Hepatitis C

The different impact of factors contributing to hepatitis C progression

Francesco Negro
University Hospitals of Geneva (Switzerland)
Lausanne – 9 octobre 2014

Natural history of hepatitis C

- From acute to persistent infection
- From no fibrosis to cirrhosis
- Development of hepatocellular carcinoma

Natural history of hepatitis C

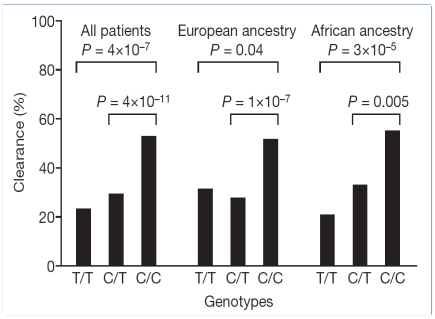
- From acute to persistent infection
- From no fibrosis to cirrhosis
- Development of hepatocellular carcinoma

Factors associated with spontaneous HCV clearance

Factor	Reference
Female sex	Bakr et al, 2006; Rao et al, 2012
Older age at infection	Vogt et al, 1999; Rerksuppaphol et al, 2004
Symptomatic hepatitis	Micallef et al, 2006
High initial viral load, rapid HVR1 sequence evolution	Liu et al, 2012
Strong antiviral T cell responses	Rehermann, 2009
Strong NK cell responses	Alter et al, 2011; Stegmann et al, 2012
Lack of coinfection with HIV	Thomson et al, 2011
KIR2DL3, HLA-C1	Khakoo et al, 2004
IFNL3	Thomas et al, 2009; Rauch et al, 2010; Tillmann et al, 2010
ApoH	Laird et al, 2014

Overall, 54-86% of adults progress to persistent HCV infection

Percentage of HCV clearance by *rs12979860* genotype near *IFNL3*



THOMAS *et al*, Nature 2009;461:798-801

Switzerland

71 reported cases py (2002-2011)
Estimated 284-355 acute HCV infections py
(incidence rate of 3.5-4.4/1000 py)[1,2]

Egypt

Estimated 100,000-500,000 acute HCV infections py
(incidence rate of 1.3-7/1000 py)[3-6]

[1]http://www.bag.admin.ch/dokumentation/publikationen
[2]FRETZ *et al*, Swiss Med Weekly 2013;143:w13793
[3]Ministry of Health and Population, Arab Republic of Egypt 2008
[4]LEHMAN & WILSON, J Viral Hepatitis 2009;16:650–8
[5]MILLER & ABU-RADDAD, Proc Natl Acad Sci U S A 2010;107:14757–62
[6]BREBAN *et al*, J Viral Hepatitis 2013;20:294-6

Natural history of hepatitis C

- From acute to persistent infection
- **From no fibrosis to cirrhosis**
- Development of hepatocellular carcinoma

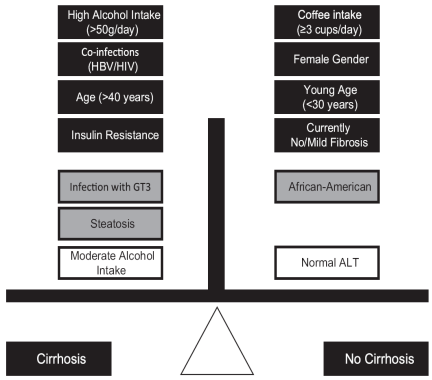
The natural history of hepatitis C is variable

Study	Design	n	Cirrhosis development	Comments
Poynard et al, 1997	Retrospective	2235	Est. 33% in 20 years	Est. 31% without cirrhosis in 50 yrs
Hissar et al, 2009	Retrospective	213	21% in 12.1 ± 8.9 years	75% HCV-3
Tong et al, 1995	Retrospective/ Prospective	131	56% cirrhosis, mean interval to cirrhosis 20.6 years	15% mortality (mean FU 3.9 yrs)
De Ledinghen et al, 2007	Retrospective/ Prospective	196 (131 with fibrosis evaluation)	6.9% cirrhosis, 21.4 ± 6.9 years from infection	92% females, all nosocomial
Kenny-Walsh, 1999	Retrospective	371 (363 with liver biopsy)	2% in 17 years	Females, mean 28-yr old at infection
Wiese et al, 2000, 2005 and 2013	Prospective	500	0.8% in 20 years; 2% in 25 years 9.3% in 35 years	Females, 16-38 yrs at infection

Adapted from MAASOUMY & WEDEMEYER, Best Pract Res Clin Gastroenterol 2012;26:401-12

Factors accelerating fibrosis progression in hepatitis C

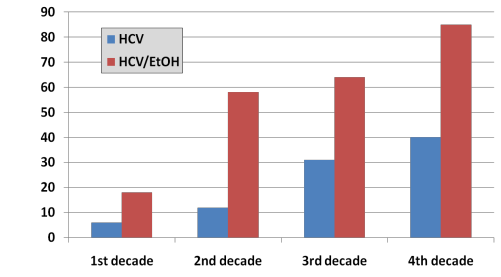
Cofactor	Reference
Histological activity	Leandro et al, 2006
Sex	Poynard et al, 1997; Kenny-Walsh, 1999; Wiese et al, 2000
Steatosis	Hourigan et al, 1998; Leandro et al, 2006
Older age at infection	Poynard et al, 1997; Vogt et al, 1999; Jara et al, 2003
Insulin resistance / T2D	Hui et al, 2003; Muzzi et al, 2005
Excess alcohol drinking	Poynard et al, 1997; Wiley et al, 1998; Hézode et al, 2003
Coinfection with HIV	Thein et al, 2008; Deng et al, 2009
Iron overload	Bonkowski et al, 2002
Tobacco / cannabis smoking	Pessione et al, 2001; Dev et al, 2006; Hézode et al 2005
HCV genotype 3	Bochud et al, 2009
PNPLA3	Valenti et al, 2001; Trépo et al, 2011; Patin et al, 2012
MHC region	Urabe et al, 2013
MERTK, TULP1, RNF7	Patin et al, 2012



MAASOUMY & WEDEMEYER, Best Pract Res Clin Gastroenterol 2012;26:401-12

Prevalence of cirrhosis in chronic hepatitis C with (n=90) or without (n=86) excess alcohol drinking*

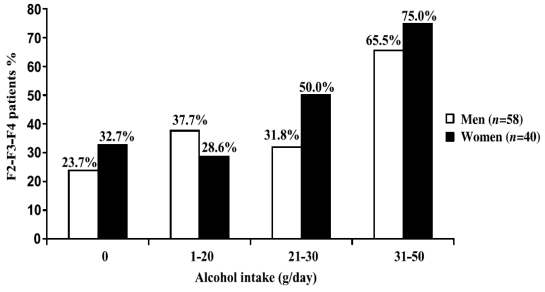
A retrospective study



*>40 g/day in women, and >60 g/day in men for >5 years

WILEY *et al*, Hepatology 1998;28:805-809

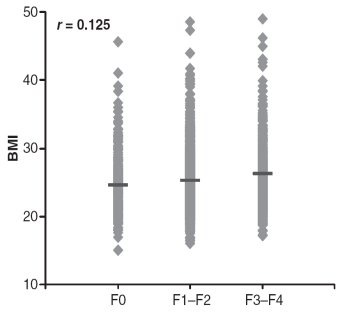
Relationship between Metavir fibrosis score and alcohol intake, by sex (n=98)



HEZODE *et al*, Aliment Pharmacol Ther 2003;17:1031-1037

BMI and fibrosis in chronic hepatitis C

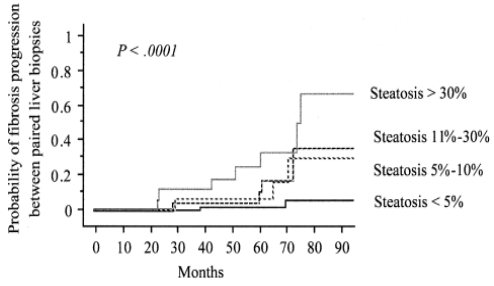
The HCV MAID Study (n = 3,068)



NEGRO & CLEMENT, *J Viral Hepat* 2009;16:681-8

Steatosis severity predicts liver fibrosis progression in chronic hepatitis C

Retrospective study on serial liver biopsies (n=135, median FU 61 mo [18-158])



FARTOUX et al, *Hepatology* 2005;41:82-87

Factors associated with severe fibrosis (stages 3-4) in chronic hepatitis C and NAFLD

HCV-3 (n=132) matched to NAFLD for age, BMI and steatosis severity (alcohol drinkers excluded)

	OR (95% CI)	P
HCV-3		
HOMA-IR	2.98 (1.13 – 7.89)	0.028
Platelet count	0.78 (0.67 – 0.92)	0.003
NAFLD		
HOMA-IR	1.16 (1.02 – 1.31)	0.021
Ferritin	1.13 (1.03 – 1.25)	0.013
Steatosis severity	3.03 (1.41 – 6.53)	0.004

BUGIANESI *et al*, Hepatology 2006;44:1648-55

Fibrogenesis in chronic hepatitis C: role of insulin resistance

- Insulin resistance/diabetes are associated with severity of fibrosis in chronic hepatitis C

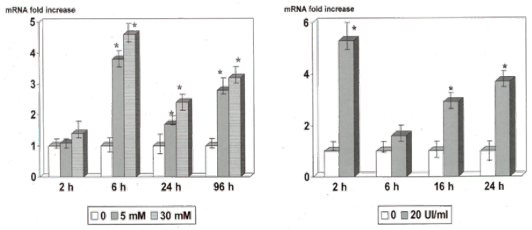
RATZIU *et al*, 2003; FARTOUX *et al*, 2005; MUZZI *et al*, 2005
LEANDRO *et al*, 2006; BUGIANESI *et al*, 2006
SVEGLIATI-BARONI *et al*, 2007

- HOMA-IR in 121 chronic hepatitis C patients with F0-F1 was higher than in 137 healthy volunteers matched for sex, BMI and waist-to-hip ratio
- By MV, the HOMA-IR score (but not steatosis) was a factor independently associated with fibrosis score (P<0.001) and progression rate (P=0.03)

HUI *et al*, Gastroenterology 2003

Insulin is Pro-Fibrogenic

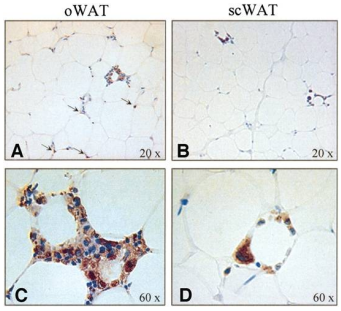
Insulin and glucose stimulate production of CTGF in hepatic stellate cells



Glucose **Insulin**

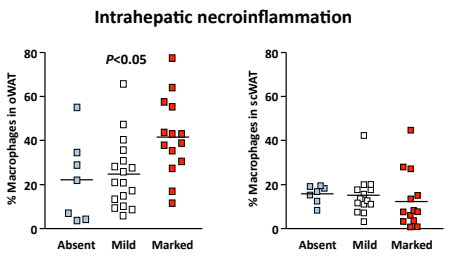
PARADIS *et al*, Hepatology 2001;34:738-744

Obese patients have significant macrophage infiltration of omental (oWAT) but not subcutaneous (scWAT) adipose tissue



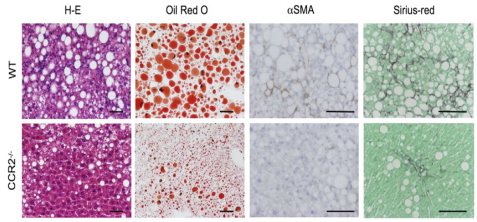
CANCELLO *et al*, Diabetes 2006;55:1554-1561

Omental macrophages are associated with liver necroinflammation



CANCELLO *et al,* Diabetes 2006;55:1554-1561

Steatosis and fibrosis are attenuated in CCR2$^{-/-}$ mice fed a choline deficient diet

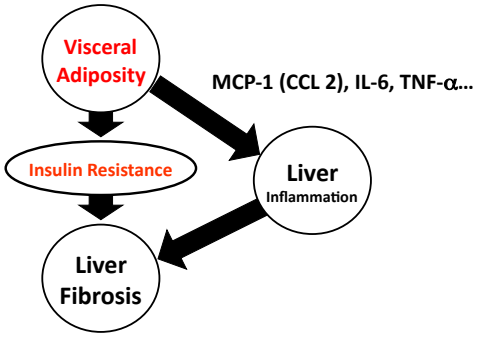


MIURA et al, *Am J Physiol* 2012;302:G1310-21

CCL2 predicts rapid fibrosis progression in HCV

FARCI et al, *Proc Natl Acad Sci USA* 2012;109:14562-7

Metabolic syndrome and liver fibrosis



Menopause and liver fibrosis progression

A prospective study (n=251)

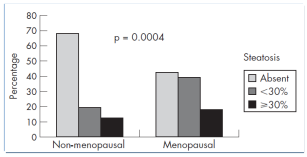


Table 3 Factors associated with moderate or severe fibrosis (multivariate analysis; n = 205)

	Modality	OR (95% CI)	p Value
Menopause	Yes	3.73 (1.7–7.8)	0.0004
	No	1	
Hormone replacement therapy	Yes	0.35 (0.1–0.8)	0.0119
	No	1	

CODES *et al,* Gut 2007;56:390-5

Estrogens protect against liver fibrosis progression

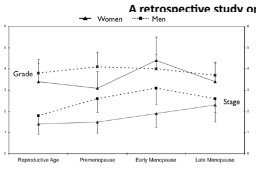
A survey on 201 HCV-infected women (157 with estimated date of infection)

Patients	METAVIR U/yr ± SE	p
Post-menopausal treated with HRT	0.099 ± 0.016	ref
Post-menopausal, untreated	0.133 ± 0.006	0.02
Pre-menopausal	0.093 ± 0.012	NS

DI MARTINO *et al,* Hepatology 2004;40:1426-33

Fibrosis severity in women worsens in parallel with increasing estrogen deprivation

A retrospective study on 701 HCV-infected patients



Factor associated with fibrosis (MV)	OR (95% CI)	p
Necroinflammation	1.506 (1.181–1.1.922)	.001
Steatosis	3.029 (1.154–7.951)	.024
ALT	1.011 (0.003–1.019)	.009
Estradiol	0.973 (0.947–0.999)	.041

VILLA *et al,* PLoS One 2012;7:e44624

Tobacco smoking is an independent factor for increased liver fibrosis score

(n = 310)

	OR (95% CI)	P
Age ≥ 46	6.3 (3.4 - 13.0)	0.0001
Male sex	1.8 (1.1 - 3.0)	0.01
Tobacco, >15 packs-years	1.9 (1.1 - 3.6)	0.03
Past alcohol abuse, >40 g/d	2.2 (0.9 - 5.0)	0.06

PESSIONE *et al,* Hepatology 2001;34:121-125

Daily cannabis smoking is a risk factor for fibrosis progression* in chronic hepatitis C

(n = 270 consecutive untreated chronic hepatitis C patients)

	OR	95% CI
Daily cannabis smoking	3.4	1.5 - 7.4
Alcohol intake >30 g/d	2.2	1.1 - 4.5
Age at contamination >40 yrs	4.0	1.9 - 8.4
Steatosis	2.0	1.0 - 4.1
Activity ≥ A2	5.4	2.9 - 10.3

*Defined as FPR > median value of 0.074 FUPY

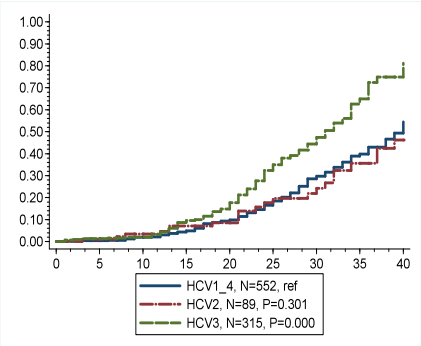
HEZODE *et al*, Hepatology 2005;42:63-71

Liver fibrosis progression in HCV/HIV coinfected patients

- 943 consecutive patients (656 HCV-monoinfected and 287 HIV/ HCV coinfected, 88% under HAART for 4.2 ± 2.4 yrs)
- Liver fibrosis evaluated by TE and biochemical indexes (APRI, FIB-4 and Forns')
- Coinfected were younger (42.9 ± 5.8 vs 52.8 ± 14.5 years), more often male, (67% vs 38%) and had more often history of IVDU (83% vs 21%)
- Advanced liver fibrosis (TE >9.5 kPa) was recognized in 18% of monoinfected and 39% of coinfected patients (p<0.005)
- By MV, factors independently associated with advanced liver fibrosis were age >45 years, BMI > 25, HIV coinfection

DE LEDINGHEN *et al*, J Viral Hepat 2011;15:427-33

Liver fibrosis progression as a function of HCV genotype



BOCHUD *et al*, J Hepatol 2009;51:655-666

Factors independently associated with rapid stage-constant FPR in HCV genotype 3

(n = 312 with assessable date of infection)

	OR	95% CI	p
Male sex	2.012	1.007 – 4.019	0.05
Age at infection	1.081	1.029 – 1.135	0.002
ALT	1.004	1.000 – 1.007	0.05
Activity	2.128	1.099 – 4.121	0.03

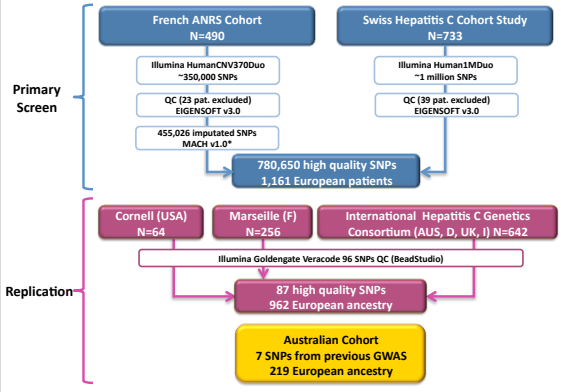
BOCHUD *et al*, J Hepatol 2009;51:655-666

GASTROENTEROLOGY 2012;143:1244–1252

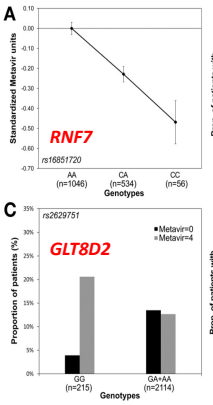
Genome-Wide Association Study Identifies Variants Associated With Progression of Liver Fibrosis From HCV Infection

ETIENNE PATIN,[1-3] ZOLTÁN KUTALIK,[3,4] JULIEN GUERGNON,[5] STÉPHANIE BIBERT,[6] BERTRAND NALPAS,[7-10] EMMANUELLE JOUANGUY,[1,2,11] MONA MUNTEANU,[12] LAURENCE BOUSQUET,[1,10] LAURENT ARGIRO,[13] PHILIPPE HALFON,[14] ANNE BOLAND,[15] BEAT MÜLLHAUPT,[16] DAVID SEMELA,[17] JEAN-FRANÇOIS DUFOUR,[18] MARKUS H. HEIM,[19] DARIUS MORADPOUR,[20] ANDREAS CERNY,[21] RAFFAELE MALINVERNI,[22] HANS HIRSCH,[23] GLADYS MARTINETTI,[24] VIJAYAPRAKASH SUPPIAH,[25] GRAEME STEWART,[26] DAVID R. BOOTH,[27] JACOB GEORGE,[28] JEAN-LAURENT CASANOVA,[1,2] CHRISTIAN BRÉCHOT,[29] CHARLES M. RICE,[30] ANDREW H. TALAL,[31] IRA M. JACOBSON,[31] MARC BOURLIÈRE,[32] IOANNIS THEODOROU,[6] THIERRY POYNARD,[33] FRANCESCO NEGRO,[34] STANISLAS POL,[1,10] PIERRE-YVES BOCHUD,[4] and LAURENT ABEL,[1,2,11] on behalf of the Swiss Hepatitis C Cohort Study Group, the International Hepatitis C Genetics Consortium, and the French ANRS HC EP 26 Genoscan Study Group

*Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Necker Medical School, INSERM Unité 980, Paris, France; [2]University Paris Descartes, Paris, France; [3]Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland; [4]Swiss Institute of Bioinformatics, Lausanne, Switzerland; [5]Laboratory of Immunity and Infection, INSERM UMR-S 945, UPMC Université Paris 6, Groupe Hospitalier Pitié-Salpêtrière AP-HP, Paris, France; [6]Infectious Diseases Service, Department of Medicine, University Hospital and University of Lausanne, Lausanne, Switzerland; [7]Département d'Hépatologie, INSERM Unité 1016, Groupe Hospitalier Cochin–Hôtel Dieu–Broca, Paris, France; [8]CIC Gilles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, and [9]Center for the Study of Hepatitis C, Rockefeller University, New York, New York; [10]Biopredictive, Paris, France; [11]Laboratoire d'Immunologie et de Génétique des Maladies Parasitaires, INSERM-UMR 906 Université de la Méditerranée, Marseilles, France; [12]Laboratoire Alphabio, Hôpital Ambroise Paré, Marseilles, France; [13]CSA, Institut de Génomique, Centre National de Génotypage, Evry, France; [14]Division of Gastroenterology and Hepatology, University Hospital, Zurich, Switzerland; [15]Division of Gastroenterology, Canton Hospital, St Gallen, Switzerland; [16]Hepatology, Department of Clinical Research, University Clinic for Visceral Surgery and Medicine, Bern, Switzerland; [17]Division of Gastroenterology and Hepatology, University Hospital, Basel, Switzerland; [18]Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland; [19]Clinica Moncucco, Lugano, Switzerland; [20]Fountaikle Hospital, Neuchâtel, Switzerland; [21]Institute for Medical Microbiology, University Hospital, Basel, Switzerland; [22]Institute of Medical Microbiology, Bellinzona, Switzerland; [23]Liver Liver Unit, Westmead Millennium Institute and Westmead Hospital, University of Sydney and University of Sydney Medical Foundation, Sydney, Australia; [24]Institute for Immunology and Allergy Research, Westmead Millennium Institute, University of Sydney, Sydney, Australia; [25]INSERM Unité 785, Liver Hepatology Centre, Paul Brousse Hospital, University Paris-XI, Villejuif, France; [26]Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, New York; [27]Service d'Hépato-gastroentérologie, Hôpital Saint-Joseph, Marseilles, France; [28]Université Pierre et Marie Curie, Service d'Hépato-gastroentérologie, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France; and [29]Divisions of Gastroenterology and Hepatology and of Clinical Pathology, University Hospital, Geneva, Switzerland



PATIN *et al*, Gastroenterology 2012;143:1244-52



RNF7
Cell-protecting agent that acts as antioxidant, protecting cells from ROS

MERTK
Clearance of apoptotic cells

GLT8D2
Glycosyltransferase regulating apoB100 levels in hepatocytes

TULP1
Interacts with MERTK during the apoptotic process

PATIN *et al*, Gastroenterology 2012;143:1244-52

Attributable Fraction

- The Attributable Fraction for each risk factor is ***the fraction of cases which would be prevented if the risk factor could be eliminated***

What is the hierarchy among all major risk factors for accelerated fibrosis progression rate in hepatitis C?

ORIGINAL ARTICLE

Impact of common risk factors of fibrosis progression in chronic hepatitis C

S Rüeger,[1,2,3] P-Y Bochud,[4] J-F Dufour,[5] B Müllhaupt,[6] D Semela,[7] M H Heim,[8] D Moradpour,[9] A Cerny,[10] R Malinverni,[11] D R Booth,[12] V Suppiah,[12,13] J George,[13] L Argiro,[14] P Halfon,[15] M Bourlière,[16] A H Talal,[17] I M Jacobson,[17] E Patin,[18,19] B Nalpas,[19,20] T Poynard,[21] S Pol,[19,20] L Abel,[18,19,22] Z Kutalik,[2,3] F Negro[23,24]

Gut 2014 Sep 11 [Epub ahead of print]

Different impact of common risk factors of fibrosis progression in chronic hepatitis C

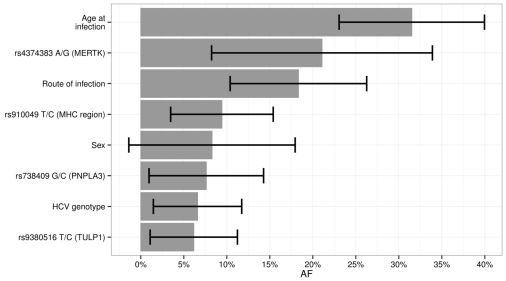
- 1493 chronic hepatitis C patients with an estimated date of infection and at least one liver biopsy
- Risk factors* for accelerated fibrosis progression rate (≥0.13 Metavir fibrosis units per year) were identified by logistic regression
- In 590 patients, the role of SNPs** previously associated with fibrosis progression by GWAS was studied
- Results replicated in 3 independent cohorts (n=1092)

*** Age at infection, sex, route of infection (IVDU *vs* non-IVDU), HCV genotype, BMI, significant alcohol drinking (≥ 20 g/day for ≥ 5 yrs), HIV coinfection and diabetes**

**** *PNPLA3*, *TULP1*, *MERTK*, *RNF7*, MHC region**

RUEGER *et al*, Gut 2014 Sep 11 [Epub ahead of print]

Attributable fraction of risk for liver fibrosis progression in chronic hepatitis C (n=590)



Most liver fibrosis progression in chronic hepatitis C is attributable to non modifiable factors

RUEGER *et al*, Gut 2014 Sep 11 [Epub ahead of print]

Attributable fraction of risk for liver fibrosis progression in 1682 chronic hepatitis C patients: a meta-analysis

(SCCS, n=590; French cohort, n=403; FR-US cohort, n=470; Sydney Cohort, n=219)

	AF (95% CI)	P*
Sex	**12.8% (7.5% - 18.1%)**	**< 0.0001**
Age at infection	**34.2% (28.4% - 40.0%)**	**< 0.0001**
Route of infection	**6.8% (1.4% - 12.2%)**	0.013
HCV genotype 3 vs. non-3	**4.0% (1.0% - 6.9%)**	0.008
rs9380516 (TULP1)	**2.9% (-0.6% - 6.4%)**	0.1
rs738409 (PNPLA3)	**7.6% (2.9% - 12.3%)**	**0.001**
***rs910049* (MHC region)**	**6.5% (2.3% - 10.8%)**	**0.003**
rs4374383 (MERTK)	**14.4% (6.5% - 22.4%)**	**0.0004**

*** Alpha is 0.00625**

RUEGER *et al*, Gut 2014 Sep 11 [Epub ahead of print]

Natural history of hepatitis C

- From acute to persistent infection
- From no fibrosis to cirrhosis
- **Development of hepatocellular carcinoma**

Risk factors for HCC in hepatitis C

Risk factor	Reference
Male sex	Fattovich et al, 2004
Steatosis	Ohata et al, 2003; Tanaka et al, 2007; Kurosaki et al, 2010
Older age	Degos et al, 2000; Fattovich et al, 2004; Lok et al, 2009
Type 2 diabetes	Hassan et al, 2002; Veldt et al, 2008; Lai et al, 2012
Excess alcohol drinking	Hassan et al, 2002; Tagger et al, 1999
Coinfection with HBV	Tagger et al, 1999
HCV genotype 1b	Bruno et al, 2007; Raimondi et al, 2009
HCV genotype 3	Nkontchou et al, 2011; Van der Meer et al, 2012
PTEN downregulation ?	Rahman et al, 2002
MICA	Kumar et al, 2011
HCP5	Lange et al, 2013
CYP2R1, GC, DHCR7	Lange et al, 2013
186-gene signature	Hoshida et al, 2013

Factors independently associated with hepatocellular carcinoma in chronic hepatitis C

(Retrospective cohort, n=1279*)

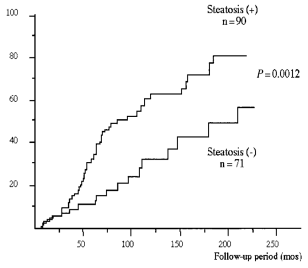
Predictor		OR (IC 95%)	P
Age	By 10-year increases	1.09 (1.05–1.13)	<0.0001
Sex	Males vs. females	2.12 (1.28–3.51)	0.004
Fibrosis stage	F3–4 vs F0–2	4.30 (2.59–7.14)	<0.0001
Severity of steatosis	≥10% vs <10%	3.04 (1.82–5.06)	<0.0001
Response to IFN-α	Non-SVR vs SVR	2.43 (1.13–5.23)	0.023
Daily alcohol drinking (g/d)	≥20 vs <20	0.50 (0.07–3.60)	0.478
Diabetes (yes/no)	present vs absent	0.75 (0.42–1.33)	0.319
BMI	≥23 vs <23	1.69 (1.02–2.86)	0.043

*Only 2 patients with HCV-3

KUROSAKI et al, *Hepatol Res* 2010;40:870-7

Steatosis predicts HCC in hepatitis C

(Retrospective study, n=126: 106 HCV-1, 17 HCV-2, 3 HCV und.)



Independent predictors of HCC: steatosis (P = 0.0135), age (P = 0.0390), cirrhosis (P = 0.0068), no IFN treatment (P = 0.0142)

(steatosis correlated with BMI, ALT and triglycerides)

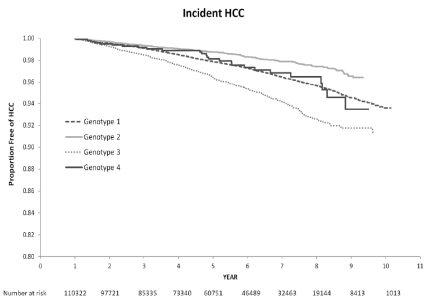
OHATA *et al,* Cancer 2003;97:3036–3043

Diabetes increases the risk of HCC in chronic hepatitis C with advanced fibrosis

- 541 chronic hepatitis C patients, Ishak scores 4-6
- 85 (16%) had diabetes
- Median FU 4.0 years (range 2.0-6.7)
- 5-year occurrence of HCC:
  - 11.4% (95% CI 3.0-19.8) if diabetes
  - 5.0% (95% CI 2.2-7.8) (P=0.013) if no diabetes
- MV Cox regression: diabetes is independently associated with HCC in patients with Ishak 6 (HR 3.28, 95% CI 1.35-7.97, P=.009)

VELDT *et al,* Hepatology 2008;47:1856-62

HCV-3 increases by 80% the risk of developing HCC vs HCV-1



KANWAL *et al,* Hepatology 2014 (in press)

Natural history of hepatitis C: what have we learned?

- Lifestyle modifications are an important staple of the management of chronic hepatitis C patients: patients should be told to drink little or no alcohol, to stop smoking, and to increase physical activity
- The most important factors accelerating the liver disease progression cannot be modified (age at infection, sex, host gene variants, HCV genotype): patients at risk should be offered antiviral therapy