Genomewide Studies Reveal Transporters as Determinants of Drug Response

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Genomewide Studies Reveal Transporters

Genetic Variants in Transporters:
- Mendelian Disease
- Common Disease and Traits
- Drug Response (ITC Polymorphisms)

- Genomewide Association Studies (GWAS) Reveal Biomarkers for Transporters
83 SLC Transporters In > 100 Mendelian Diseases

Common Disease: >150 SLC Transporters in GWAS of Human Disease

Lesinurad: Just approved

- **SLC22A12** (URAT1) and **SLC2A9** (GLUT9): Hyperuricemia and Gout, N>10,000

Key Reference

International Transporter Consortium Commentary on Clinically Important Transporter Polymorphisms

KM Giacomini\(^1\), PV Balimane\(^2\), SK Cho\(^3\), M Eadon\(^4\), T Edeki\(^5\), KM Hillgren\(^6\), S-M Huang\(^7\), Y Sugiyama\(^8\), D Weitz\(^9\), Y Wen\(^10\), CQ Xia\(^11\), SW Yee\(^1\), H Zimdahl\(^12\) and M Niemi\(^13\); on behalf of the International Transporter Consortium

Clinical Pharmacol Ther, 94: 23-26, July 2013
Genetic Polymorphisms in Drug Development

Criteria for Selection

1. Significant in genomewide association studies
2. Significant in multiple candidate gene gene studies
3. *In vitro* studies document functional changes

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Amino Acid Change</th>
<th>Europ Amer</th>
<th>African Amer</th>
<th>Asian Amer</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLCO1B1</td>
<td>V174A</td>
<td>18%</td>
<td>5%</td>
<td>12%</td>
<td>Reduced</td>
</tr>
</tbody>
</table>
SLCO1B1 Genetic Variant is Highly Associated with Statin Induced Myopathy in a GWAS

Clinical and Mechanistic Studies Validate SLCO1B1 c.521T>C, V174A

Simvastatin Levels

In Vitro Studies


SLCO1B1 Genetic Variant: What’s New?

- SLCO1B1 is associated with statin response (Postmus et al., Nature Communications (2014): GIST study)

- SLCO1B1 is associated with levels of ticagrelor active metabolite, AUSS\textsubscript{55} (PLATO Study: Varehorst et al., Eur. Heart Journal, 2015)

- SLCO1B1 is associated with methotrexate clearance (Ramsey et al., Blood (2013))
### Genetic Polymorphisms in OATP1B1 and ABCG2

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<td>SLCO1B1 c.521T&gt;Crs4149056</td>
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<td>5%</td>
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<td>Reduced</td>
</tr>
<tr>
<td>ABCG2 c.421C&gt;Ars2231142</td>
<td>Q141K</td>
<td>10%</td>
<td>1%</td>
<td>30%</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

#### Criteria for Selection

1. Significant in genomewide association studies
2. Significant in multiple candidate gene association studies
3. In vitro studies document functional changes
ABCG2 Genetic Variant is Highly Associated with Rosuvastatin Effects on Low Density Lipoprotein Levels

Highly associated variant is rs2199936 which is in 80% linkage with rs2231142.


N = 3,523

P < 10^{-14}
Clinical and Mechanistic Studies Validate ABCG2-Q141K

Rosuvastatin Levels

\[ N = 16 \text{ c.421C/C}, 12 \text{ c.421C/A}, 4 \text{ c.421A/A} \]

In Vitro Studies

ABCG2-Reference

ABCG2-Q141K


ABCG2 Genetic Variant: What’s New?

- **ABCG2** is associated with **poor response to allopurinol** (CC Wen et al., *Clin Pharmacol Ther* (2014))

  ![Graph showing ABCG2 association](image)

  \[\text{ABCG2} \quad P = 2 \times 10^{-8}\]

  \[N = 1492\]

- **Replicated in a candidate gene study**: Roberts RL, Pharmacogenomics Journal, 2015

Other: OCT1, OCT2, MATE1, OATP2B1, MRP2, CFTR
MuchFewer GWA Studies of Drugs Than GWA Studies Focused on Disease/Complex Trait

Number of GWAS Studies

Data in 2016

Giacomini KM et al., NRDD, 2017

www.genome.gov/gwastudies/
Genomewide Studies Reveal Transporters

- Genetic Variants in Transporters:
  - Mendelian Disease
  - Common Disease and Traits
  - Drug Response (ITC Polymorphisms)

Genomewide Association Studies (GWAS) Reveal Biomarkers for Transporters
In vitro Studies Trigger Clinical Drug-Drug Interaction Studies

FDA:

• OATP1B1/1B3
• OCT2, OAT1/3
• P-gp, BCRP
• MATE1

Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

- All investigational drugs
  - Determine whether investigational drug is a P-gp and/or BCRP substrate in vitro
  - Hepatic or biliary secretion major?
    - e.g., ≥25% of total clearance or unknown?
      - Yes: See Appendix, Figure A1 to determine whether an in vivo human study is needed
      - No: Determine whether investigational drug is an OATP1B1 and/or OATP1B3 substrate in vitro
  - Renal active secretion major?
    - e.g., ≥25% of total clearance or unknown?
      - Yes: See Appendix, Figure A5 to determine whether an in vivo human study is needed
      - No: See Appendix, Figure A3 to determine whether an in vivo human study is needed

- Yes: See Appendix, Figure A5 to determine whether an in vivo human study is needed

International Transporter Consortium
Current Methods Result in Many False Positives: Data for MATE1

Can we use genomewide approaches to identify biomarkers of transporters that can be used as \textit{in vivo} predictors of DDIs?

Organic Anion Transporter, OATP1B1, Is Expressed in Abundance in the Liver

Representative Pharmacologic Substrates of OATP1B1

- Simvastatin
- Pravastatin
- Rosuvastatin
- Repaglinide
- Glyburide
- Docetaxal
- Saquinavir

Goal: Use GWAS to discover endogenous metabolites of OATP1B1

- Reveal its biological role
- Use as biomarkers of potential drug-drug interactions
Discover Endogenous Metabolites of OATP1B1: Genomewide Association Studies

N > 7,000 Individuals- Blood Sample*

Metabolomic Approach

Genomewide Chip

GWAS of Each Metabolite

Which metabolites associate with SLCO1B1, 521T>C, Val174Ala?

Yee SW et al., Clin. Pharm. Ther. V100, 2016
Twelve Metabolites Associated with SNPs in the SLCO1B1 Locus Are Discovered

Yee SW et al., Clin. Pharm. Ther. V100, 2016
Validate Metabolites as Biomarkers of OATP1B1: Clinical Pharmacokinetic Studies

If a metabolite such as X-11529 is an endogenous substrate of OATP1B1, its levels will increase in patients treated with cyclosporin, an inhibitor of OATP1B1.

Yee SW et al., Clin. Pharm. Ther. V100, 2016
Validate Metabolites as Biomarkers of OATP1B1: Clinical Pharmacokinetic Studies

Yee SW et al., Clin. Pharm. Ther. V100, 2016
How will biomarker be used?

If Biomarker(s) Increases: Consider Clinical DDI Study

If No Increase: No Clinical DDI Study

Could use panel

Should be used with in vitro assays

IND Phase I Study

Measure Biomarker Before And After Drug Administration

x-11529
p=0.0017

Metabolite Intensity

Before Plus NME NME
Genomewide Conclusions

• Human genetic studies reveal that mutations in over 100 transporters are causal of Mendelian disease and polymorphisms in over 150 transporters are associated with human disease and other phenotypes.

• New GWAS have provided further evidence that polymorphisms in OATP1B1 and ABCG2 are major determinants of variation in drug response.

• Genomewide approaches have been used to discover biomarkers that associate with membrane transporters and may be predictive of clinical drug-drug interactions.
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Friday and Saturday Oral Presentations

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Marilyn Giacomini
Dietmar Weitz
Katerina Mertsch
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Sean Hsueh