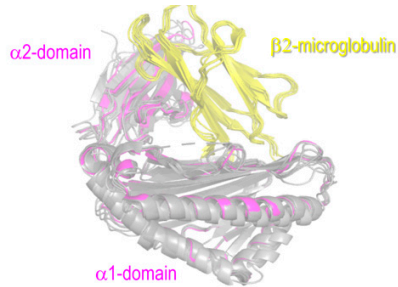


Figure S1. Graphic representation of the 3 Histidine residues in the PCSK9' CHRD (green) in contact with Glu79 of HLA-C (red).

A



Q30201 · HFE_HUMAN PDB : 1A6Z
 P10321 · HLA-C_HUMAN PDB : 6JTO
 Q53242 · HLA-A2_HUMAN PDB : 6TRN
 P01889 · HLA-B_HUMAN PDB : 1M05
 P30511 · HLA-F_HUMAN PDB : 5IJE
 P17693 · HLA-G_HUMAN PDB : 3KY0

B

HFE._10001	1	-----MGPRARPALLLLMLLQTAVLQ-----GRLLR-----SHSLHYLFMGASEQD	41
HLA-C_10002	1	-----MRVMAPRALLLLSGGLALTETWA-----CSHSMRYFDTAVSRPG	40
HLA-A_10003	1	-----MAVMAPRTLLLLSGALALTQTWA-----GSHSMRYFSTSVSRPG	40
HLA-B_10004	1	-----MLVMAPRTVLLLSAALALTETWA-----GSHSMRYFYTSVSRPG	40
HLA-E_10005	1	-MEPS-FYSSRRFPWLP RPGRVSAGSGWKRPLPGVERGRPGGEGLEPRREEGRADLSPSPPGSHSLKYFHTSVSRPG	78
HLA-F_10006	1	-----MAPRSLLLLSGALALTDTWA-----GSHSLRYFSTAVSRPG	37
HLA-G_10007	1	MKTPRMVVMAPRTLFLLLSGALTETWA-----GSHSMRYFSAAVSRPG	45
α1 domain			
HFE._10001	42	LGLSLFEALGYVDDQLFVFDH-- ESRRVE PRTPWVS RIS QMWLQLSQSLKGDHMTVDFTWIMENHNHNSK-ESHTL	118
HLA-C_10002	41	RGEPRFISVGYYDDTQFVRFDSDAASP RGE PRAPWVEQEG- PEYWDRETQYKRQAQADRVSL NLRGGYNQSEDSGSHL	119
HLA-A_10003	41	RGEPRFIAVGYYDDTQFVRFDSDAASQRMEPRAPWIEQEG- PEYWDQETRNKKAHSQTD RANLGTLRGGYNQSEDSGSHI	119
HLA-B_10004	41	RGEPRFISVGYYDDTQFVRFDSDAASPREPRAPWIEQEG- PEYWDRTQIYKAQAQTDRE SLNLRGGYNQSEAGSHTL	119
HLA-E_10005	79	RGEPRFISVGYYDDTQFVRFDNDAASPRMVPRAPWMEQEG- SEYWDRETSAR DTAQIFRVNLRTLGRGGYNQSEAGSHTL	157
HLA-F_10006	38	RGEPRYIAVEYYDDTQFLRFSDDAI PRMEPREPWVEQEG- PQYWEWTGYAKANAQTD RVALRNLL RRY NQSEAGSHTL	116
HLA-G_10007	46	RGEPRFIAMGYDDTQFVRFDSDSACPRMEPRAPWVEQEG- PEYWEETRTNKAHAQTD RMNLT LR GGYNQSEASSHTL	124
α2 domain			
HFE._10001	119	QVILGCEMQEDN-STEGYWKYGYDGDHLEFCPTLDWRAA E PRAWPT KL E WER HKIRARQNRAYL ERD CPAQQL EL	197
HLA-C_10002	120	QRMSCDGLPDGRLLRGYDQSAIDGKDYIALNEDLRSWTAADTAAQIT QR KEAARAA EQ -LRAYLEGT CV E WL RRYLEN	198
HLA-A_10003	120	QIMYGCDVGPDRFLRGYQDAYDGKDYIALNEDLRSWTAADMAAQIT KR KEAVHAA EQ -RRVYLE GR CV GL RRYLEN	198
HLA-B_10004	120	QSMYGCVDGPDGRLLRGHDQYAYDGKDYIALNEDLRSWTAADTAAQIT QR KEAARAA EQ -RRAYLE GR CV E WLRRYLEN	198
HLA-E_10005	158	QWMHGCELGPDRFLRGYEQFAYDGKDYLTNEDLRSWTAVDTAAQIS EQ KSNDA SE A EH -QRAYLE DT CV E WLHKYLEK	236
HLA-F_10006	117	QGMNGCDMGPDGRLLRGYHQHAYDGKDYISLNEDLRSWTAADTAAQIT QR FY EAE Y AEE -FRTYLE GE CL EL LLRYLEN	195
HLA-G_10007	125	QWMIGCDLGSDDRLLRGYEQYAYDGKDYIALNEDLRSWTAADTAAQIS KR KEAANVA EQ -RRAYLEGT CV E WL RRYLEN	203
HFE._10001	198	GRGVLDQVVPVLVKVTHH-VTSSVTTLCRALNYPQNIITMKWLKDKQPMDAKEFEPKDVLPNGDGTYGQWITLAVPPGE	276
HLA-C_10002	199	GKETLQRAEPKTHVTHHPLSDHEATLRCWALGFYPAEITLTWQRDGEDQ-TQDTELVEPTRPAGDGT FQ KWAAVVVP SG	277
HLA-A_10003	199	GKETLQRTDPPKTHMTHHPISDHEATLRCWALGFYPAEITLTWQRDGEDQ-TQDTELVEPTRPAGDGT FQ KWAAVVVP SG	277
HLA-B_10004	199	GKDKLERADPPKTHVTHHPLSDHEATLRCWALGFYPAEITLTWQRDGEDQ-TQDTELVEPTRPAGDRT FQ KWAAVVVP SG	277
HLA-E_10005	237	GKETLLHLEPPKTHVTHHPLSDHEATLRCWALGFYPAEITLTWQRDGEDQ-TQDTELVEPTRPAGDGT FQ KWAAVVVP SG	315
HLA-F_10006	196	GKETLQRAEDPPKAHVAHHPISDHEATLRCWALGFYPAEITLTWQRDGEDQ-TQDTELVEPTRPAGDGT FQ KWAAVVVP SG	274
HLA-G_10007	204	GKEMLQRAEDPPKTHVTHHPVFDYEATLRCWALGFYPAEITLTWQRDGEDQ-TQDVELVEPTRPAGDGT FQ KWAAVVVP SG	282
HFE._10001	277	EQRYTCQVEHFGLDQPLIVIEWPSSGTL-VIG VIS GLAV FVVI - LFIGILFI ILRKQSGSRGAMGHY VLA ERE-----	348
HLA-C_10002	278	EQRYTCMQHEGLQEPPLTSWEPSSQPTIPIM IVAGLAVLVVLAVLGAVVTAMC RRKSSGGKGG SQA ACSNSAQGS	357
HLA-A_10003	278	EQRYTCVQHEGLPKPLTLRWELSSQPTIPIV IIAGLVLLGAV-ITGAVVAVM RRKSSDRKGGSYTQAASSDSAQGS	356
HLA-B_10004	278	EQRYTCVQHEGLPKPLTLRWEPSSQSTVPIV IVAGLAVLVAVV-VIGAVVAVM RRKSSGGKGGSY SQA ACSNSAQGS	356
HLA-E_10005	316	EQRYTCVQHEGLPEPVTLRWKPASQPTIPIV IIAGLVLLGSV-VSGAVVAVIV RRKSSGGKGGSY SKA EWSDSAQGS	394
HLA-F_10006	275	EQRYTCVQHEGLPQPLILRWEQSQPTIPIV IVAGLVVLGAV-VTGAVVAVM RRKSSDRNRGSS YQA AAYSVVSGN	353
HLA-G_10007	283	EQRYTCVQHEGLPEPMLRWKQSSLPTIPIM IVAGLVVLAIV-VTGAAVVAIV RRKSSD-----	343
HFE._10001		-----	
HLA-C_10002	358	D SLIT CPA-----	366
HLA-A_10003	357	DVSLTA Q -----	365
HLA-B_10004	357	DVSLTA-----	362
HLA-E_10005	395	ESHSL-----	399
HLA-F_10006	354	LMITWSSFLFLGVLFQGYLGCLRSHSVLGRRKVGDMWILFLLWLWTSFNATFLALQSLRFGFGFRGRSFLLRSWHHLM	433
HLA-G_10007		-----	
HFE._10001		-----	
HLA-C_10002		-----	
HLA-A_10003		-----	
HLA-B_10004		-----	
HLA-E_10005		-----	
HLA-F_10006	434	KRVQIKIFD	442
HLA-G_10007		-----	

C

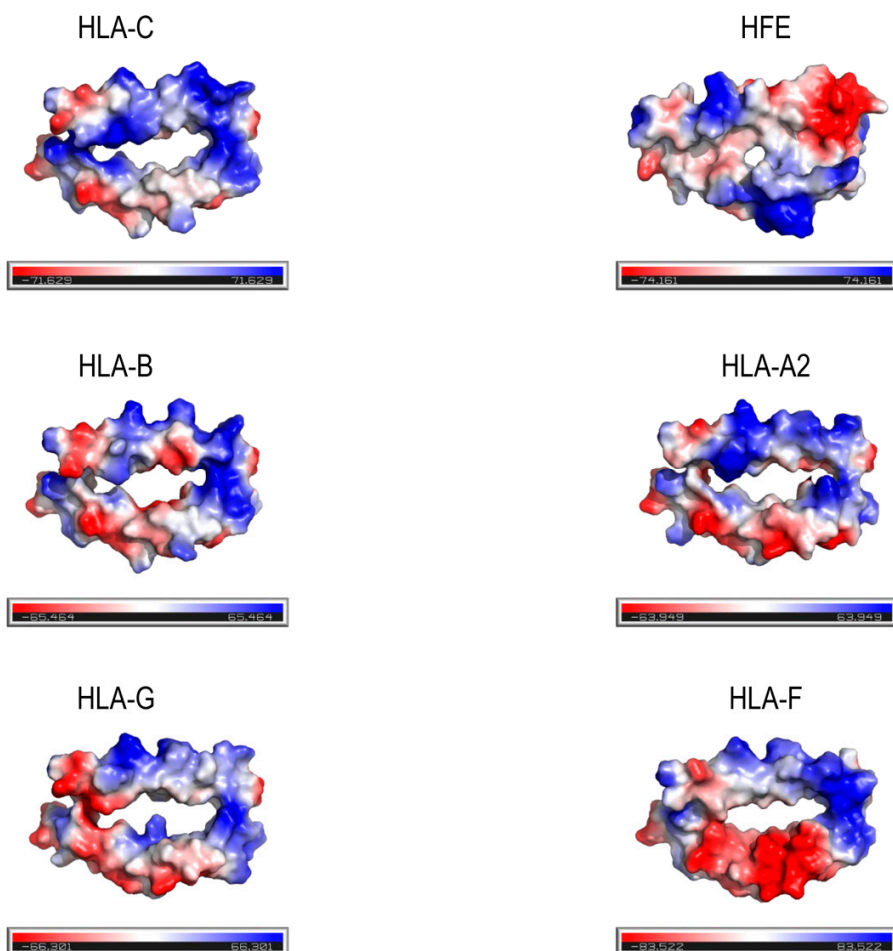


Figure S2. Structure and interaction sites of all MHC-I molecules. (A) Superimpose of the structures of the different MHC-I molecules: HFE PBD:1a6z; HLA-C PDB: 6jto (pink); HLA-A2 PBD: 6trn; HLA-B PDB: 1m05; HLA-F PDB: 5iue; HLA-G PDB: 3kyo. (B) Sequence alignment of MHC-I molecules and visualization of basic residues (highlighted in blue) and acidic residues (highlighted in red) of the antigenic pocket of MHC-I molecules. (C) Electrostatic potential of the antigenic pocket of MHC-I molecules.

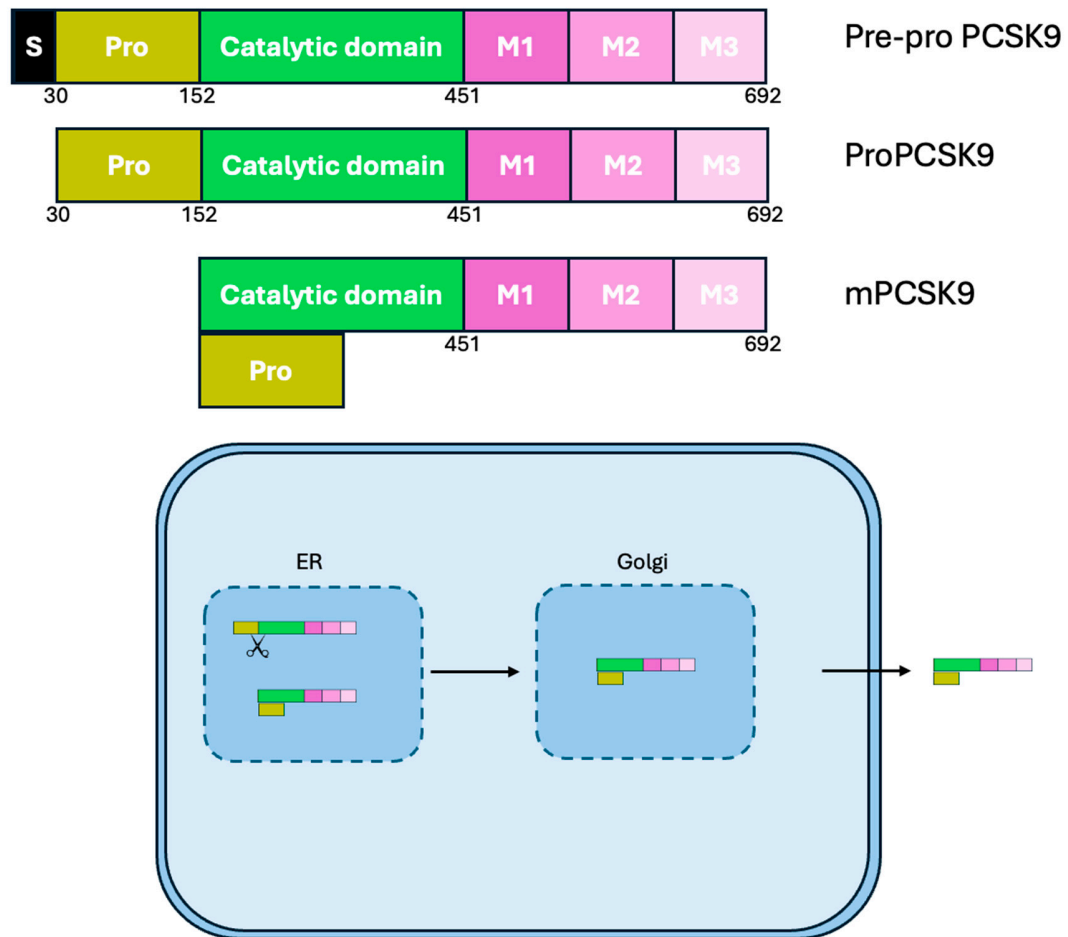


Figure S3. The schematic of different domains of PCSK9 and its trafficking in cells. The processing of PCSK9 starts with the synthesis of the 72-kDa preproPCSK9 protein (comprising 692 aa) in the ER, following with the cleavage of the signal peptide. Upon cleavage of signal peptide, proPCSK9 undergoes autocatalytic cleavage at its N-terminal (at VFAQ152↓ motif) in the ER. Nevertheless, the cleaved prodomain permanently stays non-covalently attached to the rest of the protein, even when it is secreted into the extracellular media. The heterodimer complex of PCSK9 includes a 14 kDa propeptide (aa 31-152) and a glycosylated 63 kDa (aa 153-692) mature protein (mPCSK9) that is transported to the Golgi and then secreted to the outer media.