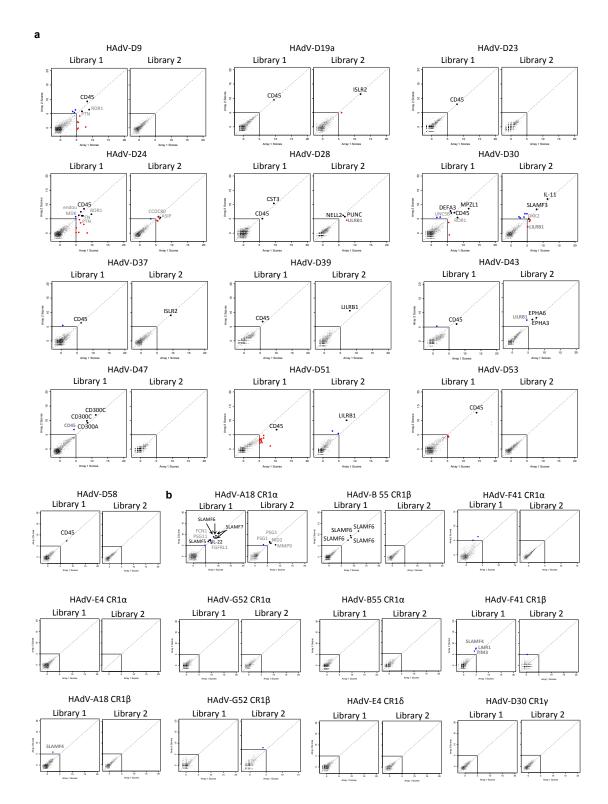
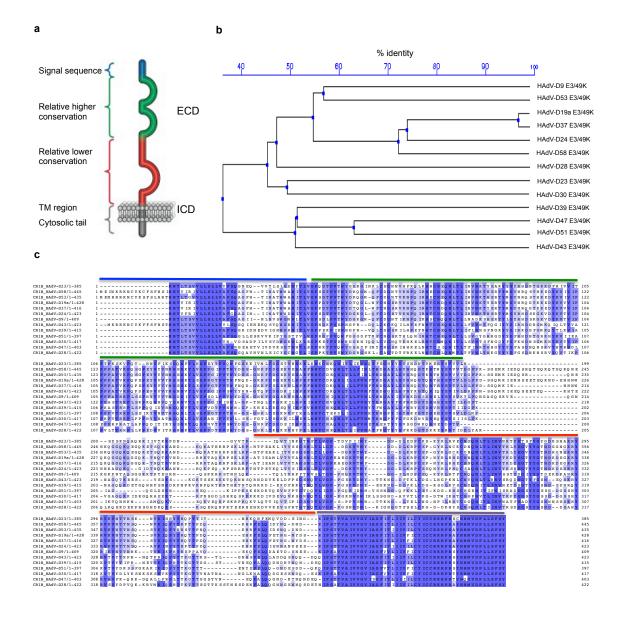


Supplementary Figure 1 (associated to Figure 1). The highly divergent HAdV E3 genes encode for predicted extracellular proteins. (a) UPGMA tree depicting the percentage of sequence identity shared by the HAdV E3 proteins analyzed in this study. (b) In silico prediction of transmembrane regions and signal peptides in the proteins encoded by the HAdV CR1 α , CR1 β , CR1 γ and CR1 δ genes. Phobius server was used to generate the plots shown.

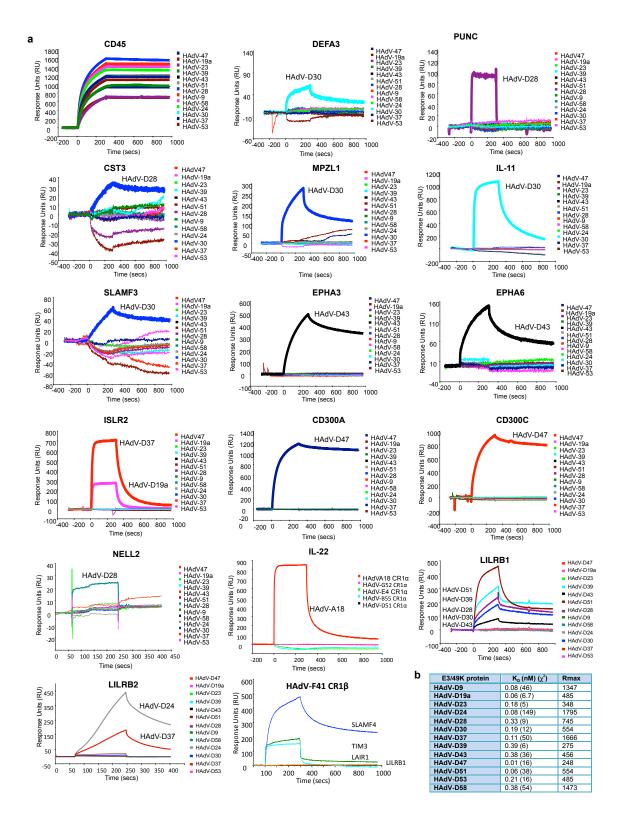


Supplementary Figure 2 (associated to Figure 2). HAdV variability imparts conserved and type-specific targeting of host receptors. (a) Intersection plots obtained for the HAdV species D E3/49K proteins selected for this study. Red and blue dots represent hits called on only a single array replicate, and black dots labeled in grey color indicate hits that were not selected for further

validation. (**b**) Intersection plots obtained for the rest of E3 proteins studied. Data were represented as in (a). The HAdV-D CR1 α , HAdV-E CR1 β and HAdV-B CR1 γ proteins were also screened; however, the results obtained for these proteins could not be analyzed due to strong non-specific binding to the microarray slides (not shown).

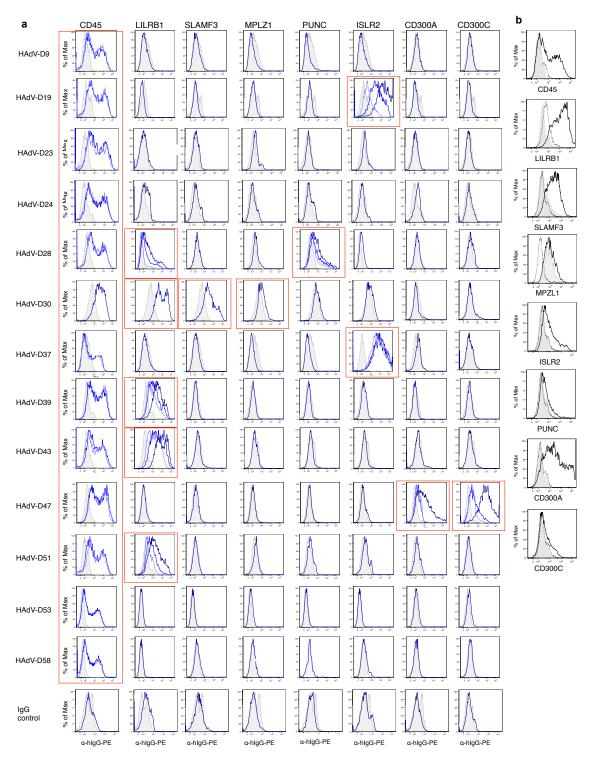


Supplementary Figure 3 (associated to Figure 2). Sequence diversity of the HAdV-D E3/49K proteins studied. (a) Schematic showing the E3/49K protein predicted structure, containing 3 predicted Ig-like domains followed by a transmembrane region and a short cytoplasmatic domain. (b) UPGMA tree showing the percentage of sequence identity shared by the 13 E3/49K proteins analyzed in this study. (c) Sequence alignment of the 13 E3/49K proteins studied. Blue bar indicates the position of the predicted signal peptide. Green bar shows the boundaries for Ig-like domains 1 and 2, which show a higher relative conservation within viral types. The region highlighted with a red bar represents the Ig-like domain 3, which shows the highest sequence variability among the E3/49K proteins. Purple bar indicates the transmembrane and the highly conserved intracellular regions. Abbreviations: ECD, extracellular domain; ICD, intracellular domain; TM, transmembrane region.



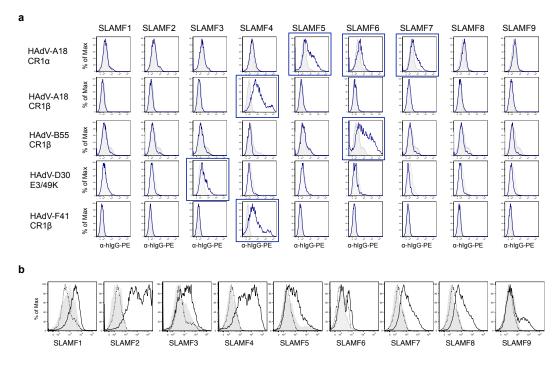
Supplementary Figure 4 (associated to Figure 2). Surface plasmon resonance validation of the E3 protein-host interactions identified and E3/49K CD45 binding affinity. (a) All E3 proteins were immobilized on sensor chips and the ECD of the indicated human proteins,

expressed as purified recombinant proteins, were run as analytes. IL-11, IL-22, LILRB1 and LILRB2 were immobilized on sensor chips and the E3 proteins were run as analytes. Analyte concentrations used in each case are as follows: CD45, 25 nM; Defensin3A, 475 nM; PUNC, 55 nM; CST3, 61 nM; NELL2, 200 nM; IL-11, nM; SLAMF3, 100 nM; EPHA3, 59 nM; EPHA6, 59 nM; ISLR2, 58 nM; CD300A, 113 nM; CD300C, 113 nM; MPZL1, 122 nM; TIM3, 500 nM; SLAMF4, 100 nM; LAIR1, 500nM. IL-11 (16-60 nM, HAdV-D30 E3/49K was run at 18 nM; IL-22 (the indicated viral proteins were injected at 500 nM); LILRB1 and LILRB2 (E3 proteins injected at 200 nM). Similar RU (4000-6000) were immobilized in all cases. Positive binders have been labeled for the ease of visualization. Assays shown are representative of two independent assays. (b) Affinity constants for the interaction between the E3/49K proteins and recombinant purified CD45RO ECD. Binding affinities are shown as K_D (nM) values. Rmax and χ^2 values indicate the goodness of the experimental fitting.

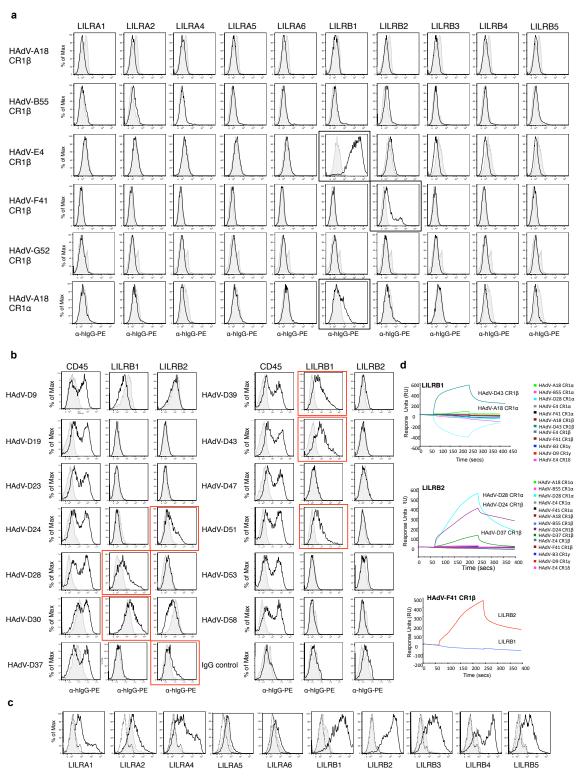


Supplementary Figure 5 (associated to Figure 2). The E3/49K proteins specifically target the cell surface receptors identified. (a) HEK293T cells were transfected with each of the receptors identified as hits and binding of soluble E3/49K proteins was analyzed by flow cytometry. Grey filled histograms represent binding of the E3/49K protein to wt cells (100 nM). Light, navy and dark blue histograms represent binding to the hit-transfected cells, at 1, 10 and

100 nM concentration, respectively. Due to binding of the HAdV-D30 E3/49K protein to non-transfected cells and for the ease of visualization, binding at one concentration is represented (100 nM). Red boxes indicate the interactions identified by the protein microarray screening. Histograms are representative of three independent assays. (b) Expression of each receptor on the surface of HEK293T cells used in a representative assay. Gray histograms show the expression of each receptor at the surface of non-transfected cells and black histograms indicate the surface expression in receptor-transfected cells, detected using specific antibodies. Dotted histogram represents isotype control binding.

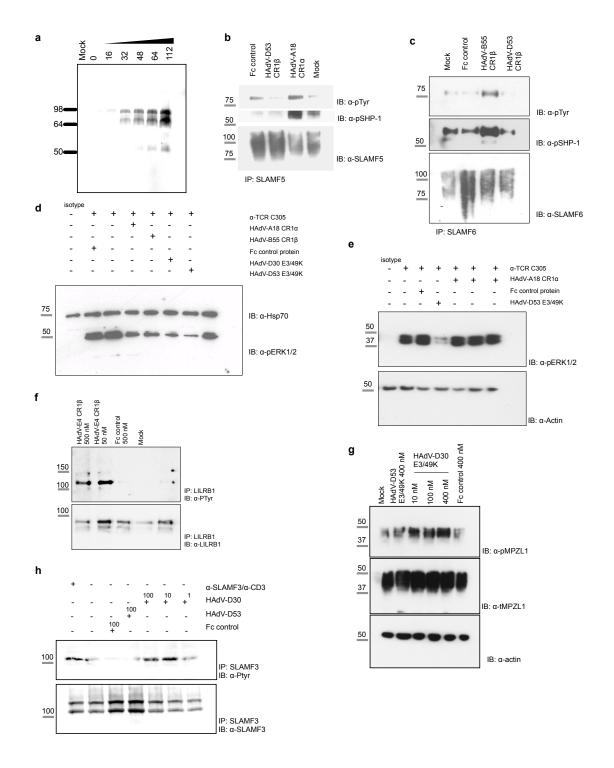


Supplementary Figure 6 (associated to Figure 5). (a) Binding of the E3 proteins to HEK293T cells expressing SLAM receptors. Grey and blue histograms represent binding to wt and SLAMF-transfected cells (200 nM), respectively. Blue boxes indicate the interactions identified. All E3 proteins were screened for binding to the SLAM receptor family; the HAdV-B CR1γ protein strongly interacted with wt cells precluding further analysis (not shown). (b) Expression of each SLAM receptor on the surface of HEK293T cells used in a representative assay. Gray histograms show the expression of each receptor at the surface of non-transfected cells and black histograms indicate the surface expression in receptor-transfected cells, detected using specific antibodies. Dotted histogram represents isotype control binding.



Supplementary Figure 7 (associated to Figure 5). Interaction of HAdV E3 proteins with the LILR family. (a) HEK293T cells were transfected with 10 LIL receptors and the binding of the indicated E3 proteins (200 nM) was analyzed by flow cytometry using an antibody directed against the Fc tag. The HAdV-E CR1β protein strongly interacted with surface LILRB1. HAdV-

F41 CR1β bound to LILRB2 whereas the HAdV-A18 CR1α targeted LILRB1. (b) Flow cytometry analysis of E3/49K binding (100 nM) to HEK293T cells transfected with LILRB1 or LILRB2. Gray and black histograms represent viral protein binding to wt and LILR-transfected cells, respectively. Red boxes indicate the interactions identified. Binding to the E3/49K proteins to all LIL receptors was analyzed by flow cytometry (not shown). (c) Histograms showing the expression of the LILR members at the surface of the cells used for the analysis. Gray histograms show the expression of each receptor at the surface of non-transfected cells. Receptor expression at the surface of transfected cells is represented by the black histograms. Dotted histograms show staining with an isotype control antibody. Assays are representative of two independent experiments. (d) Analysis of E3 protein binding to LILRB1 and LILRB2 by SPR. LILRB1 and LILRB2 ECD were immobilized on sensor chips and binding of the indicated viral proteins, injected at 200 nM, was analyzed. In the case of the HAdV-F41 CR1β protein, the viral protein was immobilized on a sensor chip and LILRB1 and LILRB2 ECDs were run as analytes (200 nM). Positive binders have been labeled on the plots for ease of visualization.



Supplementary Figure 8. Full immunoblots corresponding to the assays shown throughout the manuscript. (a) Analysis of E3/49K secretion from HAdV-D28-infected cells. Related to Fig. 3 (b) Receptor activation in SLAMF5 immunoprecipitates after stimulation with the indicated viral proteins (related to Fig. 4). (c) Receptor activation in SLAMF6 immunoprecipitates after stimulation with the indicated viral proteins (related to Fig. 4). (d) Analysis of ERK1/2

activation in Jurkat cells upon cell stimulation with an anti-TCR antibody and the indicated viral proteins (related to Fig. 4). Last lane (unlabeled) shows an additional protein not studied in the current work. (e) ERK1/2 activation in SLAMF5 KD Jurkat cells upon stimulation with the indicate proteins and an anti-TCR antibody (related to Fig. 4). (f) Receptor activation in LILRB1 immunoprecipitates upon stimulation with the indicated viral proteins. Last lane (unlabeled) shows an additional protein not studied in the current work (related to Fig. 5). (g) Activation of the receptor MPZL1 upon stimulation with the indicated viral proteins (related to Fig. 7). (h) SLAMF3 activation upon stimulation with the indicated viral proteins analyzed in receptor immunoprecipitates (related to Fig. 7). Molecular sizes are indicated in KDa.

Supplementary Table 1. List of the proteins included in the Microarrays and their corresponding UniProt ID.

Gene name	UniProt ID	Gene name	UniProt ID	Gene name	UniProt ID
A2M	P01023	ANGPTL4	Q9BY76	BGLAP	P02818
ABHD14A	Q9BUJ0	ANGPTL6	Q8NI99	BGN	P21810
ABP1	P19801	ANGPTL7	O43827	BMP10	O95393
ACE2	Q9BYF1	ANTXR1	Q9H6X2	BMP15	O95972
ACP6	Q9NPH0	APCDD1	Q8J025	BMP6	P22004
ACRV1	P26436	APCS	P02743	BMPR1A	P36894
ACVR1	Q04771	APLP1	P51693	BMPR1B	O00238
ACVR1B	P36896	APOA1	P02647	BMPR2	Q13873
ACVR1C	Q8NER5	APOA2	P02652	BOC	Q9BWV1
ACVRL1	P37023	APOA4	P06727	BOLA1	Q9Y3E2
ADAM10	O14672	APOC1	P02654	BPI	P17213
ADAM11	O75078	APOC2	P02655	BPIFA2	Q96DR5
ADAM12	O43184	APOD	P05090	BPIFB1	Q8TDL5
ADAM15	Q13444	APOE	P02649	BPIFB2	Q8N4F0
ADAMTSL1	Q8N6G6	APOF	Q13790	BSDC1	Q9NW68
ADAMTSL5	Q6ZMM2	APOH	P02749	BSG	P35613
ADCYAP1	P18509	APP	P05067	BST1	Q10588
ADIPOQ	Q15848	AREG	P15514	BST2	Q10589
ADM	P35318	ART3	Q13508	BTD	P43251
AFM	P43652	ART4	Q93070	BTLA	Q7Z6A9
AGER	Q15109	ART5	Q96L15	BTN1A1	Q13410
AGR2	O95994	ARTN	Q5T4W7	BTN2A1	Q7KYR7
AGR3	Q8TD06	ASAH1	Q13510	BTN2A2	Q8WVV5
AGT	P01019	ASGR1	P07306	BTN2A3P	Q96KV6
AHSG	P02765	ASGR2	P07307	BTN3A1	O00481
AIF1L	Q9BQI0	ASIP	P42127	BTN3A2	P78410
ALB	P02768	ASPN	Q9BXN1	BTN3A3	O00478
ALCAM	Q13740	ASTL	Q6HA08	BTNL8	Q6UX41
AMBN	Q9NP70	ATP1B1	P05026	BTNL9	Q6UXG8
AMBP	P02760	ATRAID	Q6UW56	C10orf54	Q9H7M9
AMD1	P17707	AXL	P30530	C10orf99	Q6UWK7
AMELX	Q99217	AZGP1	P25311	C11orf24	Q96F05
AMICA1	Q86YT9	B2M	P61769	C11orf68	Q9H3H3
AMIGO2	Q86SJ2	B3GNT1	O43505	C11orf83	Q6UW78
AMTN	Q6UX39	B4GALT7	Q9UBV7	C12orf39	Q9BT56
AMY1A	P04745	BAMBI	Q13145	C12orf53	Q8IYJ0
AMY1C	P04745	BCAM	P50895	C14orf37	Q86TY3
AMY2B	P19961	BCAN	Q96GW7	C15orf24	Q9NPA0
ANG	P03950	BCHE	P06276	C17orf99	Q6UX52
ANGPTL2	Q9UKU9	BCL10	O95999	C19orf18	Q8NEA5
ANGPTL3	Q9Y5C1	BDNF	P23560	C19orf38	A8MVS5

C10 - "f=0	0017/40	CDINA	CONTLIZ	CD244	000714/0
C19orf59	Q8IX19	CBLN4	Q9NTU7	CD244	Q9BZW8
C19orf63	Q5UCC4	CCDC104	Q96G28	CD27	P26842
C1orf159	Q96HA4	CCDC126	Q96EE4	CD274	Q9NZQ7
C1orf186	Q6ZWK4	CCDC134	Q9H6E4	CD276	Q5ZPR3
C1orf187	Q8NBI3	CCDC47	Q96A33	CD28	P10747
C1orf198	Q9H425	CCDC80	Q76M96	CD300A	Q9UGN4
C1orf43	Q9BWL3	CCK	P06307	CD300C	Q08708
C1orf85	Q8WWB7	CCL1	P22362	CD300E	Q496F6
C1QA	P02745	CCL11	P51671	CD300LB	A8K4G0
C1QB	P02746	CCL13	Q99616	CD300LD	Q6UXZ3
C1QTNF3	Q9BXJ4	CCL14	Q16627	CD300LF	Q8TDQ1
C1QTNF9	P0C862	CCL16	O15467	CD300LG	Q6UXG3
C1QTNF9B	B2RNN3	CCL17	Q92583	CD302	Q8IX05
C1R	P00736	CCL18	P55774	CD320	Q9NPF0
C1RL	Q9NZP8	CCL19	Q99731	CD33	P20138
C1S	P09871	CCL2	P13500	CD3D	P04234
C20orf3	Q9HDC9	CCL20	P78556	CD3E	P07766
C3	P01024	CCL21	O00585	CD3G	P09693
C3orf64	Q5NDL2	CCL22	O00626	CD4	P01730
C4BPB	P20851	CCL24	000175	CD40	P25942
C4orf26	Q17RF5	CCL25	O15444	CD40LG	P29965
C4orf34	Q96QK8	CCL26	Q9Y258	CD44	P16070
C5orf15	Q8NC54	CCL27	Q9Y4X3	CD46	P15529
C6orf15	Q6UXA7	CCL28	Q9NRJ3	CD47	Q08722
C6orf162	Q96KF7	CCL3	P10147	CD48	P09326
C6orf25	O95866	CCL3L3	P16619	CD5	P06127
C6orf58	Q6P5S2	CCL4	P13236	CD52	P31358
C6orf72	Q9NU53	CCL4L2	Q8NHW4	CD55	P08174
C7	P10643	CCL5	P13501	CD58	P19256
C8G	P07360	CCL7	P80098	CD59	P13987
C9orf11	Q9NQ60	CCL8	P80075	CD5L	O43866
CA11	O75493	CD14	P08571	CD68	P34810
CA12	O43570	CD164	Q04900	CD69	Q07108
CA14	Q9ULX7	CD164L2	Q6UWJ8	CD7	P09564
CA4	P22748	CD177	Q8N6Q3	CD72	P21854
CA6	P23280	CD180	Q99467	CD79B	P40259
CA9	Q16790	CD19	P15391	CD80	P33681
CADM1	Q9BY67	CD1D	P15813	CD83	Q01151
CADM2	Q8N3J6	CD2	P06729	CD84	Q9UIB8
CADM3	Q8N126	CD200	P41217	CD86	P42081
CALU	043852	CD200R1	Q8TD46	CD8A	P01732
CAMP	P49913	CD200R1L	Q6Q8B3	CD8B	P10966
CARTPT	Q16568	CD207	Q9UJ71	CD93	Q9NPY3
CBLN2	Q8IUK8	CD226	Q15762	CD96	P40200
CBLN3	Q6UW01	CD24	P25063	CD99	P14209

CD99L2	Q8TCZ2	CFP	P27918	CNTNAP2	Q9UHC6
CDAN1	Q8IWY9	CGA	P01215	CNTNAP4	Q9C0A0
CDCP1	Q9H5V8	CGB1	A6NKQ9	CNTNAP5	Q8WYK1
CDH1	P12830	CHAD	015335	COCH	O43405
CDH11	P55287	CHGA	P10645	COL15A1	P39059
CDH12	P55289	CHGB	P05060	COL1A2	P08123
CDH13	P55290	CHI3L1	P36222	COL3A1	P02461
CDH16	O75309	CHI3L2	Q15782	COL4A5	P29400
CDH17	Q12864	CHIA	Q9BZP6	COL8A2	P25067
CDH18	Q13634	CHIT1	Q13231	COL9A1	P20849
CDH19	Q9H159	CHL1	O00533	COLEC10	Q9Y6Z7
CDH20	Q9 НВТ6	CHODL	Q9H9P2	COLEC11	Q9BWP8
CDH24	Q86UP0	CHRDL2	Q6WN34	COLEC12	Q5KU26
CDH3	P22223	CHST14	Q8NCH0	COMP	P49747
CDH4	P55283	CLDN2	P57739	CORT	000230
CDH5	P33151	CLEC10A	Q8IUN9	CPA1	P15085
CDH6	P55285	CLEC12A	Q5QGZ9	CPA2	P48052
CDH8	P55286	CLEC12B	Q2HXU8	CPA4	Q9UI42
CDH9	Q9ULB4	CLEC17A	Q6ZS10	CPB1	P15086
CDHR1	Q96JP9	CLEC1A	Q8NC01	CPB2	Q96IY4
CDHR2	Q9BYE9	CLEC1B	Q9P126	CPQ	Q9Y646
CDHR5	Q9HBB8	CLEC2A	Q6UVW9	CR2	P20023
CDON	Q4KMG0	CLEC2B	Q92478	CRB1	P82279
CDSN	Q15517	CLEC2D	Q9UHP7	CREG1	075629
CEACAM1	P13688	CLEC2L	P0C7M8	CRELD1	Q96HD1
CEACAM19	Q7Z692	CLEC3B	P05452	CRELD2	Q6UXH1
CEACAM20	Q6UY09	CLEC4A	Q9UMR7	CRHBP	P24387
CEACAM21	Q3KPI0	CLEC4D	Q8WXI8	CRIM1	Q9NZV1
CEACAM3	P40198	CLEC4E	Q9ULY5	CRISP3	P54108
CEACAM4	O75871	CLEC5A	Q9NY25	CRISPLD2	Q9H0B8
CEACAM5	P06731	CLEC7A	Q9BXN2	CRP	P02741
CEACAM6	P40199	CLEC9A	Q6UXN8	CRTAM	095727
CEACAM7	Q14002	CLMP	Q9H6B4	CSF1	P09603
CEACAM8	P31997	CLPS	P04118	CSF1R	P07333
CECR1	Q9NZK5	CLSTN3	Q9BQT9	CSF2	P04141
CELA2A	P08217	CLU	P10909	CSF2RA	P15509
CELA3A	P09093	CLUL1	Q15846	CSF2RB	P32927
CER1	O95813	CNDP1	Q96KN2	CSF3	P09919
CES3	Q6UWW8	CNIH	B2R4P1	CSF3R	Q99062
CFB	P00751	CNPY3	Q9BT09	CSH2	P0DML3
CFHR1	Q03591	CNPY4	Q8N129	CSN2	P05814
CFHR2	P36980	CNTN2	Q02246	CSN3	P07498
CFHR3	Q02985	CNTN3	Q9P232	CSPG5	095196
CFHR5	Q9BXR6	CNTN5	O94779	CSRP2BP	Q9H8E8
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CST2	P09228	DEFB1	P60022	EFNA4	P52798
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CST4	P01034	DEFB105A	Q8WTQ1 Q8NG35	EFNB2	P52799
CST5	P28325	DEFB106A	Q8N104	EFNB3	Q15768
CST6	Q15828	DEFB108B	Q8NET1	EGF	P01133
CST7	076096	DEFB110	Q30KQ9	EGFL7	Q9UHF1
CST9L	Q9H4G1	DEFB113	Q30KQ7	EGFLAM	Q63HQ2
CTGF	P29279	DEFB114	Q30KQ7	EGFR	P00533
CTHRC1	Q96CG8	DEFB118	Q96PH6	ELN	P15502
CTLA4	P16410	DEFB119	Q8N690	ELTD1	Q9HBW9
CTRB2	Q6GPI1	DEFB121	Q5J5C9	EMB	Q6PCB8
CTRC	Q99895	DEFB127	Q9H1M4	EMCN	Q9ULC0
CTRL	P40313	DEFB132	Q7Z7B7	EMR3	Q9BY15
CTSL2	O60911	DEFB136	Q30KP8	ENDOU	P21128
CX3CL1	P78423	DEFB4A	015263	ENPEP	Q07075
CXADR	P78310	DHH	043323	ENPP5	Q9UJA9
CXCL1	P09341	DHRS9	Q9BPW9	ENPP6	Q6UWR7
CXCL10	P02778	DKK2	Q9UBU2	ENPP7	Q6UWV6
CXCL11	O14625	DKK3	Q9UBP4	EPCAM	P16422
CXCL12	P48061	DKK4	Q9UBT3	EPGN	Q6UW88
CXCL14	O95715	DKKL1	Q9UK85	EPHA2	P29317
CXCL15	Q9WVL7	DLK1	P80370	EPHA3	P29320
CXCL16	Q9H2A7	DLL1	O00548	EPHA4	P54764
CXCL17	Q6UXB2	DLL4	Q9NR61	EPHA5	P54756
CXCL2	P19875	DNASE1	P24855	EPHA6	Q9UF33
CXCL3	P19876	DPEP1	P16444	EPHA7	Q15375
CXCL5	P42830	DPP4	P27487	EPHB1	P54762
CXCL6	P80162	DPP6	P42658	EPHB2	P29323
CXCL9	Q07325	DSC1	Q08554	EPHB3	P54753
CXorf61	Q5H943	DSC2	Q02487	EPHB4	P54760
CYR61	O00622	DSCAM	O60469	ЕРНВ6	015197
CYTL1	Q9NRR1	DSG1	Q02413	EPO	P01588
CYYR1	Q96J86	DSG2	Q14126	EPOR	P19235
DAG1	Q14118	DSG4	Q86SJ6	ERBB2	P04626
DCC	P43146	ECE1	P42892	EREG	014944
DCD	P81605	ECM1	Q16610	ERMAP	Q96PL5
DCN	P07585	EDA2R	Q9HAV5	ERO1L	Q96HE7
DCT	P40126	EDAR	Q9UNE0	ERP27	Q96DN0
DDOST	P39656	EDDM3B	P56851	ERP44	Q9BS26
DDR1	Q08345	EDIL3	043854	ESAM	Q96AP7
DDR2	Q16832	EDN2	P20800	ESM1	Q9NQ30
DEFA3	P59666	EDN3	P14138	ESYT3	A0FGR9
DEFA4	P12838	EEF1D	P29692	EVI2A	P22794
DEFA5	Q01523	EFNA1	P20827	EVI2B	P34910
DEFA6	Q01524	EFNA3	P52797	F10	P00742

F11	P03951	FGF12	P61328	GAL	P22466
F11R	Q9Y624	FGF13	Q92913	GALP	Q9UBC7
F3	P13726	FGF14	Q92915	GC	P02774
F9	P00740	FGF17	O60258	GDF15	Q99988
FAIM3	O60667	FGF18	O76093	GDF5	P43026
FAM150B	Q6UX46	FGF19	O95750	GDF9	O60383
FAM151A	Q8WW52	FGF21	Q9NSA1	GDNF	P39905
FAM159A	Q6UWV7	FGF22	Q9HCT0	GFRA1	P56159
FAM171A1	Q5VUB5	FGF23	Q9GZV9	GFRA3	O60609
FAM171B	Q6P995	FGF6	P10767	GFRAL	Q6UXV0
FAM174A	Q8TBP5	FGF8	P55075	GGT1	P19440
FAM180A	Q6UWF9	FGF9	P31371	GH1	P01241
FAM187B	Q17R55	FGFBP1	Q14512	GH2	P01242
FAM189A2	Q15884	FGFBP2	Q9BYJ0	GHR	P10912
FAM19A1	Q7Z5A9	FGFBP3	Q8TAT2	GIF	P27352
FAM19A2	Q8N3H0	FGFR1	P11362	GKN1	Q9NS71
FAM19A3	Q7Z5A8	FGFR2	P21802	GKN2	Q86XP6
FAM19A4	Q96LR4	FGFR3	P22607	GNLY	P22749
FAM19A5	Q7Z5A7	FGFR4	P22455	GNRH1	P01148
FAM209A	Q5JX71	FGFRL1	Q8N441	GNRH2	O43555
FAM209B	Q5JX69	FGL1	Q08830	GP1BA	P07359
FAM3B	P58499	FIBCD1	Q8N539	GPA33	Q99795
FAM3D	Q96BQ1	FKBP11	Q9NYL4	GPC2	Q8N158
FAS	P25445	FKBP14	Q9NWM8	GPC3	P51654
FASLG	P48023	FKBP7	Q9Y680	GPC6	Q9Y625
FCAMR	Q8WWV6	FLRT1	Q9NZU1	GPHA2	Q96T91
FCER2	P06734	FLRT2	O43155	GPIHBP1	Q8IV16
FCGR2A	P12318	FLRT3	Q9NZU0	GPLD1	P80108
FCGR2B	P31994	FLT1	P17948	GPR114	Q8IZF4
FCGR3B	075015	FLT3LG	P49771	GPR56	Q9Y653
FCGRT	P55899	FLT4	P35916	GPR97	Q86Y34
FCN1	O00602	FN1	P02751	GPX7	Q96SL4
FCN2	Q15485	FNDC4	Q9H6D8	GPX8	Q8TED1
FCN3	O75636	FOLR1	P15328	GREM1	O60565
FCRL1	Q96LA6	FOLR2	P14207	GREM2	Q9H772
FCRL2	Q96LA5	FOLR3	P41439	GRN	P28799
FCRL3	Q96P31	FRZB	Q92765	GSG1	Q2KHT4
FCRL4	Q96PJ5	FSHB	P01225	GUCA2A	Q02747
FCRL5	Q96RD9	FST	P19883	GUCA2B	Q16661
FCRL6	Q6DN72	FSTL1	Q12841	GUCY2C	P25092
FCRLA	Q7L513	FSTL3	O95633	GYPA	P02724
FDCSP	Q8NFU4	FSTL5	Q8N475	GYPC	P04921
FETUB	Q9UGM5	FXYD4	P59646	GZMA	P12544
FGF1	P05230	FXYD5	Q96DB9	GZMB	P10144
FGF10	015520	FZD2	Q14332	HAPLN4	Q86UW8

HAVCR1	Q96D42	IGF1	P05019	IL1RL1	Q01638
HAVCR2	Q8TDQ0	IGF2	P01344	IL1RL2	Q9HB29
HBEGF	Q99075	IGFBP1	P08833	IL2	P60568
HEPACAM	Q14CZ8	IGFBP3	P17936	IL20	Q9NYY1
HEPACAM2		IGFBP4	P22692	IL20RA	Q9UHF4
HFE	Q30201	IGFBP5	P24593	IL20RB	Q6UXL0
HFE2	Q6ZVN8	IGFBP6	P24592	IL21	Q9HBE4
HGF	P14210	IGFBP7	Q16270	IL21R	Q9HBE5
HHIP	Q96QV1	IGFL1	Q6UW32	IL22	Q9GZX6
HHLA2	Q9UM44	IGFL3	Q6UXB1	IL22RA2	Q969J5
HPR	P00739	IGFL4	Q6B9Z1	IL23R	Q5VWK5
HRG	P04196	IGFLR1	Q9H665	IL24	Q13007
HTN3	P15516	IGSF11	Q5DX21	IL25	Q9H293
HTRA3	P83110	IGSF22	Q8N9C0	IL27RA	Q6UWB1
HTRA4	P83105	IGSF6	O95976	IL28A	Q8IZJ0
HYAL1	Q12794	IGSF8	Q969P0	IL29	Q8IU54
HYAL2	Q12891	IL10	P22301	IL2RB	P14784
IAPP	P10997	IL10RA	Q13651	IL3	P08700
IBSP	P21815	IL10RB	Q08334	IL31RA	Q8NI17
ICAM1	P05362	IL11	P20809	IL33	O95760
ICAM2	P13598	IL12B	P29460	IL36A	Q9UHA7
ICAM3	P32942	IL13RA2	Q14627	IL36G	Q9NZH8
ICOS	Q9Y6W8	IL15	P40933	IL36RN	Q9UBH0
ICOSLG	075144	IL17A	Q16552	IL4	P05112
IFI30	P13284	IL17B	Q9UHF5	IL4I1	Q96RQ9
IFNA1	P01562	IL17C	Q9P0M4	IL4R	P24394
IFNA10	P01566	IL17D	Q8TAD2	IL5	P05113
IFNA13	P01562	IL17F	Q96PD4	IL6	P05231
IFNA14	P01570	IL17RA	Q96F46	IL6ST	P40189
IFNA16	P05015	IL17RB	Q9NRM6	IL7	P13232
IFNA17	P01571	IL17RC	Q8NAC3	IL8	P10145
IFNA2	P01563	IL17RD	Q8NFM7	IL9	P15248
IFNA21	P01568	IL18	Q14116	ILDR2	Q71H61
IFNA4	P05014	IL18BP	O95998	INHBC	P55103
IFNA5	P01569	IL18R1	Q13478	INSL3	P51460
IFNA6	P05013	IL18RAP	O95256	INSL4	Q14641
IFNA7	P01567	IL19	Q9UHD0	INSL5	Q9Y5Q6
IFNA8	P32881	IL1A	P01583	INSRR	P14616
IFNAR1	P17181	IL1B	P01584	ISLR	014498
IFNAR2	P48551	IL1F10	Q8WWZ1	ISLR2	Q6UXK2
IFNB1	P01574	IL1R1	P14778	ISM2	Q6H9L7
IFNG	P01579	IL1R2	P27930	ITFG1	Q8TB96
IFNGR2	P38484	IL1RAP	Q9NPH3	ITGA10	075578
IFNW1	P05000	IL1RAPL1	Q9NZN1	ITGA5	P08648
IGDCC3	Q8IVU1	IL1RAPL2	Q9NP60	ITGB6	P18564

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ITM2A	O43736	KLRC1	P26715	LRFN5	Q96NI6
ITM2B	Q9Y287	KLRC2	P26717	LRG1	P02750
ITM2C	Q9NQX7	KLRD1	Q13241	LRIG1	Q96JA1
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IZUMO4	Q1ZYL8	KLRG1	Q96E93	LRIG3	Q6UXM1
JAG1	P78504	KLRK1	P26718	LRP10	Q7Z4F1
JAM2	P57087	KNG1	P01042	LRPAP1	P30533
JAM3	Q9BX67	L1CAM	P32004	LRRC15	Q8TF66
KAZALD1	Q96I82	LACRT	Q9GZZ8	LRRC19	Q9H756
KDELC1	Q6UW63	LAIR1	Q6GTX8	LRRC25	Q8N386
KDR	P35968	LAIR2	Q6ISS4	LRRC3	Q9BY71
KERA	O60938	LAMP2	P13473	LRRC32	Q14392
KIAA0319L	Q8IZA0	LAMP3	Q9UQV4	LRRC37A2	A6NM11
KIAA1467	A2RU67	LAMP5	Q9UJQ1	LRRC37B	Q96QE4
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KIR2DS1	Q14954	LDL		LRRN4	Q8WUT4
KIR2DS4	P43632	LDLR	P01130	LRRN4CL	Q8ND94
KIR2DS5	Q14953	LDLRAD3	Q86YD5	LRRTM1	Q86UE6
KIR3DL1	P43629	LECT1	O75829	LRRTM2	O43300
KIR3DL2	P43630	LEFTY1	075610	LRRTM3	Q86VH5
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KIRREL	Q96J84	LEPR	P48357	LRTM2	Q8N967
KIRREL2	Q6UWL6	LIF	P15018	LSAMP	Q13449
KIRREL3	Q8IZU9	LIFR	P42702	LSR	Q86X29
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KIT	P10721	LILRA4	P59901	LTB	Q06643
KITLG	P21583	LILRA5	A6NI73	LTBR	P36941
KLK1	P06870	LILRA6	Q6PI73	LUM	P51884
KLK10	O43240	LILRB1	Q8NHL6	LUZP2	Q86TE4
KLK11	Q9UBX7	LILRB2	Q8N423	LY6D	Q14210
KLK12	Q9UKR0	LILRB4	Q8NHJ6	LY6G6C	O95867
KLK13	Q9UKR3	LILRB5	075023	LY6G6D	O95868
KLK3	P07288	LINGO2	Q7L985	LY6G6F	Q5SQ64
KLK4	Q9Y5K2	LIPG	Q9Y5X9	LY6H	O94772
KLK5	Q9Y337	LIPH	Q8WWY8	LY6K	Q17RY6
KLK6	Q92876	LMAN1	P49257	LY86	O95711
KLK7	P49862	LOXL2	Q9Y4K0	LY9	Q9HBG7
KLK8	O60259	LPAL2	Q16609	LYG1	Q8N1E2
KLK9	Q9UKQ9	LPL	P06858	LYG2	Q86SG7

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LYPD2	Q6UXB3	MMP10	P09238	NFAM1	Q8NET5
LYPD3	O95274	MMP12	P39900	NFASC	O94856
LYPD5	Q6UWN5	MMP13	P45452	NGF	P01138
LYPD6	Q86Y78	MMP15	P51511	NGFR	P08138
LYPD6B	Q8NI32	MMP16	P51512	NID2	Q14112
LYSMD3	Q7Z3D4	MMP2	P08253	NLGN1	Q8N2Q7
LYVE1	Q9Y5Y7	MMP20	O60882	NLGN4X	Q8N0W4
LYZ	P61626	MMP7	P09237	NMU	P48645
LYZL2	Q7Z4W2	MMP8	P22894	NOG	Q13253
LYZL4	Q96KX0	MMP9	P14780	NOV	P48745
LYZL6	075951	MOG	Q16653	NPC2	P61916
MAG	P20916	MPL	P40238	NPDC1	Q9NQX5
MAGEA4	P43358	MPZ	P25189	NPHS1	O60500
MAGT1	Q9H0U3	MPZL1	O95297	NPPB	P16860
MAN1B1	Q9UKM7	MPZL2	O60487	NPTN	Q9Y639
MANF	P55145	MPZL3	Q6UWV2	NPY	P01303
MANSC1	Q9H8J5	MSLN	Q13421	NRCAM	Q92823
MBL2	P11226	MSMB	P08118	NRG1	Q02297
MCAM	P43121	MSR1	P21757	NRG4	Q8WWG1
MDA-LDL		MSRA	Q9UJ68	NRN1	Q9NPD7
MDGA2	Q7Z553	MSRB3	Q8IXL7	NRN1L	Q496H8
MDK	P21741	MST1	P26927	NRP2	O60462
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MEP1A	Q16819	MUC15	Q8N387	NT5E	P21589
MEP1B	Q16820	MUC20	Q8N307	NTF3	P20783
MESDC2	Q14696	MUCL1	Q96DR8	NTF4	P34130
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MFAP4	P55083	NAPSA	O96009	NTRK1	P04629
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MFGE8	Q08431	NCAM1	P13591	NTRK3	Q16288
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MFRP	Q9BY79	NCR1	O76036	NXPH1	P58417
MGP	P08493	NCR2	O95944	NXPH2	O95156
MIA	Q16674	NCR3	014931	NXPH3	O95157
MIA3	Q5JRA6	NCSTN	Q92542	NXPH4	O95158
MICB	Q29980	NDP	Q00604	OBP2A	Q9NY56
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OPCML	Q14982	PI3	P19957	PRG3	Q9Y2Y8
ORM1	P02763	PIGR	P01833	PRH1	P02810
ORM2	P19652	PIK3IP1	Q96FE7	PRH2	P02810
OSM	P13725	PILRA	Q9UKJ1	PRL	P01236
OSMR	Q99650	PILRB	Q9UKJ0	PRLR	P16471
OSTM1	Q86WC4	PIP	P12273	PRND	Q9UKY0
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OTOR	Q9NRC9	PLA2G12A	Q9BZM1	PROCR	Q9UNN8
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PCDH19	Q8TAB3	PLAT	P00750	PRSS55	Q6UWB4
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PCOLCE	Q15113	PLXNB2	O15031	PSG3	Q16557
PCYOX1L	Q8NBM8	PMCH	P20382	PSG4	Q00888
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PDCD1LG2	Q9BQ51	PNLIP	P16233	PSG6	Q00889
PDGFA	P04085	PNLIPRP2	P54317	PSG7	Q13046
PDGFC	Q9NRA1	PNOC	Q13519	PSG9	Q00887
PDGFD	Q9GZP0	PODN	Q7Z5L7	PSPN	O60542
PDGFRB	P09619	PODXL	O00592	PTGDS	P41222
PDGFRL	Q15198	PODXL2	Q9NZ53	PTGFRN	Q9P2B2
PDYN	P01213	POGLUT1	Q8NBL1	PTH	P01270
PEA15	Q15121	POMC	P01189	PTHLH	P12272
PEBP4	Q96S96	POMGNT1	Q8WZA1	PTK7	Q13308
PECAM1	P16284	PON1	P27169	PTN	P21246
PENK	P01210	POSTN	Q15063	PTPRA	P18433
PF4	P02776	PPBP	P02775	PTPRC	P08575
PGA3	PODJD8	PPY	P01298	PTPRG	P23470
PGC	P20142	PRADC1	Q9BSG0	PTPRH	Q9HD43

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PTPRO	Q16827	SCARB1	Q8WTV0	SERPINA4	P29622
PTPRR	Q15256	SCG3	Q8WYD2	SERPINA5	P05154
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PVR	P15151	SCGB1A1	P11684	SERPINA7	P05543
PVRIG	Q6DKI7	SCGB1C1	Q8TD33	SERPINA9	Q86WD7
PVRL1	Q15223	SCGB1D2	O95969	SERPINB2	P05120
PVRL2	Q92692	SCGB1D4	Q6XE38	SERPINC1	P01008
PVRL3	Q9NQS3	SCGB2A1	Q75556	SERPIND1	P05546
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QPCT	Q16769	SCGB3A2	Q96PL1	SERPINF1	P36955
QRFP	P83859	SCN1B	Q07699	SERPINF2	P08697
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RAET1L	Q5VY80	SCN3B	Q9NY72	SERPINI1	Q99574
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RARRES2	Q99969	SCPEP1	Q9HB40	SFRP1	Q8N474
Rat Tail Colla	gen	SCRG1	075711	SFRP2	Q96HF1
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RCN3	Q96D15	SDC1	P18827	SFTA2	Q6UW10
RECK	O95980	SDC2	P34741	SFTPA1B	Q8IWL2
REG1A	P05451	SDC4	P31431	SFTPA2	Q8IWL1
REG1B	P48304	SDF2L1	Q9HCN8	SFTPD	P35247
REG3A	Q06141	SECTM1	Q8WVN6	SGCA	Q16586
REG3G	Q6UW15	SELE	P16581	SGCE	O43556
REG4	Q9BYZ8	SELL	P14151	SHH	Q15465
RELT	Q969Z4	SELP	P16109	SHISA2	Q6UWI4
RET	P07949	SELPLG	Q14242	SHISA3	A0PJX4
RETN	Q9HD89	SEMA3C	Q99985	SHISA4	Q96DD7
RETNLB	Q9BQ08	SEMA3E	O15041	SIDT2	Q8NBJ9
RGMB	Q6NW40	SEMA3F	Q13275	SIGLEC10	Q96LC7
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RNASE7	Q9H1E1	SEMA4A	Q9H3S1	SIGLEC15	Q6ZMC9
RNFT2	Q96EX2	SEMA4B	Q9NPR2	SIGLEC5	O15389
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ROBO2	Q9HCK4	SEMA4G	Q9NTN9	SIGLEC7	Q9Y286
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ROR1	Q01973	SEMA6A	Q9H2E6	SIGLEC9	Q9Y336
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SLITRK1	Q96PX8	SUSD1	Q6UWL2	TLR4	O00206
SLITRK3	O94933	SUSD2	Q9UGT4	TMC2	Q8TDI7
SLITRK4	Q8IW52	SUSD4	Q5VX71	TMED1	Q13445
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SMCR7	Q96C03	TCN1	P20061	TMEM123	Q8N131
SMOC1	Q9H4F8	TCP11	Q8WWU5	TMEM130	Q8N3G9
SMOC2	Q9H3U7	TCTN2	Q96GX1	TMEM132D	Q14C87
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SPARC	P09486	TFF2	Q03403	TMEM9B	Q9NQ34
SPARCL1	Q14515	TFF3	Q07654	TMIE	Q8NEW7
SPESP1	Q6UW49	TFPI	P10646	TMIGD1	Q6UXZ0
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SPINK9	Q5DT21	TGFB3	P10600	TNFAIP6	P98066
SPINLW1	O95925	TGFBI	Q15582	TNFRSF10A	O00220
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SPOCK2	Q92563	THBS4	P35443	TNFRSF11B	O00300
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SPP1	P10451	TIGIT	Q495A1	TNFRSF14	Q92956
SPPL3	Q8TCT6	TIMD4	Q96H15	TNFRSF17	Q02223
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TNEDCE40	OONECO	VCAN	D42C44
TNFRSF19	Q9NS68	VCAN	P13611
TNFRSF1A TNFRSF1B	P19438 P20333	VEGFA VEGFB	P15692 P49765
TNFRSF1B	075509	VEGFE	P49765 P49767
TNFRSF25	Q93038	VEGFC	Q6UXI7
TNFRSF4	P43489	VIII	P98155
TNFRSF6B	095407	VLDLK VMO1	
TNFRSF8	P28908	VIVIO1 VNN1	Q7Z5L0 O95497
TNFRSF9	Q07011	VIVIVI VSIG1	Q86XK7
TNFSF10	P50591	VSIG10	Q8N0Z9
TNFSF13	075888	VSIG2	Q96IQ7
TNFSF13B	Q9Y275	VSIG2 VSIG4	Q9Y279
TNFSF13b	Q31273 Q43557	VSTM1	Q6UX27
TNFSF15	045357	VSTM2A	Q8TAG5
TNFSF18	Q9UNG2	VSTM2L	Q96N03
TNFSF8	P32971	VTCN1	Q7Z7D3
TNFSF9	P41273	VTN	P04004
TPBG	Q13641	VWC2	Q2TAL6
TPSAB1	Q15661	WBP1	Q96G27
TPST1	O60507	WFDC10A	Q9H1F0
TREM1	Q9NP99	WFDC11	Q8NEX6
TREM2	Q9NZC2	WFDC12	Q8WWY7
TREML1	Q86YW5	WFDC2	Q14508
TREML2	Q5T2D2	WFIKKN2	Q8TEU8
TREML4	Q6UXN2	WIF1	Q9Y5W5
TRH	P20396	WISP1	095388
TSKU	Q8WUA8	WISP2	O76076
TSLP	Q969D9	WNT2	P09544
TTR	P02766	XCL1	P47992
TWSG1	Q9GZX9	XCL2	Q9UBD3
TXNDC12	O95881	XPNPEP2	O43895
TXNDC15	Q96J42	XXYLT1	Q8NBI6
TYRO3	Q06418	YME1L1	Q96TA2
TYRP1	P17643	ZDHHC11	Q9H8X9
UCN2	Q96RP3	ZG16	O60844
ULBP1	Q9BZM6	ZG16B	Q96DA0
ULBP2	Q9BZM5	ZPLD1	Q8TCW7
UNC5B	Q8IZJ1		
UNC5C	095185		
UNC5D	Q6UXZ4		
UPK3BL	BOFP48		
UTS2	095399		
UTS2D	Q765I0		
VASN	Q6EMK4		
VCAM1	P19320		

Supplementary Table 2 (associated to Figure 6). Enriched GO biological process terms and corresponding p-values for the host genes targeted by the E3 proteins, split by HAdV species of the interacting E3 protein. NA indicates the absence of genes in a particular GO category, represented in grey color in Figure 6A.

GO Term		HAdV- A	HAdV- B	HAdV- D	HAdV- E	HAdV- F	New Term
GO:0051051	negative regulation of transport	-0.75	NA	-2.84	-1.42	-0.96	Inhibition of transport process
GO:0050853	B cell receptor signaling pathway	NA	NA	-2.79	NA NA	NA	B cell receptor signaling
GO:0051248	Negative regulation of protein metabolic process	-0.73	NA	-2.74	-1.39	NA	Inhibition of protein metabolism
GO:0070663	regulation of leukocyte proliferation	-0.65	NA	-2.43	-1.31	-0.85	Leukocyte proliferation
GO:0050863	regulation of T cell activation	-0.57	NA	-2.12	-1.22	-0.77	T cell activation
GO:0071396	cellular response to lipid	-0.80	NA	-2.00	-1.47	-1.01	Cellular response to lipids
GO:0050866	negative regulation of cell activation	-0.83	NA	-2.09	-1.50	-1.04	Inhibition of cell activation
GO:0002244	hematopoietic progenitor cell differentiation	NA	NA	-2.24	NA	NA	Hematopoietic progenitor cell differentiation
GO:0050852	T cell receptor signaling pathway	NA	NA	-2.24	NA	NA	T cell receptor signaling
GO:0097028	dendritic cell differentiation	-1.41	NA	-2.32	-2.11	-1.63	Dendritic cell differentiation
GO:0002820	negative regulation of adaptive immune response	-1.51	NA	-2.52	-2.20	NA	Inhibition of adaptive immune processes
GO:0002709	regulation of T cell mediated immunity	-1.27	NA	-2.03	-1.96	NA	T cell-mediated immunity
GO:0001906	cell killing	-2.14	-0.88	-2.22	-1.55	NA	Cell killing
GO:0002228	natural killer cell mediated immunity	-2.79	-1.19	-0.77	-1.88	NA	NK cell-mediated immunity
GO:0006950	response to stress	-2.09	-0.54	-0.34	-0.42	-0.48	Response to stress
GO:0032943	mononuclear cell proliferation	-0.56	NA	-2.06	-1.20	-0.75	Mononuclear cell proliferation
GO:0051607	defense response to virus	-0.83	NA	-2.09	-1.50	NA	Antiviral response
GO:0050854	regulation of antigen	NA	NA	-2.79	NA	NA	Inhibition of

	receptor-mediated signaling pathway						antigen-receptor signaling
GO:0002683	negative regulation of immune system process	-0.68	NA	-2.54	-1.34	-0.88	Inhibition of immune system processes
GO:0072511	divalent inorganic cation transport	-0.96	NA	-2.49	-1.64	-1.18	Inorganic cation transport
GO:0002764	immune response- regulating signaling pathway	-0.61	NA	-2.27	-1.26	-0.81	Regulation of immune signaling pathways
GO:0002703	regulation of leukocyte mediated immunity	-0.89	NA	-2.25	-1.56	NA	Regulation of immune signaling pathways
GO:0002703	negative regulation of transferase activity	NA	NA	-2.03	NA	NA	Inhibition of transferase activity

Supplementary Table 3 (associated to Figure 6). Disease terms from the DisGeNET database were manually collapsed to create curated terms shown in Figure 6. Table shows which disease terms were grouped together to generate the terms used for the disease association network.

Disease association, curated term	Disease association, DisGeNET term				
Bacterial and parasitic diseases	Bacterial infections and mycoses; Parasitic diseases				
Viral infection	Virus diseases				
Cancer	Neoplasms				
Nervous diseases and neurological disorders	Nervous system diseases, Behavior and behavior mechanisms				
Eye disease	Eye diseases				
Gastrointestinal diseases	Digestive system diseases, Male urogenital diseases, Female urogenital diseases and pregnancy complications				
Respiratory track disease	Respiratory track diseases, Otorhinolaryngologic diseases				
Immune disease	Immune system diseases, Hemic and lymphatic diseases				
Other	Musculoskeletal diseases; Cardiovascular diseases; Stomatognathic diseases; Congenital, hereditary and neonatal diseases and abnormalities; Skin and connective tissue diseases; Nutritional and metabolic diseases; Endocrine system diseases; Disorders of environmental origin; Animal diseases; Pathological conditions, signs and symptoms; Occupational diseases; Chemically-induced disorders; Wounds and injuries.				