Compare GWAS candidates using integrative networks

Jun Zhu, Ph. D.
Professor of Genomics and Genetic Sciences
Icahn Institute of Genomics and Multi-scale Biology
The Tisch Cancer Institute
Icahn Medical School at Mount Sinai
New York, NY

http://research.mssm.edu/integrative-network-biology/
Email: jun.zhu@mssm.edu
High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport

Gerd Assmann, Helmut Schulte, Arnold von Eckardstein, Yadong Huang

Abstract

The incidence of coronary heart disease (CHD) was assessed via the Prospective Cardiovascular Münster (PROCAM) study in 19,698 volunteer subjects aged between 16 and 65 years. An adequate incidence of atherosclerotic CHD was only found in male subjects greater than 40 years of age. The analysis and subsequent 6 year follow-up period was, therefore, confined to 4,559 male participants aged 40–64 years. In the follow-up period, 186 study participants developed atherosclerotic CHD (134 definite non-fatal myocardial infarctions (MIs) and 52 definite atherosclerotic CHD deaths including 21 sudden cardiac deaths and 31 fatal MIs). Univariate analysis revealed a significant association between the incidence of atherosclerotic CHD and high-density lipoprotein cholesterol ($P < 0.001$), which remained after adjustment for other risk factors.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial drugs and dose</th>
<th>Control</th>
<th>Follow-up (months)</th>
<th>No enrolled (No intervention, No control)</th>
<th>Statin use (%)</th>
<th>Men (No intervention, No control)</th>
<th>Mean (SD) age (years) (intervention, control)</th>
<th>White ethnicity (%)</th>
<th>Increase in HDL from baseline in active arm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dal-OUTCOMES³³ 2012</td>
<td>Dalcetrapib 600 mg daily</td>
<td>Placebo</td>
<td>31</td>
<td>15 871 (7938, 7933)</td>
<td>97</td>
<td>6365, 6436</td>
<td>60.3 (9.1), 60.1 (9.1)</td>
<td>88</td>
<td>40</td>
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<tr>
<td>Dal-PLAQUE³⁴ 2011</td>
<td>Dalcetrapib 600 mg daily</td>
<td>Placebo</td>
<td>24</td>
<td>130 (64, 66)</td>
<td>87</td>
<td>51, 55</td>
<td>62.6 (8.2), 64.6 (7.8)</td>
<td>92</td>
<td>31</td>
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<tr>
<td>Dal-VESEL³⁵ 2012</td>
<td>Dalcetrapib 600 mg daily</td>
<td>Placebo</td>
<td>8</td>
<td>476 (239, 237)</td>
<td>95</td>
<td>211, 211</td>
<td>62.3 (7.05), 61.9 (7.92)</td>
<td>NR</td>
<td>31</td>
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<tr>
<td>Define³⁶ 2010</td>
<td>Anacetrapib 100 mg daily</td>
<td>Placebo</td>
<td>18</td>
<td>1623 (811, 812)</td>
<td>99</td>
<td>629, 618</td>
<td>62.5 (8.7), 62.9 (9.0)</td>
<td>83</td>
<td>138</td>
</tr>
<tr>
<td>Illuminate³⁷ 2007</td>
<td>Torcetrapib 60 mg daily</td>
<td>Placebo</td>
<td>18</td>
<td>15 054 (7528, 7526)</td>
<td>100</td>
<td>5854, 5861</td>
<td>61.3 (7.6), 61.3 (7.6)</td>
<td>93</td>
<td>72</td>
</tr>
<tr>
<td>Illustrate³⁸ 2007</td>
<td>Torcetrapib 60 mg daily</td>
<td>Placebo</td>
<td>24</td>
<td>1188 (591, 597)</td>
<td>100</td>
<td>416, 421</td>
<td>56.9 (9.1), 57 (9.2)</td>
<td>NR</td>
<td>61</td>
</tr>
<tr>
<td>Radiance 1³⁹ 2007</td>
<td>Torcetrapib 60 mg daily</td>
<td>Placebo</td>
<td>24</td>
<td>850 (423, 427)</td>
<td>100</td>
<td>214, 232</td>
<td>46.8 (12.0), 45.2 (12.9)</td>
<td>NR</td>
<td>52</td>
</tr>
<tr>
<td>Radiance 2⁴⁰ 2007</td>
<td>Torcetrapib 60 mg daily</td>
<td>Placebo</td>
<td>20</td>
<td>752 (377, 375)</td>
<td>100</td>
<td>237, 245</td>
<td>57.9 (8.1), 56.5 (8.2)</td>
<td>NR</td>
<td>63</td>
</tr>
</tbody>
</table>

HDL=high density lipoprotein; NR=not reported.
Fig 4 The statin revolution: without background statin treatment, fibrates and niacin were found to reduce non-fatal myocardial infarction.

<table>
<thead>
<tr>
<th>Non-fatal myocardial infarction</th>
<th>No of events/total</th>
<th>Odds ratio M-H, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No background statin</td>
<td>136/1659</td>
<td>394/3332</td>
</tr>
<tr>
<td>Background statin</td>
<td>509/15 371</td>
<td>527/14 939</td>
</tr>
<tr>
<td>Test for heterogeneity: $I^2=87%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibrate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No background statin</td>
<td>773/14 236</td>
<td>1181/15 896</td>
</tr>
<tr>
<td>Background statin</td>
<td>173/2765</td>
<td>186/2753</td>
</tr>
<tr>
<td>Test for heterogeneity: $I^2=78%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CETP inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background statin</td>
<td>582/18 003</td>
<td>553/18 008</td>
</tr>
</tbody>
</table>

Daniel Keene et al. BMJ 2014;349:bmj.g4379
The cost of developing a prescription drug that gains market approval
Association vs Causality

When informed by his doctor of the correlation between fat dogs and their masters, Brian set out immediately to rectify his weight problem.

From Stephen Friend
A simple biological question: are there causal/reactive relationships?
A Bayesian network approach:

Best model
A Bayesian network approach:

Best models

Markov Equivalent models
A Bayesian network ≠ a causal structure

Markov Equivalent models

\[ B \perp C \mid A \]
Why it is so hard to model biological systems?

- The more we learn, the more complicated it becomes!

---

### Epigenetic regulation

Heritable changes in gene function that cannot be explained by changes in DNA sequence.

- DNA methylation
- Chromatin structure

### Junk DNA?

### Post transcriptional regulation

- Splicing (1981)
- RNA editing (1986)
- miRNA mediated regulation (1993)

### Post translational regulation

- Phosphorylation
- Glycosylation
- Acetylation

---

It is not one gene to one protein anymore!
Bayesian network: how to break Markov equivalent?

**Animal model:** mouse F2 intercrosses
Causal inference: genetics

Perturbations with a causal anchor

--Natural variation in a segregating population provides the same type of causal anchor

DNA Supporting Gene X

Variation in DNA leads to variation in mRNA

Variation in mRNA leads to variation in protein, which in turn can lead to disease

Central Dogma of Biology

High expression, alt splicing, codon change, etc.

Low expression, no alt splicing, no codon change, etc.

Schadt et al. Nature Genetics (2005)
A Bayesian network approach:

Best models

Markov Equivalent models
A framework for building causal networks

probabilistic graphic models

knowledge

High throughput data

Microarray data
Proteomic data
Metabolomic data
Genomics
Genetics

Medline
Biocarta/Biopathway
Biologists

Database
GUI

Hypothesis, test
Structure priors based on causality

- Estimate confidence of causality
  - Bootstrap samples for 200 times
  - Factions of causal, reactive, independent calls

- The pair is independent
  \[ p(X_a \rightarrow X_b) = 1 - \frac{\sum_{i \in FB} p(X_a \perp X_b | l_i)}{\sum_{i \in FB} 1} \]

- The pair is causa/reactive
  \[ p(X_a \rightarrow X_b) = \frac{2 \sum_i p(X_a \rightarrow X_b | l_i)}{\sum_i p(X_a \rightarrow X_b | l_i) + p(X_b \rightarrow X_a | l_i)} \]

Bayesian network: integrating genetics

- **Experimental** Hsd11b1 signature: mice treated with Hsd1 inhibitor

- **Prediction** Hsd1 signatures based on BxD data
  - **Correlation** to Hsd1
    - 10% of predicted signature overlap with experimental one
  - **BN without genetics**
    - 20% of predicted signature overlap with experimental one
  - **BN with genetics**
    - 52% of predicted signature overlap with experimental one

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Variance of OFPM explained by gene expression*</th>
<th>Mouse model</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zfp90</td>
<td>Zinc finger protein 90</td>
<td>68%</td>
<td>tg</td>
<td>Constructed using BAC transgenics</td>
</tr>
<tr>
<td>Gas7</td>
<td>Growth arrest specific 7</td>
<td>68%</td>
<td>tg</td>
<td>Constructed using BAC transgenics</td>
</tr>
<tr>
<td>Gpx3</td>
<td>Glutathione peroxidase 3</td>
<td>61%</td>
<td>tg</td>
<td>Provided by Prof. Oleg Mirochnitchenko (University of Medicine and Dentistry at New Jersey, NJ) [12]</td>
</tr>
<tr>
<td>Lactb</td>
<td>Lactamase beta</td>
<td>52%</td>
<td>tg</td>
<td>Constructed using BAC transgenics</td>
</tr>
<tr>
<td>Me1</td>
<td>Malic enzyme 1</td>
<td>52%</td>
<td>ko</td>
<td>Naturally occurring KO</td>
</tr>
<tr>
<td>Gyk</td>
<td>Glycerol kinase</td>
<td>46%</td>
<td>ko</td>
<td>Provided by Dr. Katrina Dipple (UCLA) [13]</td>
</tr>
<tr>
<td>Lpl</td>
<td>Lipoprotein lipase</td>
<td>46%</td>
<td>ko</td>
<td>Provided by Dr. Ira Goldberg (Columbia University, NY) [11]</td>
</tr>
<tr>
<td>C3ar1</td>
<td>Complement component 3a receptor 1</td>
<td>46%</td>
<td>ko</td>
<td>Purchased from Deltagen, CA</td>
</tr>
<tr>
<td>Tgfbr2</td>
<td>Transforming growth factor beta receptor 2</td>
<td>39%</td>
<td>ko</td>
<td>Purchased from Deltagen, CA</td>
</tr>
</tbody>
</table>

**Schadt et al. Nature Genetics (2005)**

**Yang et al, Nature Genetics (2009)**

Networks facilitate direct identification of genes that are causal for disease.
Prospective validation is the **gold** standard for these types of predictions.

Yang X et al, Nature Genetics, 2009
Multiple genes in a network causing diseases!

BN: simulation study

Simulation of data with network and genetics constraints

a
- Genetic map
- Rqtl
- Rcross
- genotypes
- Trait values
- Zmap
- QTLs

b
- Bayesian network (a network structure, Conditional probability density functions)
- Values of head nodes
- Values of all nodes

C
- Network reconstruction program

Bayesian network: Genetics information is critical when sample size is small

Largest improvement in recall occurs with smaller sample sizes

Integration: gain or lost?

300 samples

900 samples

300 samples

900 samples

Red: w/ Genetics

Blue: w/o Genetics

Weak signals

recall

Strong signals
A framework for data integration

probabilistic graphic models

knowledge

Medline

Biocarta/Biopathway

Biologists

High throughput data

Microarray data

Proteomic data

Metabolomic data

Genomics

Genetics

Hypothesis, test

Database

GUI
Bayesian network: integrating PPI

- 4-clique
- 3-clique

Clique community (partial clique)

Bayesian network: priors for TF or PPI complex

Introducing *scale-free priors* for TF or protein complex

\[ p(T \rightarrow g) \propto w(T) \]

\[ w(T) = \log( \sum_{g_i \in R} |r(T, g_i)| > r_{\text{cutoff}} ) \]

Integration improves network qualities

<table>
<thead>
<tr>
<th>BN</th>
<th>KO data</th>
<th>GO terms</th>
<th>TF data</th>
</tr>
</thead>
<tbody>
<tr>
<td>w/o any priors</td>
<td>125</td>
<td>55</td>
<td>26</td>
</tr>
<tr>
<td>w/ genetics priors</td>
<td>139</td>
<td>59</td>
<td>34</td>
</tr>
<tr>
<td>w/ genetics, TF and PPI priors</td>
<td>152</td>
<td>66</td>
<td>52</td>
</tr>
</tbody>
</table>

Zhu J et al., Nature Genetics, 2008
Prospective validation is the gold standard

ILV6 gives rise to large expression signature
- ILV6 KO sig enriched (p~10E-52)
- GCN4 upregulated in ILV6 KO → large signature

LEU2 KO gives rise to small expression signature
- LEU2 KO sig enriched (p~10E-18)
- GCN4 downregulated in LEU2 KO → small signature

Zhu J et al., Nature Genetics, 2008
How does LEU2 affect LEU3 activity?

LEU3 binding sites

mRNA expression

Surrogate marker for Leu3p activity
A framework for building causal networks

High throughput data

knowledge

Microarray data
Proteomic data
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Genetics

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Hypothesis, test

GUI
Yeast segregants

Synthetic complete medium
Logarithm growth
Gene expression

metabolites

Yeast segregants

Public databases

Protein-protein interactions
Transcription factor binding sites

Protein-Metabolite interactions

Bayesian network

LEU2 mRNA is causal to 2-isopropylmalate

LEU3 binding site

With metabolomic data

LEU3 regulation

- The activity of Leu3p is positively regulated by alpha-isopropylmalate (IPM), the product of the first step in leucine biosynthesis

- The degree of activation by Leu3p is Leu3p concentration dependent, and it has been shown that LEU3 gene expression is regulated by general amino acid control, which is mediated by the GCN4 transcription factor
2-isopropylmalate: mechanism of causal regulator LEU2

LEU2 genotype → LEU2 activity → 2-isopropylmalate

Transcriptional response for genes with LEU3 binding sites

LEU3 activity
Rapid Explosion of GWAS

Based on NHGRI GWAS catalog, Sept 2010
Major Challenges of GWAS

- Pinpointing the underlying susceptibility gene and biological explanation has been difficult

- The significant SNPs only explain a small portion of the genetic heritability of the complex diseases

Lusis et al, 2008; Nat Rev Genet 9, 819–830
Association to causal genes

A SNP set enrichment analysis

Knowledge based pathways and data-driven gene sets

Genetics of gene expression

GWAS

Enrichment of coronary artery disease associations

SNP P-values

Stage 1: false discovery rate < 20%
Stage 2: false discovery rate < 20%
Stage 1 & 2: false discovery rate < 5%

Collapse overlapping gene sets

B Selection and post-processing of significant gene sets

C Key driver analysis

=> CAD-associated supersets

Causal network model of gene-gene interactions

Member genes in a CAD-associated superset

Superset members overlayed on causal network

=> Gene A is a key regulator of a CAD-associated superset
Guilt by association

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes

John A Todd¹, Neil M Walker¹, Jason D Cooper¹, Deborah J Smyth¹, Kate Downes¹, Vincent Plagnol¹,
## Guilt by association

<table>
<thead>
<tr>
<th>Disease/Trait</th>
<th>GWAS_snp</th>
<th>Reported Gene(s)</th>
<th>eSNP_gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>rs10889353</td>
<td>ANGPTL3</td>
<td>ANGPTL3</td>
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<tr>
<td>Testicular germ cell tumor</td>
<td>rs210138</td>
<td>BAK1</td>
<td>BAK1</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>rs4444235</td>
<td>BMP4</td>
<td>BMP4</td>
</tr>
<tr>
<td>Serum IgE levels</td>
<td>rs2251746</td>
<td>FCER1A</td>
<td>FCER1A</td>
</tr>
<tr>
<td>Aging traits</td>
<td>rs291353</td>
<td>GNG4</td>
<td>GNG4</td>
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<tr>
<td>Multiple sclerosis</td>
<td>rs9271366</td>
<td>HLA-DRB1</td>
<td>HLA-DRB1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>rs6457617</td>
<td>MHC</td>
<td>HLA-DQA1</td>
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<tr>
<td>Type 1 diabetes</td>
<td>rs9272346</td>
<td>MHC</td>
<td>HLA-DQB1</td>
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<tr>
<td>Crohn's disease</td>
<td>rs3197999</td>
<td>MST1</td>
<td>MST1</td>
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<tr>
<td>Body mass index</td>
<td>rs10838738</td>
<td>MTCH2</td>
<td>MTCH2</td>
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<tr>
<td>HDL cholesterol, Triglycerides</td>
<td>rs7679</td>
<td>PLTP</td>
<td>PLTP</td>
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<tr>
<td>Glioma</td>
<td>rs6010620</td>
<td>RTEL1</td>
<td>RTEL1</td>
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<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>rs260461</td>
<td>ZNF544</td>
<td>ZNF544</td>
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<td><strong>Coronary disease, LDL</strong></td>
<td><strong>rs599839</strong></td>
<td><strong>CELSR2, PSRC1, MYBPHL</strong></td>
<td><strong>SORT1, PSRC1, C</strong></td>
</tr>
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<td>Lung cancer</td>
<td>rs8034191</td>
<td>CHRNA3, CHRNA5, PSMA4, LOC123688</td>
<td>PSMA4</td>
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<tr>
<td>Weight</td>
<td>rs2844479</td>
<td>AIF1, NCR3</td>
<td>BAT3</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>rs7804356</td>
<td>Intergenic</td>
<td>SKAP2</td>
</tr>
<tr>
<td>Testicular germ cell tumor</td>
<td>rs4699052</td>
<td>Intergenic</td>
<td>LOC56898</td>
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<td>Crohn's disease</td>
<td>rs6596075</td>
<td>Intergenic</td>
<td>SLC22A5</td>
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<td>Cognitive test performance</td>
<td>rs2832077</td>
<td>Intergenic</td>
<td>CCT8</td>
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<td>Systemic lupus erythematosus</td>
<td>rs10798269</td>
<td>Intergenic</td>
<td>C1orf9</td>
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<tr>
<td>Colorectal cancer</td>
<td>rs4779584</td>
<td>Intergenic</td>
<td>GREM1</td>
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<tr>
<td>Type 1 diabetes</td>
<td>rs1701704</td>
<td>RAB5B, SUOX, IKZF4, ERBB3, CDK2</td>
<td>RPS26</td>
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<td>QT interval</td>
<td>rs4725982</td>
<td>KCNH2</td>
<td>IAN4L1</td>
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<td>Intracranial aneurysm</td>
<td>rs700651</td>
<td>BOLL, PLCL1</td>
<td>PLCL1</td>
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<td>Body mass index</td>
<td>rs7498665</td>
<td>SH2B1</td>
<td>EIF3C</td>
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<td>Rheumatoid arthritis</td>
<td>rs881375</td>
<td>TRAF1, C5</td>
<td>TRAF1</td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>rs2842643</td>
<td>TFEB</td>
<td>UNC5CL</td>
</tr>
</tbody>
</table>
Our Data Supports SORT1 as the Strongest Candidate Gene

- rs599839: SORT1, p value 1.52E-56
- rs599839: PSRC1, p value 2.17E-53
- rs599839: CELSR2, p value 4.31E-23

SORT1 subnetwork is enriched for chemokine, angiogenesis, insulin signaling genes

Schadt et al., PLoS Biol., 2008; 6:e107
From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus

Kiran Musunuru1,2,3*, Alanna Strong4*, Maria Frank-Kamenetsky5, Noemi E. Lee1, Tim Ahfeldt1,6, Katherine V. Sachs4, Xiaoyu Li4, Hui Li4, Nicolas Kuperwasser1, Vera M. Ruda1, James P. Pirrucchini1,2, Brian Muchmore7, Ludmila Prokunina-Olsson7, Jennifer L. Hall2,8, Eric E. Schadt9, Carlos R. Morales10, Sissel Lund-Katz11, Michael C. Phillips11, Jamie Wong5, William Cantley5, Timothy Racie5, Kenechi G. Ejebe1,2, Marju Orho-Melander12, Olle Melander12, Victor Koteliantsky5, Kevin Fitzgerald5, Ronald M. Krauss13, Chad A. Cowan1,2, Sekar Kathiresan1,2* & Daniel J. Rader4*

Overexpression

![Image](chart_overexpression)

Knockdown

![Image](chart_knockdown)
Mouse and Rat Are Commonly Used Animal Models in Studying Human Diseases

- Understanding their conserved mechanisms is important in predicting whether drug targets identified in mouse and rat will achieve efficacy in humans.

- Identifying mechanisms that differ among them can help improve the design and interpretation of toxicity studies that involve rodent models.

- Liver is an important organ for glucose and lipid metabolism, as well as for metabolizing toxic compounds.

- Gene expression data can be organized into co-expression networks that can shed light on the functional relationship between genes.

Wang et al, PLoS Comp Bio., 2009
Comparison of multiple meta-analysis methods

Similar results were also obtained using KEGG pathways

Wang et al, PLoS Comp Bio., 2009
Conserved Modules Show Better Association with Human Lipid Traits

- Kathiresan et al. A genome-wide association study for blood lipid in the Framingham Heart Study. BMC Medical Genetics 2007, 8:SI7
- Association is defined as p-value < 0.001
- Genes were selected if marker is within ±50kb of the gene

Wang et al, PLoS Comp Bio., 2009
RXRG Is Identified as A Key Regulator that Differs Between Human and Rodent Species

- The largest sub-network consists of 11 genes, three of them, PIP5K1B, RXRG and ACSBG1, are known to be involved in lipid metabolism

- **RXRG** (Retinoid X receptor γ) is:
  - # 4 most differentially connected gene
  - Involved in 8 human specific interactions, 7 of which are with other top differentially connected genes
  - RXRG has previously been associated with hyperlipidemia
  - RXRG is a direct upstream regulator of CETP (cholesteryl ester transfer protein), which is a human specific gene that is involved in regulating HDL cholesterol

Related to hypertension  

Wang et al, PLoS Comp Bio., 2009
Meta-analysis of human, swine, and mouse liver gene expression data

Unique to human and swine
Identifying a swine subnetwork for HDL regulation

The subnetwork overlaps with candidates for GWAS diseases/traits
- electrocardiographic traits
- total cholesterol, LDL, triglycerides, obesity or weight
- fibrinogen
- Hemoglobin
- psychiatric disorders
- neurodegenerative disorders
Human adipose network

Human height

Zhu et al, BMC Genomics, 2015
Integrating diverse data is not trivial!
Check your data first!

Aknowledgements

Jiangxi Agriculture University
Lusheng Huang

UCLA
Xia Yang
Aknowledgements

Zhu lab
Seungyeul Yoo
Eunjee Lee
Li Wang
Luan Lin
Quan Long

Mount Sinai
Genomics Institute
Eric Schadt
Bin Zhang
Zhidong Tu
Charles Powell
Patrizia Casaccia

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• Canary Foundation
• Prostate Cancer Foundation
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Boston University
Avrum Spira
Joshua Campbell

U Washington
Roger Baumgarner

Berkerley
Rachel Brem

Princeton
Lenoid Kruglyak