



Are People Physically Inactive Because of Their Genes?

Introduction

To understand whether genes can influence physical activity, let's begin by making a distinction between *physical inactivity* and *level of physical activity*. Physical inactivity is a construct of great importance for a proper understanding of the relationships between behavior and risks for a number of diseases and even premature death. Indeed, a sedentary lifestyle, which is dominated by physical inactivity, has been recognized as a major risk factor for hypertension, coronary heart disease, stroke, type 2 diabetes, obesity and other conditions. The other important concept, level of physical activity, reflects the variation in activity from a small amount of light exercise performed occasionally to a large amount executed every day. Research has clearly shown that an active lifestyle, with even a moderate amount of physical activity almost every day, is quite beneficial in terms of prevention of cardiovascular events, type 2 diabetes and premature death.

Human variation in degree of physical inactivity or amount of physical activity in a typical day is quite large. For instance, physical inactivity is the way of life in quadraplegic individuals, is almost complete in people who are bedridden for some reasons or who have lost some of their mobility because of disease or senescence, and is pervasive in people who have a sedentary occupation. For instance, the amount of energy expended at rest in the reclining or sitting position is about 1500 kcal per day in a 165 lb young adult male, but energy expenditure for physical activity of any kind may range from as low as about 100 kcal (for a bedridden patient) to almost 3000 kcal or so for a couch potato, very sedentary individual. In contrast, the range of energy expenditure associated with physical activity is much larger for people who engage in voluntary regular exercise. Thus, a young male may typically expend a total of 400 to 500 kcal when he exercises for about 30 min at moderate intensity, while a professional cyclist with the same body mass competing in very demanding races (such as the Tour de France) may expend as many as 6,000 kcal per day.

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Even though this enormous range of physical activity level (and related energy expenditure) is best represented by a more or less normal distribution, it is useful for a number of purposes to categorize people in two activity phenotype groups: the physically inactive (or sedentary) group and the physically active group. It is also relevant for research and perhaps clinical purposes to use a third category, based on the distinction between those who are physically active and those who are engaging in very demanding exercise programs. However, for the purpose of this review and considering the dearth of data on the topic in general, we will focus only on the former: the physical inactivity and moderate level of physical activity phenotypes (as measured behavioral traits).

The fundamental question that we will address is whether human genetic variation contributes to the observation that there are individuals who are

reliably physically inactive and others who readily adopt and maintain a physically active lifestyle

Challenging the common dogma

Research on the determinants of a sedentary lifestyle or level of physical activity is typically rooted in paradigms that incorporate social factors, economic circumstances, time constraint, equipment and facilities, education level, etc. Despite the fact that it is never stated as such, the behaviorists engaged in this field of research assume by and large that biology has little to do with human variation in physical activity level or the adoption of a physically inactive lifestyle. To oversimplify, the underlying assumption is that individuals are born with a blank slate (to borrow from Steven Pinker's excellent book)¹, with an almost infinite ability to learn and adopt desirable behavior. For quite some time, we have expressed the view that these research paradigms needed to be broadened and enriched to include biological determinants, including genetic factors and epigenetic (see glossary) events as well. Unfortunately, the interest in the biological basis of physical activity does not have a long history as revealed by two recent papers published on the topic^{2,3}.

Several lines of evidence can be invoked to support the hypothesis that biology plays a role among the determinants of physical inactivity and physical activity levels.

- First, current models that do not incorporate biological influences account for only a moderate fraction of the variance in physical activity levels and do not discriminate fully between sedentary and physically active people.
- Second, most people who begin to exercise with the goal of becoming more physically active revert to a sedentary lifestyle. Low adherence rates diminish the public health value of regular physical activity and the preventive and therapeutic potential of regular exercise.
- Third, there are family lines with high rates of sedentary behavior as opposed to others in which all members are quite active as shown by a whole series of twin and family studies.
- Fourth, the heritability coefficients (quantitative indicators of the contribution of genetic

inheritance to human variation in a trait) for physical activity level and sedentarism are statistically significant and meaningful from a behavioral perspective.

- Fifth, the genome-wide screening studies in animal models and in one human study have identified several regions on chromosomes that appear to harbor genes and DNA sequence variants that contribute to variation in activity levels among individuals.
- Sixth, a few genes exhibiting DNA sequence differences among people have already been associated with human variation in activity level or physical inactivity.
- Seventh, there is highly suggestive evidence from animal studies that maternal nutritional status and other in utero or perinatal factors cause alterations (epigenetic events) in the levels of gene expression without altering DNA sequence, thus setting the stage for stable changes in physiology.

Reviewing the evidence for these seven lines of evidence is beyond the scope of this brief statement. However, we will highlight what we believe are the important findings and key relevant studies in the following paragraphs with an emphasis on the genetic and epigenetic aspects of the central question.

Evidence from twin studies

Much can be learned from observations made in pairs of identical (monozygotic) and fraternal (dizygotic) twins. Quite informative are the studies in which such observations were made on twin brothers or sisters who were separated for a variety of reasons early in life and who have lived apart ever since. Unfortunately no such studies have been reported for physical inactivity or level of physical activity. On the other hand, more than a dozen studies have been conducted with pairs of twin raised together and the findings from these studies have been reviewed elsewhere⁴. To illustrate the major findings from these twin observational studies, we will rely on the one performed with the largest sample size.

In a large cohort of monozygotic and dizygotic male twin pairs over 18 years of age from the Finnish Twin Registry, information on intensity and duration of activity, years of participation in a given activity,

and physical activity on the job was obtained from a questionnaire⁵. A physical activity score was generated from these variables, which was then used to compute correlations within pairs of brothers of each twin type. The correlation for the physical activity score reached 0.57 in 1,537 pairs of monozygotic twins and 0.26 in 3,507 pairs of dizygotic twins. The results indicated that heritability accounted for 62% of the physical activity score. Other twin studies have generated higher heritability estimates for indicators of physical activity levels but many more have yielded heritability values in the 40% to 50% range.

Evidence from family studies

Physical activity levels and patterns in children and their parents tend to be similar. A good number of studies have been reported on the relationships between the level of physical activity and a few on the level of sedentarism in parents and their offspring. Only a few examples will be mentioned here.

Detailed analyses of the questionnaire on physical activity habits available on 18,073 individuals living in households from the 1981 Canada Fitness Survey⁶ and from a 3-day diary obtained in 1610 subjects from 375 families in Phase 1 of the Québec Family Study generated familial correlations that ranged from 0.2 to 0.3 for various⁷ indicators of physical activity. More recently, it was reported that maximal heritabilities reached 25% for an indicator of physical inactivity and 19% for a total physical activity score⁸.

In an interesting study, 100 children, aged 4 to 7 years, and 99 mothers and 92 fathers from the Framingham Children's Study⁹ were monitored with an accelerometer for about 10 hours per day for more than one week in children and parents over the course of one year. Active fathers were 3.5 times more likely to have active offspring and active mothers were 2.0 times more likely to have active offspring than inactive fathers or mothers, respectively. When both parents were active, the children were 5.8 times more likely to be active as children of two inactive parents. These results are thus compatible with the notion that genetic or other factors transmitted across generations predispose a child to be active or inactive.

Evidence from animal models

Experimental studies in informative animal models provide several examples of how naturally occurring DNA mutations and laboratory-induced changes in key genes may affect physical activity levels and patterns. For example, mice lacking the dopamine transporter gene exhibit marked hyperactivity¹⁰, whereas dopamine receptor D2-deficient mice are characterized by reduced physical activity levels¹¹. Likewise, disruption of genes within the melanin-concentrating hormone pathway leads to hyperactivity^{12, 13}.

An intriguing example of the strong effect of a mutation in a single gene on physical activity regulation comes from the fruit fly. In two populations of flies, each exhibiting a distinct activity pattern in term of food-search behavior, those defined as *rovers* move about twice the distance while feeding compared to those qualified as *sitters*. This activity pattern is genetically determined and is regulated by a single gene, *dg2*, which encodes a cGMP-dependent protein kinase. The activity of this gene product is significantly higher in wild-type rovers than in wild type and mutant sitters, and activation of this gene reverts foraging behavior from the sitter to rover phenotype. Furthermore, overexpression of the gene in sitters changed their behavior and made them behave more like rovers¹⁴.

Evidence from genome-wide explorations

The only genome-wide linkage scan for physical activity traits available to date was carried out in the Québec Family Study cohort¹⁵. The scan was based on 432 DNA markers across the human genome (except the sex chromosomes) that were genotyped in 767 subjects from 207 families. Physical activity measures were derived from a 3-day activity diary which yielded three traits of interest: total daily activity, inactivity, moderate to strenuous activity, and from a questionnaire used to assess weekly physical activity during the past year. The strongest evidence for the presence of a gene influencing physical inactivity scores was detected on chromosome 2. Suggestive linkages with physical inactivity were also reported with markers on chromosomes 7 and 20. Several regions of the genome were linked with indicators of physical

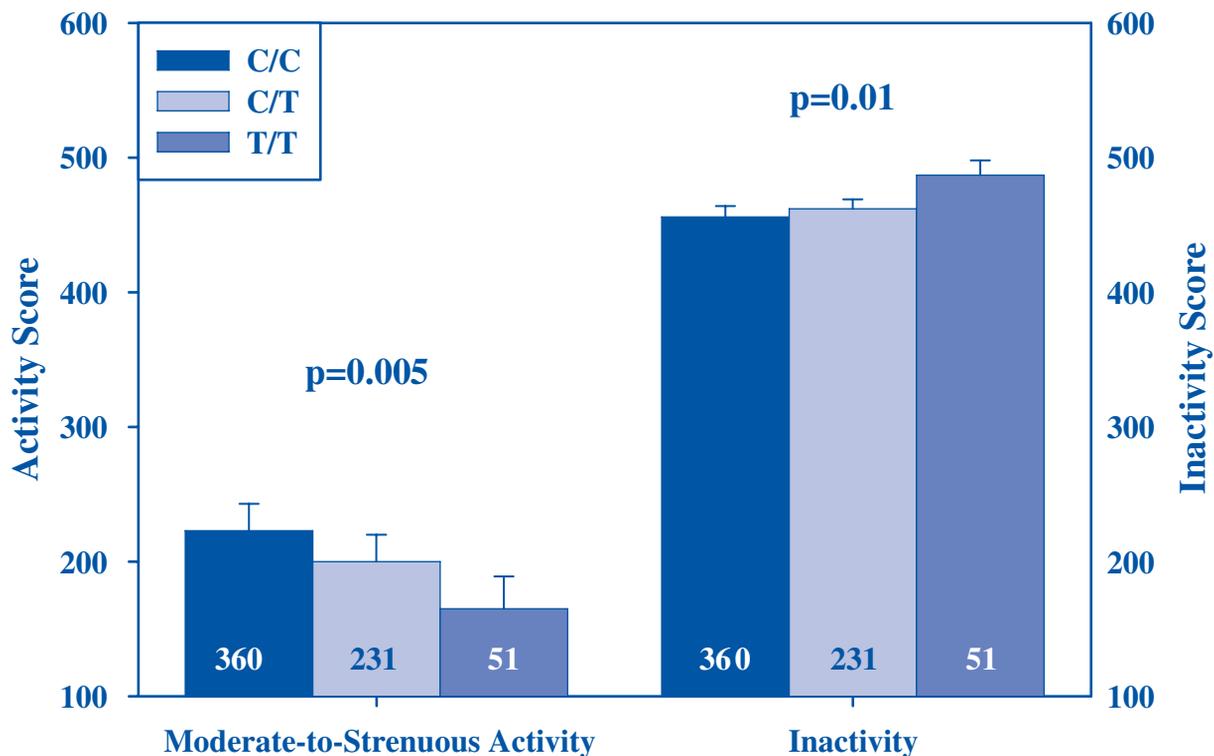


Figure 1

Moderate-to-strenuous physical activity and physical inactivity levels according to a melanocortin 4 receptor (MC4R) genotype in the Quebec Family Study cohort. The MC4R polymorphism involves two alleles, C and T, generating three genotypes: C/C, C/T, or T/T. Based on data from Loos et al.,¹⁶.

activity, including regions on chromosomes 4, 9, 11, 13 and 15.

Evidence for a role of specific genes

Up till now, only a few genes have been specifically associated with physical inactivity or physical activity traits in human studies focusing on this specific issue. These genes are the following: dopamine receptor D2 (*DRD2*), angiotensin-converting enzyme (*ACE*), leptin receptor (*LEPR*), and melanocortin 4 receptor (*MC4R*).

The associations between physical activity phenotypes and DNA sequence variation in the *DRD2* gene locus in the Québec Family Study (QFS) and the HERITAGE Family Study subjects were investigated¹⁵. In both studies, a change of cytosine to thymidine (C/T) in codon 313 of the gene was associated with physical activity levels in White

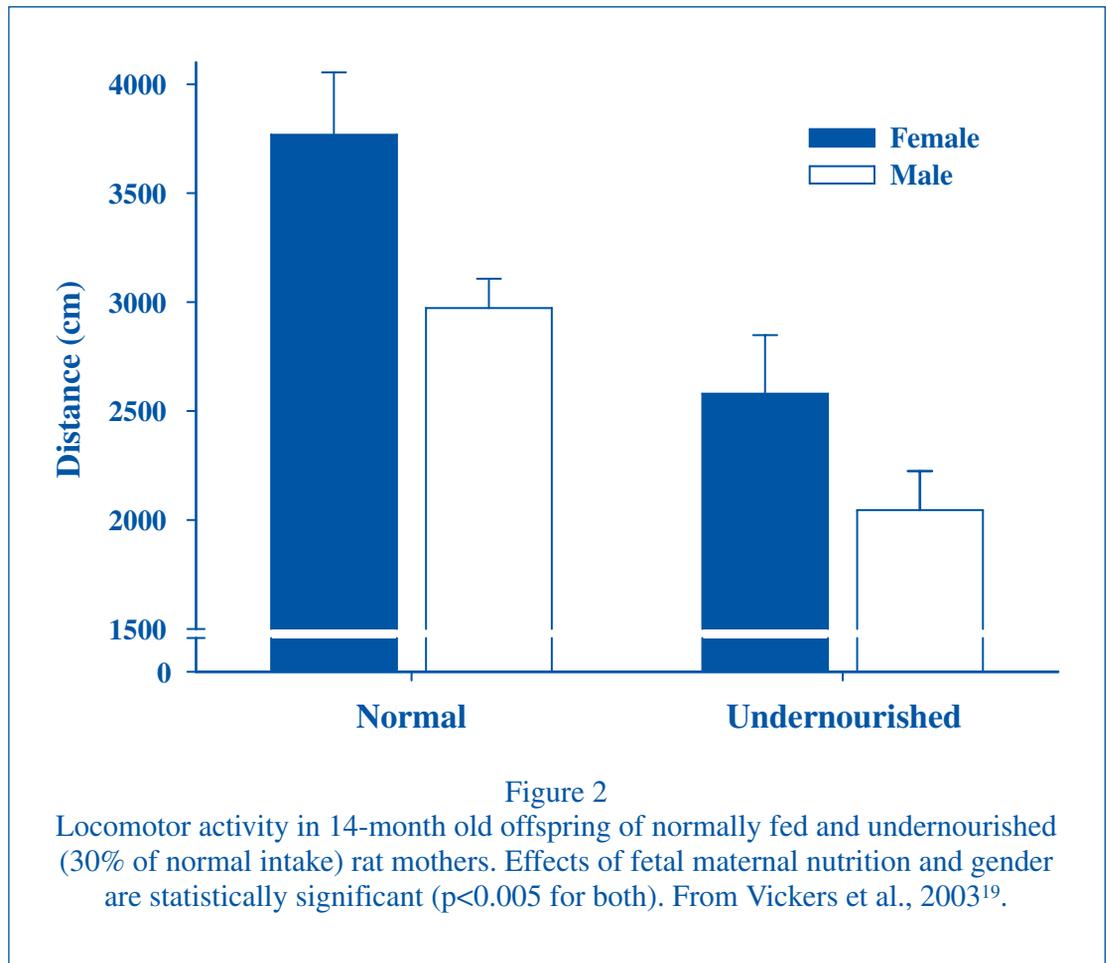
women. The QFS women with two copies of the thymidine (T) allele (the “T” form of the gene on both chromosomes) reported less weekly activity during the previous year than women with only one copy (C/T heterozygotes) or no copies (C/C homozygotes) of the “T” allele. Similarly, among the White women of the HERITAGE Family Study, the T/T homozygotes showed lower sports and work indices derived from a questionnaire than the other genotypes. Also in the QFS cohort, significant associations between a polymorphism located adjacent to the *MC4R* gene and physical activity phenotypes were reported¹⁶, with one set of homozygotes having significantly lower moderate-to-strenuous physical activity levels and higher inactivity scores than the other genotypes (Figure 1). In Pima Indians, a common glutamine (Gln) to arginine (Arg) change of amino acid 223 in the leptin receptor gene was associated with total physical

activity, with the Arg/Arg homozygotes showing 5% lower physical activity level than the Gln/Gln homozygotes¹⁷. Winnicki et al. investigated the determinants of habitual physical activity level in a group of never-treated stage I hypertensive individuals¹⁸. Physical activity was assessed by a questionnaire; the subjects were classified as sedentary or exercisers (leisure or sports activities at least once a week during the previous two months). *ACE* genotype, age, sex,

marital status, profession, and coffee and alcohol consumption were included as predictors of physical activity level in the regression model. *ACE* genotype and marital status were the strongest contributors to physical activity status, with the frequency of one gene variant being significantly higher in the sedentary group. Approximately 76% of individuals in the homozygotes for one allele were sedentary, whereas the corresponding frequency was 48% in the other homozygotic group¹⁸.

Are there epigenetic effects?

In recent years, a growing body of evidence has emphasized that DNA sequence variation is extremely important in accounting for individual differences in behavior, physiology and response to drugs or lifestyle interventions. More recently, another and very significant line of evidence indicates that chemical modification of DNA and histone proteins could translate in non-genetic phenotypic differences that often remarkably mimic



those associated with DNA sequence variants. These DNA and nucleoprotein alterations have been collectively referred to as “epigenetic events.” They begin to occur early after fertilization, are thought to take place in utero and even throughout the lifespan, are typically stable, and influence gene expression. Is there any evidence for a contribution of epigenetics to human variation in physical activity levels or physical inactivity?

No direct evidence exists for a contribution of any epigenetic alterations to physical activity level for the simple reason that the issue has not been considered yet. However, there are experimental data which are highly compatible with the hypothesis that epigenetics can influence the spontaneous level of physical activity. For instance, in one such experiment, performed in a leading New Zealand laboratory, maternal undernutrition throughout pregnancy resulted in differences in postnatal locomotor behavior¹⁹. Female Wistar rats received

only 30% of the ad libitum intake of the control females during pregnancy. The offspring of restricted mothers were significantly smaller at birth. At ages 35 days, 145 days and 420 days, the voluntary locomotor activity of the offspring of the two groups were assessed. At all ages, the offspring of the undernourished mothers were significantly less active, and the findings are illustrated in Figure 2 for the 420 days time point. These results suggested that the effects of undernutrition during pregnancy persisted during postnatal life. This effect persisted even when offspring were overnourished during postnatal life. One possible mechanism for such an effect of maternal undernutrition is via alterations in either the level of production or the sensitivity to endogenous hormones or other secreted factors during pregnancy. It is not unreasonable to hypothesize that chemical modifications superimposed on the DNA, without altering its sequence, could have played a role in the lower spontaneous physical activity level and its persistence throughout the life of the animal exposed to severe undernutrition during fetal life.

Other lines of research suggest that high-fat diets, protein restriction and other maternal dietary manipulations before and during pregnancy also have considerable consequences on the physiology and behavior of the offspring. The implications of fetal life exposures and epigenetic events on the propensity to be sedentary or physically active remain to be understood.

Summary

Research indicates that the inclination to be physically active or sedentary has a biological foundation. Twin and family studies confirm that

physical activity-related traits are characterized by familial aggregation and influenced by genetic factors. Results from animal model studies indicate that single genes can markedly influence physical activity-related behavior.

The first molecular genetic studies on physical activity traits in humans have been published during the last few years. They support the notion that it is possible to detect relatively small, yet biologically important genetic effects impacting the tendency to be sedentary or physically active at the molecular level. We are beginning to appreciate that the in utero environment and epigenetic events may play a role in postnatal physiology and behavior, but their impact on physical inactivity or physical activity level remains to be determined.

Glossary

Phenotype: It is simply a measured trait. The measured value or level of a particular character (biochemical, physiological or behavioral, e.g., physical activity level).

Genotype: The genetic constitution of an individual at the whole genome level or at a specific locus.

Allele: One of several alternative forms of a gene or DNA sequence at a specific chromosomal location (locus). At each autosomal (non-sex chromosomes) locus an individual possesses two alleles, one inherited from the father and one from the mother, and they may be the same or different.

Epigenetic: Chemical modifications superimposed on the DNA sequence. It does not change the genotype but it may influence gene expression in a stable way.

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