Muscling in on the genetics of quantitative disease traits

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OUR COMPREHENSION of how genetic factors influence a person’s susceptibility to complex disease has evolved markedly during the past 20 years. Major advances in molecular genetics technologies have contributed greatly to this process, as have improvements in phenotyping methods and statistical algorithms used in the analysis of quantitative genetics data. Although genetics studies that focus on discrete disease outcomes are valuable, they are uninformative of the disease’s etiology. One important etiological trait for a variety of health disorders is muscle wasting (sarcopenia), which frequently occurs as a consequence of aging, certain diseases, and limb immobilization following orthopedic injury. Studies that seek to disentangle the genetic from the environmental influences on muscle mass phenotypes are important as they may eventually contribute to the prevention or treatment of sarcopenia-related disorders. This invited editorial focuses on a study from the Journal of Applied Physiology by Prior et al. (11) that addresses this issue in eight large, multigenerational families from the Caribbean island of Tobago. Using advanced phenotyping and statistical analysis methods, the authors established that the heritability of lean soft-tissue mass and muscle cross-sectional area are modestly heritable traits (\(h^2 \approx 0.20\)) and that the heritability of limb-specific muscle development may vary by sex and age and that cigarette smoking, parity, and oral contraceptive use may be important environmental determinants of skeletal muscle morphology.

Skeletal muscle plays important roles in the metabolism of energy substrates, the generation of hormones required for a range of physiological processes including cell repair and signaling, and the maintenance of functional capacity and mobility. Muscle wasting (sarcopenia) frequently occurs as a consequence of aging, diseases such as anorexia nervosa, AIDS, and cancer, and limb immobilization following orthopedic injury. The consequences of sarcopenia include a decline in bone mineral density and functional capacity, and increased susceptibility to fracture, insulin resistance and dyslipidemia (1, 9, 12). Resistance exercise training is effective at delaying age-related sarcopenia and in regenerating muscle tissue following disease or injury. However, the molecular mechanisms that underlie the processes of sarcopenia and muscle regeneration are poorly understood, and safe and effective pharmacotherapy for either scenario is lacking (7).

Muscle morphology phenotypes include muscle mass, cross-sectional area, regeneration rates, and sarcopenia. Studies characterizing the heritability of these phenotypes in people from different ethnic or environmental backgrounds may yield information pointing toward the factors underlying the between-individual variation in these traits. Despite known differences in muscle morphology between ethnic groups (2), little emphasis has been placed on determining the genetic factors that underlie these differences; most heritability studies related to this topic have focused on populations of European ancestry and have used relatively imprecise anthropometric measures.

Prior and colleagues (11) describe the heritability of muscle morphology phenotypes in eight large, multigenerational families from the Caribbean island of Tobago. The study is unique in that it is the first to assess the heritability of muscle phenotypes using objective methods (dual-energy X-ray absorptiometry and computerized tomography) in extended families of recent African descent. Furthermore, the study design permitted Prior et al. (11) to partially assess the effect-modifying roles of age and sex on the heritability of muscle phenotypes. The authors conclude that lean soft-tissue mass and muscle cross-sectional area are modestly heritable traits (\(h^2 \approx 0.20\)) and that the heritability of limb-specific muscle development may vary by sex and age. The authors also conclude that cigarette smoking, parity, and oral contraceptive use may be important environmental determinants of skeletal muscle morphology.

A common misconception is that estimates of “heritability” and “genetics” are always synonymous. Because nongenetic environmental factors are often shared to a greater extent by family members than nonmembers, it is possible for a phenotype to segregate within a family in the absence of a genetic cause. One example of this is physical activity levels in children, where the influence of familial environmental factors can constrict the genetic influences on activity levels (5). A second example is adult obesity. Men and women “selectively mate,” whereby obese individuals tend to select obese partners (10). The nongenetic segregation of obesity within families can also emerge during the course of a relationship independently of mate selection; in a recently reported prospective study, people whose spouses were initially nonobese, but who subsequently became obese, were themselves at greater risk of becoming obese, seemingly because obesogenic environmental factors are shared and evolve more within than between close social networks such as families (3). The same may also be true of muscle morphology traits. Thus conventional approaches to assess heritability using collections of families, where the trait correlation within sets of highly genetically related individuals is compared with the trait correlation in sets of less genetically related individuals, can be prone to confounding, primarily because simple heritability estimates (\(h^2\)) incorporate both genetic and shared-environmental factors. Thus, if \(h^2\) is interpreted solely as the variance explained by “genetic” factors, then the role that genetic variation plays in the development of the trait may be overestimated. To circumvent this limitation in family studies requires sophisticated designs and analytical methods that partition out the genetic from the shared- and unshared-environmental variances.

In twin studies, providing zygosity is accurately determined, the genetic similarity of participants is known (for monozygotic
twins 100%, for dizygotic twins 50%, and for nontwins <50%), and the environmental factors are assumed to be the same in twins, irrespective of zygosity. By applying variance components models to twin data, it is possible to partition out the genetic from the shared- and unshared-environmental influences on a phenotype. In nontwin, multigenerational family studies, this can also be done, but the assumptions are complicated by the different levels of genetic relatedness and the fact that family members differ in age, intrauterine exposures, and other factors.

In their study, Prior et al. (11) used variance components methods to disentangle the genetic from the environmental phenotypic influences and adjusted for several factors that could confound or mediate the observed genetic effects. An important limitation of the study, however, is that several important putative confounders (e.g., physical activity) were measured using subjective methods, which are prone to error and bias. Thus, adjusting for confounders measured in this way can only partly address the problem of confounding. An additional limitation is that many other shared-environmental factors were unmeasured, which may also allow confounding to persist. These limitations are important to recognize, because, even with the more sophisticated approach the authors employ, the genetic estimates for muscle mass phenotypes may be inflated.

Even with its limitations, the study of Prior et al. (11) significantly extends the previous work undertaken on the heritability of muscle mass phenotypes. Two major strengths of the study of Prior et al. (11) are the multigenerational collection of families and the objective measures of muscle morphology. Both factors are important from the perspective of enhancing statistical power, thus increasing the possibility that true effects will be observed. However, the objective measures of muscle morphology bring a second important attribute to the table: the capacity to scrutinize the heritability of specific subcomponents of muscle; clearly, studies using crude anthropometric indexes of body composition cannot do this. The fact that this investigation focuses on an understudied population further enhances its value.

Family studies have helped form the bedrock of human disease genetics and continue to have much to offer the field. However, a more powerful and biologically specific approach involves studying cohorts of unrelated individuals who have been genotyped for selected molecular markers. The methods used in this type of study have evolved rapidly during the past 15 years, owing largely to the major technological advances that enable the measurement of many nucleotide sequence variations in individuals from large population samples. Using this approach, associations are typically assessed between variants within biologically plausible candidate genes and the level of or frequency of a disease phenotype. In the past few years, further gains have been made in extending the number of genetic variants that can be assessed in a single analysis and in reducing the related costs. The sharing of data from large-scale projects such as HAPMAP (8) has also facilitated progress. The great limitation of the molecular genetics approach, however, has been a widespread inability to reproduce reported associations, presumably because many findings are false-positive, resulting from multiple-hypothesis testing in underpowered studies. Only very recently have studies of sufficient size and marker density emerged, in which several very convincing genetic risk factors for a variety of complex disease traits have been discovered (13). Invariably, those studies, known as genome-wide association studies (GWAS), have focused on hundreds of thousands of nonspecific markers spread across the human genome, with little emphasis placed on the biological role the genes play in the phenotype’s etiology. Although GWAS for obesity-related traits have yielded very promising results (4, 6), no comprehensive reports have yet emerged focusing on well-measured muscle phenotypes. It is conceivable, therefore, that with the appropriate application of GWAS methods, tremendous progress will be made in understanding the molecular defects involved in sarcopenia and related pathologies. The combination of traditional family-based studies and state-of-the-art molecular genetics methods may further elucidate the mechanisms that underpin changes in muscle morphology and its disease sequelae.

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REFERENCES