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

• Clinical prediction model for chronic hepatitis C
Overview

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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
Genome Wide Association Studies (GWAS)

- Knowledge of haplotype patterns reduces number of SNPs required for GWAS
  - $10,000,000 \rightarrow 500,000$ - $1,000,000$
- 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
Overview

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

Dongliang Ge¹, Jacques Fellay¹, Alexander J. Thompson², Jason S. Simon³, Kevin V. Shianna¹, Thomas J. Urban¹, Erin L. Heinzen¹, Ping Qiu³, Arthur H. Bertelsen³, Andrew J. Muir², Mark Sulkowski⁴, John G. McHutchison² & David B. Goldstein¹

*IL28B* rs12979860 associated with SVR (odds ratio ~2-3) in patients of European and African ancestry
Genome-wide association of IL28B with response to pegylated interferon-α and ribavirin therapy for chronic hepatitis C

Yasuhito Tanaka1,18, Nao Nishida2,18, Masaya Sugiyama1, Masayuki Kurosaki3, Kentaro Matsuura1, Naoya Sakamoto4, Mina Nakagawa4, Masaaki Korenaga5, Keisuke Hino5, Shuhei Hige6, Yoshito Ito7, Eiji Mita8, Eiji Tanaka9, Satoshi Mochida10, Yoshikazu Murawaki11, Masao Honda12, Akito Sakai12, Yoichi Hiasa13, Shuhei Nishiguchi14, Asako Koike15, Isao Sakaida16, Masatoshi Imamura17, Kiyoaki Ito17, Koji Yano17, Naohiko Masaki17, Fuminaka Sugauchi1, Namiki Izumi3, Katsushi Tokunaga2 & Masashi Mizokami1,17

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

Vijayaprakash Suppiah1,2, Max Moldovan3, Golo Ahlenstiel4, Thomas Berg5, Martin Weltman6, Maria Lorena Abate7, Margaret Bassendine8, Ulrich Spengler4, Gregory J Dore9,10, Elizabeth Powell11,12, Stephen Riordan13, David Sheridan8, Antonina Smedile7, Vincenzo Fragomelli6, Tobias Müller5, Melanie Bahlo3, Graeme J Stewart2, David R Booth2 & Jacob George1, for the Hepatitis C Study14
Allele Frequency - *IL28B* rs12979860-C

SVR and rs12979860-C Frequency, by Ancestry

Interferon-λ

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

• Convergence of genomic discoveries!

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

<table>
<thead>
<tr>
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<th>IL28B Genotype</th>
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<tr>
<td></td>
<td>CC</td>
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<tr>
<td><strong>Overall</strong></td>
<td>69%</td>
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<tr>
<td>HCV RNA (\leq 600,000 / F0–2)</td>
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<tr>
<td>HCV RNA (\leq 600,000 / F3–4)</td>
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<td>HCV RNA &gt;600,000 / F0–2</td>
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<tr>
<td>HCV RNA &gt;600,000 / F3-4</td>
<td><strong>37%</strong></td>
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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**

<table>
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<tr>
<th>SNP</th>
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<tbody>
<tr>
<td>rs12979860</td>
<td>~3 kb upstream of TSS</td>
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<tr>
<td>rs28416813</td>
<td>5’ UTR</td>
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<tr>
<td>rs8103142</td>
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*Ge et al. Nature, 2009*
IL28A and IL28B
Amino Acid Sequence

IL28B 1 - - - - M T G D C M P V L V L M A A V L T V G A V P V A R L R G A L P D A R G C H I A Q F K S L S P Q E L Q A F K R A


IL28B 177 N L F R L L T R D L N C V A S G D L C V
IL28A 181 N L F R L L T R D L N C V A S G D L C V

How does variation in a duplicated gene cause such a large effect?
Hepatic ISG Expression
Before and After PegIFNα

A

<table>
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<tr>
<th>controls</th>
<th>pre-treatment</th>
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<td>USP18</td>
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Sarasin-Filipowicz et al. PNAS, 2008
**IL28B Genotype and Expression of Interferon Stimulated Genes**

Honda, Gastroenterology, 2010
Functional Mechanism of \textit{IL28B}

- \textit{IL28B} genotype associated with ↓ intra-hepatic ISG expression

\textit{IL28B-CC} → ↓ ISG Expression → ↑ SVR

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