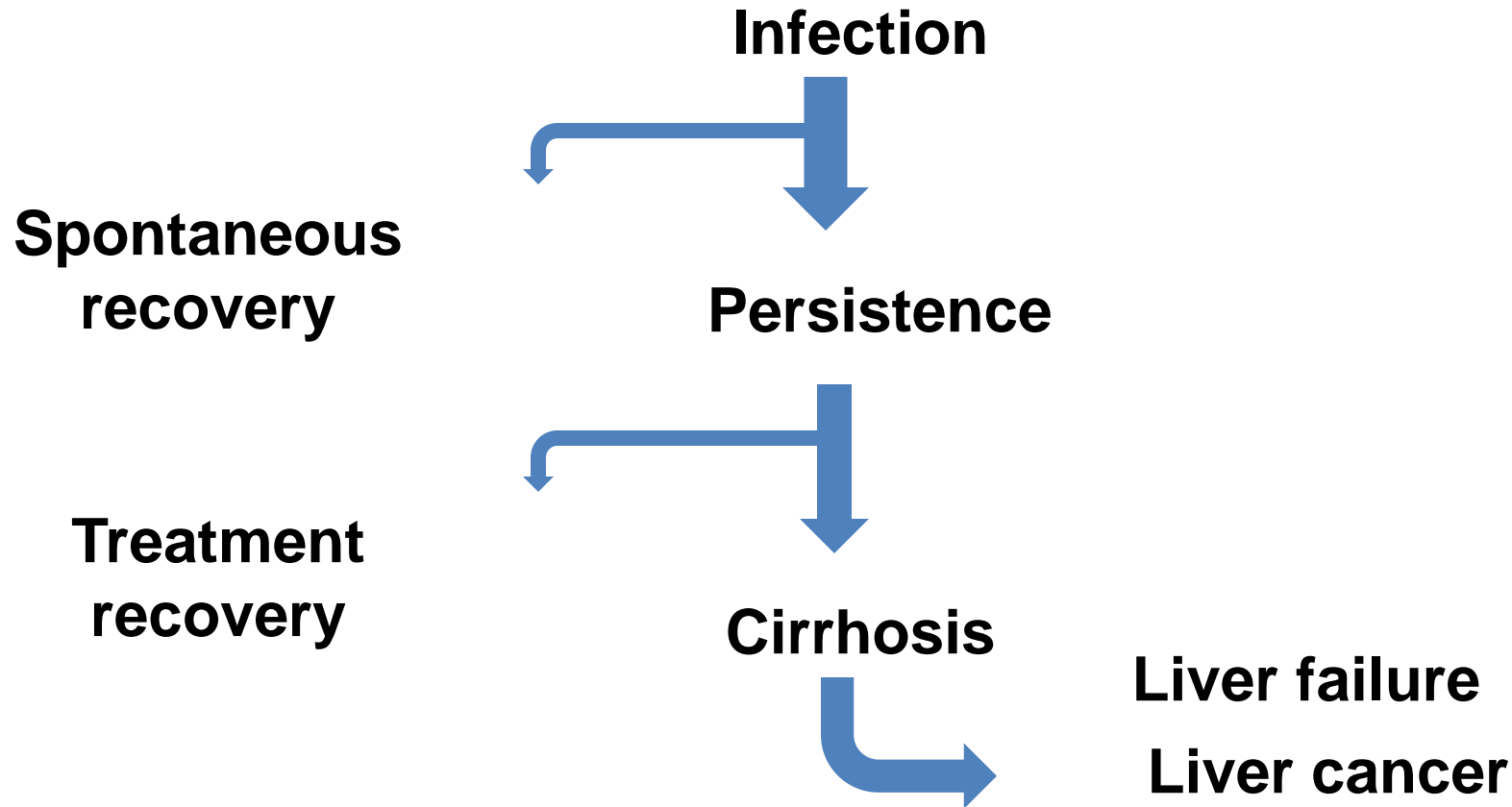


# **Translating genomics into HCV clinical practice**

**David Thomas**

# Context: HCV infection has discrete clinical outcomes that differ by race



Thomas JAMA 2000; Muir NEJM 2004

# Caucasians and HIV negative were more likely to have HCV recovery

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| <b>Factor</b>                 | <b>Adjusted Odds<br/>(95% CI)</b> | <b>Adjusted P</b> |
|-------------------------------|-----------------------------------|-------------------|
| <b>Non-Black</b>              | <b>5.15 (2.6-10.1)</b>            | <b>0.0001</b>     |
| <b>HIV positive</b>           |                                   |                   |
| <b>CD<sub>4</sub> ≥500</b>    | <b>0.58 (0.22-1.30)</b>           | <b>0.167</b>      |
| <b>CD<sub>4</sub> 200-499</b> | <b>0.54 (0.27-0.95)</b>           | <b>0.034</b>      |
| <b>CD<sub>4</sub> &lt;200</b> | <b>0.33 (0.13-0.73)</b>           | <b>0.0001</b>     |
| <b>Age &lt;45 year</b>        | <b>1.8 (0.95-3.12)</b>            | <b>0.056</b>      |
| <b>HBsAg positive</b>         | <b>2.75 (1.00 -7.64)</b>          | <b>0.058</b>      |

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**\*Multivariate logistic regression model of 95 with recovery versus 722 with persistence (Thomas et al JAMA 2000).**

## LETTERS

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## Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance

Dongliang Ge<sup>1</sup>, Jacques Fellay<sup>1</sup>, Alexander J. Thompson<sup>2</sup>, Jason S. Simon<sup>3</sup>, Kevin V. Shianna<sup>1</sup>, Thomas J. Urban<sup>1</sup>, Erin L. Heinzen<sup>1</sup>, Ping Qiu<sup>3</sup>, Arthur H. Bertelsen<sup>3</sup>, Andrew J. Muir<sup>2</sup>, Mark Sulkowski<sup>4</sup>, John G. McHutchison<sup>2</sup> & David B. Goldstein<sup>1</sup>

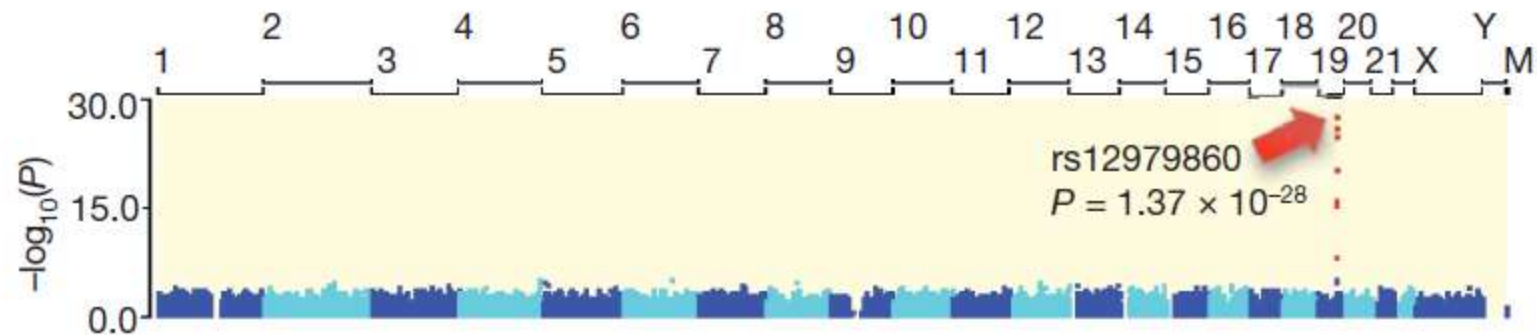


**Recovery**



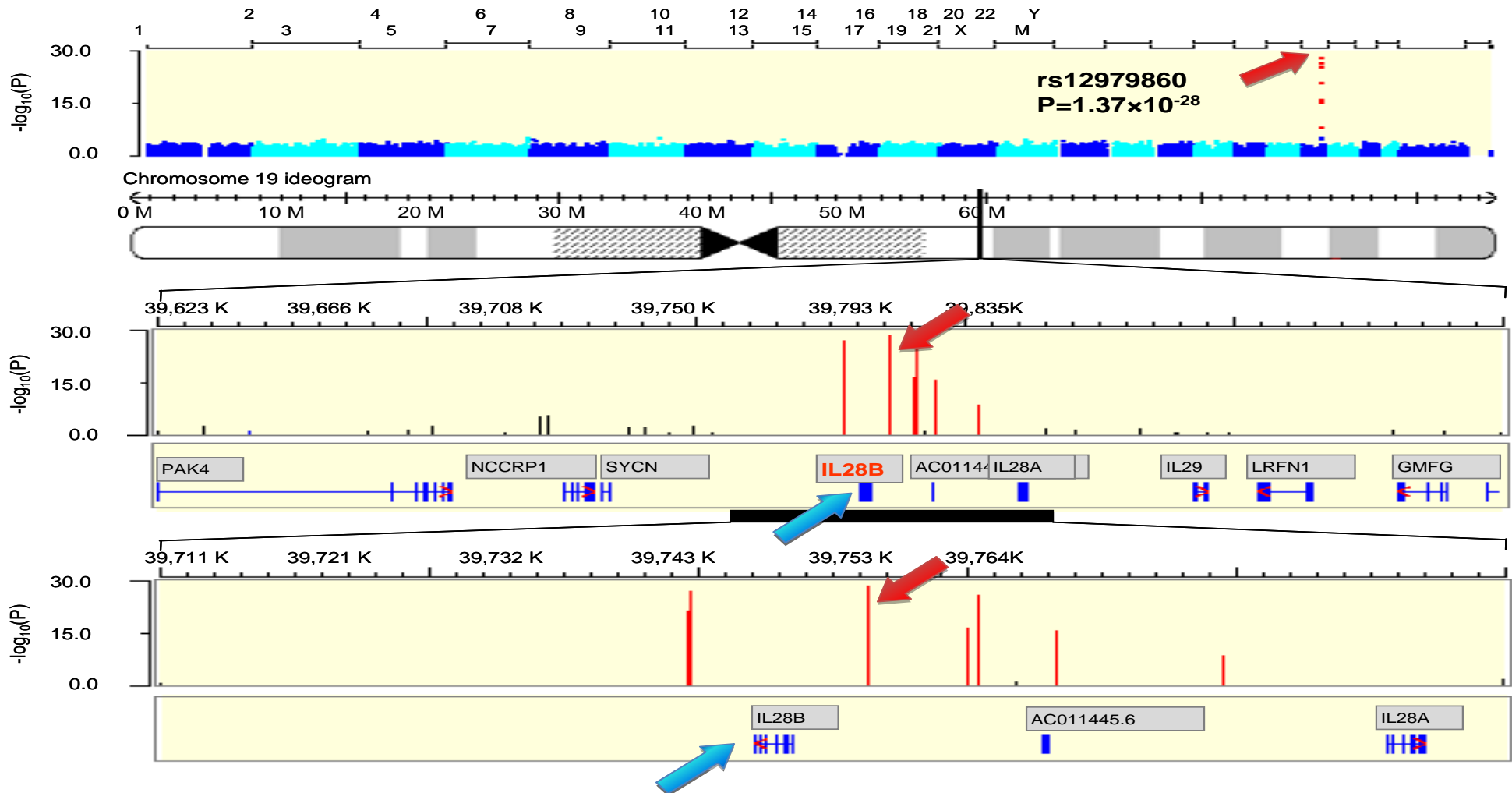
**Persistence**

# Seven SNPs within a 17-kb region around *IL28B* gene are associated with HCV recovery

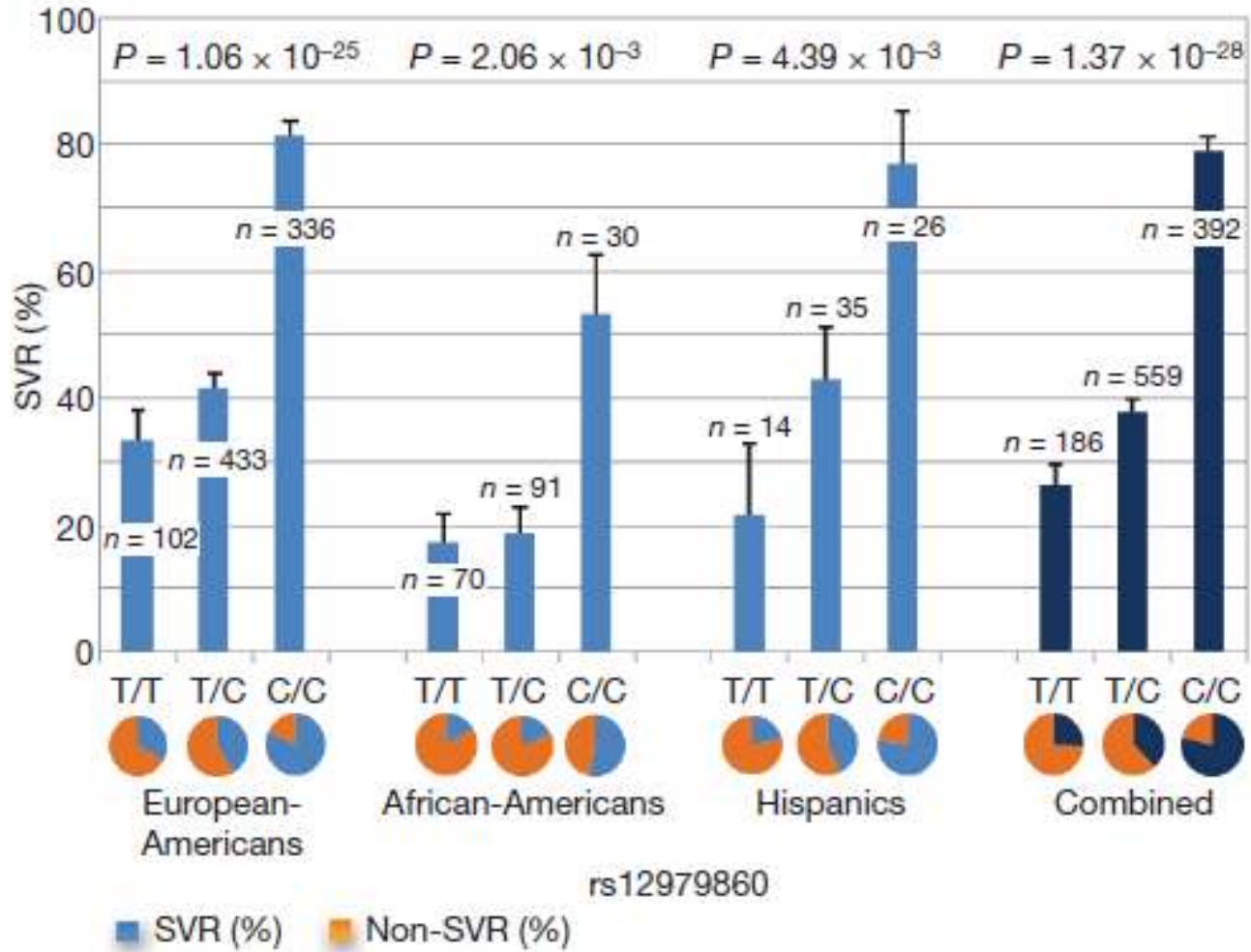


Ge, Nature, 2009; Thomas, Nature 2009; Rauch Gastroenterology 2010

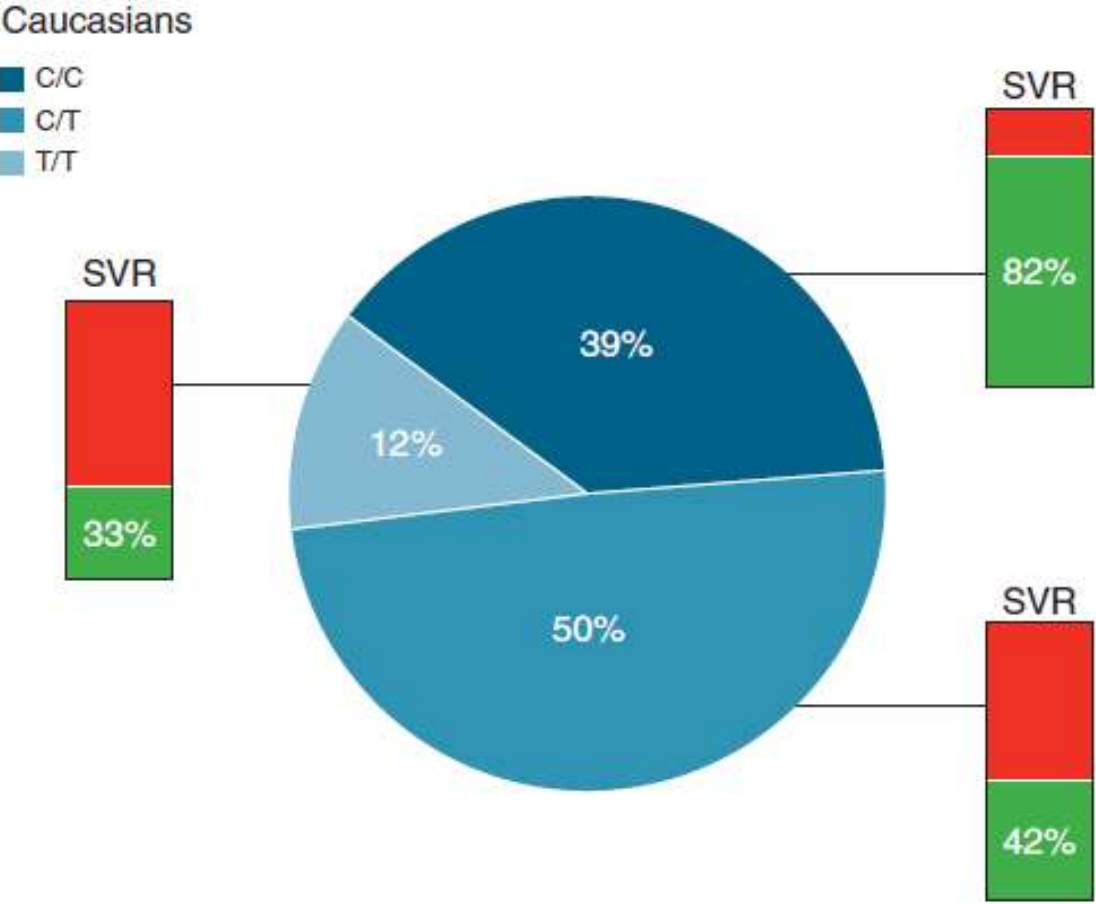
# Seven SNPs within a 17-kb region around *IL28B* gene are associated with HCV recovery



# C allele associated with PegIFN and RBV in IDEAL



# IL28b genotyping helps predict SVR in Caucasians



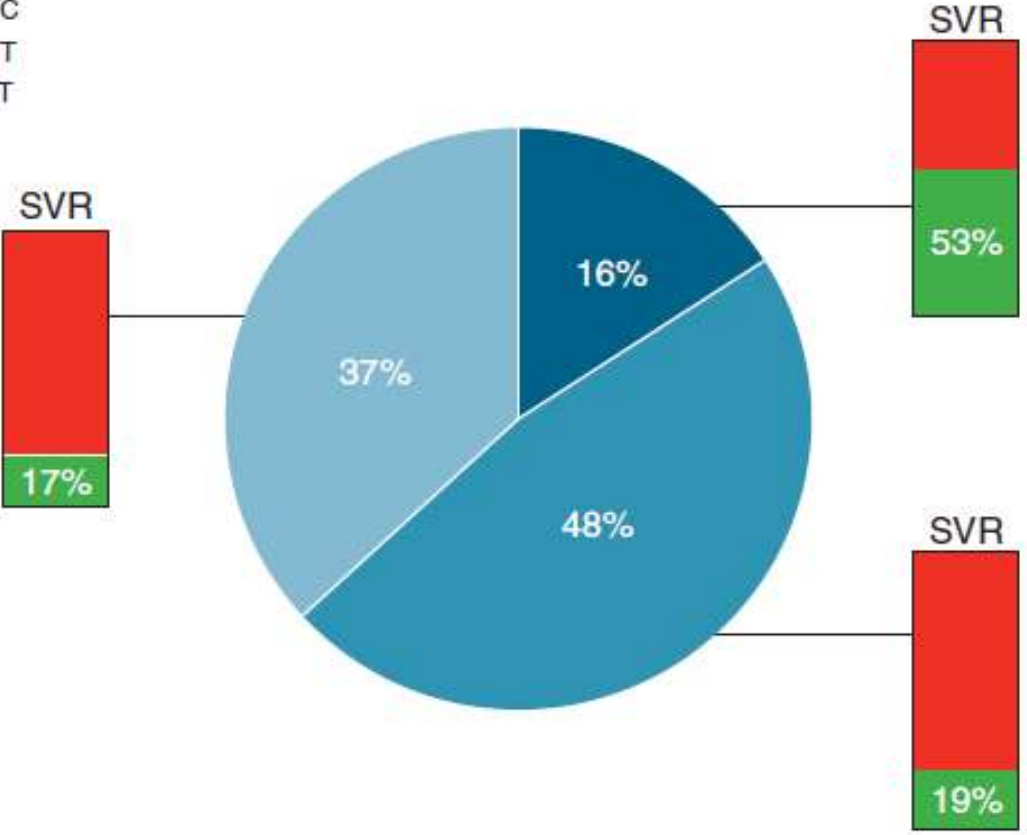
Clark Am J Gastro



# IL28b genotyping helps predict SVR in African Americans

African Americans

- C/C
- C/T
- T/T



Clark Am J Gastro

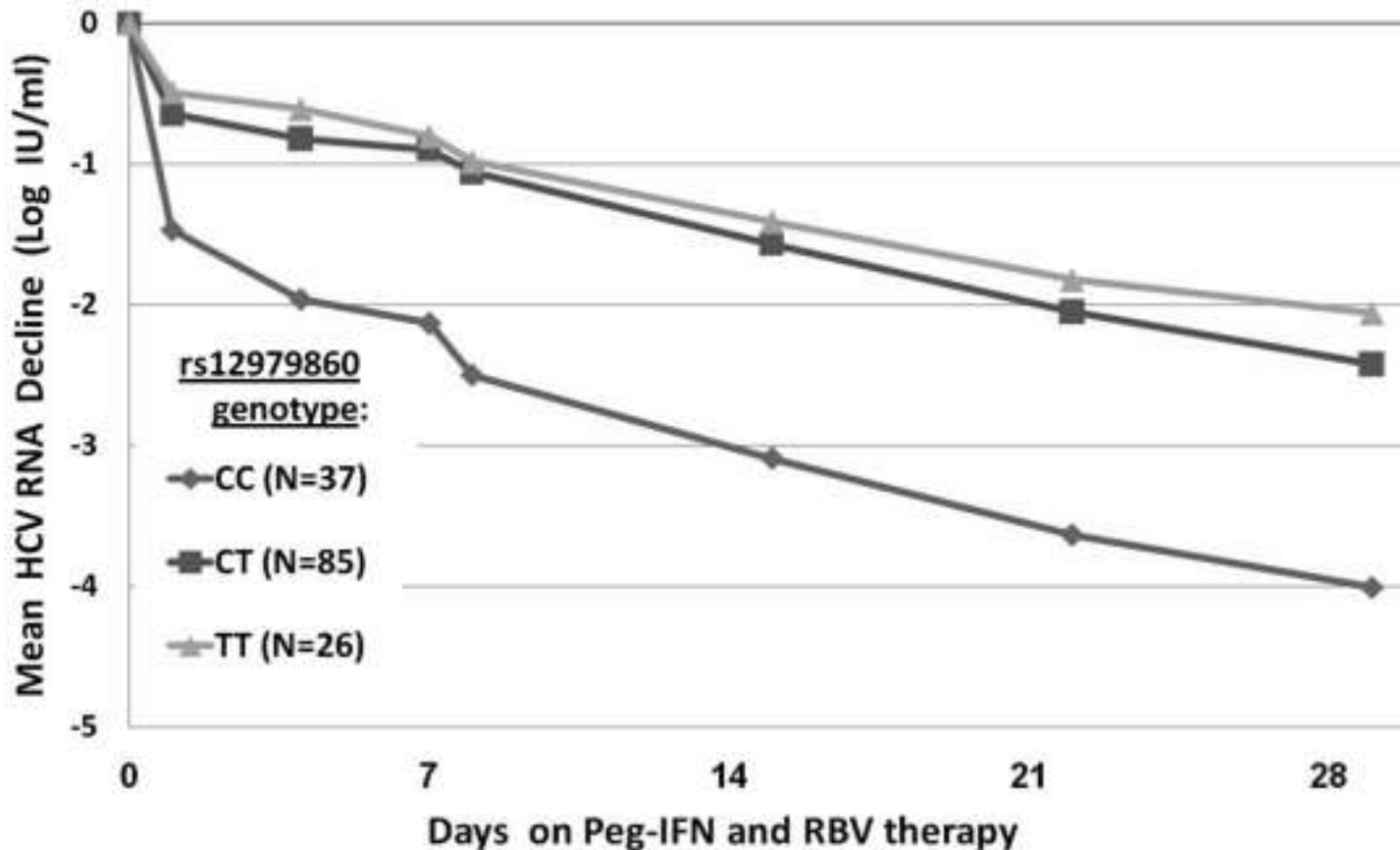
# Independent replication of the effect of genetic variation in SNPs near *IL28B* and SVR

|  | Ge et al  | Tanaka et al                         | Suppiah et al                       | Rauch et al                        |
|--|---|--------------------------------------|-------------------------------------|------------------------------------|
| Race   | Americans:<br>European; African;<br>Hispanic    | Japanese                             | European;<br>Australian             | European                           |
| SNP  | rs8099917;<br>$1.72 \times 10^{-26}$            | rs8099917;<br>$2.68 \times 10^{-32}$ | rs8099917;<br>$9.25 \times 10^{-9}$ | rs8099917;<br>$5.7 \times 10^{-8}$ |
|  | rs1297860;<br>$1.37 \times 10^{-28}$            |                                      |                                     |                                    |
| Gene   | IL28B   | IL28B                                | IL28B                               | IL28B                              |
| Adjusted odds ratio of failure by rs8099917 carriage | 5.6, Hispanic<br>6.1, African<br>7.3, Caucasian | 12.1                                 | 1.98                                | 5.2                                |

Ge D, et al. *Nature* 2009;461:399-401. Tanaka Y, et al. *Nat Genet* 2009;41:1105-9. Suppiah V, et al. *Nat Genet* 2009;41:1100-4. Rauch A, et al. *Gastroenterology* 2010; Jan 7.

# Kinetics of HCV RNA decline differ early in IL28b haplotypes

*Genotype 1 Caucasian patients*



## IL28b haplotype predicts SVR in HIV/HCV coinfected patients

**Table 2. Distribution of hepatitis C virus genotypes and treatment outcome according to rs12979860 genotypes.**

|                                   | CC<br>(N=75) | CT<br>(N=73) | TT<br>(N=16) | <i>P</i> |
|-----------------------------------|--------------|--------------|--------------|----------|
| HCV genotype [ <i>n</i> (%)]      |              |              |              |          |
| 1 (N=95)                          | 34 (45)      | 51 (70)      | 10 (63)      | 0.001    |
| 3 (N=51)                          | 35 (47)      | 14 (19)      | 2 (12)       |          |
| 4 (N=18)                          | 6 (8)        | 8 (11)       | 4 (25)       |          |
| Treatment outcome [ <i>n</i> (%)] |              |              |              |          |
| SVR (N=90)                        | 56 (75)      | 27 (37)      | 7 (44)       | <0.001   |
| NR (N=74)                         | 19 (25)      | 46 (63)      | 9 (56)       |          |

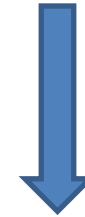
**Rallon AIDS 2010 (Pineda CID 2010, Grebley Hepatology 2010)**

# IL28B polymorphism and PegIFN/RBV + Telaprevir

81 Japanese patients with rs12979860 genotype treated with PegIFN-2b + RBV + Telaprevir (12 wk or 12 + 12 wk regimen)



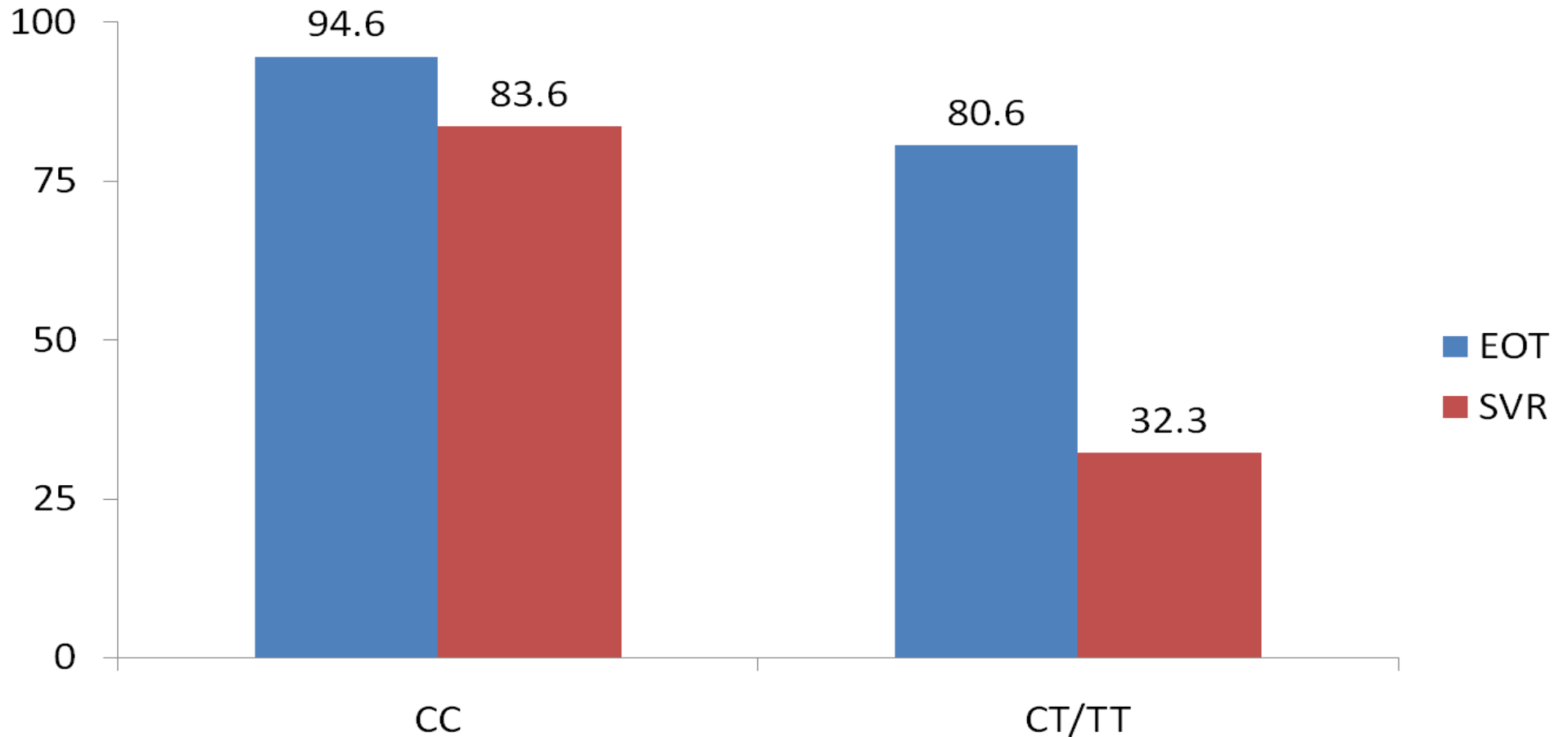
CC genotype (n = 42)  
•All 1b  
•40 Naive or relapse  
•2 Non-responder  
•30 treated with 12 + 12 regimen



CT/TT genotype (n = 34)  
•33 1b  
•15 Naive or relapse  
•19 Non-responder  
•27 treated with 12 + 12 regimen

# EOT and SVR according to rs12979860 genotype

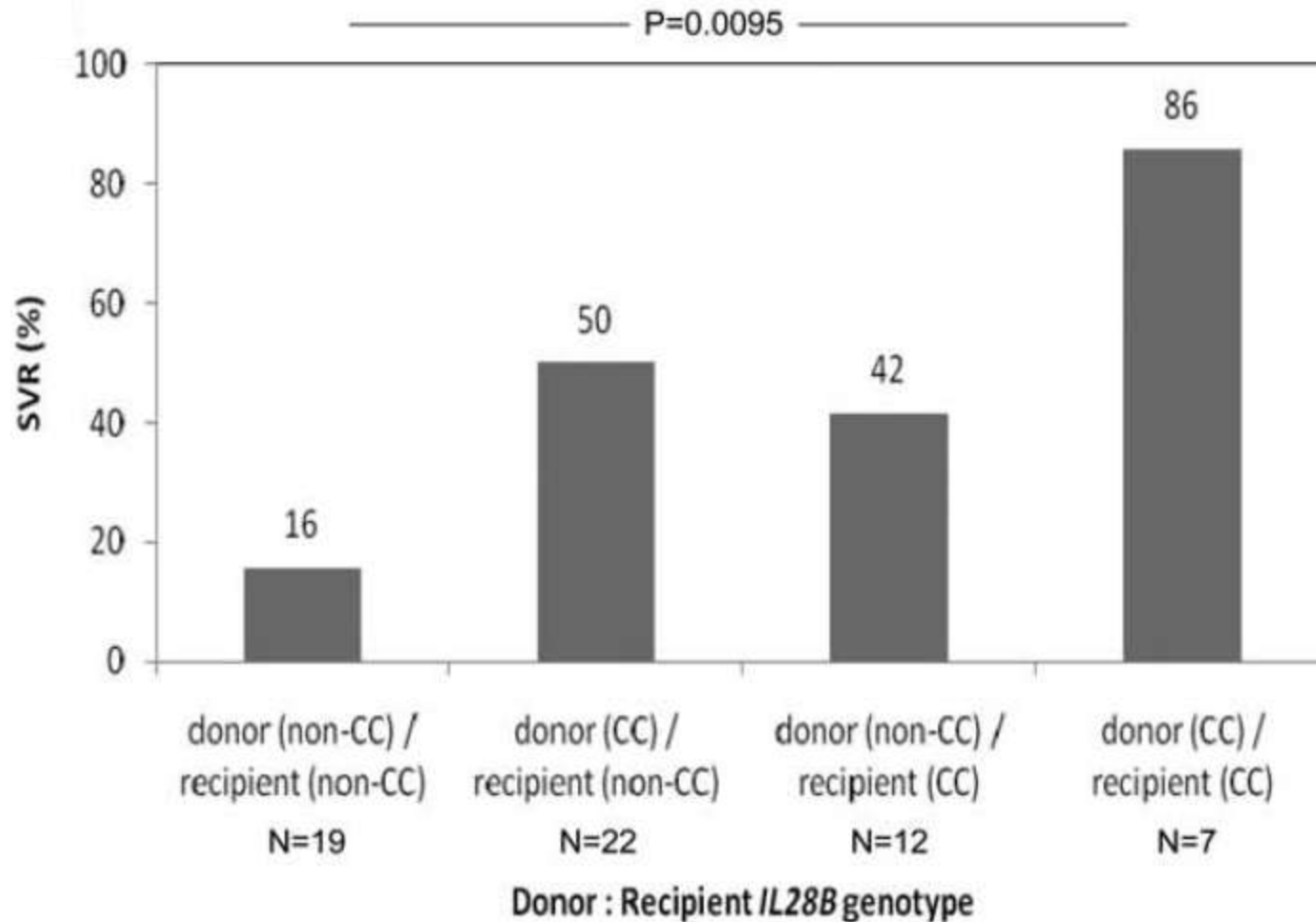
Telaprevir/PegIFN/RBV for total duration of 12 or 24 weeks



Akuta N et al. Hepatology 2010 Accepted articles; <http://www3.interscience.wiley.com/cgi-bin/fulltext/123333906/PDFSTART>

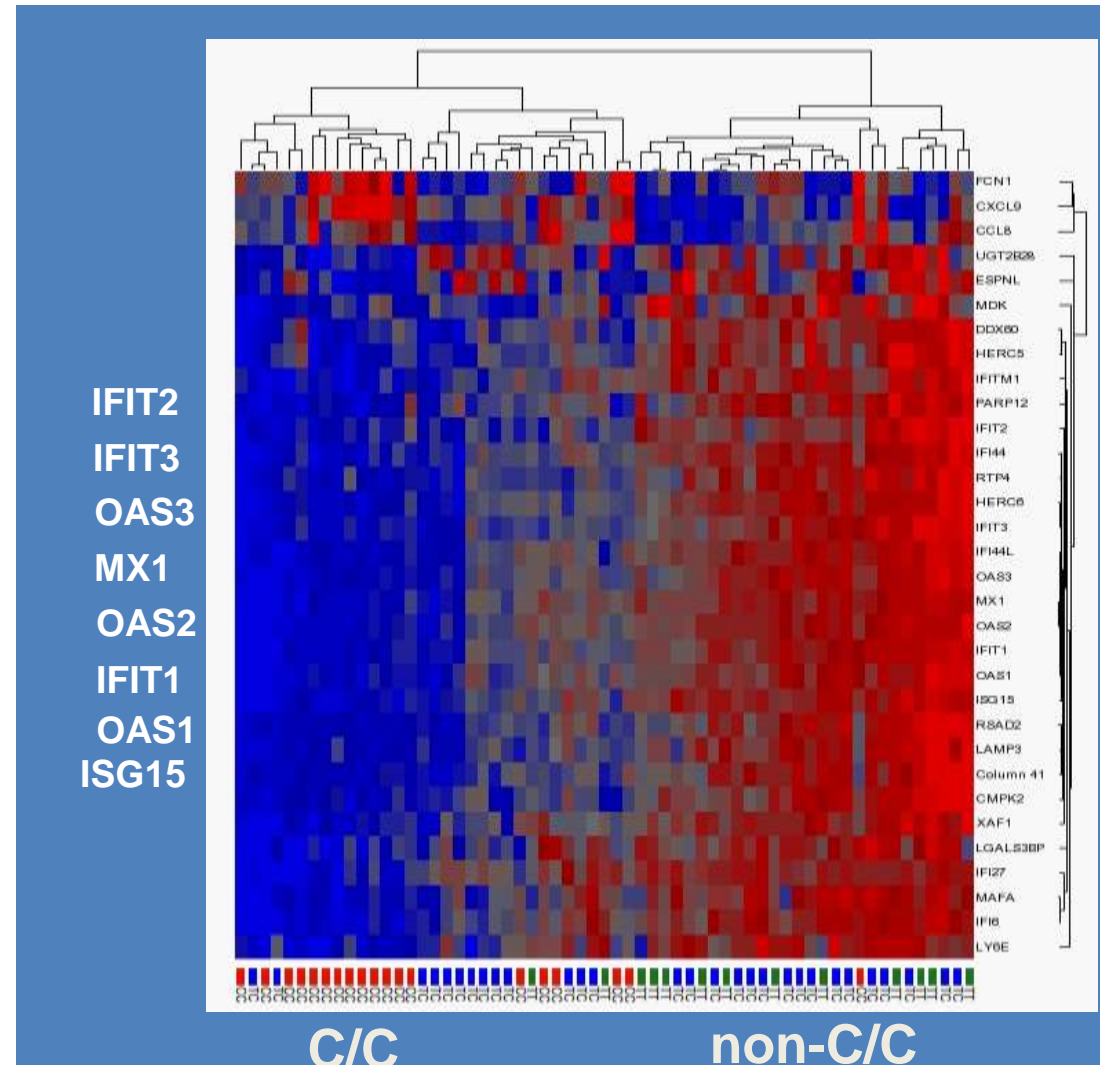
*First International Course of Translational Hepatology, Florence, 2011*

# Both donor and recipient IL28 status are important for outcome of IFN treatment after liver transplant



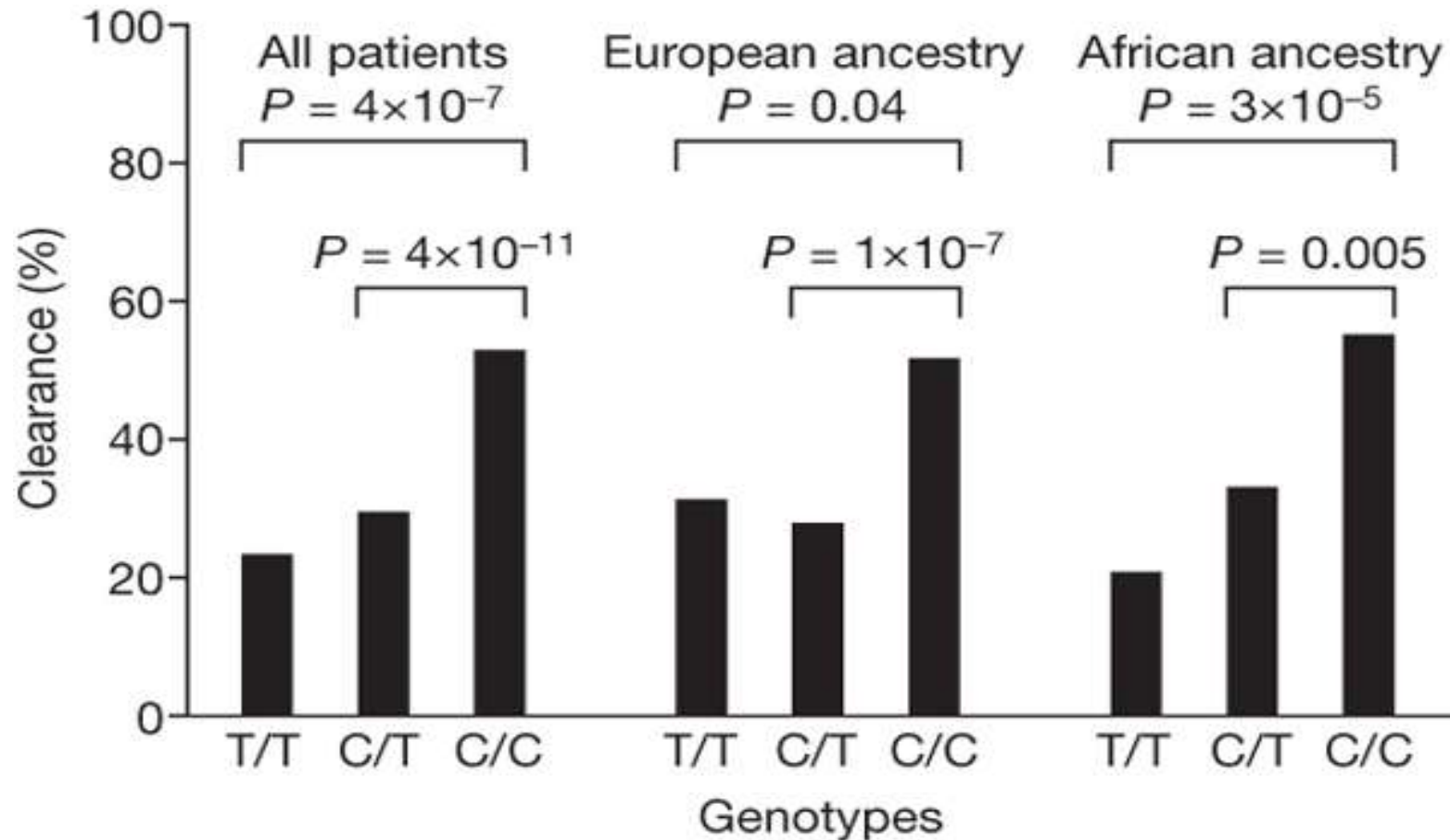
# *IL28B* genotype is associated with pre-treatment intrahepatic interferon sensitivity gene (ISG) expression

- 61 HCV-infected patients with pre-treatment liver tissue
- Measure gene expression according to rs12979860 polymorphism
- CC vs non-CC:
  - 164 genes differentially expressed
  - 32 genes:
    - differences in expression > ± 1.5-fold





# C allele associates with higher probability of spontaneous clearance of HCV



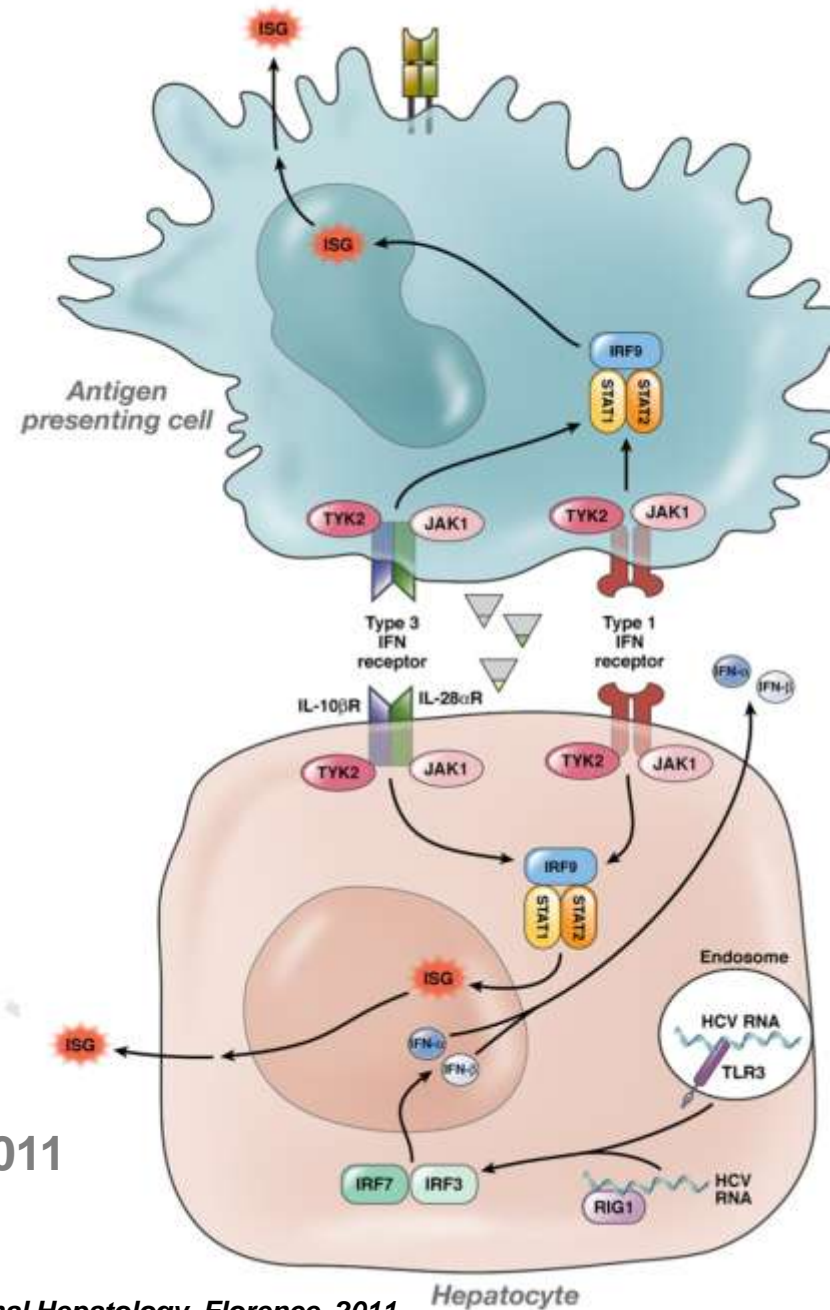
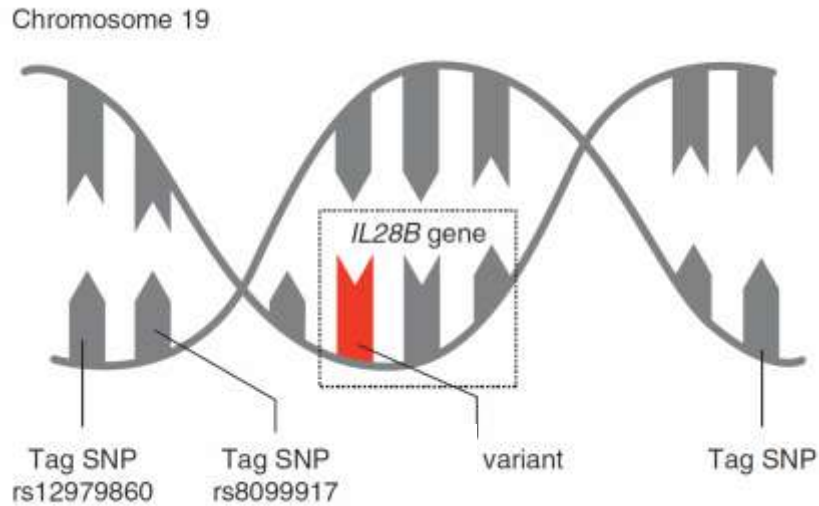
Thomas Nature 2009



# IL28b CC Affects Association of African Ancestry and HCV Persistence

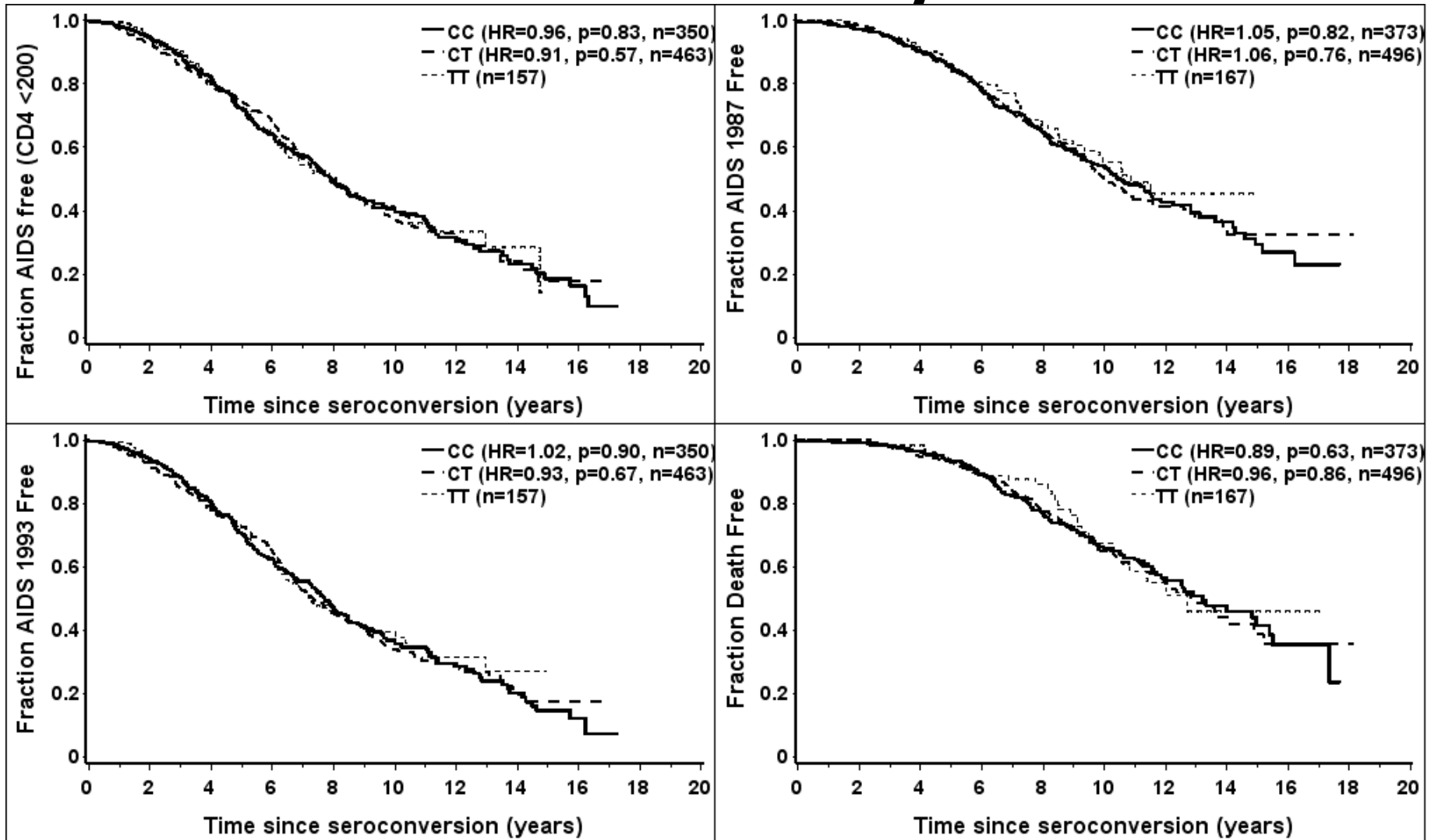
| Characteristic | OLD MODEL, OR | WITH IL28b CC (vs others) |
|----------------|---------------|---------------------------|
| EU ancestry    | 5.1           | 2.7 (1.2, 6.1)            |
| IL28b CC       | NA            | 4.1 (2.4, 7.0)            |

# Mechanism of IL28b association unknown



Balagopal Gastro 2010, Clark Am J Gastro 2011

# No association of IL28b C/T with HIV



Thio and Carrington, J Infect Dis 2010

# No association of IL28b with HBV recovery

| Genotype | Frequency in    | Frequency in       | Comparison     | OR* (95% CI)     | P    |
|----------|-----------------|--------------------|----------------|------------------|------|
|          | recovery, N (%) | persistence, N (%) |                |                  |      |
|          | N=384           | N=226              |                |                  |      |
| C        | 489 (63.7)      | 292 (64.6)         | C vs T         | 1.04 (0.82-1.33) | 0.75 |
| T/T      | 52 (13.5)       | 33 (14.6)          | C/C vs T/T     | 0.90 (0.44-1.85) | 0.77 |
| C/T      | 175 (45.6)      | 94(41.6)           | C/C vs C/T+T/T | 0.99 (0.67-1.46) | 0.95 |
| C/C      | 157 (40.9)      | 99 (43.8)          | T/T vs C/C+C/T | 1.20 (0.69-2.08) | 0.52 |

# **Clinical Applications of IL28b Testing in HCV genotype 1 infection**

- **In USA IL28b testing is commercially available**
- **Timing of treatment of acute infection**
  - **Start sooner for unfavorable genotype**
- **Timing of treatment for chronic infection**
  - **Delay for unfavorable genotype and low disease stage**
- **Clinical trials of new drugs stratified by IL28b status**

# **Clinical Applications of IL28b Testing in HCV genotype 1 infection**

- **Type of treatment**
  - **Peg and RBV without protease inhibitor for favorable genotype (80% SVR)**
- **Type of staging**
  - **Noninvasive to detect cirrhosis if favorable (like genotype 2-3)**
- **???Duration of treatment**
- **? Use of IL28b favorable liver for IL28b unfavorable recipient**



## LETTERS

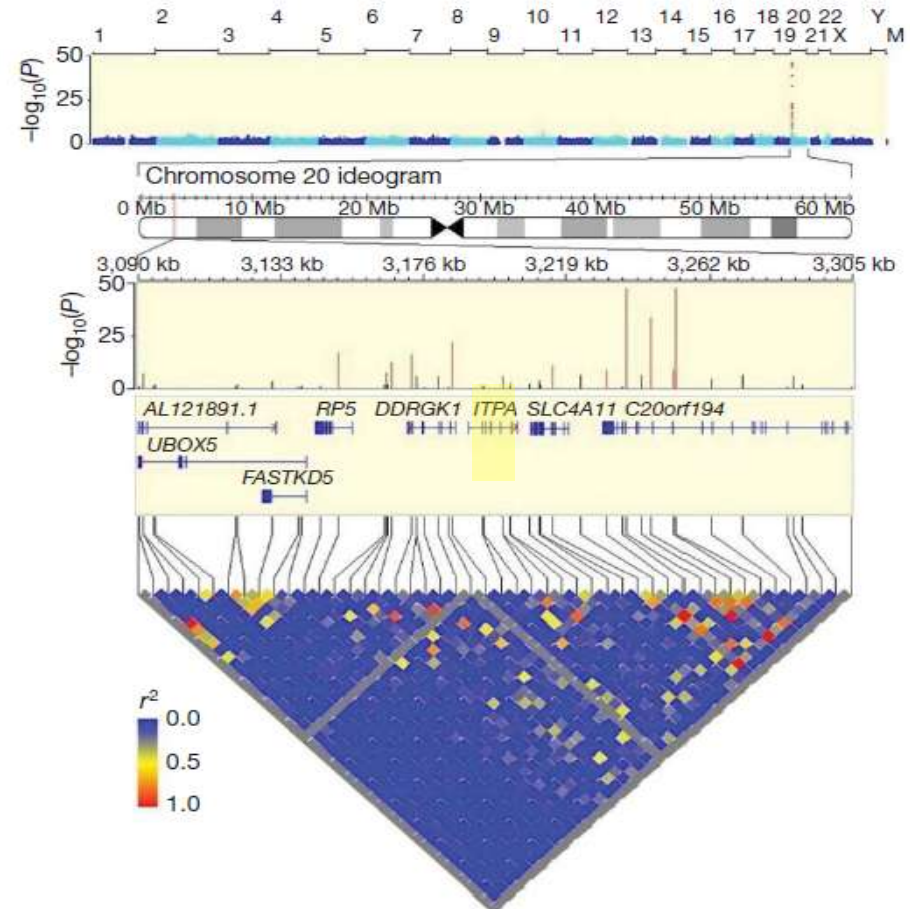
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## ***ITPA* gene variants protect against anaemia in patients treated for chronic hepatitis C**

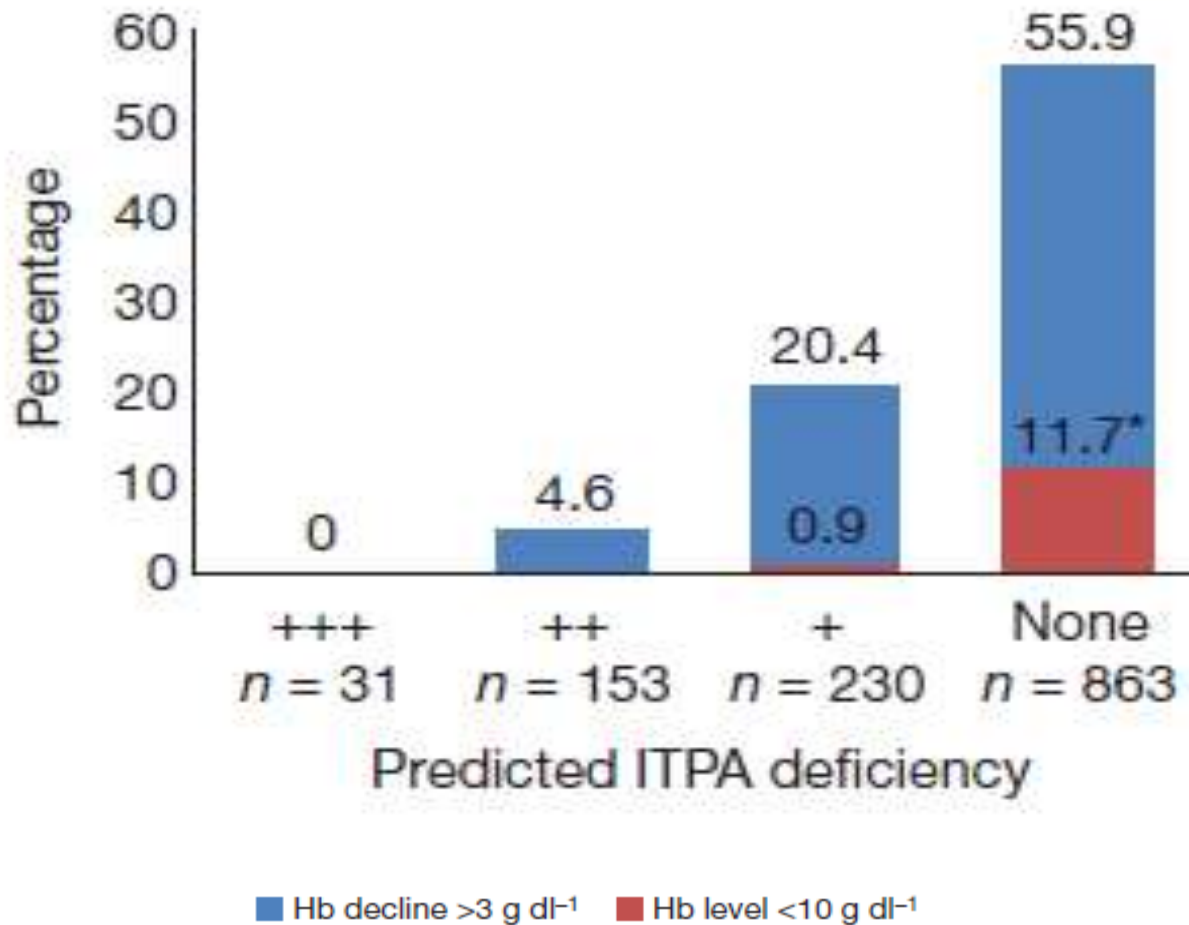
Jacques Fellay<sup>1\*</sup>, Alexander J. Thompson<sup>2\*</sup>, Dongliang Ge<sup>1\*</sup>, Curtis E. Gumbs<sup>1</sup>, Thomas J. Urban<sup>1</sup>, Kevin V. Shianna<sup>1</sup>, Latasha D. Little<sup>1</sup>, Ping Qiu<sup>3</sup>, Arthur H. Bertelsen<sup>3</sup>, Mark Watson<sup>3</sup>, Amelia Warner<sup>3</sup>, Andrew J. Muir<sup>2</sup>, Clifford Brass<sup>3</sup>, Janice Albrecht<sup>3</sup>, Mark Sulkowski<sup>4</sup>, John G. McHutchison<sup>2</sup> & David B. Goldstein<sup>1</sup>

# SNPs on chromosome 20 strongly associated with Hb decline at week 4

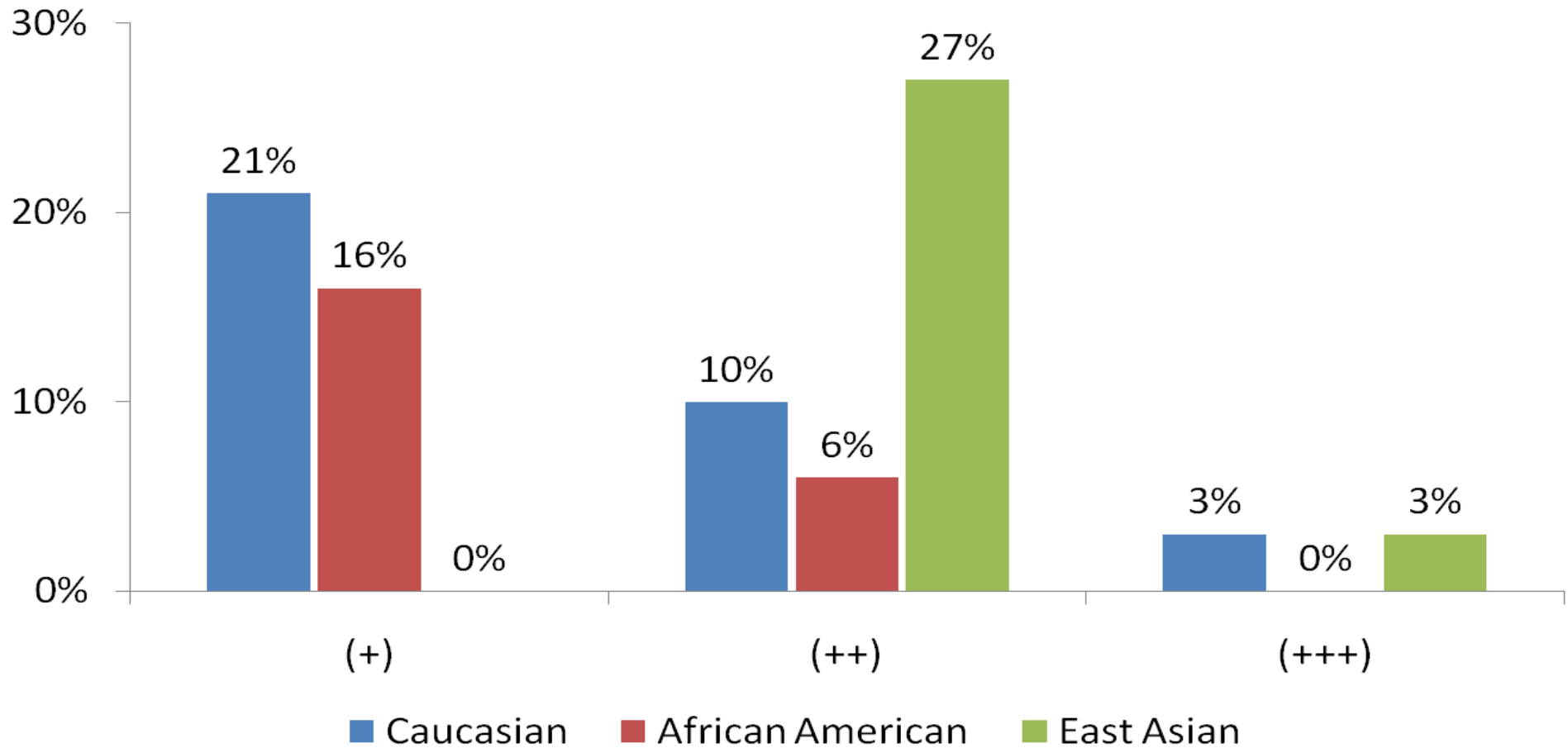
- Hemoglobin change at week 4 of PegIFN/RBV: > 3 g/dL and < 10 g/dL
- Anemia occurred in 9.1 – 11% of the population
- Among European Americans – rs6051702 had genome wide significance;  $P = 10^{-45}$ 
  - Weaker among African and Hispanic Americans
- Inosine triphosphatase (ITPA) gene
  - 2 gene mutation cause ITPA deficiency



# Predicted ITPA deficiency is associated with less Hb decline at treatment week 4

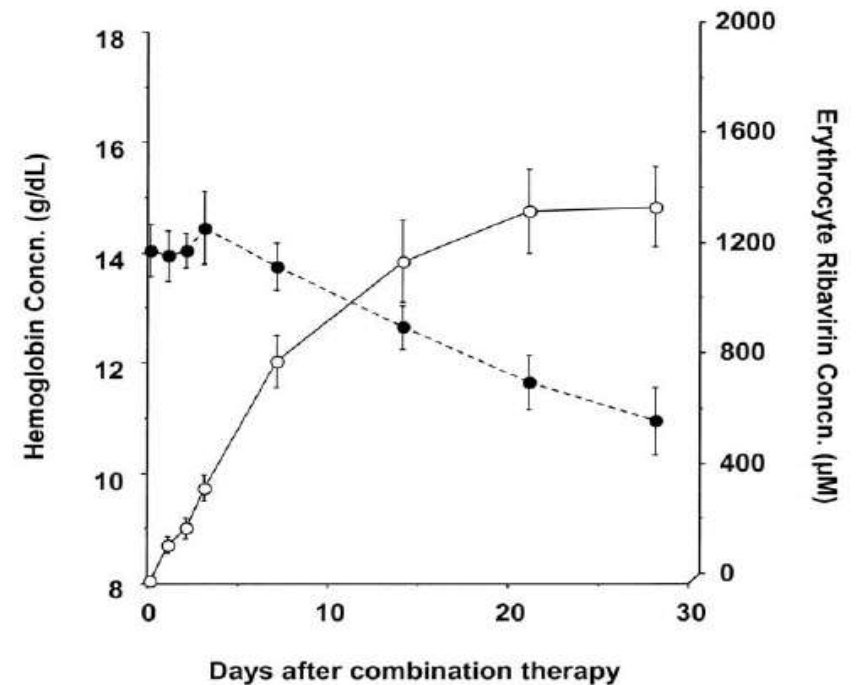


# Population Frequency of ITPA deficiency



# Protective mechanism of ITPA deficiency is not known but does not impact SVR

- RBV metabolism differs in nucleated and non-nucleated cells
- RBV-TP accumulates → deplete ATP → hemolysis
- Potential mechanism(s)
  - Accumulation of ITPA modifies the ratio of RBV-TP and ATP



# SNP at ribavirin transporter gene influences SVR post pegIFN and ribavirin

| Variable   | Multivariate            |                 |
|--|-------------------------|-----------------|
|  | OR (95% CI)             | P value         |
| Older age, years   | ...                     | ...             |
| Female sex   | ...                     | ...             |
| Advanced liver fibrosis (Metavir F3-F4)                          | ...                     | ...             |
| Baseline serum HCV-RNA level <600,000 IU/mL                      | <b>45.7 (8.7–240.5)</b> | <b>&lt;.001</b> |
| PegIFN- $\alpha$ (2a vs 2b)                                      | ...                     | ...             |
| Ribavirin dosing (1200 mg vs lower doses)                        | ...                     | ...             |
| Plasma ribavirin trough concentrations >2.5 $\mu$ g/mL at week 4 | <b>4.8 (1.3–17.1)</b>   | <b>.016</b>     |
| SLC29A1 gene polymorphisms (rs760370 genotype GG vs AG/AA)       | <b>15.9 (2.8–92.2)</b>  | <b>.002</b>     |
| Concomitant antiretroviral therapy                               | ...                     | ...             |
| Median change in hemoglobin (g/dL) from baseline to week 4       | ...                     | ...             |

# Clinical application of ITPA testing

- Not commercially available in USA
- Might inform RBV dose
- Might inform patient counseling
- Might inform timing of rEPO

# Select future areas of HCV clinical expression for genetic research

- **toxicity and effectiveness with DAA**
- **liver cancer**
- **Extrahepatic conditions**
  - **cryoglobulin vasculitis**
  - **Porphyria cutanea tarda**



# Personalized Medicine for Hepatitis C

- **IL28b gives important information on likelihood of spontaneous clearance and SVR**
- **Future applications of ITPA and other discoveries are changing**