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REVIEW

Genetic aspects of skeletal muscle strength and mass with relevance to sarcopenia

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Skeletal muscle is a highly heritable quantitative trait, with heritability estimates ranging 30–85% for muscle strength and 50–80% for lean mass. That strong genetic contribution indicates the possibility of using genetic information to individualize treatments for sarcopenia or even aid in prevention strategies through the use of genetic screening prior to the functional limitations. Though these possibilities provide the rationale for genetic studies of skeletal muscle traits, few genes have been identified that appear to contribute to variation in either skeletal muscle strength or mass phenotypes, and sarcopenia *per se* is remarkably understudied as a trait in this regard. This review examines the heritability of skeletal muscle traits, findings of linkage and genome-wide association analyses and impact of specific genes and gene-sequence variants on these traits as relevant to sarcopenia. Despite considerable work in the area, the genetic underpinnings of skeletal muscle traits remain largely unknown and the genetic aspects of sarcopenia are even less clear. Large-scale longitudinal clinical studies relying on advanced genome-wide association and other techniques are needed to provide further insights into the genes and gene variants that contribute to skeletal muscle strength and mass, and ultimately to susceptibility to sarcopenia.

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Introduction

Aging is associated with a decline in skeletal muscle strength, mass, power and physical functioning known as sarcopenia.[1] These losses have important health consequences,[2–5] including an increased risk of falls, hip fractures and functional decline.[4–6] Muscle strength is independently associated with functional ability in the elderly [5,7–9] and may explain up to 25% of the variance in overall functional ability.[10] Sarcopenia is also related to a reduction in the performance of activities of daily living,[11] which may lead to further declines in muscle mass and strength and greater reductions in the performance of those activities. The overall effect of this cycle can be a marked loss of function, predisposing older individuals to falls, injuries and disability.[12]

Although the loss of muscle mass is associated with the decline in strength with advancing age, the strength decline is much more rapid than the accompanying loss of muscle mass, indicating a decline in muscle quality.[13] In fact, the loss of muscle strength is a stronger predictor of mortality in the elderly than the loss of muscle mass.[12,14–16] The relationships of muscle mass and strength to mortality appear to lie in the higher functional capacity associated with greater muscle strength regardless of mass, resulting in an inverse association with functional limitations and disability. The consequences of sarcopenia-related disability are significant both in terms of quality of life and health-care costs related to sarcopenia, estimated to be $18.5 billion dollars in the United States for adults $\geqslant 60$ years for the year 2000.[17]

Though the losses of muscle mass and strength begin on average between 40 and 50 years of age, losses for any particular individual are difficult to predict. Sarcopenia has been reported in community-dwelling men and women <50 years,[4,5,18,19] and sarcopenia associated with compromised physical functioning occurs in nearly one in ten women aged 34–58 years,[20] providing further support for the variable onset of muscle strength losses and an indication of susceptibility to sarcopenia in some individuals. Various research groups are currently exploring the possibility that a portion of this inter-individual variability and susceptibility to early muscle losses is due to genetic factors, which is the focus of the present review. The importance of physical activity and resistance training particularly in slowing the losses of muscle mass and strength is clear[21,22] and genetic factors have been found important in this context,[23,24] but a discussion of that related literature is beyond the scope of the present review. Similarly, the present review focuses on human studies; readers are pointed to a more comprehensive review published recently[25] that discusses key findings from animal models that speak to the genetic aspects of skeletal muscle traits.

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Heritability of Skeletal Muscle Traits

Variation in skeletal muscle traits among individuals can be attributed to genetic factors, environmental factors or some interaction of both. Though the influence of environmental factors, such as physical activity and diet, have been broadly investigated, only recently studies have begun to identify the specific genetic influences on skeletal muscle traits that may explain the inter-individual trait variability. Initial studies in this regard have focused on establishing the heritability of muscle-related traits. For example, the heritability of grip strength was estimated between 30 and 50% in several early studies.[26–28] In older twins, genetic factors accounted for 65% of the variance in grip strength even after adjusting for body weight, height and age.[29] More recently, twin studies have revealed heritability values for muscle strength phenotypes ranging 30–85% depending on the conditions of the strength measure (for example, limb, contraction angle, velocity and type).[23,29–33]

With regard to skeletal muscle mass, the first direct study of lean body mass was performed by Bouchard *et al.*[34] who reported 80% heritability of lean body mass by hydrodensitometry in twin pairs. Similarly, high heritability values have been reported by many other groups using more sophisticated measurement techniques.[30,35–38] Across these studies, heritability estimates >50% are not uncommon for muscle mass measurements.

Perhaps the most relevant for this review are the studies that have examined heritability within older subjects. Several reports have demonstrated significant heritability values for muscle strength in older individuals.[29,39–43] Frederiksen and colleagues[39] reported heritability of grip strength at 50% in individuals from 46 to 96 years. Even the change in muscle strength with advancing age has been found to be heritable,[44,45] though some studies indicate that the contribution of environmental factors increases at older ages.[42,46] Overall, genetic variation explains a significant fraction of the inter-individual variability in skeletal muscle phenotypes, including muscle traits in older individuals. Despite strong evidence for a heritable component to muscle phenotypes, the genetic underpinnings of this heritability is only beginning to be known.

Linkage-Analysis and Genome-Wide Association Studies (GWASs) and Skeletal Muscle Traits

After the heritability of a trait is established, a common next step was to perform linkage-analysis studies in families, which sought to identify chromosome locations that harbor genes and gene variants that contribute to trait variation. Several such studies have been done for various measures of lean mass or muscle strength phenotypes and chromosome regions, and in some cases, specific gene loci have been identified as candidate regions.[47–51] Only one linkage study has targeted older individuals in particular. Tiainen *et al.*[42] examined 397 microsatellite markers in 94 female dizygotic twin pairs aged 66–75 years from the Finnish Twin Study on Aging. Significant linkages were reported for knee extensor isometric strength, leg extensor power and calf muscle cross-sectional area.

A few detailed linkage studies have been performed, isolating a small number of chromosome regions in order to better identify potential candidate genes.[52–54] Huygens and colleagues[53] performed a gene-targeted linkage analysis in the myostatin pathway (across 10 genes) in a young male cohort for various measures of muscle mass and strength. Significant linkage was reported for knee extension and flexion peak torque measures in the *MSTN (*myostatin), *CDKN1A* and *MYOD1* genes. The same group then performed an expanded multi-point linkage analysis in 367 young Caucasian male siblings from 145 families with nine genes involved in the myostatin signaling pathway and various measures of muscle strength.[54] Significant linkages were reported on four chromosomal regions with knee muscle strength measures. Most recently, Windelinckx and colleagues[55] performed a focused fine mapping of chromosome 12q12-14 and identified *ACVR1B* as a candidate gene for muscle strength.

Linkage analysis studies have given way recently to GWAS that can be used to identify specific gene regions in unrelated individuals by use of high-density polymorphism microarrays. In the first such GWAS for lean mass, Liu and colleagues[56] examined 379 319 polymorphisms in nearly 1000 unrelated US whites and identified two polymorphisms both located in the thyrotropin-releasing hormone receptor (*TRHR*) gene as statistically significant. Importantly, these associations were confirmed in three replication cohorts consisting of over 6000 total white and Chinese subjects. Sun *et al.*[57] recently identified several novel candidate polymorphisms underlying both appendicular lean mass and femoral neck geometric properties in a large GWAS in Chinese adults followed by independent replication in white subjects. Most recently, Hai and colleagues[58] performed a copy-number variation GWAS in this same Chinese cohort and identified the *Gremlin1* gene as significantly associated with lean mass. These studies thus contribute to the identification of specific genes and gene variants with clinically relevant influences on skeletal muscle traits important to physical function, though they are preliminary in nature and require significant replication and follow-up work to confirm their observations.

Genetic Variation and Skeletal Muscle Strength

Beyond the heritability and linkage or GWAS investigations, ultimately researchers are interested in identifying the specific genes and gene variants contributing to the genetic influence underlying these skeletal muscle traits. This section reviews specific genes that have been examined in multiple studies in relation to skeletal muscle strength measurements, focusing on genes associated with baseline strength values. Not all such genes are reviewed here, but the selected genes represent either those most studied or those with significant findings; a more comprehensive listing of genes was recently published.[25] The identification of genetic factors important to skeletal muscle strength is remarkably difficult given that multiple strength variables are commonly measured in different studies, including different muscle groups, contraction types and measurement instruments. Moreover, different genes are likely to contribute to different aspects of strength that may not be reflected across the different measurement types. All this means that for a particular gene or genotype of interest, the chances of replication across multiple studies are small. But when genes are found to be important across multiple, different strength measurements the likelihood the gene is important to muscle strength improves considerably.

Angiotensin-converting enzyme (*ACE*). *ACE* and its insertion/deletion polymorphism have been studied in relation to

skeletal muscle traits in a number of studies. Though some studies have reported significant associations with baseline muscle strength phenotypes,[59–65] there are inconsistent associations within those studies and several other investigations have not observed significant associations.[66–72] Thus, there is little evidence to suggest that *ACE* genotype is a strong contributor to inter-individual variation in skeletal muscle strength.

Alpha actinin 3 (*ACTN3*). The *ACTN3* gene has generated considerable attention following a number of cross-sectional investigations in elite athletes that pointed to a disadvantage for homozygote carriers of the R577X nonsense (X) allele in sprint and power-related activities.[73–75] When examining the breadth of studies in this area, most point to slightly lower muscle strength values in X/X vs R-allele carriers,[76–78] though not all studies support this conclusion.[69,79–81] For example, Vincent and colleagues[76] studied the R577X polymorphism in relation to isometric and isokinetic knee extensor strength in 90 young men and reported lower concentric peak torque at 300° s^{-1} in X/X compared with R/R homozygotes. The authors also reported a lower proportion of type IIx muscle fibers in X/X vs R/R homozygotes. In contrast, Norman and colleagues[80] reported no significant associations with muscle power or torque-velocity relationships among *ACTN3* genotypes in a study of 120 moderately to well-trained men and women. They were also unable to confirm the difference in fiber-type proportion reported by Vincent and colleagues. Interestingly, in a longitudinal study of 1367 older adults (70–79 years), Delmonico *et al.*[82] reported greater losses of 400 m walk time performance over 5 years in male X/X vs R-allele carriers, whereas X/X women had a 35% greater risk of lower extremity physical limitation compared with R/R women. Judson *et al.*[83] recently reported great risk of falling in older females carrying at least one X allele. The general consensus among these studies is that *ACTN3* X/X carriers have modestly lower skeletal muscle strength and power in comparison with R-allele carriers, with the work of Delmonico *et al.*[82] and most recently Judson *et al.*[83] indicating potential clinical importance for the X/X genotype in older men and women.

Ciliary neurotrophic factor (*CNTF*). Several studies have examined genetic variation in the *CNTF* gene and/or its receptor *CNTFR*. A rare null allele in the CNTF gene has been associated with muscle strength,[84,85] but the frequency of the rare A/A genotype is so low that general public health significance is unclear even while it might be clinically important for those particular individuals. Multiple polymorphisms in the *CNTFR* gene have also been studied in relation to strength variables[86,87] but no consistent findings have been observed across studies. Overall, these findings indicate the potential for significant influences of *CNTF* and *CNTFR* gene variants on skeletal muscle strength, with the rare A/A genotype in *CNTF* appearing to have the most clinical relevance.

Myostatin-related genes. Myostatin emerged as an attractive target of gene-association studies and multiple polymorphisms were identified in the human gene (*MSTN*).[88] Some investigations have reported associations with skeletal muscle strength, but the sample sizes are very small owing in part to low allele frequencies of the common polymorphisms.[89–91] Because the common polymorphisms have rare allele frequencies, any public health significance of *MSTN* genetic variation is unlikely, though it may be important for those individuals. Subsequently genes within the myostatin-signaling pathway have been examined, including the myostatin receptors (*ACVR1B* and *ACVR2B*) and follistatin, a myostatin inhibitor,[55,92,93] but again, the sample sizes of the genotype groups with significant findings were generally small, making the clinical relevance of these findings uncertain but generally not striking.

Vitamin D receptor (*VDR*). Vitamin D deficiency has been consistently associated with lower muscle strength[94] and has been discussed as a potential mechanism of sarcopenia.[95] The VDR gene has multiple polymorphisms that have been investigated but studies differ with regard to the specific polymorphisms or haplotypes examined, making comparisons difficult. VDR genetic variation has been associated with muscle strength variables in numerous studies,[96–103] though inconsistencies have been noted because of the examination of different variants. Studies having examined the BsmI locus are more mixed with regard to their findings and future studies need to incorporate the haplotype of BsmI and TaqI rather than looking at either site independently. The *VDR* FokI site is considered functional[104,105] and two studies reported higher strength in f/f compared with F/F carriers.[99,101] Thus, the *VDR* locus is a promising target that should be investigated more thoroughly in future studies.

Genetic Variation and Skeletal Muscle Mass

This section examines genes that have been studied in relation to skeletal muscle mass measurements, again focusing on frequently studied genes examined in multiple studies and associated with baseline muscle mass values.

ACE. The majority of papers examining the *ACE* insertion/deletion polymorphism have been focused on muscle strength rather than muscle mass phenotypes, though some studies have examined both.[64,67,68,70] Most have reported no association with muscle mass and it appears unlikely that *ACE* genotype contributes significantly to muscle mass phenotypes.

ACTN3. Several studies have examined the potential for the *ACTN3* R577X polymorphism to explain variability in muscle strength measures and many of those same papers have examined muscle mass variables.[76,78,80,82,106] Of those studies, only Walsh *et al.*[78] and Zempo *et al.*[106] found evidence of an association between muscle size and the *ACTN3* null X allele, indicating at best a minor role for this polymorphism in explaining inter-individual variability in this trait.

Androgen receptor (*AR*). A few studies have examined the association between the *AR* CAG-repeat polymorphism and muscle mass variables with conflicting results, with both longer repeat length[107,108] and shorter repeat length[109] being correlated with greater fat-free mass (FFM). Walsh and colleagues[108] found significant genotype associations with FFM in men from two independent cohorts and similar results were found by another group.[107] Nielsen *et al.*[109] observed opposite results but in a cohort of young men, indicating the possibility of an age interaction. Recent data indicate that the CAG-repeat sequence in the *AR* gene modulates receptor transcriptional activity and affects muscle cell development in culture.[110] Additional work is required to clarify these findings.

Myostatin-related genes. Despite the strong physiological evidence behind myostatin as a candidate gene for muscle mass traits and the importance of rare mutations in the gene on muscle mass,[111] common genetic variation in the *MSTN* gene has not been associated with muscle mass.[93,112] Studies that have examined myostatin-related genes in relation to muscle mass phenotypes have produced some minor associations[92,93] but there is little compelling evidence that *MSTN* or myostatin-related genes are major contributors to skeletal muscle mass.

TRHR. As described above, Liu and colleagues[56] identified *TRHR* as a potential candidate gene for skeletal muscle mass from the first GWAS for this trait. The authors performed separate replication studies in three cohorts consisting of over 6000 total white and Chinese subjects and consistent significant associations with lean body mass were observed in those analyses. Though only a single paper, the multiple replications pointing to *TRHR* provide strength for this as a potentially important candidate gene for muscle mass variation.

VDR. Though *VDR* genetic variation has been studied extensively in relation to muscle strength, fewer studies have focused on skeletal muscle mass. Van Pottelbergh and colleagues[113] reported associations between TaqI/ApaI haplotypes and lean mass in 271 older men (>70 years), but not in a separate group of younger men from the same study. Roth *et al.*[99] reported significant associations with the *VDR* FokI polymorphism (f and F alleles) and leg FFM in 302 older Caucasian men, with concomitant differences in muscle strength. These results provide evidence for positive association and continued interest in this gene in relation to skeletal muscle traits.

Genetic Variation and Sarcopenia

Though a number of studies have investigated specific genes and genetic variants in relation to skeletal muscle strength and mass phenotypes, only one study has specifically targeted sarcopenia *per se*. Roth and colleagues[99] analyzed the influence of *VDR* sequence variants on muscle strength and mass in a cohort of 302 older (58–93 years) Caucasian men with measures of FFM by dual-energy X-ray absorptiometry. *VDR* FokI genotype was significantly associated with different lean mass measures, with the F/F group demonstrating significantly lower mass than the F/f and f/f groups. In addition, the group categorized the men as normal or sarcopenic based on the definition of Baumgartner *et al.*,[3] which relies on a cutoff value based on appendicular FFM relative to body weight ($kg\,m^{-2}$). Logistic regression revealed a twofold higher risk for sarcopenia in *VDR* FokI F/F homozygotes than carriers of the f allele. Quadriceps muscle strength was also lower in the F/F group compared with the F/f and f/f groups, but this association was eliminated when the analysis controlled for the differences in total body lean mass. Thus, *VDR* FokI genotype was significantly associated with lean mass and sarcopenia in this cohort of older Caucasian men, with concomitant differences in muscle strength. Additional work is needed in this area.

Conclusions and Future Directions

Though high heritability values would indicate a strong genetic component, little progress has been made in identifying specific genetic contributors to skeletal muscle strength and mass phenotypes relevant to sarcopenia. Although many genes have been tentatively examined (not all reviewed here), few have been positively associated with muscle-related traits across multiple cohorts and the findings are not always consistent within any replication analyses. No genes have been replicated for association with sarcopenia itself, though *VDR* genotypes have been associated with sarcopenia in one study and with muscle strength and mass phenotypes in multiple studies.

Of those genes that have been identified, their importance to skeletal muscle-trait variation is generally small. None of the genes described above have been shown to conclusively contribute >5% of the inter-individual variation to their respective traits, and most are on the order of 1–3%. In addition to typical polymorphisms, copy number variation (multiple copies of the same gene), gene–gene interactions (multiple genes coordinated in a pathway), complex gene–environment interactions and epigenetic factors also contribute to the genetic component of inter-individual variability,[114] and these more complex phenomena are just beginning to be studied in large-scale investigations. One possible approach to addressing this complexity is the calculation of genetic predisposition scores based on multiple genetic variants.[115] Finally, it is important to recognize that genetic factors will only be one of the several contributors to sarcopenia-related traits and additional environmental and developmental factors must not be ignored when addressing future prevention and treatment strategies.[116,117]

A consideration when examining the genetic aspects of skeletal muscle traits generally and sarcopenia in particular is that of a 'threshold' level for these traits below which physical function is impaired. Once strength falls below a threshold value specific to that individual, physical function is impacted. Though such a threshold would surely be different for each individual, we can expect clinically meaningful thresholds could be established across various physical characteristics, including body composition and strength. This threshold concept has been discussed by a number of groups.[118–121] Because genetic variation will tend to have subtle influences on skeletal muscle traits, that genetic influence will tend to push muscle trait values closer to or farther away from this threshold, altering an individual's risk for impaired physical function. Identifying individuals with a genetic susceptibility to lower levels of skeletal muscle strength or mass (and who are closer to their likely threshold for physical limitation) will allow for earlier, targeted interventions to help prevent those losses. Similarly, it is important to recognize that genetic factors may have an impact on either the development of adult muscle mass and strength or the decline of these traits from their peak values in early adulthood. Different genetic influences can be envisioned for both of those traits, in effect differentiating the trajectories of muscle development from those of muscle loss. Finding these genes and developing the individualized interventions will take many years. Even if genes of only minor effect are identified that don't lend themselves directly to genetic screening and personalized medicine, those genes will point to the potential physiological pathways that can be manipulated through more typical means and thereby add to our understanding of the underlying etiology of sarcopenia.[122,123]

Conflict of Interest

The author declares no conflict of interest.

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