Advances in Exercise, Fitness, and Performance Genomics in 2011

STEPHEN M. ROTH[1], TUOMO RANKINEN[2], JAMES M. HAGBERG[1], RUTH J. F. LOOS[3,4], LOUIS PÉRUSSE[5], MARK A. SARZYNSKI[2], BERND WOLFARTH[6], and CLAUDE BOUCHARD[2]

[1]Department of Kinesiology, School of Public Health, University of Maryland, College Park, MD; [2]Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA; [3]Medical Research Council Epidemiological Unit, Institute of Metabolic Science, Cambridge, UNITED KINGDOM; [4]Charles R. Bronfman Institute for Personalized Medicine, Mount Sinai School of Medicine, New York, NY; [5]Department of Kinesiology, Laval University, Sainte-Foy, Québec, CANADA; and [6]Department of Prevention, Rehabilitation and Sports Medicine, Technical University Munich, Munich, GERMANY

ABSTRACT

ROTH, S. M., T. RANKINEN, J. M. HAGBERG, R. J. F. LOOS, L. PÉRUSSE, M. A. SARZYNSKI, B. WOLFARTH and C. BOUCHARD. Advances in Exercise, Fitness, and Performance Genomics in 2011. *Med. Sci. Sports Exerc.*, Vol. 44, No. 5, pp. 809–817, 2012. This review of the exercise genomics literature emphasizes the highest quality articles published in 2011. Given this emphasis on the best publications, only a small number of published articles are reviewed. One study found that physical activity levels were significantly lower in patients with mitochondrial DNA mutations compared with controls. A two-stage fine-mapping follow-up of a previous linkage peak found strong associations between sequence variation in the activin A receptor, type-1B *(ACVRIB)* gene and knee extensor strength, with rs2854464 emerging as the most promising candidate polymorphism. The association of higher muscular strength with the rs2854464 A allele was confirmed in two separate cohorts. A study using a combination of transcriptomic and genomic data identified a comprehensive map of the transcriptomic features important for aerobic exercise training–induced improvements in maximal oxygen consumption, but no genetic variants derived from candidate transcripts were associated with trainability. A large-scale *de novo* meta-analysis confirmed that the effect of sequence variation in the fat mass and obesity-associated *(FTO)* gene on the risk of obesity differs between sedentary and physically active adults. Evidence for gene–physical activity interactions on type 2 diabetes risk was found in two separate studies. A large study of women found that physical activity modified the effect of polymorphisms in the lipoprotein lipase (*LPL*), hepatic lipase (*LIPC*), and cholesteryl ester transfer protein *(CETP)* genes, identified in previous genome-wide association study reports, on HDL cholesterol. We conclude that a strong exercise genomics corpus of evidence would not only translate into powerful genomic predictors but also have a major effect on exercise biology and exercise behavior research. **Key Words:** GENETICS, EXERCISE TRAINING, CANDIDATE GENES, GENE–EXERCISE INTERACTION, SINGLE NUCLEOTIDE POLYMORPHISM, QUANTITATIVE TRAIT LOCUS

In this review, we continue on the success of the past two years (19,36) in which our international group of exercise genetics and genomics investigators has sought to carefully summarize the highlights of published literature from the preceding year in the area of genomics relative to exercise, fitness, and performance. Readers will recall that for several years, our group published an annual comprehensive and cumulative review of the published literature in this area but that it became too large of an effort to continue. Thus, beginning in 2010, the review evolved into a substantially shorter version, with the goal of focusing only on the strongest studies on the basis of design, sample size, phenotypes, novelty, and potential impact from the literature published in the preceding year. Thus, this review format is not intended to be a comprehensive and cumulative summary of all published literature addressing exercise genomics.

The present article is the third annual version of the highly focused review of the "scientifically strongest and substantively most important articles in exercise genomics" and covers the calendar year 2011. As described in the introduction to the first such review (36), this concise review is by design selective in choosing articles that can provide exercise and sports medicine scientists with the latest and strongest

Address for correspondence: Claude Bouchard, Ph.D., Human Genomics Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808-4124; E-mail: claude.bouchard@pbrc.edu.
Submitted for publication January 2012.
Accepted for publication February 2012.

0195-9131/12/4405-0809/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e31824f28b6

evidence in exercise genomics. The review serves the additional aims of highlighting the necessary components of a high-quality exercise genomics study. We hope that this effort will help researchers identify the vast gaps in our knowledge concerning genomics and genetics relative to exercise, fitness, and performance and thereby provide direction for future investigative efforts.

In this review, we have selected articles focusing on (a) physical activity level, (b) muscular strength and power, (c) endurance performance, (d) adiposity, (e) glucose and insulin metabolism, (f) lipid and lipoprotein metabolism, and (g) hemodynamic traits.

PHYSICAL ACTIVITY LEVEL

The year 2011 was a quiet one in terms of genetic studies on physical activity level, with the exception of a study comparing habitual activity behaviors in mitochondrial disease patients and healthy controls (3). Although the contribution of mitochondrial DNA mutations to exercise intolerance has been well documented, less is known about habitual physical activity level and sedentary behavior in these patients. Apabhai et al. (3) recruited 100 mitochondrial disease patients with confirmed mitochondrial DNA mutations and 100 individually matched (by age, sex, and body mass index (BMI)) healthy controls. The patients were categorized in four groups on the basis of the type of mutations: 47 patients had at least one point mutation, 28 had multiple deletions, 21 had single large-scale deletions, and 4 had uncharacterized genetic defects with ragged red fibers and Cox-negative staining from skeletal muscle biopsy. Physical activity level and sedentary behavior were quantified with a multisensor array that was worn for 3 d.

The results showed that although all patients were ambulatory, their activity level was significantly lower than that of controls: the patients walked more than 3000 fewer steps per day than the controls. Moreover, the patients had sedentary periods of significantly longer duration than the controls. Finally, although clinical rating of the disease severity was inversely associated with physical activity level, there were no differences in activity level between different types of mitochondrial DNA mutations. Disease severity explained 4% to 15% of the variance in activity and sedentary traits after adjusting for age, sex, and BMI.

Although this study is the first one to report lower habitual physical activity levels in mitochondrial disease patients, the findings are not surprising given the clinical spectrum of their diseases. However, the study represents an excellent illustration of the multifactorial and polygenic nature of complex traits such as habitual physical activity level and sedentary behavior. Interestingly, if the authors had tested each mutation individually, they probably would not have seen any significant associations with activity traits. However, combining a wide range of mutations that all produce a relatively uniform clinical condition provided adequate power to detect the effects on physical activity level. These particular mutations are less relevant for physical activity behavior in the general population (i.e., in individuals apparently free of mitochondrial diseases), but it is likely that multiple genes and DNA sequence variants (nuclear and perhaps even mitochondrial) affect activity and sedentary traits in the population at large.

MUSCULAR STRENGTH AND POWER

In the past year, relatively few articles were published in the area of genetics and muscular strength and power phenotypes (13,17,23,30,37,46). From these additions, two articles stand out for their unique contributions to the literature. The first, by Hughes et al. (23), examined the probability of any given individual carrying an "optimal" genotype profile across 22 polymorphisms with some prior evidence of contribution to muscular power–related phenotypes. The authors reported a very low probability (0.000003) of any person carrying all of the 22 optimal genotypes across these polymorphisms. The vast majority of people carry a genotype profile that differs by only a few alleles and genotypes from the average profile. The authors used these findings to argue that the high degree of similarity in genetic profile across individuals and the relatively few individuals with low or high numbers of favorable genotypes at these 22 loci should favor a low level of heterogeneity in muscular power–related traits in the population. Importantly, only 5 of the 22 polymorphisms have been independently replicated, so even this analysis is tentative and theoretical in nature. The results provide some insights into the challenges of using genetic information in phenotype prediction such as athletic potential. Their observations together with other published results suggest that a genetic predisposition not only arises from having favorable alleles at all loci but also can be seen in the presence of favorable alleles at a substantial fraction of all relevant loci. For instance, the latter scenario is actually strongly suggested by the results of a genome-wide association study (GWAS) of $\dot{V}O_{2max}$ trainability reviewed later in the article (9).

A second article added to our understanding of the genetic underpinnings of muscular strength phenotypes through a well-designed and comprehensive follow-up analysis of a previous linkage study (24,25). In a follow-up report, Windelinckx et al. (46) first performed a two-stage fine mapping of a previously identified linkage peak for knee extensor strength on chr12q12-14, with genotyping of 209 tagging polymorphisms in or near 74 prioritized gene targets in 500 brothers from the Leuven Genes for Muscular Strength study. Two genes were identified from this fine mapping, including activin A receptor, type 1B (*ACVR1B*). Then, a second round of genotyping was performed focused on these gene regions. Only *ACVR1B* proved interesting in the follow-up analysis. Strong associations between *ACVR1B* genotypes and knee extensor strength were observed in this follow-up analysis, with rs2854464 emerging as the most promising candidate polymorphism, such that the A allele

(allele frequency of 0.73) was associated with higher muscular strength. Importantly, the authors then performed a replication analysis of these *ACVR1B* polymorphisms in two separate cohorts and confirmed the association of higher muscular strength in rs2854464 A allele carriers.

ACVR1B encodes the activin receptor 1B that seems to be important to myostatin signaling in skeletal muscle (29), although the details are unclear. Although the rs2854464 polymorphism seems to disrupt a putative microRNA 24 (miR-24) binding site in the 3′ untranslated region of the *ACVR1B* gene, no differences in *ACVR1B* gene expression were found in a subsample of 16 individuals with different genotypes for whom skeletal muscle biopsies were available (46). The authors have thus added another strong candidate gene to those that seem to contribute to muscular strength phenotypes. Considerable work will be needed, however, to add clarity to the significance of this gene and its polymorphic variation to health- and performance-related muscular phenotypes.

ENDURANCE PERFORMANCE

In 2011, several peer-reviewed articles were published on endurance performance, mainly in elite athletes. Most of these studies (e.g., Ash et al. [4], Chiu et al. [11], Maciejewska et al. [31], and Mikami et al. [33]) were based on a case-control design and were characterized by the same limitations that we highlighted last year (19) and that were further addressed in a recent publication (6). Although some studies had replication data, the small sample size and the lack of clearly defined physiological phenotypes were consistent limiting factors (21,32). Three recently published articles were based on innovative study designs and/or unique analytic strategies with relatively large sample sizes; we are reviewing them below.

The first article by Keller et al. (26) used a combination of transcriptomics and genomics to describe the effect of endurance training on skeletal muscle phenotypes. In a prior publication by the same group, approximately 800 skeletal muscle gene transcripts were shown to be up- or downregulated by 6 wk of endurance training in sedentary subjects (43). These transcripts were identified as the training-responsive transcriptome (TRT) (43). In the more recent publication, the same group studied the potential regulatory molecules coordinating the complex network of exercise-training regulated genes using different cohorts, including 24 sedentary and healthy men who performed 6 wk of endurance training (26). In addition, genotyping was performed on 473 white subjects from the HERITAGE Family Study cohort (7), and a novel outbred rodent aerobic capacity model was studied. All three approaches were combined in an attempt to develop a more complete picture of the genetic basis of endurance performance traits.

The TRT was examined by contrasting subjects who were low or high responders to exercise training. At least 100 of the 800 TRT genes were differentially regulated between the two groups, suggesting they may be critical for the improvement of aerobic capacity. Subsequently, from a panel of 3400 single nucleotide polymorphisms (SNPs) in the HERITAGE study cohort, several DNA variants showed associations with the trainability of maximal aerobic power. However, after the conservative Bonferroni correction, none of the SNPs remained statistically significant (26). In the rat model, selected from 10 generations of high responders to aerobic training, there was evidence to the effect that in these animals, the TRT and a subset of the human high-responder genes were regulated to a greater degree in the high-responder rodents. These complex but internally consistent data were taken as evidence for a powerful gene expression program that characterizes successful adaptation to aerobic training. Interestingly, the transcripts involved belong mainly to development-, tumor biology–, and immunology-related pathways (26). From a clinical point of view, it will be interesting to see whether these findings, describing a gene-based responder status to regular exercise programs, will be replicated and eventually provide us with the foundation to individualize exercise programs in a preventive or therapeutic context.

A second new report based on a GWAS undertaken with more than 320,000 SNPs on the sample of whites in HERITAGE was recently published (9). The first finding was that a total of 39 individual SNPs were associated with $\dot{V}O_{2max}$ training response at $P < 1.5 \times 10^{-4}$, with none of the associations reaching the genome-wide significance level of 5×10^{-8}. The strongest evidence of association ($P = 1.3 \times 10^{-6}$) was observed with an SNP located in the first intron of the acyl-CoA synthetase long-chain family member 1 *(ACSL1)* gene. Subsequently, when all 39 SNPs were analyzed simultaneously in multivariate regression models, nine SNPs each accounted for at least 2% (range = 2.2% to 7.0%) of the variance ($P < 0.0001$ for all), whereas seven other SNPs each contributed between 1% and 2%. Collectively, these 16 SNPs accounted for 45% of the variance in $\dot{V}O_{2max}$ trainability. It turns out that this is a value comparable to the heritability estimate of 47% reported previously in HERITAGE (8).

Finally, a genomic predisposition score was constructed with the 21 SNPs that were entered in the final regression model, and each SNP was coded on the basis of the number of high–$\dot{V}O_{2max}$ training response alleles: the low-response allele homozygotes were assigned 0, heterozygotes received 1, and homozygotes for the high-response allele were coded as 2. Thus, the theoretical range of the genomic predisposition score was from 0 (no beneficial alleles) to 42 (two copies of the beneficial alleles at all 21 loci). The data show that the observed scores ranged from 7 to 31. Importantly, the magnitude of the difference in $\dot{V}O_{2max}$ training response between those with the lowest (9 or less, $n = 36$, mean = +221 $mL \cdot min^{-1}$) and the highest (19 or more, $n = 52$, mean = +604 $mL \cdot min^{-1}$) genomic predisposition scores was 383 $mL \cdot min^{-1}$. These observations strongly suggest that it will eventually be possible to predict in sedentary adults the magnitude of the $\dot{V}O_{2max}$ training response to be expected using a panel of genomic markers.

The third interesting publication came out of the CAREGENE (14) cohort, which comprises 935 CAD patients who completed a 3-month ambulatory supervised exercise training program with two to three (average = 2.27) 90-min training sessions per week. Before and after the training program, patients completed a maximal graded exercise test on a cycle ergometer with respiratory gas analysis. Thomaes et al. (42) investigated a set of 21 SNPs in 12 muscle-related genes in the CAREGENE subjects. A genetic predisposition score was calculated, and its predictive value was tested (42,45). In summary, they found suggestive associations for the changes in aerobic capacity with single SNPs in the ciliary neurotrophic factor *(CNTF)*, the AMP deaminase 1 *(AMPD1)*, and the glucocorticoid receptor (*GR*, now known as nuclear receptor subfamily 3, group C, member 1 [*NR3C1*]) genes. In addition, the genetic predisposition score was a significant predictor of whether a patient belonged to the responder or the nonresponder $\dot{V}O_{2max}$ gain group as a result of the training regimen (42). This publication (42) and the previous one from HERITAGE (9) emphasize that a predisposition score offers new opportunities to optimize the prediction of trainability and may have practical value in the future as suggested earlier (6).

In summary, the three publications reviewed herein represent a trend toward more powerful experimental studies with innovative designs and larger sample sizes. As suggested in our review of last year (19), the combination of transcriptomics and genomics seems to be particularly useful for the investigation of the genetic regulation of endurance performance phenotypes.

ADIPOSITY

In the past year, the list of obesity susceptibility loci grew only slightly, with one large-scale GWAS for body fat percentage identifying two new loci, near the insulin receptor substrate 1 *(IRS1)* and the sprouty homolog 2 *(SPRY2)* genes, and confirming the fat mass and obesity associated (*FTO*) locus (28). As such, the total number of obesity susceptibility loci stands currently at 52, of which 32 were primarily identified for BMI, 2 were identified for body fat percentage, 14 were identified for waist-to-hip ratio (adjusted for BMI), and 4 were identified for extreme and early-onset obesity. The two-stage design (i.e., discovery stage, followed by replication stage), the stringent significance threshold ($P < 5 \times 10^{-8}$), and the large scale that characterizes GWAS ensure that these 52 loci are unequivocally established. Despite these convincing observations, few loci have been studied in more in-depth functional experiments or detailed association analyses to gain greater insight into the mechanisms by which they contribute to obesity risk.

Because of the ever-growing scale of GWAS (e.g., the discovery stage of the latest meta-analysis for BMI included 123,865 individuals), the follow-up of these loci in epidemiological studies has become a challenging undertaking. To have sufficient statistical power, follow-up studies require sample sizes of a magnitude similar to those of the original GWAS, particularly if the outcomes of interest are impeded by inaccurate measurements. As a consequence, few studies have been able to consistently replicate the associations identified in the GWAS that counted more than 30,000 individuals, and so far, no studies have been able to show evidence that any of the obesity susceptibility loci influence body weight through association with levels of physical activity or energy expenditure.

The locus most extensively studied continues to be *FTO*, which was the first obesity susceptibility locus to be identified in 2007 by two independent studies with a discovery stage of around 4000 individuals each (16,39). The relatively small sample size needed for *FTO*'s discovery, coupled with the fact that its BMI-increasing allele is common and has the largest effect among all established obesity susceptibility loci, has greatly facilitated its replication. Variants in the first intron of *FTO* have been consistently shown to associate with a variety of obesity-related traits across all age groups and across various ethnic groups. Experimental research has suggested that *FTO* might contribute to obesity risk through peripheral mechanisms influencing energy expenditure, as well as through CNS influencing the regulation of food intake, with recent data from humans and animal models providing more evidence for the latter (44).

Of particular interest are the findings of a recent large-scale epidemiological study that examined the role of daily physical activity in the association between *FTO* and obesity risk. Since the discovery of the *FTO* locus, a growing number of studies have reported that physical activity attenuates the association between variants in the *FTO* locus and obesity-related traits (19). However, doubts arose with the publication of studies that could not confirm such an interaction between *FTO* and physical activity on obesity risk. To firmly confirm or refute this observation, Kilpeläinen et al. (27) conducted a meta-analysis based on 45 studies in adults (n = 218,166), as well as nine studies in children and adolescents (n = 19,268). Although appropriate for the study of main-effect associations, literature-based meta-analyses are not an option for interaction analyses because definitions of physical activity, statistical analyses of interaction, and reported interaction results typically differ widely across studies. Furthermore, interaction analyses are often secondary to main-effect analyses and are typically reported only when results are statistically significant, such that this literature is prone to publication bias. Therefore, in this recent study, all groups with genotype data for the *FTO* locus as well as with data on physical activity and obesity-related outcomes were invited to participate in a *de novo* meta-analysis (27). More specifically, because physical activity was assessed in different ways, it was first standardized centrally and categorized as a binary trait (physically active vs inactive) for each participating study. Subsequently, the data of each study were analyzed according to a standardized plan to achieve the greatest consistency possible across studies and to facilitate the final meta-analysis.

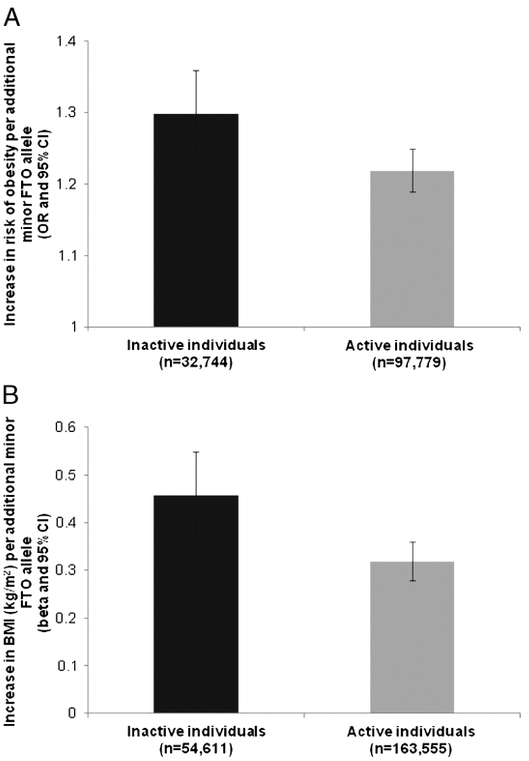

FIGURE 1—Effect of the rs9939609 variant or a proxy ($r^2 > 0.8$) on risk of obesity ($P_{interaction} = 0.001$) (A) and on BMI ($P_{interaction} = 0.005$) (B) by activity status in a random-effects meta-analysis (27). Drawn from the data reported in *PLoS Medicine*.

Consistent with early observations, the results in adults confirmed that a physically active lifestyle significantly attenuates the effect of *FTO* variation on the risk of obesity. Each additional *FTO* risk allele increases the odds of obesity by 23% ($P = 7 \times 10^{-59}$) and the BMI by 0.36 kg·m^{-2} (equivalent to 1040 g for a person 1.70 m tall) ($P = 2 \times 10^{-75}$) in the total adult population. However, the effect of *FTO* on obesity risk was significantly ($P_{interaction} = 0.001$) reduced by physical activity; i.e., each *FTO* risk allele increases the odds of obesity by 30% in the inactive individuals but only by 22% in the active individuals (Fig. 1). Consistent with the observations for obesity risk, the BMI-increasing effect of *FTO* was reduced by 30% ($P = 0.005$) in the physically active individuals (0.32 kg·m^{-2} per allele or 925 g for a 1.70-m-tall person) compared with the inactive individuals (0.46 kg·m^{-2} per allele or 1330 g for a 1.70-m-tall person) (Fig. 1). Similar interaction effects were observed for waist circumference, body fat percentage, and risk of being overweight.

Most notable was the observation that physical activity was three times more effective ($P = 0.001$) in attenuating the BMI-increasing effects of *FTO* in North Americans than in Europeans, with similar trends for other obesity-related traits. In contrast to the adult data, physical activity had no effect on the association between *FTO* variants and obesity-related traits in children and adolescents.

These findings emphasize the importance of physical activity in body weight regulation in adults, in particular in those who are genetically predisposed to obesity, and they oppose the often-held fatalist view that a genetic susceptibility is nonmodifiable. The reason for the difference in effectiveness between continents is unclear, but the often-reported lower physical activity levels and higher obesity prevalence in North Americans as compared with Europeans may play a role. Another diverging factor may be the differences in the measurement of physical activity, with more often continuous data recorded in North America and more categorical data in Europe. It remains unclear what biological mechanisms are behind the observed interaction between physical activity and *FTO* and whether the effect attenuation is observed only with physical activity or also with other lifestyle factors. Variants in the first intron of *FTO* have been shown to be associated with methylation capability, such that some have speculated that this region might be sensitive to epigenetic effects (5). Of interest are recent studies suggesting that not only physical activity but also dietary habits and energy intake might attenuate the effects of *FTO* on obesity susceptibility (2,12).

An important secondary observation from this large-scale interaction meta-analysis is the fact that variants in *FTO* are not associated with physical activity *per se* in adults ($P = 0.20$) or in children ($P = 0.6$), thus providing convincing evidence that physical activity is not the mediating factor in the association between *FTO* and obesity risk (27).

GLUCOSE AND INSULIN METABOLISM

In 2011, two studies based on reasonable sample sizes showed evidence of gene–physical activity interactions on type 2 diabetes risk (20,22). Two other studies reported that changes in glucose and/or insulin in response to lifestyle interventions were not dependent on *FTO* (15) and glucokinase regulator *(GCKR)* (35) polymorphisms.

Hivert et al. (22) tested the association between a genetic risk score (GRS) (equivalent to a genetic predisposition score) based on 34 type 2 diabetes–associated loci and the response to a lifestyle intervention program in 2843 participants of the Diabetes Prevention Program. The goals of the intensive lifestyle intervention were to achieve or maintain a weight loss of at least 7% through healthy eating and to engage in at least 150 min·wk^{-1} of physical activity. The GRS, which was created by weighing each risk allele by its reported effect size and summing the results over the 34 SNPs, was tested for its ability to predict progression to diabetes or regression toward normal glucose tolerance after 1 yr. Although no significant evidence of a GRS × lifestyle interaction was found ($P = 0.85$), the lifestyle intervention was more effective in subjects at higher genetic risk as indicated by the effect of the GRS in subjects in the highest quartile of GRS ($P < 0.0001$). Although the effect of physical activity *per se* cannot be clearly delineated from the effects of diet and weight loss, the results are of interest because they suggest that a lifestyle intervention including physical activity can attenuate the risk of developing diabetes in subjects at high genetic risk.

In the second study, He et al. (20) tested interactions between two SNPs near the *IRS1* gene (rs1522813 and rs2943641) and physical activity in relation to the risk of type 2 diabetes in two case-control studies from the Nurses' Health Study (3212 women) and the Health Professionals Follow-Up Study (2422 men). No evidence of interaction was found in men, but a significant interaction ($P = 0.017$) between physical activity (assessed as hours per week) and SNP rs1522813 was found in women. The stratified analyses comparing carriers of the A allele with the *GG* genotype revealed that among women with low levels of physical activity (low vs high levels, cutoff point of 3.0 $h \cdot wk^{-1}$), carriers of the high-risk A allele had a 39% increased risk of type 2 diabetes ($P = 0.007$), whereas among women with high levels of physical activity, the A allele was associated with a nonsignificant increased risk of 4%.

LIPID AND LIPOPROTEIN METABOLISM

During the past year, one study with a large sample size examined the interaction of genetic markers identified through GWAS with physical activity and HDL cholesterol (HDL-C) levels (1), whereas two studies with small sample sizes analyzed the associations between genetic markers and exercise-related adaptations of lipid and lipoprotein metabolism (10,40).

Numerous genes and gene variants associated with lipid levels have been identified in GWAS reports, with a recent meta-analysis of more than 100,000 individuals identifying 95 loci associated with one of four lipid traits at the genome-wide significance level ($P < 5 \times 10^{-8}$) (41). Ahmad et al. (1) tested whether the associations between 58 SNPs, from nine genes previously associated with HDL-C levels at the genome-wide level, and HDL-C levels are modified by physical activity in 22,939 women of European ancestry from the Women's Genome Health Study. Physical activity level was estimated via a questionnaire and dichotomized in the interaction models on the basis of the sample-specific median (8.8 MET-$h \cdot wk^{-1}$) cutpoints. The menopausal status of the women is not clear, although the authors noted that postmenopausal hormone use was higher in active women.

Physical activity modified the effects on HDL-C of seven SNPs at three loci, with the strongest evidence of effect observed for rs10096633 at lipoprotein lipase (*LPL*) ($P = 0.004$), rs1800588 at hepatic lipase (*LIPC*) ($P = 0.04$), and rs1532624 at cholesteryl ester transfer protein, plasma (*CETP*) ($P = 0.02$) (1). The per-minor-allele increase in HDL-C for *LIPC* SNP rs1800588 and *CETP* SNP rs1532624 was greater in active than inactive women, whereas the reverse was observed for *LPL* SNP rs10096633. The proportion of variance in HDL-C explained by the genotype–physical activity interaction ranged from 0.01% to 0.03% for the top 3 SNPs, whereas adding each SNP individually to adjusted models explained an additional 0.27% (rs10096633), 0.58% (rs1800588), or 1.99% (rs1532624) of the variance in HDL-C (1). In sensitivity analyses using physical activity–adjusted HDL-C levels and a *P* value threshold corrected for the number of genes analyzed ($P = 0.0056$), evidence of interaction remained statistically significant only for *LPL* SNP rs10096633. The study benefits from a large sample size, but it is limited by the assessment of physical activity via self-report and the incorporation of only SNPs related to HDL-C levels at the genome-wide level of significance.

In a study of 76 sedentary overweight to obese Caucasian men and women age 50–75 yr at risk for CHD, the *LIPC* −514C>T genotype-specific antiatherogenic effect of 24 wk of exercise training on VLDL and HDL occurred only in CC homozygotes and seemed to be mediated by an increase in LPL activity (10). In another study, Seip et al. (40) measured postheparin plasma lipase activities in sedentary normolipidemic men and women with the three most common apolipoprotein *(APOE)* haplotypes, $\varepsilon2/\varepsilon3$ ($n = 53$), $\varepsilon3/\varepsilon3$ ($n = 62$), and $\varepsilon4/\varepsilon3$ ($n = 52$), enrolled in 6 months of standardized aerobic exercise training. Exercise training decreased LPL activity in the *APOE* 3/3 haplotype compared with increases in haplotypes 2/3 and 4/3, independent of sex, with this difference being significant only after correcting for baseline insulin (40). However, although both studies are based on standardized exercise intervention protocols, they suffer from the limitation of small sample sizes.

HEMODYNAMIC TRAITS

In 2011, less than 10 articles were published addressing the genetics of hemodynamic phenotypes relative to acute exercise or exercise training. These articles addressed generally different genes and different phenotypes and included both cross-sectional and longitudinal studies. However, of these studies, three were of higher quality, particularly because of the size of their study populations—a critical issue especially when addressing hypotheses relative to the effect of specific genetic variants on the basis of observational data.

The three articles selected for review were epidemiological studies that were not planned for the purpose of assessing the effect of gene–physical activity interactions on hemodynamic phenotypes (18,34,38). The first article, by Sarzynski et al. (38), assessed the interactive effects of genetic variations and cardiorespiratory fitness on the development of hypertension during 20 yr in 2663 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Initial fitness levels were assessed via a treadmill test, and researchers genotyped ~100 SNPs across seven genes previously shown to be related to blood pressure (BP) or fitness. Their most consistent finding was a nominally significant interactive effect between the bradykinin receptor B2 (*BDKRB2*) rs4900318 SNP and initial fitness level on the risk of developing hypertension in both blacks and whites. However, the results were not consistent because high-fit black A homozygotes at this locus had a 44% lower risk of developing hypertension, whereas high-fit white A homozygotes had a threefold greater risk of developing hypertension. This latter finding is certainly surprising because very few, if any, previous studies have shown high-fit individuals to be at a

greater risk for any pathological cardiovascular phenotypes. Separately in blacks and whites, nominally significant SNP-by-fitness interaction effects also were found. However, none of the nominally significant differences evident in this study were statistically significant after correcting for multiple tests, despite the substantial size of the study population.

Grøntved et al. (18) published a cross-sectional study in 1214 Danish children and 1141 Estonian adolescents from the European Youth Heart Study. They genotyped four endothelial nitric oxide synthase 3 (*NOS3*) tag SNPs that captured 100% of the common genetic variation information in this gene. Habitual physical activity levels were assessed with an accelerometer and by asking four additional questions about physical activity and inactivity habits. The only nominally significant interactive effects found for BP were between the *NOS3* Glu298Asp SNP and hours of television viewing and whether the adolescents bicycled to school. However, once again, these effects were not statistically significant after accounting for the number of statistical tests performed, and no relationships whatsoever were evident with the objectively measured accelerometer physical activity data or in the population of children.

In the third study, Montasser et al. (34) in 3142 individuals in the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study typed 196 SNPs in 24 genes involved in BP-regulating pathways and assessed physical activity using a questionnaire. They initially found nominally significant relationships between SNPs in five genes (apelin receptor *[APLNR]*; *BDKRB2*; guanine nucleotide binding protein, β polypeptide 3 *[GNB3]*; nuclear receptor subfamily 3, group C, member 2 *[NR3C2]*; sodium channel, nonvoltage-gated 1, β *[SCNN1B]*) and either systolic or diastolic BP in the active, inactive, or combined groups, but these results did not directly address a gene–physical activity interaction. However, the researchers then analyzed BP levels of the active and inactive individuals relative to the number of minor alleles that an individual carried at these five loci. In this analysis, they found significant interactive effects for both systolic and diastolic BP (Fig. 2), with the relationship indicating a lower BP in active individuals as a direct function of the number of minor alleles they carried, whereas no such relationship was evident in the inactive individuals.

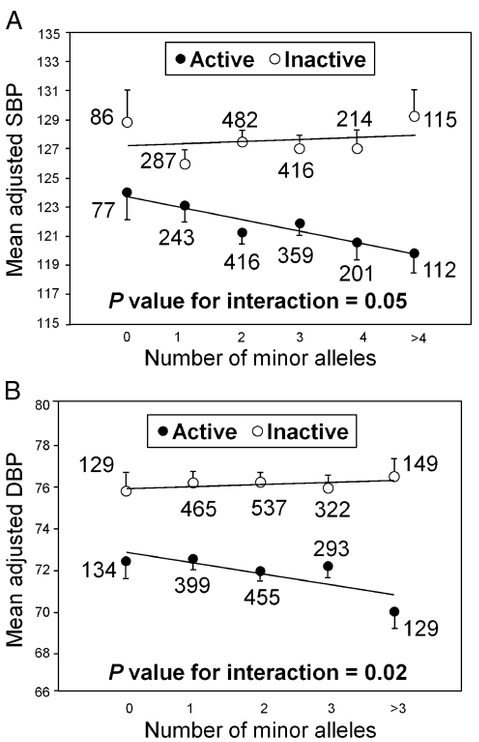

FIGURE 2—Cumulative effects of the minor alleles for all of the significant SNPs on the mean adjusted values of systolic BP (A) and diastolic BP (B). The best-fitting trend lines for each group and the *P* values for the interactions with the physical activity group are presented. The numbers of individuals are also shown next to each point (34). The figure is used with permission from the *American Journal of Hypertension*.

These studies, despite the large sample sizes involved, generated mainly nonsignificant results after correcting for the number of statistical tests performed. Thus, they failed to advance our knowledge substantially in the area of the effect of genetic variations on cardiovascular hemodynamic responses to acute exercise or habitual physical activity. This is undoubtedly a result of the fact that the studies were based on observational data and that individual genetic variants account for only a small proportion of the interindividual differences in most nonmendelian traits. However, it is important to bear in mind that these were retrospective follow-up studies based on trials that were initially not designed or powered to address genetic hypotheses relative to physical activity. Thus, perhaps what has been elucidated by these three studies is that the six "candidate" genes *(APLNR, BDKRB2, GNB3, NOS3, NR3C2, SCNN1B)* that generated at least nominally significant interactive effects with physical activity on hemodynamic phenotypes could be considered as targets for appropriately powered exercise training intervention trials to address specific directional hypotheses.

COMMENTS AND SUMMARY

Consistent with the standards defined in previous installments of this annual review, the present article emphasizes the strongest articles in exercise genomics published in 2011. As in the past, the articles reviewed were those with the strongest study designs and were characterized by reasonable sample sizes, quality of phenotype measurements and of the exercise program or physical activity exposure, adjustment for multiple testing, and quality of genotyping.

In last year's publication of "Advances in Exercise, Fitness, and Performance Genomics," we emphasized the need for appropriately powered studies to address the interactive effects of genetics and exercise training or acute exercise on any complex multifactorial physiological or pathological phenotype (19). Although no one can argue with this basic scientific tenet, we recognize that it is commonly difficult,

costly, and time-consuming to generate sample sizes of the magnitude required for sufficient statistical power to address genetic questions in acute exercise studies but even more so in complex exercise training experiments or exercise intervention trials (6).

We believe that the most significant findings of the past calendar year are the following: one study found that physical activity levels were significantly lower in patients with mitochondrial DNA mutations compared with controls. A two-stage fine-mapping follow-up of a previous linkage peak found strong associations between *ACVR1B* genotypes and knee extensor strength, with rs2854464 emerging as the most promising candidate polymorphism. The association of higher muscular strength in rs2854464 A allele carriers was confirmed in two separate cohorts. A study using a combination of transcriptomic and genomic data identified a comprehensive map of the transcriptomic features important for aerobic exercise–induced improvements in maximal oxygen consumption. However, genomic markers (tag SNPs) identified from these candidate transcripts/genes were not associated with the $\dot{V}O_{2max}$ response to exercise training. A large-scale *de novo* meta-analysis confirmed that the effect of *FTO* variation on the risk of obesity is significantly lower in physically active adults compared with sedentary people but not in children and adolescents. Evidence for gene–physical activity interactions on type 2 diabetes risk was found in two separate studies. A large study of women found that physical activity modified the effect of *LPL*, *LIPC*, and *CETP* polymorphisms, identified in previous GWAS reports, on HDL-C.

Finally, the vast majority of exercise genomic reports are based on common genetic polymorphisms, the low-hanging fruit of genomic variants. A comprehensive picture of the role of genomic differences in the inheritance of exercise-related traits will require that exercise scientists reach beyond common sequence variants and investigate other genomic structures such as rare variants, copy number variants, deletions and insertions, splice site disruptions, mutations affecting microRNAs or other small RNA molecular sequences or binding sequences, premature stop codons, enhancer recognition sequences, and undoubtedly others.

The delineation of a genomic profile predictive of a given exercise-related trait not only has the scientific and practical value associated with the ability to predict what the trait is in a sedentary state or would be with exposure to acute or regular exercise but also has the potential to illuminate the basic biology of this particular trait. Panels of genomic markers optimized for specific endophenotypes or for the prediction of the response to exercise or exercise training could dramatically affect exercise biology and generate new hypotheses on human adaptability and even evolutionary biology. In other words, a strong exercise genomics corpus of evidence would have a major effect on exercise biology and exercise behavior research.

The authors thank Ms. Allison Templet for her assistance with the preparation of the final version of the article. C.B. and T.R. are funded by the National Institutes of Health (HL-45670).

C.B. is partially funded by the John W. Barton, Sr. Endowed Chair in Genetics and Nutrition. C.B. is an adviser to Weight Watchers International and a consultant to Pathway Genomics.

The other authors have no conflicts of interest to disclose.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

1. Ahmad T, Chasman DI, Buring JE, Lee IM, Ridker PM, Everett BM. Physical activity modifies the effect of *LPL, LIPC,* and *CETP* polymorphisms on HDL-C levels and the risk of myocardial infarction in women of European ancestry. *Circ Cardiovasc Genet*. 2011;4(1):74–80.
2. Ahmad T, Lee IM, Pare G, et al. Lifestyle interaction with fat mass and obesity-associated (*FTO*) genotype and risk of obesity in apparently healthy U.S. women. *Diabetes Care*. 2011;34(3):675–80.
3. Apabhai S, Gorman GS, Sutton L, et al. Habitual physical activity in mitochondrial disease. *PLoS One*. 2011;6(7):e22294.
4. Ash GI, Scott RA, Deason M, et al. No association between *ACE* gene variation and endurance athlete status in Ethiopians. *Med Sci Sports Exerc*. 2011;43(4):590–7.
5. Bell CG, Finer S, Lindgren CM, et al. Integrated genetic and epigenetic analysis identifies haplotype-specific methylation in the *FTO* type 2 diabetes and obesity susceptibility locus. *PLoS One*. 2010;5(11):e14040.
6. Bouchard C. Overcoming barriers to progress in exercise genomics. *Exerc Sport Sci Rev*. 2011;39(4):212–7.
7. Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE family study. Aims, design, and measurement protocol. *Med Sci Sports Exerc*. 1995;27(5):721–9.
8. Bouchard C, An P, Rice T, et al. Familial aggregation of $\dot{V}O(2max)$ response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol*. 1999;87(3):1003–8.
9. Bouchard C, Sarzynski MA, Rice TK, et al. Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. *J Appl Physiol*. 2011;110(5):1160–70.
10. Brinkley TE, Halverstadt A, Phares DA, et al. Hepatic lipase gene −514C>T variant is associated with exercise training–induced changes in VLDL and HDL by lipoprotein lipase. *J Appl Physiol*. 2011;111(6):1871–6.
11. Chiu LL, Wu YF, Tang MT, Yu HC, Hsieh LL, Hsieh SS. *ACTN3* genotype and swimming performance in Taiwan. *Int J Sports Med*. 2011;32(6):476–80.
12. Corella D, Arnett DK, Tucker KL, et al. A high intake of saturated fatty acids strengthens the association between the fat mass and obesity-associated gene and BMI. *J Nutr*. 2011;141(12):2219–25.
13. Crocco P, Montesanto A, Passarino G, Rose G. A common polymorphism in the *UCP3* promoter influences hand grip strength in elderly people. *Biogerontology*. 2011;12(3):265–71.
14. Defoor J, Vanhees L, Martens K, et al. The CAREGENE study: *ACE* gene I/D polymorphism and effect of physical training on aerobic power in coronary artery disease. *Heart*. 2006;92(4):527–8.
15. Dlouha D, Suchanek P, Lanskalanskalanska V, Hubacek JA. Body mass index change in females after short-time life style intervention is not dependent on the *FTO* polymorphisms. *Physiol Res*. 2011;60(1):199–202.
16. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the *FTO* gene is associated with body mass index and

predisposes to childhood and adult obesity. *Science*. 2007;316(5826): 889–94.
17. Gineviciene V, Pranculis A, Jakaitiene A, Milasius K, Kucinskas V. Genetic variation of the human *ACE* and *ACTN3* genes and their association with functional muscle properties in Lithuanian elite athletes. *Medicina (Kaunas)*. 2011;47(5):284–90. English, Lithuanian.
18. Grøntved A, Andersen LB, Franks PW, et al. *NOS3* variants, physical activity, and blood pressure in the European Youth Heart Study. *Am J Hypertens*. 2011;24(4):444–50.
19. Hagberg JM, Rankinen T, Loos RJ, et al. Advances in exercise, fitness, and performance genomics in 2010. *Med Sci Sports Exerc*. 2011;43(5):743–52.
20. He MA, Workalemahu T, Cornelis MC, Hu FB, Qi L. Genetic variants near the *IRS1* gene, physical activity and type 2 diabetes in US men and women. *Diabetologia*. 2011;54(6):1579–82.
21. He ZH, Hu Y, Li YC, et al. Are calcineurin genes associated with athletic status? A function, replication study. *Med Sci Sports Exerc*. 2011;43(8):1433–40.
22. Hivert MF, Jablonski KA, Perreault L, et al. Updated genetic score based on 34 confirmed type 2 diabetes loci is associated with diabetes incidence and regression to normoglycemia in the Diabetes Prevention Program. *Diabetes*. 2011;60(4):1340–8.
23. Hughes DC, Day SH, Ahmetov II, Williams AG. Genetics of muscle strength and power: polygenic profile similarity limits skeletal muscle performance. *J Sports Sci*. 2011;29(13):1425–34.
24. Huygens W, Thomis MA, Peeters MW, et al. Linkage of myostatin pathway genes with knee strength in humans. *Physiol Genomics*. 2004;17(3):264–70.
25. Huygens W, Thomis MA, Peeters MW, Aerssens J, Vlietinck R, Beunen GP. Quantitative trait loci for human muscle strength: linkage analysis of myostatin pathway genes. *Physiol Genomics*. 2005;22(3):390–7.
26. Keller P, Vollaard NB, Gustafsson T, et al. A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. *J Appl Physiol*. 2011;110(1):46–59.
27. Kilpeläinen TO, Qi L, Brage S, et al. Physical activity attenuates the influence of *FTO* variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med*. 2011;8(11): e1001116.
28. Kilpeläinen TO, Zillikens MC, Stancakova A, et al. Genetic variation near *IRS1* associates with reduced adiposity and an impaired metabolic profile. *Nat Genet*. 2011;43(8):753–60.
29. Kollias HD, McDermott JC. Transforming growth factor-beta and myostatin signaling in skeletal muscle. *J Appl Physiol*. 2008;104(3): 579–87.
30. Lima RM, Leite TK, Pereira RW, Rabelo HT, Roth SM, Oliveira RJ. *ACE* and *ACTN3* genotypes in older women: muscular phenotypes. *Int J Sports Med*. 2011;32(1):66–72.
31. Maciejewska A, Sawczuk M, Cieszczyk P. Variation in the *PPARα* gene in Polish rowers. *J Sci Med Sport*. 2011;14(1):58–64.
32. Maciejewska A, Sawczuk M, Cieszczyk P, Mozhayskaya IA, Ahmetov II. The *PPARGC1A* gene Gly482Ser in Polish and Russian athletes. *J Sports Sci*. 2012;30(1):101–13.
33. Mikami E, Fuku N, Takahashi H, et al. Mitochondrial haplogroups associated with elite Japanese athlete status. *Br J Sports Med*. 2011;45(15):1179–83.
34. Montasser ME, Gu D, Chen J, et al. Interactions of genetic variants with physical activity are associated with blood pressure in Chinese: the GenSalt study. *Am J Hypertens*. 2011;24(9):1035–40.
35. Pollin TI, Jablonski KA, McAteer JB, et al. Triglyceride response to an intensive lifestyle intervention is enhanced in carriers of the *GCKR* Pro446Leu polymorphism. *J Clin Endocrinol Metab*. 2011; 96(7):E1142–7.
36. Rankinen T, Roth SM, Bray MS, et al. Advances in exercise, fitness, and performance genomics. *Med Sci Sports Exerc*. 2010;42(5): 835–46.
37. Santiago C, Ruiz JR, Rodriguez-Romo G, et al. The *K153R* polymorphism in the myostatin gene and muscle power phenotypes in young, non-athletic men. *PLoS One*. 2011;6(1):e16323.
38. Sarzynski MA, Rankinen T, Sternfeld B, Fornage M, Sidney S, Bouchard C. SNP-by-fitness and SNP-by-BMI interactions from seven candidate genes and incident hypertension after 20 years of follow-up: the CARDIA Fitness Study. *J Hum Hypertens*. 2011; 25(8):509–18.
39. Scuteri A, Sanna S, Chen WM, et al. Genome-wide association scan shows genetic variants in the *FTO* gene are associated with obesity-related traits. *PLoS Genet*. 2007;3(7):e115.
40. Seip RL, Zoeller RF, Angelopoulos TJ, et al. Interactive effects of *APOE* haplotype, sex, and exercise on postheparin plasma lipase activities. *J Appl Physiol*. 2011;110(4):1021–8.
41. Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466(7307):707–13.
42. Thomaes T, Thomis M, Onkelinx S, et al. A genetic predisposition score for muscular endophenotypes predicts the increase in aerobic power after training: the CAREGENE study. *BMC Genet*. 2011;12:84.
43. Timmons JA, Knudsen S, Rankinen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J Appl Physiol*. 2010;108(6): 1487–96.
44. Tung YCL, Yeo GSH. From GWAS to biology: lessons from FTO. *Ann N Y Acad Sci*. 2011;1220(1):162–71.
45. Williams AG, Folland JP. Similarity of polygenic profiles limits the potential for elite human physical performance. *J Physiol*. 2008;586(1):113–21.
46. Windelinckx A, De Mars G, Huygens W, et al. Comprehensive fine mapping of chr12q12-14 and follow-up replication identify activin receptor 1B (*ACVR1B*) as a muscle strength gene. *Eur J Hum Genet*. 2011;19(2):208–15.