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Supplementary webappendix

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Supplement to: Paranjape T, Heneghan H, Lindner R, et al. A 3′-untranslated region KRAS variant and triple-negative breast cancer: a case-control and genetic analysis. *Lancet Oncol* 2011; published online March 23. DOI:DOI:10.1016/S1470-2045(11)70044-4.

Supplemental Table 1:Receptor status of subtypes as used in this manuscript

Breast Cancer Subtypes	ER	PR	Her-2
Luminal A	+/-	+/-	-
Luminal B	+/-	+/-	+
Her-2 +	-	-	+
Triple Negative	-	-	-

Supplemental Table 2: Description of the three separate breast cancer case-control cohorts utilized in the study

Cohort Name	Ascertainment criteria	Available receptor status	Age (years)
Yale Case-Control			
Cases	Histologically confirmed BC cases, no prior history of cancer (except non-melanoma skin cancer) from CT, USA	ER and PR	30-80
Controls	Cancer free healthy subjects or subjects who underwent surgery for histologically confirmed benign breast disease.		35-85
Irish Cohort			
Cases	Histologically confirmed BC cases from west of Ireland	ER, PR, and HER2	30-80
Controls	Healthy females, no self-reported personal history of any cancer, no family history of breast or ovarian cancer		> 60
Yale TN cohort			
TNBC cases	Patients being treated eithe at YNHH in New Haven or at Bridgeport Hospita in Bridgeport, CT.	ER, PR, and HER2	30-85
Controls	Subjects with no prior history of cancer (except non-melanoma skin cancer)		30-80

Supplemental Table 3: Demographic variables for TNBC cases and controls from the Irish cohort versus Yale cohort using Chi-square test for categorical variable such as ethnicity and t-test for the continuous variable i.e. age

A. TNBC cases

Variable	Ireland (n = 90)	Yale (n = 140)	P value
Age	52.09 (10.66)	53.2 (13.03)	0.4995
Ethnicity			<0.0001
Caucasian (n = 166)	90 (100.00)	76 (54.29)	
African American (n = 50)	0 (0.00)	50 (35.71)	
Hispanic (n = 11)	0 (0.00)	11 (7.86)	
Asian American (n = 3)	0 (0.00)	3 (2.14)	
KRAS status			0.3863
Wild type (n = 188)	71 (78.89)	117 (83.57)	
Variant (n = 42)	19 (21.11)	23 (16.43)	

B. Controls

Variable	Ireland (n = 360)	Yale (n = 570)	P value
Age	70.78 (6.78)	55.14 (11.02)	<0.0001
Ethnicity			<0.0001
Caucasian (n = 881)	360 (100.00)	521 (91.40)	
African American (n = 44)	0 (0.00)	44 (7.72)	
Hispanic (n = 5)	0 (0.00)	5 (0.88)	
KRAS status			0.9271
Wild type (n = 780)	303 (84.17)	477 (83.68)	
Variant (n = 150)	57 (15.83)	93 (16.32)	

Supplemental Table 4: Demographic variables for the TNBC cases and controls of all ages using Chi-square test for categorical variable such as ethnicity and t-test for the continuous variable i.e. age

Demographics

Variable	Controls (n = 930)	Cases (n = 230)	P value
Age	61.20 (12.26)	52.77 (12.14)	<0.0001
KRAS			0.4293
Wild type (n = 968)	780 (83.87)	188 (81.74)	
Variant (n = 192)	150 (16.13)	42 (18.26)	
Ethnicity			<0.0001
Caucasian (n = 1047)	881 (94.73)	166 (72.17)	
African American (n = 94)	44 (4.73)	50 (21.74)	
Hispanic (n = 16)	5 (0.54)	11 (4.78)	
Asian (n = 3)	0 (0.00)	3 (1.30)	

Supplemental Table 5: Demographic variables for the premenopausal TNBC cases and controls using Chi-square test for categorical variable such as ethnicity and t-test for the continuous variable i.e. age

Demographics

Variable	**Controls (n = 250)**	**Cases (n = 111)**	**P value**
Age	45.37 (4.65)	42.70 (5.80)	<0.0001
KRAS			0.0331
Wild type (n = 300)	215 (86.00)	85 (76.58)	
Variant (n = 61)	35 (14.00)	26 (23.42)	
Ethnicity			<0.0001
Caucasian (n = 297)	219 (87.60)	78 (70.27)	
African American (n = 52)	28 (11.20)	24 (21.62)	
Hispanic (n = 9)	3 (1.20)	6 (5.41)	
Asian (n = 3)	0 (0.00)	3 (2.70)	

Supplemental Table 6: Association of the *KRAS*-variant with triple negative breast cancer cases under 51 years of age versus controls in the Irish and Yale cohorts

Irish cohort*

Variable	OR	95% CI	P value
KRAS -variant	1.933	0.942 - 3.966	0.0723

* Univariate analysis against all controls

Yale cohort

Variable	OR	95% CI	P value
KRAS -variant	2.457	1.121 - 5.384	0.0248

Multivariate Analysis, controlled for race and age

Supplemental Table 7: *KRAS*-variant differentially expressed genes within the luminal progenitor and BRCA mutant signature by LIMMA analysis in the triple negative breast cancer patients

Within luminal progenitor signature					Within the BRCA mutant like signature				
nulD	gene	logFC	p	p.adj	nulD	gene	logFC	p	p.adj
W5dWOuc9PtRXFIOHmo	SORBS2	0.77024109	0.001	0.165	reF_FiFUMuQSHaOstY	DUSP6	-1.5635473	0.000	0.06
rK6quXkuZ6dLdfeAJ4	PPP1R1B	0.75990879	0.003	0.212	Zr6CDmnTPxQt.eBl94	TFPI	0.88726644	0.001	0.11
0VIkf5B1erCKhhF3r8	EPAS1	-1.5277527	0.003	0.212	33oj15BdCIfVKZ0peg	GPRC5C	-1.3698662	0.002	0.18
W047wnl3994KR9_d_o	WFDC3	0.76664801	0.003	0.212	icmjQs6EeHSHiiSdR4	OGG1	-0.8517652	0.004	0.24
3t4p_pnl6liaI2q.l0	RAB24	0.6895776	0.009	0.338	HIpqnaOBXYjCQuJZ90	GLRX2	0.47679698	0.005	0.24
NRBiFzZZNtCuhcC9Vk	AURKB	-1.5353021	0.011	0.338	NVteQjfOacrl6gsEkI	ZNF644	1.15014517	0.005	0.24
iIrh6EzRdx8DW178mE	AKR1C3	-0.8935685	0.012	0.338	fCKeqM.Snv6e1exVLU	UNC119	0.73173575	0.006	0.24
raaukoIRSnkqp6IJBE	MATK	0.49838612	0.012	0.338	fKVEOXu10U8tW5JeCE	VPREB3	0.92362289	0.025	0.47
05UqSufN4XwS53TTro	TLR5	-1.0574883	0.014	0.338	rCOmieZudsntCKtNhw	ETFB	-1.0538852	0.025	0.47
6BVx9xJ77TR4tJHRek	RAB24	-0.8803527	0.014	0.338	lAbVmX1KWR1IlAInU4	SORD	-0.8414537	0.026	0.47
TJc6LpWwNL4e7J35ek	NCALD	-1.0265287	0.015	0.338	ul6IoQqDCFHTLinpQk	AFF1	-0.7123633	0.028	0.47
ropelTUh1SsFWDHf.0	UBE2C	-0.6930782	0.029	0.498	c57uUl4hr15e36q_ug	RBM38	0.57005612	0.029	0.47
lO0dd56nvT7T57vSoU	NCALD	-1.0912361	0.031	0.498	WQpNqrg37cE9WK0lKc	WT1	0.35637204	0.029	0.47
cRUpDfl96.fUlE_If0	FHL2	-0.9577935	0.034	0.498	xnlXiCIfDUJePscuk0	PPP1CB	0.44366224	0.031	0.47
KzhYQpF167cHVUCEOI	CAMK2N1	-0.898999	0.034	0.498	HldjlBIYc9oot4Ro3Q	ZFHX3	1.05484205	0.032	0.47
f7rBCcM59S_H1LcV64	PNMA2	0.60236064	0.035	0.498	utBKruOuCki7gAbiIo	P2RY10	0.58824966	0.033	0.47
3lN_kunvr9Ut3QhSgY	C4orf7	2.14470518	0.035	0.498	HkD7UFRVdBOKp9T.e4	AHNAK	-0.5840241	0.034	0.47
xJ1J7rjZL0S0hjUj1U	COL4A5	-1.3394053	0.038	0.498	KzhYQpF167cHVUCEOI	CAMK2N1	-0.898999	0.034	0.47
No174RVAVBCigl6guU	SLPI	1.32821488	0.038	0.498	96hSuqQp6iOSne.kjw	C14orf115	0.36249749	0.035	0.47
itHUgn.0i1NNGJFXiE	CSN3	1.69487059	0.046	0.561	Z6Lq_n546eeiqGenAs	KCNN4	0.41693431	0.035	0.47
Nrlw71O3gv5VLnEb6I	MAOA	-1.2134788	0.053	0.597	Koi5Igojafuv0V4oHo	NME1	-0.469841	0.038	0.48
Nkr_pVQH8gDQOQK56Q	MAF	0.42034031	0.057	0.597	o.7wbeUVUd0VUJ3CVU	C1orf38	0.37871966	0.039	0.48
0iuaqfpUfroIEn_qP8	PIK3R1	0.37430905	0.057	0.597	WFwa905rmw_yOTsfu4	NPTN	-0.2142517	0.046	0.54
ulQV9XRfpFIRUofPwE	ITGA5	-0.31653	0.058	0.597	WLF_H_9Ek7KuOJHRD4	CA2	0.4793348	0.049	0.54
uVwtXd.AgfeatId4JY	C1QTNF1	-1.0556671	0.061	0.598	EqRaeX9VKg13UjfBQg	BPI	0.41133271	0.051	0.54
it1ISdTSgUJApSMl4Q	HSPB8	-1.1720388	0.064	0.607	ocuFeI7ASQuqnikiko	DUSP13	0.37229168	0.056	0.54
upHrr.53YSzUQyeGno	NQO1	-0.8463655	0.067	0.607	6p1QpTggjsQpuXQsVY	STARD10	-0.640911	0.060	0.54
TgCvBIxJ2i_4kdx5CE	CPE	-0.7809367	0.075	0.651	lUfeKDoXrsER_DO7jk	KLHL2	0.40422699	0.062	0.54
fMlXdRdFU745Uq0d_c	C1QTNF1	-0.9906795	0.077	0.651	NpdZqVZSJeZWpXhZF0	NME2	-1.282517	0.065	0.54
9iGSGSK2JkpYCe9Fv8	BMP4	0.49379544	0.083	0.651	ZWm_wXShfV_ygSX92A	PUS1	-0.6502441	0.065	0.54
N_SiAbV_UdVHdNKULo	KRT15	0.97895087	0.085	0.651	upHrr.53YSzUQyeGno	NQO1	-0.8463655	0.066	0.54
fprgRN4JRzv16dwp20	NKD2	-0.4423883	0.086	0.651	uwgl3oT4cTqooEnWpU	TNNT1	0.37817669	0.068	0.54
Z1Jj2hGjuC1Rnnp1CQ	C19orf33	-0.9280315	0.087	0.651	iH79A5ONA5BdEF_ni0	MYC	-0.5960534	0.068	0.54
rdxCJV5V3vopEv8gwo	PIGR	-0.7374176	0.091	0.662	rMDue4oOgDOuSu3604	ZNF644	0.30516255	0.070	0.54
ikupIMfdEnQIwS40T0	SRPK2	0.36689011	0.097	0.680	TgCvBIxJ2i_4kdx5CE	CPE	-0.7809367	0.074	0.54
r_iBJ6cKOHcLse.k.U	TMEM45A	0.72481799	0.100	0.685	opT1IU52EnhQpTjmAo	DCI	-0.8140602	0.076	0.54
					HHS16RdB7hDSQJVFSk	INPP5J	-0.6589636	0.077	0.54
					rXfTkN64kuuSmqJSIA	DDX58	0.45766024	0.077	0.54
					ExO1zRe9Pul7konrlE	GPM6B	-0.9870874	0.080	0.55
					iK8gpErpiOJasUm9eI	CRYM	0.33291961	0.083	0.55
					ZKcgDHZH10gV39_8Go	BMPR2	0.30205644	0.084	0.55
					9dX6CEoiOHV_ghI4SU	TCF7	0.83647149	0.091	0.55
					ofV37VgjeZdy5f_Kr0	FAM129B	-0.2404329	0.096	0.55
					u5IggLilqJeJep6Jfc	ORMDL3	0.90327229	0.096	0.55
					Q1KpkXSrgegB2Fkfy4	NME2	-0.5310338	0.097	0.55
					cXSOUqt53JNLCz8kgE	SSR1	0.36145747	0.098	0.55
					rpzl_RErvrjqnviOXs	ITGB5	-0.5851932	0.099	0.55

Supplemental Table 8 : Enrichment of selected literature-derived signatures with genes identified to be *KRAS*-variant differentially expressed by LIMMA analysis in the triple negative breast cancer patients

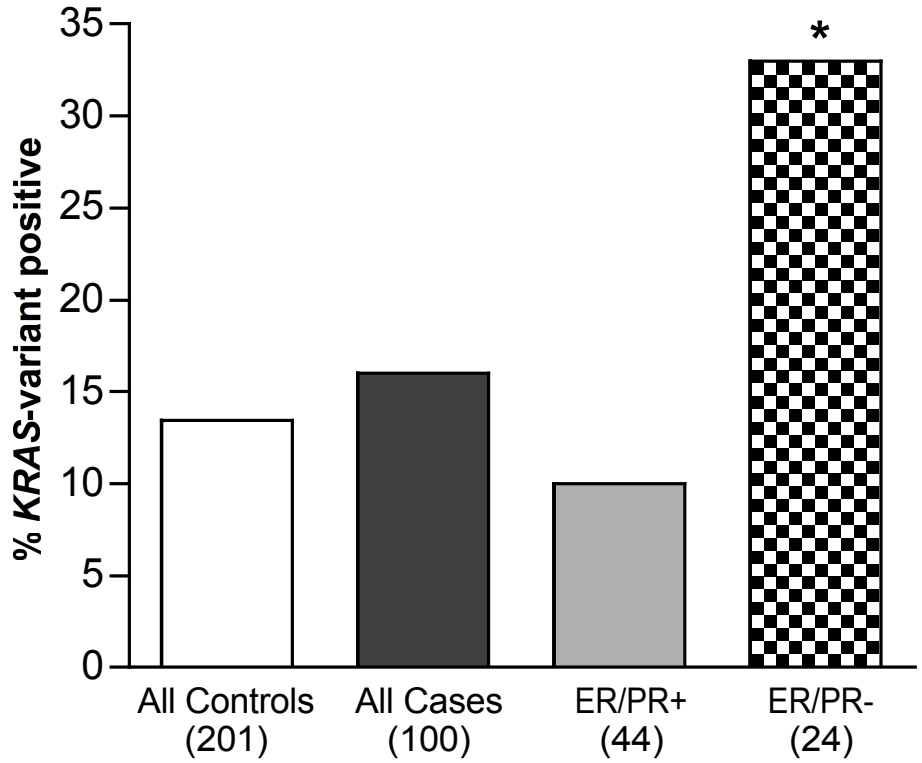
Signature	p.adj	p.raw	maxG	diff. Exp
ctnnb_bild2006	0.61600883	0.045721354	61	2
glyc_potapenko09	0.61600883	0.052426283	151	3
intrinsic_hu06	1	0.688155238	823	4
mek_dry2010	0.43918195	0.009344297	148	4
safb12_chiptargets	0.7154859	0.091338625	429	5
safb12_mrnatargets	0.64952229	0.069098116	519	6
wound.chang.down	0.51678369	0.021990795	41	2
wound.chang.up	1	0.387976745	87	1

Abbreviations : p.adj: FDR-adjusted p-value, maxG: The number of genes in the signature represented on the Illumina microarray, diff. Exp: the number of genes in that signature found to be differentially expressed.

Supplemental Table 9 : List of 50 most significantly *KRAS*-variant differentially expressed genes in the triple negative breast cancer patients identified by LIMMA analysis

nuID	gene	logFC	p-value	p.adj
xu0rGiKPdOHt8XceDM	KAL1	1.161	3.27E-006	0.060
3I179x0SbWKt66WJXg	ABHD2	1.197	3.08E-005	0.211
6p2cSR6PJ6AXXqIXE8	CHTF8	-1.762	5.41E-005	0.211
63x3kkE6KIv_7Li7qY	INSC	0.952	5.80E-005	0.211
lES9SLO6FVQLUiPlco	LIX1	0.862	7.67E-005	0.211
lno3WLlWlql4ompEqQ	BTBD3	0.892	9.30E-005	0.211
uqeojiurejf90ibdTk	SIDT2	0.704	9.45E-005	0.211
uSgLvder_5UU65g14U	CAMK2A	1.081	1.01E-004	0.211
f95JXtx_pFVFF7ye68	BAG3	-2.012	1.21E-004	0.211
rVUch7idfipSh83e9k	NA	-2.011	1.25E-004	0.211
Z6n_xvX3TtHxtHH2U0	SEL1L	1.606	1.49E-004	0.211
Bpeyv2kQv0mIgogB5c	ARMCX6	-1.394	1.62E-004	0.211
3UCajp6zXipJBv0TCo	C9orf43	0.689	1.66E-004	0.211
TYoWYd0HWC0JWR3jxc	NUP93	-1.653	1.71E-004	0.211
HkskAssd7rq8Nr_KSc	PRDM1	1.024	1.83E-004	0.211
0F8Fl88lI_7XU0efV4	TUBA1B	-0.39	1.84E-004	0.211
cKeVUq.eR61Xf9X0t8	MLH3	-1.911	1.99E-004	0.214
Kn7e.HJ5ul_hq6eE3s	ETS2	-1.661	2.27E-004	0.214
reF_FiFUMuQSHaOstY	DUSP6	-1.564	2.28E-004	0.214
ie1tIN1nl3Ulf_SV78	NA	-1.379	2.40E-004	0.214
3gq7osjnhfRUieXOVI	TNNC1	0.94	2.65E-004	0.214
rmqB9Bd3eQp7hQjlQI	CDCP1	-1.343	2.73E-004	0.214
oWlPAI4KSFnkWWXkAA	NA	-1.87	2.84E-004	0.214
ir_h054gFRKAke1Kyg	MFAP1	-1.08	3.04E-004	0.214
xU75QpS3gNep0LjXXk	NA	0.991	3.10E-004	0.214
Qepfnuoeledex5zWUg	C9orf89	-1.841	3.12E-004	0.214
KyB4s96IAUOtJH.r_I	MYNN	1.152	3.26E-004	0.214
o017n3rGln2X0laUXE	GALR3	0.764	3.34E-004	0.214
TfSd3QigkFQhvRbijY	NF2	-1.571	3.39E-004	0.214
ZHdUeJCbe61zrNBSzc	ARHGAP24	0.524	4.02E-004	0.232
NLTejns0VUSrNidBmo	HIPK1	-1.277	4.16E-004	0.232
6k8l5O.crfeULn.dL4	TMTC2	0.728	4.19E-004	0.232
ijpnYVZIUk3SE7YAI4	CMC1	-1.158	4.28E-004	0.232
W5dWOuc9PtRXFIOHmo	SORBS2	0.77	4.45E-004	0.232
3ddSK3kR1H0Tlvh3RI	TBC1D14	-1.495	4.51E-004	0.232
fadTvoHtugqBglTIXo	FAH	-1.265	4.55E-004	0.232
l0flqIh.8QdN5J1q5o	CACNG6	0.695	5.00E-004	0.244
0Ch9ek_mecjpZuSdK8	AGRN	-1.358	5.05E-004	0.244
r5VigolRK4SoglPlPU	LARP1	0.864	5.44E-004	0.247
lh1S33UT57TptL0Uh0	VPS8	-1.787	5.60E-004	0.247
6faTpd.EqRfed0r6uE	VIP	0.655	5.60E-004	0.247
QovQuig56f4ldxHnr4	NA	-1.636	5.77E-004	0.247
QdJ_t1ZKfSABUPkbuo	PWWP2B	-1.276	5.79E-004	0.247
Qp9WAlX7nu6IXQ7pE4	APEX1	-0.558	6.01E-004	0.251
l4AzSPkVV3VT16f_VU	CADM4	-1.223	6.30E-004	0.252
opX0uY0C9xuYiWWDlA	NDUFC1	-1.197	6.70E-004	0.252
QuRcd6iSQd4tSZIS4I	FAM192A	1.657	6.74E-004	0.252
rh2CVIv_u6OJKhA_eI	HMHB1	0.738	6.98E-004	0.252
xyeqUp93VRReSP3558	PCBP4	-0.742	6.99E-004	0.252
6KL5K6C6EnZIKLlk7E	MYH16	0.77	7.04E-004	0.252

Supplemental Figure 1: *KRAS*-variant in ER/PR+ versus ER/PR- premenopausal breast cancer patients



Supplemental Figure 2: Gene expression signatures associated with the *KRAS*-variant in triple negative breast cancer patient tumors