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Genetic Variant in *ACVR2B* Is Associated with Lean Mass

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Abstract

Introduction—Low lean mass (LM) is a risk factor for chronic disease, a major cause of disability and diminished quality of life, and is a heritable trait. However, relatively few specific genetic factors have been identified as potentially influencing this trait.

Methods—In this study, we selected 1,493 single-nucleotide polymorphisms (SNPs) in 155 candidate genes involved in anabolic, catabolic, growth hormone, and other related pathways, and examined their association with LM, assessed by dual energy x-ray absorptiometry, in a sample of 2,760 non-Hispanic and Hispanic White postmenopausal women from the Women's Health Initiative (WHI) Observational Study. We assessed replication of our top findings in a meta-analysis of twenty genome-wide association studies (n=38,292) conducted by the CHARGE Consortium Musculoskeletal Working Group.

Results—We identified 32 SNPs that had significant associations with LM in the WHI cohort. In the replication stage, we find that SNP rs2276541 in the activin A receptor, type IIB (*ACVR2B*) was significantly associated with LM (β=0.15; p=2.17 × 10^{-5}). *ACVR2B* codes for a receptor for a negative regulator of skeletal muscle, mysostatin, and has previously been identified in a candidate gene study as a determinant of skeletal muscle mass.

Conclusions—Our findings support a previously proposed role of *ACVR2B* allelic variation as a determinant of muscle mass and extend prior findings in men to women. Additional large-scale studies will be needed to confirm our findings in different populations.

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Supplemental Digital Content Supplement - Klimentidis et al.docx: List of candidate genes tested in the Women's Health Initiative cohort.

Keywords

muscle mass; SNP; activin A receptor; type IIB; dual energy x-ray absorptiometry

Introduction

Lean mass (LM) is an important body composition parameter, having been linked to many health outcomes such as cardiovascular disease and diabetes (35, 45, 48), and is of particular concern during the aging process, when loss of LM can impact physical function, independence, and frailty (4, 25, 28, 39). Twin and family studies have demonstrated that LM is a heritable trait (11, 19). However, relatively few specific genetic factors have been identified as potentially influencing this trait. Nevertheless, there are a number of pathways and biomarkers that have been identified as potentially regulating LM. Because LM loss is potentially preventable with lifestyle modification, knowing individual susceptibility years in advance (i.e., prior to measurable changes in LM with aging) through simple genetic testing would improve opportunities for early intervention, such as targeted physical activity interventions. Identifying the genetic factors associated with LM may also help understand the biology of muscle accrual and loss, and identify targets for pharmaceutical interventions.

Variation in LM is likely to be largely attributed to variation in catabolic and anabolic factors which affect the extent of muscle accrual and loss. Growing evidence that genetic variation influences the expression and activity of many anabolic and catabolic hormones/cytokines associated with LM suggests that inter-individual genetic variation may contribute to LM. For example, common allele variations in the genes encoding the pro-inflammatory cytokines IL-1 (8), IL-6 (13) and TNF-α (15) and their receptors have been identified and implicated as genetic determinants of individual variation in their expression and in vivo action. In addition, genes encoding growth hormone (GH) (9, 17), growth hormone receptor [GHR] (12), IGF-1 (30, 31), IGF-1 receptor (6), and IGFBP-1 (10) are also genetically variable at the population level and as such, common gene variation that affect the expression and activity of IGF-1 and GH are strongly implicated as determinants of individual differences in height, body size, muscle strength, and longevity (6, 9, 30, 31).

Based on existing evidence, we used a candidate gene-based approach to test for association of genetic variation with LM. We worked from the premise that the balance of catabolic and anabolic factors affects LM. We tested the hypothesis that polymorphisms in 155 genes which are known to be involved in the anabolic/catabolic balance, or previously found to be involved in muscle growth and atrophy are associated with LM in a sample of postmenopausal women. We also examined other genes implicated in LM through myostatin (23, 47), inflammatory (33, 36, 40), and growth hormone (9) pathways. We then examined whether identified associations could be replicated using data from twenty genome-wide association studies included in the meta-analysis conducted by the CHARGE Consortium Musculoskeletal Working Group

Methods

Study population

The study population in this analysis was drawn from the multi-ethnic cohort of 93,676 postmenopausal women enrolled in the Women's Health Initiative Observational Study (WHI-OS) between 1993 and 1998 at 40 US clinical centers (2, 3). Body composition by dual-energy X-ray absorptiometry (DXA) scans was assessed at three WHI clinical centers (Pittsburgh, PA; Birmingham, AL; Tucson-Phoenix, AZ) at baseline (n=11,393). A subset of WHI-OS participants with body composition data and stored whole-blood samples was selected for genetic analysis based on the following inclusion criteria: 1. Hispanic white or non-Hispanic white women, 2) being seen either at Tucson-Phoenix, AZ, or Pittsburgh, PA; 3) have at least two DXA scans (one at the baseline visit and one during the follow-up); 4) sufficient stored blood samples. This was an ancillary study of the Body Composition Cohort in the Women's Health Initiative (WHI). Although WHI is a multiethnic study, both the number of minority participants in the Body Composition Cohort and funding for genotyping were limited. We selected Hispanic (all) and non-Hispanic white (a random sample) women for genotyping since they were at higher risk for sarcopenia in comparison to African-Americans, and the number of Asians and Native Americans is too small to allow any subgroup analysis. More detailed descriptions of overall WHI-OS recruitment, data collection, and baseline characteristics have been previously published (2). Fasting blood samples were collected and stored for long-term storage at −70°C. All procedures and protocols were approved by the institutional review boards at each participating institution, and all participants provided written informed consent.

Replication stage

We used summary statistics from the discovery phase of the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium Musculoskeletal Working Group meta-analysis of genome-wide association studies of whole-body lean mass among 38,292 individuals (59% female) of European ancestry from 20 cohorts (WHI not included; see Supplemental Digital Content 1 for list of specific studies) with varying epidemiological study designs. LM measurements were based on DXA or bioelectrical impedance analysis. Whole-genome genotype data was imputed in each cohort up to approximately 2.5 million SNPs using either IMPUTE (18) or MACH (26). In most studies, SNPs with minor allele frequency ≤ 1%, <90% call rate, a Hardy-Weinberg equilibrium test with $p<10^{-6}$, and poor imputation accuracy (e.g. `info'<0.4) were excluded from analyses, as well as individuals with <95% call rate and ethnic outliers, as determined by principal components analysis. The association analysis was based on linear regression model including the following covariates: sex, age, age^2, height, and percent body fat. Adjustments for ancestral background (via principal components), family structure, and study-specific covariates, as needed, were also included. Fixed-effects and inverse variance-weighted meta-analyses were performed using the METAL package (44).

Phenotypes

At clinic visits, weight was measured to the nearest 0.1 kg on a balance-beam scale. Height was measured without shoes using a stadiometer to the nearest 0.1 cm. BMI was calculated

as body weight (kg) divided by height squared (m^2). Whole-body and appendicular LM and fat measurements were derived from dual-energy x-ray absorptiometry (DXA), measured at the baseline visit (QDR2000, 2000+, or 4500W; Hologic Inc, Bedford, MA). DXA-derived estimates of LM have previously been shown to correlate closely with skeletal muscle mass measured through magnetic resonance imaging (7). Standard positioning, quality-control, and analysis protocols were implemented by technicians trained and certified by the University of California, San Francisco, Bone Density Coordinating Center, San Francisco, California (7, 22). Measurements were transformed with log 2 function to fit the requirement of a normal distribution.

Genotypes

Candidate genes and SNPs were selected based on the strength of evidence from animal and cell culture studies of direct action on muscle growth and atrophy; they included: 1) published studies on biomarkers of muscle growth and atrophy, and 2) biological pathways known to be involved in anabolism and catabolism. Genotyping was performed by Illumina Inc. (San Diego, CA) on the Golden Gate platform. 1,493 SNPs from 155 genes at 21 chromosomes were genotyped. SNPs in each gene were selected based on tag SNPs ($r^2<0.8$) and > 0.1 minor allele frequency (see Table, Supplemental Digital Content 1, List of candidate genes tested in the Women's Health Initiative cohort). Of the 2,800 postmenopausal women from the Women's Health Initiative (WHI) Observational Study (2), genotyping was successfully completed on 2,760 women: 354 were Hispanic and 2,406 were non-Hispanic White. SNPs with minor allele frequency < 10%, with call rate < 5% and not in Hardy Weinberg equilibrium ($p < 0.001$) were excluded from the analysis. Any individuals whose SNP call rates were less than 95% were excluded from analysis.

Statistical Analysis

We assumed that the associations of LM with related SNPs are linear additive. Univariate regression models were used to assess the relationship between the log 2 transformed LM measurement and each SNP, and multiple linear regression models were used to evaluate this association after adjustment for age, age^2, height, and percent body fat. The covariates were selected based on their significant association with SNPs or LM at $p<0.05$. Analyses were stratified by ethnicity, and also conducted in the entire sample. To get an estimate of the effect of a SNP on lean mass in WHI, we cannot back-transform the coefficient. However, for the top SNP, we applied an approximation by multiplying the beta coefficient by the median value of the log 2 transformed LM variable.

The 32 SNPs that were nominally associated ($p<0.05$) with whole-body or appendicular LM in the non-Hispanic White WHI sample were analyzed *in silico* for association with lean muscle mass in the discovery phase of the CHARGE Consortium Musculoskeletal Working Group meta-analysis of genome-wide association studies, as described above.

Associations were considered significant if the p-value was lower than 0.0016 in the CHARGE-only analysis (i.e. Bonferroni correction for 32 tests), a conservative adjustment for multiple testing, given that there were a total of 20 genes represented among the replicated 32 SNPs.

Results

Characteristics of the WHI sample are shown in Table 1. Women in this sample (mean age=64.1 ± 7.4 years) had a mean of 37 ± 5 kg of LM, and 29.7 ± 11 kg body fat. Hispanic women were younger, shorter, had less LM and higher body fat than non-Hispanic White women (see Table 1).

Table 2 shows the 32 SNPs in 20 genes consistently associated with whole-body or appendicular LM in the non-Hispanic White WHI sample. In this table, the association between each of these 32 SNPs with whole-body LM in the WHI (entire sample and within each ethic group) and the CHARGE dataset is shown. Of these 32, five SNPs were associated with LM at a nominal significance level ($p<0.05$) in the CHARGE consortium. The lowest observed p-value was for SNP rs2276541 ($p=2.17 \times 10^{-5}$). The A allele at this SNP was associated with more LM in both WHI and CHARGE. The rs2284817 ($p=5.3 \times 10^{-4}$) is in LD ($r^2=0.79$) with rs2276541, and both of these SNPs are intronic in the *ACVR2B* gene. The association of SNP rs12439003 in the *CAPN3* gene with LM is borderline non-significant (p=0.0029 in CHARGE) according to the conservative Bonferroni threshold ($\alpha=0.0016$). The rs2276541 and rs2284817 SNP in *ACVR2B* are respectively associated with a 0.06 and 0.09 kg-per-allele difference in the WHI cohort, and a 0.15 and 0.13 difference in the CHARGE analysis. The rs12439003 SNP in the *CAPN3* gene is associated with a 0.08 and 0.18 kg-per-allele difference in the WHI and CHARGE analyses, respectively. Among Hispanics, the effects sizes were generally very similar to those observed among non-Hispanic Whites, although given the smaller sample size of Hispanic women in the study, the associations did not reach statistical significance.

Discussion

We used a candidate gene approach focused on genes involved in anabolic and catabolic pathways, and in muscle growth and atrophy. We present evidence showing that the A allele of genetic variant rs2276541 in *ACVR2B*, and potentially the A allele of variant rs12439003 in *CAPN3*, are reproducibly associated with approximately 0.1 kg greater LM.

ACVR2B codes for activin IIb, the receptor for myostatin which is a negative regulator of muscle cells(37). Knocking out ACVR2B or introducing a soluble receptor limits myostatin signaling and leads to a “double muscled” animal (23, 24). Conversely, higher myostatin has been documented with aging, and correlates with the lower muscle mass, indicative of advanced age (46). Presumably, the higher levels of myostatin are accompanied by sufficient activity or numbers of activin IIb receptors to confer the lower muscle mass, but data to support this hypothesis could not be located. In animal models, both myostatin and activin receptor IIb have been downregulated by exercise (20, 21, 41). Variation in *ACVR2B* has previously been found to be associated with skeletal muscle strength in humans (43). In that study, among men and women aged 19–90, Walsh et al. found an association between one of the major *ACVR2B* haplotypes and muscle strength in women. The SNP tagging this haplotype (rs2268757) is within 7 kb of, and in LD with, both SNPs identified in this study ($r^2=0.80$ and 0.64 with rs2276541 and rs2284817, respectively).

Calpain 3 is a muscle-specific member of the family for which mutations have previously been associated with a form of muscular dystrophy (16). Although *CAPN3* codes for a protease (catabolic side), its structural role and interaction with titin at the sarcomere level of skeletal muscle may be more important for skeletal muscle health than its proteolytic activity (16). Theoretically, it is possible that greater structural integrity contributes to higher functioning and ease of physical activity, thereby indirectly contributing to mass, as well. Much more research is needed to confirm these assertions.

It is important to note that all of the genes and SNPs that we have chosen to examine showed some prior evidence in the literature of being involved in LM variation or related pathways. Thus there are many loci previously thought to be important in LM variation (e.g. 12, 26) that do not display evidence of association in both WHI and CHARGE. For example, given the role that vitamin D plays in muscle development, previous studies have investigated variants in the vitamin D receptor (VDR) and found them to be associated with muscle mass and strength (e.g. 30, 37). Although one of these SNPs was nominally associated with LM in the WHI sample, it was not significantly associated with LM in the CHARGE replication stage. Previous candidate gene studies, although based on pathways related to muscle development, were often not replicated, stressing the importance of both replication as well as the genome-wide approach to strengthen evidence and to identify novel loci.

The strengths of our study include the use of DXA for measuring LM, which has been shown to be a reliable way of estimating skeletal muscle mass (7), the use of a biological-based approach to selecting candidate genes, and the use of a large GWAS meta-analysis for replication. To reduce potential confounding effects of height, percent fat and the impact of age on lean mass, this study has also controlled for these factors. Weaknesses of our study include a small number of Hispanic participants, and the candidate gene approach limited to a set of selected genes based on our knowledge from about 10 years ago. It is known that WHI is a selected group of postmenopausal women, so the generalizability of the finding to other gender and age groups remains to be determined. Menopause, itself, could be an important contributing factor to the genetic associations that we observe, and may explain differences between our study and the CHARGE analysis which is based on males and females from a wider age range. Specifically, menopause is associated with an accentuated decline in muscle mass, potentially associated with the menopause-related decrease in GH, IGF1 and androgens which all affect the loss of lean mass (1, 27, 32). Since women have low lean mass and older women experience menopause-related loss of lean mass, our study findings may have some uniqueness to postmenopausal women.

The effect on lean mass associated with these genetic variants is very small. As with other complex traits, each genetic variant explains very little phenotypic variation, and many hundreds or thousands of loci likely underlie this phenotypic variation. Therefore, the utility of genetic information, at least in the near future, will lie in a better understanding of molecular and physiological processes underlying muscle accrual and loss, and how lifestyle factors such as physical activity or diet may interact with these processes. As additional loci associated with LM are identified, it will be important to examine whether and how these loci interact with physical activity and diet. For example, it may be that individuals with a

certain genetic background may benefit more than others from resistance exercise with respect to maintenance, accrual, or quality of LM (5, 38).

In conclusion, genetic variation in *ACVR2B* may be important for skeletal muscle mass in non-Hispanic White postmenopausal women. Future research should explore these associations in other populations, consider sex-specific associations, and should consider both genotypes and relevant blood biomarkers simultaneously in order to gain a better understanding of the physiological and pathophysiological pathways underlying LM accrual and loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of the study participants, in the total sample size, and stratified by ethnicity.

	Total (n=2,760)	Hispanic (n=354)	Non-Hispanic White (n=2,406)
Age (years) *	64.1 ± 7.4	61.0 ± 7.3	64.5 ± 7.4
Height (cm) *	161.0 ± 6.6	158.0 ± 5.8	161.5 ± 6.6
Weight (kg)	70.3 ± 15.8	71.6 ± 16.3	70.1 ± 15.7
Whole body lean tissue mass (kg) *	37.0 ± 5.1	36.2 ± 5.2	37.06 ± 5.1
Whole body % lean tissue (%) *	55.0 ± 7.4	52.9 ± 6.8	55.3 ± 7.4
Whole body fat mass (kg) *	29.7 ± 11.1	31.5 ± 10.8	29.4 ± 11.1
Whole body % fat (%) *	42.1 ± 7.7	44.2 ± 7.1	41.7 ± 7.7

* indicates $p<0.05$ for difference between Hispanics and Non-Hispanic Whites.

Table 2

Association in WHI and CHARGE of lean mass with 32 SNPs identified in WHI.

					WHI - Non-Hispanic White			WHI - Hispanic			WHI - Total			CHARGE meta-analysis results		
Marker	**Chr.**	**Nearest Gene**	**Effect Allele**	**Other Allele**	**Effect**	**Standard Error**	**P-value**	**Effect**	**Standard Error**	**P-value**	**Effect**	**Standard Error**	**P-value**	**Effect**	**Standard Error**	**P-value**
rs2276541	3	ACVR2B	A	G	0.012	0.005	0.014	0.014	0.013	0.307	0.012	0.004	0.006	0.1543	0.0363	2.17E-05
rs2284817	3	ACVR2B	A	G	−0.018	0.005	0.0004	−0.012	0.015	0.429	−0.017	0.005	0.0005	−0.1328	0.0383	0.000528
rs12439003	15	CAPN3	A	G	0.016	0.007	0.025	0.015	0.021	0.478	0.015	0.007	0.020	0.1778	0.0596	0.002848
rs11627387	14	MTHFD1	A	G	0.010	0.005	0.047	−0.012	0.017	0.487	0.008	0.005	0.081	0.1006	0.0442	0.02298
rs7944040	11	LRP5	T	C	0.010	0.005	0.040	0.016	0.014	0.251	0.011	0.004	0.015	0.0886	0.0416	0.03314
rs8026997	15	MTHFS	T	C	0.011	0.005	0.022	0.004	0.014	0.757	0.010	0.005	0.032	0.0692	0.0376	0.06577
rs11854561	15	MTHFS	T	C	−0.011	0.005	0.039	−0.001	0.016	0.961	−0.009	0.005	0.062	−0.0673	0.0397	0.09037
rs11168292	12	VDR	C	G	−0.012	0.005	0.014	−0.014	0.016	0.387	−0.012	0.005	0.012	0.0597	0.0374	0.1102
rs3770473	2	IGFBP2	T	G	0.014	0.005	0.007	−0.010	0.014	0.495	0.011	0.005	0.021	−0.1219	0.0819	0.1366
rs3020619	17	GH1	T	C	−0.014	0.005	0.010	0.016	0.017	0.320	−0.011	0.005	0.035	−0.1442	0.1023	0.1587
rs8659	5	MTRR	A	T	−0.011	0.005	0.030	−0.004	0.014	0.797	−0.009	0.005	0.061	0.0496	0.0382	0.1938
rs2273608	14	DLK1	T	C	0.019	0.008	0.020	0.025	0.017	0.146	0.018	0.007	0.012	0.0713	0.0662	0.2814
rs7703033	5	MTRR	A	G	−0.011	0.005	0.030	0.019	0.016	0.248	−0.007	0.005	0.129	0.0349	0.04	0.3825
rs3115883	15	CAPN3	T	C	−0.011	0.005	0.027	0.016	0.015	0.272	−0.008	0.005	0.101	−0.0284	0.0419	0.4978
rs12441700	15	CAPN3	T	C	0.015	0.007	0.029	0.014	0.015	0.341	0.013	0.006	0.031	0.0305	0.0533	0.5677
rs11751539	6	SIRT5	A	T	−0.019	0.008	0.020	0.006	0.022	0.785	−0.016	0.008	0.042	−0.036	0.0708	0.6114
rs1978346	2	IGFBP5	A	G	0.011	0.005	0.020	0.003	0.014	0.808	0.011	0.005	0.017	0.0189	0.0429	0.6592
rs16959025	16	NFAT5	T	G	−0.014	0.006	0.024	−0.044	0.018	0.014	−0.017	0.006	0.002	−0.0192	0.0453	0.6717
rs10500551	16	NFAT5	T	C	0.012	0.006	0.042	0.038	0.014	0.005	0.015	0.005	0.004	0.0188	0.0451	0.6773
rs12439137	15	CYP19A1	A	G	0.016	0.007	0.028	−0.019	0.018	0.285	0.011	0.007	0.109	0.0233	0.0569	0.6822
rs326123	5	MTRR	A	G	−0.010	0.005	0.035	0.012	0.014	0.400	−0.008	0.005	0.094	0.0148	0.0389	0.7035
rs1256120	14	ESR2	A	G	0.017	0.007	0.016	0.015	0.016	0.360	0.017	0.006	0.007	−0.0209	0.0552	0.7056
rs84353	1	PAX7	T	C	0.011	0.005	0.027	−0.009	0.014	0.495	0.008	0.004	0.059	−0.0278	0.0737	0.7061
rs2813543	6	ESR1	A	G	−0.020	0.006	0.0003	0.009	0.020	0.663	−0.016	0.005	0.002	0.0079	0.0485	0.8704
rs6575806	14	RTL1	A	C	−0.013	0.005	0.017	0.011	0.018	0.517	−0.011	0.005	0.036	0.0131	0.0929	0.8883
rs162031	5	MTRR	T	C	0.015	0.006	0.008	0.007	0.015	0.655	0.014	0.005	0.011	0.0038	0.0459	0.9341

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					WHI - Non-Hispanic White			WHI - Hispanic			WHI - Total			CHARGE meta-analysis results		
Marker	**Chr.**	**Nearest Gene**	**Effect Allele**	**Other Allele**	**Effect**	**Standard Error**	**P-value**	**Effect**	**Standard Error**	**P-value**	**Effect**	**Standard Error**	**P-value**	**Effect**	**Standard Error**	**P-value**
rs8049728	16	NFAT5	T	G	0.010	0.005	0.038	0.023	0.013	0.078	0.011	0.004	0.012	−0.0025	0.036	0.9438
rs8061052	16	NFAT5	A	G	0.010	0.005	0.038	0.023	0.013	0.080	0.011	0.004	0.012	−0.0025	0.036	0.9447
rs848209	1	SPEN	T	C	−0.010	0.005	0.032	0.007	0.014	0.607	−0.007	0.004	0.093	−0.0018	0.0356	0.9601
rs12447326	16	NFAT5	T	C	0.015	0.005	0.005	0.033	0.013	0.010	0.017	0.005	0.001	0.0011	0.0403	0.9779
rs11643240	16	NFAT5	A	G	−0.014	0.005	0.006	−0.033	0.013	0.010	−0.016	0.005	0.001	0.0008	0.0403	0.985
rs1003483	11	IGF2AS	T	G	−0.011	0.005	0.023	−0.009	0.013	0.506	−0.010	0.004	0.025	0.0005	0.0426	0.9906

Abbreviations: Chr.: Chromosome; MAF: Minor allele frequency.