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Advances in Exercise, Fitness, and Performance Genomics in 2014

Ruth J. F. Loos[1], **James M. Hagberg**[2], **Louis Pérusse**[3], **Stephen M. Roth**[2], **Mark A. Sarzynski**[4], **Bernd Wolfarth**[5], **Tuomo Rankinen**[4], and **Claude Bouchard**[4]

[1]The Genetics of Obesity and Related Metabolic Traits Program, The Charles Bronfman Institute for Personalized Medicine, The Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, New York, NY

[2]Department of Kinesiology, School of Public Health, University of Maryland, College Park, MD

[3]Department of Kinesiology, Faculty of Medicine, Laval University, Ste-Foy, Québec, Canada

[4]Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA

[5]Department of Sport Medicine Humboldt University and Charité University School of Medicine, Berlin, Germany

Abstract

This is the annual review of the exercise genomics literature in which we report on the highest quality papers published in 2014. We identified a number of noteworthy papers across a number of fields. In 70 to 89 years old, only 19% of *ACE* II homozygotes exhibited significant improvement in gait speed in response to a year-long physical activity program compared to 30% of *ACE* D-allele carriers. New studies continue to support the notion that the genetic susceptibility to obesity, as evidenced by a genomic risk score (GRS; based on multiple SNPs), is attenuated by 40-50% in individuals who are physically active, compare to those who are sedentary. One study reported that the polygenic risk for hypertriglyceridemia was reduced by 30-40% in individuals with high cardiorespiratory fitness. One report showed that there was a significant interaction of a type 2 diabetes GRS with physical activity, with active individuals having the lowest risk of developing diabetes. The protective effect of was most pronounced in the low GRS tertile (HR=0.82). The interaction observed with the diabetes GRS appeared to be dependent on a genetic susceptibility to insulin resistance and not insulin secretion. A significant interaction between *PPARα* sequence variants and physical activity levels on cardiometabolic risk was observed, with higher activity levels associated with lower risk only in carriers of specific genotypes and haplotypes. The review concludes with a discussion of the importance of replication studies when very large population or intervention discovery studies are not feasible or are cost prohibitive.

Address for correspondence: Claude Bouchard, PhD, Human Genomics Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808-4124, Tel: (225) 763-2543, bouchac@pbrc.edu.

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Keywords

Genetics; single nucleotide polymorphism; genome-wide association study; genetic risk score; gene-exercise interaction; replication studies

Introduction

This publication is the 2014 installment of an annual exercise genetics and genomics review. It summarizes the best scientific papers in the calendar year 2014. As emphasized in prior years, the review focuses on the strongest publications as defined by study design, sample size, novelty, and relevance of phenotypes with potential implications for exercise science and sports medicine. The review is not a comprehensive summary of all published papers on genetics and genomics relative to exercise, physical activity, fitness, and performance, and standards for selection of papers have been explained in prior yearly installments of the publication (14, 33, 37, 38, 47).

The 2014 review is organized around the following topics: (a) physical activity behavior, (b) muscular strength and power, (c) cardiorespiratory fitness and endurance performance, (d) body weight and adiposity, (e) insulin and glucose metabolism phenotypes, (f) lipid and lipoprotein metabolism, and (g) hemodynamic traits. The paper ends with a brief discussion of the evidence and comments on the critical importance of replication studies in exercise genomics research.

Physical Activity Behavior

In 2014, even though there was no report on specific human genes and genomic variants related to physical activity behavior, one interesting study related to heritability of sedentary behavior was published. Santos et al. investigated the heritability of sedentary behavior in a cohort of 1,345 individuals (249 fathers, 327 mothers, 334 sons, and 325 daughters) from 339 Portuguese nuclear families (41). In addition, the authors tested for evidence of genotype-by-sex (GxSex) and genotype-by-age (GxAge) interactions on sedentary behavior. The mean age of children and parents was 14.5 and 44.6 years, respectively. Sedentary behavior was assessed using three different instruments: 3-day physical activity diary, Baecke physical activity questionnaire, and a short version of the International Physical Activity Questionnaire (IPAQ) to assess sedentary behavior (TV watching and sitting time from IPAQ and personal computer [PC] use time from Baecke) and low levels of physical activity (time counts and energy expenditure estimates from 3-day diaries, total physical activity from Baecke).

Heritability estimates of the sedentary behavior traits ranged from 3% to 27%. A common feature was that heritability estimates for traits directly reflecting sedentary behavior were low (3-5%) and statistically non-significant, while traits reflecting lack of physical activity were characterized by moderate heritability levels (19 – 27%, $p < 0.003$). The interaction analyses showed that, in general, both GxSex and GxAge models fit the data significantly better than models without interaction terms. Evidence of GxSex and GxAge interactions was found for TV watching and PC time, sedentary energy expenditure and physical activity

tertiles, whereas genetic correlations appeared to be stronger in men than in women, and in younger than in older individuals.

The study represents an interesting approach to evaluate if genetic background of sedentary behavior varies as a function of age or differs by sex. However, some limitations need to be kept in mind. The post-hoc power calculations showed that the study had only low to moderate power to detect GxSex interactions. The sedentary behavior traits were based on self-reported diaries and questionnaires and only some of the traits focused directly on sedentary behavior, while others reflected merely a lack of physical activity. It is vital that the findings on both GxSex and GxAge interactions be tested for replication in other cohorts.

Muscular Strength and Power

Very few articles qualify as having significantly contributed to our understanding of the genomics of muscular strength and power in 2014. Two were retained for presentation in the present review. In the first, Buford et al. (6), as part of the LIFE (Lifestyle Interventions and Independence for Elders) Research Group, examined 283 mobility-limited older men and women (70-89 yr old) who participated in a 12-month physical activity intervention that included walking, strength, and balance exercises for several days during each week. They examined whether the angiotensin converting enzyme (*ACE*) gene I/D genotype, which has been associated previously with both mobility limitation (23) and knee extensor strength response to strength training (12) in older individuals, was associated with the primary outcome measures of gait speed and performance on the short physical performance battery (SBBP). After adjustment for a number of relevant characteristics, including ACE inhibitor and angiotensin receptor blocker use, the authors found that improvements in gait speed ($P_{interaction} = 0.002$) and SBBP ($P_{interaction} = 0.02$) depended significantly on participants' *ACE* genotype. Specifically, 68% of *ACE* D-allele (D/D + I/D) carriers showed clinically significant improvements in SBBP compared to only 43% of *ACE* II homozygotes (∼20% of the population) in response to the exercise program. Similarly, only 19% of *ACE* II homozygotes exhibited a clinically significant improvement in gait speed in response to exercise compared to 30% of *ACE* D-allele carriers. Though this is a small “single gene, single polymorphism” study limited to Caucasians, the cohort is well characterized and the findings suggest a potential genotype influence on the response to regular exercise in older individuals. The findings need to be replicated in other cohorts of older men and women before one could consider its usefulness in exercise prescription as we emphasized in our review of last year (47).

In the second study, Norman et al. (31) examined the response of skeletal muscle hypertrophy signaling molecules (Akt/mTOR pathway) to acute sprint exercise across the alpha-actinin-3 (*ACTN3*) R577X nonsense single nucleotide polymorphism (SNP) genotype groups. Several studies have shown lower frequency of the *ACTN3* X/X genotype in sprint and power athletes compared to control populations (26, 49), though differences in baseline skeletal muscle properties (e.g., strength, mass) across these genotype groups have not been consistently replicated in the general population (2, 33). The authors hypothesized that the lower sprint-related performance associated with the *ACTN3* X/X genotype would be

manifest in skeletal muscle as an impaired response to an exercise stimulus. Hence, they examined the response of hypertrophy-related molecules in skeletal muscle of 18 individuals who performed a maximal sprint cycling exercise. Individuals with the *ACTN3* X/X genotype ∼20% lower increases in the phosphorylation of both mTOR (P = 0.03) and p70S6k (P = 0.01), but not of two other markers (rpS6, Akt), in response to the exercise stimulus compared to R-allele carriers. In a different group of 38 individuals, *ACTN3* X/X genotype was associated with ∼50% lower glycogen utilization in type II fibers during sprint exercise compared to R-allele carriers (P < 0.01). This study is limited by the combined analysis of multiple cohorts of individuals and the use of two similar yet different exercise stimuli across those cohorts. Additional work is needed to understand whether there are true differences in skeletal muscle signaling pathways in response to exercise challenges among *ACTN3* genotypes in humans, as well as difference in signaling events in muscle of humans compared to *Actn3* knockout mouse (27, 43).

Cardiorespiratory Fitness and Endurance Performance

In the past year, a number of articles were published on the genetics of cardiorespiratory fitness and endurance performance phenotypes. The following two papers were those that came closest to meeting our standards for this review. Both studies examined the role of genetic variation in endurance performance or maximum oxygen uptake by studying intermediate phenotypes.

Fedotovskaya et al. investigated the role of the A1470T (rs1049434) SNP in the monocarboxylate transporter 1 (*MCT1*) gene in 323 Russian athletes and 467 non-athlete controls (11). MCT1 catalyzes the transport of lactate into myocytes for oxidation and the A1470T SNP was previously shown to be associated with lactate transport rates in skeletal muscles (9, 30). Fedotovskaya et al. showed that the major allele was significantly ($P < 10^{-4}$) more prevalent among endurance athletes (71.8%) than among non-athletes (62.5%). Furthermore, among male rowers, AA homozygotes (AA 8.75 ± 1.69 mmol/L) had significantly (P = 0.005) lower blood lactate concentrations compared to T-allele carriers (AT+TT 10.26 ± 1.89 mmol/L) (11). In a small study focusing on an interesting endophenotype, Malczewska-Lenczowska et al. investigated the relation between two SNPs in the *HBB* gene and total hemoglobin mass in 82 well-trained athletes (women n = 36, men n = 46) (29). Neither of the two *HBB* SNPs showed evidence of association. While the approach is promising, and that is the reason why it is being reviewed here, much larger studies will ultimately be needed along with multiple replication studies in order to uncover genomic markers and biological pathways involved in cardiorespiratory endurance and intermediary traits of fitness and its trainability.

Body Weight and Adiposity

In the past five reviews (14, 33, 37, 38, 47), we reported on the growing evidence that the genetic susceptibility to obesity is attenuated by 20-40% in adults who are physically active compared to those who are inactive (1, 21, 25), suggesting that even those who are genetically predisposed to gain weight more easily do benefit from an active lifestyle. The genetic susceptibility was typically assessed by either a SNP in *FTO* or by combining

multiple BMI-associated loci, predominantly those discovered before 2010, into a genetic risk score (GRS). The studies we described were large, including 20,000 to more than 200,000 individuals, thus providing sufficient power and convincing evidence.

New studies reported in 2014 offered mainly corroborating observations, but including obesity-associated loci reported in 2010 (16, 45) and using longitudinal study designs. For example, a population-based study of 2,894 Han Chinese adults found that the BMI-increasing effect of a GRS, comprised of 28 BMI-associated variants, was reduced by 60% ($P_{interaction} = 0.022$) in individuals with high physical activity levels compared to individuals with low physical activity levels (50). The longitudinal 1946 British Birth Cohort, that followed 2,444 men and women from birth up to age 64 yrs, found that the genetic susceptibility assessed by a GRS of 11 BMI-associated loci was significantly ($P_{interaction} = 0.004$) attenuated by physical activity from age 53 yrs onwards, despite the fact that "being active" was loosely defined as participation in sports activities at least once a month (20). A Danish study of 3,982 individuals (mean (SD) age at baseline 46.7 (7.7) yrs), who were followed for 5 years, examined whether a GRS based on 30 BMI-associated variants associated with change in BMI over time, and whether change in physical activity during the same period influences that association (40). The GRS, while significantly associated with baseline BMI, was not associated with change in BMI during the following 5 years, and changes in physical activity levels during that timeframe had no effect on the GRS - BMI-change association (40), which is consistent with previous observations using a similar design (21). A longitudinal design has the advantage that it controls for reverse causation, but the downside is that it requires a larger sample to convincingly refute or prove interaction between genes and environment. The National Longitudinal Study of Adolescents studied 7,642 participants at the age of 16 yrs and found no evidence of an interaction between screen time and genetic susceptibility to obesity in adolescence (13). This is consistent with the observation of a large-scale meta-analysis (n > 19,000) that found that the BMI-increasing effect of *FTO* was the same in physical active and physically inactive children and adolescents (21). We have speculated before that the lack of interaction may be due to a weak association between physical activity and BMI and the relatively higher levels of physical activity in childhood and adolescence (21).

While the evidence that physical activity attenuates the genetic susceptibility to obesity is growing, in particular in adults, it remains unclear whether the attenuation is due to specific properties of physical activity as such, or whether a healthy lifestyle in general would induce similar attenuating effects. Recent large-scale studies examining the effect of dietary factors, as another proxy of a healthy lifestyle, on the association between genetic variants and obesity traits have been inconclusive. For example, a large-scale study (n > 37,000) found that the association between a GRS and BMI was significantly weaker in individuals who consumed a healthier diet (less fried food and sugar-sweetened beverages), compared to those who consumed more of the unhealthy foods (34, 35). However, a meta-analysis including data from >177,000 individuals found no evidence that *FTO*'s BMI-increasing effect is attenuated by dietary intakes (36). Similarly, the genetic susceptibility to obesity, assessed by a GRS of 16 loci, in >29,000 Swedish individuals was not influenced by dietary intake (39).

In summary, the beneficial effect of physical activity on the genetic susceptibility to obesity in adults continues to gain strength. It remains to be determined whether this is due to effects specific to physical activity or whether this is due to a healthy lifestyle in general. Furthermore, new findings confirm that the attenuating effects of physical activity only appear in (later) adulthood.

Insulin and Glucose Metabolism Phenotypes

We have retained two studies that investigated gene-physical activity interactions on the risk of type 2 diabetes (T2D) (22, 24).

Using data from the ARIC (Atherosclerosis Risk in Communities) study, Klimenditis et al. (22) examined the interaction of 65 T2D-associated SNPs with baseline physical activity level on the incidence of T2D. Over an average follow-up of 7.8 years, 821 incident cases of T2D were identified and the interaction of the T2D SNPs with baseline physical activity was examined. In addition to testing interactions with each SNP individually, the interaction was also tested with a GRS, calculated as the weighted sum of the risk alleles of all 65 SNPs. In order to gain further insight into the genetic and physiological basis of the interaction, the authors also created subsets of GRSs comprised of SNPs implicated in insulin resistance (IR), beta-cell function (BC) as well as GRSs for fasting insulin (FI) and fasting glucose (FG). When considered individually, none of the 65 SNPs showed significant evidence of interaction with physical activity after correction for multiple testing, but four SNPs showed nominally significant evidence of interaction (rs1496653 in *UBE2E2*, $P_{interaction} = 0.0009$; rs6795735 in *ADAMTS9*, $P_{interaction} = 0.014$; rs10842994 in *KLHDC5*, $P_{interaction} = 0.016$ and rs2943640 in *IRS1*, $P_{interaction} = 0.038$). Moreover, a significant interaction of the T2D-GRS with physical activity was found ($P_{interaction} = 0.016$); i.e. when the sample was stratified by tertiles of GRS, a protective effect of physical activity was found in the low GRS group only (HR = 0.82, P = 0.05). Analyses stratified by sex revealed that the interaction was significant only in women ($P_{interaction} = 0.0025$) with a protective effect of physical activity in the low GRS group (HR = 0.59, P = 0.003) compared to an increased risk in the high GRS group (HR = 1.31, P = 0.013). The interaction observed with the T2D-GRS appeared to be mainly driven through a genetic susceptibility to IR as opposed to insulin secretion, as the interaction effect was significant with the IR GRS ($P_{interaction} = 0.04$) and FI-GRS ($P_{interaction} = 0.04$), but not with the BC-GRS or the FG-GRS. Reciprocally, the association of T2D-GRS with T2D incidence was found to be stronger among individuals in the highest tertile of physical activity, which contrasts with the interaction of physical activity with the genetic risk of obesity described above, whereby the genetic risk was attenuated among physically active subjects. However, this finding is similar to that reported recently in a large case-cohort study of 12,403 incident cases of T2D and a representative sub-cohort of 16,154 individuals by Langenberg et al. (24) in which the putative effect of T2D genetic risk (based on 49 SNPs) was found to be strongest among younger, leaner and more physical active individuals (although the interaction with physical activity alone did not reach significance).

The strengths of the study by Klimentidis et al. (22) include the use of a large prospective cohort design, and also the use of a large panel of SNPs to define genetic risk. The attempt

to dissect the genetic risk by considering various GRSs based on the pathophysiological process of T2D also represents an original approach to understand the physiological basis of gene-environment interaction effects.

Lipid and Lipoprotein Metabolism

One study that examined whether cardiorespiratory fitness modified the polygenic risk for dyslipidemia was retained for this review (46). In this cross-sectional study, Tanisawa et al. measured serum levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) and fitness using a maximal graded exercise test on a cycle ergometer in 170 Japanese men aged 20-79 years (46). Subjects were divided into low-fitness and high-fitness groups according to the reference VO2max values from the prevention of lifestyle diseases, issued by the Ministry of Health, Labor, and Welfare of Japan (reference values in ml/kg/min: 39.0 for 20–39 yrs, 35.0 for 40–59 yrs, and 32.0 for 60 yrs and older). The authors genotyped 19 SNPs that met the following criteria: 1) showed genome-wide significant ($P < 5x10^{-8}$) associations with TG, LDL-C, and/or HDL-C in any genome-wide association study (GWAS) of individuals of European descent, 2) association was replicated ($P < 0.05$) in a Japanese population, and 3) minor allele frequency was >5% in the Japanese population. Three additive, weighted GRSs were calculated based on SNPs related to TG (7 SNPs), LDL-C (5 SNPs), and HDL-C (9 SNPs) and subjects were divided into tertiles (low, medium, high) for each GRS for analysis.

In adjusted models, there was a significant interaction ($P_{interaction} = 0.028$) between TG-GRS group and fitness group on TG levels. TG levels were 47 and 43 mmHg higher in the high ($P < 0.01$) and middle ($P < 0.05$) TG-GRS groups, respectively, compared to the low TG-GRS group in the low-fitness group only, while no difference in TG levels was observed between the TG-GRS groups in the high-fitness group (Figure 1).

Furthermore, the number of individuals with hypertriglyceridemia (TG ≥ 150 mg/dL) was higher in the high and middle TG-GRS groups than in the low TG-GRS group in the low-fitness group only (46). Lastly, a significant interaction ($P_{interaction} < 0.05$) between the TG-GRS and fitness was observed for body weight, as body weight was higher in the low-fitness group compared to the high-fitness group only in the high TG-GRS group. There was no interaction between GRS group and fitness group for LDL-C, HDL-C, or other lipoprotein-related traits (i.e., apolipoprotein B, apolipoprotein A-I, oxidized LDL).

In summary, the study by Tanisawa et al. found that the polygenic risk for hypertriglyceridemia was attenuated by high fitness level (46). The study is strengthened by fitness (i.e., VO2max) being directly measured and the inclusion of multiple GWAS-based SNPs/loci. However, the study is limited by its small sample size and the reliance on a cross-sectional design. Thus, it is unknown whether intrinsic fitness, acquired fitness or both is associated with the observed associations. It may be that high fitness intrinsically protects against hypertriglyceridemia regardless of TG-associated SNPs. The authors suggest that future genetic association studies, including SNPs associated with trainability of VO2max, are needed to address this issue. Moreover, the trainability of TG and SNPs associated with TG-trainability could also play a role in the observed interaction. To date no large-scale

GWAS of lipid traits in a Japanese population has been performed. Thus, although the included Caucasian-based GWAS SNPs were replicated ($P < 0.05$) in Japanese populations, given the differences in linkage disequilibrium among populations, the included SNPs may not accurately represent the loci contributing the most to the genetic architecture of lipid traits in Japanese individuals. For example, a recent study in individuals of African American, East Asian, and European ancestry performed fine-mapping of lipid GWAS loci and identified population-specific SNPs that increased the trait variance explained (48).

It will be crucial to replicate and expand these findings in other Japanese cohorts and other ancestries. Further prospective and intervention studies are needed to examine the modification of polygenic effects on lipid traits by cardiorespiratory fitness. The study by Tanisawa et al. highlights the need for more studies that examine gene-physical activity, gene-exercise, or gene-fitness interactions on lipid traits at several loci simultaneously. A genome-wide approach would allow for the identification of a panel of loci to be followed up in smaller, targeted replication studies.

Hemodynamic Traits

In 2014, half a dozen papers were published that examined the interactions between physical activity or exercise, genotypes and cardiovascular outcomes. Most were based on small sample sizes that would likely translate into a lack of statistical power to detect the magnitude of true effect sizes generally associated with SNPs, GRSs or haplotypes. Findings of such underpowered studies often turn out to be false positives or simply reflect inflated effect sizes that might result from the small sample sizes.

One study, by Halder et al. (15), had a reasonable sample size (n = 917). Using a cross-sectional study design, they assessed the effect of *PPARα* genotypes and haplotypes on the relationship between habitual physical activity levels, individual risk factors, and overall cardiometabolic risk, based on mean blood pressure (BP), waist circumference, HDL-C, glucose, and TG levels. Overall they found a significant ($P_{interaction} = 0.006$) interaction between the *PPARα* haplotype and habitual physical activity levels on cardiometabolic risk. Higher physical activity levels were associated with lower cardiometabolic risk in the overall population. However, this association was more pronounced in individuals who carried the H-23 haplotype compared to those who did not, such that at low physical activity levels the metabolic risk among H-23 carriers was higher than among non-carriers, whereas no difference in metabolic risk between the two haplotype groups was observed at high physical activity levels. A similar interaction was observed for the *PPARα* rs135542 SNP, as a stronger association between physical activity and cardiometabolic risk was observed for G-allele carriers. When individual components of the composite cardiometabolic risk score were examined, a significant interaction ($P_{interaction} = 0.05$) was found between habitual physical activity and the *PPARα* haplotype and rs135542 genotype on diastolic BP. Furthermore, they found that systolic BP ($P = 0.05$), HDL-C ($P = 0.041$), waist circumference ($P = 0.036$), and TG ($P = 0.001$) were significantly associated with H-23 haplotype in models adjusted for age, sex, education, smoking, and habitual physical activity levels. Further underscoring the need for large sample sizes in such a study is the fact that these effects account for less than 1% of the inter-individual variation in cardiometabolic

risk scores. Thus, since the effect sizes to be ascertained are generally very small, large sample sizes are required to ensure that the relationships are, in fact, true and not false positives.

Comments and Summary

As a group of collaborators, we have been reviewing the exercise genetics and genomics scientific literature for 15 years. It is obvious to us, and it should be to those who have been following the yearly installments of the reviews, that the field has grown in sophistication and that the science has become stronger. Nonetheless, exercise genomics is still in its infancy and much remains to be done before the field can be said to be competitive and mature.

The most convincing results were observed for the interaction between GRSs and physical activity on adiposity, lipid and glycemic outcomes. Specifically, we report that the genetic susceptibility to obesity and hypertriglyceridemia is attenuated in physically active individuals compared to those who are inactive. Furthermore, while physical activity is associated with lower T2D incidence, those with a higher genetic susceptibility seem to benefit the least from being physically active. However, observations tended to be less convincing for studies that examined SNPs for which the associations with exercise outcomes have been ambiguous, such the *ACE* I/D and *ACTN3* R577X, two variants that have been reported on extensively in the past. For example, while we report that, in response to exercise, *ACE* D-allele carriers were found to be more responsive than I/I homozygotes, and *ACTN3* X/X homozygotes demonstrated reduced phosphorylation of signaling molecules than R-allele carriers, overall the replication studies have been inconsistent.

One major issue that we have repeatedly addressed over the years is that of “sample size”. Exercise genomic papers were notorious for being based on small sample sizes and for being grossly underpowered. This has been one of the major reasons for the large body of contradictory results reported in the exercise science literature, which has led one of the leading journals in the field to declare a moratorium on such publications in 2012 (3). There are a number of ways to address this obvious weakness and advocating for studies based on substantially larger sample sizes is a first response strategy. We have done this several times over the last decade. Other strategies could also be helpful. Here we focus on the issue of replication.

Publication of unreliable results is not a problem unique to exercise science and exercise genomics. Indeed, the problem is pervasive in biomedical research as evidenced by the failure to replicate findings in drug studies, behavior modification interventions, nutrition and health outcomes, treatment of depression, and others (4, 7, 10, 17-19, 32). The issue is of such critical importance that the leadership of the National Institutes of Health has expressed its concern and made it public that it was looking for ways to alleviate the problem posed by findings that cannot be replicated (8). In a field in which it is extremely challenging to secure a grant large enough to ensure that the studies to be performed are adequately powered, as is the case for exercise genomics studies aimed at physical

performance and basic biological or behavioral questions, it would be appropriate to develop deliberate plans for replication.

A plan for replication of findings of a main study can take multiple forms. The most stringent replication plan calls for several laboratories working independently but within a well-defined and rigorously specified research design in order to perform exactly the same study. One example of such a very powerful but highly demanding effort is in progress in psychological science and was recently described (42). Such a comprehensive approach makes it possible in the end to undertake not only a meta-analysis of the findings from each contributing center, but also a mega-analysis as all individual data points have been gathered using exactly the same protocol. This approach is probably the most desirable, but it has the obvious limitation of cost, one that is not likely to be well received by the major funding agencies in the current budgetary climate. However, there is a precedent for this approach: this is essentially the design that was used 25 years ago in the HERITAGE Family Study in which subjects were recruited and exercise trained at four independent but deliberately coordinated clinical centers (5, 44) with the aim of addressing some of the genetic questions of the time.

Another useful albeit less costly, less demanding and less powerful approach would be to take advantage as much as possible of existing resources, such as completed studies, and to focus or re-focus them and their data on the observation in need of replication. This approach will allow for a meta-analysis of the findings at each participating laboratory. However, it is unlikely that the individual data points can be combined for a mega-analysis. An examination of this strategy is best undertaken by considering publications reviewed herein as well as other publications that were not retained for this paper. For instance, excellent examples of such an approach can be found in recent meta-analyses based on GWAS reports that have dealt with BMI and T2D (28, 45).

The studies that we summarized in this year's review can be broadly divided into two groups based on the genetic exposure examined; i.e. [1] studies that used SNPs that had been identified in large-scale GWAS and showed robust association with obesity, T2D or cardiovascular disease, and [2] studies that used SNPs located in genes that, because of their role in relevant biological pathways, were considered “candidate genes”.

The results reported for the first type of studies, using GWAS-identified SNPs, tend to be more robust and often replicate findings from preceding years. These SNPs were identified for association with common outcomes, such as BMI, glucose, insulin and lipid levels; i.e. traits that are assessed in many cohorts. As such, studies that examine the interaction between these SNPs, or a GRS, and exercise or physical activity can be based on large samples. Furthermore, summary statistics of multiple studies can also more easily be combined in meta-analyses as outcomes are assessed in standardized ways. The most convincing observations were reported for GRSs, which combine multiple SNPs to assess individuals' genetic susceptibility. As GRSs are continuous exposures that contain more variation than a single SNP, they provide greater statistical power.

Results reported for the second type of studies, i.e. those that examine a single SNP or haplotype in a gene that encodes a protein presumed to play a role in the underlying biology, have been much less successful in establishing associations and interactions. These studies often examine outcomes that are very specific and/or complex, such as power, strength, endurance, response to training and elite athlete status, which are assessed in few studies and for which not always agreed upon standardized procedures exist. Because of the specificity of the design and outcomes, these studies are much harder to replicate and summary statistics are not easily combined in traditional meta-analyses. These types of studies would benefit from so-called *de novo* meta-analyses, which requires investigators to collaborate and to harmonize outcomes, exposures and covariates and (re-)analyze associations and interactions in a standardized manner before summary statistics are combined in meta-analyses (21). Ideally, to minimize publication bias, such meta-analyses should also include data from studies that have not been published. Large-scale meta-analyses will be able to prove or refute the tested hypotheses. Furthermore, meta-regression will allow assessing which covariates contribute to the heterogeneity observed across studies.

Establishing convincing associations and interactions is only “the end of the beginning”, and a critical prerequisite to the ultimate aim, which is to translate robust observations into a better understanding of exercise biology and behavior, human performance potential and public health implications. Hence, the need for replication, reproducibility and/or well-powered studies is increasingly becoming a central aspect of science. Well planned and executed replication studies can, to some extent, attenuate what is often perceived as unattainable sample size goals in some areas of science such as exercise genomics.

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Associations among TG-GRS groups, fitness groups, and serum TG levels.

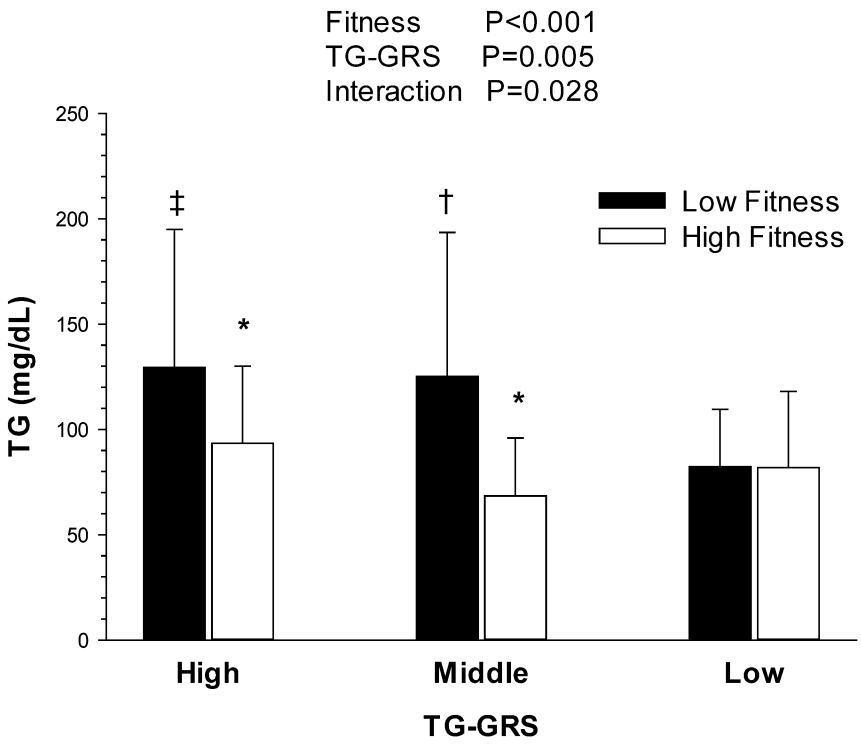

Figure 1.

Associations among TG-GRS groups, fitness groups, and serum TG levels. Data shown are means (SD). TG was log transformed for analysis (data are shown as the original values). Data were analyzed by 2-way ANCOVA with adjustment for age, BMI, current or former smoking status, history of diabetes, alcohol consumption, and saturated fat intake. TG, triglyceride; GRS, genetic risk score. *P < 0.05 vs. low-fitness subjects within the same GRS group. †P < 0.05 vs. the low-GRS group within the same fitness group. ‡P < 0.01 vs. the low-GRS group within the same fitness group. [Adapted with permission from The American Physiological Society (46)]