V vsegenomski meta analizi odkritih 56 lokusov, povezanih z mineralno kostno gostoto, in 14 lokusov, povezanih s tveganjem za zlome

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ARTICLES

nature genetics

Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture

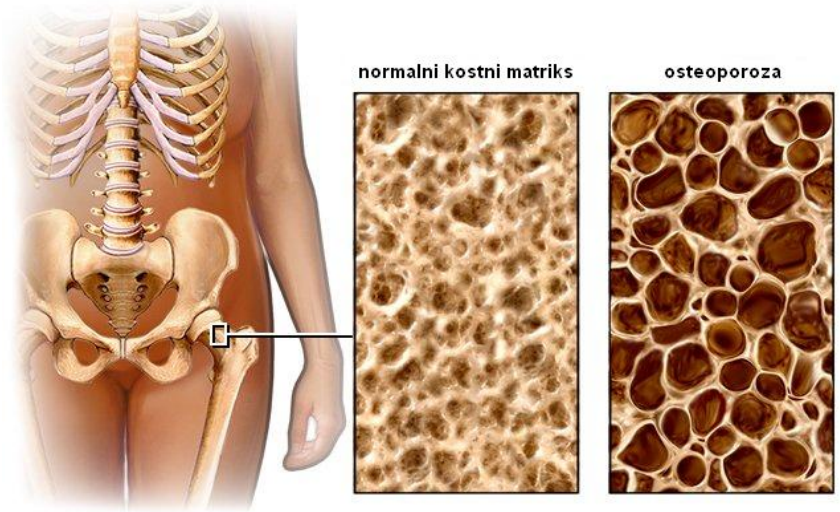
Bone mineral density (BMD) is the most widely used predictor of fracture risk. We performed the largest meta-analysis to date on lumbar spine and femoral neck BMD, including 17 genome-wide association studies and 32,961 individuals of European and east Asian ancestry. We tested the top BMD-associated markers for replication in 50,933 independent subjects and for association with risk of low-trauma fracture in 31,016 individuals with a history of fracture (cases) and 102,444 controls. We identified 56 loci (32 new) associated with BMD at genome-wide significance ($P < 5 \times 10^{-8}$). Several of these factors cluster within the RANK-RANKL-OPG, mesenchymal stem cell differentiation, endochondral ossification and Wnt signaling pathways. However, we also discovered loci that were localized to genes not known to have a role in bone biology. Fourteen BMD-associated loci were also associated with fracture risk ($P < 5 \times 10^{-4}$, Bonferroni corrected), of which six reached $P < 5 \times 10^{-8}$, including at 18p11.21 (*FAM210A*), 7q21.3 (*SLC25A13*), 11q13.2 (*LRP5*), 4q22.1 (*MEPE*), 2p16.2 (*SPTBN1*) and 10q21.1 (*DKK1*). These findings shed light on the genetic architecture and pathophysiological mechanisms underlying BMD variation and fracture susceptibility.

Osteoporosis is a disease characterized by low bone mass and micro-architectural deterioration of bone tissue leading to increased risk of fracture. The disease accounts for approximately 1.5 million new fracture cases each year, representing a huge economic burden on health care systems, with annual costs estimated to be $17 billion in the United States alone and expected to rise 50% by the year 2025 (ref. 1). Osteoporosis is defined clinically through the measurement

Discovery of BMD loci (stage 1)

We first performed a meta-analysis of multiple GWAS for BMD of the femoral neck (FN-BMD; $n = 32,961$) and lumbar spine (LS-BMD; $n = 31,800$ cases), including ~2.5 million genotyped or imputed autosomal SNPs from 17 studies of populations across North America, Europe, East Asia and Australia, with a variety of epidemiological designs and subject characteristics (Online Methods). We also

Osteoporoza



Osteoporoza

30 % žensk

12 % moških

Tveganje za zlom

40 - 53 % za ženske

13 - 22 % za moške

Zakaj se razvije osteoporoza?

OKOLJE

GENI

GEnetic Factors of OSteoporosis = GEFOS

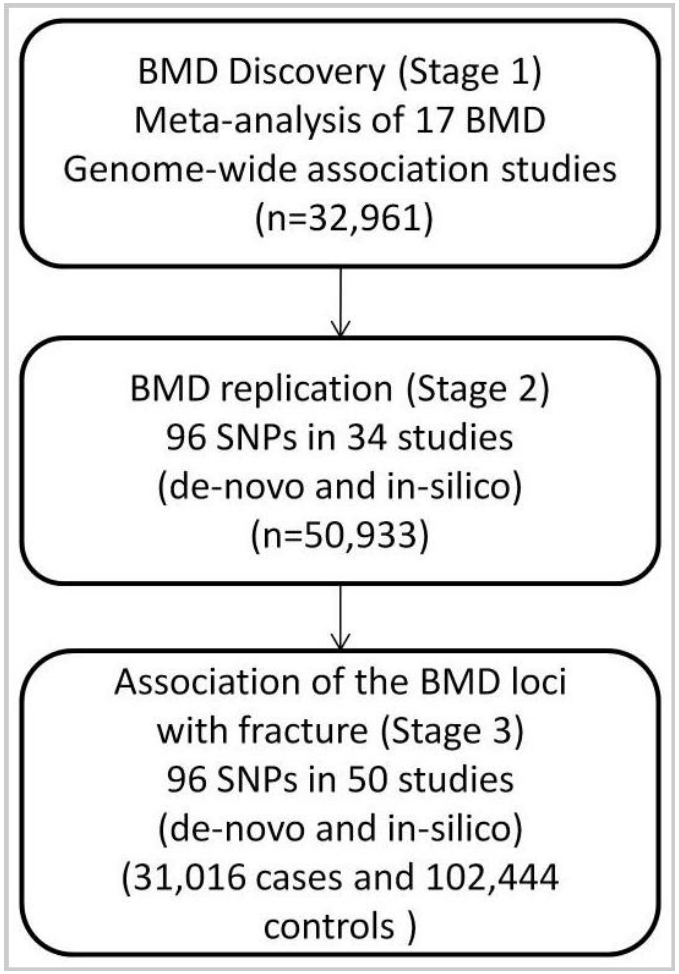
Projekt, financiran v okviru EU 7th Framework Package

19.195 preiskovancev severnoevropskega izvora
(Rotterdam study, Erasmus Rucphen Family study, Twins UK study, deCODE Genetics study, Framingham Osteoporosis study)

meta analiza podatkov iz 5 GWAS v povezavi z mineralno kostno gostoto v predelu ledvenih vretenc in vratu stegnenice

Rivadeneira F, et al. Nat Genet 2009; 41:1199-206.

Konzorcija GEFOS/GENOMOS sta združila moči...

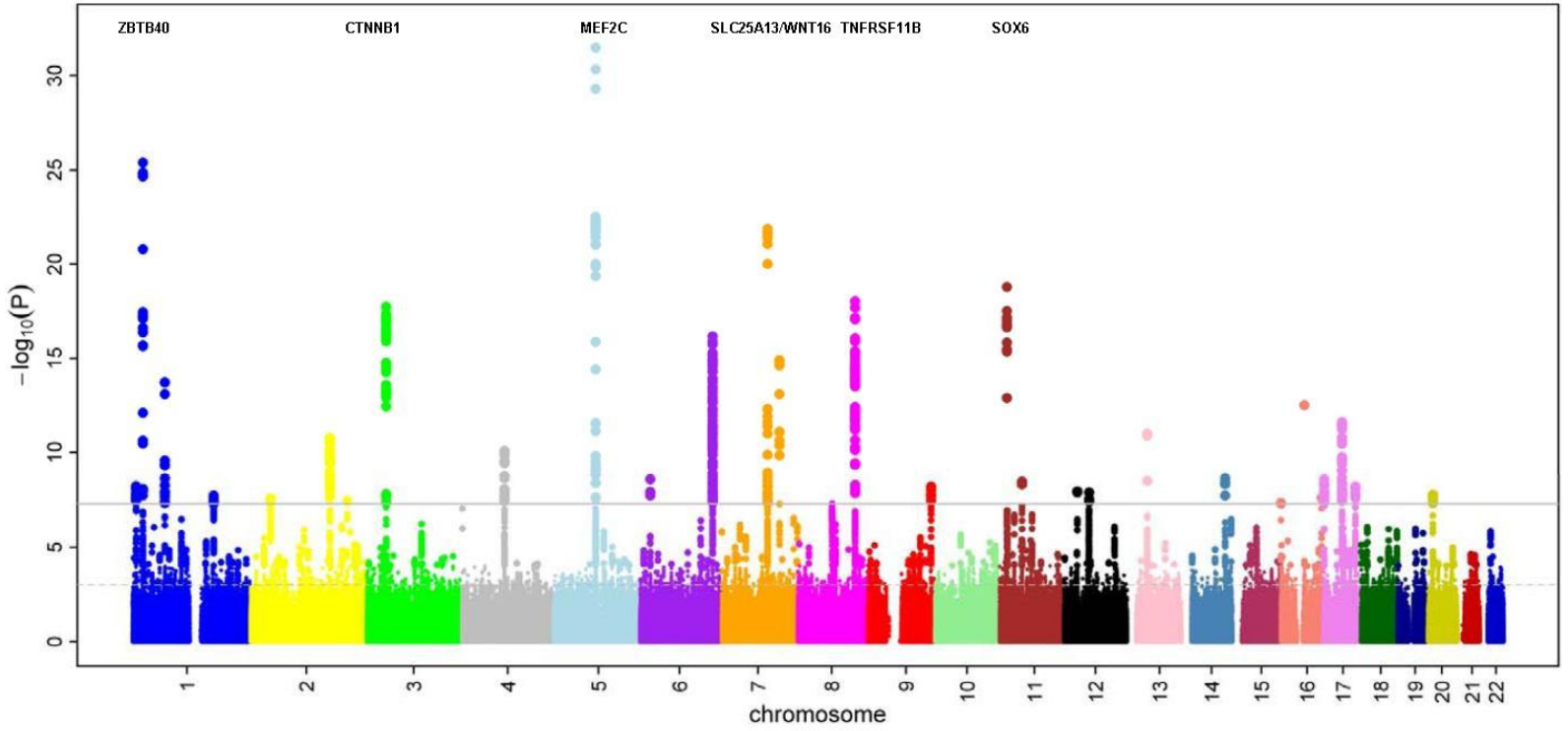


GENOMOS

GEFOS

Estrada K, et al. Nat Genet 2012; 44:491-501.

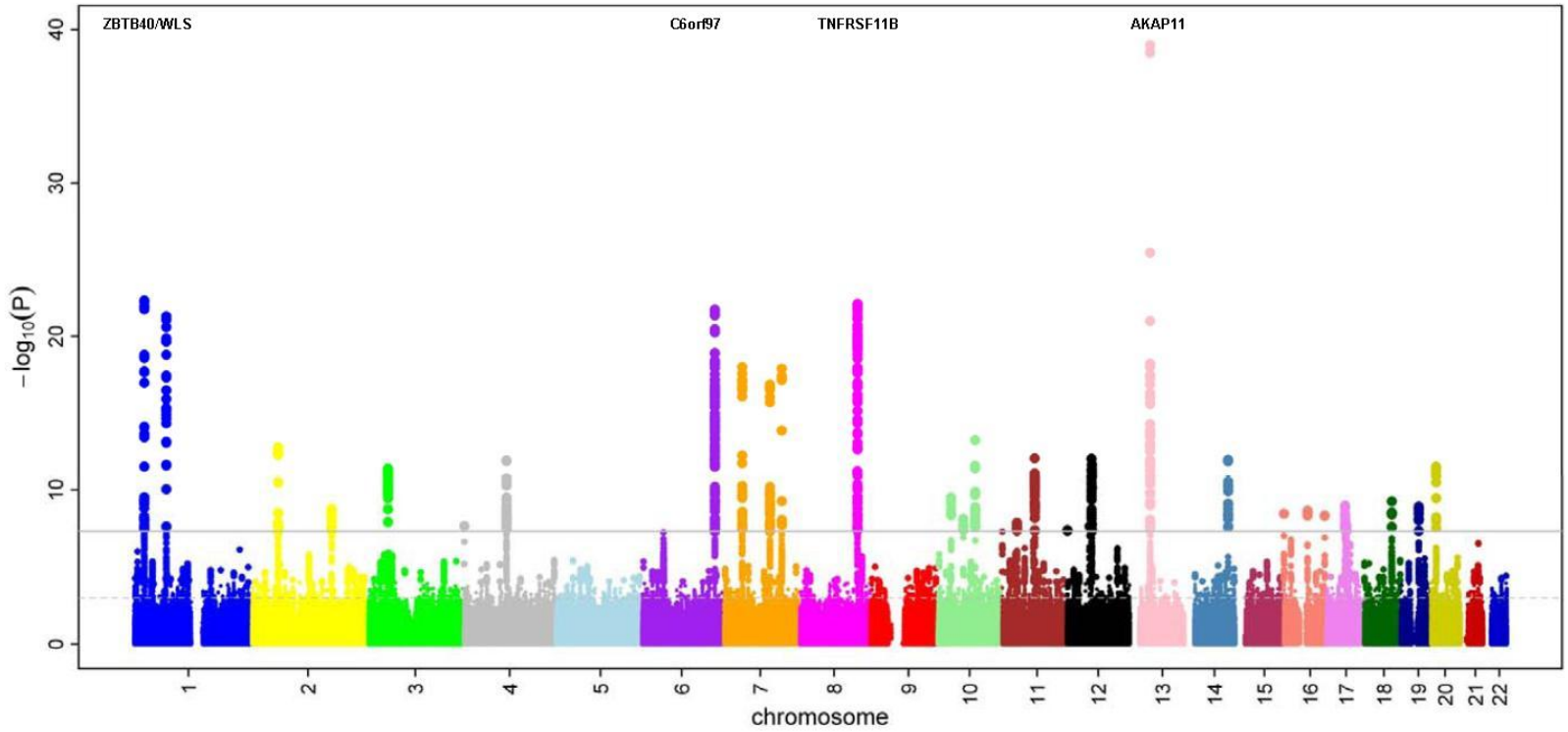
57 lokusov, povezanih z MKG vratu stegnenice (Stage 1)



Manhattan plot display loci associated with femoral neck BMD. In total, 57 BMD_fn associated loci were identified ($p<5x10^{-6}$).

Estrada K, et al. Nat Genet 2012; 44:491-501.

44 lokusov, povezanih z MKG v predelu ledvenih vretenc (Stage 1)



Manhattan plot display loci associated with lumbar spine BMD. In total, 44 BMD_ls associated loci were identified ($p<5x10^{-6}$).

Estrada K, et al. Nat Genet 2012; 44:491-501.

Locus	Closest gene/candidate	FN-BMD Stages 1 and 2 (83,894) P	LS-BMD Stages 1 and 2 (77,508) P
1q24.3	*DNM3*	**8.5×10^{-15}**	2.1×10^{-5}
2p21	*PKDCC*	**1.3×10^{-9}**	0.07
2q13	*ANAPC1*	**1.5×10^{-9}**	0.19
2q14.2	*INSIG2*	0.79	**1.2×10^{-10}**
3q13.2	*KIAA2018*	**4.1×10^{-10}**	7.6×10^{-4}
3q25.31	*LEKR1*	2.2×10^{-6}	**4.5×10^{-12}**
4p16.3	*IDUA*	**1.5×10^{-14}**	**5.2×10^{-15}**
6p21.1	*SUPT3H/RUNX2*	0.05	**5.6×10^{-11}**
6p22.3	*CDKAL1/SOX4*	**2.7×10^{-13}**	**3.6×10^{-8}**
7q31.31	*WNT16*	**5.0×10^{-40}**	**3.2×10^{-5}**
7q31.31	*C7orf58*	8.2×10^{-4}	**6.0×10^{-11}**
7q36.1	*ABCF2*	**7.3×10^{-9}**	2.2×10^{-7}
8q13.3	*XKR9/LACTB2*	**1.9×10^{-8}**	0.98
9q34.11	*FUBP3*	**3.4×10^{-22}**	6.1×10^{-8}
10p11.23	*MPP7*	0.03	**2.4×10^{-16}**
10q21.1	*MBL2/DKK1*	**1.5×10^{-8}**	**1.6×10^{-12}**
10q22.3	*KCNMA1*	0.81	**5.0×10^{-19}**
10q24.2	*CPN1*	**9.0×10^{-10}**	9.2×10^{-7}
11p14.1	*LIN7C*	0.03	**4.9×10^{-8}**
12p11.22	*KLHDC5/PTHLH*	**1.9×10^{-12}**	0.13
12p13.33	*ERC1/WNT5B*	**6.5×10^{-9}**	**5.6×10^{-12}**
12q13.12	*DHH*	3.3×10^{-7}	**1.2×10^{-15}**
12q23.3	*C12orf23*	**9.6×10^{-10}**	7.9×10^{-8}
14q32.12	*RPS6KA5*	**2.0×10^{-15}**	**1.8×10^{-14}**
16p13.11	*NTAN1*	**1.7×10^{-10}**	**2.2×10^{-9}**
16p13.3	*AXIN1*	**5.2×10^{-12}**	**1.0×10^{-16}**
16p13.3	*C16orf38/ CLCN7*	**1.5×10^{-16}**	**1.7×10^{-13}**
16q12.1	*SALL1/CYLD*	**1.9×10^{-22}**	0.04
16q12.1	*CYLD*	4.4×10^{-5}	**2.0×10^{-10}**
17p13.3	*SMG6*	**9.8×10^{-19}**	**3.4×10^{-9}**
17q24.3	*SOX9*	**1.9×10^{-11}**	0.08
18p11.21	*FAM210A*	**4.9×10^{-8}**	6.7×10^{-4}
19q13.11	*GPATCH1*	5.5×10^{-8}	**6.6×10^{-11}**
Xp22.31	*FAM9B/KAL1*	1.6×10^{-4}	**1.2×10^{-8}**

Na novo odkriti geni, ki jih do sedaj niso povezovali z razvojem osteoporoze

Estrada K, et al. Nat Genet 2012; 44:491-501.

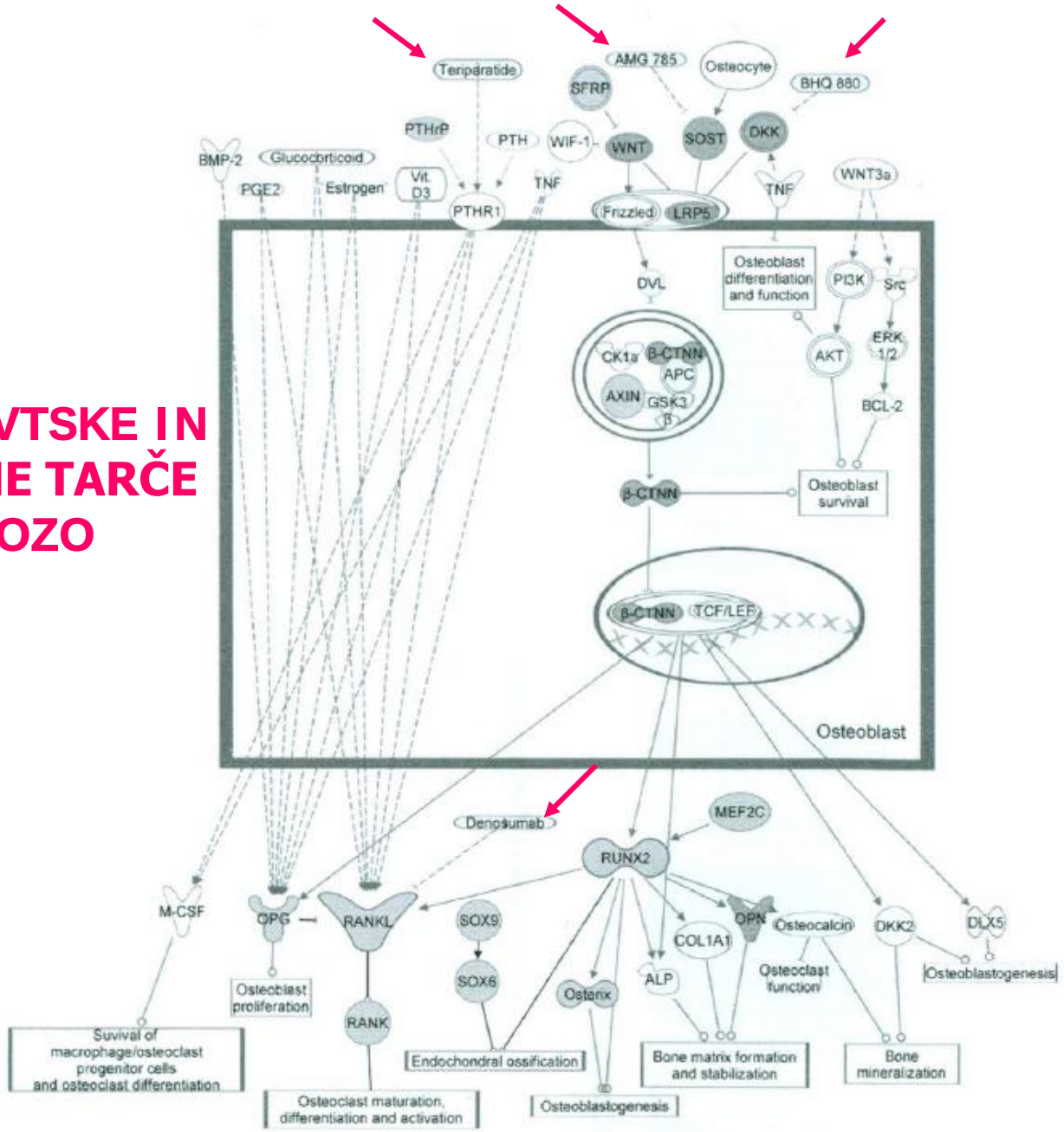
Lokusi, povezani z večjim tveganjem za zlom

Table 2 Association of identified BMD-associated loci with risk for any type of low-trauma fracture

					Meta-analysis without studies included in BMD discovery		Combined meta-analysis results			
					25,605 cases, 80,535 controls		31,016 cases, 102,444 controls			
SNP	Locus	Closest gene/candidate	Risk allele	Freq.[b]	OR (95% CI)	*P*	OR (95% CI)	*P*	Q_{het} *P*	I^2
Loci significantly associated with fracture risk at $P < 5 \times 10^{-8}$										
rs4233949	2p16.2	*SPTBN1*	G	0.63	1.07 (1.04–1.09)	1.4×10^{-7}	1.06 (1.04–1.08)	**2.6×10^{-8}**	0.36	6
rs6532023	4q22.1	*MEPE/SPP1*	G	0.67	1.06 (1.04–1.09)	8.8×10^{-7}	1.06 (1.04–1.09)	**1.7×10^{-8}**	1.00	0
rs4727338	7q21.3	*SLC25A13*	G	0.32	1.08 (1.05–1.10)	1.0×10^{-8}	1.08 (1.05–1.10)	**5.9×10^{-11}**	0.03	31
rs1373004	10q21.1	***MBL2/DKK1***	T	0.13	1.09 (1.06–1.13)	7.2×10^{-7}	1.10 (1.06–1.13)	**9.0×10^{-9}**	0.64	0
rs3736228	11q13.2	*LRP5*	T	0.15	1.09 (1.05–1.12)	2.1×10^{-6}	1.09 (1.06–1.13)	**1.4×10^{-8}**	0.78	0
rs4796995	18p11.21	***FAM210A***	G	0.39	1.06 (1.04–1.09)	6.4×10^{-7}	1.08 (1.06–1.10)	**8.8×10^{-13}**	0.12	20

Estrada K, et al. Nat Genet 2012; 44:491-501.

NOVE TERAPEVTSKE IN DIAGNOSTIČNE TARČE ZA OSTEOPOROZO



Estrada K. PhD thesis. 2012