IMPACT OF HUMAN GENETICS ON DRUG R&D

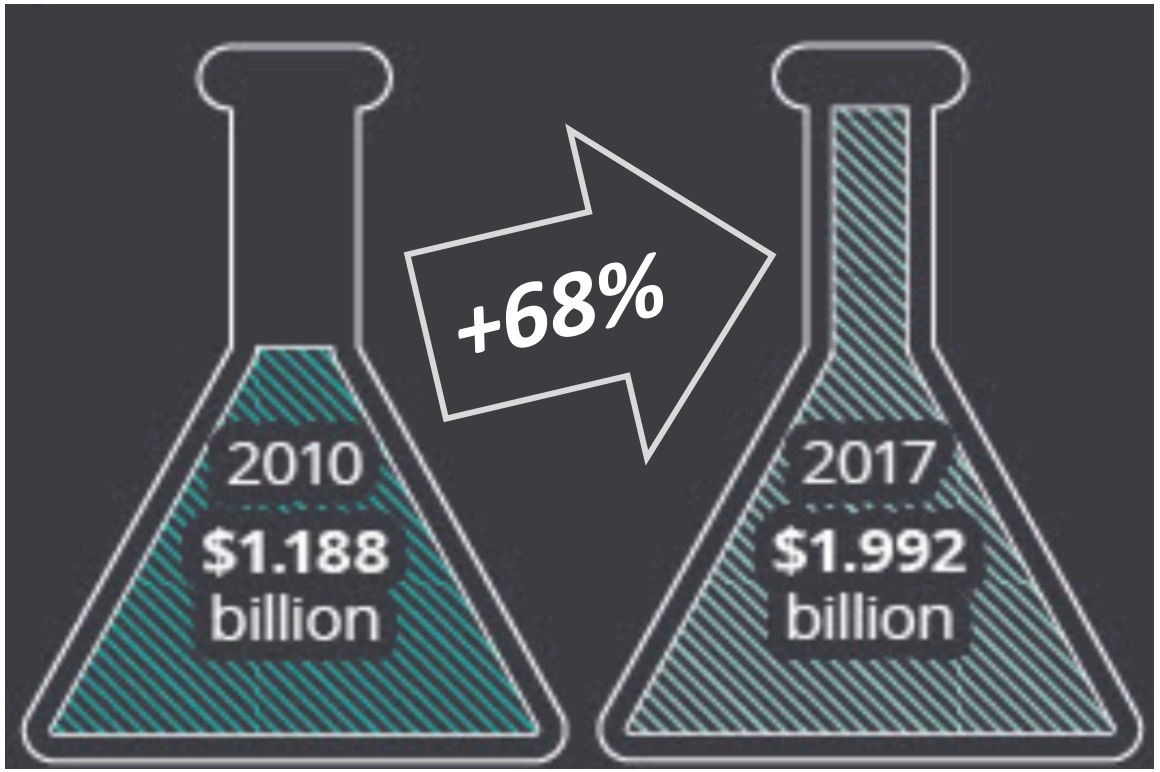
Robert Plenge

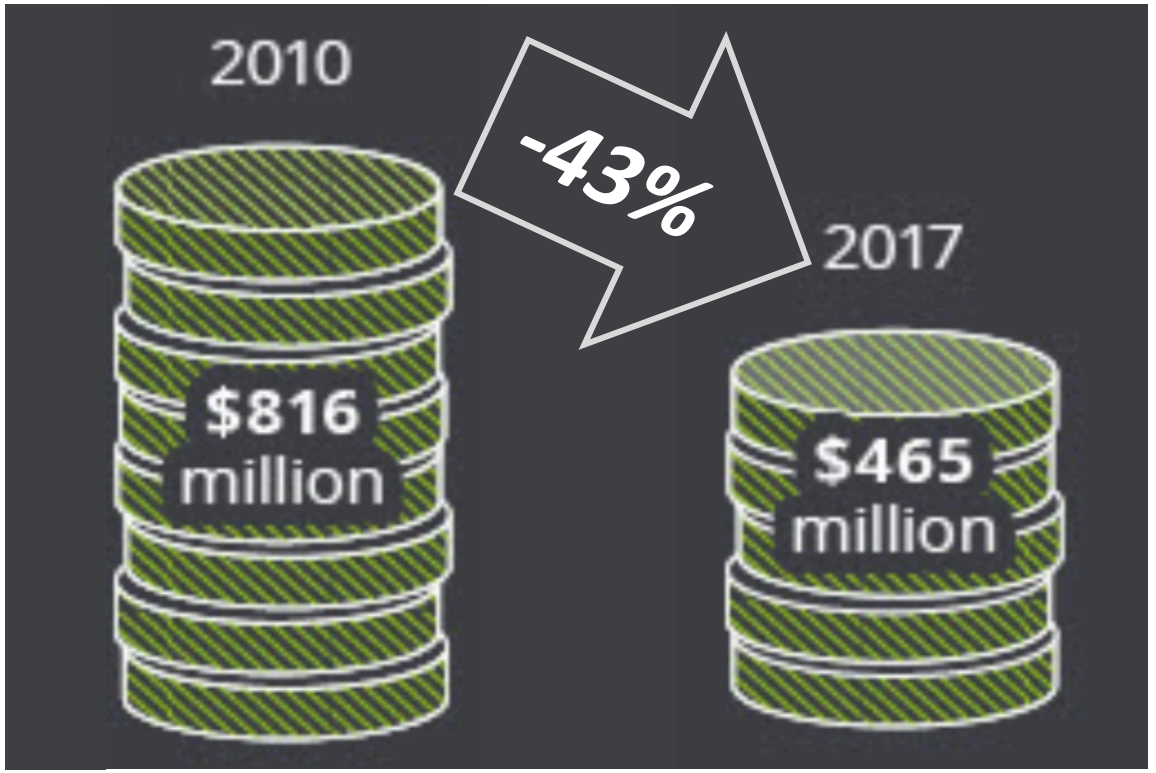
American Society of Human Genetics

October 16, 2018

The Problem

Two fundamental challenges to drug R&D





Attrition problem

Innovation problem

[Deloitte Centre for Health Solutions]

Attrition: where things go wrong and what that costs

Discovery | Pre-clinical | Phase 1 | Phase 2 | Phase 3 | Launch

1 out of 10 make it to approval

~30 → 15 → 10 → 50% → 5 → 30% → 1.5 → 70% → 1

Paul *et al. Nat Rev Drug Discovery* (2010)

Attrition: where things go wrong and what that costs

Discovery | Pre-clinical | Phase 1 | Phase 2 | Phase 3 | Launch

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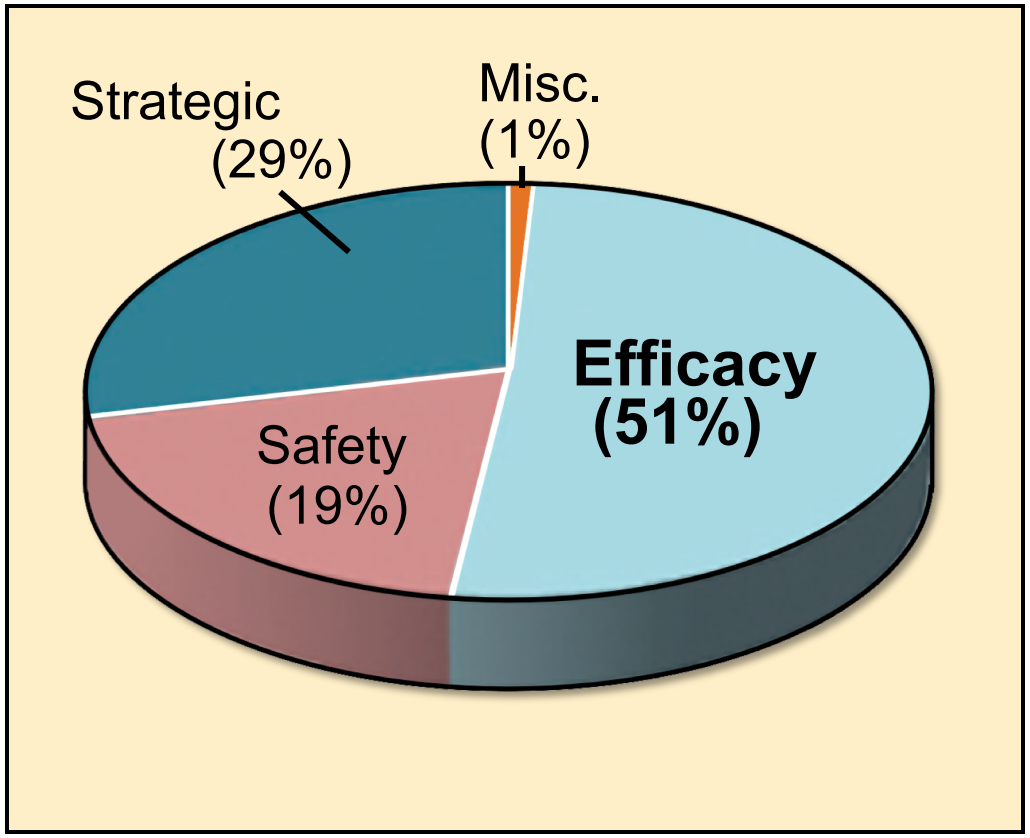
Expense and failures in Phase 2/3 that drive the cost

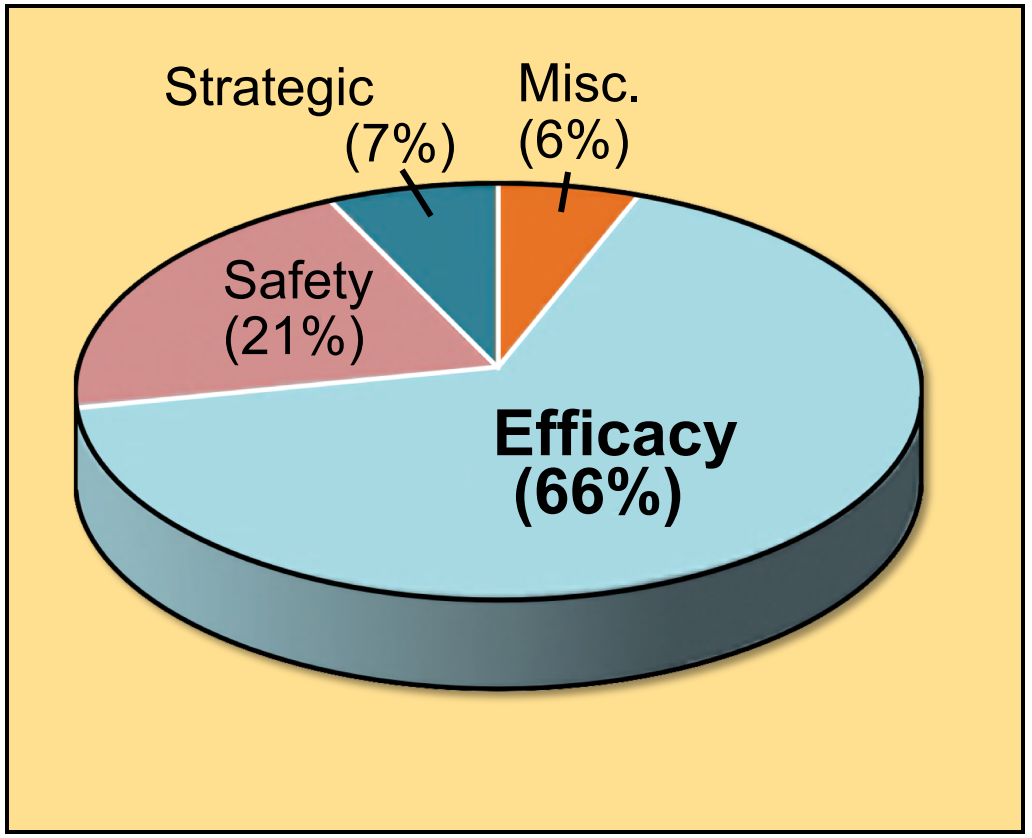
Paul *et al. Nat Rev Drug Discovery* (2010)

Most late-stage failures are due to *lack of efficacy*

Phase II failures (2008-2010)



Phase III failures (2007-2010)



Arrowsmith *Nature Reviews Drug Discovery* (2011)

Attrition: where things go wrong and what that costs

Discovery | Pre-clinical | Phase 1 | Phase 2 | Phase 3 | **Launch**

Decisions made here…

…influence success here!

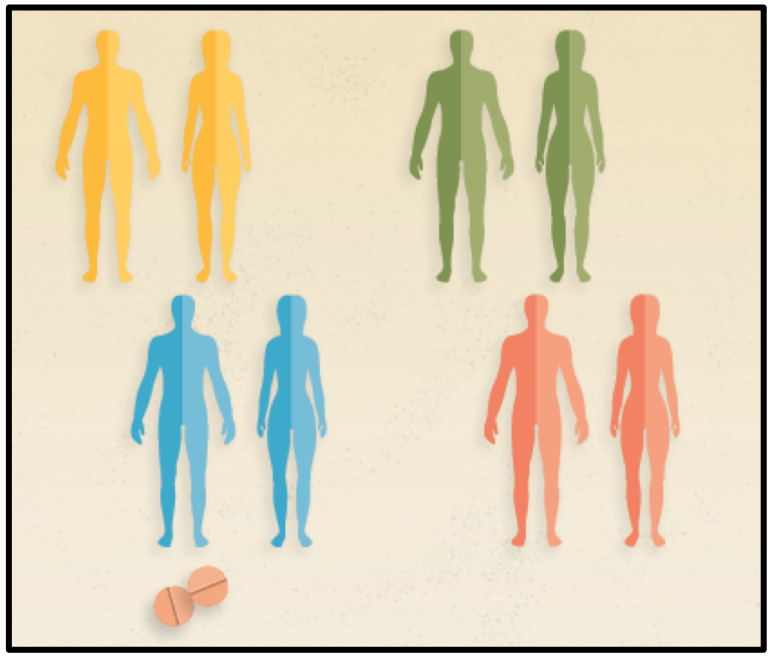
~30 → 15 → 10 → *50%* → 5 → *30%* → 1.5 → *70%* → **1**

Paul *et al. Nat Rev Drug Discovery* (2010)

A Solution

We relied on preclinical models to pick targets and estimate efficacy in heterogeneous human populations

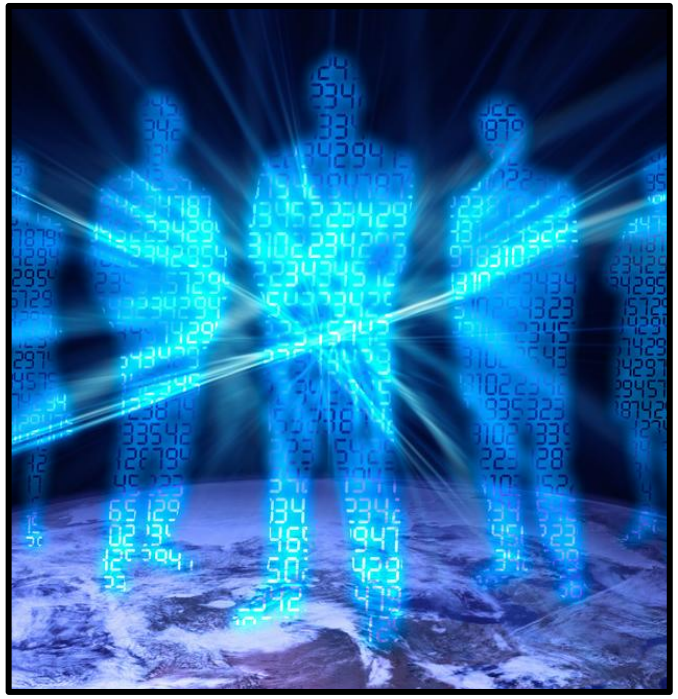
It was…

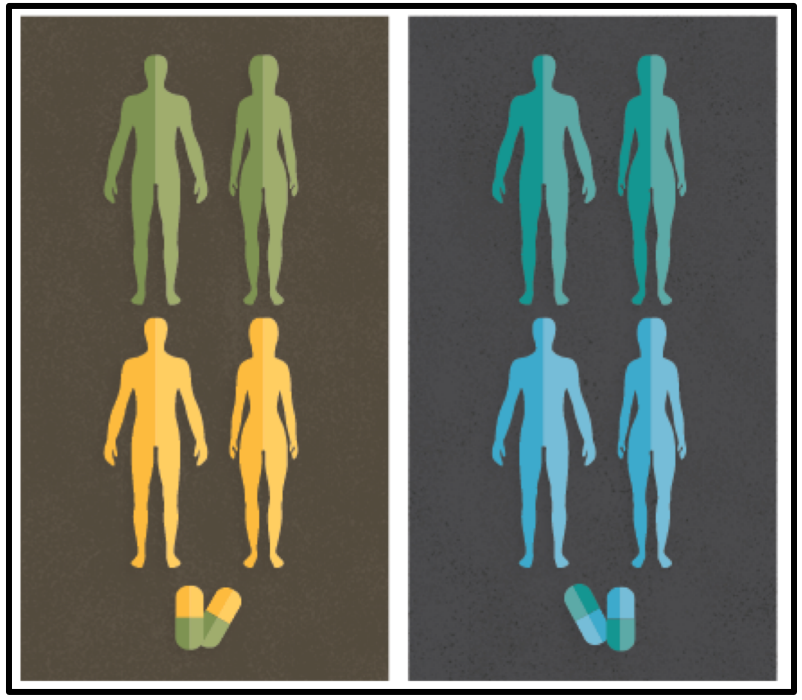


Discovery → Pre-clinical → Phase 1

Humans are the “model organism” of choice for new targets and precision medicine

But today…

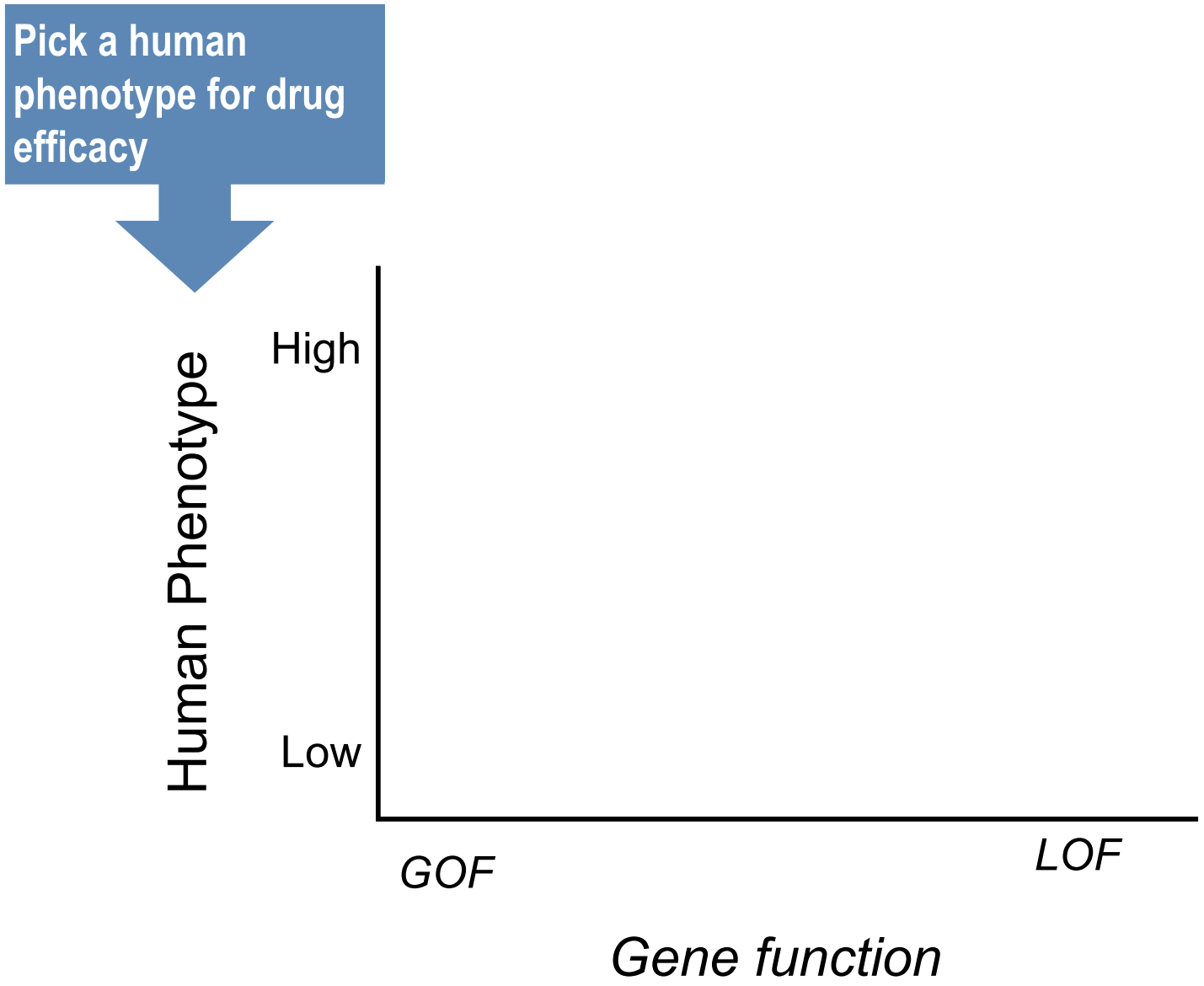




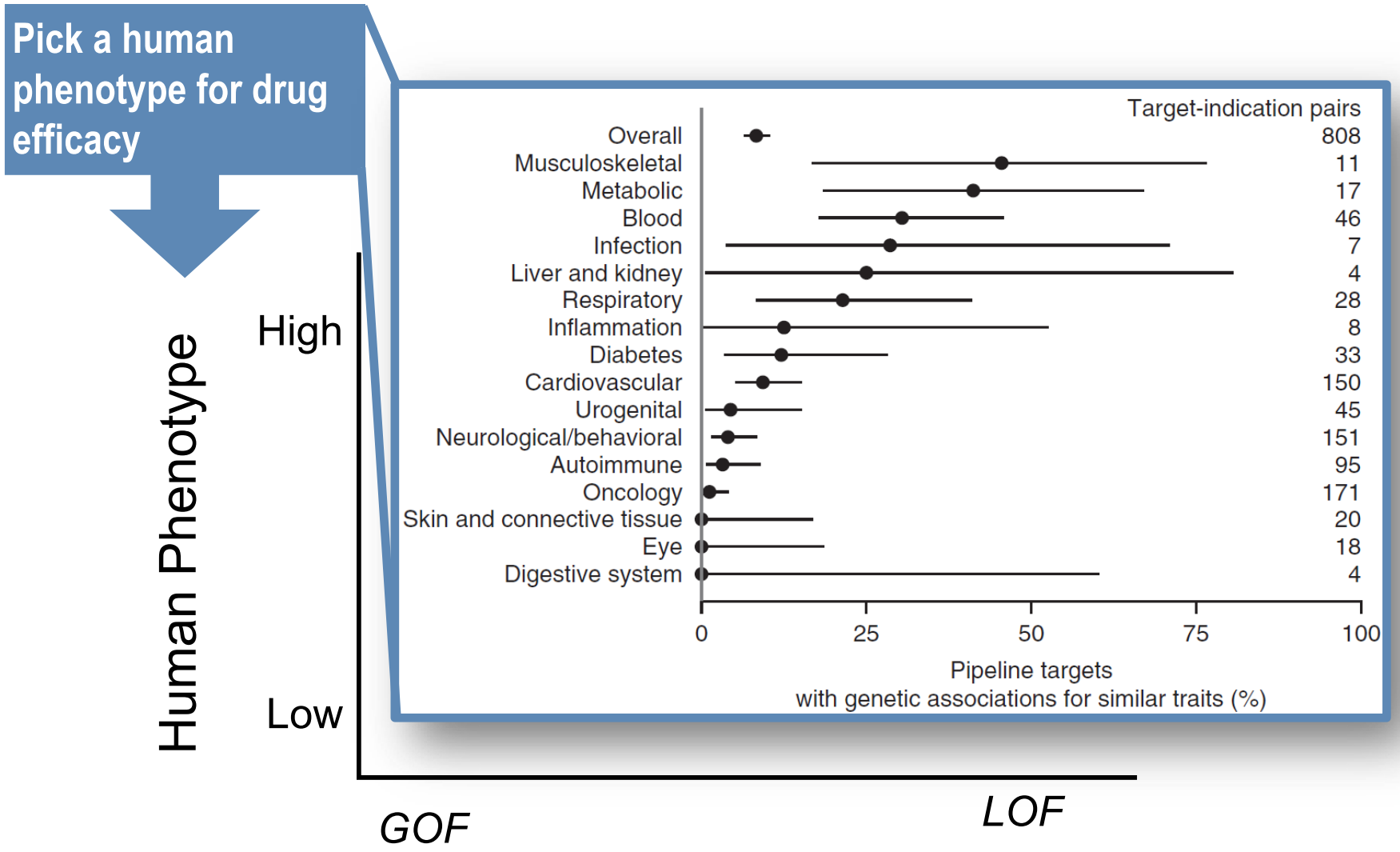
Discovery → **Pre-clinical** → **Phase 1**

Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

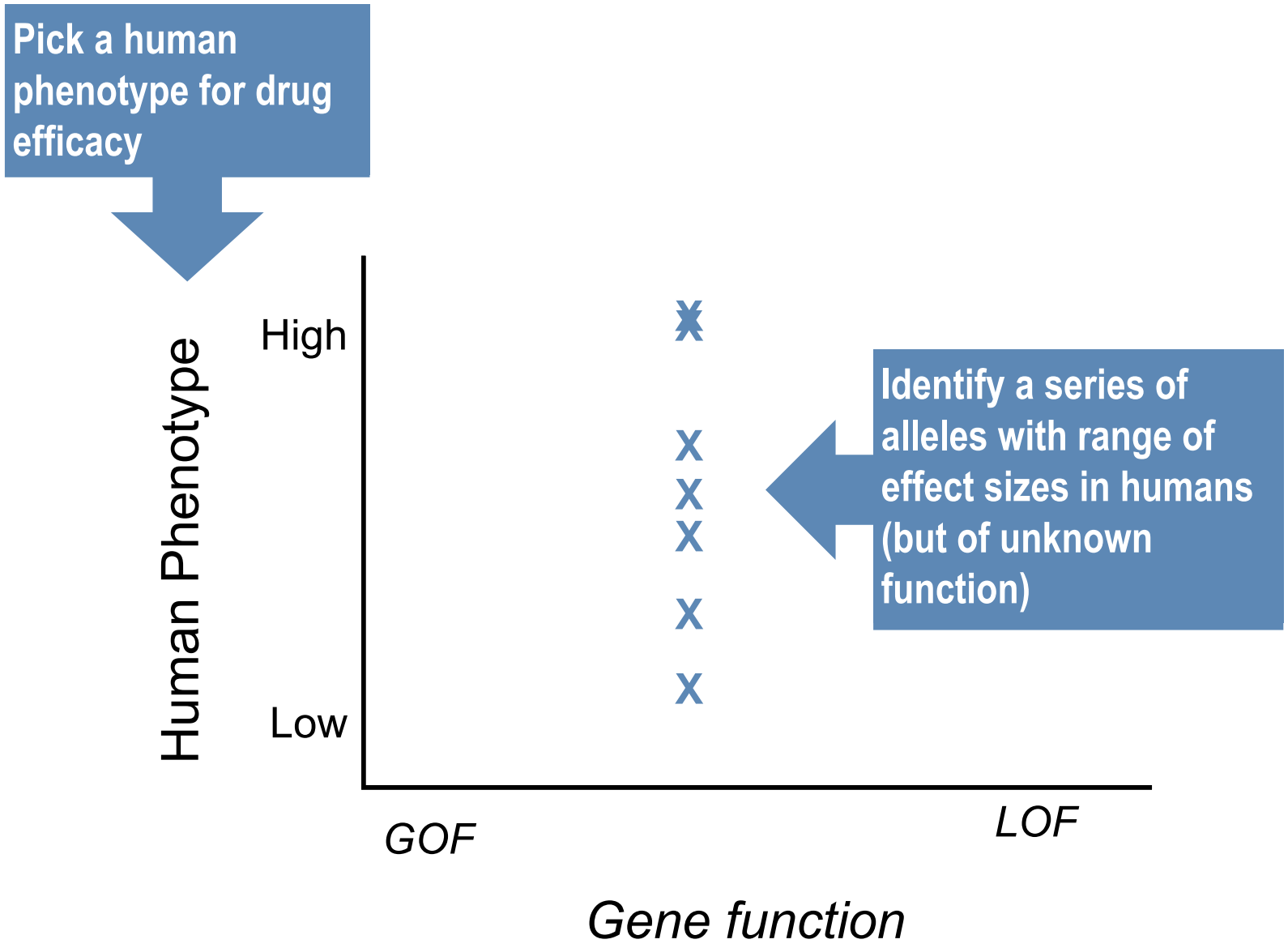
A model



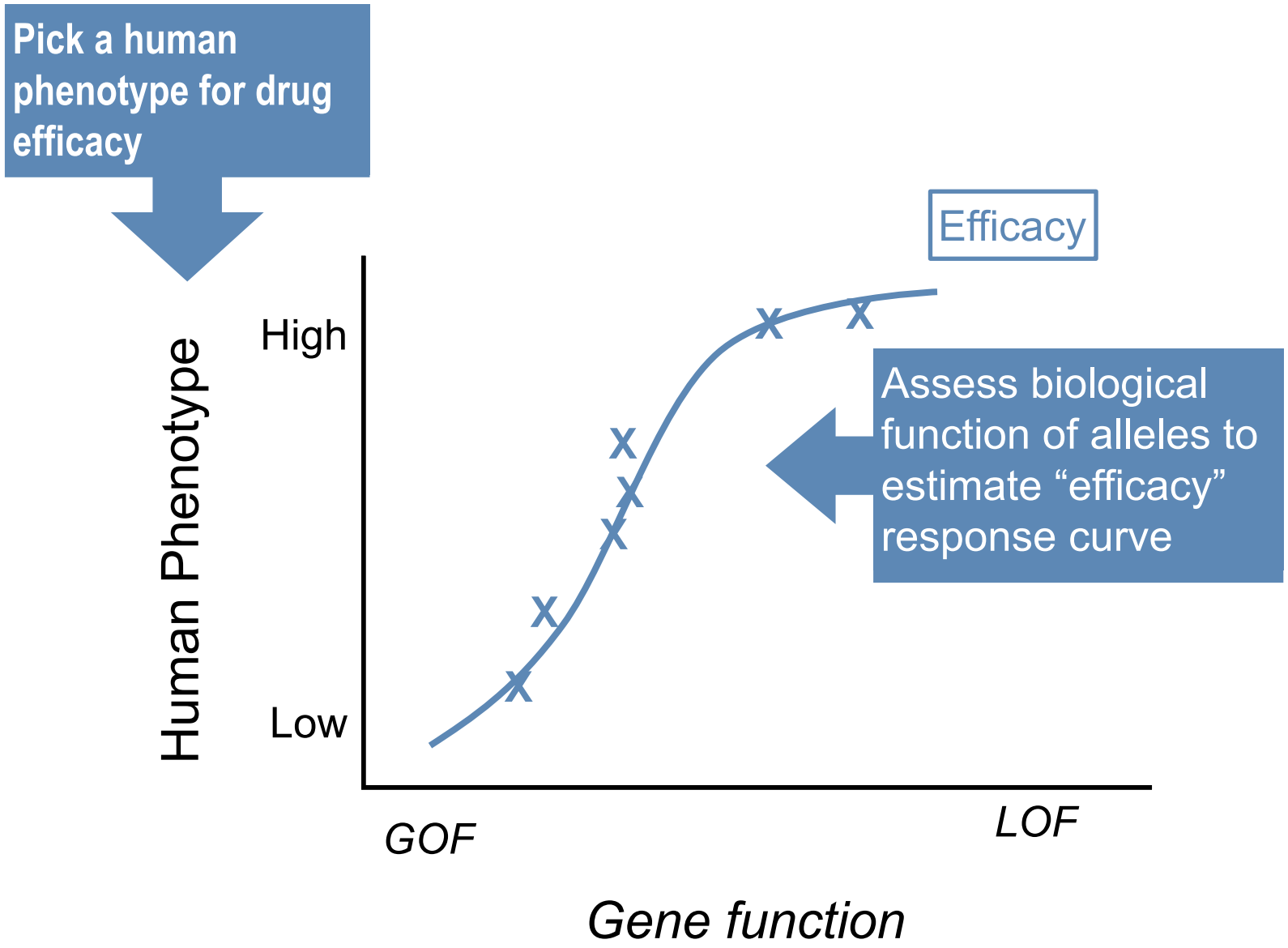
Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)



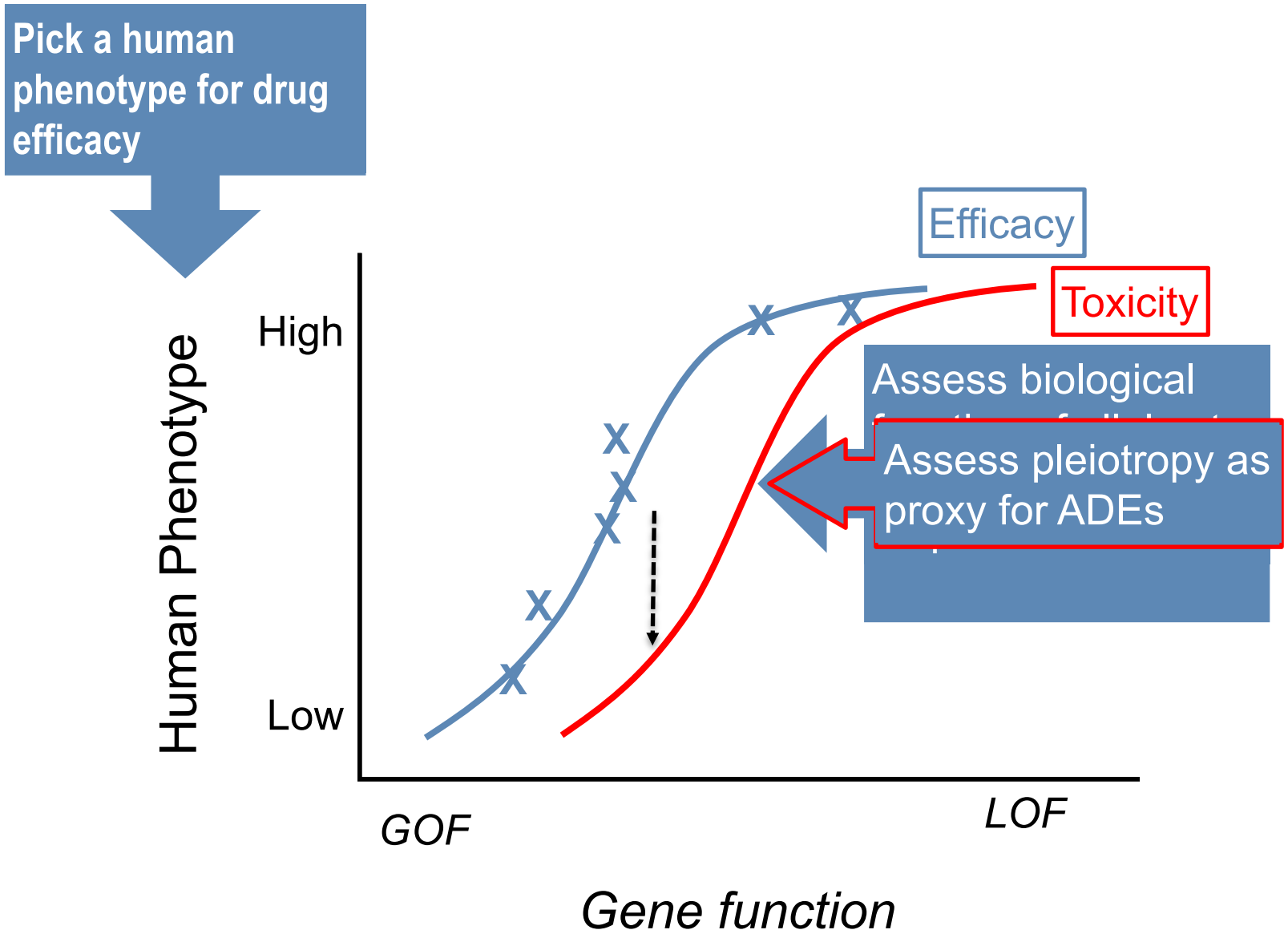
Nelson et al *Nature Genetics* 2015



Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)



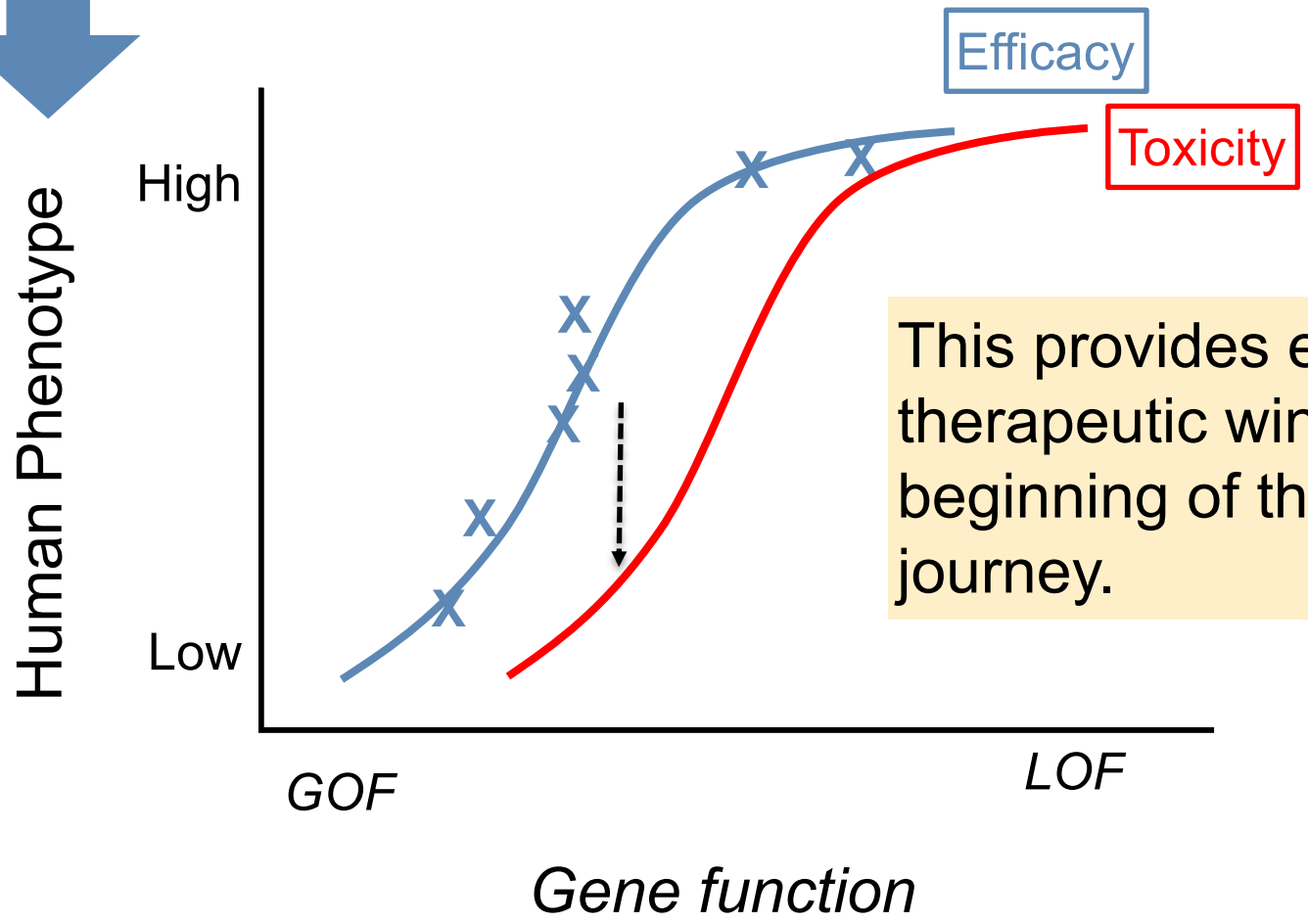
Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)



Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

New target for drug screen!

Pick a human phenotype for drug efficacy



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

Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

It is not common or rare…

It is common *and* rare variants

An example in immunology

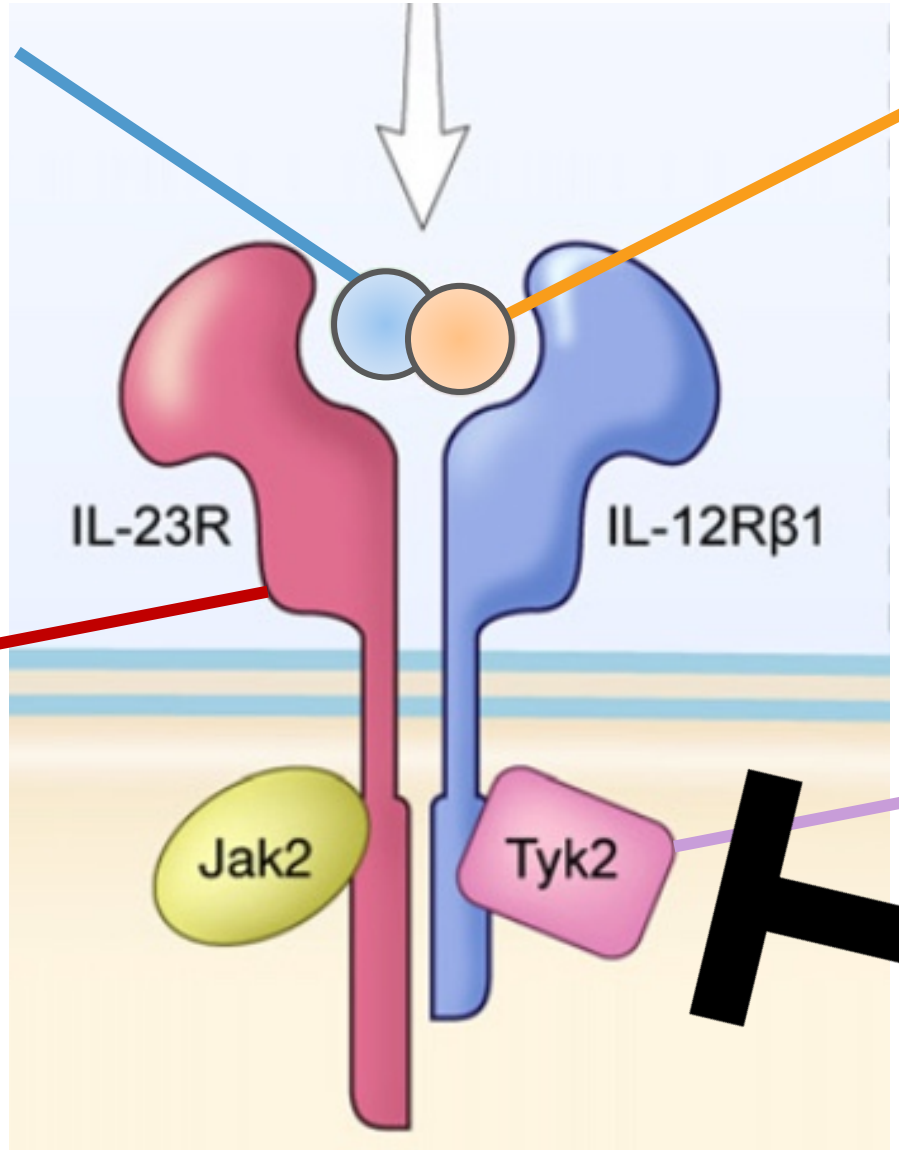
Example of allelic series model: *TYK2*

- 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)

IL12B (IL-12p40)



IL23R

TYK2

?

O'Shea and Plenge *Immunity* (2012)

nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0216-7

TYK2 gene

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

Harm-Jan Westra[1,2,3,4,5,20], Marta Martínez-Bon
Yang Luo[1,2,3,4], Nikola Teslovich[1,2,3,4], Jane Worth
Lars Klareskog[13], Solbritt Rantapaa-Dahlqvist[14]
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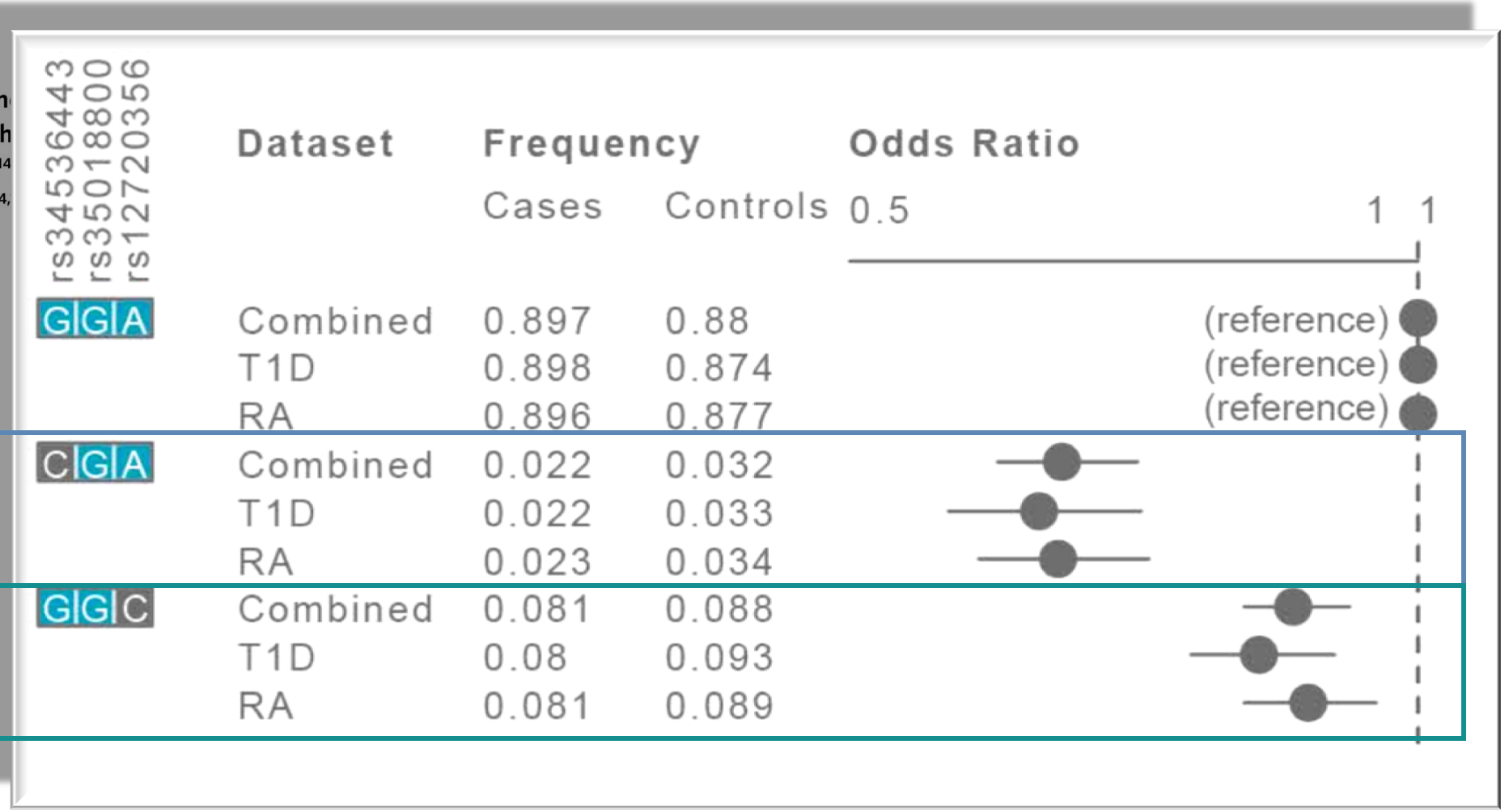
Soumya Raychaudhuri[1,2,3,4,9,19]*



P1104A

I684S

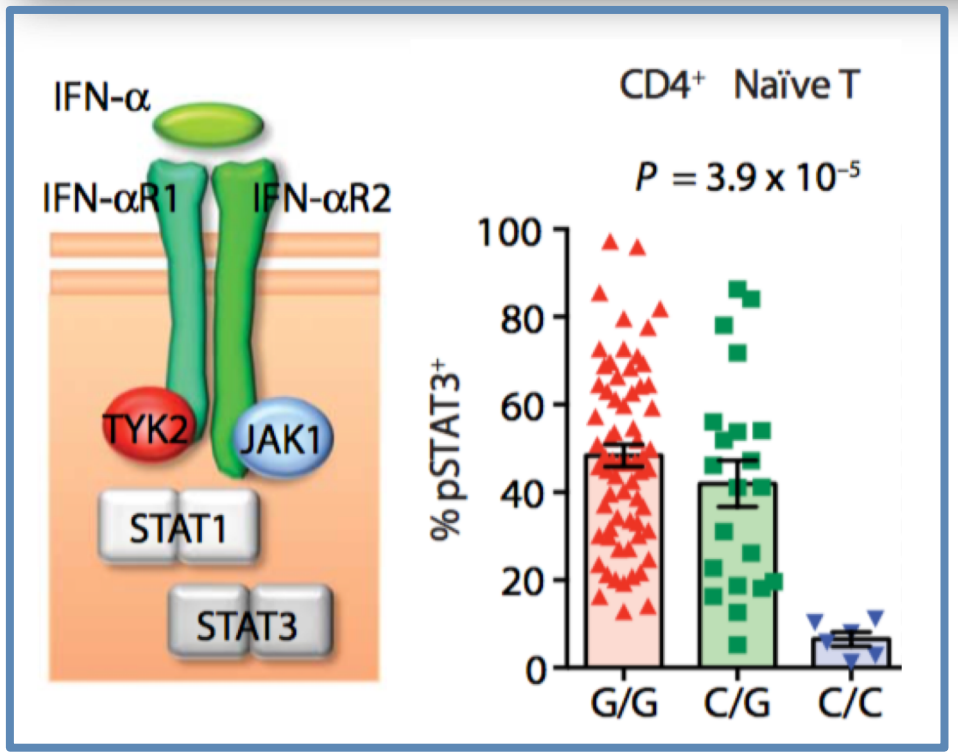
(low freq: A928V)

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

AUTOIMMUNITY

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 Fugger[1,3,4]*



P1104A allele that protects from autoimmunity is associated with ~80% loss-of-function (LoF) in C/C homozygous state

Same LoF allele has no obvious increased risk of infection

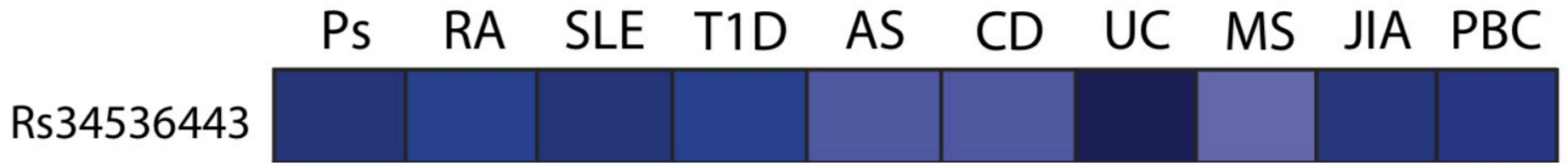
		Rs34536443 genotype			
		G/G	*G/C*	*C/C*	Total
normal	In U.K. Biobank	105,794 (90.63%)	10,689 (9.16%)	249 (0.21%)	116,732 (100%)
Infections	Mycobacterial	20 (86.96%)	3 (13.04%)	0 (0.00%)	23
	Specific bacterial (For example, *S. aureus*)	54 (90.00%)	5 (8.33%)	1 (1.67%)	60
	Specific viral (e.g. HSV, VZV, viral encephalitis)	93 (96.88%)	3 (3.12%)	0 (0.00%)	96
	Mucocutaneous candidiasis	46 (88.46%)	6 (11.54%)	0 (0.00%)	52
	Total	213 (92.21%)	17 (7.36%)	1 (0.43%)	231

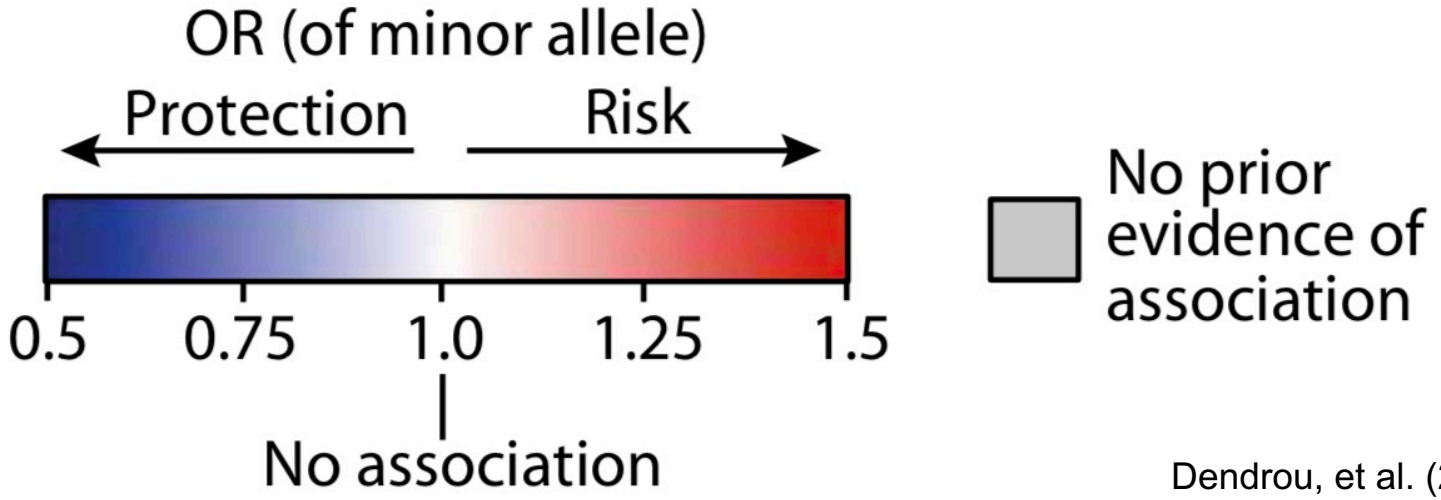
~80% LoF is *not* associated with increased infection

Dendrou, et al. (2016)
Science Translational Medicine

P1104A protects from multiple autoimmune diseases

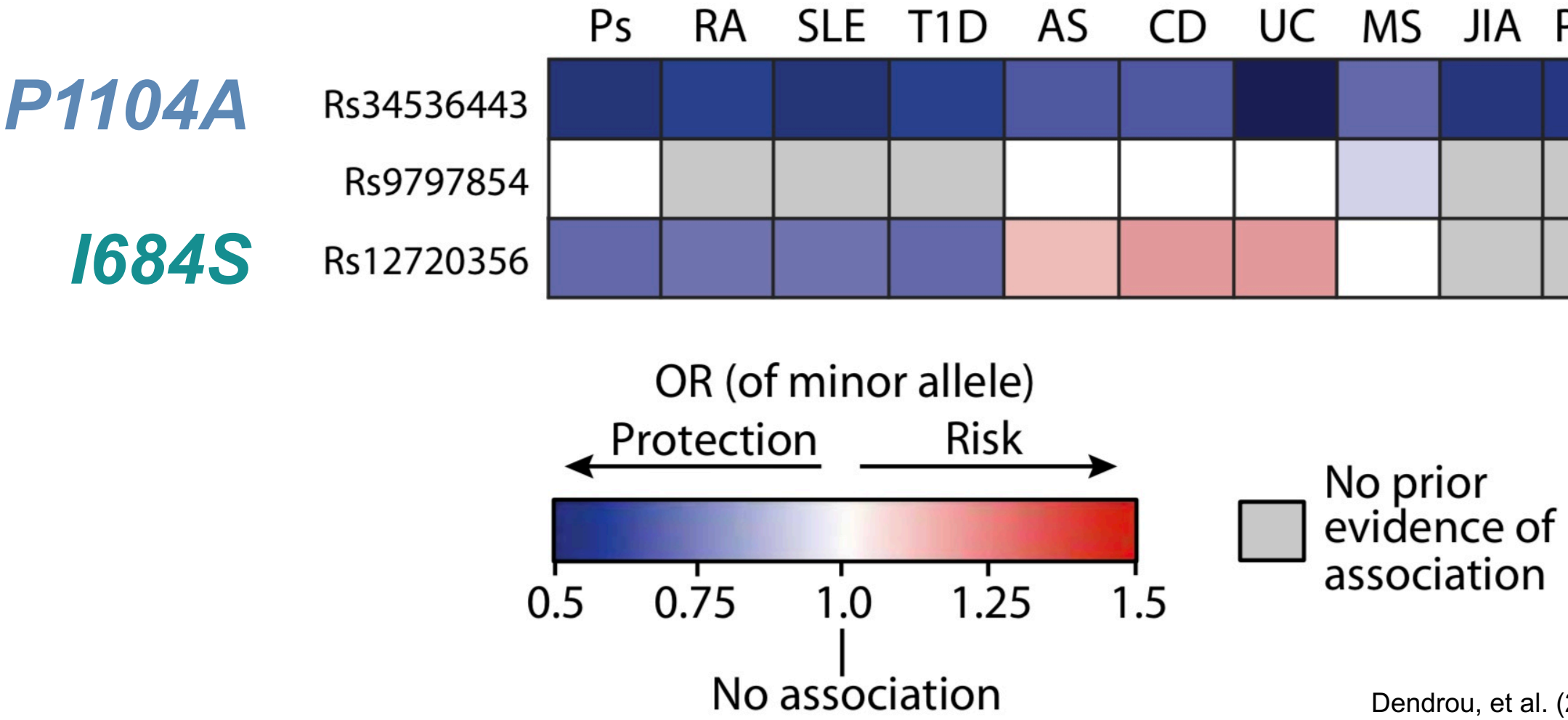
P1104A





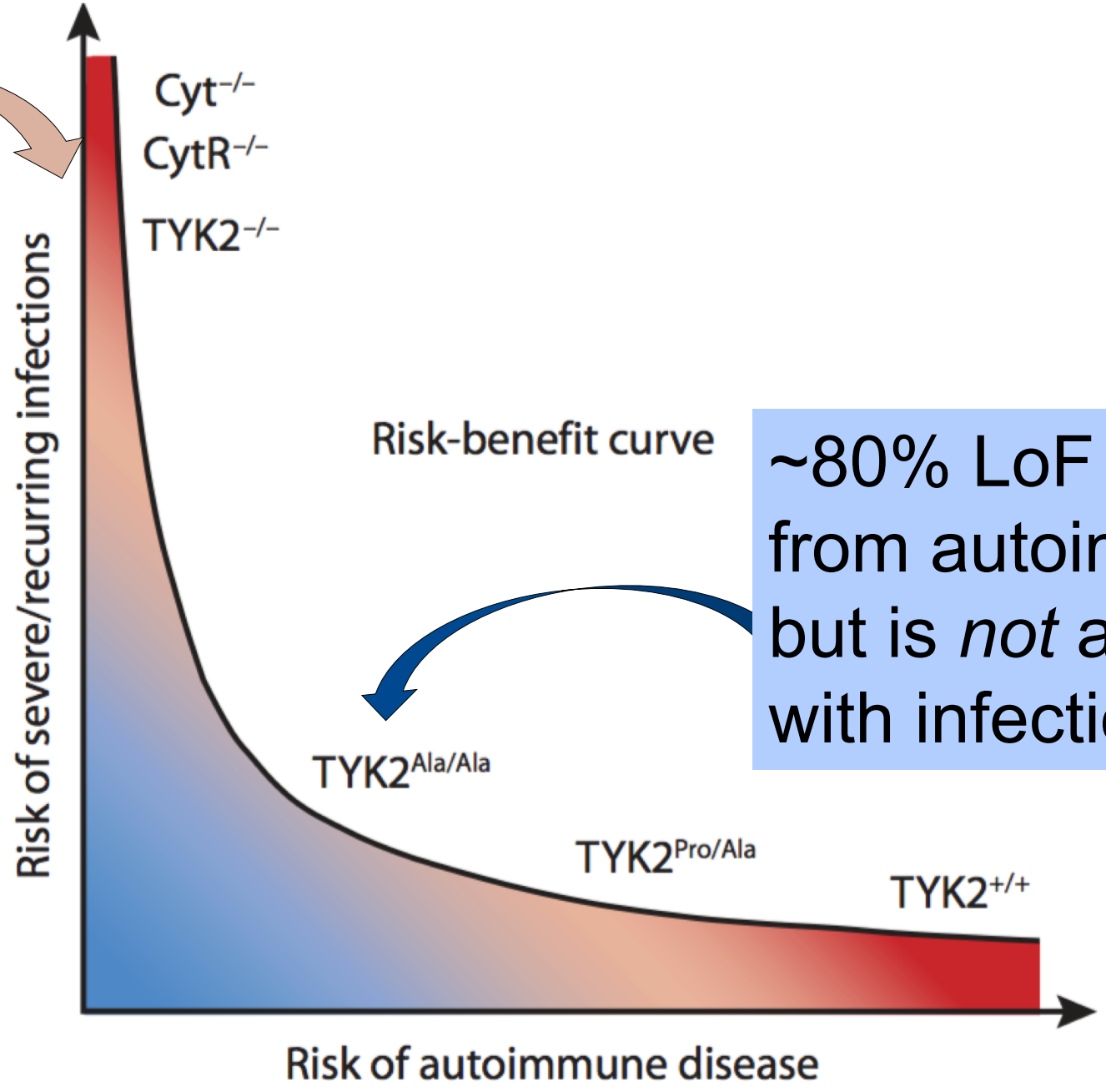
Dendrou, et al. (2016)
Science Translational Medicine

But *I684S* variant shows a more complicated pattern!

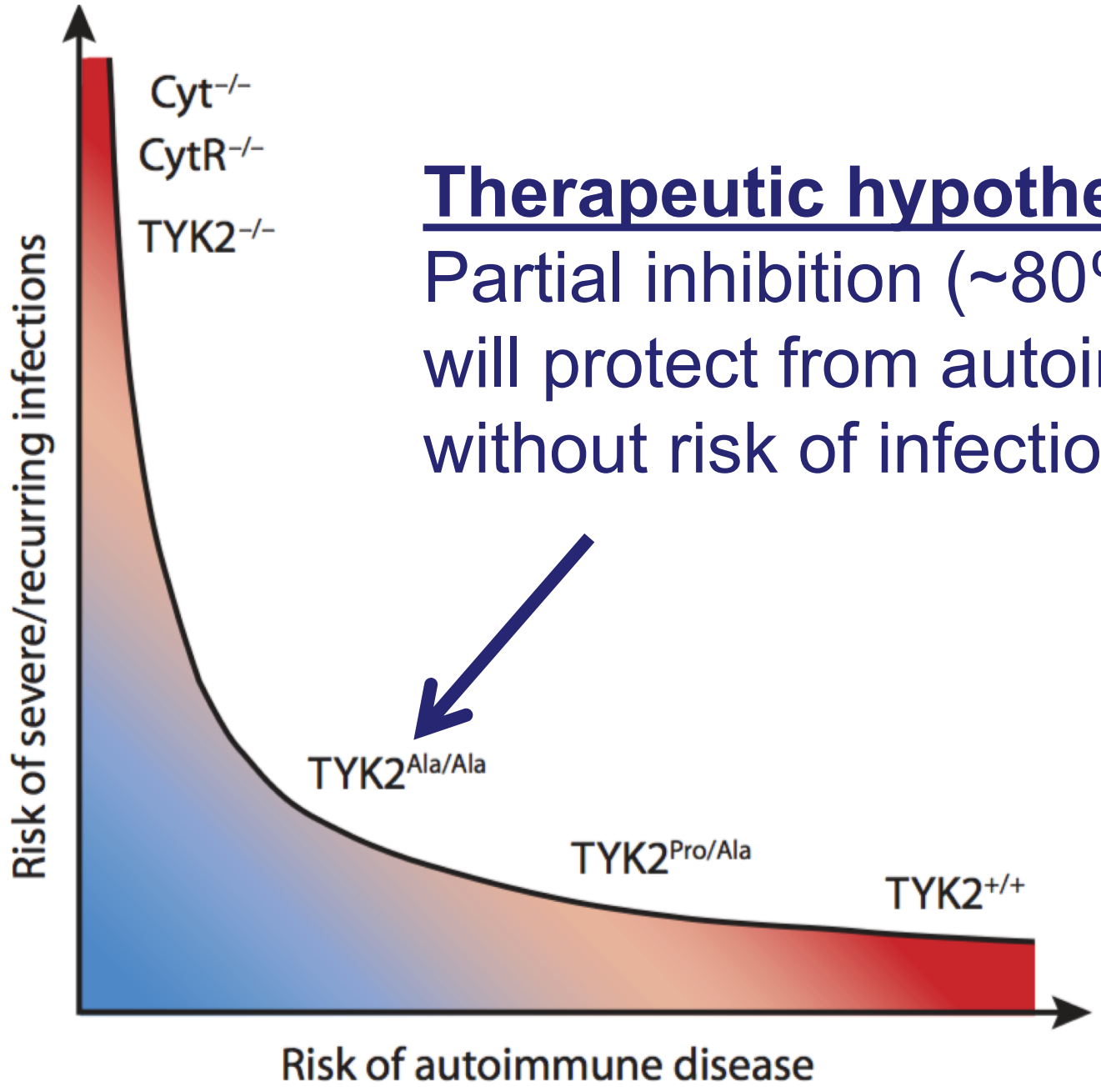


Dendrou, et al. (2016)
Science Translational Medicine

Complete TYK2 knockout increases risk of infection

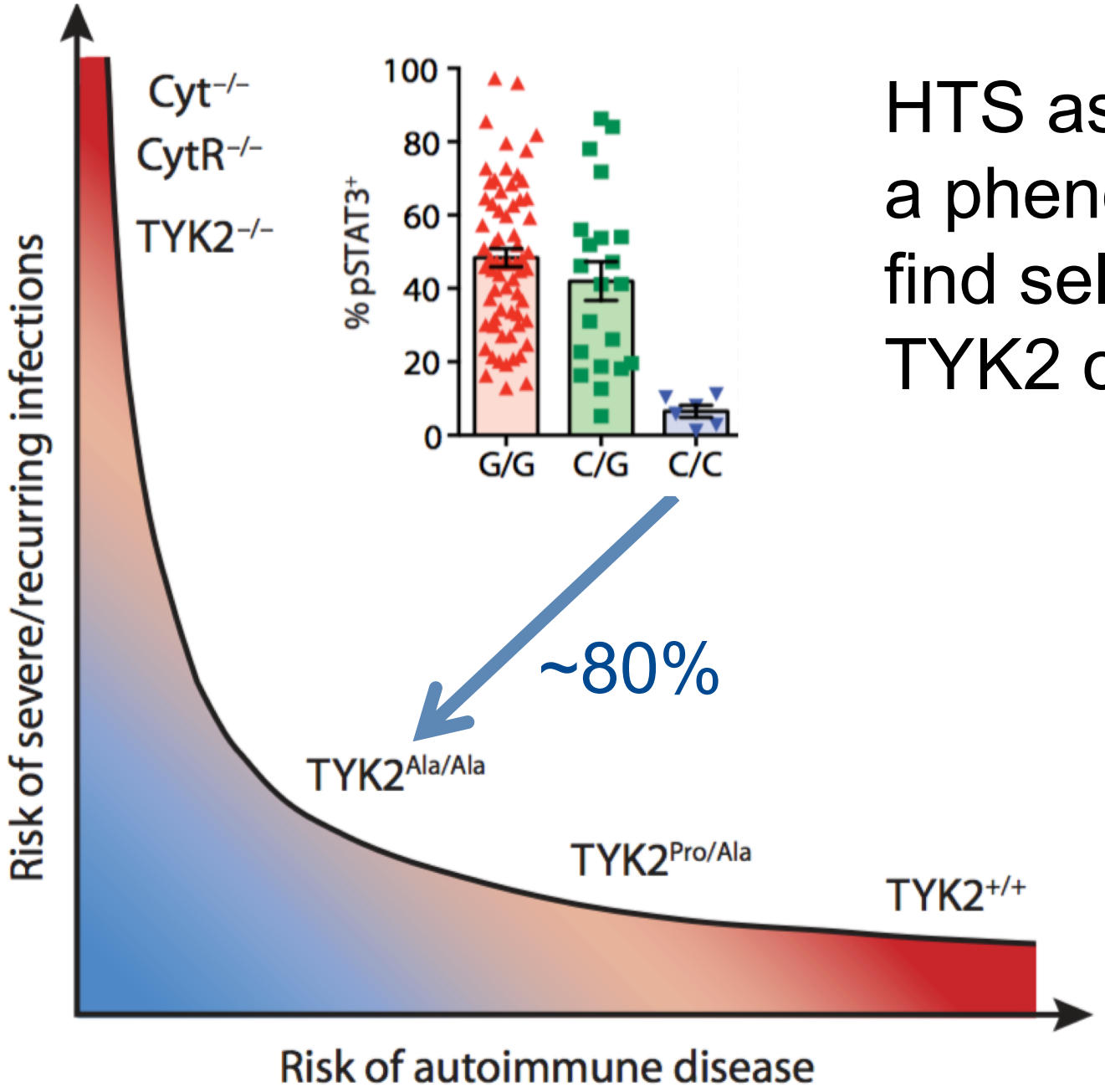


~80% LoF protects from autoimmunity but is *not* associated with infection

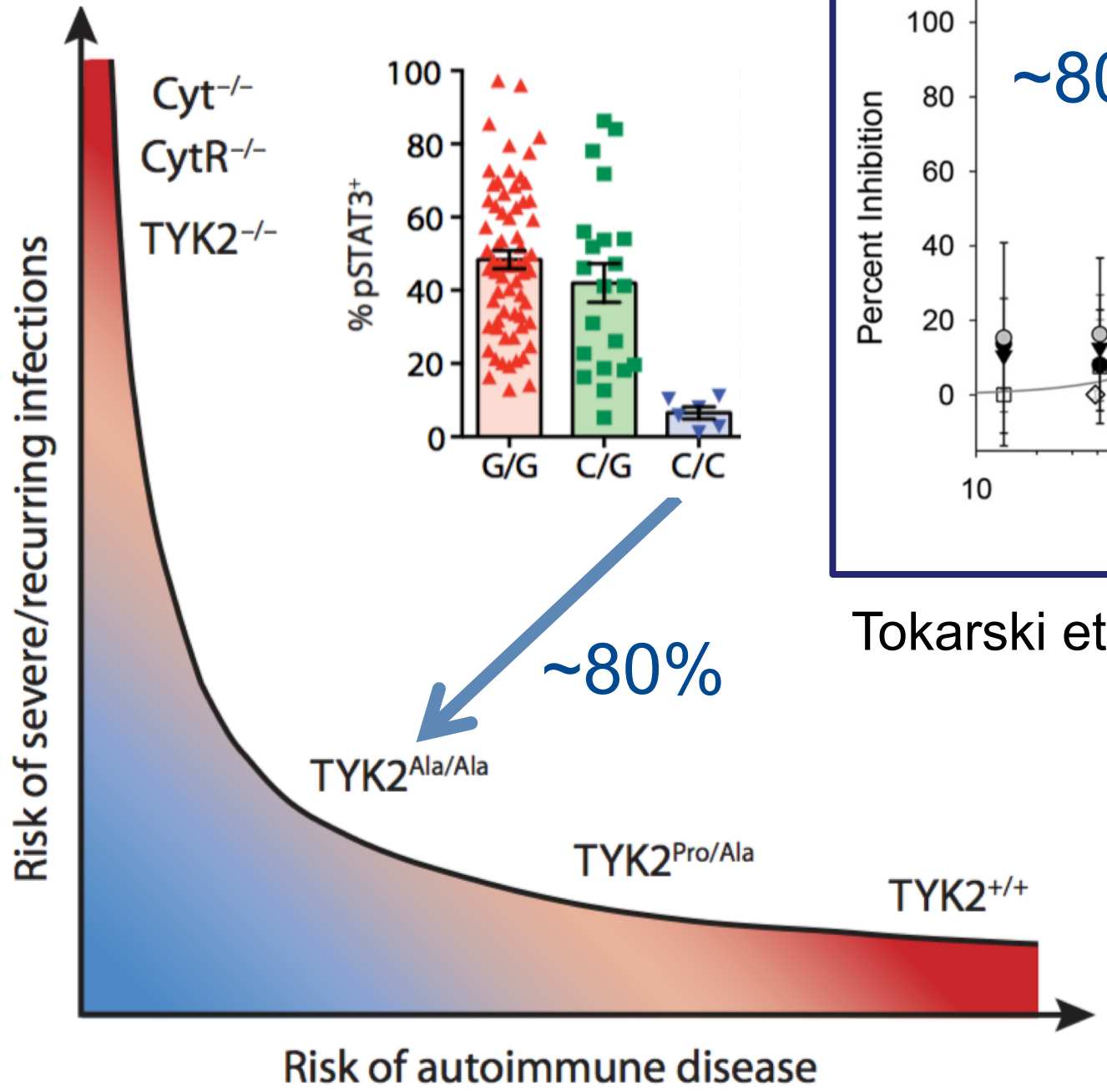


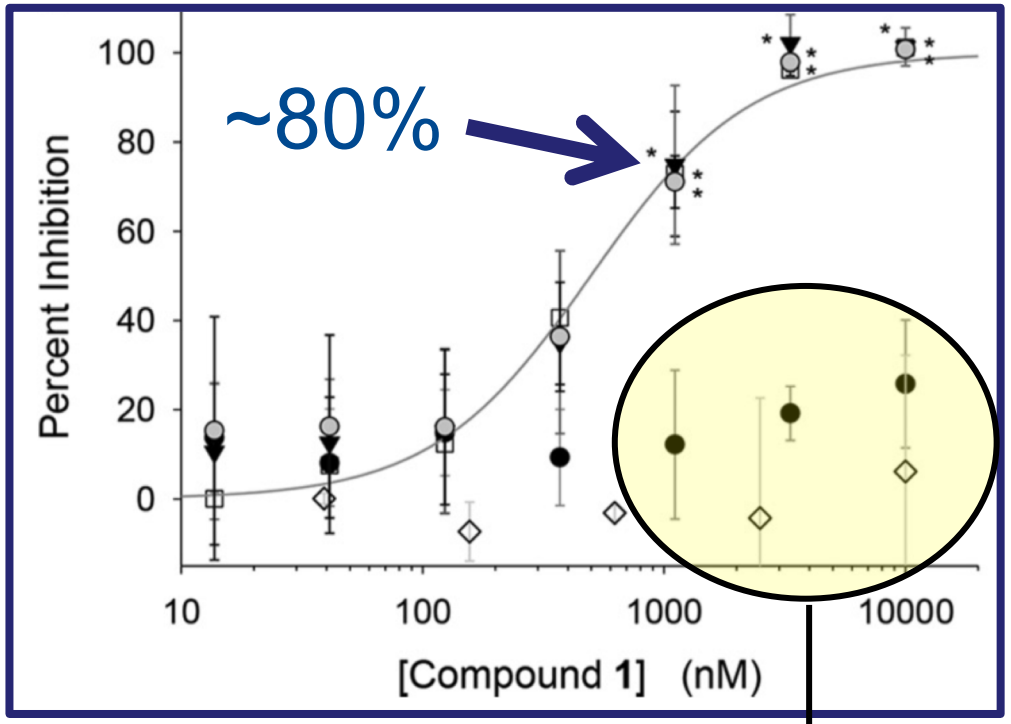
<u>Therapeutic hypothesis</u>:
Partial inhibition (~80%) of TYK2 will protect from autoimmunity without risk of infection

But matching *modality with mechanism* is challenging, especially selectivity over JAKs



HTS assay was used in a phenotypic screen to find selective inhibitors of TYK2 over other JAKs

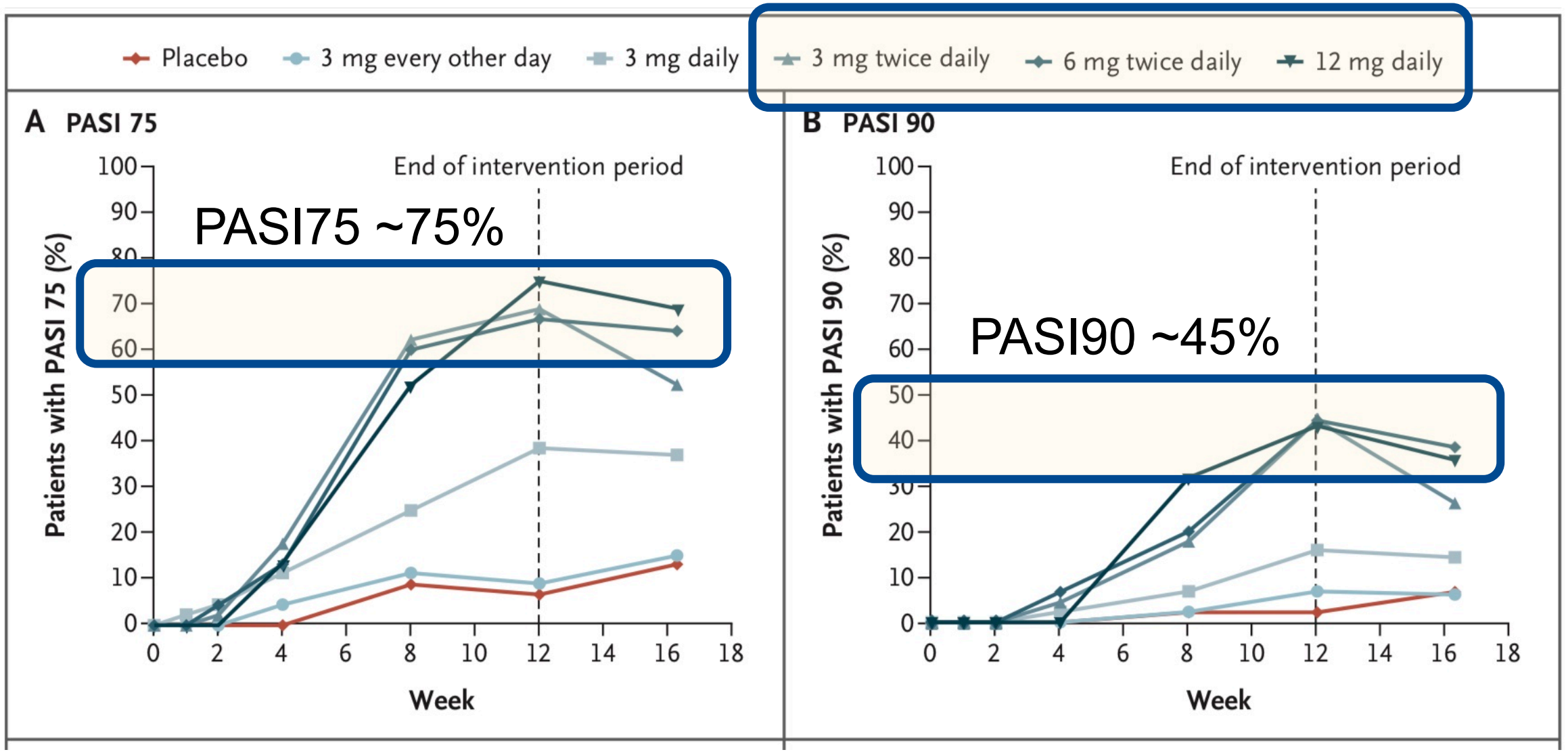




Tokarski et al (2015) *JBC*

Retains selectivity over JAKs

50-80% TYK2 inhibition safe and effective in Phase 2 (psoriasis)

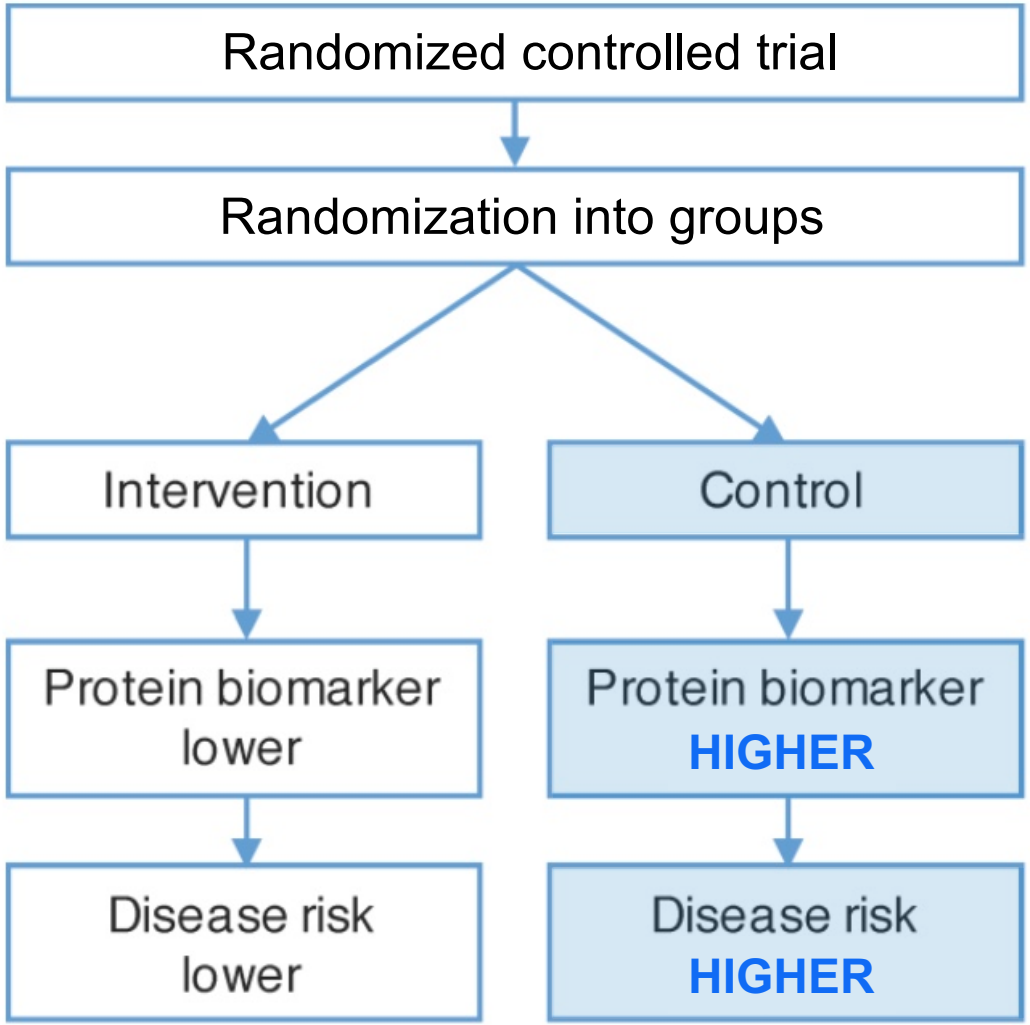


Papp et al (2018) *NEJM*

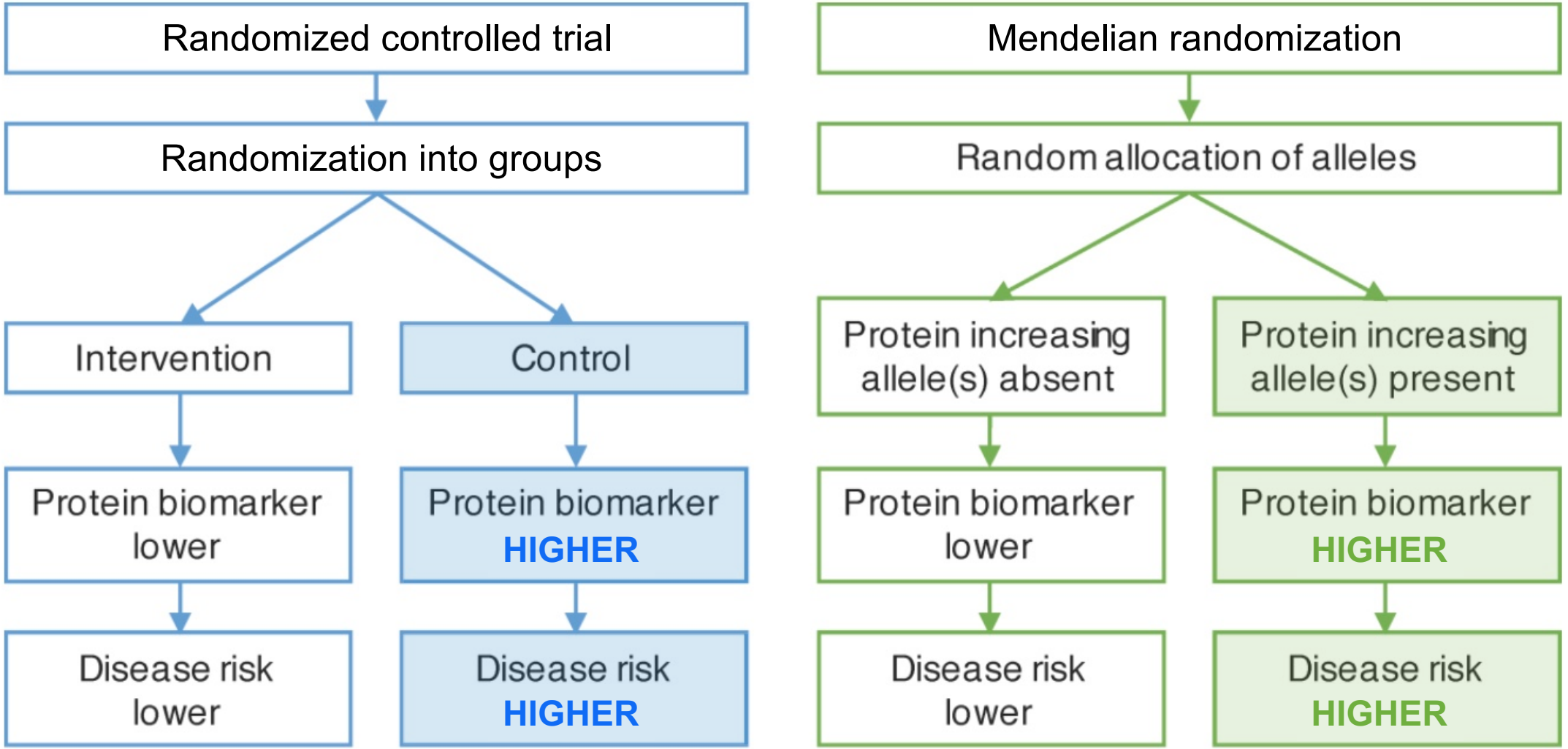
Emerging resources

Mendelian randomization

Mendelian randomization: *nature's clinical trial*

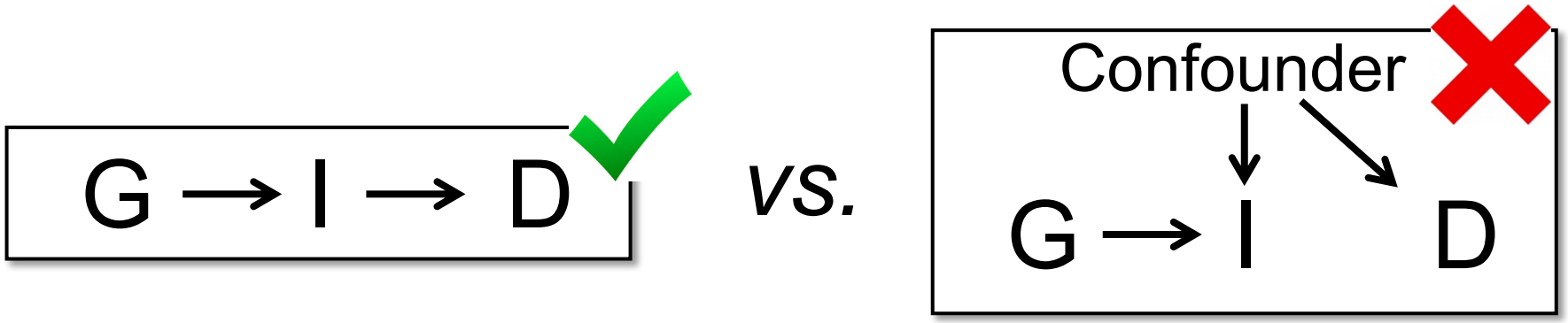


Mendelian randomization: *nature's clinical trial*

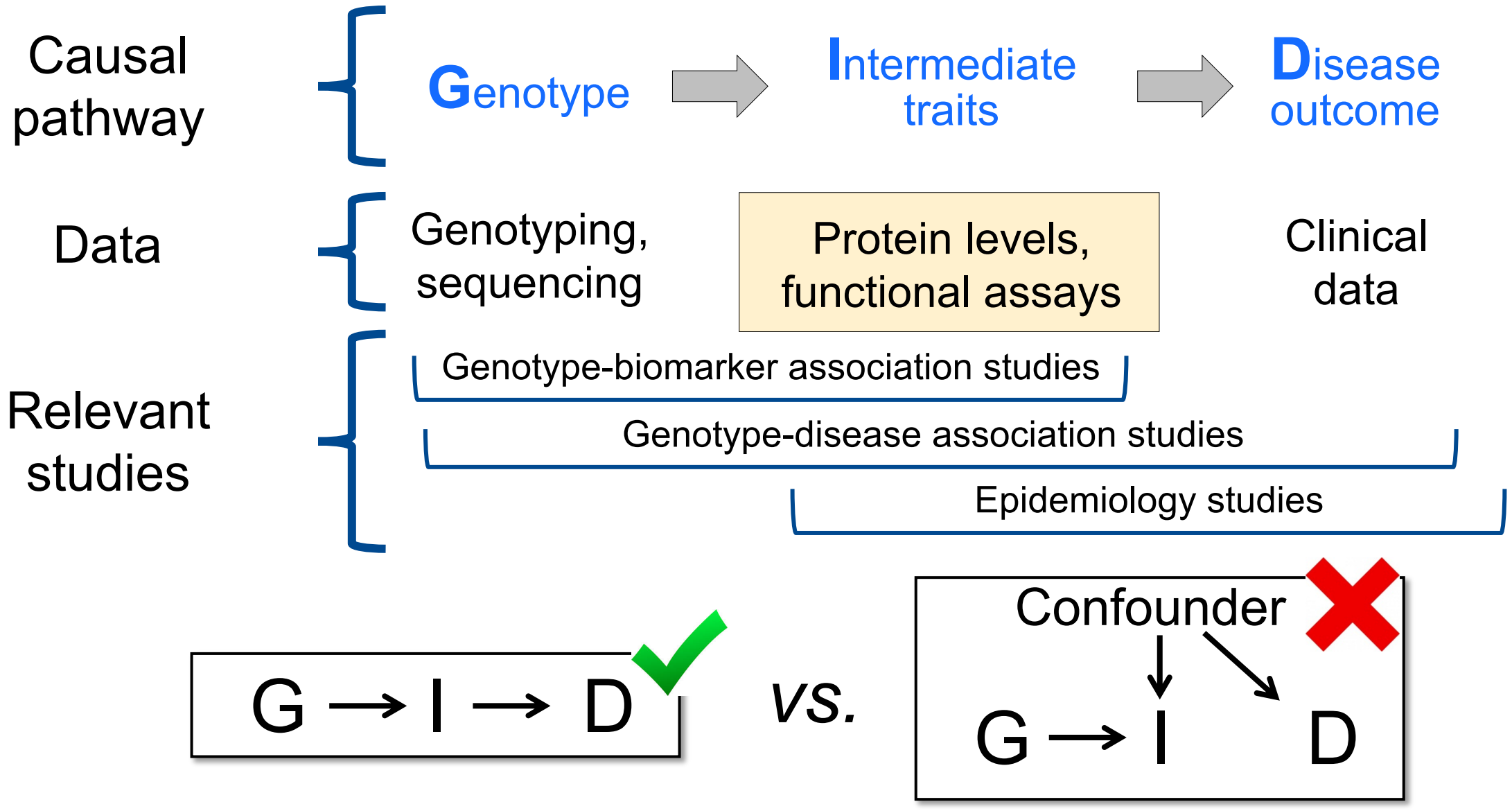


Genetics can bridge biomarker with clinical data, establishing a causal link for drug discovery

Causal pathway	**G**enotype →	**I**ntermediate traits →	**D**isease outcome
Data	Genotyping, sequencing	Protein levels, functional assays	Clinical data
Relevant studies	Genotype-biomarker association studies		
	Genotype-disease association studies		
	Epidemiology studies		



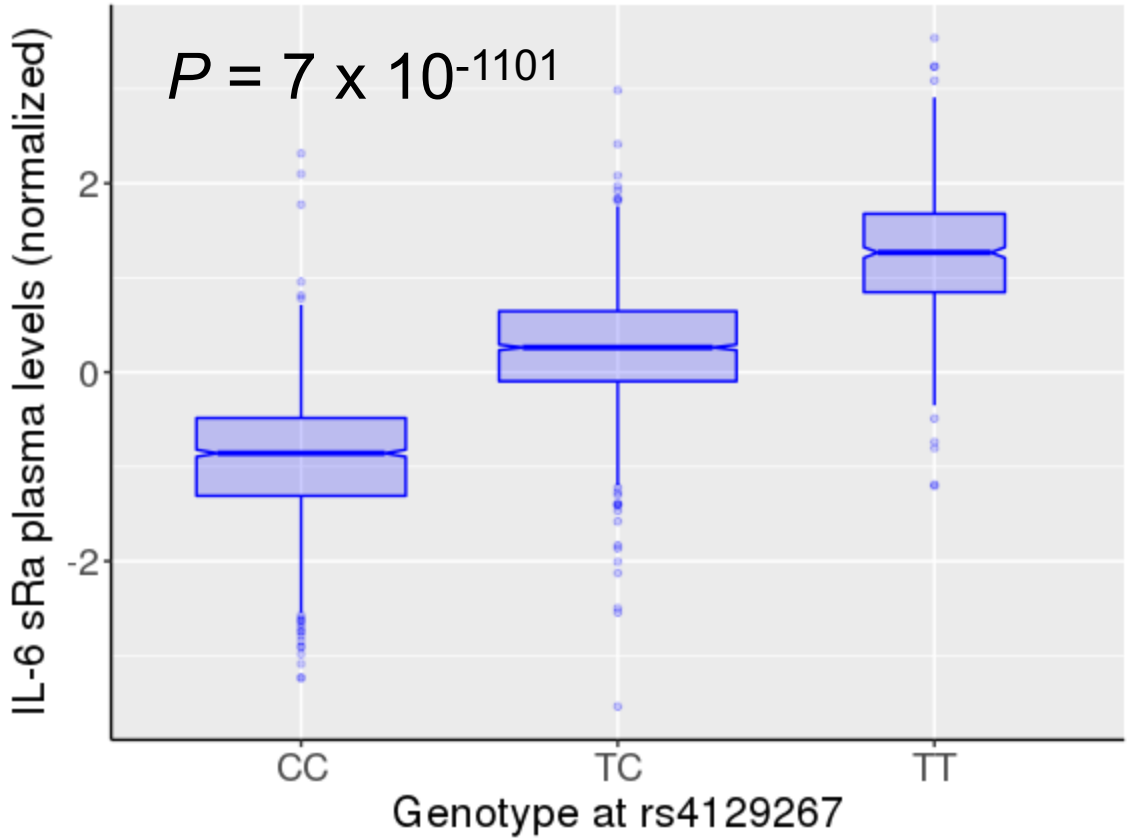
Large-scale proteomic databases are limiting



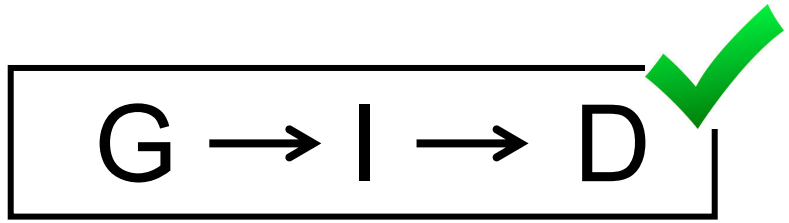
Emerging resource of pQTLs for MR

- Tested 3,622 plasma proteins in 3,301 healthy individuals from INTERVAL population cohort
- Identified 1,927 genetic associations with 1,478 proteins
- **Example**: *IL-6R* RA protective allele increases sIL-6R levels (see figure) but decreases membrane-bound IL6R
- **Therapeutic hypothesis**: preventing IL-6 signaling through IL-6R via blocking antibodies should treat RA symptoms

Sun, Maranville *et al (*2018) *Nature*



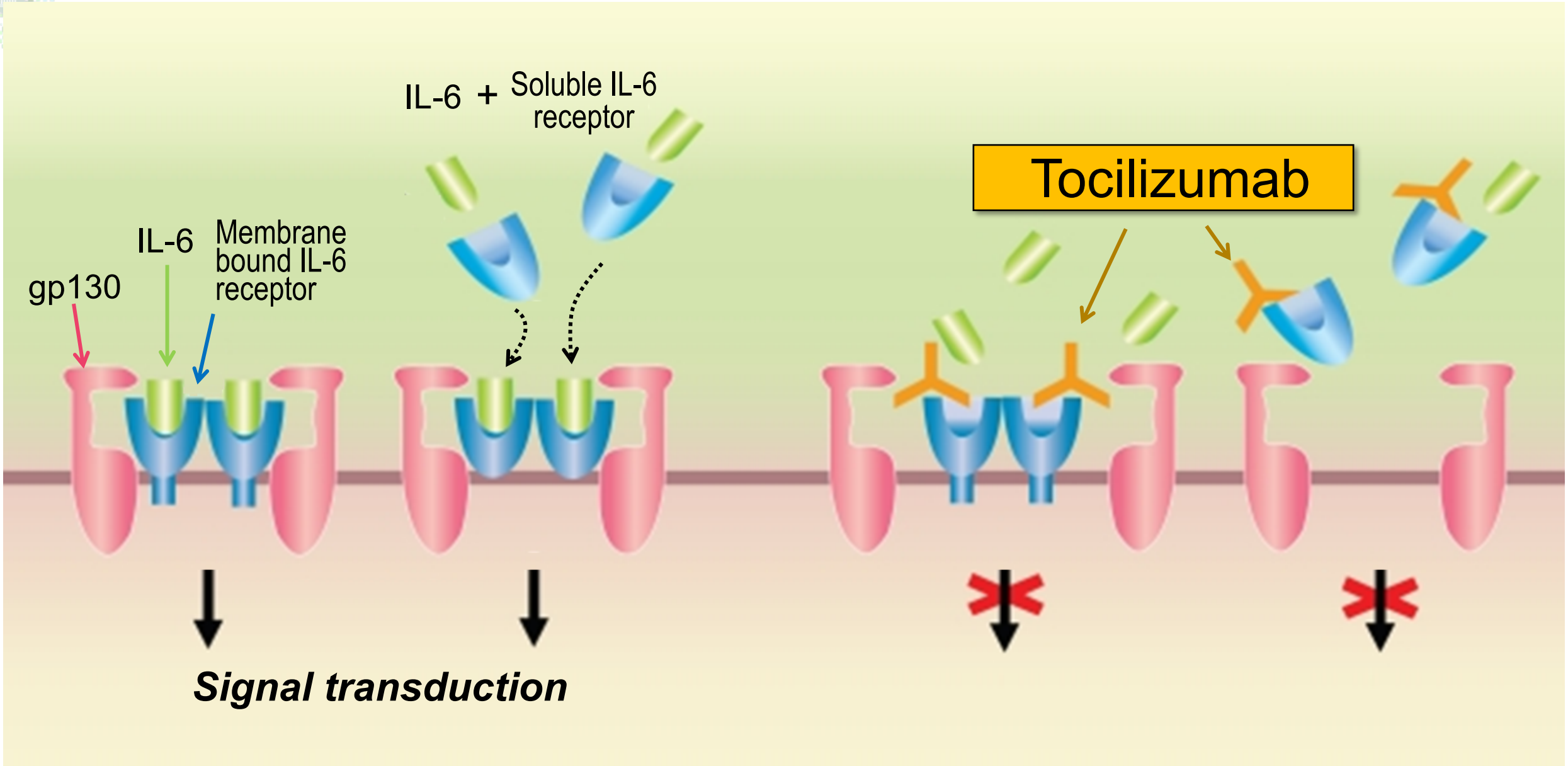
Mendelian randomization establishes a causal link between IL-6 pathway and risk of rheumatoid arthritis



IL-6R minor variant → *Less membrane IL-6R and less signaling* → *Protection from RA*

Thus, therapeutic targeting of IL-6R should be beneficial in treating RA patients

Tocilizumab mimics mutation by reducing IL-6R signaling



Phenome-wide association study (PheWAS)

Phenome-wide association studies (PheWAS)

Disease-Agnostic cohort

EHRs, Claims, Questionnaires, etc.

Clinical data

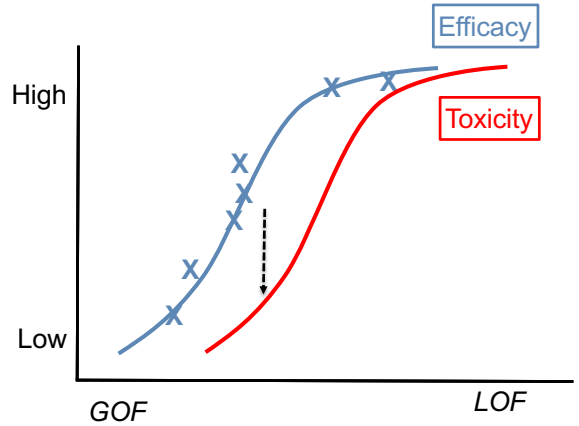
Genetic data

GWAS, exome sequencing, etc.

LoF SNP

Test association of selected SNP with clinical endpoints

- PheWAS code 1 — risk — surrogate for efficacy
- PheWAS code 2
- PheWAS code 3
- PheWAS code 4
- PheWAS code 5 — risk — surrogate for toxicity
- ⋮
- PheWAS code 500



nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0216-7

IFIH1 gene

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

Harm-Jan Westra[1,2,3,4,5,20], Marta Martínez-Bonet[4,20], Suna C
Yang Luo[1,2,3,4], Nikola Teslovich[1,2,3,4], Jane Worthington[9,10], Javi
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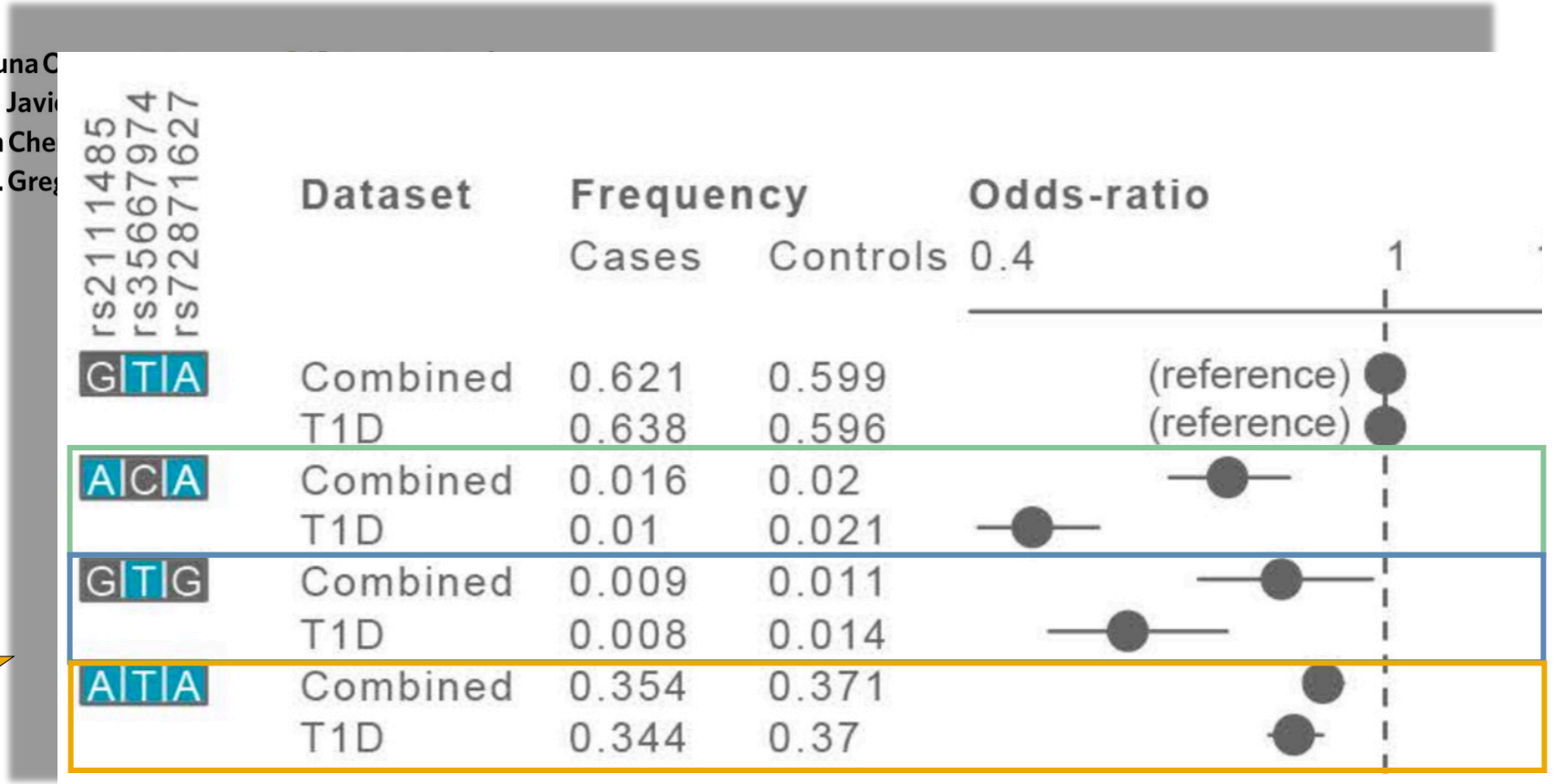
John A. Todd[17], Steve Eyre[9,10], Peter A. Nigrovic[4,18], Peter K. Greg
Soumya Raychaudhuri[1,2,3,4,9,19]*

rs35667974 – protects from T1D

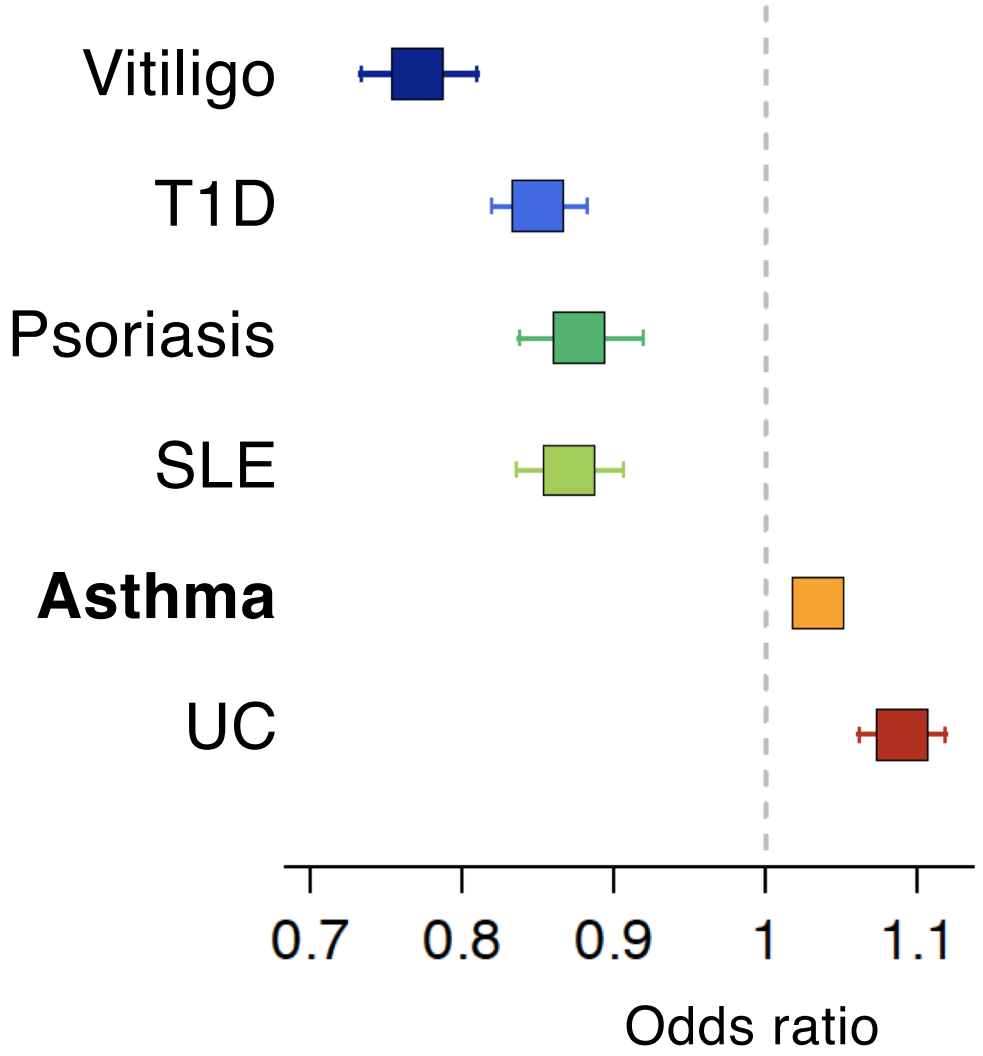
rs72871627 – protects from T1D

ATA haplotype – protects from T1D



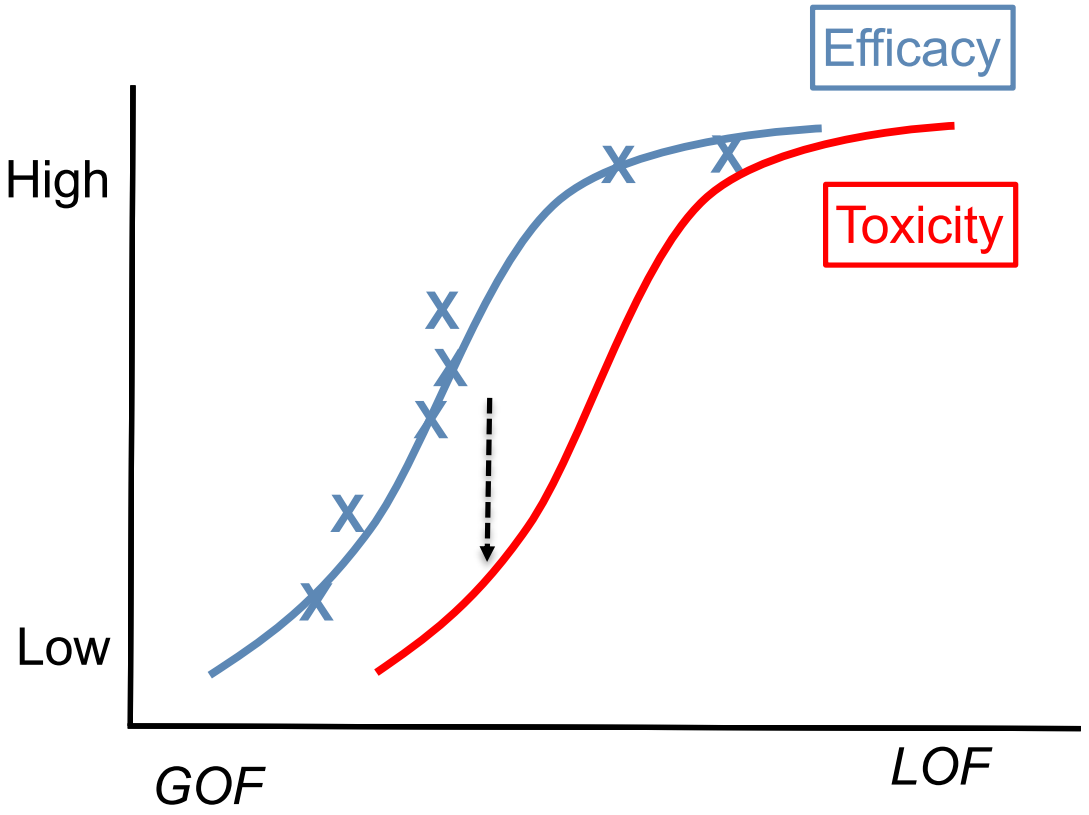
PheWAS example: *IFIH1*, autoimmunity, asthma

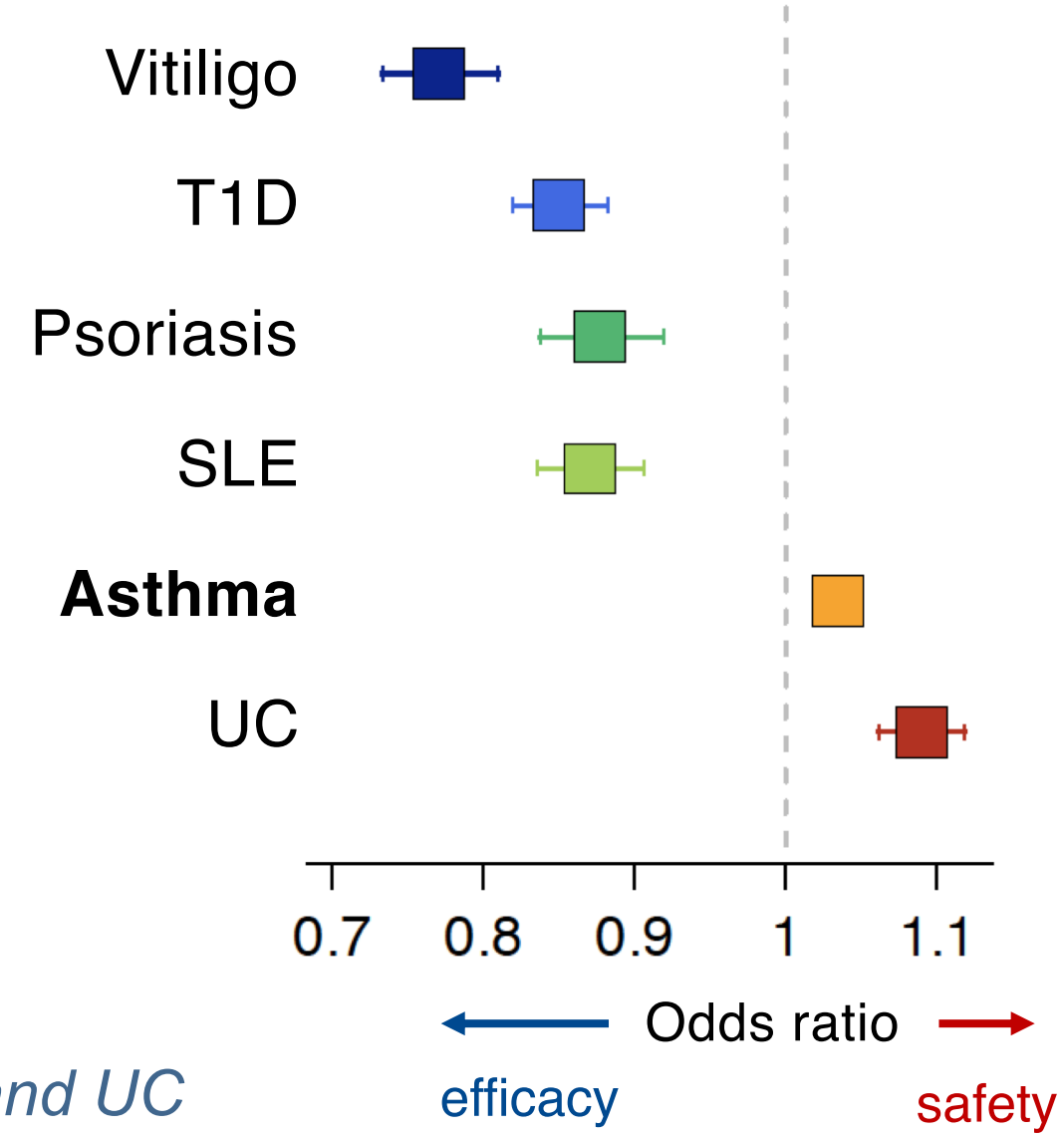
- PheWAS in ~800,000 individuals from four population cohorts
- Tested 25 SNPs for association with 1,683 clinical endpoints
- 10 novel associations discovered
- Example: *IFIH1* LOF allele protects from autoimmunity (known) but increases risk of asthma (novel finding)
- Therapeutic hypothesis: inhibiting IFIH1 may be effective in some autoimmune diseases but may make asthma worse



Diogo *et al* (2018) *Nature Communications (in press)*

Predicted impact of therapeutic inhibition of IFIH1





Beneficial effect for some autoimmune diseases, but increase risk of asthma and UC

FinnGen is a unique PheWAS resource

500,000 individuals (~10% of population)

National Registries, EHRs, etc.

Clinical data

Genetic data

Genome sequencing, Axiom array, imputation

SNP

Test association of selected SNP with clinical endpoints

PheWAS code 1

PheWAS code 2

PheWAS code 3

PheWAS code 4

PheWAS code 5

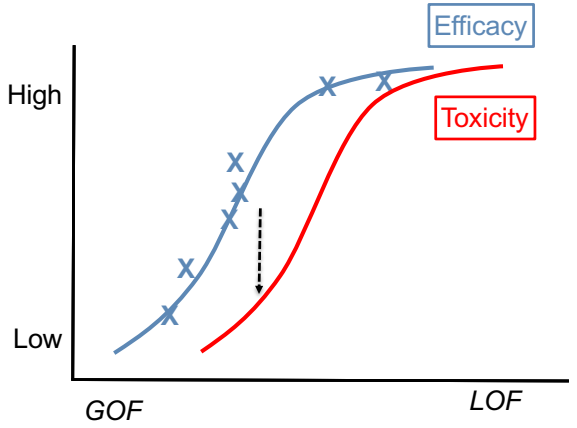
PheWAS code 500

risk

surrogate for efficacy

risk

surrogate for toxicity



In conclusion

Summary

- The pharmaceutical industry needs human genetics
- Human genetics increases probability of success >2-fold
- An “allelic series” model can be used to
  - prioritize new targets
  - match modality to mechanism
  - select pharmacodynamics biomarkers
  - determine clinical indications
- *TYK2* represents a compelling example in human immunology
- MR and PheWAS represent emerging resources
- (See back-up slides for more details!)

Questions?

@rplenge