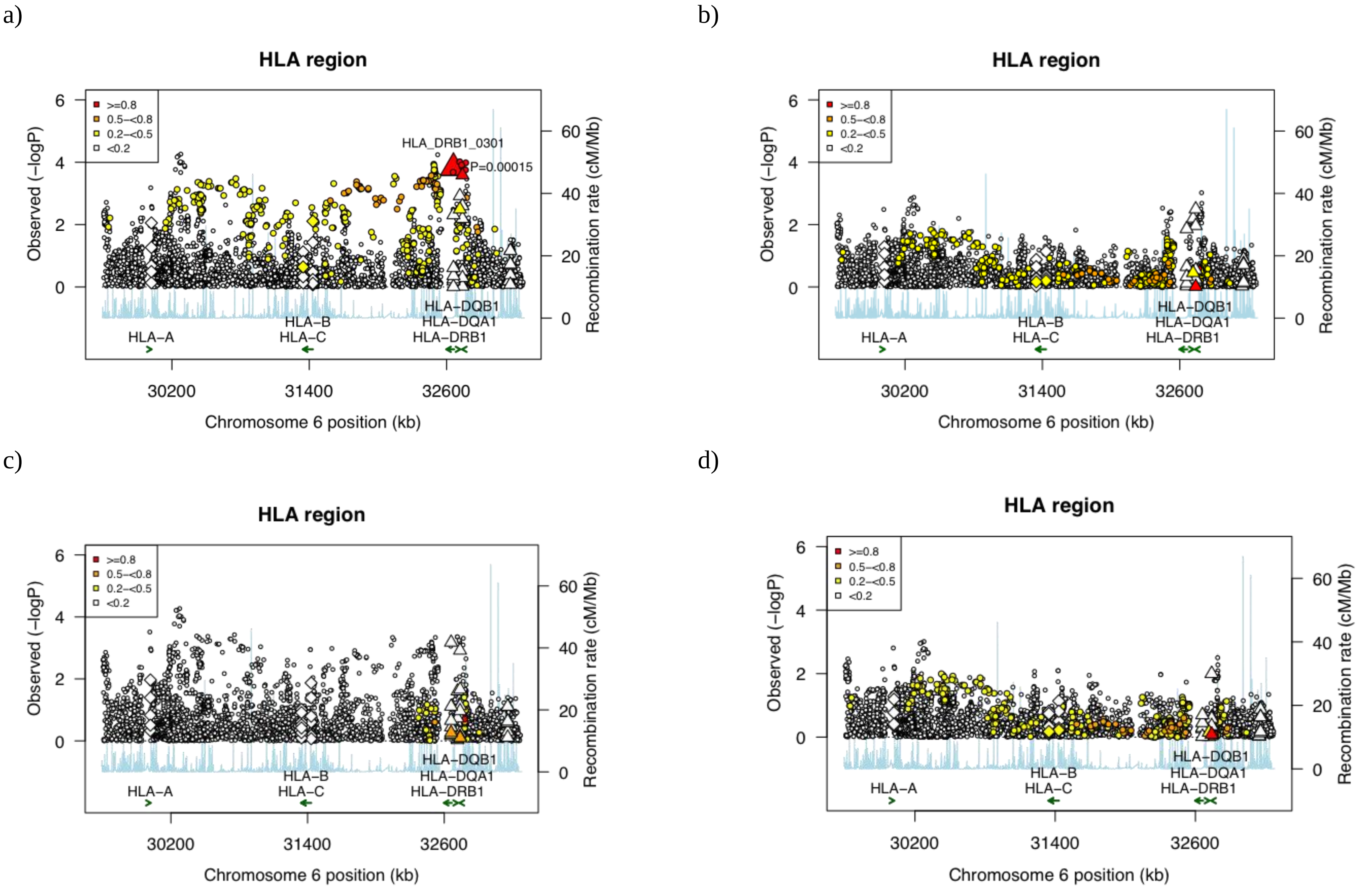
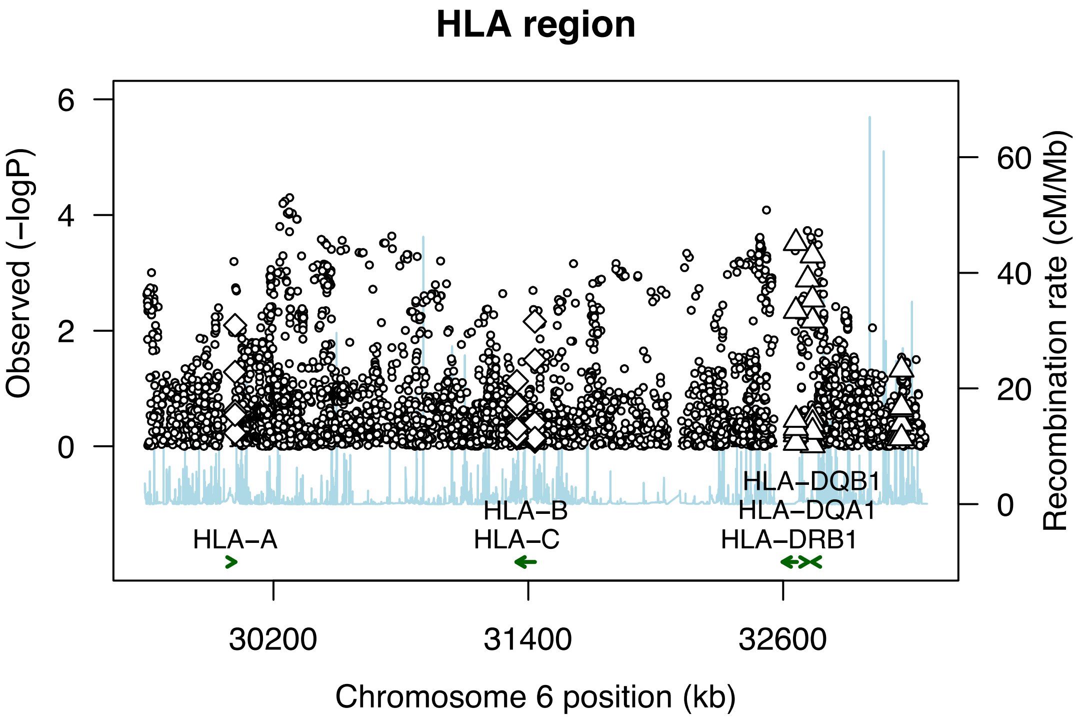
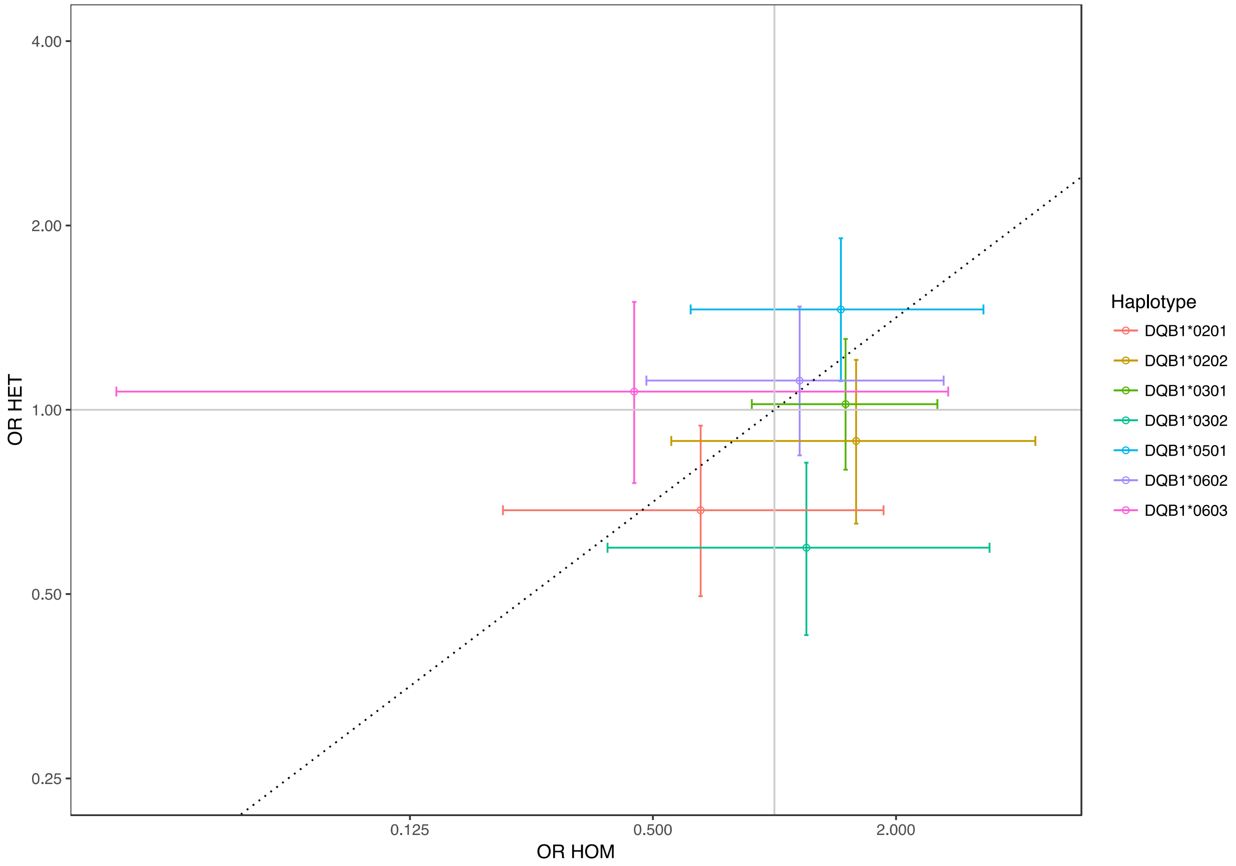
Supplementary Figure 1. Meta-analyses for a) unadjusted association analysis, b) conditional analysis adjusted for the top discovery signal, c) conditional analysis adjusted for the second signal, and d) conditional analysis adjusted for both top signals.



Supplementary Figure 2. Conditional meta-analyses adjusted for prior GWAS signal, rs1906953



Supplementary Figure 3. Scatter plot of osteosarcoma risk for homozygous haplotype carriers of DQB1 alleles plotted on the x-axis, and heterozygous haplotype carriers plotted on the y-axis for subjects in the dbGaP dataset. Associations are shown as the odds ratios for osteosarcoma risk in carriers compared to non-carriers of the haplotype. The dashed line represents a purely additive relationship, in which heterozygotes have half the risk of homozygotes (on a log-odds scale).



Supplementary Table 1. Demographics and clinical features of 207 pediatric osteosarcoma cases of European ancestry in the California Department of Public Health.

Variable	Mean (SD) or n (%)	Range
Age at diagnosis	12.4 (3.4)	4.0-19.0
Sex, male	114 (55.1%)	-
Metastasis present	21 (10.1%)	-
Tumor site in long bone	183 (88.4%)	-
Undifferentiated tumor	111 (53.6%)	-

Supplementary Table 2. HLA class I and class II allele frequencies of common variants (>0.05) in the discovery data set.

Allele	FRQ	OR	SE	P
A*0101	0.1447	0.7276	0.1766	0.071740
A*0201	0.2714	1.3510	0.1293	0.019990
A*0301	0.1416	0.6576	0.1838	0.022540
A*1101	0.0669	1.1859	0.2216	0.441800
A*2402	0.0930	1.2667	0.1927	0.219900
C*0303	0.0511	1.3490	0.2398	0.212000
C*0304	0.0795	1.1006	0.2089	0.646200
C*0401	0.1221	0.9103	0.1762	0.593900
C*0501	0.0816	1.0192	0.2080	0.927200
C*0602	0.0957	0.9568	0.1914	0.817600
C*0701	0.1445	0.9078	0.1698	0.568700
C*0702	0.1302	0.9765	0.1681	0.887600
C*1203	0.0644	1.0314	0.2378	0.896700
B*0702	0.1130	0.9328	0.1817	0.701700
B*0801	0.0976	0.5950	0.2251	0.021070
B*1501	0.0586	1.2883	0.2425	0.296100
B*3501	0.0636	1.0565	0.2423	0.820700
B*4001	0.0542	1.2436	0.2454	0.374200
B*4402	0.0877	1.1547	0.2010	0.474100
DQB1*0201	0.1062	0.5124	0.2226	0.002671
DRB1*0301	0.1055	0.5228	0.2203	0.003242
DQA1*0501	0.2396	0.7363	0.1422	0.031320
DQA1*0101	0.1549	1.3287	0.1502	0.058490
DQB1*0501	0.1318	1.2506	0.1614	0.166100
DQB1*0603	0.0624	0.7191	0.2603	0.205300
DQA1*0103	0.0712	0.7439	0.2433	0.223900

Allele	FRQ	OR	SE	P
DQB1*0302	0.1086	0.7972	0.1944	0.243600
DRB1*1301	0.0627	0.7428	0.2574	0.248100
DRB1*0101	0.0865	1.2366	0.2010	0.290700
DPB1*0101	0.0575	0.7949	0.2682	0.392000
DPB1*0301	0.0994	0.8481	0.2107	0.434100
DQB1*0301	0.1903	1.1019	0.1444	0.501500
DRB1*1501	0.1174	1.1158	0.1764	0.534600
DRB1*0401	0.0707	1.1372	0.2282	0.573200
DQB1*0602	0.1161	1.1038	0.1776	0.578000
DPB1*0201	0.1350	1.0992	0.1730	0.584600
DPA1*0103	0.7886	0.9278	0.1420	0.597800
DRB1*1101	0.0597	0.8782	0.2729	0.634100
DQB1*0202	0.0975	1.0745	0.1806	0.690900
DQA1*0102	0.1852	1.0584	0.1442	0.694000
DRB1*0701	0.1327	0.9465	0.1635	0.736800
DPB1*0401	0.4012	1.0335	0.1180	0.780200
DQA1*0201	0.1338	0.9782	0.1624	0.892100
DPA1*0201	0.1514	1.0132	0.1571	0.933300
DPB1*0402	0.1286	0.9903	0.1725	0.954900
DQA1*0301	0.1834	0.9951	0.1489	0.973900

Supplementary Table 3. Pairwise correlation of variants of 3 genes, DRB1, DQA1, and DQB1, that were identified from the top association signals, with green highlighting HLA alleles of the first signal of DRB1*0301, DQA1*0501, and DQB1*0201, and the blue highlighting HLA alleles of the second signal of DRB1*0101, DQA1*0101, and DQB1*0501.

DRB1/DQA1:

	DRB1*0101	DRB1*0301	DRB1*0401	DRB1*0701	DRB1*1101	DRB1*1301	DRB1*1501
DQA1*0101	0.981	-0.103	-0.169	-0.183	-0.134	-0.096	-0.209
DQA1*0102	-0.216	-0.151	-0.187	-0.281	-0.071	-0.158	0.978
DQA1*0103	-0.088	-0.167	-0.023	-0.196	-0.165	0.962	-0.134
DQA1*0201	-0.193	-0.295	-0.245	0.993	-0.110	-0.180	-0.280
DQA1*0301	-0.165	-0.100	0.980	-0.229	-0.141	-0.014	-0.183
DQA1*0501	-0.166	0.719	-0.161	-0.324	0.504	-0.256	-0.225

DQA1/DQB1:

DRB1/DQB1:

	DRB1*0101	DRB1*0301	DRB1*0401	DRB1*0701	DRB1*1101	DRB1*1301	DRB1*1501
DQB1*0201	-0.124	0.989	-0.097	-0.251	-0.208	-0.197	-0.214
DQB1*0202	-0.188	-0.251	-0.229	0.995	-0.085	-0.178	-0.239
DQB1*0301	-0.150	-0.200	0.282	-0.174	0.756	-0.116	-0.204
DQB1*0302	-0.118	-0.102	0.716	-0.159	-0.084	-0.050	-0.118
DQB1*0501	0.964	-0.120	-0.177	-0.183	-0.120	-0.118	-0.182
DQB1*0602	-0.210	-0.204	-0.197	-0.239	-0.104	-0.150	0.970
DQB1*0603	-0.109	-0.185	-0.035	-0.178	-0.176	0.975	-0.128

DQA1/DQB1:

	DQA1*0101	DQA1*0102	DQA1*0103	DQA1*0201	DQA1*0301	DQA1*0501
DQB1*0201	-0.147	-0.126	-0.153	-0.158	-0.162	0.572
DQB1*0202	-0.188	-0.142	-0.115	1.000	-0.222	-0.237
DQB1*0301	-0.217	-0.235	-0.149	-0.198	0.109	0.505
DQB1*0302	-0.161	-0.183	-0.092	-0.170	0.785	-0.231
DQB1*0501	0.994	-0.183	-0.122	-0.191	-0.205	-0.264
DQB1*0602	-0.200	0.983	-0.097	-0.143	-0.212	-0.259
DQB1*0603	-0.126	-0.082	0.982	-0.112	-0.116	-0.225

Supplementary Table 4. Imputation accuracy in the discovery and replication datasets for nominally significant HLA class II alleles associated with osteosarcoma risk.

HLA allele	R^2 Discovery	R^2 Replication
DRB1*0301	0.998	0.995
DQA1*0501	0.999	0.999
DQB1*0201	0.996	0.990
DRB1*0101	0.989	0.972
DQA1*0101	1.00	1.00
DQB1*0501	0.997	0.998
DQB1*0302	1.00	0.999

Supplementary Table 5. Interaction effect estimates and *P*-values for the model improvement with the inclusion of the interaction term between *DRB1*0301* and each class II allele.

Haplotype	Interaction OR (95% CI)	Interaction P_{improve}
DRB1*0101	0.44 (0.16-1.10)	8.16E-02
DRB1*0401	0.75 (0.28-1.90)	5.57E-01
DRB1*0701	1.09 (0.57-2.06)	7.98E-01
DRB1*1101	0.72 (0.22-2.22)	5.72E-01
DRB1*1301	4.44 (1.66-12.3)	2.99E-03
DRB1*1501	1.43 (0.71-2.84)	3.10E-01
DQA1*0101	0.45 (0.21-0.92)	2.94E-02
DQA1*0102	1.90 (1.03-3.48)	4.11E-02
DQA1*0103	4.40 (1.68-11.9)	2.49E-03
DQA1*0201	1.09 (0.57-2.07)	7.88E-01
DQA1*0301	0.74 (0.37-1.44)	3.78E-01
DQA1*0501	0.70 (0.40-1.15)	1.63E-01
DQB1*0201	0.96 (0.51-1.68)	8.84E-01
DQB1*0202	0.96 (0.44-2.08)	9.23E-01
DQB1*0301	0.52 (0.28-0.96)	3.54E-02
DQB1*0302	0.70 (0.25-1.80)	4.75E-01
DQB1*0501	0.51 (0.22-1.14)	1.01E-01
DQB1*0602	1.49 (0.73-3.01)	2.74E-01
DQB1*0603	3.96 (1.52-10.5)	4.76E-03
DPA1*0103	1.02 (0.67-1.56)	9.36E-01
DPA1*0201	0.91 (0.58-1.44)	6.97E-01
DPB1*0101	0.88 (0.45-1.69)	6.95E-01
DPB1*0201	1.26 (0.70-2.24)	4.39E-01
DPB1*0301	0.87 (0.44-1.66)	6.79E-01
DPB1*0401	0.82 (0.57-1.18)	2.88E-01
DPB1*0402	1.32 (0.75-2.26)	3.28E-01

Supplementary Table 6. Association analyses between HLA intragenic SNPs and osteosarcoma, stratified by dataset and combined in meta-analysis, for SNPs with meta-analysis p-value $<1.0x10^{-4}$.

	Discovery		Replication		Meta-analysis		
HLA intragenic SNP	OR	P	OR	P	OR	P	I^{2a} (%)
rs929157	0.55	4.95E-03	0.64	4.11E-03	0.61	6.82E-05	0
rs2187668	0.52	2.66E-03	0.67	8.00E-03	0.61	9.72E-05	0
rs2284189	0.52	2.65E-03	0.67	8.00E-03	0.61	9.68E-05	0
rs2517612	0.54	3.75E-03	0.64	4.06E-03	0.60	5.49E-05	0
rs2523720	0.58	7.80E-03	0.64	4.06E-03	0.61	9.70E-05	0
rs2844785	0.55	4.35E-03	0.64	4.19E-03	0.60	6.26E-05	0
rs3129890	0.81	1.15E-01	0.65	9.14E-05	0.71	5.74E-05	38.0

$^{a}I^{2}$ heterogeneity index