National Cancer Institute

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Genetic Variants in *IL28B* (INF-λ): Major Predictors of Response to INF-alfa Therapy for Chronic Hepatitis C

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The following relationships exist related to this presentation:

NONE

Major Points

- Genome wide association studies found genetic variants in *IL28B* (interferon λ3) associated with response to treatment for chronic hepatitis C

- Clinical prediction models based on *IL28B* genotype may lead to ‘personalized medicine’ for patients with chronic hepatitis C

Overview

- Hepatitis C virus (HCV)
- Genome wide association studies (GWAS)
- *IL28B* genotype and chronic hepatitis C
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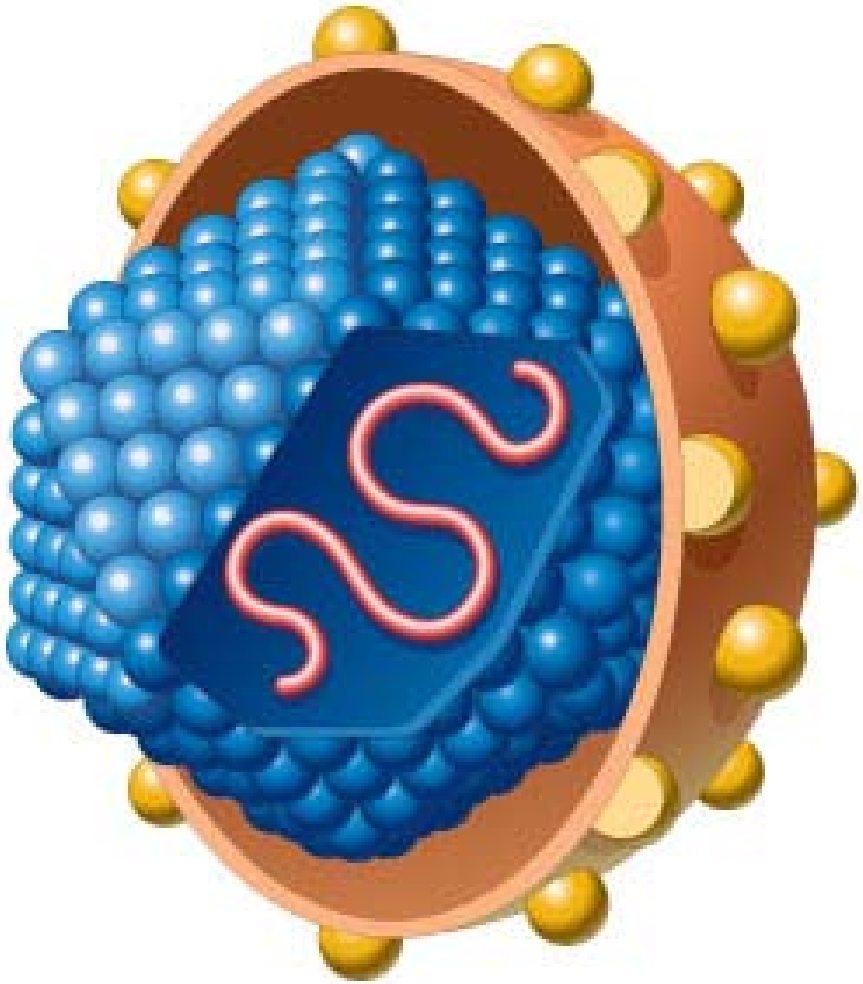
Hepatitis C Virus

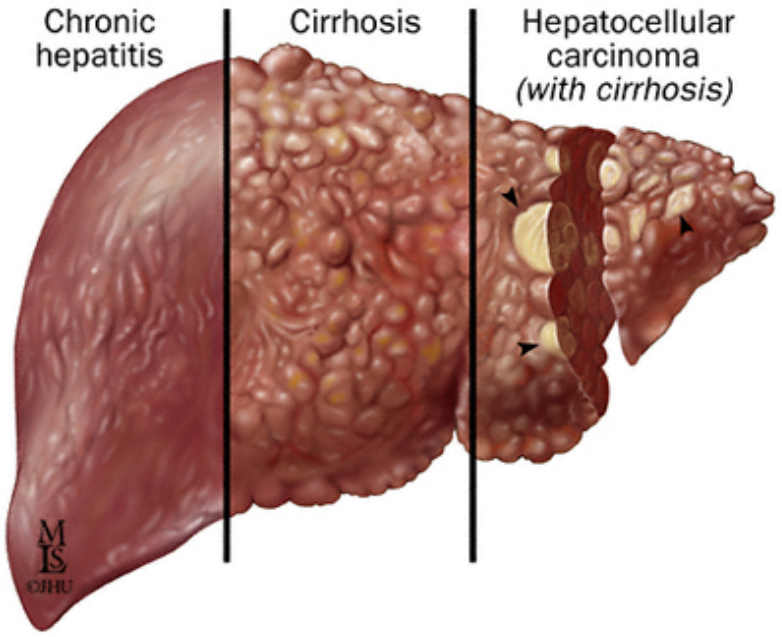


The Scientist, 2006

HCV Infection

Clinical and Public Health Considerations

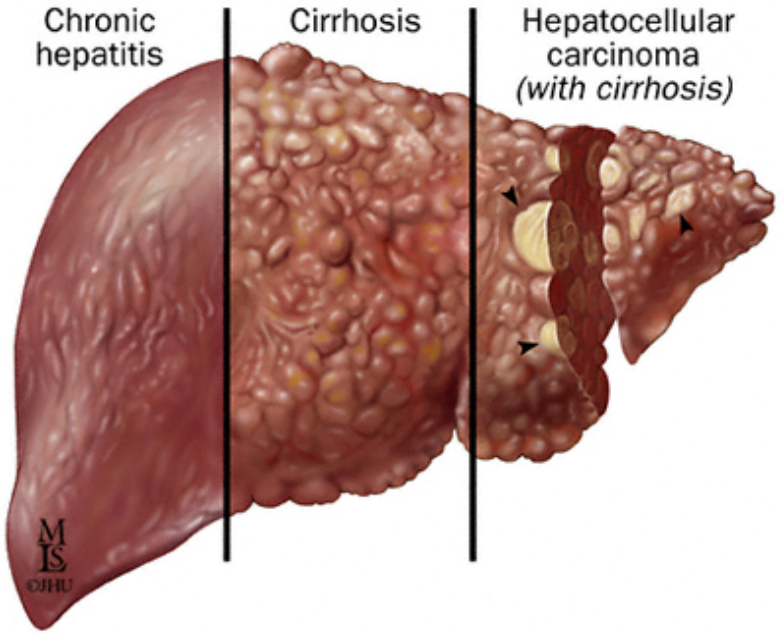
- Acute infection leads to chronic disease ~70-80% of cases
- Chronic hepatitis C burden
  - U.S. ~4 million
  - World ~170 million
- Chronic hepatitis C is leading cause of:
  - *Cirrhosis*
  - *Liver Transplantation*
  - *Hepatocellular Carcinoma*



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)
  - 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

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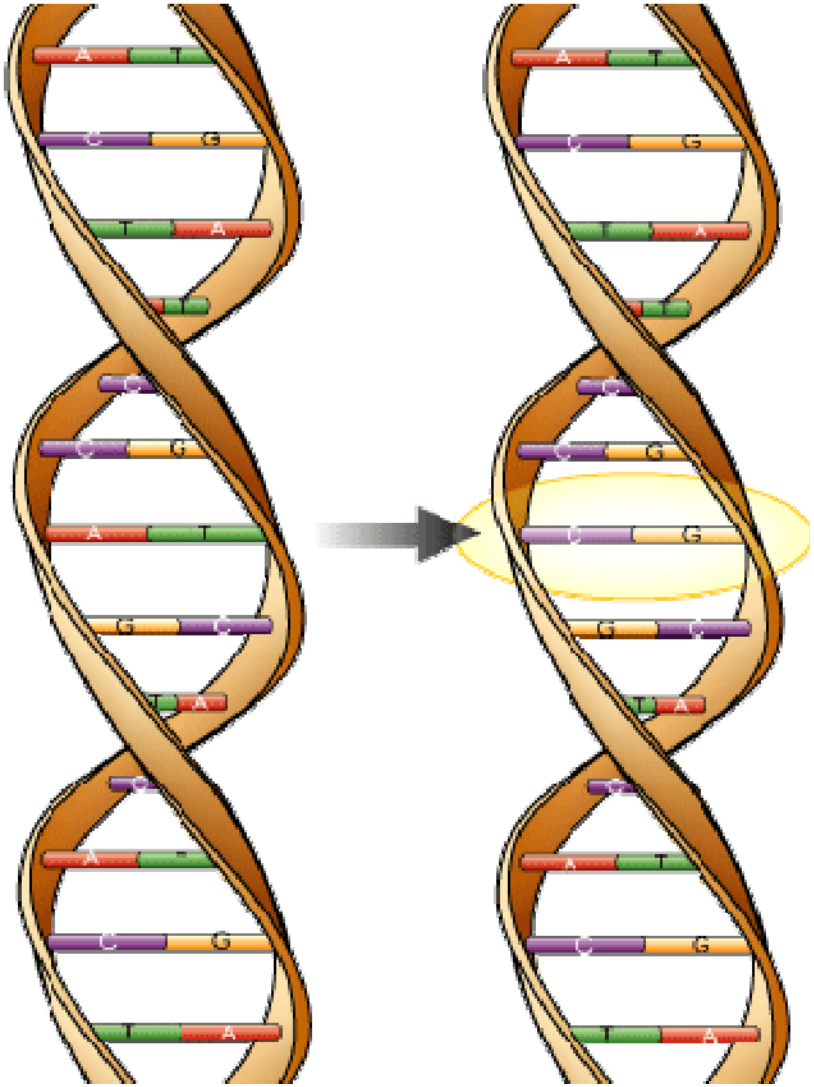
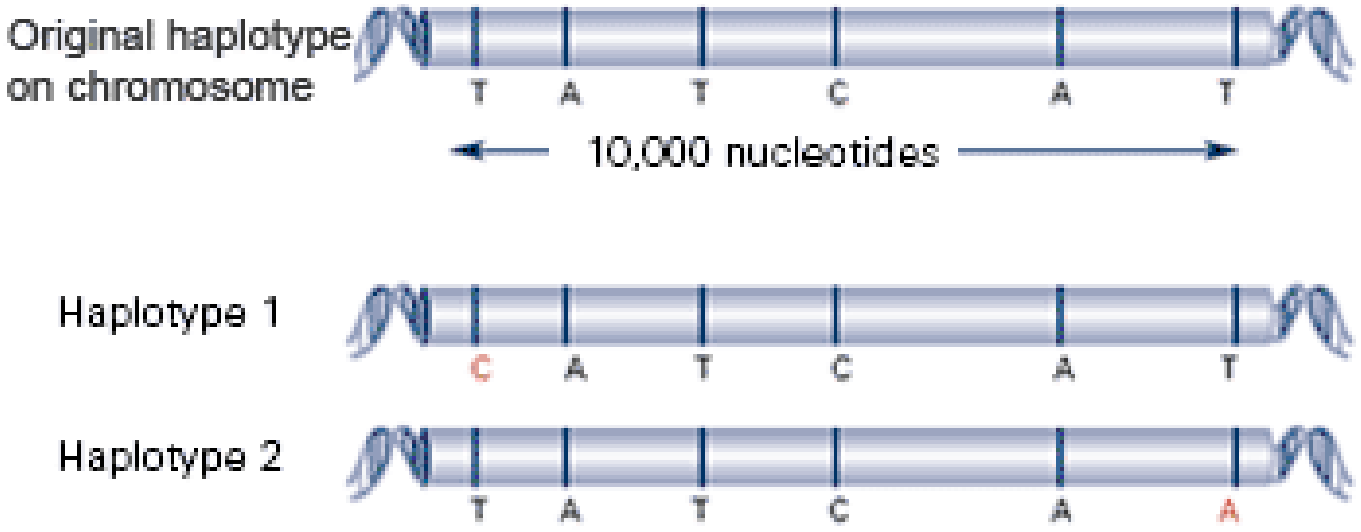
Single nucleotide polymorphism

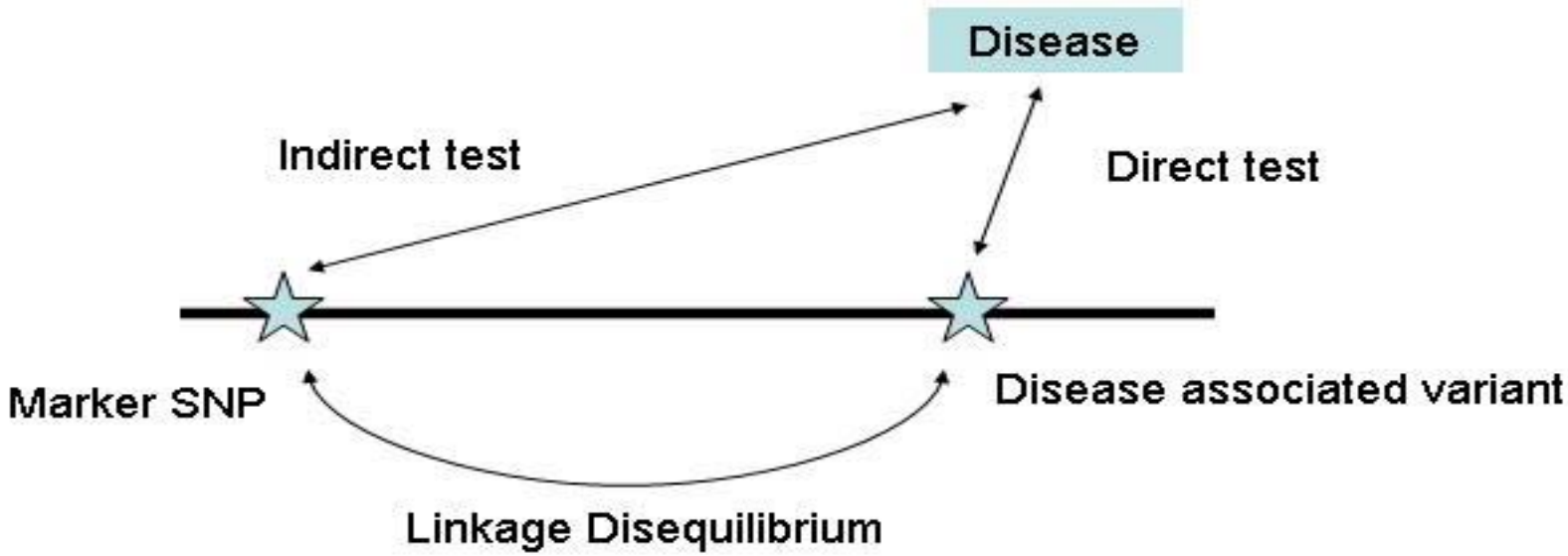



Original haplotype on chromosome
T A T C A T
10,000 nucleotides
Haplotype 1
C A T C A T
Haplotype 2
T A T C A A

Genome Wide Association Studies (GWAS)

- Knowledge of haplotype patterns reduces number of SNPs required for GWAS
  - 10,000,000 → 500,000-1,000,000
- GWAS usually requires large population to control for multiple statistical comparisons
- Identified SNPs usually only markers for 'functional' genetic variant

Use of Marker SNPs in GWAS



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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

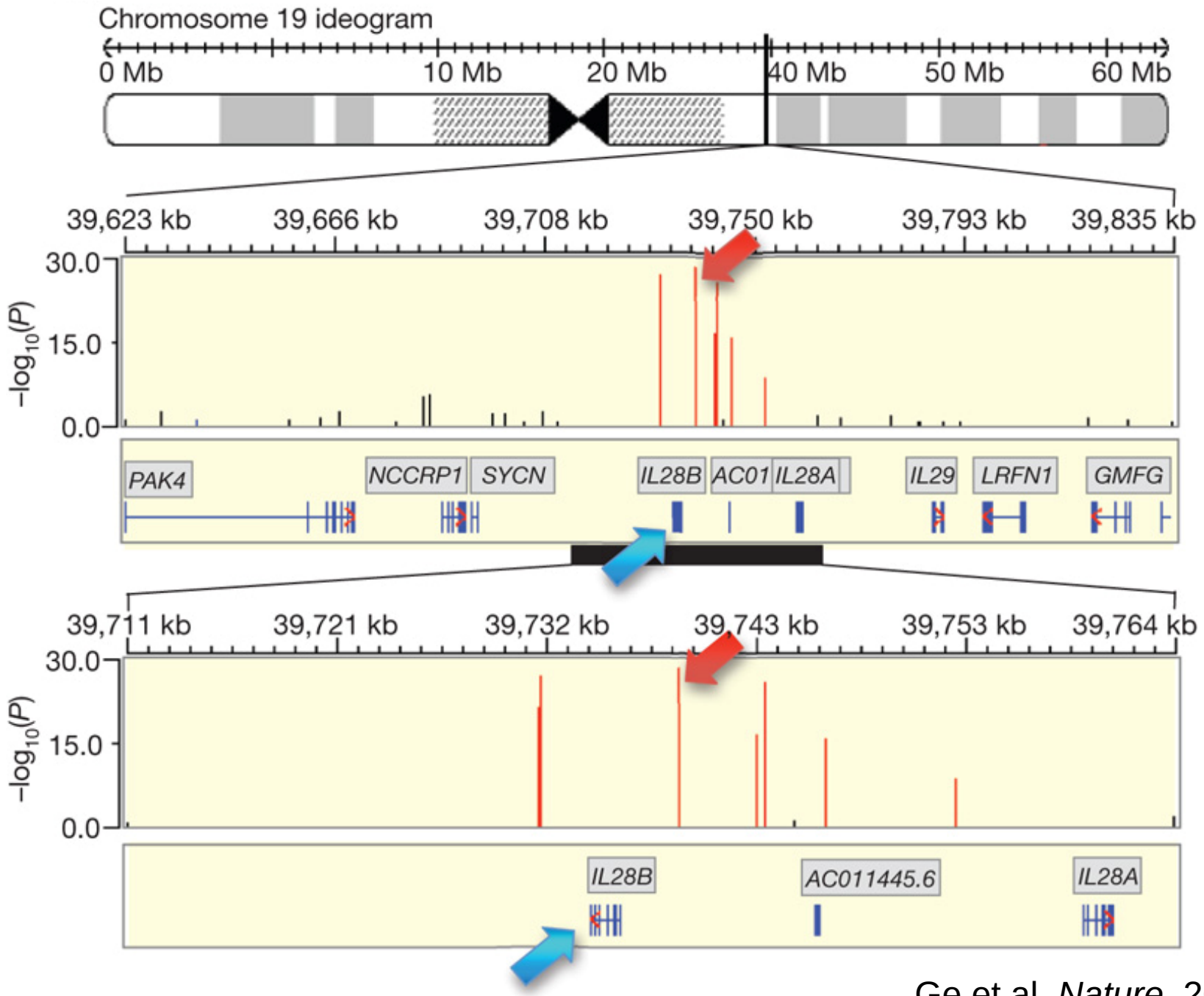
nature genetics

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]

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]

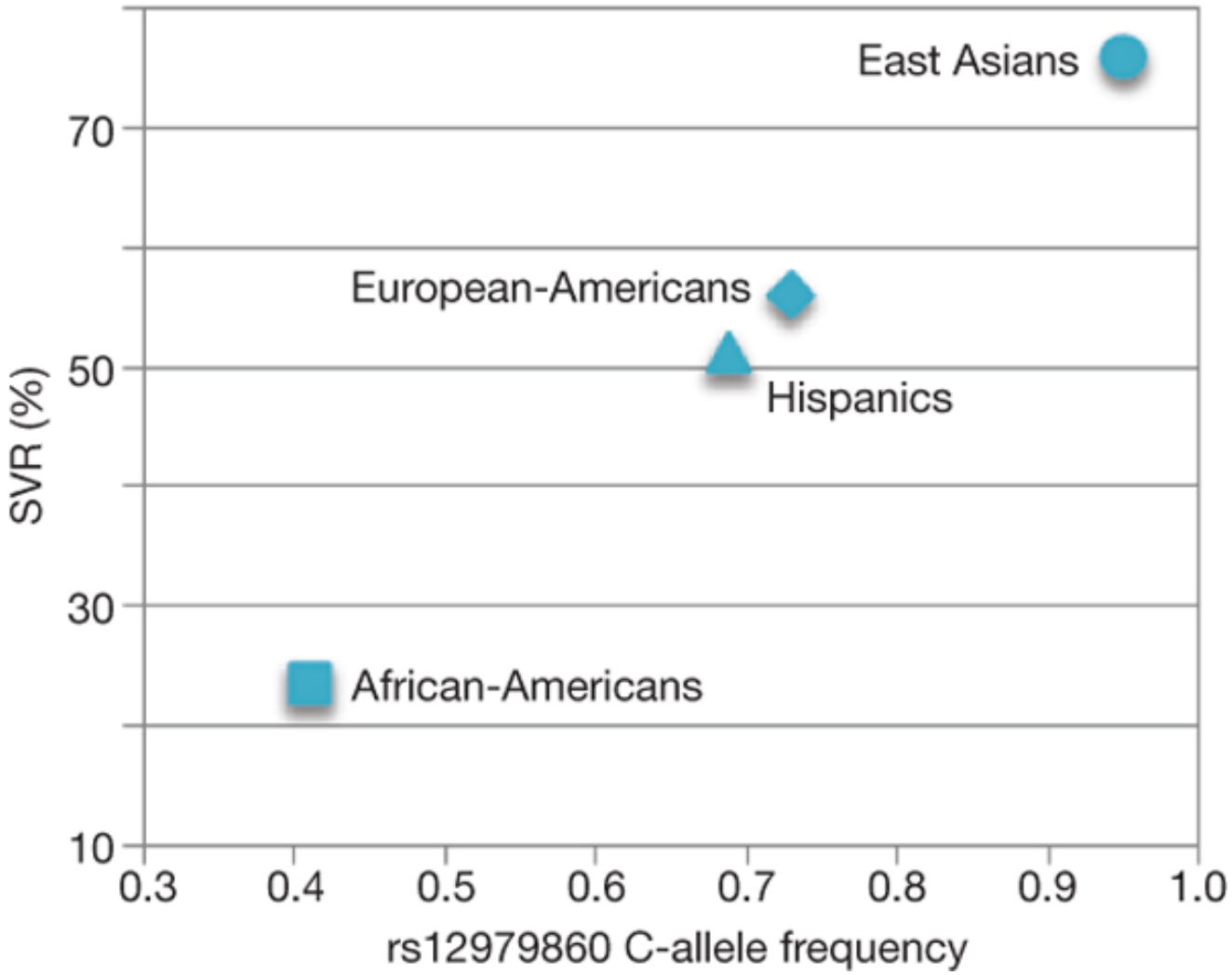


Ge et al, *Nature*, 2009

Allele Frequency - *IL28B* rs12979860-C

Thomas *et al. Nature*, 2009

SVR and rs12979860-C Frequency, by Ancestry



Ge *et al. Nature*, 2009

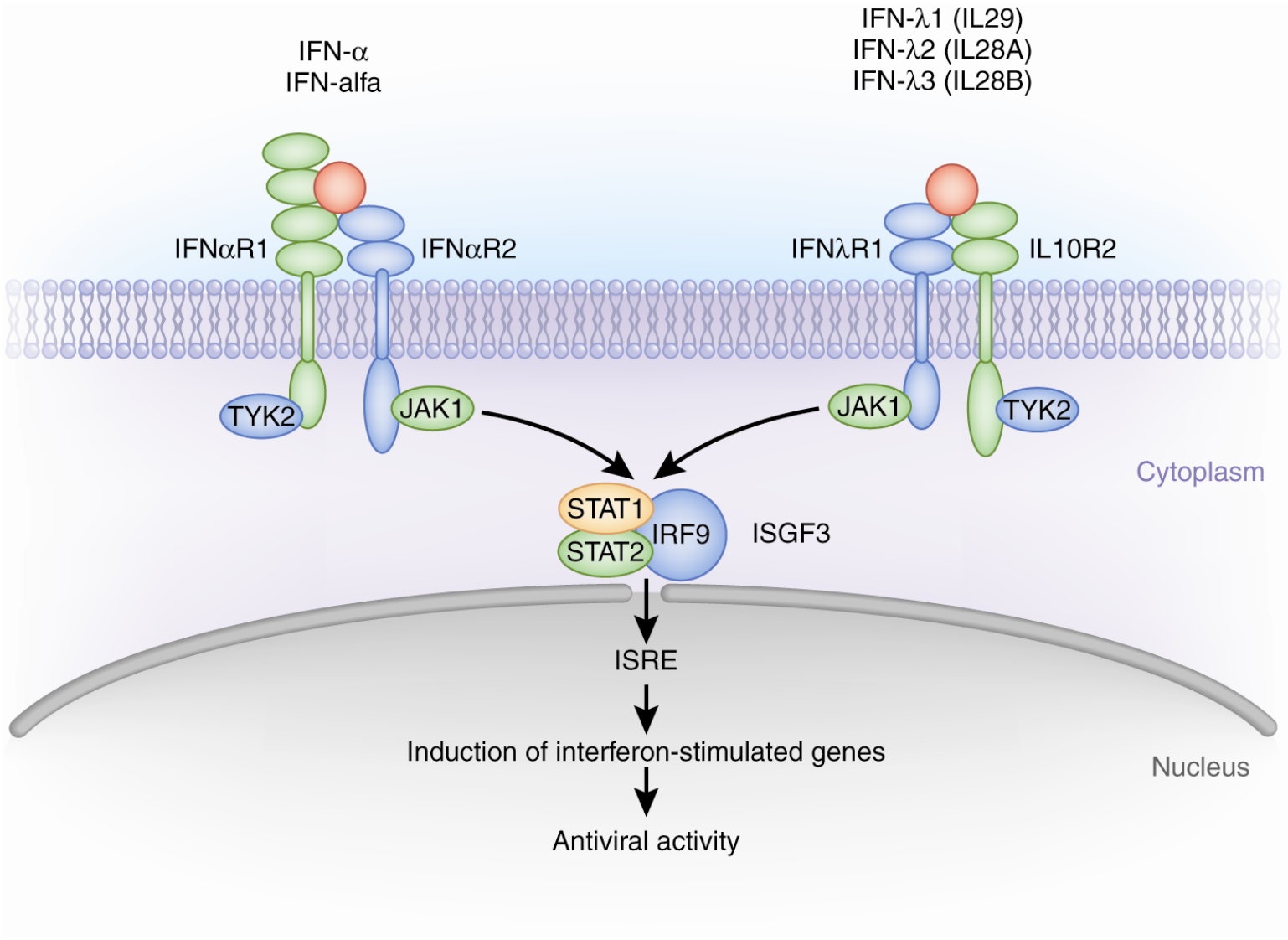
Interferon-λ

- 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

- Interferon-λ (IL29) in clinical trials for HCV
  - Fewer adverse effects?
  - Reverse effect of deleterious IL28B variant on innate immunity?

- Interferon stimulated genes are anti-proliferative as well as anti-viral

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Clinical Prediction Model for Chronic Hepatitis C

- **'Personalized medicine'** - Treatment tailored to patient's individual characteristics, including genetic makeup

- Requires statistical model to estimate probability an individual will respond to treatment

- For chronic hepatitis C, personalized clinical decisions must consider not only *IL28B* genotype, but other factors associated with SVR

SVR Rates in IDEAL Study, by *IL-28B* Genotype, HCV RNA and Fibrosis Score

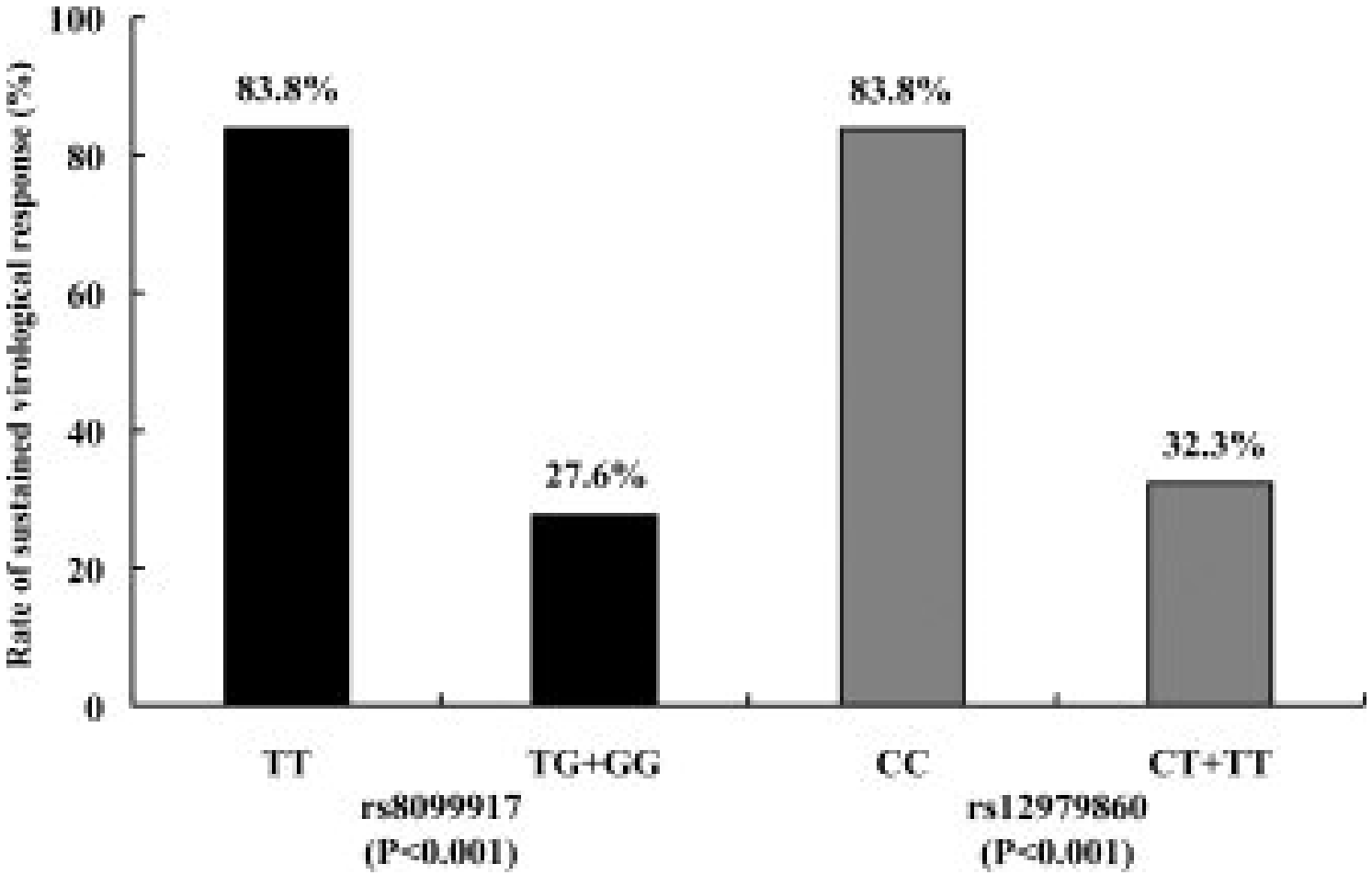
	***IL28B* Genotype**		
	CC	**CT**	**TT**
Overall	69%	33%	27%
HCV RNA ≤600,000 / F0–2	86%	63%	52%
HCV RNA ≤600,000 / F3–4	63%	25%	0%
HCV RNA >600,000 / F0–2	70%	29%	23%
HCV RNA >600,000 / F3-4	**37%**	21%	12%

Adapted from Thompson et al, Gastroenterology, 2010 (Supplementary Table 4)

IL28B Genotype-Based Model for Personalized Prediction of Response to IFN/RBV Treatment

- *IL28B* genotype alone insufficient for clinical prediction of SVR
- Model must discriminate patients who achieve SVR from those who do not
- Model must have good predictive ability

IL28B and Response to Peg-INF/Ribavirin plus Telaprevir



Akuta Hepatology, 2010

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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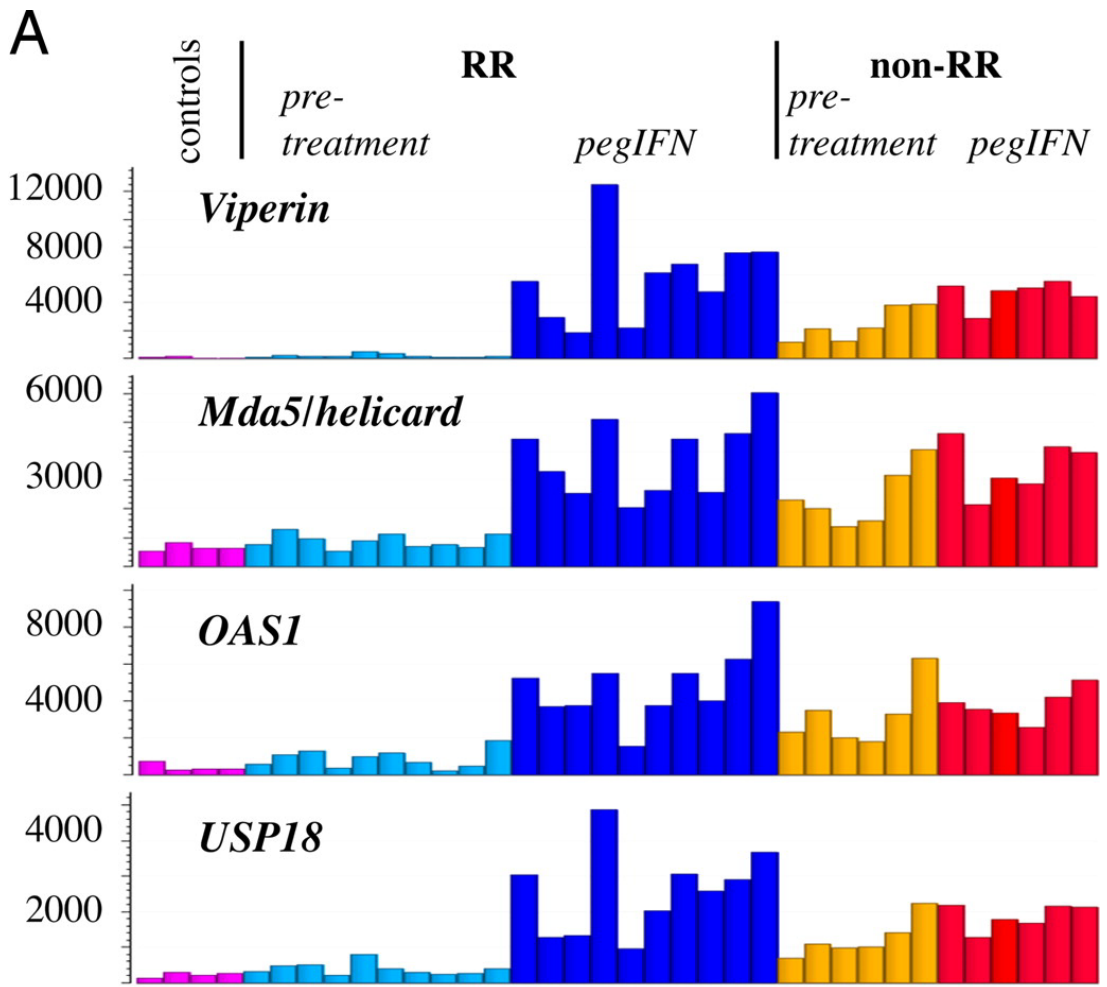
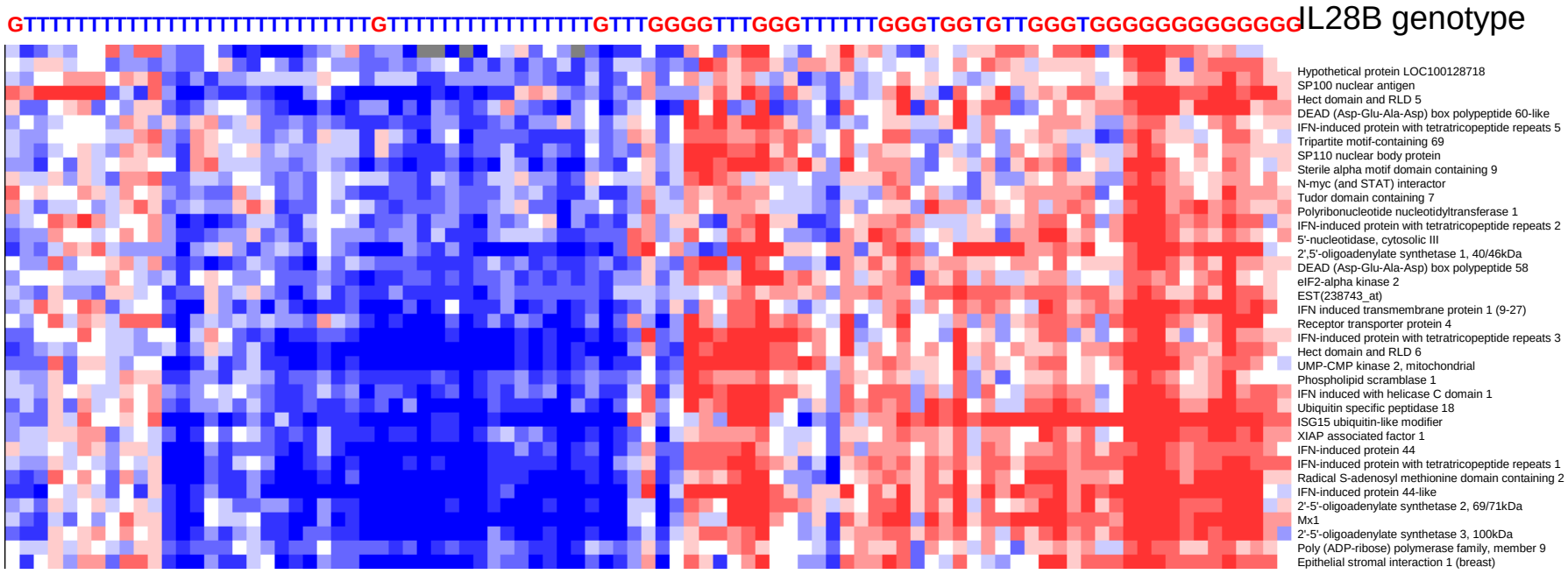
How does variation in a duplicated gene cause such a large effect?

Hepatic ISG Expression Before and After PegIFNα



Sarasin-Filipowicz et al. PNAS, 2008

IL28B Genotype and Expresson of Interferon Stimulated Genes



Honda, Gastroenterology, 2010

Functional Mechanism of *IL28B*

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

IL28B-CC→ ↓ISG Expression → ↑SVR

Honda, Gastroenterology, 2010
Thompson, EASL 2010
Dill, EASL 2010