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## Supplemental information

## Sites of vulnerability in HCV E1E2 identified

### by comprehensive functional screening

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**Figure S1. Mutations do not affect full-length E1E2 expression or incorporation into HCVpp. Related to Figures 2 and 3.** Each clone of the HCV E1E2 library was transfected into HEK-293T cells. The C-terminus of E2 was constructed with a V5 tag. (**A**) Full-length E1E2 protein expression was analyzed by intracellular staining with an anti-V5 antibody. (**B**) E1E2 protein was incorporated onto pseudoviruses (HCVpp) by co-expression of E1E2 with HIV Gagpol core and a luciferase reporter genome. Supernatants from each mutant clone were analyzed by ELISA. A mouse anti-CD81 antibody was used to capture pseudovirus particles, and linear human MAb HCV1 was used to detect E1E2 incorporation, values shown are the mean of two replicates. A chemiluminescence assay using an HRP-conjugated rabbit anti-human secondary antibody served as the readout for E1E2 incorporation. Clones with mutations in the known epitope of MAb HCV1 were omitted from the analysis.



Figure S2. Characterization of conformational anti-E1 MAbs. Related to Figure 1. (A) Binding to critical mutations is shown for E1 MAbs HCVE1-C1 and HEPC112 (Colbert et al., 2019). MAb AR5A is shown as a control, as it binds only when E1 and E2 are in complex and is sensitive to mutations that perturb E1 structure (Giang et al., 2012). Binding values are given as a percentage of MAb binding to wild-type HCV E1E2 and are plotted with error bars showing half the range (highest minus lowest binding value) of at least two measurements. (B) The critical residues for HCVE1-C1 (G311 and H312) are shown as green spheres located in the transmembrane proximal region of E1 (PDB 2KNU). The critical epitope residues of HEPC112 (R259 and R260) are shown as yellow spheres, as reported previously (Colbert et al., 2019). (C) Conformational dependence of HCVE1-C1, HEPC112, and other MAbs was determined by Western analysis. Each well was loaded with 5 µg of protein from the lysate of HCV E1E2expressing cells, followed by boiling in SDS-PAGE buffer without (-) or with DTT (+). MAbs HCVE1-C1, HEPC112 and A4 target E1, while MAbs E137 and HCV1 target E2. MAbs A4 and HCV1 recognize non-conformational epitopes, so were included as controls. (D) Neutralization by anti-E1 MAbs HCVE1-C1 and HEPC112 were assayed by incubation with wild-type HCVpp prior to infection of HEK-293T cells expressing Claudin 1. Infectivity values were normalized to the value for infectivity obtained without antibody. Values represent the mean of 2 replicates, with error bar showing the range.

#### A HCV E1 Sequence Alignment

Δ	HCV E1 Seque	ence Alignment							
Γ	HCV1a E1		40						
	HCV1b_E1	<mark>YE</mark> VRNVSGI <mark>Y</mark> HVTNDCSNSSIVYEAADMIMHTPGCVPCVRESNFSRCWV 24	10						
	HCV2a E1	APVKNISTGYMVTNDCTNDSITWQLQAAVLHVPGCVPCEKVGNTSRCWI 24	40						
	HCV3a_E1	LEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGCVPCVQDGNTSTCWT 24	40						
	HCV4a_E1	<mark>VN</mark> YRNVSGI <mark>Y</mark> HVTNDCPNSSIVYEADHHIMHLPGCVPCVREGNQSRCWV 24	10						
	HCV5a_E1	VPYRNASGVYHVTNDCPNSSIVYEADNLILHAPGCVPCVLEDNVSRCWV 24	40						
	HCV6a_E1	LTYGNSSGLYHLTNDCSNSSIVLEADAMILHLPGCLPCVRVGNQSTCWH 24	40						
	HCV7a_E1	YEVRNSSGVYHLTNDCPNASIVYETDNAILHEPGCVPCVREGNTSRCWE 24	40						
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		Fusion loop							
	HCV1a_E1	AVTPTVATRDGKLPTTQLRRHIDLLVGSATLCSALVVGDLCCSVFLVGQLFTFSPRRHWT 30	10						
	HCVID_EI	ALTPTLAARNSSIPTTTIRRHVULLVGAAALCSAMYVGULCGSVFLVSQUETFSPRRYET 30	10						
	HCV2a_E1	PVSPNVAVQQPGALTQGLRTHIUMVVMSATLCSALIVGDLCGGVMLAAQMFIVSPQHWF 30	10						
	HCV3a_E1	PVTPTVAVRIVGATTASIRSHVULLVGAATMCSALTVGDMCGAVFLVGQAFTFRPRRHQT 30	10						
	HCV4a_E1	ALTPTVAAPYIGAPLESLKSHVULMVGAATVCSGLTIGDLCGGLFLVGQMFSFRPRRHWT 30	10						
	HCV5a_EI		00						
	HCV6a_E1	AVSPTLATPNASTPATGERKHVULLAGAAVVCSSLTIGDLCGSLFLAGQUERFQPRRHWT 30	10						
	hcv/a_EI	······································	10						
		F1 stem F1 TM							
	HCV1a E1	TODCNCSIYPCHTTGHRMANDMMMNWSPTAALVVAOLLRIPOAIMDMIAGAHWGWLAGIA 3	60						
	HCV1b_E1	VODCNCSIYPGHVSGHRMAWDMMMNWSPTTALVVSOLLRIPOAVVDMVAGAHWGVLAGLA 36	60						
	HCV2a E1	VODCNCSIYPGTITGHRMAWDMMMNWSPTATMILAYAMRVPEVIIDIIGGAHWGMMFGLA 36	60						
	HCV3a_E1	VOTCNCSLYPGHLSGHRMAWDMMMNWSPAVGMVVAHVLRLPOTLFDIMAGAHWGILAGLA 36	60						
	HCV4a E1	TQDCNCSIYTGHITGHRMAWDWMMNWSPTTTLVIAQVVFIPTTLVDILSGGHWGVLVGVA 3 VQDCNCSIYSGHITGHRMAWDMMMKWSPTTALLMAQLLRIPQVVIDTIAGGHWGVLLAAA 3							
	HCV5a E1								
	HCV6a_E1	VQDCNCSIYTGHVTGHKMAWDMMMNWSPTTTLVLSSILRVPEICASVIFGGHWGILLAVA 30	50						
	HCV7a E1	VQDCNCSIYPCHVTGHRMAWDMMQNWAFALSMVAAYAVRVPGVIITTVAGGHWGVLFGLA 36	50						
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		E1 TM							
	HCV1a_E1	YFSMVGNWAKVLVVLLLFAGVDA 383							
	HCV1b_E1	YYSMVGNWAKVLIVMLLFAGVDG 383							
	HCV2a_E1	ICV2a_E1 YFSMQGAWAKVVVILLAAGVDA 383 ICV3a_E1 YFSMQGAWAKVAIINVMFSGVDA 383							
	HCV3a_E1								
	HCV4a_E1	YFSMQANWAKVILVLFLFAGVDA 383							
	HCV5a_E1	YFASTANWAKVILVLFLFAGVDG 383							
	HCV6a_E1	I EGMAGINULKVLAVLFLEAGVEA 383							
	HCV/a_EI	TEGNAGNWARVILIMLIMSGVDA 585							
-	HCV E2 Sequen	nce Alignment HVR1CNTR							
В	HCV1a	ETHVTGGNAGRTTAGLVGLLTPGAKQNIQLINTNGSW 420							
	HCV1b	HT <mark>H</mark> VTG <mark>G</mark> RVASSTQ <mark>SL</mark> VSWLSQGPSQ <mark>K1QLVNT</mark> NGSW 420							
	HCV2a	QTHTVGGSTAHNARTLTGMFSLGARQ <mark>KIQLINT</mark> NGSW 420							
	HCV3a	HTYTTGGTASRHTQ <mark>AF</mark> AGLFDIGPQQ <mark>KLQLVNT</mark> NGSW 420							
	HCV4a	ETHVSGAAVGRSTAGLANLFSSGSKQNLQLLNSNGSW 420							
	нсуба	RTHTVGGTVGQGLKSLTSFFNPGPQRQUQFVNTNGSW 420							
	нсуба	QTMIAHG-VSQTTSGFASLLTPGAKONIOLINTNGSW 419							
	ncv/a								

нсуба	QTMIAHG-VSQTTSGFASLLTPGAKQNIQLINTNGSW	419
HCV7a	ETMAVGARAAHTTGALVSLLNPGPSORIOLINTNGSW	420
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	VP2	
HCV1a	HINSTALNCNESLNTGWLAGLFYCHKENSSCOPER ASCRELTDEACGWEISYA-NG-S	478
HCV1b		170
HCVID		470
HCV2d	HINKIALNCNDSLHIGFLASLFIIHSINSSCOPERISACISILAFRVGWGALQIEDNVIN	400
нсуза	HINSTALNCNESINTGFIAGLFITHKENSTGCPORLSSCKPITFFROGWGPLTDA-NITG	479
HCV4a	HINRTALNCNDSLNTGFLASLFYTHKFNSSGCSERLACCKSLDSYGQGWGPLGVA-NISG	4/9
HCV5a	HINSTALNCNDSLQTGFIAGLMYAH <mark>KFNS</mark> SGCPERMSS <mark>CR</mark> PLAAFDQGW <mark>G</mark> TISYA-TISG	479
HCV6a	HINRTALNCNDSLQTGFLASLFYTH <mark>KFNS</mark> SCCPERMAACKPLAEFRQGW <mark>G</mark> QITHK-NVSG	478
HCV7a	HINRTALNCNDSLQTGFIAALFYTH <mark>RFNS</mark> SCCPERMASCKPLSDFDOGWCPLWYN-STER	479
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HCV1a	GLDERPYCWHYPPRPCGIVPAKSVCGPVYCFTPSPVVVGTTDRSGAPTYSWGANDTDVFV	538
HCV1b	SSD <mark>CR</mark> PY <mark>CWHYA</mark> PRPCGIVPASQVCGPVYCFTPSPVVVGTTD <mark>R</mark> FGAPTYSWGENE <mark>T</mark> DVLL	538
HCV2a	PEDMRPYCWHYPPRQCGVVSASSVCGPVYCFTPSPVVVGTTDRLGAPTYTWGENETDVFL	540
HCV3a	PSDDRPYCWHYAPRPCDIVPASSVCGPVYCFTPSPVVVGTTDARGVPTYTWGENEKDVFL	539
HCV4a	SSDDRPY <mark>CWHYAPR</mark> PCGIVPASSVCGPVYCFTPSPVVVGTTD <mark>H</mark> VGVPTYTWGENE <mark>T</mark> DVFL	539
HCV5a	PSDDKPYCWHYPPRPCGVVPARDVCGPVYCFTPSPVVVGTTDRRGCPTYNWGSNETDILL	539
HCV6a	PSDDRPYCWHYAPRPCEVVPARSVCGPVYCFTPSPVVVGTTD <mark>K</mark> RGNPTYTWGENE <mark>T</mark> DVFM	538
HCV7a	PSDORPYCWHYAPSPCGIVPAKDVCGPVYCFTPSPVVVGTTDRRGVPTYTWGENESDVFL	539
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	VR3	
HCV1a	LNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVIGCVGNNTLLCPTDCFRKYPEAT	593
HCV1b	LSNTRPPOGNWFGCTWMNSTGFTKTCGGPPCNIGGVGNNTLWCPTDCFRKHPEAT	593
HCV2a	INSTRPPOCSWEGCTWMNSTGYTKTCGAPPCRIRADENASMDLLCPTDCFRKHPDT	597
HCV3a	LKSORPPSCRWFGCSWMNSTGFLKTCGAPPCNIYGGEGNPHNESDLFCPTDCFRKHPET	599
HCV4a	INSTRUCT CONTRACTOR OF THE CONTRACT OF THE PROPERTY OF THE PRO	593
HCV5a	INNTREPACING COMMISSION AND A COMPANY AN	594
нсуба	LEGI PDD CCWECCTWMNSTGETKTCCADDCOLUDCNVNS_SANEL COTDCERKUDEA	507
HCV7a	INSTRADDOCSWECCSWMNTTCETKTCCCDDCKIDDOCA_OSNTSITCETDOFKKIEBAT	507
nev/a	INTERFORMATION INCOMPANY CONTRACTOR	221
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	* *** * **** ***:**: * **.*** :	
HCV1a		653
HCV1a	YSR CGSGPRITPRCMUPPYLMHYPCTINYTIFKVRMYVGGVEHRLEAACNWTPGPED	653
HCV1a HCV1b	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTWCCSGFWLTPRCMVDYPYRLWHYPCTVNFTVFKVRMYVGGVEHRLEAACNWTRGERCD	653 653
HCV1a HCV1b HCV2a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTVNFTVFKVRMYVGGVEHRLINAACNWTRGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVNTVIFKIRWYVGGVEHRLINAACNWTRGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVNTVIFKIRWYVGGVEHRLINAACNFTFGORCN	653 653 657
HCV1a HCV1b HCV2a HCV3a	YSRCGSGPRITPRCMVDYPYRLWHYFCTINYTIFKVRMYVGGVEHRLEAACNWTRGERC YTKCGSGPWLTPRCMVDYPYRLWHYFCTVNFVFKVRMYVGGVEHRLNAACNWTRGERC YIKCGSGPWLTPRCLIDYPYRLWHYFCTVDFLFKIRWYVGGVEHRLTAACNTRGERC YSRCGAGPWLTPRCMVDYPYRLWHYFCTVDFRLFKVRMFVGGFEHRFTAACNWTRGERC YSRCGAGPWLTPRCMVDYPYRLWHYFCTVDFRLFKVRMFVGGFEHRFTAACNWTRGERCD	653 653 657 659
HCV1a HCV1b HCV2a HCV3a HCV4a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTWCGSGFWLTPRCMVDYFYRLWHYPCTVNFTVFKVRMYVGGVEHRLAACNWTRGERCD YIKCGSGFWLTPRCLIDYPYRLWHYPCTVNYTIFKIRMYVGGVEHRLTAACNFTRGDRCN YSRCGAGFWLTPRCMVDYFYRLWHYPCTVDFRLFKVRMFVGGFEHRTAACNWTRGERCD YAKCGSGFWITPRCLIDYFYRLWHFPCTANFSVFNIRFFVGGIEHRMAAACNWTRGEVCG	653 653 657 659 653
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTVNFTVFKVRMYVGGVEHRLNAACNWTRGERCD YIKCCSGPWLTPRCLIDYPYRLWHYPCTVDTIFKIRMYVGGVEHRLTAACNFTRGORCN YSRCGAGPWLTPRCLUDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNWTRGEPCG YACCSGEPWITPRCLUDYPYRLWHPCTVDFLIRFVGGTEHRFMAACNWTRGEPCG YTRCGSGPWITPRCLUDYPYRLWHPCTVNYTIFKVRMFIGGLEHRLEAACNNTYGERCD	653 653 657 659 653 654
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV6a	YSK CGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNNTNGERCD YTN CCSGFWLTPRCMVDYPYRLWHYPCTVNFTVFKVRMYVGGVEHRLIAACNNTNGERCD YIN CCSGFWLTPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLIAACNNTNGERCD YSR CGAGPWLTPRCMVDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFAACNNTNGERCD YAR CCSGFWITPRCLIDYPYRLWHYPCTNDFSVFNIRTFVGGIEHRMQAACNNTNGERCD YTN CCSGFWITPRCLIDYPYRLWHYPCTVNTIFKVRNFTGGIEHRLAAACNNTNGERCD YOR CGSGPWITPRCLVDYPYRLWHYPCTVNTFLKKVRNFTGGIEHRLAACNNTNGERCD YOR CGSGPWITPRCLVDYAYRLWHYPCTVNTFLKKVRNFTGGIEHREAACNNTNGERCD	653 653 657 659 653 654 657
HCV1a HCV2a HCV2a HCV3a HCV4a HCV5a HCV6a HCV7a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTWCGSGPWLTPRCMVDYPYRLWHYPCTVNTTVFKVRMYVGGVEHRLTAACNWTRGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLTAACNFTRGDRCN YSRCGAGFWLTPRCMVDYPYRLWHYPCTVDFRLFKVRMFVGGTEHRMAACNWTRGERCD YAKCGSGPWITPRCLIDYPYRLWHYPCTVDTFKVRMFIGGLEHRLAACNWTRGERCD YORCGSGPWLTPRCLVHPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNWTRGERCD YORCSGPWTTPRCLVDYAYRLWHYPCTVNTIFKVRMFIGGLEHRFDVACNWTRGERCD YSRCGSGPWLTPRCVHYPYRLWHYPCTVNTFHKVRNFVGGTEHRFDACNWTRGERCD YSRCGSGPWLTPRCMVHYPYRLWHYPCTVNTFHKVRNFVGGTEHRFDACNNTRGERCD	653 653 657 659 653 654 657 657
HCV1a HCV2a HCV2a HCV3a HCV4a HCV5a HCV6a HCV7a	YSHCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTHGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTVNTVFKVRMYVGGVEHRLNAACNWTHGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVDTIFKIRNYVGGVEHRLTAACNWTHGERCD YSHCGAGPWLTPRCLUDYPYRLWHYPCTVDFLFKVRMFVGGTEHRFTAACNWTHGERCD YARCGSGPWITPRCLUDYPYRLWHPCTVNTIFKIRNYVGGTEHRFDAACNWTHGERCD YCCGSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGLEHRLEAACNWTHGERCD YSHCGSGPWLTPRCLVHYPYRLWHYPCTVNTTIKKVRMFVGGTEHRFDVACNWTHGERCD YSHCGSGPWLTPRCLVHYPYRLWHYPCTVNTTIKKVRMFVGGTEHRFDVACNWTHGERCD	653 653 657 659 653 654 657
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV5a HCV6a HCV7a	YSR CGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRCERCD YTKCSGSGPWLTPRCMVDYPYRLWHYPCTVNTVFKVRMYVGGVEHRLIAACNWTRCERCD YIK CGSGFWLTPRCLIDYPYRLWHYPCTVNTTIFKIRMYVGGVEHRLTAACNWTRCERCD YSR CGAGFWLTPRCLIDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNWTRCERCD YNRCCSGFWLTPRCLUDYPYRLWHFPCTNNTIFKVRNFTGLEHRLEAACNWTRCERCC YC CGSGFWLTPRCLWHYPRLWHYPCTVNTFTKVRNFTGLEHRLEAACNWTRCERCE YSR CGSGFWLTPRCLWHYPRLWHYPCTVNFTLHKVRNFTGGEHRELAAACNWTRCERCD YSR CGSGFWLTPRCLWHYPRLWHYPCTVNFTLHKVRNFTGGEHRELAAACNWTRCERCE YSR CGSGFWLTPRCLWHYPRLWHYPCTVNFTLHKVRNFTGGEHRELAAACNWTRCERCD **********	653 653 657 659 653 654 657 657
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV5a HCV6a HCV7a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YIRCGSGPWLTPRCMVDYPYRLWHYPCTVNTVFKVRMYVGGVEHRLIAACNWTRGERCD YIRCGSGPWLTPRCLIDPYRLWHYPCTVNTFIKIRWYGGVEHRLIAACNWTRGERCD YSRCGAGPWLTPRCLUDPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNWTRGERCD YARCGSGPWITPRCLUDYPYRLWHYPCTVNTFIKVRMFIGGLEHRLEAACNWTRGERCD YCCGSGPWITPRCLUDYYRLWHYPCTVNTFIKVRMFIGGLEHRLEAACNWTRGERCD YSCGSGPWITPRCLUDYARLWHYPCTVNTFIKVRMFIGGLEHRLEAACNWTRGERCD YSCGSGPWITPRCLUDYARLWHYPCTVNTFIKVRMFIGGLEHRLEAACNWTRGERCD YSCGSGPWITPRCLUDYARLWHYPCTVNTFIKVRMFIGGLEHRLEAACNWTRGERCD YSCGSGPWITPRCLUDYARLWHYPCTVNTFIKVRMFIGGLEHRLEAACNWTRGERCD YSCGSGPWITPRCLUDYARLWHYPCTVNTFIKVRMFIGGLEHRLEAACNWTRGERCD YSCGSGPWITPRCLUDYARLWHYPCTVNTFIHKVRLYIGVEHRLDAACNWTRGERCD ************************************	653 653 657 659 653 654 657 713
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV5a HCV7a HCV1a HCV1a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTBGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTVNTVFKVRMYVGGVEHRLNAACNWTBGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNWTBGERCD YSRCGSGPWITPRCLIDYPYRLWHPPCTVDFRLFKVRMFVGGIEHRFDAACNWTBGERCD YSRCGSGPWITPRCLUDYPYRLWHPPCTVNTTIFKVRMFIGGIEHRFDAACNWTBGERCD YSRCGSGPWITPRCLUDYPYRLWHPPCTVNTTIFKVRMFIGGIEHRFDAACNWTBGERCD YSRCGSGPWITPRCLUMYPYRLWHPPCTVNTTIFKVRMFIGGIEHRFDAACNWTBGERCD YSRCGSGPWITPRCLUMYPYRLWHYPCTVNFTLHKVRMFIGGIEHRFDAACNWTBGERCD YSRCGSGPWITPRCLUMYPYRLWHYPCTVNFTLHKVRMFIGGIEHRFDAACNWTBGERCD XSRCGSGPWITPRCUMYPYRLWHYPCTVNFTLHKVRNFIGGVEHRFDAACNWTBGERCD XSRCGSGPWITPRCUMYPYRLWHYPCTVNFTLHKVRNFIGGVEHRFDAACNWTBGERCD XSRCGSGPWITPRCUMYPYRLWHYPCTVNFTLHKVRNFIGGVEHRFDAACNWTBGERCD XSRCGSGPWITPRCUMYPYRLWHYPCTVNFTLHKVRNFIGGVEHRFDAACNWTBGERCD XSRCGSGPWITPRCUMYPYRLWHYPCTVNFTLHKVRNFIGGVEHRFDAACNWTBGERCD XSRCGSGPWITPRCUMYPYRLWHYPCTVNFTLHKVRNFIGGVEHRFDAACNWTBGERCD XSRCGSGPWITPRCUMYPYRLWHYPCTVNFTLHKVRNFIGGVEHRFDAACNWTBGERCD	653 653 657 659 653 654 657 657 713 713
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV6a HCV7a HCV1a HCV1b HCV1b	YSICGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNNTRGERCD YTRCGSGPWLTPRCMVDYPYRLWHYPCTVNFTVFKVRMYVGGVEHRLIAACNNTRGERCD YIRCGSGPWLTPRCLIDYPYRLWHYPCTVNTFIKIRNYVGGVEHRLIAACNNTRGERCD YSICGAGPWLTPRCMVDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNNTRGERCD YARCGSGPWITPRCLIDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNNTRGERCD YGRCGSGPWITPRCLVDYPYRLWHYPCTVNTIFKVRNFTGGEHRLEAACNNTRGERCD YGRCGSGPWITPRCLVDYAINHPPCTVNTFIKVRNFTGGEHRLEAACNNTRGERCD YSRCGSGPWITPRCLVDYAINHPPCTVNTFIKVRNFTGGEHRLEAACNNTRGERCD YSRCGSGPWITPRCLVDYAINHPPCTVNTFIKVRNFTGGEHRLEAACNNTRGERCD YSRCGSGPWITPRCLVDYAINHPPCTVNTFIKVRNFTGGEHRLEAACNNTRGERCD Storregion LEDRDRSELSPLLSTTOWOVIECSTTIPALSTGLIHLMONTVDVOVIGGSSIASWA LEDRDRSELSPLLSTTEWAILPCTYSDIPALSTGLIHLMONTVDVOVIGGSSIASWA	653 657 659 653 654 657 657 713 713 717
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV6a HCV7a HCV1a HCV1b HCV1b HCV2a HCV2a	YSRCCSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTHGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTVNTYIFKVRMYVGGVEHRLNAACNWTHGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLTAACNTHGERCD YSRCGSGPWITPRCLIDPYRLWHYPCTVNTIFKIRMYVGGEHRFTAACNWTHGERCD YACCSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNWTHGERCD YSRCGSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNWTHGERCD YSRCGSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNWTHGERCD YSRCGSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNWTHGERCD YSRCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNWTHGERCD YSRCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNWTHGERCD SSRCSSGPWITPRCLUDYAYRLWHYPCTVNTIFKKRWFIGGLEHRCDACNWTHGERCD LEDRDRSELSPLLSTTEWGILPCSTTIPALSTCLIHLWONTUDVOYNGCSSTASWA LEDRDRSELSPLLSTTEWGILPCSTTIPALSTCLIHLWONTUDVOYNGCSSAVSFA LEDRDRSCSPLLBSTTEWGILPCSTTIPALSTCLIHLWONTUDVOYNGCSSAVSFA	653 657 659 653 654 657 657 713 713 713 717
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV6a HCV7a HCV1a HCV1b HCV1b HCV2a HCV3a HCV4a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTVNTVIFKVRMYVGGVEHRLEAACNWTRGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNWTRGERCD YSRCGSGPWLTPRCLIDYPYRLWHYPCTVNTIFKIRNYVGGFEHRFTAACNWTRGEVCG YTRCSSGPWITPRCLUDYPYRLWHPPCTVNTTIFKVRNFTGGLEHRLEAACNWTRGEVCG YTRCSGGPWTPRCLUDYPYRLWHPPCTVNTTIFKVRNFTGGLEHRLEAACNWTRGEVCG YSRCGSGPWITPRCLUDYAYRLWHPPCTVNTTIFKVRNFTGGLEHRLEAACNWTRGEVCG YSRCGSGPWITPRCLUDYAYRLWHPPCTVNTTIFKVRNFTGGLEHRLEAACNWTRGEVCG YSRCGSGPWITPRCLUPYRTUHYPCTVNTTIFKVRNFTGGLEHRLEAACNWTRGEVCG SCRCGSGPWITPRCLUPYRTUHYPCTVNTTIFKVRNFTGGLENGLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGLENGLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGLENGLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGLENGLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGVENRLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGVENRLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPTTIFLNKVRUPYGGVENRLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGVENRLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGVENRLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGVENRLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPCTVNTTIFKVRNFTGGVENRLACNWTRGEVCG SCRCGSGPWITPRCUPYRTUHYPTTUHYTIFVNT SCRTTGGON LEDRORSELSPILLSTTGWGIPCSFTTPALSTGLINLANNVDVQVINGGSAVNSFA LEDRORSELSPILLSTTGWITPCTTVSDIPALSTGLINLANNVDVQVINGGSAVNSFA LEDRORSELSPILLSTGWGIPCSFTTPALSTGLINLANNVDVQVINGGSAVNSFA	653 657 659 653 654 657 713 713 713 717 719 713
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV6a HCV7a HCV1a HCV1b HCV2a HCV3a HCV2a HCV3a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNNTRGERCD YTNCCSGFWLTPRCMVDYPYRLWHYPCTVNTVFKVRMYVGGVEHRLIAACNNTRGERCD YSRCGAGPWLTPRCMVDYPYRLWHYPCTVNTFIKIRNYVGGVEHRLIAACNNTRGERCD YSRCGAGPWLTPRCLIDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNNTRGERCD YARCCSGFWITPRCLIDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNNTRGERCD YCRCGSGFWITPRCLUDYPYRLWHYPCTVNTIFKVRNFTGGLEHRLEAACNNTRGERCD YCRCGSGFWLTPRCLVHYPYRLWHYPCTVNTFIKVRNFTGGEHRLEAACNNTRGERCD YSRCGSGFWLTPRCLVDYPYRLWHYPCTVNTFIKVRNFTGGEHRLEAACNNTRGERCD YSRCGSGFWLTPRCLVDYAYRLWHYPCTVNTFIKVRNFTGGEHRLEAACNNTRGERCD YSRCGSGFWLTPRCLVDYAYRLWHYPCTVNTFIKVRNFTGGEHRLEAACNNTRGERCD * ***** *****************************	653 657 659 653 654 657 657 713 713 717 719 713 714
HCV1a HCV2a HCV2a HCV5a HCV5a HCV5a HCV6a HCV1a HCV1b HCV2a HCV2a HCV3a HCV3a HCV5a HCV5a HCV5a	YSR CGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTBGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLIAACNWTBGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVDFLFKVRMYVGGVEHRLTAACNWTBGERCD YSR CGSGPWLTPRCLUDYPYRLWHYPCTVNTIFKIRMYVGGTEHRFTAACNWTBGERCD YNCCSGPWLTPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGLEHRLEAACNWTBGERCD YDCCSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFIGGLEHRLEAACNWTBGERCD YSS CGSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFIGGLEHRLEAACNWTBGERCD SS CGSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRNFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRNFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRNFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRNFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRNFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRNFIGGTEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRLVIGGEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRLVIGGEHRFDVACNWTBGERCD SS CGSGPWLTPRCUHYPYRLWHYPCTVNTTIHKVRLVIGGEHRFDVACNWTBGERCD LEDRORSELSPLLLSTTENAILPCTYSTPALSTCLIHLMNLVDVQTYLGGESAUNSFA LEDRORSELSPLLLSTTENAILPCTYSTPALSTCLIHLMNUVDVQTYLGGESAUNSFA LEDRORSELSPLLLTTAVGILPCSTTPALSTCLIHLMNUVDVQTYLGGESAUNSFA LEDRORSELSPLLLTTAVGILPCSTTPALSTCLIHLMNUVDVQTYLGGESAUNSFA LEDRORSESPLLLSTENAILPCTSTPALSTCLIHLMNUVDVQTYLGGESAUNSFA	653 657 659 653 654 657 657 713 713 713 713 719 713 714 717
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV7a HCV1a HCV1b HCV1b HCV2a HCV3a HCV4a HCV5a HCV4a HCV5a HCV4a	YSRCGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTKCGSGPWITPRCMVDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLAAACNWTRGERCD YIRCGSGPWITPRCLIDYPYRLWHYPCTVDFRLFKVRMYVGGFEHRFTAACNWTRGERCD YAKCGSGPWITPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGFEHRFTAACNWTRGEVCG YTRCGSGPWITPRCLUDYPYRLWHYPCTVNTTIFKVRMFTGGLEHRLEAACNWTRGEVCG YTRCGSGPWITPRCLUDYPYRLWHYPCTVNTTIFKVRMFTGGLEHRLEAACNWTRGEVCG YCCGSGPWITPRCLUDYAYRLWHYPCTVNTTIFKVRMFTGGLEHRLEAACNWTRGEVCG YCRCGSGPWITPRCLUDYAYRLWHYPCTVNTTIFKVRMFTGGLEHRLEAACNWTRGEVCG YCRCGSGPWITPRCLUDYAYRLWHYPCTVNTTIFKVRMFTGGLEHRLEAACNWTRGEVCG YSRCGSGPWITPRCMHYPYRLWHYPCTVNTTIFKVRMFTGGLEHRLEAACNWTRGERCD ************************************	653 657 659 653 654 657 713 713 717 719 713 714 717
HCV1a HCV2a HCV2a HCV4a HCV5a HCV6a HCV7a HCV1b HCV1b HCV1b HCV2a HCV3a HCV4a HCV4a HCV4a HCV5a HCV4a HCV5a	YSRCGSGPRITPRCMUDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTKCGSGPWITPRCMUDYPYRLWHYPCTVNTIFKVRMYVGGVEHRLIAACNWTRGERCD YIRCGSGPWITPRCLUPYRLWHYPCTVNTIFKIRMYVGGVEHRLTAACNTRGERCD YSRCGSGPWITPRCLUPYRLWHYPCTVNTIFKIRMYVGGTEHRFTAACNWTRGEPC YARCGSGPWITPRCLUPYRLWHYPCTVNTIFKVRMFIGLEHRAQAACNWTRGEPC YSRCGSGPWITPRCLUPYRLWHYPCTVNTIFKVRMFIGLEHRAQAACNWTRGEPC YSRCGSGPWITPRCLUPYRLWHYPCTVNTIFKVRMFIGLEHRAQAACNWTRGEPC YSRCGSGPWITPRCLUPYRLWHYPCTVNTIFKVRMFIGLEHRAQAACNWTRGEPC YSRCGSGPWITPRCLUPYRTWHYPCTVNTIFKVRMFIGGLEHRLAACNNTRGEPC SSCCSGPWITPRCLUPYRTWHYPCTVNTIFKVRMFIGGLEHRLAACNNTRGEPC SSCCSGPUTPRCVUPYRTWHYPCTVNTIFKVRMFIGGLEHRLAACNNTRGEPC SSCCSGPUTPRCVUPYRTWHYPCTVNTIFKVRMFIGGLEHRLAACNNTRGEPC SSCCSGPUTPRCVUPYRTWHYPTRUHYPCTVNTIFKVRNFIGGLEHRLAACNNTRGEPC SSCCSGPUTPRCVUPYRTWIPYRTWATHFTVIL SSCCSGPUTPRCVUPYRTWIPYRTWATHFT SSCCSFFILSTTUPALING SSCCSFFILSTTWAILPCSTTIPALSTCLINLNNUVDVOYINGCSSANSFA LEDRDRSELSFLHSTTENAILPCSTTWFALSTCLINLNNUVDVOYINGCSANSFA LEDRDRSELSFLHSTTENAILPCSTTPALSTCLINLNNUVDVOYINGGSANSWA LEDRDRSELSFLHSTTENAILPCSTTPALSTCLINLNNUVDVOYINGGSANSWA LEDRDRSELSFLHSTTENAILPCSTPALSTCLINLNNUVDVOYINGGSANSWA LEDRDRSELSFLHSTTENAILPCSTPALSTCLINLNNUVDVOYINGGSANSWA LEDRDRSELSFLHSTTIFAILPCSTPALSTCLINLNNUVDVOYINGSSINSWA	653 657 659 653 657 657 713 713 717 719 713 714 717 717
HCV1a HCV1b HCV2a HCV3a HCV5a HCV5a HCV6a HCV1b HCV1b HCV2a HCV2a HCV2a HCV3a HCV4a HCV5a HCV5a HCV5a	YSR CGSGPRITPRCMVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCD YTKCGSGPWITPRCMVDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLIAACNWTRGERCD YIKCGSGPWITPRCLIDYPYRLWHYPCTVDTPLFKVRMYVGGVEHRLTAACNWTRGERCD YARCGSGPWITPRCLUDYPYRLWHYPCTVDTIFKIRMYVGGTEHRFAACNWTRGEVCG YNCGSGPWITPRCLUDYPYRLWHYPCTVNTIFKIRMYVGGTEHRFAACNWTRGEVCG YSRCGSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGIEHRLEAACNWTRGEVCG YSRCGSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGIEHRLEAACNWTRGEVCG YSRCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKRVRMFIGGIEHRLEAACNWTRGEVCG YSRCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRMFIGGIEHRFDAACNWTRGEVCG YSRCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRFIGUEHRLEAACNWTRGEVCG SSCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRFIGGIEHRFDAACNWTRGEVCG SSCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRFIGGIEHRFDAACNWTRGEVCG SSCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRFIGUEHRLDAACNWTRGEVCG SSCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRIVIGUEHRLDAACNWTRGEVCG SSCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRIVIGUEHRLDAACNWTRGEVCG SSCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRIVIGUEHRLDAACNWTRGEVCG SSCGSGPWITPRCLUDYAYRLWHYPCTVNTIFKKVRIVIGUEHRLDAACNWTRGEVCG SSCGSGPWITPRCLUDYAYRWYYXWHYPCTVNTIFKKVRIVIGUE SSCGSGPWITPRCLUDYAYRWYYXWHYPCTVNTIFKKVRIVIGUEHRLDAACNWTRGEVCG LEDRORSCLSPLLUSTTEWAILPCSTVPIALSTGLIHLWNIVDVOYLYGGSAVSA LEDRORSCLSPLLUSTTEWAILPCSTVPIALSTGLIHLWNIVDVOYLYGGSAVSWA LEDRORSCLSPLLUTTAWGILPCSTTPPALSTGLIHLWNIVDVOYLYGGSAVSWA LEDRORSCLSPLLUSTTEWAILPCSTVPIALSTGLIHLWNIVDVOYLYGGSAVSWA LEDRORSCLSPLLUSTTEWAILPCSTVPIALSTGLIHLWNIVDVOYLYGGSAVSWA LEDRORSCLSPLLUSTTEWAILPCSTVPIALSTGLIHLWNIVDVOYLYGGSAVSWA	653 657 659 653 654 657 713 713 717 719 713 714 717 717
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV7a HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV4a HCV5a HCV4a HCV5a HCV4a HCV5a HCV4a	YSK CGSGPRITPRCMVDYPYRLWHYPCTINTIFKVRMYVGGVEHRLEAACNKTBGERCD YTKCGSGPWITPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLTAACNKTBGERCD YSK CGSGPWITPRCLIDYPYRLWHYPCTVDFRLFKVRMFVGGFEHRFTAACNKTBGERCD YSK CGSGPWITPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGFEHRFTAACNKTBGERCD YSK CGSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGEHRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYPYRLWHYPCTVNTIFKVRMFIGGEHRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFKVRMFIGGEHRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFKVRMFIGGEHRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRMFIGGEHRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRMFIGGEHRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRMFIGGEHRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRMFIGGEHRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRMFIGGEKRELEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRMFIGGVEHRLEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRNFIGGVEHRLEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRNFIGGVEHRLEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRNFIGGVEHRLEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRNFIGGVEHRLEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRNFIGGVEHRLEAACNKTBGERCD YSK CGSGPWITPRCLUDYAYRLWHYPCTVNTIFLHKVRNFIGGVEHRLEAACNKTBGERCD HEDRORSELSPLLISTTEWAILPCTYSDIPALSTGLIHLKNNVDVOVYNGGSAWSFA LEDRORSELSPLLISTTEWAILPCTYSDIPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORSELSPLLISTTEWAILPCSTTPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORSELSPLLISTTEWAILPCSTTPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORSELSPLLISTTEWAILPCSTTPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORVELSPLLISTTEINAILPCSTTPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORVELSPLLISTTEWAILPCSTPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORVELSPLLISTTEWAILPCSTTPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORVELSPLLISTTEWAILPCSTPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORVELSPLLSTTEINAILPCSTPALSTGLIHLNNVDVOVYNGGSAWSFA LEDRORVELSPLLSTTEWAILPCSCLWMILISTAAC	653 657 659 654 657 657 713 717 719 713 714 717 717
HCV1a HCV1b HCV2a HCV3a HCV5a HCV5a HCV6a HCV1b HCV1b HCV1b HCV2a HCV4a HCV4a HCV4a HCV5a HCV6a HCV7a HCV6a HCV7a	YSR CCSGPRITPRCMVDYPYRLWHYPCTINTIFKVRMYVGGVEHRLEAACNWTBGERCD YTKCGSGPWITPRCMVDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLIAACNWTBGERCD YIR CCSGPWITPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLIAACNWTBGERCD YSR CCSGPWITPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGVEHRFTAACNWTBGERCD YAR CCSGPWITPRCLUPYPRLWHYPCTVNTIFKIRMYVGGTEHRFDAACNWTBGERCD YSR CCSGPWITPRCLUPYPRLWHYPCTVNTIFKIRMYVGGTEHRFDAACNWTBGERCD YSR CCSGPWITPRCLUPYPRLWHYPCTVNTIFKIRMYVGGTEHRFDAACNWTBGERCD YSR CCSGPWITPRCLUPYPRLWHYPCTVNTIFKIRMYVGGTEHRFDAACNWTBGERCD YSR CCSGPWITPRCLUPYPRLWHYPCTVNTIFKIRVRHFUGGLEHRLAACNNTGERCD Stan region LEDRORSELSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSSTASWA LEDRORSELSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSAWSFA LEDRORSELSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEHRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEHRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEHRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEHRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEHRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEHRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEHRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEHRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEBRORSCHSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEBRORSCHSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSGAWGWA LEBRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSAWGWA LEBRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSAWGWA LEBRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSAWGWA LEBRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSAWGWA LEBRORVSLSPLLISTTEWGILPCSTTIPALSTGLIHLANNVUDVOYLYGGSAWGWA LEBRORVSLSPLLISTTEWGILPCSCUMMILISGABA TAG	653 657 659 654 654 657 713 717 719 717 714 717 717
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV6a HCV1b HCV1b HCV2a HCV4a HCV5a HCV5a HCV5a HCV5a HCV7a HCV1a HCV1b HCV2a	YSR CCSG PRITPRCMVDYPYRLWHYPCTINTIFKVRMYVGGVEHRLEAACNWTBGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTVNTIFKVRMYVGGVEHRLAACNWTBGERCD YSR CCSGFWLTPRCLIDYPYRLWHYPCTVDFLFKVRMYVGGVEHRLTAACNWTBGERCD YSR CCGSGPWLTPRCLUDYPYRLWHYPCTVDFLFKVRMFUGGIEHRPAACNNTBGERCD YSR CCSGFWLTPRCLUDYPYRLWHYPCTVNTIFKVRMFUGGIEHRFAACNNTBGERCD YSR CCSGFWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFUGGIEHRFAACNNTBGERCD YSR CCSGFWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFUGGIEHRFAACNNTBGERCD YSR CCSGFWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFUGGIEHRFAACNNTBGERCD YSR CCSGFWLTPRCUHYPYRLWHYPCTVNTTIHKVRMFUGGIEHRFAACNNTBGERCD ************************************	653 657 659 653 654 657 657 713 713 717 719 713 714 717 717
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV6a HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV4a HCV7a HCV4a HCV7a	YSR CGSGPRITPRCMVDYPYRLWHYPCTINTJIFKVRMYVGGVEHRLEAACNFTBGERCD YTKCGSGPWLTPRCLUDYPYRLWHYPCTUNTJIFKVRMYVGGVEHRLTAACNFTBGERCD YSR CGSGPWLTPRCLUDYPYRLWHYPCTUNTJIFKVRMYVGGFEHRETAACNFTBGERCD YSR CGSGPWLTPRCLUDYPYRLWHYPCTUNTJIFKVRMFTGGEHRENLAACNFTBGERCD YARCGSGPWLTPRCLUDYPYRLWHYPCTUNTJIFKVRMFTGGEHRENLEAACNNTBGERCD YCCGSGPWUTPRCLUDYPYRLWHYPCTUNTJIFKVRMFTGGEHRENLEAACNNTBGERCD YCR CGSGPWLTPRCLUHYPYRLWHYPCTUNTJIFKVRMFTGGEHRENLEAACNNTBGERCD YSR CGSGPWLTPRCLUHYPYRLWHYPCTUNTJIFKVRMFTGGEHRENLEAACNNTBGERCD YSR CGSGPWLTPRCUHYPYRLWHYPCTUNTJIFKVRMFTGGEHRENLEAACNNTBGERCD YSR CGSGPWLTPRCUHYPYRLWHYPCTUNTJIFKVRMFTGGEHRENLAACNNTBGERCD ************************************	653 657 659 653 654 657 657 713 717 719 713 717 717 717 717
HCV1a HCV1b HCV2a HCV3a HCV5a HCV5a HCV6a HCV1a HCV1b HCV2a HCV4a HCV4a HCV7a HCV4a HCV7a HCV1a HCV1b HCV2a HCV1b HCV1b HCV2a HCV1b HCV2a HCV1b HCV2a HCV1b HCV2a	YSR CCSGPRITPRCMVDYPYRLWHYPCTINTIFKVRMYVGGVEHRLEAACNKTRGERCD YTKCSGSGWLTPRCMVDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLAACNKTRGERCD YIKCSGSGWLTPRCLIDYPYRLWHYPCTVNTIFKIRMYVGGVEHRLAACNKTRGERCD YSR CCSGFWITPRCLIDPYRLWHYPCTVNTIFKIRMYVGGTEHRFJAACNKTRGERCD YAR CCSGFWITPRCLIDPYRLWHYPCTVNTIFKIRMYVGGTEHRFJAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRMFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CCSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CSSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CSSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLEHRLAACNKTRGERCD YSR CSSGFWITPRCLUDPYRLWHYPCTVNTIFKVRNFIGGLENG LEDRDRSELSPLLUSTTEWAILPCSTPTPALSTGLIHLKNIVDVOYLYGGSACWSWA LEDRDRSELSPLLUSTTEWAILPCSTPTPALSTGLIHLKNIVDVOYLYGGSACWSWA LEDRDRSELSPLLUSTTEWAILPCSTPTPALSTGLIHLKNIVDVOYLYGGSACWSWA LEDRDRAES PLUFSTTOISILPCSTTPALSTGLIHLKNIVDVOYLYGGSACWSWA LEDRDRVUSSELNUSTTEWAILPCSTPTPALSTGLIHLKNIVDVOYLYGGSACWSWA LEDRDRVUSSELNUSTTEWAILPCSTPTPALSTGLIHLKNIVDVOYLYGGSACWSWA LEDRDRVUSSELNUSTTEWAILPCSTPTPALSTGLIHLKONVDVOYLYGGSACWSWA LEDRDRVUSSELNUSTTEWAILPCSTPTPALSTGLIHLKONVDVOYLYGGSACWSWA LEDRDRVUSSELNUSTTEWAILPCSTPTPALSTGLIHLKONVDVOYLYGGSACWSWA LEDRDRVUSSELNUSTTEWAILPCSTPTPALSTGLIHLKONVDVOYLGSSIVSUSSIVSUS LEDRDRVUSSELNUSTEWACCCUMMILIGAACA 746 NWEWVULFFLLAADARVCACUMMILIGAACA 750 NGWEWVULFFLLAADARVCACUMMILIGAACA 752 NUEWVULFFLLAADARVSAULMINNSOTEA 752	653 657 659 653 654 657 713 717 719 713 717 719 713 717 717
HCV1a HCV1b HCV2a HCV3a HCV4a HCV5a HCV7a HCV1a HCV1b HCV2a HCV4a HCV5a HCV4a HCV7a HCV1a HCV1a HCV1a HCV1a HCV1a HCV1a HCV1a HCV1a	YSR CCSG PRITPRCMVDYPYRLWHYPCTINTIFKVRMYVGGVEHRLEAACNWTBGERCD YTKCGSGPWLTPRCMVDYPYRLWHYPCTUNTIFKVRMYVGGVEHRLTAACNWTBGERCD YIKCGSGPWLTPRCLIDYPYRLWHYPCTVDFLFKVRMYVGGVEHRLTAACNWTBGERCD YSR CGSGPWLTPRCLIDYPYRLWHYPCTVDFLFKVRMFVGGFEHRFTAACNWTBGERCD YAKCGSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFVGGEHRFDAACNWTBGERCD YSR CGSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFVGGEHRFDAACNWTBGERCD YSR CGSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFVGGTEHRFDAACNWTBGERCD YSR CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGTEHRFDAACNWTBGERCD YSR CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGTEHRFDAACNWTBGERCD XSR CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGTEHRFDAACNWTBGERCD XSR CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGTEHRFDAACNWTBGERCD XSR CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGGEHRFDAACNWTBGERCD XSR CGSGPWLTPRCUHHPYRLWHYPCTVNTTIFKVRMFVGGGEHRFDAACNWTBGERCD XSR CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGGEWRJAACNWTSGERCD XSR CGSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGGEWRJACN LEDRORSELSPLLUSTTEWGILPCSTTIPALSTGLIHLMONTUDVOYING GSAVNSFA LEDRORSELSPLLUSTTEWGILPCSTTIPALSTGLIHLMONTUDVOYING GSAVNSFA LEDRORSELSPLLUSTTEWGILPCSTTIPALSTGLIHLMONTUDVOYING GSAVNSFA LEDRORSELSPLLUSTTEWGILPCSTTIPALSTGLIHLMONTUDVOYING SSAVNSFA LEDRORSELSPLLUSTTEWGILPCSTTIPALSTGLIHLMONTUDVOYING SSAVNSFA LEDRORSELSPLLUSTTEWGILPCSTTIPALSTGLIHLMONTUDVOYING SSAVNSFA LEDRORSELSPLLUSTTEWGILPCSTTIPALSTGLIHLMONTUDVOYING SSAVNSFA LEDRORSELSPLLUSTTEWGALDEGSTTIPALSTGLIHLMONTUDVOYING SSAVNSFA LEDRORVELSPLLUSTTEWGALDEGSTTIPALSTGLIHLMONTUDVOYING SSAVNSFA LEDRORVELSPLLUSTTEWGALDEGSTTIPALSTGLIHLMONTUDVOYING SSAVNSFA LEDRORVELSPLLUSTTEWGALDEGSTTIPALSTGLIHLMONTUDVOYING SSATLSN 	653 657 659 653 654 657 713 717 717 717 713 714 717 717
HCV1a HCV2a HCV3a HCV5a HCV5a HCV6a HCV7a HCV1b HCV1b HCV2a HCV4a HCV5a HCV6a HCV7a HCV6a HCV7a	YSR CCSGPRITPRCMVDYPYRLWHYPCTINTIFKVRMYVGGVEHRLEAACNWTBGERCD YTKCGSGPWITPRCLUPYPRLWHYPCTUNTIFKIRMYVGGVEHRLIAACNWTBGERCD YICCSGFWITPRCLUPYPRLWHYPCTUNTIFKIRMYVGGVEHRLAACNWTBGERCD YSR CCSGFWITPRCLUPYPRLWHYPCTUNTIFKIRMYVGGVEHRFTAACNWTBGERCD YACCSGFWITPRCLUPYPRLWHYPCTUNTIFKIRMYVGGTEHRFDAACNWTBGERCD YSR CCSGFWITPRCLUPYPRLWHYPCTUNTIFKURMFUGGLEHRLAACNNTGERCD YSR CCSGFWITPRCLUPYPRLWHYPCTUNTIFKURMFUGGLEHRLAACNNTGERCD YSR CCSGFWITPRCLUPYPRLWHYPCTUNTIFKURMFUGGLEHRLAACNNTGERCD YSR CCSGFWITPRCLUPYPRLWHYPCTUNTIFKURMFUGGTEHRFDAACNNTGERCD ************************************	653 657 659 659 657 657 713 713 717 719 713 714 717 717
HCV1a HCV2a HCV2a HCV5a HCV5a HCV5a HCV6a HCV1a HCV1b HCV2a HCV4a HCV5a HCV5a HCV7a HCV1a HCV1b HCV2a HCV7a HCV1a HCV1a HCV1a HCV1a HCV1a HCV1a HCV7a	YSR CCSGPRITPRCMVDYPYRLWHYPCTINTIFKVRMYVGGVEHRLEAACNWTBGERCD YTKCSGSGWLTPRCMVDYPYRLWHYPCTUNTIFKVRMYVGGVEHRLAACNWTBGERCD YIKCSGSGWLTPRCLIDYPYRLWHYPCTVDFVFKVRMYVGGVEHRLTAACNWTBGERCD YSR CCGSGPWLTPRCLUDYPYRLWHYPCTVDFLFKVRMFVGGFEHRFTAACNWTBGERCD YAKCGSGPWLTPRCLUDYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFTAACNWTBGERCD YSR CCSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFTAACNWTBGERCD YSR CCSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFTAACNWTBGERCD YSR CCSGPWLTPRCLUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFTAACNWTBGERCD YSR CCSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFDAACNWTBGERCD YSR CCSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFDAACNWTBGERCD YSR CCSGPWLTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFDAACNWTBGERCD SSC CSGPULTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFDAACNWTBGERCD YSR CCSGPULTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFDAACNWTBGERCD YSR CCSGPULTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFDAACNWTBGERCD YSR CCSGPULTPRCUHYPYRLWHYPCTVNTTIFKVRMFVGGFEHRFDAACNWTBGERCD SSC SSC SPLLUSTTENQILPCSTTIPALSTCLIHLMONLUDVOYLGG SAANKA LEDRDRSELSPLLUSTTENQILPCSTTIPALSTCLIHLMONLUDVOYLGG SAANKA LEDRDRSELSPLLUSTTENAIDPCTSTIPALSTCLIHLMONLUDVOYLGG SAANKSFA LEDRDRSELSPLLUSTTENAIDPCSTTIPALSTCLIHLMONLUDVOYLGG SAANSA LEDRDRSELSPLLUSTTENAIDPCSTTIPALSTCLIHLMONLUDVOYLGG SAANSA LEDRDRSELSPLLUSTTENAIDPCSTTIPALSTCLIHLMONLUDVOYLGG SAANSA LEDRDRSELSPLLUSTTENAIDPCSTTIPALSTCLIHLMONLUDVOYLGG SAANSA LEDRDRSELSPLLUSTTENAIDPCSTTIPALSTCLIHLMONLUDVOYLGG SAANSA LEDRDRAESSPLLUSTTENAIDPCSTTIPALSTCLIHLMONLUDVOYLGG SAANSA LEDRDRAESSPLLUSTTENAIDSEN TWEEVULFILLADARVCSCLMMILLISDAEA 746 NWEWVULFILLADARVCSCLMMILLISDAEA 750 NWEWVULFILLADARVCSCLMMILLISDAEA 750 NWEWVULFILLADARVCSCLMMILLISDAEA 750 NWEWVULFILLADARVCSCLMMILLISDAEA 750 NWEWVULFILLADARVCSCLMMILLISDAEA 750 NWEWVULFILLADARVCSCLMMILLISDAEA 750 NWEWVULFILLADARCTCTULMILLISTVEA 750 NWEWVULFILLADARCTCTULMILLISTVEA 750	653 657 659 653 654 657 657 657 713 713 717 717 717 717 717

**Figure S3. Sequence conservation of HCV Env polyprotein across HCV genotypes. Related to Figure 3.** (A) Sequence alignment for HCV E1 glycoprotein. (B) Sequence alignment for HCV E2 glycoprotein. Critical residues for E1E2 assembly are highlighted in yellow, those for infectivity in blue. ClustalW alignment was performed using parental sequence HCV1a isolate H77 together with reference sequences for each genotype recommended by the International Committee on Taxonomy of Viruses. Regions of structure- and sequence-related importance are denoted. Subtype/genotype, isolate/locus, accession # (reference): 1b, HPCJCG, D90208 (Kato et al., 1990); 2a, HPCPOLP, D00944 (Han and Houghton, 1992; Hotta et al., 1994; Okamoto et al., 1991); 3a, HPCEGS, D17763 (Sakamoto et al., 1994); 4a, ED43, Y11604 (Chamberlain et al., 1997a); 5a, EUH1480, Y13184 (Chamberlain et al., 1997b); 6a, EUHK2, Y12083 (Adams et al., 1997); 7a, QC69, EF108306 (Murphy et al., 2015).

				Neutralization Ability							
MAb (Ref.)	Type Region		pitope Critical Residues	Test	Tested Genotypes	Cross- reactivity	Fraction of 1a Strains Neutralized <sup>a</sup>	Potency	Mechanism	Class	
Broadly Neutralizing MAbs											
AP33 (Owsianka et al., 2005)	NC	E2 cNTR	L413, N415, G418, W420	HCVpp	1a, 1b, 2a, 2b, 3-6	All tested	N/D	High	CD81 interaction	bNAb	
AR2A (Giang et al., 2012; Law et al., 2008)	С	E2 AR2	K628	HCVpp, HCVcc	1a, 1b, 2a, 2b, 3-6	1a, 2a, 2b, 4-5	N/D	Variable	Post- attachment	bNAb	
AR3A (Giang et al., 2012; Law et al., 2008)	С	E2 AR3	T425, N428, G436, W437, L438, F442, Y485, W529, G530, D535, W616	HCVpp, HCVcc	1a, 1b, 2a, 2b, 3-6	All tested	N/D	Variable	CD81 binding, pre-/post- attachment	bNAb	
AR3B (Law et al., 2008)	С	E2 AR3	T425, L427, N428, W437, G440, F442, D520, W529, G530, D535, W616	HCVpp, HCVcc	1a, 1b, 2a, 2b, 4-5	All tested	N/D	Variable	CD81 binding	bNAb	
AR3C (Law et al., 2008)	С	E2 AR3	T425, N428, W437, L438, F442, Y443, W529, G530, D535, W616	HCVpp, HCVcc	1a, 1b, 2a, 2b, 4-5	All tested	N/D	Variable	CD81 binding	bNAb	
AR3D (Law et al., 2008)	С	E2 AR3	T425, L427, N428, G436, W437, G440, F442, D520, W529, G530, D535, W616	HCVpp, HCVcc	1a, 1b, 2a, 2b, 4-5	All tested	N/D	Variable	CD81 binding	bNAb	
AR4A (Torrents de la Peña et al., 2021)	С	E2 stem	I696	HCVpp, HCVcc	1a, 1b, 2a, 2b, 3-6	1a, 2a, 4a, 5a, 6a	N/D	Variable	Pre-/post- attachment	bNAb	
AR5A (Giang et al., 2012)	С	E2 stem	K628, R630, L665	HCVpp, HCVcc	1a, 1b, 2a, 2b, 3-6	1a, 1b, 2a, 4-6	N/D	Variable	Pre-/post- attachment	bNAb	
e20 (Castelli et al., 2017; Mancini et al., 2009)	С	E2 AR3	T425, L427, N428, W437, F442, W529, G530, W616	HCVpp, HCVcc	1a, 1b, 2a, 2b, 4-5	1a, 1b, 2a, 2b, 4	N/D	Variable	CD81 binding	bNAb	
e137 (Castelli et al., 2017; Perotti et al., 2008)	С	E2 AR3	T425, N428, N430, S432, W437, L438, G530	HCVpp, HCVcc	1a, 1b, 2a, 2b, 3-6	1a, 1b, 2b, 4	N/D	Variable	CD81 binding	bNAb	
H77.39 (Sabo et al., 2011)	NC	E2 cNTR	N415, G418, W420	FFU assay	1-6	1-5	N/D	High	CD81 and SR-B1 binding early post- attachment	bNAb	
HCV1 (Broering et al., 2009; Kong et al., 2012)	NC	E2 cNTR	L413, G418, W420	HCVpp	1a, 1b, 2b, 3a, 4a	All tested	N/D	High	CD81 binding	bNAb	
HEPC3 (Bailey et al., 2017)	С	E2 AR3	T425, L427, N428, W437, A499, D520, G530	HCVcc	1a, 1b, 2-6	1a, 1b, 2a, 4a, 5a, 6a	16/19	High	CD81 binding	bNAb	
HEPC13 (Bailey et al., 2017)	С	E2 AR3	T425, L427, N428, W437, A499, D520, G530	HCVcc	1a, 1b, 2-6	1a, 1b, 2a, 4a, 5a, 6a	16/19	High	CD81 binding	bNAb	
HEPC74 (Bailey et al., 2017; Jankowski et al., 2018)	С	E2 AR3	N428, G530, D535	HCVcc	1a, 1b, 2-6	1a, 1b, 2a, 4a, 5a, 6a	17/19	Variable	CD81 binding	bNAb	
HEPC43 (Bailey et al., 2017)	С	E2 AR3	T425, L427, N428, G436, W437, L438, G440, F442, Y443, A499, G517, T519,	HCVcc	1a, 1b, 2-6	1a, 1b, 2a, 4a, 5a, 6a	17/19	Variable	CD81 binding	bNAb	

# Table S1. Antibodies used in this study. Related to Figures 2, 3

			D520, Y527, W529, G530, D535, W616							
IGH505 <sup>c</sup> (Meunier et al., 2008; Wahid and Dubuisson, 2013)	NC	E1 stem	H316, W320, M323	HCVpp	1a, 1b, 2-6	1a, 1b, 2a, 4a, 5a, 6a	N/D	High (excl. weak 2a)	Post- binding	bNAb
IGH526 (Meunier et al., 2008; Wahid and Dubuisson, 2013)	NC	E1 stem	H316, A319, W320, M323, M324	HCVpp	1a, 1b, 2-6	1a, 1b, 2a, 4a, 5a, 6a	N/D	Variable	Post- binding	bNAb
	1			Neutraliz	zing MAbs			1	Γ	1
e301 (Burioni et al., 2002; Castelli et al., 2017)	С	E2 AR3	T425, L427, N428, W437, L438, G440, F442, D520, W529, G530, D535, W616	VSV/ HCV	1a, 1b	1a, 1b	N/D	Moderate	CD81 binding	NAb
e509 (Castelli et al., 2017; Sautto et al., 2012)	С	E2 AR3	T425, L427, N428, G436-L438, G440, F442, W529, G530, D535, Y594, W616, C620	HCVpp	1a, 1b, 2a	1a	N/D	High	CD81 binding	NAb
H77.16 (Keck et al., 2016; Sabo et al., 2011)	N C	E2 HVR1	P405-K408, N410-I411	FFU assay	1a, 2a	1a	N/D	High	SR-B1 binding early post- attachment	NAb
H77.28 (Sabo et al., 2011)	N C	E2 AR1	D535, T542-P544	FFU assay	1a, 2a	1a	N/D	Weak	Pre- attachment	NAb
HEPC98 (Bailey et al., 2017; Mankowski et al. 2018)	NC	E2 HVR1	L402, P405, K408	HCVpp panel	1a, 1b	1a, 1b	6/19	Variable	Pre- attachment	NAb
HEPC108 (Colbert et al., 2019)	С	E2 AR1	R543, P545, N548, Y594, G635	HCVpp panel	1a, 1b	1a, 1b	15/19	Variable	Unknown	NAb
HEPC111 (Colbert et al., 2019)	С	E2 stem	W672, L666	HCVpp panel	1a, 1b	1a, 1b	14/19	Variable	Pre-/post- attachment	NAb
HEPC112 (Colbert et al., 2019)	С	E1	R259, R260	HCVpp panel	1a, 1b	1a	7/19	Variable	Unknown	NAb
HEPC122 (Colbert et al., 2019)	С	E2 AR3	I422, L441, H445, Y527, W529, W616, C620	HCVpp panel	1a, 1b	1a, 1b	13/19	High/ variable	CD81 binding	NAb
HEPC146 (Colbert et al., 2019)	C	E2 AR3	G517, T534, W529	HCVpp panel	1a, 1b	1a, 1b	16/19	High/ variable	Pre-/post- attachment	NAb
HEPC 151-1 (Colbert et al., 2019)	С	E2 AR3	W529	HCVpp panel	1a, 1b	1a, 1b	16/19	High	CD81 binding	NAb
HEPC 151-2 (Colbert et al., 2019)	C	E2 AR1	R543-P545, N548, Y594, G635	HCVpp panel	1a, 1b	1a	9/19	Variable	Unknown	NAb
HEPC153 (Colbert et al., 2019)	С	E2 AR3	N423, L427, N430, S432, W437, L441, F442, R455, G517, Y527, W529, W616	HCVpp panel	1a, 1b	1a, 1b	17/19	High	CD81 binding	NAb
HEPC154 (Colbert et al., 2019)	С	E2 AR3	N430, S432, W437, F442	HCVpp panel	1a, 1b	1a, 1b	14/19	High/ variable	CD81 binding	NAb
HEPC158 (Colbert et al., 2019)	С	E2 AR1	R543, P544, P545, N548, Y594, G635	HCVpp panel	1a, 1b	1a	9/19	Variable	Unknown	NAb

Non-neutralizing MAbs										
AR1A (Law et al., 2008)	С	E2 AR1	T519, T542, P544, P545, G547, N548, Y632	HCVpp, HCVcc	1a, 1b, 2a, 2b, 4, 5	N/D	N/D	N/A	N/A	Non- NAb
AR1B (Ball et al., 2014; Law et al., 2008)	С	E2 AR1	P544, P545, G547, N548	HCVpp, HCVcc	1a, 1b, 2a, 2b, 4, 5	N/D	N/D	N/A	N/A	Non- NAb
e8 (Castelli et al., 2014)	С	E2 AR1	T542, P544, P545, G547, N548, V633	VSV/ HCV	1b	N/D	N/D	N/A	N/A	Non- NAb
e10 (Bugli et al., 2001; Castelli et al., 2014)	С	E2 AR3	T425, P498, A499, T519, D520, R521, G530	Unknown	1a	N/D	N/D	N/A	N/A	Non- NAb
H60 (Castelli et al., 2014)	С	E2 AR1, HVR2	G470, I472, Y474, R543, P544, P545, Y594	Unknown	1a	N/D	N/D	N/A	N/A	Non- NAb
H77.47 (Sabo et al., 2011)	С	E2 AR1	R543-L546	FFU assay	1a, 2a	N/D	N/D	N/A	N/A	Non- NAb
HEPC50 (Bailey et al., 2017)	С	E2 AR1	R543, P544, P545, G547, Y594, C597, G598, Y632	HCVpp panel	1a, 1b	N/D	0/19	N/A	N/A	Non- NAb
HEPC46 (Bailey et al., 2017; Mankowski et al., 2018)	С	E2 AR1	N541, T542, R543, P544, P545, L546, G547, N548, Y594, C597, G598, V633	HCVpp panel	1a, 1b	N/D	0/19	N/A	N/A	Non- NAb
S1 (Giang et al., 2012)		E2 stem	\$512, Y632	N/D	N/A	N/A	N/A	N/A	N/A	E2 stem
AB (Giang et al., 2012)	С	E2 stem	R630, E641	N/D	N/A	N/A	N/A	N/A	N/A	E2 stem
HCVE1-C1 (this manuscript)	С	E1 stem	G311, H312	HCVpp	1a	N/D	N/D	N/A	N/A	Non- NAb

<sup>a</sup>For 1a/1b panel tests, "fraction of 1a strains neutralized" refers to the number of strains of genotype 1a HCVpp that were neutralized by the MAb compared to all tested strains. In the original characterization of MAbs from (Colbert et al., 2019) the same data used here to identify critical binding residues were analyzed more broadly to recognize binding residues and also residues that might be important for the local structure of the MAb binding site. Abbreviations: AR1-5, antigenic regions 1-5; cNTR, conserved N-terminal region; C, conformational; NC, non-conformational; NTR, N-terminal region; N/D, not determined; N/A, not applicable.

Stage	Protein	Region <sup>a</sup>	Critical Residues
Folding	E1	Unknown	D218, I220, H222, G225, C226, V227, P228, C229,
			V230, R231, E232, G233, C238, W239, V242, V246,
			T248, D250, G251, L253, P254, L258, D263, R297,
			H298, T300, Q302, C304, N305*, C306, H352, G354,
			F378, D382
Folding	E1	N-terminus	C207, N209*, I212, E215
Folding	E1	Putative IFL	D279
Folding	E2	Front layer	T425*, N428, C429
Folding	E2	β-sandwich	<i>C494</i> , I496, V497, A499, V502, <i>C503</i> , G504, P505,
			V506, Y507, C508, F509, P511, V514, V516, T518,
			F537, N540*, F550, G551, C552, W554, M555, N556*,
			G559, T561, C564, G565, C569
Folding	E2	CD81BL	D520, G523, G530, D535
Folding	E2	Back layer	G600, W602, I603, C607, M608, V609, D610, Y611,
			R614, H617, Y618, P619, T621, N623*, T625*, H638,
			L640, A642, A643, <i>C644</i>
E1E2 dimer assembly	E1	N-terminus	Y201, T204, N205, D206
E1E2 dimer assembly	E2	Unknown	C381, C585
E1E2 dimer assembly	E2	Back layer	C459, C486
E1E2 dimer assembly	E2	β-sandwich	W487, R543, P544, P545, W549
E1E2 dimer assembly	E2	Stem	<i>C</i> 652, R657, D658, <i>C</i> 677, F679, L692, D698, Q700
CD81 LEL binding	E2	cNTR	W420
CD81 LEL binding	E2	Front layer	I422, S424, L427, N430*, S432*, G436, W437, L438,
			G440, L441, F442, Y443
CD81 LEL binding	E2	β-sandwich	V515
CD81 LEL binding	E2	CD81BL	T519, T526, Y527, W529
CD81 LEL binding	E2	Back layer	W616
Infectivity	E1	E1 cleavage	Y192, Q193
Infectivity	E1	Unknown	R259, H261, T292, P310, G311, I313
Infectivity	E1	Putative IFL	\$273, Y276, G282, F285, L286
Infectivity	E1	Stem	M318, W320, M322, M323, W326, P328, A330, A331,
			L332, V333, V334, L337, R339, M347
Infectivity	E1	TM	V355, F362, M364, N367, L377
Infectivity	E2	HVR1, SR-B1	H386, G390, G398, L399, N410, I411
Infectivity	E2	cNTR	Q412, I414, T416
Infectivity	E2	Front layer	K446, F447, S449, G451, L456
Infectivity	E2	VR2	R460, G470, R483
Infectivity	E2	Back layer	Y489, P490, T593, R596, W646, R648, G649
Infectivity	E2	β-sandwich	R492, N541, L546
Infectivity	E2	CD81BL	R521, T534*
Infectivity	E2	igVR	G572, L579
Infectivity	E2	Stem	L662, S663, L665, L666, L667, S668, T669, T670, Q671,
			W672, L675, T681, L682, L685, S686, T687, G688, H691,
			H693, I696, V697, Y701, L702, Y703, V705, S707, I709,
			A710, I714, K715
Infectivity	E2	TM	L722, L735, W736, Q743

 Table S2. Critical residues for E1E2 structure and function. Related to Figures 2, 3.

Critical cysteines are italicized; \* residues in glycosylation sequences are denoted by asterisks. Abbreviations: CD81BL, CD81 binding loop; cNTR, conserved N-terminal domain; HVR1, hypervariable region 1; igVR, intergenotypic variable region; IFL, internal fusion loop; LEL, long extracellular loop; SR-B1, scavenger receptor B type 1 binding site; TM, transmembrane domain.

<sup>a</sup>Regions of the HCV Env sequence or structure were identified from the literature and reflect the current consensus based on all available experimental evidence (Akbar and Jusoh, 2013; Drummer et al., 2006; Drummer et al., 2007; Flint et al., 1999; Lavillette et al., 2007; Tong et al., 2017).