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HCV GT-6a-consensus 5' - untranslated region (5'-UTR) and the first 48 nucleotides of core:

GCCAGCCCCTTAACGGGGCGACTCCGCCATTATCACTCCCCTGTGAGGAACTACTGTCTT  
CACGCAGAAAGCGTCTAGCCATGGCGTTAGTATGAGTGTCGTACAGCCTCCAGGCCCCCCC  
CTCCCGGGAGAGCCATAGTGGTCTGCGGAACCGGTGAGTACACCGGAATTGCCAGGATGA  
CCGGGTCCTTTCCATTGGATCAAACCCGCTCAATGCCTGGAGATTTGGGCGTGCCCCCGCA  
AGACTGCTAGCCGAGTAGCGTTGGGTTGCGAAAGGCCTTGTGGTACTGCCTGATAGGGTGC  
TTGCGAGTGCCCCGGGAGGTCTCGTAGACCGTGCATCATGAGCACACTTCCAAAACCCCAA  
AGAAAAACCA

HCV GT-6a consensus sub-genomic sequence (NS3-NS5B):

GCTCCCATCACCGCGTATGCGCAGCAGACGAGGGGCCTAGTCGGCACCATTGTGACCAGCC  
TAACCGGGCGTGACAAAAATGAGGTCGAAGGGGAGGTACAGGTGGTCTCCACGGCTACCC  
AATCCTTCCTGGCGACCTCCATTAACGGTGTTCATGTGGACTGTTTATCATGGGGCCGGTTCA  
AAGACTCTCGCTGGACCGAAAGGACCAGTGTGTCAAATGTACACCAATGTGGACAAGGAC  
CTAGTAGGATGGCCATCTCCCCGGGAGCAAGGTCGCTCACCCCATGTACTTGTGGCTCTA  
GTGACCTCTATCTGGTCACGAGGGAGGCCGACGTTATCCCCGCAAGGCGCAGGGGTGACA  
ACCGTGCTGCCCTCCTCTCTCCTAGGCCATAAGCACCTTGAAAGGCTCCTCGGGAGGCC  
CATTATGTGTCCCTCGGGGCACGTTGTGGGACTCTTCCGAGCTGCCGTATGCACAAGGGGT  
GTAGCAAATCCTTAGATTTTATCCAGTGGAAAACATGGAGACGACTATGCGCTCTCCCT  
CATTACAGACAACCTCCACGCCGCCTGCGGTGCCCCAGACCTATCAGGTAGGGTATCTGCA  
CGCACCAACAGGCAGCGGAAAGAGCACCCGTGTTCCGGCGGCGTACGCTAGCCAGGGCTA  
CAAGGTGTTGGTCTTGAACCCATCGGTGGCGGCAACGCTTAGCTTTGGCTCTTATATGAGGC

AAGCTTACGGCGTGGAGCCGAATGTCCGGACCGGGGTCAGGACTGTAACCACAGGGGGCG  
CTATCACGTA CTCCACATATGGGAGATTCTTGGCCGATGGGGGATGTTCCGGAGGAGCGTA  
CGACATCATCATCTGTGATGAGTGCCACTCCACAGACCCTACGACGGTGTGGGCATTGGC  
ACGGTTCTCGACCAGGCTGAGACTGCCGGGGTTCGCCTTACTGTGCTCGCAACAGCAACGC  
CGCCGGGTTCTGTCACTGTCCCCATCCTAACATAACAGAGACAGCCCTCCCGACTACGGG  
AGAAATACCATTTTATGGAAAGGCCATCCCCCTTGAGTACATCAAAGGGGGGAAGACATCTC  
ATATTCTGTCACTCAAAGAAGAAGTGCGATGAGCTGGCCGGGAAACTGAAGTCACTCGGCT  
TAAACGCCGTCGCATTCTACAGAGGTGTCGATGTGTCCGTCATCCCCACCTCGGGCGATGT  
CGTCGTCTGCGCAACAGACGCCCTTATGACCGGCTACACAGGCGATTTTCGATTCCGTCATC  
GACTGTAACGTAGCCGTGACACAGGTGGTGGATTTTCAGCTTGGACCCAACATTTTCCATAG  
AGACTACCACCGTCCCTCAGGATGCGGTATCACGGAGCCAACGACGAGGCCGCACGGGGC  
GGGGTAAACCGGGGGTGTACAGATTTGTCTCCCAAGGGGAGAGGCCTTCGGGTATGTTCGA  
CACCGTCGTCCTGTGTGAGGCTTATGACACGGGATGCGCGTGGTACGAACTAACCCCTTCT  
GAAACAACCTGTCAGGTTGAGGGCCTATATGAACACTCCTGGCCTTCCCGTATGCCAAGACC  
ACCTGGAATTTTGGGAAGGCGTGTTTACTGGCTTGACTCACATAGACGCCCACTTTCTGTCT  
CAGACGAAGCAGGGGGGTGAGAACTTCGCGTACCTCGTGGCATAACCAGGCTACAGTGTGC  
GCCAGGGCCAAAGCCCCCCCCGCCTTCTTGGGATACGATGTGGAAGTGTCTCATCAGACTCA  
AACCCACCCTTACCGGCCCACTCCACTTTTGTATCGGCTGGGGGCGTCCAAAATGAGAT  
AATAACAACCCATCCAATAACCAAATACATCATGACCTGTATGTCTGCGGATTTGGAGGTT  
ATCACCAGCACATGGGTCCTCGTGGGTGGAGTCCTAGCCGCGCTCGCAGCCTACTGCTTGT  
CAGTGGGCTGTGTTGTCATCTGTGGCAGGATAACTTTGACTGGCAAGCCTGCTGTTGTCCCT  
GATCGCGAGATCTTATAACCAGCAATTTGACGAGATGGAGGAGTGCTCTAGGCACATCCCCT  
ACCTCGCTGAGGGCCAGCAGATCGCCGAACAGTTCAGACAAAAGGTGTTGGGACTCCTCCA

AGCGAGCGCTAAGCAGGCAGAAGAAGCTGAAGCCTGCTGTCCATTCCGCGTGGCCTAGGGT  
GGAGGAGTTTTGGAGGAAACACATGTGGAACCTTGTTCAGCGGGATTTCAGTACTTGGCGGGC  
TTATCCACTCTGCCCCGGCAACCCAGCCGTGGCATCATTGATGTCATTTACAGCGTCGCTGAC  
CAGTCCTCTGAGGACTTCTCAGACCCTGCTCCTCAACATACTCGGCGGCTGGATAGCCACC  
CAAGTGGCTCCCCCCCCCGCGTCTACAGCTTTTGTTCGTGAGCGGTCTAGCAGGAGCCACGG  
TTGGAAGCATCGGGCTCGGGAGGGTGTGGTTGATGTGCTCGCCGGATAACGGAGCCGGTGT  
GTCGGGTGCTCTAGTCGCTTTCAAGATCATGAGCGGCGAGTGCCCGACCACGGAAGACATG  
GTCAATCTGCTACCCGCGCTGTTGTCGCCAGGGGCTCTCGTGGTGGGGGTTCGTGTGTGCTGC  
CATCTTAAGACGCCACGTTGGCCCTGCTGAGGGTGCTAACCAGTGGATGAACAGGCTAATA  
GCCTTTGCATCAAGAGGCAACCACGTGTCCCCGACGCACTACGTGCCTGAGACTGACGCGT  
CAAAAAATGTGACTCAGATACTCACTTCTCTTACCATCACCAGCCTACTCCGTAGATTACAT  
CAGTGGGTCAATGAAGACACGGCCACCCCTTGCCTACCTCATGGTTACGCGACGTGTGGG  
ACTGGGTGTGTACAGTGTTATCTGATTTTAAAGTATGGCTGCAAGCCAACTTCTCCCTCGC  
CTGCCGGGGATCCCCTTCTCTCGTGCCAAACGGGATATAGGGGAGTCTGGGCAGGGGACG  
GGGTGTGCCACACCACTTGTACCTGTGGGGCCGTGATAGCTGGACACGTCAAAAATGGCAC  
CATGAAAATCACAGGGCCCAAGACATGCAGTAACACTTGGCACGGGACTTTTCCAATCAAC  
GCCACCACTACCGGCCCCAGCACACCACGACCAGCCCCCACTATCAGCGCGCTCTTTGGC  
GGGTATCTGCCGAGGACTACGTTGAGGTACGGAGGTTGGGCGACTGCCACTATGTGGTAGG  
GGTCACTGCTGAAGGGTTGAAGTGCCCTTGCCAGGTGCCTGCGCCTGAATTCTTCACTGAG  
GTCGATGGCGTGAGGATACACCGTTACGCGCCACCTTGCAAGCCCTTGCTCAGGGACGAAG  
TGACTTTCTCTGTGGGTCTTTCAAACACTATGCCATAGGGTTCGCAGCTCCCTTGCGAGCCAGAG  
CCTGACGTGACCGTAGTCACCTCAATGCTCACAGACCCACGCACATCACCGCAGAGACGG  
CAGCACGGCGGTTGAAGAGGGGGTCCCCCCCCCTCCTTAGCCAGCTCTTCGGCCATCCAGCT

GTCTGCACCGTCCCTCAAGGCTACTTGCACAACCTTCCAAAGACCACCCGGACATGGAACTC  
ATCGAGGCCAACCTCCTTTGGAGGCAGGAGATGGGAGGCAACATCACTCGAGTCGAGTCA  
GAGAACAAAGTTGTAGTACTTGACTCCTTTGAGCCTCTAACCGCTGAGTATGACGAGAGGG  
AAATCTCAGTATCAGCTGAGTGCCATAGGCCACCCAGGCACAAATTCCCTCCAGCTCTCCC  
AATATGGGCCAGGCCTGACTACAATCCACCTCTCTACAAGCATGGCAAATGCCCGGATAC  
GAGCCTCCAGTCGTGTCTGGGTGTGCCGTCGCCCCACCTAAACCGGCACCAATTCCCCCGC  
CGAGGCGGAAGAGGCTAGTGCACCTTGGATGAGTCCACGGTCTCGCACGCCTTGGCGCAGCT  
CGCCGACAAGGTATTTGTGGAGAGTAGTAGTGACCCAGGACCTAGTTCAGACTCGGGACTA  
TCAATAACCAGTCCCGTTCCACCTGCCCAACAACACCGGACGACGCCTGCTCAGAAGCAG  
AGTCCTATAGCTCAATGCCCCCTCTTGAGGGGGAGCCTGGTGACCCTGACCTAAGCTCAGG  
CTCTTGGTCCACTGTGAGCGATCAGGACGACGTCGTGTGTTGTTCCATGTCCTATTCCTGGA  
CGGGGGCTCTAATAACACCATGTGCTGCGGAGGAGGAGAAGCTTCCAATAAATCCCCTGAG  
CAACTCCCTCATAAGACACCATAACATGGTGTATTCCACCACATCACGCAGCGCCAGCCTC  
CGCCAGAAGAAGGTACATTTGACAGAGTGCAAGTGTTTCGACCAACATTATCAGGATGTAC  
TAAAGGAGATTAAGCTTCGAGCGTCCACGGTGCAGGCGAAGCTCCTATCCATAGAGGAAG  
CCTGCGACCTCACACCATCGCACTCAGCCCGGTCCAAATATGGGTATGGTGCACAGGACGT  
TAGAAGCCATGCTAGCAAGGCCGTTGACCACATCCGCTCCGTGTGGGAGGACTTGCTAGAA  
GACTCTGATACCCCAATTCCCACGACCATCATGGCTAAGAATGAAGTCTTCTGCGTAGATC  
CGTCGAAGGGTGGACGCAAGCCGGCACGCCTAATAGTTTACCCAGACTTGGGCGTGCGGGT  
CTGCGAGAAGATGGCCCTATACGACGTGACGCGGAAGTTACCACAGGCCGTGATGGGTTC  
GCATACGGATTCCAGTACTCCCCTAACCAGAGGGTTGAGTACTTGCTCAAAATGTGGCGGT  
CAAAGAAGGTGCCCATGGGCTTTTCTTACGACACCAGGTGTTTTGATTCAACCGTCACCGA  
GCGGGATATCCGGACTGAGAACGACATCTATCAGTCTTGCCAGCTGGATCCCGTGGCAAGG

AAGGCAGTATCATCCCTAACAGAACGGCTCTACGTAGGCGGCCCCATGGTAAACTCCAAGG  
GACAGTCATGTGGCTACCGTAGATGCCGCGCCAGTGGGGTGCTGCCACGAGCATGGGAA  
ACACCCTCACATGCTATCTGAAGGCACAGGCCGCCTGCAGGGCGGCCAACATCAAGGACT  
GTGACATGTTGGTGTGCGGAGATGACTTAGTGGTCATTTGTGAGAGTGCTGGCGTCCAGGA  
GGACACTGCGTCACTGCGAGCATTACGGATGCTATGACCAGGTA CT CAGCTCCCCCTGGA  
GACGCCCCGCAACCTACGTATGACCTTGAGCTCATAACATCGTGCTCATCCAATGTCTCCGT  
CGCCACGACGGCAATGGGAAGAGATATTACTACCTCACACGTGACTGTACCACTCCACTT  
GCGCGGGCCGCCTGGGAGACAGCCCGCCACACTCCAGTCAATTCGTGGTTGGGCAACATCA  
TTATGTTTGCCCCACGATATGGGTGCGTATGGTTCTGATGACCCATTTTTTCTCCATCCTCC  
AGTCGCAAGAACAATTGGAGAAAGCACTCGACTTTGACATCTACGGAGTGACCTATTCCGT  
CTCTCCACTTGATCTCCCAGCAATCATTCAACGACTCCATGGCATGGCAGCATTITCACTCC  
ACGGATACTCTCCAGTTGAGCTCAATAGGGTAGGGGCTTGCCTCAGGAAACTTGGGGTACC  
TCCCTTGCGAGCCTGGAGACATCGAGCCAGAGCTGTCAGAGCCAAACTCATTGCCCAAGGG  
GGGAAAGCGGCTATATGCGGTAAGTACCTCTTCAACTGGGCGGTGAAGACCAAATAAAA  
CTCACTCCATTGGTCTCCGCGAGCAAGCTTGACTTATCAGGCTGGTTCGTGGCAGGCTACGA  
CGGGGGGGACATTTATCACAGCGTGTCCCAGGCTCGACCCCGTCTCTTACTCCTTGGCCTAC  
TCCTACTCACCGTAGGGGTAGGCATCTTTTTGCTCCCCGCTCGGTAG

**FIG S1.** Nucleotide sequences of the pGT6a-cons replicon. A plasmid (pGT6a-cons) encoding a subgenomic Hepatitis C virus (HCV) genotype (GT)-6a replicon was constructed for phenotypic analysis following the method described by Yu et al (1) with a few modifications. Briefly, A subgenomic GT-6a consensus (GT-6a-cons) sequence was calculated by comparing 21 GT-6a genome sequences available in the usHCVdb (Table S2) and synthesized (Integrated DNA Technologies,

Coralville, IA). The synthesized GT-6a-cons 5'-untranslated region (5'-UTR) plus the first 48 nucleotides of the core region and the NS3-NS5B polyprotein region (including the sequence encoding the NS5A amino acid substitution S232I) were cloned into the Con1 replicon (2) to replace the GT-1b 5-UTR and NS3-NS5B sequences using the regular cloning technology.

**TABLE S1.** HCV GT-6 NS3, NS5A and NS5B primers to amplify and sequence patient-derived NS3, NS5A and NS5B coding regions

Name (NS3-)	NS3 Sequence	Name (NS5A-)	NS5A Sequence	Name (NS5B-)	NS5B Sequence
6a-F	TTCTCYCCCATGGA GAAGAA	6a-F1	TCACCAGCCTACT CCGTAGA	6a-F1	GGGAGCCTGGTGACC CTGACCT
6a-R1	TTCCCATAYGTGGA GTACGT	6a-F2	GTGGGTCAATGAA GACACG	6a-F2	TCTTGGTCCACTGTG AGCGGTG
6a-R2	CGGGTGCTCTTTCC RCTGCC	6a-R1	TAGCAAGTCCTCC CACACGGAG	6a-R1	CAAAAAGATGCCTAC CCCTAC
6e-F	TTCTCGCCTATGGA GAAGAA	6a-R2	GGACGCTCGAAGC TTGATCTCC	6a-R2	AGTAGGAGTAGGCC AAGGAGTAA
6e-R1	TTTCCATAGGTAGA RTAGGT	6e-F1	TTTAAGATCATGA GCGGCGA	6e-F1	GAGCCCGGAGACCCC GACTTAAG
6e-R2	TTCGTGCTTTTCCC RCTGCC	6e-F2	TGGATGAAYAGGC TCATAGC	6e-F2	GGCATCGTGGTCCAC AGTCAGC
6f-F	GCCCCATAACAGC CTACCATC	6e-R1	CGCCCTCTTCTCGC ACACCC	6e-R1	AAGGAAGATGCCTAC CCCTAC
6f-R	TGATCTCATAGTGG TCTCCATG	6e-R2	TGTCCACACAAAA CACCTCA	6elrs-R2	AGTAGGAGTAGGCA CAGGAGTAA
6g-F	GCACCAATCACGG CCTACGCC	6f-F1	CTTCGGAGACTCC ACGAGTGGAT	6f-F1	CATGGTCTACGGTCA GTGATG
6g-R	GGACCGCATRGTY GTCTCCATG	6f-F2	CAACGGAGATTGG ACAACCTCCA	6f-F2	TGAGGATGACGCAA ACAGCAG

Name (NS3-)	NS3 Sequence	Name (NS5A-)	NS5A Sequence	Name (NS5B-)	NS5B Sequence
6l-F1	TTCTCCCCTATGGA GAAGAA	6f-R1	TCTACGCGCTGCT TAGGCGAG	6f-R	GAGCAGGAAGCAGA AAGATGCC
6l-F2	TTCTCCCCTATGGA GACCAA	6f-R2	AGGCGAGTACTGG AAGCCGTA	6g-F	ATGTCCTACTCATGG ACGGGAGCCCT
6l-R1	TTGCCATAGGTAGA ATAGGT	6g-F	ACATGGCTYCGAG ACATCTGG	6g-R	GGGCGGGGAGCAAA AAGATGCCTACC
6l-R2	TTAGTGCTCTTGCC ACTGCC	6g-R	TCCYAGAGCTGA CTGTGGACC	6l-F1	GGAGATCCGGACCTT AGCTCGG
6o-F1	TTCTCCCCTATGGA GAAGAA	6l-1R	GGCCCTCTTCTCG CACACCC	6l-F2	CCACAGTCAGTGAGG AGGACGA
6o-F2	GCYGCTTGCGGCG ACATACTT	6l-F1	TTCGAGGGGTAAT CATGTATCG	6l-R1	GGGCAGGGAGCAGA AAGATGCC
6o-R1	TTGCCATAGGTGGA ATATGT	6l-F2	ACGTGCCTGAAAC TGACACTTC	6o-F1	AACCCGGGGATCCGG ACTTGGA
6o-R2	TTCGTGCTCTTTCC RCTGCCAGT	6l-R2	TATCGACGCAAAA CACCTCA	6o-F2	CGGGATCCTGGTCCA CGGTCAG
6p-F	GCCCCATTACGGC CTACCACC	6o-F1	AAAAATGTGATGA CCATACT	6o-R1	AGCAAAAAGATGCCT ACCC
6p-R	AGACCGCATGGTA GTCTCCATG	6o-F2	TGATGACCATACT CAGTTCC	6o-R2	GAGTAGGAGTAGGC ACAGGAGT
6q-F	TTCTCTCCTATGGA GAAGAA	6o-R1	TCCACCCGCTGCT TAGGCGAG	6p-F1	ATGTCGTA CTCTGG ACTGGGGCTCT
6q-R1	TTCCCATAGGTGGA GTATGT	6o-R2	AGGCGAGTACTGG AAGCCATA	6p-R1	GAGCGGGAAGCAAA AAGATGCC

Name (NS3-)	NS3 Sequence	Name (NS5A-)	NS5A Sequence	Name (NS5B-)	NS5B Sequence
6q-R2	CTTGGTGCTCTTAC CACTGCC	6p-F	ACTTGGTTAAGAG ACATTTGG	6q-F1	CCTGAGCTCTGGCTC GTGGTC
6r-F	TTCTCACCCATGGA GAAGAA	6p-R	TCCTCCTCGCTGA CCGTCGACC	6q-F2	TGGTCTACAGTCAGT GAGGA
6r-R1	TTGCCATATGTGGA ATAGGT	6q-F1	TTCAARATCATGA GCGGGGA	6q-R1	CAAAAAGATCCCTAC CCCTAC
6r-R2	CTTGGTGCTCTTAC CGCTGCC	6q-F2	GGGCCAACCAGTG GATGAAC	6q-R2	AGTAGGAGTAGGAA CAGGAGGAA
6s-F	TTCTCGCCTATGGA GAAGAA	6q-R1	GGCTTTCTTCTCGC ATACCC	6r-F1	ACCACTCGAGGGCGA ACCTG
6s-R1	TTGCCATAGGTAGA GTATGT	6q-R2	GGTCTACGCAAAA CACCTCA	6r-F2	TTGGTCCACGGTCAG TGACGA
6s-R2	TTTAGTACTCTTCC CGCTACC	6r-R1	TGCTCGCTTCTCGC ATACCC	6r-R1	CAGGAAAATGCCTAC CCCTAC
		6r-R2	CGTCCACACAGAA CACCTCA	6s-F1	GTGATCCCGACCTCG ATTCGG
		6r-F1	GCTTTCAAGATCA TGAGCGG	6s-F2	TGGGCTACCGTCAGT GAAGA
		6r-F2	CACGCACTATGTG CCTGAGAC	6s-R1	CAAGATGACGCCTAC CCCTAC
		6s-F1	GCGTTCAAGATCA TGAGCGG		
		6s-F2	GGGGCCAACCAGT GGATGAA		

Name (NS3-)	NS3 Sequence	Name (NS5A-)	NS5A Sequence	Name (NS5B-)	NS5B Sequence
		6s-R1	TGCCCTTTTCTCGC ACACCC		
		6s-R2	GCTCTACACAGAA CACCTCA		

F, forward primer; GT, genotype; R, reverse primer

**TABLE S2.** USHCVDB HCV GT-6 sequences used in baseline polymorphism analyses

Accession			Accession			Accession		
Number	GT	Country	Number	GT	Country	Number	GT	Country
AY859526*#	6a	Hong Kong	D84263*	6d	Vietnam	JX183555*	6l	Vietnam
DQ859971	6a	China	DQ314805*	6e	China	JX183556*	6l	Vietnam
HQ639936*#	6a	China	EU408326*	6e	United States	DQ835767*	6m	Thailand
KC441486	6a	China	EU246931*	6e	Vietnam	DQ835765*	6m	Thailand
KC441485	6a	China	EU246932*	6e	Vietnam	DQ835766*	6m	Thailand
HQ912955*#	6a	China	DQ835760*	6f	Thailand	DQ835763*	6m	Thailand
HQ912954*#	6a	China	DQ835764*	6f	Thailand	AY878652*	6n	China
KC844037*#	6a	China	EU246936*	6f	Thailand	DQ278894*	6n	China
KC441480	6a	China	HM042087	6f	Thailand	DQ835768*	6n	Thailand
KC441481	6a	China	HM042085	6f	Thailand	EU246937*	6n	Thailand
KC441482	6a	China	HM042086	6f	Thailand	EU246938*	6n	Thailand
KC441483	6a	China	HM042088	6f	Thailand	KC191671*	6n	Malaysia
KC441484	6a	China	HM042090	6f	Thailand	EF424627*	6o	Canada
KC441477	6a	China	HM042089	6f	Thailand	EU408327*	6o	United States

Accession			Accession			Accession		
Number	GT	Country	Number	GT	Country	Number	GT	Country
KC441478	6a	China	HM042093	6f	Thailand	EU246934*	6o	Vietnam
KC441479	6a	China	HM042091	6f	Thailand	EF424626*	6p	Canada
KC844038*#	6a	China	HM042092	6f	Thailand	DQ155560*	6p/2i	Vietnam
DQ480513*#	6a	Hong Kong	HM042094	6f	Thailand	EF424625*	6q	Canada
DQ480516*#	6a	Hong Kong	HM042095	6f	Thailand	EU408328*	6r	Canada
DQ480523*#	6a	Hong Kong	HM042096	6f	Thailand	EU408329*	6s	Canada
DQ480514*#	6a	Hong Kong	DQ314806*	6g	Hong Kong	EU246939*	6t	Vietnam
DQ480515*#	6a	Hong Kong	D63822*	6g	Indonesia	EF632069*	6t	Vietnam
DQ480518*#	6a	Hong Kong	D84265*	6h	Vietnam	EF632070*	6t	Vietnam
DQ480519*#	6a	Hong Kong	DQ835762*	6i	Thailand	EF632071*	6t	Vietnam
DQ480520*#	6a	Hong Kong	EU246935*	6i	Thailand	EU408331*	6u	China

Accession			Accession			Accession		
Number	GT	Country	Number	GT	Country	Number	GT	Country
DQ480521*#	6a	Hong Kong	DQ835770*	6i	Thailand	EU246940*	6u	Vietnam
DQ480522*#	6a	Hong Kong	DQ835761*	6j	Thailand	EU798761*	6v	China
DQ480517*#	6a	Hong Kong	DQ835769*	6j	Thailand	FJ435090*	6v	China
DQ480524*#	6a	Hong Kong	AY878651*	6k	China	EU798760*	6v	China
DQ480512*#	6a	Hong Kong	DQ278893	6k	China	EU158186*	6v	China
Y12083*#	6a	Hong Kong	AY878650*	6k	China	EU643834*	6w	Taiwan
EU246930*#	6a	Vietnam	DQ278891	6k	China	EU643836*	6w	Taiwan
NC 009827*	6b	Thailand	D84264*	6k	Vietnam	DQ278892*	6w	China
D84262*	6b	Thailand	EF424628*	6l	United States	EU408330*	6xa	China
EF424629*	6c	Thailand	EU246933*	6l	Vietnam	EU408332*	6xa	China

GT, genotype

\* Sequences used in the NS3 and NS5B polymorphism analyses

# Sequences used to calculate the GT-6a subgenomic consensus sequence

**TABLE S3.** Source and HCV GT-6 subtypes of patient-derived samples

Patient Sample Identification	Source	Country	Segregation to usHCVdb Sequences	HCV GT-6 Subtypes		
				NS3	NS5A	NS5B
BMS-1	Monash Univ (10MMC)	AU		a	a	a
BMS-2	Boca Biolistics (11Boca)	ND	AY859526,	a	a	a
BMS-3	Boca Biolistics (22Boca)	ND	Y12083	a	a	a
BMS-4	SeraCare Life Sci (6a-16)	ND		NA	a	NA
BMS-5	ALLY-1 (AI444215) (3)	US		e	e	e
BMS-6	Monash Univ (5MMC)	AU		e	e	e
BMS-7	Monash Univ (8MMC)	AU		e	e	e
BMS-8	Boca Biolistics (12Boca)	ND	DQ314805	e	e	e
BMS-9	Boca Biolistics (14Boca)	ND		e	e	e
BMS-10	Boca Biolistics (15Boca)	ND		e	e	e
BMS-11	Boca Biolistics (18Boca)	ND	DQ835760	f	f	f
BMS-12	UNITY-4 (AI443123-1) (4)	TW		g	g	g
BMS-13	UNITY-4 (AI443123-2) (4)	TW		g	g	g
BMS-14	UNITY-4 (AI443123-3) (4)	TW	D63822	g	g	g
BMS-15	UNITY-4 (AI443123-4) (4)	TW		g	g	g

Patient Sample Identification	Source	Country	Segregation to usHCVdb Sequences	HCV GT-6 Subtypes		
				NS3	NS5A	NS5B
BMS-16	Monash Univ (1MMC)	AU		l	l	l
BMS-17	Boca Biolistics (13Boca)	ND	EF424628	l	l	l
BMS-18	Boca Biolistics (21Boca)	ND		l	l	l
BMS-19	Boca Biolistics (20Boca)	ND	EF424627	o	o	o
BMS-20	UNITY-2 (AI443113) (5)	US	EF424626	p	p	p
BMS-21	Monash Univ (3MMC)	AU	EF424625	q	q	q
BMS-22	Monash Univ (4 MMC)	AU	EU408328	r	r	r
BMS-23	Monash Univ (2MMC)	AU		s	s	s
BMS-24	Monash Univ (6 MMC)	AU	EU408329	s	s	s
BMS-25	Monash Univ (7MMC)	AU		s	s	s

AU, Australia; BMS, Bristol-Myers Squibb; NA, not available; ND, not determined; Sci, Sciences; TW, Taiwan;  
US, United States; Univ, university

**TABLE S4.** Prevalence of HCV GT-6 subtypes by NS3 polymorphisms and country

GT-6 Subtype	NS3 Seqs	Country	NS3 Seqs with Noted Polymorphisms	NS3 Polymorphisms				
				V36	K80	A156	D168	I170
6a	24	AU (n=1), CN	20					
		(n=5), HK (n=15),	1				E	
		VN (n=1), ND (n=2)	1					V
			1			L		
			1				Q	
6b	2	TH	2		Q			
6c	1	TH	1		Q		V	
6d	1	VN	1	L	Q		V	
6e	10	AU (n=2), CN	10	I	Q			V
		(n=10), US						
		(n=2), VN (n=2), ND (n=3)						
6f	4	TH (n=3), ND (n=1)	4	L	Q			V

GT-6 Subtype	NS3 Seqs	Country	NS3 Seqs	NS3 Polymorphisms				
			with Noted Polymorphisms	V36	K80	A156	D168	I170
6g	6	HK (n=1), ID	4		Q			
		(n=1),TW (n=4)	1	L	Q			V
			1	L	Q		E	V
6h	1	VN	1		Q			A
6i	3	TH	3		Q			V
6j	2	TH	2		Q			V
6k	3	CN (n=2), VN (n=1)	3		Q			V
6l	7	AU (n=1), US (n=1),	5		Q			V
		VN (n=3), ND (n=3)	1	L	Q			V
			1		Q	V		V
6m	4	TH	4		Q			
6n	6	CN (n=2), MY	6		Q			V
		(n=1), TH (n=3)						
6o	4	CA (n=1), US (n=1), VN (n=1),ND (n=1)	4	I	Q			V

GT-6 Subtype	NS3 Seqs	Country	NS3 Seqs with Noted Polymorphisms	NS3 Polymorphisms				
				V36	K80	A156	D168	I170
6p	3	CA (n=1), US (n=1), VN (n=1)	3		Q			V
6q	2	AU (n=1), CA (n=1)	1	I	Q			V
			1	L	Q			V
6r	2	AU (n=1), CA (n=1)	2		Q			V
6s	4	AU (n=3), CA (n=1)	4	L	Q			V
6t	4	VN	4	L	Q			V
6u	2	CN (n=1), VN (n=1)	2		Q			V
6v	4	CN	4		Q			V
6w	3	CN (n=1), TW (n=2)	3	L	Q			V
6xa	2	CN	2		Q			V

No., number; Seqs, sequences

Country codes: AU: Australia; CA: Canada; CN: Mainland China; HK: Hong Kong; ID: Indonesia; MY: Malasia;  
 ND: Not Determined; TH: Thailand; TW: Taiwan; US: United States; VN: Vietnam

**TABLE S5.** Susceptibility of HCV GT-6 NS3 polymorphisms at residue positions associated with NS3 drug resistance

	<b>ASV</b>		<b>SMV#</b>		<b>GZV#</b>		<b>BMS-986144*</b>	
	EC <sub>50</sub>	EC <sub>90</sub>	EC <sub>50</sub>	EC <sub>90</sub>	EC <sub>50</sub>	EC <sub>90</sub>	EC <sub>50</sub>	EC <sub>90</sub>
	(±SD)	(±SD)	(±SD)	(±SD)	(±SD)	(±SD)	(±SD)	(±SD)
<b>RAS</b>	nM	nM	nM	nM	nM	nM	nM	nM
WT-cons	48 (5.5)	130 (27)	54 (6.2)	96 (16)	3.6 (0.4)	8.1 (0.9)	9.0 (1.1)	15 (2)
D168E	300 (16)	513 (38)	1355 (95)	1583 (79)	19 (1.2)	22 (0.1)	18 (1.2)	21 (1.6)
K80Q	7.1 (0.2)	18 (0.2)	3.5 (0.1)	6.4 (0.1)	1.1 (0.2)	2.2 (0.1)	3.9 (0.0)	7.5 (0.1)
K80Q- D168E	296 (4)	672 (28)	95 (0.6)	194 (0.5)	6.7 (0.6)	20 (1.1)	9.1 (0.4)	17 (0.1)
K80Q- I170A	13 (1.1)	29 (0.2)	6.5 (0.5)	13 (2.2)	1.6 (0.3)	3.3 (0.6)	4.7 (0.4)	8.8 (0.1)
V36L- K80Q- D168E	168 (11)	347 (35)	71 (1.5)	167 (19)	4 (0.1)	12 (1)	8.5 (0.5)	16 (0.5)

ASV, asunaprevir; GZV, rgazoprevir; SMV, simeprevir; WT-cons, wild-type consensus sequence for GT-6a

\* BMS-986144 is a pan-genotypic NS3 protease P1-P3 macrocycle (6)

# Clinical resistance profiles for simeprevir (SMV) and grazoprevir (GZV) are described in FDA-approved product labels (7, 8)

NS3-K80L resulted in similar  $EC_{50/90}$  values as K80Q; No replication data was available for A156V

NS3 substitutions were introduced into the HCV GT-6a NS3-NS5B consensus sequence. Experiments with the different NS3 inhibitors were tested in parallel and results represent the average of three independent experiments each performed in duplicate. When testing HCV GT-6a replicon variants, susceptibility assays using the HCV GT-6a-cons was performed in parallel.

**TABLE S6.** Prevalence of HCV GT-6 subtypes by NS5B polymorphisms and country

GT-6 Subtype	NS5B Seqs	Country	NS5B Seqs with Noted Polymorphs	NS5B Polymorphisms					
				L159	S282	L392	V421	V494	P495
6a	24	AU (n=1), CN (n=5),	19						
		HK (n=15), VN	4				A		
		(n=1), ND (n=2)	1					L	
6b	2	TH	2					A	
6c	1	TH	1					A	
6d	1	VN	1					A	
6e	10	AU (n=2), CN	6					A	
		(n=10), US (n=2),	4			I	A		
		VN (n=2), ND (n=3)							
6f	4	TH (n=3), ND (n=1)	4					A	
6g	6	HK (n=1), ID (n=1),	2					A	
		TW (n=4)	3			I			
			1				A		

GT-6 Subtype	NS5B Seqs	Country	NS5B Seqs	NS5B Polymorphisms					
			with Noted Polymorphs	L159	S282	L392	V421	V494	P495
6h	1	VN	1						A
6i	3	TH	3						A
6j	2	TH	2						A
6k	3	CN (n=2), VN (n=1)	3						A
6l	7	AU (n=1), US (n=1), VN (n=3), ND (n=3)	7						A
6m	4	TH	4						A
6n	6	CN (n=2), MY (n=1), TH (n=3)	6						A
6o	4	CA (n=1), US (n=1), VN (n=1), ND (n=1)	3 1					?	A A
6p	3	CA (n=1), US (n=1), VN (n=1)	3						A
6q	2	AU (n=1), CA (n=1)	1 1				I		A A

GT-6 Subtype	NS5B Seqs	Country	NS5B Seqs with Noted Polymorphs	NS5B Polymorphisms					
				L159	S282	L392	V421	V494	P495
6r	2	AU (n=1), CA (n=1)	2					A	
6s	4	AU (n=3), CA (n=1)	1					A	
			3	F				A	
6t	4	VN	4					A	
6u	4	CN (n=3), VN (n=1)	4					A	
6v	4	CN	4					A	
6w	3	CN (n=1), TW (n=2)	1						
			1					M	
			1	C			M		

No., number; Polymorphs, polymorphisms; Seqs, sequences

Country codes: AU: Australia; CA: Canada; CN: Mainland China; HK: Hong Kong; ID: Indonesia; MY: Malasia; ND: Not Determined; TH: Thailand; TW: Taiwan; US: United States; VN: Vietnam

**TABLE S7.** Susceptibility of HCV GT-6 NS5B polymorphisms at residue positions associated with NS5B drug resistance

	<b>BCV</b>		<b>SOF</b>		<b>BMS-929075</b>	
	<b>(Thumb-1 Inhibitor)</b>		<b>(Nucleotide Inhibitor)</b>		<b>(Palm Inhibitor)*</b>	
	EC <sub>50</sub> (±SD)	EC <sub>90</sub> (±SD)	EC <sub>50</sub> (±SD)	EC <sub>90</sub> (±SD)	EC <sub>50</sub> (±SD)	EC <sub>90</sub> (±SD)
<b>RAS</b>	nM	nM	nM	nM	nM	nM
WT-cons	64 (8)	312 (13)	60 (24)	266 (30)	13 (2)	71 (8)
V494A	495 (132)	2654 (234)	68 (5)	315 (11)	15 (2)	70 (2)
P495L	>5000	>5000	86 (6)	421 (37)	7.2 (0.3)	39 (5)
L392I	664 (69)	2723 (94)	80 (6)	338 (20)	14 (0)	61 (8)

BCV, beclabuvir; SOF, sofosbuvir; WT-cons, wild-type consensus sequence for GT-6a

BCV is a thumb Site I inhibitor, sofosbuvir SOF is a nucleoside inhibitor while BMS-929075 is a primer grip inhibitor usually impacted by substitutions at C316, S365 and M414 (9)

NS5B substitutions were introduced into the HCV GT-6a NS3-NS5B consensus sequence. No replication data was available for -L392I+V494A. Experiments with the different NS5B inhibitors were tested in parallel and results represent the average of three independent experiments each performed in duplicate. When testing HCV GT-6a replicon variants, susceptibility assays using the HCV GT-6a-cons was performed in parallel.

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