

Genetic Determinants in HCV

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April 27, 2011



Disclosure

My presentation includes
discussion of medications under
investigation

Background - Treatment

- Anti-viral agents offer potential for viral eradication
 - termed Sustained Virologic Response (SVR)
- Treatment leading to SVR is beneficial
 - SVR reduces liver-related morbidity, mortality
 - SVR reduces all-cause mortality
 - In HCV mono-infection
 - In HIV/HCV coinfection

Singal Clin Gastroenterol Hepatology 2010 Berenguer Hepatology 2009 Backus Clin Gastroenterol Hepatology 2011

Only 1 Therapy

- **PegIFN α injections + RBV pills**
 - IFN immunomodulator
 - RBV nucleoside analogue active against several viruses
 - Do not specifically inhibit enzymes critical in HCV replication
- **Ineffective**
 - SVR < 50% G1 pts. (75% pts U.S.)
- **Toxic**
 - Many adverse effects, numerous contraindications
 - Minority pts. treated
- **Treatment decisions complex**
 - Based on determinants that help predict viral response
 - Degree fibrosis



Many Factors Contribute to Response

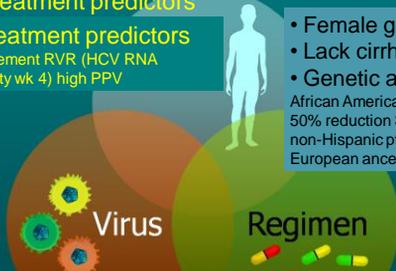
Pre-treatment predictors

On-treatment predictors

- Achievement RVR (HCV RNA negativity wk 4) high PPV

- Female gender
- Lack cirrhosis
- Genetic ancestry

African American pts.
50% reduction SVR vs.
non-Hispanic pts.
European ancestry



- Genotype: G 2,3 > sensitive to therapy vs. G1
- Low HCV RNA level

3/11/2011 FCIB-HCV DRUG 24

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Host genetic associations with SVR

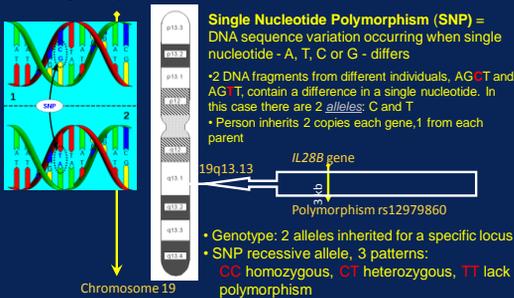
- **Limitations of pretreatment characteristics**
 - Do not accurately predict treatment response G1 pts.
 - Do not adequately explain variation in response
 - Variability, especially between pts. different ancestral groups, suggested that human genetic variability may explain differences
- **Role of immunomodulator IFN α in treating HCV driven search for genetic associations between components of immune system + outcome therapy**
 - Human genome > 3.3 billion base pairs
 - > 10 million of these may vary in nucleotide sequence between individuals
 - ? Find variation that results in heightened susceptibility to IFN?
- **2009: Interleukin 28 Beta (IL28B) gene**
- **3 independent groups researchers in different parts of the world described IL28B as being highly predictive of response to pegIFN/RBV in G1 HCV-monoinfected treatment-naïve pts.**

Ge Nature 2009 Suppiah Nat Gen 2009 Tanaka Nat Gen 2009 Clark Am J Gastro 2011

Objectives

1. Understand key recent advances in genomics and hepatitis C virus
2. Describe the biological importance of IL28B genotypes
3. Understand the clinical relevance of genetic variation in IL28B

2009: Breakthrough in HCV Pharmacogenomics A Polymorphism on Chromosome 19 Predicts SVR



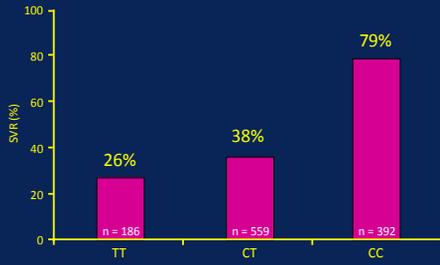
Ge D, et al. *Nature*. 2009;461:399-401. Chromosome 19 graphic courtesy of Oak Ridge National Laboratory. Available at: <http://www.ornl.gov/sci/techresources/meetings/ecr2/olsen.gif>.

Ge et al. 1st published report

- Conducted genome-wide association study to investigate genetic predictors treatment response
 - using 1,137 North American HIV-negative pts. with chronic HCV G1 who had entered a clinical trial of pegIFN/RBV
- Possession favorable gt CC at IL28B associated with 2.5-fold increase SVR rate compared with non-favorable gt (CT/TT)

Ge D, Fellay J, Thompson A, Simon J, Shianna K, Urban T, Heitzman E, Qui P, Bertelsen A, Muir A, Sulkowski M, McHutchison J, Goldstein D. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;461:399-401

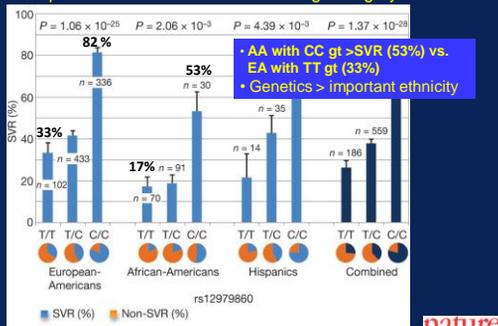
IL28B Genotype and SVR All Patients



Ge Nature 2009

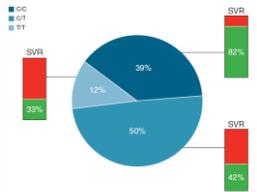
Percentage of SVR by IL28B gts

CC gt associated with increase SVR ethnic groups
Response rates lower for AAs in each gt category



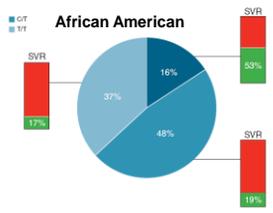
• AA with CC gt >SVR (53%) vs. EA with TT gt (33%)
• Genetics > important ethnicity

European American



• CC gt more common European Americans (39%) than African Americans (16%)

African American



• Difference in frequency CC gt thought to account for half of observed ethnic variation in treatment response

Ge Nature 2009 Clark Am J Gastro 2011

Regional Distribution of IL28B CC Genotype

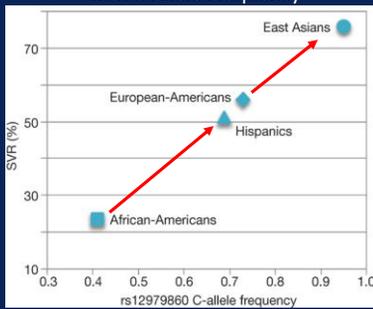
Pie charts show frequency of the C (green) and T (blue) alleles

Higher frequency C allele East Asians, >70% CC
Explains why pts. Asian ancestry, despite prevalence G1, highest SVR rates



Thomas Nature, 2009 Reprinted by permission from Macmillan Publishers Ltd Ge Nature 2009

SVR Rates Across Population Groups Display Concordance with C-Allele Frequency



Ge Nature 2009 doi:10.1038/nature08309

nature

Findings replicated in studies of other clinical cohorts around world

Confirmed:

- Carriage 2 favorable alleles strongly, but not fully, predicts SVR
- 1 or 2 non-favorable alleles does not completely predict non-response

Clinical perspective: Compare impact IL28B and conventional predictors SVR

- Vs. Pre-treatment factors, IL28B
 - Overrides HCV viral load, degree fibrosis, ancestry
 - Comparable or > viral genotype
 - IL28B status (CC vs. non-CC) strongest predictor SVR
- Vs. On-treatment parameters, RVR stronger predictor

Tanaka 2009 Supplah 2009 Ge 2009 Thomas Nature 2009 Chung Gastro 2010 Thompson Gastro 2010

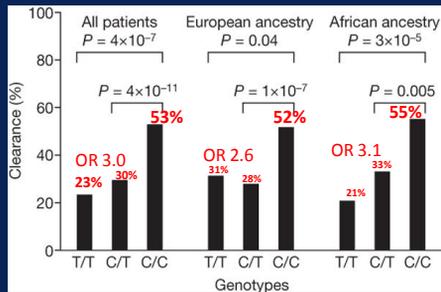
Spontaneous Clearance

- Following HCV infection, natural (spontaneous) viral clearance (without therapy) occurs 25% pts. within 1st 3-6 mos.
- Ge et al: C allele frequency reduced in chronically infected vs. matched controls
 - Suggested association between C allele + higher rate natural clearance
- Thomas: CC gt associated with spontaneous clearance in untreated pts. following acute HCV infection
 - Spontaneous clearance rates CC pts. 2-3X those for CT/TT
 - Holds for pts. coinfecting with HIV and HBV
- C = cure/clearance
- Implicated IL28B as having primary role in resolving HCV
 - IL28B important not only in response to IFN-based therapy, but in
 - Pathogenesis
 - Host immune response to HCV

Ge 2009 Thomas Nature 2009 Thomas Rauch Gastroenterology 2010

Percentage Spontaneous HCV Clearance by Host gt

Overall clearance rate: CC 53% vs. CT/TT 28%



Similar clearance rates among individuals of European, African ancestry

DL Thomas 2009 nature

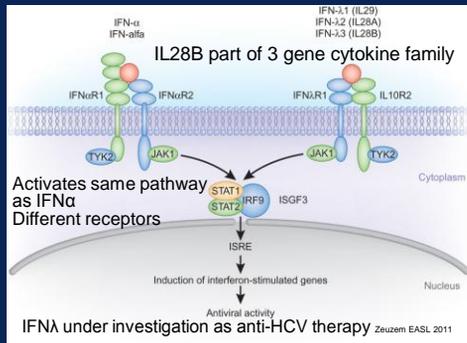
Many investigations in retrospective cohorts of pts. treated with pegIFN/RBV whose DNA had been collected, stored

CC gt associated with...

- Higher SVR rates
 - HIV/HCV coinfecting pts.
 - G 2 and 3 pts. ?
 - Association weaker in comparison to G1
 - Non-responders
 - Liver Transplant setting
 - Higher SVR with HCV treatment post-liver transplantation when CC variant occurs in either recipient or donor liver
 - CC donor livers might be preferentially allocated to HCV pts.
- Higher RVR rates – enhanced on-treatment viral kinetics
- Spontaneous clearance among infected infants born to G1 women

Pineda CID 2010 Rallon AIDS 2010 Moghaddam Hepatology 2011 Stättmayer Clinical Gastro and Hepatology 2011 Araujo JAIDS 2011 Chevaliez Gastro 2011 Ruiz-Extremera Hepatology 2011 Charlton Hepatology 2011

Mechanism IL28B?



Kotenko Nat Immunol 2003 Sheppard Nat Immunol 2003 O'Brien Nature Genetics 2009

How might IL28B be used in clinical practice?

- **Licensed PCR assay for IL28B available in US since July 2010**
 - Multiple vendors (LabCorp, Quest, Roche Molecular etc), cost \$300
 - Test performed on whole blood sample
 - Result reported as CC, CT or TT
 - Use existing billing codes (83891, 83898, 83896x2, 83912) for reimbursement
- **Help predict groups with very high or low likelihood SVR**
Ex: Increase number of potential responders who receive therapy
 - Throughout the world, treatment for HCV has poor uptake, often due to pt. + physician concerns about efficacy, tolerability
 - Knowledge CC gt could motivate pts. undergo treatment, adhere to treatment; motivate providers to treat
- **HCV treatment about to change**
 - Threshold revolution in HCV therapy, introduction of direct acting antiviral agents (DAAs), inhibit enzymes critical to HCV replication
 - Lead to higher cure rates
- **TRUE goal/Another goal DAAs – get rid IFNα**
- **Could have used IL28B 10 yrs ago**

IL28B Incorporated Development DAAs

- **Clinical trials pegIFN/RBV + DAAs stratified by IL28B gt**
 - Avoid significant numbers CC pts. being randomized unequally into different arms of a study
 - Ensure promising results which may be due to genetic susceptibility to IFNα component of regimen not attributed to potency of new drug
- **Studies new DAAs required to establish if IL28B variants will change clinical practice recommendations**
- **1 published study evaluating predictive role IL28B with DAAs**
 - Small cohort pts. receiving telaprevir, experimental PI, + pegIFN/RBV. SVR rates:
 - 83% CC subjects
 - 32% non-CC subjects
- **Suggests IL28B gt may be predictive of SVR in treatment with PIs plus pegIFN/RBV**

Akuta Hepatology 2010

Early in Study of Role IL28B gt with DAAs

46th Annual Meeting of European Association for Study of the Liver (EASL) Berlin, March 30-April 3 2011

- With potent DAAs, will importance IL28B disappear?
 - IL28B gt Not Associated With SVR in Treatment-Experienced Pts. Receiving Telaprevir-Based Triple Therapy
 - Similar SVR Rates in IL28B CC, CT or TTs
- Will IL28B predict subpopulations may receive shorter course therapy?
 - Telaprevir substantially improved SVR rates across all IL28B gts in ADVANCE trial
 - Greatest improvement in SVR occurred in CT/TT pts.
 - SVR 90% CC
 - Potential for shorter treatment duration
 - Studies planned evaluating 12-wk PI-based regimens in G1 CC pts.
 - IL28B gt Predicts Likelihood of Shortened Therapy in SPRINT-2 and RESPOND-2 Phase III Boceprevir Trials

Pol EASL 2011 Poordad EASL 2011 Jacobson EASL 2011

IFN-free regimens

- DAAs cannot be used as monotherapy because resistance develops
 - At least 1st generations will be used in combination with IFNα/RBV
 - We will soon be called to decide whether our pts. should be treated with
 - Current SOC
 - PegIFN/RBV plus DAA
 - Wait for IFN-free DAA cocktail
 - Decision may be easier with IL28B
 - G1 non-CC pts. without fibrosis
 - Avoid current SOC
 - Stuck with IFN while
 - Many may not benefit from DAAs
 - Drug interactions, lack access
 - Yrs away from Atripla for HCV
- 
- Theoretically IL28B gt not expected to have major impact on efficacy IFN-free, combination DAA regimens
 - Currently being explored
 - Whether in future pts. may be selected on basis of genetic make-up to undergo IFN-free treatment remains to be demonstrated

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Genetics and HCV

Towards a Personalized Treatment ?

- Role IL28B in clinical practice?
- Role as new treatments become available?
 - Will IL28B be part of FDA labeling for DAAs?
 - HCV treatment paradigm will continue to shift
 - Both clinicians and pts. must stay on top of these changes that will influence treatment decisions
- IL28B gt alone insufficient in predicting SVR
 - Should never be used to deny pt. HCV treatment
- Mathematical clinical prediction models based on IL28B gt and clinical characteristics (e.g. fibrosis) under development
 - Goal: Computer-based tool
 - Provide pts. and providers with personalized prediction of treatment success



Romero-Gomez Liver Int. 2011 Walk Hepatology 2009 O'Brien Hepatology 2010 Medrano CID 2010

IL28B Gt: A Major Discovery Leads to Many New Scientific Questions

- **Investigation IL28B gene family active area of study**
 - Is this a marker of IFN response beyond HCV?
 - Implications for other diseases with IFN-based regimens (e.g. HBV, melanoma)?
- **Half of pts. achieving SVR do not carry favorable IL28B gt**
 - What other genetic contributors involved?
- **Other SNPs under study: Ex. ITPA Deficiency Testing**
 - Recent identification 2 SNPs within the inosine triphosphate pyrophosphatase (ITPA) gene protective against RBV-induced hemolytic anemia
 - Genetic Test for ITPA gt may be available soon
 - Guide decision-making for pts. in whom RBV avoided/given lower doses because of risks for developing anemia

Romero-Gomez Liver Int. 2011; Volk Hepatology 2009; O'Brien Hepatology 2010; Medrano CID 2010

Will payers require CC pts. be initially treated without DAAs to see if they have RVR, likely to respond to SOC?



Summary and Conclusions

- Recent studies have shown genetic variations at the IL28B gene on chromosome 19 strongly correlate with
 - Susceptibility to pegIFN α /RBV therapy
 - Natural ability to clear HCV
- Associations similar in persons with and without HIV coinfection
- Ethnic differences SVR mostly related to different frequencies of CC gt
- Associations led to clinical genetic tests to help guide antiviral treatment
 - IL28B gt expected to impact treatment anytime IFN α used
 - Impact with DAAs may be attenuated vs. current SOC
 - Present and near future scenario, RVR selects best candidate to SVR
- **Limit costs, support rational use IL28B**
 - Increase number of pts. for whom treatment beneficial
 - Minimize treatment among those in whom it may be deleterious
- **Additional prospective studies IL28B needed to clarify its value**

Mangia Digestive and Liver Disease 2011
