Authors and Disclosures

Tuomo Rankinen[1], Stephen M. Roth[2], Molly S. Bray[3], Ruth Loos[4], Louis Pérusse[5], Bernd Wolfarth[6], James M. Hagberg[2], and Claude Bouchard[1]

[1]Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA; [2]Department of Kinesiology, School of Public Health, University of Maryland, College Park, MD; [3]Department of Epidemiology, Heflin Center for Genomic Sciences, Clinical Nutrition Center, University of Alabama at Birmingham, Birmingham, AL; [4]Medical Research Council Epidemiological Unit, Institute of Metabolic Science, Cambridge, UNITED KINGDOM; [5]Division of Kinesiology, Department of Preventive Medicine, Laval University, Ste-Foy, Québec, CANADA; and [6]Preventive and Rehabilitative Sports Medicine, Technical University Munich, Munich, GERMANY

Address for correspondence:
Claude Bouchard, Ph.D., or Tuomo Rankinen, Ph.D., Human Genomics Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808-4124; E-mail: bouchac@pbrc.edu or rankint@pbrc.edu.

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Advances in Exercise, Fitness, and Performance Genomics

Tuomo Rankinen; Stephen M. Roth; Molly S. Bray; Ruth Loos; Louis Pérusse; Bernd Wolfarth; James M. Hagberg; Claude Bouchard

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Abstract and Introduction

Abstract

An annual review publication of the most significant articles in exercise, fitness, and performance genomics begins with this article, which covers 2 yr, 2008 and 2009. The review emphasizes the strongest articles as defined by sample size, quality of phenotype measurements, quality of the exercise program or physical activity exposure, study design, adjustment for multiple testing, quality of genotyping, and other related study characteristics. With this avowed focus on the highest quality articles, only a small number of published articles are reviewed. Among the most significant findings reported here are a brief overview of the first genome-wide association study of the genetic differences between exercisers and nonexercisers. In addition, the latest results on the actinin alpha 3 (*ACTN3*) R577X nonsense polymorphism are reviewed, emphasizing that no definitive conclusion can be reached at this time. Recent studies that have dealt with mitochondrial DNA haplogroups and endurance performance are described. Published reports indicating that physical activity may attenuate the effect of

the fat mass and obesity associated (*FTO*) gene risk allele on body mass index are reviewed. Articles that have tested the contributions of specific genes to the response of glucose and insulin metabolism traits to regular exercise or physical activity level are considered and found to be generally inconclusive at this stage. Studies examining ethnic differences in the response of blood lipids and lipoproteins to exercise training cannot unequivocally relate these to apolipoprotein E (*APOE*) genotypes. Hemodynamic changes with exercise training were reported to be associated to sequence variation in kinesin heavy chain (*KIF5B*), but no replication study is available as of yet. We conclude from this first installment that exercise scientists need to prioritize high-quality research designs and that replication studies with large sample sizes are urgently needed.

Introduction

During the past decade, we published seven versions of a human gene map for fitness and performance-related traits, beginning with the first version in 2000[54] and ending with the last installment in 2009.[4] Several reasons have motivated us to continue our effort but to redirect it into a different format. The yearly update of the gene map became increasingly large, which required a growing number of precious printed pages in the journal. Moreover, the constant expansion of the entries in the map became increasingly difficult to manage by our team of collaborators without being able to count on dedicated resources. Finally, entries in the map were based on a mixture of weak and good studies. We collectively felt that it would be better to find a formula allowing us to emphasize the best studies as they truly add to the body of evidence and are therefore most likely to advance the field of exercise genomics. The result of this interrogation exercise is the current review article.

Our group of colleagues from institutions in the United States, Canada, and Europe intends to publish a yearly review of the scientifically strongest and substantively most important articles in exercise genomics. Over time, science is going to drive the specific content areas of the review. We will be primarily guided by the quality of the published studies. The boundaries of the topic areas theoretically covered by the annual review are quite broad. Any trait relevant to exercise, fitness, and performance is of interest and could be retained for the review. For instance, genes and genomic markers involved in exercisers versus nonexercisers, level of physical activity, and energy expenditure of activity or time spent in a sedentary state would be of interest. Performance-related phenotypes could include cardiorespiratory endurance, elite endurance athlete status, muscle strength, other muscle performance traits, and exercise intolerance of variable degrees. As for health-related fitness traits, the review could incorporate studies focusing on hemodynamic traits such as exercise heart rate (HR), blood pressure (BP), and heart morphology; exercise and body composition; exercise and insulin and glucose metabolism; and exercise and blood lipid, lipoprotein, inflammatory markers, or hemostatic factors. We will not review even an excellent article unless there was an exercise-related issue addressed in the publication.

Several reports have dealt with the conditions defining a sound and a strong association study between genomic markers and complex human traits.[10] These considerations will guide us in the selection of the publications to be incorporated in the yearly review. For instance, there is a general agreement on the fact that genotype-phenotype associations are influenced by sample size, quality of the phenotype and genotype measurements,

quality of the exercise or activity exposure, study design, adjustment for multiple testing, and population stratification. Of particular interest is the issue of the sample size used in an initial study as well as in subsequent replication efforts. Most studies in the exercise genomic field defined in the broad sense are underpowered and cannot therefore establish a definitive genotype-phenotype relationship. Because the effect size of a given gene on fitness or performance-related traits is thought to be generally small, the sample size necessary to achieve robust statistical significance to capture such effect sizes reliably will be large.

In exercise genomic studies, the phenotype of interest can typically be reliably measured. Minimizing the phenotypic error variance (also known as random variance, noise variance) is vital for a successful genetic study. This is not a negligible issue because the lower the error variance, the easier it is to capture the portion of phenotypic variance that is attributable to genetic factors. Conversely, the larger the error variance, the bigger the sample size needed to isolate the genetic variance reliably. The same is true for the "exposure to exercise" variable. If the study deals with the response to exercise and the subjects are exercise trained with a well-controlled, fully monitored and adequately standardized program, the sample size required to have sufficient power will be lower than that in a situation where subjects are asked to exercise on their own at home during their leisure time. However, despite the importance of the above considerations, they should not be used as a license to undertake studies with small sample sizes. Globally, the studies published to date in exercise genomics are underpowered and should have been based on much larger sample sizes, often at least 10 times larger than actually used. And even if a study generates a small *P* value for a genotype-phenotype association, the results should be interpreted with caution until additional large replication studies confirm the initial finding.

In assessing the quality of a report, one should also consider whether multiple testing was taken into account in reporting and interpreting results. Other issues to ponder include population stratification or some other uncontrolled factors, including nonrandom genotyping errors, which could have created a spurious association. It is important to verify whether the design of the study and the analytical approaches were appropriate and sufficiently described to allow replication in another laboratory. It is also useful to recognize that there is a strong tendency to publish studies with positive results. Indeed, in the end, very few negative studies reach publication. Likewise, it is often challenging to publish results that are statistically significant but indicate an association that is in the opposite direction of that reported in the original study. This strong bias diminishes the value of using published reports on a given gene-phenotype association to produce a meaningful meta-analysis with the hope that the latter will compensate somehow for the chronic lack of statistical power in the individual studies. In this regard, it would benefit the scientific community if editors and reviewers would make sure that good quality studies regardless of the final outcome (negative or positive) would have an equal chance to get published, either in print or online.

In summary, we intend to be highly selective in the choice of published articles that will be considered for inclusion in this annual review. By focusing on the highest quality publications, by reviewing them critically, and by drawing the attention of exercise scientists and sports medicine specialists on the potential implications of the findings of such articles, we hope to promote the best exercise genomic science and to further the

translational process to other exercise science laboratories and all exercise settings. We welcome comments and suggestions as we move forward with this initiative.

Genes and Physical Activity Level

Studies on the genetics of physical activity level are not extensive, but available evidence from twin and family studies suggests that genetic factors contribute significantly to the propensity of being sedentary or physically active. In this regard, the most comprehensive twin study on physical activity was published a few years ago. Data from seven large twin studies were pooled to create a cohort of 37,051 twin pairs: 13,676 monozygotic pairs, 17,340 same-sex dizygotic (DZ) pairs, and 6035 opposite-sex DZ pairs.[66] Information on exercise participation was derived from questionnaires, and the final outcome variable was dichotomized as exercisers and nonexercisers, with exercisers being defined as individuals who reported at least 60 min of weekly activity with a minimum intensity of 4 METs. The mean prevalence of exercise participation was 44% in men and 35% in women. The intrapair resemblance in exercise participation was significantly higher in monozygotic twins than that in DZ twins.[66] Furthermore, correlations among same-sex DZ twins tended to be greater than that in opposite-sex DZ pairs. The most parsimonious model from structural equation model fitting revealed that variance in exercise participation was explained by additive genetic and nonshared environmental effects in all but one subgroup. The median heritability estimates across all groups reached 62%.[66] These estimates are in line with the observations from previous studies with smaller number of twins.[53]

However, data on genes and DNA sequence variants contributing to the genetic variance in physical activity are scarce. An important step forward in molecular genetics of activity behavior was achieved in 2009 with the publication of the first genome-wide association study (GWAS) on habitual physical activity level.[13] The report included results from two cohort studies: 1644 unrelated individuals from The Netherlands Twin Register and 978 subjects living in Omaha, Nebraska. Leisure-time physical activity level was quantified using questionnaires, and MET-hours were calculated on the basis of the type, the frequency, and the duration of reported activities. Work and commuting-related (e.g., biking to work) activities as well as activities such as gardening were not included in the MET-hour calculations. Subjects who reported at least 4 $MET \cdot h \cdot wk^{-1}$ were classified as exercisers, whereas those with less than four weekly MET-hours were considered as nonexercisers. Prevalence of exercisers was 49.5% and 62.6% in the Dutch and the American cohorts, respectively. The exerciser or nonexerciser classification was used as the primary phenotype for the genome-wide association analyses. The GWAS single-nucleotide polymorphism (SNP) genotyping was done using Perlegen (Mountain View, CA) and Affymetrix (Santa Clara, CA) platforms in the Dutch (435,291 SNP) and the American (381,000 SNP) cohorts, respectively. To standardize the SNP from the two different platforms, approximately 2.5 million SNP from the International HapMap Caucasian database were imputed in both cohorts. After various quality control procedures, the final genotype data set included 1.6 million SNP. The proportion of genotyped SNP was 17.5% and 18.9% in the Dutch and American cohorts, respectively. Genome-wide association analyses were done using logistic regression models with sex and age as covariates. The analyses were conducted first separately in each study, and the results were then combined using meta-analytic methods.

None of the 1.6 million SNP reached the commonly used threshold of genome-wide significance ($P = 5 \times 10^{-8}$). However, SNP in three genomic regions showed *P* values less than 1×10^{-5} (Table 1). The strongest evidence of association was observed on chromosome 10q23.2 at the 3'-phosphoadenosine 5'-phosphosulfate synthase 2 (*PAPSS2*) gene locus: the odds ratio (OR) for being an exerciser was 1.32 ($P = 3.81 \times 10^{-6}$) for the common T-allele of SNP rs10887741 (imputed in both cohorts). *PAPSS2* encodes an enzyme involved in sulfation of various molecules, including glycosaminoglycans. Mechanisms by which *PAPSS2* affects exercise participation are unknown, but mutations in the *PAPSS2* have been reported to cause spondyloepimetaphyseal dysplasia, which is characterized by short stature and short limbs both in humans and in mice.[70] The other two SNP with $P < 1 \times 10^{-5}$ were rs12612420 ($P = 7.61 \times 10^{-6}$, OR = 1.43; imputed in both cohorts), which is located about 12 kb upstream of the first exon of the DNA polymerase-transactivated protein 6 (*DNAPTP6*) gene, and rs8097348 ($P = 6.68 \times 10^{-6}$, OR=1.36; imputed in both cohorts), which is located about 236 kb upstream of chromosome 18 open reading frame 2 (*C18orf2*). The authors also investigated the associations with previously reported physical activity candidate genes and physical activity linkage regions. The strongest candidate gene association was detected with SNP rs12405556 ($P = 9.7 \times 10^{-4}$, OR = 1.24; imputed) at the leptin receptor (*LEPR*) locus. However, the pooled *P* value reflected mainly the strong association observed in the American cohort ($P = 9.79 \times 10^{-5}$; $P = 0.226$ in the Dutch sample). The strongest association among the previously identified linkage regions was found on chromosome 15q13 with SNP rs8036270 ($P = 4.61 \times 10^{-5}$) in the gamma-aminobutyric acid A receptor, gamma 3 (*GABRG3*) gene locus.

[CLOSE WINDOW]

Table 1. Most significant findings from a genome-wide association study (GWAS) for exercise participation.

SNP	Chr	Map [a]	Closest Gene [b]	Pooled *P* [c]	Pooled OR	Dutch *P*	American *P*
rs12612420	2	201,158,122	SPATS2L (12.5 kb)	7.61×10^{-6} (7.65×10^{-5})	1.43 (1.22–1.67)	8.81×10^{-4}	0.0022
rs10887741	10	89,443,310	PAPSS2 (intron 1)	3.81×10^{-6} (6.26×10^{-6})	1.32 (1.17–1.49)	0.0034	1.34×10^{-4}
rs8097348	18	1,595,021	C18orf2 (235 kb)	6.68×10^{-6} (6.99×10^{-5})	1.36 (1.19–1.56)	3.67×10^{-4}	0.0054

On the basis of data from De Moor et al. (13).
[a] Location of the SNP on the basis of the NCBI dbSNP Build 37.1 database.
[b] Distance to the gene is given in parentheses.
[c] First *P* value is from a model adjusted for age and sex and corresponds to the odds ratio (OR) given in the next column (also cohort-specific *P* values are adjusted for age

and sex).
P value in parentheses is from a model adjusted also for body mass index.

The GWAS reported by De Moor et al.[13] is the first comprehensive search for genes contributing to the propensity to be physically active. The major advantage of the GWAS strategy is that it covers the entire genome uniformly and thereby is not restricted by *a priori* hypotheses as is the case in candidate gene studies. On the other hand, a critical feature in the GWAS approach is replication: findings of an individual study should be tested in other large cohorts with a similar phenotype and study design. If the associations are replicated, the case for the contribution of a gene and DNA sequence variant to the trait of interest becomes considerably stronger. It would be a major advance if we could have a comprehensive picture of the molecular genetic architecture of relevant habitual physical activity traits in the next few years. Because several large cohort studies have habitual physical activity questionnaire data available in combination with recently completed genome-wide SNP genotyping, new informative data should become available in the future.

Genes and Muscular Strength and Power

The major story in the genetic aspects of muscular strength and power continues to be the investigation of the R577X nonsense polymorphism in the *ACTN3* gene. First reported by Yang et al.[75] as having a disadvantage for sprint and power-related athletes, the X/X genotype (i.e., alpha-actinin-3 protein deficiency) has been associated with sprint and power-related performance in several studies.[19,20,44,45,49,57,75] These initial studies prompted the exploration of specific quantitative traits underlying the genotype association with performance, specifically examining various aspects of muscular strength, mass, and power.[12,14,15,41,59,73,74] These subsequent studies have generated less consistent findings than the initial investigations, which were focused almost solely on elite athletes.

Because the expression of *ACTN3* is limited to type II muscle fibers, investigators have begun to evaluate whether or not fiber-type proportions or fiber characteristics are altered in X/X individuals deficient in alpha-actinin-3 protein. An *ACTN3* knockout mouse model has been developed, and several investigations have been performed that tend to support the findings in humans that alpha-actinin-3 deficiency alters muscle performance, potentially through alterations in fiber-type characteristics and metabolism.[9,39,40] The first study reported lower concentric peak torque at $300°\cdot s^{-1}$ in X/X compared with R/R homozygotes.[73] Importantly, a lower proportion of type IIx muscle fibers in X/X versus R/R homozygotes, the first evidence in humans that performance differences may be tied to alterations in muscle fiber characteristics, was observed. Unfortunately, the sample size of the entire cohort for the study was only 90, with 43 subjects examined for fiber-type proportions.

In 2009, Norman et al.[47] examined muscle strength, power, gene expression, and fiber-type proportions as well as fat-free mass (FFM) in a study of 120 moderately to well-trained men and women. In general, their measurement techniques were good, including well-validated methods of examining muscle strength, power, and fiber type; only the FFM measurement (estimated by skinfolds) is lacking in precision, reflecting that FFM was not an emphasis of the study. The authors reported no significant associations with muscle power or torque-velocity relationships among *ACTN3* genotypes or with FFM.

As shown in Figure 1, absolutely no differences were found between the R577X genotype groups for Wingate cycle power output in either men or women nor were there any differences in knee extensor isokinetic force at several velocities in a small subset of men. Importantly, Norman et al.[47] were also unable to confirm the differences in fiber-type proportion reported by Vincent et al..[73] The data on fiber type were obtained in a large number of fibers, but only in 63 men and women. The proportion of type I fibers were (mean (SD)) 55% (12), 57% (12), and 54% (17); of type IIa fibers were 32% (12), 34% (10), and 35% (14); and of type IIx fibers (reported as type IIb fibers) were 12% (10), 8% (5), and 11% (12) in X/X, R/X, and R/R, respectively. Similar findings were reported for each sex separately. As the authors conclude, in regularly physically active men and women, "*ACTN3* genotype is not an important determinant of muscle power or sprint performance".[47]

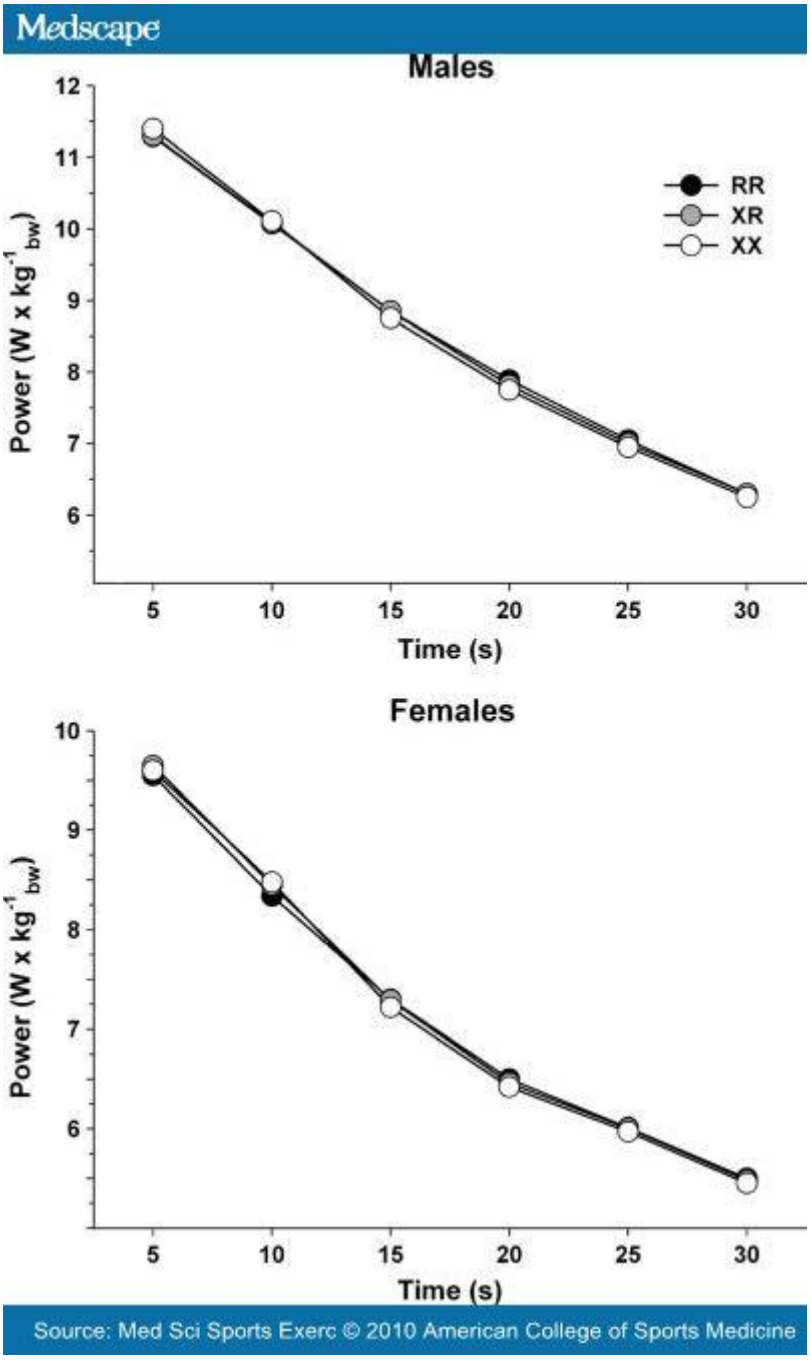

Figure 1. The data show Wingate cycle power output for the three ACTN3 genotype groups for men and women separately. No significant differences were observed. Reproduced from Norman et al. (47) by permission of the American Physiological Society.

Despite its strengths of careful measurements and extensive biopsy characterization, the study of Norman et al.[47] is quite limited in sample size for the analysis of muscle strength and power, and the emphasis on moderately to well-trained individuals adds a degree of training-induced variability that might be confounding their results. However, the fiber-type data certainly suggest that any effect of alpha-actinin-3 deficiency on fiber-type proportion is modest at best. Such specific studies have not been performed in elite-level athletes, which by definition are a small population. Much larger studies and randomized controlled trials of muscular performance and skeletal muscle fiber structure and metabolism are necessary to shed light on the true effect of the alpha-actinin-3 deficiency in both athletes and general population.

The general consensus among all these studies, if such a consensus is possible, is that *ACTN3* X/X homozygotes may have modestly lower skeletal muscle strength and power in comparison with R-allele carriers. Because the most consistent findings are found in studies of elite athletes, with generally inconclusive or negative findings in the studies of recreationally trained or untrained individuals, the importance of R577X may be limited to individuals with years of high-level training and performance levels approaching elite status. Although Delmonico et al.[15] have argued for the potential clinical relevance of *ACTN3* genotype in older individuals, the inconsistency across studies indicates that such a conclusion is currently tentative at best.

Other genes were also considered over the last 2 yr. Liu et al.[37] published the first GWAS focused on skeletal muscle traits. Although muscle strength was not the focus of their investigation, the researchers identified a pair of SNP in the *TRHR* gene that were strongly associated with lean body mass (by dual-energy x-ray absorptiometry) in a study of >350,000 SNP examined in nearly 1000 unrelated U.S. whites. These two polymorphisms were then consistently replicated in multiple cohorts consisting of over 6000 white and Chinese subjects. The *TRHR* gene encodes the thyrotropin-releasing hormone receptor. Because of the importance of thyroid hormone in skeletal muscle development,[35,46,63] the *TRHR* gene is thus recognized as an important candidate gene for future investigation, with potential consequences for the correlated traits of muscle strength and power.

Genes and Cardiorespiratory Endurance

Most of the endurance performance-related genetic studies have focused on genes encoded by the nuclear genome, whereas mitochondrial genes have received less attention. Scott et al.[60] analyzed mitochondrial haplotypes, which had been tentatively associated with elite endurance performance in prior studies, to determine why East African runners tend to dominate in middle- and long-distance events.[6,17,45] The purpose of their study was to compare the frequencies of several mitochondrial DNA (mtDNA) haplogroups found in elite Kenyan athletes with those in the general Kenyan population. DNA samples were obtained from 221 national level Kenyan athletes (N) and 70 international Kenyan athletes (I), with 85 members of the general Kenyan population serving as a control group (C). The mtDNA haplogroups were classified by

sequencing 340 bases of the hypervariable section (HVS I) and genotyping known restriction sites in the mtDNA.[33] The haplogroup distribution of the national (P = 0.023) and international athletes ($P < 0.001$) differed significantly from that of the Kenyan controls. Furthermore, the international athletes showed a greater proportion of L0 haplogroups (C = 15%, N = 18%, I = 30%) and lower proportion of L3* haplogroups (C = 48%, N = 36%, I = 26%). Although a higher number of international level athletes originated from the Rift Valley province relative to controls (C = 20%, N = 65%, I = 81%), subjects from this province did not differ in haplogroup distribution from other regions (P = 0.23). Likewise, Bantu subjects did not differ from Nilotic subjects (P = 0.12), although Nilotic languages were overrepresented among the athletes. The authors concluded that Kenyan international level athletes differed in their mtDNA haplogroup distribution from the general Kenyan population. This suggests that mtDNA haplogroups may be associated with elite Kenyan distance running. However, the authors point out that although the outstanding performance of the East African runners might be in part influenced by specific genetic factors, potentially associated to the mtDNA, the genetic background alone does not explain their endurance performance accomplishments.

A series of studies on the basis of a cohort of 74 endurance athletes, 81 sprinters, and 240 nonathlete controls was published in 2009. Borderline significant associations were reported between DNA sequence variants in the GA-binding protein transcription factor, alpha subunit (*GABPA*), peroxisome proliferator-activated receptor gamma coactivator 1 alpha (*PPARGC1A*), and guanine nucleotide binding protein (G-protein) beta polypeptide 3 (*GNB3*) genes and endurance athlete status.[21–23] In addition, *post hoc* subgroup analyses on the basis of international versus national level competition participation history of the endurance athletes revealed some suggestive interactions between peroxisome proliferator-activated receptor delta (*PPARD*) and *PPARGC1A* variants.[21] The main limitation of these reports is the small effective sample size. For example, the lower frequency of the *PPARGC1A* 482Ser allele in the endurance athletes reflected the fact that no Ser482Ser homozygotes were found, although at least six homozygotes would have been expected on the basis of the Hardy-Weinberg equilibrium.[21] The small number of athletes that were available for the analyses makes it difficult to evaluate whether the results reflect true association or an artifact related to the limited sample size (e.g., genotyping problem, population stratification issue, etc.).

Genes, Exercise, and Adiposity

The field of adiposity and obesity genetics has made great strides forward, thanks to the success of the GWAS approach. During the past 3 yr, large-scale high-resolution GWAS have identified at least 15 genetic loci reproducibly associated with obesity-related traits.[38] Of these validated obesity-susceptibility loci, the *FTO* locus was identified first in 2007, and therefore its molecular and physiological characteristics as well as its public health implications have been examined more extensively than is the case for the other loci. To date, genetic variation in the *FTO* locus confers the largest effect on body mass index (BMI) and risk of obesity.[38] Each additional *FTO* risk allele increases BMI by 0.30–0.75 $kg \cdot m^{-2}$ (equivalent to ~0.97–2.4 kg in weight for a person 1.80 m tall) and risk of obesity by 1.2–1.3 odds, at least in individuals of white European descent.

Despite intensive research during the past 2 yr, *FTO*'s physiological role in the regulation of energy balance is not yet well understood. Nevertheless, there is currently little or no evidence that genetic variation in *FTO* increases the susceptibility to obesity through a reduction of physical activity. Data from animal studies have provided support for a role of *FTO* in the central[26,65] as well as the peripheral[11,24] regulation of the energy balance. Two recent studies in mice consistently showed that loss of *Fto* function, either by complete gene knockout[24] or by a single point mutation,[11] results in reduced total weight and adipose tissue. Both studies found that basal energy expenditure in the transgenic mice was increased through increased sympathetic nervous system activity, whereas locomotor activity remained unchanged[11] or was even decreased.[24] Studies in children and in adults that aimed to disentangle the adiposity-increasing mechanisms of *FTO* partially support the observations in mice. So far, none have reported association of genetic variation in *FTO* with reduced physical activity levels[3,8,28,72] or reduced resting energy expenditure.[3,8,18,29,64] Although the absence of association between *FTO* variation and physical activity levels may be "real," studies have typically been small ($n < 1000$), and measurements of lifestyle factors have been imprecise. Consequently, the statistical power to prove or to refute an association has likely been low. We can therefore conclude that there is currently little evidence that genetic variation in the *FTO* gene increases adiposity and risk of obesity through reduced physical activity. However, future large-scale studies with precise measurement of physical activity are needed to confirm the absence of association.

Examining the direct association between *FTO* and physical activity levels can increase our understanding of the physiological pathways through which *FTO* mediates its effect on obesity susceptibility. However, these studies do not give us the whole story about *FTO*'s implications on public health. The latter can be addressed in part through gene-lifestyle interaction studies that examine whether *FTO*'s genetic effect on obesity susceptibility is attenuated by increased physical activity. In the population-based Inter99 study of 5554 Danish men and women (mean (SD) age = 46.2 (7.9) yr) for whom physical activity data were obtained through self-reported questionnaires, the difference in BMI between the wild-type allele homozygotes and the risk-allele homozygotes was 1.1 $kg \cdot m^{-2}$ ($P = 1 \times 10^{-9}$).[1] However, in individuals who reported to be physically inactive (1.95 ± 0.3 $kg \cdot m^{-2}$), this difference was three to four times larger ($P_{\text{interaction}} = 0.007$) than that in individuals who reported to be moderately (0.69 $kg \cdot m^{-2}$) to intensively (0.47 $kg \cdot m^{-2}$) physically active. These findings are consistent with those observed in 704 Old Order Amish individuals (mean (SD) age = 43.6 (3.4) yr).[51] Although the sample size was relatively small, physical activity was measured over seven consecutive days using activity accelerometers, which provide a more precise assessment than questionnaires and thus more statistical power to identify interactions. In this study, each additional *FTO* risk allele increased the BMI by 0.75 $kg \cdot m^{-2}$ ($P < 0.001$). In the low physical activity group (i.e., less than average), the additive effect of the *FTO* risk allele was 49% greater (1.12 $kg \cdot m^{-2}$ per allele, $P < 0.001$) than that in the high physical activity group (0.30 $kg \cdot m^{-2}$ per allele, $P = 0.29$; Fig. 2).

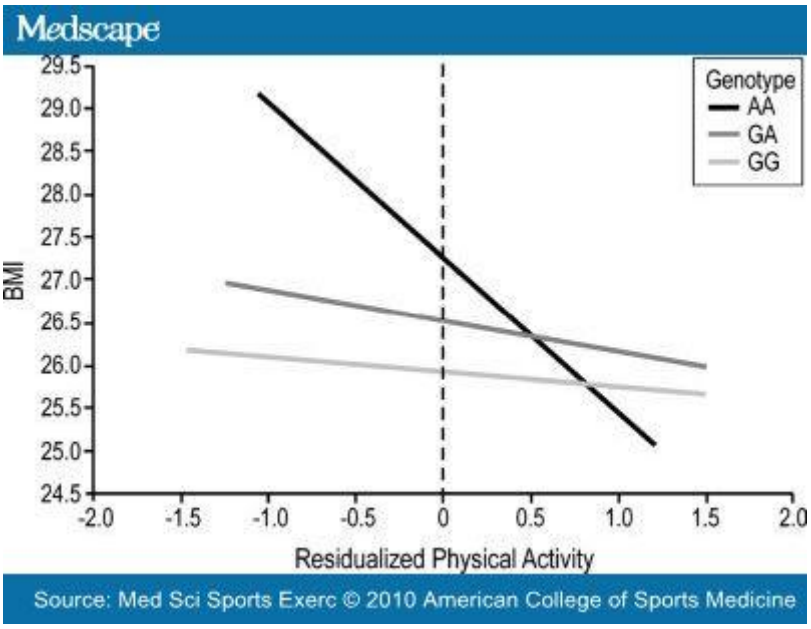

Figure 2. Predicted BMI as a function of adjusted physical activity levels. The inverse association between physical activity and BMI is more pronounced in AA-homozygotes than that in G-allele carriers of the FTOvariant (rs1861868). Reproduced from Rampersaud et al. (51). [Arch Intern Med. 2008;168:1791–7; copyright © 2008 American Medical Association. All rights reserved.]

A significant interaction ($P_{\text{interaction}} = 0.004$) was also observed in 20,374 individuals of the EPIC-Norfolk study (mean (SD) age = 58.8 (9.3) yr).[72] Although physical activity was measured by questionnaire, the strength of this study lies in its large sample size. Although in the total sample each additional *FTO* risk allele increased the BMI by 0.31 $kg \cdot m^{-2}$ ($P < 0.001$), the increase was only 0.25 $kg \cdot m^{-2}$ in physically active individuals but 0.44 $kg \cdot m^{-2}$ (or 76% larger) in physically inactive individuals. Even larger differences between low and high physical activity groups were observed in 4839 individuals (mean age = ~57.5 yr) of the Malmo Diet and Cancer study.[62] In subjects who reported high leisure-time physical activity levels, no association between *FTO* variation and BMI was observed ($\beta = 0.05$ $kg \cdot m^{-2}$ per allele, $P = 0.97$), whereas in those who reported low physical activity levels, each *FTO* risk allele increased the BMI by 0.4 $kg \cdot m^{-2}$ ($P = 0.003$) ($P_{\text{interaction}} = 0.05$). Further support for an *FTO*-physical activity interaction came from a study in French middle-aged adults and in Finnish children and adolescents.[7] So far, only one large-scale and thus well-powered population-based study in 15,925 men and women (mean (SD) age = 45.5 (6.9) yr) from southern Sweden did not observe an effect attenuation of the *FTO*-BMI association by physical activity ($P_{\text{interaction}} = 0.71$).[30] The reasons for the discrepant observations are unclear. The average age of this Swedish population is similar to those of previous observational studies, and although the average BMI was slightly lower, interactions remained insignificant when analyses were performed in overweight individuals only. The relatively small main effect of *FTO* on BMI (0.13 $kg \cdot m^{-2}$ per allele) and the potentially higher than average physical activity levels observed in this population may explain the absence of interaction.

Results of exercise and lifestyle intervention studies have been less consistent than those of observational studies. One study reported resistance to body fat loss in the *FTO* risk-allele homozygotes during a 20-wk endurance training program,[56] whereas the

opposite was observed in overweight women during a 6-month moderate-intensity exercise program,[42] and no interaction was observed in the diabetes prevention studies.[25,34] Despite the often well-controlled interventions, sample sizes of these studies were typically small, study participants were often overweight, variation in weight change was relatively small, and the main effect of *FTO* on weight change was often small or insignificant. All these factors may have limited the power to identify a gene-physical activity interaction effect. However, the results from the HERITAGE Family Study, which has the largest sample size, highly standardized training program with 100% compliance, and directly measured body composition phenotype, raise an interesting question for future studies:[56] although regular physical activity may be able to prevent or slow down the *FTO* genotype-related weight gain as suggested by the observational studies, exercise training may be less effective in losing the already gained fat mass in the *FTO* risk-allele homozygotes than in those who do not carry the allele.

Taken together, most of the observational studies suggest that physical activity could potentially attenuate in part the effect of *FTO* variation on BMI. This is an important observation with public health implications because it challenges the determinist view that a genetic susceptibility to obesity is unmodifiable. It should be noted, however, that 1) the absolute contribution of *FTO* to variation in BMI is rather small (<2%), even among physically inactive individuals, and 2) the literature may be biased as negative interaction results may not be reported as often as positive ones. Therefore, a large-scale meta-analysis of published and unpublished data is warranted for an unbiased evaluation of the *FTO*-physical activity interaction hypothesis.

Insulin and Glucose Metabolism Phenotypes

Over the last 2 yr, a total of seven articles analyzed genetic associations between candidate genes and the response of glucose and insulin metabolism phenotypes to exercise and/or habitual physical activity.[5,31,32,43,50,58,68] Among these studies, two tested association taking into account potential interactions with physical activity level,[5,58] but only one found significant evidence of such an effect. Ruchat et al.[58] tested association between two SNP in the hepatocyte nuclear factor 4 alpha (*HNF4A*) gene and glucose, insulin, and C-peptide plasma levels measured in the fasting state and during an oral glucose tolerance test in 528 nondiabetic adult subjects from the Quebec Family Study. Significant evidence of gene × physical activity interaction was found for 2-h glucose levels and glucose area under the curve ($P < 0.0001$), for insulin area under the curve ($P < 0.003$), and for fasting C-peptide levels ($P = 0.03$). The interaction with physical activity was independent of BMI, suggesting that regular exercise can reduce the risk of diabetes independent of changes in adiposity.

Three studies reported evidence of association between polymorphisms in the peroxisome proliferator-activated receptor gamma (*PPARG*),[32] *PPARD*,[68] and ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*)[43] genes and the response of type 2 diabetes-related traits to a lifestyle intervention program. Because of its large sample size (3548 compared with 479 and 156 in the other studies), the study of Moore et al.[43] is probably the most significant of these three studies. The authors examined the impact of the *ENPP1* K121Q polymorphism on diabetes incidence (3-yr follow-up) as well as insulin secretion and sensitivity at baseline and after treatment with a lifestyle intervention in the Diabetes Prevention Program. The goals of the

lifestyle intervention consisted of reducing caloric intake, decreasing dietary fat to 25% fat, and adding 150 min·wk^{-1} of moderate-intensity physical activity to achieve and maintain at least a 7% weight loss. They found that carriers of the Q risk allele at the *ENPP1* K121Q polymorphism have an increased incidence of diabetes (hazard ratio = 1.38, $P = 0.01$) and that this increased risk was eliminated by lifestyle modification (hazard ratio = 0.89, $P = 0.5$). The effects of this polymorphism on changes in indices of insulin secretion and insulin sensitivity after 1 yr of intervention were not significant.[43] The major limitation of these lifestyle modification studies is that the intervention is not standardized and monitored, which makes it difficult to evaluate the impact of exercise *per se* on the phenotypes under investigation.

A final study investigated the effects of short-term exercise training on skeletal muscle ATP synthesis assessed using magnetic resonance spectroscopy and insulin sensitivity assessed from an oral glucose tolerance test and tested the hypothesis that the responses are modulated by polymorphisms in two genes regulating mitochondrial function, *PPARGC1A* and NADH dehydrogenase (ubiquinone) 1 beta subcomplex 6 (*NDUFB6*).[31] The authors studied 24 nonobese first-degree relatives of type 2 diabetes patients and 12 control subjects. The subjects performed three 10-min bouts of cycling exercise at an intensity set at 90% of the workload that induced hyperventilation during an incremental exercise test. The study end points were measured before and 48 h after the exercise bouts. The results showed that in some relatives of type 2 diabetes patients, there is a resistance to the stimulation of ATP synthesis and absence of improvements in insulin sensitivity in response to exercise and that these individuals carry a risk polymorphism in the *NDUFB6* gene from the respiratory chain complex I related to ATP synthesis. Unfortunately, the small sample size of the study precludes any firm conclusion regarding the role of this genetic variant at this time.

Genes, Exercise, and Lipid and Lipoprotein Metabolism

Numerous genes and gene variants with well-documented roles in lipid metabolism and associations to lipid levels in humans have also been shown to play a role in lipid response to exercise and physical activity.[4] One of these genes is the *APOE* gene. Although the *APOE* epsilon variant, which is actually a haplotype of two different exonic SNP, demonstrates different allele frequencies across populations, its association with total cholesterol, cholesterol fractions, and other serum lipids is fairly consistent across studies.[67] Several studies have reported significant changes in blood lipid components (HDL_2-C, LPL_A, ApoB/AI ratio, LDL/HDL ratio, TC/HDL ratio) after exercise that vary with *APOE* genotype, but none of them have examined racial/ethnic differences in lipid response.[27,61,69] It is an interesting hypothesis that the effects of *APOE* genotype may be differentially modified by exercise training depending on race/ethnicity.

Obisesan et al.[48] analyzed genotype at the well-studied epsilon variant in the *APOE* gene as a mediator of plasma lipid response to exercise training. Subjects in the study participated in a supervised, progressive exercise training program consisting of three sessions per week for 6 months. A total of 149 subjects (120 whites and 29 blacks), age 50–75 yr, completed the training protocol. Both plasma lipid concentrations and lipoprotein particle size were determined for all subjects before and after exercise training. Although both black and white in the *APOE* 2/3 group (contained genotypes 2/2, 2/3, and 3/3) experienced no significant within-group differences in total and

subfraction measures of plasma HDL-C or HDL-C particle size, there was a significant interaction between race/ethnicity and genotype for HDL-C particle size and HDL-C subfractions.[48] Black *APOE* 2/3 group experienced approximately 2.5 times the increase in particle size compared with white 2/3 group (0.26 ± 0.06 vs 0.10 ± 0.03 nm, $P = 0.015$) after exercise training.[48] In addition, black *APOE* 2/3 carriers had greater exercise-training-induced improvements in the HDL-C subfractions compared with whites.[48] There were no racial differences in training responses for *APOE* epsilon 4 allele carriers (genotypes 3/4 and 4/4, two individuals with genotype 2/4 were excluded).

In contrast, a study reported previously by Leon et al.[36] examined differences in lipid response to aerobic exercise training in black and white men and women from the HERITAGE Family Study and found that white women with the 2/2 or 2/3 genotype experienced the greatest changes of any race/gender group in plasma total HDL-C and HDL-C subfractions after exercise training, with significant differences after training also observed for total cholesterol in white men with the 2/2, 2/3, or 2/4 genotypes; differences in ApoA1 levels were the only significant change reported in black women with APOE 2/4 compared with other genotypes. The inconsistencies in race/ethnicity response differences between the two reports described above may be explained by dissimilarities in the age and/or baseline fitness level of the subjects, differences in the assays used to measure the lipid fractions (e.g., the study of Obisesan et al.[48] was the first to use NMR spectroscopy to identify HDL particle size), and differences in the training regimen used in each study but more importantly by the differences in sample sizes. For instance, the study by Obisesan et al.[48] included only 22–29 black subjects with exercise training data (depending on phenotype), whereas in the HERITAGE Family Study, 250 blacks completed the training program. This is another indication that statistical power matters.

Genes, Exercise, and Cardiovascular Phenotypes

It appears that roughly 20 articles were published in the last 2 yr addressing interactions between physical activity, genetics, and cardiovascular (CV) hemodynamic phenotypes. What follows is a summary of three of these articles, selected for presentation because they are the strongest studies representing the range of research reports generally encompassed within this section. Most other studies were not selected for presentation because they had small sample sizes or addressed gene-physical activity interactions in a single disease in a single ethnic group and thus would have less overall public health impact.

An early genome-wide linkage study from Rankinen et al.[52] in the white HERITAGE families found linkage for the response of submaximal exercise stroke volume (SV) to endurance training at the 10p11.2 and 2q31-q32 loci. In 2003, Rankinen et al.[55] interrogated the 2q31-q32 locus more intensely and identified titin (*TTN*) as a novel candidate gene for the submaximal exercise SV training response. In 2009, Argyropoulos et al.[2] and the HERITAGE coworkers further studied the linkage between the 10p11 locus and the response of submaximal exercise SV to exercise training in one of the most comprehensive gene-physical activity studies reported to date.

Argyropoulos et al.[2] first typed additional microsatellites to further interrogate the 10p11 locus and found that the best linkage existed within a range of 7 Mb from 30 to 37 Mb on this chromosome. *In silico* searching indicated that there were 16 known genes within that chromosomal region, and a total of 90 SNP were then genotyped across these known genes. These results indicated that SNP within the *KIF5B* and integrin beta 1 (*ITGB1*) genes were associated with the submaximal exercise SV response to exercise training. However, *KIF5B* SNP were much more strongly and consistently associated with this CV phenotype. *KIF5B* was perceived as a plausible candidate gene for CV responses to exercise training because kinesins in general are part of a superfamily of molecular motors that help to move different cellular vesicles and organelles. *KIF5B* in particular has been shown to help transport K+ channels and mitochondria. The investigators then resequenced the *KIF5B* gene and found eight SNP within the promoter region that had minor allele frequencies >5%. Their initial molecular studies showed that *KIF5B* was expressed in numerous adult human tissue types and also in numerous components of the heart. They then transfected different *KIF5B* promoter haplotypes into two cell lines and found significant activity differences among three of the seven haplotype combinations they studied. Finally, they assessed mitochondrial localization and biogenesis during states of both *KIF5B* overexpression and underexpression in undifferentiated C12C12 cells. Silencing of the gene resulted in reduced mitochondrial activity in the transfected cells as well as the perinuclear accumulation of mitochondria. Overexpression led to increased mitochondrial activity. Thus, their overall conclusion on the basis of linkage and association studies and functional studies is that common genetic variations in the promoter of the *KIF5B* gene affect gene expression, hence mitochondrial biogenesis, and finally submaximal exercise SV changes resulting from endurance exercise training. This is a very important and strong study because of the large sample size in the initial human studies and the depth the investigators went to study the functional aspects of specific genetic variants they believed to be important.

Dias et al.[16] studied the impact of the Glu298Asp endothelial nitric oxide synthase (*NOS3*) polymorphism on regulation of muscle blood flow at rest and during isometric handgrip exercise. The investigators *a priori* selected subjects to have 15 Glu298Glu homozygotes, 9 Asp298Asp homozygotes, and 9 Glu298Asp heterozygotes matched for age, sex, BMI, and plasma lipoprotein-lipid profiles. Baseline BP, HR, forearm blood flow, and forearm vascular conductance were similar among the three *NOS3* genotype groups. HR and BP responses to isometric handgrip also did not differ significantly among the genotype groups. However, Asp298Asp homozygotes did not increase forearm vascular conductance or forearm blood flow during the exercise, whereas the heterozygote and the Glu298Glu homozygote groups had significant and substantive increases in both of these CV response phenotypes during the exercise. Further isometric handgrip studies with infusions of phentolamine, an alpha adrenergic blocker, and L-N^G monomethylarginine (l-NMMA), an endothelial NOS inhibitor, provided evidence that this differential vasodilatory response among Glu298Asp *NOS3* genotype groups was the result of alterations in *NOS3* function and NO-induced vasodilation, not sympathetic vasoconstriction. This study is an example where the genetics issues are dealt with in a simple and straightforward fashion; however, the physiology phenotypes assessed are highly mechanistic and allow one to draw quite strong conclusions despite the small sample sizes used. The problem with this type of study is that when a second polymorphism that impacts this CV phenotype is identified, the number of study groups

required to address the potential interactive nature of these loci begins to increase exponentially.

Finally, the study by Vimaleswaran et al.[71] is a genetic epidemiology study assessing the impact of habitual levels of energy expenditure on the relationship between *NOS3* polymorphisms and BP. They typed 11 *NOS3* polymorphisms, including all of those considered common variants in this gene, in 726 individuals in a prospective cohort study of type 2 diabetes and related metabolic disorders in the United Kingdom. They used a previously validated method of ambulatory HR recordings to estimate habitual nonresting energy expenditure (NREE). An intronic variant (IVS25+15 G→A) was associated with both systolic and diastolic BP, and both of these relationships were significantly affected by NREE. The beneficial effects of the GG genotype at this locus were statistically evident only in individuals who were in the highest tertile of NREE (Fig. 3), with the benefits averaging 3–5 mm Hg for both systolic and diastolic BP. They concluded that eventually individuals could be specifically directed to physical activity interventions to maintain or to reduce BP on the basis of their genotype at this locus.

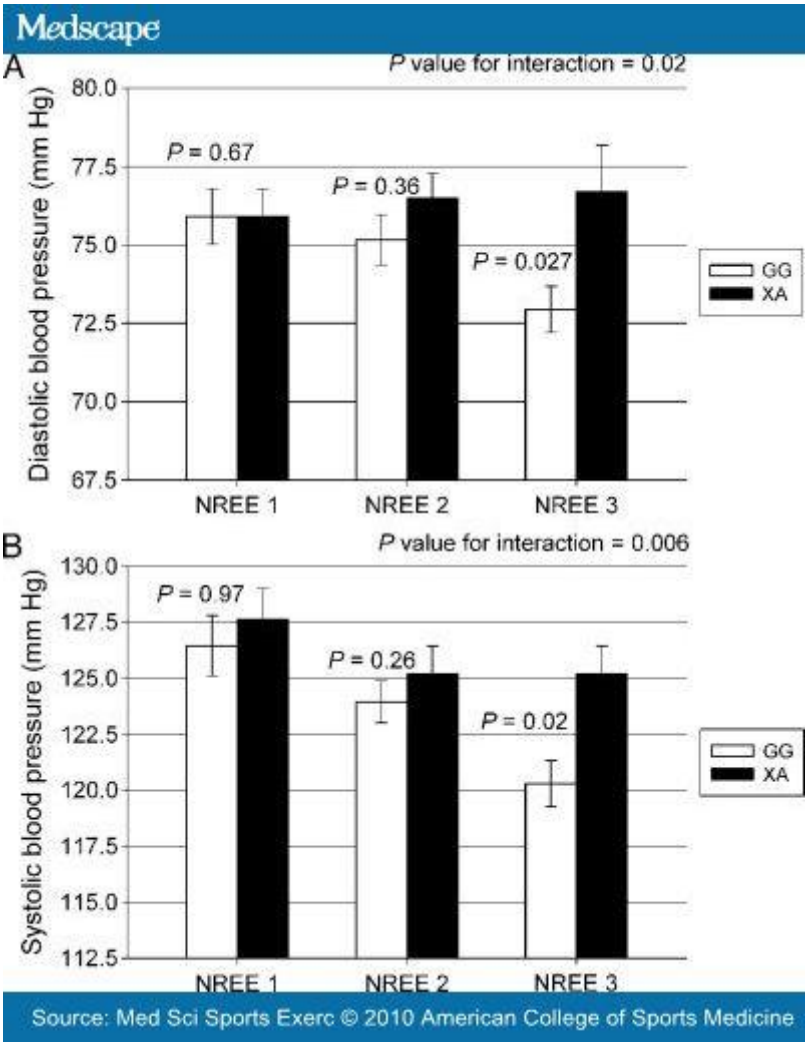

Figure 3. A. Interaction of nonresting energy expenditure (NREE) (sex-specific tertiles of energy expenditure per kilogram) and IVS25+15 SNP on diastolic BP. B. I interaction of NREE and IVS25+15 SNP on systolic BP. Reproduced with permission from the Macmillan Publishers Ltd: Vimaleswaran KS, Franks PW, Barroso I, et al.

Habitual energy expenditure modifies the association between NOS3 gene polymorphisms and blood pressure. Am J Hypertens. 2008;21:297–302, copyright © 2008.

Summary and Conclusions

The review emphasizes the strongest articles in exercise genomics published in 2008 and 2009. The selection of the articles retained was made on the basis of sample size, quality of phenotype measurements, quality of the exercise program or physical activity exposure, study design, adjustment for multiple testing, quality of genotyping, and other related study characteristics. This focus on the highest quality articles accounts for the fact that only a small number of publications are reviewed. A brief overview of the first GWAS of the genetic differences between exercisers and nonexercisers is presented. Three genomic hits are of particular interest for future investigations. The latest results on the *ACTN3* R577X nonsense polymorphism are reviewed emphasizing that no definitive conclusion can be reached at this time. Recent studies that have dealt with mtDNA haplogroups and endurance performance are described. Published reports indicating that physical activity may attenuate the effect of the *FTO* risk allele on BMI are reviewed. Articles that have tested the contributions of specific genes on the response of glucose and insulin metabolism traits to regular exercise or physical activity level are considered and found to be generally inconclusive at this stage. Ethnic differences in the response of blood lipids and lipoproteins to exercise training cannot be unequivocally related to *APOE* genotypes. Hemodynamic changes with exercise training were reported to be associated to sequence variation in *KIF5B*, but no replication study is available as of yet. We conclude from this first installment that exercise scientists need to prioritize high-quality research designs and that replication studies with large sample sizes are urgently needed.

[CLOSE WINDOW]

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