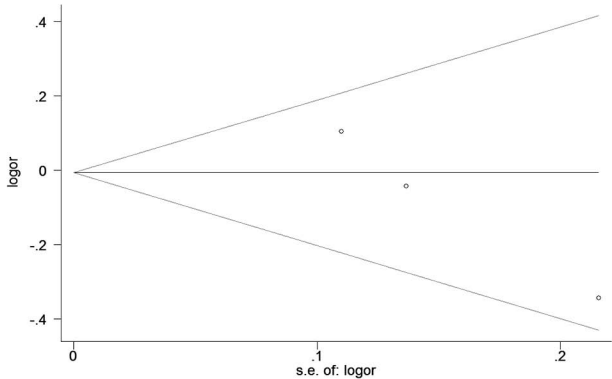


Begg's funnel plot with pseudo 95% confidence limits



Study %

ID OR (95% CI) Weight

Xu2014 1.19 (0.54, 2.61) 50.38

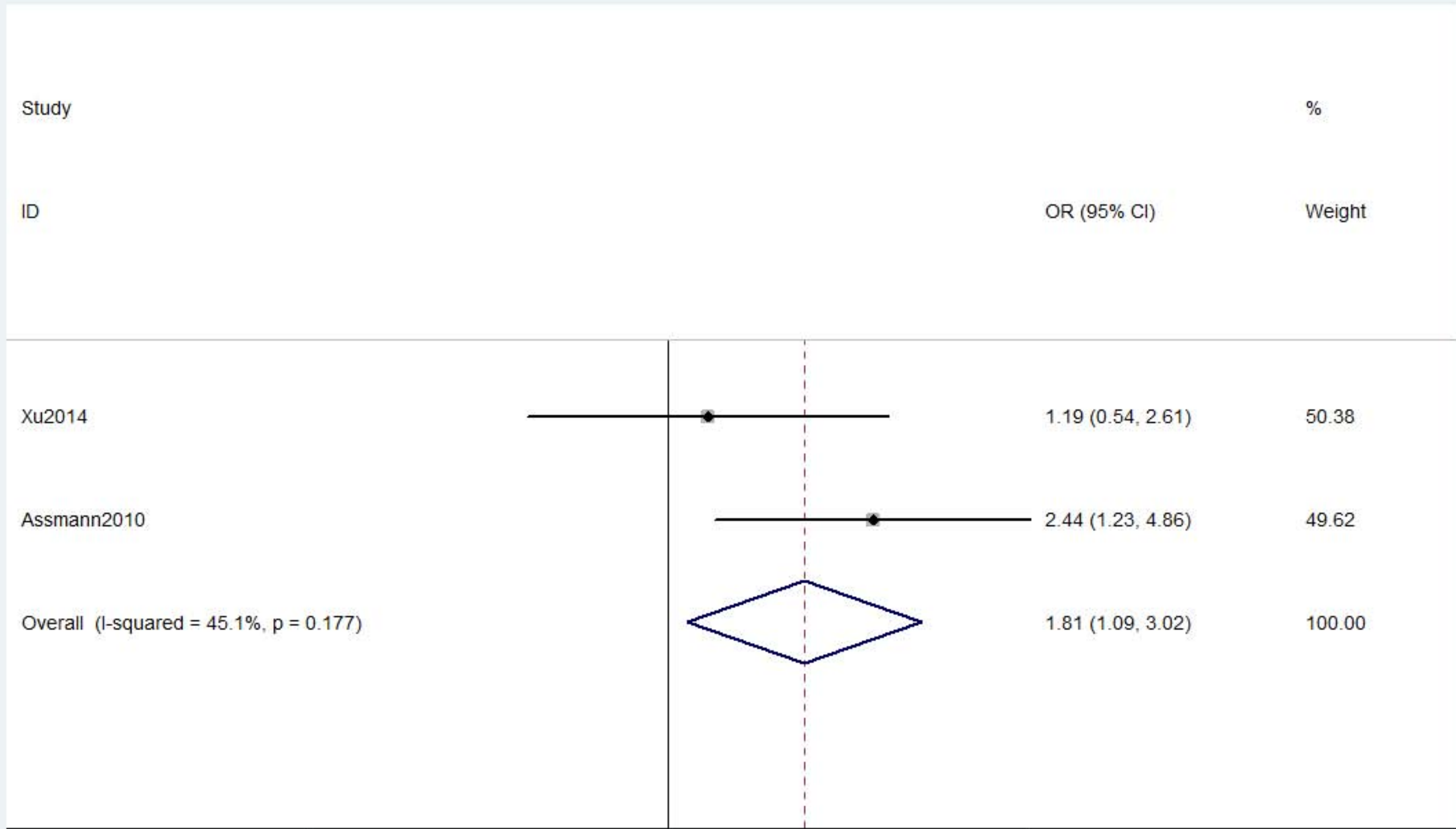
Assmann2010 2.44 (1.23, 4.86) 49.62

Overall (I-squared = 45.1%, p = 0.177) 1.81 (1.09, 3.02) 100.00

.206

1

4.86



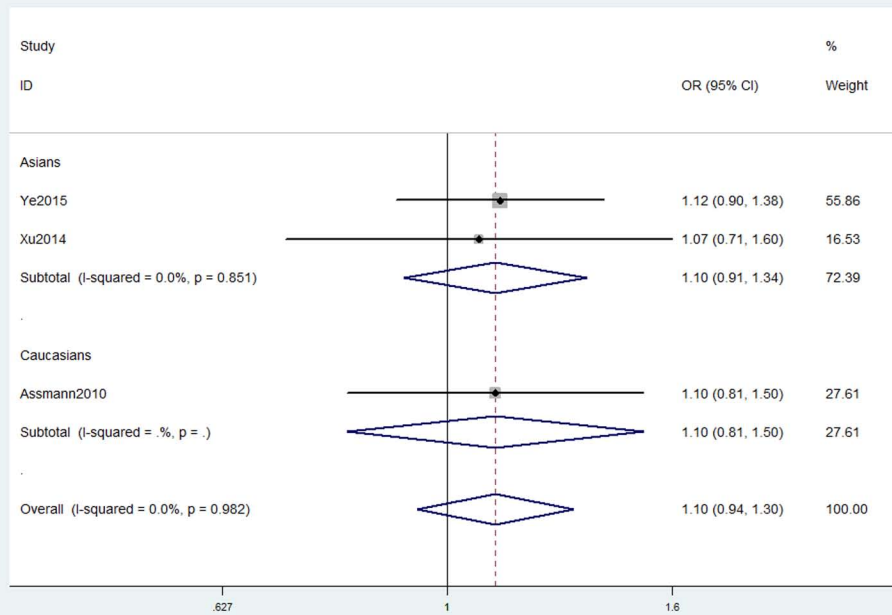
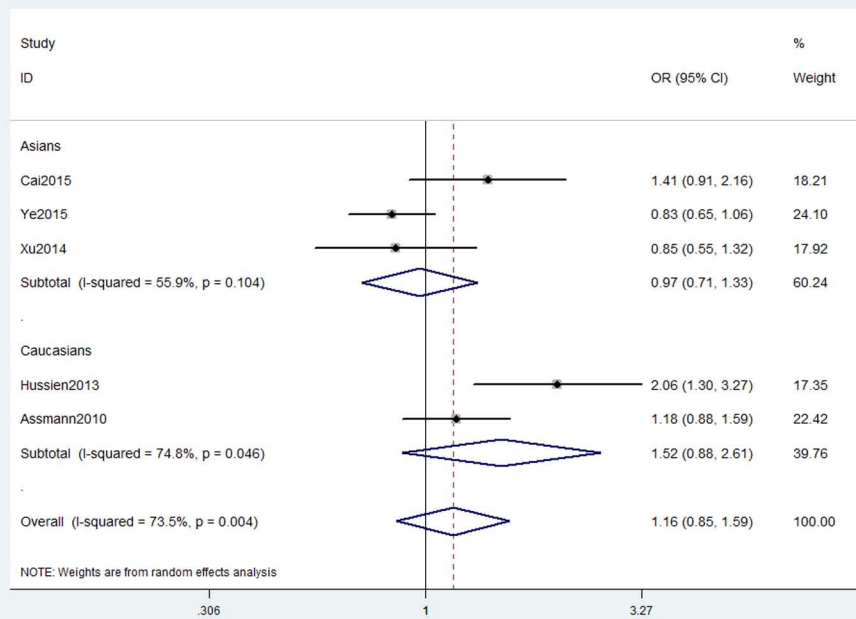


Table S1 Stratified analyses between rs1805034 polymorphism and the risk of RA

Variable	Genotype (case/control)			OR (95% CI); <i>P</i> *				
	rs1805034	TT	TC	CC	TC vs. TT	CC vs. TT	CC+TC vs. TT	CC vs. TC+TT
Sex								
Male	65/104	72/75	9/19	1.54(0.98,2.40); 0.060	0.76(0.32,1.78); 0.524	1.38(0.90,2.12); 0.143	0.62(0.27,1.41); 0.254	
Female	201/282	181/249	43/56	1.02(0.78,1.33); 0.884	1.08(0.70,1.67); 0.737	1.03(0.80,1.32); 0.814	1.07(0.70,1.62); 0.759	
Age								
≤55	129/178	136/160	31/33	1.17(0.85,1.62); 0.332	1.30(0.76,2.22); 0.346	1.19(0.88,1.62); 0.258	1.20(0.72,2.01); 0.492	
>55	137/208	117/164	21/42	1.08(0.79,1.49); 0.625	0.76(0.43,1.34); 0.340	1.02(0.75,1.38); 0.913	0.73(0.42,1.27); 0.265	
rs531564	CC	CG	GG	GC vs. CC	GG vs. CC	GG+GC vs. CC	GG vs. GC+CC	

OR = odds ratio; 95%CI = 95% confidence interval. *Significant *P* values if ≤ 0.05 .

Table S2 Comparison of studied data according to RANK genotypes in all RA cases.

rs1805034		RA(n=573)				<i>P</i>
		TC+CC(n=305)		TT(n=266)		
Age	Years, Mean \pm SD	54.02 \pm 15.63		55.07 \pm 14.47		0.407
Sex	Male/Female, (n, %)	73/224	23.9/76.1	65/201	24.4/75.6	0.969
ESR	mm/h, Mean \pm SD	33.08 \pm 24.66		34.35 \pm 25.95		0.549
RF	Positive/Negative, (n, %)	240/65	78.7/21.3	214/52	80.5/19.5	0.603
anticcp	Positive/Negative, (n, %)	149/156	48.9/51.1	150/116	56.4/43.6	0.072
CRP	mg/L, Mean \pm SD	27.29 \pm 33.41		29.49 \pm 40.49		0.477
DAS28	Mean \pm SD	4.28 \pm 1.53		4.31 \pm 1.41		0.806
Functional class	I+II/ III+IV, (n, %)	175/130	57.4/42.6	152/114	57.1/42.9	0.955

Table S3 Comparison of studied data according to RANK genotype in all RA cases.

rs1805034		RA(n=573)		TC+TT(n=519)		P
		CC(n=52)				
Age	Years, Mean \pm SD		51.56 \pm 17.13		54.81 \pm 14.86	0.139
Sex	Male/Female, (n, %)	9/43	17.3%/82.7%	137/382	26.4%/73.6%	0.152
ESR	mm/h, Mean \pm SD		32.58 \pm 27.58		33.78 \pm 25.04	0.744
RF	Positive/Negative, (n, %)	7/45	13.5%/86.5%	110/409	21.2%/78.8%	0.188
anticcp	Positive/Negative, (n, %)	24/28	46.2%/53.8%	248/271		0.822
CRP	mg/L, Mean \pm SD		34.51 \pm 42.11		27.69 \pm 36.28	0.204
DAS28	Mean \pm SD		4.10 \pm 1.36		4.31 \pm 1.49	0.317
Functional class	I+II/ III+IV, (n, %)	30/22	57.7%/42.3%	297/222	57.2%/42.7%	0.948

Table S4 Comparison of studied data according to RANK genotypes in all RA cases.

rs1805034		RA(n=573)						<i>P</i>
		TT (n=266)		TC (n=253)		CC (n=52)		
Age	Years, Mean ± SD	55.07 ± 14.47		54.53 ± 15.29		51.56 ± 17.13		0.128
Sex	Male/Female, (n, %)	65/201	24.4%/75.6%	72/181	27.1%/72.9%	9/43	17.3%/82.7%	0.207
ESR	mm/h, Mean ± SD	34.35 ± 25.95		33.18 ± 24.08		32.58 ± 27.58		0.620
RF	Positive/Negative, (n, %)	214/52	80.5%/19.5%	195/58	77.1%/22.9%	45/7	86.5%/13.5%	0.267
anticcp	Positive/Negative, (n, %)	150/116	56.4%/43.6%	121/132	47.8%/52.2%	28/24	53.8%/46.2%	0.145
CRP	Mg/L, Mean ± SD	29.49 ± 40.49		25.80 ± 31.22		34.51 ± 42.11		0.130
DAS28	Mean ± SD	4.31 ± 1.41		4.32 ± 1.56		4.10 ± 1.36		0.364
Functional class	I+II/ III+IV, (n, %)	152/114	57.1%/42.9%	145/108	57.3%/42.7%	30/22	57.7%/42.3%	0.997

Table S5 The association of genetic risk score of rs1805034, rs531564 polymorphisms with risk of RA.

Variable	Case (n = 574)	Control (n = 804)	OR (95% CI)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> value
	N (%)	N (%)				
First (-1.5-0)	126	241	0.67(0.50,0.88)	0.005	0.66(0.49,0.87)	0.004
Second (0)	204	260	1	-	1.0	-
Third (0-0.5)	241	270	1.14(0.88,1.46)	0.317	1.13(0.88,1.46)	0.344

The genotyping for rs1805034 and rs531564 was successful in: 571 cases and 771 controls

Adjusted for sex and age

*Bold values are statistically significant ($P < 0.05$)

Table S6. Characteristics of included studies

Author	Year	Nationality	Sample size (Female/Male)		Age (mean)		Study Gene	Study SNPs	Genotype method	NOS	HWE
			case	control	case	control					
Mohamed	2016	Egypt	172 (female)	176 (female)	57.4	55.1	RANK	rs1805034	PCR-RFLP	6	N
							RANKL	rs9525641	PCR-RFLP	6	N
Xu	2014	China	201(171/30)	200(172/28)	51.9	53.5	RANKL	rs2277438	LDR-PCR	6	Y
							OPG	rs2073618	LDR-PCR	6	Y
								rs3102735	LDR-PCR	6	Y
								rs7984870	MALDI-TOF MS	5	Y
Zhang	2013	China	329 (274/82)	697(496/201)	53.6	53.5	RANKL	rs7984870	MALDI-TOF MS	5	Y
Assmann	2010	Germany	534(392/142)	519(186/333)	49.1	34.8	RANK	rs1805034	TaqMan	5	Y
								rs35211496	TaqMan	5	Y
							RANKL	rs9533156	TaqMan	5	Y
								rs2277438	TaqMan	5	Y
								rs1054016	TaqMan	5	Y
							OPG	rs3102735	TaqMan	5	Y
								rs2073618	TaqMan	5	Y
Zavala	2015	Mexico	81(female)	52(female)	49.9	NA	OPG	rs2073617	PCR-RFLP	5	Y
								rs3134070	PCR-RFLP	5	Y
								rs3134069	PCR-RFLP	5	Y
Cai	2015	China	205(175/30)	171(97/74)	48.5	41.6	OPG	rs3102735	PCR	6	Y
								rs3134069	PCR	6	Y
Ye	2015	China	574(427/147)	804(599/205)	54.5	55.7	OPG	rs3102735	MALDI-TOF MS	6	Y
								rs2073618	MALDI-TOF MS	6	Y
Hussien	2013	Saudi Arabia	200(female)	150(female)	57.3	57.1	OPG	rs3102735	PCR-RFLP	5	Y
This study	2018	China	574(427/147)	804(599/205)	54.5	55.7	RANK	rs1805034	MALDI-TOF MS	6	Y

Table S7. Genotype distributions of RANK, RANKL, OPG polymorphisms in the included studies

NA, not available; HB, hospital-based; PB, population-based.

Gene & SNP	Author&Year	SOC	Ethnicity	Allele		CASE			CONTROL			Association with RA
				1	2	11	12	22	11	12	22	
RANK rs1805034	Mohamed2016	PB	Caucasians	T	C	87	61	24	74	69	33	Increased risk
	Assmann2010	HB	Caucasians	T	C	154	235	132	148	264	104	Not related
	This study2018	HB	Chinese	T	C	266	253	52	386	324	75	Not related
RANK rs35211496	Assmann2010	HB	Caucasians	C	T	368	128	23	330	165	21	Decreased risk
RANKL rs2277438	Xu2014	PB	Asians	A	G	95	90	15	99	77	12	Not related
	Assmann2010	HB	Caucasians	A	G	342	136	28	360	140	12	Increased risk
RANKL rs7984870	Zhang2013	HB	Chinese	C	G	90	152	78	175	344	175	Not related
RANKL rs9525641	Mohamed2016	PB	Caucasians	T	C	76	65	31	73	69	34	Not related
RANKL rs9533156	Assmann2010	HB	Caucasians	T	C	165	248	101	142	249	123	Not related
RANKL rs1054016	Assmann2010	HB	Caucasians	G	T	178	242	98	161	242	107	Not related
OPG rs3102735	Cai2015	HB	Asians	T	C	127	63	15	119	49	3	Increased risk
	Ye2015	PB	Asians	T	C	418	142	12	546	220	22	Not related
	Xu2014	PB	Asians	T	C	146	50	4	131	51	6	Not related
	Hussien2013	PB	Caucasians	T	C	116	59	25	111	36	3	Increased
	Assmann2010	HB	Caucasians	T	C	410	116	7	410	99	5	Not related
OPG rs2073618	Ye2015	PB	Asians	G	C	296	238	37	430	305	53	Not related
	Xu2014	PB	Asians	G	C	107	77	16	102	70	13	Not related
	Assmann2010	HB	Caucasians	G	C	98	276	154	103	266	143	Not related
OPG rs3134069	Zavala2015	PB	Caucasians	A	C	66	10	1	41	11	0	Not related
	Cai2015	HB	Asians	A	C	177	27	1	144	25	2	Not related
OPG rs2073617	Zavala2015	PB	Caucasians	C	T	28	26	11	9	29	13	Increased risk
OPG rs3134070	Zavala2015	PB	Caucasians	C	T	52	18	2	39	11	2	Not related