

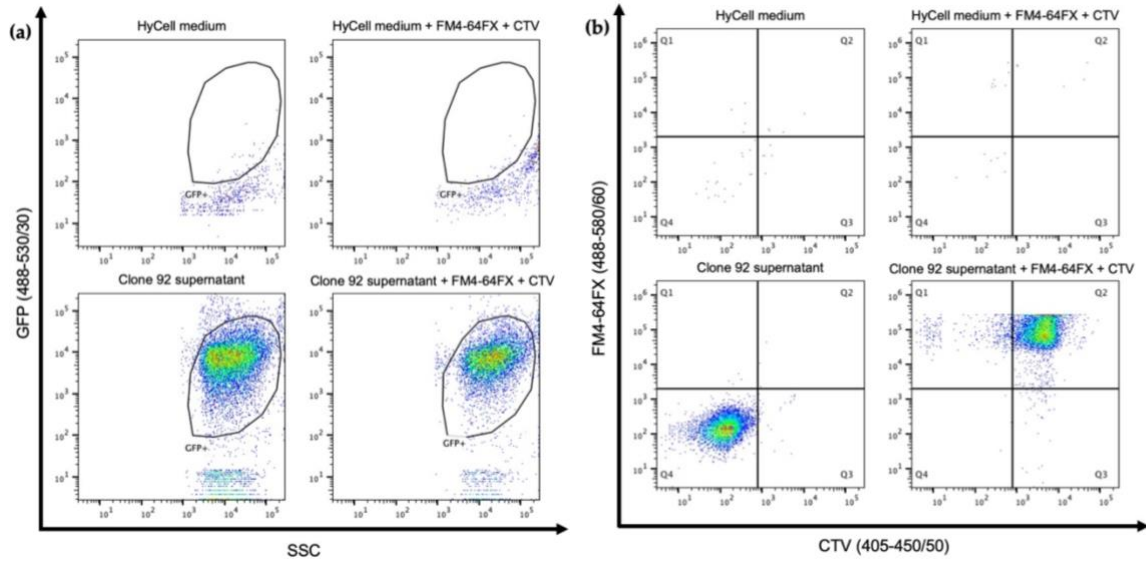


Figure S1. Analysis of Clone 92 supernatant by flow virometry. (a) GFP+ particles are depicted in the gate. The sample shown here as demonstration is $C^{92}EV_{sup}$ from day 7 of culture. (b) Double-positive events are in Q2. The sample shown here as demonstration is $C^{92}EV_{sup}$ from day 7 of culture.

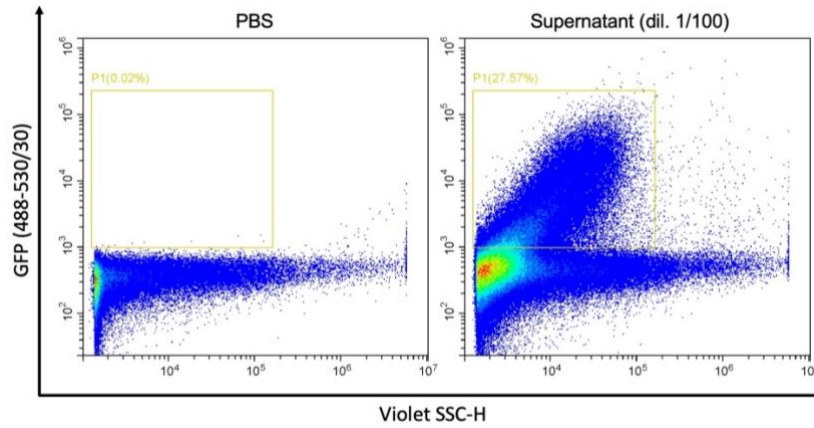


Figure S2. Flow virometry density plots showing size (violet side scatter) and green fluorescence (GFP) in the negative control PBS and an in-process Clone 92 sample (here supernatant at a dilution factor of 100). The gating P1 corresponds to GFP+ events (distribution indicated between brackets).

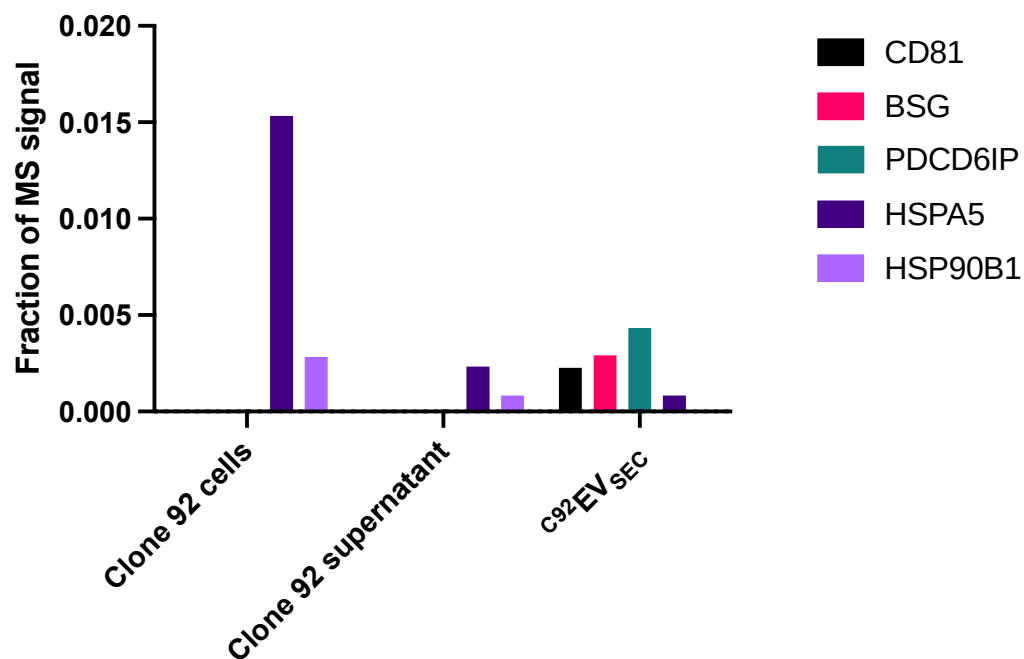


Figure S3. Enrichment of C92EVSEC shown by the increase in signal for CD81, BSG, and PDCD6IP and the depletion of cellular protein in EVs shown by a decrease in signal for HSPA5 and HSP90B1 compared to parent cells.

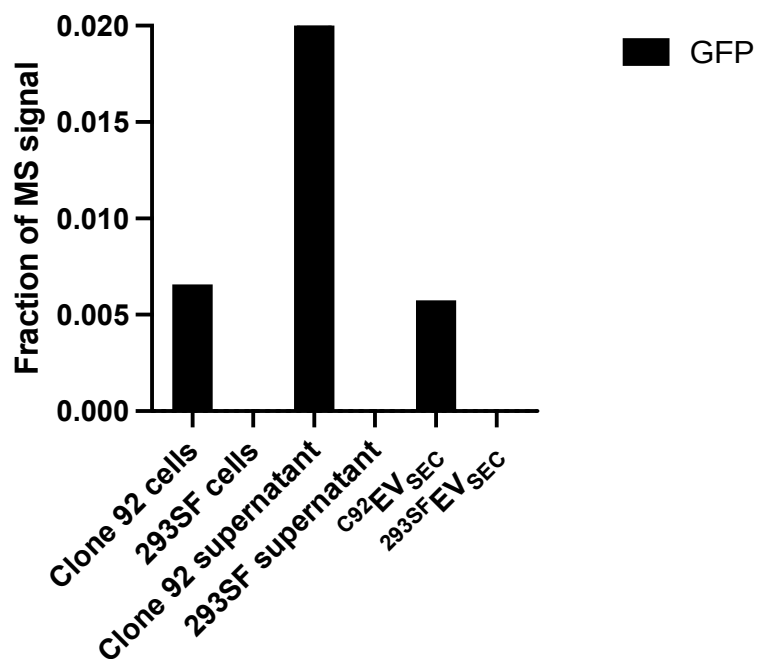


Figure S4. Presence of GFP in cells, supernatant and EVs from Clone 92.

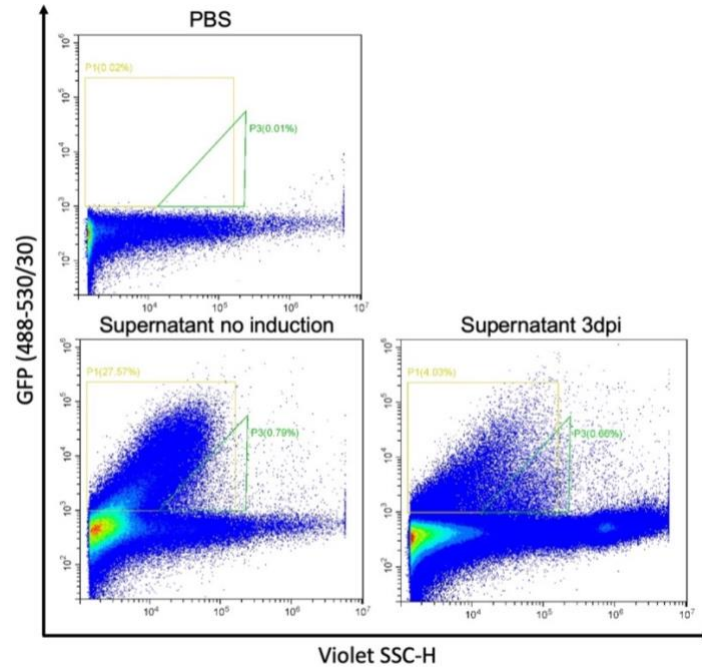


Figure S5. Flow virometry density plots showing size (violet side scatter) and green fluorescence (GFP) in the negative control PBS and in Clone 92 supernatants. The gating P1 corresponds to GFP+ events (distribution indicated between brackets) and P3 corresponds to large particles.

Table S1. List of all proteins identified in C92EV_{UC} and C92EV/LV_{UC} with a Mascot score > 30 and more than 1 peptide.

Only in C92EV _{UC}	Only in C92EV/LV _{UC}	Overlap C92EV _{UC} and C92EV/LV _{UC}
SYDE2	ASB2	USF3
RGPD3	SMARCA2	DCDC2B
FHOD3	DOCK6	STAG1
HEATR5B	C10ORF120	MAGI2
TRMT12	ZNF814	COL4A1
CASC3	TNRC6B	SMU1
AVEN	LRRK1	KLHL34
SNTB1	PDE4B	ADAMTS17
CHRD	ATN1	MPDZ
PIK3R2	KAZN	PATJ
SVBP	C16ORF62	SHC2
DLC1	HDAC4	HIST1H1C
PPM1H	HIVEP1	ZNF469
AKAP7	KLHL18	NSUN4
GLDN	DEPDC1	TTBK1
KMT2E	CDYL	BASP1
FMN2	UBE3B	CCDC63
PCOLCE2	ERAP2	HIST1H1E
RIPOR1	NEFM	HIST2H2AA3
CTU2	DDX17	ATP5PF
P2RY11	PES1	COL3A1

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
SLC22A10	RIOX1	TUBB6
NTRK3	MON1B	TUBB2B
BMS1	TNNI1	TUBB4B
SPATA31E1	BIRC6	TUBB
TEX13C	GLYCTK	JAK1
SETDB1	EXOC3	HSPG2
FAM120C	ARCN1	STIM1
AASS	AUTS2	PLXNA4
GJC2	RBM28	STK33
DNAJC17	PUM3	BANK1
PHLDB1	BRWD1	MOCOS
SKOR1	RPL14	UBC
CCDC177	ARID5B	UTRN
P3H1	POMGNT1	HIST3H2BB
PCNX2	ADGRL1	RAD54L
UTY	SYTL4	FASN
SPG11	MEIOB	COBL
PPP1R10	ODF2	RAB11FIP4
SRRM3	JAKMIP3	KIF27
MTR	NPR2	PIWIL2
CCDC13	SYMPK	CENPE
SRRM2	PVALB	AGBL3
FBXO21	FAM234A	ARMH1
MBD1	HECTD4	RFC1
DGKD	LNP1	SOX12
GOLGA4	ITPRID2	ABHD12
GRPEL2	HNRNPU	PDCD6IP
DNTTIP2	KLC3	RRBP1
ATG4C	SYNE2	SCG2
GMCL1	RAD51D	HIST1H1D
EWSR1	RPLP0	LENG8
UGGT2	DENND3	ENTHD1
SGSM2	RAD17	PKM
NOL8	FCHO2	OLFM4
MRPS27	CARMIL1	LGALS3BP
CCSER2	KDM3A	UBA1
ERICH6	CAMTA2	ITGA6
TYRO3	PPEF2	GCSH
WWC2	FAM129C	CCDC73
MCIDAS	RPL11	DOK1
CYP2J2	DDX27	PIK3C2B
PLBD1	CRYBG1	APC2
DBF4	U2AF1	APC
ENDOG	DHX33	RACK1
ESYT2	PDE12	CABLES2
KATNB1	HNRNPH1	GPR158
DDX54	MSH3	GALNT11
APBB1	RPL18	WDR7

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
NPAT	RPS20	DMXL1
RBM5	OOEP	TUBB3
RBM10	AMBRA1	CENPJ
PCDHA1	SETD2	ASPM
AKT3	GTPBP10	KIAA1107
CBLB	SFPQ	STX18
OGT	NPY5R	PCARE
RBM7	TRIM11	MYH6
CHD1L	NBEAL2	ATP2A2
NFRKB	ACAD10	CCDC88B
PCDHAC2	DNAH3	MED12
NEDD1	FAM81B	GARNL3
ZFP92	PRMT1	MRPL3
EHMT2	ANKRD26	CCT3
TMEM125	SLF1	HNRNPL
TRAV26-2	HIST2H2BD	USP37
USP36	RPS18	ESYT1
NIM1K	TRIM77	STOX2
OBSCN	YARS	GVINP1
ZNF594	ARHGAP32	HNRNPA1
SSH1	RALGAPA2	HIST1H2BN
SOWAHC	DIAPH2	HIST1H2BM
ZNF462	METTL26	COL5A2
TENM1	INPP4A	RNF168
PDCD11	ACACB	ROS1
SNX20	RHOA	ALB
TMEM199	CLIP1	EHMT1
ABCF2	MAD1L1	SMARCA5
PHF3	NAV2	USP24
TRIM37	RPL4	ZMAT3
CNGA3	MAST2	EIF2B2
IDI2-AS1	ZNF318	RFX2
THOP1	RTFDC1	NDUFAF4
AOPEP	VPS18	SLC45A1
DNHD1	SYDE1	MARCKS
TTC13	SHROOM1	CSN1S1
SIM1	RP1L1	KIT
KLHL38	TDO2	LRRK2
MYO18A	NLRP14	FLG
SRP54	ANLN	RPL29
ADGRV1	ARMCX5	TBRG4
ARID4A	MYCBP2	GFP
IQSEC2	GPALPP1	RSAD1
INPPL1	LMTK3	TNFAIP1
FOXRED1	KIR3DL3	DSCAM
RAB3IP	DIAPH3	ZNF142
SEL1L3	AK7	PTPRT
ATG14	RBBP8	LRFN4

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
ZNF638	COL9A3	MTHFD1
ZBTB40	RAD50	CROCC2
RITA1	POLR3C	PCGF2
CCDC7	AXIN1	COL25A1
RABEP1	WDR36	NCAPD3
KCTD18	JPH1	LACTB
MYO6	ATP10B	TALDO1
DNAH14	INTS10	PARP1
RIC3	POMC	PXDN
MINK1	MRPL4	DNAH9
SCARB1	ATP5PO	KDM5C
SDCBP	EIF2S2	INTS1
NLRP3	ARHGEF2	PDE4D
AHNAK	CALML4	SRCAP
RBMXL2	GPRIN1	KIF5C
CTNNB1	KDM4D	RNASEH2B
EML6	HMG20B	TUBA1A
BCAS3	RPS2	KCTD10
TNIK	VPS11	ATP2A1
CD163L1	TRMT5	DNAH1
GLDC	MKI67	SSPO
TDRD6	ZKSCAN5	RPA1
ANXA11	RPS3A	LMNA
ROBO4	ARHGEF17	KCTD16
FLOT1	SECISBP2	MARCKSL1
TDRD5	SCD5	HNRNPC
PLD3	PEG3	SYNRG
AP2A2	ABCA12	PGK1
HTRA1	EVC2	TUSC1
MESP2	CCER1	MDK
VPS13D	ERBIN	RBBP6
NEB	CEP89	TRPC3
EPS8L1	PWP2	MACF1
DMXL2	SAFB	AKAP3
COL6A2	HNRNPM	SYNE1
CSMD1	OSGIN2	ZNHIT2
LRP1	OR2T1	ZBED9
DYNC2H1	ADGRL2	C12ORF57
RYR1	FAM243A	VPS33B
NIN	NFKBIL1	GAL3ST4
PDE3A	RPS27	HSPA1A
PLCL1	PLD2	WEE1
ALX1	PSRC1	AKAP12
USP42	CALCOCO1	DNAJA4
MYO1A	ZNF764	TMEM132A
CCDC158	IQCJ-SCHIP1	ZC3H18
PCDHA10	CEP112	PTGFRN
SLC26A4	FGF4	CACNA1E

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
C1QB	CUL9	PKLR
LCA5	DNM1	RPGRIP1
SYCP1	MTHFD1L	APOE
PLCE1	FARSB	SCAP
SRI	GPR50	LONRF3
COL2A1	CTPS1	COL23A1
TOLLIP	PCF11	REV1
UNC13A	RANBP2	CNOT11
SYCP2	JAM3	FOXF2
SLC2A12	MTHFSD	PROCA1
ARG1	PCBP2	NUP153
HIBADH	HACD1	KMT2D
CACNA1F	PLXNB1	OXNAD1
FGD6	WDR3	GUSB
SUMO1	FAM89A	HMCN1
LAMA5	RPS26	ARNTL2
LPO	MAP7D3	DPP6
FAM135A	ALMS1	PDLIM5
	PUSL1	HYDIN
	CDC5L	SCN9A
	RPL13	UTP18
	RAI1	LRBA
	INTS4	NBEA
	KIF28P	SLC22A7
	KARS	ATP1A1
	HES2	TEX10
	SF3B3	EIF2S3
	RPLP2	EPM2A
	MPHOSPH9	CWF19L2
	EIF4G3	GCN1
	HPCAL4	ACTG1
	NKTR	DSP
	IFT88	NFKBIE
	BCAR3	ACTC1
	PRPF19	CPT1B
	CCDC66	C2ORF16
	ZNF236	RAN
	IQUB	ACTBL2
	RPS8	DNAH11
	ZC3H11B	FAM43A
	NPHP3	ALKBH8
	RPL22	SHROOM3
	GAB2	TNRC18
	ZBTB39	CLU
	TOPAZ1	EYS
	BICD1	TMCO5B
	RPS11	RPL23A
	NOP58	AHCY

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
	MAP10	FSIP2
	DENND5A	DSG1
	FBXO15	PRODH
	TEDC2	IQCE
	ZNF644	FGA
	COG5	SRCIN1
	RPL36	ACACA
	CLIP4	IQGAP2
	C9ORF66	ZNF397
	ZC3H3	CD81
	SOX6	RPH3A
	PNN	ANAPC4
	RABEP2	GTF3C1
	JRK	PCDHB3
	GOLGA8S	HSP90AA1
	EIF2B4	UNC80
	TRAF3IP1	RPTN
	STRAP	COX4I2
	FGFR2	TAF1
	FGFR4	MECOM
	KIAA0753	RPS16
	CLK1	EXPH5
	CEP162	MTERF3
	IRF2BP1	TSPAN7
	NMT1	CCT6B
	RPL10	HSPA1L
	DIS3	PIK3C2A
	MCM4	MYO15A
	MMTAG2	GFAP
	NLRC3	KIAA1109
	SLIT1	CAPS
	KMT2A	TTN
	TCF20	SPEN
	RPS23	ATAD5
	TOGARAM1	HNRNPK
	CCDC196	HMGNI
	SUMF1	DARS
	UNC13D	JMJD1C
	ARID4B	PNPLA8
	COL27A1	PTPN14
	SCAF4	ARNTL
	IRAK1BP1	PRC1
	RPL23	PPL
	CCDC69	CLTC
	HMBS	C1ORF167
	SPTY2D1	PPP1R9B
	PCDHB11	GAPDH
	SPATA31D1	A1BG

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
	SRSF2	CGNL1
	RPL3	MAP4K4
	HIRIP3	PSMG3
	SHTN1	PSMD2
	JPH3	CKAP5
	RPS17	FARSA
	SSRP1	PRKDC
	SRSF8	PLEC
	ARHGEF10L	NAALAD2
	RAPH1	TRIP12
	QARS	SYNPO2
	HNRNPD	EXOC3L1
	CDAN1	OPTN
	DYNC1I2	NPEPPS
	RPL19	NUP50
	EID3	HECW2
	NPBWR2	FPGT
	CCDC88C	ZNF775
	NEXMIF	ALPK3
	TIAM1	LMNB2
	SRSF1	HSPA8
	GMPS	PDPR
	TET2	RNF213
	RPL8	ZSWIM4
	EIF5B	COPB1
	COL5A3	MUC16
	EXOC8	GPCPD1
	MICALCL	ADAM15
	INSRR	MFGE8
	GPAT4	CD6
	SART3	CCDC186
	SRM	LAMA1
	MRPL46	SMC2
	IGF2BP3	YWHAQ
	ZNF404	GOLIM4
	SON	L3HYPDH
	POLD1	FAM160A2
	DMAC2	HSPA2
	COL11A1	C2CD3
	DNAJC11	ULK2
	ERVK-21	HMG5
	RPS6	MFN1
	CGN	SNW1
	ELOVL7	SVIL
	ILF2	RPS3
	HNRNPA3	HSP90AB1
	SDE2	ZFP28
	PRRC2B	FAT2

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
	FRMPD3	SPATA2
	TEX15	PSMD3
	SLC24A1	CEP44
	POLG	PYGL
	GPR119	ENO1
	ISPD	ZNF804A
	EGLN1	ITPR3
	TTF1	HMG2
	ABCB4	CFAP65
	PCLAF	PPP1R12C
	LEO1	SDHB
	MED4	RIMS1
	FN3KRP	CEP350
	TSGA10	NFE4
	ATG7	RRP15
	UBN2	MYO9A
	CFAP100	LIPE
	RPL35	APOB
	SERPINA12	CHD9
	C5ORF51	HSPA5
	SRSF4	SPTBN5
	NAA38	UBAP1
	MED25	TPP1
	OGA	KIAA1217
	CCDC83	ALPL
	KIF2B	SMARCA4
	RBM33	MUC19
	EID2	TENM3
	RASL11B	STRN3
	FNDC1	SOX11
	HUNK	ATP1A3
	ICAM3	ATP1A2
	SCN10A	RPS5
	TGOLN2	ANKRD18A
	ACTR1A	TECTA
	PYGM	OR4N2
	TCP1	MYH7B
	EEF1A1	NONO
	ASL	FAM136A
	XRCC6	GBF1
	PLIN2	RAB11FIP1
	CCT4	KIF22
	POLK	CROCC
	ASH1L	RBMXL3
	MYL2	UHRF1BP1L
	CCT6A	LRRC47
	SPINK5	VIM
	MYO7A	PRELID3B

Only in C ⁹² EV _{UC}	Only in C ⁹² EV/LV _{UC}	Overlap C ⁹² EV _{UC} and C ⁹² EV/LV _{UC}
	PHGDH	EEF2
	PSMB6	MYH4
	CLVS2	MYH8
	ALOX12	MYH7
	CCT2	MYH1
	ZNF503	TUBGCP3
	CCT5	DNAH17
	TYW1B	CABIN1
	POTEKP	CBX8
	KPNB1	RNF6
	ATP6AP1	KIAA1671
	H2AFV	GOLGA6C
	GNB2	DHX36
	GNB1	NME2
	CLIC6	CKB
	FMR1	IGF2R
	TC2N	HSPA6
	ERCC6L2	VCL
	RUVBL1	UBA2
	LRP4	POTEI
	SLC12A3	POTEE
	NPTN	PSMD11
	UNC13C	SFSWAP
	EIF4A1	ACLY
	NEK10	PCLO
	SCN11A	IQSEC1
	BRIP1	ASPH
	TRAP1	TOP2A
	FCN2	CFL1
	KIF3A	NF2
	UNC5D	POLQ
	LRRCC1	ABHD16A
	RREB1	PGBD5
	GLYAT	LGB
	ARHGEF1	PPIA
	H1FOO	ANXA2
	ITGB1	WDR87
	APOH	GNG12
	ARF3	CIT
	TKTL2	AHNAK2
	BSG	TF
	COL17A1	LONP1
	CEP104	TCF7L2
	USP31	EMILIN3
	AOX1	TXLNG
	PPP1R3A	SARS2
	SMC5	RAP1A
	TJP2	PCDHA8

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
	NAV3	MAP1B
	TRANK1	TUBA3E
	NT5E	TGM3
	DNAH10	TAGAP
	CHD2	RPS14
	FAT3	ZNF514
	CLIC1	PPM1D
	NOX5	TRIM3
	MSN	PDE4DIP
	P2RX4	LARS
	CMPK2	CARD14
	PRX	EZR
	FMNL1	SLTM
	PACSIN1	MYH13
	DHX37	AGAP9
	EIF3A	EEF1G
	PPP2R1A	EEA1
	RPS15A	RBM12
	HNRNPR	ZNF205
	ERP44	RUFY1
	LTB4R	HDLBP
	PRDM15	EIF3B
	PROM1	UHRF1
	DCXR	SACS
	CALB1	COL4A2
	DTX3L	PM20D1
	YWHAG	CCT8
	PRDX1	ENO3
	RUVBL2	CHD7
	PDCD10	ALAD
	PRDX6	LZTS3
	RDX	ASCC3
	PSMD13	HLA-A
	PTPRK	CAMTA1
	RPL30	FLG2
	DHX9	DCD
	FLNA	FEZF1
	PSMA1	RPS13
	PFKP	NMT2
	APRT	CSN1S2
	PTPRZ1	ZFYVE26
	NRXN1	RBBP4
	YWHAE	PDIA4
	TPI1	SPECC1L
	FBN1	FO XK1
	FAM83F	ANK3
	LDHA	GOLGB1
	COL18A1	CTNNA2

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
	PCBP1	CTNNA1
	MAGI3	PTPRB
	XPO7	TNRC6A
	ZNF853	UHMK1
	DDX5	NFX1
	ARHGAP22	TRIM28
	COL4A4	PRAMEF20
	ZNF415	SYNJ1
	COL5A1	ANKHD1
	KANK3	QRICH2
	PSMC2	VWA8
	TDRD9	ENOX1
	CDK1	PLXNB3
	NPM1	GRIK2
	CHCHD3	GNAS
	PFKL	TDRD15
	NKX6-1	MRPS22
	CAPZA1	STN1
	XIRP1	RRM1
	CLIP2	EIF4A3
	SHROOM2	KMT2B
	SLC16A1	MPC2
	FILIP1	WWC3
	RTN1	RPSA
	CDC42	ARHGAP23
	MIA3	ENAH
	LDHB	MRPL52
	PSMA3	CCT7
	HLA-C	PSMC5
	MYO16	FEZF2
	HNRNPA2B1	CILP2
	MYH10	SMYD2
	MYH9	GNAI1
	STAU1	MVK
	PSMD12	NCOR2
	EIF3C	MYO7B
	PPP1CA	GNPAT
	CDH6	KLHL12
	ZNRF1	DHTKD1
	STOM	DSCAML1
	COPA	ALDOA
	RPS10	ZNF516
	CRYBG3	LMF1
	PA2G4	UBE2M
	HSP90AA5P	XPO1
	EPRS	SRRT
	PSMD7	RPL12
	ARF5	AP4E1

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
	AMY1A	DGKG
	RAC1	HRNR
	TEX14	DYNC1H1
	PPP2CA	TOP1
	GLT8D2	SAMM50
	PKN2	TNS1
	COBLL1	GNG5
	HLA-G	SPTAN1
	ABT1	FAM200A
	DDX39B	CLTCL1
	PSMD1	ABCA2
	DDX3Y	ZNF746
	PSMD6	NASP
	FAM186B	TH
	PSMD14	SLC1A5
	GLUD1	ERVK-9
	PKD1L1	WDR33
	GRIP1	EIF3F
	DNAH6	CAPN5
	STYK1	VPS13C
	SLC6A3	UROC1
	ACAT2	PASK
	BPI	PPP1R12A
	RAB1A	M6PR
	BUB3	ACSF2
	AFP	HIP1
	FSCN1	MCM2
	RPL10A	SPAST
	SORCS1	GOLGA5
	FBN2	SETD1A
	RBM44	EEF2K
	PSMC6	ATIC
	ERVK-19	RPS4X
	LIFR	LIMCH1
	PAN3	DIP2A
	GART	RHOA
	SPEF2	TERT
	MICAL3	PARD6A
	ARF6	KCNH5
	IGF2BP1	PRAG1
		ANXA1
		TYMSOS
		PLK1
		F13A1
		POLN
		AGER
		KCNA7
		XRCC5

Only in ^{C92} EV _{UC}	Only in ^{C92} EV/LV _{UC}	Overlap ^{C92} EV _{UC} and ^{C92} EV/LV _{UC}
		PENK
		SIPA1L1
		TMEM214
		EDC4
		MRPS5
		GNAI3
		SLC26A8
		CUEDC1
		RNF8
		DACT1
		ASPRV1
		CCNF
		EIF3L
		MUCL3
		TPR
		DNAH7
		INCENP
		IQCC
		KCNMA1
		CSE1L
		C1ORF94
		GTF3C5
		VAMP3
		MRPL51
		TMTC1
		MYH3
		KCNJ9
		DST
		RAB21
		NEDD4
		KIF3C
		ZZEF1
		ATP1A4
		NOP53
		AKR7A2