The A1330V polymorphism of the low-density lipoprotein receptor-related protein 5 gene (LRP5) associates with low peak bone mass in young healthy men.

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Adult
Alleles
Bone Density - genetics
Calcifediol - blood
Finland
Fractures, Bone - etiology - genetics
Gene Frequency
Humans
LDL-Receptor Related Proteins - genetics
Low Density Lipoprotein Receptor-Related Protein-5
Male
Military Personnel
Osteoporosis - etiology - genetics
Parathyroid Hormone - blood
Polymorphism, Single Nucleotide
Risk factors

Abstract: Polymorphisms in the gene coding for low-density lipoprotein receptor-related protein 5 (LRP5) contribute to variation in bone mass in the general population. Whether this is due to influence on bone mass acquisition or on bone loss thereafter has not been established.

We studied the association of LRP5 polymorphisms with peak bone mass in young men. The study included 235 Finnish men, aged 18.3 to 20.6 years. Lifestyle factors and fracture history were recorded. Bone mineral content (BMC), density (BMD) and scan area were measured for the lumbar spine and proximal femur by dual energy X-ray absorptiometry (DXA). Blood and urine were collected for determination of bone turnover markers, serum 25-OHD and PTH. Genomic DNA was extracted from peripheral blood for genetic analysis of LRP5. Ten single nucleotide polymorphisms in LRP5 were analyzed and correlated with bone parameters.

Only the A1330V polymorphism of LRP5 significantly associated with bone parameters. In comparison with subjects with the AlaAla genotype (n=215), those with AlaVal genotype (n=20) had lower femoral neck BMC (P=0.029) and BMD (P=0.012), trochanter BMC (P=0.0067) and BMD (P=0.015), and total hip BMC (P=0.0044) and BMD (P=0.0089). Fracture history was similar for the genotypes.

The polymorphic valine variant at position 1330 of LRP5 was significantly associated with reduced BMC and BMD values in healthy young Finnish men. The results provide evidence for the crucial role of LRP5 in peak bone mass acquisition.

PubMed ID: 17223614 View in PubMed

[Alimentary risk factors of osteoporosis].

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Author:	V M Kodentsova
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Source:	Vopr Pitan. 2009;78(1):22-32
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Keywords:	Age Factors
	Bone Density - genetics - physiology
	Calcium - administration & dosage
	Cardiovascular Diseases - complications
	Food - standards
	Gastrointestinal Diseases - complications
	Humans
	Malnutrition - complications
	Motor Activity - physiology
	Osteoporosis - etiology - genetics - metabolism
	Risk factors
	Russia
	Vitamins - administration & dosage
Abstract:	The data on of alimentary risk factors of osteoporosis have been observed. The frequency of decreased bone mineral density, vitamin and calcium diet content and sufficiency with vitamins evaluated by means of blood serum level determination among patients suffering from chronic diseases (of cardiovascular system, gastrointestinal tract, osteopenia and osteoporosis).
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An Sp1 binding site polymorphism in the COLIA1 gene predicts osteoporotic fractures in both men and women.

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Adult
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Biological Markers - analysis
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Denmark - epidemiology
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Male
Middle Aged
Osteoporosis - complications - epidemiology - genetics
Polymerase Chain Reaction
Polymorphism, Genetic - genetics
Predictive value of tests
Regression Analysis
Sex Factors
Spinal Fractures - epidemiology - etiology - genetics

Abstract:

Genetic factors play an important role in the pathogenesis of osteoporosis, and recent studies have shown that a polymorphic Sp1 binding site in collagen type I alpha1 (COLIA1) gene is associated with bone mass and vertebral fractures in women from the U.K. Information on the predictive value of the COLIA1 Sp1 polymorphism in other populations is limited, however, and no studies have yet been performed in osteoporotic males. In view of this, we analyzed COLIA1 genotypes in relation to bone density and biochemical markers of bone turnover and the presence of osteoporotic fractures in a case-control study of Danish men and women. COLIA1 genotype was determined by polymerase chain reaction analysis of genomic DNA extracted from peripheral blood samples and related to bone mass, biochemical markers of bone turnover, and the presence of fracture in a study of 375 osteoporotic vertebral fracture patients and normal controls. There was no significant effect of COLIA1 genotype on bone mass or biochemical markers when data from the control group (n = 195) and fracture group (n = 180) were analyzed separately. However, the genotype distribution was significantly different in the fracture cases compared with age-matched controls (chi2 = 16.48, n = 249,p = 0.0003) due mainly to over-representation of the ss genotype in the fracture patients (14.3% vs. 1.4%), equivalent to an odds ratio for vertebral fracture of 11.83 (95% confidence interval 2.64-52.97) in those with the ss genotype. Similar differences in genotype distribution between osteoporotic patients and controls were observed in both men (chi2 = 11.52, n = 95, p = 0.0032, OR = 2.04) and women (chi2 = 6.90, n = 154, p = 0.032, OR = 1.37). In keeping with the above, logistic regression analysis showed that the ss genotype was an independent predictor of osteoporotic fracture (p = 0.028). This study confirms that the COLIA1 Sp1 polymorphism is significantly associated with osteoporotic vertebral fractures. The association is seen in both men and women, and the effect on fracture risk appears to be partly independent of bone mineral density. Our results raise the possibility that genotyping at the Sp1 site could be of clinical value in identifying individuals at risk of osteoporotic fractures in both genders.

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9738510 View in PubMed

Association and linkage disequilibrium analyses suggest genetic effects of estrogen receptor alpha and collagen IA1 genes on bone mineral density in Caucasian women.

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Bone Density - genetics
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Estrogen Receptor alpha
European Continental Ancestry Group - genetics
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Fingers - radiography
Haplotypes - genetics
Humans
Linkage Disequilibrium - genetics
Male
Middle Aged
Nuclear Family
Polymerase Chain Reaction
Polymorphism, Restriction Fragment Length
Receptors, Estrogen - genetics
Russia

Abstract: Estrogen receptor alpha (ER alpha) and collagen IA1 (COLIA1) genes have been suggested as possibly implicated in reduced bone mineral density (BMD). The present study investigated the occurrence of association and linkage disequilibrium between radiographic hand BMD and polymorphic alleles of ER alpha and COLIA1 genes, in human pedigrees of a Chuvasha population in Russia. The study sample included 463 members of 113 pedigrees, mostly nuclear families. We performed association and transmission disequilibrium test (TDT) analyses of the combined PvuII and XbaI RFLPs alleles on the same chromosome (haplotype) of the ER alpha gene with BMD Z scores of cancellous or cortical bone in the hand phalanges. The association analyses were performed separately for both genders in the parental generation, i.e., 'fathers' (n = 114; average age 64.2 y) and 'mothers' (n = 122; average age 62.7 y). The Px haplotype was associated significantly with lower BMD Z scores in 'mothers' only. The difference between subjects who carried one or two copies of the Px haplotype and those lacking it was 0.68 Z scores, P = 0.003 and 0.51 Z scores, P = 0.025 for cancellous and cortical bone, respectively. Multiple linear regression model with age, height, weight, and Px haplotype status as predictors explained 26.7% and 28.3% of the total observed variance in BMD with Px haplotype as independent predictor explaining 5.9%; P = 0.002 and 3%; P = 0.028 (cancellous and cortical bone, respectively). Results of t-TDT for triads of two parents and just one of their female offspring (but not male offspring) suggested the existence of linkage disequilibrium between the two loci of Px haplotype and BMD trait (P = 0.047). No association was found between polymorphic alleles of COLIA1 gene and BMD, but 'mothers' with combined genotypes of Px haplotype of ER alpha gene and "s" allele of COLIA1 gene had the lowest mean Z scores (-0.944 and -0.788 for cancellous and cortical bone, respectively). We conclude that the Px haplotype of the ER alpha gene is associated with low BMD values in females, as the phenotype is gender dependent (the association was not observed in males), and the "s" allele of COLIA1 gene in combination with this haplotype contributes to reduced BMD.

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Association study of common variants in the sFRP1 gene region and parameters of bone strength and body composition in two independent healthy Caucasian male cohorts.

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Bone and Bones - physiology
Cohort Studies
Denmark
European Continental Ancestry Group - genetics
Genetic Predisposition to Disease
Genetic Variation
Genotype
Humans
Intercellular Signaling Peptides and Proteins - genetics
Male
Membrane Proteins - genetics
Middle Aged
Osteoporosis - genetics
Polymorphism, Single Nucleotide
Young Adult

Abstract: Bone mineral density (BMD) and bone strength are predictive parameters for the development of osteoporosis and related fracture later in life. Although it is well known that BMD and bone strength have a high heritability, not much of the variation is already explained. Mice models showed that sFRP1 has an influence on bone formation. Therefore this study aimed to investigate the effect of common genetic variation on BMD and bone strength in Caucasian men of different ages. Using HapMap we selected 13 tagSNPs which tag most common genetic variation in and around sFRP1 and we genotyped these SNPs in the young cohort of the Odense Androgen Study (OAS). The OAS includes a total of 1383 Danish men from two different age groups ([20-29 years]: N=783; [60-74 years]: N=600) and is well characterised. The subjects were phenotyped for BMD at several sites, and additionally for body composition and hip geometry parameters. Based on the results of the young cohort we selected three SNPs for further analysis in the complete OAS population. To conclude we tried to replicate the results of two SNPs in an independent population of 994 Belgian men. We found a strong association for rs9694405 with BMI as well in both cohorts separately as in the whole OAS population. Further we found rs4736965 associated with several hip geometry parameters in the same population. However we were not able to replicate those results in the Belgian population. At last we found in the OAS population age specific effects for rs10106678 with whole body BMD and waist to hip ratio.

PubMed ID: 22178351 View in PubMed

Association study of polymorphisms in the SOST gene region and parameters of bone strength and body composition in both young and elderly men: data from the Odense Androgen Study.

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Body Composition - genetics
Body mass index
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Bone Morphogenetic Proteins - genetics
Cohort Studies
Denmark
Femur Neck - physiology
Genetic Association Studies
Genetic Markers - genetics
Genotype
Humans
Low Density Lipoprotein Receptor-Related Protein-5 - genetics
Male
Middle Aged
Polymorphism, Genetic

Abstract: By means of different genetic association studies the SOST gene, encoding sclerostin, has repeatedly been suggested to regulate bone mineral density (BMD) and osteoporosis susceptibility. This study aimed at a further understanding of the importance of two previously studied single-nucleotide polymorphisms in the SOST gene, rs10534024 (SRP3) and rs9902563 (SRP9), in the Odense Androgen Study (OAS) cohort. This cohort includes a total of 1,383 Danish men from two different age groups, 20-29 years (n = 783) and 60-74 years (n = 600), and is well characterized. Subjects were phenotyped for BMD at several sites and additionally for body composition and hip geometric parameters. In a combined analysis of the young and the elderly OAS, no associations were found for SRP3 either with BMD or with hip geometry. Instead, we found that this polymorphism had a relatively large effect on weight (-1.149 kg) and body mass index (-0.389 kg/m(2)) (P = 0.021 and 0.006 under a codominant model). For SRP9, a significant association was found for femoral neck BMD (+0.020 g/cm(2), P = 0.020) and a trend toward significance for hip geometry (buckling ratio of the narrow neck) but only when considering a recessive effect of the minor allele (C). No age-specific effects were found for either of the two SNPs. In summary, we are the first to find interesting associations between SRP3 and body composition. For SRP9, we replicated a site-specific association with femoral neck BMD. In addition, we report a novel association for this polymorphism with hip geometry.

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Association with replication between estrogen-related receptor gamma (ESRRgamma) polymorphisms and bone phenotypes in women of European ancestry.

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Aged, 80 and over
Bone Density - genetics
Estrogen Replacement Therapy
Female
Femur Neck - pathology - ultrasonography
Genetic Association Studies - statistics & numerical data
Genetic Predisposition to Disease
Haplotypes
Heel - pathology - ultrasonography
Humans
Lumbar Vertebrae - pathology - ultrasonography
Middle Aged
Ontario - epidemiology
Osteoporosis - epidemiology - genetics - ultrasonography
Phenotype
Polymorphism, Genetic
Polymorphism, Single Nucleotide
Quebec - epidemiology
Receptors, Estrogen - genetics

Abstract: Osteoporosis is a bone disease characterized by low bone mineral density (BMD), a highly heritable polygenic trait. Women are more prone than men to develop osteoporosis owing to a lower peak bone mass and accelerated bone loss at menopause. Lack of estrogen thus is a major risk factor for osteoporosis. In addition to having strong similarity to the estrogen receptor 1 (ESR1), the orphan nuclear estrogen-related receptor gamma (ESRRgamma) is widely expressed and shows overlap with ESR1 expression in tissues where estrogen has important physiologic functions. For these reasons, we have undertaken a study of ESRRgamma sequence variants in association with bone measurements [heel quantitative ultrasound (QUS) by measurements of broadband ultrasound attenuation (BUA), speed of sound (SOS), and stiffness index (SI) and dual-energy X-ray absorptiometry (DXA) at the femoral neck (FN) and lumbar spine (LS)]. A silent variant was found to be associated with multiple bone measurements (LS, BUA, SOS, and SI), the p values ranging from .006 to .04 in a sample of 5144 Quebec women. The region of this variant was analyzed using the HapMap database and the Gabriel method to define a block of 20 kb. Using the Tagger method, eight TagSNPs were identified and genotyped in a sample of 1335 women. Four of these SNPs capture the five major block haplotypes. One SNP (rs2818964) and one haplotype were significantly associated with multiple bone measures. All SNPs involved in the associations were analyzed in two other sample sets with significant results in the same direction. These results suggest involvement of ESRRgamma in the determination of bone density in women.

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Body composition and bone mineral density in children with premature adrenarche and the association of LRP5 gene polymorphisms with bone mineral density.

https://arctichealth.org/en/permalink/ahliterature148293

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	Body Composition
	Bone Density - genetics
	Child
	Cross-Sectional Studies
	Female
	Femur Neck - anatomy & histology
	Finland
	Humans
	LDL-Receptor Related Proteins - genetics
	Low Density Lipoprotein Receptor-Related Protein-5
	Male
	Pituitary Gland - growth & development
	Polymorphism, Genetic
	Reference Values
	Spine - anatomy & histology
Abstract:	Precocious increase in adrenal androgen production is the hallmark of premature adrenarche (PA). Adrenal androgens have anabolic properties.
	The objective of the study was to test whether body composition and bone mineral density (BMD) are altered in PA and study whether genetic variation in low-density lipoprotein receptor-related protein 5 (LRP5) affects BMD in PA.
	This was a cross-sectional study.
	The study was conducted at a university hospital.
	The study included 126 prepubertal children (64 with PA, 10 boys; 62 non-PA controls, 10 boys). Femoral neck and lumbar spine areal and calculated volumetric BMD (dual energy X-ray absorptiometry), body composition (bioimpedance), serum 25-hydroxyvitamin D, and markers of bone turnover and calcium homeostasis were compared between the PA and control groups. Single-nucleotide polymorphisms of LRP5 were determined and associated with BMD.
	Children with PA had higher femoral neck and lumbar spine BMD(areal) than the controls (Z-score 0.56 vs. -0.09, P
PubMed ID:	19789208 View in PubMed

Bone mineral density is associated with estrogen receptor gene polymorphism in men.

https://arctichealth.org/en/permalink/ahliterature191578

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Estrogen Receptor alpha
Female
Genotype
Haplotypes - genetics
Humans
Male
Middle Aged
Polymorphism, Restriction Fragment Length
Receptors, Estrogen - genetics
Russia
Sex Factors

Abstract: In order to identify genetic effects of allelic variation on bone mineral density (BMD), association studies have been performed recently. Examining the relation between PvuII and XbaI restriction fragment length polymorphism (RFLPs) at the estrogen receptor (ER alpha) gene and BMD, in women or men, have yielded conflicting results. We analyzed the association between this polymorphism and BMD Z score values of cancellous bone at the 3rd finger in 344 members of nuclear families of European population, Chuvasha, living in Russia. The population sample included 183 males, aged 18-84, and 161 females, aged 23-79. The analysis has been performed separately for both sexes and for both generations (parents and offspring). We used a novel direct haplotyping method, which determines simultaneously each of the PvuII and XbaI RFLPs and their relation to each other. The haplotypes were represented as the combination of both polymorphic sites on the same chromosome, by using P/p and X/x for PvuII and XbaI restriction sites, respectively. The subjects were classified into 3 groups of genotypes: A = PXPX (homozygote for the PX haplotype); B = PXPx, PXpx (the heterozygotes for the PX haplotype); C = PxPx, Pxpx, pxpx (genotypes that are lacking the PX haplotype). The PXPX genotype (A) was associated with higher BMD Z score values in comparison to the genotypes that are lacking the PX haplotype (C), in total males [0.618 vs. -0.133 (p = 0.004)] and for the "sons" generation [0.724 vs. -0.198 (p = 0.02)]. Similar tendency was observed for the "fathers" generation (0.539 vs. -0.085), though the difference did not approach statistical significance (p = 0.087). These findings were not found in the female samples, nor in the "mothers" or "daughters" generations. The question if there are differences in the mode of action of estrogen through its receptor on bone mass, between the genders or between the males' generations, have to be further investigated.

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Common genetic variation in the DKK1 gene is associated with hip axis length but not with bone mineral density and bone turnover markers in young adult men: results from the Odense Androgen Study.

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Body Weights and Measures
Bone Density - genetics
Bone Remodeling - genetics
Cohort Studies
Denmark
Epistasis, Genetic
Genetic Association Studies
Genetic Predisposition to Disease
Genetic Variation - physiology
Hip - anatomy & histology
Hip Fractures - genetics
Humans
Intercellular Signaling Peptides and Proteins - genetics
Linkage Disequilibrium
Male
Polymorphism, Single Nucleotide - physiology
Young Adult
Abstract: LRP5 was recently confirmed as an important susceptibility gene for osteoporosis. Our objective was to evaluate the effect of DKK1 polymorphisms on bone mineral density (BMD), hip geometry, and bone turnover. DKK1 is a secreted protein that binds to LRP5/6 receptors and inhibits canonical Wnt signaling. Using HapMap, we selected three SNPs covering the genetic variation in a 13.53-kb region comprising DKK1. The Odense Androgen Study is a population-based study comprising 783 Caucasian men aged 20-29 years. BMD and hip structural parameters were available for study. Bone turnover markers were used as a secondary end point. All analyses were repeated after adjusting for covariables and in subgroups according to physical activity. We found no significant association between DKK1 and BMD or markers of bone turnover; however, a significant association (P = 0.012) was found for rs1569198 with hip axis length (HAL), independent of BMD and height. Moreover, the association seemed to be driven by the non-sedentary subgroup (P = 0.004). Haplotype analysis further confirmed the association of rs1569198 with HAL. Furthermore, we obtained indications for interaction between DKK1 and LRP5 genotypes for different hip geometry parameters. As almost all variance within the DKK1 gene was covered, we conclude that common variation in this gene does not markedly influence BMD or bone turnover markers in young men. In this population, however, a common SNP in DKK1 does have a significant effect on HAL, implying a possible effect on hip fracture risk in the general population. This finding could be of interest but needs replication in independent populations.

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