according to the viral response in genotype 2a infection, did not differ significantly in our study. Amino acid 70 and 91, which have been reported to vary according to viral response to PEG-IFN/RBV therapy in genotype 1b infection, were conserved irrespective of the outcome.

Comparison of amino acid variation between the SVR and non-SVR patients across HCV "regions" using sliding window analysis

Fig.2c shows the combined result of sliding window analysis for study groups 1 and 2, this approach was used to detect differing HCV amino acid "regions", rather than single amino acid positions, between the SVR and the non-SVR patients. According to the result, four regions were notably associated with the final outcome (p-values less than 1/1000). Core aa 110, detected as a single amino acid position discriminating between the SVR and the non-SVR patients, was also identified as one of these regions. Because core aa 110 was already known for its strong correlation with the response as above, the region was excluded from further analysis. Among the other three regions, only NS5A aa 2258-2306 showed significant differences in the two independent study groups (Table 2b). Interestingly, the NS5A region overlapped the PKR-binding domain, which includes the interferon sensitivity determining region (ISDR). Fig.2d shows the aligned sequences of amino acids around 2258-2306 of HCV NS5A. As with previous studies, variations in the ISDR were also significantly more frequent in SVR patients.

Multivariate analysis to detect independent factors contributing to the SVR

Multivariate analysis revealed that variation of core aa 110, the total number of

substitutions within NS5A aa 2258-2306, and total ribavirin dose ≥80% were finally identified as the independent variables influencing the final outcome (odds ratio 24.7, 11.5 and 16.0; $p = 0.02, 0.03$ *and* 0.02, Table 3).

Biological relevance of variation in core and NS5A in this study group

To determine biological relevance of core aa110 and NS5A aa2258-2306, we investigated their relationship with clinical background factors. Multiple variations in the NS5A region aa 2258-2306 were significantly related to pretreatment HCV RNA titer ($p=9E-05$, Fig. 3 and Table 4a). Interestingly, variation of the core aa110 was significantly associated with the patients' age ($p=0.03$, Table 4b).

DISCUSSION

In this study, based on analysis of complete HCV ORF sequences and comparison of SVR and non-SVR patients in two independent study groups, we have shown that amino acid variations in the core and NS5A correlate most significantly with the final outcome in the treatment for genotype 2a chronic hepatitis C. The study is unique in that the patients studied were all Japanese, excluding any affect of racial differences and providing a clearer analysis of the viral differences.

From the analysis of the characteristics of patients infected with genotype 2a HCV, it was clear that most non-SVR patients responded to the PEG-IFN/RBV therapy at least transiently, given that most of these non-SVR patients (89%) achieved EVR. This result demonstrated that most non-SVR patients were relapser, but were not null-responders as observed frequently among genotype 1b patients treated with PEG-IFN/RBV therapy. Therefore, we compared the different viral responses according to the final outcome of SVR or non-SVR.

Variation of core aa 110 was identified as the single amino acid residue most significantly related to the final outcome ($p=5E-05$). In recent studies of treatment of genotype 1b infection with PEG-IFN/RBV, amino acid variation in the core region was reported to be associated with response. It is interesting that the core region was also identified as an HCV gene associated with the response to PEG-IFN/RBV therapy of genotype 2a infection, although the amino acid residues of core in genotype 1b were different, being aa 70 and aa 91. It is also interesting that amino acids aa 70 and aa 91 are conserved as arginine and leucine, respectively, in genotype 2a, as reported to be associated with favorable PEG-IFN/RBV responses in genotype 1b infection, consistent with the association with a high SVR rate in genotype 2a infection. Very recently, a

correlation was reported between amino acid variations in the core region and viral responses of genotype 2a HCV infection (20). Though the result seems discrepant from our study, we suspect the inconsistent results were at least partially attributable to the different groups used in comparison: we compared the difference between non-SVR patients and SVR patients while they compared the difference between non-SVR and RVR patients.

In systemic searching for the viral "regions" associated with the treatment outcome, NS5A aa2258-2306 was identified by two independent studies. Interestingly, the region overlaps the PKR-binding domain (PKR-BD), including the ISDR, in which the number of amino acid substitutions is known to be related to the response to IFN-based therapy in genotype 1b, and also in genotype 2a (17-18). Therefore, we also confirmed that total number of substitutions in the ISDR and PKR-BD is significantly associated with the final outcome in this group of patients when the two studies were combined.

Some viral regions other than core and NS5A also showed the potential association with the final outcome. Viral single amino acid substitutions of aa 773 in p7, aa 2099 in the NS5A, and aa 3013 in NS5B, or viral regions in E1 aa 400-403 and in E2 aa 724-744 were more frequent in SVR. However, because these were not extracted as significant in one of the two studies when analyzed separately, additional studies are needed to confirm the association with the final outcome. On the other hand, we could not find an association with the final outcome and the PePHD or IRRDR, including the V3 regions (data not shown) reported 1b HCV infection (21-22).

It is interesting that the variation of the core region showed the clear association with age. The younger patients with core aa 110T showing favorable

responses while the older patients with core aa 110 non-T showed unfavorable responses. It is possible that different response rates according to the patients' ages in genotype 2a infection might have been related to the core substitutions, although further study is needed. In NS5A, it was reported that the variations within the PKR-binding region, including those within the ISDR, can disrupt the NS5A-PKR interaction, possibly rendering HCV sensitive to the antiviral effects of interferon (23). Clinically, the number of substitutions within the region has been reported to correlate with the serum HCV RNA level (12). We also confirmed that the number of substitutions within the NS5A aa 2258-2306 was significantly associated with the pretreatment HCV RNA titers.

Multivariate analysis of the combined group of patients showed that variation of core aa 110, NS5A aa 2258-2306, and total ribavirin dose ≥80% were independent variables associated with the final outcome (Table. 3). The association of ribavirin dose and HCV relapse rate was reported previously (24) and that result was confirmed in this study. On the other hand, the total PEG-IFN dosage was not identified when it was administered at greater than 60% of the initially scheduled amount. Indeed, when the drug dosage is excluded, the strongest association was seen in the viral elements of core and NS5A, revealing the importance of these two regions in the treatment of genotype 2a HCV infection with PEG-IFN/RBV therapy.

On the other hand, our study still has some limitations. In recent studies, IL28B single nucleotide polymorphisms were reported to be correlated significantly with the treatment response in genotype 1b HCV infections (25-26). In genotype 2a HCV infection, a correlation was also reported to exist between the IL28B SNP and the treatment response (27). However, we could not investigate the association of the IL28B

single nucleotide polymorphisms in the treatment response in genotype 2a HCV infections. In addition, the number of analyzed patients was rather small, especially in non-SVR patients.

In conclusion, by comprehensive investigation of the complete HCV ORF in patients showing different responses to PEG-IFN/RBV therapy, we have demonstrated that amino acid variation in the core and NS5A are significantly associated with the final outcome of treatment of genotype 2a chronic hepatitis C. Considering this result, determination of those HCV regions before treatment might provide further benefits for the patients infected with genotype 2a HCV.

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FIGURE LEGENDS

Fig.1 Number of amino acid substitutions per sample in the sustained viral responders (SVR) and the non-sustained viral responders (non-SVR) group.

The numbers of variations, relative to a population consensus, that were unique to either SVR or non-SVR patients are shown for the full open reading frame (ORF) (Fig.1, left) and for each HCV protein (Fig.1, right).

Fig.2a Different amino acid usages at each viral amino acid position between the sustained viral responders (SVR) and the non-sustained viral responders (non-SVR) patients.

Amino acid variation was determined between SVR and non-SVR patients by Fisher's exact probability test. The longitudinal axis shows the - logP value.

Fig.2b Sequence alignment in the core region.

Dashes indicate amino acids identical to the consensus sequence and substituted amino acids are shown by standard single letter codes.

Fig.2c Sliding window analysis.

Viral regions affecting treatment outcome are shown as red spots. There are four hot spots: at core amino acid 110, amino acids 400-403 (i.e. the hyper variable region) in Envelope2 (E2) region, amino acids 724-743 in E2 and amino acids 2258-2306 in the nonstructural (NS)5A.

Fig.2d Sequence alignment amino acids in the nonstructural (NS)5A around amino acids 2258 to 2306.

Dashes indicate amino acids identical to the consensus sequence and substituted amino acids are shown by standard single letter codes.

Fig.3 Correlation between pretreatment HCV RNA levels and the number of substitutions in the NS5A region aa 2258 to 2306.

Spearman's correlation coefficient by rank test is demonstrated.

Table

Table 1. Baseline Characteristics of All Patients (Group 1 and 2)

Characteristic	SVR (n = 58)			non-SVR (n = 20)			*P* value△
	Group 1 (n = 36)	Group 2 (n =22)	Combined (n = 58)	Group 1 (n = 7)	Group 2 (n = 13)	Combined (n = 20)	
Gender(Male/Female)	20 / 16	9 / 13	29 / 29	4 / 3	5 / 8	9 /11	0.80†
Age(yrs)	50.0 ± 12.5*	57.3 ± 10.0	52.4 ± 12.1	55.0 ± 9.7	59.8 ± 6.4	58.1 ± 7.8	0.058‡
ALT(IU/l)	86.6 ± 86.6	71.2 ± 50.4	80.5 ± 74.2	52.9 ± 29.3	88.1 ± 90.1	75.8 ± 75.5	0.81‡
Platelet($x10^4/mm^3$)	20.8 ± 6.2	19.0 ± 5.2	20.1 ± 5.8	14.7 ± 7.1	19.1 ± 4.9	17.6 ± 6.0	0.11‡
Fibrosis score(0-2 / ≥3)§	34 / 1	19 / 2	53 / 3	4 / 3	11 / 2	15 / 5	0.049†
HCV RNA(KIU/ml)	760(2-3100)**	340(54-3600)	550(12-3600)	1300 (350-30000)	1400 (180-5000)	1300 (180-30000)	0.002‖
IFN dose(≥80% / 60-80%)¶	28 / 4	21 / 1	49 / 5	4 / 3	11 / 2	15 / 5	0.12†
Ribavirin dose(≥80% / 60-80%)¶	27 / 5	17 / 5	44 / 10	4 / 3	5 / 8	9 / 11	0.003†
RVR rate (%)	87.5	54.5	74.1	33.3	46.1	42.1	0.022†
EVR rate (%)	100	100	100	66.7	100	89.4	0.07†

* : mean ± SD ** : median (range) † : Fisher's exact probability test ‡ : Student t test ‖ : Mann-Whitney's U test △: *P* values between all SVR (n = 58) vs. all non-SVR (n = 20)

Several clinical charcteristics listed below were unavailable in some patients

§ : SVR : n = 56 (35 in group1, 21 in group2), non-SVR : n = 17 (7 in group1, 10 in group2) ¶ : SVR : n = 54 (32 in group1, 22 in group2)

Table 2a. Variations in each Amino Acid Position and SVR rate

Position		Group 1 (n = 43)	*P* value	Group 2 (n = 35)	*P* value	Combined (n = 78)	*P* value
Core aa 110	T	100% (19 / 19)	0.01	92.9% (13 / 14)	0.004	97% (32 / 33)	5E - 05
	non T	70.8% (17 / 24)		42.9% (9 / 21)		57.8% (26 / 45)	
p7 aa 773	V	77.4% (24 / 31)	0.16	53.6% (15 / 28)	0.03	66.1% (39 / 59)	0.002
	non V	100% (12 /12)		100% (7 / 7)		100% (19 / 19)	
NS5A aa 2099	R	92.9% (13 / 14)	0.40	91.7% (11 / 12)	0.01	92.3% (24 / 26)	0.01
	non R	79.3% (23 / 29)		47.8% (11 / 23)		65.4% (34 / 52)	
NS5B aa 3013	L	78.9% (26 / 33)	0.17	47.8% (11 / 23)	0.01	66.1% (37 / 56)	0.008
	non L	100% (10 / 10)		91.7% (11 / 12)		95.5% (21 / 22)	

Table 2b. Number of Amino Acid Substitutions in each Region and SVR rate

Region		Group 1 (n = 43)	*P* value	Group 2 (n = 35)	*P* value	Combined (n = 78)	*P* value
E2 aa 400-403	mutation ≥2	89.3% (25 / 28)	0.22	100% (11 / 11)	0.002	92.3% (36 / 39)	0.0005
	mutation 0-1	73.3% (11 / 15)		45.8% (11 / 24)		56.4% (22 / 39)	
E2 aa 724-743	mutation ≥1	100% (28 / 28)	0.0002	72% (18 / 25)	0.12	86.8% (46 / 53)	0.0006
	no mutation	53.3% (8 / 15)		40% (4 / 10)		48% (12 / 25)	
ISDR(aa 2213-2248)	mutation ≥2	100% (15 / 15)	0.08	86.7% (13 / 15)	0.02	93.3% (28 / 30)	0.003
	mutation 0-1	75% (21 / 28)		45% (9 / 20)		62.5% (30 / 48)	
NS5A aa 2258-2306	mutation ≥5	100% (19 / 19)	0.01	84.2% (16 / 19)	0.006	92.1% (35 / 38)	0.0006
	mutation 0-4	70.8% (17 / 24)		37.5% (6 / 16)		57.5% (23 / 40)	

Table 3. Multivariate Logistic Regression Analysis

Factor	Odds (95% CI)	*P* value
Age	1.01 (0.91-1.13)	0.85
HCV RNA	1.00 (1.00-1.00)	0.09
Fibrosis score ≥3/0-2	2.37 (0.21-26.7)	0.48
RVR achievement	3.46 (0.54-22.1)	0.19
Ribavirin dose ≥ 80%	16.0 (1.66-153)	0.02
Core aa 110 T	24.7 (1.72-353)	0.02
NS5A aa 2258-2306 mutations 0-4/≥5	11.5 (1.23-108)	0.03

Table 4a. Baseline Characteristics of Patients with NS5A aa 2258-2306 mutations 0-4 or ≥5 (Group 1 and 2)

Characteristic	Mutation 0-4 (n = 40)	Mutation ≥5 (n = 38)	*P* value
Gender (Male/Female)	22 / 18	16 / 22	NS†
Age (yrs)	54.3 ± 11.4*	53.5 ± 11.5	NS‡
ALT (IU/l)	73.8 ± 70.3	85.3 ± 78.7	NS‡
Platelet ($x10^4/mm^3$)	18.0 ± 5.9	21.0 ± 5.7	0.03‡
Fibrosis score (0-2 / ≥3)§	33 / 5	33 / 2	NS†
HCV RNA (KIU/ml)	1100 (99 - 30000) **	380 (12 - 5000)	0.02‖
IFN dose (≥80% / 60-80%)¶	31 / 8	33 / 2	NS†
Ribavirin dose (≥80% / 60-80%)¶	25 / 14	28 / 7	NS†
RVR rate (%)	65.8	62.9	NS†
EVR rate (%)	94.7	100	NS†
Relapse rate (%)	35.9	7.9	0.002†
SVR rate (%)	57.5	92.1	0.0006†

*: mean ± SD, †: Fisher's exact probability test , ‡: Student t test, §: Mutation 0-4 : n = 38, mutation ≥5 : n = 35,

**: median (range), ‖: Mann-Whitney's U test, ¶: Mutation 0-4 : n = 39, mutation ≥5 : n = 35

Table 4b. Baseline Characteristics of Patients with Core 110 T or N/S (Group 1 and 2)

Characteristic	Core 110 T (n = 33)	Core 110 N/S (n = 45)	*P* value
Gender (Male/Female)	18 / 15	20 / 25	NS†
Age (yrs)	50.4 ± 13.0*	56.4 ± 9.5	0.032‡
ALT (IU/l)	64.5 ± 48.2	88.8 ± 86.2	NS‡
Platelet ($x10^4/mm^3$)	19.3 ± 4.9	19.5 ± 6.6	NS‡
Fibrosis score (0-2 / ≥3)§	30 / 1	36 / 6	NS†
HCV RNA (KIU/ml)	580 (54 - 3600) **	980 (12 - 30000)	NS‖
IFN dose (≥80% / 60-80%)¶	26 / 3	38 / 7	NS†
Ribavirin dose (≥80% / 60-80%)¶	23 / 6	30 / 15	NS†
RVR rate (%)	72.4	59.1	NS†
EVR rate (%)	100	95.5	NS†
Relapse rate (%)	3.0	38.6	9E-05†
SVR rate (%)	97.0	57.8	5E-05†

*: mean ± SD, †: Fisher's exact probability test , ‡: Student t test, §: Core 110 T : n = 31, Core 110 N/S : n = 42,

**: median (range), ‖: Mann-Whitney's U test, ¶: Core 110 T : n = 29