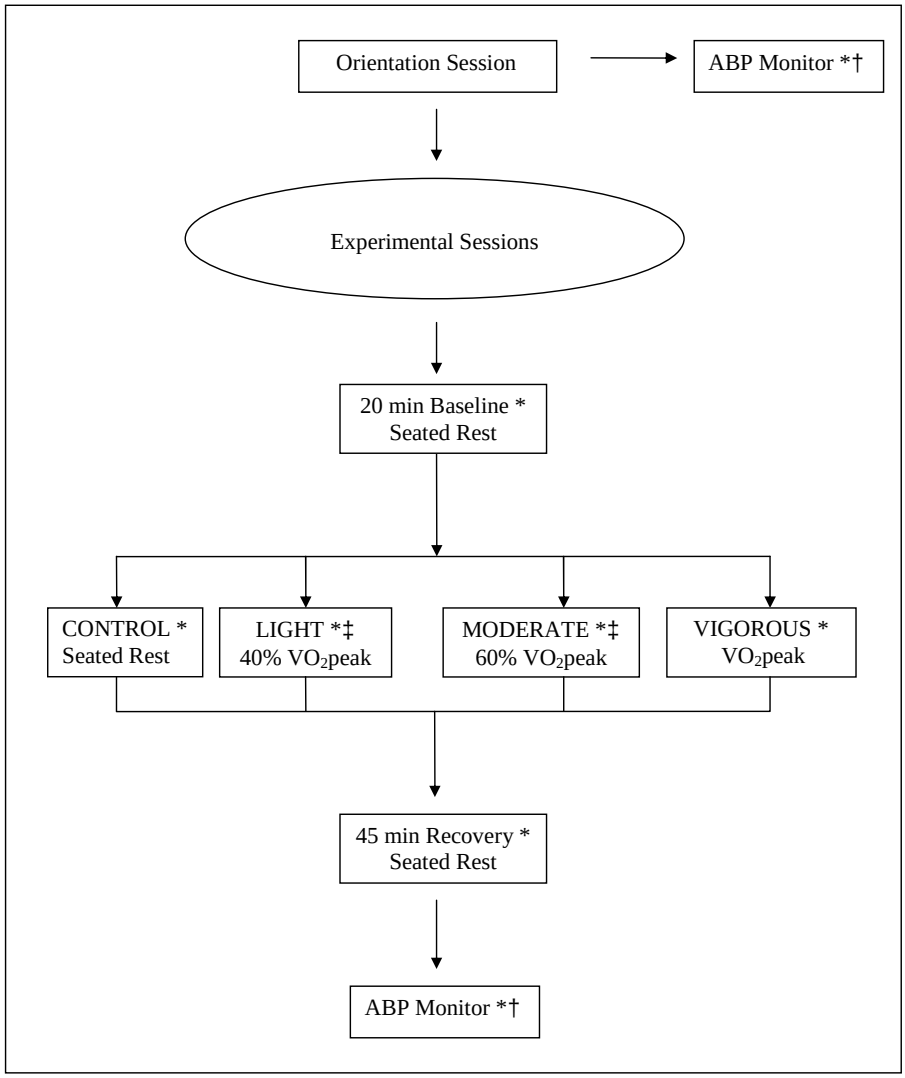

Fig. (1). Study design overview. ABP, ambulatory blood pressure; VO_2peak, peak oxygen consumption; * Blood pressure and heart rate taken throughout (see text for details); † Worn until waking the next morning; ‡ Includes 5 min warm-up and 5 min cool down periods to total 40 min of exercise. Reprinted from Eicher JD, Maresh CM, Tsongalis GJ, Thompson PD, Pescatello LS. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. Am Heart J 2010 Sep; 160(3): 513-520.

published previously [23, 30, 58-60], and they were described in detail in our initial review [25]. The genetic determinants examined in our most recent study were three renin angiotensin aldosterone system (RAAS) polymorphisms: angiotensin 1 converting enzyme (*ACE*) insertion/deletion (rs4646994); angiotensin II receptor, type 1 (*AGTR1*) 1166 A>C (rs5186); and intron-2 conversion of aldosterone synthase (*CYP11B2*) (rs1799998). We also investigated adducin 1 alpha (*ADD1*) Gly460Trp (rs4961), guanine nucleotide-binding protein system alpha subunit (*GNAS*) 393 T>C (rs7121), endothelial nitric oxide synthase (*ENOS*) -786 T>C (rs2070744), apolipoprotein E (*APOE*) polymorphism at amino acid position 112 and/or 158 (E2, E3, and E4) (rs4712), and the insertion/deletion of a HindIII restriction enzyme site polymorphism on the Y chromosome (*Y-HindIII*) (rs9786271).

Table **3** contains a summary of our series of studies examining the genetic and clinical correlates of PEH performed at LIGHT, MODERATE and VIGOROUS intensity [23, 30, 31, 58-60]. The vision for exercise genomics is to eventually use genetic and clinical information to personalize ExR_x to maximize the efficiency of exercise as a therapeutic modality in the prevention, treatment, and control of hypertension. Thus, we constructed genetic and clinical profiles of men who lowered (exercise responders) and did not lower BP (exercise nonresponders) after acute aerobic exercise with hierarchical binary logistic regression. We used findings from our prior work [23, 30, 31, 58-60] to define a LIGHT responder as men with an average BP change from baseline that was reduced $\geq$ 1 mmHg after LIGHT compared to non-exercise control over 9 hr; and all else were classified as LIGHT nonresponders. Similarly, MODERATE responders were defined as men with an average BP change from baseline that was reduced $\geq$ 1 mmHg after MODERATE compared to non-exercise control

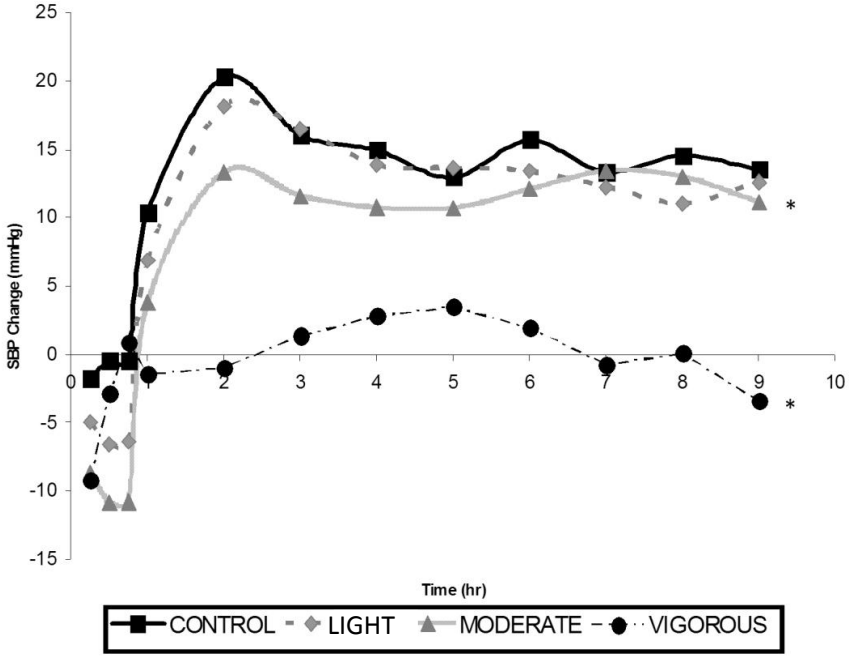

Fig. (2). Awake systolic blood pressure change from baseline (Mean±SEM) at hourly intervals over 9 h after control and exercise compared with baseline values. VO_2peak, peak oxygen consumption; CONTROL, non-exercise session of seated rest; LIGHT, 40% VO_2peak; MODERATE, 60% VO_2peak; VIGOROUS, VO_2peak; * $p \leq 0.001$ exercise treatment versus non-exercise control. Reprinted from Eicher JD, Maresh CM, Tsongalis GJ, Thompson PD, Pescatello LS. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. Am Heart J 2010 Sep; 160(3): 513-520.

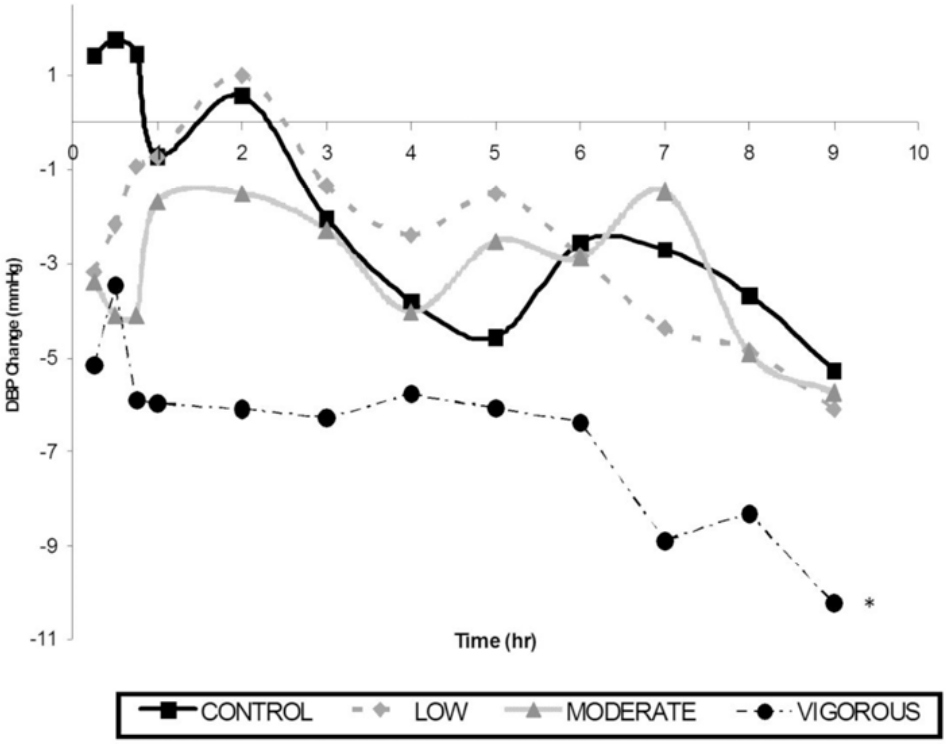

Fig. (3). Awake diastolic blood pressure change from baseline (Mean±SEM) at hourly intervals over 9 h after control and exercise compared with baseline values. VO_2peak, peak oxygen consumption; CONTROL, non-exercise session of seated rest; LIGHT, 40% VO_2peak; MODERATE, 60% VO_2peak; VIGOROUS, VO_2peak; * $p \leq 0.001$ exercise treatment versus non-exercise control. Reprinted from Eicher JD, Maresh CM, Tsongalis GJ, Thompson PD, Pescatello LS. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. Am Heart J 2010 Sep; 160(3): 513-520.

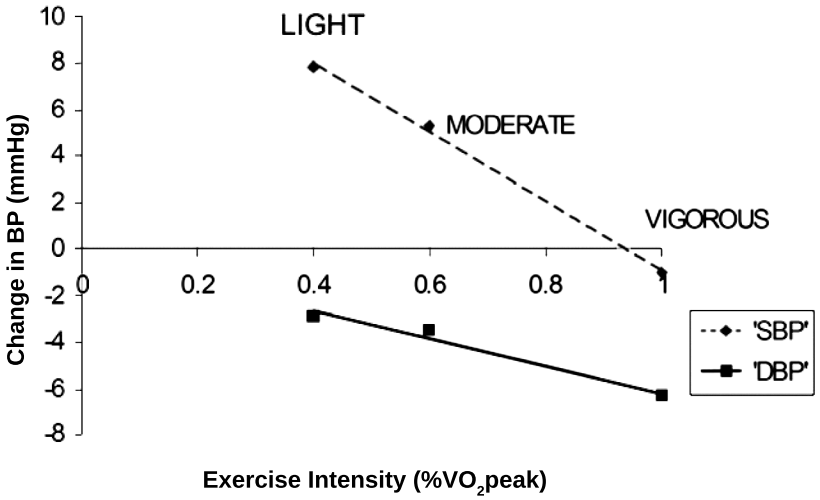

Fig. (4). Linear regression of average BP change from baseline following LIGHT, MODERATE, and VIGOROUS. SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; VO_2peak, peak oxygen consumption; SBP: y=-14.9x+14.0, R^2=0.998; DBP: y=-5.9x-0.3, R^2=0.969 ($p<0.01$). Reprinted from Eicher JD, Maresh CM, Tsongalis GJ, Thompson PD, Pescatello LS. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. Am Heart J 2010 Sep; 160(3): 513-520.

over 9 hr; and all else were classified as MODERATE nonresponders.

Binary logistic regression determined the genetic and clinical profile of LIGHT responders (n=30) and nonresponders (n=13), and MODERATE responders (n=31) and nonresponders (n=13). This logistic regression model classified 28 out of 30 men as LIGHT responders with a sensitivity of 93.3%, 9 out of 12 men as LIGHT nonresponders with a specificity of 75.0%, and explained 41.0% (Cox and Snell R^2) to 58.0% (Nagelkerke R^2) of the variability in the BP response to LIGHT exercise. Similarly, this statistical model classified 27 out of 31 men as MODERATE responders with a sensitivity of 87.1%, 10 out of 13 men as MODERATE nonresponders with a specificity of 69.2%, and explained 41.4% (Cox and Snell R^2) to 58.9% (Nagelkerke R^2) of the variability in the BP response to MODERATE exercise. A binary logistic regression analysis was not possible following VIGOROUS exercise as the number of non-responders was too small (n=7). However, continuous multiple variable linear regression determined genetic and clinical correlates of the BP response following VIGOROUS exercise, accounting for 27.0% of the variability in SBP and 46.4% in the DBP response (Table **3**).

Notably, RAAS genetic variants and *ADD1* Gly460Trp (rs4961) associated with the BP response to acute aerobic exercise, independent of the level of physical exertion. Consistent with our findings, Alioglu *et al.* [33] previously reported *ADD1* Gly460Trp (rs4961) associated with the peak SBP response to VIGOROUS walking and jogging (a treadmill GEST) among 49 middle-aged men and women with hypertension. Additionally Santana *et al.* [32] reported *ACE* insertion/deletion (rs4646994) associated with the BP response following MODERATE (20 min cycling at 90% anaerobic threshold) and VIGOROUS (a cycling GEST) among 30 older men and women with hypertension. RAAS genetic variants and *ADD1* Gly460Trp (rs4961) are important regulators of BP, renal sodium reabsorption, and extracellular volume maintenance [61-64]. These candidate gene findings suggest the renal system is important in the regulation of the BP response immediately following aerobic exercise. Future work should replicate these results in larger samples as well as investigate the mechanisms by which renal genetic variants may modulate PEH.

Furthermore, in our studies clinical correlates of the metabolic syndrome, i.e., fasting lipids, lipoproteins and glucose associated with PEH, regardless of the intensity of the exercise bout (Table **3**). The metabolic syndrome and hypertension have a common underlying pathophysiology of insulin resistance and hyperinsulinemia, heightened activation of the sympathetic nervous system, and increased sodium reabsorption [65-68]. These disorders result in increased peripheral vasculature resistance, impaired glucose tolerance, dyslipidemia, and endothelial dysfunction. In addition, *APOE* E2, E3, and E4 (rs4712) and *Y-HindIII* (rs9786271) correlated with the BP response following VIGOROUS, suggesting pathways involved with lipid metabolism also modulate PEH. Genes on this locus of the Y chromosome have been associated with BP regulation and lipid physiology in mice [69, 70]. Thus, genetic and clinical biomarkers of the metabolic syndrome should be further investigated as modulators of PEH. If confirmed to associate with PEH, they may be eventually used to profile people who respond and do not respond to the antihypertensive effects of acute aerobic exercise.

We also observed an association between baseline nitric oxide (NO) levels and PEH following VIGOROUS (partial r^2=0.130, p=0.004) (Table **3**) [31]. Increased blood flow during exercise imposes laminar shear stress on the

Table 3. Genetic and Clinical Correlates of Post-exercise Blood Pressure Response to LIGHT, MODERATE, and VIGOROUS Exercise [23, 30, 31, 58-60, 122]

Variable	B	Partial r^2	*p*
LIGHT (40% VO_2peak) Systolic and Diastolic Blood Pressure*			
C-Reactive Protein	-21.54 ± 10.413	0.187	0.039
High-density Lipoprotein	-0.090 ± 0.074	0.118	0.221
Metabolic Syndrome†	1.540 ± 1.588	0.045	0.332
Family History§	-1.866 ± 1.301	0.074	0.151
# RAAS risk alleles‖	0.729 ± 1.080	0.018	0.499
ADD1 Gly460Trp#	-2.692 ± 1.492	0.108	0.071
GNAS 393 T>C**	1.453 ± 1.197	0.030	0.225
Total Model		**0.580**	**0.002**
MODERATE (60% VO_2peak) Systolic and Diastolic Blood Pressure*			
Baseline Blood Pressure	-0.068 ± 0.048	0.084	0.156
High Density Lipoprotein	-0.269 ± 0.113	0.097	0.017
Metabolic Syndrome†	-2.853 ± 1.516	0.018	0.060
Family History§	-3.100 ± 1.388	0.123	0.025
# RAAS risk alleles‖	1.662 ± 1.159	0.170	0.152
ADD1 Gly460Trp#	1.491 ± 1.281	0.004	0.244
ENOS 786 T>C††	-2.666 ± 1.491	0.093	0.074
Total Model		**0.589**	**0.001**
VIGOROUS (100% VO_2peak) Systolic Blood Pressure†			
Nitric Oxide	-319.4 ± 104.2	0.130	0.004
Y-HindIII Ins/Del§§	-7.384 ± 3.319	0.098	0.032
# RAAS risk alleles‖	-6.416 ± 3.305	0.042	0.060
Total Model		**0.270**	**0.008**
VIGOROUS (100% VO_2peak) Diastolic Blood Pressure†			
Glucose	-0.378 ± 0.126	0.142	0.005
Fibrinogen	4.421 ± 2.264	0.080	0.059
VO_2 peak	-0.415 ± 0.173	0.086	0.022
APOE E2, E3, E4‡‡	-4.003 ± 1.647	0.071	0.021
ADD1 Gly460Trp#	5.815 ± 2.539	0.085	0.029
Total Model		**0.464**	**0.001**

*Binary logistic regression model previously published [23] distinguishing exercise responders (LIGHT n=30, MODERATE n=31) and nonresponders (LIGHT n=13, MODERATE n=13). Responders, the average change in blood pressure from baseline $\leq$1 mmHg less after exercise compared to nonexercise control over 9 hr; all else were as nonresponders. r^2 values refer to Nagelkerke pseudo R^2, a descriptive measure of goodness of fit in logistic regression similar to the r^2 concept of linear regression [136].

†Multiple variable linear regression model of average change in blood pressure from baseline over 9 hr among n=44 participants. Binary logistic regression for VIGOROUS was not possible as too few participants were non-responders (n=7). The sample size of LIGHT (n=43), MODERATE (n=44), and VIGOROUS (n=44) differed slightly due to genetic and clinical markers not being obtained on all participants in each of the three statistical models.

‡ Metabolic Syndrome=absent (n=27) or present (n=17) by National Cholesterol Education Adult Treatment Panel III Criteria [2].

§ Family History=self disclosed family history of hypertension among first degree relatives no (n=22) or yes (n=22).

‖RAAS Risk Alleles, 0–2 risk alleles (n = 21) or $\geq$3 risk alleles (n = 23) from three polymporhisms of the renin-angiontensin system. Polymorphisms were angiotensin 1 converting enzyme (*ACE*) insertion/deletion (rs4646994); angiotensin II receptor, type 1 (*AGTR1*) 1166 A>C (rs5186); and intron-2 conversion of aldosterone synthase (*CYP11B2*) (rs1799998)

adducin 1 alpha (*ADD1*) Gly460Trp (rs4961), Gly/Gly (n = 33) or Gly/Trp (n = 11)

**guanine nucleotide-binding protein system alpha subunit (*GNAS*) 393 T>C (rs7121); TT/TC (n = 33) vs CC (n = 10).

††endothelial nitric oxide synthase (*ENOS*) -786 T>C (rs2070744); TT/TC (n=23) vs CC (n=21).

§§ apolipoprotein E (*APOE*) polymorphism at amino acid position 112 and/or 158 (E2, E3, and E4) (rs4712); E3/E3 (n=21), E2 carrier (n=5), or E4 carrier (n=14).

‡‡insertion/deletion of HindIII restriction enzyme site on the Y chromosome (*Y-HindIII*) (rs9786271); insertion/insertion (n=25) or insertion/deletion (n=18).

endothelium, which increases endothelial nitric oxide synthase (ENOS) activity and the production, release, and bioavailability of NO [71, 72]. NO provokes relaxation of the vessel smooth muscle which decreases peripheral vascular resistance and possibly contributes to PEH [73, 74]. A recent review by Halliwill *et al.* [44] indicates other vasodilator mechanisms contribute to PEH, namely histamine receptor activation. Nonetheless ENOS and NO are involved in the regulation of BP as well as the cardiovascular response to exercise [75], and may account for some of the variability in the BP response following acute [31, 76] and chronic exercise [77, 78].

Additionally we found *ENOS* -786 T>C (rs2070744) tended to influence BP response to MODERATE. SBP tended to be 5.3±2.4 mmHg lower after MODERATE versus non-exercise control over 9 h among carriers of the *ENOS* -786 C risk allele (n=23) compared to those with *ENOS* -786 TT (n=21) (partial r^2=0.093, p=0.074) (Table **3**) [30]. *ENOS* -786 T>C (rs2070744) is located in 5' promoter region of the *ENOS* gene. The *ENOS* -786 C risk allele is associated with decreased promoter activity reducing ENOS activity and production of NO, and subsequently, yielding higher resting BP [79, 80]. Similarly, the *ENOS* -786 C allele is also associated with increased responsiveness to atorvastatin, a medication that upregulates ENOS as does exercise [81, 82]. These findings support the notion people with risk alleles in major BP regulatory pathways are responsive to anti-hypertensive therapeutic interventions such as exercise and statin pharmacological therapy despite their unfavorable genetic predispositions towards hypertension and cardio-vascular disease. This hypothesis should be further investigated among larger samples, as well as with respect to other genetic variants in BP regulatory pathways.

We also recently explored relationships among the peak SBP response to a GEST or VIGOROUS and clinical and genetic indicators of endothelial function [29]. *ENOS* -786 T>C (rs2070744) (partial r^2=0.040, p=0.024), % brachial artery reactivity change at 1 min (partial r^2=0.093, p=0.020), fasting glucose (partial r^2=0.062, p=0.014), resting NO (partial r^2=0.037, p=0.064), and age (partial r^2=0.009, p=0.014) explained 24.1% of the GEST peak SBP response (p=0.043). Thus, genetic and clinical indicators of endothelial function appeared to explain a clinically significant portion of the peak SBP response to a GEST. *ENOS* -786 T>C (rs2070744) explained 4% of the variability in the peak SBP response. Among carriers of the *ENOS* C risk allele (n=24), peak SBP was 11.1±5.0 mmHg higher than men with the *ENOS* TT genotype (n=24) (partial r^2=0.040, p=0.024). As stated previously, the *ENOS* C risk allele is associated with reduced bioavailability of NO and higher resting BP [74, 79, 80]. Individuals with reduced bioavailability of NO and higher resting BP exhibit reduced peripheral vasodilation during exercise [83] possibly resulting in an exaggerated peak SBP response to a GEST or VIGOROUS [83, 84].

Our finding regarding the *ENOS* -786 C risk allele association with the peak SBP response to a GEST [29] is in contrast to our previous finding regarding *ENOS* -786 C risk allele association with the SBP response following MODERATE over 9 h [30]. Specifically, the *ENOS* -786 C risk allele associated favorably with the SBP response following MODERATE but unfavorably with the peak SBP response to a GEST. These apparent contradictory findings illustrate the challenges of confirming genotype-phenotype associations among exercise genomic studies. There are an increasing number of reports either failing to replicate a previously reported risk allele phenotype association, or replicating the association but in the reverse direction.

This lack of replication could be caused by many factors. First, lack of replication could be due to differences in study designs, such as exercise intensity (e.g., MODERATE [30] versus VIGOROUS [29]) and the timing of BP measurement (e.g., during [30] versus after exercise [29]). Second, the lack of replication could be due to low statistical power, as common SNPs typically explain just a small proportion of the variability of the response of health-related phenotypes to exercise. These relatively small effect sizes require larger sample sizes (typically $n \geq 1{,}000$) than exercise genomic studies to date have included [85]. Third, genetic variants not tested or controlled for could possibly have much stronger associations with the health-related phenotype than the genetic variant being tested contributing to the large amount of "missing heritability" that remains unaccounted for [86]. Fourth, interactive effects of multiple genetic variants, i.e., epistasis [87], may account for a substantial portion of the missing heritability of health-related phenotypes beyond what can be explained by individual genetic variants. In addition, the notion that non-additive interactive effects can inflate a trait's heritability levels, known as "phantom heritability," is hypothesized to hinder standard genetic association analyses from explaining the full genetic contributions to phenotypes of interest [88]. Fifth, heritable factors not measured that affect the transcription, translation, and regulation of genes may negate or even reverse associations between individual SNPs and phenotypes, a concept known as the "flip-flop" phenomenon [89]. These factors include DNA methylation, modification of histones surrounding the DNA, micro RNAs (miRNAs), other non-coding RNAs that affect translational regulation (e.g., long non-coding RNAs), and proteomic factors (Fig. **5**) [90, 91] that are discussed later in this review.

Exercise Training Studies

The previous section focused on genetic studies of the BP response to acute exercise. Now, we will focus on two studies that examined the influence of *ENOS* genetic variants on the BP response to exercise training. Sponton *et al.* [45] studied the influence of *ENOS* -786 T>C (rs2070744) on the BP response to aerobic exercise training among 55 postmenopausal, overweight women with pre-hypertension. Subjects completed 60 min of moderate intensity (50%-70% heart rate reserve), cycle exercise 3 $d \cdot wk^{-1}$ for 6 months. Women carrying the *ENOS* -786 C risk allele (n=41) reduced SBP/DBP following training by 8.4±2.2/7.0±1.3 mmHg, while non-carriers (n=14) reduced SBP/DBP by

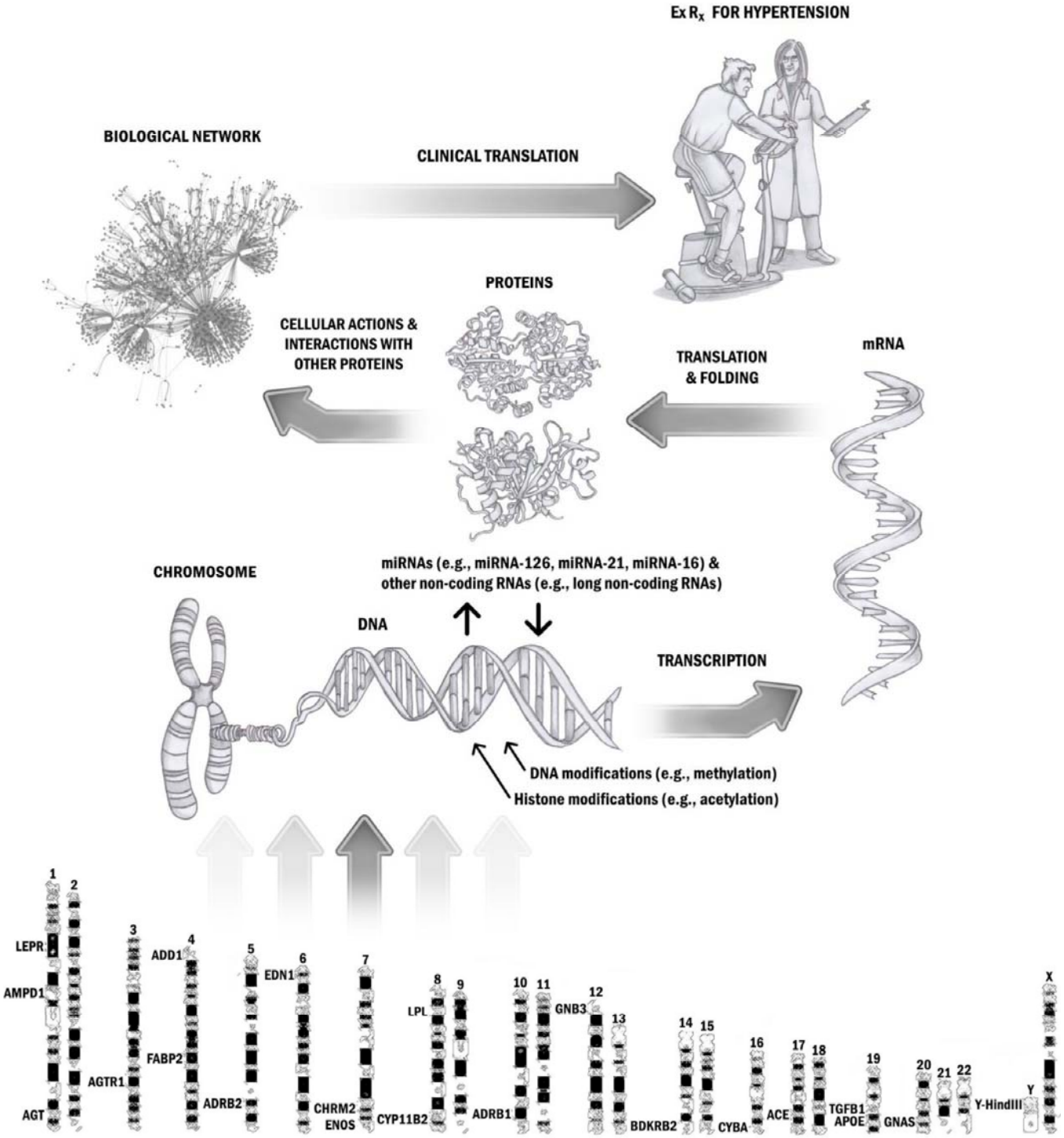

Fig. (5). A conceptual model linking DNA sequence variation, factors affecting gene expression, proteomics, biological systems, and the ExR_x for hypertension. Arrows indicate species/factor/process being regulated or affected.

11.3±3.2/10.4±1.8 mmHg ($p<0.05$). Consistent with our studies [29, 30], these results indicate *ENOS* -786 T>C (rs2070744) influences the BP response to exercise. However, the direction of the C risk allele association with the BP response to MODERATE aerobic exercise training agrees with our findings following MODERATE but not VIGOROUS acute aerobic exercise.

Zago *et al.* [46] examined the influence of *ENOS* -786 T>C (rs2070744) and the amino acid change *ENOS* Glu298Asp (*ENOS* -894 G>T, rs1799983) at exon 7 on the BP response to aerobic exercise training among 118 middle-aged adults with pre-hypertension (gender unspecified). Subjects completed 20-40 min of moderate intensity

(50-70% VO_2peak), aerobic exercise 3 $d \cdot wk^{-1}$ for 6 months. Zago *et al*. [46] found subjects carrying both the *ENOS* -786 C and -894 T risk alleles significantly reduced SBP and DBP following exercise training. However, among subjects with *ENOS* -786 TT and/or -894 GG common genotype(s), BP was not different pre to post exercise training.

Thus, Zago *et al.* [46] demonstrated an interactive gene effect between *ENOS* -786 T>C and -894 G>T on the BP response to aerobic exercise training, but no independent effect of either variant as in our findings [29, 30] and those of Sponton *et al.* [45] and Rankinen *et al.* [52]. Indeed, the studies of Augeri *et al.* [30], Olson *et al.* [29], Rankinen *et al.* [52], Sponton *et al.* [45], and Zago *et al.* [46] indicate that *ENOS* -786 T>C (rs2070744) and *ENOS* -894 G>T (rs1799983) modulate the BP response to acute and chronic aerobic exercise. At the same time, contradictions exist among the studies regarding the direction and interactions among associated alleles. Furthermore, several other reports indicate the *ENOS* -786 T>C (rs2070744) [47, 48] and *ENOS* -894 G>T (rs1799983) [47, 49] did not influence the BP response to aerobic exercise training among postmenopausal women with normal BP [47] as well as prehypertension [48, 49]. Thus, similar to the acute exercise studies reviewed in the previous section, candidate gene association studies of BP response to exercise training suffer from lack of replication [92]. The remainder of this review will discuss the many possible explanations which could underlie these discrepancies.

THE PROMISES AND CHALLENGES OF EXERCISE GENOMICS

The study of genomic factors and the identification of responders and nonresponders to exercise interventions based upon genetic information has increased dramatically over the past 10 yr [93]. Moreover, experts believe these are key areas of research that will drive advancements in exercise science in the 21st century [94]. Important reasons for undertaking work in exercise genomics are: (1) exercise scientists can use genetic information to identify physiological pathways underlying the responses and adaptations to exercise; and (2) clinicians and sport medicine professionals will ultimately be able to use genetic information to individualize ExR_x to maximize the effectiveness of exercise as a therapeutic option to prevent, treat, and manage chronic diseases and conditions such as hypertension [92, 95].

Despite the promise of exercise genomics advancing basic and clinical science, work identifying genetic and clinical determinants of the response of health-related phenotypes to exercise has advanced more slowly than originally envisioned [92]. There are a number of potential reasons for this slow advancement in exercise genomics that have resulted in contradictory findings and ultimately "missing heritability" or the failure to identify genetic variants that explain the genetic components of disease and/or inherited traits [86].

These Reasons Include

- Often times a limited set of common SNPs within a limited set of candidate genes were examined. As we describe in the forthcoming section, the recently developed approaches of GWAS and next-generation sequencing are more comprehensive and should be applied to the response of health-related phenotypes to exercise such as BP. GWAS and next-generation sequencing afford the opportunity to test not only a greater number of common SNPs but also rare variants, non-coding and intergenic variants, and structural variants such as copy number variants. These types of variations have emerged as important heritable factors in complex diseases and traits such as hypertension and should be explored in future work [86]. Furthermore, investigating a limited set of SNPs results in selection biases and limits the possibility to elucidate important interactive effects of multiple genetic variants, i.e., epistasis [87]. In fact, these interactive gene effects may account for a substantial portion of a phenotype's heritability that cannot be explained by individual genetic variants [88] and can even reverse the association of individual risk alleles with phenotypes [89], as described in the previous section.

- Most exercise genomics studies, including those reviewed in this article, may lack the statistical power to test their hypotheses, leading to inconsistent findings. Statistical power depends upon significance threshold, expected effect size, sample size, and precision of measurements, all of which pose significant challenges in exercise genomics studies. First, significance thresholds must be stringent to account for the multiple testing of a large number of genetic variants, and therefore the need to adjust for multiple hypothesis testing. Second, common SNPs typically explain just a small proportion of the variability of exercise phenotypes. These relatively small effect sizes require large sample sizes (typically $n \geq 1{,}000$) to detect statistical differences [85]. Yet, all studies included in this review enrolled $n \leq 118$ participants so they may have been underpowered to detect an association. Third, precise measurement of exercise phenotypes is difficult, particularly as sample sizes increase. GWAS and next-generation sequencing studies have partially addressed these issues by including larger sample sizes [86, 96], although they require even greater statistical power than candidate gene association studies due to the larger number of genetic variants tested for significance.

- Sex and race frequently confound relationships between genotype and phenotype [87, 97-99]. For example, allele frequencies often differ by genetic ancestry and population substructure [87, 100]. These population structural differences have plagued genetic association studies with false positives and inconsistent results due to inadequate control for population stratification and poor study design. Studies reviewed in this manuscript exemplify

such study design issues: our studies enrolled subjects of European descent [23, 29-31, 58-60], Rankinen *et al.* [52] examined a racially diverse subject population in the HERITAGE study [52], and Sponton *et al.* [45] and Zago *et al.* [46] enrolled subjects from Brazil. Furthermore, our studies enrolled men [23, 29-31, 58-60], Rankinen *et al.* [52] men and women, Sponton *et al.* [45] women, and Zago *et al.* [46] subjects of unspecified sex. Therefore, the results from exercise genomics studies could be limited by both population stratification and sex effects.

- Researchers have focused on studying genetic variation without until recently investigating the heritable alterations in gene regulation including DNA methylation, histone modifications, micro RNAs (miRNAs), other non-coding RNAs (e.g., long non-coding RNAs), and proteomic factors that affect the transcription, translation, and regulation of genes (Fig. **5**) [90, 91]. These various modes of gene and protein regulation have recently been shown to have substantial effects upon physiological functions as well as heritable traits and disease [90, 91]. Such heritable alterations in gene regulation may be another factor accounting for directional reversal of risk allele phenotype associations [89] such as those observed by studies reviewed in this manuscript.

- The phenotypes and mechanistic pathways being examined are biologically complex so that the phenotypes being examined should be assessed carefully with a hypothesis-driven, functional approach, and often times are not [90-92, 101]. Furthermore, the recently developed approaches of GWAS and next-generation sequencing are often not hypothesis-driven. For this reason, there remains a considerable amount of missing heritability left unexplained [86, 92], or explained in individual studies that require replication [102, 103].

Replication has become the hallmark of exercise genomics studies [92]. A different approach that may improve the ability to confirm findings among exercise genomic studies is to examine genetic variants that emerge from GWAS that have biological plausibility for the genotype-phenotype associations being examined [104-106]. In this way, GWAS can generate hypotheses for future hypothesis-driven work. A recent development that may further improve replication among studies is utilizing next generation sequencing to densely genotype entire regions surrounding variants initially identified through GWAS and/or candidate gene association studies to associate with the health-related phenotype of interest [96]. This approach is based upon the premise that the variants functionally influencing the phenotype will be in close proximity to variants identified to be associated with the phenotype being examined, termed *linkage disequilibrium.* Furthermore, emerging statistical approaches designed specifically for genotypic data now consider neighboring variants in sequenced regions jointly to perform more powerful association tests than typically done in candidate gene association studies [107, 108]. Finally, the ability to replicate findings among studies maybe improved by testing the interaction among genetic variants that will explain a greater proportion of heritability than do variants examined individually. Gene interactions can be investigated by summing the number of risk alleles to create genetic risk scores that are tested for the associations with health-related phenotypes of interest [102, 103, 109, 110].

- Even among biologically plausible candidate genes that repeatedly associate with relevant phenotypes, functionality and interaction among specific genetic variants remain poorly understood [111]. However next-generation sequencing could rectify this problem by allowing investigators to not only explore a greater number of candidate variants, but also identify functional variants and elucidate their possible interaction networks [112].

- There exists a bias towards publishing studies with positive findings regarding the exercise-induced genotype phenotype associations [90-92, 101]. As stated above, these genetic variants may not be responsible for the associations that emerged but may merely be a marker due to linkage disequilibrium.

It is important to note the BP candidate gene association exercise studies included in this updated review are subject to many of these same limitations. For these many reasons, exercise genomic studies are limited by a large number of genetic variants explaining a small amount of heritability, a lack of replication, and ultimately, a large proportion of heritability left unexplained. Nonetheless, recent work from our laboratory [23, 29-31, 58-60], HERITAGE [50-54], and others [22, 27, 45, 46, 101, 113] suggests the possibility that some of the genetic determinants associated with the BP response to acute and chronic exercise reside in the RAAS, NO synthase, and other BP regulatory pathways.

Taken in context with past studies, to date, there are 25 polymorphisms reported associated with the BP response to a single bout of acute (i.e., PEH) [23, 30, 33, 58-60] or chronic exercise (i.e., an exercise training program) [45, 46, 50-52, 54, 114-121]. Many of these polymorphisms were found in major BP regulatory systems including the: 1) Renal System [*ACE* (rs4340), *ADD1* (rs4961), angiotensinogen (*AGT*) (rs699), *AGTR1* (rs5186), and *CYP11B2* (rs1799998)]; 2) Sympathetic Nervous System [adenosine monophosphate deaminase 1 (*AMPD1*) (rs17602729), adrenergic receptor, beta 1 (*ADRB1*) (rs1801253), adrenergic receptor, beta 2 (*ADRB2*) (rs1042714), cholinergic receptor (*CHRM2*) (rs324640, rs8191992), *GNAS* (rs7121), and guanine nucleotide binding protein, beta polypeptide 3 (*GNB3*) (rs5443)]; and 3) Nitric Oxide Synthase Pathway and/or Vascular Function [endothelin 1 (*EDN1*) (rs5370, rs2070699, rs5369), *ENOS* (rs2070744), and transforming growth factor, beta 1 (*TGFB1*) (rs1800470)]. Others were related to established and emerging cardiovascular disease risk factors implicated in the etiology of hypertension: 1) Dyslipidemia [*APOE* (rs7412), *APOE* (rs429358), fatty acid binding protein 2 (*FABP2*) (rs1799883), and lipoprotein lipase (*LPL*) (rs328)]; 2) Obesity [leptin receptor (*LEPR*) (rs1137100)]; and 3) Inflammatory Biomarkers [cytochrome b-245 alpha

polypeptide (*CYBA*) (rs4673, rs1049255) and cytochrome P450 superfamily (*CYP2D6*) (rs1065852)].

We have also found a major clinical determinant of the BP response to exercise is having one or more components of the metabolic syndrome [122]. In our studies, depending upon the multivariate regression model used, these genetic and clinical factors accounted for 27% to 59% of the variability in the BP response to exercise [23]. Our research and that of others suggest a personalized approach to exercise prescription for lowering BP based upon genetic and clinical information is warranted among individuals with hypertension, although there remain significant challenges to overcome and discoveries to be made before such a vision becomes a reality.

A VISION FOR THE FUTURE OF GENOMICS IN THE PRESCRIPTION OF EXERCISE FOR HYPERTENSION

The recent Report of the National Heart, Lung, and Blood Institute Working Group on Epigenetics and Hypertension acknowledged that while hypertension clearly has a heritable component, current genomics research has failed to explain the basis of this heritability [90]. However, exercise genomics aims not to investigate the genetic basis of hypertension but rather the genetic basis of the interaction between hypertension and exercise. Moreover, the failure to account for a majority of the heritability of hypertension may be failure to account for exercise and other environmental factors (e.g., diet, stress, smoking) interacting with genes to influence BP [22]. Future studies should account for the interactions among genes and the response of health-related phenotypes to exercise such as BP. At the same time, the limitations of the existing studies as discussed in this review should be addressed. This could be done in several ways.

First, GWAS technology has enabled investigators to study millions of variants at one time, including common, rare, non-coding, intergenic, and structural genetic variants [86]. GWAS have successfully identified risk genes and variants of complex health-related phenotypes such as age-related macular degeneration [86]. Thus, GWAS could aid in identifying new genes that contribute to BP response to exercise and rectify the limited scope of the existing candidate gene studies reviewed above. Previous GWAS from the HERITAGE study have identified individual genetic variants as well as combined genetic risk scores associated with the aerobic capacity [102] and submaximal heart rate response to exercise [103]. These findings illustrate the promise of GWAS and combined genetic risk scores to contribute to exercise genomics. However, as discussed in the previous section GWAS should be followed up by further hypothesis-driven approaches. Such approaches include replication in independent samples, examination of the strongest biologically plausible variants for the genotype-phenotype associations being examined [104-106], and next generation sequencing of regions surrounding variants initially identified through GWAS [107, 108]. Moreover next-generation sequencing will allow investigators to identify functional variants and elucidate their possible interaction networks [112].

The GWAS approach could also benefit from comparisons between individuals who exhibit the most favorable versus the most unfavorable BP responses to exercise. Bouchard *et al.* [24] recently reported that 12% of the individuals in HERITAGE increased their SBP by at least 10 mmHg following exercise training, while a similar proportion reduced their SBP by at least 10 mmHg (Fig. **6**). Similar findings occurred for other cardiovascular disease risk factors including fasting insulin, plasma triglycerides, and high density lipoprotein cholesterol. The authors issued an urgent call for studies exploring genetic and other predictors of favorable versus unfavorable exercise response. This new information would allow health care professionals to rightfully prescribe exercise as antihypertensive therapy to individuals likely to lower BP with exercise, and recommend alternative therapeutic options to the subset of individuals not likely to lower BP with exercise.

There is also a need to move beyond the contribution of genetic variants and also analyze the effects of heritable factors that influence gene expression on BP phenotypes. Moreover, animal model studies suggest exercise is an environmental factor interacting specifically with such factors. Fernandes *et al.* [123] measured resting BP, miRNA-126, miRNA-21, and miRNA-16 in two groups of spontaneously hypertensive rats before and after a 10 wk intervention. One group trained for 10 wk by swimming, while the other group remained sedentary. The trained rats with hypertension achieved greater reductions in BP as well as significantly different changes in the expression of all three miRNAs compared with the sedentary rats with hypertension. The changes in miRNA levels in the trained hypertensive rats were accompanied by significant elevations in vascular endothelial growth factor and the antiapoptotic protein Bcl-2, supporting the role of these miRNAs in exercise-induced improvements in angiogenesis and vascular integrity. These results suggest that these miRNAs may modulate the BP response to exercise in rats and should be explored in humans.

In vitro experiments on human endothelial cells have identified miRNAs that alter the regulation of angiogenesis, redox signaling, and vascular integrity [124]. Since all of these cardiovascular phenotypes contribute to the regulation of BP, it is possible that alterations in the sequences of regulatory miRNAs could be a mechanism underlying the BP response to exercise. In addition to miRNAs, Baccarelli *et al.* [91] described several gene regulatory factors, including DNA methylation and histone modifications that influence cardiovascular phenotypes in both animals and humans. The cardiovascular phenotypes associated with these factors include increased levels of inflammatory biomarkers [125], aortic fatty streaks [126], vascular lesions [127], overall dysregulated inflammation and atherosclerosis [128], and hypertension [129, 130]. Thus, these regulatory factors affecting gene expression may well influence BP

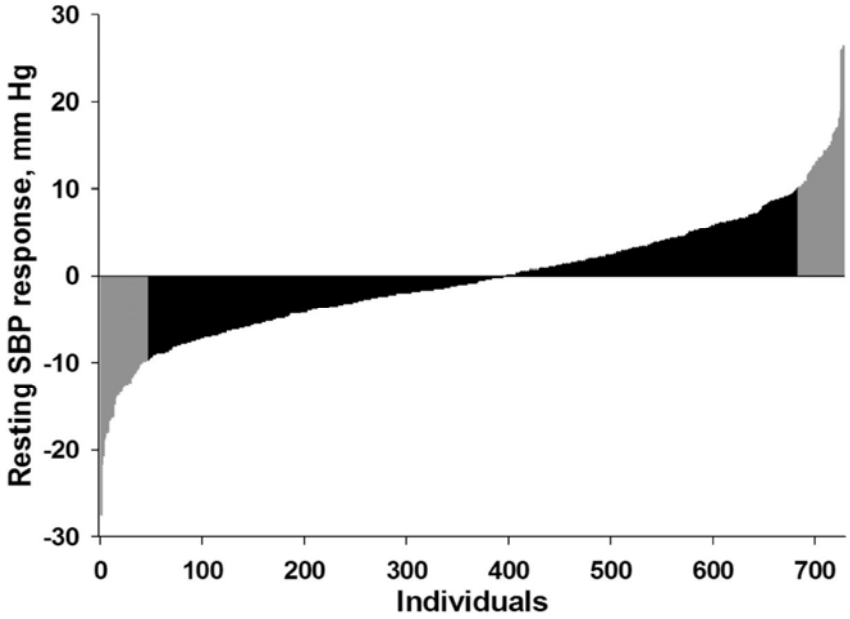

Fig. (6). Distribution of response to the HERITAGE exercise program with adverse and favorable responders highlighted in gray. SBP, systolic blood pressure. Adapted with permission from Bouchard C, Blair SN, Church TS, Earnest CP, Hagberg JM, Hakkinen K, *et al*. Adverse metabolic response to regular exercise: is it a rare or common occurrence? PLoS One 2012; 7(5): e37887.

response to exercise in humans and should be explored in future studies.

Finally, future research should also examine the biological significance of proteins encoded by genetic variants associated with BP response to exercise by studying their translation, folding, cellular actions, and interaction with other proteins in biological networks [131]. Keller *et al.* recently undertook a study to identify biological networks modulating the aerobic capacity response to exercise training [132]. They first compiled a panel of proteins known to be translated by mRNAs that were: a) differentially expressed after versus before 6 wk of aerobic exercise training for 4 $d \cdot wk^{-1}$ cycling at 70% VO_2peak, for 45 $min \cdot d^{-1}$ among young sedentary men [133], b) differentially expressed after versus before exercise training to a greater extent in the most versus least favorable aerobic capacity responders to the exercise training, and/or c) differentially expressed in rats bred for high versus low aerobic capacity.

Next, the authors searched a bioinformatics database for the biological networks reported to involve the greatest numbers of these proteins, assigning highest priority to the networks involving proteins meeting more than one of the inclusion criteria for their panel. This analysis revealed the biological network most likely associated with aerobic capacity response to exercise training was integrin signaling, followed by immune cell regulatory processes. The authors concluded future studies investigating determinants of the aerobic capacity response to exercise training should include biomolecular analysis of integrin signaling and immune cell regulatory processes. More recently, this group performed a similar analysis following a resistance exercise training intervention, concluding the biological network most strongly associated with the muscle hyperterophy response to resistance training was retinoic acid signaling [134]. This work illustrates the need to study not only DNA sequence variation and factors affecting gene expression, but also the behavior and interactions among the proteins encoded by these genes. A complete understanding of the link between genes and clinical translational applications such as the ExR_x for hypertension will similarly require *interomics*, or the integration of genomics, transcriptomics, proteomics, and systems biology (Fig. **5**) [91, 135].

Clearly, identification of clinical and genetic determinates of the BP response to acute and chronic aerobic exercise with the ultimate goal of personalized exercise prescription to maximize the efficiency of exercise as antihypertensive therapy is in its infancy. Yet, work to date indicates genetic variants associated with hypertension that are involved with major BP regulatory processes including sodium and fluid homeostasis, vascular function, inflammation, thrombosis and haemostasis, and energy and lipid metabolism also associate with the BP response to acute and chronic exercise. Interestingly, some of these associations appear dependent on the intensity of the exercise bout. Identification of clinical and genetic biomarkers associated with the BP response to acute and chronic exercise may allow clinicians to eventually prescribe exercise regimes that will optimize the use of exercise as antihypertensive therapy when considering the patient's clinical presentation and treatment goals, and the benefits and risks of the dose of exercise. At the same time, the limitations in exercise genomics will be overcome with new discoveries that remain to be made [85, 87, 90-92, 101].

Exercise will continue to be recommended to nearly all people for its numerous health benefits. However, exercise genomics will eventually enable sport medicine professionals and clinicians to refine ExR_x for subgroups of people to maximize the effectiveness of exercise as therapeutic option for the management and treatment of their hypertension and other chronic diseases and health conditions. For example, clinical and genetic information will be obtained on an individual such as that shown in Table **3** that profile those likely and not likely to respond to exercise as antihypertensive therapy. As studies examining the important interactive effects of multiple genetic variants and the heritable alterations in gene regulation, including DNA methylation, histone modifications, miRNAs, other non-coding RNAs (e.g., long non-coding RNAs), and proteomic factors that affect the transcription, translation, and regulation of genes [90, 91] are completed, this new information can also inform clinical decision making when prescribing exercise for targeted health outcomes such as lower BP. The ultimate goal is for health care professionals to prescribe exercise for individuals with hypertension identified to respond favorably to the BP lowering effects of exercise, and recommend other therapeutic options to individuals with hypertension identified to not respond favorably to antihypertensive effects of exercise.

The National Institutes of Health recently issued a funding opportunity announcement for Genomic Medicine Pilot Demonstration Projects (RFA-HG-12-006). The objective of this initiative is to support projects designed to demonstrate feasibility and develop methods for incorporating an individual's genetic profile into his or her clinical care. Such initiatives could eventually expand to the realm of ExR_x not only for hypertension but other diseases and health conditions shown to benefit from a physically active lifestyle. However, because of the complexities surrounding exercise genomics, a personalized ExR_x based upon genetic and clinical information for a targeted health outcome remains a vision of the future.

CONCLUSIONS

Hypertension is a major public health problem in the United States and world. Exercise is recommended to prevent, treat, and control hypertension at present with a generic "one size fits all" approach. Yet, there is considerable individual variability in the BP response to exercise due to genetic and environmental factors that are not well understood. The work summarized in this updated review indicates genetic and clinical information may eventually be used to characterize people who do and do not respond to exercise as antihypertensive therapy. Ultimately, exercise scientists and clinicians will be able to individualize ExR_x to optimize the use of exercise as a therapeutic modality for the prevention, treatment, and control of hypertension as well as other diseases and health conditions that benefit from a physically active lifestyle. Uncovering genetic and clinical determinants of the immediate antihypertensive effects of exercise will also improve our understanding of the biology of predispositions to disease processes such as hypertension.

DISCLOSURES

This manuscript is an updated version of our previously published manuscript: Pescatello LS. The promises and challenges of the use of genomics in the prescription of exercise in hypertension. Curr Hypertens Rev 2010; 6(1): 32-43.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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