National Cancer Institute

Interferon-Alfa, Interferon-λ and Hepatitis C: Applying Genomics to Infectious Disease

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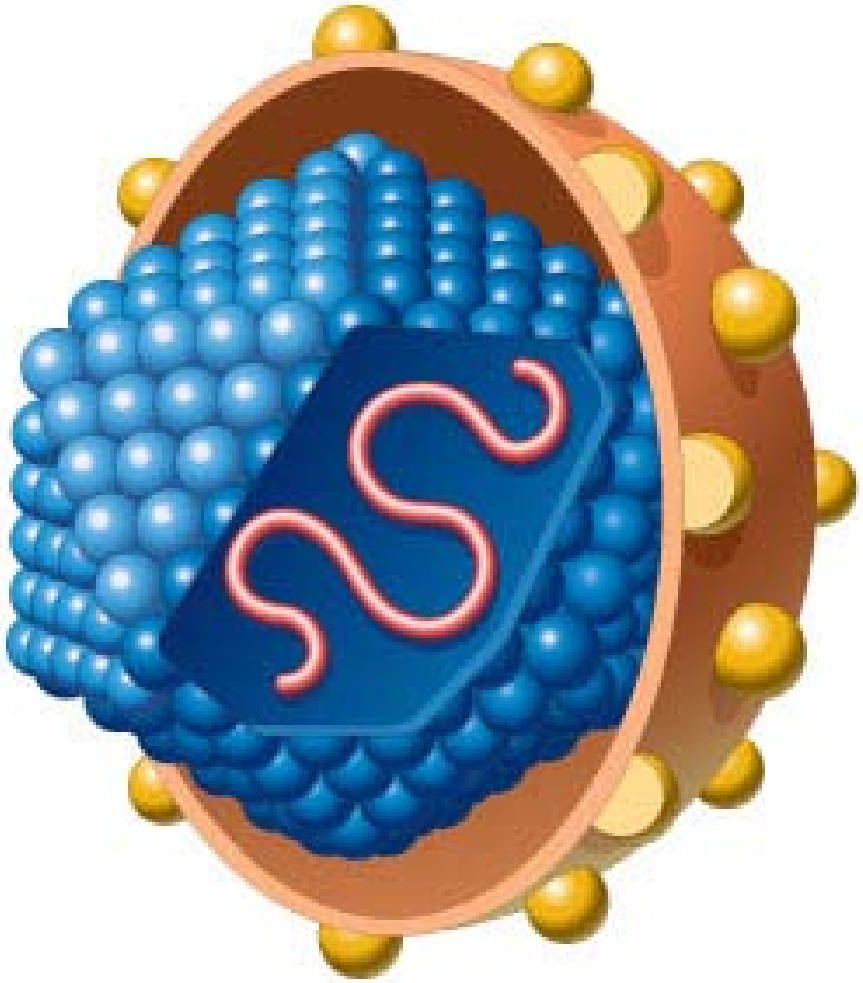
National Institutes of Health

Overview

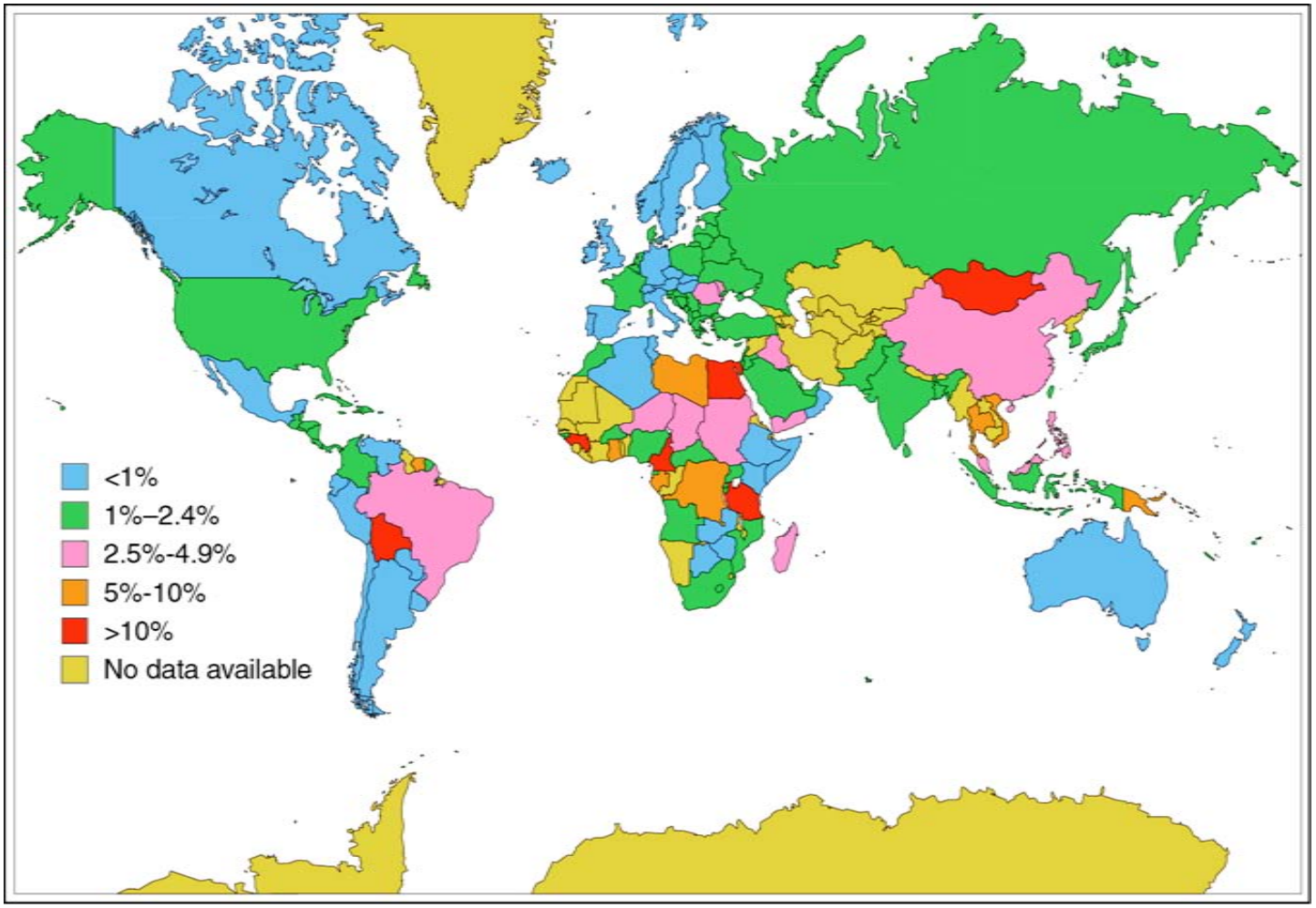
- Infection with hepatitis C virus (HCV) is important public health problem
- Successful anti-viral therapy can prevent HCV-associated morbidity and mortality
- Genomic discoveries regarding *IL28B* (interferon-λ3) have improved our understanding of HCV infection and could improve treatment of HCV-infected patients

Hepatitis C Virus



The Scientist, 2006

HCV Infection Prevalence



~ 170 million are chronically infected

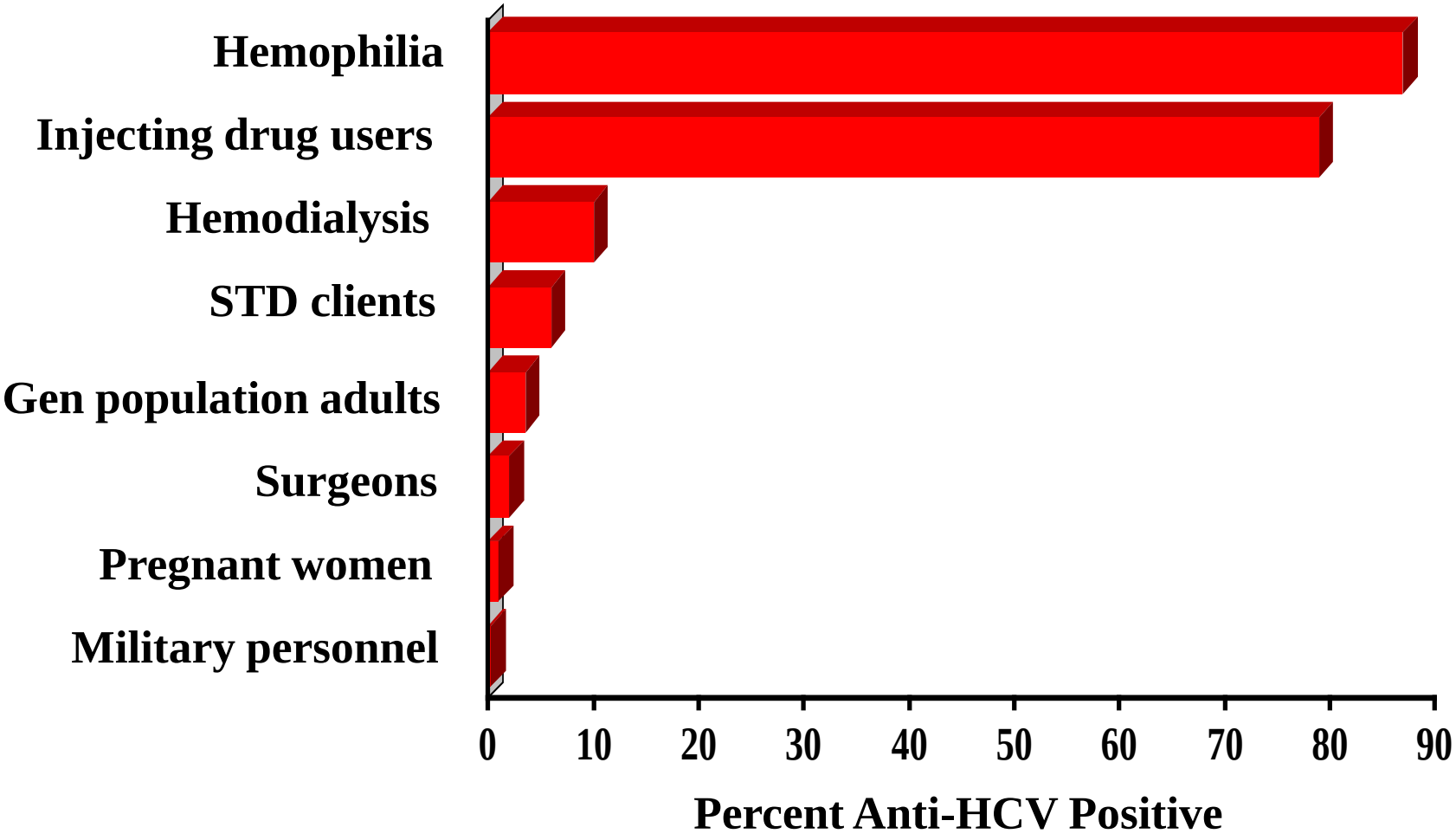
WHO. *Wkly Epidemiol Rec*. 2000

Number Persons with HCV Infection United States

Population	Ever Infected *No. (95% CI)*	Currently Infected *No. (95% CI)*
	(Millions)	
NHANES (1999-2002)	4.1 (3.4, 4.9)	3.2 (2.7, 3.9)
Other Populations	1.1 (0.7, 1.6)	0.9 (0.6, 1,3)
Total	5.2 (4.1, 6.5)	4.1 (3.3, 5.2)

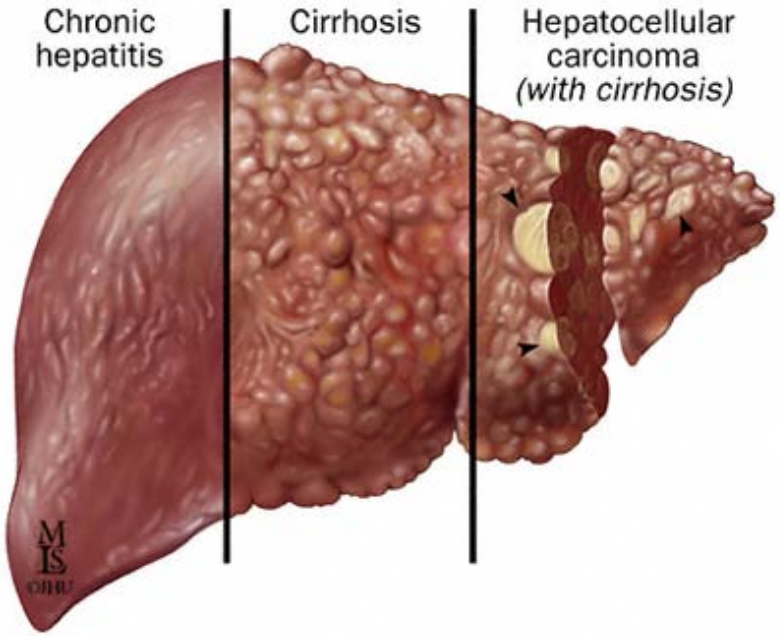
Edlin Hepatology 2005; 42: 213A

HCV Prevalence, by Risk Group



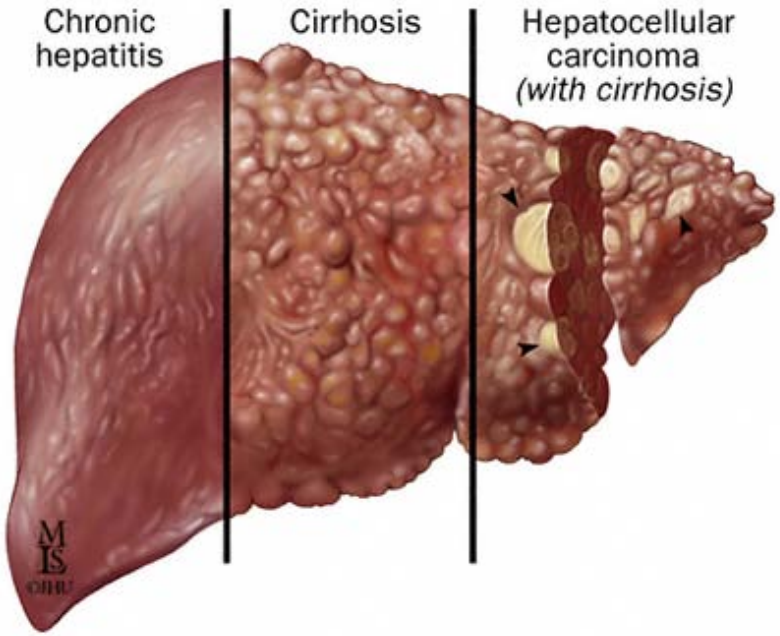
HCV Infection
Clinical and Public Health Considerations

- Acute infection leads to chronic disease ~70-80% of cases
- Chronic hepatitis C is leading cause of:
  - *Cirrhosis*
  - *Liver Transplantation*
  - *Hepatocellular Carcinoma*



HCV Infection
Clinical and Public Health Considerations

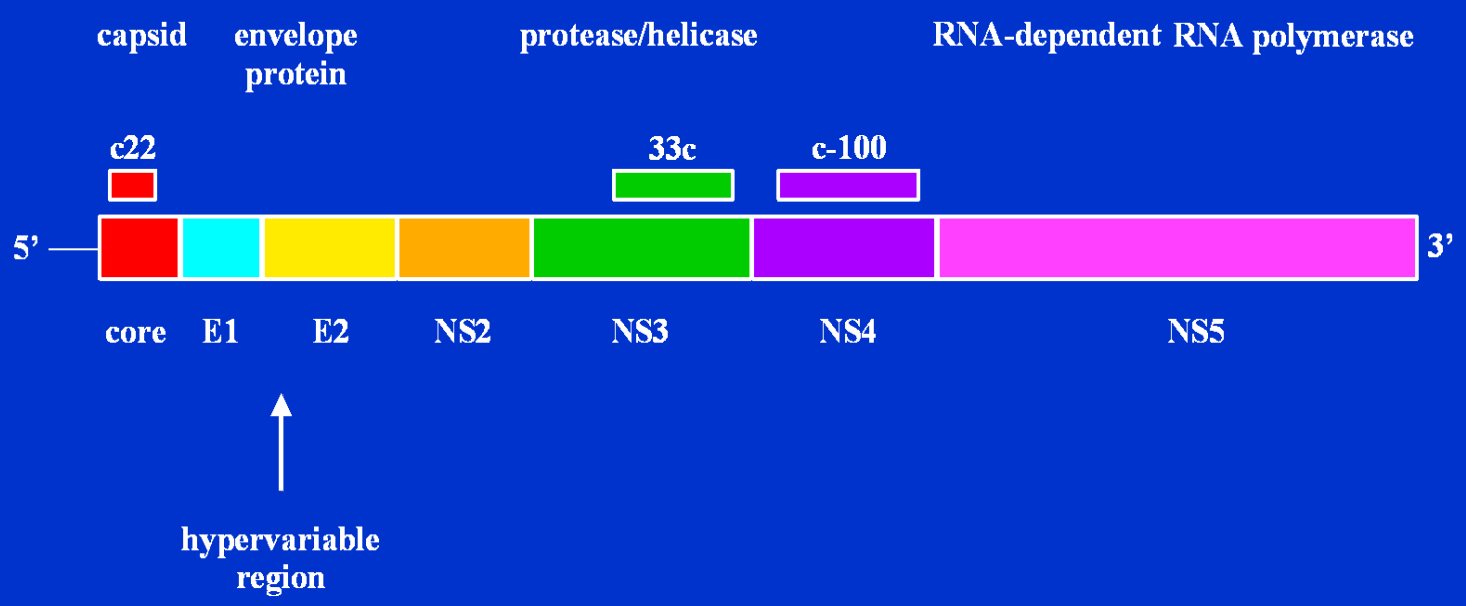
- No vaccine
- Successful treatment greatly reduces risk of liver cancer and end stage liver disease



Treatment of Chronic Hepatitis C

- Current treatment regimen
  - Pegylated-interferon-alfa plus ribavirin (48 weeks)
  - Frequent adverse effects
  - Sustained virological response (SVR) ~45%
    - Varies by viral genotype and other factors

Hepatitis C Virus



Treatment of Chronic Hepatitis C

- Current treatment regimen
  - Pegylated-interferon-alfa plus ribavirin (48 weeks)
  - Sustained virological response (SVR) ~45%

- 'Direct-acting' agents on near horizon
  - ↑ SVR to ~75% (in combination with pegylated-interferon-alfa / ribavirin)
  - Treatment failure → resistant HCV strains

nature genetics

IL28B is associated with response to chronic hepatitis C interferon-α and ribavirin therapy

Vijayaprakash Suppiah[1,2], Max Moldovan[3], Golo Ahlenstiel[4], Thomas Berg[5], Martin Weltman[6], Maria Lorena Abate[7], Margaret Bassendine[8], Ulrich Spengler[4], Gregory J Dore[9,10], Elizabeth Powell[11,12], Stephen Riordan[13], David Sheridan[8], Antonina Smedile[7], Vincenzo Fragomeli[6], Tobias Müller[5], Melanie Bahlo[3], Graeme J Stewart[2], David R Booth[2] & Jacob George[1], for the Hepatitis C Study[14]

- *IL28B* rs8099917 associated with SVR in patients of European ancestry

nature genetics

Genome-wide association of *IL28B* with response to pegylated interferon-α and ribavirin therapy for chronic hepatitis C

Yasuhito Tanaka[1,18], Nao Nishida[2,18], Masaya Sugiyama[1], Masayuki Kurosaki[3], Kentaro Matsuura[1], Naoya Sakamoto[4], Mina Nakagawa[4], Masaaki Korenaga[5], Keisuke Hino[5], Shuhei Hige[6], Yoshito Ito[7], Eiji Mita[8], Eiji Tanaka[9], Satoshi Mochida[10], Yoshikazu Murawaki[11], Masao Honda[12], Akito Sakai[12], Yoichi Hiasa[13], Shuhei Nishiguchi[14], Asako Koike[15], Isao Sakaida[16], Masatoshi Imamura[17], Kiyoaki Ito[17], Koji Yano[17], Naohiko Masaki[17], Fuminaka Sugauchi[1], Namiki Izumi[3], Katsushi Tokunaga[2] & Masashi Mizokami[1,17]

reserved.

- *IL28B* rs8099917 strongly associated with SVR in Japanese patients (odds ratio ~12)

doi:10.1038/nature08309 nature

LETTERS

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

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

- *IL28B* rs12979860 associated with SVR (odds ratio ~2-3) in patients of European and African ancestry

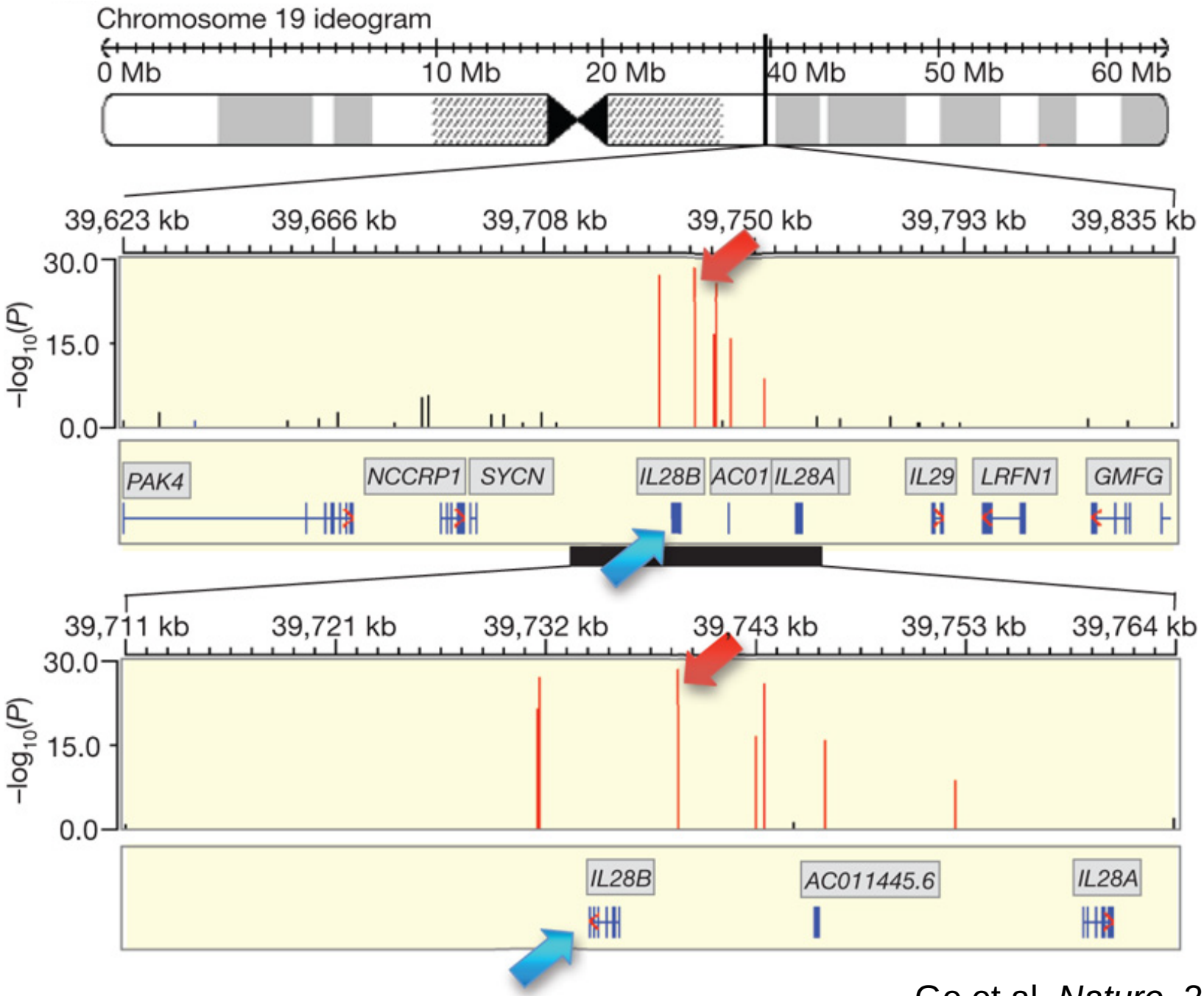
doi:10.1038/nature08463 nature

LETTERS

Genetic variation in *IL28B* and spontaneous clearance of hepatitis C virus

David L. Thomas[1]*, Chloe L. Thio[1]*, Maureen P. Martin[2]*, Ying Qi[2], Dongliang Ge[3], Colm O'hUigin[2], Judith Kidd[4], Kenneth Kidd[4], Salim I. Khakoo[5], Graeme Alexander[6], James J. Goedert[7], Gregory D. Kirk[8], Sharyne M. Donfield[9], Hugo R. Rosen[10], Leslie H. Tobler[11], Michael P. Busch[11], John G. McHutchison[12], David B. Goldstein[3] & Mary Carrington[2,13]

- *IL28B* rs12979860 associated with spontaneous clearance of HCV in subjects of European and African ancestry (odds ratio ~2-3)

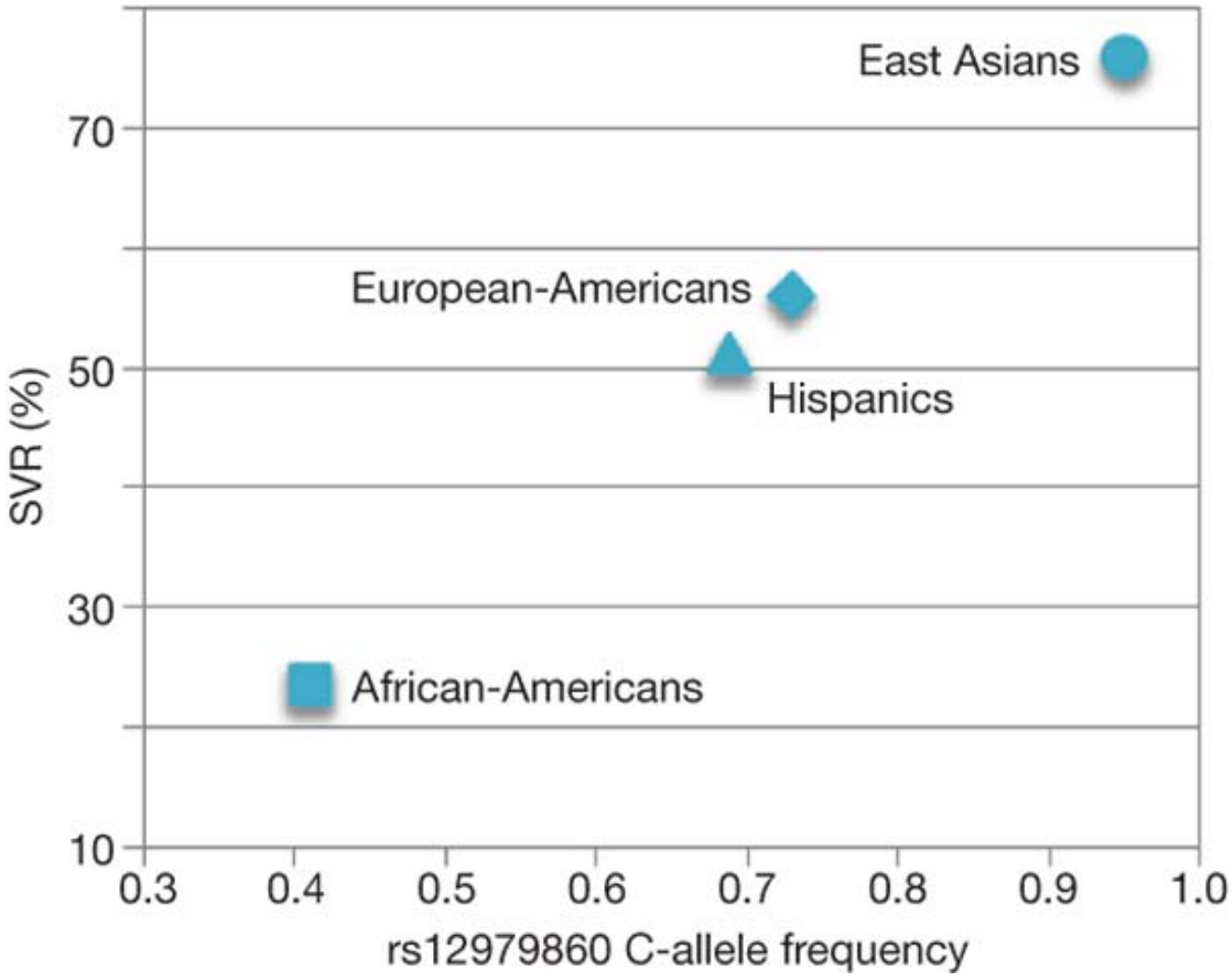


Ge et al, *Nature*, 2009

Allele Frequency - *IL28B* rs12979860-C

Thomas *et al. Nature*, 2009

SVR and rs12979860-C Frequency, by Ancestry



Ge *et al. Nature*, 2009

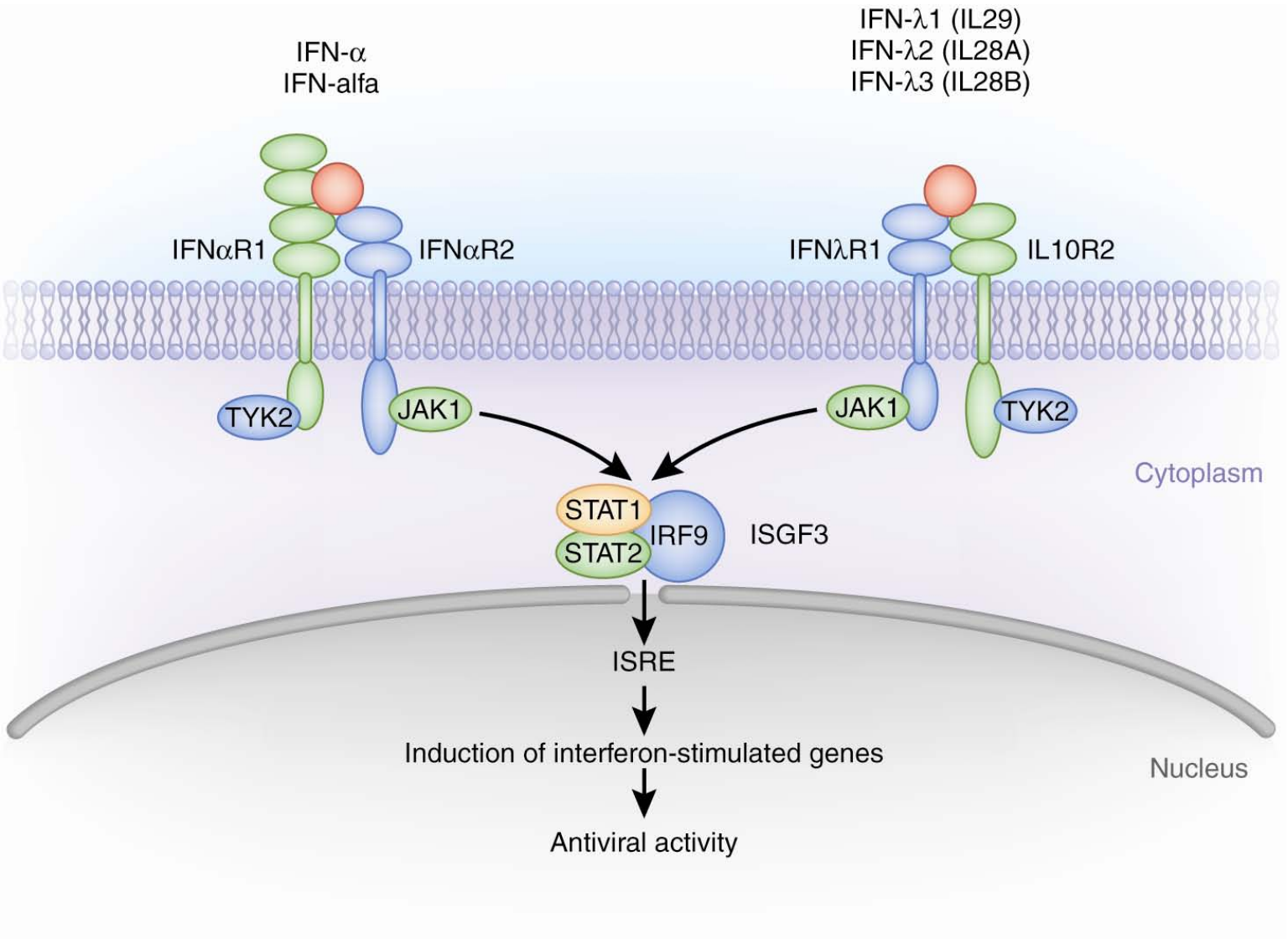
Interferon-λ

- Cytokine family discovered via computational prediction from genomic sequence
  - *IL29* (interferon-λ1)
  - *IL28A* (interferon-λ2)
  - *IL28B* (interferon-λ3)

- Convergence of genomic discoveries!

Kotenko *et al. Nat. Immunol* 2003

Sheppard *et al. Nat. Immunol* 2003



O'Brien, *Nature Genetics*, 2009

Interferon-λ

- Anti-proliferative

- PEG-IL29 already in early trials for HCV
  - Fewer adverse effects?
  - Reverse effect of deleterious IL28B variant on innate immunity?

IL28B Function

- Identity of functional variant(s)?
- Functional mechanism?

IL28B SNPs

SNP	Location
rs12979860	~3 kb upstream of TSS
rs28416813	5’ UTR
rs8103142	Lys70Arg

Ge *et al. Nature*, 2009

IL28A and *IL28B* Amino Acid Sequence

```
IL28B    1 - - - - MTGDCMPVLVLMAAVLTVTGAVPVARLRGALPDARGCHIAQFKSLSPQELQAFKRA
IL28A    1 MKLDMTGDCTPVLVLMAAVLTVTGAVPVARLHGALPDARGCHIAQFKSLSPQELQAFKRA

IL28B   57 KDALEESLLLKDCKCRSRLFPRTWDLRQLQVRERPVALEAELALTLKVLEATADTDPALG
IL28A   61 KDALEESLLLKDCRCHSRLFPRTWDLRQLQVRERPMALEAELALTLKVLEATADTDPALV

IL28B  117 DVLDQPLHTLHHILSQLRACIQPQPTAGPRTRGRLHHWLHRLQEAPKKESPGCLEASVTF
IL28A  121 DVLDQPLHTLHHILSQFRACIQPQPTAGPRTRGRLHHWLYRLQEAPKKESPGCLEASVTF

IL28B  177 NLFRLLTRDLNCVASGDLCV
IL28A  181 NLFRLLTRDLNCVASGDLCV
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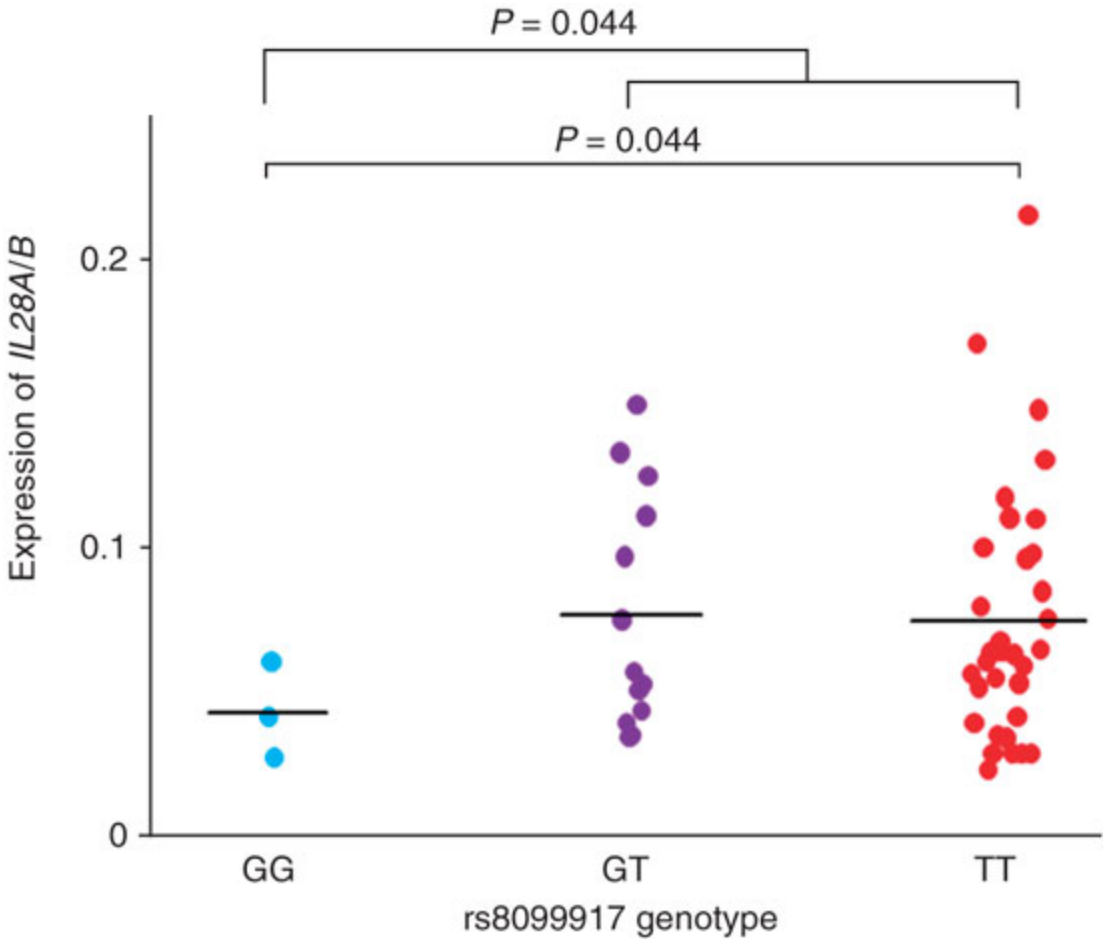
How does variation in a duplicated gene cause such a large effect?



Suppiah, Nature Genetics, 2009

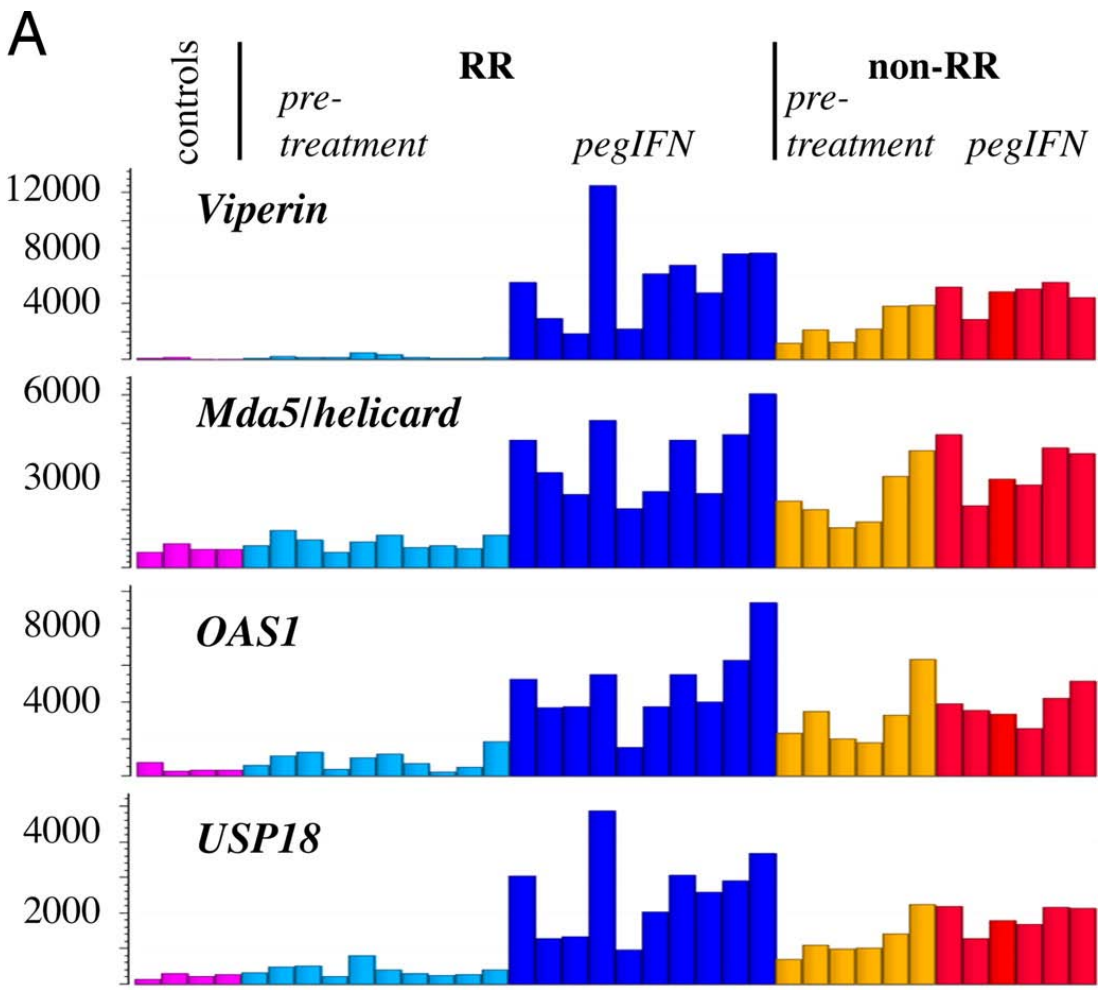
Functional Mechanism of *IL28B*

- Previous ***genomic*** studies of gene expression
  - ↑expression IFN-stimulated genes (ISGs) ***pre-treatment*** associated with ↓ SVR

- Activation of the endogenous IFN system may impede response to therapy by inducing a refractory state of the IFN signaling pathway

Chen Gastroenterology, 2005
Sarasin-Filipowicz, PNAS, 2008

Hepatic ISG Expression Before and After PegIFNα



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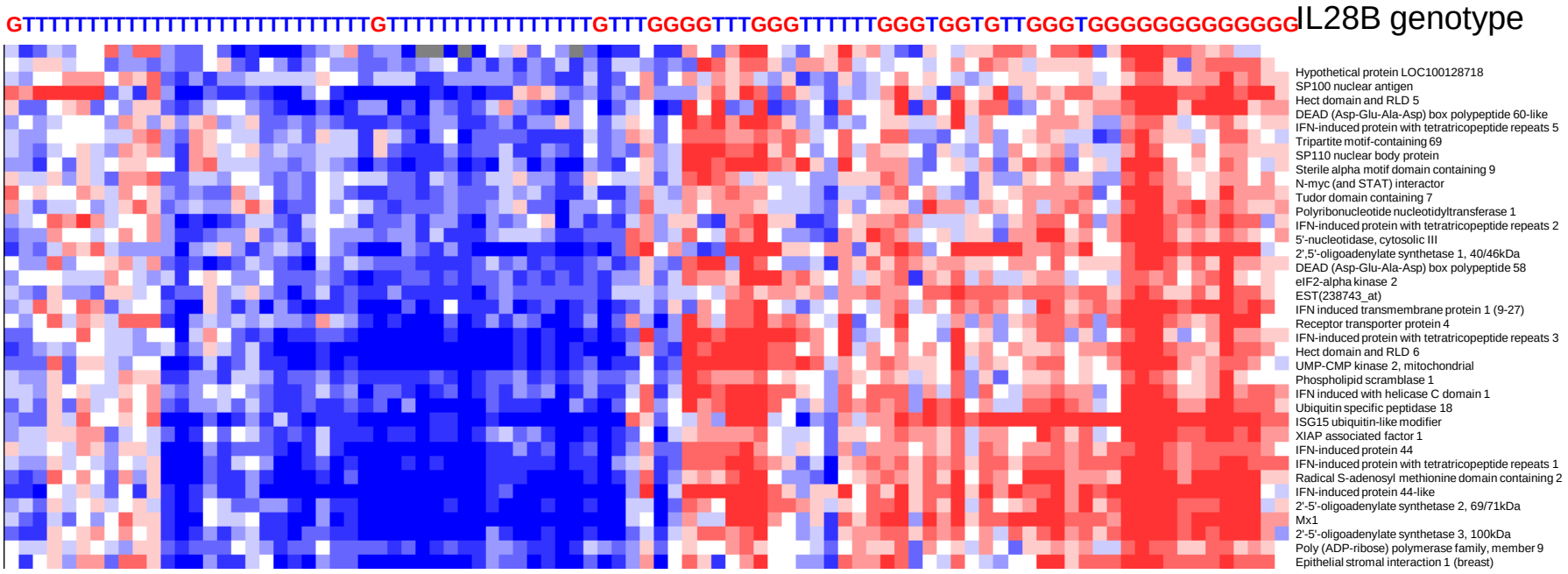
Sarasin-Filipowicz et al. PNAS, 2008

IL28B Genotype and Expresson of Interferon Stimulated Genes


GTTT

Functional Mechanism of *IL28B*

- *IL28B* genotype associated with ↓ intra-hepatic ISG expression

IL28B-CC→ ↓ISG Expression → ↑SVR

Honda, Gastroenterology, in press
Thompson, EASL 2010
Dill, EASL 2010

Interferon-Alfa, Interferon-λ and Hepatitis C *Summary*

- *IL28B* genotype affects:
  - Spontaneous HCV clearance
  - Response to HCV treatment

Interferon-Alfa, Interferon-λ and Hepatitis C
Conclusions

- Specific genetic variant(s) responsible for these effects not yet known, but function may involve effect on ongoing expression of interferon stimulated genes

Interferon-Alfa, Interferon-λ and Hepatitis C
Conclusions

- Application of integrated genomic approaches to infectious diseases may yield discoveries with potential for clinical translation