Cardiorespiratory Fitness, BMI, and Risk of Hypertension: The HYPGENE Study

TUOMO RANKINEN[1], TIMOTHY S. CHURCH[2,5], TREVA RICE[3], CLAUDE BOUCHARD[1], and STEVEN N. BLAIR[4,5]

[1]Human Genomics Laboratory and [2]Preventive Medicine Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA; [3]Division of Biostatistics and Department of Psychiatry, Washington University School of Medicine, St. Louis, MO; [4]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC; and [5]Cooper Institute, Dallas, TX

ABSTRACT

RANKINEN, T., T. S. CHURCH, T. RICE, C. BOUCHARD, and S. N. BLAIR. Cardiorespiratory Fitness, BMI, and Risk of Hypertension: The HYPGENE Study. *Med. Sci. Sports Exerc.*, Vol. 39, No. 10, pp. 1687–1692, 2007. **Introduction:** Cardiorespiratory fitness and regular physical activity are inversely associated with the risk of hypertension, and exercise training has been shown to lower elevated blood pressure (BP). Genetic factors contribute significantly to the interindividual differences in endurance training-induced changes in BP. However, similar data on the genotype-by-fitness interactions on the risk of hypertension are scarce. **Methods:** In 2000, we started a systematic collection of blood samples from all consenting subjects of the Aerobics Center Longitudinal Study (ACLS) with a goal to generate a resource for studies addressing genotype-by-fitness interaction effects on various health-related end points. Here, we introduce the rationale and design of the first study based on the ACLS genetics resource focusing on hypertension as the health outcome (HYPGENE study), and we report the associations of cardiorespiratory fitness and body mass index (BMI) with the risk of hypertension. All HYPGENE subjects (N = 1234) were healthy and normotensive at their first clinic visit. Cases (N = 629) developed hypertension during the follow-up period (mean 8.7 yr), whereas controls (N = 605) remained normotensive (mean follow-up 10.1 yr). **Results:** Cardiorespiratory fitness was the strongest predictor of the hypertension risk, with each maximal metabolic equivalent unit being associated with a 19% lower risk (95% confidence interval [95% CI], 12–24%). Each baseline BMI unit was associated with a 9% higher hypertension risk (95% CI, 4–13%). However, the association of BMI was greatly attenuated (odds ratio 1.04 [95% CI, 0.99–1.09]) when fitness also was included in the model. **Conclusions:** The HYPGENE study will provide an excellent resource to address hypotheses regarding the genetic basis of hypertension while taking cardiorespiratory fitness level into account.
Key Words: GENOTYPE, RISK FACTOR, PHYSICAL ACTIVITY, CASE–CONTROL STUDY, BLOOD PRESSURE

Essential hypertension, the chronic elevation of blood pressure of unknown origin, represents approximately 90% of all hypertension diagnoses. It has been estimated that 65 million people in the United States have high blood pressure, and it is well documented that hypertension is a major risk factor for stroke and heart disease (28). However, blood pressure is a modifiable risk factor. Several traits, such as diet, physical activity, cardiorespiratory fitness, body weight, and psychosocial stress have been shown to affect blood pressure levels, both acutely and chronically.

Prospective epidemiological studies have shown a lower risk of developing hypertension in physically fit (2,3,6,27) and physically active (10,12,13,19,20) individuals compared with unfit and sedentary individuals. Several intervention studies have reported clinically significant reductions in systolic and diastolic blood pressure (SBP and DBP, respectively) after moderate-intensity aerobic exercise training (8,11,22,29). The average training-induced reductions in SBP and DBP have varied from 2 to 11 mm Hg and from 1 to 8 mm Hg, respectively (7,8,11,16,17,29). The magnitude of training responses have increased as a function of initial BP levels (8), being more pronounced in patients with mild to moderate hypertension than in normotensive subjects.

Excess body weight also is associated with an increased risk of developing hypertension (9,14), whereas weight loss has been shown to lower blood pressure (14,18). For example, in the Nurses' Health Study, both baseline BMI

Address for correspondence: Tuomo Rankinen, Ph.D., Human Genomics Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808; E-mail: rankint@pbrc.edu.
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and BMI at age 18 yr were strong predictors of risk for hypertension (14). Each baseline BMI unit was associated with a 12% higher risk of future development of hypertension. In addition, long-term (12–50 yr) weight change after age 18 yr was strongly associated with hypertension risk. Compared with weight-stable women, those who lost at least 2.1 kg had a significantly lower risk, whereas women who gained weight showed a higher risk for hypertension (14).

Interestingly, some individuals become hypertensive despite a physically active lifestyle and/or a normal body weight, whereas some people who are sedentary and/or overweight and may still have blood pressure in an optimal range. Similarly, whereas exercise training and weight loss lower blood pressure on average, there are significant interindividual differences in blood pressure responses. For example, in the HERITAGE Family Study, SBP and DBP measured during steady-state submaximal (50 W) exercise decreased on average by 7 and 3.5 mm Hg, respectively, in response to exercise training (30). However, the responses varied from marked decreases to no changes, or, in some cases, even to slight increases (5,30). The underlying mechanisms for interindividual variation in the effects of regular physical activity are still poorly understood, but two main factors contributing to the variation in training-induced changes in hemodynamic traits are initial phenotype level and familial aggregation (5). The HERITAGE Family Study has shown that heritabilities of endurance training–induced changes in hemodynamic phenotypes vary between 20 and 40%, and some of the classic hypertension candidate genes also seem to affect the training responses (24,25). However, similar data on the contribution of genetic variation to the antihypertensive effect of moderate and high levels of cardiorespiratory fitness are scarce, mainly because of the paucity of suitable data sets to explore such questions. In 2000, the Human Genomics Laboratory of the Pennington Biomedical Research Center in collaboration with the Aerobics Center Longitudinal Study (ACLS) investigators started a systematic banking of blood samples from all consenting ACLS participants, with the goal of generating a suitable resource to address hypotheses related to cardiorespiratory fitness-by-genotype interactions on various health outcomes.

The purpose of this paper is to introduce the ACLS-based genetics resource, describe the design and methods of the first study targeting hypertension as an end point (HYPGENE study), and report the associations of cardiorespiratory fitness and body mass index with the risk of developing hypertension in the HYPGENE cohort.

SUBJECTS AND METHODS

ACLS genetics collaboration. The ACLS is an ongoing epidemiology study conducted at the Cooper Institute in Dallas, TX, and composed of patients who come to the Cooper Clinic for preventive medical examinations. Examinations date back to 1970; to date, the database is composed of over 200,000 patient visits from over 80,000 individual patients. A unique aspect of the ACLS is that the majority of participants performed a maximal exercise test on a treadmill allowing for the accurate quantification of cardiorespiratory fitness. Many peer-reviewed papers have been published from the ACLS data including the landmark 1989 publication on cardiorespiratory fitness and mortality (4), which has received over 1200 citations. Thus, the ACLS is a well-established, well-characterized database to investigate fitness-related issues.

A systematic banking of blood samples from all consenting ACLS participants started in spring 2000. All subjects gave a written informed consent to send their samples to other institutions for storage and genetic analyses. The samples consisted of EDTA anticoagulated blood samples that were left over after standard clinical chemistry assays were performed as part of the clinic examination. The blood samples were removed from the clinic labeled tubes and transferred to a new cryotube that was labeled with the subject's ACLS ID number and collection date (all personal identifiers were removed). The samples were immediately frozen and stored at −80°C until shipped in dry ice to the Human Genomics Laboratory in Baton Rouge, LA for final storage. Collection of these samples ended in May 2006, and the final inventory includes samples from 19,900 ACLS participants. The majority of these participants had clinic visits and data for years before the examination when their blood sample for DNA banking was collected. The HYPGENE study protocol has been approved by the institutional review boards of the Pennington Biomedical Research Center and the Cooper Institute.

Selection of cases and controls. The first study based on the new ACLS genetic resource focuses on hypertension and is entitled the HYPGENE study. The aim of the HYPGENE study is to investigate the contributions of DNA sequence variation in candidate genes, cardiorespiratory fitness, and body mass index, as well as their interactions, to the incidence of hypertension. A total of 13,600 individuals, of whom 6800 had at least two clinic visits, were available in the ACLS DNA bank at the time when the HYPGENE cases and controls were selected.

All eligible ACLS subjects for the HYPGENE study were required to be healthy with resting blood pressure 134/86 mm Hg or less at their first clinic visit. Subjects with diagnosed hypertension or other chronic disease (cardiovascular disease, stroke, type I or type II diabetes mellitus, cancer, arthritis, etc.) as well as subjects with any blood pressure affecting medication at first clinic visit were excluded. All eligible subjects were required to have at least two clinic visits with a minimum of 2 yr apart. Cases were defined as subjects who developed hypertension during the follow-up. Hypertension was defined as physician-diagnosed hypertension with medication to lower

TABLE 1. Baseline characteristics of the cases and controls.

	Cases	Controls	*P* Value
Number of subjects	629	605	
Sex (male/female)	519/117	453/152	0.004
Age (yr)	43.3 (9.2)	42.7 (8.9)	0.273
BMI ($kg \cdot m^{-2}$)	25.1 (3.2)	24.1 (3.1)	< 0.0001
Maximal METs	11.7 (2.0)	12.3 (2.0)	< 0.0001
Treadmill time (min)	18.0 (5.0)	19.4 (5.0)	< 0.0001
SBP (mm Hg)	117.3 (8.7)	110.5 (9.2)	< 0.0001
DBP (mm Hg)	77.7 (6.0)	73.8 (7.0)	< 0.0001
Follow-up (yr)	8.7 (6.4)	10.1 (7.0)	0.0002

METs, metabolic equivalents, calculated from treadmill time (see Methods for details); SBP, systolic blood pressure; DBP, diastolic blood pressure.

blood pressure or resting systolic blood pressure 140 mm Hg or more and/or diastolic blood pressure 90 mm Hg or more on a follow-up clinic visit. Controls were required to remain normotensive (blood pressure < 130/85 mm Hg, as defined by the national and international recommendations when project was started (15,31)) and otherwise healthy throughout the follow-up period. That is, controls were selected among the "survivors" rather than from all subjects at baseline (21). All cases and controls were confirmed via review of clinical records.

The controls were selected randomly using a sex-specific frequency matching protocol within 5-yr baseline age strata (age at first clinic visit) and allowing up to 20% oversampling within the sex-by-age strata. The main goal was to obtain cases and controls that were of similar age at baseline (first clinic visit). We chose not to use a strict matching routine for control selection in order to avoid restrictions and potential complications that such an approach could induce on statistical analyses with candidate gene DNA sequence variation markers. As Table 1 shows, our frequency matching routine worked well and there is no difference in baseline age between the cases and controls. Minor differences in potential confounding factors such as sex and follow-up time can be accommodated in statistical models by including them as covariates. An incidence-density sampling design for the controls would have provided a direct sample of the base population, and the odds ratio would have been a direct estimate of the hypertension rate ratio (21,26). However, because our "effective" sampling base was restricted to ACLS subjects with DNA samples, the incidence–density sampling among these subjects would not have provided a sufficient sample size. We also considered selecting four controls for each case (1:4 case–control ratio) to obtain greater precision for the risk estimates. Although the number of cases needed for a given statistical power would be slightly lower with 1:4 than with 1:1 matching, the total sample size would be considerably greater. Because availability of cases was not a limiting factor in the ACLS cohort, we decided to use 1:1 matching to keep the costs of molecular genetic studies at a reasonable level.

Baseline phenotype measurements. Cardiorespiratory fitness was assessed by a maximal exercise test following a modified Balke protocol (1). Subjects began walking at 88 $m \cdot min^{-1}$ (3.3 mph) with no elevation. After the first minute, the incline was increased to 2% and then by 1% each minute thereafter until the 25th minute. For the few individuals still able to continue the test beyond 25 min, the elevation was maintained at 25%, but the speed was increased by 5.4 $m \cdot min^{-1}$ (0.2 mph) each minute to the end of the test. The test was terminated when the subject was exhausted or if the physician stopped the test for medical reasons. Time to completion on the treadmill was used to estimate maximal metabolic equivalents using the following formula: METs = [1.44 × (minutes on treadmill) + 14.99]/3.5. Time on the treadmill test with this protocol is highly correlated ($r = 0.92$) with measured maximal oxygen uptake (23). Thus, the maximal METs in this study provide a reasonable surrogate for maximal aerobic power. Body mass and stature were measured using a standard physician's scale and stadiometer, and the BMI ($kg \cdot m^{-2}$) was calculated.

Statistical methods. Differences in continuous and class variables between cases and controls were assessed with *t*-tests and chi-square tests, respectively. Logistic regression modeling was used to assess the contribution of baseline age, sex, follow-up time, cardiorespiratory fitness (treadmill time) and body mass index (BMI) to the risk of hypertension. The final model included all five independent variables. All fitness and BMI associations presented in the results section are adjusted for age, sex, follow-up time, and BMI (for fitness) or fitness (for BMI), unless otherwise stated. Fitness and BMI were modeled both as continuous traits and as class variables (sex-specific quartiles).

RESULTS

Baseline characteristics of cases and controls are summarized in Table 1. The mean age of cases and controls was 43 yr at baseline. The average follow-up time until diagnosis of hypertension was 8.7 (SD 6.4) years in cases, whereas it reached 10.1 (SD 7.0) years in controls. The controls had a 0.6-unit-greater maximal MET count (1.4-min-longer treadmill time) and a 1.0-unit-lower BMI than cases at baseline (Table 1). Subjects were clearly normotensive at baseline, with mean resting blood pressure 114/76 mm Hg. However, mean systolic and diastolic blood pressure levels were, respectively, 6.8 and 3.9 mm Hg lower in controls than in cases. Of the cases, 382 (61%) were confirmed on the basis of hypertension diagnosis and medication, 177 (28%) had elevated DBP, 35 (5.5%) had elevated SBP, and 35 (5.5%) had both elevated SBP and DBP. In the follow-up visit, the mean SBP and DBP levels in the controls were 113 (8.5) mm Hg and 75 (5.9) mm Hg, respectively, and all controls had resting blood pressure levels of 128/84 mm Hg or less.

Results of the logistic regression models for the risk of hypertension using fitness (METs) and BMI as continuous variables and adjusting for baseline age, sex, and follow-up time are presented in Table 2. Cardiorespiratory fitness showed the strongest association with hypertension risk

TABLE 2. Results of logistic regression models for the risk of hypertension in all subjects and by sex, using fitness and body mass index as continuous variables.

	OR (95% CI)	*P* Value
All		
Age (yr)	0.99 (0.97–1.00)	0.1
Fitness (METs)	0.81 (0.76–0.88)	< 0.01
BMI (kg·m^{-2})	1.04 (0.99–1.09)	0.1
Follow-up (yr)	0.97 (0.96–0.99)	< 0.01
Sex	2.06 (1.42–3.00)	< 0.01
Men		
Age (yr)	0.99 (0.97–1.00)	0.12
Fitness, METs	0.84 (0.78–0.91)	< 0.01
BMI (kg·m^{-2})	1.04 (0.99–1.10)	0.17
Follow-up (yr)	0.97 (0.95–0.99)	< 0.01
Women		
Age (yr)	0.98 (0.95–1.02)	0.35
Fitness, METs	0.68 (0.55–0.83)	< 0.01
BMI (kg·m^{-2})	1.01 (0.92–1.11)	0.84
Follow-up (yr)	0.96 (0.92–1.01)	0.12

OR, odds ratio; CI, confidence interval; METs, metabolic equivalents, calculated from treadmill time (see Methods for details).

among all subjects as well as in sex-specific models. Each 1-MET increment in fitness level was associated with 19% (95% CI, 12–24%), 16% (95% CI, 9–22%), and 32% (17–45%) risk reductions in all subjects, men, and women, respectively (Table 2). When the cohort was divided in quartiles on the basis of sex-specific MET cutoffs, the third and fourth quartiles had 58% (95% CI, 41–71%) and 63% (95% CI, 47–75%) lower risk of hypertension compared with the first quartile (Fig. 1).

Each baseline BMI unit was associated with a 9% higher risk of hypertension (OR 1.09 [95% CI, 1.04–1.13]) after adjusting for age, sex, and follow-up time. However, the association of BMI was greatly weakened (OR 1.04 [0.99; 1.09]) when fitness also was included in the model (Table 2). Logistic regression models using sex-specific BMI quartiles revealed that the hypertension risk did not increase linearly as a function of BMI level. As depicted in Figure 2, the increased risk was evident only in the highest BMI quartile. Subjects in quartile 4 had a more than twofold risk of becoming hypertensive compared with those in quartile 1 in an age-, sex-, and follow-up time–adjusted model. However, inclusion of cardiorespiratory fitness in the model reduced the risk estimate to OR 1.53 (95% CI, 1.07–2.18).

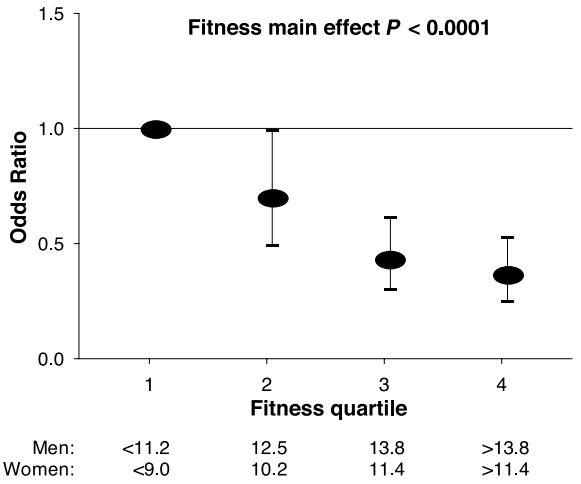

FIGURE 1—Risk of hypertension across sex-specific quartiles of cardiorespiratory fitness in the HYPGENE study. Least fit individuals (quartile 1) were used as a reference group, and the odds ratios are adjusted for age, sex, follow-up time, and body mass index. Upper cutoffs (METs) of quartiles 1, 2, and 3 for men and women are given below the figure.

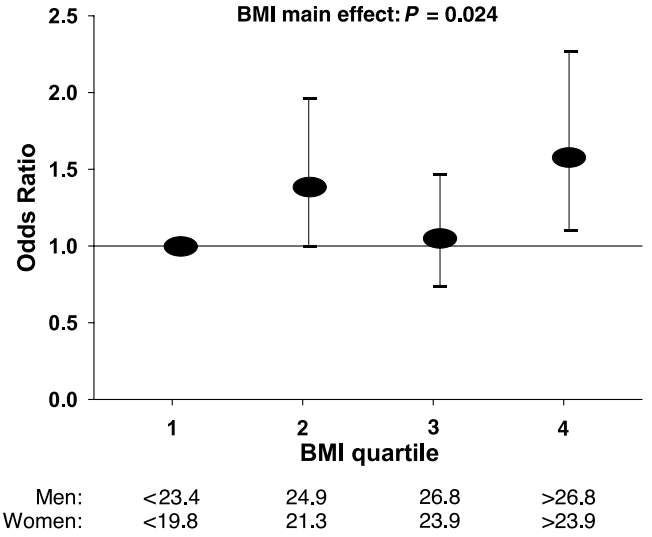

FIGURE 2—Risk of hypertension across sex-specific quartiles of body mass index in the HYPGENE study. Leanest individuals (quartile 1) were used as a reference group, and the odds ratios are adjusted for age, sex, follow-up time, and cardiorespiratory fitness. Upper cutoffs of quartiles 1, 2, and 3 for men and women are given below the figure.

DISCUSSION

The protective effects of higher levels of cardiorespiratory fitness and regular physical activity against elevated blood pressure and hypertension have been demonstrated in several observational studies and intervention trials (22). Being unfit has been associated with a 1.5- to 2.2-fold risk of developing hypertension compared with fit individuals (3,6,27), whereas in sedentary subjects the hypertension risk has been reported to be 1.35 to 1.73 times greater than in those who are physically active (10,13,20). Our observations in the HYPGENE cohort agree well with the risk estimates from earlier studies. The 63% lower risk in the highest fitness quartile compared with the lowest quartile would translate into a 2.7-fold greater risk of hypertension in the least fit (1st quartile) when the most fit (4th quartile) subjects are used as a reference group.

Although higher levels of fitness are clearly associated with a lower risk of hypertension in the HYPGENE cohort, a detailed inspection of the distribution of cases and controls across the fitness level continuum showed that 37% of the subjects in the highest fitness decile became hypertensive, and one third of the subjects in the lowest decile remained normotensive during the follow-up period (Fig. 3). In other words, individuals with equally high levels of cardiorespiratory fitness experienced different

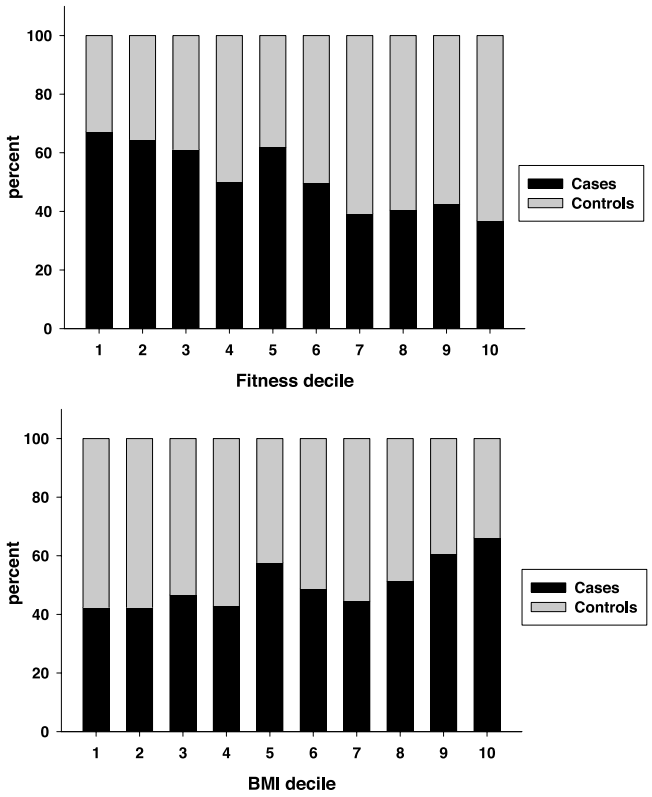

FIGURE 3—Distribution of cases and controls across the deciles of cardiorespiratory fitness (*upper panel*) and body mass index (*lower panel*) in the HYPGENE study.

disease outcomes. This pattern is akin to the interindividual differences in responsiveness of various risk factors, including blood pressure, to standardized and controlled exercise training programs (5). Identifying the sources of this type of variation is vital for a better understanding of both the (patho)physiological processes leading to hypertension and the mechanisms by which higher levels of cardiorespiratory fitness protect against hypertension. The ultimate benefit would be more efficient use of physical activity in prevention and treatment of hypertension. Identification of "high responders" would allow physicians to use regular physical activity as a primary treatment in these patients. On the other hand, "low responders" would provide a target population for exercise scientists to explore other types of training programs that may be more effective for these individuals.

Body weight gain and obesity are strong risk factors for high blood pressure and hypertension, and in the HYPGENE cohort, higher BMI was also associated with greater hypertension risk. Our estimate of a 9% age-, sex-, and follow-up time–adjusted hypertension risk per unit of BMI is similar to the 12% risk estimate reported in the Nurses Health Study (14). However, in our data, the contribution of baseline BMI to the hypertension risk was attenuated substantially when cardiorespiratory fitness was added to the regression model. Moreover, the risk of hypertension was not linearly associated throughout the BMI distribution. As depicted in Figure 3, the greater prevalence of cases over controls started to emerge only in BMI deciles 9 and 10 (i.e., BMI > 27.3 $kg \cdot m^{-2}$ in men and BMI > 24.6 $kg \cdot m^{-2}$ in women). One possible explanation for the smaller than expected association of BMI to the risk of hypertension may be that the HYPGENE subjects were, by and large, of normal weight during their first clinic visit. Moreover, our observation that the higher prevalence of cases occurs only at the upper end of the BMI distribution supports the notion that the risk of hypertension starts to increase at BMI levels that are clearly in the overweight range.

Our observations regarding the contribution of cardiorespiratory fitness and body mass index to the risk of hypertension provide a good foundation for the pursuit of the primary aims of the HYPGENE study: to investigate the contribution of DNA sequence variation in functional candidate genes, and the genotype-by-fitness interactions to the risk of hypertension. First, the average protective effect of cardiorespiratory fitness on hypertension seen in this cohort provides an excellent basis to test genotype-by-fitness interactions. Second, the fact that we can effectively control for a major physiological predictor of hypertension risk will greatly improve our chances to detect the genotype main effects that are independent of fitness level and that may contribute to the development of hypertension among fit individuals or to the protection against elevated blood pressure in the unfit subjects. Third, the relative leanness of the cohort will work to our advantage by reducing the confounding effect of excess body weight to the genotype main effect and genotype-by-fitness interaction analyses. Finally, the large number of retrospectively confirmed incident cases and healthy controls will give us adequate statistical power to explore the contribution of DNA sequence variation to the risk of hypertension independent of and interacting with cardiorespiratory fitness.

In summary, using the longitudinal design of the ACLS cohort, we have generated a case–control study with 638 new, incident hypertensive cases and 605 healthy controls with similar follow-up times. Our data confirm that cardiorespiratory fitness is a significant predictor of the risk of hypertension, whereas the effect of body weight emerges only in the overweight range. The HYPGENE cohort will provide an excellent resource to address hypotheses regarding the genetic basis of hypertension while taking cardiorespiratory fitness levels into account.

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