

Supplemental Table 1. The list of variants with their respective scores for each variant classifier

Gene	DNA	Protein	Align-GVGD		Polyphen-2	CADD	MAPP		Frequency (ESP)	Domain
			Mammals ^a	3 S/P ^b			Mammals ^a	3 S/P ^b		
ATM	c.136-139 del CATT	frameshift	FS	FS	1	21.8	45.4	45.4	0	1
ATM	c.170 G>A	W57X	X	X	1	36	45.4	45.4	0	1
ATM	c.295 A>G	S99G	Class C55	Class C0	0.997	28.8	9.08	2.41	0.000154	0
ATM	c.363 delA	frameshift	FS	FS	1	36	45.4	45.4	0	1
ATM	c.544 G>C	V182L	Class C0	Class C0	0.002	12.03	10.22	4.77	0.008004	0
ATM	c.936 A>C	L312F	Class C15	Class C15	1	19.5	12.59	12.59	0	0
ATM	c.1229 T>C	V410A	Class C65	Class C25	0.434	15.88	27.75	19.81	0.00177	0
ATM	c.G1464T	W488C	Class C65	Class C65	0.653	14.15	29.05	29.05	0.000077	0
ATM	c.1810 C>T	P604S	Class C65	Class C0	0.635	15.46	17.5	4.5	0.004003	0
ATM	c.2021 A>G	H674R	Class C0	Class C0	0	4.044	6.96	3.51	0.000077	0
ATM	c.2158 C>T	R720C	Class C0	Class C0	0	10.15	3.6	2.92	0	0
ATM	c.2494 C>T	R832C	Class C0	Class C0	0	9.764	1.91	1.77	0.000154	0
ATM	c.3004 G>T	G1002C	Class C0	Class C0	0.002	8.811	3.42	6.66	0	0
ATM	c.3295 G>A	D1099N	Class C0	Class C0	0.002	9.962	2.37	1.39	0	0
ATM	c.3925 G>A	A1309T	Class C0	Class C0	0.009	15.47	8.56	4.95	0.001077	0
ATM	c.3963 G>A	M1321I	Class C0	Class C0	0.003	9.956	6.1	2.1	0	0
ATM	c.4388 T>G	F1463C	Class C65	Class C65	1	24.2	17.91	17.91	0.001154	0
ATM	c.4424 G>T	Y1475C	Class C25	Class C25	0.874	11.19	8.85	8.45	0	0
ATM	c.4724 G>A	R1575H	Class C25	Class C25	1	25.4	14.41	14.41	0	0
ATM	c.4949 A>G	N1650S	Class C0	Class C0	0	2.775	1.05	1.32	0.000077	0
ATM	c.5071 A>C	S1691R	Class C0	Class C0	0.001	9.876	3.72	4.19	0.002154	0
ATM	c.5089 A>G	T1697A	Class C0	Class C0	0.001	2.424	17.04	3.2	0.000154	0
ATM	c.5267 C>G	T1756R	Class C15	Class C0	0.054	8.393	33.46	2.63	0	0
ATM	c.5713 insT	frameshift	FS	FS	1	40	45.4	45.4	0	1
ATM	c.5882 A>G	Y1961C	Class C65	Class C65	1	23	23.02	23.02	0.000154	1
ATM	c.5890 A>G	K1964E	Class C15	Class C0	0.053	12.9	20.1	13.14	0	1
ATM	c.5906 A>T	D1969V	Class C35	Class C0	0.242	13.97	25.01	5.76	0	1
ATM	c.5932 G>T	E1978X	X	X	1	49	45.4	45.4	0	1
ATM	c.5975 A>C	K1992T	Class C65	Class C0	0.73	17.27	27.99	16.51	0.000231	1
ATM	c.6067 G>A	G2023R	Class C65	Class C25	1	30	36.52	45.39	0.002308	1
ATM	c.6088 A>G	I2030V	Class C15	Class C0	0	8.212	12.49	5.81	0.005001	1
ATM	c.6235 G>A	V2079I	Class C0	Class C0	0.002	9.681	4.05	2.45	0.006001	1
ATM	c.6437 G>C	S2146T	Class C0	Class C0	0	0.87	2.16	1.38	0.003925	1
ATM	c.6482 G>A	R2161H	Class C0	Class C0	0.503	19.29	7.16	6.29	0	1
ATM	c.6551 G>C	S2184T	Class C0	Class C0	0.109	14.82	5.08	2.65	0.000154	1
ATM	c.6574 T>G	S2192P	Class C65	Class C0	0.015	4.401	39.26	4.22	0	1
ATM	c.6820 G>A	A2274T	Class C55	Class C55	1	35	33.24	33.24	0	1

ATM	c.6860 G>C	G2287A	Class C0	Class C0	0.216	12.31	3.75	4.4	0.000077	1
ATM	c.6919 C>T	L2307F	Class C15	Class C0	0.999	22.4	12.59	7.04	0.001846	1
ATM	c.6995 T>C	L2332P	Class C25	Class C0	0.005	5.623	21.58	2.37	0.008463	1
ATM	c.6998 C>A	T2333K	Class C0	Class C0	0.005	11.5	30.09	31.23	0.000077	1
ATM	c.7004 C>T	T2335I	Class C0	Class C0	0.004	16.79	4.02	5.75	0.000231	1
ATM	c.7174 C>T	R2392W	Class C65	Class C65	1	25.1	22.31	22.31	0.000231	1
ATM	c.7187 C>G	T2396S	Class C55	Class C0	0.095	13.57	11.33	1.85	0.000231	1
ATM	c.7187C>G	T2396S	Class C55	Class C0	0.095	13.57	11.33	1.85	0.000231	1
ATM	c.7271 T>G	V2424G	Class C65	Class C65	1	26.1	23.22	23.22	0.000077	1
ATM	c.7271T>G	V2424G	Class C65	Class C65	1	26.1	23.22	23.22	0.000077	1
ATM	c.7390 T>C	C2464R	Class C65	Class C0	0.838	5.902	34.86	10.39	0.000462	1
ATM	c.7475 T>G	L2492R	Class C65	Class C45	1	24	33.02	31.81	0.000077	1
ATM	c.7636_7644del9	SRI2546_2548del3	IFD	IFD	1	19.45	40.7	34.66	0	1
ATM	c.7638-7646 del9	RIS2547-2549del	IFD	IFD	1	19.45	40.7	41.72	0	1
ATM	c.7740 A>C	R2580S	Class C0	Class C0	0.001	7.937	4.86	5.16	0	1
ATM	c.7775 C>G	S2592C	Class C65	Class C65	1	17.69	20.41	20.41	0	1
ATM	c.7867 C>A	L2623I	Class C0	Class C0	1	29.2	15.46	15.46	0	1
ATM	c.7870 T>G	C2624G	Class C65	Class C65	0.999	23.8	15.41	15.41	0	1
ATM	c.7912 T>G	W2638G	Class C65	Class C15	0.964	10.94	23.29	11.35	0	1
ATM	c.7999 A>G	M2667V	Class C15	Class C0	0.179	13.49	30.01	7.51	0	1
ATM	c.8006 T>C	I2669T	Class C65	Class C65	0.999	20.8	19.6	19.6	0	1
ATM	c.8011 -6 T>G	NA	intronic	intronic	0	2.559	0	0	0	0
ATM	c.8268_8268+4 del5	splice donor deletion	splice	splice	1	11.96	45.4	45.4	0	1
ATM	c.8269 -5 T>G	splice	splice	splice	1	6.733	45.4	45.4	0	1
ATM	c.8285 A>G	Q2762R	Class C35	Class C0	0.961	29	33.7	7.16	0	1
ATM	c.8481 T>G	F2827L	Class C15	Class C15	1	25.3	12.82	12.82	0	1
ATM	c.8494 C>T	R2832C	Class C65	Class C45	1	23.2	29.01	20.28	0	1
ATM	c.8732 C>G	T2911S	Class C0	Class C0	0.212	14.61	3.53	3.04	0	1
ATM	c.8734 A>G	R2912G	Class C65	Class C65	1	20.7	25.9	25.9	0.000231	1
ATM	c.8741 T>C	I2914T	Class C65	Class C65	1	25.1	19.6	19.6	0	1
ATM	c.8773 G>A	G2925S	Class C55	Class C55	1	35	7.5	7.5	0	1
ATM	c.8938 C>A	L2980I	Class C0	Class C0	0.148	9.526	15.46	2.88	0	1
ATM	c.9078_9079 insA	frameshift	IFD	IFD	1	43	44.95	43.98	0	1
ATM	c.9086 G>A	G3029D	Class C65	Class C15	0.011	12.26	35.86	37.66	0.000308	1
ATM	c.9139 C>T	R3047X	IFD	IFD	1	50	43.98	43.98	0	1
BARD1	c.33 G>T	Q11H	Class C0	Class C0	0.41	13.17	2.38	2.04	0.001608	0
BARD1	c.57 G>C	E19D	Class C0	Class C0	0.083	12.36	8.64	7.82	0	0
BARD1	c.73 G>C	A25P	Class C0	Class C0	0.876	15.92	10.89	10.94	0	0
BARD1	c.90 T>A	G30G	SYN	SYN	0	3.557	0.86	1.97	0.000805	1
BARD1	c.216 -21T>G	NA	intronic	intronic	0	4.3	0	0	0	0

BARD1	c.216 T>C	C53C	SYN	SYN	0	10.75	0.15	0.15	0	1
BARD1	c.221 G>T	C74F	Class C65	Class C65	1	19.7	21.32	21.32	0	1
BARD1	c.279 A>G	Q93Q	SYN	SYN	0	8.479	0.62	0.94	0.000154	1
BARD1	c.281 A>C	D94A	Class C65	Class C65	1	20	29.51	29.51	0	1
BARD1	c.326 G>A	S109N	Class C45	Class C0	0.988	17.82	14.09	3.67	0	1
BARD1	c.346C>T	H116Y	Class C35	Class C0	0.006	12.26	10.85	3.25	0.000231	1
BARD1	c.348 T>C	H116H	SYN	SYN	0	8.504	0.93	1.99	0.000308	1
BARD1	c.600 A>G	A200A	SYN	SYN	0	0.22	3.97	5.19	0	0
BARD1	c.609 A>C	G203G	SYN	SYN	0	0.36	3.1	2.25	0.008996	0
BARD1	c.632T>C	L211S	Class C35	Class C35	0.999	17.75	16.77	18.85	0	0
BARD1	c.690 C>G	D230E	Class C0	Class C0	0.028	9.815	5.24	2.86	0	0
BARD1	c.716 T>A	L239Q	Class C0	Class C0	0.014	2.114	2.22	2.87	0.000154	0
BARD1	c.722 C>G	S241C	Class C15	Class C15	0.999	13.17	1.3	2.3	0	0
BARD1	c.882 G>A	R294R	SYN	SYN	0	8.827	1.72	2.4	0	0
BARD1	c.1339 C>G	L447V	Class C25	Class C25	0.998	16.89	25.8	25.8	0.000154	0
BARD1	c.1347 A>G	Q449Q	SYN	SYN	0	7.22	0.11	2.4	0.000231	0
BARD1	c.1364 A>G	N455S	Class C45	Class C45	1	18.38	13.4	13.4	0	0
BARD1	c.1395 +50T>C	NA	intronic	intronic	0	5.779	0	0	0.001231	0
BARD1	c.1409 A>G	N470S	Class C0	Class C0	0.339	8.571	3.78	5.52	0	0
BARD1	c.1429 G>A	V477M	Class C15	Class C15	1	24.5	24.43	24.43	0	0
BARD1	c.1491 A>G	P497P	SYN	SYN	0	8.669	0.14	0.14	0	0
BARD1	c.1586 G>A	R529Q	Class C35	Class C35	0.998	10.28	14.43	14.43	0	0
BARD1	c.1613 G>A	S538N	Class C0	Class C0	0	0.007	1.25	1.43	0.000077	0
BARD1	c.1678A>G	M560V	Class C0	Class C0	0	1.319	6.31	4.65	0	0
BARD1	c.1738 G>A	E580K	Class C0	Class C0	0.041	9.977	5.4	2.55	0.004767	1
BARD1	c.1835 A>T	D612V	Class C35	Class C0	0.015	6.447	24.1	2.69	0.000077	1
BARD1	c.1904 -10T>C	NA	intronic	intronic	0	13.96	0	0	0	1
BARD1	c.1933 T>C	C645R	Class C0	Class C0	0.001	2.457	5.85	2.53	0.022913	1
BARD1	c.1955 A>G	E652G	Class C65	Class C65	1	24	28.23	28.23	0	1
BARD1	c.1957 A>G	I653V	Class C0	Class C0	0.001	9.207	5.48	6.67	0	1
BARD1	c.1972 C>T	R658C	Class C35	Class C35	0.995	24	23.61	20.58	0.00592	1
BARD1	c.1977 A>G	R659R	SYN	SYN	0	8.834	0.59	0.99	0.002384	1
BARD1	c.1989 C>T	N663N	SYN	SYN	0	7.497	0.09	0.09	0	1
BARD1	c.2002 -11C>T	NA	intronic	intronic	0	11.61	0	0	0	1
BARD1	c.2161 G>A	A721T	Class C0	Class C0	0.999	17.3	13.1	15.95	0	1
BARD1	c.2191 C>G	R731G	Class C65	Class C0	0.992	19.7	25.9	3.78	0.002076	1
BARD1	c.2212 A>G	I738V	Class C0	Class C0	0.027	9.469	5.48	6.67	0.006689	1
BARD1	c.2235 T>C	Y745Y	SYN	SYN	0	4.321	1.16	1.36	0	1
BARD1	c.2279 C>T	S760L	Class C65	Class C65	1	24.8	28.64	28.64	0	0
BARD1	c.2282 G>A	S761N	Class C0	Class C0	0.007	14.35	2.86	2.25	0.001461	0

CHEK2	c.14C>T	S5L	Class C0	Class C0	0.011	12.92	9.98	14.03	0.000077	1
CHEK2	c.74T>C	V25A	Class C0	Class C0	0	0.272	4.86	2.91	0	1
CHEK2	c.254C>T	P85L	Class C0	Class C0	0.728	12.03	26.92	2.37	0.002384	1
CHEK2	c.283C>T	R95X	X	X	1	37	45.4	45.4	0	1
CHEK2	c.320 -5T>A	NA	intronic	intronic	0	11.93	0	0	0.000384	1
CHEK2	c.349A>G	R117G	Class C65	Class C65	1	19.93	25.9	25.9	0.000154	1
CHEK2	c.381A>G	E127E	SYN	SYN	0	4.791	1.49	2.42	0	1
CHEK2	c.405delA	K135delA	FS	FS	1	24.3	45.4	45.4	0	1
CHEK2	c.410G>A	R137Q	Class C0	Class C0	0.027	12.54	11.22	2.45	0.000077	1
CHEK2	c.444+24c>T	NA	intronic	intronic	0	5.15	0	0	0.001538	1
CHEK2	c.470T>C	I157T	Class C65	Class C25	0.514	21.1	19.6	14.55	0.001615	1
CHEK2	c.474A>C	A158A	SYN	SYN	0	11.2	1.69	1.5	0	1
CHEK2	c.474A>G	A158A	SYN	SYN	0	11.18	1.69	1.5	0	1
CHEK2	c.538C>T	R180C	Class C65	Class C25	0.64	17.36	29.01	9.34	0.001077	1
CHEK2	c.539G>A	R180H	Class C25	Class C0	0.125	12.53	14.41	2.99	0	1
CHEK2	c.575C>T	S192L	Class C65	Class C15	0.899	16.82	28.64	13.99	0	1
CHEK2	c.592+50a>T	NA	intronic	intronic	0	2.498	0	0	0.002846	1
CHEK2	c.593 -14C>T	NA	intronic	intronic	0	8.971	0	0	0.000233	1
CHEK2	c.593 -20delTCT	NA	intronic	intronic	0	0	0	0	0	1
CHEK2	c.593 -45T>A	NA	intronic	intronic	0	5.903	0	0	0	1
CHEK2	c.593-6 InsCCTT	NA	intronic	intronic	0	0	0	0	0	1
CHEK2	c.651A>G	R217R	SYN	SYN	0	9.542	0.14	1.36	0	1
CHEK2	c.663C>G	I221M	Class C0	Class C0	0.953	17.5	15.7	5.14	0.000155	1
CHEK2	c.688G>T	A230S	Class C65	Class C15	0.076	19.88	23.39	6.45	0	1
CHEK2	c.715G>A	E239K	Class C55	Class C15	0.985	24	19.98	9.44	0.000154	1
CHEK2	c.727T>C	C243R	Class C65	Class C0	0.887	19.81	34.86	27.77	0.000077	1
CHEK2	c.751A>T	I251F	Class C15	Class C15	1	25.4	10.65	10.65	0	1
CHEK2	c.792+62 delAA	NA	intronic	intronic	0	0	0	0	0	1
CHEK2	c.793 -17T>C	NA	intronic	intronic	0	11.37	0	0	0	1
CHEK2	c.823G>T	E275X	X	X	1	49	45.4	45.4	0	1
CHEK2	c.847 -10C>G	NA	intronic	intronic	0	11.2	0	0	0	1
CHEK2	c.911T>C	M304T	Class C65	Class C55	0.999	19.47	25.97	18.59	0	1
CHEK2	c.917G>C	G306A	Class C55	Class C55	1	27.3	22.05	22.05	0	1
CHEK2	c.931G>A	D311N	Class C0	Class C0	0.005	14.33	13.96	3.26	0	1
CHEK2	c.967A>C	T323P	Class C35	Class C0	0.995	21.3	43.72	13.2	0	1
CHEK2	c.1036C>T	R346C	Class C65	Class C65	1	21.1	29.01	29.01	0	1
CHEK2	c.1037G>A	R346H	Class C25	Class C25	1	34	14.41	14.41	0	1
CHEK2	c.1054A>T	N352Y	Class C65	Class C65	1	25.8	20.2	20.2	0	1
CHEK2	c.1065G>A	L355L	SYN	SYN	0	4.288	0.13	0.13	0	1
CHEK2	c.1100delC	T367delC	FS	FS	1	42	45.4	45.4	0	1

CHEK2	c.1111C>T	H371Y	Class C35	Class C35	0.011	16.74	12.32	14.91	0	1
CHEK2	c.1138delCT	L380delCT	FS	FS	1	42	45.4	45.4	0	1
CHEK2	c.1182A>T	E394D	Class C35	Class C35	1	19.09	13.31	13.31	0	1
CHEK2	c.1216C>T	R406C	Class C15	Class C15	0.745	15.7	19.52	15.39	0	1
CHEK2	c.1253T>G	F418C	Class C65	Class C65	1	23.3	17.91	17.91	0	1
CHEK2	c.1263delT	L421delT	FS	FS	1	41	45.4	45.4	0	1
CHEK2	c.1276C>T	P426S	Class C65	Class C65	1	27.3	17.5	17.5	0	1
CHEK2	c.1312G>T	D438Y	Class C65	Class C25	0.999	21.2	21.06	9.42	0.000308	1
CHEK2	c.1313A>G	D438G	Class C65	Class C15	0.661	20.1	20.85	10.68	0	1
CHEK2	c.1336A>G	N446D	Class C15	Class C0	0.003	9.55	29.27	3.69	0	1
CHEK2	c.1343T>G	I448S	Class C65	Class C65	0.124	11.73	20.83	20.83	0.006766	1
CHEK2	c.1427C>T	T476M	Class C65	Class C15	1	19.54	29.5	23.02	0.000401	1
CHEK2	c.1451C>T	P484L	Class C65	Class C65	0.999	25.8	26.92	26.92	0	1
CHEK2	c.1491T>C	D497D	SYN	SYN	0	5.179	1.88	2.95	0	1
CHEK2	c.1528C>T	Q510X	X	X	1	47	45.4	45.4	0	1
CHEK2	c.1534C>G	L512V	Class C0	Class C0	0	3.416	3.1	3.33	0	1
CHEK2	c.1542 +11T>A	NA	intronic	intronic	0	2.948	0	0	0.022796	1
CHEK2	c.1542 +92A>G	NA	intronic	intronic	0	3.726	0	0	0	1
CHEK2	c.1556G>T	R519L	Class C25	Class C25	0.61	16.9	21.16	20.41	0	1
MRE11A	c.1-42G>A	NA	intronic	intronic	0	14.46	0	0	0.000077	0
MRE11A	c.18A>T	A6A	SYN	SYN	0	0.694	2.55	3.32	0	0
MRE11A	c.19C>G	L7V	Class C25	Class C0	0.004	8.845	25.8	6.38	0	0
MRE11A	c.21-12T>C	NA	intronic	intronic	0	17.76	0	0	0	0
MRE11A	c.21-17C>T	NA	intronic	intronic	0	15.68	0	0	0	0
MRE11A	c.37T>C	F13L	Class C15	Class C0	0.402	12.79	12.82	7.26	0	1
MRE11A	c.120C>T	L40L	SYN	SYN	0	5.058	1.09	3.58	0.000539	1
MRE11A	c.162T>C	F54F	SYN	SYN	0	8.823	0.11	0.11	0	1
MRE11A	c.259C>T	R87W	Class C65	Class C15	1	17.06	22.31	11.19	0	1
MRE11A	c.463C>T	R155C	Class C65	Class C35	0.89	22.4	29.01	18.41	0	1
MRE11A	c.529G>C	A177P	Class C25	Class C25	1	24.7	38.15	38.15	0	1
MRE11A	c.660-7G>T	NA	intronic	intronic	0	13.4	0	0	0	1
MRE11A	c.704A>G	D235G	Class C65	Class C65	1	25.4	20.85	20.85	0	1
MRE11A	c.826C>T	P276S	Class C0	Class C0	0.998	26.8	6.38	6.04	0	1
MRE11A	c.846-12T>C	NA	intronic	intronic	0	6.496	0	0	0	1
MRE11A	c.846-20T>G	NA	intronic	intronic	0	6.152	0	0	0	1
MRE11A	c.940C>T	L314L	SYN	SYN	0	9.282	0.13	0.13	0.000154	1
MRE11A	c.1074A>G	P358P	SYN	SYN	0	10.64	0.14	0.14	0	1
MRE11A	c.1084C>G	L362V	Class C25	Class C25	0.856	18.34	25.8	25.8	0	1
MRE11A	c.1096C>A	R366R	SYN	SYN	0	13.01	0.14	0.69	0	1
MRE11A	c.1238A>G	N413S	Class C45	Class C0	0.947	19.01	13.4	4.35	0	1

MRE11A	c.1281A>T	L427F	Class C0	Class C0	0.87	20.6	9.32	3.53	0	1
MRE11A	c.1442C>T	T481I	Class C65	Class C0	0.999	29.2	33.48	10.24	0	1
MRE11A	c.1443A>G	T481T	SYN	SYN	0	9.867	0.19	1.56	0	1
MRE11A	c.1462C>T	R488C	Class C65	Class C65	1	19.65	29.01	29.01	0.000077	0
MRE11A	c.1504C>T	R502C	Class C65	Class C35	0.028	16.07	29.01	17.61	0.000077	0
MRE11A	c.1508G>A	R503H	Class C0	Class C0	0.007	14.93	5.75	4.35	0	0
MRE11A	c.1564-18delTCT	NA	intronic	intronic	0	0	0	0	0	0
MRE11A	c.1667A>G	N556S	Class C0	Class C0	0.001	7.308	3.28	2.3	0.000462	0
MRE11A	c.1811G>A	R604H	Class C0	Class C0	0.002	5.527	2.66	2.54	0.000231	0
MRE11A	c.1852A>G	M618V	Class C15	Class C0	0.025	12.99	30.01	6.51	0.000154	0
MRE11A	c.1897C>G	R633G	Class C0	Class C0	0.001	6.68	5.3	7.63	0	0
MRE11A	c.1927-9C>A	NA	intronic	intronic	0	4.056	0	0	0	0
MRE11A	c.1995-19delTGTGTTTTGTTTT	NA	intronic	intronic	0	0	0	0	0	0
MRE11A	c.2049G>A	G683G	SYN	SYN	0	0.413	0.12	0.12	0	0
MRE11A	c.2054A>G	D685G	Class C35	Class C0	0.191	14.43	17.47	3.63	0	0
MRE11A	c.2070+2T>A	NA	intronic	intronic	0	10.44	0	0	0	0
MRE11A	c.2109delAAGAAGAAA	frameshift	IFD	IFD	0	13.73	37.49	31.21	0	0
MRE11A	c.2113A>G	R705G	Class C15	Class C0	0.1	13	12.68	3.53	0	0
NBN	c.1-2C>T	NA	intronic	intronic	0	3.515	0	0	0	0
NBN	c.37+3A>T	NA	intronic	intronic	0	7.684	0	0	0	0
NBN	c.104T>C	I35T	Class C65	Class C65	0.999	22	21.74	21.62	0	1
NBN	c.127C>T	R43*	X	X	1	25.3	45.4	45.4	0.000077	1
NBN	c.425A>G	N142S	Class C0	Class C0	0.129	11.05	7.02	4.26	0.000077	1
NBN	c.426T>C	N142N	SYN	SYN	0	9.874	0.54	1.4	0.000154	1
NBN	c.456G>A	M152I	Class C0	Class C0	0.999	24.9	21.99	21.99	0.000077	1
NBN	c.464T>C	V155A	Class C65	Class C65	0.982	20.7	27.75	27.75	0	1
NBN	c.591insTTGDe113	frameshift	FS	FS	1	28.9	45.4	45.4	0	1
NBN	c.628G>T	V210F	Class C0	Class C0	0.215	12.43	7.11	5.19	0.001001	0
NBN	c.671G>A	G224E	Class C65	Class C65	1	21.1	35.36	35.36	0	0
NBN	c.804delGT	frameshift	FS	FS	1	17.34	45.4	45.4	0	1
NBN	c.950T>A	M317K	Class C45	Class C0	0.814	14.7	31.58	25.87	0	1
NBN	c.954T>A	T318T	SYN	SYN	0	9.618	1.2	1.78	0	1
NBN	c.1065C>T	S355S	SYN	SYN	0	0.1	0.75	0.62	0	0
NBN	c.1176A>G	K392K	SYN	SYN	0	3.512	0.94	1.26	0	0
NBN	c.1202C>G	P401R	Class C0	Class C0	0.03	0.634	25.23	3.07	0	0
NBN	c.1222A>G	K408E	Class C0	Class C0	0.722	10.69	5.41	5.48	0.002768	0
NBN	c.1301C>A	T434N	Class C0	Class C0	0.698	13.87	7.15	7.28	0	0
NBN	1398-19delC	NA	intronic	intronic	0	0	0	0	0	0
NBN	c.1398-9insT	NA	intronic	intronic	0	0	0	0	0	0
NBN	c.1509T>G	N503K	Class C0	Class C0	0.835	13.76	2.24	1.41	0	0

NBN	c.1720 T>A	L574I	Class C0	Class C0	0.085	5.199	3.58	3.72	0.000615	0
NBN	c.2235-18C>T	NA	intronic	intronic	0	14.87	0	0	0.0014	0
NBN	c.2235-18C>T	NA	intronic	intronic	0	14.87	0	0	0.0014	0
RAD50	c.24C>T	S8S	SYN	SYN	0	12.06	0.12	0.12	0.000154	1
RAD50	c.113A>G	N38S	Class C45	Class C45	1	30	13.4	13.4	0	1
RAD50	c.129G>A	T43T	SYN	SYN	0	16.26	0.19	0.19	0	1
RAD50	c.250C>G	L84V	Class C25	Class C0	1	21.4	25.8	24.81	0	1
RAD50	c.260G>A	R87H	Class C25	Class C0	0.962	15.33	14.41	10.56	0.000154	1
RAD50	c.280A>C	I94L	Class C0	Class C0	0	15.56	7.01	8.94	0.003537	1
RAD50	c.379G>A	V127I	Class C25	Class C0	0.999	20.1	11.96	5.57	0.001768	1
RAD50	c.412C>T	R138X	X	X	1	36	45.4	45.4	0	1
RAD50	c.511G>T	A171S	Class C65	Class C0	0.098	13.15	23.39	2.22	0	0
RAD50	c.552-1G>A	NA	intronic	intronic	0	19.33	0	0	0	0
RAD50	c.572C>T	T191I	Class C65	Class C0	0.584	19.41	33.48	5.11	0.004536	1
RAD50	c.597A>C	Q199H	Class C15	Class C0	1	19.09	14.36	14.01	0	0
RAD50	c.671G>A	R224H	Class C0	Class C0	1	20.5	8.23	1.81	0.000615	0
RAD50	c.715G>C	E239Q	Class C0	Class C0	0.978	16.98	13.82	2.73	0	0
RAD50	c.741A>G	E247E	SYN	SYN	0	7.999	0.92	1.95	0	0
RAD50	c.756+5C>T	NA	intronic	intronic	0	1.684	0	0	0	0
RAD50	c.756+6delT	NA	intronic	intronic	0	0	0	0	0	0
RAD50	c.757-12C>A	NA	intronic	intronic	0	9.495	0	0	0	0
RAD50	c.785T>G	L262H	Class C65	Class C0	0.202	24	20.32	3.17	0.000077	0
RAD50	c.885+5G>A	NA	intronic	intronic	0	13.35	0	0	0	0
RAD50	c.921A>G	L307L	SYN	SYN	0	7.949	1.28	1.71	0.000538	0
RAD50	c.943G>T	V315L	Class C25	Class C0	0.777	21.8	20.81	4.73	0.001999	0
RAD50	c.980G>A	R327H	Class C25	Class C0	0.994	27.7	14.41	3.66	0.002384	0
RAD50	c.1094G>A	R365Q	Class C0	Class C0	0.013	15.29	5.73	2.03	0.000308	0
RAD50	c.1246-10A>G	NA	intronic	intronic	0	0.022	0	0	0	0
RAD50	c.1277A>G	Q426R	Class C35	Class C35	0.992	24.2	33.7	33.7	0.000308	0
RAD50	c.1336A>G	K446E	Class C55	Class C0	1	24.7	23.7	16.55	0.000154	0
RAD50	c.1456C>T	R486C	Class C25	Class C15	0.752	17.94	20.93	7.76	0.000077	0
RAD50	c.1670C>G	S557C	Class C15	Class C0	0.996	20	18.06	5.44	0	0
RAD50	c.1713C>T	P571P	SYN	SYN	0	9.889	0.14	0.78	0	0
RAD50	c.1794-59A>C	NA	intronic	intronic	0	12.18	0	0	0	0
RAD50	c.1875C>G	Y625X	X	X	1	37	45.4	45.4	0	1
RAD50	c.1878A>G	E626E	SYN	SYN	0	8.423	0.16	1.17	0	0
RAD50	c.1911T>A	D637E	Class C35	Class C0	0.972	21.3	23.98	5.93	0.000154	1
RAD50	c.2025C>T	D675D	SYN	SYN	0	7.498	0.15	2.97	0.028141	1
RAD50	c.2047G>A	V683I	Class C25	Class C0	0.635	15.23	11.96	1.48	0.000077	1
RAD50	c.2054delAG	Q685fs	FS	FS	1	38	45.4	45.4	0	1

RAD50	c.2091C>T	V697V	SYN	SYN	0	9.127	0.74	3.96	0.001153	1
RAD50	c.2163A>G	K721K	SYN	SYN	0	9.862	1.5	1.54	0	1
RAD50	c.2173C>T	R725W	Class C65	Class C35	0.981	23.3	22.31	18.98	0.000077	1
RAD50	c.2283A>G	I761M	Class C0	Class C0	0.212	11.68	15.7	9.86	0	0
RAD50	c.2288G>A	R763H	Class C0	Class C0	0.004	15.11	5.06	2.36	0.000154	0
RAD50	c.2397G>C	Q799H	Class C15	Class C0	0.966	24.3	14.36	5.57	0.000384	0
RAD50	c.2525T>C	V842A	Class C65	Class C0	0.048	13.26	27.75	5.55	0.000308	0
RAD50	c.2750C>T	T917I	Class C15	Class C0	0.001	12.85	6.59	2.73	0	0
RAD50	c.2837A>T	D946V	Class C35	Class C0	0.029	11.58	23.09	6.45	0	0
RAD50	c.2841T>C	I947I	SYN	SYN	0	8.619	0.1	1.42	0	0
RAD50	c.2910C>T	D970D	SYN	SYN	0	7.222	0.9	2.49	0.004204	0
RAD50	c.2938del5	L980fs	FS	FS	1	41	45.4	45.4	0	1
RAD50	c.3036+37T>C	NA	intronic	intronic	0	7.01	0	0	0	0
RAD50	c.3036+5G>A	NA	intronic	intronic	0	11.14	0	0	0.000616	0
RAD50	c.3037-3T>C	NA	intronic	intronic	0	9.988	0	0	0.006	0
RAD50	c.3153G>A	L1051L	SYN	SYN	0	7.995	0.13	1.65	0.004154	0
RAD50	c.3165-4A>T	NA	intronic	intronic	0	7.717	0	0	0.000923	0
RAD50	c.3165-8T>G	NA	intronic	intronic	0	2.824	0	0	0.002693	0
RAD50	c.3239G>A	G1080D	Class C65	Class C0	0.804	25.4	35.86	9.73	0	0
RAD50	c.3260A>G	H1087R	Class C0	Class C0	0	4.723	7.03	0.97	0	0
RAD50	c.3278G>A	R1093Q	Class C35	Class C0	0.265	17.12	14.43	2.45	0	0
RAD50	c.3311A>G	Y1104C	Class C25	Class C25	0.942	20.6	8.34	7.58	0	0
RAD50	c.3363G>T	L1121L	SYN	SYN	0	8.752	0.13	0.13	0	1
RAD50	c.3476-12delITTC	NA	intronic	intronic	0	0	0	0	0	0
RAD50	c.3496C>T	R1166W	Class C65	Class C0	0.999	24.4	22.31	4.79	0	1
RAD50	c.3790C>T	L1264F	Class C15	Class C15	1	32	12.59	12.59	0	1
RAD50	c.3836G>A	R1279H	Class C25	Class C0	0.982	33	14.41	3.6	0.000154	1
RAD50	c.3852delGAAA	E1284fs	IFD	IFD	1	38	44.34	40.7	0	1
RAD50	c.3879C>T	I1293I	SYN	SYN	0	7.962	1.86	1.91	0.003306	1
RAD50	c.3902A>G	K1301R	Class C0	Class C0	0.001	15.75	2.1	2.07	0	0
RAD51	c.-1 dupA	unknown	intronic	intronic	0	14.41	0	0	0	1
RAD51	c.-2 -19A>G	NA	intronic	intronic	0	5.169	0	0	0.000461	1
RAD51	c.108 C>T	N36N	SYN	SYN	0	9.624	2.26	1.34	0.000077	1
RAD51	c.414 T>C	H138H	SYN	SYN	0	16.07	0.12	0.54	0	1
RAD51	c.449 G>A	R150Q	Class C0	Class C0	0	9.975	2.33	1.54	0.001384	1
RAD51	c.531 -31C>T	NA	intronic	intronic	0	6.909	0	0	0	1
RAD51	c.645 G>A	R215R	SYN	SYN	0	14.49	2.4	1.06	0.000154	1
RAD51	c.671 C>G	A224G	Class C0	Class C0	0.927	35	9.35	5.58	0.000077	1
RAD51	c.720 C>G	A240A	SYN	SYN	0	10.47	2.04	1.83	0.000154	1
RAD51	c.895 +33G>A	NA	intronic	intronic	0	0	0	0	0	1

RAD51	c.895 +5delG	NA	intronic	intronic	0	0	0	0	0	1
RAD51	c.976 A>G	M326V	Class C0	Class C0	0	5.798	11.2	4.53	0	1
RINT1	c.43-12delTTC	NA	intronic	intronic	0	0	0	0	0.0092	1
RINT1	c.43-20C>G	NA	intronic	intronic	0	9.827	0	0	0	1
RINT1	c.177C>T	F59F	SYN	SYN	0	12.21	0.11	1.24	0.000154	1
RINT1	c.281C>G	T94R	Class C65	Class C65	1	20.7	37.76	37.76	0	1
RINT1	c.301A>G	K101E	Class C55	Class C0	0.935	16.27	23.7	5.97	0	1
RINT1	c.319T>G	L107V	Class C25	Class C0	0.985	16.48	25.8	7.33	0	1
RINT1	c.376C>T	H126Y	Class C0	Class C0	0.028	6.361	2.26	2.87	0.000308	1
RINT1	c.388G>A	A130T	Class C0	Class C0	0.01	9.408	8.8	3.32	0.000538	1
RINT1	c.399C>T	S133S	SYN	SYN	0	1.297	1.38	0.94	0.000077	1
RINT1	c.413C>T	A138V	Class C65	Class C0	0.234	13.92	35.49	6.61	0.000384	1
RINT1	c.501A>T	Q167H	Class C15	Class C0	0.014	13.52	14.36	3.51	0	1
RINT1	c.543C>T	T181T	SYN	SYN	0	9.692	0.19	1.51	0	1
RINT1	c.690-15A>G	NA	intronic	intronic	0	0.019	0	0	0.000077	1
RINT1	c.732C>T	I244I	SYN	SYN	0	6.717	1.15	0.68	0.006074	1
RINT1	c.736C>A	P246T	Class C0	Class C0	0.418	12.74	4.45	2.64	0	1
RINT1	c.778G>T	A260S	Class C0	Class C0	0	4.759	4.31	2.16	0	1
RINT1	c.782C>T	P261L	Class C65	Class C0	0.001	7.221	26.92	2.69	0.000154	1
RINT1	c.891T>C	P297P	SYN	SYN	0	8.597	0.14	1.81	0	1
RINT1	c.1025T>C	M342T	Class C45	Class C0	0.003	7.485	22.41	2.88	0.000308	1
RINT1	c.1121G>A	R374Q	Class C35	Class C35	1	36	14.43	14.43	0	1
RINT1	c.1256C>G	P419R	Class C0	Class C0	0.997	17.98	27.5	27.41	0.000077	1
RINT1	c.1270A>T	S424C	Class C15	Class C15	0.034	14.35	5.02	6.25	0	1
RINT1	c.1334-5delA, c.1334-1_1335delGTT	IFR	IFD	IFD	1	21.2	43.15	43.15	0	1
RINT1	c.1377C>T	A459A	SYN	SYN	0	10.56	0.23	0.23	0.000154	1
RINT1	c.1385C>T	S462L	Class C65	Class C15	0.997	18.39	28.64	16.77	0	1
RINT1	c.1428A>G	P476P	SYN	SYN	0	10.1	0.14	1.06	0	1
RINT1	c.1449G>T	M483I	Class C0	Class C0	0.105	14.59	21.99	21.99	0	1
RINT1	c.1453C>T	L485L	SYN	SYN	0	6.03	0.13	0.13	0	1
RINT1	c.1465A>G	I489V	Class C0	Class C0	0.212	16.67	9.59	9.87	0	1
RINT1	c.1519G>A	E507K	Class C55	Class C0	0.837	23.9	19.98	4.73	0.000077	1
RINT1	c.1562C>T	T521I	Class C65	Class C0	0.969	19.98	33.48	10.08	0	1
RINT1	c.1656T>C	D552D	SYN	SYN	0	9.369	0.15	1.38	0	1
RINT1	c.1672-3C>T	NA	intronic	intronic	0	12.25	0	0	0	1
RINT1	c.1949C>T	P650L	Class C65	Class C15	0.997	14.16	26.92	14.45	0	1
RINT1	c.1962G>A	T654T	SYN	SYN	0	0.01	0.91	2.3	0.001384	1
RINT1	c.1985T>C	L662S	Class C65	Class C55	0.997	23.9	22.76	19.82	0.000154	1
RINT1	c.2003T>C	F668S	Class C55	Class C0	0.015	10.68	16.4	2.6	0.003767	1
RINT1	c.2036T>C	V679A	Class C0	Class C0	0	5.292	6.42	1.83	0	1

RINT1	c.2067+6T>A	NA	intronic	intronic	0	10.85	0	0	0.008381	1
RINT1	c.2090A>G	N697S	Class C45	Class C45	0.966	21.6	13.4	13.4	0	1
RINT1	c.2128C>T	R710W	Class C65	Class C65	1	21.2	22.31	22.31	0	1
RINT1	c.2159G>T	C720F	Class C65	Class C0	0.999	23.3	21.32	17.68	0	1
RINT1	c.2176T>C	Y726H	Class C65	Class C35	0.866	24.3	16.52	17.35	0.000231	1
RINT1	c.2179T>C	F727L	Class C15	Class C15	0.998	32	12.82	12.82	0	1
RINT1	c.2184A>G	K728K	SYN	SYN	0	12.4	0.14	0.14	0.000077	1
RINT1	c.2193A>G	K731K	SYN	SYN	0	8.839	0.14	0.14	0	1
RINT1	c.2253G>T	L751L	SYN	SYN	0	6.883	0.13	1.03	0	1
RINT1	c.2276C>T	P759L	Class C25	Class C15	0.015	17.59	24.42	22.59	0.006766	1
RINT1	c.2361G>A	W787*	IFD	IFD	1	40	43.98	43.98	0	1
RINT1	c.2362C>T	P788S	Class C65	Class C0	0.999	27.8	17.5	3.71	0	1
XRCC2	c.1-1G>A	NA	Class C65	Class C65	1	13.74	36.3	36.3	0	1
XRCC2	c.40-16T>C	NA	intronic	intronic	0	14.8	0	0	0.001231	1
XRCC2	c.46G>T	A16S	Class C65	Class C0	0.584	15.35	23.39	8.62	0	1
XRCC2	c.49C>T	R17X	X	X	1	37	45.4	45.4	0	1
XRCC2	c.181C>A	L61I	Class C0	Class C0	0.604	17.26	15.46	15.46	0	1
XRCC2	c.271C>T	R91W	Class C65	Class C65	1	14.77	22.31	22.31	0	1
XRCC2	c.283A>G	I95V	Class C0	Class C0	0.013	0.61	3.96	5.81	0.000231	1
XRCC2	c.651_652delITG	C217X	IFD	IFD	1	11.76	43.98	43.98	0	1
XRCC2	c.693G>T	W231C	Class C65	Class C65	1	16.34	29.05	29.05	0	1
XRCC2	c.808T>G	F270V	Class C45	Class C45	1	19.47	17.61	17.61	0.002692	1

^aPMSAs include protein sequences from Human through *Ornithorynchus anatinus*; ^b3 S/P=3 substitutions per position: Human through 3 substitutions per position pMSA depth, which was different for each gene: *ATM*, *Brachiostoma floridae*; *BARD1*, *Xenopus*; *CHEK2*, *Danio rerio*; *MRE11A*, *Brachiostoma floridae*; *NBN*, *Anolis carolinensis*; *RAD50*, *Drosophila melanogaster*; *RAD51*, *Arabidopsis thaliana*; *RINT1*, *Strongylocentrotus purpuratus*; *XRCC2*, *Danio rerio*;

Supplemental Table 2. A listing of the regions used for the domain boundaries rMS inclusion
Summed Length

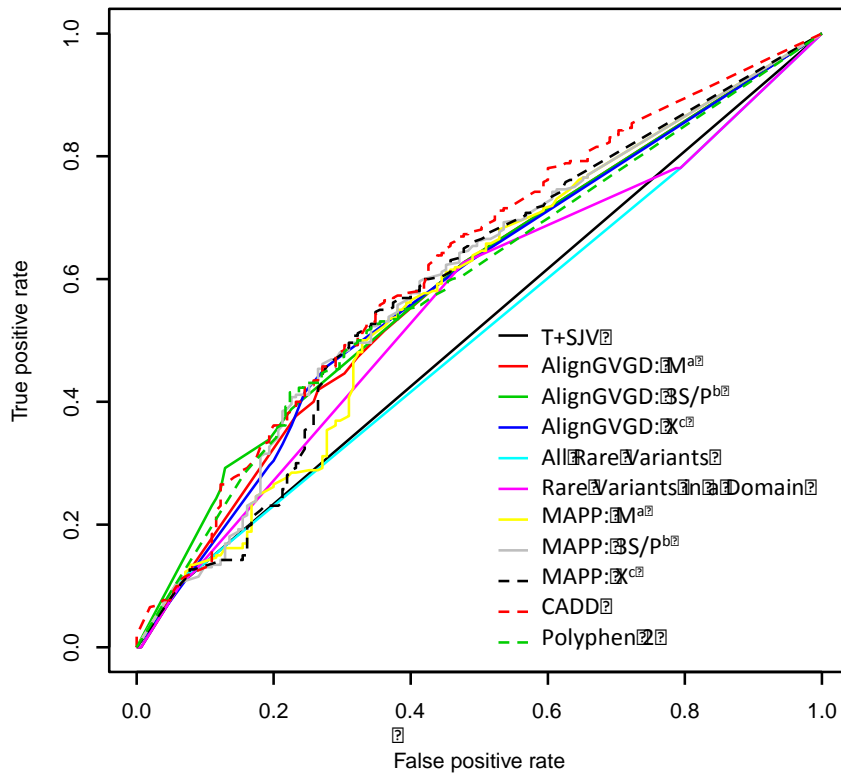
Genes	mRNA Assession	Protein Assession	Gene Length, a	Summed Length of Domain, a	Domain Region
<i>ATM</i>	NM_000051.3	NP_000042.3	3056	1,097 (36%)	1960+ (includes FAT and FATC)
<i>BARD1</i>	NM_000465.3	NP_000456.2	777	273 (35%)	26-119 (RING & BRCA1 interaction); 568-748 (BRCT)
<i>CHEK2</i>	NM_007194.3	NP_009125.1	543	543 (100%)	Entire Gene
<i>RAD51</i>	NM_002875.4	NP_002866.2	339	339 (100%)	Entire Gene
<i>RINT1</i>	NM_021930.4	NP_068749.3	792	792 (100%)	Entire Gene
<i>XRCC2</i>	NM_005431.1	NP_005422.1	280	280 (100%)	Entire Gene
<i>MRE11A</i>	NM_005591.3	NP_005582.1	708	497 (70%)	13-482 (Phosphoesterase; RAD50 interaction); 568-594 (GAR)
<i>RAD50</i>	NM_005732.3	NP_005723.2	1312	455 (35%)	3-166 (ATPase); 189-198 (MRE11A interaction); 635-734 (Zinc hook); 1117-1297 (ATPase)
<i>NBN</i>	NM_002485.4	NP_002476.2	754	369 (49%)	1-110 (FHA); 111-206 & 227-334 (BRCT); 640-662, 681-691 & 734-754 (MRE11A interaction)

Supplemental Table 3. ROC curve estimates for each variant classifier

Variant Classifier: pMSA depth	Observation	AUC
Align-GVGD: M ^a	416	0.5926
Align-GVGD: 3 S/P ^b	416	0.6025
MAPP: M ^a	416	0.5817
MAPP: 3 S/P ^b	416	0.6000
CADD	416	0.6235
Polyphen2	416	0.5941
All Rare Variants	416	0.5105
All Rare Variants in Domains	416	0.5596
Truncations and Splice Junction Variants	416	0.5193

^aM=Mammals: Human through *Ornithorynchus anatinus* pMSA depth; ^b3 S/P=3 substitutions per position: Human through 3 substitutions per position pMSA depth, which was different for each gene: *ATM*, *Brachiostoma floridae*; *BARD1*, *Xenopus*; *CHEK2*, *Latimeria chalumnae*; *MRE11A*, *Brachiostoma floridae*; *NBN*, *Anolis carolinensis*; *RAD50*, *Drosophila melanogaster*; *RAD51*, *Arabidopsis thaliana*; *RINT1*, *Strongylocentrotus purpuratus*; *XRCC2*, *Danio rerio*; ^cX=*Xenopus*: Human through *Xenopus* pMSA depth.

Supplemental Figure 1. ROC curves for each variant classifier. ^aM=Mammals: Human through *Ornithorynchus anatinus* pMSA depth; ^b3S/P: Human through 3M pMSA depth, which was different for each gene: *ATM*, *Brachiostoma floridae*; *BARD1*, *Xenopus*; *CHEK2*, *Danio rerio*; *MRE11A*, *Brachiostoma floridae*; *NBN*, *Anolis carolinensis*; *RAD50*, *Drosophila melanogaster*; *RAD51*, *Arabidopsis thaliana*; *RINT1*, *Strongylocentrotus purpuratus*; *XRCC2*, *Danio rerio*; ^cX=Xenopus: Human through *Xenopus* pMSA depth. T+SJV: Truncations and Splice Junction Variants



Supplemental Table 4. Correlations between missense analysis programs for rare key-domain missense variants. Adjusted R² and (P-values).

	MAPP ^a	CADD	Polyphen-2	Synthetic Consensus
Align-GVGD ^a	0.43(8.84X10 ⁻¹⁸)	0.19(8.40X10 ⁻⁸)	0.27(1.07X10 ⁻¹⁰)	0.64(4.07X10 ⁻³¹)
MAPP ^a	X	0.15(3.18X10 ⁻⁶)	0.26(2.49X10 ⁻¹⁰)	0.47(2.81X10 ⁻²⁰)
CADD	X	X	0.56(2.36X10 ⁻²⁵)	0.55(8.62X10 ⁻²⁵)
Polyphen-2	X	X	X	0.59(1.84X10 ⁻²⁷)

^aProtein Multiple Sequence Alignments were from Human through 3S/P

Supplemental Table 5. Combined Odds Ratio Estimates from Case-Control Mutation Screening of ATM, CHEK2, and NBN

Analysis	Distinct Variants	Control(%)	Case(%)	Adjusted OR ^a (CI)	P-value
Noncarrier	43	1,054(94.02)	1,192(91.90)	Reference	
Carrier of Rare Missense Outside of Domain	19	22(1.96)	9(0.69)	0.33(0.15-0.74)	7.28X10 ⁻³
Carrier of Truncation or Splice Junction Variant	17	6(0.54)	24(1.85)	4.20(1.69-10.44)	0.0020
Rare Missense Substitutions: MAPP					
rMS < 11	29	21(1.87)	22(1.70)	1.08(0.58-2.02)	0.8104
rMS ≥ 11	45	18(1.61)	50(3.86)	2.73(1.56-4.79)	4.55X10 ⁻⁴
Rare Missense Substitutions: Align-GVGD					
rMS < C35	46	31(2.77)	42(3.24)	1.47(0.90-2.40)	0.1234
rMS ≥ C35	28	8(0.71)	30(2.31)	3.19(1.43-7.13)	4.65X10 ⁻³
Rare Missense Substitutions: CADD					
rMS < 23	51	29(2.59)	48(3.70)	1.59(0.98-2.60)	0.0611
rMS ≥ 23	23	10(0.89)	24(1.85)	2.60(1.22-5.57)	0.0136
Rare Missense Substitutions: PolyPhen-2					
rMS < 0.9	35	22(1.96)	28(2.16)	1.32(0.73-2.38)	0.3556
rMS ≥ 0.9	39	17(1.52)	44(3.39)	2.51(1.40-4.49)	1.96X10 ⁻³
Total	153	1,121	1,297		

^aAdjusted for race/ethnicity and study center; CI=95% Confidence Interval

Supplemental Table 6. Missense Analysis Program Overlap

Variant Classifier	Control (%)	rMS/T+SJV	Case (%)	rMS/T+SJV	Adjusted OR ^a	(CI)	P-Value
Only NBN, CHEK2, and ATM							
Carrier of T+SJV	6 (0.5)		24 (1.9)		4.20	(1.69-10.44)	0.0020
One or More	23 (2.1)	3.83	52 (4.0)	2.17	2.22	(1.33-3.72)	0.0023
Two or More	13 (1.2)	2.17	37 (2.9)	1.54	2.59	(1.35-5.00)	0.0044
Three or More	11 (1.0)	1.83	31 (2.4)	1.29	2.77	(1.36-5.63)	0.0050
All Four	2 (0.2)	0.33	12 (0.9)	0.50	6.14	(1.34-28.14)	0.0194
BARD1-MRE11A-RAD50-RAD51-RINT1-XRCC2							
Carrier of T+SJV	3 (0.3)		3 (0.2)		1.07	(0.20-5.60)	0.9401
One or More	13 (1.2)	4.33	44 (3.4)	14.67	2.53	(1.33-4.83)	0.0047
Two or More	5 (0.4)	1.67	34 (2.6)	11.33	4.90	(1.87-12.84)	0.0012
Three or More	3 (0.3)	1.00	21 (1.6)	7.00	5.25	(1.52-18.14)	0.0088
All Four	0 (0.0)	0.00	8 (0.6)	2.67			<0.000 ^a
All Nine Genes							
Carrier of T+SJV	9 (0.8)		27 (2.1)		3.31	(1.53-7.16)	2.36X10 ⁻³
One or More	34 (3.0)	5.67	93 (7.2)	3.88	2.37	(1.57-3.60)	4.56X10 ⁻⁵
Two or More	18 (1.6)	3.00	70 (5.4)	2.92	3.18	(1.85-5.46)	2.68X10 ⁻⁵
Three or More	14 (1.2)	2.33	52 (4.0)	2.17	3.27	(1.77-6.04)	1.51X10 ⁻⁴
All Four	2 (0.2)	0.33	20 (1.5)	0.83	8.61	(1.96-37.81)	4.35X10 ⁻³

^a P-value from Fisher's Exact Test

Supplemental Table 7. Excluding a single gene from the 9 gene ensemble

Variant Classifier	Control (%)	rMS/T+SJV	Case (%)	rMS/T+SJV	Adjusted OR ^a	(CI)	P-Value
Dropping BARD1							
Non-carrier	1,014 (90.45)		1,140 (87.90)		Reference		
rMS Outside of Domain	50 (4.46)		44 (3.39)		0.77	(0.50-1.18)	0.2298
Carrier of T+SJV	6 (0.54)		10 (0.77)		1.80	(0.63-5.15)	0.2718
rMS Inside of Domain							
Align-GVGD	9 (0.80)	1.50	35 (2.70)	3.50	3.25	(1.52-6.96)	0.0024
MAPP	20 (1.78)	3.33	56 (4.32)	5.60	2.42	(1.42-4.15)	0.0012
CADD	15 (1.34)	2.50	42 (3.24)	4.20	2.48	(1.34-4.58)	0.0038
Polyphen2	25 (2.23)	4.17	63 (4.86)	6.30	2.13	(1.31-3.47)	0.0024
Overlap of Two	16 (1.43)	2.67	53 (4.09)	5.30	2.82	(1.58-5.06)	4.84E-04
Dropping MRE11A							
Non-carrier	994 (88.67)		1,098 (84.66)		Reference		
rMS Outside of Domain	55 (4.91)		44 (3.39)		0.75	(0.49-1.15)	0.1868
Carrier of T+SJV	9 (0.80)		27 (2.08)		3.24	(1.49-7.01)	0.0029
rMS Inside of Domain							
Align-GVGD	11 (0.98)	1.22	48 (3.70)	1.78	3.58	(1.81-7.05)	2.37E-04
MAPP	25 (2.23)	2.78	74 (5.71)	2.74	2.69	(1.67-4.34)	4.82E-05
CADD	15 (1.34)	1.67	44 (3.39)	1.63	2.68	(1.45-4.93)	1.60E-03
Polyphen2	30 (2.68)	3.33	76 (5.86)	2.81	2.25	(1.44-3.52)	3.67E-04
Overlap of Two	18 (1.61)	2.00	62 (4.78)	2.30	2.96	(1.71-5.12)	9.96E-05
Dropping RAD50							
Non-carrier	1,016 (90.63)		1,125 (86.74)		Reference		
rMS Outside of Domain	37 (3.30)		22 (1.70)		0.54	(0.31-0.94)	0.0298
Carrier of T+SJV	6 (0.54)		25 (1.93)		4.53	(1.83-11.23)	0.0011
rMS Inside of Domain							
Align-GVGD	10 (0.89)	1.67	46 (3.55)	1.84	3.79	(1.87-7.69)	2.22E-04
MAPP	24 (2.14)	4.00	72 (5.55)	2.88	2.71	(1.67-4.41)	5.85E-05
CADD	13 (1.16)	2.17	40 (3.08)	1.60	2.97	(1.55-5.68)	0.0010
Polyphen2	25 (2.23)	4.17	71 (5.47)	2.84	2.55	(1.58-4.11)	1.34E-04
Overlap of Two	17 (1.52)	2.83	60 (4.63)	2.40	3.01	(1.72-5.28)	1.18E-04
Dropping RAD51							
Non-carrier	1,000 (89.21)		1,096 (84.50)		Reference		
rMS Outside of Domain	49 (4.37)		40 (3.08)		0.75	(0.48-1.16)	0.1940
Carrier of T+SJV	9 (0.80)		27 (2.08)		3.31	(1.53-7.16)	0.0024
rMS Inside of Domain							
Align-GVGD	11 (0.98)	1.22	49 (3.78)	1.81	3.62	(1.84-7.13)	2.02E-04
MAPP	26 (2.32)	2.89	78 (6.01)	2.89	2.63	(1.65-4.21)	5.28E-05

CADD	14	(1.25)	1.56	48	(3.70)	1.78	3.05	(1.64-5.67)	4.25E-04
Polyphen2	27	(2.41)	3.00	81	(6.25)	3.00	2.57	(1.63-4.07)	5.47E-05
Overlap of Two	17	(1.52)	1.89	70	(5.40)	2.59	3.38	(1.95-5.87)	1.54E-05
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Dropping RINT1									
Non-carrier	1,009	(90.01)		1,121	(86.43)		Reference		
rMS Outside of Domain	50	(4.46)		41	(3.16)		0.72	(0.46-1.12)	0.1428
Carrier of T+SJV	9	(0.80)		27	(2.08)		3.26	(1.51-7.05)	0.0027
rMS Inside of Domain									
Align-GVGD	9	(0.80)	1.00	42	(3.24)	1.56	3.75	(1.78-7.90)	5.02E-04
MAPP	22	(1.96)	2.44	68	(5.24)	2.52	2.72	(1.64-4.52)	1.06E-04
CADD	13	(1.16)	1.44	39	(3.01)	1.44	2.85	(1.48-5.48)	0.0017
Polyphen2	24	(2.14)	2.67	69	(5.32)	2.56	2.48	(1.52-4.04)	2.69E-04
Overlap of Two	16	(1.43)	1.78	61	(4.70)	2.26	3.14	(1.77-5.58)	9.12E-05
<hr/>									
Dropping XRCC2									
Non-carrier	1,010	(90.10)		1,106	(85.27)		Reference		
rMS Outside of Domain	45	(4.01)		40	(3.08)		0.81	(0.51-1.27)	0.3561
Carrier of T+SJV	9	(0.80)		26	(2.00)		3.14	(1.44-6.81)	0.0039
rMS Inside of Domain									
Align-GVGD	11	(0.98)	1.22	45	(3.47)	1.73	3.31	(1.67-6.56)	6.11E-04
MAPP	21	(1.87)	2.33	70	(5.40)	2.69	2.84	(1.70-4.75)	6.56E-05
CADD	10	(0.89)	1.11	44	(3.39)	1.69	3.66	(1.80-7.45)	3.49E-04
Polyphen2	21	(1.87)	2.33	72	(5.55)	2.77	2.82	(1.70-4.70)	6.50E-05
Overlap of Two	13	(1.16)	1.44	63	(4.86)	2.42	3.83	(2.06-7.12)	2.11E-05

^aAdjusted for ethnicity and study center. OR=Odds Ratio; CI=95% Confidence Interval; rMS=rare missense substitution; T+SJV = Truncation or Splice Junction Variant.

Supplemental Table 8. Previously reported associated SNPs and corresponding breast cancer risk in the multiple papers used for reference in comparison of our dataset and risk estimates for non-Caucasians.

Locus	SNP	Allele ^a	Caucasian ^h			Recent African Ancestry ^j			Latina ^k				East Asian ^l		
			MAF ^b	OR ^c	Observed MAF	AF ^d	OR ^c	Observed MAF	AF ^d	Heterozygous OR	Homozygous OR	Observed MAF	AF ^d	OR ^c	Observed MAF
1p11.2	rs11249433	A/G	0.40	1.09	0.45	0.101	1.07	0.16		1.13 ^f		0.27	0.03	1.16	0.06
CASP8	rs1045485	G/C	0.13	0.97	0.12		0.97 ^g	0.05		0.97 ^g		0.06		0.97 ^g	0.00
2q35	rs13387042	A/G	0.49	0.88	0.46	0.251	1.01 ^c	0.30	0.67	0.85 ^e	0.67 ^c	0.59	0.90	0.94	0.88
SLC4A7	rs4973768	C/T	0.47	1.10	0.49	0.35	1.06	0.39		1.11 ^f		0.59	0.19	1.11	0.23
5p12	rs10941679	A/G	0.25	1.13	0.26	0.189	0.94	0.22		1.11 ^f		0.36	0.48	1.08	0.53
MAP3K1	rs889312	A/C	0.28	1.12	0.28	0.34	0.93	0.33	0.43	1.04	1.09	0.41	0.52	1.05 ^c	0.43
ESR1	rs2046210	G/A	0.41	1.08	0.38	0.627	1.02	0.58		1.18 ^f		0.33	0.34	1.27	0.39
8q24	rs13281615	A/G	0.41	1.09	0.42	0.44	1.00	0.44		1.06 ^f		0.60	0.52	1.03	0.51
CDKN2A/B	rs1011970	G/T	0.17	1.06	0.18	0.342	0.90	0.26		1.06 ^f		0.33	0.08	1.06	0.12
ANKRD16	rs2380205	C/T	0.44	0.98	0.38	0.584	1.03 ^e	0.57		0.98 ^f		0.28	0.11	0.98	0.13
ZNF365	rs10995190	G/A	0.16	0.86	0.18	0.168	1.14 ^e	0.17		0.96 ^f		0.10	0.02	1.06	0.04
ZMIZ1	rs704010	C/T	0.38	1.08	0.40	0.076	1.04	0.08		1.07 ^f		0.45	0.29	1.05 ^c	0.40
FGFR2	rs2981578	T/C	0.50 ⁱ	1.24 ⁱ	0.48	0.871	1.24	0.86		1.22 ^f		0.52		1.19 ^j	0.62
LSP1	rs3817198	T/C	0.31	1.07	0.33	0.159	0.85	0.17	0.20	1.02	1.20	0.21	0.13	1.07	0.10
11q13	rs614367	C/T	0.15	1.21	0.15	0.128	1.09	0.15		1.25 ^f		0.08		1.29	0.03
RAD51L1	rs999737	C/T	0.23	0.92	0.23	0.033	1.07 ^e	0.06	0.17	1.01	1.17	0.18	0.00	1.08	0.00
TOX3	rs3803662	G/A	0.26	1.24	0.29	0.516	0.96	0.42	0.41	1.27	1.25	0.42	0.64	1.15 ^c	0.54
COX11	rs6504950	G/A	0.28	0.94	0.28	0.346	1.11 ^e	0.35		0.96 ^f		0.21	0.07	0.98	0.15

^aMajor/Minor Allele; ^bMAF=Minor Allele Frequency in controls; ^cOR=Per allele OR; ^dAF=Risk Allele Frequency; ^eThe alternative allele was determined as the risk allele, so the reciprocal of the published OR was used; ^fLatian OR = (Caucasian OR + East Asian OR)/2; ^gMinority OR could not be found, so Caucasian was used; ^hMichailidou, K. *et al.* (2013). N=10,052 cases and 12575 controls; ⁱMeyer, K. B. *et al.* (2013). N=89,050 Caucasians, N=13,983 East Asians; ^jHuo, D. *et al.* (2012). N= 1509 cases and 1383 controls; ^kFejerman, L. *et al.* (2013). N= 603 cases and 730 controls; ^lZheng, W. *et al.* (2013). N= 6,000+ cases and 6,000+ controls