Impact of Human Genetics on Drug R&D

Robert Plenge
Roadmap for “genetic dose-response” portal
Common Disease Consortium
December 3, 2018
The problem
Which targets, when perturbed therapeutically, have a beneficial effect in humans?

How do these targets differ from standard-of-care?
“Allelic series” model
Pick a human phenotype for drug efficacy

Gene function

Pick a human phenotype for drug efficacy

- **Gene function**
  - GOF
  - LOF

- **Human Phenotype**
  - High
  - Low

- **Biological RA risk genes**
- **Drug target genes**
- **Direct PPI**

Pick a human phenotype for drug efficacy

Identify a series of alleles with range of effect sizes in humans (but of unknown function)
Pick a human phenotype for drug efficacy

Gene function

High

Low

GOF

LOF

“variant to function”

Assess biological function of alleles to estimate “efficacy” response curve

Efficacy

Human Phenotype

Gene function
Pick a human phenotype for drug efficacy

Gene function

Efficacy

Toxicity

Assess biological function to estimate "efficacy" response curve

Assess pleiotropy as proxy for ADEs

"Biobanks"
New target for drug screen!

This provides evidence for the therapeutic window at the beginning of the drug discovery journey.

Pick a human phenotype for drug efficacy

<table>
<thead>
<tr>
<th>Gene function</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOF</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>LOF</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Toxicity

Efficacy
Not common or rare…
Not coding or regulatory…

…range of alleles that perturb target function to estimate impact in humans
An example in immunology
TYK2 is an intracellular signaling molecule (next slide)

Rare, complete human knockout is associated with immunodeficiency and risk of infection

Common protein coding alleles reduce TYK2 function and protect from risk of autoimmune disease (e.g., psoriasis, RA, SLE, IBD)

Same common alleles do not increase risk of infection
IL23 signaling and psoriasis

IL23A (IL-23p19)  IL23R

IL12B (IL-12p40)  TYK2

O'Shea and Plenge *Immunity* (2012)
IL23 signaling and psoriasis

**IL23A** (IL-23p19)

**IL12B** (IL-12p40)

**TYK2**
Fine-mapping and functional studies highlight potential causal variants for rheumatoid arthritis and type 1 diabetes

Harm-Jan Westra\textsuperscript{1,2,3,4,5,20}, Marta Martínez-Bonmatí\textsuperscript{1,2,3,4}, Nikola Teslovič\textsuperscript{1,2,3,4}, Jane Worth\textsuperscript{1}, Lars Klareskog\textsuperscript{2}, Solbritt Rantapaa-Dahlqvist\textsuperscript{2,4}, John A. Todd\textsuperscript{7}, Steve Eyre\textsuperscript{6,10}, Peter A. Nigrovic\textsuperscript{8}, Soumya Raychaudhuri\textsuperscript{1,2,3,4,9,19,*}

\textbf{TYK2 gene}

\begin{itemize}
  \item \textbf{P1104A}
  \item \textbf{I684S}
  \item (low freq: A928V)
\end{itemize}
Fine-mapping and functional studies highlight potential causal variants for rheumatoid arthritis and type 1 diabetes

Harm-Jan Westra, Marta Martínez-Bonmatí, Yang Luo, Nikola Teslovič, Jane Worth, Lars Klareskog, Solbritt Rantapaa-Dahlqvist, John A. Todd, Steve Eyre, Peter A. Nigrovic, Soumya Raychaudhuri.

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<tr>
<th>Dataset</th>
<th>Frequency</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>Combined</td>
<td>0.897</td>
<td>0.88</td>
</tr>
<tr>
<td>T1D</td>
<td>0.898</td>
<td>0.874</td>
</tr>
<tr>
<td>RA</td>
<td>0.896</td>
<td>0.877</td>
</tr>
<tr>
<td>Combined</td>
<td>0.022</td>
<td>0.032</td>
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<td>0.081</td>
<td>0.088</td>
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P1104A

I684S

(low freq: A928V)
P1104A allele that protects from autoimmunity is associated with ~80% loss-of-function (LoF) in C/C homozygous state.
Resolving TYK2 locus genotype-to-phenotype differences in autoimmunity

Calliope A. Dendrou,1 Adrian Cortes,1,2 Lydia Shipman,1 Hayley G. Evans,1 Kathrine E. Attfield,3 Luke Jostins,2 Thomas Barber,1 Gurman Kaur,3 Subita Balaram Kuttikkatte,3 Oliver A. Leach,1 Christiane Desel,1 Soren L. Faergeman,1,4 Jane Cheeseman,5 Matt J. Neville,5,6 Stephen Sawcer,7 Alastair Compston,7 Adam R. Johnson,8 Christine Everett,8 John I. Bell,9 Fredrik Karpe,5,6 Mark Ultsch,8 Charles Eigenbrot,8 Gil McVean,2 Lars Fugger1,3,4*
Same LoF allele has no obvious increased risk of infection

<table>
<thead>
<tr>
<th>Infections</th>
<th>Rs34536443 genotype</th>
<th></th>
<th></th>
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<th>Total</th>
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<tr>
<td></td>
<td>G/G</td>
<td>G/C</td>
<td>C/C</td>
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<tr>
<td>In U.K. Biobank</td>
<td>105,794 (90.63%)</td>
<td>10,689 (9.16%)</td>
<td>249 (0.21%)</td>
<td>116,732 (100%)</td>
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<td>Mycobacterial</td>
<td>20 (86.96%)</td>
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<td>Specific bacterial (For example, S. aureus)</td>
<td>54 (90.00%)</td>
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<td>Specific viral (e.g. HSV, VZV, viral encephalitis)</td>
<td>93 (96.88%)</td>
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<td>Mucocutaneous candidiasis</td>
<td>46 (88.46%)</td>
<td>6 (11.54%)</td>
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<td>Total</td>
<td>213 (92.21%)</td>
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~80% LoF is not associated with increased infection

Dendrou, et al. (2016)
Science Translational Medicine
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Dendrou, et al. (2016)
*Science Translational Medicine*
Complete TYK2 knockout increases risk of infection. 

~80% LoF protects from autoimmunity but is not associated with infection.
Therapeutic hypothesis: Partial inhibition (~80%) of TYK2 will protect from autoimmunity without risk of infection.

Dendrou, et al. (2016)
Science Translational Medicine
50-80% TYK2 inhibition safe and effective in Phase 2 (psoriasis)

PASI 75 ~75%

PASI 90 ~45%

Papp et al (2018) NEJM
Gaps remain (towards a “federated ecosystem of interoperable data custodians”)
Roadmap to build “genetic dose-response” portal

- Genetic architecture of human disease
  - fine-mapping of CVAS signals and co-localization across traits
  - continued sequencing of rare, Mendelian diseases (e.g., PID)
  - human knockout project (e.g., dbLoF)
  - exome sequencing in case-control cohorts (e.g., RVAS)

- Functional interrogation (“V2F”)
  - high-throughput assessment of mutations
  - scRNA-seq in disease tissues at population scale
  - Mendelian randomization on QTLs

- Pleiotropy (“Biobanks”)
  - integrated population-based biobanks
  - quantitative traits as biomarkers

- Data analysis
  - statistical methods to model dose-response
  - data integration and visualization engine

- Major limitations: reductionist, linear and need for multiple variants
  - phenotypic screens based on PRS / cell states / AI, other “leapfrog” technologies

Incentive: genetics portal would automatically run these analyses for investigators
Questions?

@rplenge