Supplementary Table 1 Comparison of somatic variants detected by target sequencing and by whole-exome sequencing (GRCh37/hg19)

DetectionType	Sample name	Chr	Start	Reference allele	Alternative allele	Gene	Annotation	VAF in target sequencing	Comment
Exome sequencing only	KU22CR	3	37061889	C	T	*MLH1*	nonsynonymous SNV	41.1	excluded by target sequencing with VAF 40-60%
Exome sequencing only	KU66	5	112175676	AG	-	*APC*	frameshift deletion	43.7	excluded by target sequencing with VAF 40-60%
Exome sequencing only	KU65	8	90967512	T	-	*NBN*	frameshift deletion	19.6	detected in 15 samples
Exome sequencing only	KU13	11	108196929	A	C	*ATM*	nonsynonymous SNV	48.3	excluded by target sequencing with VAF 40-60%
Exome sequencing only	KU22CR	12	58143257	G	C	*CDK4*	nonsynonymous SNV	42.0	excluded by target sequencing with VAF 40-60%
Exome sequencing only	KU12	17	7578291	T	G	*TP53*	splice-site variant	49.1	excluded by target sequencing with VAF 40-60%
Exome sequencing only	KU25B	17	41234534	T	C	*BRCA1*	nonsynonymous SNV		not detected by target sequencing
Exome sequencing only	KU66	17	7577093	C	T	*TP53*	nonsynonymous SNV	43.5	excluded by target sequencing with VAF 40-60%
Common	KU26	5	112176046	A	-	*APC*	frameshift deletion	19.0	
Common	KU59	5	112151262	G	A	*APC*	nonsynonymous SNV	27.7	
Common	KU61	5	112176863	C	T	*APC*	stopgain	89.2	
Common	KU68	5	112175594	A	T	*APC*	stopgain	82.4	
Common	KU22CR	7	6038813	G	A	*PMS2*	stopgain	31.1	
Common	KU41	10	89692911	G	A	*PTEN*	nonsynonymous SNV	30.7	
Common	KU64	10	89717705	C	T	*PTEN*	nonsynonymous SNV	12.5	
Common	KU65	10	89717672	C	T	*PTEN*	stopgain	26.5	
Common	KU66	10	89693003	A	-	*PTEN*	frameshift deletion	30.1	
Common	KU65	10	89717770	A	-	*PTEN*	frameshift deletion	24.6	
Common	KU66	10	89717770	A	-	*PTEN*	frameshift deletion	31.3	
Common	KU65	10	88677067	C	A	*BMPR1A*	synonymous SNV	32.8	
Common	KU14	11	108183170	C	G	*ATM*	nonsynonymous SNV	37.4	
Common	KU44	16	68844112	G	A	*CDH1*	nonsynonymous SNV	23.5	
Common	KU52	17	7577506	C	A	*TP53*	nonsynonymous SNV	30.7	
Common	KU59	17	7578442	T	C	*TP53*	nonsynonymous SNV	30.0	
Common	KU65	17	7577536	T	C	*TP53*	nonsynonymous SNV	29.1	
Common	KU65	17	7578389	G	A	*TP53*	nonsynonymous SNV	27.1	
Common	KU64	17	41247895	C	T	*BRCA1*	nonsynonymous SNV	22.7	
Common	KU09	18	48604696	G	T	*SMAD4*	synonymous SNV	23.0	
Common	KU09	18	48604697	A	G	*SMAD4*	nonsynonymous SNV	23.3	
Target sequencing only	KU65	2	48027123	T	G	*MSH6*	nonsynonymous SNV	27.8	germline in exome sequencing with matched leukocyte
Target sequencing only	KU26	9	21971122	G	A	*CDKN2A*	nonsynonymous SNV	65.2	germline in exome sequencing with matched leukocyte

VAF: variant allele frequency;SNV: single nucleotide variant

Supplementary Table 2 Tumor characteristics at CRPC diagnosis in the germline variant study (*n* = 549).

Factor	Group	All patients	Pathogenic germline *BRCA1, BRCA2, PALB2 or ATM* mutations	
			yes	no
		n = 549	*n* = 29	*n* = 520
Acquisition of castration resistance (%)	no	82 (16.9)	2 (8.0)	80 (17.4)
	yes	404 (83.1)	23 (92.0)	381 (82.6)
	NA	63	4	59
PSA at CRPC (median [IQR]) (ng/mL)		3.16 [2.23, 6.68]	3.17 [2.03, 10.25]	3.16 [2.23, 6.62]
Non-metastatic CRPC (%)	no	214 (80.8)	12 (85.7)	202 (80.5)
	yes	51 (19.2)	2 (14.3)	49 (19.5)
	NA	284	15	269
Lung metastasis at CRPC (%)	no	241 (90.9)	13 (92.9)	228 (90.8)
	yes	24 (9.1)	1 (7.1)	23 (9.2)
	NA	284	15	269
Liver metastasis at CRPC (%)	no	253 (95.5)	14 (100.0)	239 (95.2)
	yes	12 (4.5)	0 (0.0)	12 (4.8)
	NA	284	15	269
Use of ARPI (%)	no	202 (41.8)	7 (28.0)	195 (43.1)
	yes	281 (58.2)	18 (72.0)	263 (56.9)
	NA	66	4	62
Use of docetaxel (%)	no	269 (55.7)	9 (36.0)	260 (57.1)
	yes	214 (44.3)	16 (64.0)	198 (42.9)
	NA	66	4	62
Use of platinum chemotherapy (%)	no	409 (84.7)	17 (68.0)	392 (85.7)
	yes	74 (15.3)	8 (32.0)	66 (14.3)
	NA	66	4	62
Possible NE change (%)	no	318 (84.8)	15 (88.2)	303 (84.8)
	yes	57 (15.2)	2 (11.8)	55 (15.2)
	NA	174	12	162

CRPC: castration-resistant prostate cancer; ARPI: androgen receptor pathway inhibitor; NE: neuroendocrine; NA: not available

Supplementary Table 3 The list of germline mutations (GRCh37/hg19)

Chromosome	Start	Reference allele	Alternative allele	Gene	Transcript	Variant	Protein alteration	Annotation	Pathogenic or likely pathogenic by ClinVar
13	32930744	C	T	*BRCA2*	NM_000059	c.7615C>T	p.Gln2539*	stop gain	yes
13	32920978	C	T	*BRCA2*	NM_000059	c.6952C>T	p.Arg2318*	stop gain	yes
13	32920978	C	T	*BRCA2*	NM_000059	c.6952C>T	p.Arg2318*	stop gain	yes
13	32912089	CTG	C	*BRCA2*	NM_000059	c.3599_3600delGT	p.Cys1200fs	frameshift deletion	yes
13	32914065	CAATT	C	*BRCA2*	NM_000059	c.5576_5579delTTAA	p.Ile1859fs	frameshift deletion	yes
13	32912062	GA	G	*BRCA2*	NM_000059	c.3572delA	p.Lys1191fs	frameshift deletion	yes
13	32914839	AC	A	*BRCA2*	NM_000059	c.6348delC	p.Cys2117fs	frameshift deletion	yes
13	32914065	CAATT	C	*BRCA2*	NM_000059	c.5576_5579delTTAA	p.Ile1859fs	frameshift deletion	yes
13	32914065	CAATT	C	*BRCA2*	NM_000059	c.5576_5579delTTAA	p.Ile1859fs	frameshift deletion	yes
13	32911297	TAAAC	T	*BRCA2*	NM_000059	c.2808_2811delACAA	p.Ala938fs	frameshift deletion	yes
13	32912062	GA	G	*BRCA2*	NM_000059	c.3572delA	p.Lys1191fs	frameshift deletion	yes
13	32912091	G	GTT	*BRCA2*	NM_000059	c.3600_3601insTT	p.Asn1201fs	frameshift insertion	yes
13	32914065	CAATT	C	*BRCA2*	NM_000059	c.5576_5579delTTAA	p.Ile1859fs	frameshift deletion	yes
13	32914137	C	A	*BRCA2*	NM_000059	c.5645C>A	p.Ser1882*	stop gain	yes
13	32914065	CAATT	C	*BRCA2*	NM_000059	c.5576_5579delTTAA	p.Ile1859fs	frameshift deletion	yes
13	32914065	CAATT	C	*BRCA2*	NM_000059	c.5576_5579delTTAA	p.Ile1859fs	frameshift deletion	yes
13	32914065	CAATT	C	*BRCA2*	NM_000059	c.5576_5579delTTAA	p.Ile1859fs	frameshift deletion	yes
13	32913558	C	CA	*BRCA2*	NM_000059	c.5073dupA	p.Trp1692fs	frameshift insertion	yes
13	32913359	C	T	*BRCA2*	NM_000059	c.4867C>T	p.Gln1623*	stop gain	no
17	41244777	TTAAC	T	*BRCA1*	NM_007294	c.2767_2770delGTTA	p.Val923fs	frameshift deletion	yes
17	41245157	TTC	T	*BRCA1*	NM_007294	c.2389_2390delGA	p.Glu797fs	frameshift deletion	yes
16	23640993	ATG	A	*PALB2*	NM_024675	c.2480_2481delCA	p.Thr827fs	frameshift deletion	yes
16	23640959	A	G	*PALB2*	NM_024675	c.2514+2T>C		splice-site variant	yes
16	23649452	T	C	*PALB2*	NM_024675	c.49-2A>G		splice-site variant	yes
16	23649206	GACAA	G	*PALB2*	NM_024675	c.172_175delTTGT	p.Gln60fs	frameshift deletion	yes
16	23641529	TTAAGA	T	*PALB2*	NM_024675	c.1941_1945delTCTTA	p.His647fs	frameshift deletion	yes
11	108203577	CTTATA	C	*ATM*	NM_000051	c.7886_7890delTATTA	p.Ile2629fs	frameshift deletion	yes
11	108160488	C	T	*ATM*	NM_000051	c.4396C>T	p.Arg1466*	stop gain	yes
11	108100052	T	G	*ATM*	NM_000051	c.331+2T>G		splice-site variant	yes
11	108100052	T	G	*ATM*	NM_000051	c.331+2T>G		splice-site variant	yes
11	108201061	TGGA	T	*ATM*	NM_000051	c.7430_7432delGAG	p.Gly2477del	disruptive inframe deletion	no
17	46805561	C	T	*HOXB13*	NM_006361	c.395G>A	p.Gly132Glu	missense variant	yes
17	46805561	C	T	*HOXB13*	NM_006361	c.395G>A	p.Gly132Glu	missense variant	yes
17	46805561	C	T	*HOXB13*	NM_006361	c.395G>A	p.Gly132Glu	missense variant	yes
17	46805561	C	T	*HOXB13*	NM_006361	c.395G>A	p.Gly132Glu	missense variant	yes
17	46805561	C	T	*HOXB13*	NM_006361	c.395G>A	p.Gly132Glu	missense variant	yes
17	46805561	C	T	*HOXB13*	NM_006361	c.395G>A	p.Gly132Glu	missense variant	yes
17	46805906	C	A	*HOXB13*	NM_006361	c.50G>T	p.Gly17Val	missense variant	yes
17	46805561	C	T	*HOXB13*	NM_006361	c.395G>A	p.Gly132Glu	missense variant	yes
17	46805561	C	T	*HOXB13*	NM_006361	c.395G>A	p.Gly132Glu	missense variant	yes
17	59761166	C	CA	*BRIP1*	NM_032043	c.3240dupT	p.Ala1081fs	frameshift insertion	no
17	59760966	AT	A	*BRIP1*	NM_032043	c.3440delA	p.Asn1147fs	frameshift deletion	no
8	90993753	T	G	*NBN*	NM_002485	c.172-2A>C		splice-site variant	no
3	37042464	GT	G	*MLH1*	NM_000249	c.227delT	p.Val76fs	frameshift deletion	no
9	21971179	G	T	*CDKN2A*	NM_000077	c.179C>A	p.Ala60Glu	missense variant	yes

fs: frameshift; *: stop gain

Supplementary Table 4 The list of somatic mutations

Chromosome	Start	Reference allele	Alternative allele	Gene	Transcript	VAF (%)	Variant	Protein alteration	Annotation
13	32954272	-	A	*BRCA2*	NM_000059	35.6	c.9247dupA	p.Val3082fs	frameshift insertion
17	41231398	T	C	*BRCA1*	NM_007300	65.4	c.A4376G	p.Gln1459Arg	nonsynonymous SNV
16	23641023	A	C	*PALB2*	NM_024675	37.1	c.T2452G	p.Phe818Val	nonsynonymous SNV
11	108218086	G	A	*ATM*	NM_000051	18.2	c.G8665A	p.Asp2889Asn	nonsynonymous SNV
11	108115721	A	C	*ATM*	NM_000051	14.0	c.A869C	p.His290Pro	nonsynonymous SNV
11	108201068	G	-	*ATM*	NM_000051	26.9	c.7435delG	p.Glu2479fs	frameshift deletion
17	7573983	C	G	*TP53*	NM_000546	12.6	c.G1044C	p.Leu348Phe	nonsynonymous SNV
17	7578280	G	A	*TP53*	NM_000546	33.3	c.C569T	p.Pro190Leu	nonsynonymous SNV
17	7579592	T	C	*TP53*	NM_000546	22.5	c.97-2A>G		splice-site variant
17	7578446	-	G	*TP53*	NM_000546	25.9	c.483dupC	p.Ile162fs	frameshift insertion
17	7577609	C	G	*TP53*	NM_000546	71.4	c.673-1G>C		splice-site variant
17	7577568	C	A	*TP53*	NM_000546	22.9	c.G713T	p.Cys238Phe	nonsynonymous SNV
17	7579333	-	G	*TP53*	NM_000546	15.7	c.353dupC	p.Thr118fs	frameshift insertion
17	7576848	AGTACC	-	*TP53*	NM_000546	39.4	c.993_993del	p.Gln331fs	frameshift deletion
5	112175951	-	A	*APC*	NM_000038	65.7	c.4661dupA	p.Glu1554fs	frameshift insertion
5	112177265	C	-	*APC*	NM_000038	10.2	c.5974delC	p.Pro1992fs	frameshift deletion
5	112175970	A	-	*APC*	NM_000038	27.2	c.4679delA	p.Glu1560fs	frameshift deletion
10	89690827	-	G	*PTEN*	NM_000314	28.1	c.235dupG	p.Thr78fs	frameshift insertion
10	89624272	-	AA	*PTEN*	NM_000314	15.7	c.46_47insAA	p.Tyr16_Gln17delinsX	stop gain
16	68849455	ACGTAGCAGTG	-	*CDH1*	NM_004360	22.4	c.1358_1368del	p.His453fs	frameshift deletion
22	29115382	C	A	*CHEK2*	NM_007194	38.7	c.683+1G>T		splice-site variant
2	48027319	A	G	*MSH6*	NM_000179	11.4	c.A2197G	p.Met733Val	nonsynonymous SNV
2	47705512	C	T	*MSH2*	NM_000251	28.5	c.C2312T	p.Ala771Val	nonsynonymous SNV

VAF: variant allele frequency; fs: frameshift; *: stop gain; SNV: single nucleotide variant