Supplementary Materials and Methods

Analysis of HCVpp Envelope Glycoprotein Expression

Expression of HCV glycoproteins was characterized in HEK 293T producer cells and HCVpp purified through a 20% sucrose cushion ultracentrifugation as described.¹ Immunoblots of HCV glycoproteins were performed using anti-E1 11B7 and anti-E2 AP33 mAbs as described.²

Cellular Binding of Envelope Glycoproteins

Envelope glycoprotein-expressing HEK 293T cells were lysed in phosphate-buffered saline by 4 freezing and thawing cycles. Cell debris and nuclei were removed by low-speed centrifugation and supernatants containing native intracellular E1E2 complexes were used for binding studies. Huh7.5.1, shCD81-, or shCD13-Huh7.5 cells (2×10^5 cells per well) were seeded in 96-well plates. After incubation with lysates containing patient-derived E1E2 proteins, Huh7.5.1 target cells were first incubated with mAb AP33 (10 µg/mL) and then with phycoerythrinconjugated anti-mouse Ab (5 µg/mL, BD Biosciences). Bound E2 was analyzed by flow cytometry as described.³

Construction of Plasmids for Production of Chimeric HCVcc Expressing Patient-Derived Envelopes

Genotype 1 JFH-based HCVcc chimeras expressing the structural proteins of patient-derived viruses were produced as previously described for Con1/C3-JFH1-V2440L.^{4,5} Briefly, the complementary DNA region encoding for the HCV core to the first transmembrane domain of NS2 (C3 junction site) from variant VL was inserted into pFK-Con1/C3-JFH1-V2440L using fusion polymerase chain reaction with Pfu DNA polymerase (Agilent Technologies, Massy, France) and standard cloning procedures using appropriate restriction sites including BsmI and AvrII. The obtained construct was designated *VL/JFH1*. The VL/JFH1 encoding sequence was used as a template to insert individual and combined mutations using the QuikChange II XL site-directed mutagenesis kit (Agilent Technologies) as described previously.¹

Galanthus nivalis Capture Enzyme-Linked Immunosorbent Assay

Binding of HMAb CBH-23 to viral envelopes was analyzed using an enzyme-linked immunosorbent assay with HCVpp as a capture antigen as described.⁶ HCVpp expressing the E1E2 glycoproteins of HCV variants or control pseudoparticles with absent HCV envelope glycoprotein expression were partially purified and enriched through ultracentrifugation as described.¹ Purified particles were quantified as described previously.¹ Partially purified HCVpp or control pseudoparticles were captured onto *Galanthus nivalis* (GNA)-coated microtiter plates as described.⁶ Soluble E2 (derived from strain HCV-H77 and expressed in 293T cells as described previously³) was used as a positive control for antibody binding. Neutralizing human anti-E2 antibody CBH-23 (25 μ g/mL diluted in phosphate-buffered saline) then was added to captured HCVpp or soluble E2 (1 h at room temperature). After washing and removal of nonbound antibody, mAb binding to HCV envelopes was detected using horseradish-peroxidase anti-human IgG (GE Healthcare, Orsay, France) at a concentration of 1/3000 for 1 hour at room temperature, followed by incubation with 1-step Turbo TMB– enzymelinked immunosorbent assay (Thermo Fisher Scientific, Illkirch, France) for color development. Absorbance was measured at 450 nm using a microplate reader Softmax program (Molecular Devices, Sunnyvale, CA).

Bioinformatics

Multiple sequence alignment of complete E2 proteins was performed using the European HCV databases (http://euhcvdb.ibcp.fr).⁷ Two amino acid repertoires were computed with all E2 sequences of provisional/ confirmed genotype 1b using the *ComputeRepertoire* tool as part of the euHCVdb *Extract* tool (http://euhcvdb. ibcp.fr).

Results

Prevalence of the Identified Mutations in a Large Genomic Database of Viral Isolates

Bioinformatic sequence analysis of a large panel of 2074 HCV strains within the European HCV database further supports the potential relevance of the identified positions for pathogenesis of HCV infection in general.7 Residues F, S, and R are observed much more frequently at positions 447, 458, and 478 than L, G, and C. F and S are the most predominant residues at positions 447 and 458 in the large majority of 1b strains, respectively (F447 all, 98.4%; 1b, 96.2%; S458 all, 94%; 1b, 90.3%; Supplementary Figure 5). The position 478 is variable but R (all, 2.4%; 1b, 10.8%) is more frequent than C (all, 0.2%; 1b, 0.9%) (Supplementary Figure 5). The high prevalence of identified residues supports their functional relevance for virus survival and selection because more structurally and functionally relevant residues will be observed more frequently. These data suggest that the epitope containing the identified residues at positions 447, 458, and 478 is responsible not only for viral evasion from autologous antiviral antibodies during LT but also may contribute to viral evasion in chronic HCV infection in general.

References

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binding steps and membrane fusion. Gastroenterology 2008;135:1719–1728.

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Supplementary Figure 1. Actual viral infectivity of HCVpp derived from variants VL, VC, and VA shown as relative light units (RLU) of luciferase reporter gene expression. (*A* and *B*) Comparative analysis of viral entry of HCVpp shown in Figure 1. Results are expressed in RLUs plotted in a logarithmic scale. The threshold for a detectable infection in this system is indicated by *dashed lines*. The detection limit for positive luciferase reporter protein expression was 3×10^3 RLU/assay, corresponding to the mean ± 3 standard deviations of background levels (ie, luciferase activity of naive noninfected cells or cells infected with pseudotypes without HCV envelopes).^{1,1,2,13} Background levels of the assay were determined in each experiment. Means \pm standard deviation from at least 4 independent experiments performed in triplicate are shown. Significant differences in HCVpp entry VC, VA, and VL wild-type and mutant variants are indicated (* $P \le .05$; **P < .001). Ctrl, control; HVR, hypervariable region; V, viral variant.



Supplementary Figure 2. Positions 447, 458, and 478 modulate binding of envelope glycoproteins to CD81 expressed at the cell surface. Binding of native E1E2 complexes expressed from patient-derived complementary DNAs to Huh7.5 cells with silenced CD81 expression (described in Figure 3) was detected by flow cytometry. Results are expressed as the percentage of E1E2 binding compared with shCD13-Huh7.5 control cells. Means \pm standard deviation from 3 independent experiments performed in triplicate are shown. Significant differences in binding between variants are indicated (**P < .001).



Supplementary Figure 3. Differences in viral entry are not caused by impaired HCVpp production. (*A*) Analysis of envelope glycoprotein expression. Protein expression was analyzed by immunoblotting as described in the Materials and Methods section. Molecular markers (in kilodaltons) are indicated on the *right*. (*B*) Transfection efficiency during HCVpp production. Transfection efficiency was analyzed for each variant and quantified by determining luciferase expression in HEK 293T producer cells expressed as a normalized percentage compared with control transfected cells. (*C*) Envelope glycoprotein expression in HCVpp. HCVpp were purified as described previously^{1,2} and subjected to immunoblot as described in panel *A*. (*D*) Lentiviral p24 antigen expression was analyzed by enzyme-linked immunosorbent assay (ELISA) and is indicated as optical density (OD) values at 450 nm. (*E*) Cellular binding of E2 derived from patient-derived or H77 and HCV-J strains. Binding of native E1E2 complexes to Huh7.5.1 cells was detected as described in Supplementary Materials and Methods. Results are expressed as delta mean fluorescence intensity (ΔMFI) ± standard deviation. One representative experiment of 3 is shown. Da, dalton; MW, molecular weight.

			HCVpp entry, %						
Antibody	Reference	Epitope, amino acid	VL	VC	VCVL458+478	VLVC ₄₅₈₊₄₇₈	VA	VAVL ₄₄₇	VLVA ₄₄₇
AP33	8	412-423	6 ± 3	12 ± 1	3 ± 1	11 ± 5	2 ± 1	5 ± 1	3 ± 1
IGH461	9	436–448	58 ± 4	56 ± 8	51 ± 7	53 ± 3	55 ± 2	56 ± 6	52 ± 7
16A6	9	523-530	76 ± 10	74 ± 8	83 ± 9	82 ± 2	73 ± 9	74 ± 4	81 ± 9
CBH-2	10	Domain B, conformational 431, 523–540	60 ± 5	8 ± 5	65 ± 6	9 ± 5	39 ± 8	61 ± 4	39 ± 10
CBH-5	10	Domain B, conformational 523–540	71 ± 2	10 ± 4	73 ± 7	8 ± 1	36 ± 5	59 ± 7	47 ± 8
CBH-23	Keck and Foung, unpublished data	Domain C, conformational	97 ± 9	21 ± 6	98 ± 13	14 ± 3	32 ± 7	53 ± 12	44 ± 3
HC-1	11	Domain B, conformational 523–540	73 ± 5	31 ± 9	81 ± 10	27 ± 9	2 ± 1	2 ± 1	77 ± 1

Supplementary Table 1. Neutralization of Patient-Derived and Chimeric HCVpp by Monoclonal Anti-Envelope Antibodies

NOTE. HCVpp produced from isolates shown in Figure 1 were incubated with mAbs (10 μ g/mL) for 1 hour at 37°C. HCVpp-antibody complexes then were added to Huh7.5.1 cells. Viral epitopes targeted by the respective antibody, percentage of HCV entry in the presence of antibody (strains VL, VC, VCVL₄₅₈₊₄₇₈, VLVC₄₅₈₊₄₇₈, VA, VAVL₄₄₇, and VLVA₄₄₇), and source or reference of antibody are shown. Means \pm standard deviation from at least 3 experiments, each performed in triplicate, are shown.

V, viral variant.



Supplementary Figure 4. Binding of neutralizing anti-E2 HMAb CBH-23 to patient-derived envelope glycoproteins expressed on HCVpp as capture antigens in an enzyme-linked immunosorbent assay (ELISA). HCVpp expressing envelope glycoproteins of variants VL, VA, VC, VLVA₄₄₇, and VLVC₄₅₈₊₄₇₈ were used as capture antigens on GNA-coated ELISA plates. Control (Ctrl) pseudoparticles with absent HCV envelope glycoprotein expression and recombinant soluble E2 (sE2 derived from strain H77)¹⁴ served as negative and positive controls, respectively. Anti-E2 CBH-23 reactivity was detected as described in the Supplementary Materials and Methods section and is indicated as optical density (OD) values at 450 nm. Means ± standard deviation from 1 representative experiment are shown.

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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	26	54	F	1a	$3.38 imes10^6$	20	400	20
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	27	47	M	3a	$6.16 imes 10^{5}$	100	3200	3200
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	28	43	М	1a	$5.75 imes10^6$	20	800	200
3054M2c 4.67×10^5 10010032003151M1a 6.16×10^6 1004001003239M4a 1.12×10^6 202008003362F4f 2.88×10^6 20800203446M4k 3.54×10^5 20201003654M2c 4.67×10^5 20032001003654M2c 4.67×10^5 20032001003734M3a 7.94×10^4 20400203930F1b 1.00×10^6 202004004047F1b 2.29×10^6 1004002004152M1a 1.73×10^6 20032002004346M1a 4.34×10^6 20032002004346M1a 4.34×10^6 20032002004529F1a 1.08×10^5 20016002004645M3a 2.78×10^5 2032002004645M3a 2.68×10^6 1001001005040M3a 2.68×10^6 1003002005148F1a 1.00×10^5 208002005237M1a $1.84 \times $	29	51	М	4a	$1.44 imes 10^{6}$	100	400	400
31 51 M $1a$ 6.16×10^6 100 400 100 32 39 M $4a$ 1.12×10^6 20 200 800 20 33 62 F $4f$ 2.88×10^6 20 800 20 34 46 M $4k$ 3.54×10^5 20 20 100 35 42 M $1a$ 9.54×10^5 200 220 100 36 54 M $2c$ 4.67×10^5 200 220 100 37 34 M $3a$ 3.23×10^6 20 200 400 39 30 F $1b$ 1.00×10^6 20 200 400 40 47 F $1b$ 1.03×10^6 200 3200 400 41 52 M $1a$ 1.73×10^6 200 3200 400 41 52 M $1a$ 1.68×10^6 200 3200 200 43 46 M $1a$ 4.34×10^6 200 3200 200 44 66 F $1b$ 3.89×10^5 200 1600 200 45 29 F $1a$ 1.08×10^6 20 3200 200 46 45 M $3a$ 2.46×10^6 100 3200 200 48 55 M $1a$ 8.81×10^6 100 100 100 50 40 M $3a$ 2.46×10^6 <td>30</td> <td>54</td> <td>M</td> <td>2c</td> <td>4.67×10^{5}</td> <td>100</td> <td>100</td> <td>3200</td>	30	54	M	2c	4.67×10^{5}	100	100	3200
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	31	51	М	1a	$6.16 imes10^6$	100	400	100
3362F4f 2.88×10^6 20800203446M4k 3.54×10^5 20201003542M1a 9.54×10^5 4008004003654M2c 4.67×10^5 20032001003734M3a 3.23×10^6 20201003847M3a 7.94×10^4 20400204047F1b 1.00×10^6 20032004004152M1a 1.73×10^6 20032002004152M1a 1.45×10^6 320032002004346M1a 4.34×10^6 2008004004466F1b 3.89×10^5 20016002004529F1a 1.08×10^5 4004002004855M1a 8.81×10^6 2032002004855M1a 8.81×10^6 208001004953M1a 1.84×10^6 1001001005040M3a 2.46×10^6 10032002005148F1a 1.00×10^5 208002005237M1a 1.84×10^6 8008002005347M3a 6.8×10	32	39	М	4a	1.12×10^{6}	20	200	800
3446M4k 3.54×10^5 20201003542M1a 9.54×10^5 4008004003654M2c 4.67×10^5 20032001003734M3a 3.23×10^6 20201003847M3a 7.94×10^4 20400203930F1b 1.00×10^6 2022004004047F1b 2.29×10^6 1004002004152M1a 1.73×10^6 20032002004234M1b 1.45×10^6 320032002004346M1a 4.34×10^6 2008004004466F1b 3.89×10^5 20016002004529F1a 1.08×10^5 4004002004645M3a 2.78×10^5 202002004855M1a 8.81×10^6 1001001005040M3a 2.46×10^6 10032002005148F1a 1.00×10^5 208002005237M1a 1.64×10^6 1001002005347M3a 6.8×10^6 10016004005437M1a $1.84 \times $	33	62	F	4f	2.88×10^{6}	20	800	20
3542M1a 9.54×10^5 4008004003654M2c 4.67×10^5 20032001003734M3a 3.23×10^6 20201003847M3a 7.94×10^4 20400203930F1b 1.00×10^6 202004004047F1b 2.29×10^6 1004002004152M1a 1.73×10^6 20032004004234M1b 1.45×10^6 320032002004346M1a 4.34×10^6 2008004004466F1b 3.89×10^5 20016002004529F1a 1.08×10^5 4004002004645M3a 2.78×10^5 202002004855M1a 1.46×10^6 2032002005040M3a 2.46×10^6 1001001005040M3a 2.46×10^6 10032002005148F1a 1.00×10^5 208002005237M1a 1.84×10^6 8008002005347M3a 6.8×10^6 1001001005437M1a $1.84 \times $	34	46	M	4k	3.54×10^{5}	20	20	100
3654M2c 4.67×10^5 20032001003734M3a 3.23×10^6 20201003847M3a 7.94×10^4 20400203930F1b 1.00×10^6 202004004047F1b 2.29×10^6 1004002004152M1a 1.73×10^6 20032004004234M1b 1.45×10^6 320032002004346M1a 4.34×10^6 2008004004466F1b 3.89×10^5 20016002004529F1a 1.08×10^5 4004002004645M3a 2.78×10^5 202002004765F4f 1.46×10^6 203200204855M1a 8.81×10^6 20300205040M3a 2.46×10^6 1001001005148F1a 1.00×10^5 20800205237M1a 1.84×10^6 1003002005347M3a 6.8×10^6 1001008005565F1b 2.18×10^6 1001008005645F1a 3.93×10^6	35	42	M	1a	9.54×10^{5}	400	800	400
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	36	54	M	2c	4.67×10^{5}	200	3200	100
3847M3a 7.94×10^4 20400203930F1b 1.00×10^6 202004004047F1b 2.29×10^6 1004002004152M1a 1.73×10^6 20032004004234M1b 1.45×10^6 320032002004346M1a 4.34×10^6 2008004004466F1b 3.89×10^5 20016002004529F1a 1.08×10^5 4004002004645M3a 2.78×10^5 202002004855M1a 8.81×10^6 203200204855M1a 8.81×10^6 1001001005040M3a 2.46×10^6 1001001005148F1a 1.00×10^5 20800205237M1a 5.08×10^6 10016004005437M1a 5.08×10^6 10016004005565F1b 2.18×10^6 1001008005645F1a 3.93×10^6 160016004005749M4a 2.06×10^6 80032002005830M1b 7.2	37	34	M	3a	3.23×10^{6}	20	20	100
3930F1b 1.00×10^6 202004004047F1b 2.29×10^6 100 400 200 4152M1a 1.73×10^6 200 3200 400 4234M1b 1.45×10^6 3200 3200 200 4346M1a 4.34×10^6 200 800 400 4466F1b 3.89×10^5 200 1600 200 4529F1a 1.08×10^5 400 400 200 4645M3a 2.78×10^5 20 200 200 4855M1a 8.81×10^6 20 3200 200 4855M1a 1.15×10^6 100 100 100 5040M3a 2.46×10^6 100 3200 200 5148F1a 1.00×10^5 20 800 200 5237M1a 1.84×10^6 800 800 200 5347M $3a$ 6.8×10^6 100 1600 400 5437M1a 1.84×10^6 800 800 200 5565F $1b$ 2.18×10^6 100 100 400 5749M $4a$ 2.06×10^6 800 3200 200 5830M $1b$ 7.21×1	38	47	М	3a	$7.94 imes 10^{4}$	20	400	20
4047F1b 2.29×10^6 1004002004152M1a 1.73×10^6 20032004004234M1b 1.45×10^6 320032002004346M1a 4.34×10^6 2008004004466F1b 3.89×10^5 20016002004529F1a 1.08×10^5 4004002004645M3a 2.78×10^5 202002004765F4f 1.46×10^6 203200204855M1a 8.81×10^6 1001001005040M3a 2.46×10^6 10032002005148F1a 1.00×10^5 20800205237M1a 5.08×10^6 10016004005437M1a 1.84×10^6 8008002005565F1b 2.18×10^6 1001008005645F1a 3.93×10^6 160016004005749M4a 2.06×10^6 80032002005830M1b 7.21×10^5 1008002005931M3a 6.67×10^6 201001006037M1a 6	39	30	F	1b	1.00×10^{6}	20	200	400
4152M1a 1.73×10^6 200 3200 4004234M1b 1.45×10^6 3200 3200 200 4346M1a 4.34×10^6 200 800 400 4466F1b 3.89×10^5 200 1600 200 4529F1a 1.08×10^5 400 400 200 4645M3a 2.78×10^5 20 200 200 4765F4f 1.46×10^6 20 3200 20 4855M1a 8.81×10^6 20 800 100 4953M1a 1.15×10^6 100 100 100 5040M $3a$ 2.46×10^6 100 3200 200 5148F1a 1.00×10^5 20 800 200 5237M1a 5.08×10^6 100 1600 400 5347M $3a$ 6.8×10^6 100 1600 400 5565F $1b$ 2.18×10^6 100 1600 400 5749M $4a$ 2.06×10^6 800 3200 200 5830M $1b$ 7.21×10^5 100 800 5931M $3a$ 6.66×10^6 100 200 200 5931M $3a$ 6.66×10^6 <	40	47	F	1b	2.29×10^{6}	100	400	200
4234M1b 1.45×10^6 3200 3200 200 4346M1a 4.34×10^6 200 800 400 4466F1b 3.89×10^5 200 1600 200 4529F1a 1.08×10^5 400 400 200 4645M3a 2.78×10^5 20 200 200 4765F4f 1.46×10^6 20 3200 200 4855M1a 8.81×10^6 20 800 100 4953M1a 1.15×10^6 100 100 100 5040M3a 2.46×10^6 100 3200 200 5148F1a 1.00×10^5 20 800 200 5237M1a 5.08×10^6 100 1600 400 5437M1a 1.84×10^6 800 800 200 5565F1b 2.18×10^6 100 1600 400 5749M4a 2.06×10^6 800 3200 200 5830M1b 7.21×10^5 100 800 200 5931M3a 6.66×10^6 100 200 200 60 37 M1a 6.70×10^6 20 100 100	41	52	M	1a	1.73×10^{6}	200	3200	400
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	42	34	M	1b	1.45×10^{6}	3200	3200	200
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	43	46	М	1a	$4.34 imes10^6$	200	800	400
4529F1a 1.08×10^5 4004002004645M3a 2.78×10^5 202002004765F4f 1.46×10^6 203200204855M1a 8.81×10^6 208001004953M1a 1.15×10^6 1001001005040M3a 2.46×10^6 10032002005148F1a 1.00×10^5 20800205237M1a 5.08×10^6 204002005347M3a 6.8×10^6 10016004005437M1a 1.84×10^6 8008002005565F1b 2.18×10^6 1001008005645F1a 3.93×10^6 160016004005749M4a 2.06×10^6 80032002005830M1b 7.21×10^5 1008002005931M3a 6.66×10^6 1002002006037M1a 6.70×10^6 20100100	44	66	F	1b	3.89×10^{5}	200	1600	200
46 45 M $3a$ 2.78×10^5 20 200 200 47 65 F $4f$ 1.46×10^6 20 3200 20 48 55 M $1a$ 8.81×10^6 20 800 100 49 53 M $1a$ 1.15×10^6 100 100 100 50 40 M $3a$ 2.46×10^6 100 3200 200 51 48 F $1a$ 1.00×10^5 20 800 20 52 37 M $1a$ 5.08×10^6 100 1600 400 53 47 M $3a$ 6.8×10^6 100 1600 400 54 37 M $1a$ 1.84×10^6 800 800 200 55 65 F $1b$ 2.18×10^6 100 100 800 56 45 F $1a$ 3.93×10^6 1600 1600 400 57 49 M $4a$ 2.06×10^6 800 3200 200 58 30 M $1b$ 7.21×10^5 100 800 200 59 31 M $3a$ 6.66×10^6 100 200 200 60 37 M $1a$ 6.70×10^6 20 100 100	45	29	F	1a	1.08×10^{5}	400	400	200
4765F4f 1.46×10^6 203200204855M1a 8.81×10^6 208001004953M1a 1.15×10^6 1001001005040M3a 2.46×10^6 10032002005148F1a 1.00×10^5 20800205237M1a 5.08×10^6 204002005347M3a 6.8×10^6 10016004005437M1a 1.84×10^6 8008002005565F1b 2.18×10^6 1001008005645F1a 3.93×10^6 16004005749M4a 2.06×10^6 80032002005830M1b 7.21×10^5 1008002005931M3a 6.66×10^6 1002002006037M1a 6.70×10^6 20100100	46	45	M	3a	2.78×10^{5}	20	200	200
M M	47	65	F	4f	1.46×10^{6}	20	3200	20
4953M1a 1.15×10^6 1001001005040M3a 2.46×10^6 100 3200 2005148F1a 1.00×10^5 20800205237M1a 5.08×10^6 204002005347M3a 6.8×10^6 10016004005437M1a 1.84×10^6 8008002005565F1b 2.18×10^6 1001008005645F1a 3.93×10^6 160016004005749M4a 2.06×10^6 80032002005830M1b 7.21×10^5 1008002005931M3a 6.66×10^6 1002002006037M1a 6.70×10^6 20100100	48	55	M	1a	8.81×10^{6}	20	800	100
5040M3a 2.46×10^6 100 3200 2005148F1a 1.00×10^5 20800205237M1a 5.08×10^6 204002005347M3a 6.8×10^6 10016004005437M1a 1.84×10^6 8008002005565F1b 2.18×10^6 1001008005645F1a 3.93×10^6 160016004005749M4a 2.06×10^6 80032002005830M1b 7.21×10^5 1008002005931M3a 6.66×10^6 1002002006037M1a 6.70×10^6 20100100	49	53	M	1a	1.15×10^{6}	100	100	100
51 48 F $1a$ 1.00×10^5 20 800 20 52 37 M $1a$ 5.08×10^6 20 400 200 53 47 M $3a$ 6.8×10^6 100 1600 400 54 37 M $1a$ 1.84×10^6 800 800 200 55 65 F $1b$ 2.18×10^6 100 100 800 56 45 F $1a$ 3.93×10^6 1600 1600 400 57 49 M $4a$ 2.06×10^6 800 3200 200 58 30 M $1b$ 7.21×10^5 100 800 200 59 31 M $3a$ 6.66×10^6 100 200 200 60 37 M $1a$ 6.70×10^6 20 100 100	50	40	M	3a	2.46×10^{6}	100	3200	200
52 37 M $1a$ 5.08×10^6 20 400 200 53 47 M $3a$ 6.8×10^6 100 1600 400 54 37 M $1a$ 1.84×10^6 800 800 200 55 65 F $1b$ 2.18×10^6 100 100 800 56 45 F $1a$ 3.93×10^6 1600 1600 400 57 49 M $4a$ 2.06×10^6 800 3200 200 58 30 M $1b$ 7.21×10^5 100 800 200 59 31 M $3a$ 6.66×10^6 100 200 200 60 37 M $1a$ 6.70×10^6 20 100 100	51	48	F	1a	1.00×10^{5}	20	800	20
1- $1 1-2$ $1-2$ $1-2$ $1-2$ $1-20$ <	52	37	M	1a	5.08×10^{6}	20	400	200
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	53	47	M	3a	6.8×10^{6}	100	1600	400
55 65 F $1b$ 2.18×10^6 100 100 800 56 45 F $1a$ 3.93×10^6 1600 100 400 57 49 M $4a$ 2.06×10^6 800 3200 200 58 30 M $1b$ 7.21×10^5 100 800 200 59 31 M $3a$ 6.66×10^6 100 200 200 60 37 M $1a$ 6.70×10^6 20 100 100	54	37	M	1a	1.84×10^{6}	800	800	200
56 45 F $1a$ 3.93×10^6 160 160 400 57 49 M $4a$ 2.06×10^6 800 3200 200 58 30 M $1b$ 7.21×10^5 100 800 200 59 31 M $3a$ 6.66×10^6 100 200 200 60 37 M $1a$ 6.70×10^6 20 100 100	55	65	F	1h	2.18×10^{6}	100	100	800
57 49 M $4a$ 2.06×10^6 1000 1000 400 58 30 M $1b$ 7.21×10^5 100 800 200 59 31 M $3a$ 6.66×10^6 100 200 200 60 37 M $1a$ 6.70×10^6 20 100 100	56	45	F	1a	3.93×10^{6}	1600	1600	400
58 30 M $1b$ 7.21×10^5 100 800 200 59 31 M $3a$ 6.66×10^6 100 200 200 60 37 M $1a$ 6.70×10^6 20 100 100	57	49	M	4a	2.06×10^{6}	800	3200	200
59 31 M $3a$ 6.66×10^6 100 200 200 60 37 M $1a$ 6.70×10^6 20 100 100	58	.30	M	1h	7.21×10^5	100	800	200
60 37 M 1a 6.70×10^6 20 100 100	59	31	M	3a	6.66×10^{6}	100	200	200
	60	37	M	1a	6.70×10^{6}	20	100	100

Supplementary Table 2. Characteristics of Patients and Viruses Used for Neutralization Studies

					HCVpp neutralization titer, 1/dilution		
Patient number	Age, y	Sex	Genotype	Viral load, IU/mL	VL	VC	VA
61	49	М	1a	$3.16 imes10^5$	20	800	20
62	43	Μ	1	$6.83 imes10^5$	20	20	20
63	69	Μ	1b	$4.7 imes10^5$	20	20	200
64	48	Μ	1a	$3.28 imes10^6$	20	3200	100
65	46	Μ	Зa	$8.55 imes10^5$	20	800	100
66	51	Μ	1b	$1.07 imes10^6$	20	200	1600
67	43	Μ	1b	$4.27 imes10^5$	20	100	800
68	36	Μ	Зa	$1.14 imes10^6$	20	800	20
69	53	F	1b	$3.06 imes10^5$	20	400	20
70	24	F	Зa	$1.29 imes10^6$	20	20	20
71	63	Μ	1b	$3.01 imes10^6$	100	200	100
72	44	Μ	1	$1.10 imes10^5$	20	3200	200
73	28	Μ	Зa	$1.85 imes10^{6}$	20	3200	20
74	54	Μ	1b	$1.29 imes10^5$	20	3200	20
75	17	F	1b	$2.41 imes10^5$	20	20	200
76	40	Μ	Зa	$1.26 imes10^6$	20	20	100
77	35	Μ	1b	$8.89 imes10^5$	20	20	800
78	36	F	6a	$1.4 imes10^7$	20	100	400
79	70	F	1b	$1.13 imes10^5$	100	100	400
80	62	Μ	1a	$2.68 imes10^6$	100	200	20
81	70	Μ	1b	$2.85 imes10^5$	20	200	3200
82	63	Μ	1b	$1.95 imes10^5$	200	400	400
83	33	Μ	1a	$1.76 imes10^6$	100	200	800
84	35	Μ	1a	$2.78 imes10^6$	20	20	200
85	60	F	1	$6.39 imes10^5$	20	200	100
86	57	Μ	Зa	$1.22 imes10^{6}$	200	3200	400
87	60	Μ	1	$3.6 imes10^6$	100	3200	20
88	49	Μ	4	$2.24 imes10^{6}$	20	1600	20
89	37	Μ	4	$9.35 imes10^5$	100	800	100
90	55	Μ	1a	$3.77 imes10^6$	20	3200	100
91	47	Μ	1a	$2.36 imes10^6$	20	1600	20
92	72	Μ	За	$3.83 imes10^5$	20	400	20
93	79	Μ	1b	$2.81 imes10^5$	100	1600	100
94	58	F	1b	$6.58 imes10^5$	100	3200	200
95	50	Μ	За	$6.07 imes10^5$	20	3200	100
96	67	F	1b	$4.13 imes10^5$	100	800	20
97	49	Μ	За	$5.22 imes10^5$	200	400	200
98	53	F	1b	$2.31 imes10^6$	20	400	1600
99	37	Μ	1a	$1.87 imes10^5$	100	3200	200
100	54	F	4a	$9.23 imes10^5$	20	200	100
101	39	М	1a	$1.76 imes10^5$	100	800	200
102	51	F	2b	$1.10 imes 10^{6}$	100	3200	800

Supplementary Table 2. Characteristics of Patients and Viruses Used for Neutralization Studies

NOTE. HCVpp were incubated with anti-HCV-positive sera from 102 patients with chronic HCV infection (ClinicalTrial.gov identifier NCT00638144). Patient number, age, sex, viral genotype, and load in serum are indicated. HCVpp-antibody complexes were added to Huh7.5.1 cells and infection was analyzed as described in Figure 4. Calculation of neutralization and determination of background and thresholds for neutralization were performed as described in Figure 6. Neutralization titers obtained by end point dilution are indicated for each variant. Means from at least 3 independent experiments, each performed in triplicate, are shown. V, viral variant.

	HCV	HCVcc neutralization titer, 1/dilution				
Patient number	VL	VLVC ₄₅₈₊₄₇₈	VLVA ₄₄₇			
11	400	1600	800			
28	20	1600	800			
33	20	400	400			
35	400	1600	1600			
36	200	1600	3200			
45	800	1600	800			
65	20	1600	1600			
66	20	3200	800			
68	20	1600	1600			
94	100	3200	800			
98	100	800	3200			
99	100	3200	1600			

Supplementary Table 3. HCVcc Neutralization Titers

NOTE. Results were confirmed using chimeric HCVcc expressing the HCV envelope glycoproteins depicted in Figure 7 and using 12 representative sera from patients. Neutralization assays were performed using a similar protocol as described in Supplementary Tables 2 and 3. Means from at least 3 independent experiments, each performed in triplicate, are shown. V, viral variant.



Supplementary Figure 5. Distribution of residues at positions 447, 458, and 478 of HCV E2 sequences in the European HCV databases. Distribution of residues at positions 447, 458, and 478 for HCV complete E2 sequences from all subtypes (black) and from subtype 1b only (white) within the European Hepatitis C Virus databases⁷ (available: http://euhcvdb.ibcp.fr). F and S are the predominant residue at positions 447 and 458 (F447, 98.4%; 1b, 96.2%; S458 all, 94%; 1b, 90.3%). The position 478 is variable (it belongs to HVR2) but R (all, 2.4%; 1b, 10.8%) is more frequent than C (all, 0.2%; 1b, 0.9%).