研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ
泉　並木	ウイルスおよび宿主因子に基づいたC型肝炎の治療	森正樹、下瀬川徹、金子周一、松本俊治、寺田弘司	消化器疾患の最新医療	先端医療技術研究所	東京	2011	104-107
泉　並木	健康診断で肝臓の数値が気になるとき読む本	泉　並木	健康診断で肝臓の数値が気になるとき読む本	幻冬舎	東京	2011	全部
泉　並木	肝癌の治療	林紀夫、日比紀文、上西紀夫、下瀬川徹	Annual Review消化器2012	中外医学社	東京	2012	174-184
泉　並木	ウイルス肝炎の治療戦略　序文	工藤正俊、泉　並木	ウイルス肝炎の治療戦略	診断と治療社	東京	2010	vii
三浦美香、前川伸哉、門倉信、末木良太、小馬瀬一樹、進藤浩子、進藤邦明、雨宮史武、中山康弘、植竹智義、井上泰輔、坂本穣、榎本信幸	肝発癌に関連するC型肝炎ウイルス遺伝子領域とIL28B SNP の解析	小俣政男	第 18 回浜名湖シンポジウム記録集消化器疾患と幹細胞；その基礎と臨床	アークメディア	日本	2011年	171－177

雑誌

発表者氏名	論文タイトル名	発表誌名	巻・号	ページ	出版年
正木尚彦	ウイルス肝炎検診と病診連携の重要性と進めかた	Medical Practice	28 巻 8 号	1453-1457	2011

Ito K, Higami K, Masaki N, Sugiyama M, Mukaide M, Saito H, Aoki Y, Sato Y, Imamura M, Murata K, Nomura H, Hige S, Adachi H, Hino K, Yatsuhashi H, Orito E, Kani S, Tanaka Y, Mizokami M.	The rs8099917 polymorphism, determined by a suitable genotyping method, is a better predictor for response to pegylated interferon-alpha/ ribaviriin therapy in Japanese patients than other SNPs associated with IL28B.	J Clin Microbiol	49 巻 5 号	1853-1860	2011
Tamada Y, Yatsuhashi H, Masaki N, Nakamuta M, Mita E, Komatsu T, Watanabe Y, Shimada M, Hijioka T, Satoh T, Mano Y, Komeda T, Takahashi M, Kohno H, Ota H, Hayashi S, Miyakawa Y, Abiru S, Ishibashi H.	Hepatitis B virus strains of subgenotype A2 with an identical sequence spreading rapidly from the capital region to all over Japan in patients with acute hepatitis B.	Gut			2011 Nov 7. [Epub ahead of print]
Asahina Y, Izumi N et al.	Association of gene expression involving innate immunity and genetic variation in interleukin 28B with antiviral response.	Hepatol	55	20-9	2012
Kurosaki M, Izumi N, et al.	Data mining model using simple and readily available factors could identify patients at high risk for hepatocellular carcinoma in chronic hepatitis C.	J Hepatol	In press		2012
Kurosaki M, Izumi N, et al.	Relationship between polymorphysms of the inosine triphosphate gene and anemia or outcome after treatment with pegylated interferon and ribavirin.	Antivir Ther	16	685-94	2011
Itakura J, Izumi N et al.	Changes days can predict the undetectable time in hepatitis C viral load during first 14 point of serum viral laod by pegylated interferon and ribavirin therapy.	Hepatol Res	41	217-24	2011

Watanabe S, Izumi N et al.	Cancer preventive effect of pegylated interferon α-2b plus ribavirin in a real-life clinical setting in Japan: PERFECT interim analysis.	Hepatol Res	41	955-64	2011
Shindo H, Enomoto N, Izumi N et al.	Characterization of naturally occurring protease inhibitor-resistance mutations in genotype 1b hepatitis C virus patients	Hepatol Int	In press		2011
Kurosaki M, Izumi N, et al.	Sequences in the interferon sensitivity-determining region and core region of hepatitis C virus impact pretreatment prediction of response to PEG-interferon plus ribavirin: data mining analysis.	J Med Virol	83	445-52	2011
Izumi N, Asahina Y et al.	Predictiors of virological response to a combination therapy with pegylated interferon plusu ribavirin including virus and host factors.	Hepat Res Treat	2010	703602	2010
Kurosaki M, Izumi N, et al.	Pre-treatment prediction of response to pegylated-interferon plus ribavirin for chronic hepatitis C using genetic polymorphism in IL28B and viral factors.	J Hepatol	54	439-48	2011
Kurosaki M, Izumi N, et al.	Hepatic steatosis in chronic hepatitis C is a significant risk factor for developing hepatocellular carcinoma independent of age, sex, obesity, fibrosis stage and response to interferon therapy.	Hepatol Res	40	870-7	2010
Asahina Y, Izumi N, et al.	Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection.	Hepatology	52	518-27	2010
Kurosaki M, Izumi N, et al.	A predictive model of response to peginterferon ribavirin in chronic hepatitis C using classification and regression tree analysis.	Hepatol Res	40	251-60	2010

Itakura J, Izumi N et al.	Reproducibility and usability of chronic virus infection model using agent-based simulation; comparing with a mathematical model.	Biosystems	99	70-8	2010
Hiramatsu N, Izumi N, et al.	Pretreatment prediction of anemia progression by pegylated interferon alpha-2b plus ribavirin combination therapy in chronic hepatitis C infection: decision-tree analysis.	J Gastroenterol	46	1111-9	2011
Tsuchiya K, Izumi N et al.	Expression of keratin 19 is related to high recurrence of hepatocellular carcinoma after radiofrequency ablation.	Oncology	80	278-88	2011
Kuzuya T, Izumi N et al.	Early decrease in α-fetoprotein but not des-γ-carboxy prothrombin predicts sorafenib efficacy in patients with advanced hepatocellular carcinoma.	Oncology	81	251-8	2011
Kawaguchi T, Izumi N et al.	Branched-chain amino acids as pharmacological nutritients in chronic liver disease.	Hepatology	54	1063-70	2011
Izumi N	Prediction and prevention of intrahepatic recurrence of hepatocellular carcinoma.	Hepatol Res	In press		2012
Izumi N	Recent advances of radiofrequency ablation for early hepatocellular carcinoma	J Gastroenterol Hepatol	26	115-22	2011
Tamada Y, Yatsuhashi H, Masaki N, Nakamuta M, Mita E, Komatsu T, Watanabe Y, Muro T, Shimada M, Hijioka T, Satoh T, Mano Y, Komeda T, Takahashi M, Kohno H, Ota H, Hayashi S, Miyakawa Y, Abiru S, Ishibashi H.	Hepatitis B virus strains of subgenotype A2 with an identical sequence spreading rapidly from the capital region to all over Japan in patients with acute hepatitis B	Gut.			2011 (in press)

Miyaaki H, Ichikawa T, Yatsuhashi H, Taura N, Miuma S, Usui T, Mori S, Kamihira S, Tanaka Y, Mizokami M, Nakao K.	Suppressor of cytokine signal 3 and IL28 genetic variation predict the viral response to peginterferon and ribavirin	Hepatol Res	41(12)	1216-1222	2011
Kawaguchi T, Kakuma T, Yatsuhashi H, Watanabe H, Saitsu H, Nakao K, Taketomi A, Ohta S, Tabaru A, Takenaka K, Mizuta T, Nagata K, Komorizono Y, Fukuizumi K, Seike M, Matsumoto S, Maeshiro T, Tsubouchi H, Muro T, Inoue O, Akahoshi M, Sata M.	Data mining reveals complex interactions of risk factors and clinical feature profiling associated with the staging of non-hepatitis B virus/non-hepatitis C virus-related hepatocellular carcinoma	Hepatol Res	41(6)	564-571	2011
Ozawa E, Abiru S, Nagaoka S, Yano K, Komori A, Migita K, Yatsuhashi H, Taura N, Ichikawa T, Ishibashi H, Nakao K.	Ferritin/alanine aminotransferase ratio as a possible marker for predicting the prognosis of acute liver injury	J Gastroenterol Hepatol	26(8)	1326-1332	2011
Ito K, Higami K, Masaki N, Sugiyama M, Mukaide M, Saito H, Aoki Y, Sato Y, Imamura M, Murata K, Nomura H, Hige S, Adachi H, Hino K, Yatsuhashi H, Orito E, Kani S, Tanaka Y, Mizokami M.	The rs8099917 Polymorphism, Determined by a Suitable Genotyping Method, is a Better Predictor for Response to Pegylated Interferon-{alpha}/Ribavirin Therapy in Japanese Patients than Other SNPs Associated with IL28B	J Clin Microbiol	49(5)	1853-1860	2011

Matsuda T, Marugame T, Kamo KI, Katanoda K, Ajiki W, Sobue T; The Japan Cancer Surveillance Research Group.	Cancer Incidence and Incidence Rates in Japan in 2006: Based on Data from 15 Population-based Cancer Registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project.	Jpn J Clin Oncol	42(2)	139-147	2012
Katanoda K, Ajiki W, Matsuda T, Nishino Y, Shibata A, Fujita M, Tsukuma H, Ioka A, Soda M, Sobue T.	Trend analysis of cancer incidence in Japan using data from selected population-based cancer registries.	Cancer Sci	103(2)	360-368	2012
Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T; Japan Cancer Surveillance Research Group.	Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) project.	Jpn J Clin Oncol	41(1)	139-47	2011
Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T; Research Group of Population-Based Cancer Registries of Japan.	Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study.	Jpn J Clin Oncol	41(1)	40-51	2011
東尚弘、祖父江友孝、西本寛.	臓器がん登録の現状.—臓器がん登録の実態についての調査報告—.	外科治療	104(2)	169-176	2011
祖父江友孝.	がん登録の進歩.	腫瘍内科	7(1)	56-61	2011
Shimbo. T, Nagata-Kobayashi S, Masaki N, Study Group Developing Nationwide Database of Hepatitis Japan	Cost-Effectiveness of Peginterferon and Ribavirin for Elderly Patients with Chronic Hepatitis C: Results Based on the Nationwide Hepatitis Registration in Japan.	Value in Health	14(7)	A395	2011

Kawaoka T, Hayes CN, Ohishi W, Ochi H, Maekawa T, Abe H, Tsuge M, Mitsui F, Hiraga N, Imamura M, Takahashi S, Kubo M, Tsunoda T, Nakamura Y, Kumada H, Chayama K.	Predictive value of the IL28B polymorphism on the effect of interferon therapy in chronic hepatitis C patients with genotypes 2a and 2b.	J Hepatol	54(3)	408-14.	2011
Abe H, Hayes CN, Ochi H, Maekawa T, Tsuge M, Miki D, Mitsui F, Hiraga N, Imamura M, Takahashi S, Kubo M, Nakamura Y, Chayama K.	IL28 variation affects expression of interferon stimulated genes and peg-interferon and ribavirin therapy.	J Hepatol	54(6)	1094-101	2011
Hashimoto Y, Ochi H, Abe H, Hayashida Y, Tsuge M, Mitsui F, Hiraga N, Imamura M, Takahashi S, Nelson Hayes C, Ohishi W, Kubo M, Tsunoda T, Kamatani N, Nakamura Y, Chayama K.	Prediction of response to peginterferon-alfa-2b plus ribavirin therapy in Japanese patients infected with hepatitis C virus genotype 1b.	J Med Virol	83(6)	981-8	2011
Azakami T, Hayes CN, Sezaki H, Kobayashi M, Akuta N, Suzuki F, Kumada H, Abe H, Miki D, Tsuge M, Imamura M, Kawakami Y, Takahashi S, Ochi H, Nakamura Y, Kamatani N, Chayama K.	Common genetic polymorphism of ITPA gene affects ribavirin-induced anemia and effect of peg-interferon plus ribavirin therapy.	J Med Virol	83(6)	1048-57	2011

Hiraga N, Abe H, Imamura M, Tsuge M, Takahashi S, Hayes CN, Ochi H, Tateno C, Yoshizato K, Nakamura Y, Kamatani N, Chayama K.	Impact of viral amino acid substitutions and host interleukin-28b polymorphism on replication and susceptibility to interferon of hepatitis C virus.	Hepatology	54(3)	764-71	2011
酒井明人、荒井邦明、金子周一	肝臓癌の予防とサーベイランス	G.I.Research	19	334-341	2011
Honda M, Takehana K, Sakai A, Tagata Y, Shirasaki T, Nishitani S, Muramatsu T, Yamashita T, Nakamoto Y, Mizukoshi E, Sakai Y, Yamashita T, Nakamura M, Shimakami T, Yi M, Lemon SM, Suzuki T, Wakita T, Kaneko S; Hokuriku Liver Study Group	Malnutrition impairs interferon signaling through mTOR and FoxO pathways in patients with chronic hepatitis C	Gastroenterology	141	128-140	2011
Kadokura M, Maekawa S, Sueki R, Miura M, Komase K, Shindo H, Amemiya F, Uetake T, Inoue T, Sakamoto M, Nakagawa M, Sakamoto N, Watanabe M, Enomoto N	Analysis of the complete open reading frame of hepatitis C virus in genotype 2a infection reveals critical sites influencing the response to peginterferon and ribavirin therapy.	Hepatol Int	5(3)	789-99	2011

Kadokura M, Maekawa S, Sueki R, Miura M, Komase K, Shindo H, Amemiya F, Uetake T, Inoue T, Sakamoto M, Nakagawa M, Sakamoto N, Watanabe M, Enomoto N	Analysis of the complete open reading frame of genotype 2b hepatitis C virus in association with the response to peginterferon and ribavirin therapy.	PLoS One	6(9):e24514. Epub		2011
Shindo H, Maekawa S, Komase K, Sueki R, Miura M, Kadokura M, Shindo K, Amemiya F, Kitamura T, Nakayama Y, Inoue T, Sakamoto M, Okada SI, Asahina Y, Izumi N, Honda M, Kaneko S, Enomoto N	Characterization of naturally occurring protease inhibitor-resistance mutations in genotype 1b hepatitis C virus patients.	Hepatol Int	Aug 18.Epub ahead of print		2011
Miura M, Maekawa S, Kadokura M, Sueki R, Komase K, Shindo H, Ohmori T, Kanayama A, Shindo K, Amemiya F, Nakayama Y, Kitamura T, Uetake T, Inoue T, Sakamoto M, Okada S, Enomoto N	Analysis of viral amino acids sequences and the IL28B SNP influencing the development of hepatocellular carcinoma in chronic hepatitis C.	Hepatol Int	2011 Aug 17.Epub ahead of print		2011

Ⅳ. 研究成果の刊行物・別刷

ウイルス肝炎検診と病診連携の重要性と進めかた

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はじめに●

厚生労働省の推定(2010年)によると，現在わが国には約350万人の肝炎ウイルスキャリアが存在する．その内訳は，B型肝炎ウイルスキャリアが約110～140万人，C型肝炎ウイルスキャリアが約190～230万人であるが，実際慢性肝炎以上に進行している患者数はB型肝炎で約7万人(慢性肝炎5万人，肝硬変・肝癌2万人)，C型肝炎で約37万人(慢性肝炎28万人，肝硬変・肝癌9万人)と見積もられており，それ以外の人は無症候性キャリアにとどまっているか，あるいは，肝炎ウイルスに感染していることすら自覚していないものと考えられる．いうまでもなく，ウイルス肝炎検診の主目的はこれら感染未自覚者を新たに掘り起こすことである．

肝炎総合対策のこれまでの概要●

これまで国は数々の肝炎対策を打ち出してきた(表1)．その中でも特記すべき施策として，平成14年から18年までの5年間全国で行われた節目検診，節目外検診があり，肝炎ウイルス検査を無料で行うことにより，潜在的患者の掘り起こしを全国規模で展開した．その検診結果は厚生労働省による報道発表資料(http://www.mhlw.go.jp/houdou/2007/10/h1003-1.html)として公開されているが，この5年間にC型肝炎ウイルス検診受診者はのべ8,634,509人に達し，うち99,950人(1.16%)が「現在，C型肝炎ウイルスに感染している可能性がきわめて高い」と判定され，一方，B型肝炎ウイルス検診受診者はのべ8,704,587人でうち100,983人(1.16%)が「陽性」と判定された．しかし，その結果が検診受診者に通知されたにもかかわらず，厳密な意味での二次精検を目的とした医療機関への受診率は約40%にとどまったものと推定されており，インターフェロンなどの抗ウイルス療法まで受けた患者数はさらに少なく，検診

表1　これまでの国の肝炎対策

・昭和39年	「献血の推進について」閣議決定
・昭和47年	献血血液に対してHBs抗原検査導入
・昭和61年	B型慢性肝炎に対するインターフェロンの保険適用
・平成4年	C型慢性活動性肝炎に対するインターフェロンの保険適用(初回)
・平成13年	「肝炎に関する有識者会議」報告書取りまとめ
・平成14年	「C型肝炎緊急総合対策」を開始 保健所，老健事業，政管健保，健保組合，職域の検診に肝炎ウイルス検査を導入 (～平成18年)節目検診(老人保健事業)・節目外検診
・平成17年	「C型肝炎対策等に関する専門家会議」
・平成18年	「C型肝炎対策等の一層の推進について」取りまとめ 肝炎ウイルス検査の実施，検査体制の強化，診療体制の整備
・平成19年	「全国C型肝炎診療懇談会報告書―都道府県における肝炎検査後肝疾患診療体制に関するガイドライン―」 与党PT「新しい肝炎総合対策の推進について」取りまとめ 肝炎ウイルス検査の促進，インターフェロン治療のための環境整備，研究の推進
・平成20年1月	「薬害肝炎被害者救済特別措置法」の成立
・平成20年4月～	「B型・C型慢性肝炎に対するインターフェロン治療費助成の開始」
・平成21年11月	「肝炎対策基本法」の成立
・平成22年4月～	「B型・C型慢性肝疾患に対する医療費助成の拡充」

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●平成14年度から行われた節目(外)検診における二次精検受診率は約40%であった.
●現在,全国47都道府県に70肝疾患診療連携拠点病院が指定されている.
●各自治体では二次医療圏ごとに専門医療機関を指定している.

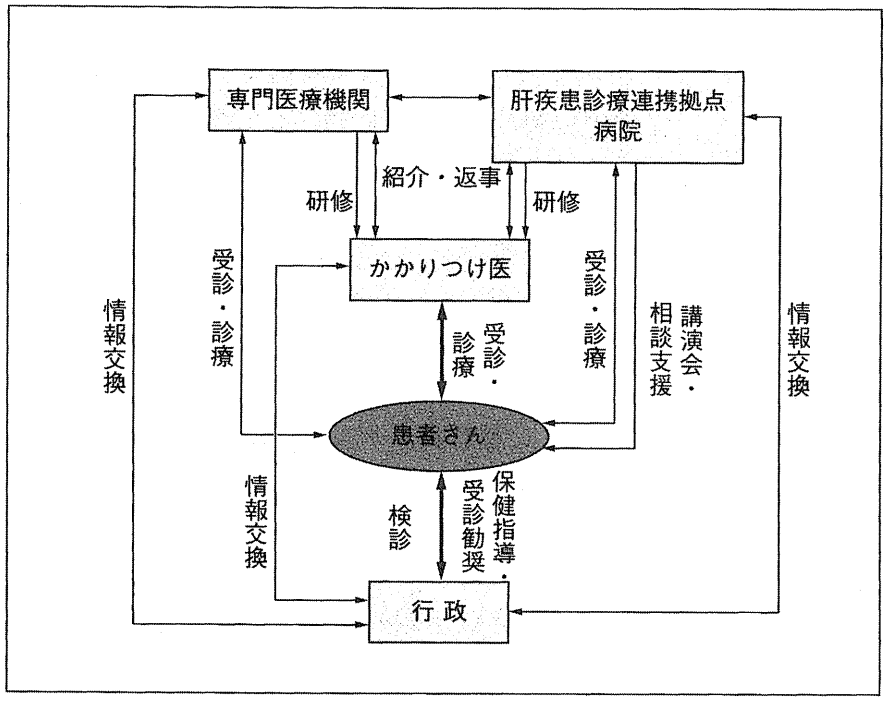


図1 都道府県における肝疾患診療ネットワーク
(都道府県における肝炎検査後肝疾患診療体制に関するガイドライン:2007年1月,厚生労働省)

表2 肝疾患診療連携拠点病院と専門医療機関が満たすべき資格要件

1)肝疾患診療連携拠点病院
① 肝疾患に係る一般的な医療情報の提供
② 都道府県内の専門医療機関などに関する情報の収集や提供
③ 医療従事者や地域住民を対象とした研修会や講演会の開催や肝疾患に関する相談支援
④ 肝疾患に関する専門医療機関と協議の場の設定
2)専門医療機関
① 専門的な知識を持つ医師による診断と治療方針の決定
② インターフェロンなどの抗ウイルス療法
③ 肝癌の高危険群の同定と早期診断

の効果は当初期待されたほどではなかった.さらに,解決されるべき課題として,肝疾患診療体制が全国において必ずしも同等のレベルではないという現状があった.これら諸問題に対処するために,平成19年1月「都道府県における肝炎検査後肝疾患診療体制に関するガイドライン」が厚生労働省により取りまとめられ,各都道府県においてかかりつけ医と患者を支援するネットワークを行政側,医療側含めて構築しようとする施策が打ち出された.「かかりつけ医と患者」は診療の最小単位であるが,かかりつけ医は必ずしも肝疾患診療に精通しているわけではない.これを支援するために,本ガイドラインでは,各都道府県に原則1ヵ所の肝疾患診療連携拠点病院を設置するとともに,二次医療圏ごとに専門医療機関を指定し,さらに行政側も参加するという診療ネットワークの構築を提言した(**図1**).これらの施設指定を受けるために必要とされる資格要件を**表2**に示す.特に,肝疾患診療連携拠点病院の資格要件を満たすためには複数名の専門医(特に肝臓専門医)が常勤する基幹病院であることが必然的に求められる.平成23年4月現在,全国47都道府県に70施設が肝疾患診療連携拠点病院の指定を受けているが

●肝炎情報センターは都道府県における肝疾患診療ネットワークを支援する組織である.
●今後の肝炎総合対策は肝炎対策基本法に基づいて決定される.

(国立国際医療研究センター肝炎情報センターホームページURL：http://www.ncgm.go.jp/center/index.html)，その内訳をみると，国立大学法人が34病院，公立・私立大学が24病院，その他(国立病院機構，県立病院，一般病院など)が12病院となっている．なお，肝疾患患者数が多く広域に分布しているなどの理由で，複数の拠点病院が指定されている自治体もある．さらに，都道府県単位の活動を支援するシステムとして，国立国際医療センター(現，国立国際医療研究センター)に平成20年11月肝炎情報センターが設置された(千葉県市川市)．その果たすべき役割として三つのミッションがある[1]．第一に「インターネットなどによる最新情報提供」であり，平成20年12月には肝疾患医療に関する診療ガイドライン，肝炎診療をめぐる国内外の情報などを「一般向け，医療従事者向け，および，肝臓専門医向け」に発信するためのホームページを立ち上げた．第二に「拠点病院間での情報共有を支援する」ことで，肝疾患診療連携拠点病院で構成する連絡協議会を年に2回開催し，拠点病院事業における問題点の解決を目指した話し合いを行っている．第三に，肝疾患診療連携拠点病院などに勤務する医療従事者(医師，看護師，相談員ほか)を対象とした「研修」の企画・立案・推進を行っている．

肝炎検診の重要性●

平成22年1月に施行された肝炎対策基本法は肝炎対策に関してきわめて包括的な内容となっている．これを具体的施策として実現するために，平成22年6月から5回にわたって患者団体代表者ほか各界の有識者を交えた肝炎対策推進協議会が開催され，その肉づけが図られた．その結果が「肝炎対策の推進に関する基本的な指針[2]」としてまとめられている．その第3には「肝炎検査の実施体制及び検査能力の向上に関する事項」として取り上げられており，① 今後，肝炎ウイルス検査の受検者数把握のための調査・研究が必要であること，② 国民に対して肝炎に関する正しい知識の普及啓発，③ 肝炎検診の効果についての検証，さらに，④ 肝炎医療に携わる者に対して肝炎ウイルス検査に関する知見修得のための研修の機会を確保することなどを求めている．このように肝炎検診の重要性が強調される所以は，「一生に一度」肝炎検診を受けさえすれば肝炎ウイルスキャリアであることが判明し，そのことによって慢性肝炎から肝硬変・肝癌へ進展する患者の囲い込みが可能となるからである．筆者が所属する病院において2001～2006年の6年間に入院した544例の肝硬変患者の成因を調査したところ[3]，B型肝炎9.4%，C型肝炎69.8%，B＋C型肝炎2.6%とウイルス肝炎関連が80%以上を占め，特にC型肝炎関連が70%以上であった．さらに，この期間の肝癌371例の成因では，B型肝炎10.5%，C型肝炎75.5%，B＋C型肝炎3.0%と肝癌の90%は肝炎ウイルス感染が原因で，特にC型肝炎関連が75%を占めていた(**図2**)．したがって，肝疾患関連死を抑制するためには，肝炎ウイルス感染の有無を早期に把握することがきわめて重要であることは容易に理解されよう．

肝炎検診の実際●

肝炎検診を精密検査受診につなげ，さらには根本的な治療である抗ウイルス療法の施行率を上げることにより肝硬変・肝癌への進展を抑制せねばならない．その作業過程において，いかに地道な労力が要求されるものか，行政はもちろん病診連携の関与がいかに重要であるかについて，石川県における具体的事例[4]を紹介したい．

肝炎ウイルス検診が開始された平成14年度か

●わが国における肝硬変，肝癌の成因の80～90%は肝炎ウイルス感染である．
●肝臓専門医数が少なく，かつ，偏在している地域では自治体全体の精検レベルの底上げが必要となる．

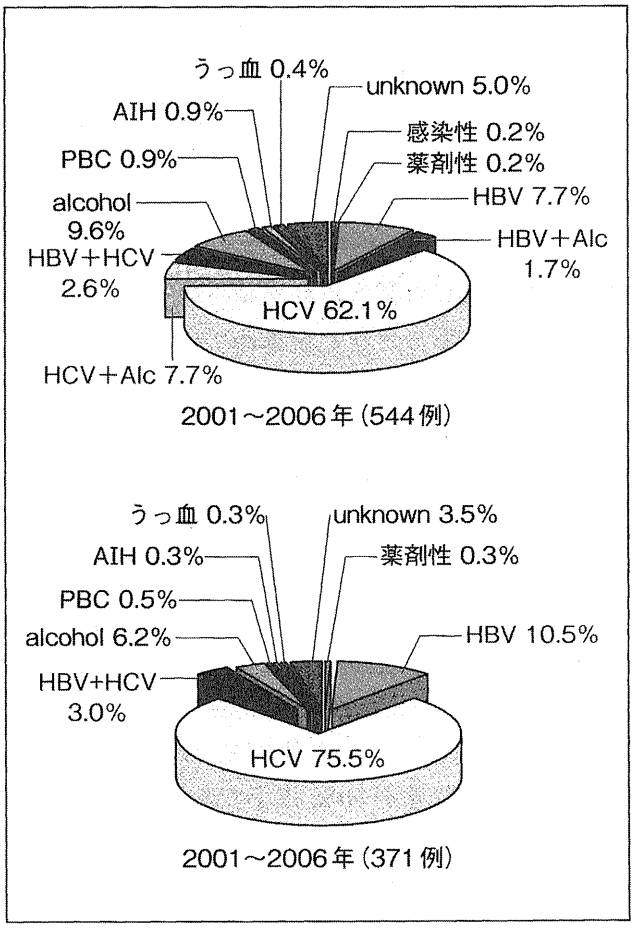


図2　肝硬変（上段）・肝癌（下段）の成因
（国立国際医療研究センター病院；2001～2006年）

表3　石川県肝炎ウイルス検診の7本の柱

1）検診へ行政が関与することの通知と同意
2）精密検査を全県下で統一
3）住民，検診・精密検査担当医に対する手引きの作成
4）精密検査での画像検査を義務づけ
5）全症例に対する事例検討会の開催
6）前年度陽性者に対する保健師による事後調査
7）保健師などを対象とした研修会の開催

（文献4）より引用）

ら石川県では，県健康福祉部，保健所などの行政，検診を担当する医師会，学識経験者，検査センターをメンバーとして肝炎協議会を設置し，肝炎診療体制の確立に取り組んできた．石川県では消化器肝臓専門医が常勤する総合病院が都市部に集中しているため，精密検査受診率の低下が予想された．これを回避するために，精密検査を行う医療機関を敢えて指定せずに，県全体の精検レベルの底上げをするという画期的な方針をとった．具体的な7本の柱を**表3**に示す．初年度には画像検査未施行例11%，「追跡調査の必要なし」との診断例が4%存在したが，① 診断名の改訂（「異常なし」を「無症候性キャリア」へ変更），② 1例ごとの事例検討会において画像検査の重要性を強調，③ 診断の手引きの作成などにより著明な改善を認めたという．特に，事例検討会については，その後石川県の肝疾患診療連携拠点病院に指定されている金沢大学医学部附属病院消化器内科スタッフの精力的な取り組みの賜物であると聞いている．その結果，インターフェロン施行率は平成14年度から18年度の5年間で4.6%→7.9%→23.5%→35.3%→31.0%と有意に上昇したことが報告されている．しかし，精検受診率が南加賀地方で低いこと，さらに，全地域において男性，特に65歳未満で低いことが問題点として指摘されている（**図3**）．このような疫学的解析を行うことによってはじめて，受診勧奨を推進すべき対象が明らかとなると同時に，行政に対する施策提言が可能になるものと考えられる．

おわりに●

平成23年度政府予算では肝炎総合対策に238億円が割り当てられており，うち，肝炎ウイルス検査の促進分が55億円と前年度に比し倍増している．特定感染症検査等事業として，保健所における肝炎ウイルス検査の受診勧奨と検査体制の整備が図られるが，特に，出張型検診の実施に1億円が計上されている点は新たな試みとして注目に値する．さらに健康増進事業として，市町村にお

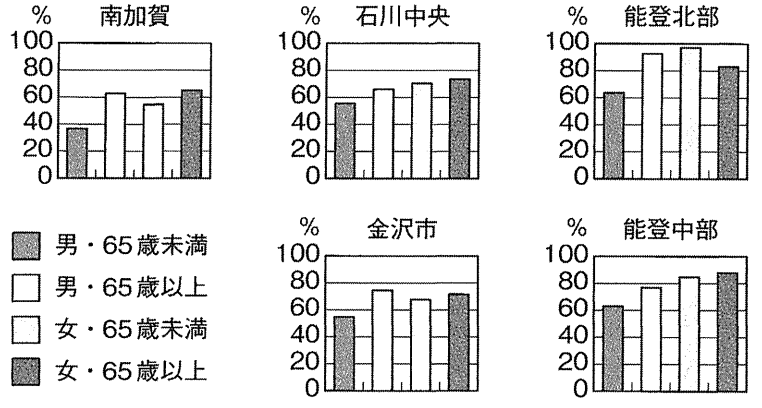
●IFN治療を効率的に推進するためには，地域ごとの特性を考慮した肝炎対策の立案と運用が必要である．

●ウイルス肝炎検診の推進には肝疾患診療ネットワークの活用が有効である．

図3　石川県肝炎ウイルス検診における精密検査受診状況(平成14～18年度分)
金沢大学附属病院消化器内科　酒井明人先生のご厚意による
(文献4)より引用)

精検受診率

	65歳未満	65歳以上	計(性別)
男性	70/131 (53.4%)	216/292 (74.0%)	286/423 (67.6%)
女性	205/285 (71.9%)	418/557 (75.0%)	623/842 (74.0%)
計	275/416 (66.1%)	634/849 (74.7%)	909/1,265 (72.0%)



ける肝炎ウイルス検診等(節目検診)の実施に32.3億円が計上されており，検査未受検者への受検促進の一層の強化が図られるものと期待される．これらの施策をわが国全体に浸透させるためには，これまで構築されてきた肝疾患診療ネットワークが有効に活用されるべきである．

文　献

1) 正木尚彦：肝炎情報センターの役割．特集　肝疾患の地域医療連携．肝胆膵 **61** (5)：721-729, 2010
2) 肝炎対策の推進に関する基本的な指針．http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/hourei.html
3) 長沖祐子ほか：肝硬変の予後に関する実態調査—1990～1997年と2001～2006年との比較—．肝硬変の成因別実態2008，恩地森一ほか編，中外医学社，東京，p.116-120，2008
4) 酒井明人ほか：石川県の取り組み．特集　肝疾患の地域医療連携．肝胆膵 **61** (5)：753-761，2010

Association of Gene Expression Involving Innate Immunity and Genetic Variation in Interleukin 28B With Antiviral Response

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Innate immunity plays an important role in host antiviral response to hepatitis C viral (HCV) infection. Recently, single nucleotide polymorphisms (SNPs) of *IL28B* and host response to peginterferon α (PEG-IFNα) and ribavirin (RBV) were shown to be strongly associated. We aimed to determine the gene expression involving innate immunity in *IL28B* genotypes and elucidate its relation to response to antiviral treatment. We genotyped *IL28B* SNPs (rs8099917 and rs12979860) in 88 chronic hepatitis C patients treated with PEG-IFNα-2b/RBV and quantified expressions of viral sensors (*RIG-I, MDA5*, and *LGP2*), adaptor molecule (*IPS-1*), related ubiquitin E3-ligase (*RNF125*), modulators (*ISG15* and *USP18*), and *IL28* (*IFNλ*). Both *IL28B* SNPs were 100% identical; 54 patients possessed rs8099917 TT/rs12979860 CC (*IL28B* major patients) and 34 possessed rs8099917 TG/rs12979860 CT (*IL28B* minor patients). Hepatic expressions of viral sensors and modulators in *IL28B* minor patients were significantly up-regulated compared with that in *IL28B* major patients (≈3.3-fold, $P < 0.001$). However, expression of *IPS-1* was significantly lower in *IL28B* minor patients (1.2-fold, $P = 0.028$). Expressions of viral sensors and modulators were significantly higher in nonvirological responders (NVR) than that in others despite stratification by *IL28B* genotype (≈2.6-fold, $P < 0.001$). Multivariate and ROC analyses indicated that higher *RIG-I* and *ISG15* expressions and *RIG-I/IPS-1* expression ratio were independent factors for NVR. IPS-1 down-regulation in *IL28B* minor patients was confirmed by western blotting, and the extent of IPS-1 protein cleavage was associated with the variable treatment response. *Conclusion:* Gene expression involving innate immunity is strongly associated with *IL28B* genotype and response to PEG-IFNα/RBV. Both *IL28B* minor allele and higher *RIG-I* and *ISG15* expressions and *RIG-I/IPS-1* ratio are independent factors for NVR. (HEPATOLOGY 2012;55:20-29)

Infection with hepatitis C virus (HCV) is a common cause of chronic hepatitis, which progresses to liver cirrhosis and hepatocellular carcinoma in many patients.[1] Pegylated interferon α (PEG-IFNα) and ribavirin (RBV) combination therapy has been used to treat chronic hepatitis C (CH-C) to alter the natural course of this disease. However, 20% patients are nonvirological responders (NVR) whose HCV-RNA does not become negative during the 48 weeks of PEG-IFNα/RBV combination therapy.[2] In a recent genome-wide association study, single nucleotide polymorphisms (SNPs) located near interleukin 28B

Abbreviations: CH-C, chronic hepatitis C; γ-GTP, γ-glutamyl transpeptidase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HCV, hepatitis C virus; HMBS, hydroxymethylbilane synthase; IL28, interleukin 28; IPS-1, IFNβ promoter stimulator 1; ISG15, interferon-stimulated gene 15; MDA5, melanoma differentiation associated gene 5; NVR, nonvirological responders; PEG-IFNα, pegylated interferonα; SNP, single nucleotide polymorphism; RIG-I, retinoic acid-inducible gene I; RBV, ribavirin; RNF125, ring-finger protein 125; ROC, receiver operator characteristic; SVR, sustained viral responder; TVR, transient virological responder; USP18, ubiquitin-specific protease 18; VR, virological responder.

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(*IL28B*) that encodes for type III IFNλ3 were shown to be strongly associated with a virological response to PEG-IFNα/RBV combination therapy.[3-5] In particular, the rs8099917 TG and GG genotypes were shown to be strongly associated with a null virological response to PEG-IFNα/RBV.[3] However, mechanisms involving resistance to PEG-IFNα/RBV have not been completely elucidated.

The innate immune system has an essential role in host antiviral defense against HCV infection.[6] The retinoic acid-inducible gene I (RIG-I), a cytoplasmic RNA helicase, and related melanoma differentiation associated gene 5 (MDA5) play essential roles in initiating the host antiviral response by detecting intracellular viral RNA.[7,8] The IFNβ promoter stimulator 1 (IPS-1)—also called the caspase-recruiting domain adaptor inducing IFNβ, mitochondrial antiviral signaling protein, or virus-induced signaling adaptor—is an adaptor molecule. IPS-1 connects RIG-I sensing to downstream signaling, resulting in *IFNβ* gene activation.[9-12] RIG-I sensing of incoming viral RNA has been shown to be modified by LGP2,[8,13] a helicase related to RIG-I and MDA5 lacking caspase-recruiting domain. The ubiquitin ligase ring-finger protein 125 (RNF125) has been shown to conjugate ubiquitin to RIG-I, MDA5, and IPS-1 and this suppresses the functions of these proteins.[14] Further, these molecules are ISGylated by the IFN-stimulated gene 15 (ISG15), a ubiquitin-like protein,[15] and ISG15 is specifically removed from ISGylated protein by ubiquitin-specific protease 18 (USP18) to regulate the RIG-I/IPS-1 system.[16,17] Moreover, the NS3/4A protease of HCV specifically cleaves IPS-1 as part of its immune-evasion strategy.[9,18] Therefore, the RIG-I/IPS-1 system and its regulatory systems have essential roles in the innate antiviral response.

Recently, we demonstrated that baseline intrahepatic gene expression levels of the RIG-I/IPS-1 system were prognostic biomarkers of the final virological outcome in CH-C patients who were treated with PEG-IFNα/RBV combination therapy.[19] We found that up-regulation of *RIG-I* and *ISG15* and a higher expression ratio of *RIG-I/IPS-1* could predict NVR for subsequent treatment with PEG-IFNα/RBV combination therapy.[19] However, association of gene expression involving innate immunity and genetic variation of *IL28B* has not yet been elucidated. Hence, the aim of this study was to determine gene expression involving the innate immune system in different genetic variations of *IL28B* and elucidate the relation of gene expression to final virological outcome of PEG-IFNα/RBV combination therapy in CH-C patients.

Patients and Methods

Patients. Among histologically proven CH-C patients admitted at the Musashino Red Cross Hospital, 88 patients with HCV genotype 1b and a high viral load (>5 log IU/mL by TaqMan HCV assay; Roche Molecular Diagnostics, Tokyo, Japan) were included in the present study (Table 1). Patients with decompensated liver cirrhosis, autoimmune hepatitis, or alcoholic liver injury were excluded. No patient had tested positive for hepatitis B surface antigen or anti-human immunodeficiency virus antibody or had received immunomodulatory therapy before enrollment. Forty-two patients had been enrolled in a previous study that determined hepatic gene expression involving innate immunity.[19] Written informed consent was obtained from all patients and the study was approved by the Ethical Committee of Musashino Red Cross Hospital in accordance with the Declaration of Helsinki.

Treatment Protocol. The patients were administered subcutaneous injections of PEG-IFNα-2b (PegIntron, MSD, Whitehouse Station, NJ) at a dose of 1.5 $\mu g\ kg^{-1}\ week^{-1}$ for 48 weeks. RBV (Rebetol, MSD) was administered concomitantly over this treatment period, administered orally twice daily at 600 mg/day for patients who weighed less than 60 kg and 800 mg/day for patients who weighed between 60-80 kg. The dose of PEG-IFNα-2b was reduced to 0.75 $\mu g\ kg^{-1}\ week^{-1}$ when either neutrophil count was less than $750/mm^3$ or platelet count was less than $80 \times 10^3/mm^3$. The dose of RBV was reduced to 600 mg/day when the hemoglobin concentration decreased to 10 g/dL. More than 80% adherence was achieved in all patients.

Measurement of Hepatic Gene Expression. Liver biopsy was performed immediately before initiating

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Potential conflict of interest: Nothing to report.

Additional Supporting Information may be found in the online version of this article.

Table 1. Patient Characteristics and *IL28B* Genotype

	IL28B Major*	*IL28B* Minor†	*P*-value‡
Patients, n	54	34	
Age (SD), year	58.8 (10.0)	59.1 (10.3)	0.918§
Sex, n (%)			0.051‖
Male	13 (24.1)	15 (44.1)	
Female	41 (75.9)	19 (55.9)	
BMI (SD), kg/m^2	22.7 (3.5)	23.5 (3.6)	0.193§
ALT (SD), IU/L	61.3 (50.7)	62.4 (44.7)	0.962§
γ-GTP (SD), IU/L	36.7 (25.9)	57.3 (52.4)	0.010§
LDL-cholesterol (SD), mg/dL	103.3 (29.8)	91.8 (26.9)	0.067§
Hemoglobin (SD), g/dL	14.1 (1.4)	14.4 (1.3)	0.186§
Platelet count (SD), ×10^{3}3/μL	161 (6.4)	163 (4.4)	0.489§
Fibrosis stage, n (%)			0.532‖
F1, 2	38 (70.4)	26 (76.5)	
F3, 4	16 (29.6)	8 (23.5)	
Viral load (SD), ×10^{63} IU/mL	1.7 (1.4)	1.9 (2.0)	0.788§
%HCV core 70 & 91 a.a. double mutation¶	8.9	43.5	0.001‖
%ISDR wild**	43.5	51.7	0.486‖
Viral response, n (%)			<0.001‖
SVR	17 (31.5)	13 (38.2)	
TVR	26 (48.1)	3 (8.8)	
NVR	11 (20.4)	18 (52.9)	

Unless otherwise indicated, data are given as mean (SD).

*rs8099917 TT and rs12979860 CC.

†rs8099917 TG and rs12979860 CT.

BMI, body mass index; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDL-C, low-density lipoprotein cholesterol; HCV, hepatitis C virus; ISDR, interferon sensitivity determining region; SVR, sustained virological response; TVR, transient virological response; NVR, nonvirological response.

‡Comparison between *IL28B* major and minor genotypes.

§Mann-Whitney *U* test.

‖Chi-square test.

¶HCV core mutation was determined in 68 patients.

**ISDR was determined in 75 patients.

the therapy. After extraction of total RNA from liver biopsy specimens, the messenger RNA (mRNA) expression of the positive and negative cytoplasmic viral sensor (*RIG-I, MDA5*, and *LGP2*), the adaptor molecule (*IPS-1*), the related ubiquitin E3-ligase (*RNF125*), the modulators of these molecules (*ISG15* and *USP18*), and *IFNλ* (*IL28A/B*) was quantified by real-time quantitative polymerase chain reaction (PCR) using target gene-specific primers. In brief, total RNA was extracted by the acid-guanidinium-phenol-chloroform method using Isogen reagent (Nippon Gene, Toyama, Japan) from the liver biopsy specimen, which was 0.2-0.4 cm in length and 13G in diameter. Complementary DNA (cDNA) was transcribed from 2 μg of total RNA template in a 140-μL reaction mixture using the SYBR RT-PCR Kit (Takara Bio, Otsu, Japan) with random hexamer. Real-time quantitative PCR was performed using Smart Cycler version II (Takara Bio) with the SYBR RT-PCR Kit (Takara Bio) according to the manufacturer's instructions. Assays were performed in duplicate and the expression levels of target genes were normalized to the expressions of glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) gene and hydroxymethylbilane synthase (*HMBS*), an enzyme that is stable in the liver, as quantified using real-time quantitative PCR as internal controls. For accurate normalization, a set of two housekeeping genes was used in the present study. Sequences of the primer sets were as follows: *RIG-I*, 5′-AAAGCATGCA TGGTGTTCCAGA-3′, 5′-TCATTCGTGCATGCTC ACTGATAA-3′; *MDA5*, 5′-ACATAACAGCAACATG GGCAGTG-3′, 5′-TTTGGTAAGGCCTGAGCTGG AG-3′; *LGP2*, 5′-ACAGCCTTGCAAACAGTACAAC CTC-3′, 5′-GTCCCAAATTTCCGGCTCAAC-3′; *IPS-1*, 5′-GGTGCCATCCAAAGTGCCTACTA-3′, 5′-CAGC ACGCCAGGCTTACTCA-3′; *RNF125*, 5′-AGGGCA CATATTCGGACTTGTCA-3′, 5′-CGGGTATTAAAC GGCAAAGTGG-3′; *ISG15*, 5′-AGCGAACTCATCT TTGCCAGTACA-3′, 5′-CAGCTCTGACACCGACA TGGA-3′; *USP18*, 5′-TGGTTCTGCTTCAATGACT CCAATA-3′, 5′-TTTGGGCATTTCCATTAGCACT C-3′; *IFNλ*: 5′-CAGCTGCAGGTGAGGGA-3′, 5′-G GTGGCCTCCAGAACCTT-3′; *GAPDH*, 5′-GCACC GTCAAGGCTGAGAAC-3′, 5′-ATGGTGGTGAAGA CGCCAGT-3′; *HMBS*, 5′-AAGCGGAGCCATGTCT GGTAAC-3′, 5′-GTACCCACGCGAATCACTCTCA-3′.

Genotyping for* IL28B *(rs8099917 and rs12979860) Polymorphism. Genetic polymorphism in a tagged SNP located near the *IL28B* gene (rs8099917 and rs12979860) was determined by direct sequencing of PCR-amplified DNA. In brief, after extraction from whole blood samples, genomic DNA was amplified by PCR. Sequences of the primer sets were: rs8099917, 5′-ATCCTCCTCTCATCCCTCA TC-3′, 5′-GGTATCAACCCCACCTCAAAT-3′; rs129 79860, 5′-GGACGAGAGGGCGTTAGAG-3′, 5′-AG GGACCGCTACGTAAGTCAC-3′.

Both strands of the PCR products were sequenced by the dye terminator method using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Chiba, Japan); nucleotide sequences were determined by a capillary DNA sequencer ABI3730xl (Applied Biosystems). Homozygosity (rs8099917 GG and rs12979860 TT) or heterozygosity (rs8099917 TG and rs12979860 CT) of the minor sequence was defined as having the *IL28B* minor allele, whereas homozygosity for the major sequence (rs8099917 TT and rs12979860 CC) was defined as having the *IL28B* major allele.

Western Blotting. Western blotting was performed using samples from 14 patients (six from *IL28B* major patients and eight from *IL28B* minor patients) as described.[19] In brief, liver biopsy specimens of

approximately 10 mg were homogenized in 100 μL of Complete Lysis-M (Roche Applied Science, Penzberg, Germany). Next, 30 μg of protein was separated by NuPAGE 4%-12% Bis-Tris gels (Invitrogen, Carlsbad, CA) and blotted on polyvinylidene difluoride membranes. The membranes were immunoblotted with anti-RIG-I (Cell Signaling Technology, Danvers, MA) or anti-IPS-1 (Enzo Life Science, Farmingdale, NY), followed by anti-β-actin (Sigma Aldrich, St. Louis, MO). After immunoblotting with horseradish peroxidase-conjugated secondary antibody, signals were detected by chemiluminescence (BM Chemiluminescence Blotting Substrate, Roche Applied Science, Mannheim, Germany). Optical densitometry was performed using ImageJ software (NIH, Bethesda, MD). Naive Huh7 cells were used for a positive control for full-length IPS-1, and cells transfected with HCV-1b subgenomic replicon[20] were used for a positive control for cleaved IPS-1.

Definitions of Response to Therapy. A patient negative for serum HCV-RNA during the first 6 months after completing PEG-IFNα-2b/RBV combination therapy was defined as a sustained viral responder (SVR), and a patient for whom HCV-RNA became negative at the end of therapy and reappeared after completion of therapy was defined as a transient virological responder (TVR). A patient for whom HCV-RNA became negative at the end of therapy (SVR + TVR) was defined as a virological responder (VR). A patient whose HCV-RNA did not become negative during the course of therapy was defined as an NVR. HCV-RNA was determined by TaqMan HCV assay (Roche Molecular Diagnostics).

Statistical Analysis. Categorical data were compared using the chi-square test and Fisher's exact test. Distributions of continuous variables were analyzed by the Mann-Whitney *U* test for two groups. All tests of significance were two-tailed and $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics and* IL28B *Genotype. Table 1 shows patient characteristics according to *IL28B* genotype. SNPs at rs8099917 and rs12979860 were 100% identical; 54 patients were identified as having the major alleles (rs8099917 TT/rs12979860 CC; *IL28B* major patients) and the remaining 34 had the minor alleles (rs8099917 TG/rs12979860 CT; *IL28B* minor patients). Patients having a minor homozygote (rs8099917 GG or rs12979860 TT) were not found in this study, which is consistent with a recent report of the rarity of a minor homozygote in Japanese patients.[3] *IL28B* minor patients were significantly associated with a higher γ-glutamyl transpeptidase (γ-GTP) level and higher frequency of mutations at amino acid positions 70 and 91 of the HCV core region (glutamine or histidine mutation at amino acid position 70; methionine mutation at amino acid position 91). NVR rate was significantly higher in *IL28B* minor patients than in *IL28B* major patients.

Gene Expression Involving Innate Immunity and* IFNλ *in the Liver. Hepatic expression levels of cytoplasmic viral sensors (*RIG-I, MDA5*, and *LGP2*) were significantly higher in *IL28B* minor patients than in *IL28B* major patients (Fig. 1). Similarly, expressions of *ISG15* and *USP18* were significantly higher in *IL28B* minor patients than in *IL28B* major patients (Fig. 1). In contrast, the hepatic expression of the adaptor molecule (*IPS-1*) was significantly lower in *IL28B* minor patients than that in *IL28B* major patients (Fig. 1). Hepatic expression of *RNF125* was similar among *IL28B* genotypes (Fig. 1). *IFNλ (IL28A/B)* expression was higher in *IL28B* minor patients, but not statistically significant (Fig. 1). Because expression of *RIG-I* and *IPS-1* were negatively correlated, the expression ratio of *RIG-I/IPS-1* in *IL28B* minor patients was significantly higher than in *IL28B* major patients (Fig. 1).

Next, to assess the relationship between baseline hepatic gene expression and treatment efficacy, we compared levels of gene expression involving innate immunity and *IFNλ* based on the final virological response (Fig. 2). Overall, hepatic expressions of cytoplasmic viral sensors and the ISG15/USP18 system in NVR patients were significantly higher than those in VR patients. In a similar but opposite manner, hepatic expressions of *IPS-1* and *RNF125* in NVR patients were significantly lower than that in VR patients, and the expression of *IFNδ* was higher in NVR patients, but the differences were not statistically significant. Expression ratio of *RIG-I/IPS-1* was significantly higher in NVR patients than that in VR patients.

Because hepatic expressions of the RIG-I/IPS-1 and ISG15/USP18 systems were significantly related both to *IL28B* minor and NVR patients, *RIG-I* and *ISG15* expression levels and the *RIG-I/IPS-1* ratio between VR and NVR patients were further stratified by *IL28B* genotype (Fig. 3). Even in the subgroup of *IL28B* minor patients, the expressions of *RIG-I* and *ISG15* were significantly higher in NVR patients than those in VR patients. Similar tendencies were observed in a subgroup of *IL28B* major patients, in whom the *RIG-I/IPS-1* expression ratio was significantly higher in

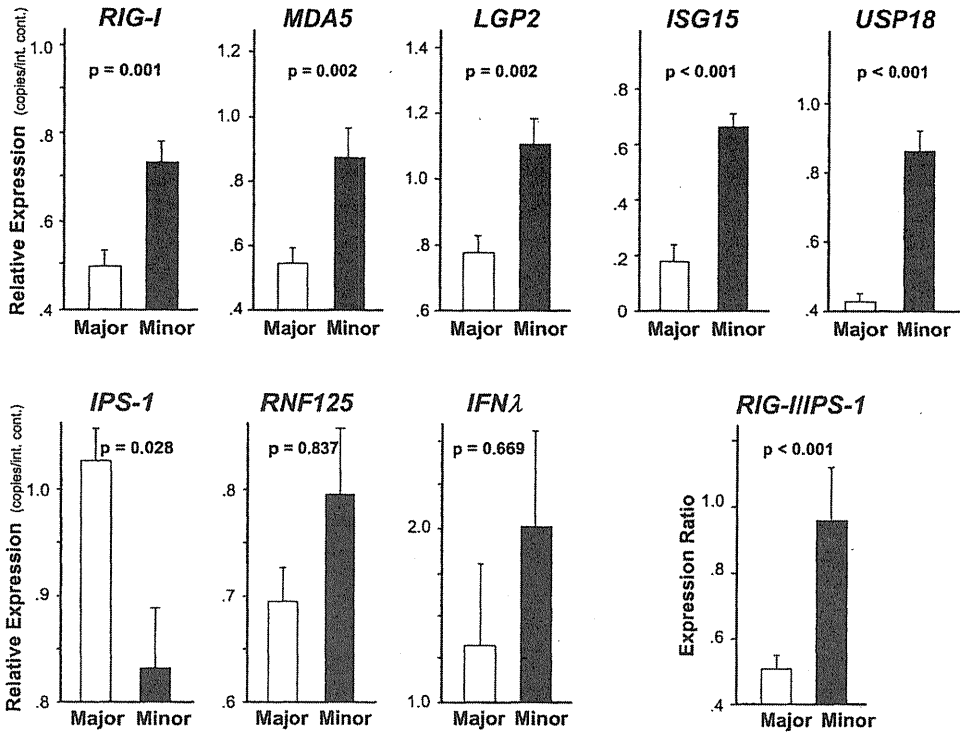

Fig. 1. Comparison of hepatic gene expression levels between *IL28B* major (rs8099917 TT/rs12979860 CC, n = 54) and *IL28B* minor patients (rs8099917 TG/rs12979860 CT, n = 34). Expression levels of cytoplasmic viral sensors (*RIG-I*, *MDA5*, and *LGP2*), modulators (*ISG15* and *USP18*), an adaptor (*IPS-1*), negative regulators (*RNF125*) and *IFNλ*, and expression ratio of the *RIG-I/IPS-1* are shown. Error bars indicate standard error. The *P*-values were determined by the Mann-Whitney *U* test.

NVR patients than in VR patients. However, in patients of the same virological response subgroup, *RIG-I* and *ISG15* expression levels and *RIG-I/IPS-1* ratio were higher in *IL28B* minor patients, and the difference in *ISG15* expression in subgroup of VR and NVR patients and that in *RIG-I/IPS-1* ratio in subgroup of VR patients was statistically significant between *IL28B* genotypes (Fig. 3).

Receiver Operator Characteristic (ROC) Analysis. To determine the usefulness of these gene quantifications and *IL28B* genotyping as predictors of NVR, an ROC analysis was conducted (Fig. 4A). The area under the ROC curve for *RIG-I* and *ISG15* expressions and *RIG-I/IPS-1* expression ratio was 0.712, 0.782, and 0.732, respectively, suggesting that quantification of these gene transcripts is useful for

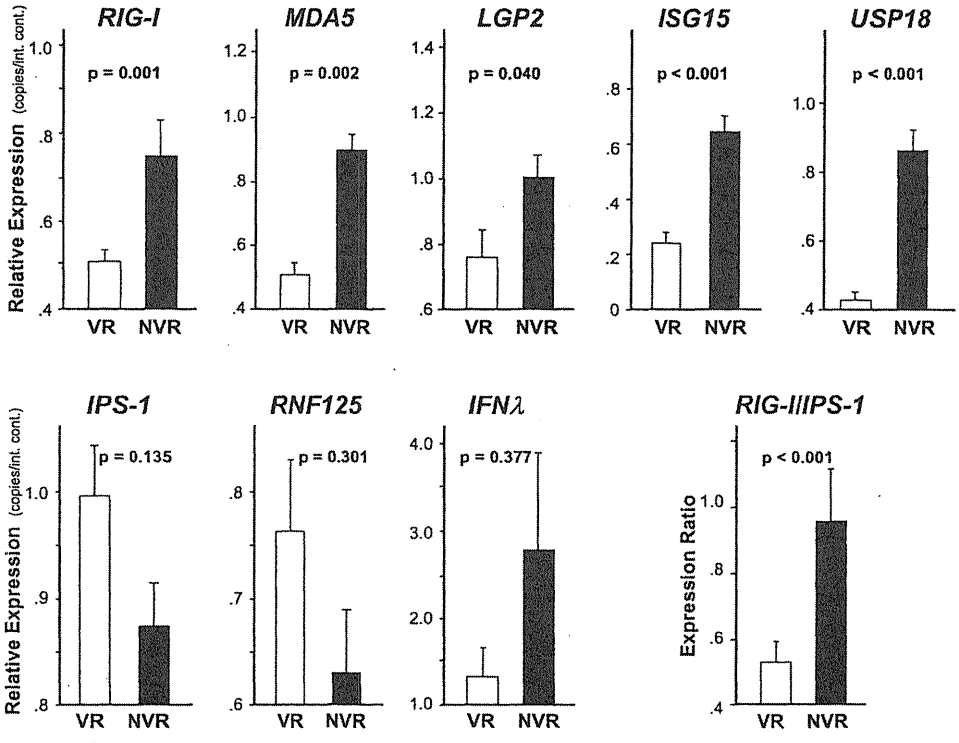

Fig. 2. Comparison of hepatic gene expression levels between virological responders (VR, n = 60) and nonvirological responders (NVR, n = 28). Expression levels of cytoplasmic viral sensors (*RIG-I*, *MDA5*, and *LGP2*), modulators (*ISG15* and *USP18*), an adaptor (*IPS-1*), negative regulators (*RNF125*) and *IFNλ*, and *RIG-I/IPS-1* expression ratio are shown. Error bars indicate standard error. The *P*-values were determined by the Mann-Whitney *U* test.