IMPACT OF HUMAN GENETICS ON DRUG R&D



Robert Plenge

Roadmap for "*genetic dose-response*" portal

Common Disease Consortium

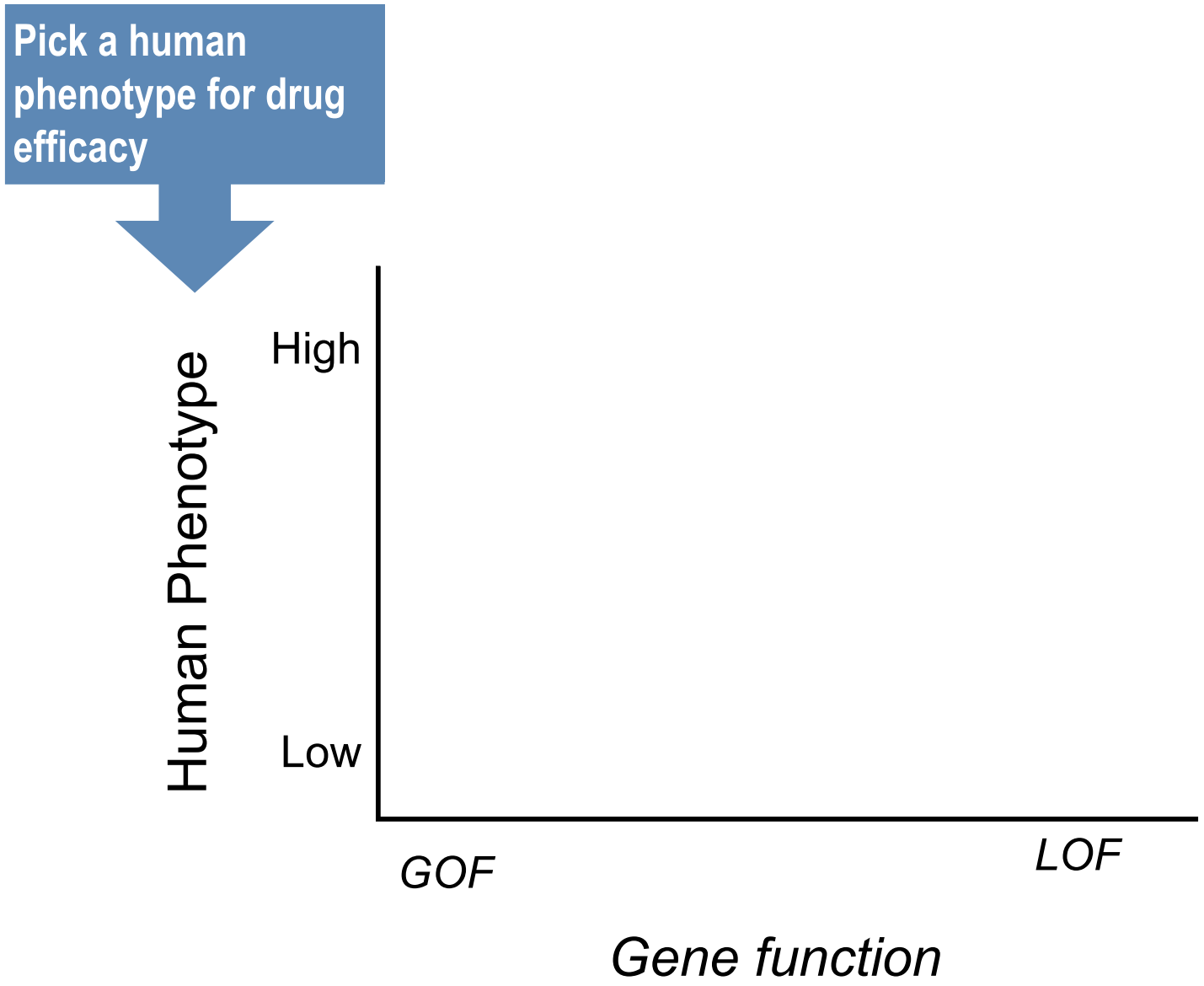
December 3, 2018

The problem

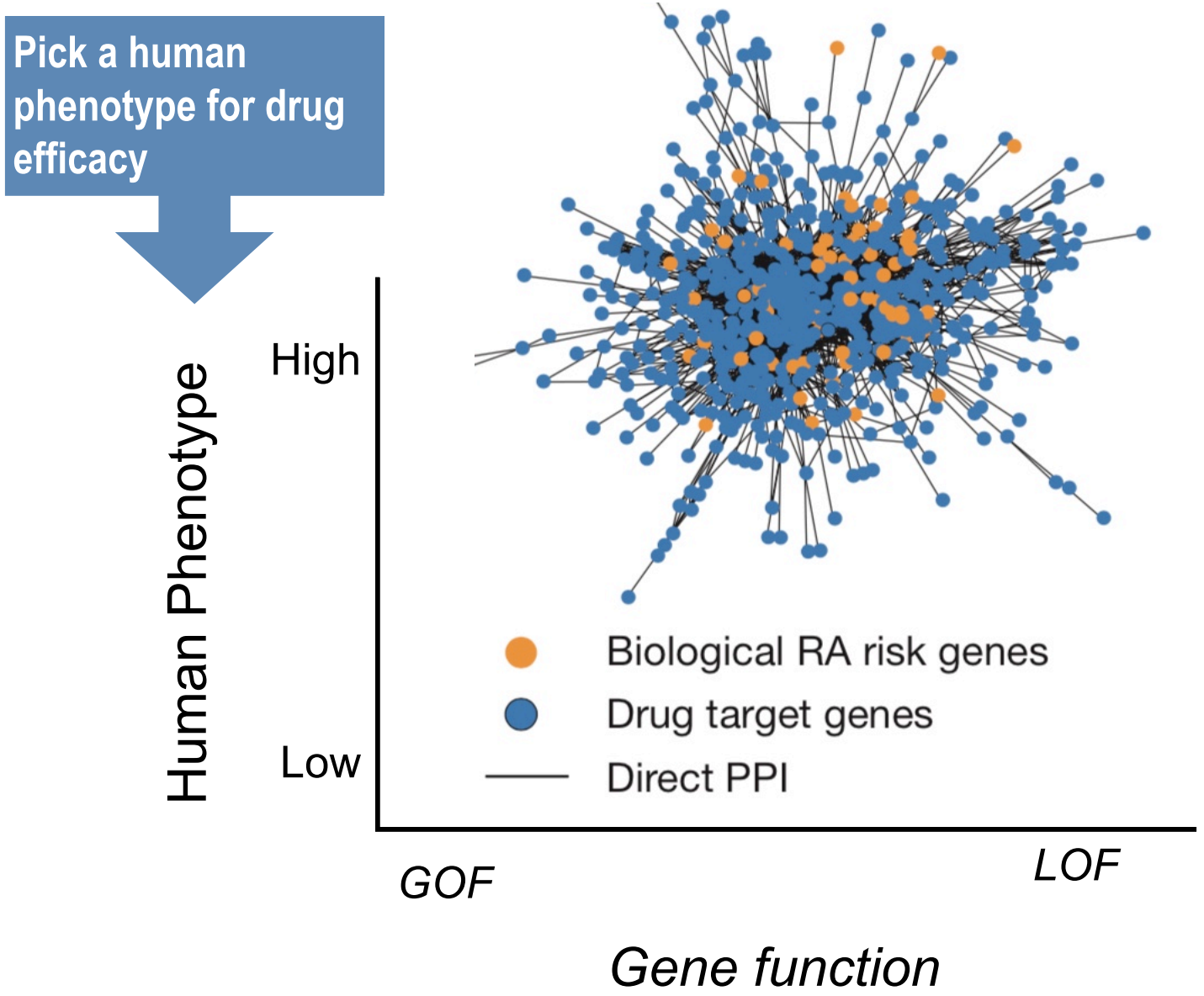
Which targets, when perturbed therapeutically, have a beneficial effect in humans?

How do these targets differ from standard-of-care?

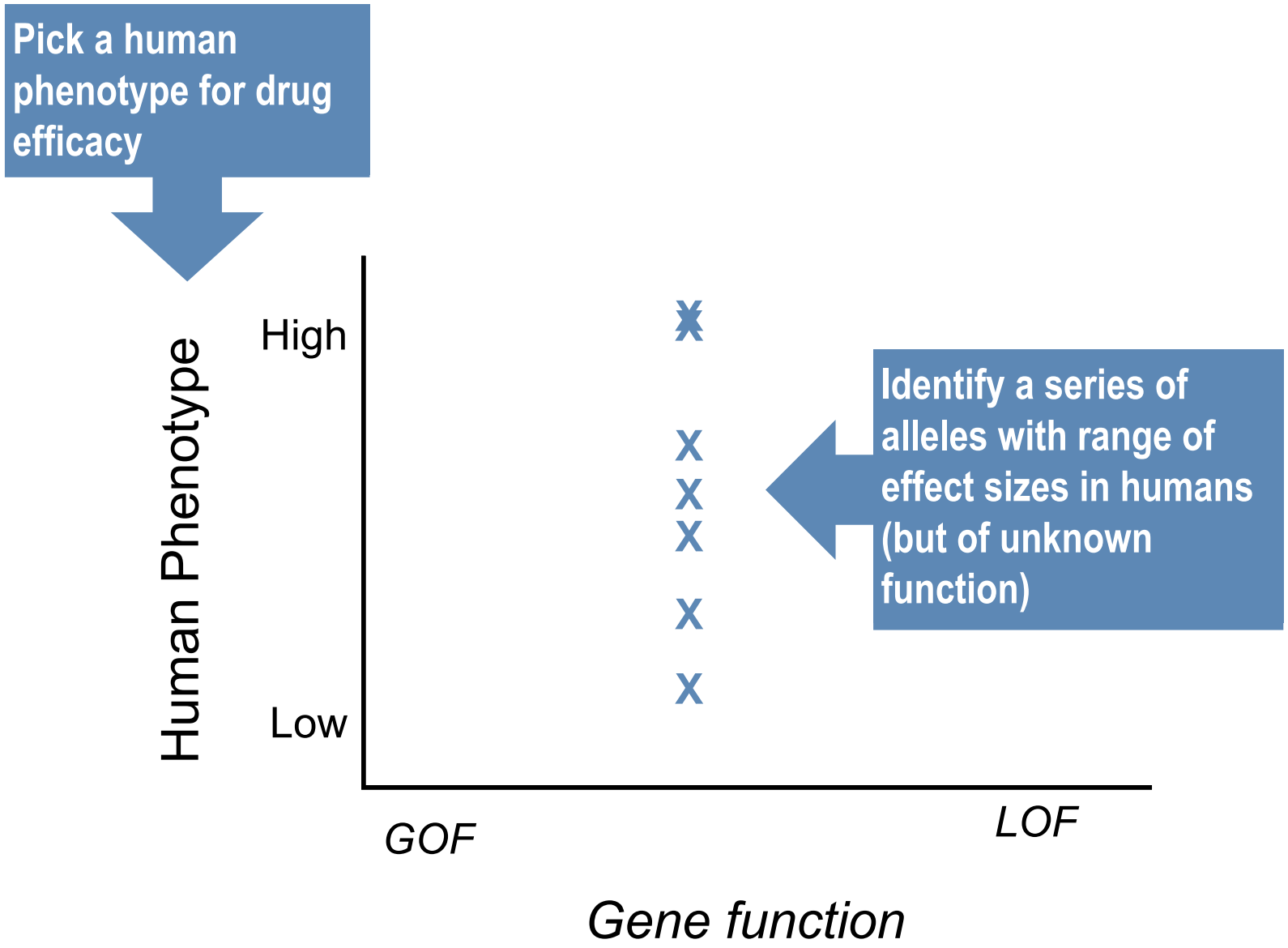
“*Allelic series*” model



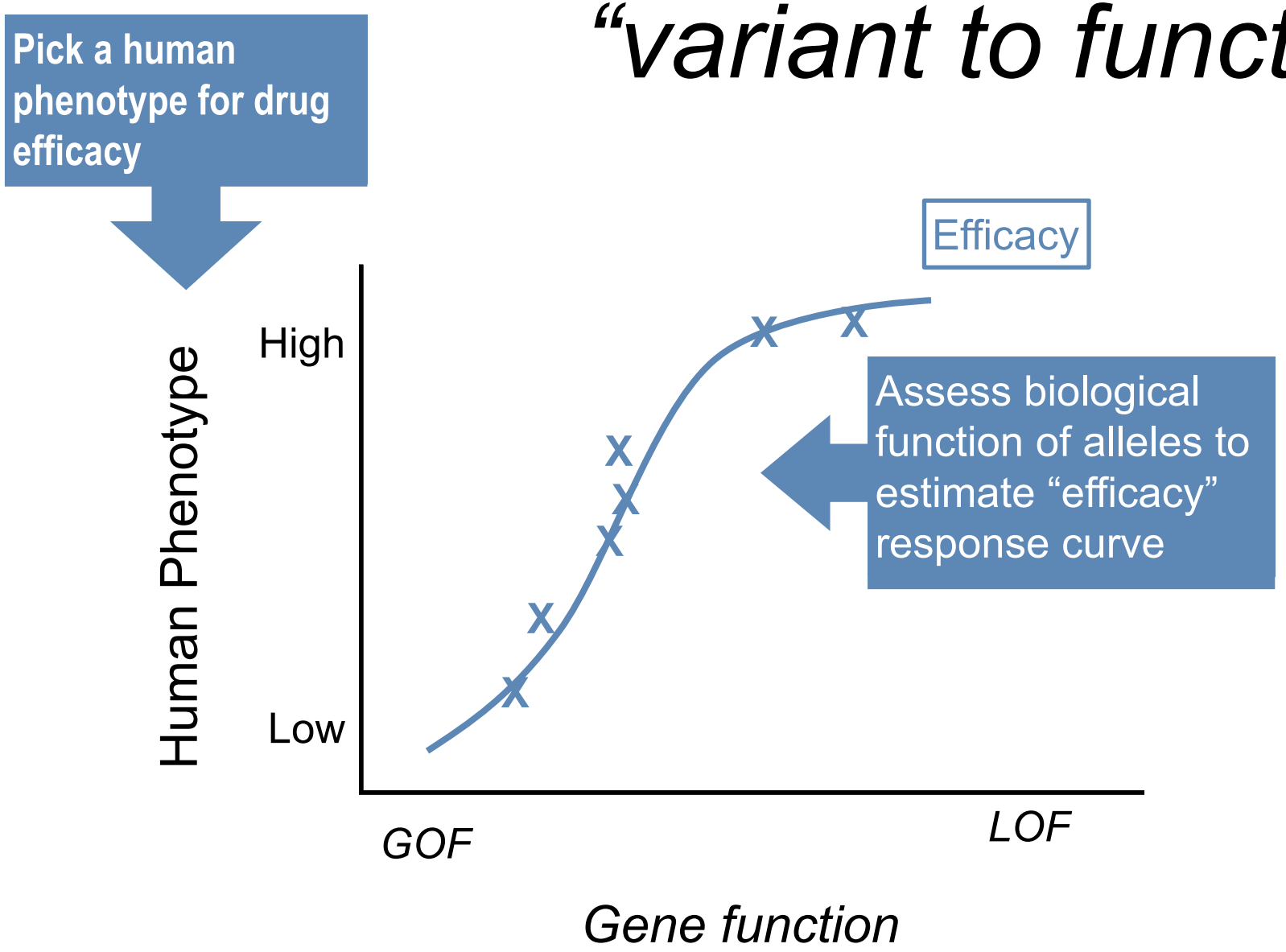
Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)



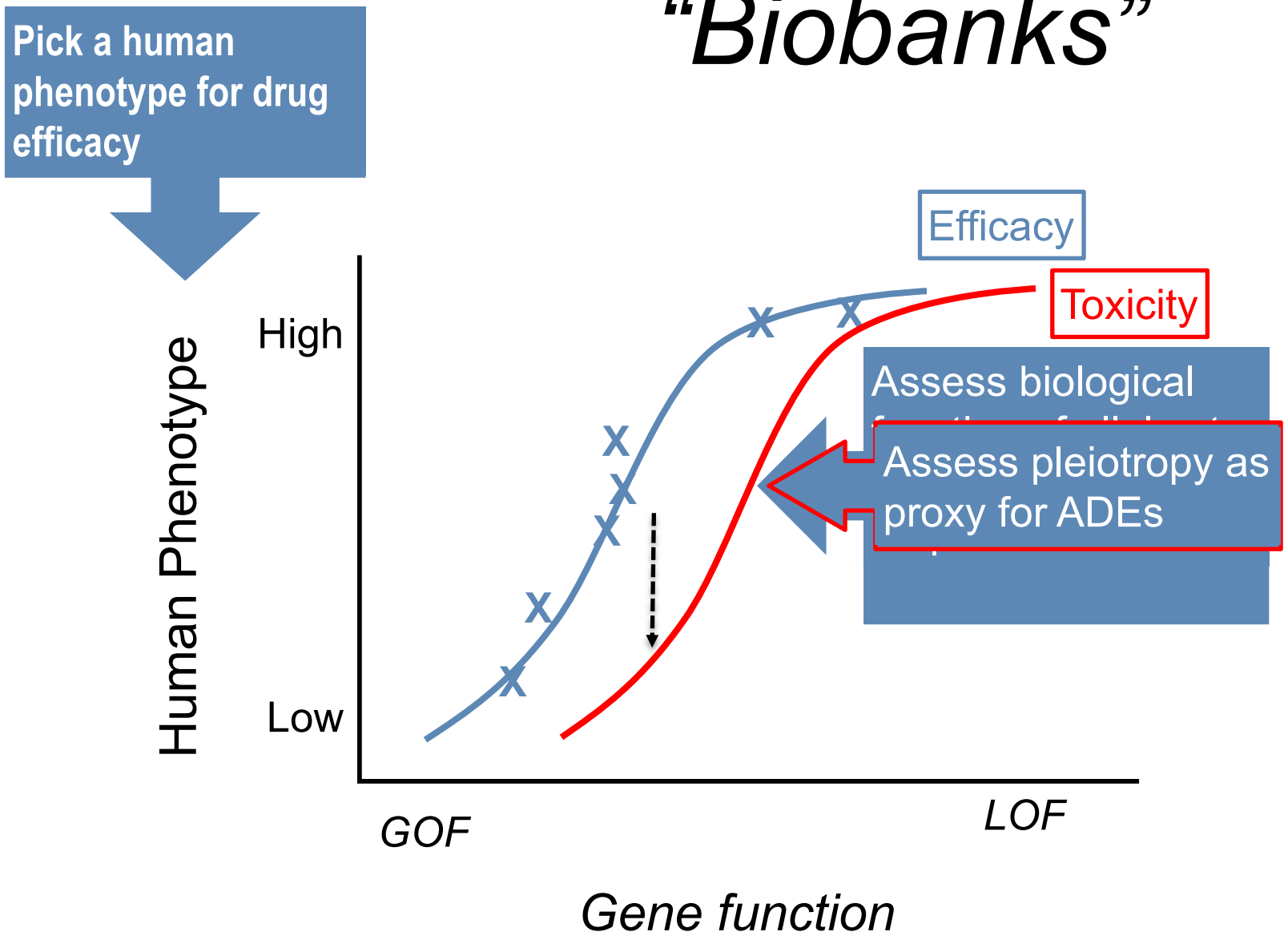
Okada et al *Nature* (2013)


Pick a human phenotype for drug efficacy
Human Phenotype
High
Low
Identify a series of alleles with range of effect sizes in humans (but of unknown function)
GOF
LOF
Gene function

"variant to function"

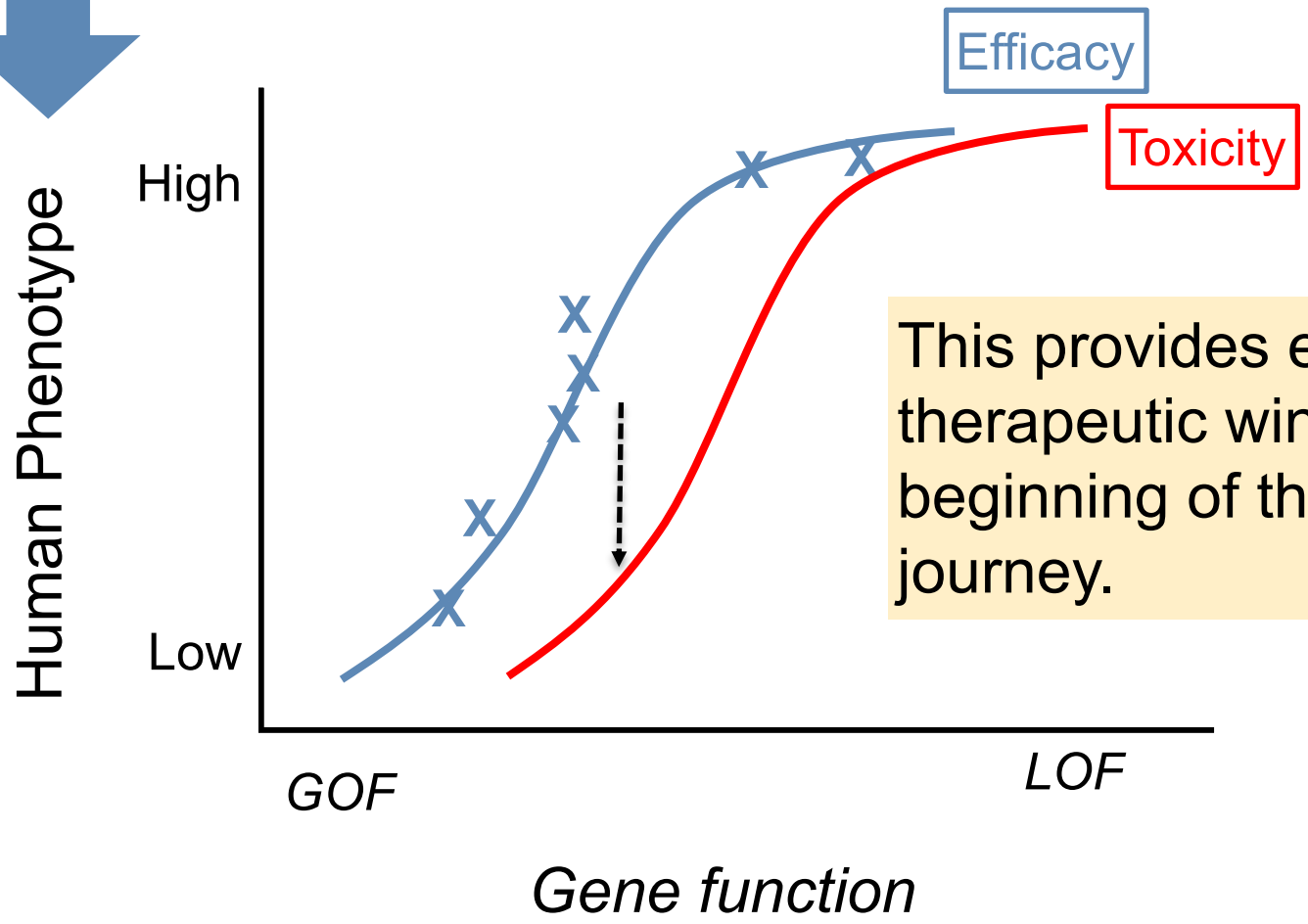


"Biobanks"


Pick a human phenotype for drug efficacy
Efficacy
Toxicity
Assess biological
Assess pleiotropy as proxy for ADEs
High
Low
Human Phenotype
GOF
LOF
Gene function

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.

Not common or rare…
Not coding or regulatory…

…range of alleles that perturb target function to estimate impact in humans

An example in immunology

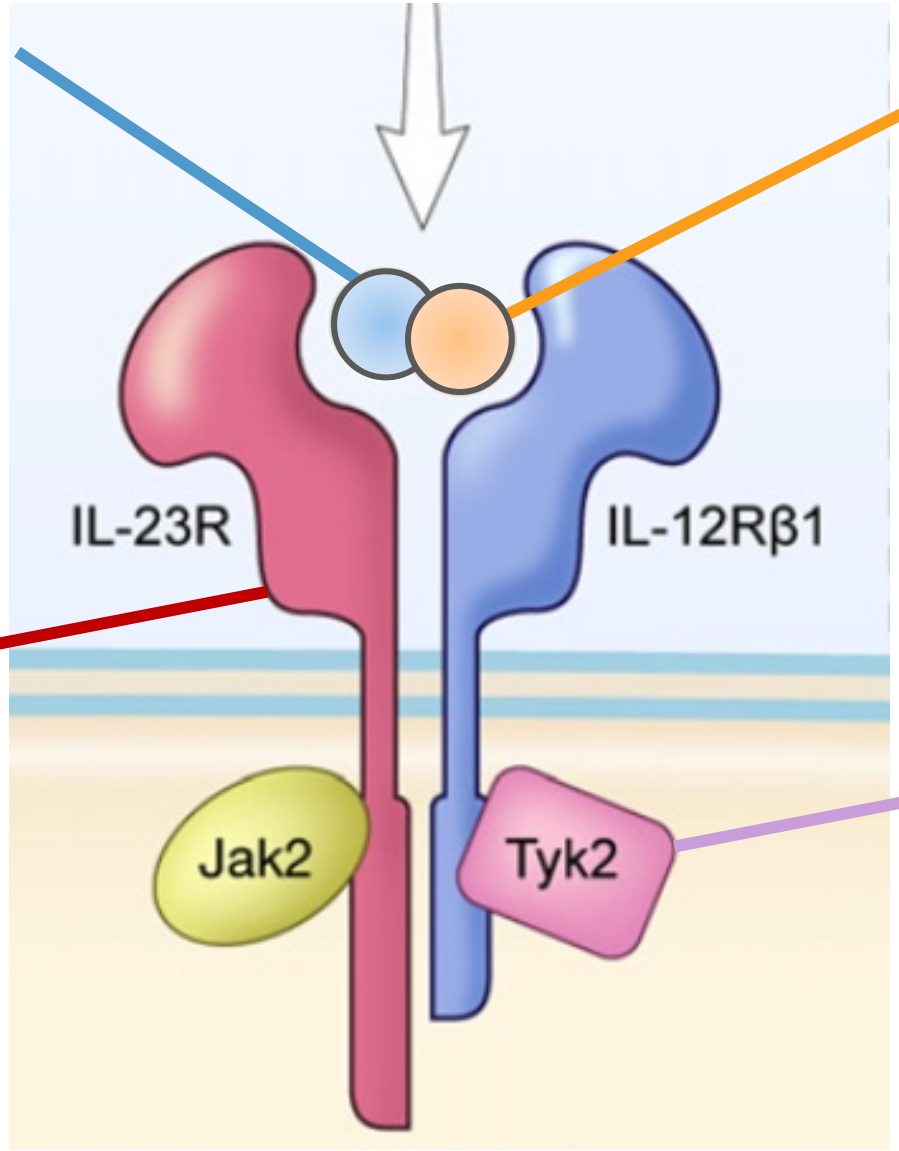
Example of allelic series model: *TYK2*

- 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)

IL23 signaling and psoriasis

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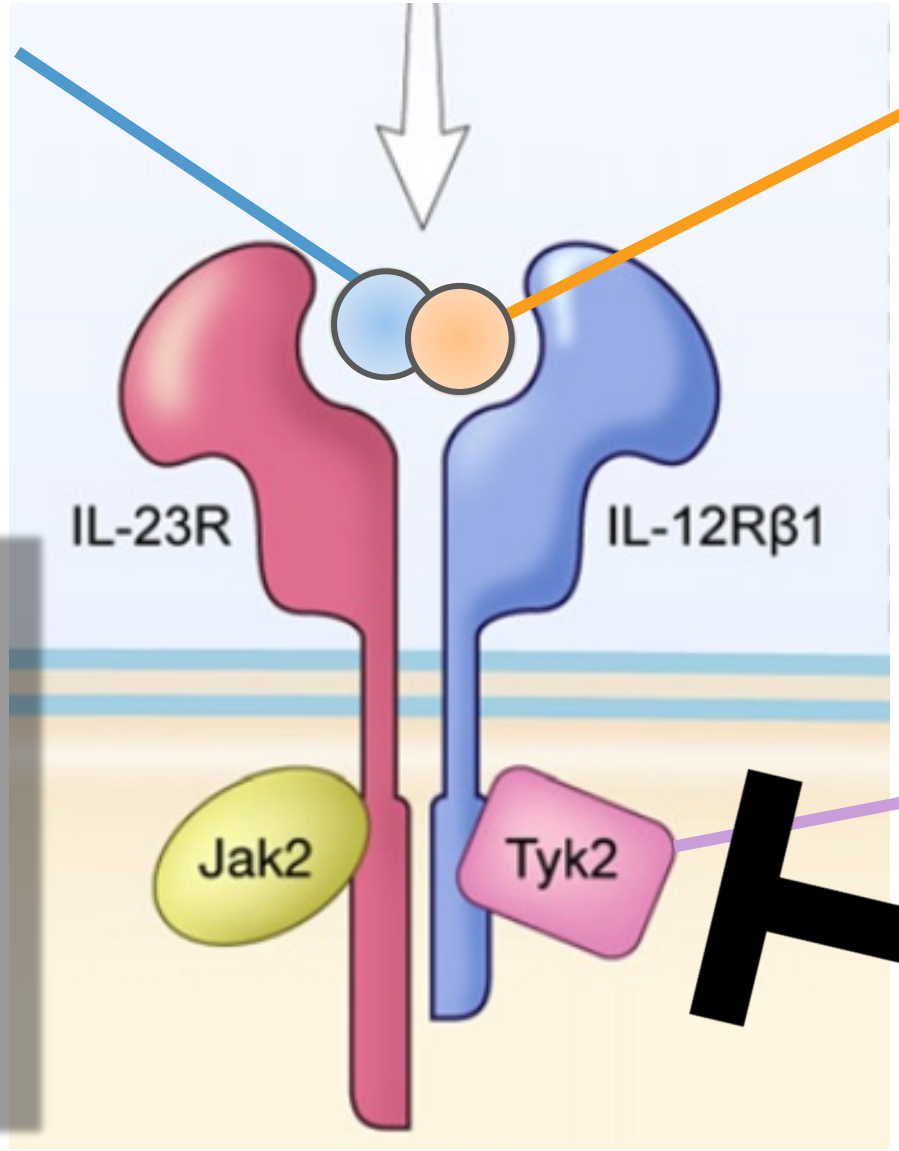
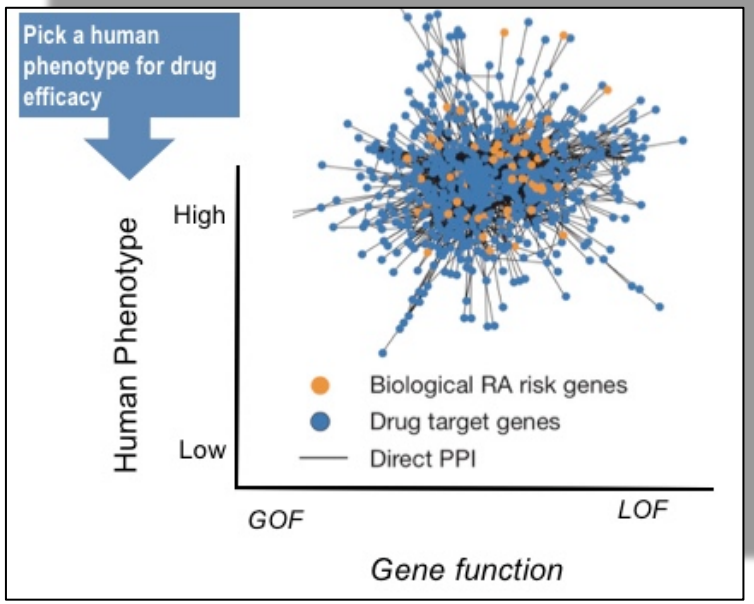


IL12B (IL-12p40)

TYK2

?



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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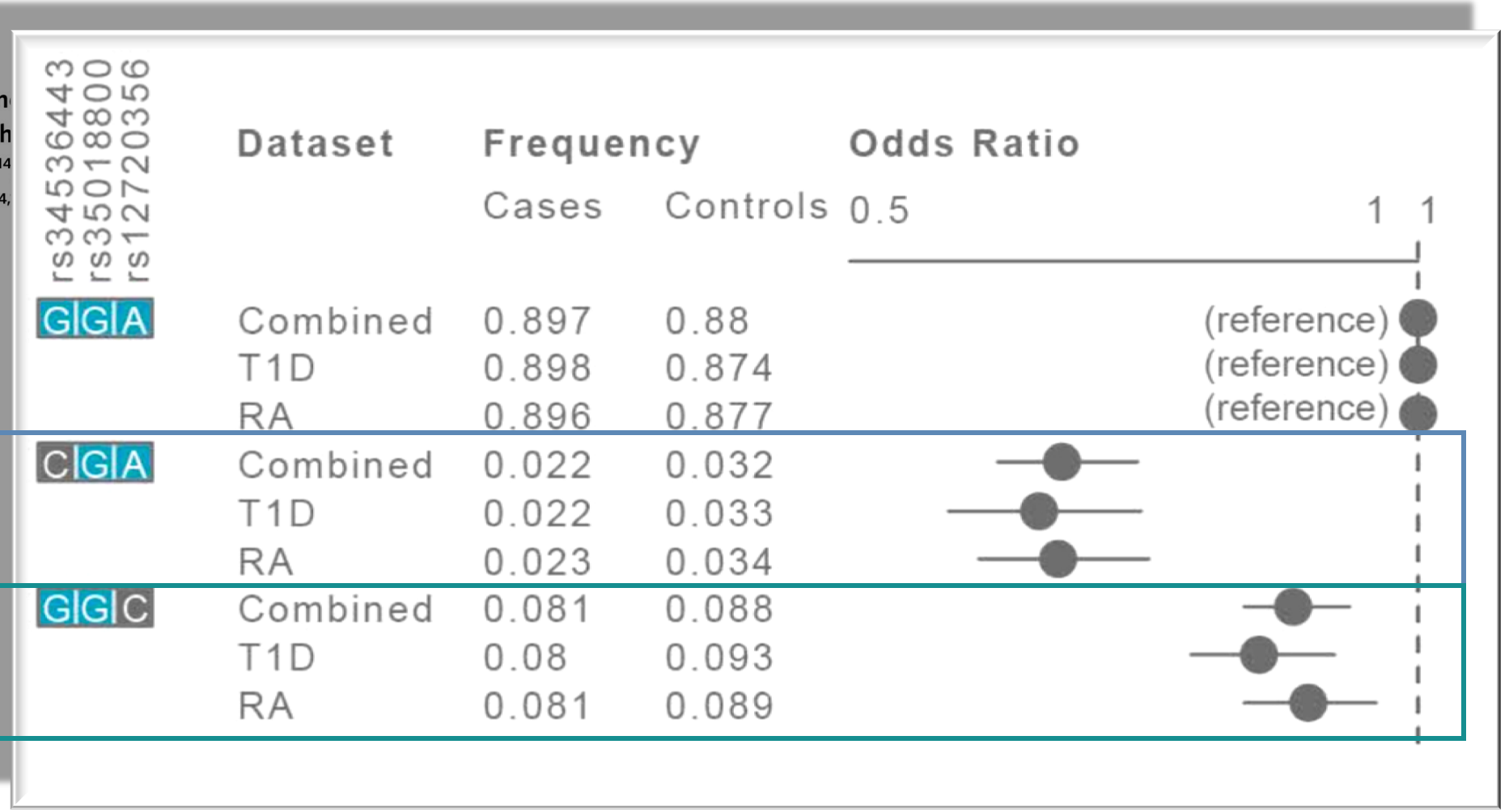

P1104A

I684S

(low freq: A928V)

nature genetics

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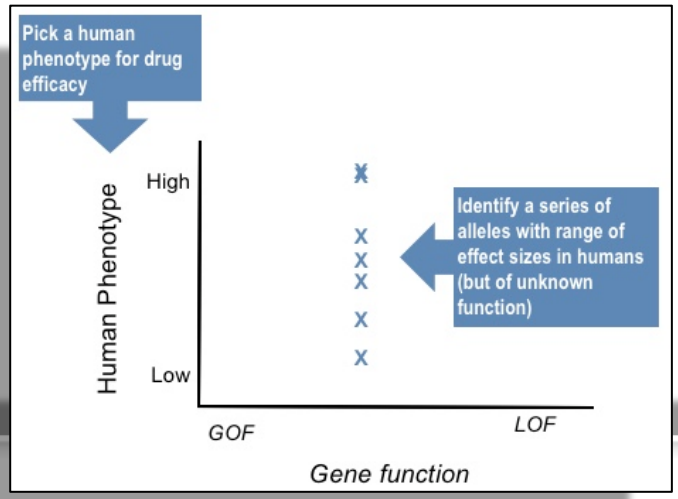


rs34536443 rs35018800 rs12720356	Dataset	Frequency Cases	Frequency Controls	Odds Ratio
G G A	Combined	0.897	0.88	(reference)
	T1D	0.898	0.874	(reference)
	RA	0.896	0.877	(reference)
C G A	Combined	0.022	0.032	
	T1D	0.022	0.033	
	RA	0.023	0.034	
G G C	Combined	0.081	0.088	
	T1D	0.08	0.093	
	RA	0.081	0.089	

P1104A

I684S

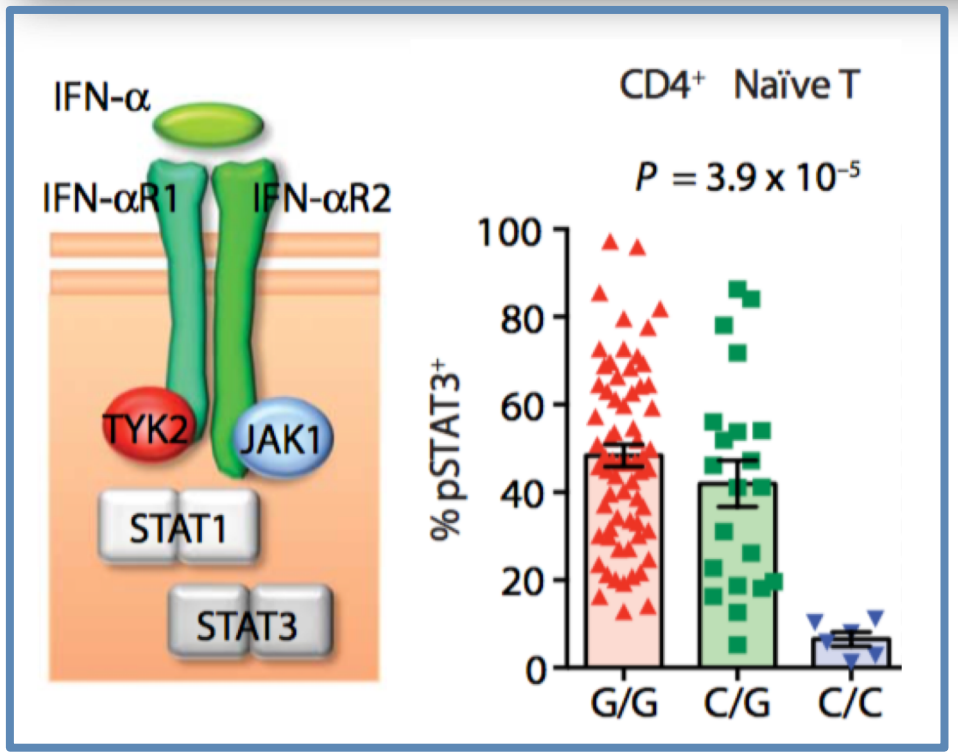
(low freq: A928V)

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

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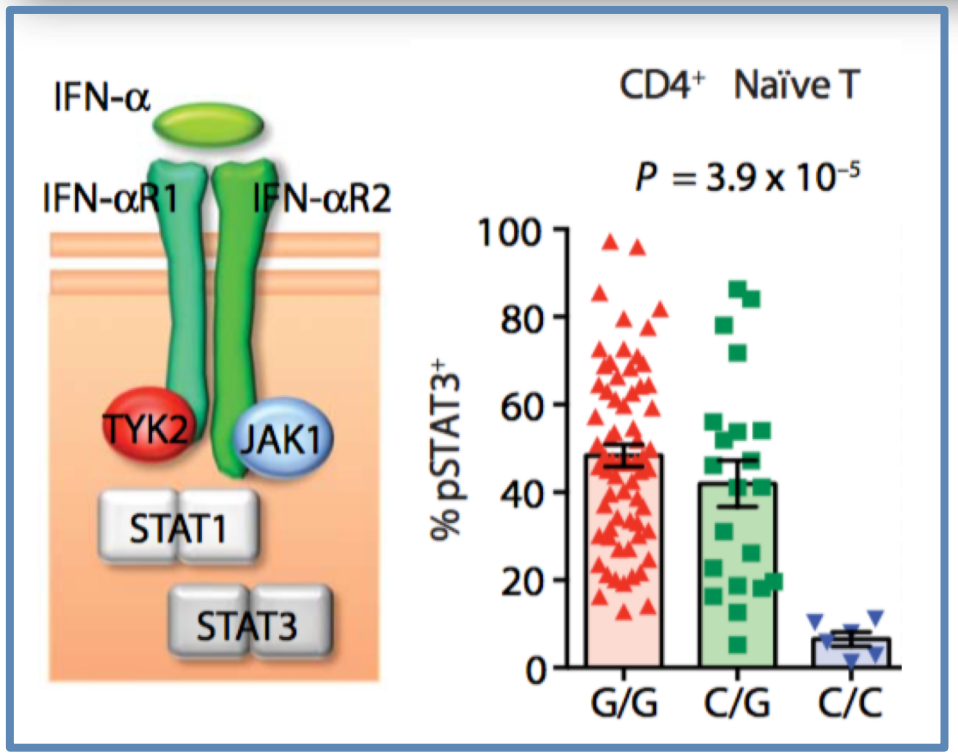

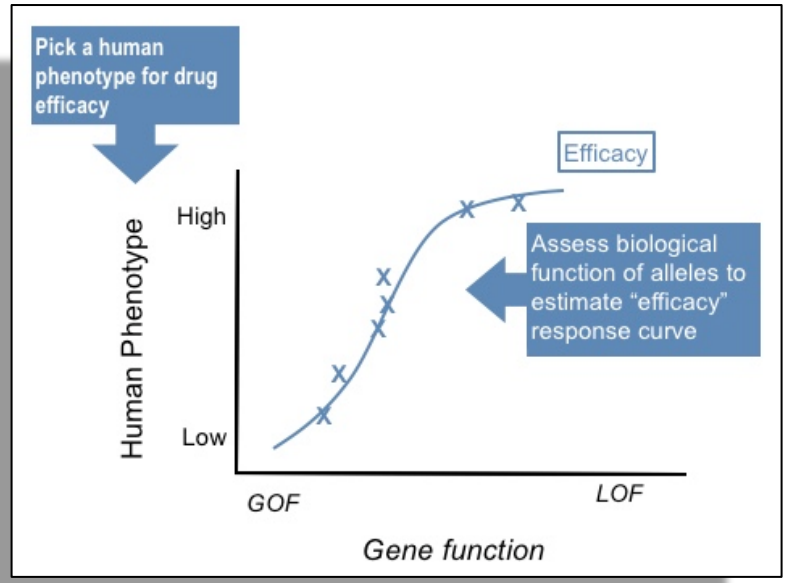

Same LoF allele has no obvious increased risk of infection

		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

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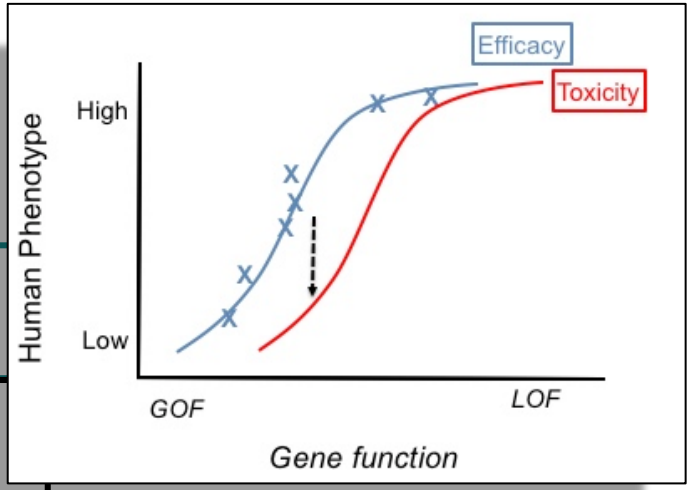
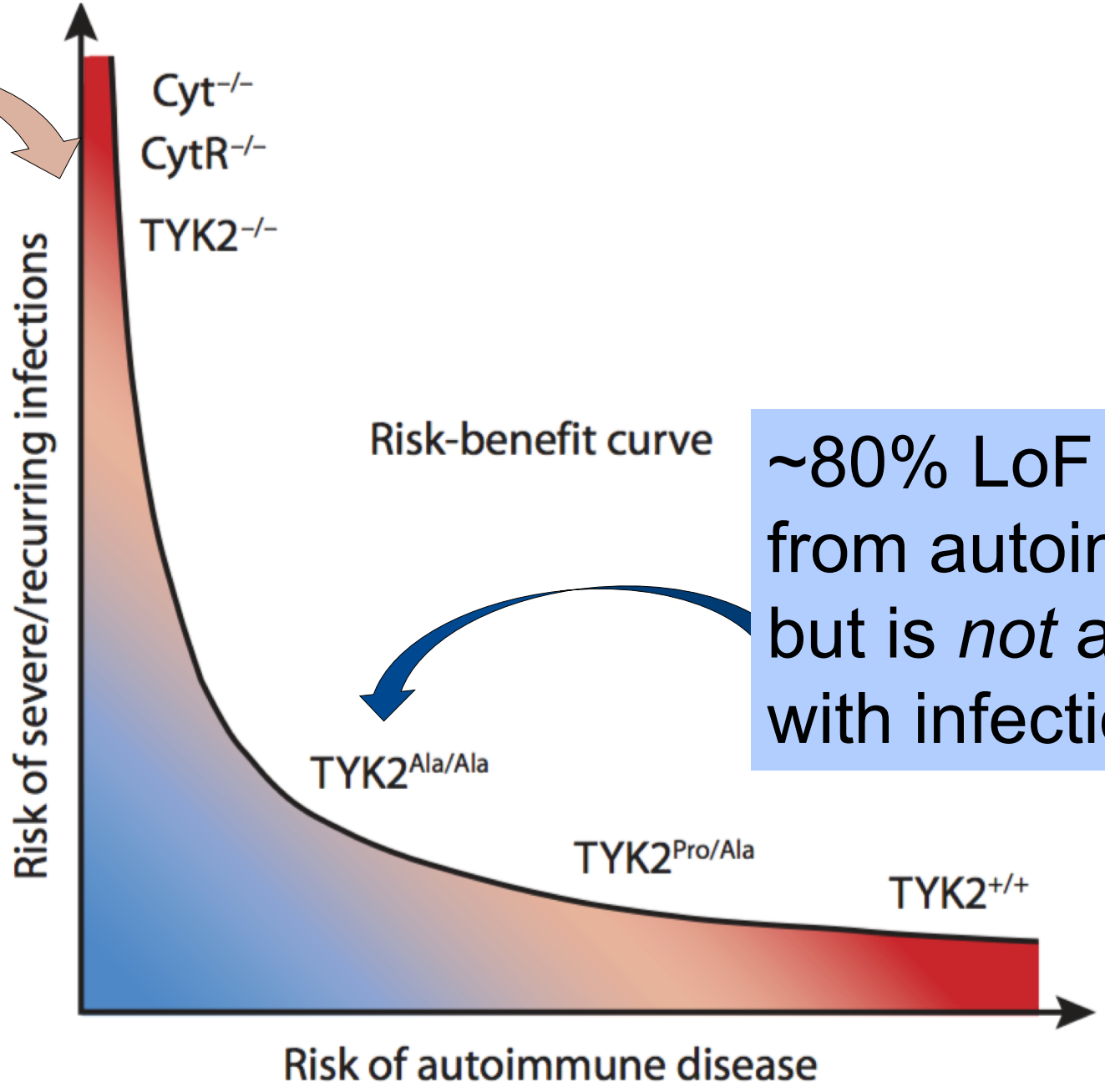


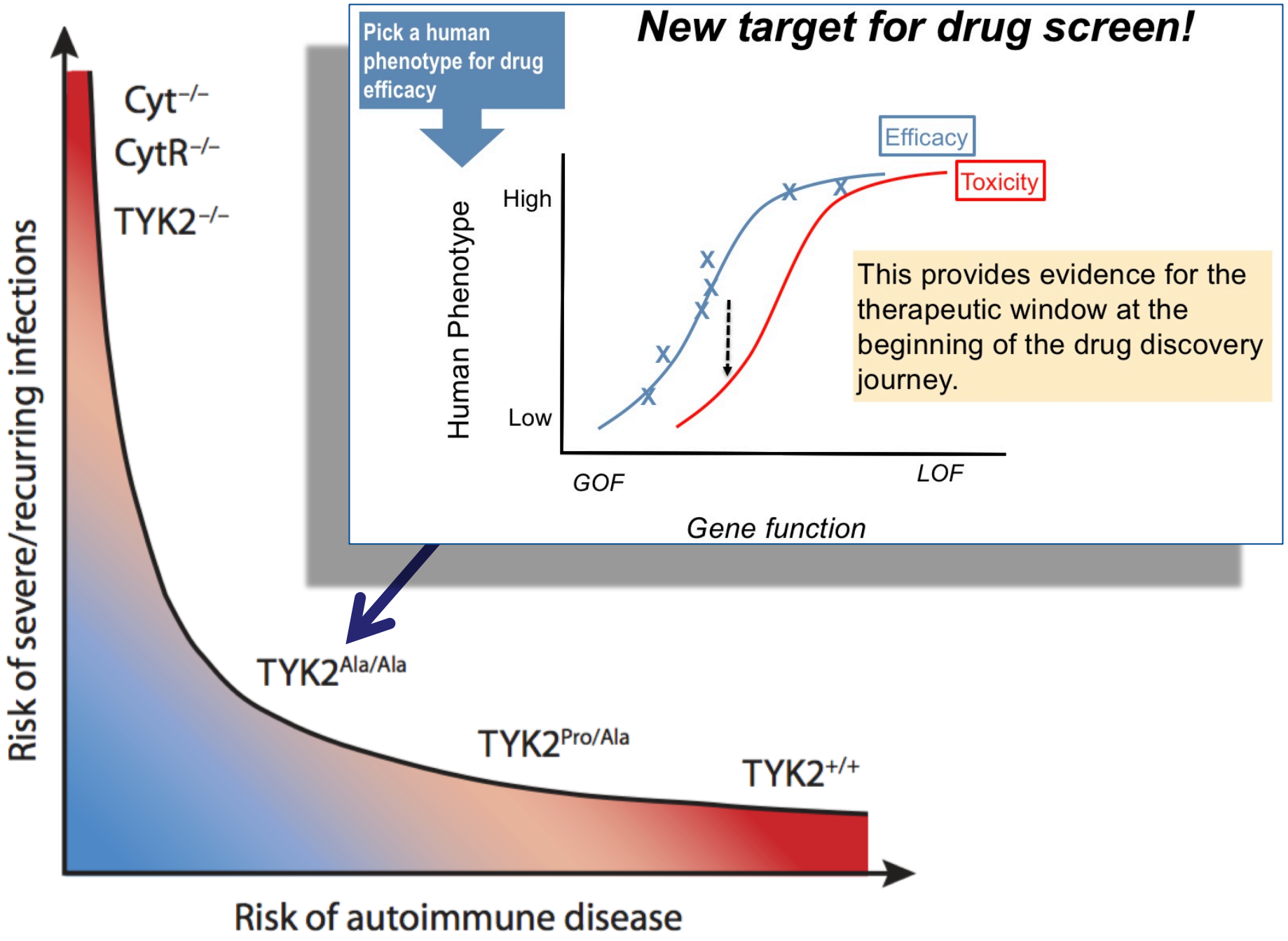
Dendrou, et al. (2016)
Science Translational Medicine

Complete TYK2 knockout increases risk of infection



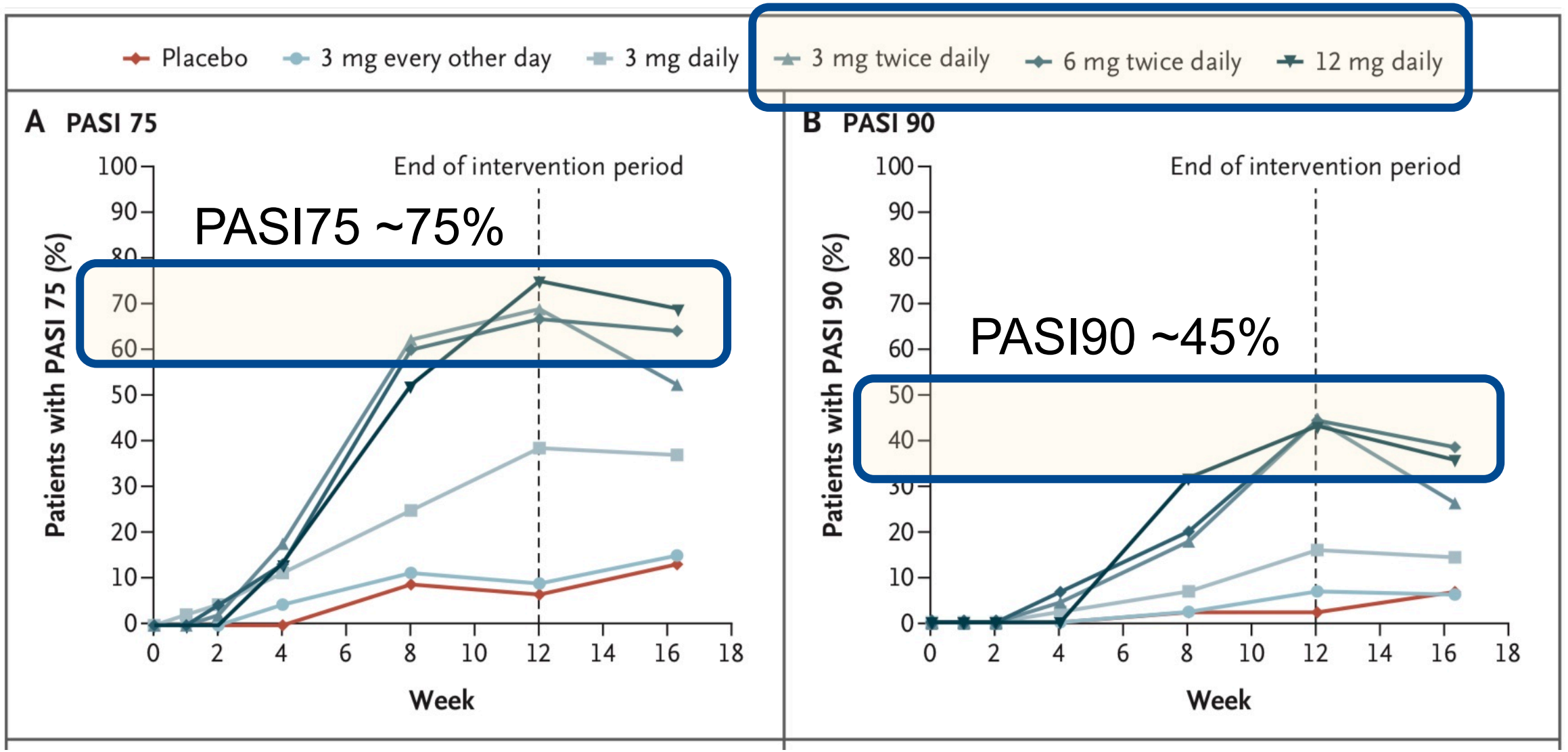
~80% LoF protects from autoimmunity but is *not* associated with infection

Dendrou, et al. (2016)
Science Translational Medicine



Dendrou, et al. (2016)
Science Translational Medicine

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



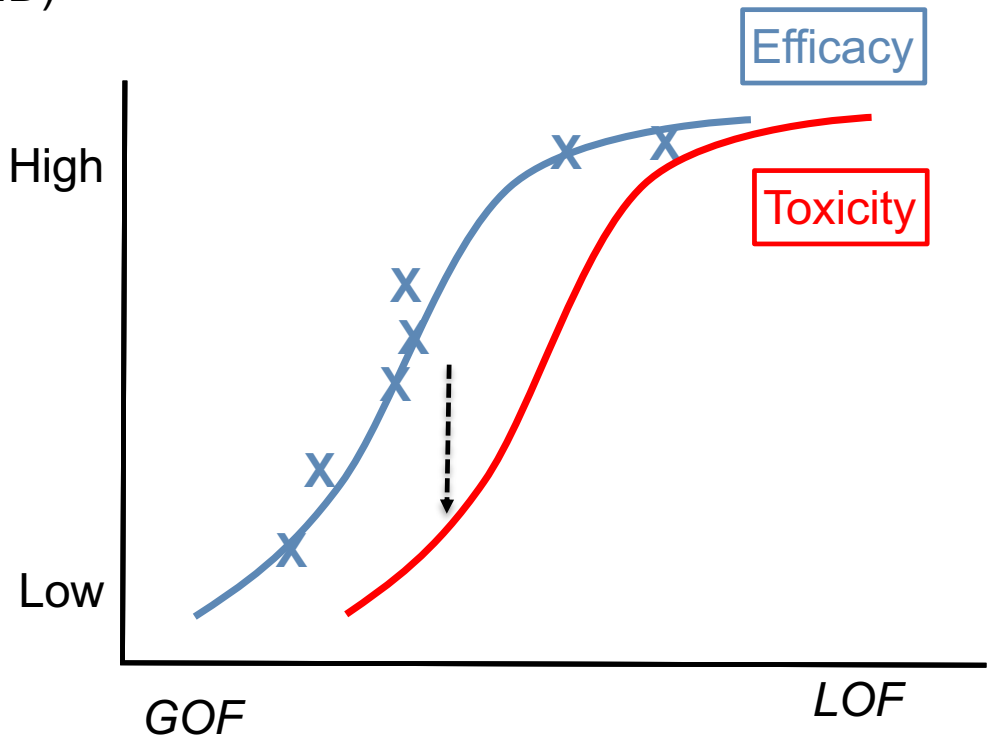
Papp et al (2018) *NEJM*

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