The expression of miRNAs is associated with tumour genome instability and predicts the outcome of ovarian cancer patients treated with platinum agents

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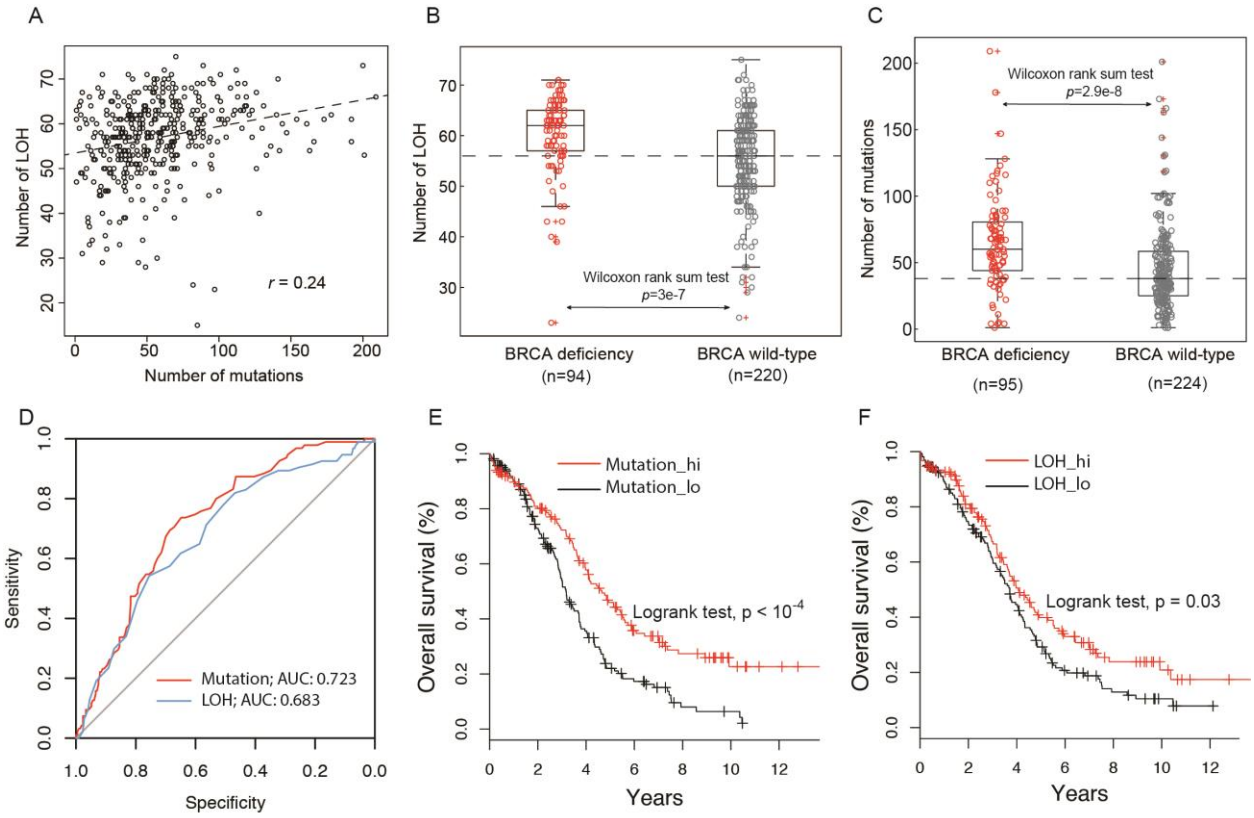
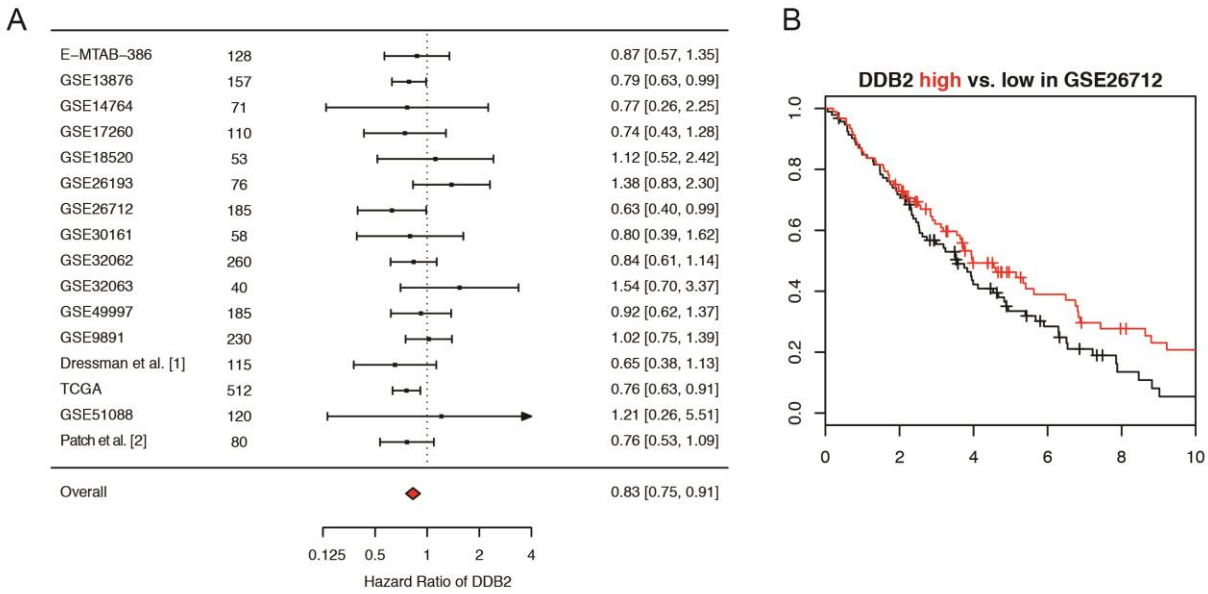


Supplementary Figure 1. Defining the appropriate measures for genome instability in ovarian cancer. (**A**) The number of mutations is correlated with the number of LOH in ovarian cancer (r=0.24). (**B**) The number of LOH is significantly correlated with *BRCA1/2* deficiency (including germline or somatic mutations and epigenetic siliencing events of *BRCA1/2*) in ovarian cancer genome. (**C**) The number of mutations is significantly correlated with *BRCA1/2* deficiency in ovarian cancer genome ($p < 0.01$). (**D**) ROC curves showing the predictive performance using the frequency of mutation and LOH to identify BRCA deficient tumors. (**E**) Kaplan-Meier overall survival curves showing the association between mutation freuqncy (high vs. low) and clinical outcome of ovarian cancer. (**F**) Kaplan-Meier overall survival curves showing the association between LOH freuqncy (high vs. low) and clinical outcome of ovarian cancer.



Supplementary Figure 2. The prognostic value of platinum responsive genes. (**A**) An example of the meta-analytic strategy. The prognostic value of gene DDB2 in ovarian cancer is estimated by leveraging 16 transcriptome datasets. Segments show 95% CIs, and the red diamonds show the fixed-effects meta-analysis summaries of HRs over all the datasets.We repeated the same strategy on the 80 platinum responsive genes (Supplementary Table 2). (**B**) Kaplan-Meier overall survival curves showing the association between expression of DDB2 and clinical outcome of ovarian cancer in the dataset GSE26712 (logrank p = 0.07).

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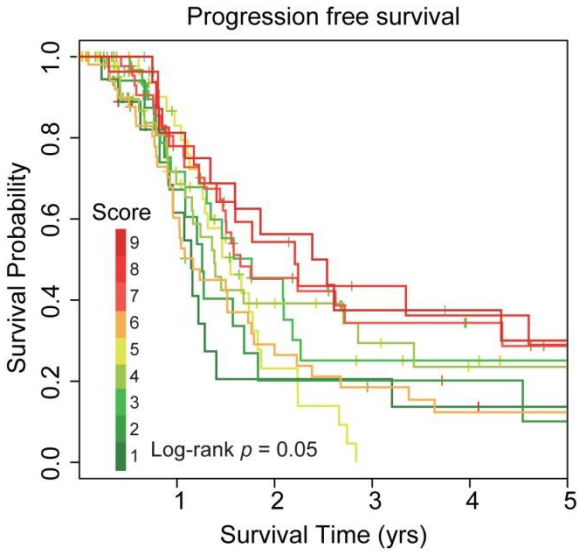

Supplementary Figure 3. Favorable progression free survival is associated with increasing value of score based on the expression of the 10 miRNAs.

Supplementary table 1. Literatures supporing miRNA_targets

microRNA	Target	Pathway	PMID	Reference
miR-100	ATM	ATM	20869334	[1]
miR-101	ATM	ATM	20617180	[2]
miR-18	ATM	ATM	21980462	[3]
miR-421	ATM	ATM	20080624	[4]
miR-146	BRCA1	HR	21472990	[5]
miR-182	BRCA1	HR	21195000	[6]
miR-195	CHEK1	ATM	21778430	[7]
miR-497	CHEK1	ATM	24464213	[8]
miR-182	CHEK2	ATM	21195000	[6]
miR-106	H2AX	ATM	19597473	[9]
miR-138	H2AX	ATM	21693595	[10]
miR-17	H2AX	ATM	19597473	[9]
miR-20	H2AX	ATM	19597473	[9]
miR-215	H2AX	ATM	19597473	[9]
miR-24	H2AX	ATM	19377482	[11]
miR-93	H2AX	ATM	19597473	[9]
miR-193	mcl-1	ATM	23546867	[12]
miR-16	UNG2	BER	23228472	[13]
miR-199	UNG2	BER	23228472	[13]
miR-34	UNG2	BER	23228472	[13]
miR-361	VEGF	BER	24865854	[14]
let-7	E2F2	DDS	20418948	[15]
miR-185	ATR	DDS	23807228	[16]
miR-106	E2F1	DDS	17135268	[17]

miR-17	E2F1	DDS	18836483	[18]
miR-20	E2F1	DDS	18836483	[18]
miR-34	p53	DDS	24884974	[19]
miR-449	E2F1	DDS	19833767	[20]
miR-93	E2F1	DDS	17135268	[17]
miR-106	p21	DDS	20878953	[21]
miR-17	p21	DDS	20190813	[22]
miR-192	p21	DDS	19074875	[23]
miR-215	p21	DDS	20190813	[22]
miR-93	p21	DDS	20190813	[22]
miR-181	p27	DDS	19273599	[24]
miR-221	p27	DDS	17627278	[25]
miR-222	p27	DDS	17627278	[25]
miR-125	p53	DDS	19293287	[26]
miR-25	p53	DDS	20542001	[27]
miR-30	p53	DDS	20542001	[27]
miR-491	p53	DDS	23519249	[28]
miR-504	p53	DDS	20542001	[27]
miR-98	p53	DDS	21880462	[29]
miR-221	p57	DDS	18521080	[30]
miR-222	p57	DDS	23447020	[31]
miR-302	p63	DDS	19342891	[32]
miR-92	p63	DDS	19608627	[33]
miR-29	p85	DDS	19079265	[34]
miR-502	p53	DDS	24374662	[35]
miR-301	p63	DDS	24398967	[36]
miR-373	RAD23B	HR	19141645	[37]

miR-96	RAD51	HR	22761336	[38]
miR-210	RAD52	HR	19141645	[37]
miR-373	RAD52	HR	19141645	[37]
miR-34	SIRT1	HR	18755897	[39]
miR-151	RhoGDIA	HR	20305651	[40]
miR-301	PTEN	HR	21393507	[41]
miR-18	MDM2	MMR	23365201	[42]
miR-192	MDM2	MMR	20951946	[43]
miR-194	MDM2	MMR	20951946	[43]
miR-215	MDM2	MMR	20951946	[43]
miR-25	MDM2	MMR	22431589	[44]
miR-32	MDM2	MMR	22431589	[44]
miR-661	MDM2	MMR	24141721	[45]
miR-155	MLH1	MMR	20351277	[46]
miR-155	MSH2	MMR	20351277	[46]
miR-21	MSH2	MMR	21078976	[47]
miR-21	MSH6	MMR	21078976	[47]
miR-28	Nm23-H1	MMR	22240480	[48]
miR-324	GLI1	MMR	24706306	[49]
miR-124	CDK2	NER	19404929	[50]
miR-302	CDK2	NER	21062975	[51]
miR-372	CDK2	NER	21646351	[52]
miR-885	CDK2	NER	21233845	[53]
miR-124	CDK6	NER	18607543	[54]
miR-29	CDK6	NER	20086245	[55]
miR-449	CDK6	NER	19833767	[20]
miR-521	CSA	NER	18668526	[56]

miR-192	ERCC3	NER	21672525	[57]
miR-192	ERCC4	NER	21672525	[57]
miR-23	FANCG	NER	21750350	[58]
miR-96	REV1	NER	22761336	[38]
miR-211	MMP-9	NER	23183822	[59]
miR-505	AKT3	NHEJ	22051041	[60]
let-7	c-myc	OTHER	19574298	[61]
miR-15	BCL2	OTHER	16166262	[62]
miR-16	BCL2	OTHER	16166262	[62]
miR-205	BCL2	OTHER	23612742	[63]
miR-34	BCL2	OTHER	17656095	[64]
miR-372	CCNA1	OTHER	21646351	[52]
miR-16	Cdc25A	OTHER	19536137	[65]
miR-21	Cdc25A	OTHER	19738433	[66]
miR-322	Cdc25A	OTHER	20462953	[67]
miR-424	Cdc25A	OTHER	20462953	[67]
miR-449	Cdc25A	OTHER	19833767	[20]
miR-503	Cdc25A	OTHER	20462953	[67]
miR-29	CDC42	OTHER	19079265	[34]
miR-145	c-myc	OTHER	19202062	[68]
miR-15	Cyclin D	OTHER	18931683	[69]
miR-16	Cyclin D	OTHER	18931683	[69]
miR-15	Cyclin E	OTHER	19117988	[70]
miR-16	Cyclin E	OTHER	19944013	[71]
miR-29	Cyclin E	OTHER	21551130	[72]
miR-122	Cyclin G1	OTHER	19584283	[73]
miR-101	DNA-PKcs	OTHER	20617180	[2]

miR-128	Wee1	OTHER	20668041	[74]
miR-155	Wee1	OTHER	20668041	[74]
miR-195	Wee1	OTHER	22190509	[75]
miR-516	Wee1	OTHER	20668041	[74]
miR-16	Wip1	OTHER	20668064	[76]
miR-29	Wip1	OTHER	21522133	[77]
miR-320	SMAR1	OTHER	23876508	[78]
miR-28	Cyclin D	OTHER	22240480	[48]
miR-25	REV3L	TLS	22349819	[79]
miR-32	REV3L	TLS	22349819	[79]
miR-26	Cyclin-D	OTHER	19524505	[80]
miR-26	Cyclin-E	OTHER	19524505	[80]
miR-122	Cyclin-G	OTHER	17616664	[81]
miR-122	BCL-w	OTHER	18692484	[82]
miR-195	Cyclin-D	OTHER	19441017	[83]
miR-195	CDK6	NER	19441017	[83]
miR-195	E2F3	DDS	19441017	[83]
miR-221	PTEN	HR	19962668	[84]
miR-222	PTEN	HR	19962668	[84]
miR-29	mcl-1	ATM	17404574	[85]
miR-101	mcl-1	ATM	19155302	[86]
miR-127	BCL6	OTHER	18645025	[87]
miR-28	BRCA1	ATM	18645025	[87]
miR-22	CDK6	NER	21502362	[88]
miR-22	SIRT1	HR	21502362	[88]
miR-133	MMP-9	NER	24714873	[89]
miR-126	VEGF	BER	19223090	[90]

miR-718	VEGF	BER	24815691	[91]
miR-200	VEGF	BER	21357793	[92]
miR-145	AKT3	NHEJ	24781864	[93]
miR-489	AKT3	NHEJ	24686007	[94]
miR-17	AKT1	NHEJ	24658544	[95]
miR-20	AKT1	NHEJ	24658544	[95]
miR-122	AKT3	NHEJ	24244539	[96]
miR-29	AKT3	NHEJ	23764849	[97]
miR-133	GLI1	MMR	24443799	[98]
miR-202	GLI1	MMR	23936094	[99]

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Supplementary table 3. Platinum response genes.

genes	Freq	pvalue	HR	95CI_L	95CI_U	FDR
CETN2	16	6.55E-05	0.85610681	0.79323251	0.92396474	0.00383719
DDB2	16	9.84E-05	0.82811098	0.75312267	0.91056586	0.00383719
ERCC8	16	0.00021334	1.20665604	1.0924418	1.33281131	0.00554678
RAD17	14	0.0013993	1.22008984	1.07992007	1.37845314	0.02728626
H2AFX	15	0.00285759	0.89207466	0.82757779	0.96159806	0.03828652
HLTF	15	0.00294512	1.1195468	1.03923884	1.20606062	0.03828652
ERCC1	15	0.00516841	1.15294936	1.04348766	1.27389357	0.05759091
UBE2B	15	0.00595789	1.15503288	1.04227886	1.27998466	0.05808941
RAD9A	15	0.01262431	0.87588808	0.78926737	0.97201525	0.1094107
C17orf70	13	0.01781211	0.84748503	0.73906987	0.97180375	0.13893444
BRCA2	16	0.02126229	1.11547506	1.01642279	1.22418015	0.15076893
FANCI	15	0.03140362	0.92855928	0.86794205	0.99341003	0.17859631
RBBP8	14	0.03182755	0.925793	0.86285694	0.99331955	0.17859631
UBE2V2	14	0.03205575	1.11473167	1.00935341	1.23111159	0.17859631
FANCA	15	0.04528682	0.90560708	0.82183257	0.99792126	0.23549149
PALB2	16	0.06057379	0.89964902	0.80557477	1.00470917	0.27792681
TP53BP1	16	0.05803354	1.12124685	0.99611208	1.26210145	0.27792681
RAD54L	16	0.0700907	0.92771627	0.85537468	1.00617601	0.27839393
BLM	16	0.06488312	0.92644385	0.85426175	1.0047251	0.27839393
C19orf40	13	0.07138306	1.10179646	0.99159792	1.22424161	0.27839393
POLK	12	0.08387875	1.0966335	0.98773005	1.21754425	0.31154963
REV3L	16	0.09696642	1.07634238	0.9867807	1.17403282	0.34379004
RAD50	16	0.12519074	1.07608678	0.97980402	1.18183099	0.42145029
CHEK2	11	0.12967701	0.92119596	0.82841034	1.02437399	0.42145029
RAD54B	14	0.15263609	0.9490986	0.88352794	1.01953557	0.42520055
FBXO18	12	0.14162552	1.09508784	0.97015894	1.23610402	0.42520055
FANCB	11	0.14905536	1.09843978	0.96691187	1.24785927	0.42520055
NBN	15	0.14906728	1.06075768	0.97908147	1.14924743	0.42520055
FANCG	3	0.18728913	0.90284053	0.77559226	1.05096591	0.50374318
CLSPN	10	0.20551931	0.93172347	0.835099	1.03952781	0.51784498
FANCL	16	0.2257273	0.94798143	0.86949024	1.03355823	0.51784498
ATRIP	5	0.22087084	0.86852576	0.69306518	1.08840699	0.51784498
HUS1	14	0.21054872	1.06654702	0.96422919	1.17972217	0.51784498
RAD18	11	0.21294758	1.08084874	0.95638172	1.22151434	0.51784498
POLH	14	0.26355831	0.93945272	0.8420209	1.04815856	0.54409944
CHEK1	15	0.26374471	0.95704159	0.88611115	1.03364979	0.54409944
WDR48	15	0.26507409	1.06085251	0.95617444	1.1769903	0.54409944
TOP2A	16	0.26285499	1.03038382	0.97778735	1.08580952	0.54409944
BRCA1	16	0.28178661	1.04349836	0.96564687	1.12762631	0.56357321
FANCF	16	0.29669238	0.95103062	0.86544641	1.04507828	0.57855014
ERCC2	15	0.31559874	1.06563222	0.94121534	1.20649545	0.60040737
RAD52	16	0.34828958	1.04301858	0.95513989	1.13898264	0.60370194
XPA	16	0.33620824	1.05769587	0.94343541	1.18579454	0.60370194
POLI	16	0.34156359	0.95951198	0.88117119	1.04481768	0.60370194
TOPBP1	16	0.32960081	1.04418641	0.95725335	1.13901431	0.60370194

ATR	15	0.36584832	0.95912587	0.87617756	1.04992695	0.60715253
UBE2N	14	0.35826359	1.04806228	0.94818277	1.15846287	0.60715253
ERCC5	16	0.39232984	1.04576436	0.94385525	1.15867671	0.63753598
ATM	16	0.42572344	0.96667542	0.88932796	1.05075002	0.66597227
RNF8	15	0.44668897	0.96427751	0.87803403	1.05899211	0.66597227
ERCC3	16	0.46105772	0.96104964	0.86470305	1.06813131	0.66597227
DDB1	16	0.44691025	0.9546292	0.84697358	1.07596853	0.66597227
FANCC	16	0.4609922	0.9593408	0.85910441	1.07127233	0.66597227
XRCC3	15	0.43155054	0.95368604	0.84739572	1.07330853	0.66597227
RAD23B	15	0.48026358	0.97438689	0.90665651	1.04717696	0.68110108
RAD23A	15	0.51700041	1.03028754	0.94137447	1.12759847	0.72010772
FANCM	9	0.53302936	0.95316624	0.81973571	1.1083156	0.72940859
XAB2	16	0.54482562	1.03079423	0.93440982	1.13712068	0.73269652
TP53	15	0.57328071	0.98665733	0.94159878	1.03387207	0.75789653
XPC	15	0.59870014	0.97098171	0.87012529	1.08352842	0.77831018
MDC1	16	0.65707162	0.9795337	0.89407174	1.07316476	0.84018994
RAD1	16	0.67176284	0.98096259	0.89751309	1.0721711	0.845121
ERCC6	16	0.68378831	1.02461462	0.91146948	1.15180502	0.84659505
BRIP1	15	0.74140492	0.9866812	0.91115202	1.06847131	0.85043506
USP1	16	0.74089942	0.98706151	0.91373493	1.06627251	0.85043506
FANCE	16	0.73722943	0.98308433	0.88983573	1.08610474	0.85043506
RAD51C	16	0.73385857	1.0129429	0.94056676	1.09088834	0.85043506
SHFM1	12	0.72853796	1.01954817	0.91396145	1.13733296	0.85043506
FANCD2	12	0.75758903	1.01640425	0.91662838	1.12704081	0.85640499
MAD2L2	12	0.77412735	1.0146967	0.91846403	1.12101221	0.86259905
REV1	15	0.78877847	1.01426551	0.9144195	1.12501377	0.86654536
SHPRH	12	0.81041584	1.01336934	0.90916679	1.12951489	0.87795049
MUS81	16	0.83598101	1.01333702	0.89388811	1.14874771	0.89323999
MRE11A	16	0.85117687	1.00826913	0.9251549	1.09885019	0.89718643
RAD51	16	0.89212949	0.99447952	0.9180128	1.0773156	0.92781467
XRCC2	15	0.91114667	0.99499328	0.91103284	1.08669147	0.93512421
UBE2I	16	0.9740197	1.00156294	0.91171708	1.10026272	0.98666931
ERCC4	15	0.99519205	0.99967076	0.89813468	1.11268571	0.99519205
RAD51L1	0	NA	NA	NA	NA	NA
RAD51L3	0	NA	NA	NA	NA	NA