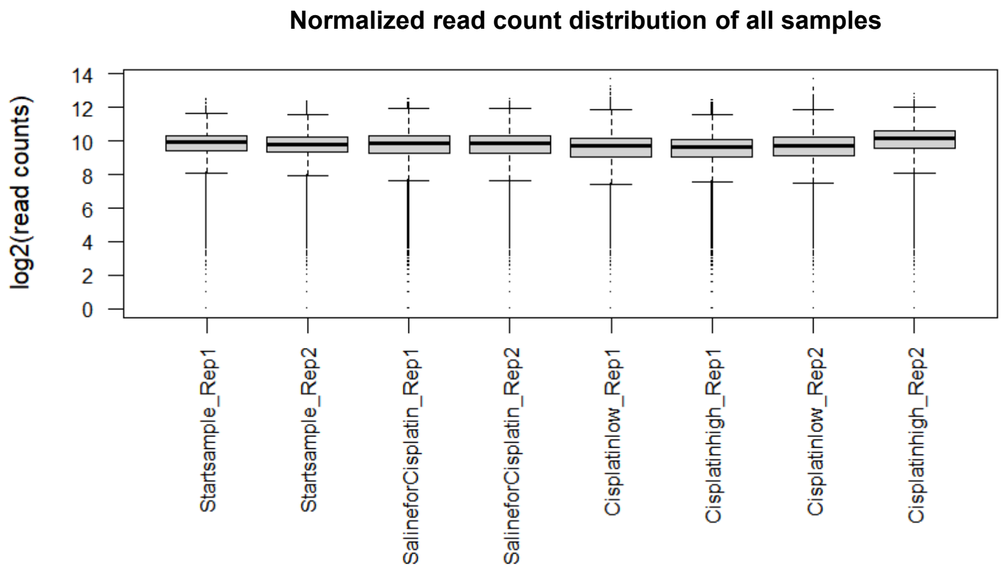
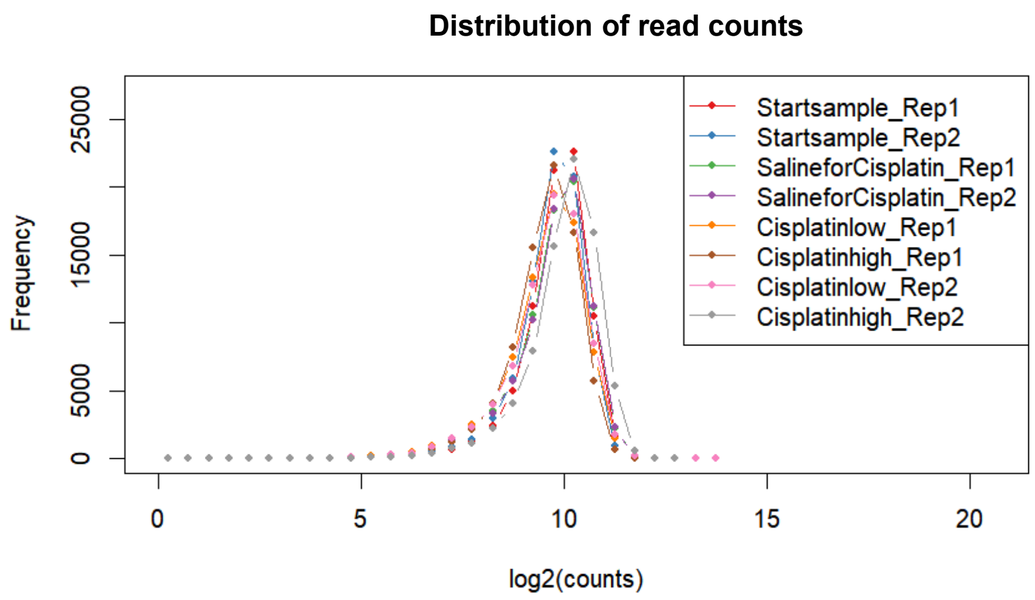
Figure S1

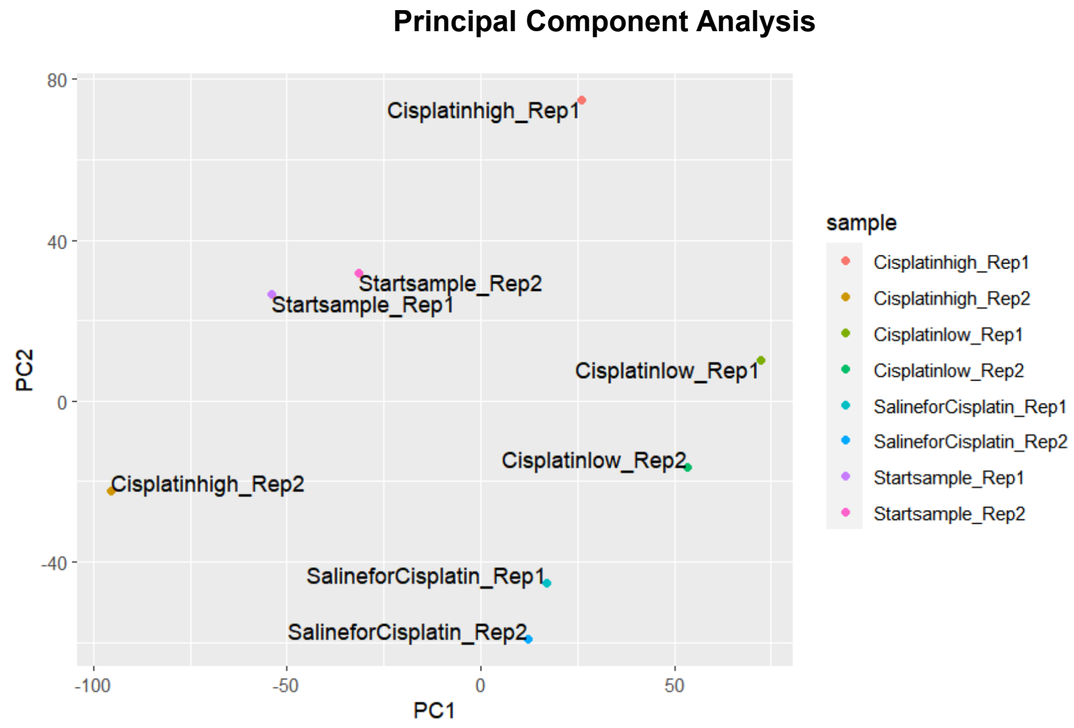
(A)



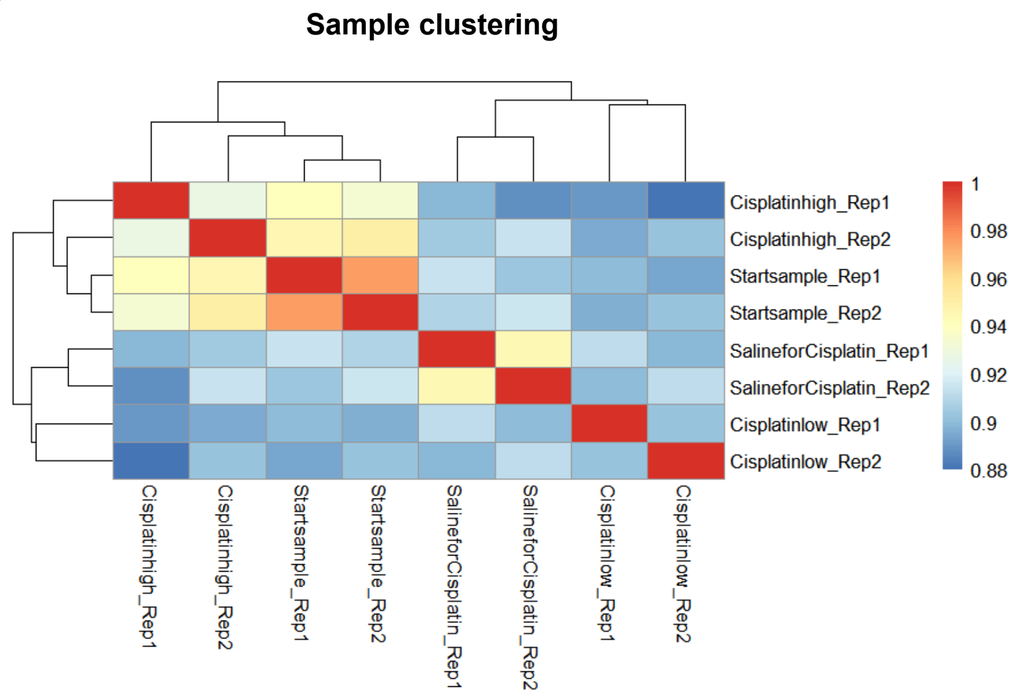
(B)



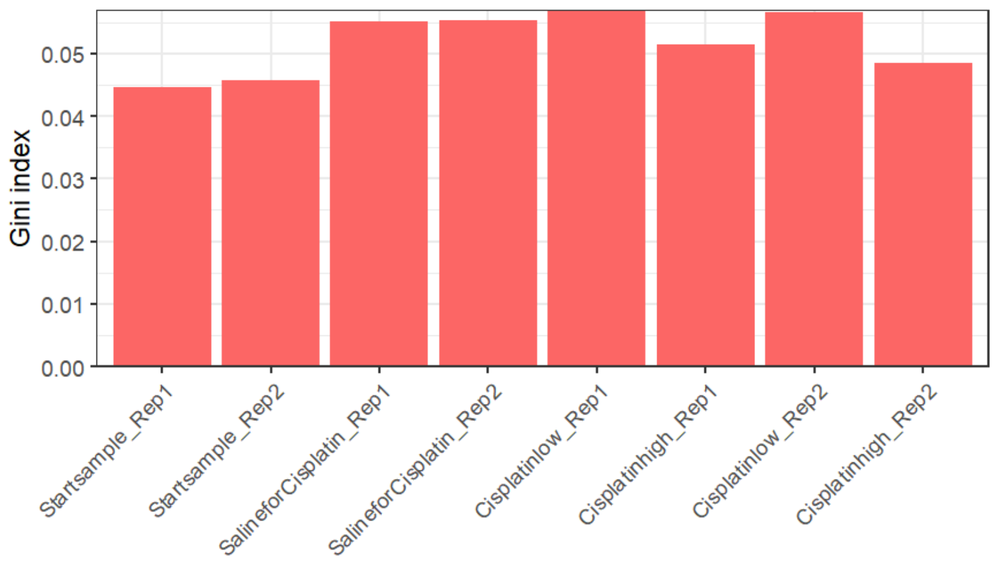
(C)



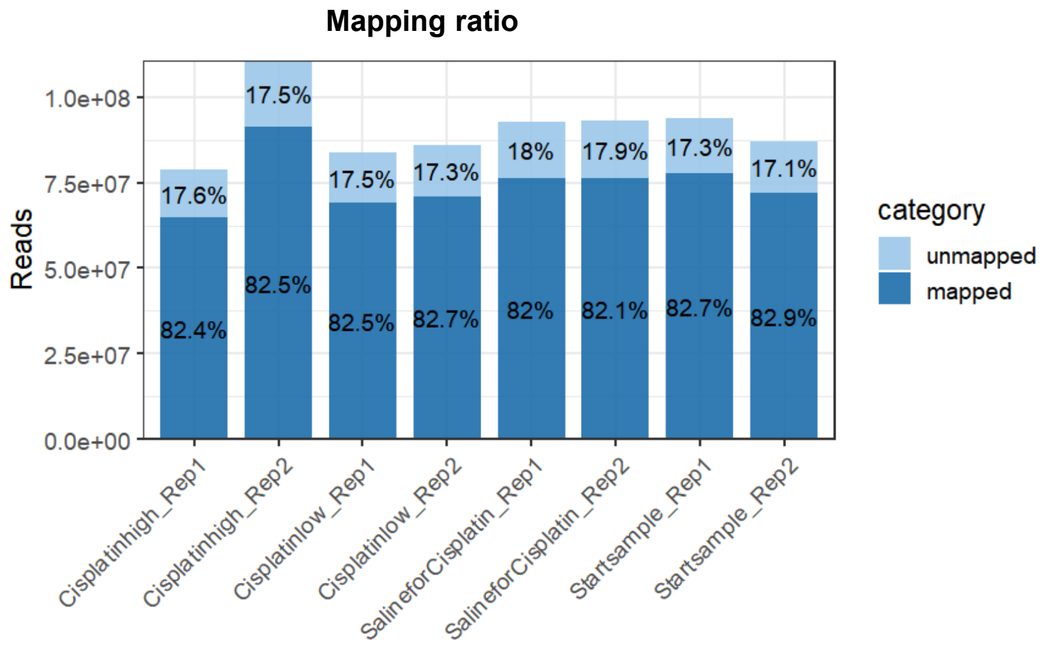
(D)



(E)



(F)

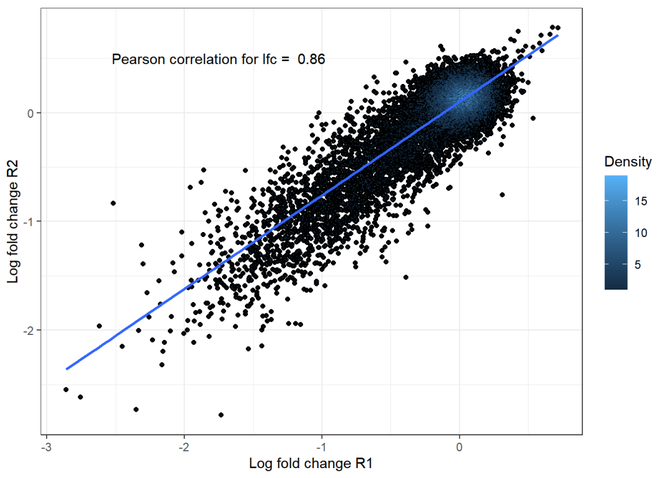


(G)

Label	Reads	Mapped	Percentage	Total gRNAs	Zerocounts	GiniIndex
Startsample_Rep1	94023063	77744860	0.8269	77441	28	0.04456
Startsample_Rep2	87008878	72115575	0.8288	77441	30	0.04572
SalineforCisplatin_Rep1	92943246	76223547	0.8201	77441	49	0.05521
SalineforCisplatin_Rep2	93143862	76464265	0.8209	77441	46	0.05529
Cisplatinlow_Rep1	83695888	69076722	0.8253	77441	45	0.05702
Cisplatinhigh_Rep1	78890138	64972695	0.8236	77441	63	0.05144
Cisplatinlow_Rep2	85995677	71102237	0.8268	77441	50	0.05662
Cisplatinhigh_Rep2	110778348	91411905	0.8252	77441	47	0.04850

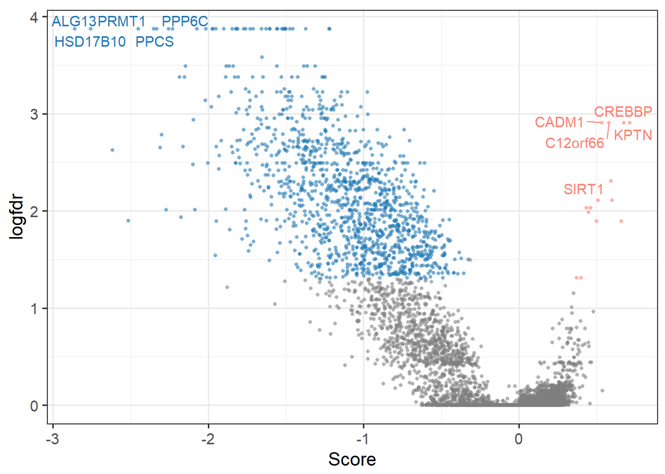
Figure S2

(A)

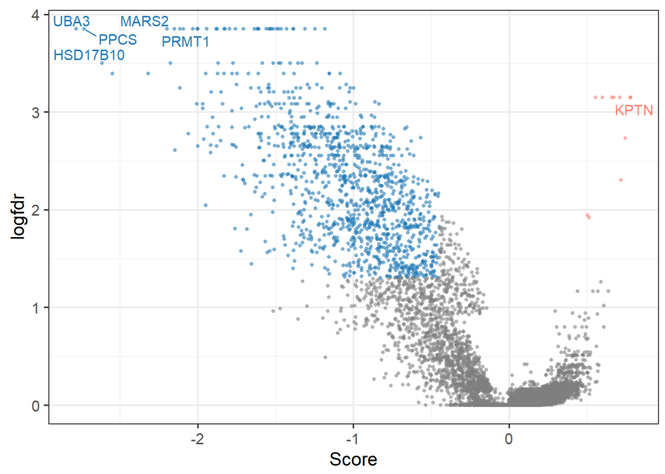


(B)

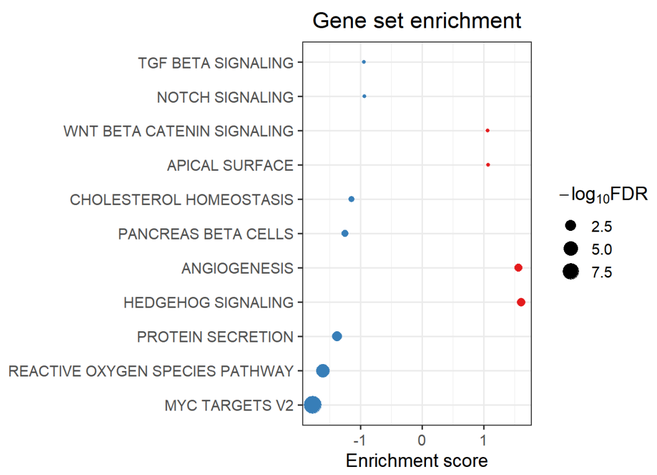
Replicate 1

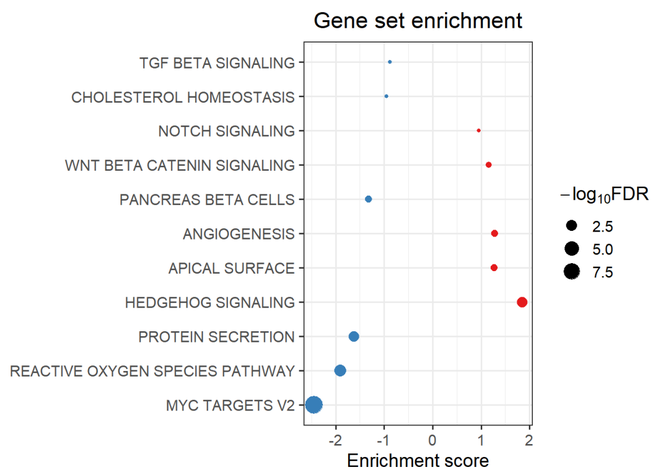


Replicate 2

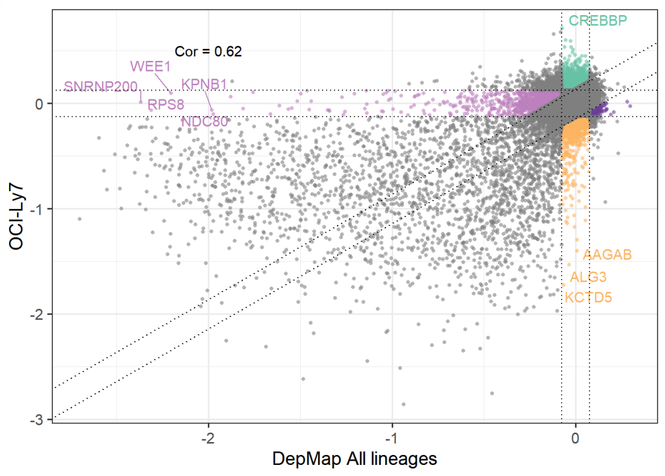


(C)

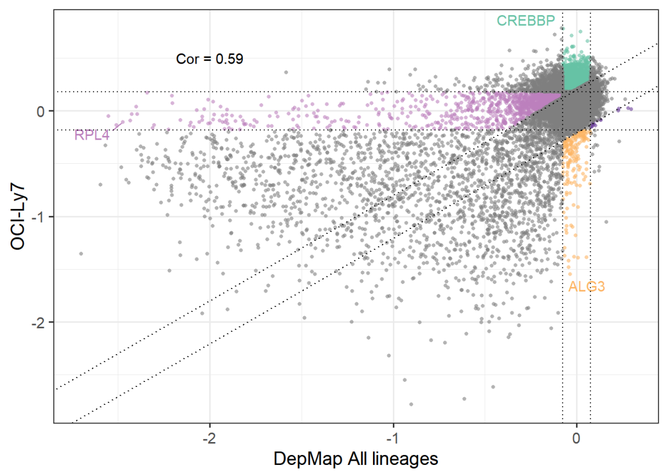




(D)

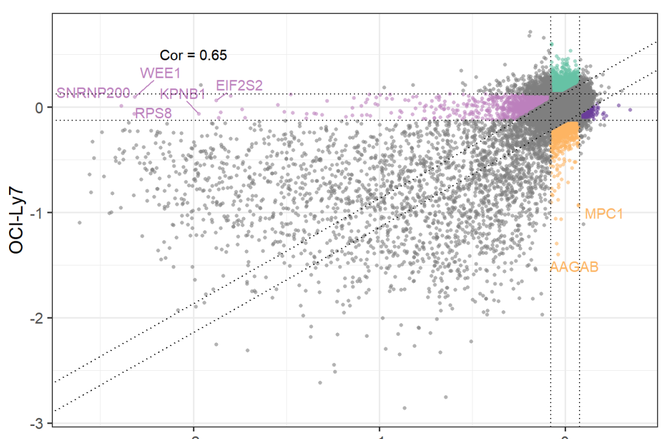


	DepMap_Lower	DepMap_Middle	DepMap_Top
R1_Lower	2174	526	2
R1_Middle	1448	11990	35
R1_Top	42	388	1

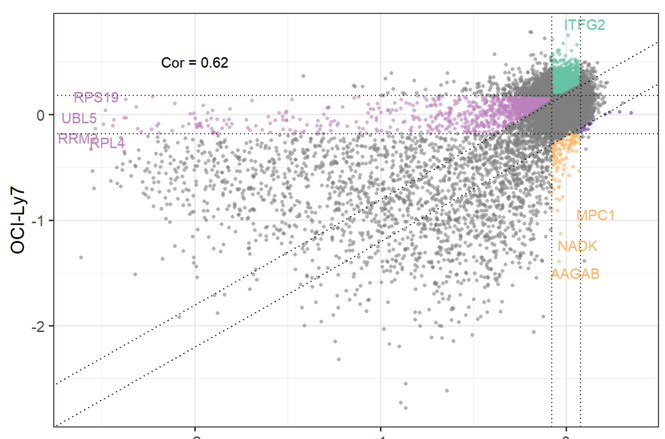


	DepMap_Lower	DepMap_Middle	DepMap_Top
R2_Lower	1673	188	1
R2_Middle	1948	12157	36
R2_Top	43	559	1

(E)

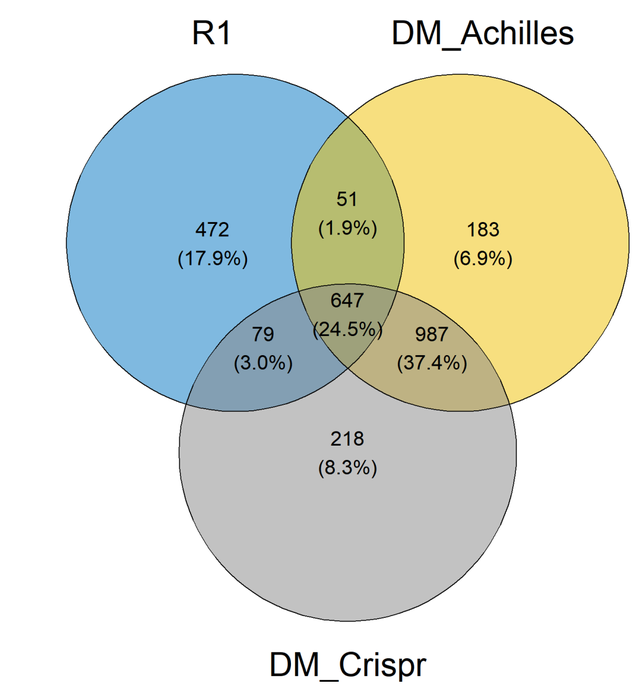


	DepMap_Lower	DepMap_Middle	DepMap_Top
R1_Lower	2251	451	0
R1_Middle	1245	12173	55
R1_Top	34	395	2



	DepMap_Lower	DepMap_Middle	DepMap_Top
R2_Lower	1740	122	0
R2_Middle	1748	12342	51
R2_Top	42	555	6

(F)



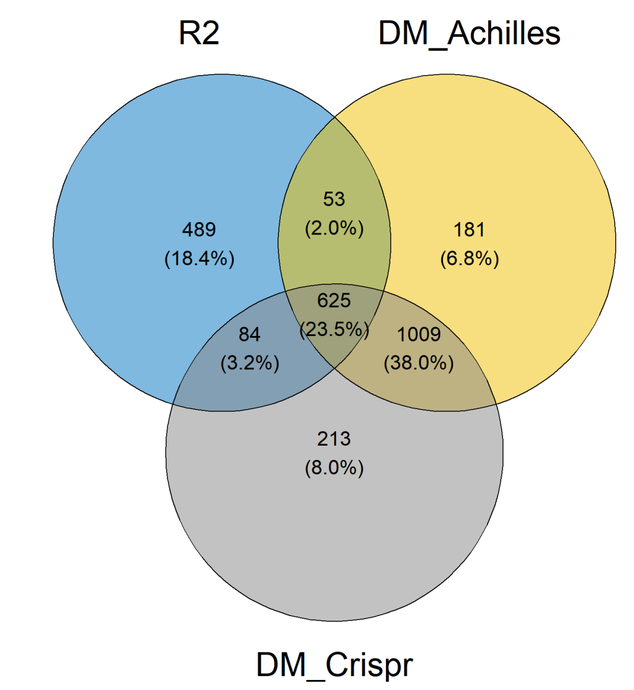
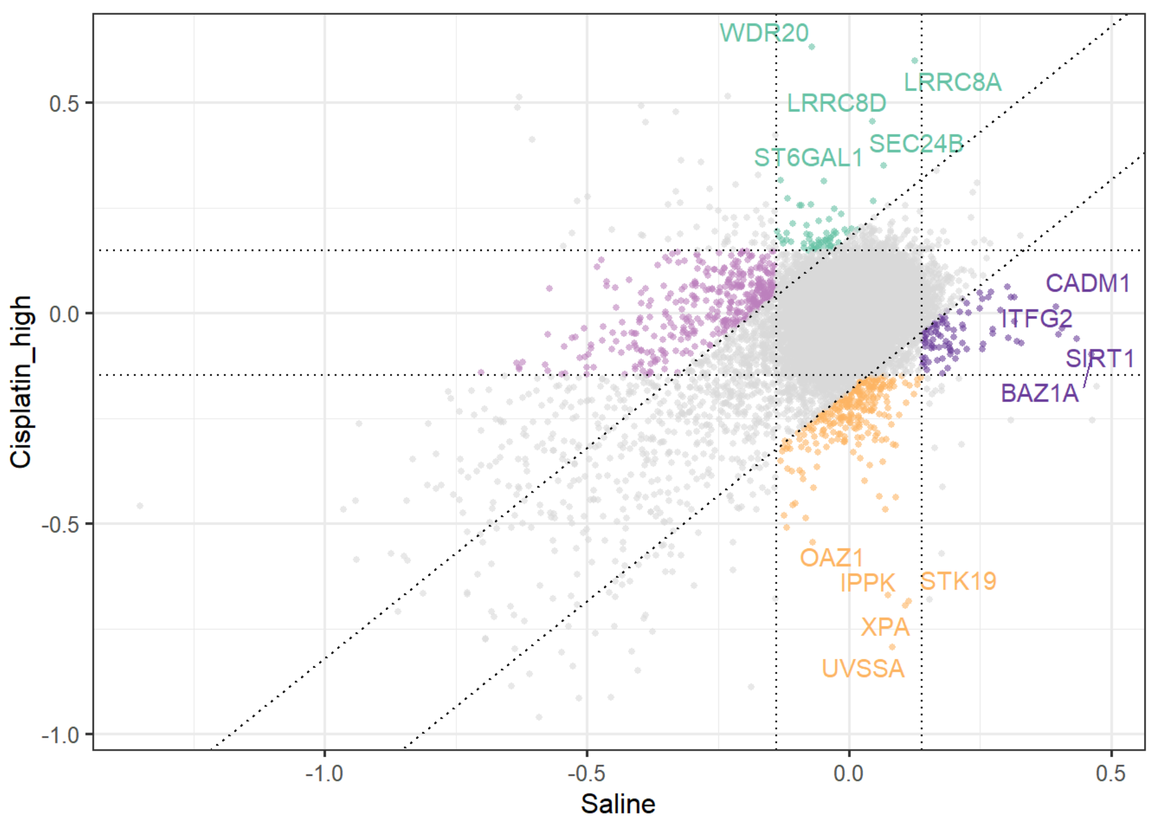


Figure S3


WDR20
LRRC8A
LRRC8D
SEC24B
ST6GAL1
CADM1
ITFG2
SIRT1
BAZ1A
OAZ1
IPPK
STK19
XPA
UVSSA
0.5
0.0
-0.5
-1.0
Cisplatin_high
-1.0
-0.5
0.0
0.5
Saline

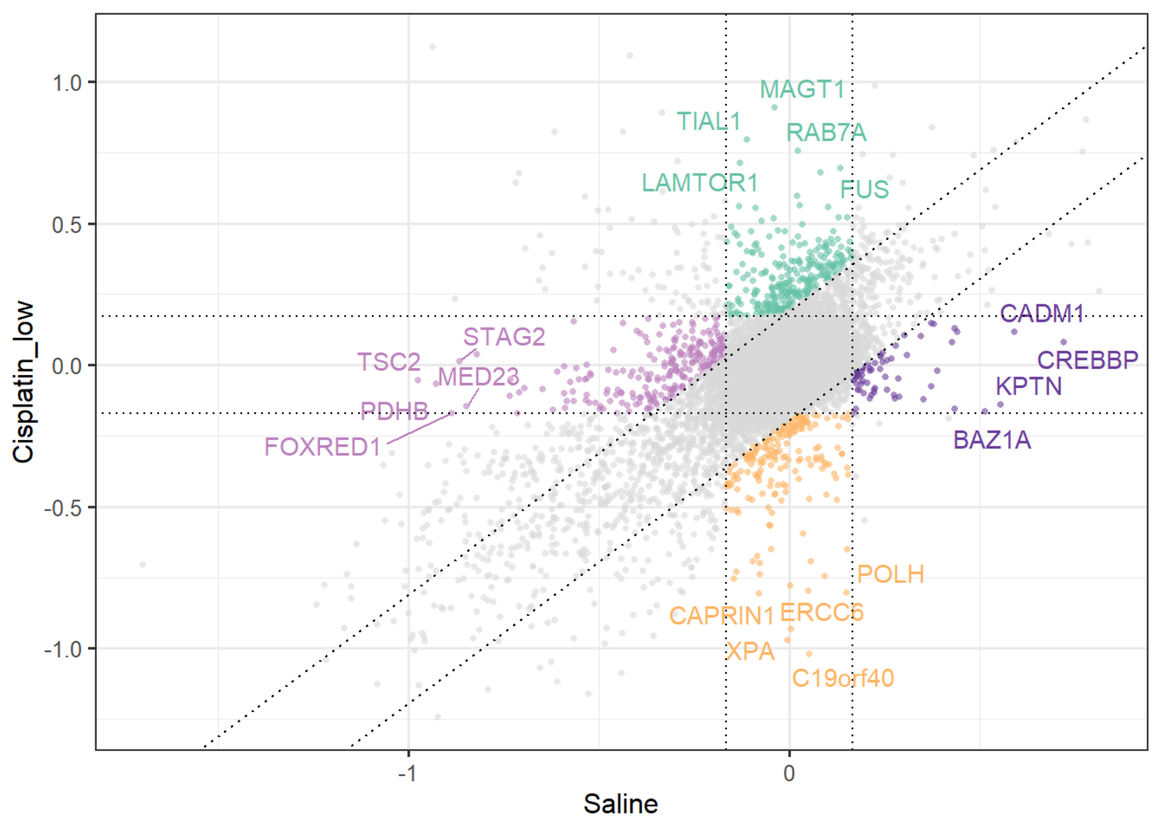
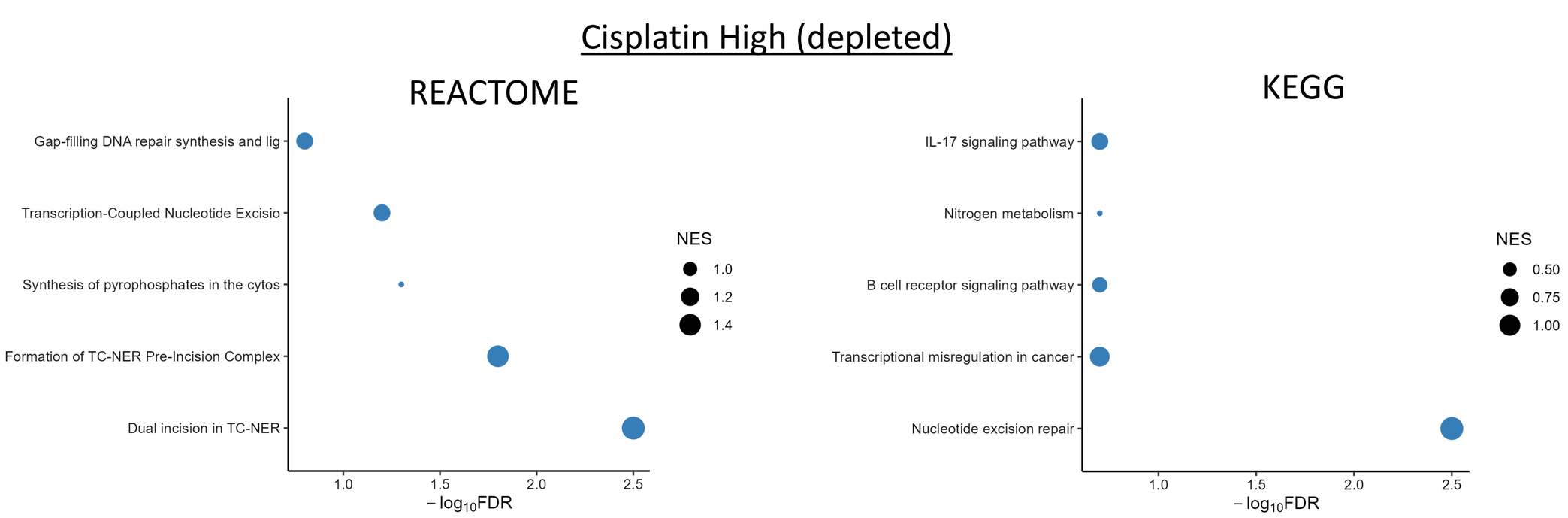
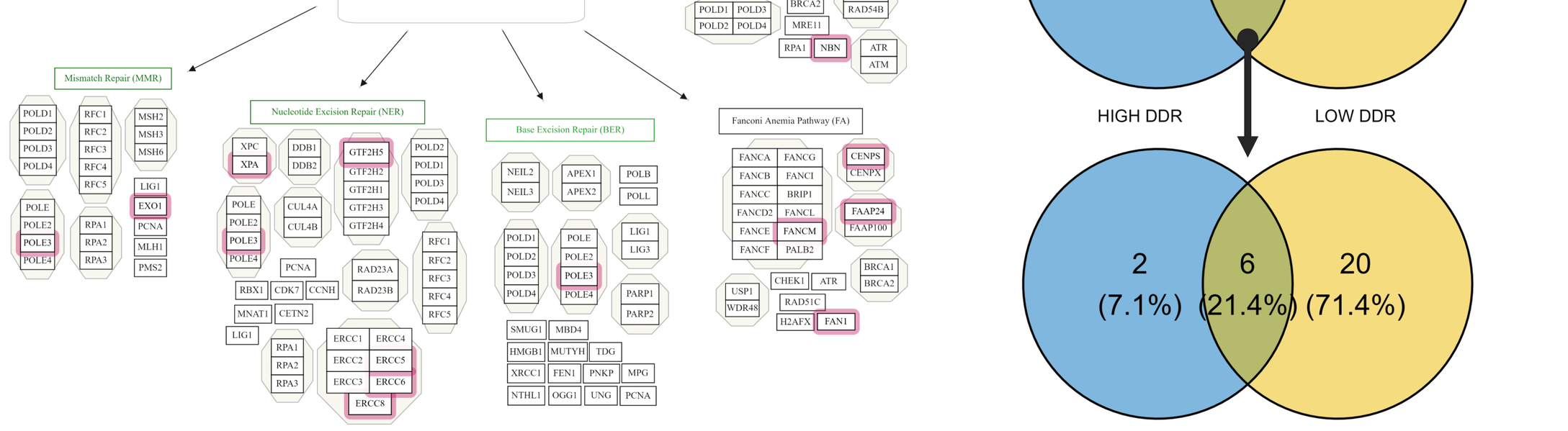

MAGT1
TIAL1
RAB7A
LAMTOR1
FUS
CADM1
STAG2
TSC2
MED23
CREBBP
KPTN
PDHB
FOXRED1
BAZ1A
POLH
CAPRIN1
ERCC5
XPA
C19orf40
1.0
0.5
0.0
-0.5
-1.0
Cisplatin_low
-1
0
Saline

Figure S4

(A)



(B)



(C)

(D)

(E)

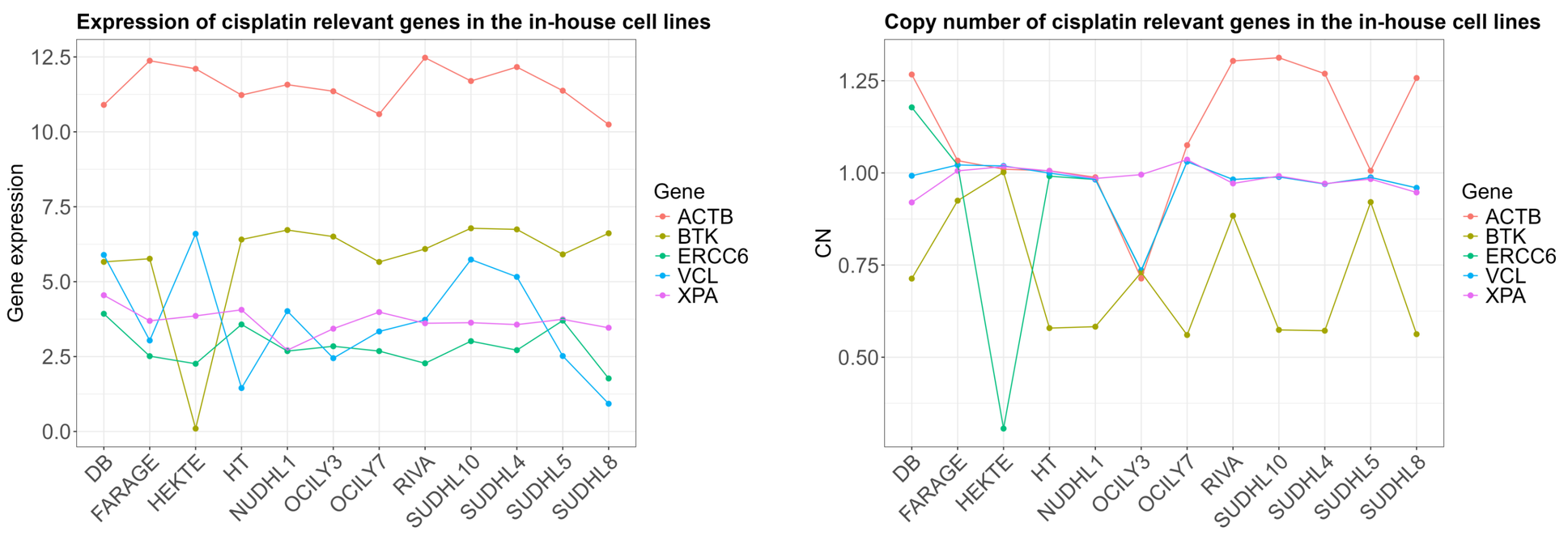
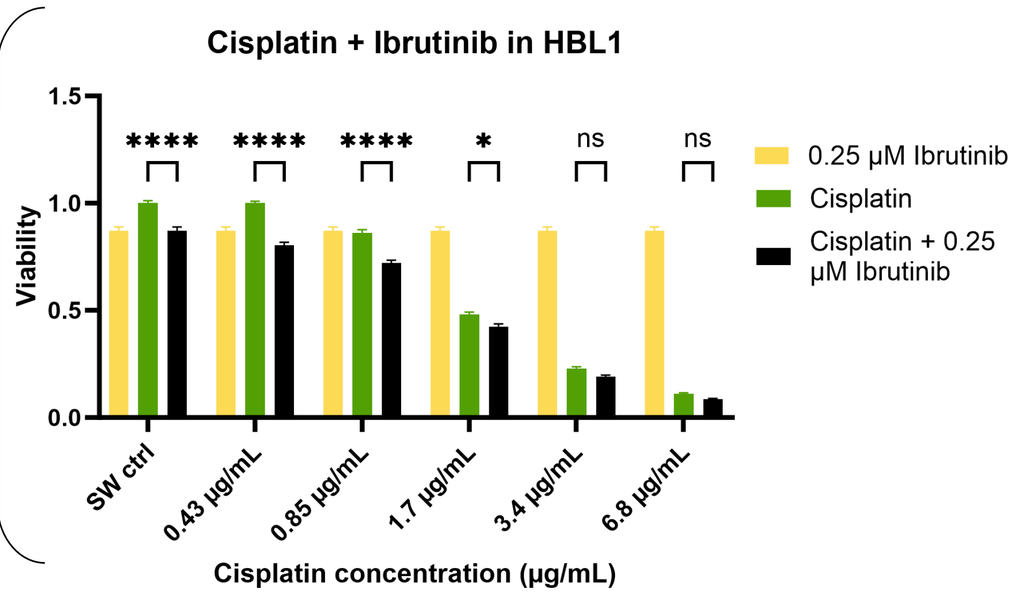


Figure S5

(A)

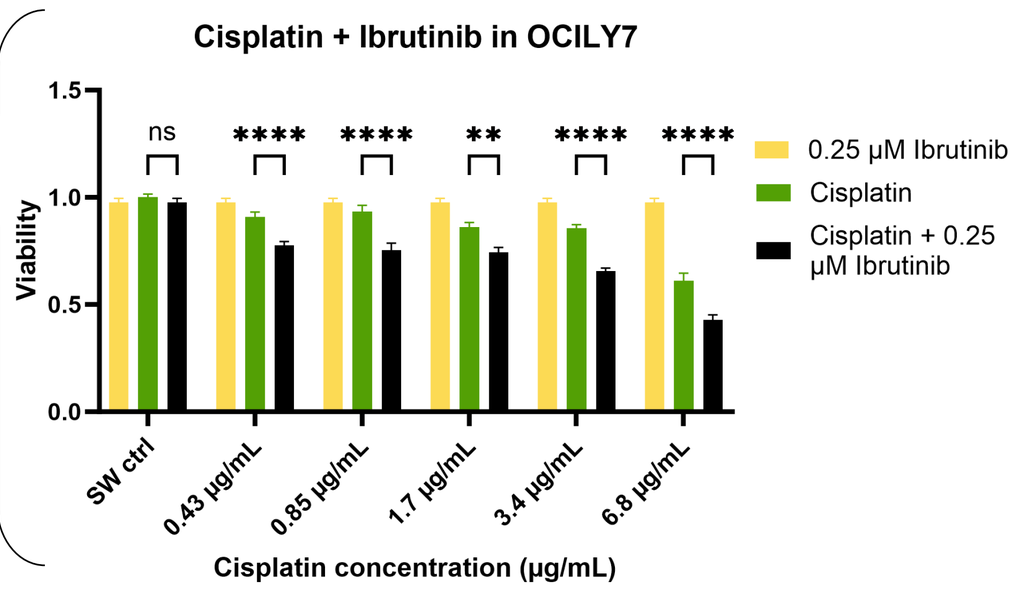
HBL1

IBR \ CIS	0 µg/mL	0.43 µg/mL	0.85 µg/mL	1.7 µg/mL	3.4 µg/mL	6.8 µg/mL
0 µM	1.00	1.00	0.86	0.49	0.23	0.11
0.25 µM	0.86	0.8 (Bliss: -0.06)	0.72 (Bliss: -0.02)	0.42 (Bliss: 0.01)	0.19 (Bliss: -0.01)	0.09 (Bliss: -0.01)
1 µM	0.82	0.81 (Bliss: -0.01)	0.73 (Bliss: 0.02)	0.45 (Bliss: 0.06)	0.24 (Bliss: 0.05)	0.12 (Bliss: 0.03)
4 µM	0.76	0.76 (Bliss: -0.01)	0.71 (Bliss: 0.05)	0.53 (Bliss: 0.16)	0.32 (Bliss: 0.15)	0.16 (Bliss: 0.07)
16 µM	0.61	0.58 (Bliss: -0.02)	0.56 (Bliss: 0.04)	0.46 (Bliss: 0.16)	0.32 (Bliss: 0.18)	0.16 (Bliss: 0.09)
32 µM	0.25	0.26 (Bliss: 0.01)	0.25 (Bliss: 0.04)	0.22 (Bliss: 0.1)	0.15 (Bliss: 0.09)	0.07 (Bliss: 0.05)



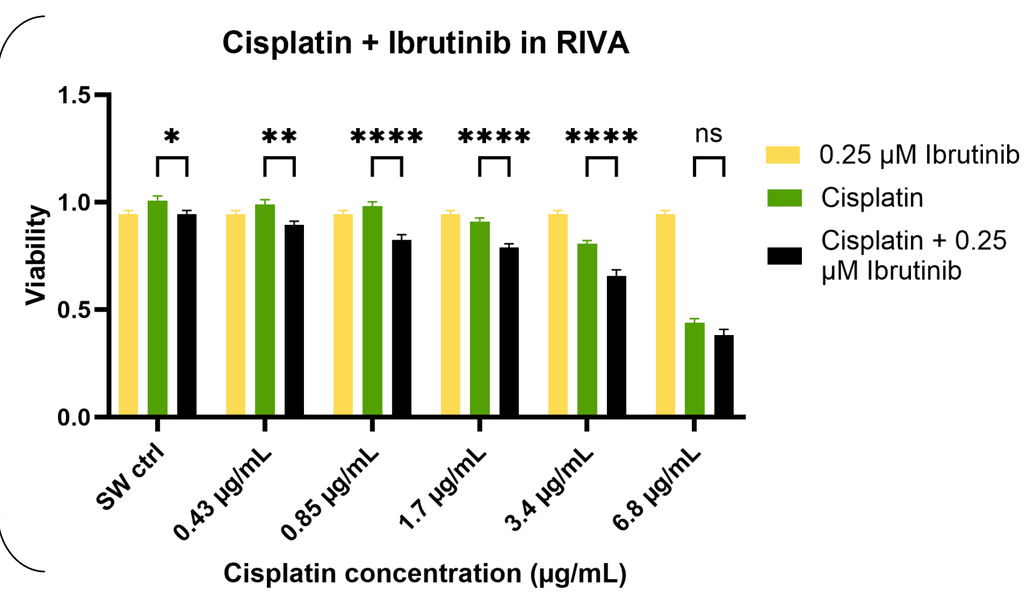
OCILY7

IBR \ CIS	0 µg/mL	0.43 µg/mL	0.85 µg/mL	1.7 µg/mL	3.4 µg/mL	6.8 µg/mL
0 µM	1.00	0.91	0.95	0.84	0.86	0.60
0.25 µM	0.98	0.8 (Bliss: -0.1)	0.73 (Bliss: -0.2)	0.74 (Bliss: -0.08)	0.66 (Bliss: -0.18)	0.43 (Bliss: -0.16)
1 µM	0.90	0.74 (Bliss: -0.09)	0.66 (Bliss: -0.19)	0.71 (Bliss: -0.05)	0.66 (Bliss: -0.12)	0.44 (Bliss: -0.1)
4 µM	0.62	0.55 (Bliss: -0.01)	0.49 (Bliss: -0.09)	0.52 (Bliss: 0)	0.47 (Bliss: -0.06)	0.36 (Bliss: 0)
16 µM	0.36	0.34 (Bliss: 0.01)	0.34 (Bliss: -0.01)	0.4 (Bliss: 0.1)	0.35 (Bliss: 0.04)	0.27 (Bliss: 0.05)
32 µM	0.09	0.14 (Bliss: 0.05)	0.13 (Bliss: 0.04)	0.14 (Bliss: 0.06)	0.08 (Bliss: 0)	0.07 (Bliss: 0.01)



RIVA

IBR \ CIS	0 µg/mL	0.45 µg/mL	0.85 µg/mL	1.7 µg/mL	3.4 µg/mL	6.8 µg/mL
0 µM	1.00	0.99	0.98	0.92	0.80	0.44
0.25 µM	0.93	0.87 (Bliss: -0.04)	0.84 (Bliss: -0.07)	0.8 (Bliss: -0.06)	0.65 (Bliss: -0.09)	0.36 (Bliss: -0.04)
1 µM	0.83	0.8 (Bliss: -0.02)	0.77 (Bliss: -0.04)	0.76 (Bliss: -0.01)	0.65 (Bliss: -0.02)	0.43 (Bliss: 0.07)
4 µM	0.74	0.74 (Bliss: 0)	0.71 (Bliss: -0.02)	0.7 (Bliss: 0.02)	0.61 (Bliss: 0.02)	0.5 (Bliss: 0.18)
16 µM	0.66	0.65 (Bliss: 0)	0.65 (Bliss: 0)	0.62 (Bliss: 0.01)	0.59 (Bliss: 0.06)	0.55 (Bliss: 0.26)
32 µM	0.39	0.36 (Bliss: -0.02)	0.36 (Bliss: -0.02)	0.29 (Bliss: -0.07)	0.36 (Bliss: 0.05)	0.3 (Bliss: 0.13)



SUDHL5

IBR \ CIS	0 µg/mL	0.2125 µg/mL	0.425 µg/mL	0.85 µg/mL	1.7 µg/mL	3.4 µg/mL
0 µM	1.00	1.03	0.91	0.58	0.17	0.06
0.25 µM	0.93	0.78 (Bliss: -0.17)	0.74 (Bliss: -0.11)	0.46 (Bliss: -0.08)	0.08 (Bliss: -0.08)	0.01 (Bliss: -0.05)
1 µM	0.86	0.79 (Bliss: -0.09)	0.73 (Bliss: -0.05)	0.51 (Bliss: 0.01)	0.13 (Bliss: -0.01)	0.05 (Bliss: -0.01)
4 µM	0.72	0.66 (Bliss: -0.08)	0.63 (Bliss: -0.03)	0.45 (Bliss: 0.03)	0.15 (Bliss: 0.02)	0.04 (Bliss: -0.01)
16 µM	0.40	0.42 (Bliss: 0)	0.36 (Bliss: -0.01)	0.24 (Bliss: 0)	0.09 (Bliss: 0.02)	0.04 (Bliss: 0.01)
32 µM	0.03	0.04 (Bliss: 0.01)	0.04 (Bliss: 0.01)	0.03 (Bliss: 0.01)	0.03 (Bliss: 0.03)	0.02 (Bliss: 0.02)

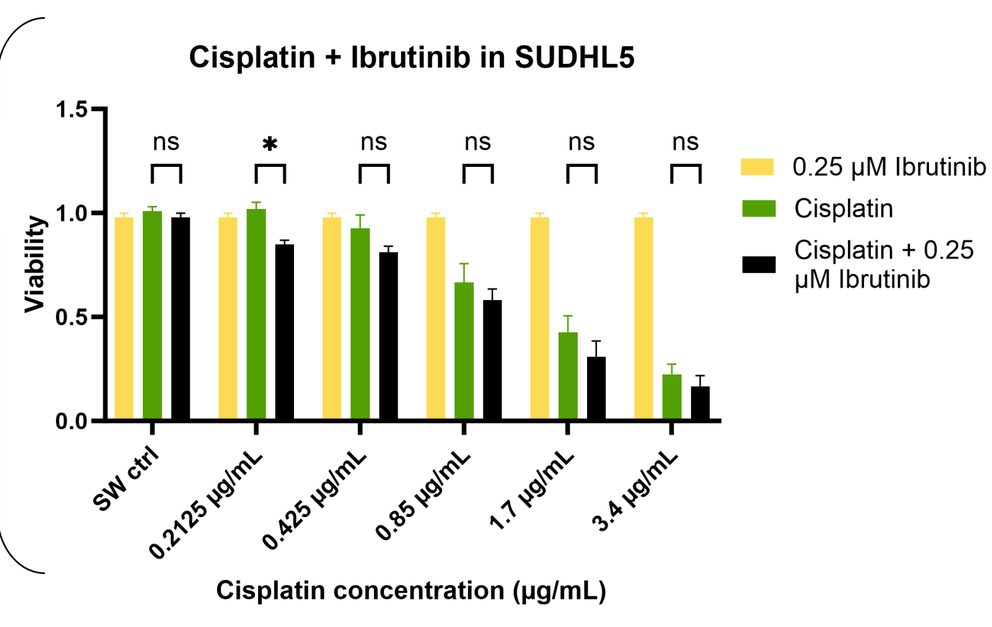
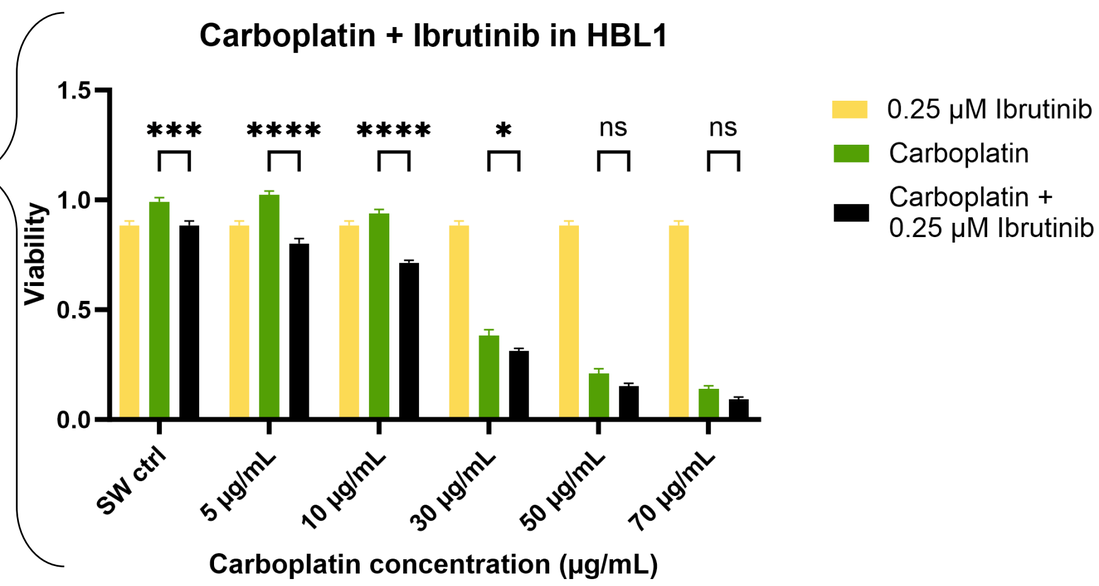


Figure S5

(B)

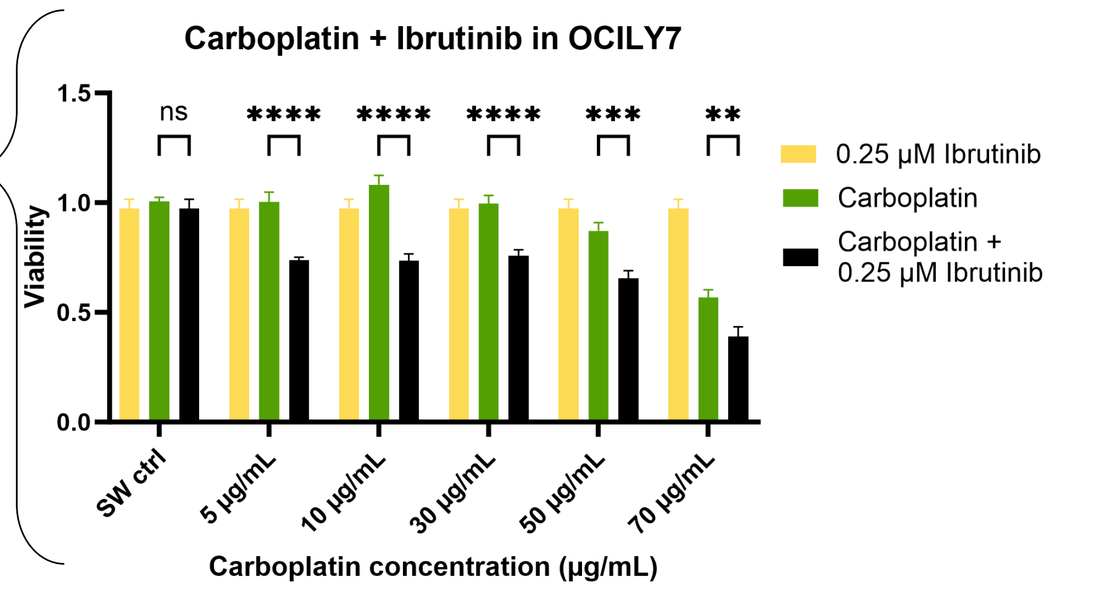
HBL1

IBR \ CAR	0 µg/mL	5 µg/mL	10 µg/mL	30 µg/mL	50 µg/mL	70 µg/mL
0 µM	1.00	1.02	0.94	0.38	0.21	0.14
0.25 µM	0.88	0.8 (Bliss: -0.1)	0.71 (Bliss: -0.12)	0.31 (Bliss: -0.03)	0.15 (Bliss: -0.03)	0.09 (Bliss: -0.03)
1 µM	0.86	0.79 (Bliss: -0.09)	0.72 (Bliss: -0.08)	0.33 (Bliss: 0.01)	0.18 (Bliss: 0)	0.13 (Bliss: 0.01)
4 µM	0.80	0.72 (Bliss: -0.09)	0.65 (Bliss: -0.1)	0.37 (Bliss: 0.06)	0.23 (Bliss: 0.06)	0.17 (Bliss: 0.06)
16 µM	0.61	0.56 (Bliss: -0.06)	0.52 (Bliss: -0.06)	0.35 (Bliss: 0.12)	0.22 (Bliss: 0.1)	0.14 (Bliss: 0.06)
32 µM	0.30	0.29 (Bliss: -0.02)	0.23 (Bliss: -0.05)	0.15 (Bliss: 0.04)	0.08 (Bliss: 0.02)	0.06 (Bliss: 0.01)



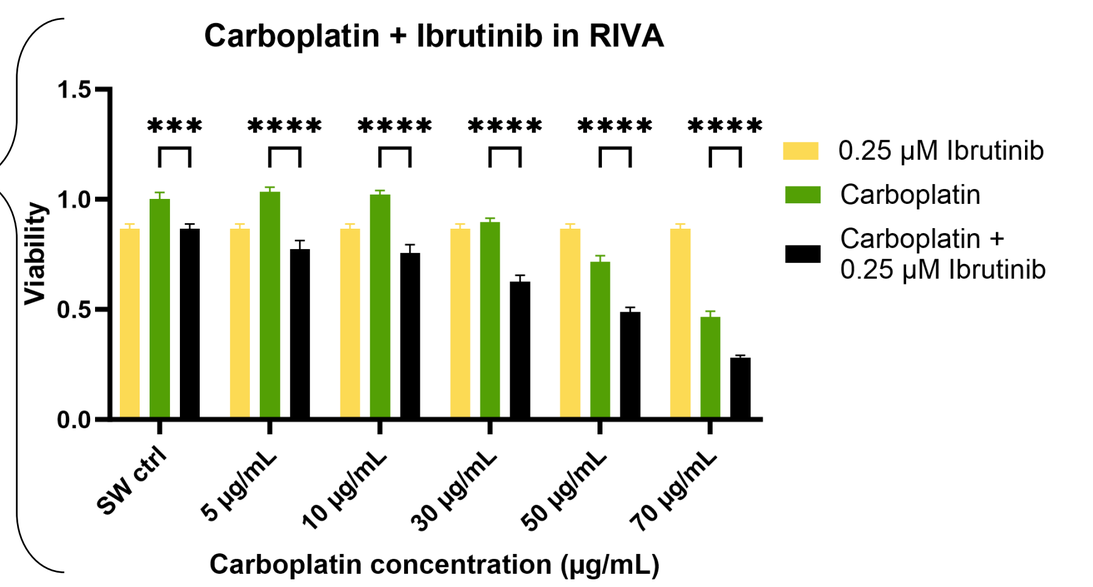
OCILY7

IBR \ CAR	0 µg/mL	5 µg/mL	10 µg/mL	30 µg/mL	50 µg/mL	70 µg/mL
0 µM	1.00	1.00	1.09	1.00	0.87	0.57
0.25 µM	0.98	0.74 (Bliss: -0.24)	0.73 (Bliss: -0.33)	0.76 (Bliss: -0.21)	0.66 (Bliss: -0.19)	0.39 (Bliss: -0.16)
1 µM	0.96	0.72 (Bliss: -0.25)	0.71 (Bliss: -0.34)	0.75 (Bliss: -0.21)	0.65 (Bliss: -0.19)	0.38 (Bliss: -0.17)
4 µM	0.79	0.63 (Bliss: -0.17)	0.58 (Bliss: -0.28)	0.6 (Bliss: -0.19)	0.52 (Bliss: -0.17)	0.31 (Bliss: -0.14)
16 µM	0.58	0.51 (Bliss: -0.08)	0.48 (Bliss: -0.15)	0.45 (Bliss: -0.13)	0.39 (Bliss: -0.12)	0.25 (Bliss: -0.08)
32 µM	0.14	0.15 (Bliss: 0.02)	0.14 (Bliss: -0.01)	0.09 (Bliss: -0.04)	0.08 (Bliss: -0.04)	0.05 (Bliss: -0.02)



RIVA

IBR \ CAR	0 µg/mL	5 µg/mL	10 µg/mL	30 µg/mL	50 µg/mL	70 µg/mL
0 µM	1.00	1.03	1.02	0.90	0.72	0.47
0.25 µM	0.87	0.77 (Bliss: -0.12)	0.76 (Bliss: -0.13)	0.63 (Bliss: -0.15)	0.49 (Bliss: -0.13)	0.28 (Bliss: -0.12)
1 µM	0.79	0.7 (Bliss: -0.11)	0.7 (Bliss: -0.11)	0.62 (Bliss: -0.09)	0.51 (Bliss: -0.05)	0.37 (Bliss: 0)
4 µM	0.70	0.67 (Bliss: -0.06)	0.64 (Bliss: -0.07)	0.58 (Bliss: -0.05)	0.49 (Bliss: -0.01)	0.4 (Bliss: 0.07)
16 µM	0.61	0.59 (Bliss: -0.05)	0.58 (Bliss: -0.05)	0.55 (Bliss: -0.01)	0.48 (Bliss: 0.04)	0.41 (Bliss: 0.13)
32 µM	0.35	0.34 (Bliss: -0.02)	0.33 (Bliss: -0.03)	0.31 (Bliss: -0.01)	0.28 (Bliss: 0.02)	0.25 (Bliss: 0.08)



SUDHL5

IBR \ CAR	0 µg/mL	2.5 µg/mL	5 µg/mL	7.5 µg/mL	15 µg/mL	30 µg/mL
0 µM	1.00	0.85	0.69	0.39	0.13	0.08
0.25 µM	0.88	0.67 (Bliss: -0.08)	0.45 (Bliss: -0.15)	0.27 (Bliss: -0.07)	0.07 (Bliss: -0.04)	0.02 (Bliss: -0.05)
1 µM	0.83	0.69 (Bliss: -0.01)	0.5 (Bliss: -0.07)	0.3 (Bliss: -0.02)	0.08 (Bliss: -0.02)	0.06 (Bliss: 0)
4 µM	0.82	0.63 (Bliss: -0.07)	0.48 (Bliss: -0.09)	0.3 (Bliss: -0.03)	0.08 (Bliss: -0.03)	0.04 (Bliss: -0.02)
16 µM	0.35	0.27 (Bliss: -0.02)	0.18 (Bliss: -0.06)	0.11 (Bliss: -0.02)	0.05 (Bliss: 0.01)	0.03 (Bliss: 0.01)
32 µM	0.05	0.04 (Bliss: 0)	0.03 (Bliss: 0)	0.03 (Bliss: 0.01)	0.03 (Bliss: 0.02)	0.02 (Bliss: 0.02)

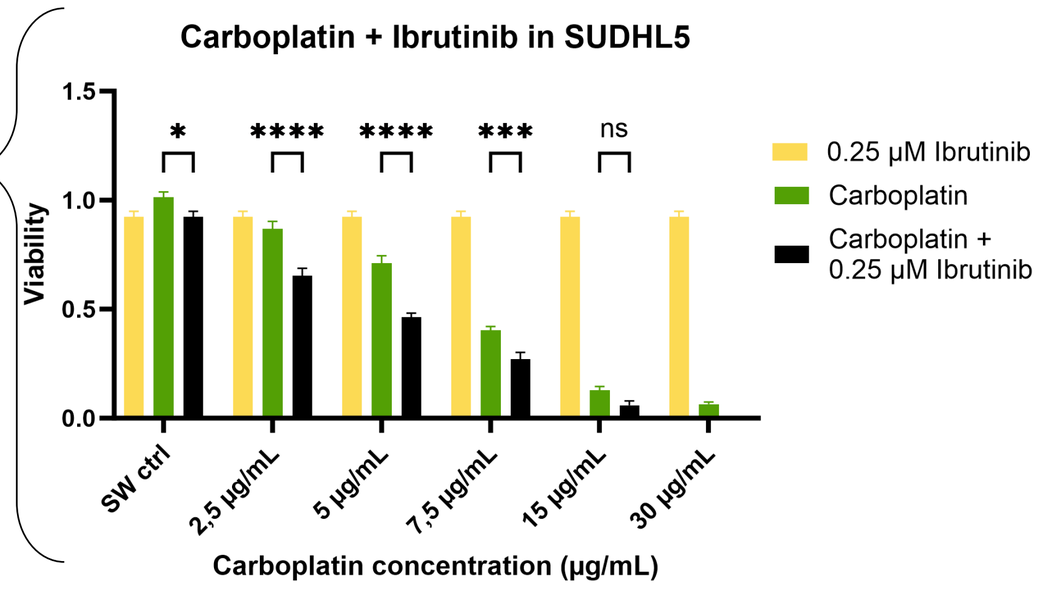
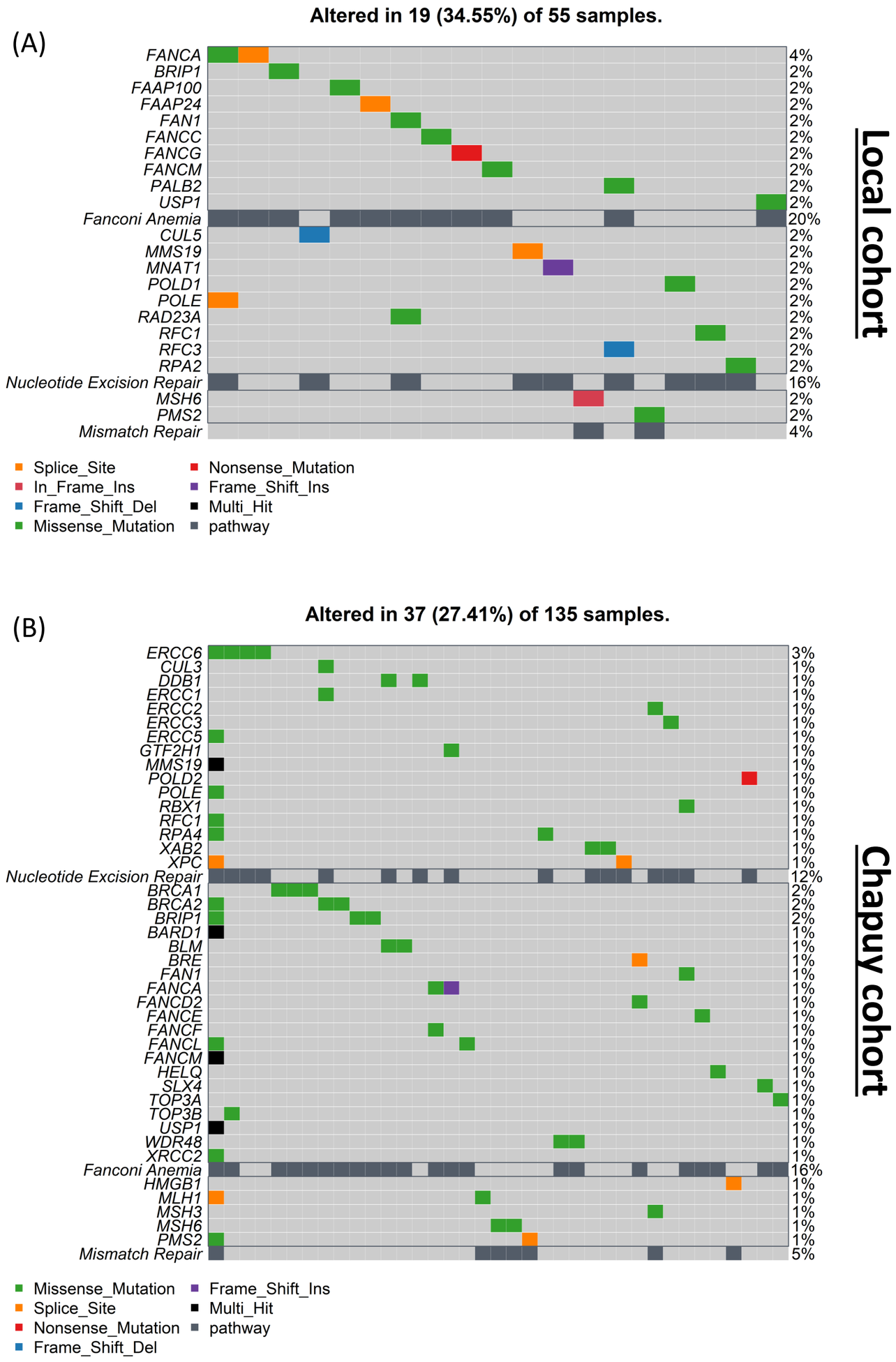


Figure S6


(A)
Altered in 19 (34.55%) of 55 samples.
FANCA 4%
BRIP1 2%
FAAP100 2%
FAAP24 2%
FAN1 2%
FANCC 2%
FANCG 2%
FANCM 2%
PALB2 2%
USP1 2%
Fanconi Anemia 20%
CUL5 2%
MMS19 2%
MNAT1 2%
POLD1 2%
POLE 2%
RAD23A 2%
RFC1 2%
RFC3 2%
RPA2 2%
Nucleotide Excision Repair 16%
MSH6 2%
PMS2 2%
Mismatch Repair 4%
Local cohort
Splice_Site
In_Frame_Ins
Frame_Shift_Del
Missense_Mutation
Nonsense_Mutation
Frame_Shift_Ins
Multi_Hit
pathway
(B)
Altered in 37 (27.41%) of 135 samples.
ERCC6 3%
CUL3 1%
DDB1 1%
ERCC1 1%
ERCC2 1%
ERCC3 1%
ERCC5 1%
GTF2H1 1%
MMS19 1%
POLD2 1%
POLE 1%
RBX1 1%
RFC1 1%
RPA4 1%
XAB2 1%
XPC 1%
Nucleotide Excision Repair 12%
BRCA1 2%
BRCA2 2%
BRIP1 2%
BARD1 1%
BLM 1%
BRE 1%
FAN1 1%
FANCA 1%
FANCD2 1%
FANCE 1%
FANCF 1%
FANCL 1%
FANCM 1%
HELQ 1%
SLX4 1%
TOP3A 1%
TOP3B 1%
USP1 1%
WDR48 1%
XRCC2 1%
Fanconi Anemia 16%
HMGB1 1%
MLH1 1%
MSH3 1%
MSH6 1%
PMS2 1%
Mismatch Repair 5%
Chapuy cohort
Missense_Mutation
Splice_Site
Nonsense_Mutation
Frame_Shift_Del
Frame_Shift_Ins
Multi_Hit
pathway
(C)
Altered in 26 (54.17%) of 48 samples.
ERCC5 8%
CUL4A 6%
ERCC1 4%
POLE 4%
RFC4 4%
ERCC2 2%
ERCC4 2%
GTF2H5 2%
LIG1 2%
POLD3 2%
RFC5 2%
XPA 2%
Nucleotide Excision Repair 27%
MSH3 8%
MLH1 6%
MSH2 2%
PMS1 2%
PMS2 2%
Mismatch Repair 17%
BRCA1 4%
BRIP1 4%
FANCD2 4%
PALB2 4%
TELO2 4%
APITD1 2%
BARD1 2%
BLM 2%
BRCA2 2%
FANCA 2%
FANCE 2%
FANCG 2%
FANCL 2%
FANCM 2%
HELQ 2%
XRCC2 2%
Fanconi Anemia 33%
TCGA cohort
Missense_Mutation
Splice_Site
Nonsense_Mutation
In_Frame_Del
Frame_Shift_Del
Multi_Hit
pathway