



Hsu, Y. H., Estrada, K., Evangelou, E., Ackert-Bicknell, C., Akesson, K., Beck, T., Brown, S. J., Capellini, T., Carbone, L., Cauley, J., Cheung, C. L., Cummings, S. R., Czerwinski, S., Demissie, S., Econs, M., Evans, D., Farber, C., Gautvik, K., Harris, T., ... Karasik, D. (2019). Meta-Analysis of Genomewide Association Studies Reveals Genetic Variants for Hip Bone Geometry. *Journal of Bone and Mineral Research*, 34(7), 1284-1296. Article e3698. <https://doi.org/10.1002/jbmr.3698>

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Meta-analysis of Genome-Wide Association Studies Reveals Genetic Variants for Hip Bone Geometry M18060388

Table 1 : Discovery, Replication and Joint analysis results

Stage	DISCOVERY N=18,719									REPLICATION N=9000+				COMBINED N=27,053			Functional annotation
phenotype	chr	POSITION	top SNP	freq	zscore	P	Het.I ²	Direction.x	gene(s)	freq	zscore	P	HetI ²	freq	zscore	P-value	
FNL	5	4,380,853	rs261179	0.75	5.288	1.23E-07	0	+++++	IRX1, ADAMTS16	0.7538	1.302	0.01834	0	0.756	5.582	2.37E-08	intergenic
NNW	5	176,460,183	rs6556301	0.36	-5.681	1.35E-08	21.3	--+	FGFR4,NSD1,R AB24	0.3644	-1.078	0.0176	73.1	0.364	-5.583	2.37E-08	intergenic
NNZ	11	68,618,111	rs7102273	0.72	5.348	8.88E-08	16.7	+++++	LRP5,PPP6R3,GAL *	0.7322	2.937	0.00332	28.2	0.724	6.595	4.25E-11	intergenic
NNW	12	28,596,065	rs11049605	0.30	5.458	4.80E-08	0	+++++	CCDC91	0.3125	4.361	#####	57.2	0.306	6.908	4.93E-12	intronic
FNL	21	35,634,458	rs8129030	0.64	-4.769	1.85E-06	30.4	-----+?-	RUNX1	0.6306	-0.677	0.108	0	0.638	-4.732	2.23E-06	intergenic

Bold font: p-values <5E-08

Table 2: Hip Geometry associations (p<0.000005) with genes previously associated with BMD

SNP	Region	Chr_pos	Reported Gene(s)	Mapped gene	PUBMEDID	First Author	Journal	HSA Zscore	HSA P-value	HSA phenotype
rs2450083	8q24.12	119051303	TNFRSF11B	TNFRSF11B - COLEC10	24945404	Kemp JP	Plos Genet	3.648	1.800E-06	NNW
rs7108738	11p15.2	15688538	SOX6	INSC - SOX6	22504420	Estrada K	Nat Genet	-5.000	7.600E-07	NNZ
rs3736228	11q13.2	68433827	LRP5	LRP5	22504420	Estrada K	Nat Genet	-6.000	1.430E-06	NNZ

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Table 3: Top Hip Geometry SNPs associations with Adult Stature

Stage	DISCOVERY							HEIGHT (GIANT consortium)	
phenotype	chr	POSITION	top SNP	freq	zscore	p	in/near gene(s)	SNP	P-value
FNL	5	4380853	rs261179	0.76	5.288	1.23E-07	IRX1, ADAMTS16	rs261179	5.85E-01
NNW	5	176460183	rs6556301	0.36	-5.681	1.35E-08	FGFR4,NSD1,RAB24	rs6556301	4.16E-04
NNZ	11	68618111	rs7102273	0.72	5.348	8.88E-08	LRP5,PPP6R3,GAL	rs7102273	1.33E-01
NNW	12	28596065	rs11049605	0.30	5.458	4.80E-08	CCDC91	rs11049605	2.53E-12
FNL	21	35634458	rs8129030	0.6401	-4.769	1.85E-06	RUNX1	rs8129030	8.99E-01

Bold font: p-values <5E-08

Table 4: Most significant hip geometry SNP associations with any type of fracture

HG GWAS							Any type of fracture GWAS				
phenotype	chr	top SNP	freq	Zscore	P	in/near gene(s)	A1	A2	beta	se	P
FNL	5	rs261179	0.7558	5.288	1.23E-07	IRX1, ADAMTS16	t	c	-0.001	0.01	0.91
NNW	5	rs6556301	0.3642	-5.681	1.35E-08	FGFR4,NSD1,RAB24	t	g	0.016	0.01	0.07
NNZ	11	rs7102273	0.7243	5.348	8.88E-08	LRP5, PPP6R3,GAL *	t	c	-0.037	0.01	7.46E-05
NNW	12	rs11049605	0.3042	5.458	4.80E-08	CCDC91	t	g	0.010	0.01	0.25
FNL	21	rs8129030	0.6379	-4.769	1.85E-06	RUNX1	a	t	0.003	0.01	0.71

Table 5: Correlations of candidate gene transcripts with Hip Geometry traits

Affy ID	Gene symbol	NSA		Neck Length		NN Width		NN Sect Mod	
		r	P value	r	P value	r	P value	r	P value
238125_at	ADAMTS16	0.07	0.518	0.13	0.234	-0.13	0.251	0.20	0.082
1570571_at	CCDC91	-0.02	0.893	-0.10	0.388	-0.10	0.358	-0.17	0.121
218545_at	CCDC91	0.12	0.271	-0.03	0.759	0.12	0.277	-0.08	0.491
1554962_a_at	FGFR4	-0.09	0.430	0.04	0.736	-0.04	0.729	0.10	0.384
211237_s_at	FGFR4	0.00	0.994	-0.01	0.942	0.04	0.712	0.21	0.057
208129_x_at	LOC100506403 /// LOC101928269 /// RUNX1	-0.09	0.427	0.06	0.596	0.07	0.518	0.27	0.014
209359_x_at	LOC100506403 /// LOC101928269 /// RUNX1	-0.18	0.101	0.05	0.654	-0.12	0.289	0.23	0.041
209360_s_at	LOC100506403 /// LOC101928269 /// RUNX1	-0.09	0.443	0.00	0.998	-0.08	0.463	0.09	0.415
210365_at	LOC100506403 /// LOC101928269 /// RUNX1	-0.03	0.792	0.11	0.331	0.01	0.920	-0.01	0.956
210805_x_at	LOC100506403 /// LOC101928269 /// RUNX1	0.00	0.986	0.05	0.633	-0.10	0.388	-0.07	0.528
211180_x_at	LOC100506403 /// LOC101928269 /// RUNX1	-0.14	0.230	-0.01	0.934	-0.14	0.216	0.14	0.212
209468_at	LRP5	-0.05	0.634	-0.04	0.722	-0.01	0.930	-0.09	0.428
229591_at	LRP5	-0.07	0.520	0.24	0.036	0.03	0.781	0.03	0.814
219084_at	NSD1	0.13	0.269	-0.08	0.461	0.06	0.605	0.10	0.389
225654_at	NSD1	0.20	0.072	-0.03	0.817	0.15	0.185	0.33	0.003
235760_at	NSD1	0.07	0.519	-0.16	0.149	0.05	0.629	0.04	0.740
243612_at	NSD1	-0.05	0.679	0.05	0.639	-0.13	0.234	-0.08	0.495
217928_s_at	PPP6R3	-0.07	0.530	0.03	0.814	0.02	0.830	0.14	0.231
222467_s_at	PPP6R3	-0.11	0.350	0.01	0.922	-0.13	0.242	0.08	0.466
232312_at	PPP6R3	0.04	0.720	-0.04	0.749	-0.13	0.241	-0.20	0.078
225251_at	RAB24	0.05	0.680	-0.03	0.814	-0.01	0.931	0.03	0.800

Bold font: correlations with p-values <0.05

Table 6: Expression QTLs (eQTLs) from trans-iliac biopsies

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SNP	chr	position	geneprobe	beta	t statistics	p-value
rs261179	5	4,380,853	---			>0.05
rs261189	5	4,325,585	---			>0.05
rs6556301	5	176,460,183	PDLIM7	0.121297105	2.952509835	4.99E-03
rs2164198	8	69,577,442	CPA6	0.048952917	2.207793024	3.24E-02
rs12545316	8	68,687,255	---			>0.05
rs7102273	11	68,618,111	PPP6R3	0.191649382	-3.63881459	7.03E-04
rs10843164	12	28,569,714	CCDC91	0.124429445	-2.444584818	1.85E-02

Bold font: p-values <0.05

Table 7: Expression of candidate genes in murine bone cells

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		osteoblast (calvarial)	osteoclast	Osteoblast Modules <i>(Farber et al.)</i>
top SNP	gene(s)			
rs261179	IRX1	increase-plateau	0	
rs261189	ADAMTS16	0	1	
rs6556301	FGFR4	0	0	
	NSD1	0	1	
	RAB24	slight decrease	1	
rs7102273	LRP5	increase	1	6, 9
	PPP6R3	0	1	6
	GAL	0	0	
rs11049605	CCDC91	0	1	
rs8129030	RUNX1	0	1	