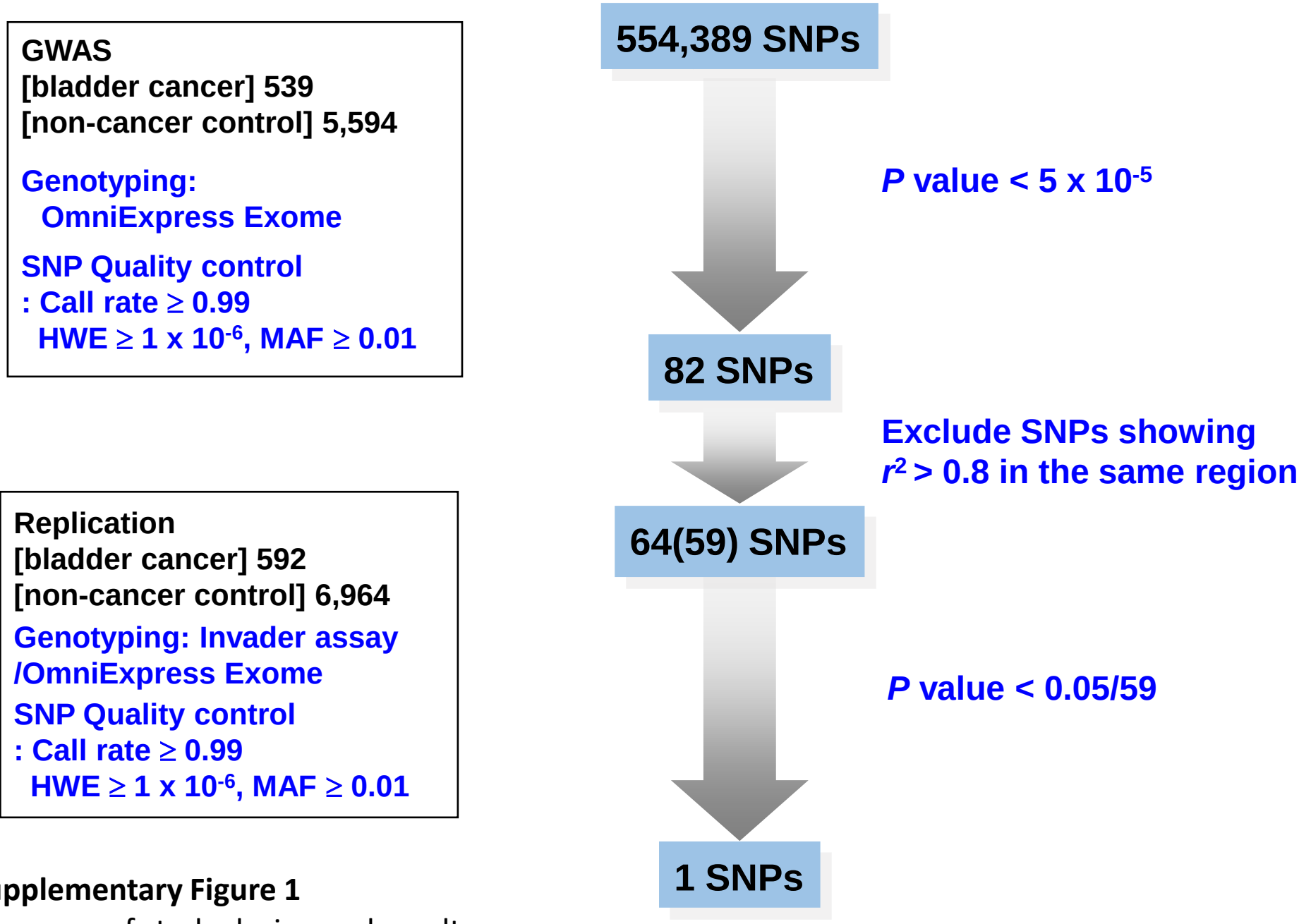
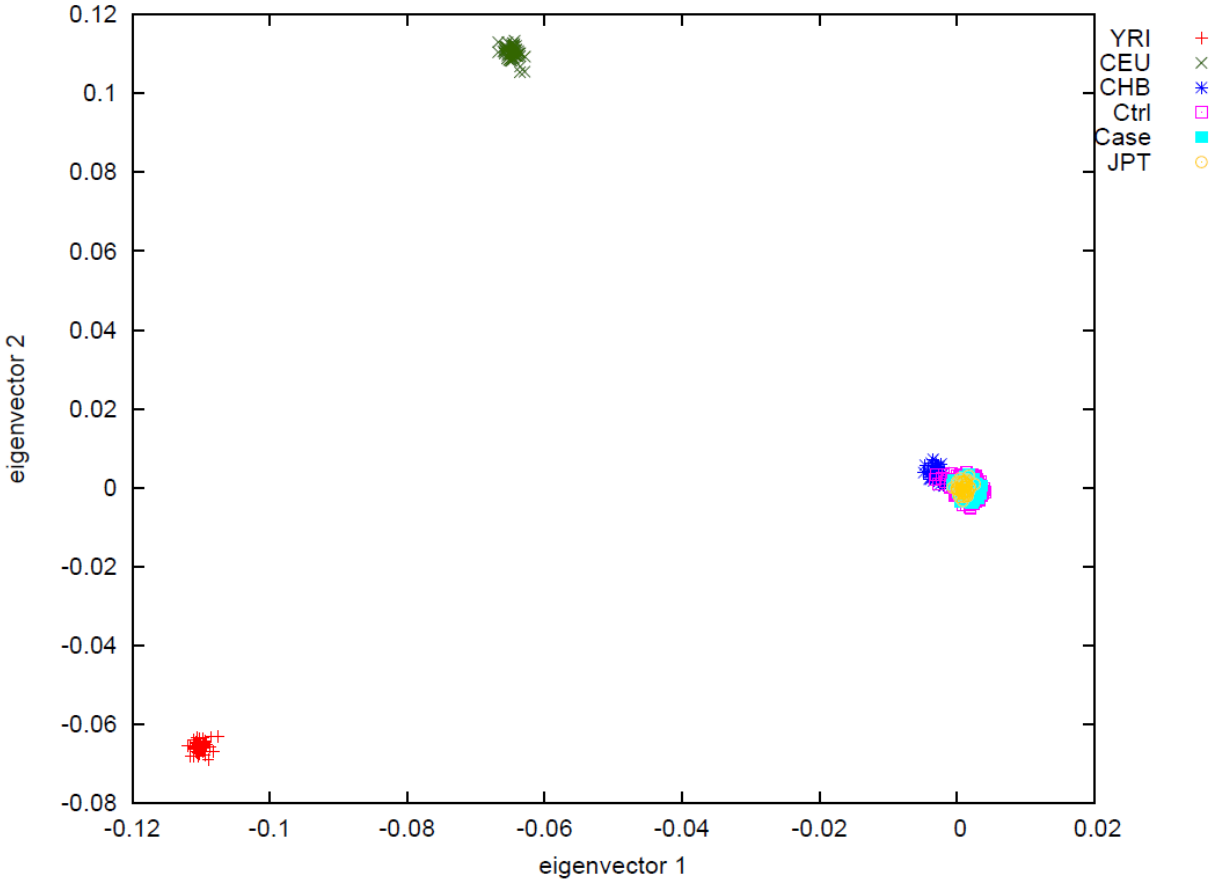
Supplementary Figure 1



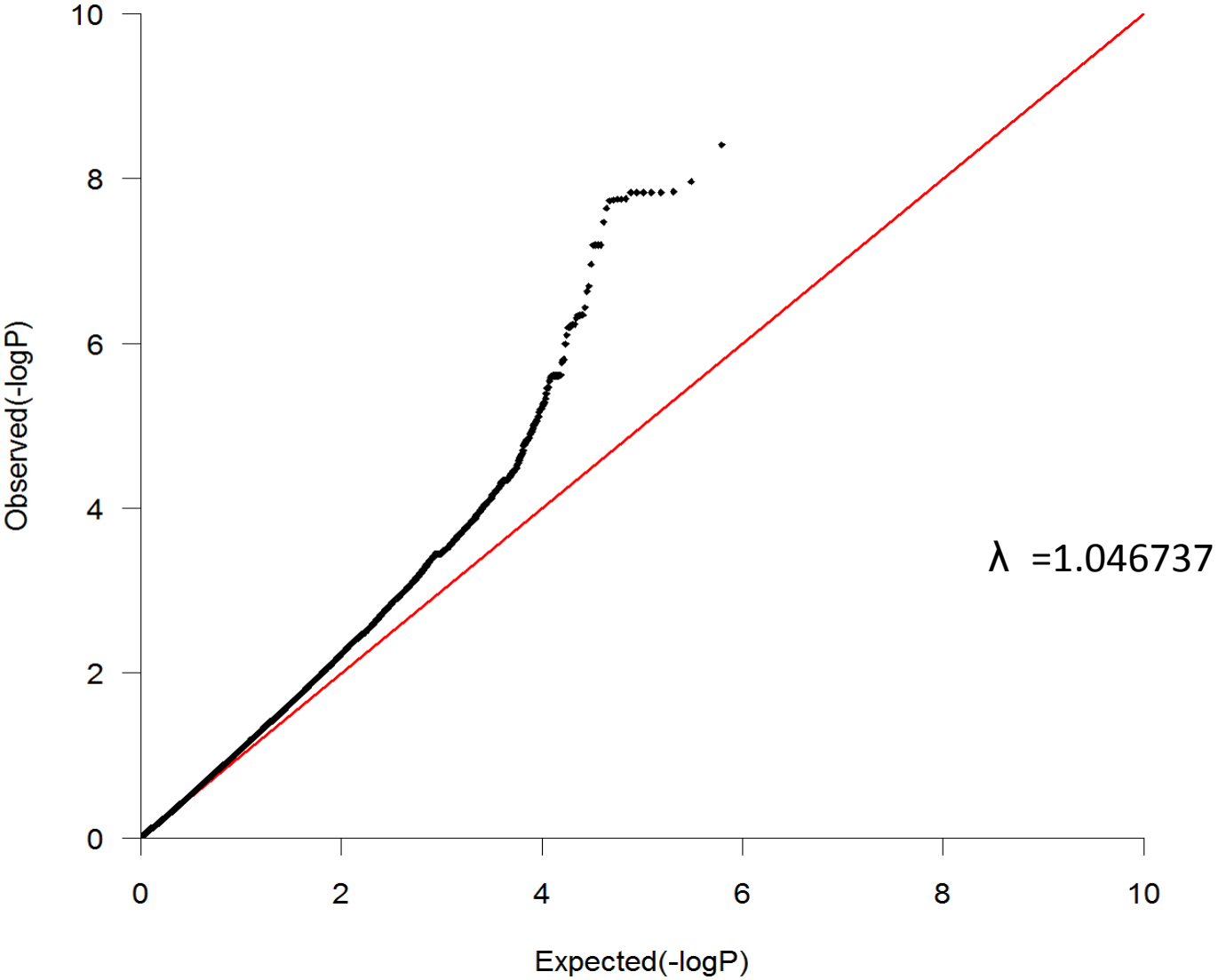
Supplementary Figure 1
Summary of study design and results.

Supplementary Figure 2



Supplementary Figure 2 Principal Component Analysis (PCA) plots showing the distribution of case and control used in the GWAS. Case and control samples of this study with four reference populations from the HapMap database which include Europeans (represented by Caucasian from UTAH, CEU), Africans (represented by Yoruba from Ibadan, YRI) and East Asians (represented by Japanese from Tokyo, JPT, and Han Chinese from Beijing, CHB). All samples used in GWAS were of Asian ancestry.

Supplementary Figure 3



Supplementary Figure 3 Quantile-quantile plots for test statistics (Cochran-Armitage trend test). Black dots are the uncorrected test statistics (λ = 1.046737). SNPs of MAF=0 or HWE < 10^{-6} in controls were excluded from analysis.

Supplementary Table 1. Characteristics of study population.

Stage	Platform	Number of samples	Female (%)	Age (mean +/- SD)
GWAS (Japanese)				
Cases[a]	Illumina Ominiexpress exome	539	19.40%	68.62 +/- 11.10
Controls[b,c]	Illumina Ominiexpress + Illumina Human Exome	5594	39.20%	56.92 +/- 14.10
Replication 1 (Japanese)				
Cases[a]	Invader assay	592	17.30%	70.16 +/- 10.99
Controls[b,d]	Illumina Ominiexpress exome	6964	47.00%	44.47+/- 18.17
Replication 2[e] (Europeans)				
Cases	Illumina Human 1M-Duo/ Illumina Human 610 Quad	3508	15.42%	66.95 +/- 7.87
Controls		5101	17.35%	65.06 +/- 8.61

[a] Bladder cancer samples were collected from 11 hospitals: Iwate Medical University, Okayama University, Kochi Medical School, Kyoto Prefectural University of Medicine, Kanazawa University, Yamagata University, University of Tsukuba, Nagoya City University, Gifu University, Kagoshima University, and Ehime University. [b]Control samples were obtained from Biobank Japan Project. Samples with previous history of cancer were exclued from analysis. [c] Control samples include healthy volunters (n=1,919) and patients with cerebral aneurysm, chronic obstructive pulmonary disease, glaucoma. [d]Control samples for replication 1 include patients with nephrolithiasis, epilepsy, atopic dermatitis, nephotic syndrome, and Grave's disease. [e]NCI-GWAS study in individuals with bladder cancer and controls of European ancestry (Rothman et al, Nat Genet, 2010).

Supplementary Table 2. Summary of GWAS

SNP	chr	Position	gene	relativeloc	case			control			*P*trend	allele	
					11	12	22	11	12	22		1	2
rs6933607	6	33743997	*LEMD2*	0	1	79	451	96	1338	4147	1.76×10^{-8}	T	C
rs1075379	6	33737800	*LEMD2*	1190	451	79	1	4146	1337	96	1.79×10^{-8}	T	C
rs943466	6	33731787	*LEMD2*	7203	1	83	447	97	1367	4110	3.39×10^{-8}	A	G
rs3828783	6	33767727	*MLN*	0	1	75	455	83	1264	4231	1.10×10^{-7}	T	C
rs942636	6	33651129	*ITPR3*	0	1	65	465	59	1162	4357	2.02×10^{-7}	A	G
rs11759011	6	33650812	*ITPR3*	0	1	64	466	56	1151	4374	2.35×10^{-7}	A	G
rs1416476	1	187500338	*FDPSP1*	-31851	3	34	494	1	177	5401	4.96×10^{-7}	T	C
rs2092449	1	210585575	*HHAT*	0	25	190	316	168	1513	3895	7.94×10^{-7}	T	C
rs2296329	6	33650743	*ITPR3*	0	405	119	7	3721	1683	176	2.87×10^{-6}	A	G
rs1048943	15	75012985	*CYP1A1*	0	370	144	17	3321	1956	304	4.09×10^{-6}	A	G
rs961266	15	54471130	*UNC13C*	0	406	118	7	4683	859	34	4.67×10^{-6}	A	G
rs334446	18	69059944	*LOC100505776*	127256	312	174	44	3690	1674	215	5.53×10^{-6}	T	C
rs16972486	15	75066008	*CSK*	-8417	10	138	383	259	1801	3519	5.80×10^{-6}	A	G
rs11543198	15	74912328	*CLK3*	0	16	140	375	283	1913	3385	6.22×10^{-6}	A	G
rs8041357	15	74869438	*ARID3B*	0	375	140	16	3386	1912	283	6.41×10^{-6}	A	G
rs1763382	10	29308480	*RPL21P93*	-120027	91	265	175	1354	2795	1432	6.89×10^{-6}	T	G
rs2257127	14	69060068	*RAD51B*	0	436	86	9	4043	1420	118	7.73×10^{-6}	A	G
rs7081804	10	29312885	*RPL21P93*	-124432	126	276	129	1007	2738	1829	7.83×10^{-6}	T	C
rs925864	2	21451176	*LOC100287183*	133595	312	190	29	3759	1649	171	8.72×10^{-6}	A	G
rs16975754	15	96419749	*LOC100507311*	276895	25	192	314	178	1574	3821	9.39×10^{-6}	A	G
rs11687850	2	21394682	*APOB*	-127737	21	174	336	127	1440	4009	9.96×10^{-6}	T	C
rs10826553	10	29300987	*RPL21P93*	-112534	124	278	129	1004	2741	1836	1.06×10^{-5}	A	G
rs11599857	10	29306940	*RPL21P93*	-118487	129	278	124	1835	2739	1005	1.11×10^{-5}	T	C
rs11637142	15	85295927	*ZNF592*	0	390	132	9	4530	995	53	1.19×10^{-5}	A	G
rs249299	16	9470037	*RPL21P119*	-219259	46	228	257	337	2009	3234	1.20×10^{-5}	A	C
rs1773877	10	29302946	*RPL21P93*	-114493	90	265	176	1329	2800	1452	1.25×10^{-5}	A	G
rs212282	4	111986708	*LOC391686*	-119723	196	252	83	2518	2441	602	1.44×10^{-5}	A	G
rs10466058	10	29312679	*RPL21P93*	-124226	128	276	127	1802	2736	1025	1.45×10^{-5}	A	G
rs4711253	6	31007081	*MUC22*	3902	33	216	282	257	1810	3514	1.47×10^{-5}	A	C
rs11637505	15	87636301	*AGBL1*	64018	17	193	320	164	1473	3925	1.47×10^{-5}	T	C
rs4812591	20	40994026	*PTPRT*	0	170	247	113	2196	2552	831	1.56×10^{-5}	A	G
rs9469583	6	33717770	*IP6K3*	-3008	30	172	329	173	1503	3905	1.62×10^{-5}	T	C
rs16937767	8	49457532	*RPL29P19*	159780	48	216	267	313	1991	3277	1.64×10^{-5}	T	C
rs2891639	8	49441535	*RPL29P19*	143783	53	216	262	335	2042	3199	1.68×10^{-5}	A	G
rs2028973	6	25138627	*CMAHP*	-7	3	49	479	47	921	4613	1.71×10^{-5}	T	C
rs8038822	15	54473080	*UNC13C*	0	293	206	31	3600	1758	222	1.75×10^{-5}	A	C
rs4924385	15	40037021	*FSIP1*	0	119	278	134	1740	2704	1132	2.00×10^{-5}	A	G
rs1193329	8	19153728	*SH2D4A*	-17353	222	239	70	2766	2339	473	2.12×10^{-5}	T	C
rs97458	2	21327635	*APOB*	-60690	334	176	21	3971	1472	130	2.12×10^{-5}	A	G
rs2071354	6	33044388	*HLA-DPA1*	0	429	96	5	4039	1438	102	2.22×10^{-5}	T	C
rs2512081	11	78819123	*ODZ4*	0	148	258	125	1940	2694	947	2.26×10^{-5}	A	G
rs34503701	6	30960221	*MUC21*	2546	11	155	365	85	1187	4307	2.29×10^{-5}	A	T
rs4280941	6	162250522	*PARK2*	0	321	192	18	3893	1536	147	2.34×10^{-5}	T	C
rs10056970	5	109405571	*LOC100289673*	184371	37	218	276	665	2443	2450	2.44×10^{-5}	A	G
rs950283	1	94567223	*ABCA4*	0	172	266	93	2295	2550	735	2.52×10^{-5}	T	C
rs4775587	15	63270157	*LOC100287243*	0	78	245	208	555	2398	2625	2.63×10^{-5}	T	C
rs10435421	7	136339058	*PSMC1P3*	-59515	359	148	24	4141	1324	103	2.67×10^{-5}	T	C
rs2512043	8	98987918	*MATN2*	0	71	250	210	1081	2700	1793	2.85×10^{-5}	A	G
rs987870	6	33042880	*HLA-DPA1*	0	429	97	5	4041	1436	104	2.89×10^{-5}	T	C
rs16958932	16	69534636	*CYB5B*	34469	246	231	54	3050	2158	372	2.90×10^{-5}	T	C
rs1773879	10	29300299	*RPL21P93*	-111846	35	206	290	593	2414	2574	3.04×10^{-5}	T	G
rs515135	2	21286057	*APOB*	-19112	8	143	380	65	1074	4442	3.31×10^{-5}	A	G
rs11999408	9	28427729	*LINGO2*	0	6	66	459	71	1146	4363	3.39×10^{-5}	A	G
rs2512080	11	78818226	*ODZ4*	0	148	260	123	1943	2691	946	3.43×10^{-5}	T	C
rs2171582	17	3364303	*SPATA22*	0	137	244	150	1745	2695	1134	3.49×10^{-5}	T	C
rs1003576	20	41003699	*PTPRT*	0	168	260	101	2242	2533	806	3.55×10^{-5}	T	C
rs6796317	3	63927739	*ATXN7*	0	372	144	15	4323	1176	82	3.63×10^{-5}	A	G
rs6942045	6	33351696	*RPL35AP4*	5437	19	150	362	278	2034	3268	3.68×10^{-5}	T	C
rs936613	8	63530880	*NKAIN3*	0	304	199	28	2740	2321	518	3.69×10^{-5}	T	C
rs1480190	8	63581067	*NKAIN3*	0	23	196	312	474	2255	2836	3.69×10^{-5}	A	G
rs9388539	6	127230163	*RSPO3*	-209885	232	237	62	2913	2213	454	3.71×10^{-5}	T	C
rs863002	1	159174920	*DARC*	0	16	118	397	53	1018	4508	3.81×10^{-5}	A	G
rs6566535	18	69110583	*LOC100505776*	76617	43	183	304	214	1805	3553	3.89×10^{-5}	A	C
rs11634320	15	85172183	*SCAND2*	-2508	8	128	395	56	959	4566	3.91×10^{-5}	A	C
rs11638290	15	85227636	*SEC11A*	0	11	135	385	59	1071	4444	3.98×10^{-5}	A	G
rs3937008	18	32618893	*MAPRE2*	0	55	243	233	908	2616	2053	4.00×10^{-5}	T	G
rs2569217	5	171860077	*SH3PXD2B*	0	218	249	64	2818	2233	520	4.06×10^{-5}	A	G
rs2925076	5	109415961	*LOC100289673*	194761	271	222	37	2430	2453	674	4.15×10^{-5}	T	C
rs10734961	12	129068616	*TMEM132C*	0	106	249	176	798	2520	2253	4.23×10^{-5}	A	G
rs1257282	14	99828776	*SETD3*	35307	1	50	480	2	298	5279	4.29×10^{-5}	A	G
rs606699	6	10358695	*LOC442161*	7049	455	72	4	5069	491	15	4.36×10^{-5}	A	G
rs884174	18	45821931	*C18orf12*	42723	324	184	23	3851	1588	141	4.42×10^{-5}	A	C
rs6134687	20	12830779	*LOC100505515*	-100309	2	97	432	21	659	4900	4.53×10^{-5}	A	C
rs17751112	15	63270333	*LOC100287243*	0	73	238	220	504	2354	2723	4.62×10^{-5}	T	C
rs7251736	19	45618902	*LRRC68*	0	371	144	16	4308	1182	90	4.63×10^{-5}	A	G
rs755228	10	76829374	*DUPD1*	-11102	136	278	117	1898	2706	977	4.63×10^{-5}	T	C
rs10765734	11	95090828	*LOC100129203*	123260	290	202	39	2554	2426	600	4.74×10^{-5}	T	C
rs3803403	15	85383145	*ALPK3*	0	391	127	10	4522	1004	53	4.77×10^{-5}	C	G
rs863006	1	159177748	*DARC*	1458	16	118	397	54	1021	4504	4.82×10^{-5}	A	G
rs1051168	15	85200520	*NMB*	0	9	131	391	59	1001	4512	4.84×10^{-5}	A	C
rs11877772	18	39396802	*LOC100301521*	-2109	227	244	59	1997	2636	948	4.93×10^{-5}	T	G
rs9962989	18	69133367	*LOC100505776*	53833	348	149	34	3946	1513	117	4.94×10^{-5}	A	G

We analyzed 539 bladder cancer cases and 5594 controls at GWAS stage. Chr.,chromosome; Postion in the NCBI Build 36.3. [a]P values were obtained from Cochrane-Armitage trend test.

Supplementary Table 3. Result of replication analyses

SNP	case			control			[a]*P*trend	[b]OR (95% C.I.)
	11	12	22	11	12	22		
rs6933607	7	119	466	91	1477	5396	0.49	1.07 (0.89-1.29)
rs3828783	6	113	473	81	1370	5512	0.64	1.05 (0.86-1.27)
rs942636	8	101	482	68	1241	5651	0.99	1.00 (0.82-1.22)
rs1416476	0	20	572	4	244	6716	0.77	1.07 (0.68-1.7)
rs2092449	23	187	382	208	1993	4755	0.040	0.85 (0.74-0.99)
rs2296329	421	139	19	4915	1859	187	0.50	0.94 (0.8-1.12)
rs961266	500	85	7	5879	1034	44	0.72	1.04 (0.84-1.29)
rs334446	379	190	21	4490	2196	275	0.96	1.00 (0.86-1.16)
rs16972486	15	165	412	280	2228	4453	0.0032	1.27 (1.08-1.49)
rs11543198	21	158	413	316	2382	4265	1.22×10^{-4}	1.36 (1.16-1.59)
rs1763382	132	289	171	1692	3449	1822	0.12	1.10 (0.98-1.24)
rs2257127	449	125	17	5174	1643	147	0.67	0.96 (0.81-1.14)
rs7081804	126	271	179	1311	3348	2305	0.10	0.90 (0.8-1.02)
rs925864	398	175	19	4627	2122	215	0.77	0.98 (0.84-1.14)
rs16975754	8	214	370	220	1982	4733	0.09	0.88 (0.75-1.02)
rs11687850	14	149	429	145	1793	5024	0.99	1.00 (0.85-1.18)
rs11637142	479	105	8	5633	1248	77	0.87	1.02 (0.84-1.24)
rs249299	54	210	327	388	2606	3969	0.044	0.87 (0.76-1)
rs4711253	32	195	364	361	2419	4183	0.61	1.04 (0.9-1.2)
rs4812591	242	259	90	2637	3270	1057	0.31	0.94 (0.83-1.06)
rs9469583	20	188	383	198	1878	4884	0.009	0.82 (0.7-0.95)
rs16937767	34	221	337	384	2487	4093	0.42	0.94 (0.82-1.08)
rs2891639	37	223	332	400	2564	3992	0.48	0.95 (0.83-1.09)
rs2028973	3	80	507	77	1161	5726	0.02	1.33 (1.06-1.66)
rs4924385	159	298	134	2058	3435	1468	0.16	1.09 (0.97-1.23)
rs1193329	308	237	46	3427	2933	602	0.17	0.91 (0.8-1.04)
rs2071354	461	121	9	5347	1511	103	0.56	0.95 (0.79-1.14)
rs2512081	214	277	101	2507	3266	1188	0.96	1.00 (0.88-1.13)
rs34503701	18	114	459	141	1616	5206	0.37	1.09 (0.91-1.3)
rs4280941	394	183	15	4858	1939	167	0.13	1.12 (0.96-1.31)
rs950283	242	254	95	2915	3128	921	0.20	1.08 (0.96-1.23)
rs4775587	50	256	285	763	3053	3148	0.053	1.14 (1-1.29)
rs10435421	421	162	8	5128	1666	155	0.43	1.07 (0.91-1.26)
rs2512043	112	285	195	1240	3413	2306	0.66	0.97 (0.86-1.1)
rs16958932	305	233	53	3731	2714	519	0.20	1.09 (0.96-1.24)
rs1773879	57	233	301	753	3029	3181	0.024	1.16 (1.02-1.32)
rs11999408	14	119	456	110	1314	5538	0.13	0.87 (0.72-1.04)
rs2171582	180	283	128	2113	3351	1474	0.89	1.01 (0.89-1.14)
rs6796317	442	139	11	5424	1437	99	0.06	1.18 (0.99-1.41)
rs6942045	26	195	371	321	2446	4190	0.28	1.08 (0.94-1.25)
rs936613	298	248	46	3496	2875	593	0.75	0.98 (0.86-1.12)
rs1480190	42	238	312	541	2784	3633	0.67	1.03 (0.9-1.18)
rs9388539	307	235	49	3562	2844	557	0.86	0.99 (0.87-1.13)
rs863002	6	109	477	79	1266	5619	1.00	1.00 (0.82-1.22)
rs6566535	22	204	363	298	2396	4267	0.72	1.03 (0.89-1.19)
rs11634320	7	105	479	79	1200	5685	0.73	0.97 (0.79-1.18)
rs11638290	9	111	472	90	1338	5531	0.99	1.00 (0.83-1.21)
rs3937008	104	263	223	1103	3290	2560	0.79	0.98 (0.87-1.11)
rs10734961	90	275	226	989	3266	2693	0.61	0.97 (0.86-1.09)
rs1257282	0	29	561	7	383	6574	0.44	1.16 (0.79-1.71)
rs606699	529	60	3	6293	652	15	0.30	1.15 (0.88-1.49)
rs884174	404	168	19	4733	2027	198	0.99	1.00 (0.86-1.17)
rs6134687	2	85	504	35	888	6038	0.40	0.91 (0.72-1.14)
rs7251736	441	141	10	5291	1560	113	0.44	1.07 (0.9-1.27)
rs755228	191	290	109	2401	3400	1163	0.19	1.08 (0.96-1.22)
rs10765734	276	239	77	3225	3018	721	0.41	1.05 (0.93-1.2)
exm1184743	465	103	7	5630	1254	79	0.97	1.00 (0.82-1.22)
rs1051168	8	104	478	81	1260	5612	0.95	1.01 (0.83-1.22)
rs11877772	208	289	95	2449	3400	1114	0.98	1.00 (0.89-1.13)

We analyzed 592 bladder cancer cases and 6,964 controls at replication stage. [a]P values were obtained from Cochrane-Armitage trend test. [b]Odd ratio with 95% confidence interval was shown using allele 1 as a reference.

Supplementary Table 4. Replication analysis in Europeans

	GWAS in Japanese, n=6112			
rs8041357	cases, n (%) N=531	controls, n (%) N=5581	OR (95% CI)	[a]*P* -value
G	172 (16.2)	2478 (22.2)	referent	
A	890 (83.8)	8684 (77.8)	1.48 (1.25-1.75)	6.41×10^{-6}
GG	16 (3.01)	283 (5.07)	referent	
AG	140 (26.4)	1912 (34.3)		
AA	375 (70.6)	3386 (60.7)	1.56 (1.28-1.89)	6.67×10^{-6}
	Replication 2 - NCI GWAS1 in Europeans, n=8609			
rs8041357	cases, n (%) N=3508	controls, n (%) N=5101	OR (95% CI)	[a,b]*P* -value
G	219 (3.12)	380 (3.72)	referent	
A	6797 (96.88)	9822 (96.28)	1.19 (1.004-1.42)	0.045
GG	8 (0.23)	6 (0.12)	referent	
AG	203 (5.79)	368 (7.21)		
AA	3297 (93.99)	4727 (92.67)	1.23 (1.03-1.47)	0.025

[a] *P* -values for an additive and recessive models. [b] Adjusted for age, sex, study center, smoking (ever/never) and significant EVs.

Supplementary Table 5. Imputation analysis of 15q24 locu

SNP	CHR	POS	Allele Risk/Non risk	Risk allele freq Case	Risk allele freq Cont.	Rsqr	OR	P-VALUE	gene	relative loc
rs59797898	15	74716080	T/C	0.8257	0.7689	0.897	1.48	1.03×10^{-5}	*SEMA7A*	0
rs7174305	15	74728998	C/G	0.8237	0.7644	0.8938	1.50	4.63×10^{-6}	*SEMA7A*	-2699
rs80343857	15	74750946	T/C	0.8384	0.7804	0.9041	1.51	5.13×10^{-6}	*UBL7*	0
rs12442548	15	74764791	A/G	0.8379	0.7807	0.8855	1.52	5.37×10^{-6}	*LOC440288*	0
rs189260882	15	74795830	C/T	0.9069	0.8714	0.638	1.78	3.61×10^{-5}	*LOC440288*	22197
rs78706301	15	74808869	C/A	0.8266	0.7706	0.8296	1.53	5.66×10^{-6}	*ARID3B*	-24679
rs12437988	15	74829821	C/T	0.8372	0.7779	0.9627	1.49	6.50×10^{-6}	*ARID3B*	-3727
rs8041357	15	74869438	T/C	0.838	0.7779	0.9997	1.47	6.41×10^{-6}	*ARID3B*	0
rs12443108	15	74895827	A/G	0.8249	0.7626	0.949	1.49	3.17×10^{-6}	*CLK3*	-4886
rs11543198	15	74912328	G/A	0.838	0.7779	1	1.47	6.22×10^{-6}	*CLK3*	0
rs75388839	15	74930402	A/G	0.8258	0.7667	0.9679	1.46	1.06×10^{-5}	*EDC3*	0
rs1048943	15	75012985	T/C	0.8323	0.7702	0.9997	1.48	4.09×10^{-6}	*CYP1A1*	0
rs17861110	15	75022463	C/G	0.8321	0.7696	0.9762	1.49	3.13×10^{-6}	*CYP1A1*	-4586
rs17861115	15	75025332	C/T	0.8416	0.7808	0.9111	1.54	1.89×10^{-6}	*CYP1A1*	-7455
rs149798731	15	75030331	C/T	0.846	0.7915	0.7724	1.61	2.37×10^{-6}	*CYP1A2*	-10853
rs16972208	15	75032587	G/A	0.8256	0.7612	0.9356	1.53	1.24×10^{-6}	*CYP1A2*	-8597
rs17861140	15	75034922	G/A	0.8251	0.7612	0.9371	1.52	1.56×10^{-6}	*CYP1A2*	-6262
rs2069514	15	75038220	G/A	0.8256	0.7615	0.9397	1.52	1.42×10^{-6}	*CYP1A2*	-2964
rs1350194	15	75052062	A/T	0.8312	0.7648	0.9521	1.55	5.80×10^{-7}	*CYP1A2*	3121
rs61620875	15	75052233	C/T	0.8312	0.7648	0.9523	1.55	5.81×10^{-7}	*CYP1A2*	3292
rs117429208	15	75058402	C/T	0.8482	0.7876	0.9812	1.51	3.73×10^{-6}	*CYP1A2*	9461
rs4488423	15	75059387	T/G	0.8483	0.7877	0.9815	1.51	3.82×10^{-6}	*CYP1A2*	10446
rs12437562	15	75060346	C/G	0.8487	0.7887	0.9861	1.50	4.71×10^{-6}	*CYP1A2*	11405
rs16972381	15	75061524	G/A	0.8488	0.7889	0.9877	1.50	4.99×10^{-6}	*CYP1A2*	12583
rs59567621	15	75062405	T/C	0.8489	0.7891	0.9892	1.50	5.25×10^{-6}	*CSK*	-12020
rs58322828	15	75063742	A/G	0.8542	0.7961	0.9739	1.51	6.24×10^{-6}	*CSK*	-10683
rs16972486	15	75066008	C/T	0.851	0.7921	0.9984	1.49	5.80×10^{-6}	*CSK*	-8417
rs56992651	15	75067012	C/T	0.8511	0.7922	0.9968	1.49	6.85×10^{-6}	*CSK*	-7413
rs58050869	15	75067625	C/T	0.8511	0.7922	0.9965	1.49	6.85×10^{-6}	*CSK*	-6800
rs77979355	15	75070518	G/A	0.8413	0.7797	0.979	1.50	3.73×10^{-6}	*CSK*	-3907

We analyzed 539 bladder cancer cases and 5581 controls at GWAS stage. Chr.,chromosome; Position in the NCBI Build 37. [a]P values were obtained from allele dosage test.