Curso Nutrigenomica y Avanzado

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Departamento de Formación Instituto Nutrigenomica

Nutrigenómica y osteoporosis

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1. Introducción de la importancia de la genética osteoporosis.
2. Polimorfismos en el gen del receptor de la vitamina D
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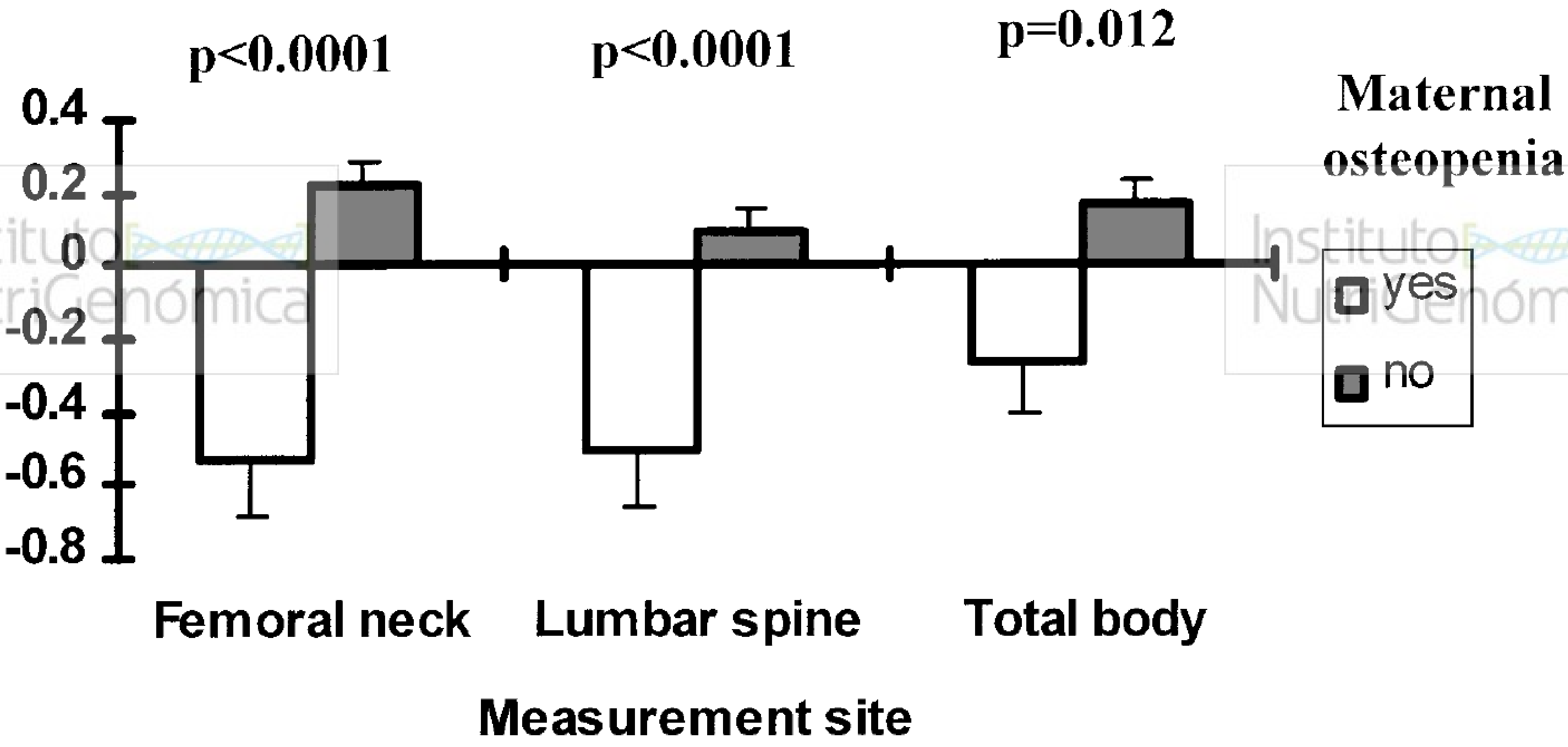
4. Polimorfismos en el gen del receptor de estrógenos
5. Metabolismo lipídico y osteoporosis
6. Vitaminas del complejo B, estrés oxidativo y osteoporosis

Associations between maternal peak bone mass and bone mass in prepuberal male and female children

(Jones & Nguyen, 2000)
J Bone Miner Res 15:1998-2004



Genes asociados con variaciones en la masa ósea

	Gen	Proteína
Hormonas y receptores calciotrópicos	*VDR*	Receptor de la vitamina D
	ER-α	Receptor de estrógenos-α
	ER-β	Receptor de estrógenos-β
	CT	Calcitonina
	CTR	Receptor de la calcitonina
	PTH	Paratohormona
	PTHR1	Receptor de la paratohormona 1
	CYP19	Aromatasa
	GCCR	Receptor de glucocorticoide
	CaSR	Receptor sensible al calcio
	AR	Receptor de andrógenos
Citoquinas, factores de crecimiento	*TGF-β1*	Factor transformador del crecimiento-β1
	IL-6	Interleukina-6
	IGF-1	Factor de crecimiento similar a la inuslina 1
	IL-1ra	Receptor antagonista de la interleukina-1
	OPG	Osteoprotegerina
	TNF-α	Factor de necrosis tumoral-α
	TNFR2	Receptor 2 del factor de necrosis tumoral
Proteínas de la matriz ósea	*COLIA1*	Colágeno tipo I α1
	COLIA2	Colágeno tipo I α2
	BGP	Osteocalcina
	MGP	Proteína Gla de matriz
	AHSG	α-2-HS-glycoproteina

Nutrigenómica y osteoporosis

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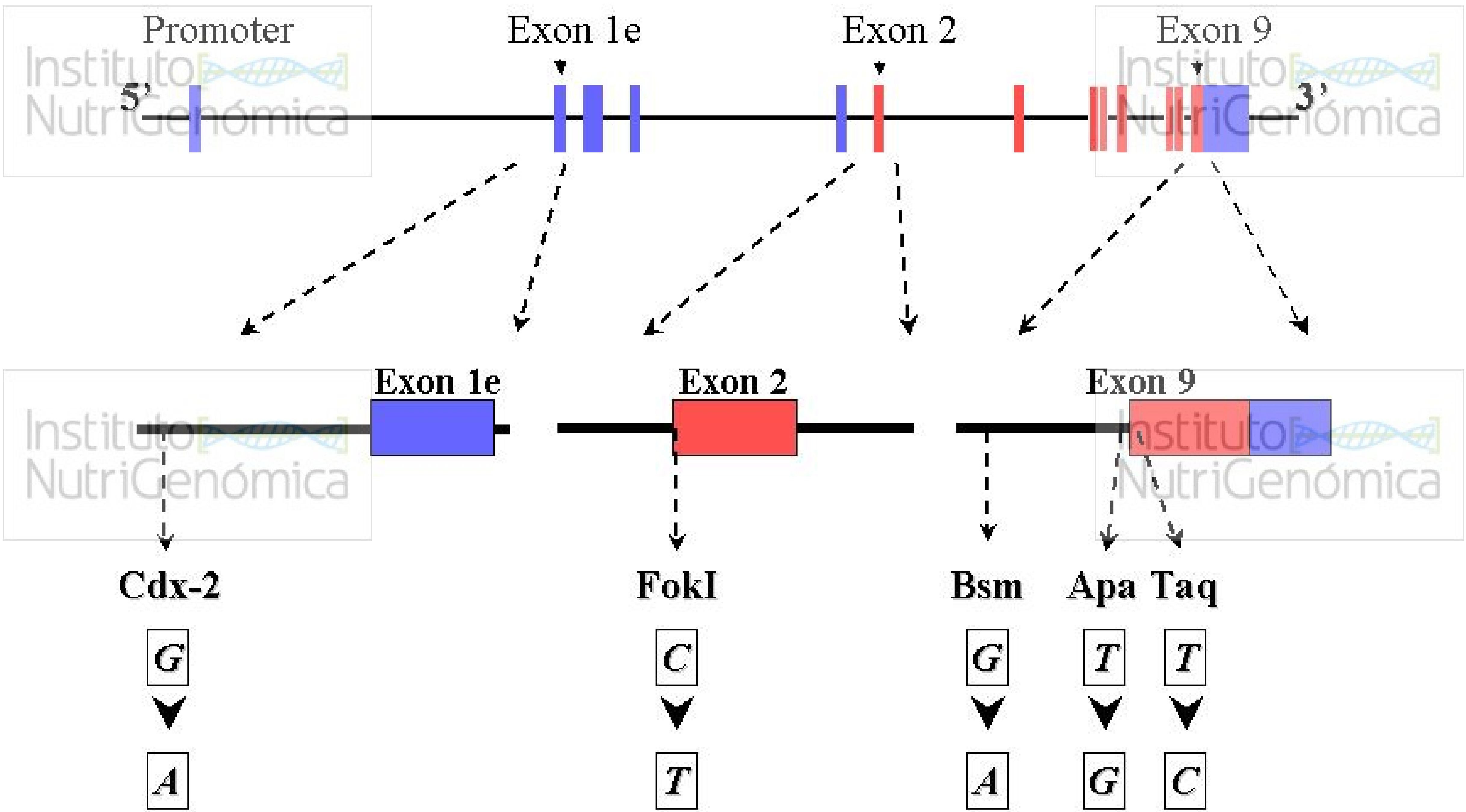
Receptor de la Vitamina D *(VDR)*



The association between vitamin D receptor gene polymporphism and bone mineral density at the spine, hip and whole-body in premenopausal women.

(Salomone et al, 1996)

Osteoporosis International, 6:63-68

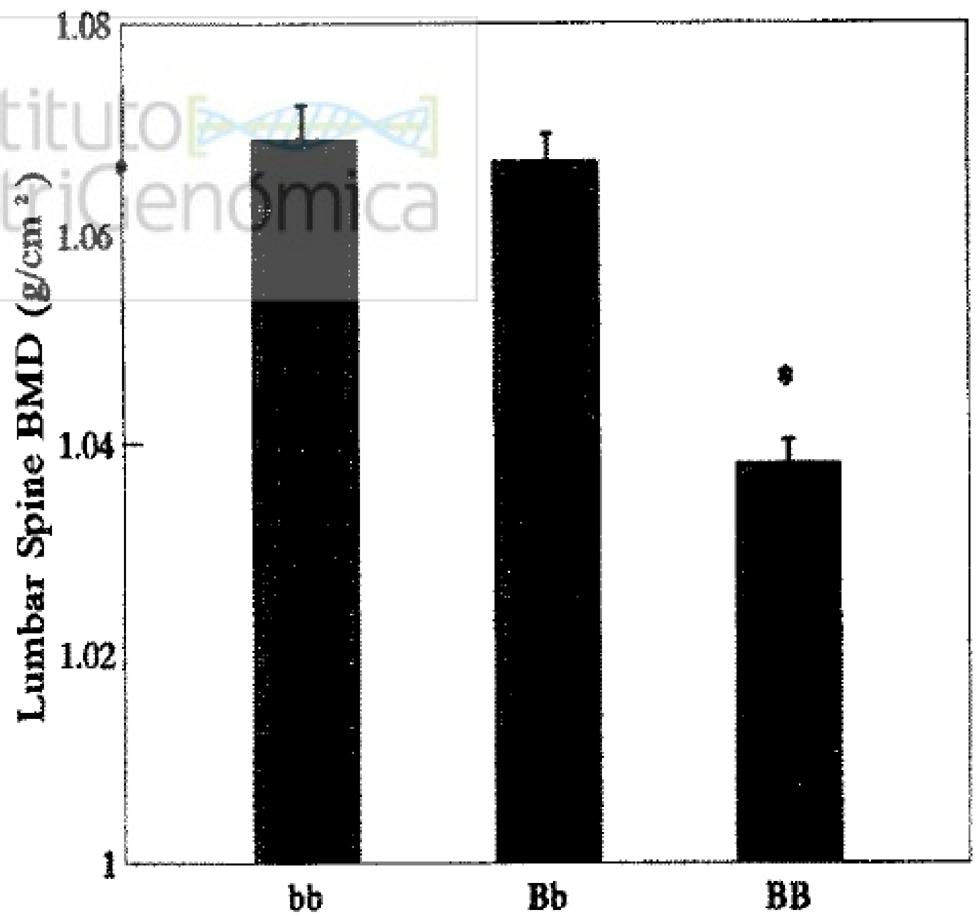
rs1544410

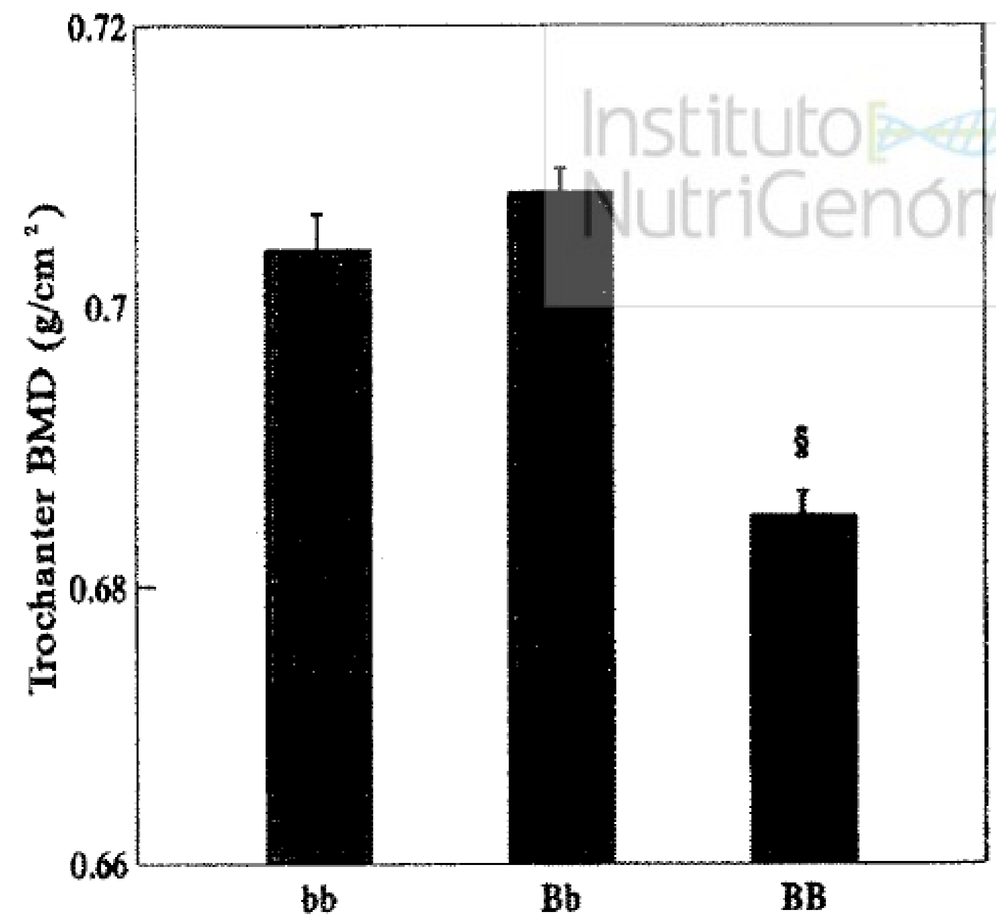
*Bms*I

bb: AA

bB: AG

BB: GG

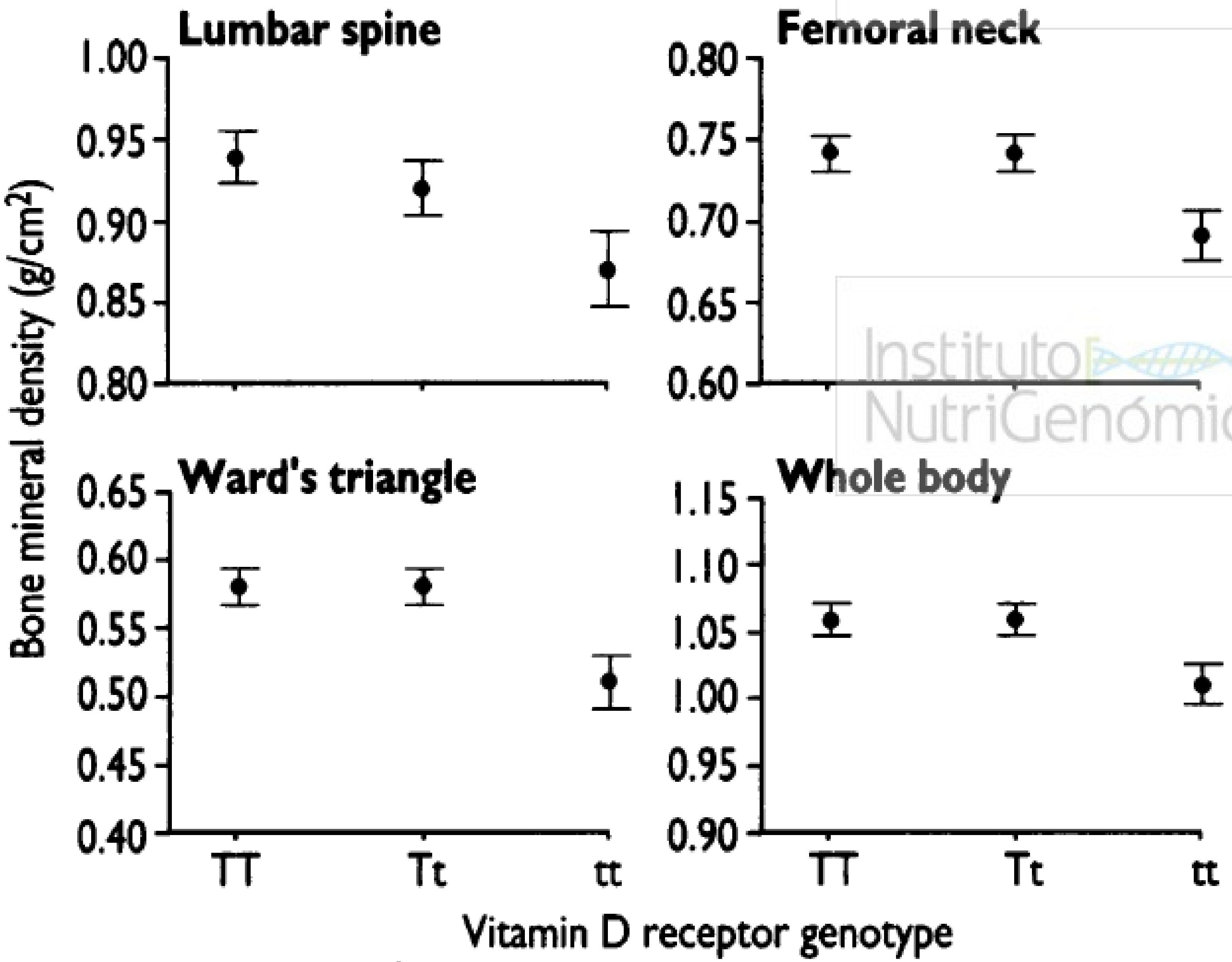




Influence of vitamin D receptor genotype on bone mineral density in postmenopausal women: a twin study in Britain

(Spector et al, 1995)
BMJ 310:1357-1360

*Taq*I

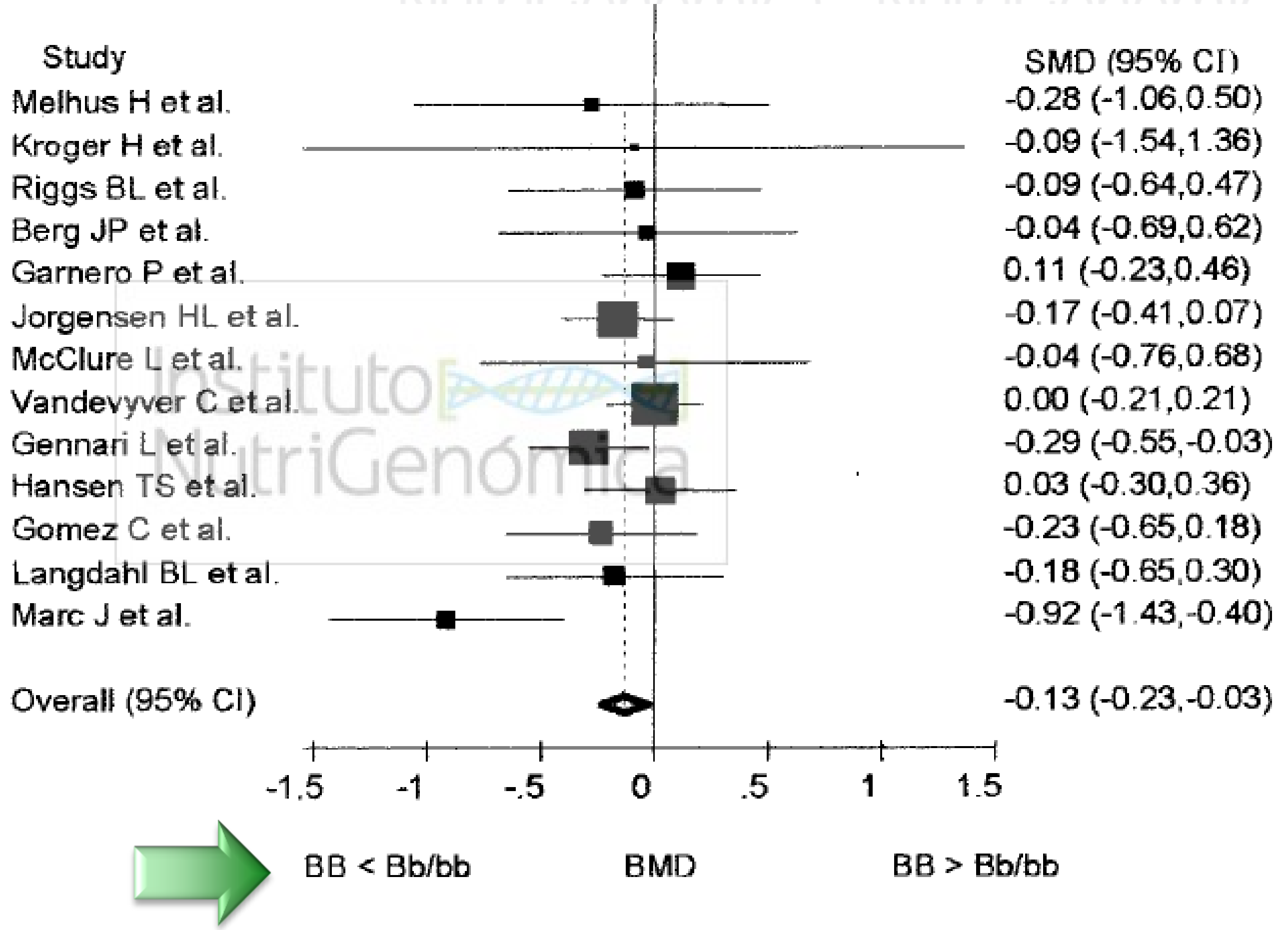


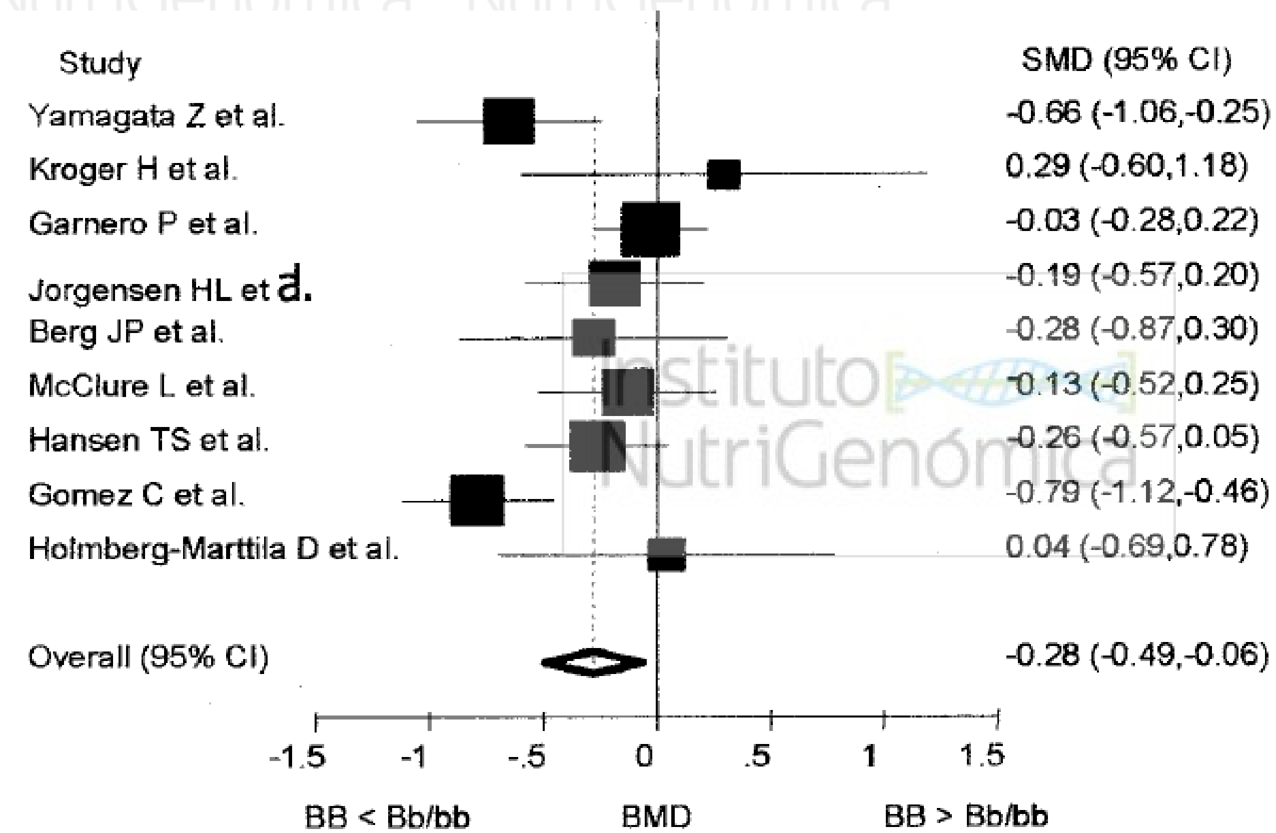
Meta-analysis of molecular association studies: vitamin D receptor gene polymorphism and BMD as a case study

(Thakkinstian et al, 2004)

J Bone Miner Res 19:419-428

BmsI





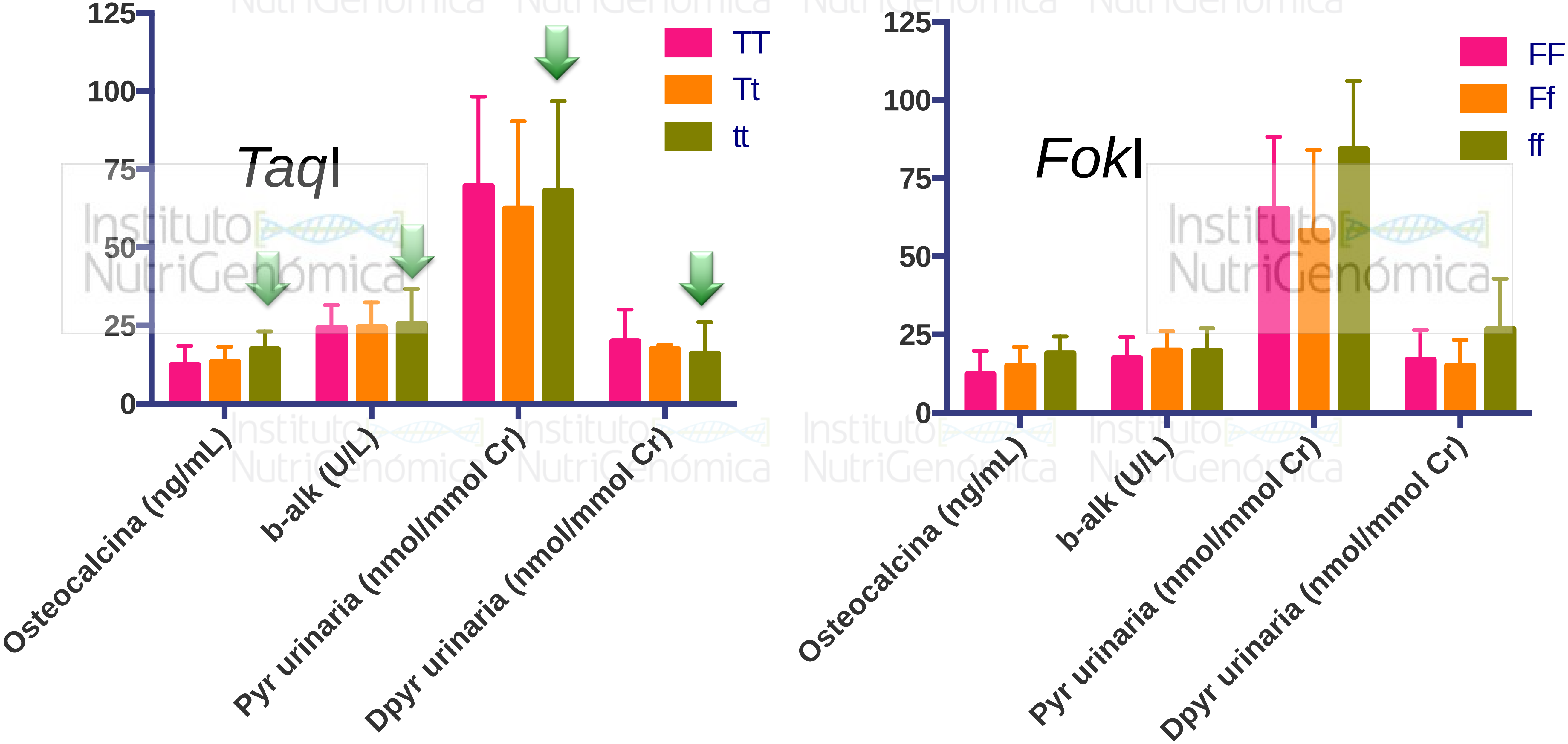
Transverales

Longitudinales

An assessment of genetic markers as predictors of bone turnover in healthy adults

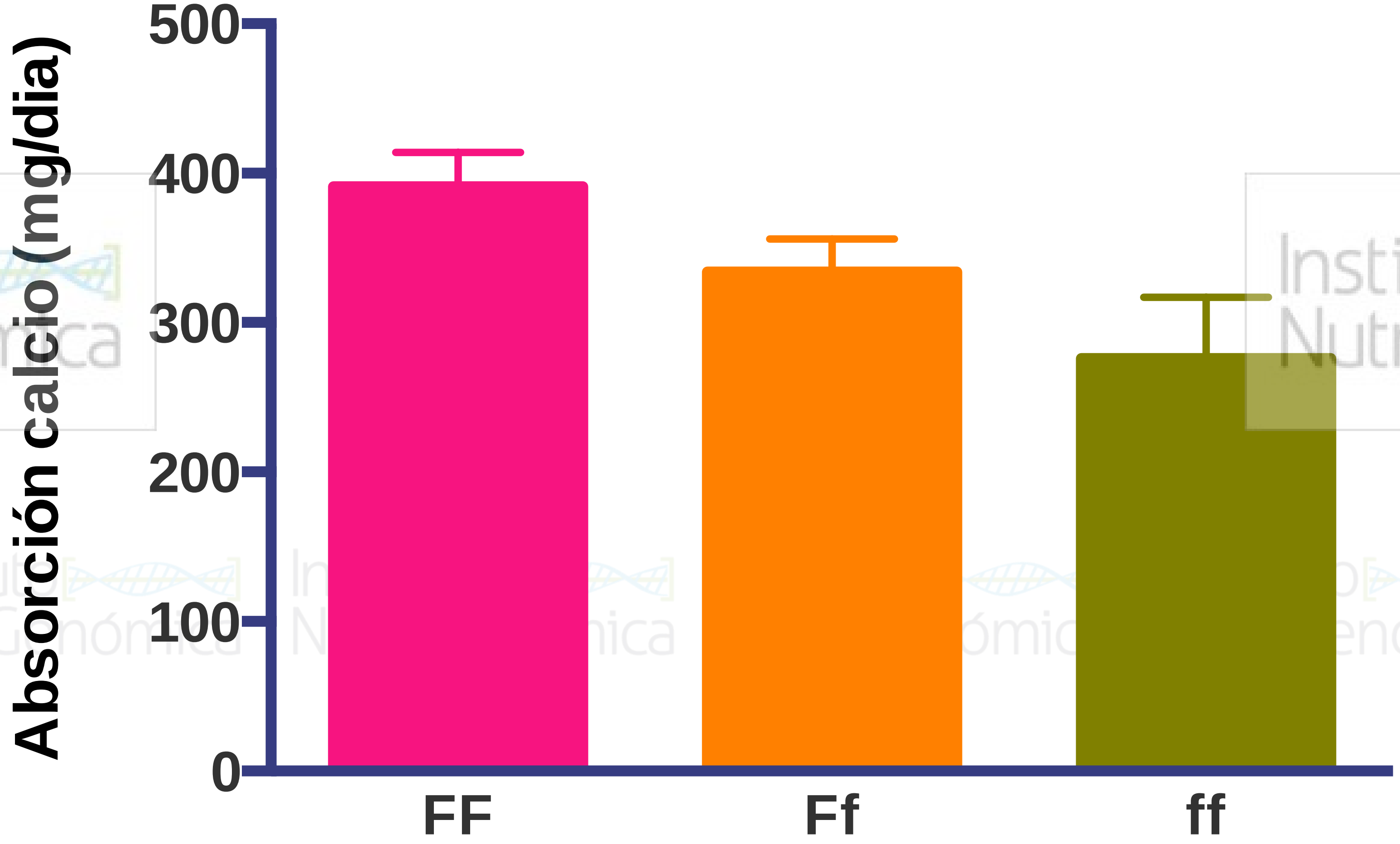
(Sheehan et al, 2001)

J Endocrinol Invest 24:236-245



Vitamin D receptor gene *Fok*1 polymorphism predicts calcium absorption and bone mineral density in children

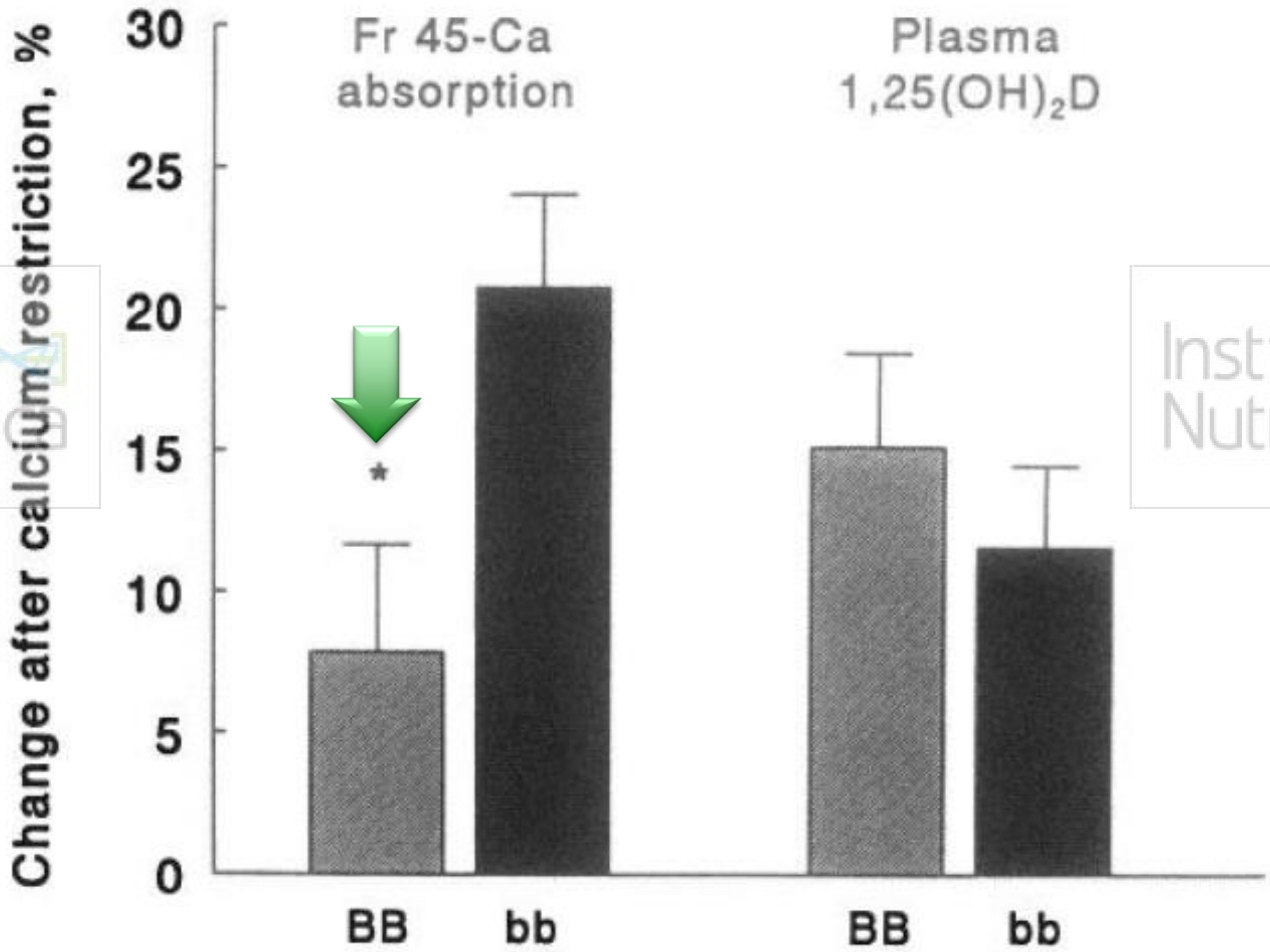
(Ames et al, 1999)
J Bone Miner Res 14;740-746



Calcium absorption on high and low calcium intakes in relation to vitamin D receptor genotype

(Dawson-Hughes et al, 1995)
J Clin Endocrinol Metab 80:3657-3661

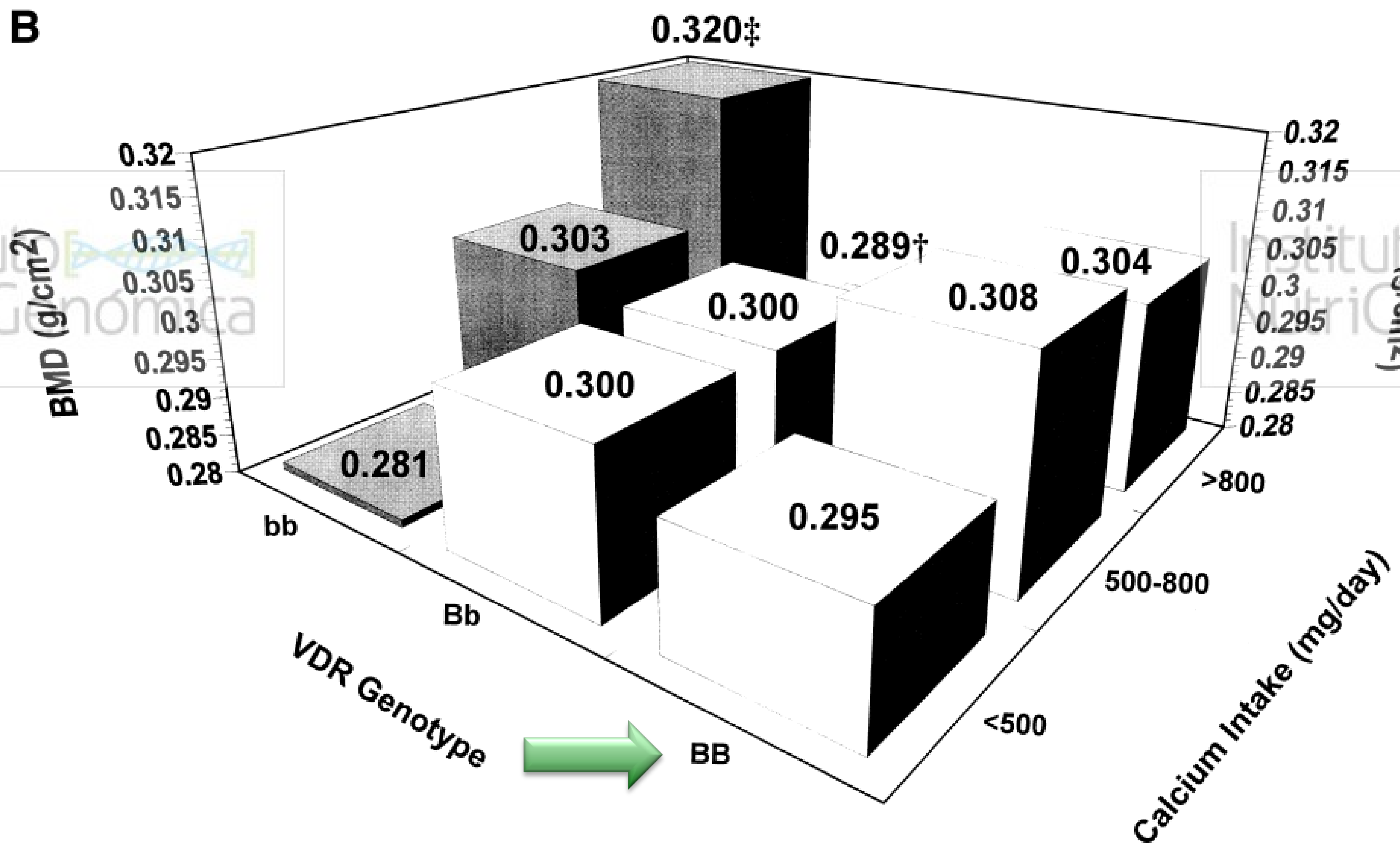
*Bms*I



The BsmI vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density

(Kiel et al, 1997)

J Bone Miner Res, 12:1049-1057



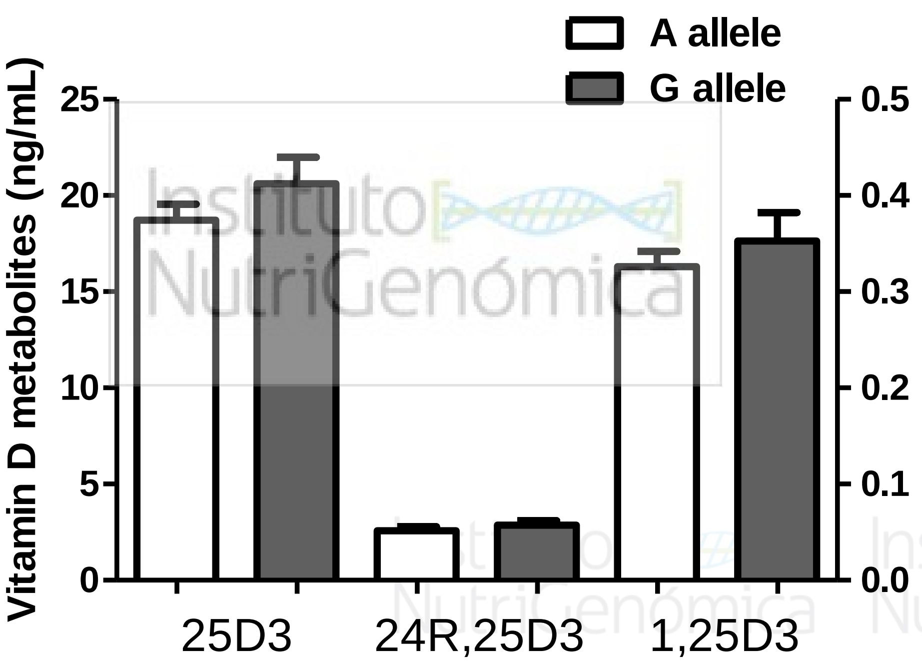
Vitamin D receptor *Bsm*I polymorphism modulates soy intake and 25-hydroxyvitamin D supplementation benefits in cardiovascular disease risk factors profile.

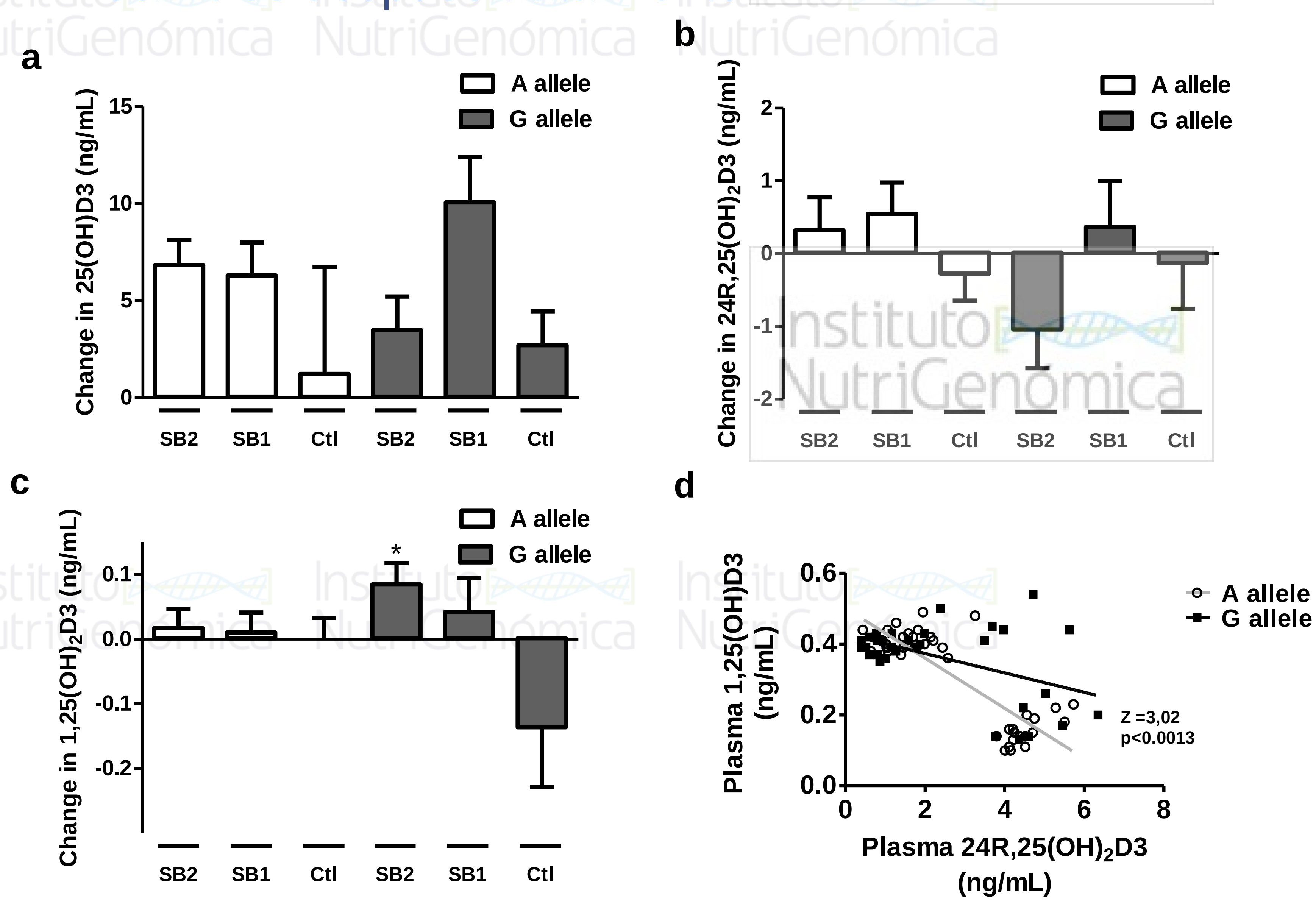
(Serrano et al, 2013)

Genes & Nutrition 8:561-569

Cambios después tratamiento

Inicio estudio

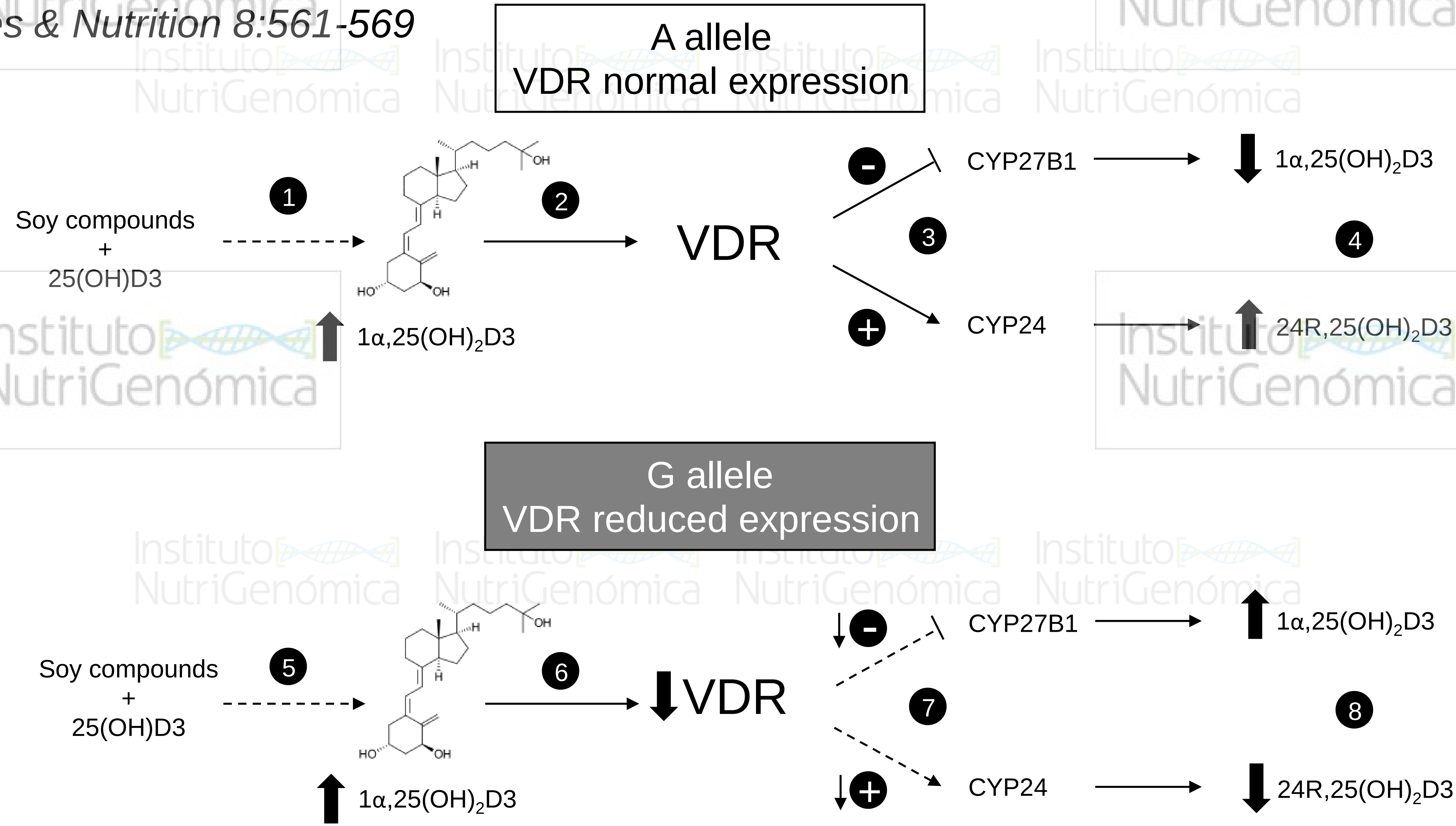




Alelo G: BB

Vitamin D receptor *Bsm*I polymorphism modulates soy intake and 25-hydroxyvitamin D supplementation benefits in cardiovascular disease risk factors profile.

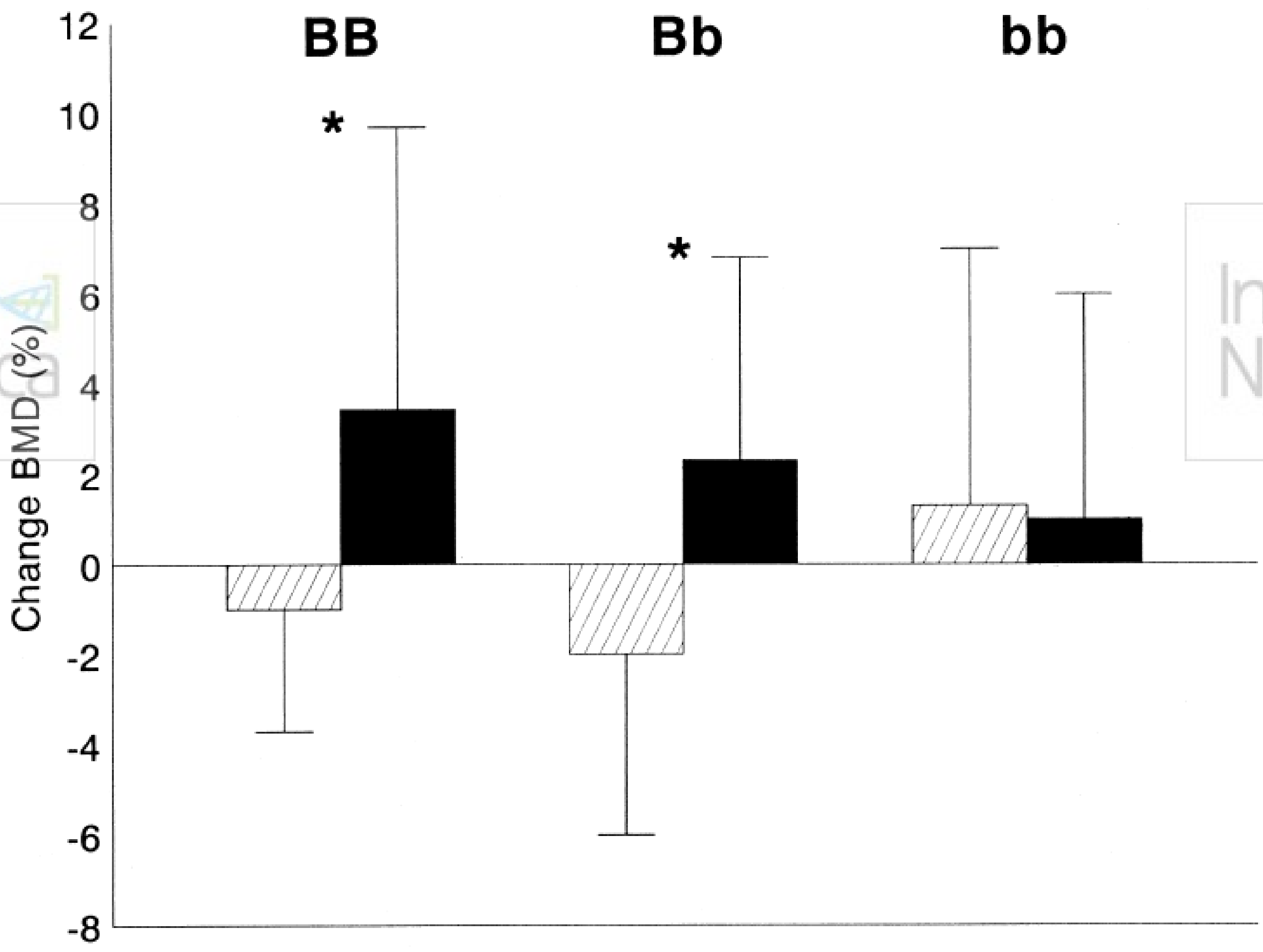
(Serrano et al, 2013)
Genes & Nutrition 8:561-569



The effect of vitamin D supplementation on the bone mineral density of the femoral neck is associated with vitamin D receptor genotype

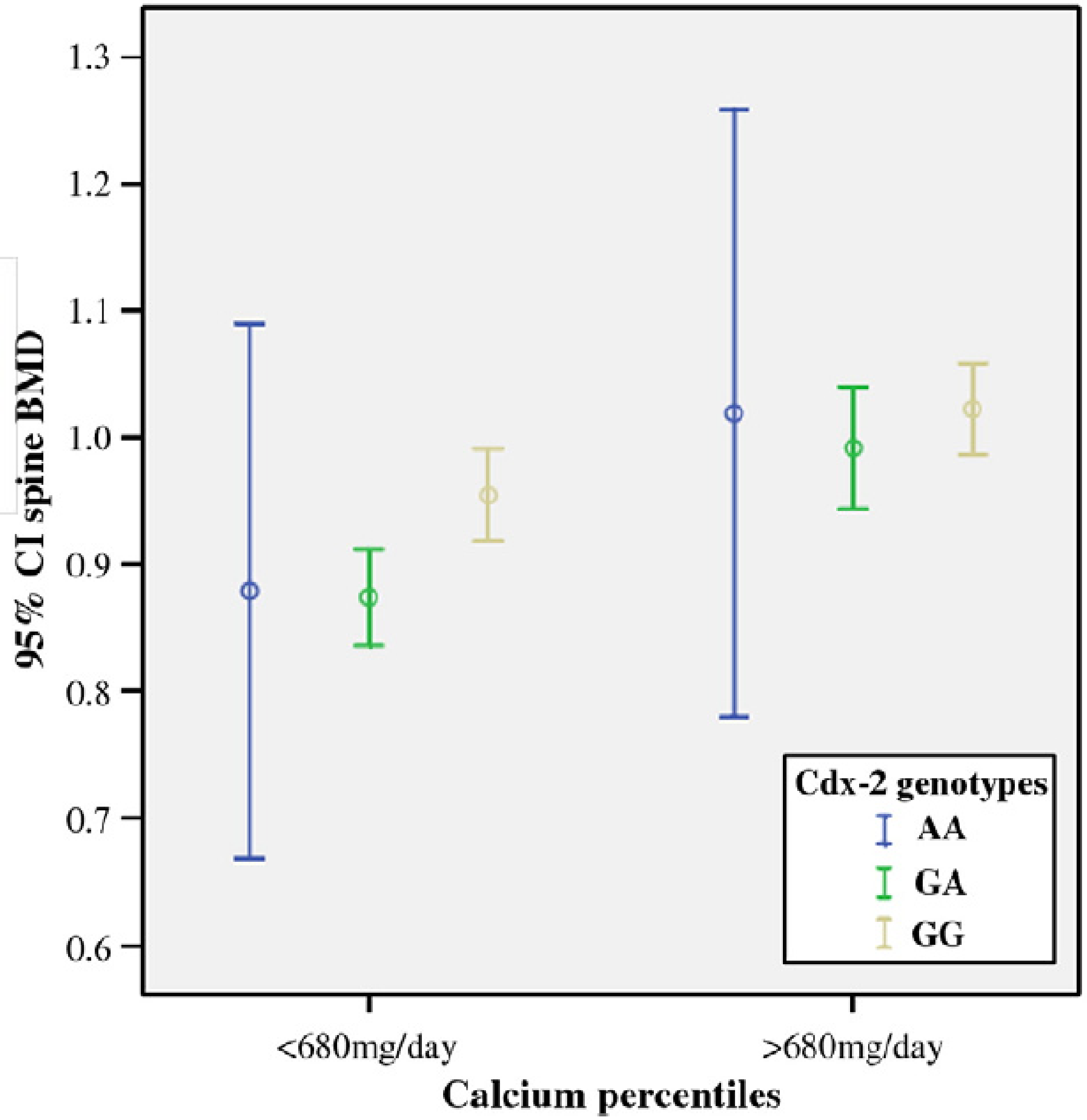
(Graafmans et al, 1997)

J Bone Miner Res 12:1241-1245



The role of vitamin D receptor gene polymorphisms in the bone mineral density of Greek postmenopausal women with low calcium intake

(Stathopoulou et al, 2011)
J Nutr Biochem, 22:752-757



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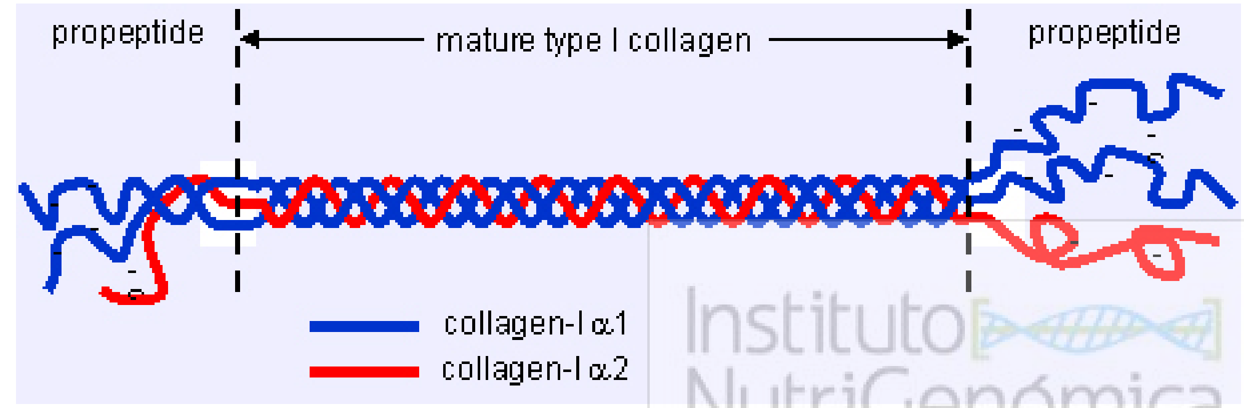
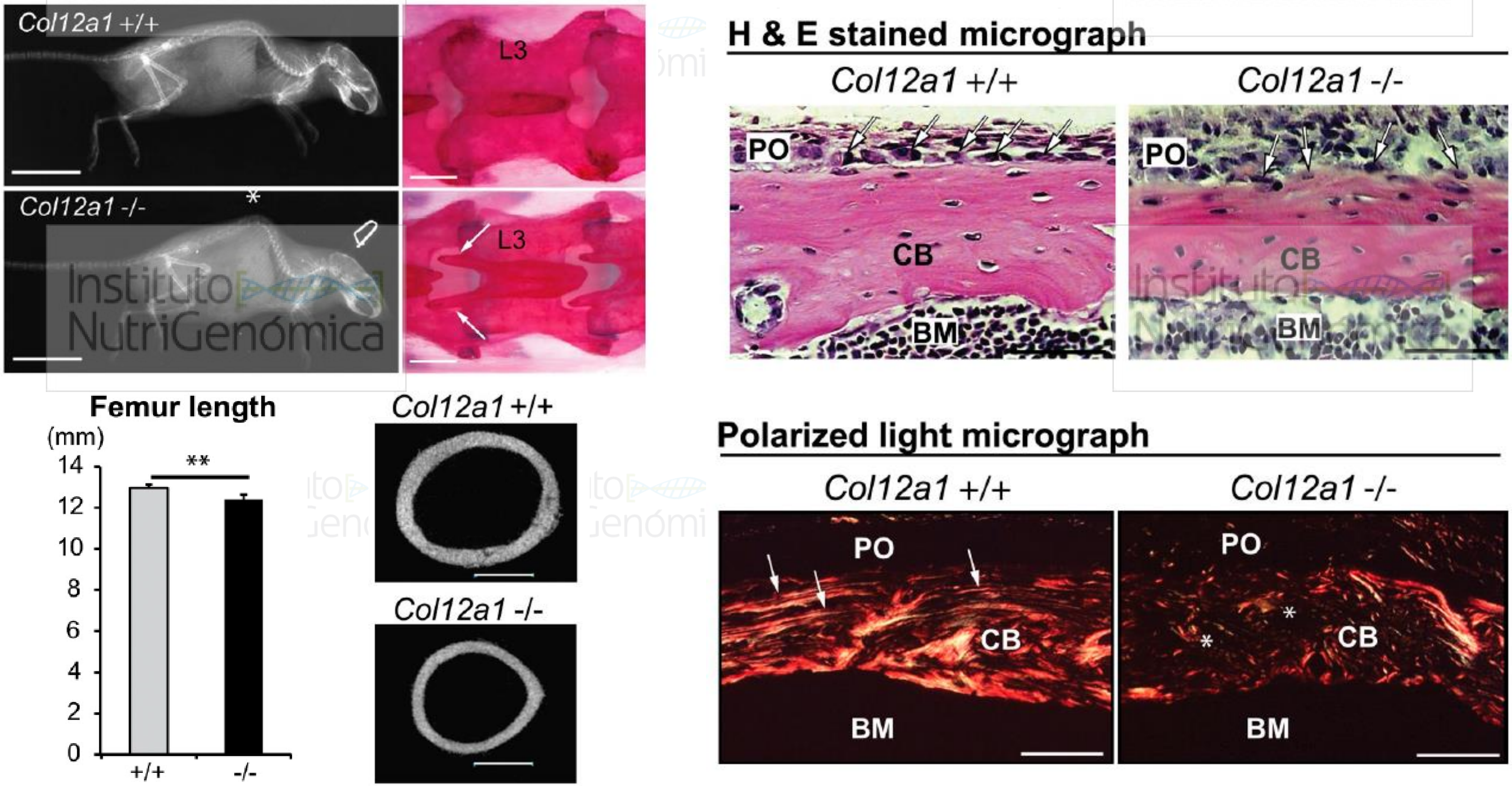
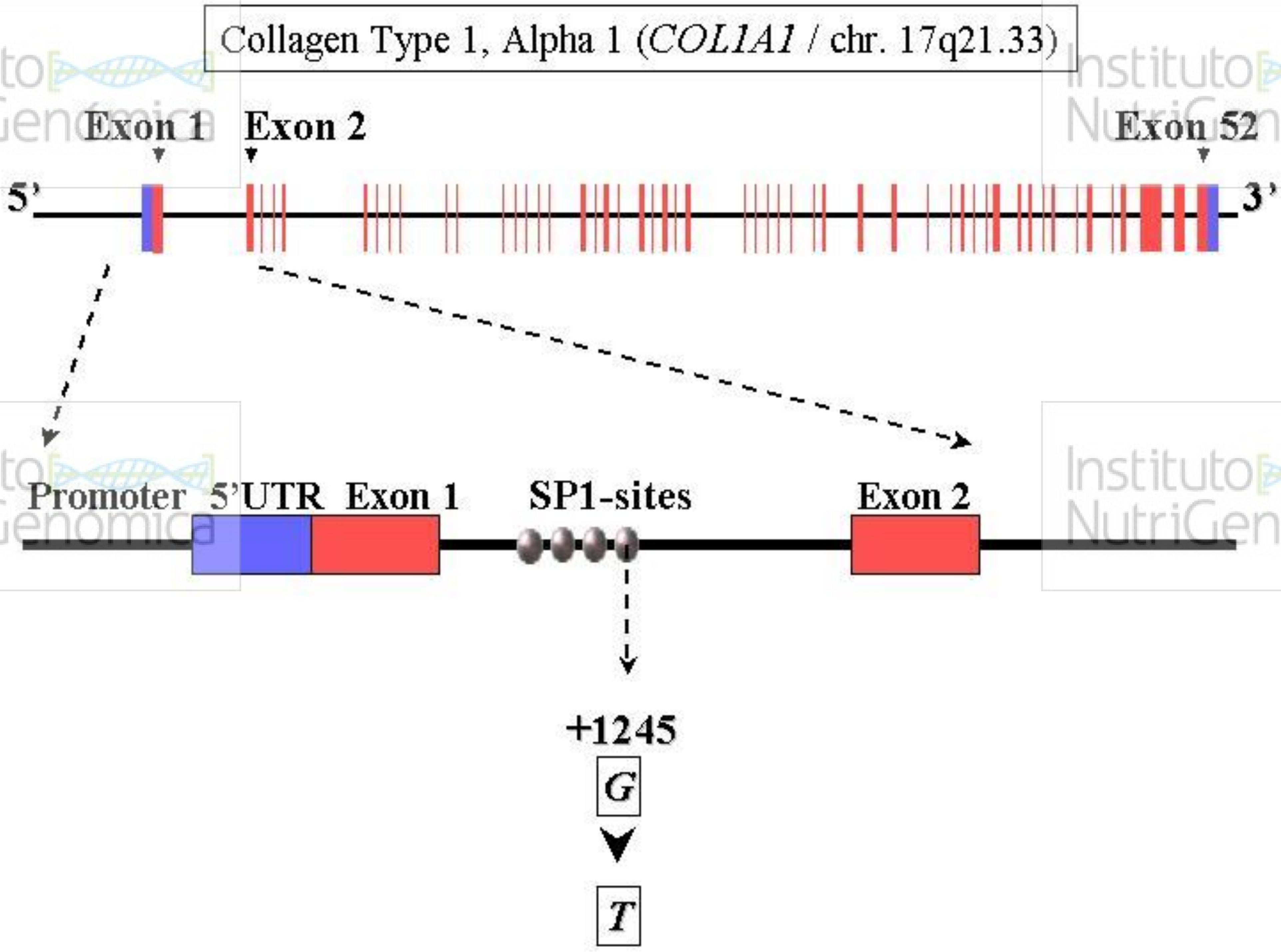
Funciones colágeno tipo 1-α1







Collagen Type 1, Alpha 1 (COL1A1 / chr. 17q21.33)
Exon 1
Exon 2
Exon 52
5'
3'
Promoter
5'UTR
Exon 1
SP1-sites
Exon 2
+1245
G
T

A COL1A1 Sp1 binding site polymorphism predispose to osteoporotic fracture by affecting bone density and quality.

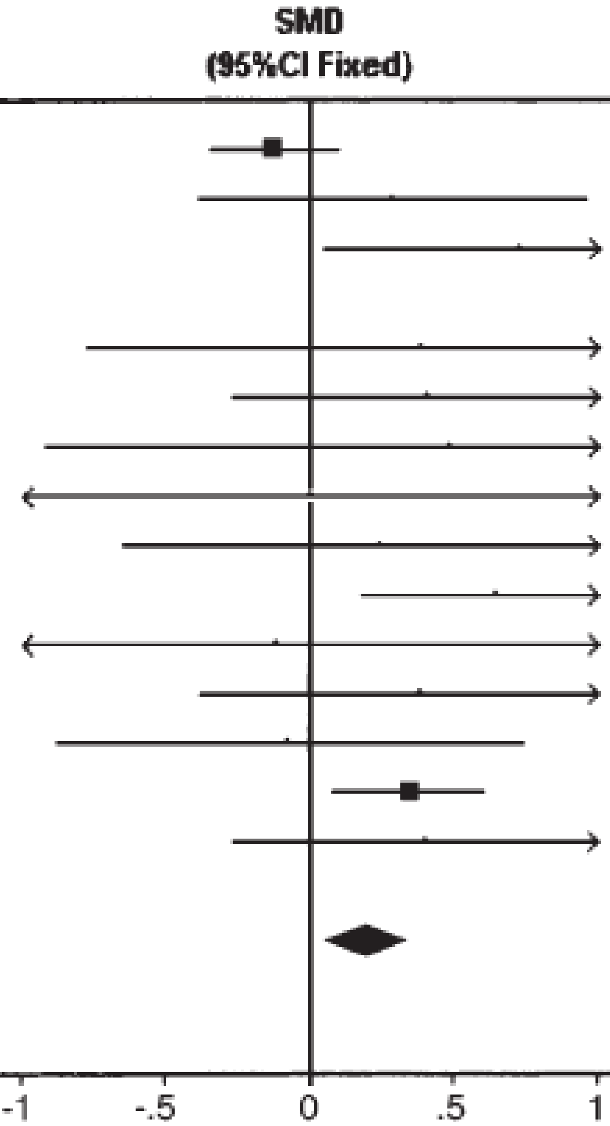
(Mann et al, 2001)

J Clin Invest 107:899-907.

Comparison: 01 BMD and Genotype
Outcome: 02 LS BMD SS vs ss

Study	SS n	SS mean(sd)	ss n	ss mean(sd)	Weight %	SMD (95%CI Fixed)
Braga 2000	349	0.82(0.16)	98	0.84(0.18)	36.1	-0.12[-0.35,0.10]
Garnero 1998	134	1.01(0.10)	9	0.98(0.16)	4.0	0.29[-0.39,0.96]
Grant 1996a	124	0.88(0.19)	9	0.74(0.16)	3.9	0.74[0.06,1.42]
x Grant 1996b	63	0.85(0.07)	1	0.82(0.00)	0.0	Not Estimable
Hampson 1998	47	1.13(0.15)	3	1.07(0.17)	1.3	0.39[-0.78,1.56]
Harris 2000	155	1.16(0.25)	9	1.06(0.12)	4.0	0.41[-0.27,1.08]
Heegard 2000	94	0.80(0.10)	2	0.75(0.16)	0.9	0.49[-0.91,1.89]
Hustmyer 1999	58	1.19(0.13)	4	1.19(0.11)	1.8	0.00[-1.01,1.01]
Keen 1999	113	0.96(0.16)	5	0.92(0.09)	2.3	0.25[-0.64,1.15]
Langdahl 1998	214	0.85(0.22)	20	0.71(0.13)	8.5	0.65[0.19,1.11]
Liden 1998	93	0.89(0.19)	3	0.91(0.21)	1.4	-0.10[-1.25,1.05]
McGuigan 2000	124	0.77(0.15)	7	0.71(0.19)	3.1	0.39[-0.37,1.16]
Sowers 1999	172	1.29(0.16)	6	1.30(0.15)	2.7	-0.06[-0.88,0.75]
Uitterlinden 1998a	1194	1.03(0.17)	58	0.97(0.19)	26.0	0.35[0.09,0.61]
Weichetova 2000	173	0.87(0.12)	9	0.82(0.12)	4.0	0.41[-0.26,1.09]
Total(95%CI)	3107		243		100.0	0.20[0.07,0.34]

Test for heterogeneity chi-square=17.37 df=13 p=0.18
Test for overall effect z=2.92 p=0.004

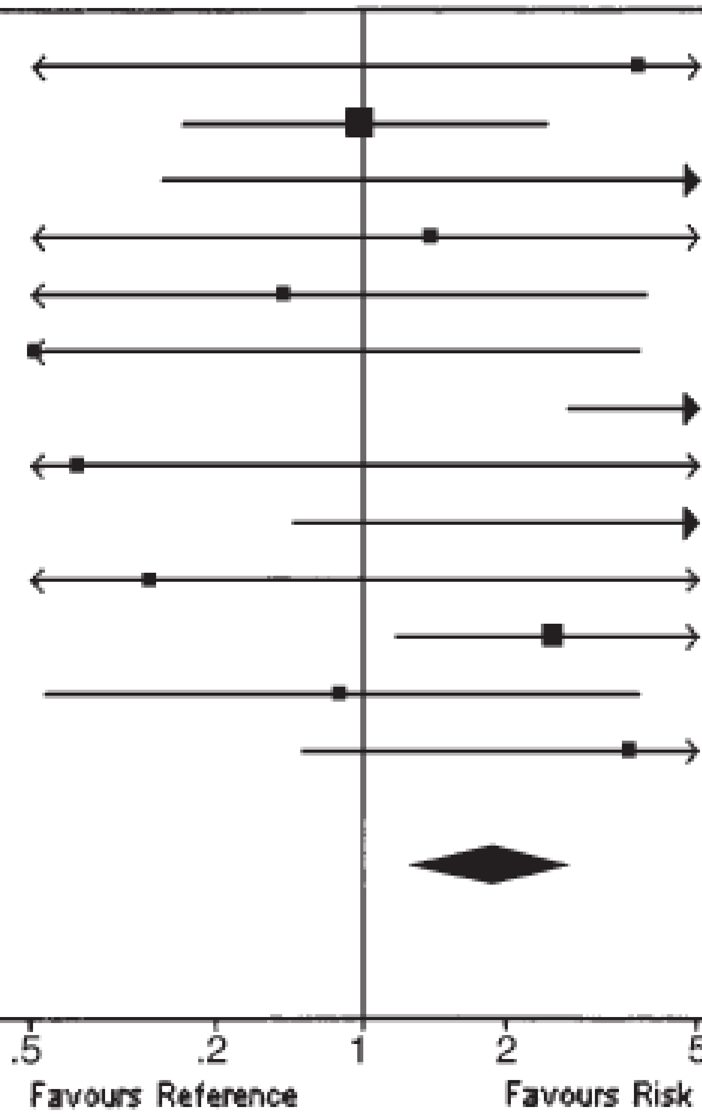


Comparison: 02 Fracture and Genotype
Outcome: 02 Fracture SS vs ss

Study	Cases n/N	Controls n/N	OR (95%CI Fixed)	Weight %	OR (95%CI Fixed)
Alvarez 1999	1 / 20	0 / 24		1.2	3.77[0.15,97.74]
Braga 2000	6 / 44	92 / 671		26.8	0.99[0.41,2.42]
Grant 1996a	3 / 55	0 / 55		1.3	7.40[0.37,146.74]
Heegard 2000	0 / 16	2 / 117		1.7	1.40[0.06,30.46]
Hustmyer 1999	2 / 56	4 / 78		8.8	0.69[0.12,3.88]
Keen 1999	0 / 55	5 / 130		9.0	0.21[0.01,3.78]
Langdahl 1998	15 / 105	2 / 144		4.0	11.83[2.64,52.97]
Liden 1998	0 / 36	3 / 67		6.7	0.25[0.01,5.02]
McGuigan 2000	6 / 93	1 / 88		2.6	6.00[0.71,50.88]
Roux 1998	0 / 50	4 / 167		5.7	0.36[0.02,6.80]
Uitterlinden 1998a	8 / 111	50 / 1667		15.9	2.51[1.16,5.44]
Uitterlinden 1998b	2 / 74	42 / 1399		11.3	0.90[0.21,3.76]
Weichetova 2000	7 / 126	2 / 126		5.2	3.65[0.74,17.91]
Total(95%CI)	50 / 841	207 / 4733		100.0	1.86[1.28,2.70]

Test for heterogeneity chi-square=18.60 df=12 p=0.099

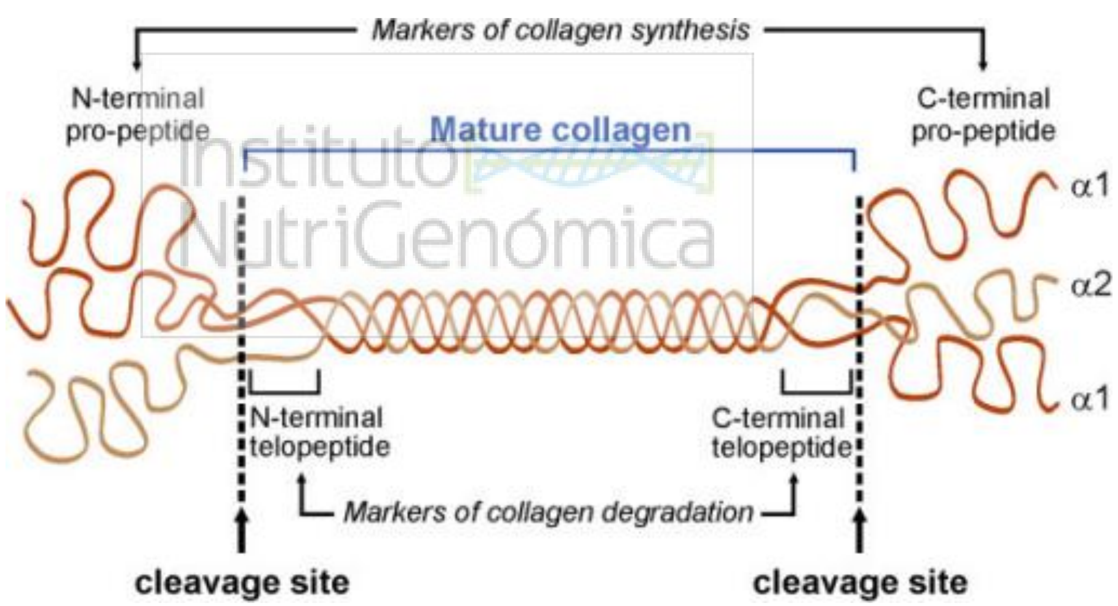
Test for overall effect z=3.26 p=0.001

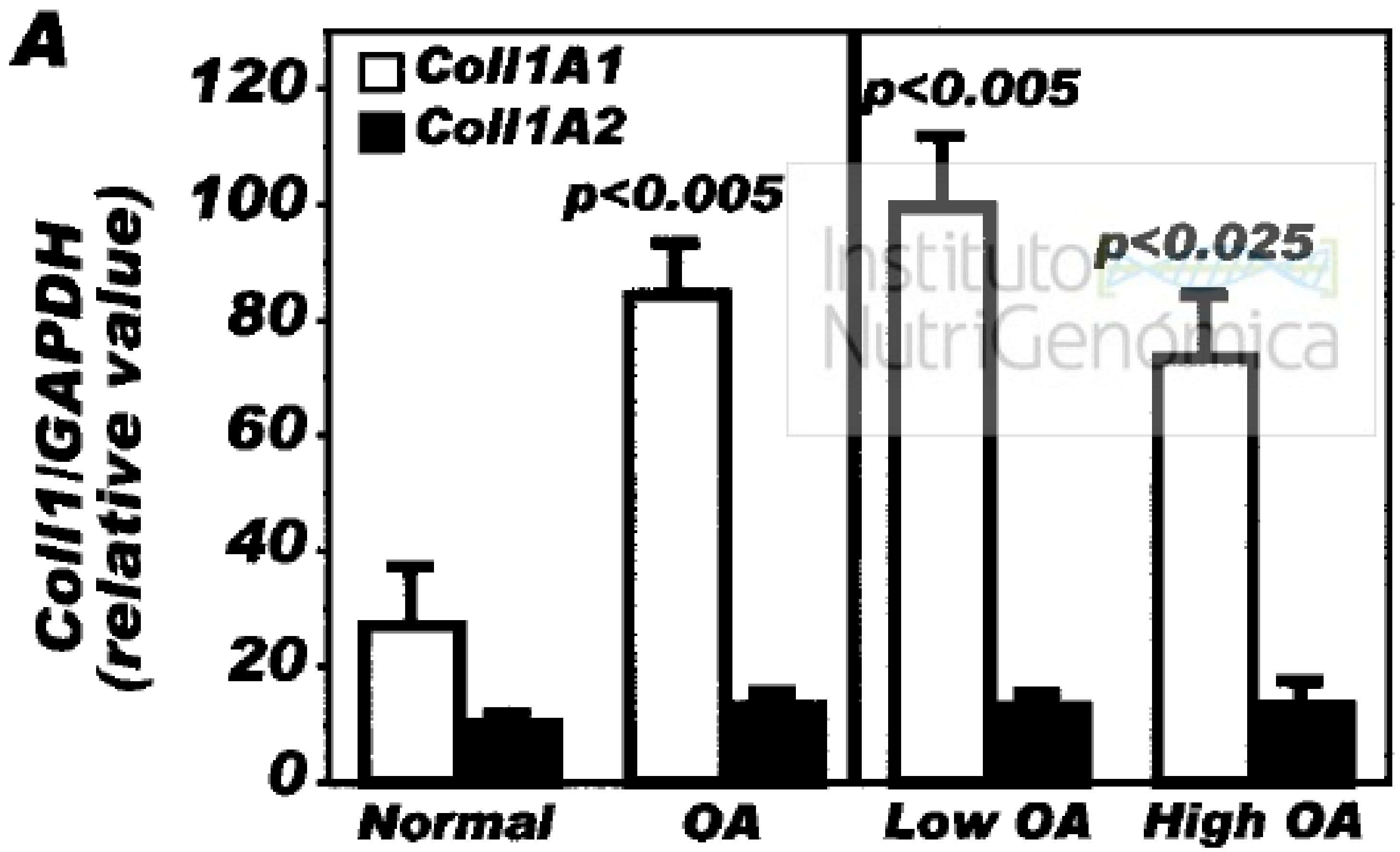


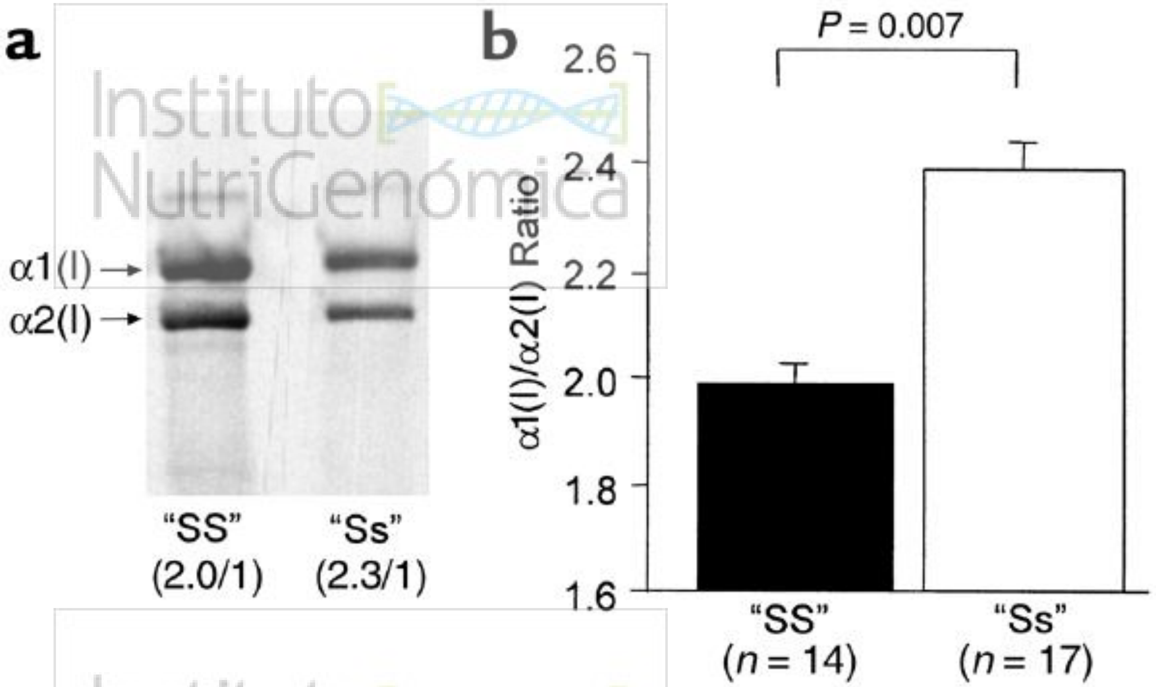
Altered mineralization of human osteoarthritic osteoblast is atribubutable to abnormal type I collagen production

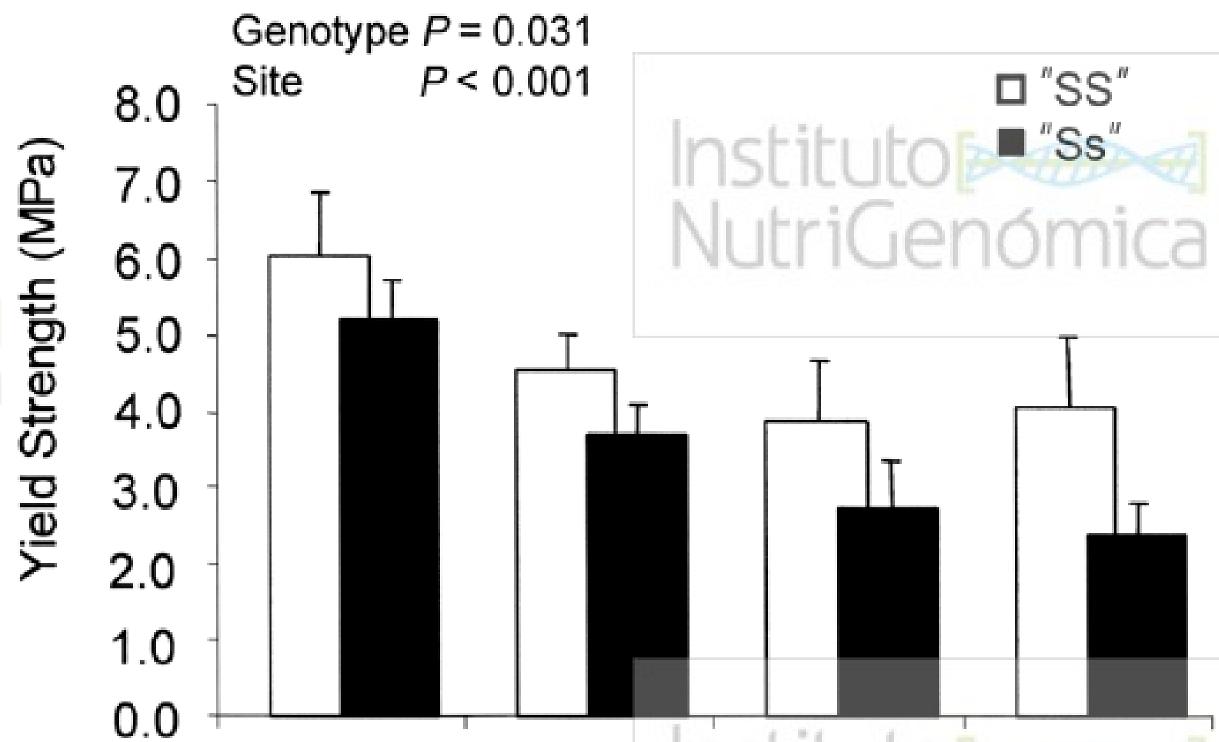
(Couchourel et al, 2009)

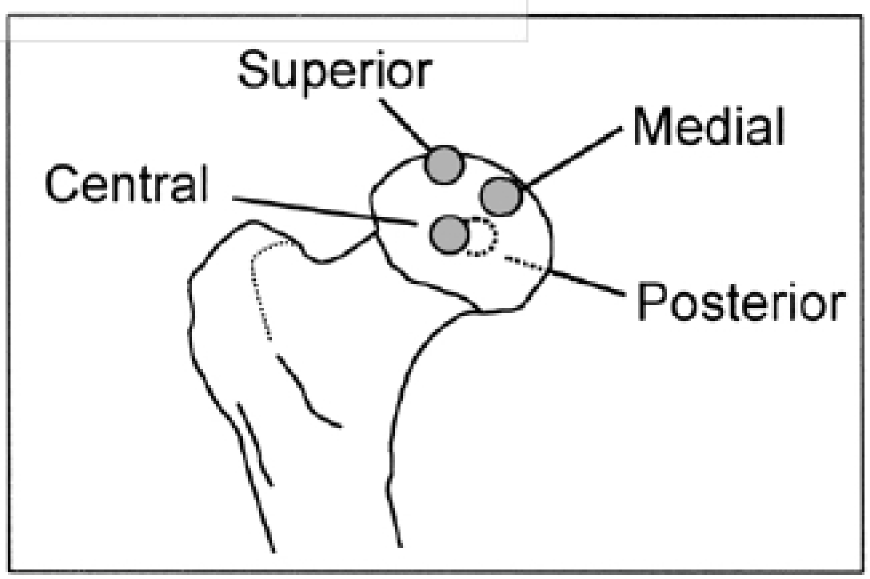
Arthritis & Rheumatism, 60:1438-1450

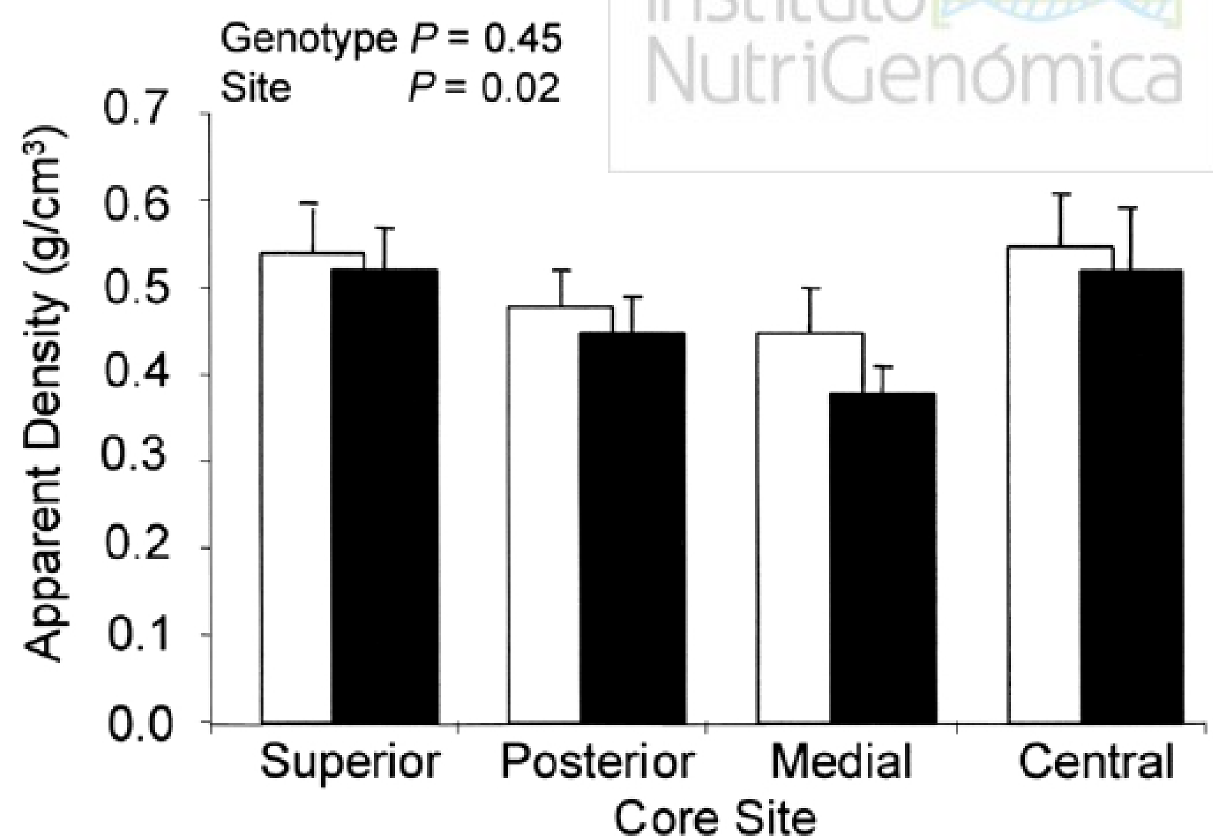





a
b
α1(I) →
α2(I) →
"SS"
(2.0/1)
"Ss"
(2.3/1)
P = 0.007
α1(I)/α2(I) Ratio
2.6
2.4
2.2
2.0
1.8
1.6
"SS"
(n = 14)
"Ss"
(n = 17)


Genotype P = 0.031
Site P < 0.001
"SS"
"Ss"
Yield Strength (MPa)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

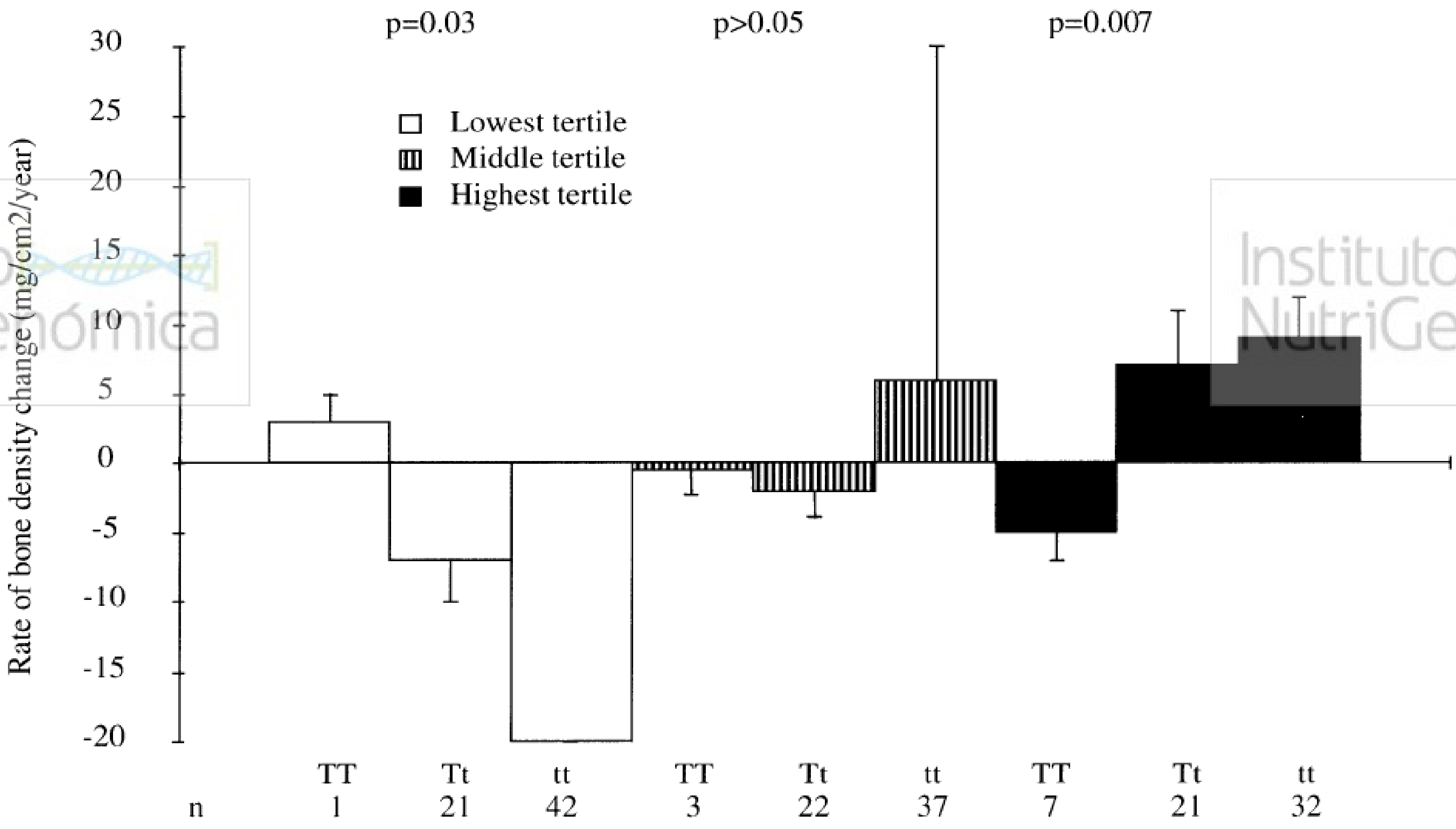

Superior
Medial
Central
Posterior


Genotype P = 0.45
Site P = 0.02
Apparent Density (g/cm³)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Superior
Posterior
Medial
Central
Core Site

Genetic control of bone density and turnover: role of the collagen 1α1, estrogen receptor, and vitamin D receptor genes

(Brown et al, 2001)

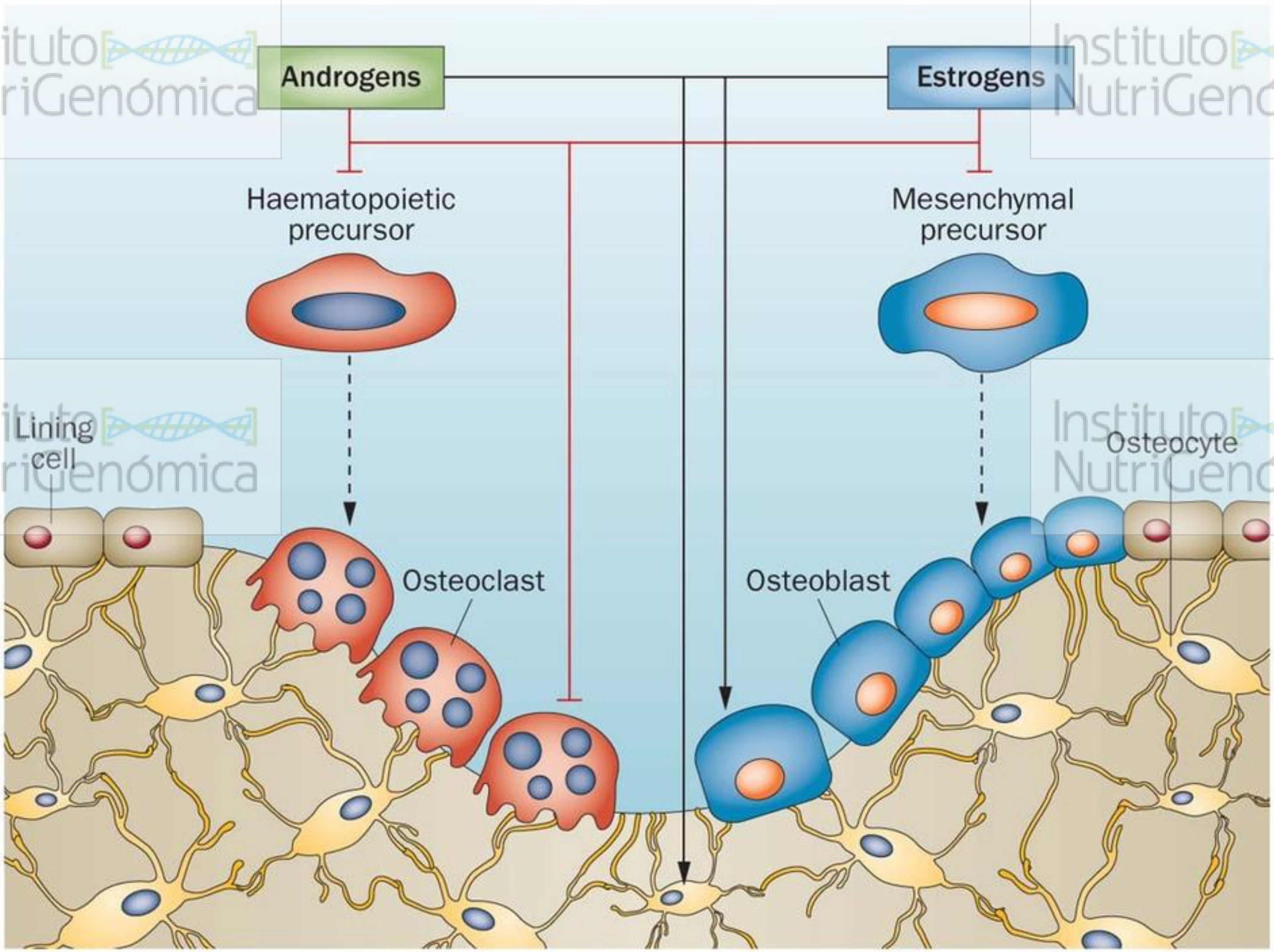
J Bone Miner Res 16:758-764

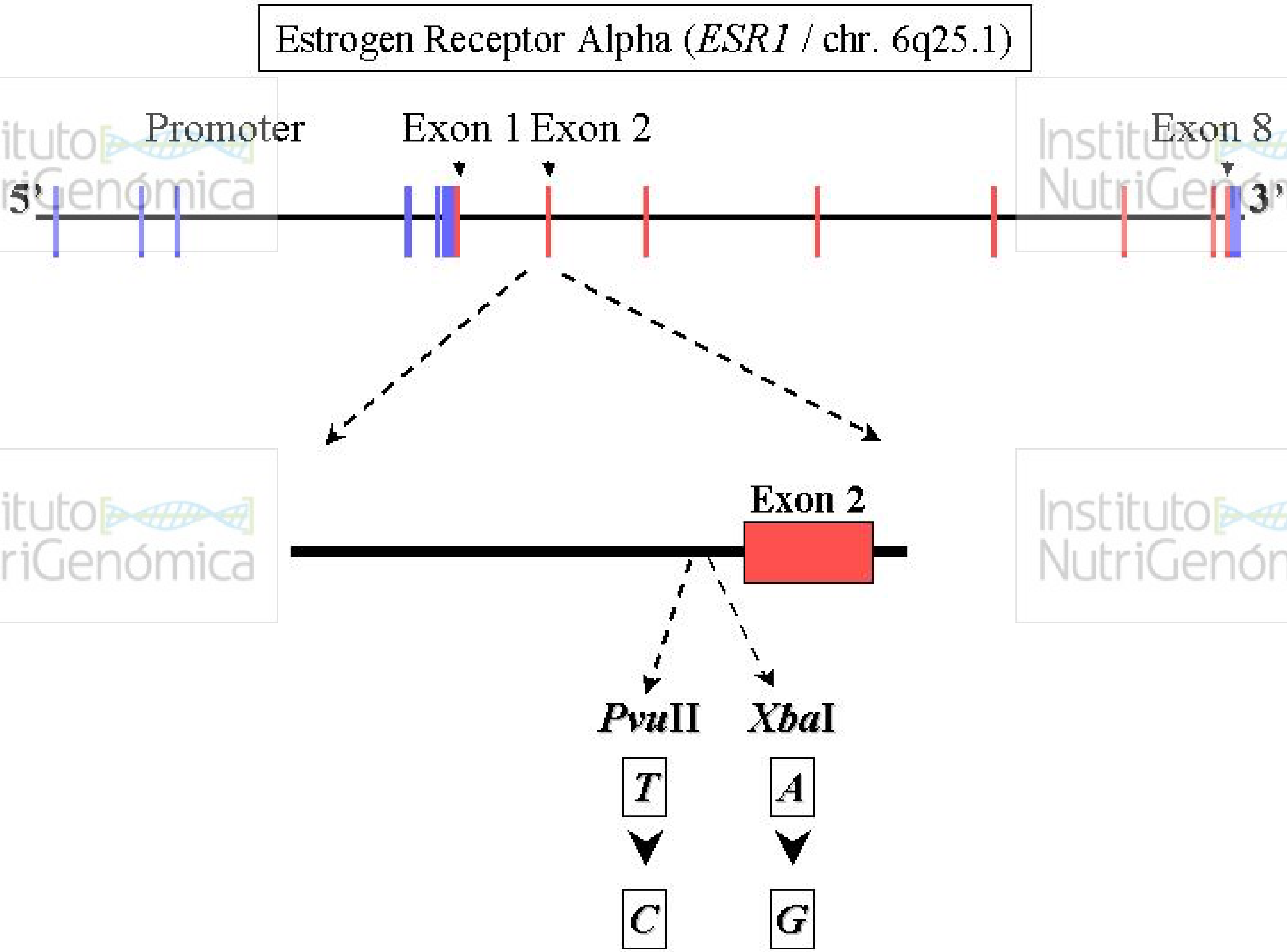


Nutrigenómica y osteoporosis

Índice

Función de los estrógenos en la formación del hueso

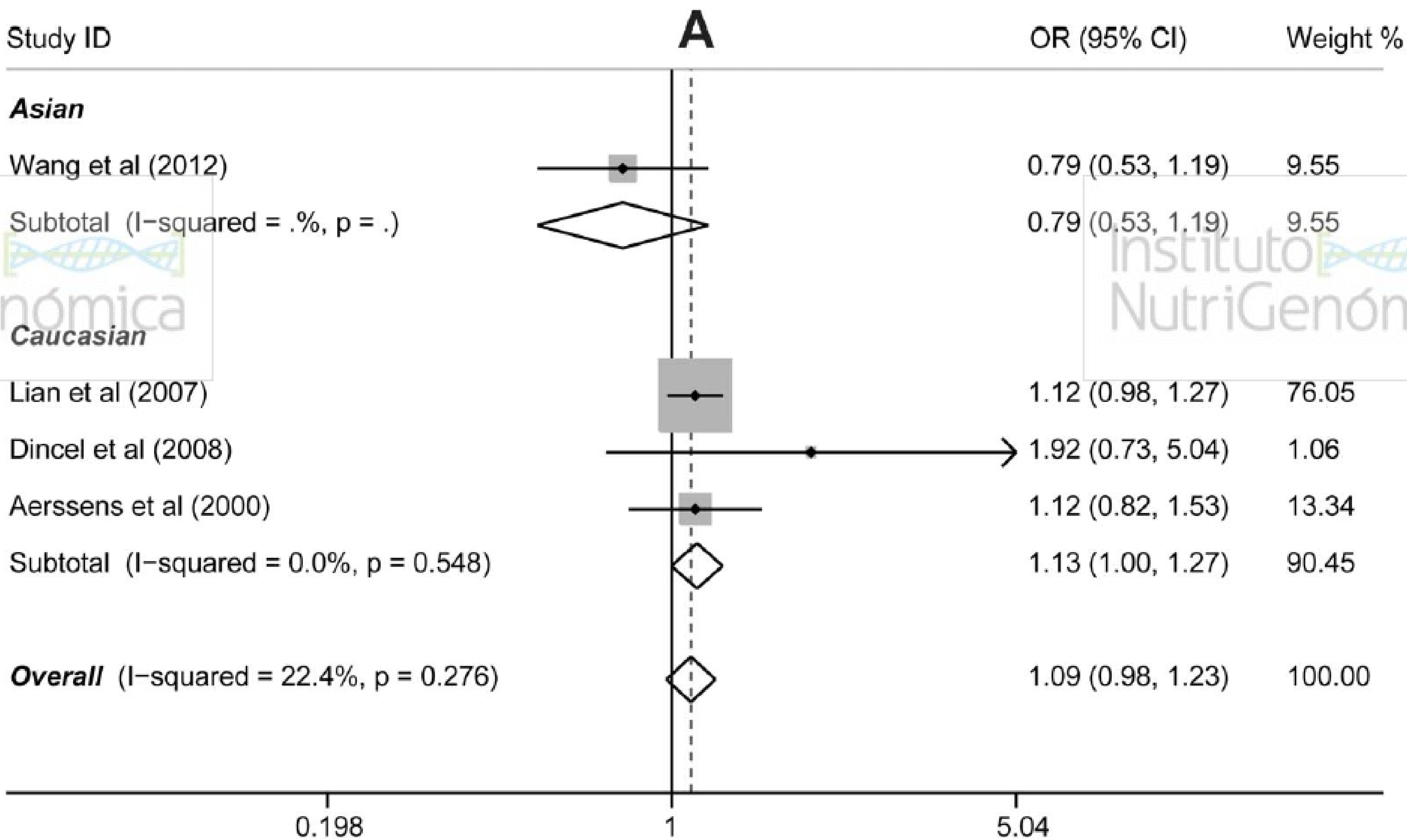



Estrogen Receptor Alpha (*ESR1* / chr. 6q25.1)
Promoter
Exon 1
Exon 2
Exon 8
5'
3'
Exon 2
*Pvu*II
*Xba*I
T
A
C
G

Association between estrogen receptor alpha gene (ESR1) Pvull (C/T) and XbaI (A/G) polymorphism and hip fracture risk: Evidece from a meta-analysis

(Tang et al, 2013)
Plos One 8:e82806

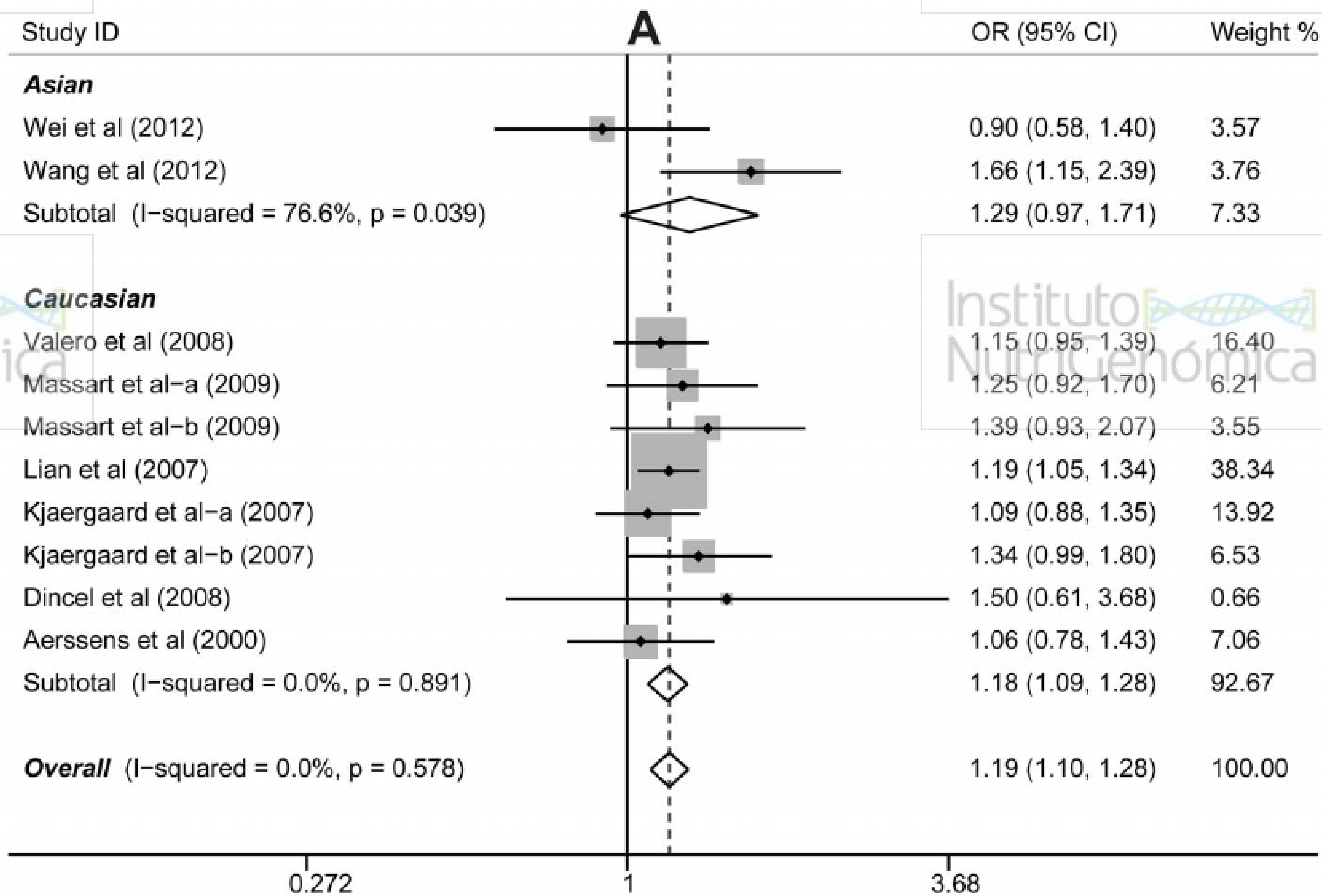
*Xba*I Alelo G vrs A



Association between estrogen receptor alpha gene (ESR1) Pvull (C/T) and XbaI (A/G) polymorphism and hip fracture risk: Evidece from a meta-analysis

(Tang et al, 2013)
Plos One 8:e82806

PvuII
Alelo T vrs C

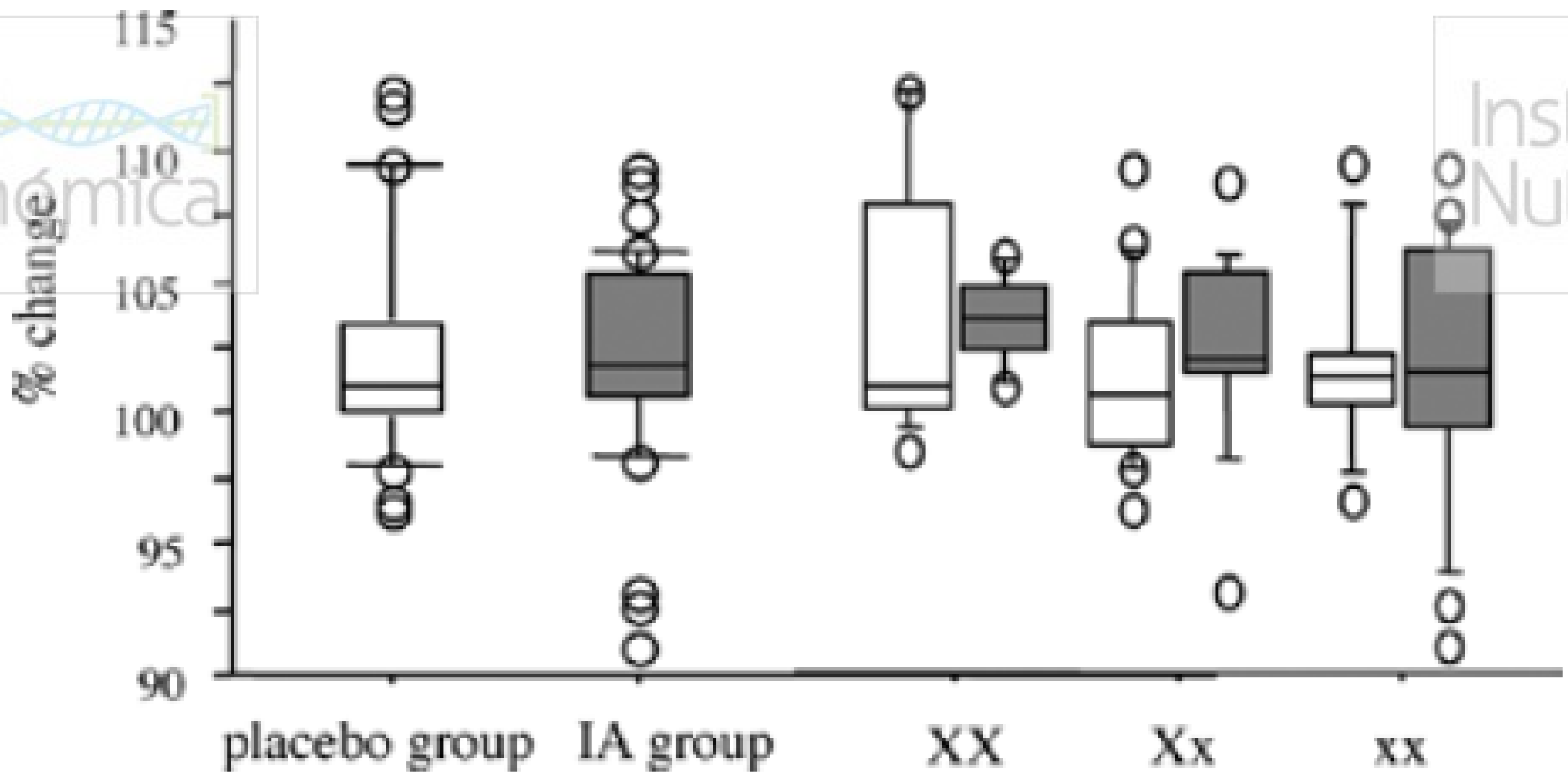


Alterations in bone turnover by isoflavone aglycone supplementation in relation to estrogen receptor α polymorphism.

(Katsuyama et al, 2010)
Molecular medicine reports: 3:531-535.

Suplemento con 30 mg/día de isoflavonas
Durante 3 meses

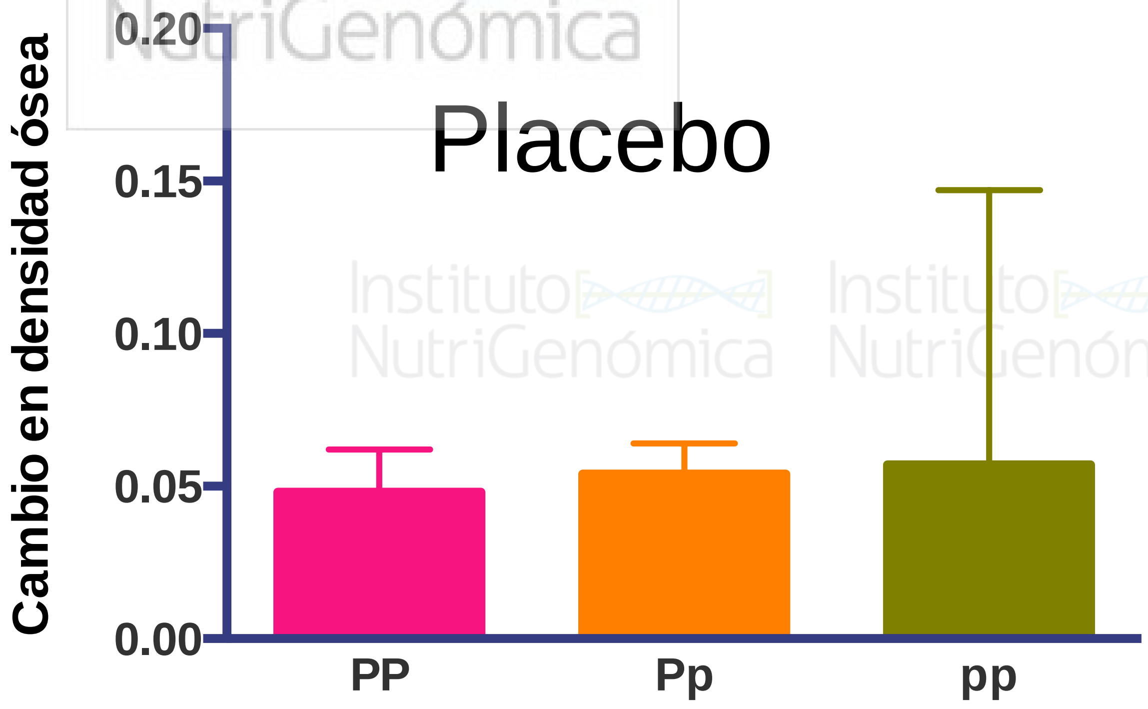
*Xba*I

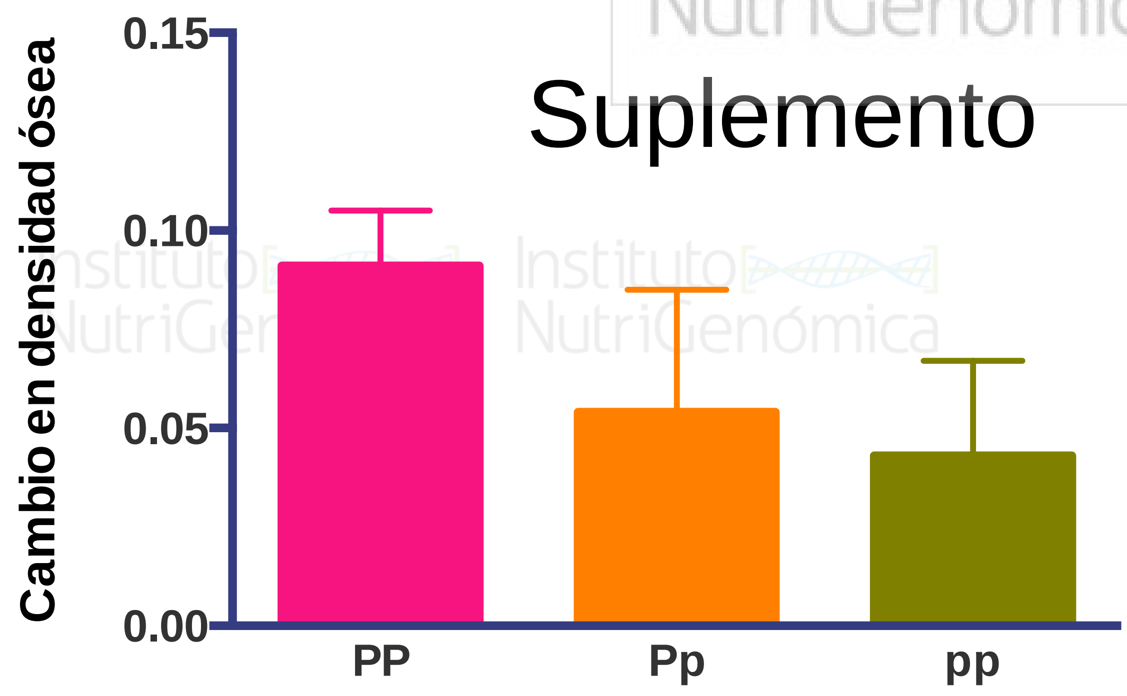


Association of estrogen receptor-α gene PvuII polymorphisms with the effect of calcium supplementation on skeletal development in chinese pubertal girls

(Yang et al, 2009)
Biomed Environ Sci 22:480-487.

Suplementación diaria durante 1 año con
- 250 mg carbonato de calcio
- 60 IU vitamina D





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3. Polimorfismos en el gen del colágeno tipo 1-α1

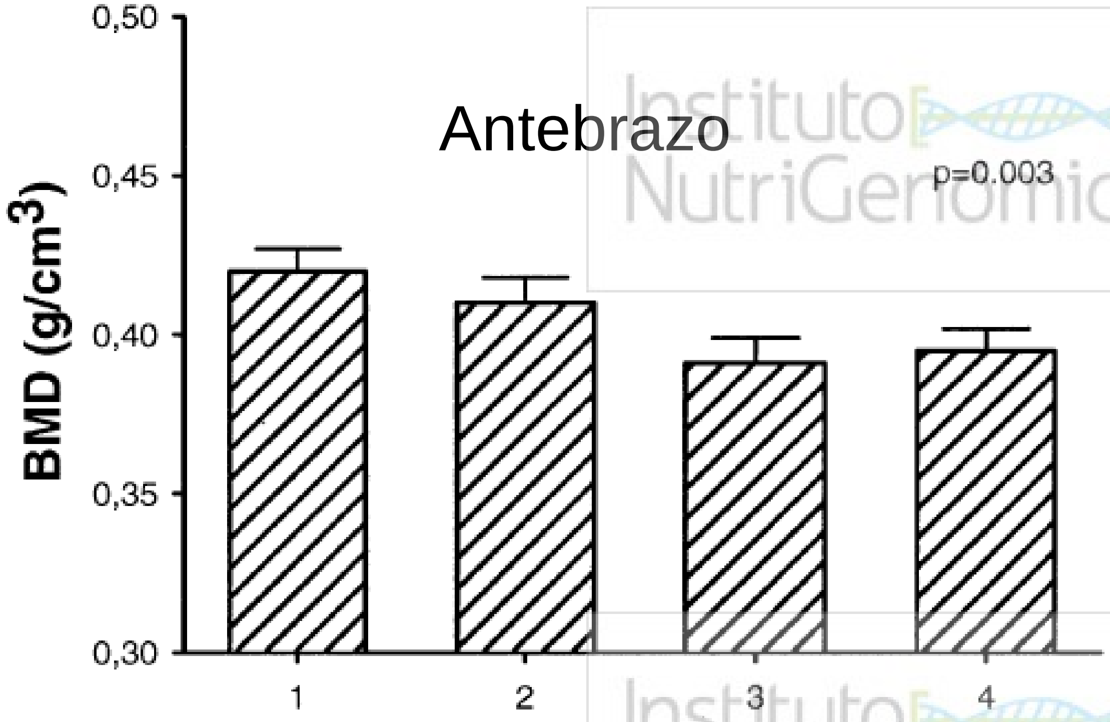
4. Polimorfismos en el gen del receptor de estrógenos

5. **Metabolismo lipídico y osteoporosis**

6. Vitaminas del complejo B, estrés oxidativo y osteoporosis

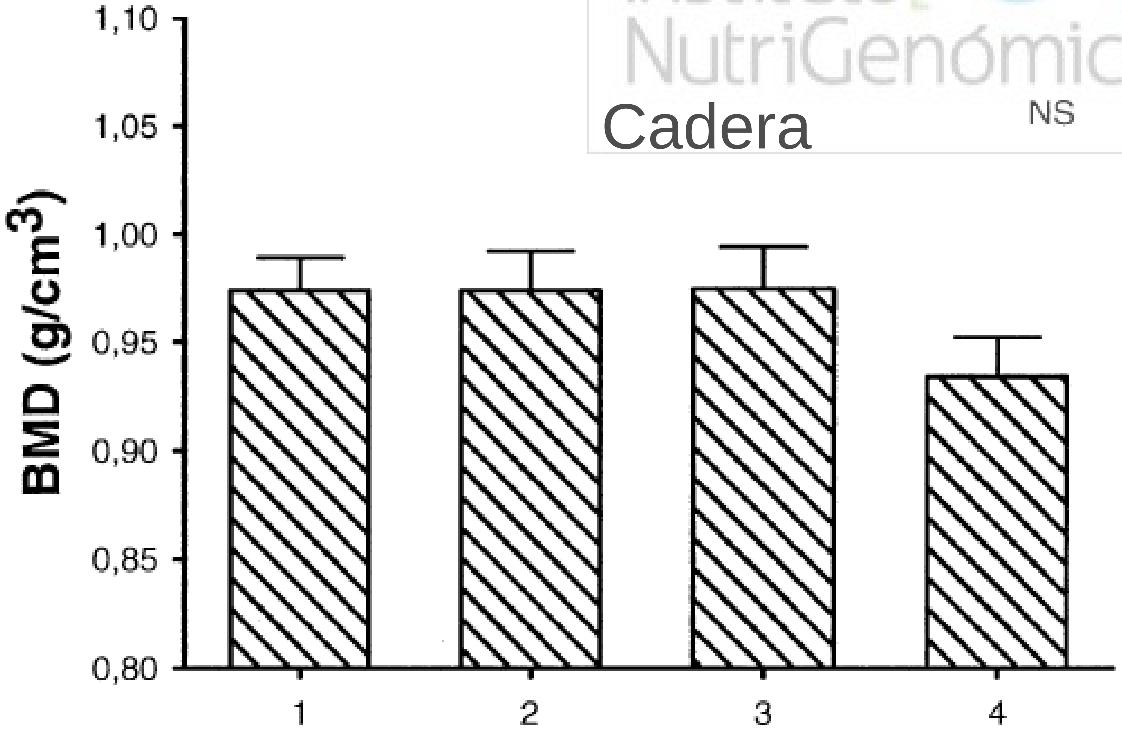
Does serum cholesterol contribute to vertebral bone loss in postmenopausal women?

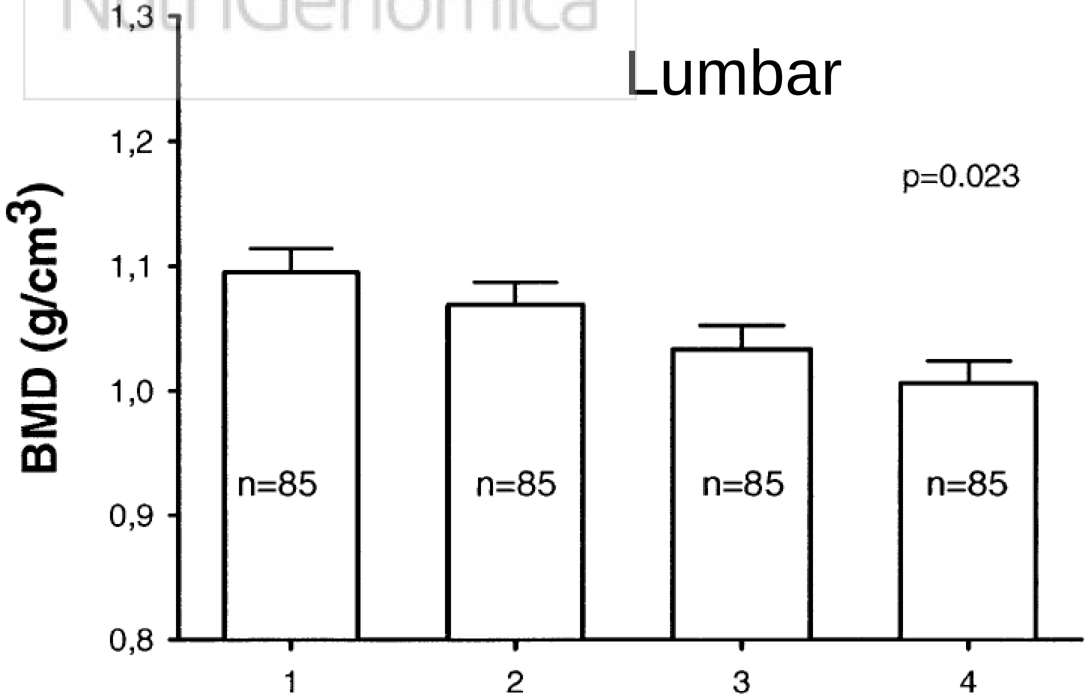
(Tanko et al, 2003)
Bone 32:8-14



Colesterol total

Q1: 193 mg/dL
Q2: 232 mg/dL
Q3: 265 mg/dL
Q4: 310 mg/dL

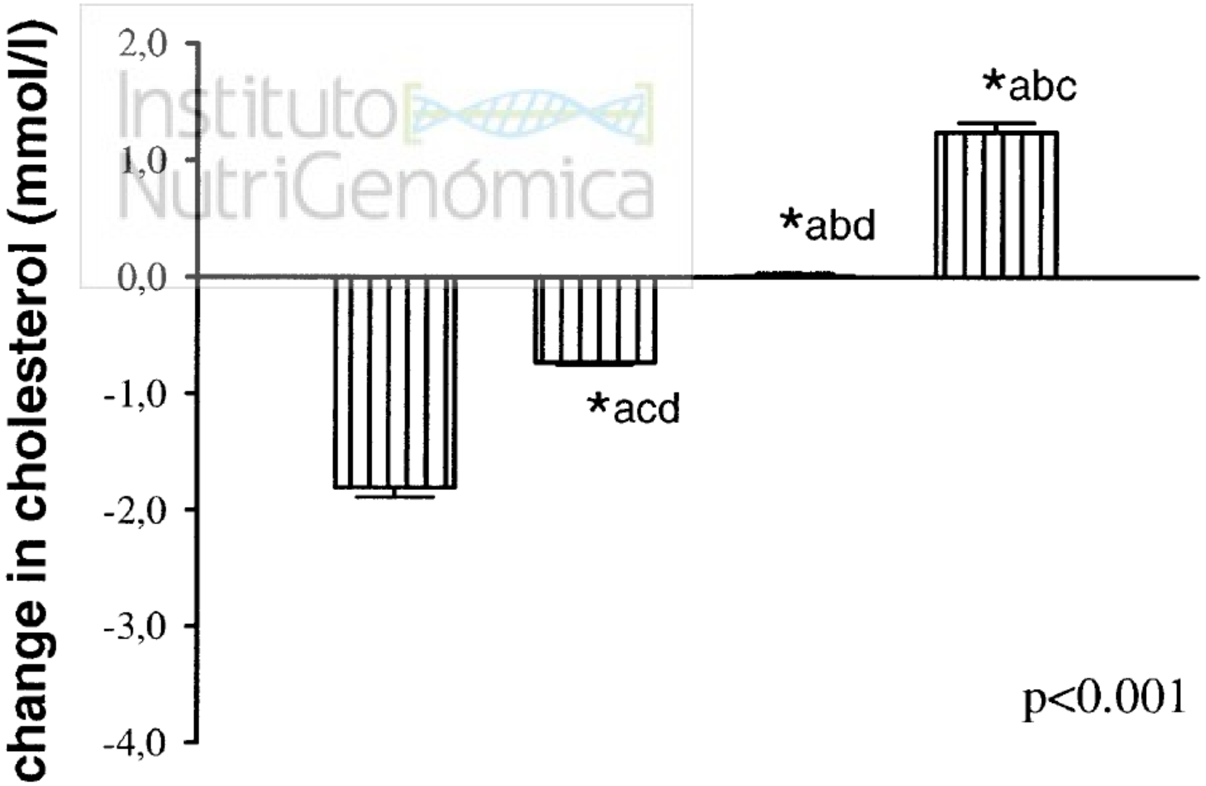


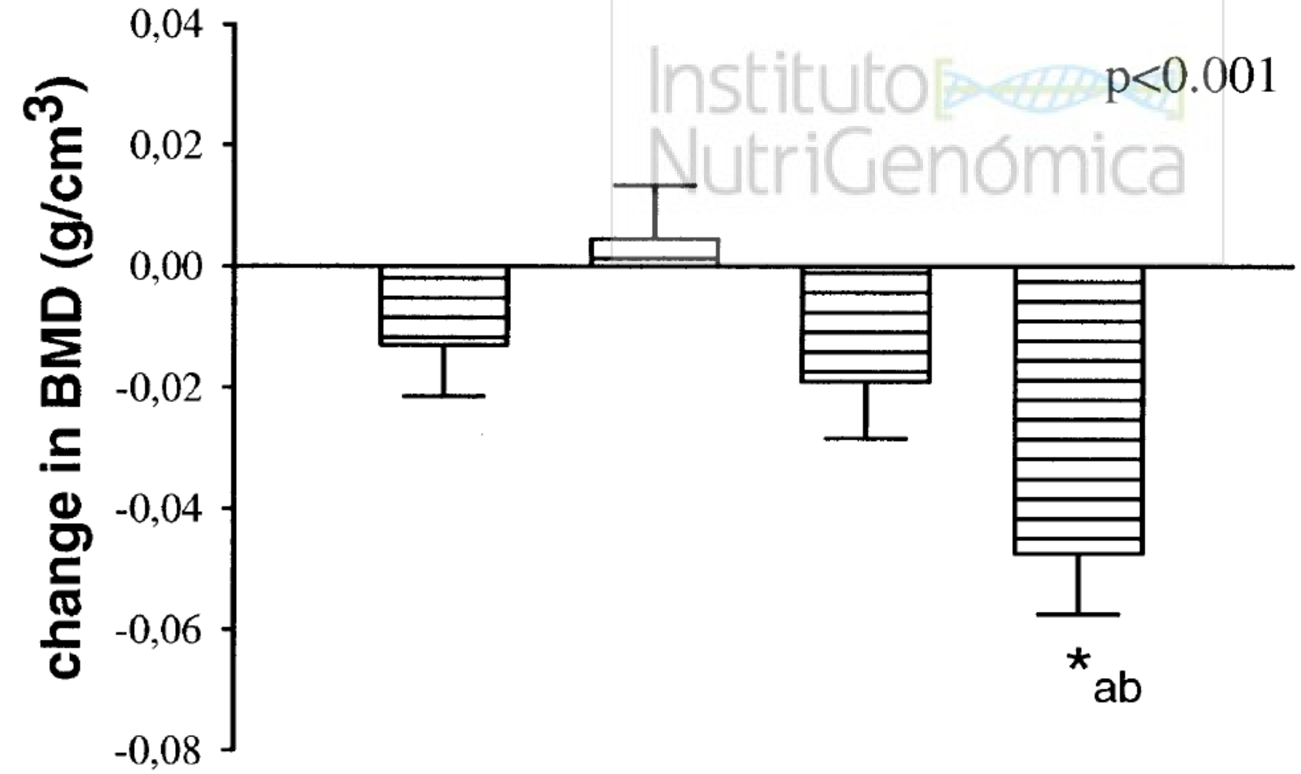


Does serum cholesterol contribute to vertebral bone loss in postmenopausal women?

(Tanko et al, 2003)
Bone 32:8-14

Seguimiento de 8 años…

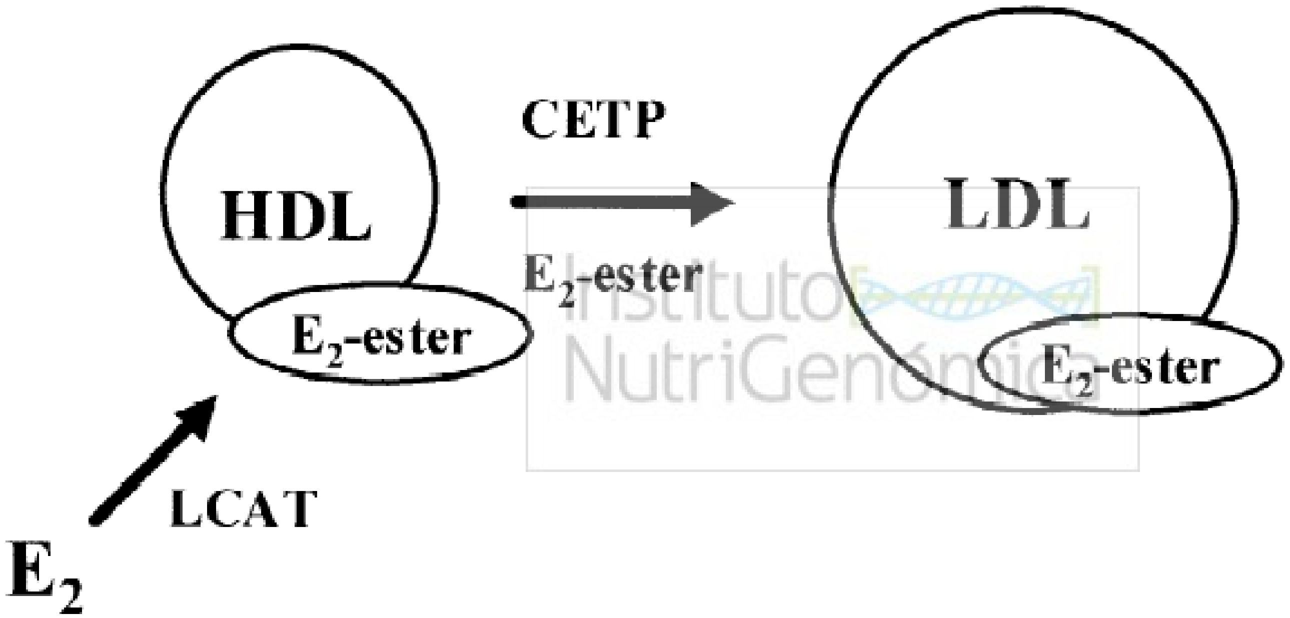




HDL cholesterol and bone mineral density: Is there a genetic link?

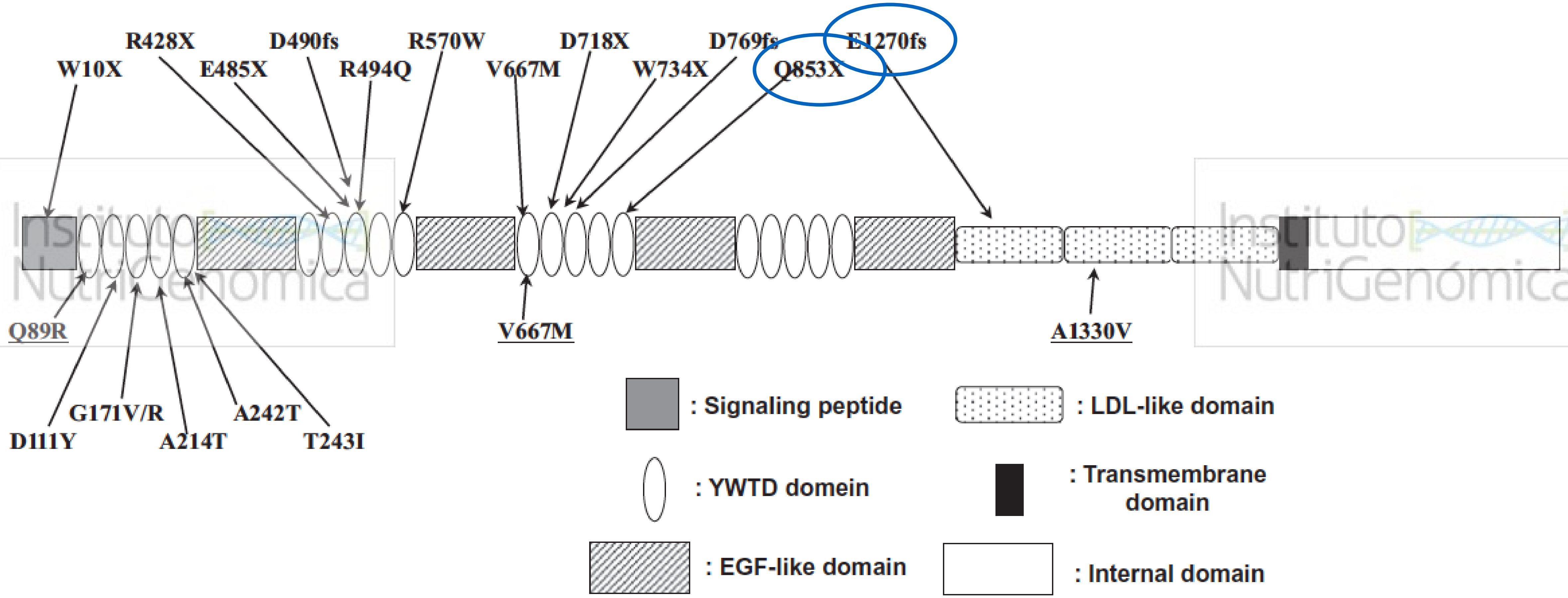
(Ackert-Bicknell, 2012)
Bone 50:525-533

Gen	Nombre
ABCG8	ATP-binding cassette, sub-family G, member 8
APOE	Apolipoprotein E
ESR1	Estrogen receptor 1 (alpha)
GHRH	Growth hormone releasing hormone
IL6	Interleukin 6
MTHFR	5,10 methylenetetrahydrofolate reductase
PON1	Paraoxonase 1
PPARG	Peroxisome proliferator activated receptor gamma
TNF	Tumor necrosis factor



LDL Receptor-Related Protein 5 (LRP5) affects bone accrual and eye development

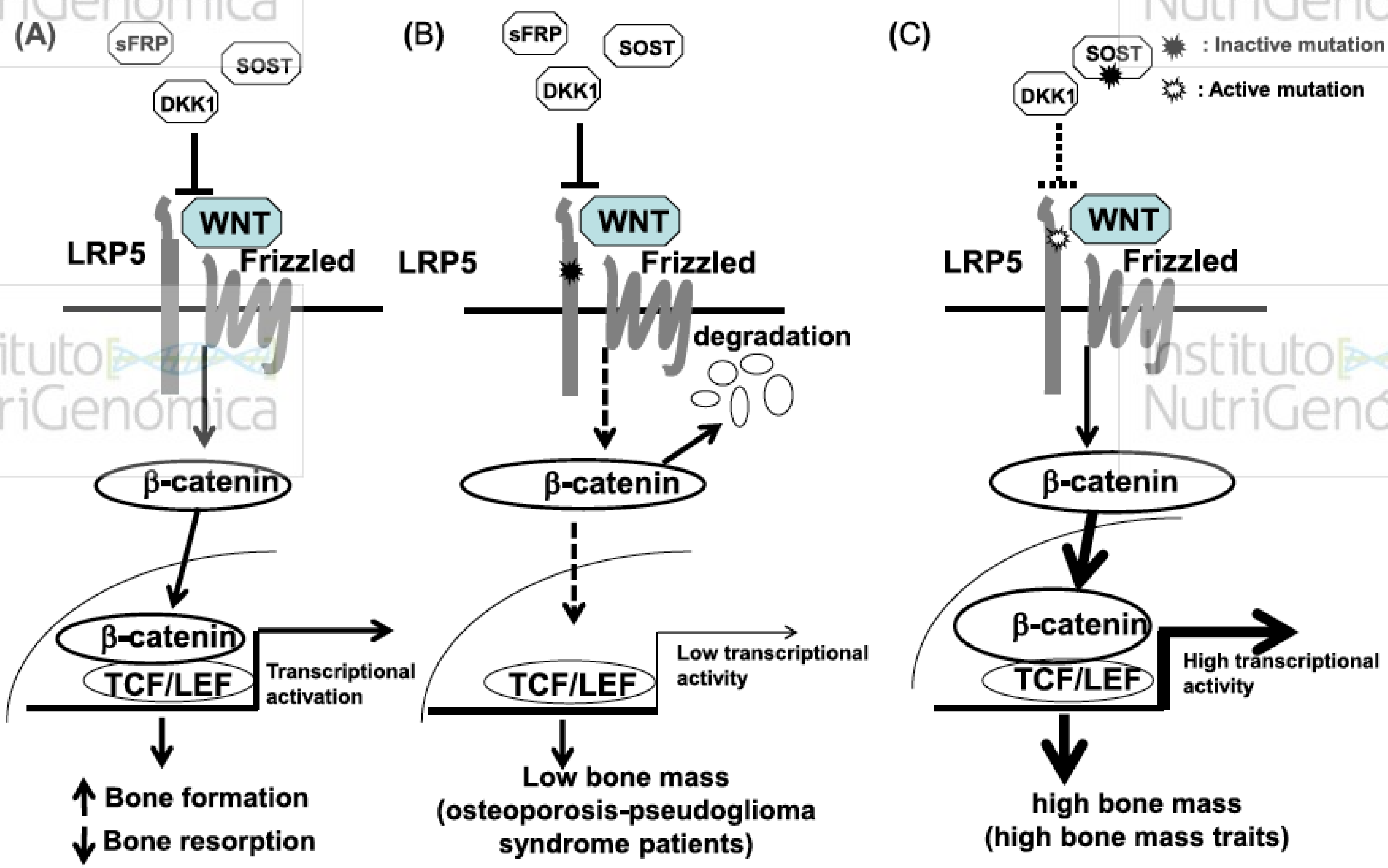
(Gong et al, 2001)
Cell 107:513-523



Genetics of osteoporosis

(Urano & Inoue, 2014)

Biochem Biophys Res Comm 452:287-293



Nutrigenómica y osteoporosis

Índice

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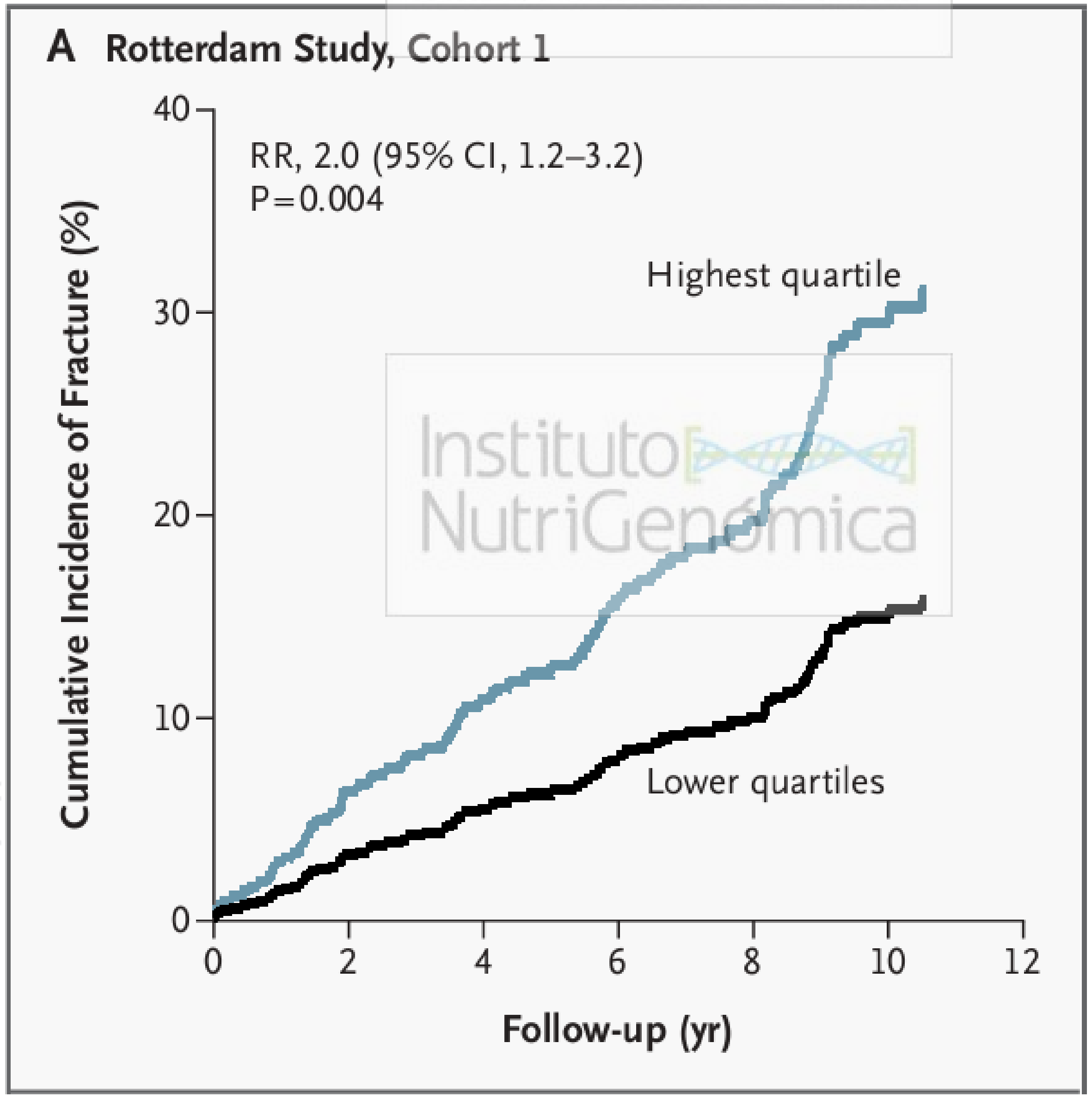
Homocysteine Levels and the Risk of Osteoporotic Fracture

Joyce B.J. van Meurs, Ph.D., Rosalie A.M. Dhonukshe-Rutten, M.Sc., Saskia M.F. Pluijm, Ph.D., Marjolein van der Klift, M.D., Ph.D., Robert de Jonge, Ph.D., Jan Lindemans, Ph.D., Lisette C.P.G.M. de Groot, Ph.D., Albert Hofman, M.D., Ph.D., Jacqueline C.M. Witteman, Ph.D., Johannes P.T.M. van Leeuwen, Ph.D., Monique M.B. Breteler, M.D., Ph.D., Paul Lips, M.D., Ph.D., Huibert A.P. Pols, M.D., Ph.D., and André G. Uitterlinden, Ph.D.

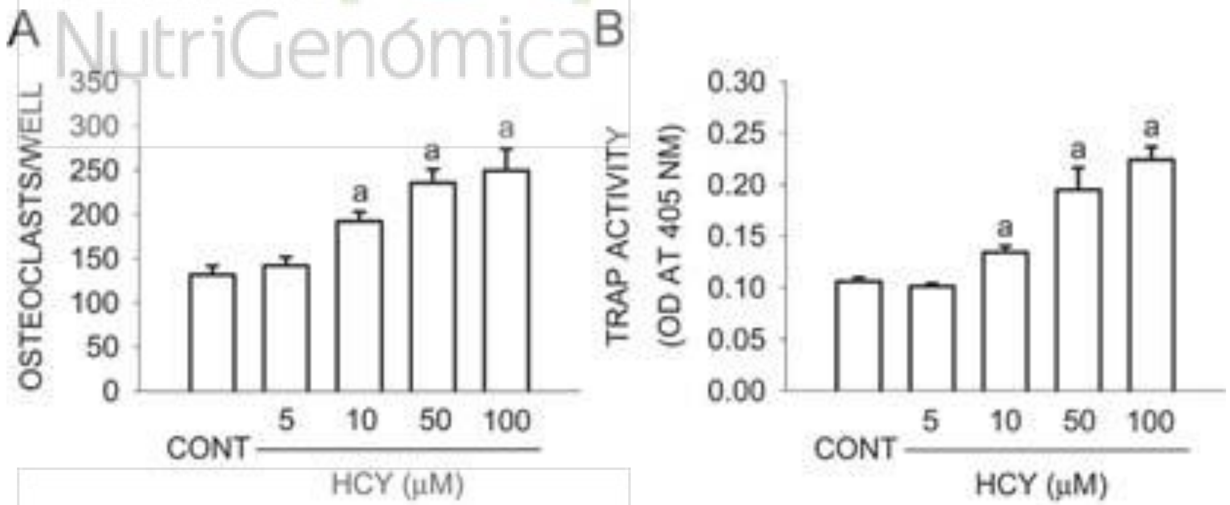
Table 4. Relative Risks and Population Attributable Risks for Independent Risk Factors for Incident Fracture.*

Factor	Relative Risk (95% CI)	Population Attributable Risk (95% CI)
		%
Age >75 yr	2.3 (1.7–3.1)	31 (25–48)
BMD, lowest quartile	1.6 (1.1–2.3)	13 (2–25)
Current smoker	1.6 (1.1–2.3)	10 (4–23)
Fall in previous year†	1.9 (1.2–2.7)	20 (10–35)
Dementia and cognitive impairment†	2.5 (1.5–4.1)	15 (7–30)
Homocysteine level, highest quartile	1.9 (1.4–2.6)	19 (10–29)



Homocysteine Enhances Bone Resorption by Stimulation of Osteoclast Formation and Activity Through Increased Intracellular ROS Generation

Jung-Min Koh,[1,2] Young-Sun Lee,[2,3] Yang Soon Kim,[3] Duk Jae Kim,[1] Hong-Hee Kim,[4] Joong-Yeol Park,[1] Ki-Up Lee,[1] and Ghi Su Kim[1]



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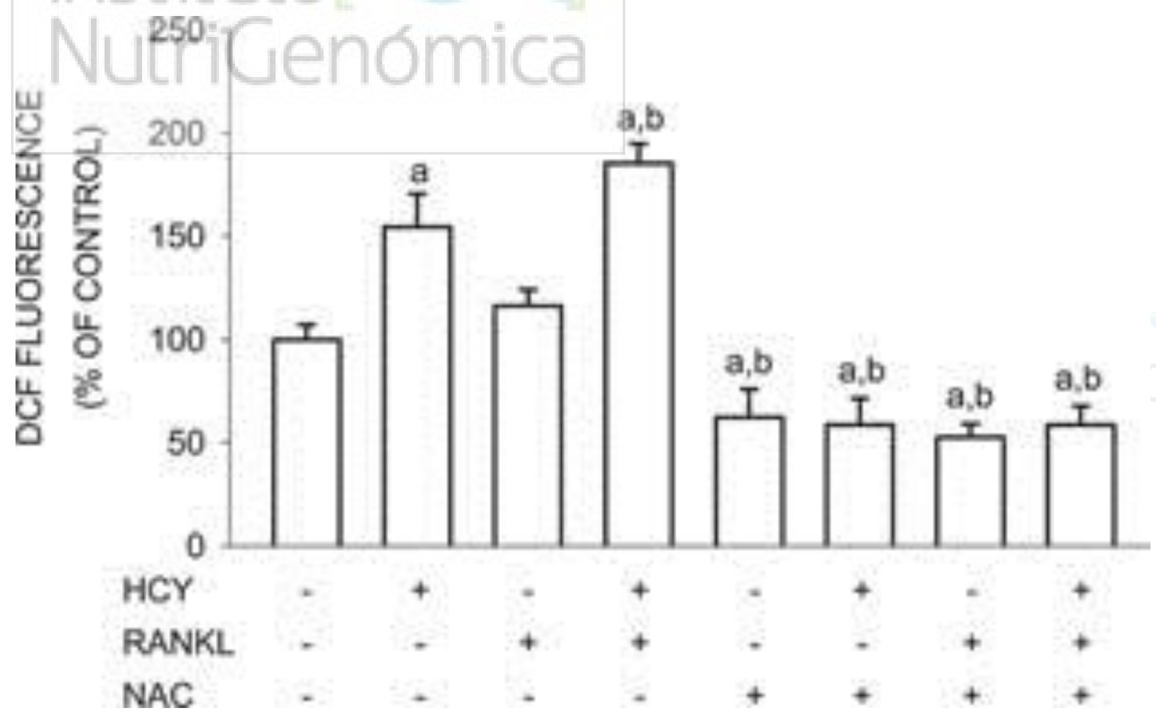

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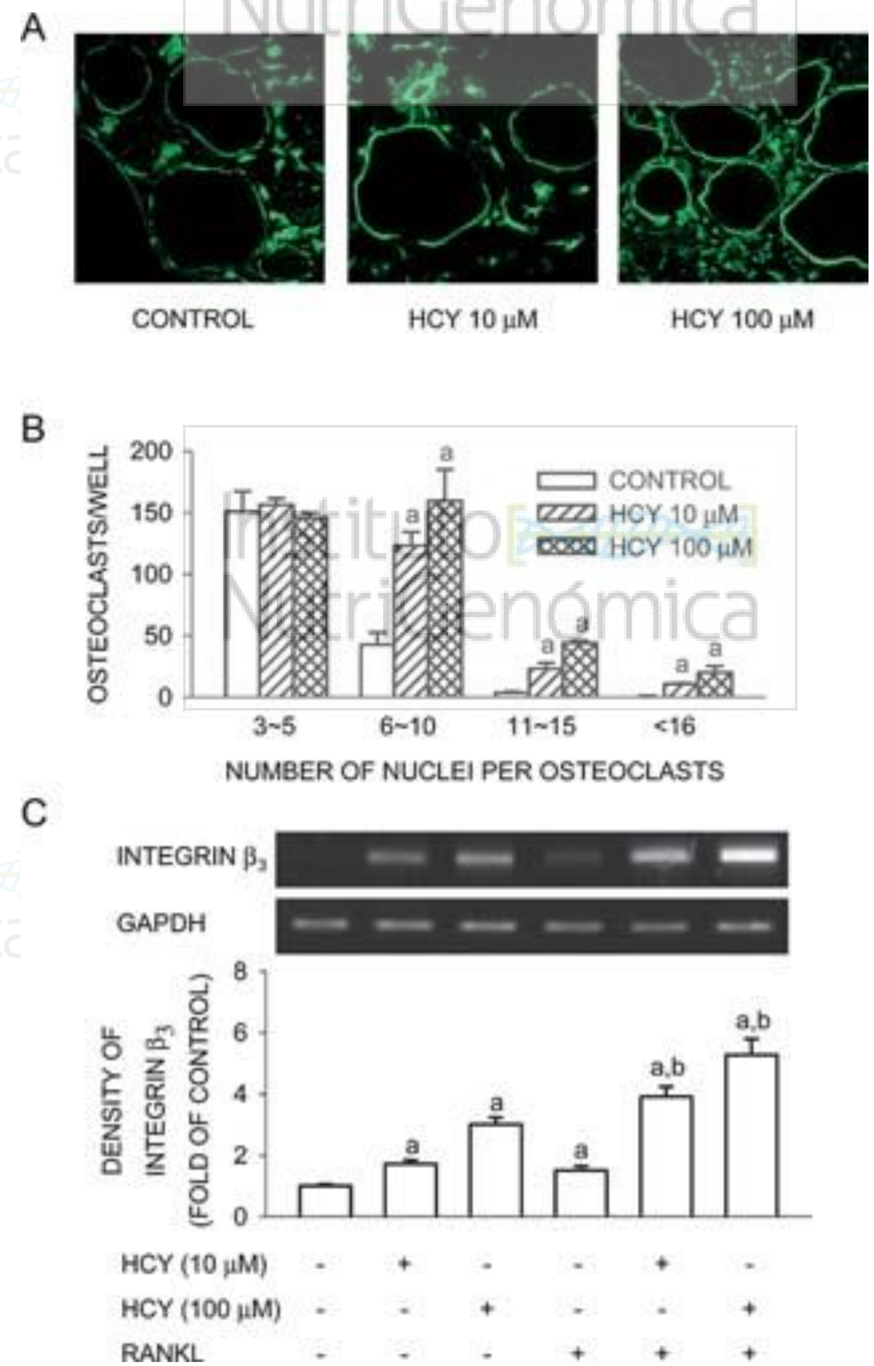


Journal of Bone and Mineral Research
Volume 21, Issue 7, pages 1003-1011, 15 MAY 2006 DOI: 10.1359/jbmr.060406
http://onlinelibrary.wiley.com/doi/10.1359/jbmr.060406/full#fig4

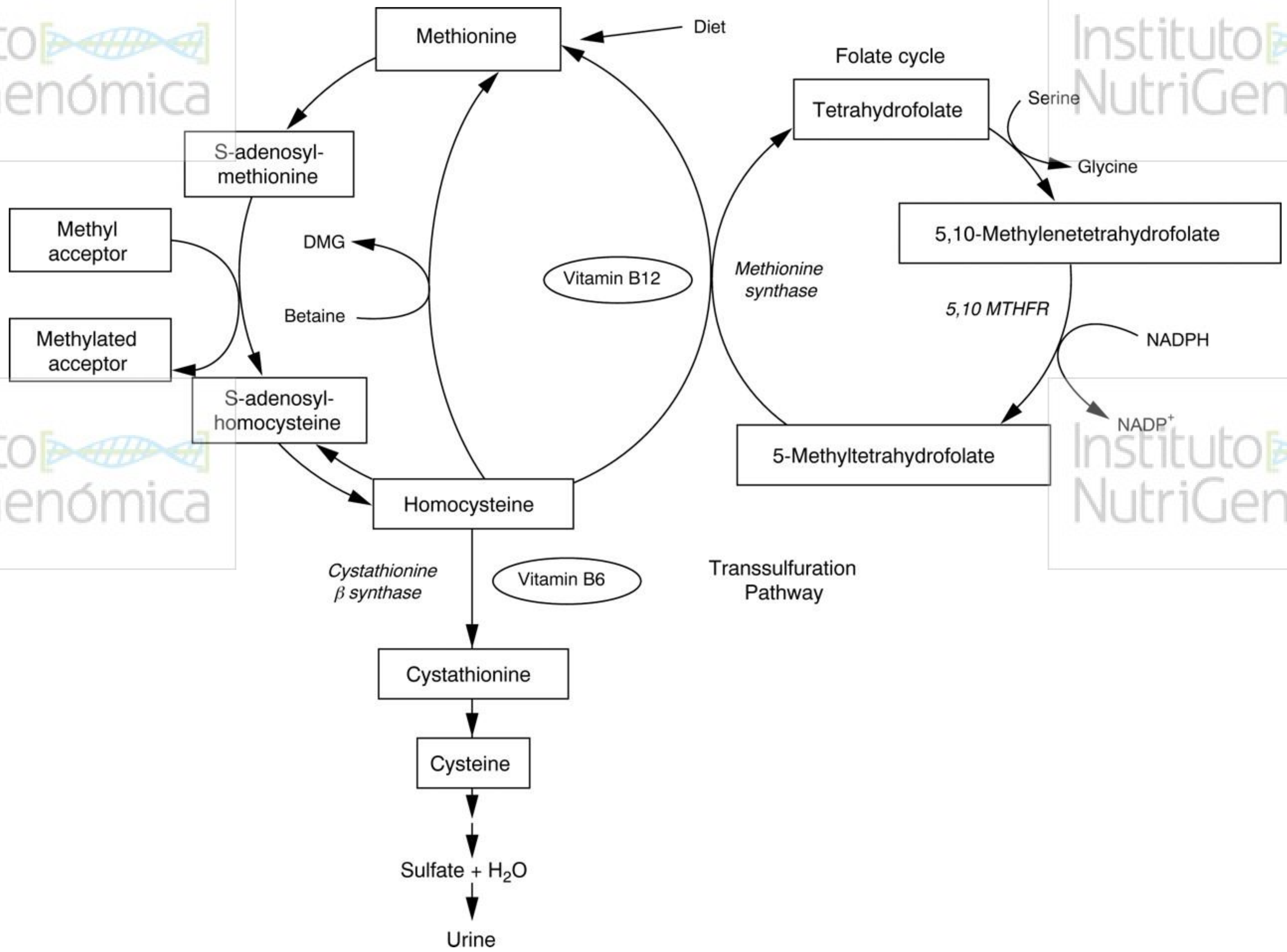
A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase

(Frosst et al, 1995)
Nat Genet 10:111-113

Table 1 Correlation between MTHFR genotype and enzyme activity, thermolability and plasma homocysteine level

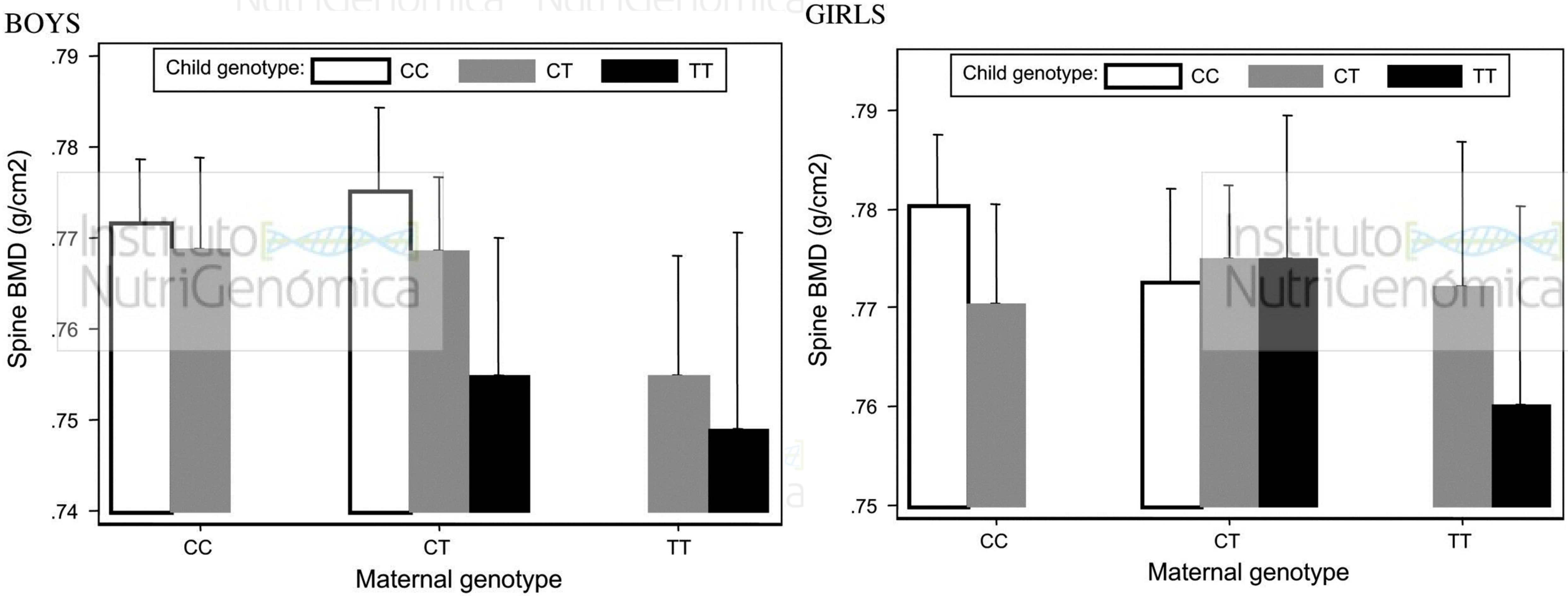
	Genotype −/− *n*=19	+/− *n*=9	+/+ *n*=12
Specific activity[a,b] (nmol CH_2O/mg protein/hr)	22.9±1.7 (11.8–33.8)	15.0±0.8 (10.2–18.8)	6.9±0.6 (2.6–10.2)
Residual activity after heating[a,b] (%)	66.8±1.5 (55–76)	56.2±2.8 (41–67)	21.8±2.8 (10–35)
Plasma homocysteine[a,c] (µM)(after fasting)	12.6±1.1 (7–21)	13.8±1.0 (9.6–20)	22.4±2.9 (9.6–42)
Plasma homocysteine[a,c] (µM)(post-methionine load)	41.3±5.0[d] (20.9–110)	41±2.8 (29.1–54)	72.6±11.7[e] (24.4–159)

Vitaminas del complejo B y osteoporosis



Insights into the programming of bone development from the Avon Longitudinal Study of Parents and Children (ALSPAC)

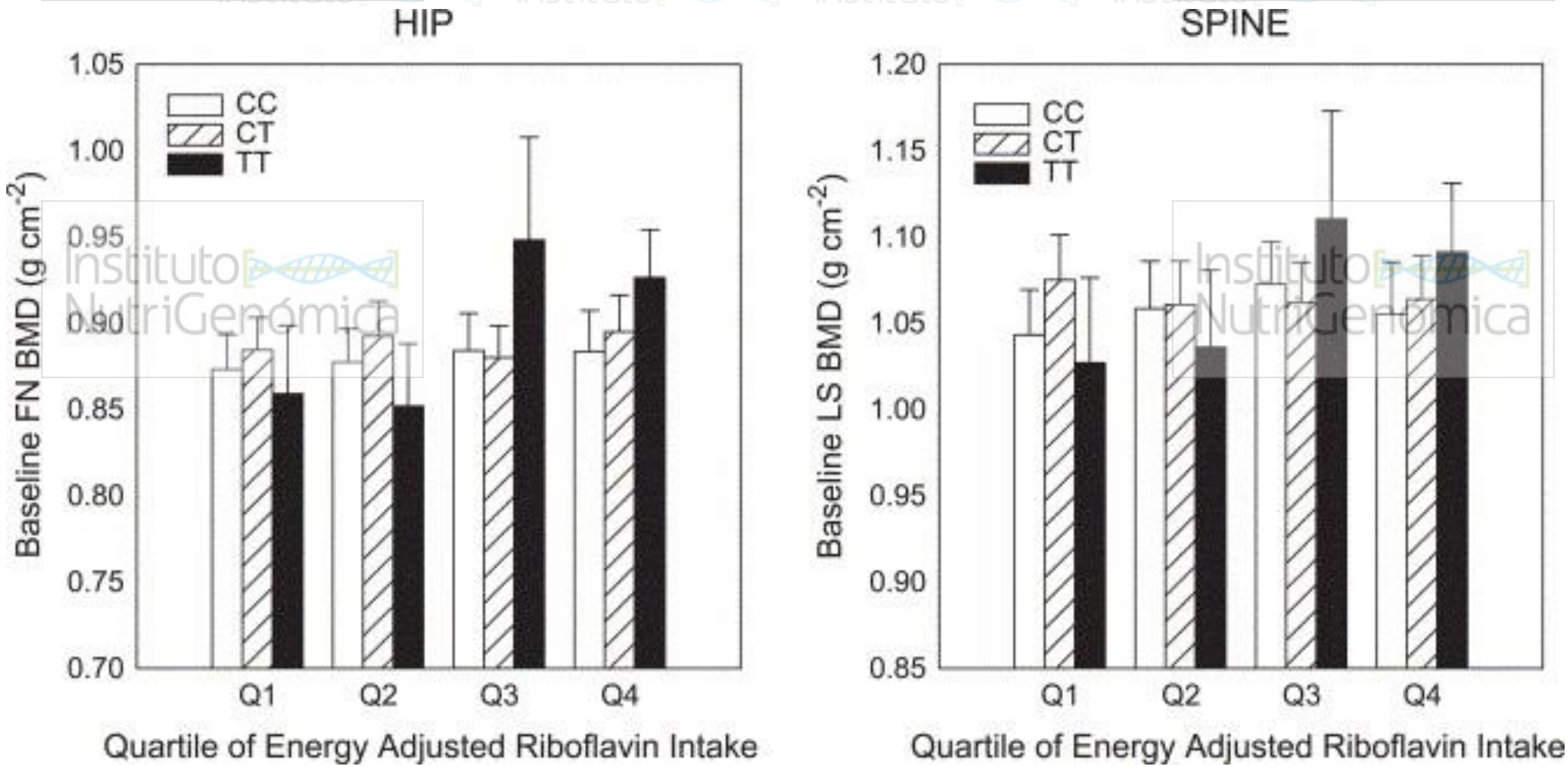
(Steer & Tobias, 2011)
Am J Clin Nutr 94(6 Suppl):1861S-1864S



Mean (95% CI) spine bone mineral density (BMD) for mother-child combinations of MTHFR C677T genotype adjusted for child age, height, and weight for boys and girls separately (n = 1015 and 997, respectively).

Methylenetetrahydrofolate reductase polymorphism interacts with riboflavin intake to influence bone mineral density

(McDonald et al, 2004)
Bone 35:957-964



Marked decreased in plasma antioxidants in aged osteoporotic women: results of a cross-sectional study

(Maggio et al, 2003)
J Clin Endocrinol Metab 88:1523-1527

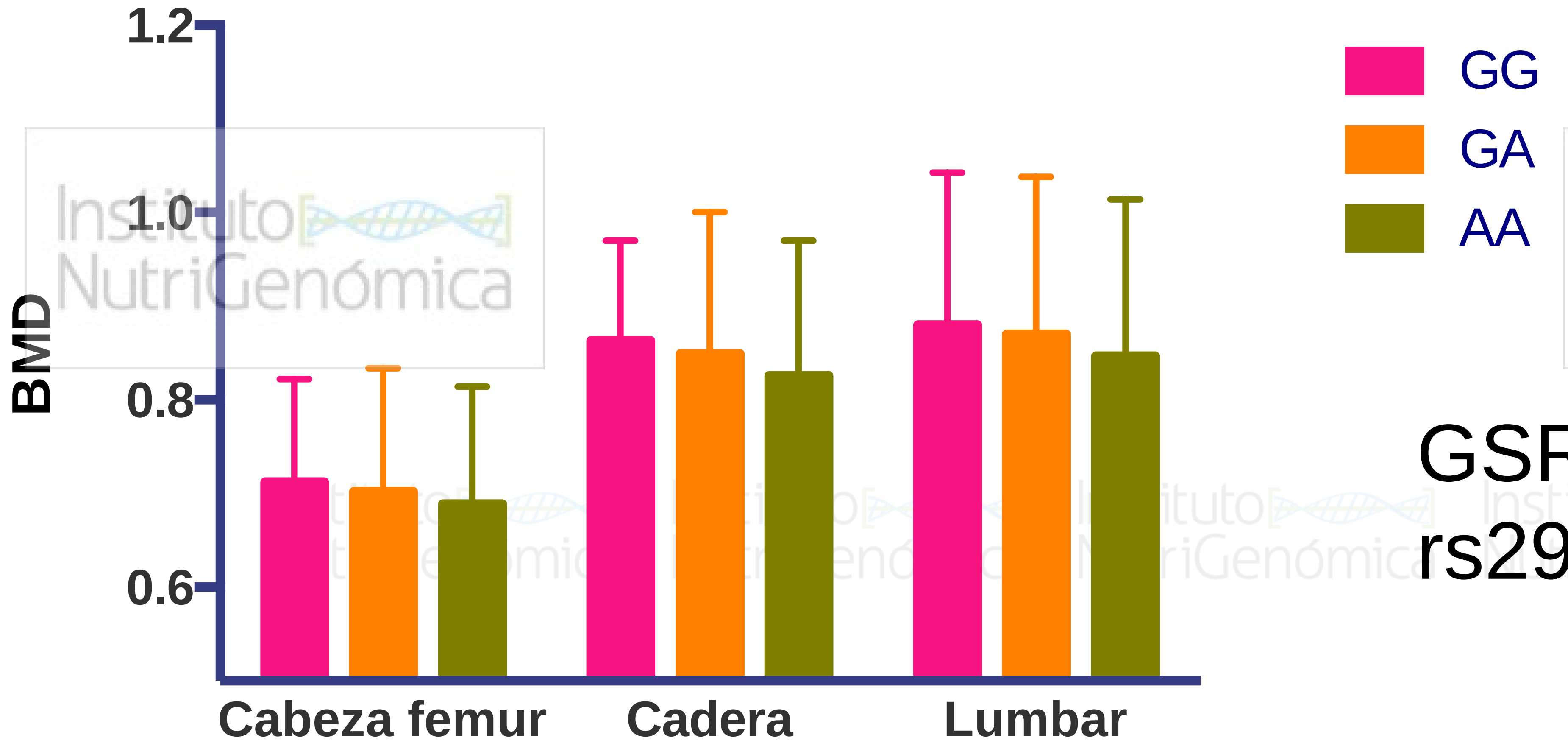
	Osteoporosis	**Control**
Vitamina C plasmática (microM)	30 ± 3,7	55,5 ± 13,1
Vitamina E plasmática (microM)	46,7 ± 5	62,8 ± 8,76
SOD (U/mL)	24,22 ± 3,8	31,38 ± 3,1
MDA (microM)	1,13 ± 0,54	0,77 ± 0,35
NO (micromol(g Hb)	0,33 ± 0,24	0,21 ± 0,13

Role of antioxidant systems, lipid peroxidation, and nitric oxide in postmenopausal osteoporosis

(Ozgocmen et al, 2006)
Mol Cell Biochem 295:45-52

Antioxidant enzymes GSR, SOD1, SOD2, and CAT gene variants and bone mineral density values in postmenopausal women: a genetic association analysis

(Jurkovic et al, 2012)
Menopause 19:368-376



GSR
rs2978663

Conclusiones en este apartado

1. Los heredabilidad de la osteoporosis es evidente desde edades tempranas.

2. En los casos del poseer alelos de riesgo la mejor terapia nutricional parece ser la suplementación de calcio y vitamina D.

3. Algunos otros compuestos como isoflavonas de la soja podrían contribuir a incrementar los niveles de vitamina D.

4. Existen otros factores asociados como el metabolismo de lípidos y el estado antioxidante que pueden predisponer al desarrollo de osteoporosis