

Genetics of Regular Exercise and Sedentary Behaviors

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Studies on the determinants of physical activity have traditionally focused on social factors and environmental barriers, but recent research has shown the additional importance of biological factors, including genetic variation. Here we review the major tenets of this research to arrive at three major conclusions: First, individual differences in physical activity traits are significantly influenced by genetic factors, but genetic contribution varies strongly over age, with heritability of leisure time exercise behavior ranging from 27% to 84% and heritability of sedentary behaviors ranging from 9% to 48%. Second, candidate gene approaches based on animal or human QTLs or on biological relevance (e.g., dopaminergic or cannabinoid activity in the brain, or exercise performance influencing muscle physiology) have not yet yielded the necessary evidence to specify the genetic mechanisms underlying the heritability of physical activity traits. Third, there is significant genetic modulation of the beneficial effects of daily physical activity patterns on strength and endurance improvements and on health-related parameters like body mass index. Further increases in our understanding of the genetic determinants of sedentary and exercise behaviors as well as the genetic modulation of their effects on fitness and health will be key to meaningful future intervention on these behaviors.

■ **Keywords:** twin studies, animal studies, gene by exercise interaction

Despite the well-documented benefits of physical activity for health (Berlin & Colditz, 1990; De Moor et al., 2008; Knab et al., 2009; Knab & Lightfoot, 2010; Lee et al., 2012; Morris et al., 1980; Samitz et al., 2011; Stubbe et al., 2006) and the often repeated public health recommendations (Haskell et al., 2007; Kohl III et al., 2012), a large proportion of adults worldwide do not engage in sufficient physical activity to maintain an optimal cardiorespiratory fitness level (Hallal et al., 2012) or to maintain muscle mass and function. Compared to a few generations ago, obligatory physical activity during work is restricted to jobs still requiring manual labor; for example, farming, cleaning, and construction work. Even in manual labor, mechanization and tool-use have strongly reduced the need for prolonged or vigorous physical work. Transportation is mostly passive and it is no longer required to walk for prolonged periods of time, while pavements and strollers have obviated the need to carry young children across uneven terrain. Recreation in free time that used to involve large amounts of dancing

and making music has been replaced by sedentary activities like reading, watching TV and computer time. The bulk of modern-day moderate to vigorous activity, particularly in the most modernized societies, is more and more of a voluntary nature, prominently including regular exercise activities in leisure time.

In contrast to total physical activity, measurement of regular voluntary exercise behavior can be reliably done by self-report in adolescents and adults (De Moor et al., 2008; Haase et al., 2004; Stubbe et al., 2006). This allows it to be assessed in large-scale longitudinal survey studies, where it may not always be feasible to use more objective

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measurements of exercise activity — for instance, by accelerometers or pedometers. A focus on leisure time exercise behavior is additionally advantageous in view of the existence of good animal models to study the genetics of voluntary exercise behavior (De Moor et al., 2008; Gomes et al., 2009; Kelly et al., 2014; Knab et al., 2009; Knab & Lightfoot, 2010). Large-scale survey studies of voluntary leisure time exercise behaviors have shown the existence of vast individual differences across a wide range of countries (Haase et al., 2004; Steptoe et al., 1997; Stubbe et al., 2006; van der Aa et al., 2010). Large individual differences in spontaneous exercise are also found in experimental studies in rodents both across, but even within, different strains.

As leisure time exercise behavior is largely voluntary, it presents by its very nature a modifiable behavior. However, the opposite end of the physical activity spectrum, sedentary behavior, is also receiving increasing attention as an additional and possibly independent target for behavioral intervention. Whereas sedentary behavior has long been regarded as the absence of regular voluntary exercise behavior, a number of studies have now shown this to be incorrect. Daily time spent on moderate to vigorous exercise activity and time spent on sitting activities are only weakly correlated (Pate et al., 2008; van der Aa et al., 2010). In addition, negative health outcomes, including high BMI, have been reported to follow from sedentary behaviors, independent of physical activity levels (Chinapaw et al., 2011; Lakerveld et al., 2013; Proper et al., 2011; Scheers et al., 2013; van der Ploeg et al., 2012). In fact, the Sedentary Behaviour Research Network has suggested using the term ‘inactive’ for those not meeting specific physical activity guidelines (Sedentary Behaviour Research Network, 2012) and to reserve sedentary for behaviors that are done in a sitting or reclining posture and do not consume more energy than 1.5 of the resting metabolic rate. Therefore, we cannot assume that the factors causing individual differences in regular exercise behavior are equivalent to the factors causing individual differences in sedentary behavior.

To increase the success of intervention on both of these important health behaviors, much research is being devoted to their determinants. The bulk of these studies have attempted to explain low levels of exercise and high levels of sedentariness in terms of psychological, social and environmental barriers. This ignores the overwhelming recent evidence that genetic factors also play an important role in sedentary and exercise behaviors. A major impetus for the recent attention to biological factors in the understanding of individual differences in voluntary exercise behavior has come from animal studies. Two good genetic models are available in rodents. First, selective breeding for spontaneous high wheel-running activity can greatly enhance existing within-strain differences in this voluntary behavior, thereby increasing the genetic variation that is specifically related to the drive to exercise (Kelly et al.,

2014; Rezende et al., 2009). Second, there is considerable variation in spontaneous wheel-running among genetically well-characterized inbred strains of rats and mice, which can be exploited in genetic analysis (Lightfoot et al., 2010). In humans, twin studies have been the main model demonstrating the contribution of genetic factors to regular voluntary exercise activities and more recently also to sedentary time (e.g., TV, computer time).

Heritability of Leisure Time Exercise Behavior

Regular involvement in voluntary exercise behavior clearly ‘runs in the family,’ such that the chance of one family member being a regular exerciser increases the chance of all other family members to be, or to become, an exerciser. This often observed familial resemblance partly represent the many environmental influences that are shared within a family (‘nurture’) and they partly represent genetic influences (‘nature’). Twin studies can separate these two mechanisms by comparing the resemblance in exercise behavior between monozygotic (MZ) and dizygotic (DZ) twins. When twins are reared together they share part of their environment and this sharing of the family environment is the same for MZ and DZ twins. Shared environmental factors would include factors like parenting style, parental attitudes, family functioning, neighborhood characteristics or the family’s financial means. The important difference between MZ and DZ twins is that the former share virtually all of their genotypes, whereas the latter share on average only half of the genotypes segregating in that family (Falconer and Mackay, 1996). This distinction is the basis of the classical twin study.

If the resemblance in exercise or sedentary behavior within MZ pairs is larger than in DZ pairs, this suggests that genetic factors influence the behavior. These genetic factors can be either additive, representing the sum of all linear effects of the genetic loci that influence the trait of interest, or non-additive when they include dominance (interaction between two alleles at the same locus) and epistatic (interaction between alleles at different loci) effects. If the resemblance in sedentary or exercise behavior is as large in DZ twins as it is in MZ twins, in spite of their differential genetic resemblance, this points to shared environmental factors (C) as the cause of family resemblance in the behavior (Boomsma et al., 2002). The extent to which MZ and DZ twins do not resemble each other is ascribed to the person-specific (or non-shared) environmental factors (E). These include all unique experiences such as differential jobs or lifestyle, accidents or other life events, and in childhood, differential treatment by the parents, and non-shared friends and peers. Broad sense heritability of exercise is defined as the relative proportion of the total variance explained by additive and non-additive genetic factors and is often presented as a percentage by multiplying this ratio by

a hundred. The percentage of variance ascribed to shared environmental and unique environmental factors can be computed in a similar manner.

Two of the largest twin registries with longitudinal data on leisure time exercise behavior are the Netherlands and the Finnish Twin Registries. Focusing specifically on voluntary exercise behaviors, the Netherlands Twin Registry has shown that throughout the lifespan, participation in sports and leisure time exercise activities like jogging, fitness clubs, regular swimming shows substantial heritability, with estimates seldom below 30% and as high as 84% in adolescence (de Moor et al., 2011; Stubbe et al., 2005; 2006, Stubbe & de Geus, 2008; van der Aa et al., 2010, Vink et al., 2011). The presence of substantial genetic influences on leisure time physical activity is confirmed in full in Finland. Figure 2 in Aaltonen et al. (2014) very nicely summarizes an impressive body of work done in adolescent and adult Finnish twins. From age 16 to 35, heritability estimates varied between 31% and 42%. Many other twin studies in different countries have confirmed the importance of genetic factors in leisure time exercise activity (de Vilhena e Santos et al., 2012).

Although the exact patterns may be country specific, the bulk of twin studies converge on three other main findings (De Moor & de Geus, 2012; Huppertz et al., 2012). First, in childhood and adolescence there is a clear influence of the shared environment on individual differences in exercise behavior, apart from the contribution of genetic factors. Second, the influence of person-specific environmental influences tends to increase across the adult age span from lowest levels in (late) adolescence to higher levels in adults, such that from the middle age and up the unique environment is the major contributor to individual differences in leisure time exercise activities. Third, significant sex differences exist in the heritability estimates, particularly in childhood and adolescence. This suggests that the motivational factors influencing exercise behavior are both sex and age specific. For example, exercise ability ('Am I good at this?') may play a large role in adolescence but be less relevant in adulthood, whereas expected health benefits will instead be more important to the adult exerciser. An example of a potential cause in sex differences is that losing weight may be a somewhat stronger motive for female exercisers than males, who in turn may want to 'look in shape.'

Aaltonen et al. (2014) addressed this question empirically in their Finnish longitudinal dataset. Motivational factors underlying voluntary engagement in regular exercise were assessed with a modified version of the Recreational Exercise Motivation Measure. Among both adolescent and adults, those who had been consistently active rated the effects of exercise on mastery, physical fitness, and psychological wellbeing higher than persons who had been consistently inactive over time. In younger twins, additional motivational factors were found, related to appearance, enjoyment and willingness to look better and be fitter than

others, and to the social aspect of exercising. A question complicating these findings is whether the individual differences in these motives could themselves be influenced by genetic factors. If so, they could contribute to the heritability of regular exercise behavior — by the indirect route of influencing motivation. Of note, a recent study of the Netherlands Twin Registry showed that the perceived health benefits, which were higher in exercisers, were indeed heritable, and the genetic factors influencing perceived health benefits of exercise overlapped with those influencing actual exercise behaviors (Huppertz et al., 2014b). An important remaining question is whether the larger *perceived* health benefits in exercisers reflect true differences in *obtained* benefits. We return to the topic of differential sensitivity to exercise benefits later on.

Heritability of Sedentary Behavior

So far, just a few studies have specifically addressed the heritability of sedentary behavior. Four studies used accelerometer data in a modest sized twin samples (den Hoed et al., 2013; Fisher et al., 2010; Franks et al., 2005; Joosen et al., 2005), whereas only two studies addressed survey based sedentary behaviors (van der Aa et al., 2012). In 9- to 12-year-old twins, accelerometer data showed no genetic contribution and strong shared environment effects, explaining 55% of the variance in sedentary time. Survey data showed that shared environmental influences on individual differences in sedentary behaviors diminish during the transition from adolescence to early adulthood. Results based on the Dutch sample showed sex differences in genetic architecture, with larger heritability estimates for boys than for girls both during early adolescence (boys: 35%; girls: 19%) and early adulthood (boys: 48%; girls: 34%). The Add Health data provide no evidence for sex differences and show a stable pattern of heritability across the adolescent age range (32–34%). In middle-aged twins, using accelerometer data, den Hoed et al. (2013) found that 31% of the variance in the time spent in sedentary behavior was heritable. The remaining variance was predominantly explained by unique environmental factors and random error, whereas shared environmental factors played only a marginal role.

Two recent papers readdressed the topic of genetic and environmental determination of sedentary behavior in large adolescent and adult twin samples. In an adolescent US sample, Haberstick et al. (2014) assessed the average time spent weekly on a variety of leisure time activities including both exercise-related activities and passive sedentary activities consisting of just sitting around, watching TV, or listening to music. Out of the average 6 hours of leisure time activities, adolescents spent 1.5 hours in these passive activities. Variation in the time spent passively was accounted for by genetic (boys: 9%; girls: 36%), shared environmental (boys: 16%; girls: 18%), and person-specific environmental (boys: 76%; girls: 47%) factors. The results deviate partly

from those by van der Aa et al. (2010), who found a much lower contribution of person-specific factors in boys (only 36%). This may be due to the definition of passive leisure time by Haberstick et al. (2014). In contrast to van der Aa et al (2010), they did not include measures of time spent on computer and video games, which are common activities among adolescents, and perhaps more so for boys than girls. This difference in the definition of sedentary time between the two studies could indeed impact more on the heritability of sedentary time in boys compared to that in girls.

Piirtola et al. (2014) used the fourth wave in the Finnish Twin Cohort to address the heritability of a wide range of self-reported sitting behaviors, including sitting time at work, at home watching television or videos, at home at the computer, in a vehicle or elsewhere. Sitting time was on average 7 hours per day in both sexes, and, as expected, increased sitting time was associated with higher BMI. They report a heritability estimate of 35% for total sitting time from self-report, which is in keeping with heritability of accelerometer data in the study by den Hoed et al. (2013) in a similar age group (31%).

Candidate Genes

Having established relatively high heritability for exercise behaviors and a significant contribution to sedentary behavior, at least from adolescence onward, it would be expected that some of the genetic variants involved in these phenotypes might have been identified. Unfortunately, no genes that influence exercise behavior have been detected at the level of ‘proof beyond reasonable doubt.’ For sedentary behavior, no meaningful candidate gene findings have emerged at all (de Vilhena e Santos et al., 2012). For exercise behavior, a number of genomic regions have been implied by genome-wide linkage or genome-wide association studies and significant association to a number of candidate genes has been reported (de Geus & De Moor, 2011; De Moor & de Geus, 2012). However, it has become clear that candidate gene studies suffer from a winner’s curse and that large-scale replication is needed before we can trust these findings to be anything other than false positives (Sullivan, 2007).

It is not only mandatory that the genotype-phenotype associations are confirmed by repeated independent replication; functional annotation studies should furthermore confirm that the genotype induces a functional effect on protein function, the level of its expression, or its posttranslational fate and, ideally, that manipulation of the genotype alters the phenotype. Animal studies are crucial for this type of in-depth research into the genetic mechanisms. In contrast to humans, all tissues are accessible and the shorter life expectancy of rodents provides further advantage when studying effects of exercise on aging processes and long-term health outcomes. Two models have been used in the

study of exercise genetics. First there is considerable variation in the amount and duration of spontaneous bouts of running in genetically well-characterized inbred strains of both rats and mice when given free access to a running wheel. Second, selective breeding for high wheel-running activity can greatly enhance existing within-strain genetic differences specifically related to exercise (Kelly et al., 2014; Rezende et al., 2009).

Two genes for exercise behavior (*Drd1*, regulating dopamine levels and *Nhlh2*, regulating β -endorphin levels) have survived experimental scrutiny using these animal models (Dawes et al., 2014), but at least three recent articles show that support for the rest of the handful of positional and theoretical candidate genes that have been identified so far has not been overwhelming. Dawes et al. (2014) investigated cross-strain genomic variation and gene expression differences between low-active C3H/HeJ and high-active C57L/J inbred mice in nine of the genes with reported direct or indirect association to physical activity: actinin 2 (*Actn2*), actinin 3 (*Actn3*), calsequestrin 1 (*Casq1*), dopamine receptor 2 (*Drd2*), leptin receptor (*Lepr*), melacortin 4 receptor (*Mcr4*), myostatin (*Mstn*), 3'-phosphoadenosine 5'-phosphosulfate 2 (*Papss2*) and glucose transporter 4 (*Glut4*). First, between-strain structural genomic differences were identified in the haplotypes of *Actn2*, *Casq1*, *Drd2*, *Lepr*, and *Papss2*, but all SNPs differing between low-active and high active mice were non-coding, not in promoter regions, and not linked to known miRNA targets. Next, gene expression was assessed in the nucleus accumbens as the most important brain structure involved in rewarding aspects of exercise, and the soleus muscle as the typical type-II fibre muscle employed in the endurance running discriminating these strains. As an important innovation they compare the strains not only in the typical free-access-to-wheel running setting, but also in a setting where wheel-running was disabled for both strains to avoid the confounding effects on gene expression of the wheel running itself. Augmented gene expression for *Casq1* and *Mstn* was seen in the high-active strain but only when they had free access to the wheel, suggesting that the expression was driven by the exercise itself rather than genetic variation underlying the innate drive to exercise. In the most pure comparison of the strains in the wheel-locked cages none of the ‘candidate genes’ were differentially expressed between inherently low- and high-active mice in soleus or nucleus accumbens.

Using their proteomics approach, Ferguson et al. (2014), could not confirm a dopaminergic contribution to the heritability of voluntary wheel running in the same low-/high-active strain contrast and experimental setup used by Dawes et al. (2014). They compared the global proteome signatures obtained from the nucleus accumbens of the C3H/HeJ and C57L/J inbred mice strains. There were only seven proteins differentially expressed between the strains (personal communication). Under housing conditions of equal wheel

running, mice bred for low wheel-running activity showed overexpression of four proteins related to neural stress, whereas mice bred for high wheel-running activity overexpressed proteins that impact on metabolism and have a neuroprotective effect. Again, proteins encoded by none of the previous suggested functional relevant or positional candidate genes were different between the strains. Also, in spite of the previously observed evidence that CB₁ receptors on VTA GABAergic terminals exert a permissive control on rodent voluntary running performance (Dubreucq et al., 2013) and the clearly differential wheel running response to dopaminergic-acting drugs in these inbred strains of mice (Knab et al., 2012) no strain differences were seen in the protein levels of the dopamine receptor 1 and endocannabinoid receptor 1. Specific Western blotting also did not reveal strain differences in the expression of the constituting *Drd1* and *Cr1* genes. In spite of the plausibility of the involvement of the dopaminergic and endocannabinoid pathways, the genetic differences between the low- versus high-active strains may not be primarily expressed in the most likely components of these pathways, that is, their receptors.

The idea that obvious dopaminergic candidate genes may not be involved in the heritability of voluntary exercise behavior was reinforced by Huppertz et al. (2014a) using a large human sample. A number of candidate alleles of VNTRs and SNPs in eight genes with a known function in the dopaminergic reward system were selected for their known effects on dopamine levels and dopamine transmission. Data on weekly metabolic equivalents of task (MET) spent on exercise activities and at least one SNP/VNTR were available for 8,768 Dutch individuals aged from 7 to 50 years. None of the genetic variants were associated with exercise behavior ($p > .02$), despite sufficient power to detect even small effects. Also combining all variants into a polygenic risk score did not yield a significant association of dopaminergic genetic variation to leisure time exercise behavior.

An overall conclusion of these candidate gene studies is that an a priori focus on pathways that are believed to be functionally relevant based on known biology may not serve us well. Instead an agnostic approach may be better. We support the plea of Huppertz et al. (2014a) for large genome-wide association (GWA) studies to help unravel the genetic pathways that affect this health-enhancing behavior. Although a part of the heritability estimated from twin studies remains missing, large-scale meta-analysis GWA studies have successfully identified a flurry of genetic variants for health behaviors such as smoking and alcohol intake and for disease risk factors like BMI, and glucose or disease outcomes like diabetes and schizophrenia (<http://www.genome.gov/GWAStudies/>). An international consortium that brings together cohorts with genome-wide SNP data and data on exercise and sedentary phenotypes is direly needed. That consortium should seek links to animal researchers early on to be able to rapidly annotate GWAS derived hits functionally with regard to transcrip-

tional expression, transcription regulation, proteomic, and transgenic follow-up studies. Fortunately, the perspective is very good. At least for voluntary exercise we have an excellent rodent model and, in general, physical (in)activity is a phenotype that can be assessed with high precision in many species, ranging from fruit fly to mammals. Thus a GWA+animal consortium would be in a good position to better understand the genetic determinants of sedentary and exercise behaviors.

Effects of Exercise That May Be Modulated By Genotype

Research into the determinants of exercise behavior and its role in healthy aging is an important item on the agenda of many governments and their health research funding agencies worldwide, of which the European Horizon 2020 program on ‘Health, demographic change and wellbeing’ is a good example (<http://ec.europa.eu/programmes/horizon2020/en/h2020-section/health-demographic-change-and-wellbeing>). The core assumption driving these programs is that increasing exercise behavior has some beneficial effects on all individuals, that is, that ‘Exercise = Medicine,’ a hypothesis to which we fully ascribe. However, it is now also clear that the extent of the beneficial effects of exercise will be very different between individuals and that genetic factors explain part of this individual response sensitivity. The best example is provided by the effects of exercise on exercise ability itself. Folk wisdom, sometimes unfortunately copied by scientists, holds that a person’s fitness level represents a good measure of that persons’ exercise behavior. However, the relationship between exercise capacity and total physical activity is low to moderate in both human and animal studies (Lightfoot, 2013). This relationship increases when it is made more specific; for instance, between regular vigorous activity and endurance capacity, or between regular strength training and strength phenotypes, or most specifically between sport-specific skills training and actual performance. Here, too, the relation is far from perfect and we predict that the cause is a large variation in ‘trainability’ that is in part caused by genetic variation. A clear demonstration of this gene-by-exercise interaction is provided by the HERITAGE study by Bouchard and colleagues (Bouchard, 2012; Bouchard & Rankinen, 2001). In over 200 families, both parents and two or more adult biological offspring were recruited, tested on multiple fitness traits, exercise-trained in the laboratory with the same program for 20 weeks, and retested on the same traits. This large-scale training study showed an astounding variation in the response to exercise. A heritability estimate of 47% was obtained for the training-induced increase in maximal oxygen consumption (VO₂max) during exhaustive exercise, that is, the trainability of aerobic fitness (Bouchard et al., 1999).

Genetic differences in trainability do not only apply to aerobic fitness. Pescatello et al. (2013) describe the main findings of the FAMuSS study, which set out to determine whether 500 selected candidate genes influenced baseline muscle size and strength in 1,300 young health men and women, as well as the increase in muscle size (MRI) and strength (maximal elbow flexor contraction) in response to a 12-week progressive unilateral resistance training program of the non-dominant arm with the dominant arm as a comparison. In keeping with similar findings for the effects of endurance training on VO_2max , very large individual differences in the training response were found, with changes in maximal voluntary biceps contraction ranging from a 25% decrease to a 145% increase in strength (paralleled by cross-sectional muscle area changes of -5% to $+55\%$). Over 15 genetic variants were found to be associated with basal strength or strength trainability, although sex-specific or ethnicity findings were common and the published papers focused on a few genes at a time. This means that full experiment-wise correction for multiple testing was not applied and some of the findings may be false positives — which does not detract from the value of this original pioneer study but instead should encourage replication studies. Because the FAMuSS study was ‘ahead of time,’ it used a candidate gene approach limited to Taqman based SNP typing. In hindsight, exome sequencing or a $> 1\text{M}$ SNP array would have provided a more valuable genetic resource.

In the Portuguese Health Family Study (FAMS), Santos et al. (2014) show that the genetic predisposition to fat accumulation is significantly modulated by the amount of daily physical activity. To demonstrate this gene \times physical activity interaction, they use two elegant and converging methods that use the contrast between within and between family variance in waist circumference, body and trunk fat percentages, and BMI. First, they test whether the heritability of these traits is different at low or high levels of energy expenditure. Second, exploiting an old idea of Falconer to test for gene \times environment interaction (Falconer, 1952), they test the genetic correlation between body composition traits at low or high daily energy expenditure. If this genetic correlation is not equal to one, different genes influence body composition at low versus high levels of energy expenditure. In contrast to most previous studies, Santos et al. (2014) found that genetic variance in all body composition traits increases with higher levels of daily energy expenditure. This is puzzling. Possibly, this may reflect the use of a detailed assessment of 3-day total daily energy expenditure rather than instruments geared more towards leisure time exercise behaviors. It may be expected that food consumption will increase in parallel with daily energy expenditure. In that case, their results may have partly detected a gene \times energy intake interaction. We have to concur with Santos et al. (2014) that there is a clear necessity to continue efforts to unravel the effects of the various physical activity

traits on the expression of genetic variance in body composition.

Alessio et al. (2014) used a rat model to test whether exercise modulates the normal aging of the heart muscle. They compare the whole genome gene expression profile as well as cardiac proteomics signature of rats aged 3 months and 16 months. They did so in rats housed in standard laboratory cages that traveled a daily distance of 161 meters a day and rats with free access to wheel running that traveled 10 (!) times this distance. Measurements were taken sufficiently long after the last exercise to reflect acute effects of last wheel running. There were ~ 230 genes differentially expressed at age 3 and age 16 months, mostly related to vascular function, homeostasis, oxidative stress and cholesterol. Surprisingly few ($n = 15$) genes that were part of the age-modulated gene expression profile showed a difference between sedentary and exercising rats. In general, at both ages no large differences were found in gene expression between sedentary and exercising rats. Much more evidence was found for an exercise effect on the proteomics signature. Levels for 103 proteins varied between the sedentary and exercising animals. Levels of proteins involved in binding, sugar metabolic processes and vascular regulation decreased more with age in sedentary rats. Levels increased with age in exercising rats for proteins involved in ATP metabolic processes and vascular function. The larger differences seen by proteomics compared to transcriptomics analysis may reflect miRNA interactions, post-translational modifications, and protein degradation or unpredicted protein-protein interactions. Although this is not the focus of this review, we note that these results question the ecological validity of transcriptomics and proteomics results obtained from rats housed in standard cages. Rats are innately motivated to exercise and restricting this drive has measurable biological effects, resulting in non-trivial increases in the risk for high blood cholesterol, high body weight, hypertension and tumor genesis (Alessio et al., 2009).

Ludlow et al. (2013) performed a systematic review of the studies on the effects of regular exercise behavior on telomere biology. Telomere length is a major marker of aging and telomere-driven senescent cells importantly contribute to the gradual loss of tissue regenerative capacity. In highly mitotic cells this process is counteracted by telomerase activity that in turn is regulated by the telomere-binding protein shelterin. Although results are not unanimous, the evidence clearly points to a telomere-protective effect of regular exercise. The mechanisms are far from straightforward. In skeletal muscle and immune cells, long-term high intensity exercise actually shortens average telomere length. This disadvantage is offset by upregulation of telomerase activity and changes in abundance of shelterin and DNA damage response and repair proteins. These teloprotective effects of telomerase and shelterin may specifically target the critically shortened telomeres. Interestingly, such effects again appear to be modulated by genotype (Ludlow et al., 2008).

Reflective of their own careful work in this area Ludlow et al. (2013) place clear caveats on the temporary conclusion that regular exercise slows cellular aging by reducing the rate of age-associated telomere shortening. Studies have been difficult to compare because of the different age ranges used and the methods of telomere length determination, which show substantial lab and sample preparation variation. Tissue specificity of the association between exercise and telomere biology has not sufficiently been delineated. Moreover, a practical problem in establishing causality is that telomere length changes very slowly (e.g., years) and controlled randomized exercise trials of this duration are not a feasible option. A potential alternative would be to use Mendelian randomization techniques (Lawlor et al., 2008) to test whether increased levels of regular exercise indeed could be causal for telomere biology. Telomere length and telomerase activity show heritable individual differences with heritability for telomere length estimated at 70% and for telomerase activity at 81% (Broer et al., 2013; Kosciolk & Rowley, 1998). Under a unidirectional causal model, the genetic variants leading to higher levels of regular exercise behavior should also be associated with longer telomeres (whereas the reverse need not be true).

Taken together, the papers reviewed above confirm that the effects of regular leisure time exercise may be strongly modulated by genotype. Perhaps even more than finding the genes causing individual differences in exercise and sedentary behaviors, identifying the genetic variants that cause genetic modulation of its effects on fitness and health traits may prove key to meaningful future intervention on these behaviors. In many instances, we may expect to find an overlap. The genetic variants that increase health benefits of exercise (e.g., strong gain in fitness, or large weight loss) may be exactly the ones that caused the individual to remain involved in regular exercise in the first place.

The Future Fate of Exercise and Sedentary Genes

A major recent change in the human environment is the abundant food availability. Already it is known that overfeeding reduces physical activity in multiple animal models and humans alike (Lightfoot, 2013). In fact, the association of high BMI and low daily energy expenditure may be only partly due to mechanical and social effects of overweight, but also reflect a direct effect of caloric intake on the activity drive. In a provocative essay, Lightfoot (2013) argues that the reverse is also true, that underfeeding was a major driver to select genotypes leading to an innate physical activity drive. As a titillating example, it is observed that the *GUCY1A2* gene, which is a foraging gene in drosophila and lies downstream of a physical activity related mouse QTL, may also be the cause of the hyperactivity seen in anorexia nervosa patients.

At an evolutionary scale this means that the direct link between caloric restriction and the need for prolonged physical activity, perhaps more so for farming societies than hunter/gatherers, has acted to increase the frequency of physical activity enhancing genetic variants. Being active meant being fed. However, this evolutionary model also suggests that genetic changes are afoot in societies with abundant food availability. Our current technology and the abundance of food have removed the need for the innate physical activity drive. As overweight and low physical activity in many modernized human societies have no, or only weak, negative effects on reproductive success, the pressure to stay fit and active is relaxed. Just as exercise does not produce benefits to the same extent in all genotypes, sedentary behavior may not exert detrimental effects to the same extent in all genotypes. Selection pressure may therefore shift to genotypes that protect against the early health-deterioration effects of an all-encompassing sedentariness.

Should scientists passively await the rise of *Homo sedentaris*? Or should they keep engaged in research on the genetics of regular exercise and sedentary behaviors? We gladly leave this to the wisdom of the readership, but also admit to a clear bias towards the latter.

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