cancers

Supplementary Materials

SNP-SNP Interaction in Genes Encoding PD-1/PD-L1 Axis as a Potential Risk Factor for Clear Cell Renal Cell Carcinoma

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Table S1. Genotype distribution of investigated *PDCD1* and *PD-L1* polymorphisms in Renal Cell Carcinoma (RCC) patients and controls.

Gene	**Polymorphisms**	**Genotype**	**RCC patients (N = 237)**			**Controls (N = 256)**			**OR (CI95%)**	***p***
			N	**%**	**HWE**	**N**	**%**	**HWE**		
PDCD1 (PD-1)	rs36084323 (PD-1.1)	GG	229	96.6	p = 0.070; f = −0.017	249	97.3	p = 0.824; f = −0.014	1	χ^2 = 0.171; p = 0.679
		GA	8	3.4		7	2.7		1.23 (0.45; 3.34)	
		AA	0	0.0		0	0.00		–	
	rs11568821 (PD-1.3)	GG	188 43	79.3	p = 0.075; f = 0.116	206	80.5	p = 0.445; f = 0.048	1	χ^2 = 0.592; p = 0.744
		GA	43	18.1		46	18.0		1.02 (0.65; 1.62)	
		AA	6	2.5		4	1.6		1.58 (0.47; 5.35)	
	rs2227981 (PD-1.5)	CC	80	33.8	p = 0.713; f = 0.024	82	32.0	p = 0.361; f = −0.057	1	χ^2 = 0.814; p = 0.666
		CT	113	47.7		132	51.6		0.88 (0.59; 1.30)	
		TT	44	18.6		42	16.4		1.07 (0.64; 1.81)	
	rs10204525 (PD-1.6)	GG	195	82.3	p = 0.454; f = −0.049	208	81.2	p = 0.037; f = 0.131	1	χ^2 = 3.275; p = 0.194
		GA	41	17.3		42	16.4		1.04 (0.65; 1.47)	
		AA	1	1		6	2.3		0.25 (0.04; 1.47)	
	rs7421861	TT	107	45.1	p = 0.072; f = 0.117	99	38.7	p = 0.142; f = −0.052	1	χ^2 = 5.325; p = 0.063
		TC	95	40.1		129	50.4		0.68 (0.47; 1.00)	
		CC	35	14.8		28	10.9		1.15 (0.66; 2.03)	
PD-L1	PD-L1 (rs822335)	CC	84	35.9	p = 0.105; f = −0.106	102	40.5	p = 0.429; f = 0.050	1	χ^2 = 3.022; p = 0.221
		CT	122	52.1		112	44.4		1.32 (0.90; 1.94)	
		TT	28	12.0		38	15.1		0.90 (0.51; 1.58)	
	PD-L1 (rs4143815)	GG	107	45.7	p = 0.282; f = 0.070	122	48.41	p = 0.455; f = 0.047	1	χ^2 = 0.655; p = 0.721
		GC	97	41.5		103	40.88		1.07 (0.73; 1.57)	
		CC	30	12.8		27	10.71		1.26 (0.71; 2.25)	
	PD-L1 (rs4742098)	AA	136	58.1	p = 0.628; f = 0.032	137	54.4	p = 0.737; f = −0.021	1	χ^2 = 0.777; p = 0.678
		AG	83	35.3		99	39.3		0.85 (0.58; 1.23)	
		GG	15	6.4		16	6.3		0.95 (0.45; 1.97)	
	PD-L1 (rs10815225)	GG	185	79.1	p = 0.941; f = 0.005	214	84.92	p = 0.064; f = 0.117	1	χ^2 = 3.389; p = 0.184
		GC	46	19.7		34	13.49		1.56 (0.96; 2.52)	
		CC	3	1.3		4	1.59		0.90 (0.22; 3.69)	

Table S2. Analysis of linkage disequilibrium (r^2) between genetic variants located in *PDCD1* gene.

Controls				
	rs11568821	**rs2227981**	**rs10204525**	**rs7421861**
rs36084323	0.001	0.010	0.118	0.000
rs11568821	–	0.057	0.004	0.176
rs2227981	–	–	0.082	0.372
rs10204525	–	–	–	0.053
ccRCC patients				
	rs11568821	**rs2227981**	**rs10204525**	**rs7421861**
rs36084323	0.002	0.012	0.120	0.009
rs11568821	–	0.102	0.013	0.242
rs2227981	–	–	0.064	0.343
rs10204525	–	–	–	0.051

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Table S3. Analysis of linkage disequilibrium (r^2) between genetic variants located in *PD-L1* gene.

	Controls		
	rs4143815	**rs4742098**	**rs10815225**
rs822335	0.006	0.000	0.054
rs4143815	–	0.537	0.019
rs4742098	–	–	0.064
	ccRCC patients		
	rs4143815	**rs4742098**	**rs10815225**
rs822335	0.125	0.058	0.066
rs4143815	–	0.558	0.003
rs4742098	–	–	0.021

Table S4. *PDCD1* haplotype analysis in relation to ccRCC risk.

***PDCD1* haplotype**					**ccRCC patients N (%)**	**Controls N (%)**	**χ^2**	**p**	**OR (CI95%)**
rs36084323	**rs7421861**	**rs11568821**	**rs2227981**	**rs10204525**					
G	C	A	C	C	48.7 (11.7)	51.1 (10.0)	0.750	0.386	1.20 (0.79; 1.82)
G	T	G	C	C	89.4 (21.5)	106.1 (20.7)	0.096	0.757	1.05 (0.76; 1.44)
G	C	G	C	C	90.0 (21.6)	130.1 (25.4)	1.749	0.186	0.81 (0.60; 1.11)
G	T	G	T	C	145.3 (34.9)	166.2 (32.5)	0.696	0.404	1.12 (0.85; 1.48)
G	T	G	T	T	28.8 (6.9)	43.1 (8.4)	0.706	0.401	0.81 (0.50; 1.32)
					global χ^2 = 3.167; p = 0.530				

Significant results were bolded

Table S5. Rs7421861 x rs10815225 interaction - observed and expected genotype distributions in ccRCC patients and control subjects.

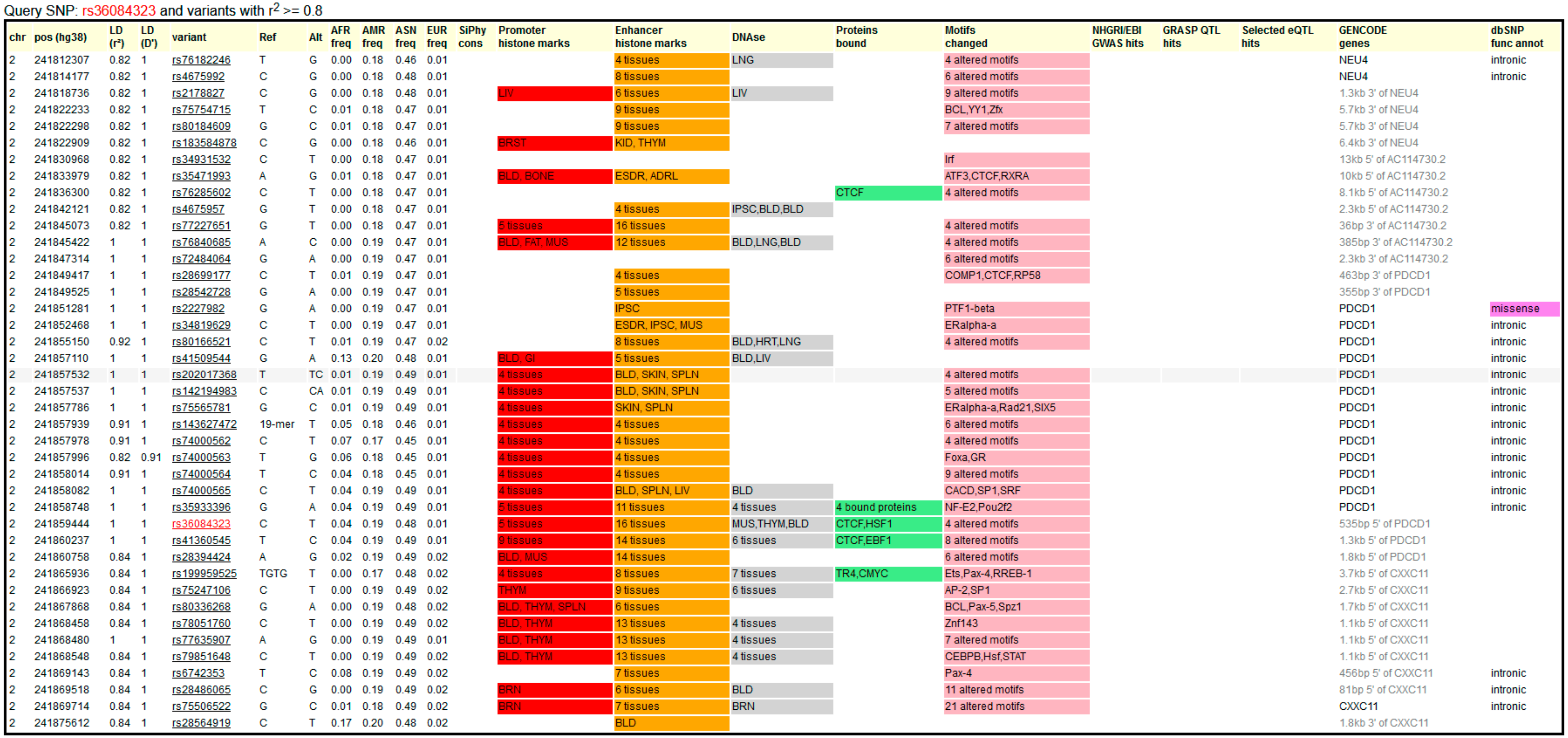
ccRCC patients											
Observed					**Expected**					χ^2	*p*
Genotype		**rs7421861**			**Genotype**		**rs7421861**				
		TT+CC	**TC**	**∑**			**TT+CC**	**TC**	**∑**		
rs10815225	**GG**	92	71	163	**rs10815225**	**GG**	99.39	63.61	163.0	**6.873**	**0.009**
	GC+CC	33	9	42		**GC**	25.61	16.39	42.0		
	∑	125	80	205		**∑**	125.0	80.0	205.0		
Controls											
Observed					**Expected**					χ^2	*p*
Genotype		**rs7421861**			**Genotype**		**rs7421861**				
		TT+CC	**TC**	**∑**			**TT+CC**	**TC**	**∑**		
rs10815225	**GG**	109	105	214	**rs10815225**	**GG**	106.15	107.85	214.0	1.006	0.316
	GC+CC	16	22	38		**GC+CC**	18.85	19.15	38.0		
	∑	125	127	252		**∑**	125	127	252.0		

In ccRCC patient group there is a difference between observed and expected number of genotypes ($p = 0.009$). while in controls the observed number of genotypes did not differ from the expected ($p = 0.316$). Significant results were bolded.

Table S6. List of Assays used in the study to perform genotyping of examined SNP.

Gene	Polymorphism	Assay ID
PDCD1	rs36084323G>A	C__57931321_10
	rs7421861T>C	C__26891639_10
	rs11568821G>A	C__57931290_10
	rs2227981C>T	C__57931286_20
	rs10204525G>A	C____172862_20
PD-L1	rs10815225 G>C	C___1348557_30
	rs822335 C>T	C___7590674_10
	rs4143815 G>C	C__31941235_10
	rs4742098 A>G	C__27957750_10

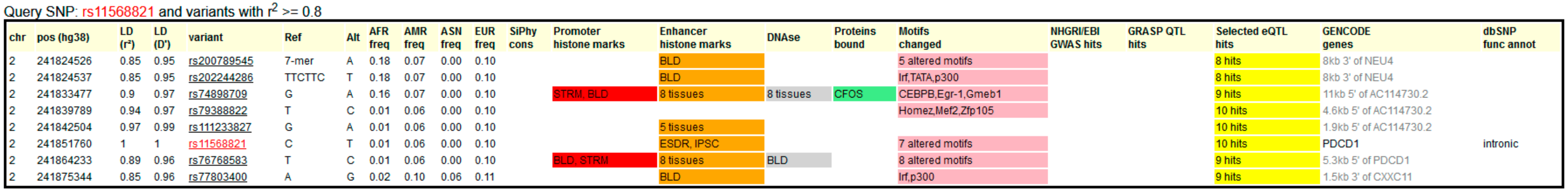
A



Query SNP: rs36084323 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
2	241812307	0.82	1	rs76182246	T	G	0.00	0.18	0.46	0.01			4 tissues	LNG		4 altered motifs				NEU4	intronic
2	241814177	0.82	1	rs4675992	C	G	0.00	0.18	0.48	0.01			8 tissues			6 altered motifs				NEU4	intronic
2	241818736	0.82	1	rs2178827	C	G	0.00	0.18	0.48	0.01		LIV	6 tissues	LIV		9 altered motifs				1.3kb 3' of NEU4	
2	241822233	0.82	1	rs75754715	T	C	0.01	0.18	0.47	0.01			9 tissues			BCL,YY1,Zfx				5.7kb 3' of NEU4	
2	241822298	0.82	1	rs80184609	G	C	0.01	0.18	0.47	0.01			9 tissues			7 altered motifs				5.7kb 3' of NEU4	
2	241822909	0.82	1	rs183584878	C	G	0.00	0.18	0.46	0.01		BRST	KID, THYM							6.4kb 3' of NEU4	
2	241830968	0.82	1	rs34931532	C	T	0.00	0.18	0.47	0.01						Irf				13kb 5' of AC114730.2	
2	241833979	0.82	1	rs35471993	A	G	0.01	0.18	0.47	0.01		BLD, BONE	ESDR, ADRL			ATF3,CTCF,RXRA				10kb 5' of AC114730.2	
2	241836300	0.82	1	rs76285602	C	T	0.00	0.18	0.47	0.01					CTCF	4 altered motifs				8.1kb 5' of AC114730.2	
2	241842121	0.82	1	rs4675957	G	T	0.00	0.18	0.47	0.01			4 tissues	IPSC,BLD,BLD						2.3kb 5' of AC114730.2	
2	241845073	0.82	1	rs77227651	G	T	0.00	0.18	0.47	0.01		5 tissues	16 tissues			4 altered motifs				36bp 3' of AC114730.2	
2	241845422	1	1	rs76840685	A	C	0.00	0.19	0.47	0.01		BLD, FAT, MUS	12 tissues	BLD,LNG,BLD		4 altered motifs				385bp 3' of AC114730.2	
2	241847314	1	1	rs72484064	G	A	0.00	0.19	0.47	0.01						6 altered motifs				2.3kb 3' of AC114730.2	
2	241849417	1	1	rs28699177	C	T	0.01	0.19	0.47	0.01			4 tissues			COMP1,CTCF,RP58				463bp 3' of PDCD1	
2	241849525	1	1	rs28542728	G	A	0.00	0.19	0.47	0.01			5 tissues							355bp 3' of PDCD1	
2	241851281	1	1	rs2227982	G	A	0.00	0.19	0.47	0.01			IPSC			PTF1-beta				PDCD1	missense
2	241852468	1	1	rs34819629	C	T	0.00	0.19	0.47	0.01			ESDR, IPSC, MUS			ERalpha-a				PDCD1	intronic
2	241855150	0.92	1	rs80166521	C	T	0.01	0.19	0.47	0.02			8 tissues	BLD,HRT,LNG		4 altered motifs				PDCD1	intronic
2	241857110	1	1	rs41509544	G	A	0.13	0.20	0.48	0.01		BLD, GI	5 tissues	BLD,LIV						PDCD1	intronic
2	241857532	1	1	rs202017368	T	TC	0.01	0.19	0.49	0.01		4 tissues	BLD, SKIN, SPLN			4 altered motifs				PDCD1	intronic
2	241857537	1	1	rs142194983	C	CA	0.01	0.19	0.49	0.01		4 tissues	BLD, SKIN, SPLN			5 altered motifs				PDCD1	intronic
2	241857786	1	1	rs75565781	G	C	0.01	0.19	0.49	0.01		4 tissues	SKIN, SPLN			ERalpha-a,Rad21,SIX5				PDCD1	intronic
2	241857939	0.91	1	rs143627472	19-mer	T	0.05	0.18	0.46	0.01		4 tissues	4 tissues			6 altered motifs				PDCD1	intronic
2	241857978	0.91	1	rs74000562	C	T	0.07	0.17	0.45	0.01		4 tissues	4 tissues			4 altered motifs				PDCD1	intronic
2	241857996	0.82	0.91	rs74000563	T	G	0.06	0.18	0.45	0.01		4 tissues	4 tissues			Foxa,GR				PDCD1	intronic
2	241858014	0.91	1	rs74000564	T	C	0.04	0.18	0.45	0.01		4 tissues	4 tissues			9 altered motifs				PDCD1	intronic
2	241858082	1	1	rs74000565	C	T	0.04	0.19	0.49	0.01		4 tissues	BLD, SPLN, LIV	BLD		CACD,SP1,SRF				PDCD1	intronic
2	241858748	1	1	rs35933396	G	A	0.04	0.19	0.49	0.01		5 tissues	11 tissues	4 tissues	4 bound proteins	NF-E2,Pou2f2				PDCD1	intronic
2	241859444	1	1	rs36084323	C	T	0.04	0.19	0.48	0.01		5 tissues	16 tissues	MUS,THYM,BLD	CTCF,HSF1	4 altered motifs				535bp 5' of PDCD1	
2	241860237	1	1	rs41360545	T	C	0.04	0.19	0.49	0.01		9 tissues	14 tissues	6 tissues	CTCF,EBF1	8 altered motifs				1.3kb 5' of PDCD1	
2	241860758	0.84	1	rs28394424	A	G	0.02	0.19	0.49	0.02		BLD, MUS	14 tissues			6 altered motifs				1.8kb 5' of PDCD1	
2	241865936	0.84	1	rs199959525	TGTG	T	0.00	0.17	0.48	0.02		4 tissues	8 tissues	7 tissues	TR4,CMYC	Ets,Pax-4,RREB-1				3.7kb 5' of CXXC11	
2	241866923	0.84	1	rs75247106	C	T	0.00	0.19	0.49	0.02		THYM	9 tissues	6 tissues		AP-2,SP1				2.7kb 5' of CXXC11	
2	241867868	0.84	1	rs80336268	G	A	0.00	0.19	0.48	0.02		BLD, THYM, SPLN	6 tissues			BCL,Pax-5,Spz1				1.7kb 5' of CXXC11	
2	241868458	0.84	1	rs78051760	C	T	0.00	0.19	0.49	0.02		BLD, THYM	13 tissues	4 tissues		Znf143				1.1kb 5' of CXXC11	
2	241868480	1	1	rs77635907	A	G	0.00	0.19	0.49	0.01		BLD, THYM	13 tissues	4 tissues		7 altered motifs				1.1kb 5' of CXXC11	
2	241868548	0.84	1	rs79851648	C	T	0.00	0.19	0.49	0.02		BLD, THYM	13 tissues	4 tissues		CEBPB,Hsf,STAT				1.1kb 5' of CXXC11	
2	241869143	0.84	1	rs6742353	T	C	0.08	0.19	0.49	0.02			7 tissues			Pax-4				456bp 5' of CXXC11	intronic
2	241869518	0.84	1	rs28486065	C	G	0.00	0.19	0.49	0.02		BRN	6 tissues	BLD		11 altered motifs				81bp 5' of CXXC11	intronic
2	241869714	0.84	1	rs75506522	G	C	0.01	0.18	0.49	0.02		BRN	7 tissues	BRN		21 altered motifs				CXXC11	intronic
2	241875612	0.84	1	rs28564919	C	T	0.17	0.20	0.48	0.02			BLD							1.8kb 3' of CXXC11	

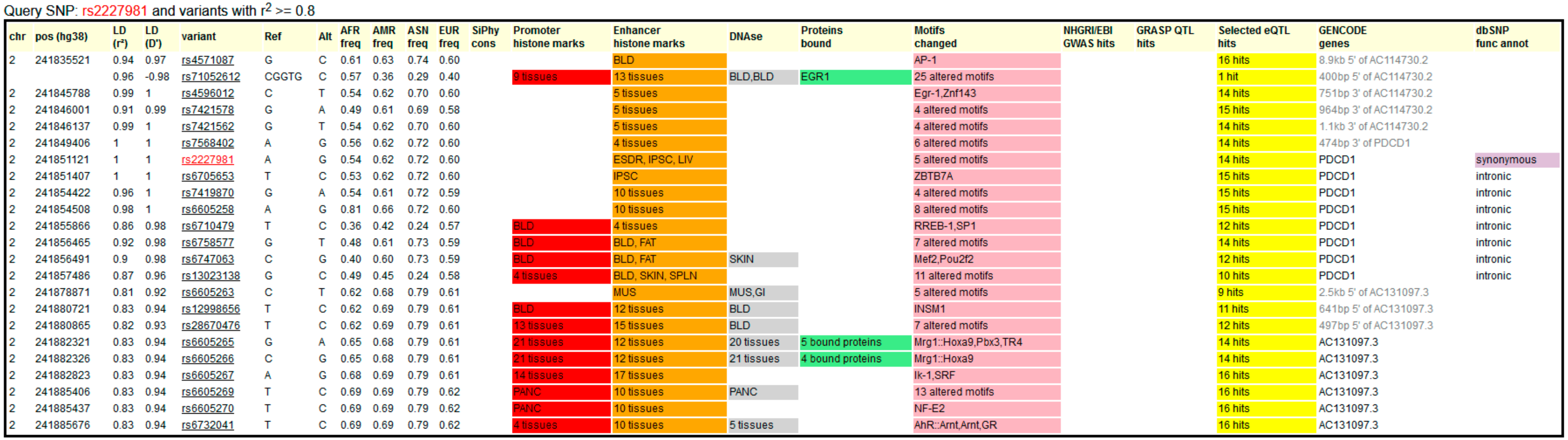
B



Query SNP: rs11568821 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
2	241824526	0.85	0.95	rs200789545	7-mer	A	0.18	0.07	0.00	0.10			BLD			5 altered motifs			8 hits	8kb 3' of NEU4	
2	241824537	0.85	0.95	rs202244286	TTCTTC	T	0.18	0.07	0.00	0.10			BLD			Irf,TATA,p300			8 hits	8kb 3' of NEU4	
2	241833477	0.9	0.97	rs74898709	G	A	0.16	0.07	0.00	0.10		STRM, BLD	8 tissues	8 tissues	CFOS	CEBPB,Egr-1,Gmeb1			9 hits	11kb 5' of AC114730.2	
2	241839789	0.94	0.97	rs79388822	T	C	0.01	0.06	0.00	0.10						Homez,Mef2,Zfp105			10 hits	4.6kb 5' of AC114730.2	
2	241842504	0.97	0.99	rs111233827	G	A	0.01	0.06	0.00	0.10			5 tissues						10 hits	1.9kb 5' of AC114730.2	
2	241851760	1	1	rs11568821	C	T	0.01	0.06	0.00	0.10			ESDR, IPSC			7 altered motifs			10 hits	PDCD1	intronic
2	241864233	0.89	0.96	rs76768583	T	C	0.01	0.06	0.00	0.10		BLD, STRM	8 tissues	BLD		8 altered motifs			9 hits	5.3kb 5' of PDCD1	
2	241875344	0.85	0.96	rs77803400	A	G	0.02	0.10	0.06	0.11			BLD			Irf,p300			9 hits	1.5kb 3' of CXXC11	

C

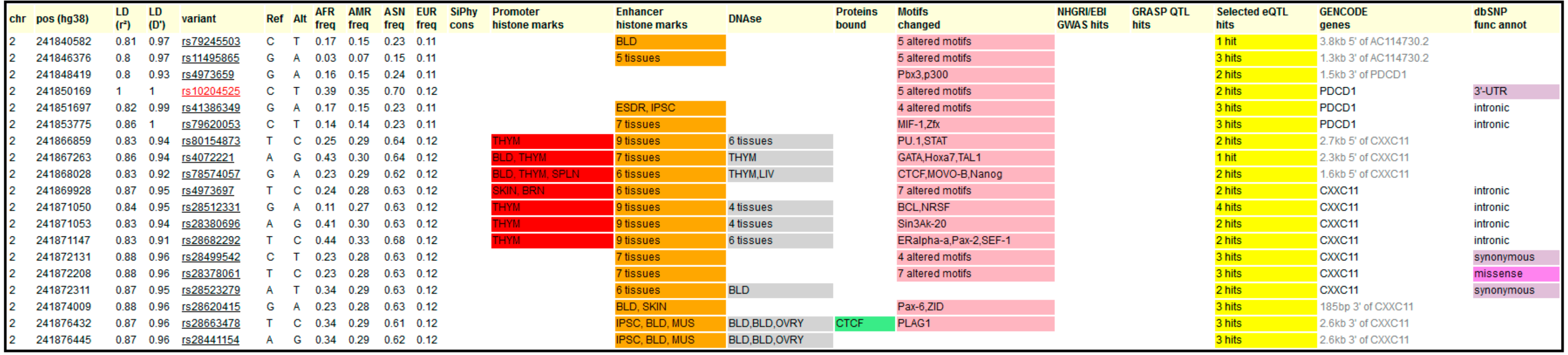


Query SNP: rs2227981 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
2	241835521	0.94	0.97	rs4571087	G	C	0.61	0.63	0.74	0.60			BLD			AP-1			16 hits	8.9kb 5' of AC114730.2	
		0.96	-0.98	rs71052612	CGGTG	C	0.57	0.36	0.29	0.40		9 tissues	13 tissues	BLD,BLD	EGR1	25 altered motifs			1 hit	400bp 5' of AC114730.2	
2	241845788	0.99	1	rs4596012	C	T	0.54	0.62	0.70	0.60			5 tissues			Egr-1,Znf143			14 hits	751bp 3' of AC114730.2	
2	241846001	0.91	0.99	rs7421578	G	A	0.49	0.61	0.69	0.58			5 tissues			4 altered motifs			15 hits	964bp 3' of AC114730.2	
2	241846137	0.99	1	rs7421562	G	T	0.54	0.62	0.70	0.60			5 tissues			4 altered motifs			14 hits	1.1kb 3' of AC114730.2	
2	241849406	1	1	rs7568402	A	G	0.56	0.62	0.72	0.60			4 tissues			6 altered motifs			14 hits	474bp 3' of PDCD1	
2	241851121	1	1	rs2227981	A	G	0.54	0.62	0.72	0.60			ESDR, IPSC, LIV			5 altered motifs			14 hits	PDCD1	synonymous
2	241851407	1	1	rs6705653	T	C	0.53	0.62	0.72	0.60			IPSC			ZBTB7A			15 hits	PDCD1	intronic
2	241854422	0.96	1	rs7419870	G	A	0.54	0.61	0.72	0.59			10 tissues			4 altered motifs			15 hits	PDCD1	intronic
2	241854508	0.98	1	rs6605258	A	G	0.81	0.66	0.72	0.60			10 tissues			8 altered motifs			15 hits	PDCD1	intronic
2	241855866	0.86	0.98	rs6710479	T	C	0.36	0.42	0.24	0.57		BLD	4 tissues			RREB-1,SP1			12 hits	PDCD1	intronic
2	241856465	0.92	0.98	rs6758577	G	T	0.48	0.61	0.73	0.59		BLD	BLD, FAT			7 altered motifs			14 hits	PDCD1	intronic
2	241856491	0.9	0.98	rs6747063	C	G	0.40	0.60	0.73	0.59		BLD	BLD, FAT	SKIN		Mef2,Pou2f2			12 hits	PDCD1	intronic
2	241857486	0.87	0.96	rs13023138	G	C	0.49	0.45	0.24	0.58		4 tissues	BLD, SKIN, SPLN			11 altered motifs			10 hits	PDCD1	intronic
2	241878871	0.81	0.92	rs6605263	C	T	0.62	0.68	0.79	0.61			MUS	MUS,GI		5 altered motifs			9 hits	2.5kb 5' of AC131097.3	
2	241880721	0.83	0.94	rs12998656	T	C	0.62	0.69	0.79	0.61		BLD	12 tissues	BLD		INSM1			11 hits	641bp 5' of AC131097.3	
2	241880865	0.82	0.93	rs28670476	T	C	0.62	0.69	0.79	0.61		13 tissues	15 tissues	BLD		7 altered motifs			12 hits	497bp 5' of AC131097.3	
2	241882321	0.83	0.94	rs6605265	G	A	0.65	0.68	0.79	0.61		21 tissues	12 tissues	20 tissues	5 bound proteins	Mrg1::Hoxa9,Pbx3,TR4			14 hits	AC131097.3	
2	241882326	0.83	0.94	rs6605266	C	G	0.65	0.68	0.79	0.61		21 tissues	12 tissues	21 tissues	4 bound proteins	Mrg1::Hoxa9			14 hits	AC131097.3	
2	241882823	0.83	0.94	rs6605267	A	G	0.68	0.69	0.79	0.61		14 tissues	17 tissues			Ik-1,SRF			16 hits	AC131097.3	
2	241885406	0.83	0.94	rs6605269	T	C	0.69	0.69	0.79	0.62		PANC	10 tissues	PANC		13 altered motifs			16 hits	AC131097.3	
2	241885437	0.83	0.94	rs6605270	T	C	0.69	0.69	0.79	0.62		PANC	10 tissues			NF-E2			16 hits	AC131097.3	
2	241885676	0.83	0.94	rs6732041	T	C	0.69	0.69	0.79	0.62		4 tissues	10 tissues	5 tissues		AhR::Arnt,Arnt,GR			16 hits	AC131097.3	

D

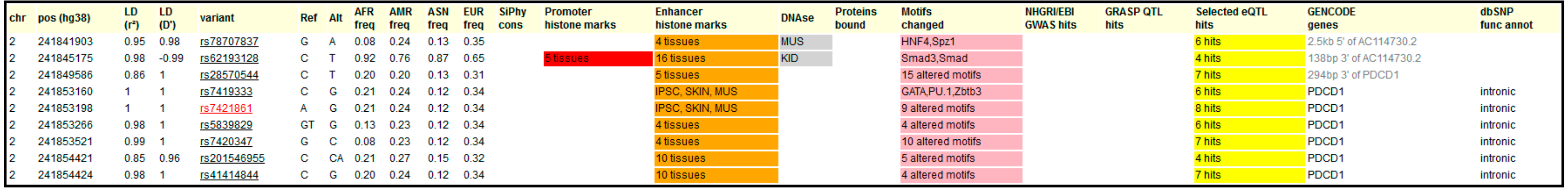
Query SNP: rs10204525 and variants with r^2 >= 0.8



chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
2	241840582	0.81	0.97	rs79245503	C	T	0.17	0.15	0.23	0.11			BLD			5 altered motifs			1 hit	3.8kb 5' of AC114730.2	
2	241846376	0.8	0.97	rs11495865	G	A	0.03	0.07	0.15	0.11			5 tissues			5 altered motifs			3 hits	1.3kb 3' of AC114730.2	
2	241848419	0.8	0.93	rs4973659	G	A	0.16	0.15	0.24	0.11						Pbx3,p300			2 hits	1.5kb 3' of PDCD1	
2	241850169	1	1	rs10204525	C	T	0.39	0.35	0.70	0.12						5 altered motifs			2 hits	PDCD1	3'-UTR
2	241851697	0.82	0.99	rs41386349	G	A	0.17	0.15	0.23	0.11			ESDR, IPSC			4 altered motifs			3 hits	PDCD1	intronic
2	241853775	0.86	1	rs79620053	C	T	0.14	0.14	0.23	0.11			7 tissues			MIF-1,Zfx			3 hits	PDCD1	intronic
2	241866859	0.83	0.94	rs80154873	T	C	0.25	0.29	0.64	0.12		THYM	9 tissues	6 tissues		PU.1,STAT			2 hits	2.7kb 5' of CXXC11	
2	241867263	0.86	0.94	rs4072221	A	G	0.43	0.30	0.64	0.12		BLD, THYM	7 tissues	THYM		GATA,Hoxa7,TAL1			1 hit	2.3kb 5' of CXXC11	
2	241868028	0.83	0.92	rs78574057	G	A	0.23	0.29	0.62	0.12		BLD, THYM, SPLN	6 tissues	THYM,LIV		CTCF,MOVO-B,Nanog			2 hits	1.6kb 5' of CXXC11	
2	241869928	0.87	0.95	rs4973697	T	C	0.24	0.28	0.63	0.12		SKIN, BRN	6 tissues			7 altered motifs			2 hits	CXXC11	intronic
2	241871050	0.84	0.95	rs28512331	G	A	0.11	0.27	0.63	0.12		THYM	9 tissues	4 tissues		BCL,NRSF			4 hits	CXXC11	intronic
2	241871053	0.83	0.94	rs28380696	A	G	0.41	0.30	0.63	0.12		THYM	9 tissues	4 tissues		Sin3Ak-20			2 hits	CXXC11	intronic
2	241871147	0.83	0.91	rs28682292	T	C	0.44	0.33	0.68	0.12		THYM	9 tissues	6 tissues		ERalpha-a,Pax-2,SEF-1			2 hits	CXXC11	intronic
2	241872131	0.88	0.96	rs28499542	C	T	0.23	0.28	0.63	0.12			7 tissues			4 altered motifs			3 hits	CXXC11	synonymous
2	241872208	0.88	0.96	rs28378061	T	C	0.23	0.28	0.63	0.12			7 tissues			7 altered motifs			3 hits	CXXC11	missense
2	241872311	0.87	0.95	rs28523279	A	T	0.34	0.29	0.63	0.12			6 tissues	BLD					2 hits	CXXC11	synonymous
2	241874009	0.88	0.96	rs28620415	G	A	0.23	0.28	0.63	0.12			BLD, SKIN			Pax-6,ZID			3 hits	185bp 3' of CXXC11	
2	241876432	0.87	0.96	rs28663478	T	C	0.34	0.29	0.61	0.12			IPSC, BLD, MUS	BLD,BLD,OVRY	CTCF	PLAG1			3 hits	2.6kb 3' of CXXC11	
2	241876445	0.87	0.96	rs28441154	A	G	0.34	0.29	0.62	0.12			IPSC, BLD, MUS	BLD,BLD,OVRY					3 hits	2.6kb 3' of CXXC11	

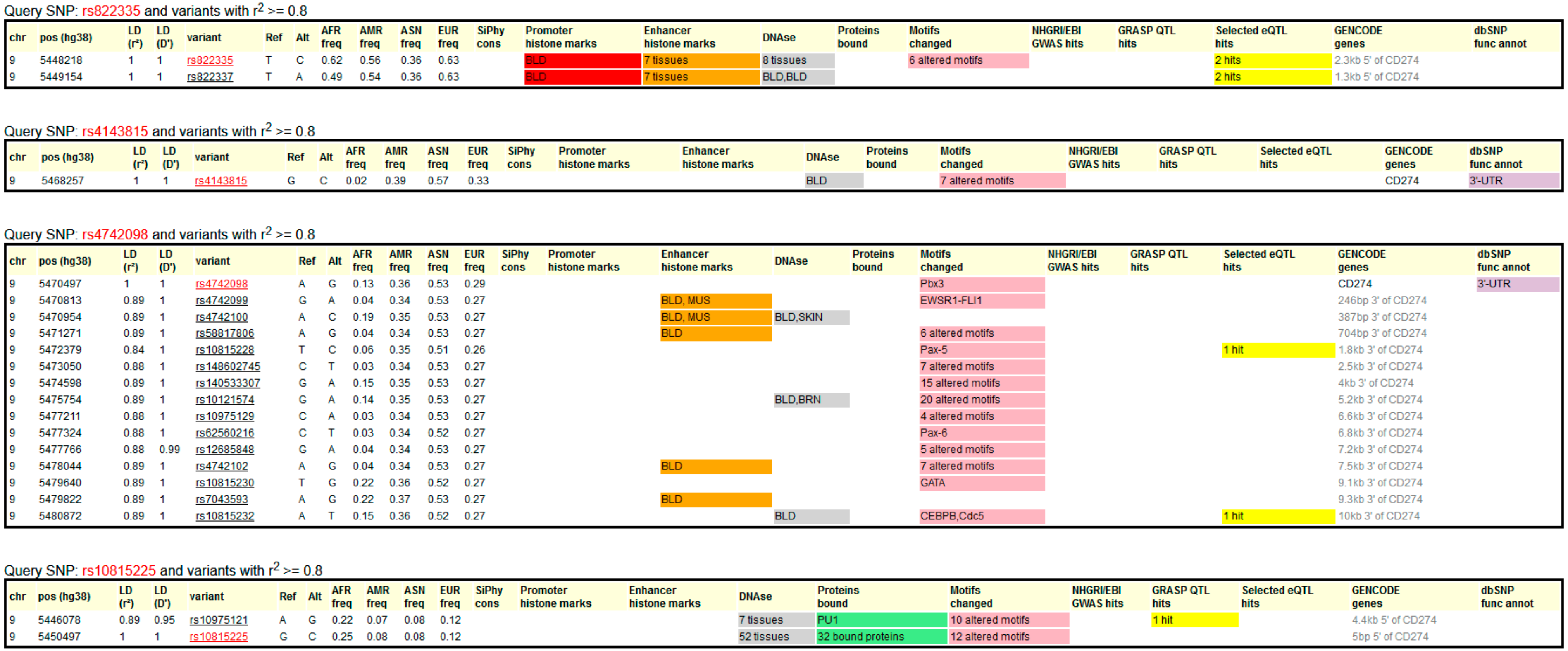
E

Query SNP: rs7421861 and variants with r^2 >= 0.8



chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
2	241841903	0.95	0.98	rs78707837	G	A	0.08	0.24	0.13	0.35			4 tissues	MUS		HNF4,Spz1			6 hits	2.5kb 5' of AC114730.2	
2	241845175	0.98	-0.99	rs62193128	C	T	0.92	0.76	0.87	0.65		5 tissues	16 tissues	KID		Smad3,Smad			4 hits	138bp 3' of AC114730.2	
2	241849586	0.86	1	rs28570544	C	T	0.20	0.20	0.13	0.31			5 tissues			15 altered motifs			7 hits	294bp 3' of PDCD1	
2	241853160	1	1	rs7419333	C	G	0.21	0.24	0.12	0.34			IPSC, SKIN, MUS			GATA,PU.1,Zbtb3			6 hits	PDCD1	intronic
2	241853198	1	1	rs7421861	A	G	0.21	0.24	0.12	0.34			IPSC, SKIN, MUS			9 altered motifs			8 hits	PDCD1	intronic
2	241853266	0.98	1	rs5839829	GT	G	0.13	0.23	0.12	0.34			4 tissues			4 altered motifs			6 hits	PDCD1	intronic
2	241853521	0.99	1	rs7420347	G	C	0.08	0.23	0.12	0.34			4 tissues			10 altered motifs			7 hits	PDCD1	intronic
2	241854421	0.85	0.96	rs201546955	C	CA	0.21	0.27	0.15	0.32			10 tissues			5 altered motifs			4 hits	PDCD1	intronic
2	241854424	0.98	1	rs41414844	C	G	0.20	0.24	0.12	0.34			10 tissues			4 altered motifs			7 hits	PDCD1	intronic

Figure S1. Linkage disequilibrium (LD) blocks generated with application of HaploReg v4.1 presenting SNPs being in strong LD (r^2>0.8) with A) rs36084323G>A (PD-1.1). B) rs11568821G>A (PD-1.3). C) rs2227981C>T (PD-1.5). D) rs10204525G>A (PD-1.6). E) rs7421861T>C.



Query SNP: rs822335 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
9	5448218	1	1	rs822335	T	C	0.62	0.56	0.36	0.63		BLD	7 tissues	8 tissues		6 altered motifs			2 hits	2.3kb 5' of CD274	
9	5449154	1	1	rs822337	T	A	0.49	0.54	0.36	0.63		BLD	7 tissues	BLD,BLD					2 hits	1.3kb 5' of CD274	

Query SNP: rs4143815 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
9	5468257	1	1	rs4143815	G	C	0.02	0.39	0.57	0.33				BLD		7 altered motifs				CD274	3'-UTR

Query SNP: rs4742098 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
9	5470497	1	1	rs4742098	A	G	0.13	0.36	0.53	0.29						Pbx3				CD274	3'-UTR
9	5470813	0.89	1	rs4742099	G	A	0.04	0.34	0.53	0.27			BLD, MUS			EWSR1-FLI1				246bp 3' of CD274	
9	5470954	0.89	1	rs4742100	A	C	0.19	0.35	0.53	0.27			BLD, MUS	BLD,SKIN						387bp 3' of CD274	
9	5471271	0.89	1	rs58817806	A	G	0.04	0.34	0.53	0.27			BLD			6 altered motifs				704bp 3' of CD274	
9	5472379	0.84	1	rs10815228	T	C	0.06	0.35	0.51	0.26						Pax-5			1 hit	1.8kb 3' of CD274	
9	5473050	0.88	1	rs148602745	C	T	0.03	0.34	0.53	0.27						7 altered motifs				2.5kb 3' of CD274	
9	5474598	0.89	1	rs140533307	G	A	0.15	0.35	0.53	0.27						15 altered motifs				4kb 3' of CD274	
9	5475754	0.89	1	rs10121574	G	A	0.14	0.35	0.53	0.27				BLD,BRN		20 altered motifs				5.2kb 3' of CD274	
9	5477211	0.88	1	rs10975129	C	A	0.03	0.34	0.53	0.27						4 altered motifs				6.6kb 3' of CD274	
9	5477324	0.88	1	rs62560216	C	T	0.03	0.34	0.52	0.27						Pax-6				6.8kb 3' of CD274	
9	5477766	0.88	0.99	rs12685848	G	A	0.04	0.34	0.53	0.27						5 altered motifs				7.2kb 3' of CD274	
9	5478044	0.89	1	rs4742102	A	G	0.04	0.34	0.53	0.27			BLD			7 altered motifs				7.5kb 3' of CD274	
9	5479640	0.89	1	rs10815230	T	G	0.22	0.36	0.52	0.27						GATA				9.1kb 3' of CD274	
9	5479822	0.89	1	rs7043593	A	G	0.22	0.37	0.53	0.27			BLD							9.3kb 3' of CD274	
9	5480872	0.89	1	rs10815232	A	T	0.15	0.36	0.52	0.27				BLD		CEBPB,Cdc5			1 hit	10kb 3' of CD274	

Query SNP: rs10815225 and variants with r^2 >= 0.8

chr	pos (hg38)	LD (r^2)	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	NHGRI/EBI GWAS hits	GRASP QTL hits	Selected eQTL hits	GENCODE genes	dbSNP func annot
9	5446078	0.89	0.95	rs10975121	A	G	0.22	0.07	0.08	0.12				7 tissues	PU1	10 altered motifs		1 hit		4.4kb 5' of CD274	
9	5450497	1	1	rs10815225	G	C	0.25	0.08	0.08	0.12				52 tissues	32 bound proteins	12 altered motifs				5bp 5' of CD274	

Figure S2. Linkage disequilibrium (LD) blocks generated with application of HaploReg v4.1 presenting SNPs being in strong LD (r^2>0.8) with rs822335C>T. rs4143815G>C. rs4742098A>G. rs10815225G>C.

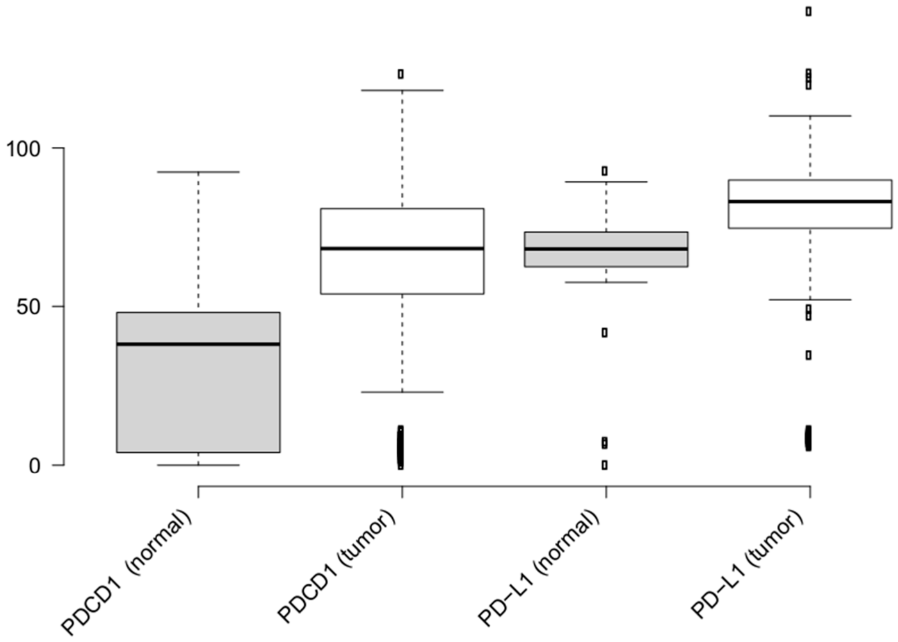


Figure S3. *PDCD1* and *PD-L1* overexpression in ccRCC tissues as compared to control tissues.