Genetic determinants of bone mineral density loss in Aromatase inhibitors treatment

Rodríguez-Sanz. M[1], Prieto-Alhambra. D[2], Servitja. S[3], Torres. E[1], Mellibovsky. L[1], Garrigós. L[3], García-Giralt. N[1], Balcells. S[4], Grinberg. D[4], Díez-Pérez. A[1], Tusquets. I[3] and Nogués. X[1]

[1]URFOA-IMIM, Red Temática de Investigación Cooperativa en Envejecimiento y Fragilidad (RETICEF), Instituto de Salud Carlos III FEDER, Barcelona, SPAIN, [2]University of Oxford, UNITED KINGDOM, [3]Medical Oncology Department, Parc de Salut Mar, Barcelona, SPAIN, [4]Genetics department, Universitat de Barcelona,CIBERER, Spain

Purpose

Aromatase inhibitors (AI) treatment of estrogen receptor positive breast cancer in postmenopausal women results in bone loss due to estrogen depletion. This study aims to identify genetic variants associated with bone mineral density (BMD) loss during AI treatment.

Methods

Single nucleotide polymorphisms (SNPs) were selected in genes involved in BMD determination according to three different hypotheses: Vitamin D and estrogen signaling pathway, genes previously associated with BMD and fractures in a GWAs study (Estrada K et al, Nature Genetics, 2012) and finally AI CYP450 metabolizer subunits. Selected SNPs were genotyped in 280 Caucasian, postmenopausal women with early breast cancer, candidates for adjuvant treatment with AI. Paired T-tests were used to assess changes in BMD at the three sites measured: Lumbar spine (LS), femoral neck (FN) and total hip (TH). Multivariate linear regression analyses were performed to test the association between the selected SNPs and absolute BMD loss after 1 year of follow-up. All models were adjusted for body mass index, years since menopause and baseline BMD. Regarding the SNPs in genes of vitamin D signaling, potential confounding for baseline vitamin D concentrations was assessed.

Results

After 1 year on AI therapy, participants experienced a significant 1.42 % [95 % CI 0.93–1.91 %] bone loss at LS (0.014 g/cm^2 [0.009–0.019], P<0.0001), 1.16 % [95 % CI 0.62–1.70 %] bone loss at FN (0.009 g/cm^2 [0.005–0.013], P<0.0001) and 0.72 % [95 % CI 0.30–1.14 %] bone loss at TH (0.007 g/cm^2 [0.003–0.010], P=0.01). Fig. 1.

Under the hypothesis of Vitamin D and estrogen signaling, rs2544037 in VDR gene and rs6013897 in CYP24A1 gene reached significant p-values (P=0.04 and P=0.01 respectively) for the association with LS BMD loss. The same SNP in VDR, as well as rs11907350 in CYP24A1 were associated (P=0.02) with FN BMD loss. For the analyses of genes previously associated with BMD, rs7851693 in FUBP3 showed significant p-value (P=0.01) and rs163879 in DCDC5 showed a borderline p-value (P=0.06) for the association with LS BMD loss. Finally, rs4986894 in CYP2C19 gene and rs9332982 in CYP4A11 gene, both involved in AI metabolization, obtained significant results in the association with LS BMD loss (P=0.01 and P=0.004 respectively). Fig. 2

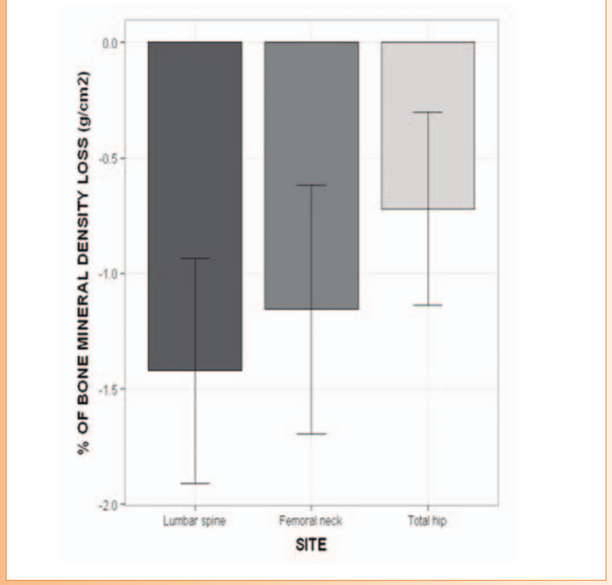

Figure 1. Percentage of Bone mineral density loss at the three common sites after 1 year of AI treatment.

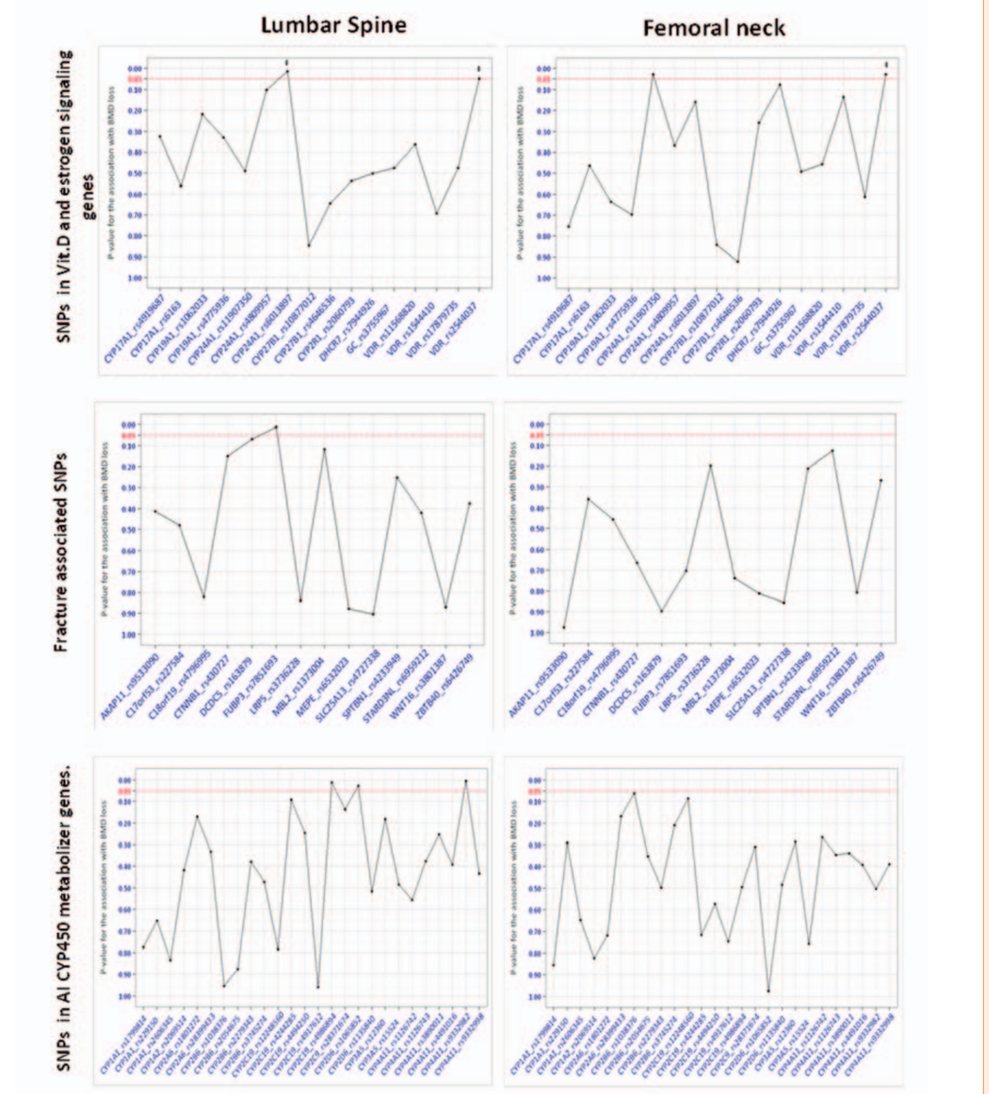

Figure 2. P-values for the association of BMD loss at LS and FN with SNPs in genes: A) Of Vitamin D and estrogen signaling pathway, B) Previously associated with fracture in a GWAs study and C) Of AI CYP450 metabolizer subunits. Dominant model.
* Recessive model.

Conclusions

SNPs in VDR, CYP24A1, FUBP3, DCDC5, CYP4A11 and CYP2C19 genes appeared significantly associated with BMD loss during AI treatment. None of the 3 tested hypothesis stands out from the others, suggesting that bone loss during AI therapy is determined by an interaction of genes involved in several metabolic pathways: Vitamin D and estrogens signaling, AI-metabolization by CYP450 as well as BMD and fracture gene determinants

Hospital del Mar

Parc de Salut MAR Barcelona