

James M. Hagberg

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Exercise genes? And no, not Levi's 501s!

James M. Hagberg

Department of Kinesiology, School of Public Health, University of Maryland, College Park, Maryland

GENETIC STUDIES have generally focused on clinical or pathological phenotypes, such as obesity and diabetes. Now accumulating evidence indicates that our behaviors also have a strong genetic basis! The data presented by Lightfoot et al. in this issue of the *Journal of Applied Physiology* (6a) strengthen the belief that physical activity (PA) as a behavior has a genetic basis.

The first report of a genetic effect on behavior appears to be in 1975 in the classic genetic model *Drosophila melanogaster* (fruit flies), where different walking behaviors were found to have heritability of 7–26% (2). A 1985 study in Norwegian twins reported that the behavior of smoking was highly heritable (9). And in a 1988 Australian twin study, smoking, PA, alcohol intake, and dietary habits were all more closely related in monozygous than dizygous twins (5), indicating a potential genetic basis.

Additional early evidence of the heritability of PA levels came in 1989 from Perusse and colleagues (10), who reported that PA levels had heritability of 29% in the Quebec Family Study. A 2006 study in ~37,000 twin pairs from 7 European Union countries reported 62% heritability for achieving >60 min/wk of moderate-intensity exercise (12). Similar heritability for wheel running activity in mice has been reported previously (7).

Now that it is clear that PA as a behavior is heritable, what specific genes underlie this relationship? The first genomewide linkage study for PA levels, in 2003 (11), typed 432 markers across the genome in the Quebec Family Study and found 8 chromosomal loci (2p22–p16, 20q13.1, 4q28.2, 9q31.1, 11p15, 15q13.3, with 7p11.2 and 13q22–q31 being linked to 2 PA phenotypes) that had either promising or suggestive linkage with various PA and inactivity indexes. In 2006 Cai and colleagues (1) reported that chromosomal locus 18q was linked to PA and inactivity indexes and dietary intake in Hispanic siblings. De Moor and colleagues (4) then found that locus 19p13.3 was linked to achieving >60 min/wk of PA in a large Dutch twin study, with the relationship being stronger in women. They followed this up by typing ~1.6 million single nucleotide polymorphisms (SNPs) in ~2,600 adults and reported that significant associations were evident for 37 SNPs in the 3'-phosphoadenosine 5'-phosphosulfate synthase (PAPSS2) gene (10q23–q24) and in two intergenic regions at 2q33.1 and 18p11.32 (3). However, they also found no evidence for replication of 6 loci previously associated and 12 loci previously linked with habitual PA levels, including the 19p13.3 locus they previously identified.

A number of studies in mice have also identified chromosomal loci linked or associated with voluntary wheel running. One important fact to keep in mind is the incredible level of voluntary activity in mice, where the average distance run/day

in the present study is 5.5 kilometers! Clearly an incredible feat for such a diminutive species! Such distances covered daily by us much larger humans would probably “cure” most of the epidemic diseases facing the world, including obesity and type 2 diabetes. Also important is the fact that across the 38 strains of mice the range of running distances/day amounted to a ~27-fold difference, from 0.4 to 11 km/day!

In 2008 Lightfoot and colleagues (8) assessed quantitative trait loci (QTL) in two mice strains that differed in voluntary wheel running by approximately threefold. They found one significant and three suggestive QTL for duration, one significant and four suggestive QTL for distance, and two significant and six suggestive QTL for running speed. Their most striking result was that a fairly small region of chromosome 13 was significantly associated with all three running phenotypes! A 2010 study by Kelly et al. (6) identified 32 significant and 13 suggestive QTL associated with wheel running in a reciprocal cross of mice with genetic propensity for increased exercise and another inbred mouse strain.

The present virtual “tour de force” study assessed haplotype associations between ~8.2 million SNPs and 3 wheel running phenotypes in 448 mice across 38 strains (6a). They identified three QTL significantly linked to running distance in the entire population, another four significant only in males, and another two significant only in females. They found only one QTL associated with running duration, and it was only present in females. No QTL were linked with running speed. However, they did not replicate their previous findings of three significant running phenotype linkages on chromosome 13!

So where does all this information about chromosomal loci and QTL for PA as a behavior in animals and humans lead us? I would contend—still very confused!!! But clearly, voluntary PA as a behavior is heritable, and the good news is that a substantial number of chromosomal loci and genes have been reported to be linked to it. However, the bad news is that there is no replication of these loci, even within the same model (mice, human) and the same laboratory.

This lack of replication and the identification of numerous putative “exercise” genes should not surprise us. After all, the same lack of replication has been evident for such widely studied phenotypes as obesity and type 2 diabetes, and these studies also have identified a wide range of putative candidate genes. The data on PA genes combined with those from the search for obesity and diabetes genes do tell one very clear story—that laboratory animals and we as humans are highly complex, and this complexity extends to the genetic basis for our behaviors. It is also important to keep in mind that this complexity is most likely what has kept the human race alive and evolving over the course of our history. If we had not been this complex, we probably would have become extinct by now!

So what do these results relating to the genetics of exercise behavior mean for us in the here and now? What if, and this is a very big “if” based on what we know at present, in the future a genetic screen for voluntary exercise participation is developed? With that information, one could divide a population

Address for reprint requests and other correspondence: J. Hagberg, Dept. of Kinesiology, School of Public Health, Univ. of Maryland, College Park, MD 20742-2611 (e-mail: hagberg@umd.edu).

into four groups as a function of those with and without the “exercise genes” and those who currently are or are not exercising. Clearly, those already active individuals who carry the “exercise genes” would need the least ongoing effort for them maintain their exercise habits on a long-term basis. On the other hand, those active individuals not carrying the “exercise genes” may need additional personal, social, and medical support for them to maintain their activity habits.

What then might be done for those individuals who are currently not exercising? Clearly, we would expect some small proportion of even these individuals to carry the “exercise genes,” as these are susceptibility and not deterministic genes, and this information could help motivate them to begin and maintain a PA program to optimize their future health. So what about those sedentary individuals who do not carry the “exercise genes”? Hopefully this information will not provide them with simply another reason not to exercise, because “it just isn’t in my genes”! What may be needed is an alternative starting point to Bandura’s Five Stages of Change behavioral model—where the individual receives some level of “genetic counseling” to indicate that these are only susceptibility, and not deterministic Mendelian, genes. Perhaps such an alternative initial step for these individuals will help them progress more rapidly from the precontemplative to the action stages for a regular PA program that will also optimize their future health.

DISCLOSURES

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