

Vitamin D Receptor Genotype Is Associated With Fat-Free Mass and Sarcopenia in Elderly Men

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We investigated the association of vitamin D receptor (VDR) genotype with fat-free mass (FFM) in a cohort of 302 older (aged 58–93 years) Caucasian men who underwent body composition analysis by dual-energy X-ray absorptiometry, and completed questionnaires addressing comorbidities, physical activity, and dietary intake. All participants were genotyped for a VDR translation start site (FokI) polymorphism [FF (37.7%), Ff (48.4%), and ff (13.9%)] and the previously studied BsmI polymorphism [BB (24.9%), Bb (37.7%), and bb (37.4%)]. The BsmI polymorphism was not associated with FFM in any analysis; however, the FokI polymorphism was significantly associated with total FFM, appendicular FFM, and relative (kg/m^2) appendicular FFM (all $p < .05$), with the FF group demonstrating significantly lower FFM than the Ff and ff groups (e.g., total FFM: FF = 57.6 ± 0.4 , Ff = 59.4 ± 0.4 , ff = 59.4 ± 0.7 kg; $p < .02$). Age-adjusted logistic regression revealed a 2.17-fold higher risk for sarcopenia (defined previously as appendicular FFM $< 7.26 \text{ kg}/\text{m}^2$) in FF homozygotes (95% CI [confidence interval] = 1.19–3.85; $p = .03$) compared to men with one or more f alleles. The VDR translation start site (FokI) polymorphism is significantly associated with FFM and sarcopenia in this cohort of older Caucasian men.

AGING is associated with a gradual loss of muscle mass and strength (1,2), leading to sarcopenia and significant decrements in physical function, metabolic impairments, and disability (2,3). Diminished muscle strength has also been associated with mortality in older adults (4,5). Although numerous mechanisms have been proposed, the events leading to sarcopenia are unclear and likely multifactorial, encompassing hormonal, neurological, nutritional, environmental, and genetic factors, and their interactions (6).

One environmental factor associated with age-related losses in muscle function is vitamin D status, with low blood levels of vitamin D associated with muscle weakness and atrophy of type II muscle fibers (7,8). The receptor for 1,25-dihydroxyvitamin D [1,25(OH)₂D], VDR (vitamin D receptor), is expressed in skeletal muscle and is an important mediator of 1,25(OH)₂D effects on muscle contractility (9). A T/C transition polymorphism in exon 2 of VDR (10) alters the translation initiation start site, such that individuals with the C allele (designated “F”) initiate translation at a second initiation site downstream of the initiation site of individuals with the T allele (designated “f”) (11). Thus, individuals with the T allele synthesize the full-length VDR protein (427 amino acids), while individuals with the C allele synthesize a slightly truncated version of the VDR protein (424 amino acids). The truncated F isoform of the VDR protein has been shown to have greater transcriptional activation of reporter genes *in vitro* (11,12) and more efficient interaction with a key transcription factor (13) than the longer f isoform. Additional polymorphisms have been identified in the VDR gene (e.g., BsmI, TaqI, and ApaI polymorphisms), but none have known functional significance (10).

Muscle mass and strength are highly heritable (14–16), although the genes that contribute to variation in these phenotypes have not been clearly identified. Previous work has indicated an association between sequence variation in the VDR gene and muscle strength in women (17,18), and body weight and fat-free mass (FFM) in men (19). In the present work, we studied the association of total body mass, nonosseous FFM, and muscle strength with both the translation start site (FokI) polymorphism and the BsmI polymorphism in the VDR gene in 302 older men from the Study of Osteoporotic Risk in Men (STORM) (20). We chose to study the BsmI site because it has been the focus of the bulk of existing literature in this area (17,18,21), and the FokI site because of its functional significance. In previous work, the B allele of the BsmI polymorphism has been inconsistently associated with greater muscle strength, which we sought to confirm. For the FokI site, we hypothesized that the f allele would be associated with reduced muscle mass and strength.

METHODS

Participants

From February 1991 to February 1992, a total of 523 community-dwelling Caucasian men attended a clinic examination for STORM, a study of the determinants of bone density in men aged 50 years and older (20). Participants were recruited primarily from population-based lists of age-eligible voters in the Monongahela Valley (30 miles southeast of Pittsburgh, Pennsylvania). We excluded men who were unable to walk without the assistance of

another person or who had undergone a bilateral hip replacement. Of the 523 men who participated in the baseline examination, 302 provided peripheral blood leukocytes for DNA extraction and genotyping at subsequent clinic visits, and form the basis of the present analyses. Written informed consent was obtained from all participants, and the University of Pittsburgh Institutional Review Board approved the protocol.

Genotyping

High-molecular-weight genomic DNA was isolated from peripheral lymphocytes using standard techniques. Participants were genotyped for the VDR FokI and BsmI restriction sites as previously described (17,22), and grouped as FF, Ff, and ff, and BB, Bb, and bb genotypes, respectively.

Body Composition

Whole-body soft tissue composition was measured by dual-energy X-ray absorptiometry (DXA) with the array mode (Hologic QDR 2000; Hologic, Inc., Waltham, MA). DXA measurements were made by a certified technician using DXA software and standardized procedures for patient positioning. The system software provided the mass of fat-free soft tissue, fat, and bone mineral for both the whole body and specific regions. Appendicular muscle mass was considered equivalent to the sum of FFM in both the right and left arms and legs. Appendages were isolated from the trunk and head by using DXA regional computer-generated default lines with manual adjustment. As previously described by Baumgartner and colleagues (23), both appendicular and total FFM values were made relative to body height squared (kg/m^2) to address the strong correlation among these variables with height. Similarly, sarcopenia was defined as relative appendicular muscle mass $<7.26 \text{ kg}/\text{m}^2$, which is below two standard deviations from the mean of a young non-Hispanic white reference population used by Baumgartner and colleagues (23).

Muscle Strength Testing

Quadriceps strength was measured using the Bodymaster Isometric Dynamometer (Dublin, CA) and Jackson Evaluation System (Lafayette Instrument Co., Lafayette, IN). Participants had one practice trial and two test trials on each leg. A trial consisted of 4 seconds of contraction, with force measurements recorded during the last 3 seconds. Peak and average torque in pounds were displayed at the end of each trial. Testing was performed with the participant seated and strapped into the machine with arms folded across the chest. The padded lever arm was positioned so that it contacted the participant's shin just proximal to the foot. The trial began when the participant was instructed to bring his shin gently to the pad until tension was felt (knee extended to 125°). The examiner then instructed the participant to begin pushing and extend the leg with a maximum effort throughout the 4-second period. Verbal encouragement was offered by the examiner.

Hormone Assays

All men were instructed to fast overnight to minimize lipemia on the morning of the examination. Blood was

drawn between 08:00 and 12:00 hours, and serum was frozen at -70°C until first thawed for hormone assays. Samples for $1,25(\text{OH})_2\text{D}$ analysis were sent directly from storage to the analytical laboratory (Esoterix, Calabasas Hills, CA) without thawing, and were measured by a radio-receptor assay using a procedure similar to Reinhardt and colleagues (24). Intraassay and interassay coefficients of variation, respectively, averaged 6.5% and 10.5%.

Total testosterone was measured by radioimmunoassay after extraction and purification by LH-20 column chromatography (25). Bioavailable testosterone was determined by an ammonium sulfate precipitation process that separated the sex hormone-binding globulin-bound steroid from albumin-bound and free steroid (26).

Other Measures

Body weight was measured to the nearest 0.1 kg after removal of shoes and heavy outer clothing on a calibrated balance beam scale. Height was measured to the nearest 0.1 cm after removal of shoes, at the peak of a deep inhalation, using a wall-mounted Harpenden stadiometer (Holtain, Dyved, U.K.). The average of two height measurements was used in statistical analysis. Body mass index (kg/m^2) was calculated from height and weight measurements. Participants also completed a self-administered questionnaire, which was reviewed with the participant in the clinic by a trained interviewer. In addition to medical history, we asked participants if they engaged in rigorous exercise at least once per week, currently smoked cigarettes, and drank alcohol. Dietary intake was assessed by the 1995 revision of the National Cancer Institute–Block Health Habits and History Questionnaire (27,28). We measured physical activity using a modified Paffenbarger Scale (29), in which participants reported the frequency and duration of their participation per week during the past year in 33 different physical activities. The activities were assigned energy expenditures according to previously reported methods (30). Total physical activity, expressed in kilocalories expended per day, was calculated by adding kilocalories expended in the 33 recreational activities.

Statistics

Deviation from expected Hardy Weinberg equilibrium was calculated using Chi-square analysis. Chi-square analysis was also used to determine differences in the expected frequency of sarcopenic men within each genotype group. For testing associations between VDR genotype and FFM and muscle strength variables, an initial analysis was performed separately for the BsmI and FokI polymorphisms for each phenotype measure using a multiple regression model that included all potential covariates. This strategy was repeated with the inclusion of both BsmI and FokI genotypes within the same model. Covariates with a p value $>.10$ were then removed from each model, and a second analysis was performed using analysis of covariance (ANCOVA), which included VDR genotype group, age, total fat, physical activity, and any covariates not excluded from the initial regression model. Statistical significance for the ANCOVA models was accepted at $p < .05$. Analysis of variance models were used to test for differences in physical

Table 1. Subject Characteristics by Vitamin D Receptor FokI Genotype

VDR Genotype Group	FF	Ff	ff	<i>p</i> Value
<i>N</i>	114	146	42	—
Age (y)	73.1 ± 0.7	73.0 ± 0.6	72.2 ± 1.1	.76
Height (cm)	173 ± 0.6	173 ± 0.5	173 ± 0.9	.96
Body weight (kg)	81.4 ± 1.1*	85.0 ± 1.0	86.9 ± 1.8	.02
BMI (kg/m ²)	27.2 ± 0.3*	28.1 ± 0.3	29.3 ± 0.6	.01
Total fat mass (kg)	20.2 ± 0.6 [†]	21.3 ± 0.5	22.7 ± 1.0	.07
Percent body fat (%)	24.8 ± 0.4	25.0 ± 0.4	26.0 ± 0.7	.27
Caloric intake (kcal/d)	1891 ± 58	1827 ± 51	1775 ± 96	.53
Protein intake (g/d)	77.8 ± 2.6	74.4 ± 2.3	72.3 ± 4.3	.45
Physical activity (kcal/d)	242 ± 28	225 ± 25	202 ± 46	.74
1,25(OH) ₂ D (pg/mL)	48.0 ± 1.3	49.6 ± 1.2	47.3 ± 2.2	.54

Notes: Data are least squares means ± SE (standard error).

**p* < .05 compared with both Ff and ff genotype groups.

[†]*p* < .05 versus ff genotype group only.

VDR = Vitamin D receptor; BMI = body mass index.

characteristics among VDR genotype groups. Logistic regression analysis with age adjustment was used to estimate the odds ratios and 95% confidence intervals (CI) for the association between VDR genotype and the prevalence of sarcopenia. Data presented are least squares means ± SE (standard error).

RESULTS

A total of 297 men were genotyped for the VDR BsmI polymorphism (74 BB, 112 Bb, and 111 bb), and 302 men were genotyped for the FokI polymorphism (114 FF, 146 Ff, and 42 ff). For BsmI, the frequency of the less-common B allele was *q* = .44, and the genotype frequencies (BB: 24.9%, Bb: 37.7%, and bb: 37.4%) differed from those expected by Hardy Weinberg equilibrium (*p* < .01). For FokI, the frequency of the less common f allele was *q* = .38, and the genotype frequencies (FF: 37.7%, Ff: 48.4%, and ff: 13.9%) did not differ from those expected by Hardy Weinberg equilibrium (*p* = .91).

In all analyses, the BsmI polymorphism was not significantly associated with any body composition or strength phenotype, and all data are shown relative to the FokI polymorphism. As shown in Table 1, no significant differences were observed among FokI genotype groups for age, height, daily physical activity, total caloric or protein intake, 1,25(OH)₂D levels, or percent body fat; however, significantly lower total body mass and body mass index were observed in the FF compared with the Ff and ff genotype groups (both *p* ≤ .02). Approximately 25% of men reported vitamin D supplementation; that proportion did not differ significantly by FokI genotype, and vitamin D supplementation was not a significant covariate in any analysis.

As shown in Table 2, significant FokI genotype differences were observed for each of the FFM phenotype measures. For all soft tissue FFM variables, the FF group exhibited significantly lower FFM than both the Ff and ff groups in ANCOVA models that adjusted for age, bioavailable testosterone, serum vitamin D levels, cigarette smoking, total fat, height (for unadjusted variables), and physical activity (all *p* < .05; Table 2). Based on the

Table 2. Soft Tissue Fat-Free Mass Variables by Vitamin D Receptor FokI Genotype

VDR Genotype Group	FF	Ff	ff	<i>p</i> Value
Appendicular muscle mass (kg)	23.4 ± 0.2*	24.4 ± 0.2	24.1 ± 0.4	.009
Relative appendicular muscle mass (kg/m ²)	7.8 ± 0.1*	8.1 ± 0.1	8.1 ± 0.1	.001
Total FFM (kg)	57.6 ± 0.4*	59.4 ± 0.4	59.4 ± 0.7	.002
Relative total FFM (kg/m ²)	19.2 ± 0.1*	19.8 ± 0.1	19.9 ± 0.2	.003

Notes: Data are least squares means ± SE (standard error) adjusted for age, total fat, physical activity, bioavailable testosterone, serum 1,25(OH)₂D levels, cigarette smoking, and height (for unadjusted FFM variables).

**p* < .05 versus Ff and ff groups.

VDR = Vitamin D receptor; FFM = fat-free mass.

adjusted R square values, FokI genotype accounted for 1.1% of the variance in total FFM, 1.3% of appendicular FFM (asm), 1.9% of the relative total FFM (kg/m²), and 2.1% of the relative appendicular FFM (rasm) in multiple regression models that included the covariates (all *p* < .05). The addition of the BsmI polymorphism to regression or ANCOVA models did not improve or change the significance associated with the FokI polymorphism for any FFM variable.

Vitamin D levels did not differ by FokI genotype (Table 1). We further evaluated the interaction between serum concentrations of 1,25(OH)₂D, FokI genotype, and FFM using ANCOVA. We found no significant interactions between FokI genotype and serum vitamin D levels for any soft tissue FFM phenotype (data not shown).

We further analyzed the relationship between FokI genotype and soft tissue FFM by classifying the men as “normal” or “sarcopenic.” Men with relative appendicular FFM values <7.26 kg/m² were categorized as sarcopenic based on previous criteria (23). The overall prevalence of sarcopenia among these older men was 24.8%. We evaluated the frequencies of the FokI genotype groups among men with normal appendicular skeletal muscle mass (*n* = 227) and those who were sarcopenic (*n* = 75). Chi-square analysis revealed a significant difference in the expected frequency of sarcopenic men, with higher-than-expected numbers in the FF group (*p* = .03; Figure 1). Similarly, age-adjusted logistic regression analysis revealed a significant association between FokI genotype and the presence of sarcopenia (Figure 1; *p* = .03). Men with the FF genotype demonstrated a 2.17-fold higher risk of sarcopenia (95% CI: 1.19–3.85) than men with the ff genotype, independent of age. The BsmI polymorphism was not associated with the presence of sarcopenia.

FokI genotype was significantly associated with quadriceps average and peak strength values (*p* < .05; Table 3). However, adjusting for genotype-related differences in FFM eliminated the association between FokI genotype and muscle strength.

DISCUSSION

To our knowledge, the present study is the first to demonstrate an association between the translation initiation start site (FokI) polymorphism in the VDR gene with soft

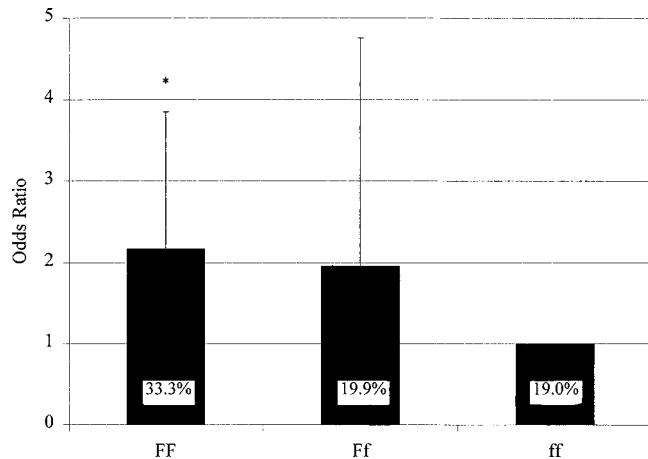


Figure 1. Prevalence of sarcopenia by vitamin D receptor FokI genotype. The figure shows odds ratios and 95% confidence intervals for FokI genotype groups, with the ff group acting as the reference. Odds ratios were determined by logistic regression analysis with adjustment for age. * $p = .03$ versus ff. Within each bar, the percentage of sarcopenic men is shown for each genotype group. The FF group (33.3%) had a significantly higher frequency of sarcopenic men as determined by Chi-square analysis ($p = .03$) than the Ff and ff groups. There were 38 sarcopenic and 76 normal men in the FF group, 29 sarcopenic and 117 normal men in the Ff group, and 8 sarcopenic and 34 normal men in the ff group.

tissue FFM in older men. The current report is also the first to describe a risk allele for the presence of sarcopenia among older adults. Men with the FF genotype exhibited significantly lower total body mass and FFM than men with the Ff and ff genotype, as well as a greater prevalence of sarcopenia, equivalent to a twofold increased risk. Moreover, the lower FFM among men with the FF genotype resulted in significantly lower quadriceps muscle strength, although this association was no longer statistically significant after adjusting for differences in FFM. The BsmI polymorphism was not associated with any FFM or strength measure. These results will need to be verified in other populations including women and men of other race/ethnic backgrounds, but nonetheless suggest that the VDR locus may contribute to interindividual variation in muscle mass and susceptibility to sarcopenia.

Although the heritabilities of both lean body mass and muscle strength have been well described (14–16), the identification of specific genes and allelic variants contributing to these phenotypes is in its infancy. Allelic variants in only a few genes have been associated with muscle-related phenotypes to date, including ciliary neurotrophic factor (31), ciliary neurotrophic factor receptor (32), myostatin (33), type I collagen (34), angiotensin-I converting enzyme (35,36), vitamin D receptor (17–19), and insulin-like growth factor I (37). The successful sequencing of the human genome will significantly advance our efforts to identify functional sequence variation contributing to muscle phenotypes. These efforts may ultimately lead to the use of genetic information to identify individuals at the greatest risk of sarcopenia before the onset of disability. The identification of genes contributing to sarcopenia risk will be facilitated by our growing understanding of the physiological mechanisms

Table 3. Muscle Strength Values by Vitamin D Receptor FokI Genotype

	FF	Ff	ff	<i>p</i> Value
Average quadriceps strength (kg)				
Unadjusted	33.0 ± 1.3*	36.5 ± 1.2	40.6 ± 2.2	.01
Adjusted ^a	34.4 ± 1.3	35.6 ± 1.1	39.7 ± 2.1	.12
Peak quadriceps strength (kg)				
Unadjusted	37.7 ± 1.3 [†]	40.3 ± 1.2	43.2 ± 2.1	.08
Adjusted ^a	39.4 ± 1.2	39.2 ± 1.1	41.8 ± 2.0	.52
Grip strength (kg)				
Unadjusted	31.6 ± 0.5	30.7 ± 0.5	30.2 ± 0.9	.28
Adjusted ^a	31.9 ± 0.5 [‡]	30.5 ± 0.5	30.1 ± 0.9	.08

Notes: ^aData are least squares means ± SE (standard error) adjusted for appendicular muscle mass.

* $p = .004$ versus ff; $p = .058$ versus Ff.

[†] $p = .03$ versus ff.

[‡] $p = .047$ versus Ff; $p = .071$ versus ff.

underlying sarcopenia. The combination of genetic information and environmental risk factors may eventually be used to identify those at increased risk and to develop novel risk assessment and individually tailored prevention and treatment programs. The rationale for studying VDR polymorphisms here was based on the findings that vitamin D is important for both muscle strength and muscle morphology, as well as the knowledge that the VDR protein is expressed in muscle and is critical for the action of 1,25(OH)₂D in muscle (9). Subsequent studies, based on considerably larger sample sizes, will need to address the anticipated complex interactions among multiple genes and environmental influences on sarcopenia.

The results of the present study provide evidence for a recessive risk allele for sarcopenia in elderly Caucasian men, such that men homozygous for the FokI F allele (FF; 38%) demonstrated an approximately twofold risk of being sarcopenic, as defined by Baumgartner and colleagues (23). In addition, multiple measures of FFM were significantly lower in the FF compared with the Ff and ff groups, which resulted in significantly lower quadriceps muscle strength. Other investigations have examined the potential association between VDR genotypes and muscle phenotypes, although only one has studied the FokI polymorphism, which is the only polymorphism known to influence VDR protein structure and function. Van Pottelbergh and colleagues (19) reported no association between VDR FokI genotype and three indices of muscle strength in a group of young and older men; however, body weight was significantly different between the FF and ff groups, though the direction of difference was not reported. In addition, analysis of a VDR TaqI and Apal haplotype that did not include the FokI site showed a significant association with both body weight and FFM in the older men, although the FFM measure appears to have included osseous tissue (19). Geusens and colleagues (17) reported 23% greater quadriceps muscle strength in elderly women homozygous for the absence of the BsmI site (B allele) located in the intron separating exons VIII and IX of the VDR gene compared with the bb genotype group. That same group confirmed this association

in a smaller sample of elderly women (18), but it was unclear whether the same participants were included in both analyses. A separate study could not confirm the results of Geusens and colleagues (17) and reported no association between the BsmI VDR variant and trunk muscle torque in Japanese women (21), although the muscle strength measure was quite different between the studies. The BsmI polymorphism was not associated with FFM, muscle strength, or sarcopenia in the present study. Additional work will be required to clarify the discrepancies of these studies. Nevertheless, the totality of results from the present study and previous work provide evidence of an association between allelic variation at the VDR locus and muscle phenotypes.

The molecular basis for the association observed for the FokI polymorphism in the present study is uncertain and cannot be addressed by the current study. The f isoform of VDR is the full-length isoform and has been shown to have a decreased ability to induce transcription compared to the truncated F isoform (11,12). The f allele has also been associated with lower bone density in several but not all studies (10). To our knowledge, the present data are the first to examine this allele in the context of sarcopenia. Based on previous findings in the bone literature, we hypothesized that the f allele would be associated with reduced muscle mass and strength; however, we observed the opposite association in the present study. How the higher activity attributed to the F allele would be manifest as lower FFM in the FF genotype group is presently unclear, although uncertainty remains regarding the potential functional significance of this polymorphism in skeletal muscle. Whitfield and colleagues and Jurutka and colleagues (12,13) have performed several experiments aimed at addressing the functional significance of multiple alleles within VDR and have generally shown a strong correlation between VDR genotype and VDR activity. Their work, however, points to the interaction of the translation start site (FokI) polymorphism with a mononucleotide (poly A; A_n) variant in the 3' untranslated region of VDR (12), which may influence VDR gene transcription. In the present investigation, we did not estimate VDR haplotypes, a shortcoming of the experimental design, but rather relied on ANCOVA models to analyze the contribution of each polymorphism individually and multiple regression to address the contribution of both selected VDR loci simultaneously to the phenotypes of interest. It will be important in future studies to evaluate the association of other VDR allelic variants and VDR haplotype blocks on muscle mass and strength.

Summary

We present data showing a significant association between the VDR FokI (F/f) polymorphism and the presence of sarcopenia in older Caucasian men. To our knowledge, this is the first risk allele for sarcopenia to be identified, which will require validation in additional populations and in women.

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