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Driven to Be Inactive?—The Genetics of Physical Activity

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Abstract

The health implications of physical inactivity, including its integral role in promoting obesity, are well known and have been well documented. Physical activity is a multifactorial behavior with various factors playing a role in determining individual physical activity levels. Research using both human and animal models in the past several years has clearly indicated that genetics is associated with physical activity. Furthermore, researchers have identified several significant and suggestive genomic quantitative trait loci associated with physical activity. To date, the identities of the causal genes underlying physical activity regulation are unclear, with few strong candidate genes. The current research provides a foundation from which future confirmatory research can be launched as well as determination of the mechanisms through which the genetic factors act. The application of this knowledge could significantly augment the information available for physical activity behavior change interventions resulting in more efficient programs for those predisposed to be inactive.

I. Introduction

Research has convincingly demonstrated the benefits of physical activity on health and disease.[1] Despite this evidence, the prevalence of physical activity is continuing to decline with directly measured data suggesting that less than 5% of adults engage in moderate activity on a regular basis.[2] Researchers recognize that physical inactivity is a risk factor for many health outcomes such as cardiovascular disease, diabetes, some forms of cancer, and obesity.[3] For example, the population attributable risk increases significantly for several chronic diseases such as stroke (24.3%), hypertension (13.8%), and Type 2 diabetes (21.1%), due to physical inactivity and the risk for hypertension (34%), and Type 2 diabetes (28.6%) increases even more due to obesity.[4] Consequently, physical inactivity has been held responsible for approximately two million deaths per year worldwide[5] and is defined as an actual cause of chronic diseases by the Centers for Disease Control and Prevention.[6] The percentage of the total population of the United States that is physically inactive[2] far exceeds the percentage of those who smoke (19.7%), are hypertensive (27.5%), or have elevated total cholesterol (37.5%).[7] Therefore, the investigation of the causes and mechanisms of physical inactivity should be considered an area of critical importance for our national health policy[6] especially in regards to the prevention and treatment of obesity.

Physical activity can be defined as any daily movement of the body and exists on a continuum ranging from frank inactivity to constant movement. Physical activity can consist of numerous types of activity such as household chores, occupational tasks, leisure activity, sports, and care-giving duties. While the preponderance of research has focused on determining the demographic, social, psychological, and environmental factors affecting physical activity, a growing body of literature using both human and animal models has demonstrated significant genetic influence on physical activity.[8–13] Given that genetic factors are often an important determinant in limiting the response and rate of response to a physiological stressor, it would be advantageous to determine the genetic influences on physical activity so that this knowledge can be used to limit or augment the role of genetic factors on activity.

II. The Heritability of Physical Activity

Heritability is the influence of genetic factors on the variance of any phenotype between individuals;[14] in our case, we are interested in the mechanisms of how genetic factors influence physical activity. However, first, it is important to determine whether genetics actually play a role. Estimates of the magnitude of the heritable influence on any phenotype is expressed as values that range from zero to one (or 0–100%) with a value of zero indicating no influence of heredity with mainly environmental effects influencing that trait[15] and a value of one indicating that all individual variance in the characteristic of interest arose from genetic factors.[16] These heritability estimates are usually derived from either broad-sense and/or narrow-sense heritability equations. Narrow-sense heritability estimates the amount of phenotypic variation in physical activity that is transmitted from parent to child and since just parental transmission is involved, the estimates of narrow-sense heritability are thought to include only additive genetic effects and are lower (i.e., more conservative) than other measures of heritability.[17] Narrow-sense heritabilities are often calculated using offspring–parent regression. Conversely, the contribution of all genetic factors to the phenotypic variation in physical activity is considered broad-sense heritability. Because all genetic factors are considered, including additive and dominant effects, this estimate is higher than narrow-sense heritabilities and thus considered a more liberal estimation of heritability.[17–19]

Research designs that have investigated physical activity heritability have fallen into two general camps: those using human subjects and those using animal models. Within the human subjects' side of the literature, both family resemblance models and twin studies have been used. Determining familial resemblance in physical activity is an approach that primarily uses human families and examines the variance in activity amongst parents and children. One of the earliest family studies of physical activity was the Quebec Family Study in 300 families.[20] In this study, the investigators determined that genetic factors explained 20–29% of the familial resemblance in habitual physical activity as measured with 3-day activity survey data. In a second phase of this study, physical activity was assessed using 3-day activity diaries and a 1-year recall questionnaire in 200 families.[21] In this phase, heritability estimates were lower (16–25%) and were explained more completely by a combination of common environment and genetic factors. Interestingly, the inactivity phenotype, based on a lack of activity reported in the subjects' activity diaries, had a slightly

higher heritability level than past and current physical activity levels. A further extension of the family resemblance design was a study by Sallis and coworkers that examined physical activity in 95 Anglo families and 111 Mexican-American families from the San Diego Family Health Project using a 7-day recall questionnaire. They found moderate correlations (0.25–0.55) of familial aggregation for kilocalories expended per day and 0.20–0.35 correlations for vigorous leisure physical activity.[22]

Similar to the values reported by Simonen *et al*.,[21] heritability estimates from the Southwest Ohio Family Study[23] were 0.17–0.26 for sport and leisure physical activity across 521 relatives. Activity in this study was measured by the Baecke Questionnaire of Habitual Physical Activity. Supporting the general trend toward more modest heritability estimates, the Canada Fitness Survey observed low familial correlations (0.08–0.38) for physical activity level in 13,804 individuals.[24] Exhibiting an even lower heritability of activity, a study of 1364 Mexican-Americans family members did not demonstrate a significant familial effect (9%) on physical activity levels as determined by a 7-day recall questionnaire.[25] Interestingly, while all of the family studies that have used indirect means to estimate activity have reported lower estimations of activity heritability, the Viva la Familia Study that used accelerometers to measure activity in 631 Hispanic parents and 1030 of their children found generally higher ranges of heritability (0.32–0.60) for physical activity.[26] Similarly, in the Framingham Children's Study, Moore *et al*.[27] found that when using the Caltrac accelerometer to measure physical activity in 100 children and parents, the children were 5.8 times likely to be active if both parents were active. Thus, the majority of the family resemblance studies have shown activity heritability estimates in the range of 0.25. Future family studies of activity heritability should follow the lead of Butte *et al*.[26] and Moore *et al*.[27] and employ methods that give a more direct estimation of daily activity to eliminate this potential source of deflation in the heritability estimates.

Monozygous twins are genetically identical and therefore phenotypic differences between pairs are assumed to be due to environmental factors and/or measurement error.[28] Dizygous pairs are approximately 50% genetically identical and thus, in conjunction with monozygous twins, can further illuminate the contribution of common versus unique environmental factors on physical activity.

One of the first twin studies to consider physical activity using a twin design was a Finnish study that measured physical activity from recall.[29] One thousand five hundred and thirty-seven monozygotic (MZ) and 3507 dizygotic (DZ) male twin pairs were asked the amount, intensity, and duration of current physical activity and the number of years of activity in adult life. Intraclass correlations were 0.57 for MZ twins and 0.26 for DZ twins, with an overall age adjusted of 0.62 and a common environmental effect of zero.[29] While not stated, these results suggested a 38% contribution of unique environmental effects and/or measurement error. These heritability estimates are naturally higher than the majority of those seen in the family studies due to the use of the more liberal broad-sense heritability statistics. However, several years later, as a continuation from the Finnish study using a cohort of the male MZ twins, familial aggregation still accounted for a large portion (43%) of exercise participation in adulthood suggesting that childhood influences might have affected these subjects' physical activity through their lifespan.[30] Other extensive twin

studies since Kaprio *et al*.'s[29] study have also reported higher levels of heritability than seen in the family studies. For example, a twin study of over 3000 male MZ and DZ pairs from the Vietnam Era Twin Registry assessed physical activity levels using questionnaires and determined that there was genetic influence in physical activity levels since the MZ pairs had higher correlations than the DZ pairs.[11] Specifically, the activity questionnaires regarding intense physical activity resulted in heritability estimates of 39–58%, with the activity index of "running at least 10 miles per week" having a significant genetic component (53%). The heritability estimates resulting from the moderate exercise portion of the questionnaire were generally lower, but all were significant, with a 38% heritability estimate for the overall index of moderate activity.

The largest twin study to date examined exercise participation survey responses from 13,676 MZ and 23,375 DZ pairs 19–40 years old, from seven different countries (total n = 85,198).[31] This study found that heritability for leisure-time exercise participation of at least 60 min per week ranged from 27% to 71% depending on the nationality and sex of the subject.[31] Males in Norway had the lowest activity heritability (27%) whereas females in the United Kingdom (UK) had the highest heritability (71%). The median exercise participation heritability for all countries adjusted for sex was 62%. However, a study of 1003 MZ and 386 DZ twins comparing a higher threshold (150 min per week) to a lower threshold (60 min per week) of exercise participation found that unique environmental and genetic factors accounted for 55% and 45%, respectively, of the variance for the lower threshold.[32] The higher threshold (150 min) had 72% and 28% of the variance accounted for by unique and common environmental factors, respectively, suggesting that genetic influence on exercise might be dependent on duration. Therefore, while both genetics and unique environmental factors appear to contribute significantly to exercise participation, common environmental factors may have a stronger influence on higher duration of activity.

There has been ambiguity in the literature regarding whether there is differential heritability of activity in males and females. With a sizable cohort (over 5000 MZ and 8000 DZ male and female twins), the Swedish Twin Study reported significant genetic heritability of physical activity levels using a question about leisure-time activity over the past year. Heritability of physical activity levels between the sexes was similar, being reported as 57% for males and 50% for females, while the unique environmental factors accounted for 40% in males and 44% in females and influence of common environmental factors ranged between 3% and 6%.[33] In contrast, in a study of over 400 Portuguese twin pairs, 12–25 years old, researchers demonstrated that males had a higher genetic influence for leisure-time physical activity assessed by a questionnaire than females (63% vs. 32%).[34] The male pairs had no significant common environmental influence and 37% arose from unique environmental factors. However, females, while exhibiting similar unique environmental influences as males (30%), showed a significant common environmental influence on activity (38%). The finding of differential heritability of activity was originally suggested by Boomsma *et al*.[35] when they examined sports participation by a single question in a group 44 MZ and 46 DZ Dutch twins aged 14–20 years.[35] They found that heritability was 77% for the males and 35% for females, which is consistent with Maia and colleagues' estimates.[34] Supporting the lack of common environment influence in male twins were

findings from the Leuven Longitudinal Study on over 180 Flemish 15-year-old male and female twins.[36] Using a single question survey, variation in sports participation in males was explained 83% by genetic factors and 17% by common environmental factors. However, in females, genetic factors explained 44% and environmental factors explained 54% of the variance for sport participation. Only a small percentage (2%) of the variation was explained by unique environmental factors. Thus, in a large number of twin studies, there are reported higher levels of activity heritability with a lack of consensus regarding differential heritability in males versus females.

Interestingly, there is early evidence that the potential difference in male and female heritability of activity may be more complex and involve environmental factors. In a three-generation study, physical activity patterns showed no association between twins, their parents, and their grandparents, as assessed by questionnaires.[37] While there were no generational associations in activity level, there were strong correlations in MZ boys (0.72) and MZ girls (0.64) in activity levels. Thus, the authors suggested that the lack of association between intergenerational physical activities might be due to social changes over time and not necessarily due to the transmission of genetic factors. Furthermore, a twin study of 62 MZ and 38 DZ pairs aged 4–10 years found that additive genetic factors did not explain any variance in physical activity level or physical activity energy expenditure after adjustment for body weight, indicating that body weight was actually the factor genetically controlled and not activity.[38] Both Aarnio *et al*.[37] and Franks *et al*.[38] results may be partially explained by Stubbe *et al*.'s[13] findings that before the age of 18, genetics played virtually no part in determining physical activity, but rather activity levels were due primarily to common environmental influence.

Much like the family resemblance studies, the majority of the twin studies have used indirect estimations of physical activity, usually very-short activity recall surveys. Recall surveys of physical activity are well known to grossly overestimate actual physical activity levels,[39] and thus, because the phenotype is inaccurate, it is probable that the heritability estimates may also be inaccurate. Therefore, direct measures of activity are important to integrate in twin studies. However, the use of direct measures necessarily decreases the number of human subjects that can be tested. Thus, researchers have to determine whether the error controlled with directly measuring physical activity outweighs the lower statistical power associated with the necessarily more limited sample sizes that arise from directly measuring activity. An elegant example of these issues and the resulting effect on activity heritability estimates is the study by Joosen *et al*.,[28] where physical activity was measured by accelerometry and energy expenditure was measured using doubly labeled water in both a respiration chamber and free-living conditions. In this study, genetic factors accounted for 72% and 78% of the variance in activity-induced energy expenditure and physical activity, respectively, during free-living conditions in 12 MZ and 8 DZ twins. Broad-sense estimates of heritability of activity in the free-living conditions suggested that 92% of the individual variance in activity was explained by genetics. While these estimates were generally higher than those seen using survey methods, the very low number of subjects (20 twin pairs) used for these heritability estimates makes them suspect. Further twin studies where activity is

measured using direct methods are required to resolve the wide range of heritability estimates present in the literature.

It is clear that human studies using family and twin models have confirmed that there is a genetic component to physical activity. However, there are large inconsistencies in the reported magnitude of the association between heritability and activity. While it is possible that the range of genetic heritability of activity will actually vary significantly due to individual differential genetic regulation, we also cannot dismiss the possibility that the large range is due to inconsistencies and measurement error associated with the various phenotypes and measurements of physical activity. Additionally, the requirement for literally thousands of subjects to provide sufficient statistical power is also responsible for the confusion found in the published literature on this topic. Thus, to control for some of these limitations, other researchers have turned to animal models to consider the heritability of activity.

Animal models can be a practical resource to measure heritability of voluntary physical activity, since most environmental conditions can be standardized. Additionally, the use of inbred and selectively bred mice provides the ability to measure genetic variability in large cohorts that have homozygous genomes and using breeding schemes, researchers can introduce “controlled heterozygosity” of the genome with the ability to determine from which parent arose particular genomic regions and genes. Additionally, with the shorter lifespans of many animals, and in particular rodents, extensive breeding designs and lifespan-length measures can be used. Furthermore, measures of physical activity are generally easy to conduct and robust; wheel running activity, which has been claimed as the best analogue of human voluntary activity,[40] has been used since the early 1920s providing a deep and rich literature base.

One of the earliest studies of the heritability of activity in mice found narrow-sense heritability to be 0.20 in two inbred lines of house mice.[41] A few years later, a larger study found broad-sense heritability for 24- to 48-h activity measures ranging from 0.26 to 0.29 for 26 inbred strains.[42] Similarly, Lightfoot *et al*. found overall broad-sense heritabilities for 21 days of wheel running activity of 0.25, 0.18, and 0.14 for duration, distance, and average velocity, respectively, in 14 strains of inbred mice.[43] In addition, another study measured wheel running in seven strains of male inbred mice and demonstrated slightly higher broad-sense heritability estimates of 0.42, 0.39, and 0.24 for duration, distance, and average speed, respectively.[44] Thus, in these mouse strain screen designs, it was shown that genetics played a significant role in determining physical activity levels. However, these estimates were generally broad-sense in nature and did not consider the amount of transmissibility from parents to the offspring.

Using a research design that selectively bred mice for high wheel running activity, Swallow and coworkers[45] observed lower heritabilities of activity after 10 generations of selective breeding, demonstrating a mean narrow-sense heritability of 0.19 and an adjusted value for within-family selection of 0.28. When Swallow and colleagues[45] estimated heritability using broad-sense methods, they found values of 0.46 for males and 0.53 for females with an average of 0.49 for full sibs in generation 0. These values were similar to those derived from

a larger study using 310 F_2 mice produced from high active C57L/J and low active C3H/HeJ inbred progenitor mice. In this study, reported broad-sense heritability estimates of 0.59, 0.50, and 0.47 for duration, distance, and average wheel running speed, respectively, were reported.[46]

Similar to human work by Boomsma *et al*.[35] and Maia *et al*.,[34] differential heritabilities of activity by sex were also observed by Lightfoot *et al*.[43] These investigators showed 12% genetic influence of activity for females and 31% for males in the amount of distance run daily. Interestingly, there has also been noted an influence of sex on activity with female mice running longer, further, and faster in several studies.[43,47,48] Whether this sex effect on activity is caused by genetic regulation is not clear.[46]

Human and animal research has made it apparent that physical activity is partly heritable, but the variations in study design make it difficult to estimate the exact magnitude of heritability on physical activity. Human studies have mainly used subjective measures that tend to overestimate physical activity whereas wheel running as a measure of physical activity in mice is consistent and repeatable.[43,49–51] Since the genetic homology between humans and mice is significant,[52] the heritability of physical activity found in mice may have implications for understanding the role of genetic variation in spontaneous activity in humans.

III. Heritability of Physical Activity across the Lifespan

Given the difficulty and expense of tracking people for long periods of time, the majority of activity heritability studies that have employed human designs have not considered possible changes in the heritability of activity with age. Since the data are clear that activity decreases with age in both humans and animals,[53–56] it is interesting to consider whether genetic influence on activity is altered across the lifespan and as a result, may be a factor in the age-related decrease in activity. Thus, while difficult, a few studies have attempted to address this question.

Using a simple binary question (“Do you participate in sports regularly?”), a study using the Netherlands Twin Registry found in over 2600 Dutch male and female twin pairs, aged 13–20 years, that sport participation decreased with age.[13] Common environmental factors were found to significantly influence sport participation from ages 13 to 16 years, whereas this pattern was reversed with sports participation almost entirely associated with heritability after the age of 18. In addition, a study that examined lifetime exercise participation in 147 MZ and 153 DZ male twins aged 35–70 years from the Finnish Twin Cohort showed heritability increased from 17% in adolescence to 51% in adulthood.[57]

The finding of an increase in genetic influence on activity with aging has been supported by the one existing animal study on the topic that was released almost simultaneously with the study by Stubbe *et al*.[13] Turner *et al*.[58] examined physical activity through the first 9 months of the lifespan (approximately 35% of the lifespan) in female mice from 10 inbred strains. In this model, overall physical activity measured by wheel running distance decreased throughout a 26-week time period. However, average broad-sense heritabilities for wheel running distance increased from 41% at 12 weeks of age to 76% at 30 weeks of age, after

which the heritabilities dropped to the mid-60% range for the last 6 weeks of the experiment. These findings, in conjunction with those from the two human studies, suggest that the genetic influence on physical activity tends to increase with age.

IV. Genomic Locations Associated with Physical Activity

While it is interesting to debate the level of heritability associated with activity as discussed above, differences in activity quantification, the model used, and the contributions of age, disagreements about the precise magnitude of activity heritability are likely to persist. However, it is safe to say that genetic factors do influence physical activity. This brings us to the genetic mechanisms that are involved with the regulation of physical activity. Given the size of both the human and mouse genomes, an intermediary step has been to identify the genomic regions associated with activity. The determination of these genomic locations—called quantitative trait loci (QTL)—provides a foundation from which gene identification efforts and mechanistic studies can be launched.

Researchers have found significant and suggestive genomic locations for physical activity using both rodent and human models. In rodents, the best analogue for human voluntary activity has been considered to be wheel running.[39] Using a cohort of 310 F_2 mice derived from high active C57L/J and low active C3H/HeJ mice, Lightfoot *et al*.[46] identified four significant QTL, three of which colocalized on chromosome 13 (*DUR13.1*, *DIST13.1*, and *SPD13.1*) and one on chromosome 9 (*SPD9.1*) associated with speed of activity. The chromosome 13 QTL accounted for approximately 6% of the variability and the *SPD9.1* QTL accounting for approximately 11% of the variability in the speed of activity. However, the four significant QTL and 14 suggestive QTL in this study only explained 11–34% of the phenotypic variance (depending on the activity index used), indicating there were other QTL or genetic factors that explained additional variance in physical activity levels. Subsequently, Leamy *et al*.,[59] using the same F_2 database,[46] uncovered a significant number of epistatic QTL indicating that any consideration of activity QTL would need to account for potential interaction between genes. Interestingly, Leamy and coworkers noted that the inclusion of these epistatic QTL, none of which was significant by itself, explained between 18% and 36% of the variance in physical activity. Thus, the combination of the direct effect QTL[46] with the epistatic QTL,[59] explained most of the genetic variance in physical activity in this F_2 model. Interestingly, there were minimal relationships between any of the activity indices and weight of the animals.

However, Leamy proposed that perhaps there were various pleiotropic models that described the relationship between weight and physical activity indices arising even in the controlled heterozygosity of the F_2 generation. Leamy and coworkers[60] discovered 19 relationship QTL (relQTL) associated with pleiotropic relationship of the physical activity traits (distance, duration, and speed) and body weight. Seventy-nine percent of these relQTL influenced the relationship between one of the physical traits and body weight. In addition, the relQTL had 40 significant interactions with 31 of the epistatic QTL that had been discovered earlier.[59] Therefore, Leamy and coworkers observed that even in a population where controlled genomic heterozygosity was introduced using breeding schemes, there were at least three different models describing the genetic pleiotropic relationship between

activity indices (i.e., distance, duration, and speed) and weight, leading to a rather complex picture of the genetic relationship between activity and weight.

Using mice from the unique selective breeding model of Garland and Kelly,[61] both Nehrenberg and coworkers[62] and Hartmann and colleagues[63] have identified additional QTL associated with physical activity. First, Hartmann and colleagues[63] identified a QTL on chromosome 11 that is strongly associated with the recessive mini-muscle phenotype that Garland's lab group has discovered in their high active animals. When controlling for the influence of this QTL, Nehrenberg and colleagues[60] also discovered QTL associated with high activity on chromosomes 5, 6, and 7. While several of these QTL overlap with those previously discovered by Lightfoot and colleagues,[46] several are unique and provide additional regions for candidate gene exploration.

While more difficult and necessarily requiring large cohorts of subjects, there have been efforts to identify genomic QTL associated with activity in humans. In an earlier, smaller genome-wide scans in humans, Cai and coworkers[64] identified one highly significant QTL on chromosome 18q associated with sedentary activity in Hispanic American children. Colocalizing within this QTL, the authors suggested that the melanocortin-4 receptor (*MC4R*) gene was a potential gene linked with physical activity in their cohort. In a larger genome-wide association study (GWAS) that was part of the Quebec Family Study, Simonen *et al*. observed one significant and several suggestive linkages for physical inactivity and activity.[65] In Simonen *et al*.'s study,[65] the significant QTL was on chromosome 2 (2p22–p16) and suggestive linkages were found on chromosomes 7p11.2 and 20q13.1 for physical inactivity, chromosomes 11p15 and 15q13.3 for time spent in physical activity, chromosomes 13q22–q31 for total daily physical activity, and chromosomes 4q28.2, 7p11.2, 9q31.1, and 13q22–q31 for moderately strenuous activity.

Recently, the most extensive of the human GWAS was published. De Moor *et al*.[66] studied 2622 adults of European ancestry using an exercise participation survey and a moderately dense single nucleotide polymorphism (SNP) map of 1,607,535 measured or imputed common SNPs. This GWAS revealed 37 novel SNPs for exercise participation clustered in three distinct genomic regions. The QTL containing the majority of the associated SNPs colocated with the *PAPSS2* gene on chromosome 10q23.2, while the other two QTL fell in intergenic areas on chromosomes 2 (2q33.1) and 18 (18p11.32). Beside the potential for novel QTL discovery, the strength of this type of study was the ability to cross-reference previously suggested potential candidate genes to determine if these genes colocalized within the genomic region of the QTL. In this study, De Moor and colleagues found that while not significant, suggestive associations were found with the location of the leptin receptor (*LEPR*) gene and the *GABRG3* gene on chromosome 15 (15q12–13). However, none of the other potential candidate genes that had been suggested earlier angiotensin-converting enzyme (*ACE*), calcium sensing receptor (*CASR*), *CYP19A1*, dopamine receptor 2 (*DRD2*), and *MC4R* [67,66,69,70–72] localized within any of the three significant QTL found in this study.

Surprisingly, when considered in total, there are few (> 10) significant QTL that have been associated with physical activity. While it is possible that there are actually just a few genes

that influence physical activity level, the likelihood is that the existing models have had limited power to detect numerous less-powerful QTL that may play a role in regulating physical activity; this is a point that has been made by both De Moor *et al*.[66] and Lightfoot *et al*.[46] and a point that needs to be addressed by using a GWAS approach and much larger datasets. However, the available data do provide identification of genomic regions that presumably contain candidate genes associated with physical activity level.

V. Potential Candidate Genes for Physical Activity

Once potential QTL are found, it is tempting to declare candidate genes based solely on apparent functional relevance and localization within these QTL. While these criteria are important, they have led to a less than stellar track record of identifying causal genes from QTL studies.[73] Therefore, additional criteria should be used to sort through potential candidate genes before a gene's candidacy for involvement in a complex trait such as physical activity is made.[74] Additional candidate criteria can take several forms, ranging from demonstration of haplotype differences in gene structure to actual phenotypical changes due to gene manipulation. As such, multiple genes have been speculated to be involved in physical activity; however, few at this time present multiple lines of evidence to confirm their candidacy as being part of the regulatory mechanisms of physical activity.

Several studies have suggested that dopaminergic function is part of the biological regulation of physical activity in both animal and human studies.[67,75,76] Pharmacologically based studies have demonstrated that altered dopaminergic function in selectively bred high active mice was at least partially responsible for the high activity of these mice.[75,76] Injection with dopamine reuptake blockers cocaine and GBR 12909[75] and subsequently ritalin and apomorphine[76] resulted in altered wheel running activity in the high active mice leading to identification of dopamine receptor 1 (*Drd1*) as a potential physical activity-regulating gene. Supporting this hypothesis, Knab *et al*.[51] found significant differences in expression level between the high (C57L/J) and low (C3H/HeJ) active mice for both *Drd1* and tyrosine hydroxylase (*TH*) dopaminergic genes in the nucleus accumbens independent of wheel running exposure, but no difference for dopamine receptors 2–5 genes and the dopamine transporter gene (*Dat*). Supporting the suggestion of *Drd1* as a gene regulating physical activity, regional haplotype analysis conducted by Ceaser *et al*.[77] found differences in *Drd1* haplotype distributions between high active C57L/J mice and low active C3H/HeJ mice. These three independent lines of research, in conjunction with the well-known functional relevance of *Drd1* in locomotor disorders (e.g., Parkinson's) and the location of the *Drd1* gene in one of the QTL identified by Lightfoot *et al*.,[46] suggest that *Drd1* is an appropriate candidate gene for further investigation regarding its role in physical activity regulation.

In addition to *Drd1*, there is some evidence that *DRD2* is also a potential candidate gene for activity regulation. In fact, *Drd2* localizes to a genomic area that was identified as an epistatic QTL[59] and a *DRD2* gene polymorphism was found to be associated with past physical activity in white women in the Quebec Family and HERITAGE Family studies.[67] Subsequently, in a cohort of selectively bred high active mice, the *Drd2* gene was expressed at a 20% higher rate than in a control group[78] with an additional study showing that *Drd2*

gene knockout mice exhibited reduced locomotor activity compared to wild-type mice.[79] However, there have been no differences reported in either *Drd2* expression or haplotype structure between high and low active mouse strains.[51,77] Furthermore, *DRD2* was also not replicated by the only GWAS using over one million SNP in Dutch and American adults.[66] Thus, while certainly a compelling candidate gene, further evidence is needed to strengthen the case of *DRD2* as a gene regulating activity level.

Another potential candidate gene regulating physical activity is the *Nhlh2* gene.[80] While relatively new, the *Nhlh2* gene has been known to be associated with leptin, and its encoded protein is a precursor to the formation of endorphins, both potentially functionally relevant to activity levels.[80] It has been shown that running wheel activity in *Nhlh2* knockout mice (N2KO) was reduced by approximately 50% as compared to wild-type mice;[80] further, *Nhlh2* is located on chromosome 3 and colocalizes with one of the epistatic physical activity QTL identified by Leamy *et al*.[59] Thus, *Nhlh2* has functional relevance to physical activity, localizes within one of the identified QTL, exhibits partial haplotype differences between high and low active mice,[77] and, when manipulated, directly affects physical activity. Thus, *Nhlh2* is a good candidate for further investigation of its activity-regulating effects.

Several other genes have been suggested as potential candidate genes regulating physical activity. While these genes may in fact be involved in activity regulation, evidence at this time is lacking to confidently declare them candidate genes. For example, Stefan *et al*.[68] found in Pima Indians that the Arg223-encoding allele of the *LEPR* gene predisposed to lower energy expenditure and physical activity levels compared to individuals with the Gln223-encoding allele. Another study showed that *LEPR* was related to physical activity energy expenditure in young boys.[81] However, *LEPR* does not localize into any of the significant QTL in either human[66] or mouse[46,59] and does not show haplotype differences between high and low active animals.[77]

Another potential candidate gene regulating physical activity is the *MC4R* gene.[69] Using a cohort from the Quebec Family Study, the *MC4R* gene on chromosome 18 was determined to be associated with past and current physical activities measured using a questionnaire and 3-day activity diary,[69] and individuals with the homozygous (T/T) or heterozygous (C/T) variation of *MC4R* were significantly more inactive than individuals with the homozygous (C/C) allele. Furthermore, a study of Hispanic children that measured physical activity using accelerometry suggested that a mutation of *MC4R*, which colocalized to a QTL for chromosome 18q, was associated with activity levels.[64] However, *MC4R* did not colocalize to any of the QTL identified in the larger human GWAS[66] or in any of the identified animal QTL. Thus, while *MC4R* shows promise as a candidate gene, further evidence is needed.

To this point, the majority of suggested candidate genes are postulated to work in a central manner, usually affecting or altering the “motivation” of exercise through the reward system. However, when the gene for glucose transporter 4 (*Slc2a4*, also known as *Glut-4*) was overexpressed in fast-twitch skeletal muscle of mice, these mice ran four times farther than control mice.[82] The authors speculated that the increase in muscle glucose availability secondary to the increased transport might be the reason the mice were able to sustain higher wheel running. Supporting this hypothesis, a study using highly active selectively bred mice

reported that *Slc2a4* expression was 2.4-fold higher in the gastrocnemius[83] as compared to the control mice. Additionally, *Slc2a4* colocalizes with one of the QTL (chromosome 11, 40 cM) associated with physical activity.[62] Like *MC4R, LEPR,* and *DRD2, SLC2A4* continues to be a viable potential candidate gene and awaits further confirmatory evidence.

Other potential candidate genes have been identified as possibly associated with physical activity. In a bone mineral density study of 97 Caucasian girls with a mean age of 16.9 ± 1.2 years, the girls with the S allele for *CASR* were found to be less physically active.[70] In a study of 355 mild hypertensive men and women, the *ACE* gene was linked to leisure physical activity.[71] Individuals with DD polymorphism were more inactive and individuals with the II polymorphism for *ACE* engaged more frequently in sport activities.[71] Additionally, an aromatase (*CYP19*) gene polymorphism was associated with physical activity at baseline in a study of 331 early postmenopausal women.[72] Even though these possible associations were significant, none of these genes localize to any of the association sites discovered by De Moor *et al*.,[66] and only the mouse variants of *Cyp19* and *Ace* map to QTL discovered in mouse models.[46,59] Thus, with available evidence ambiguous at best, additional work is needed to further understand the relationship between *CASR, ACE,* and *CYP19* and physical activity.

Given the suggestion by Leamy *et al*.[60] of potential pleiotropic relationships between weight and activity, a few of the potential candidate genes for physical activity have been linked with obesity. A study of *Nhlh2* transcription factor knockout mice (N2KO) showed that a reduction in voluntary wheel activity led to weight gain in male N2KO mice after 12 weeks.[80,84] Other authors have shown that access to a running wheel and genetic differences in activity level are not necessarily related to the caloric intake of an animal, nor protective of body mass or body fat.[85] However, *Nhlh2* is known to have transcriptional control of *MC4R*,[80] of which polymorphisms in the *MC4R* gene have been associated with obesity and reduced physical activity in several studies.[64,69,86] An example of this association was shown in the Quebec Family Study where the inactive offspring in the cohort that had the *MC4R-C-2745T* variant had a lower body mass index (BMI); however, there was no association between inactivity and BMI in the parents.[69] While associated with *MC4R*, the *Nhlh2* gene is also known to be associated with leptin, a key regulator of food intake and energy expenditure.[87] In Pima Indians, individuals homozygotic for the leptin (*LEPR*) receptor Arg223-encoding allele had lower physical activity levels along with larger fat cell size.[68] Taken together, these findings, in conjunction with Leamy and coworkers' recent suggestion of the pleiotropic nature of the genes involved in weight maintenance and activity,[60] suggest that there is a complex relationship between physical activity and obesity that may involve genetic determinants. However, the lack of localization of many of the attractive candidate genes (e.g., *MC4R, LEP, LEPR*, etc.) within any published physical activity QTL greatly increases the complexity of the interpretation of these relationships. Future research will need to not only confirm these relationships, but further delineate potential mechanistic pathways involved.

VI. Summary

There are still considerable limitations and differences in study design, methodology, culture, and cohort composition that make determining an exact magnitude of the heritability on activity level and subsequent effects on obesity, difficult. However, in general, it appears that genetics has a moderate influence on physical activity level. Additionally, there is early evidence that age and sex may both be regulators of the heritability of activity. The initial genomic maps that exist associating specific genomic locations with activity, while limited at this early stage, provide a foundation from which further efforts to identify genes and mechanisms of regulation can be launched. Furthermore, research suggests that the full range of physical activity levels (inactivity to vigorous) may be regulated by different genomic regions. In particular, while the genetic structures responsible for physical activity regulation remain unknown, new genetic and molecular methods are making identification of specific physical activity genes an attainable goal. *DRD1* and *NHLH2* have the most evidence linking them with activity, while *SLC2A4 and PAPSS2* appear to be promising candidate genes with several other genes, while attractive as potential candidate genes, still lacking clear evidence of their involvement with activity. In addition, growing evidence supports a complex and pleiotrophic genetic association between physical activity and body weight regulation; however, the amount, nature, and mechanism(s) of these genetic associations are still undefined.

When the genetic regulators of physical activity are identified, this knowledge could significantly impact health promotion strategies focused on increasing physical activity levels and decreasing obesity. Knowledge of the genetic mechanisms associated with spontaneous physical activity level could lead to individualized programs and behavior change strategies tailored for those predisposed to be inactive. Besides the positive influence on the currently estimated cost of physical inactivity to our health care system ($507 billion per year)[88], an increase in physical activity levels would provide increases in both quality and quantity of life for all citizens.

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