Molecular Target Discovery in IBD

Canada Future Directions in IBD
November 2025

Dermot McGovern

Cedars Sinai

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@doc_ibd

Disclosures

Consultant: Mirador Therapeutics

Patents: anti-TL1A therapy in IBD and other IMIDs

Disease Targets Grounded in Human Genetics Have Higher Success Rate

- Human genetics support for a target can significantly increase success probability in the clinic

Table 1 The relative value of genetic support for the probability that a target-indication pair progresses along the drug development pipeline, based on historical drug trial information

	p(progress|genetic support)/(progress|no genetic support)		
Progression	GWASdb and OMIM	GWASdb	OMIM
Phase I to phase II	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.9)
Phase III to approval	1.1 (1.0–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.3)
Phase I to phase III	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.9 (1.5–2.3)
Phase I to approval	2.0 (1.6–2.4)	1.8 (1.3–2.3)	2.2 (1.6–2.8)

Values give the ratio of the probability of a target-indication pair progressing given genetic support to the probability of progressing without genetic support; 95% confidence intervals are given in parentheses.

- Recent FDA-approved therapeutics tend to be supported by genetic evidence

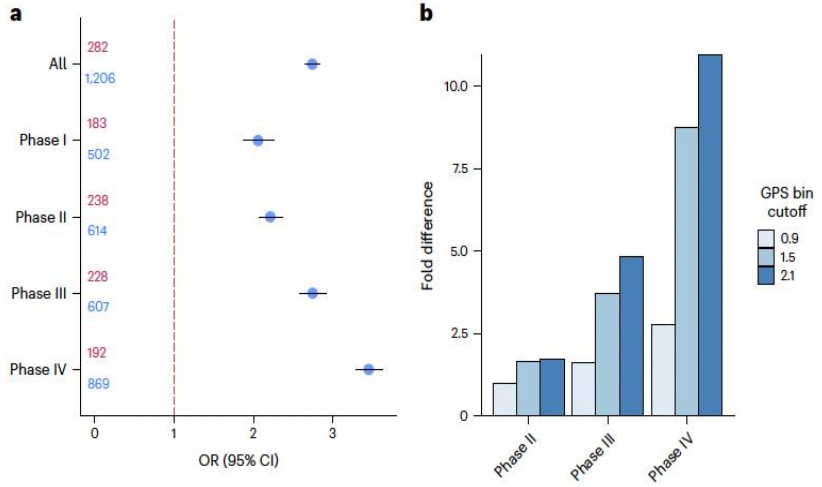
Nelson, et al. *Nature genetics* 2015. Minikelet al. *Nature* 2024: Rusina, et al. *Nature reviews Drug Discovery* 2023

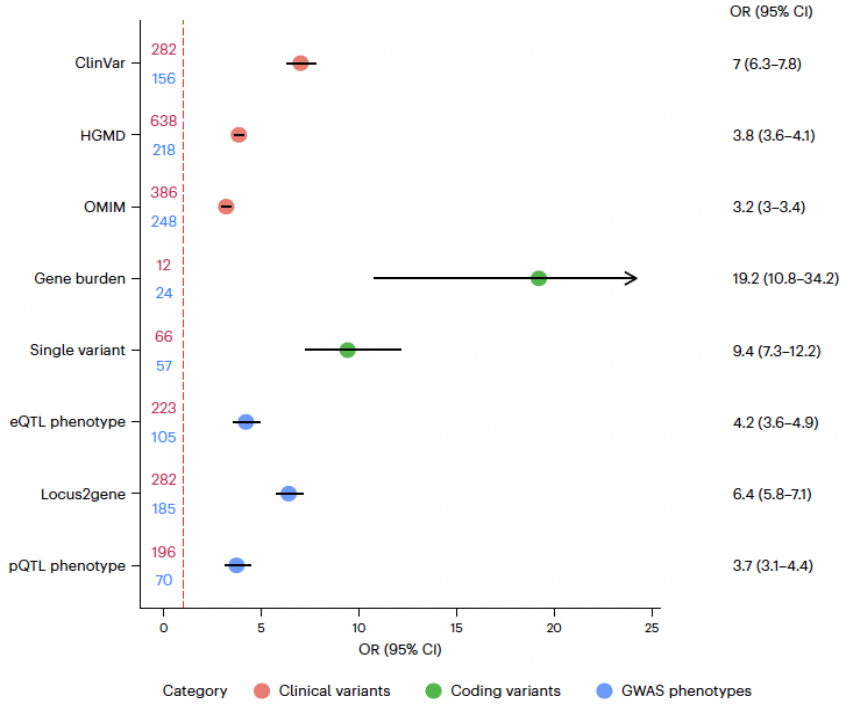
nature genetics

Article https://doi.org/10.1038/s41588-023-01609-2

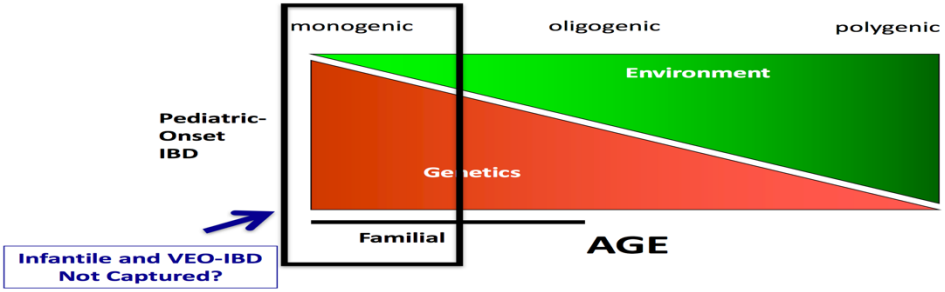
Development of a human genetics-guided priority score for 19,365 genes and 399 drug indications

AI Framework combining genetic (8 features), gene & protein expression data, drug indications to develop a Genetic Priority Score (GPS)

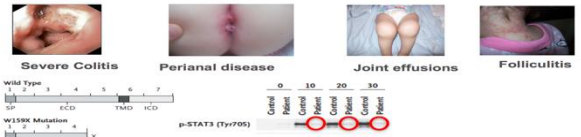




Monogenic Forms of IBD: n =1 'Therapeutic' interventions



- Presented in 1st year of life with severe colitis
- Multiple enterocutaneous fistulae, recurrent folliculitis, recurrent infections, impaired wound healing



Hematopoietic stem cell therapy can be curative

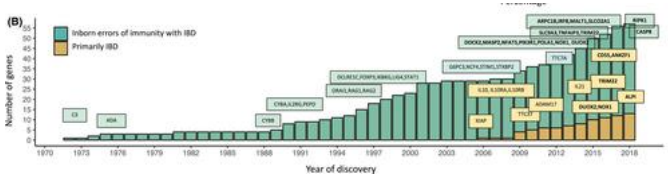


Table 3
Potential "actionable": gene defects recognized in VEO-IBD

Gene Defect	Potential Therapeutic Approach	Contraindications to Therapy
IL10 and IL 10 receptor	HSCT likely curative[80,91]	
FOXP3, IL2RA, CTLA4, MALT1	HSCT likely curative[92]	
XIAP	HSCT likely curative[60]	
SH2D1A	HSCT likely curative[93]	
DCLRE1C	HSCT likely curative[94]	
ZAP70	HSCT likely curative[95]	
WAS	HSCT likely curative[96]	
CGD *CYBB, CYBA, NCF1, NCF2, NCF4*	HSCT likely curative[97] Leukine antibiotics, IL-1 receptor antagonist (Anakinra), possible use to bridge to HSCT or if HSCT not available[98,99]	Anti-TNF contraindicated: increase risk of severe infections, may be fatal[100]
EPCAM		HSCT not helpful[101]
TTC7A		HSCT not helpful[102]
Mevalonate kinase deficiency, *NLRC4* gene defects, IL-10 R deficiency	IL-1 targets[29]	
NLRC4	IL-18, ILR inhibition[103]	
LRBA deficiency	CTLA4 fusion protein: Abatacept (possible use to bridge to HSCT)[104]	
STAT1	HSCT *or* Janus kinase inhibitor Ruxolitinib[105]	

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Pazmandi et al, Immunological Reviews, 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Common Diseases in Clinical Cohorts — Not Always What They Seem

~10,000 subjects from UK Biobank with a dx of MS, IBD, AD

2.86% with MS diagnosis
1.12% with IBD diagnosis
2.50% with AD diagnosis

"Carried a rare variant that contributes to molecular diagnosis of a monogenic disorder"

Validation in Phase 3 studies of: **ADA** (UC and CD), **UPA** (UC), **RISA** (UC and CD)

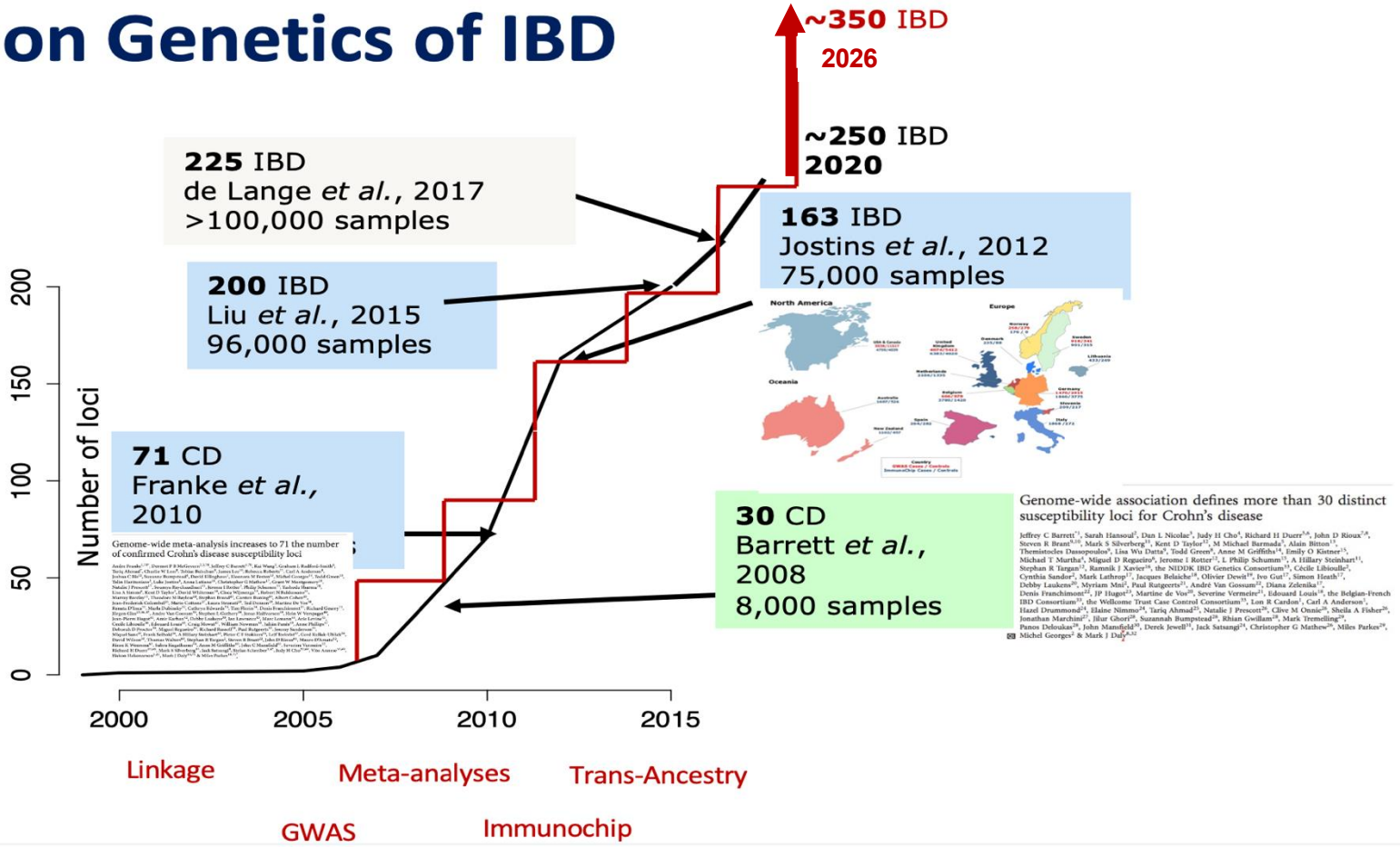
- 1480 IBD - 4.73% carried a rare 'monogenic' variant

- **ADA:** 31/33 (94%) variant +ve: 94% no clinical or endoscopic remission within a year ❌
- **UPA:** 7/10 variant +ve: no endoscopic remission at week 8 (none at week 52) ❌
- **RISA:** 4/17 variant +ve: endoscopic remission at 12 weeks ✅

Case: 60 yrs, woman with CD in SERENE CD: clinical response, no endoscopic response

- Heterozygous for likely *ACTG2* pathogenic variant - autosomal-dominant familial visceral myopathy

Updates on Genetics of IBD



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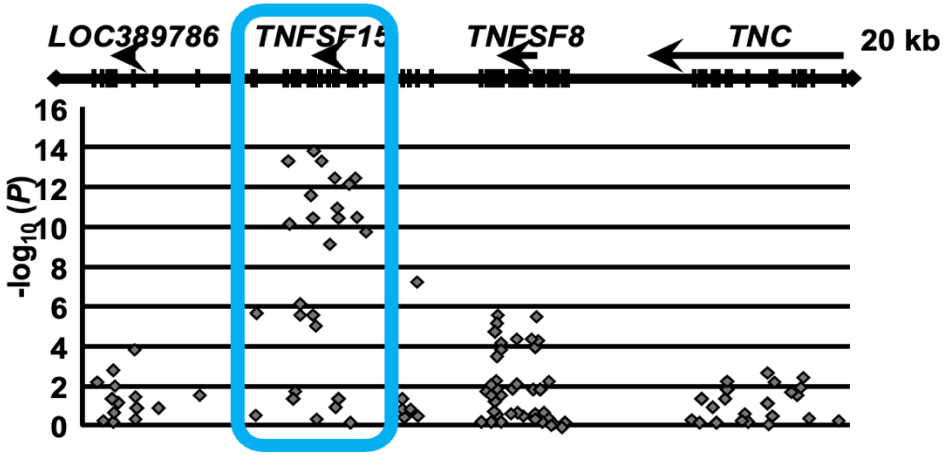
Single nucleotide polymorphisms in *TNFSF15* confer susceptibility to Crohn's disease

Human Molecular Genetics, 2005, Vol. 14, No. 22 **3499–3506**
doi:10.1093/hmg/ddi379
Advance Access published on October 13, 2005

Single nucleotide polymorphisms in *TNFSF15* confer susceptibility to Crohn's disease

Keiko Yamazaki[1], Dermot McGovern[2,3], Jiannis Ragoussis[2], Marta Paolucci[2], Helen Butler[2], Derek Jewell[2,3], Lon Cardon[2], Masakazu Takazoe[4], Torao Tanaka[4], Toshiki Ichimori[5], Susumu Saito[6], Akihiro Sekine[6], Aritoshi Iida[6], Atsushi Takahashi[7], Tatsuhiko Tsunoda[7], Mark Lathrop[8] and Yusuke Nakamura[1,6,*]



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Yamazaki, K., et al. 2005. *Hum Mol. Gen*. 14:3499.

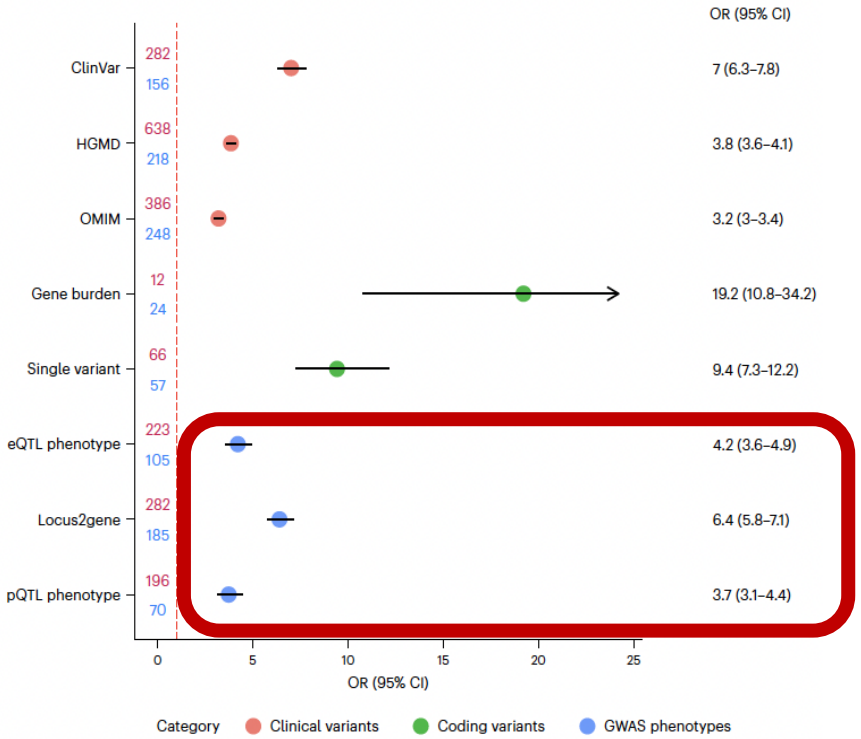
nature genetics

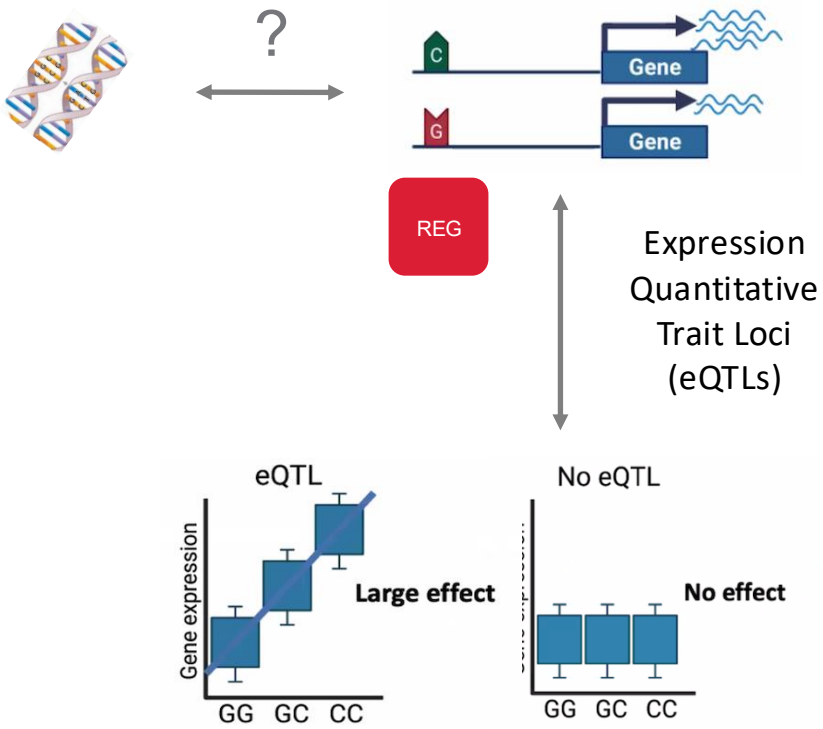
Article

https://doi.org/10.1038/s41588-023-01609-2

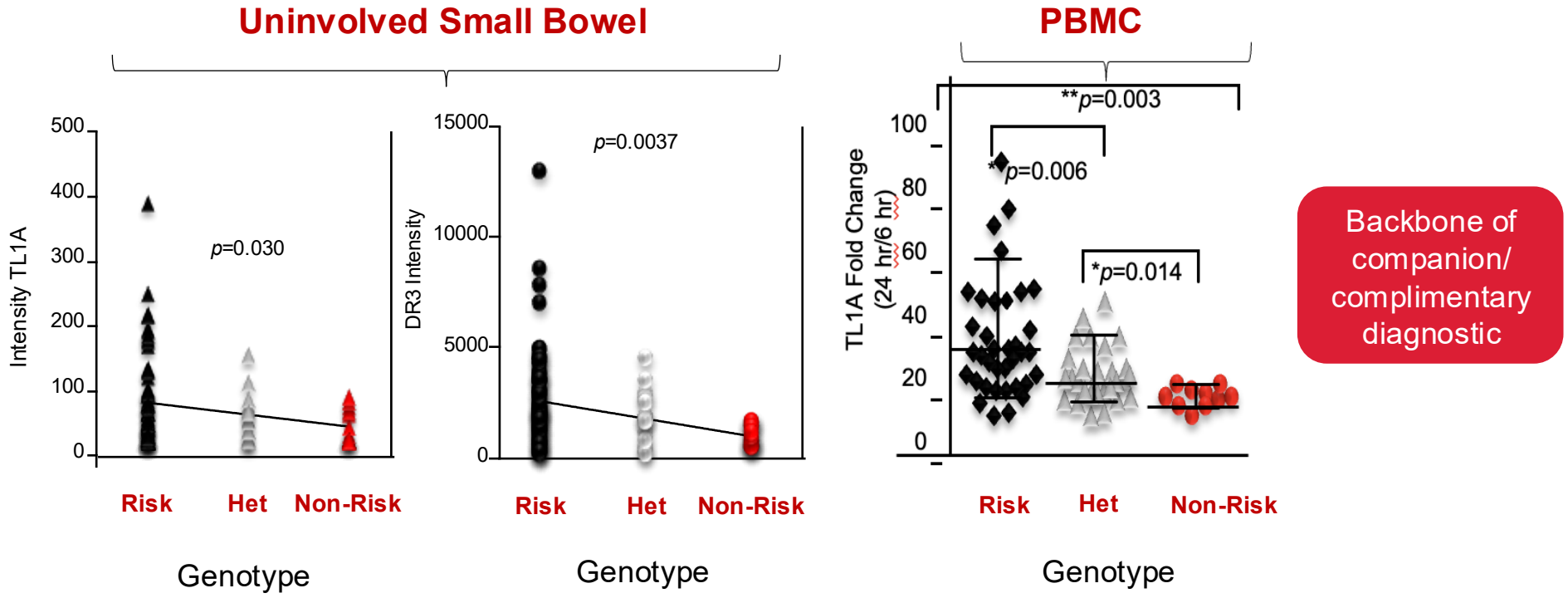
Development of a human genetics-guided priority score for 19,365 genes and 399 drug indications

Linking Genetics to Target Genes





Functional Genomics: *TNFSF15* Genotype is Associated with Magnitude of TL1A Induction and Expression of DR3



Backbone of companion/ complimentary diagnostic

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Bilsborough, J., et al. *unpublished*.

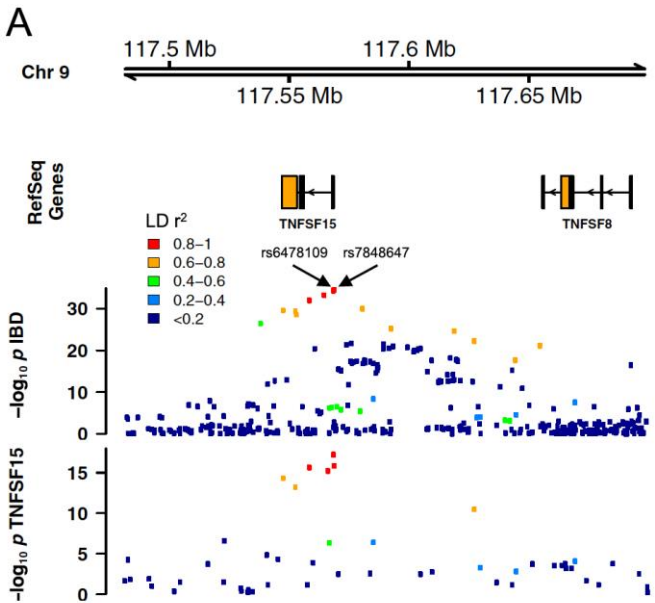
PLOS GENETICS

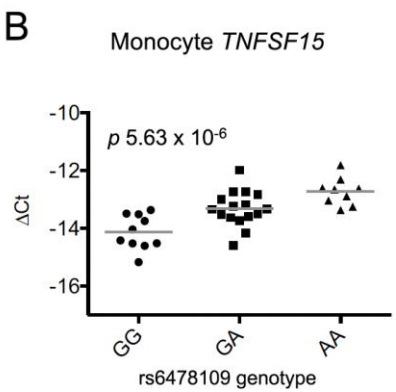
RESEARCH ARTICLE

Reduced monocyte and macrophage *TNFSF15*/TL1A expression is associated with susceptibility to inflammatory bowel disease

[redacted]

1 Department of Medicine, University of Cambridge School of Clinical Medicine, University of Cambridge,





rs6478109

A (EUR minor allele) = IBD protective

G (EUR major allele) = IBD risk

TNFSF15/TL1A Findings in Human Disease

Genetic Variation in *TNFSF15*:

Associated with Stricturing CD in EUR

Barrett et al. *Am J. Pathology*, 2012

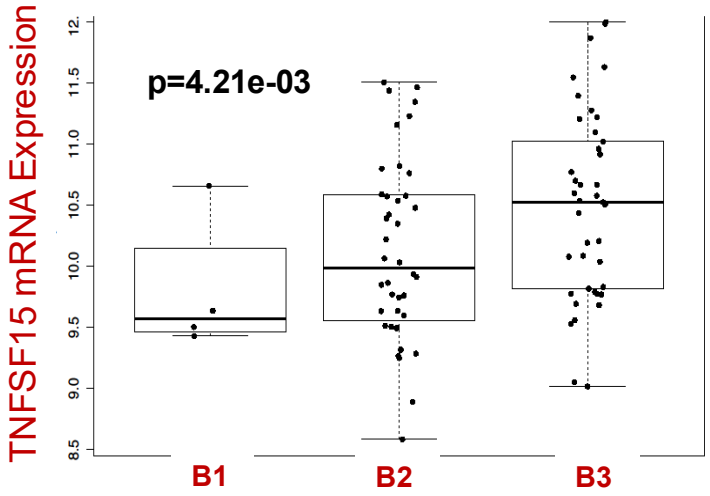
Associated with Stricturing CD in JPN

Hirano A, et al. *Inflamm Bowel Dis* 2013

Associated with MRUC in EUR

Haritunians T, et al. *Inflamm Bowel Dis* 2010

Increased *TNFSF15* mRNA in B2 and B3 small bowel CD

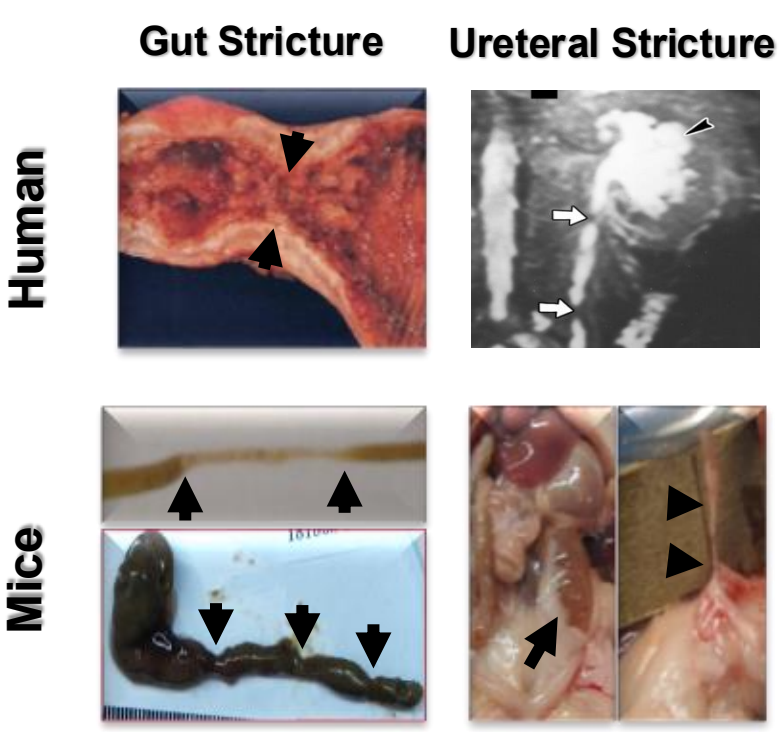


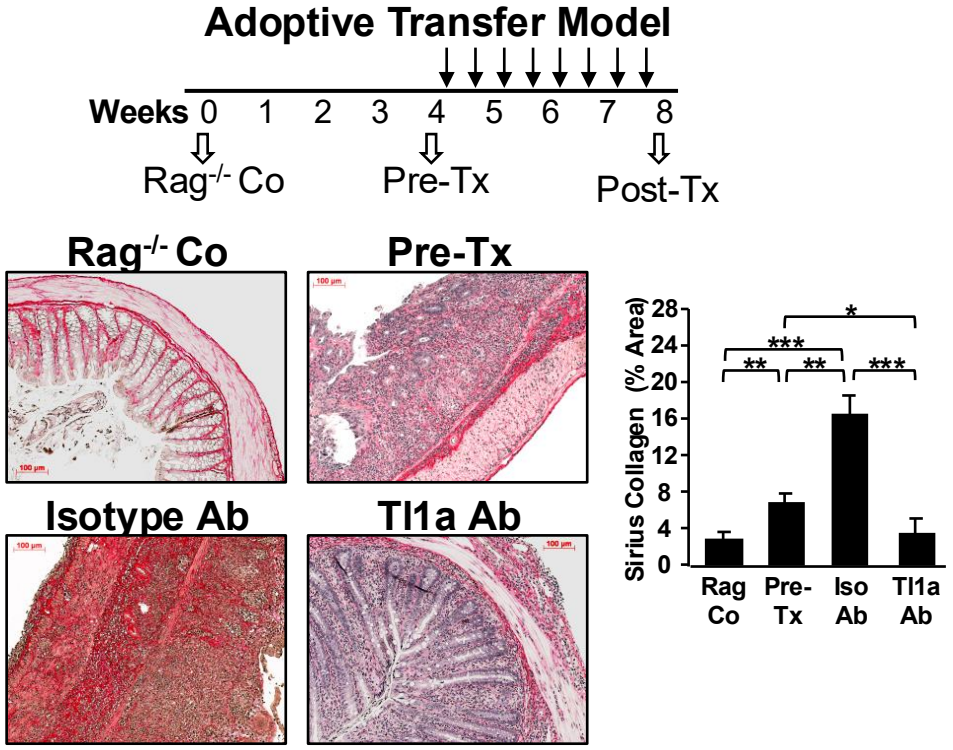
B1= inflammatory CD, B2= structuring CD, B3= Internal Penetrating CD

Potdar, A., et al. *unpublished*.

TL1A Tg Mice: CD Phenotypic Copy

Reversal of Chronic Fibrosis by Anti-TL1A Antibody





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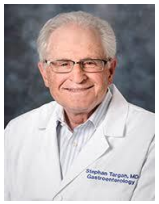
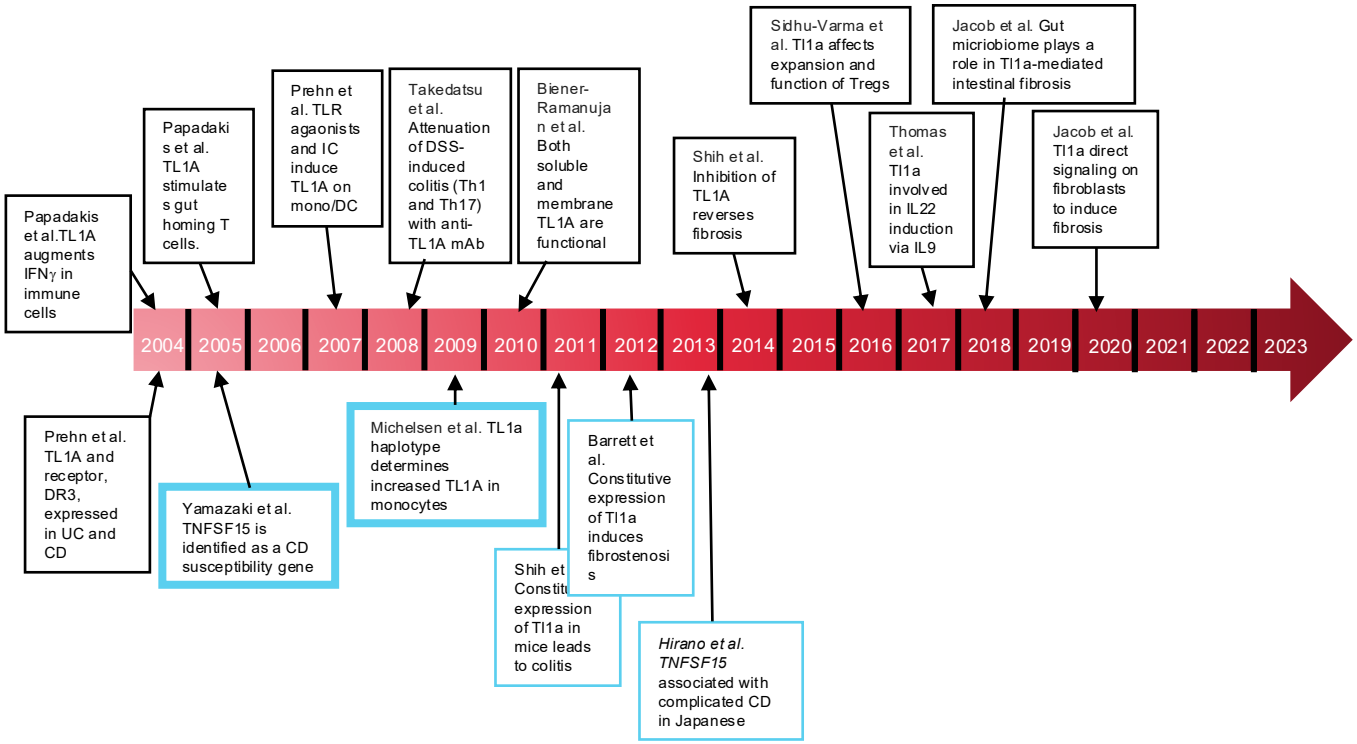
Shih et al. PLoS, 2011, Shih et al. *Gastroenterology,* 2012, Barrett et al *Am J. Pathology*., 2012, Libo. Micro & ImmunEu J., 2013. Shih, D, et al. *Mucosal Immunology* 2014

TL1A (*TNFSF15*) Biological Validation Timeline

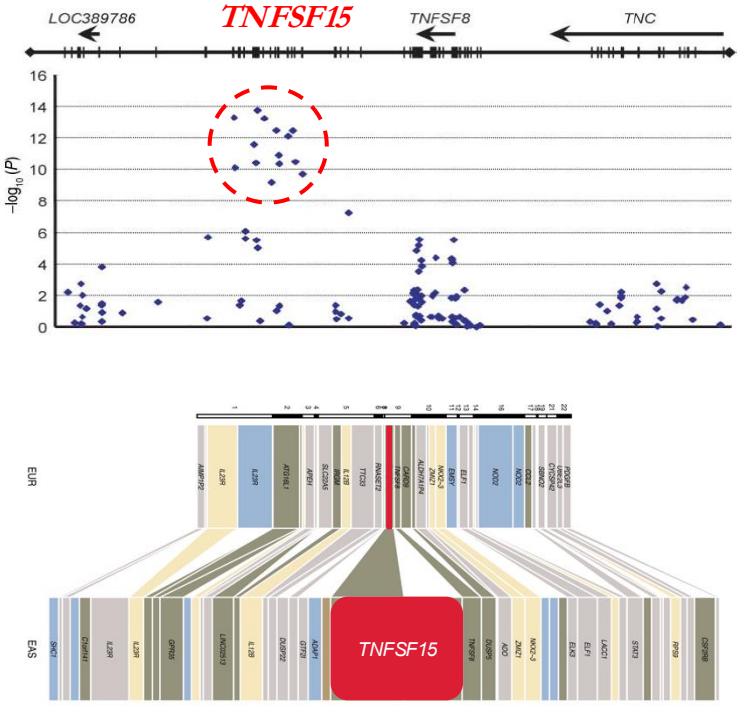


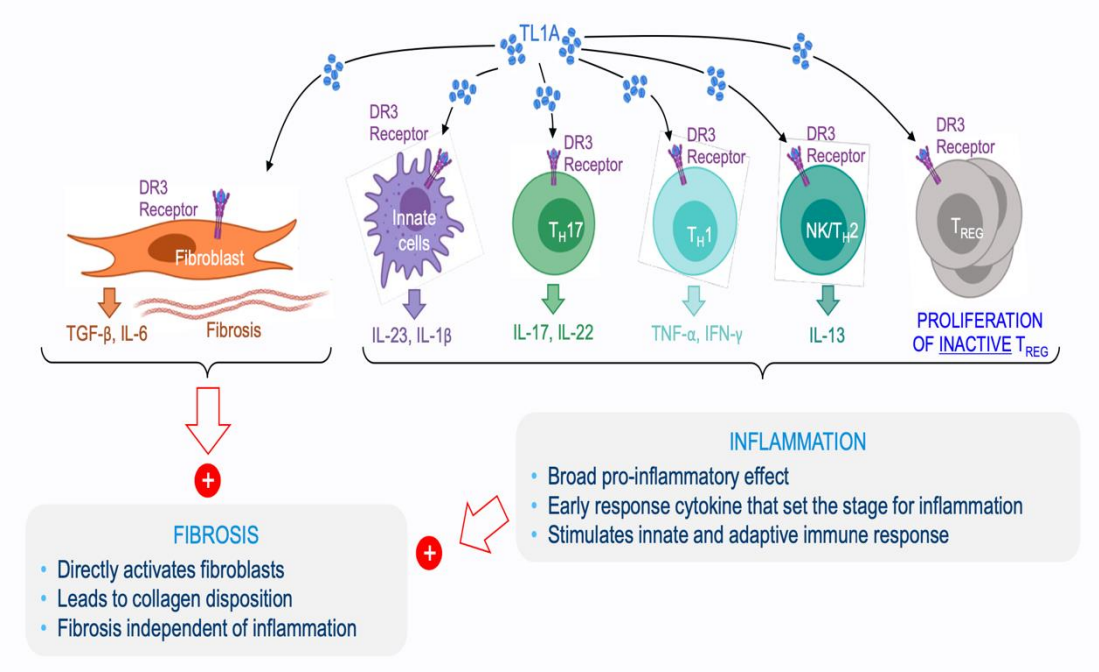
Stephan Targan

Janine Bilsborough



From Genetic Association to Functional Characterization: ~15 years





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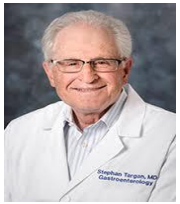
Subsequent Events That Brought anti-TL1A To Patients

- CSMC 3D unit makes anti-TL1A antibody
- Precision IBD spun out from CSMC to develop anti-TL1A antibody in IBD
- Precision IBD becomes Prometheus Biosciences to optimize antibody and companion diagnostic
- Prometheus Biosciences ‘days from going bust’
- Prometheus Bio., IND, Phase 1 study, and Phase II trials in UC/CD

TL1A (*TNFSF15*) Biological Validation & Drug Development Timeline

Janine Bilsborough



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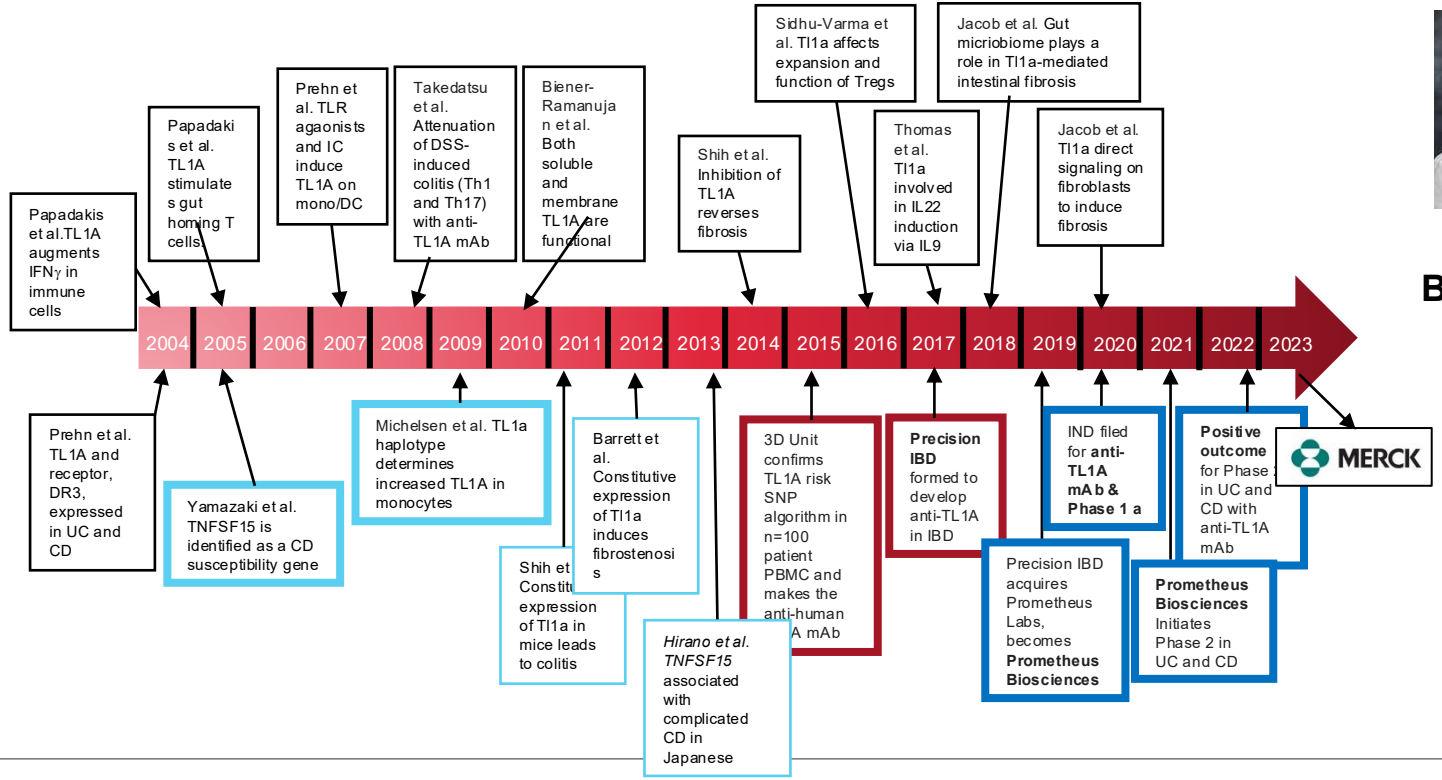
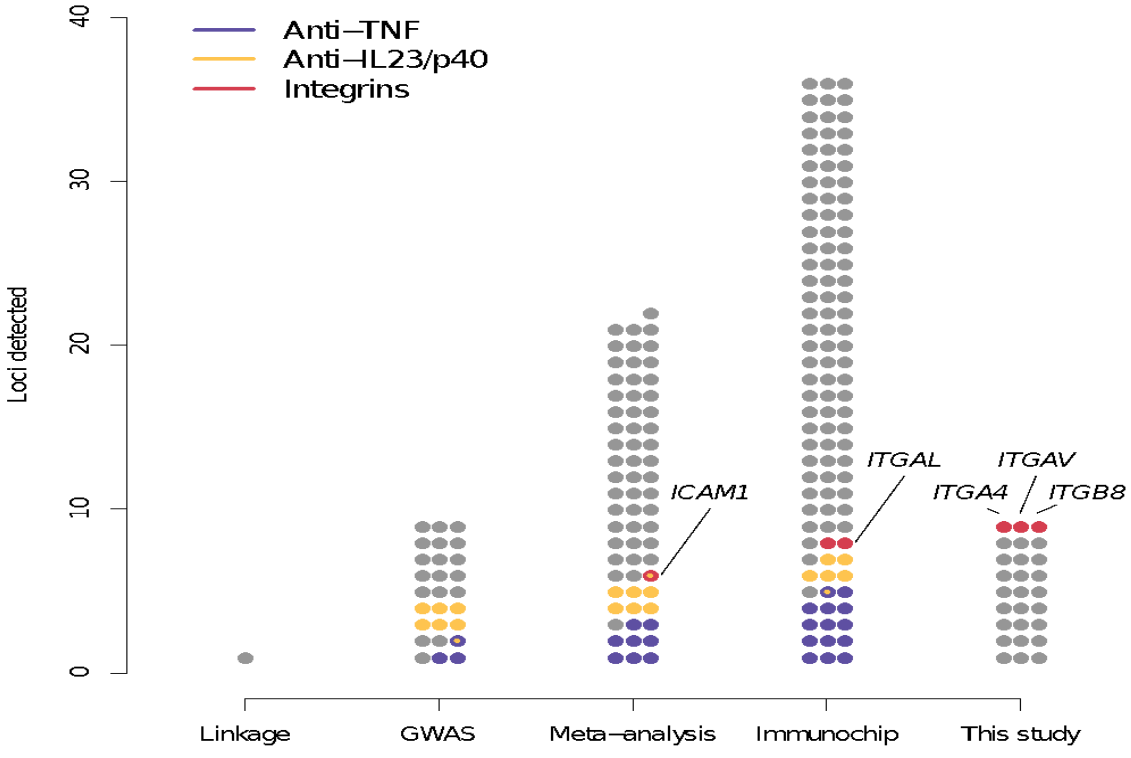


Genetic Clues for Therapeutics in IBD



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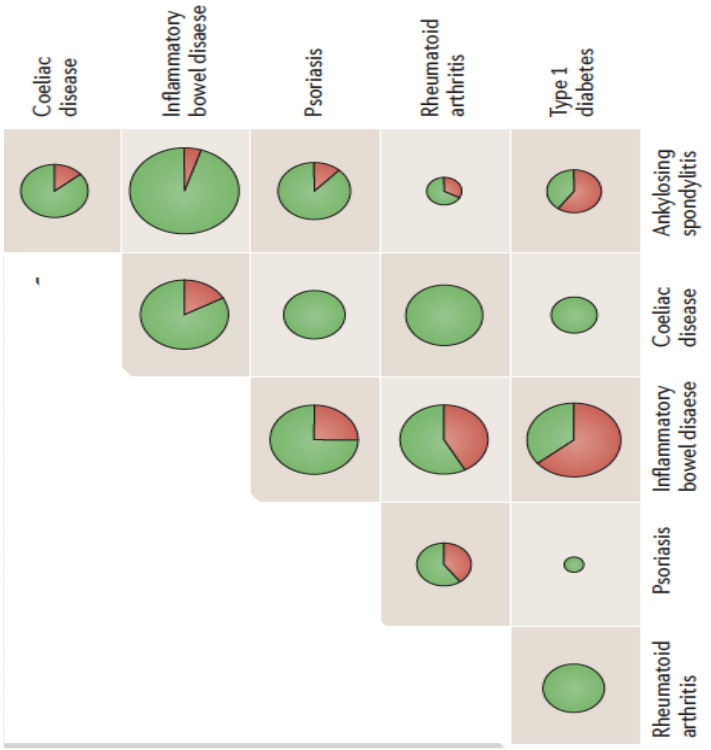
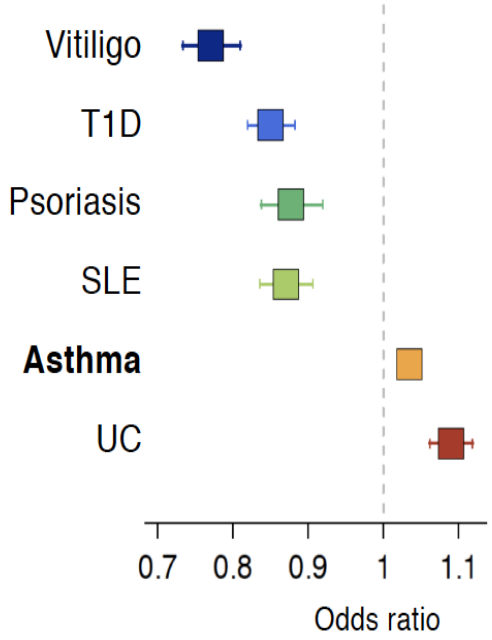
de Lange, et al *Nat Genet*, 2017

Pleiotropy and Discordance





IFIH1 LOF allele and IMDs

Plenge et al, Nature Review Drug Development, 2013, Jostins et al. Nature 2012, Parkes et al, Nature Reviews 2013

(re)Defining IMIDS and IBD

All IBD patients

IBD1

CD with Stricturing Disease

IBD2

CD with Perianal Disease

IBD3

CD Non-Responsive to Anti-TNF

IBD4

UC Non-Responsive to Anti-TNF

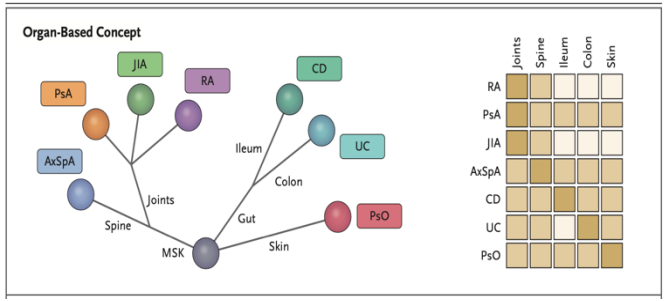
IBD5

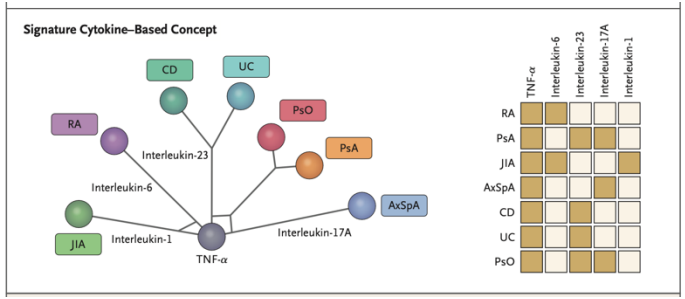
Medically Refractive UC

IBD6……

Etc.…

Late Onset Disease (UC)





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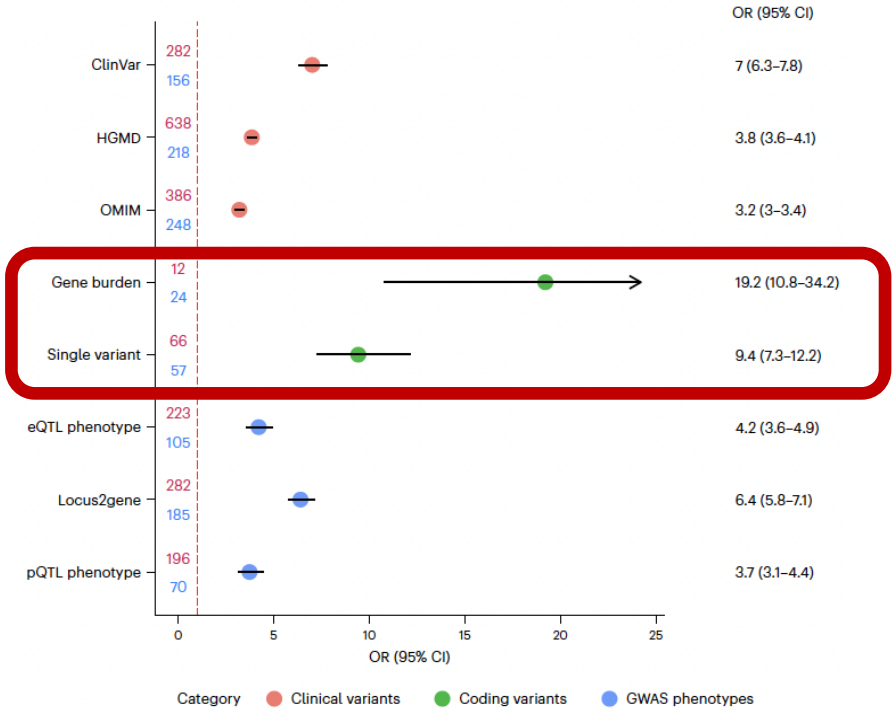
Schett et al NEJM 2021

nature genetics

Article

https://doi.org/10.1038/s41588-023-01609-2

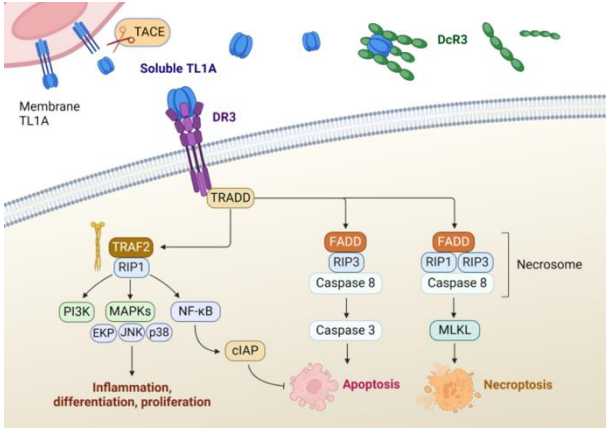
Development of a human genetics-guided priority score for 19,365 genes and 399 drug indications



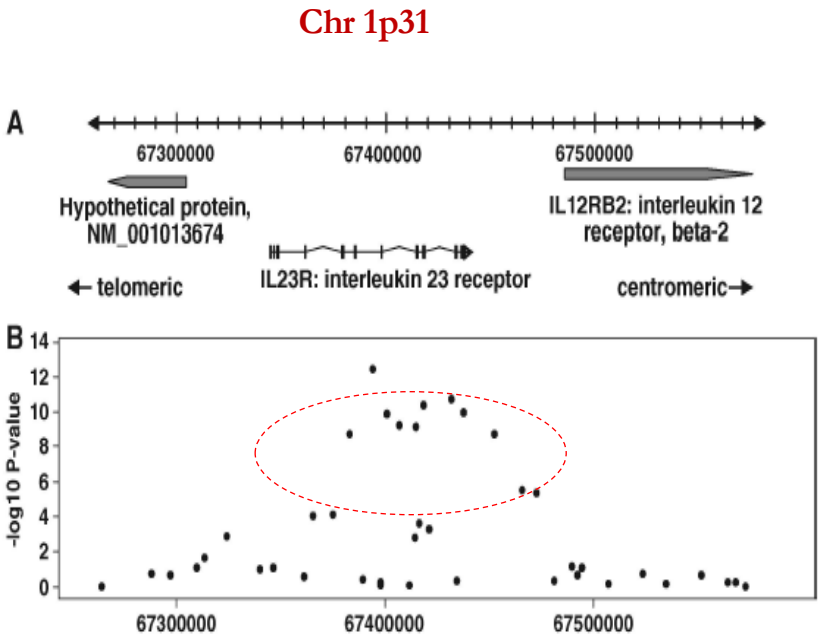
OR – 19.2

OR – 9.4

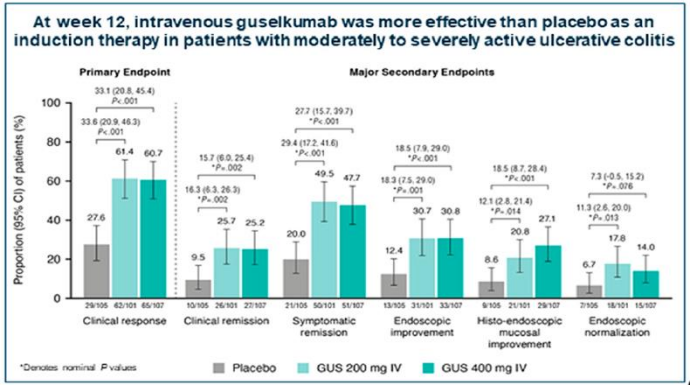
Gene Burden Test in latest IIBDGC WES Study of ~86k IBD & ~500k Controls implicates ***DCR3*** **(*TNFRSF6B*)** in IBD susceptibility



2006: CD GWAS identifies *IL23R* → New therapeutics



- Coding Variant
- LOF
- Protective



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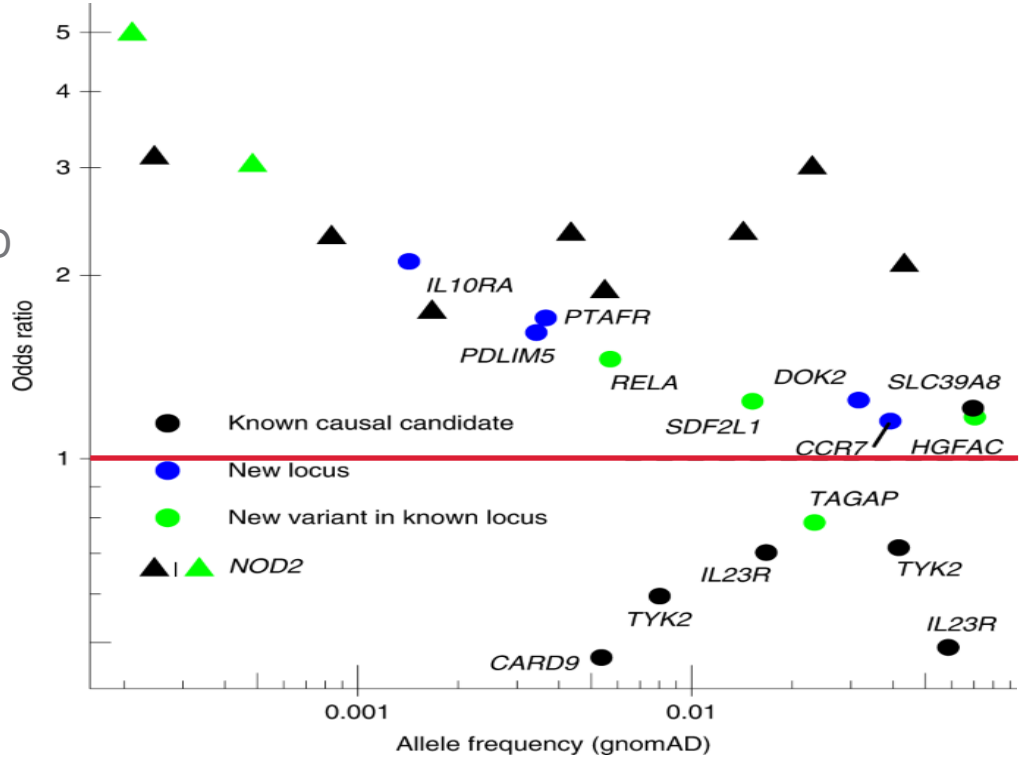
Duerr et al, *Cell* 2006, Laurent Peyrin-Biroulet et al, *Gastroenterology* 2023

Large-scale sequencing identifies multiple genes and rare variants associated with Crohn's disease susceptibility

>30000 CD and >80000 controls

- 45 coding variants significantly associated
- 10 genes identified as causal genes for CD



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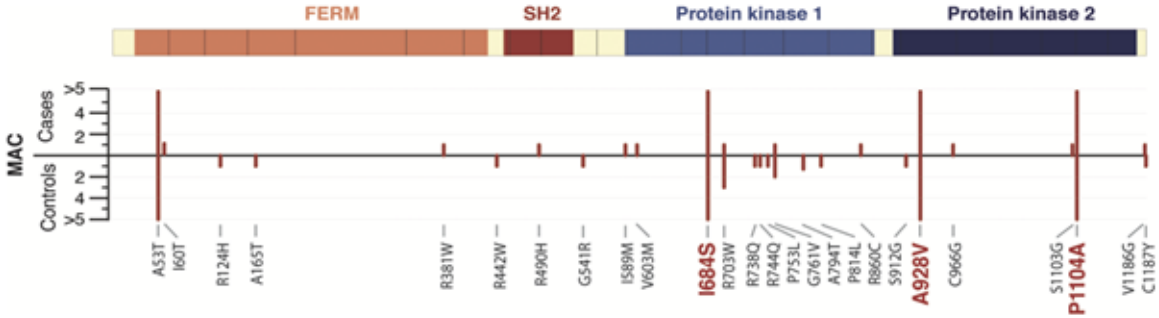
Aleksejs Sazonovs et al, Nature Genetics 2022

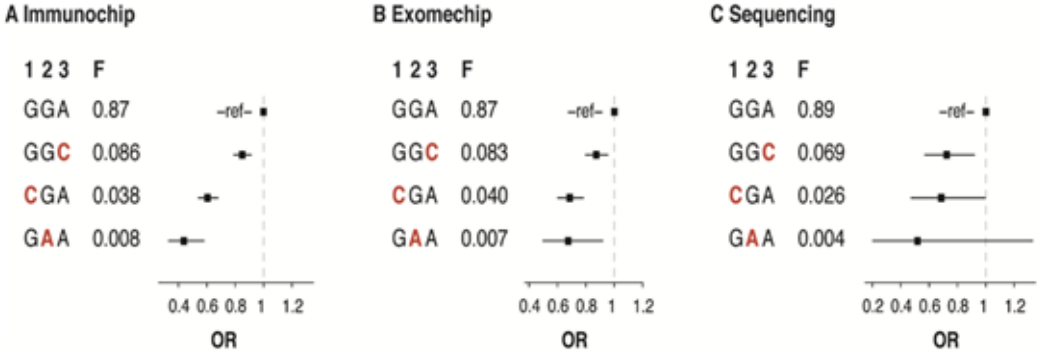
RESEARCH ARTICLE

TYK2 Protein-Coding Variants Protect against Rheumatoid Arthritis and Autoimmunity, with No Evidence of Major Pleiotropic Effects on Non-Autoimmune Complex Traits

TKY2 - 3 Protein-coding Variants Protect vs RA

1: P1104A
2: A982V
3: I684S
F: haplotype frequency





Pleiotropy

- All 3 variants showed protection vs Lupus
- 2/3 showed protection vs IBD

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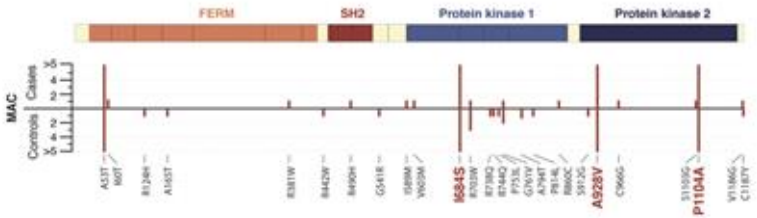
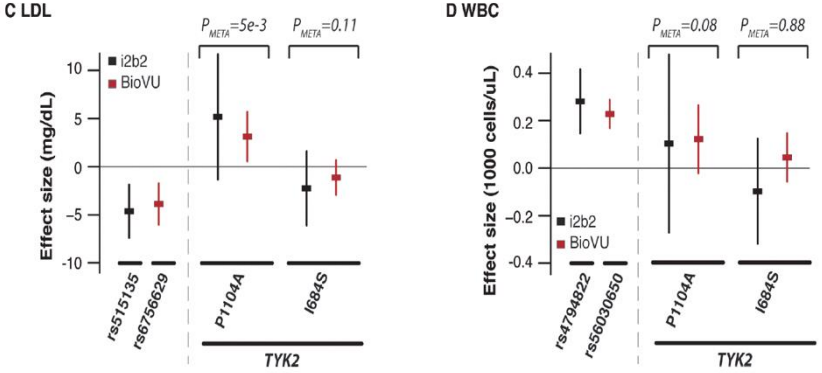
Diogo D et al. *Plos Genetics* 2023

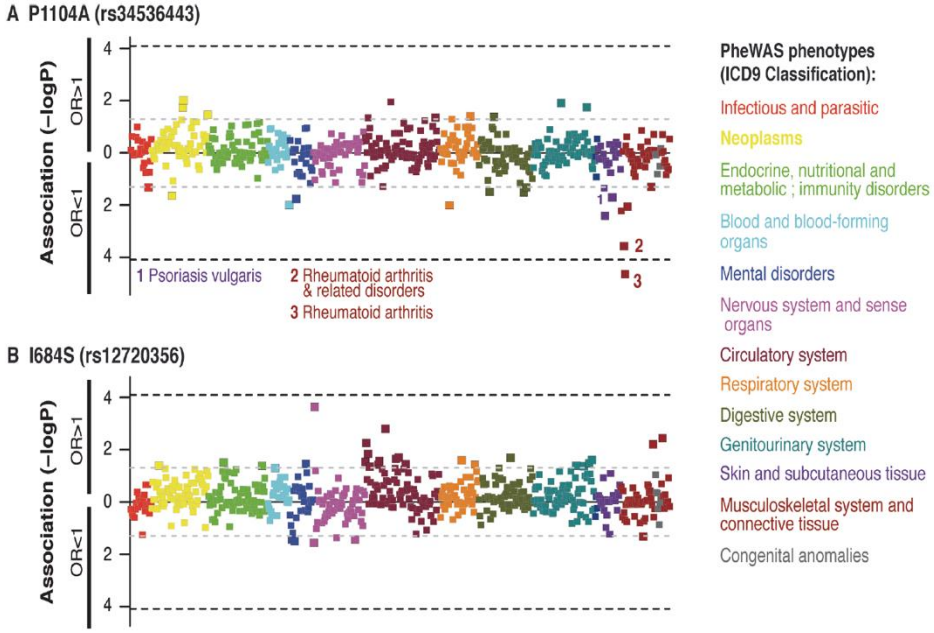
RESEARCH ARTICLE

TYK2 Protein-Coding Variants Protect against Rheumatoid Arthritis and Autoimmunity, with No Evidence of Major Pleiotropic Effects on Non-Autoimmune Complex Traits

TKY2 - 3 Protein-coding Variants Protect vs RA







Suggestive evidence association between A928V & pneumonia OR = 1.54, P = 0.004

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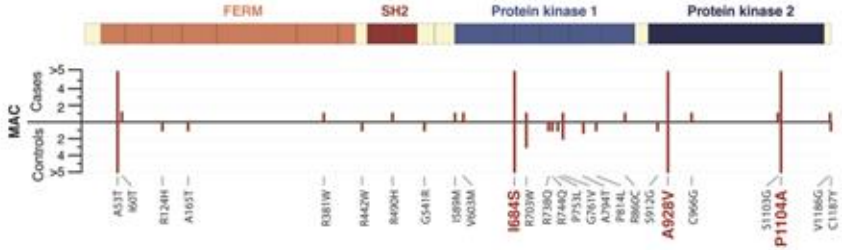
Diogo D et al. *Plos Genetics* 2023

TYK2 I684S: disease specific mechanisms

TYK2	P1104A	2.8184E-43	-0.2307
TYK2	A928V	4.0738E-17	-0.3413
TYK2	I684S	9.12E-24	0.144



TYK2 kinase domain (P1104A/A928V):

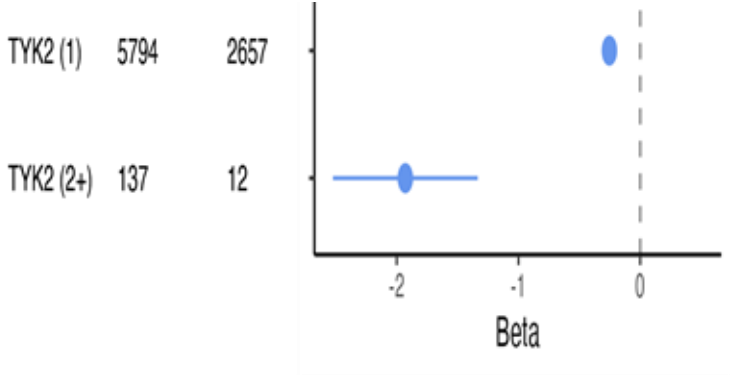
- Strong dose-dependent protection
- No fitness cost in healthy controls
- Homozygotes almost “immune” to IBD

Pseudokinase domain coding variants (I684S):

- Risk for IBD but protective for other autoimmune diseases

→ Domain location determines functional consequence?

→ Tissue-specific effects?



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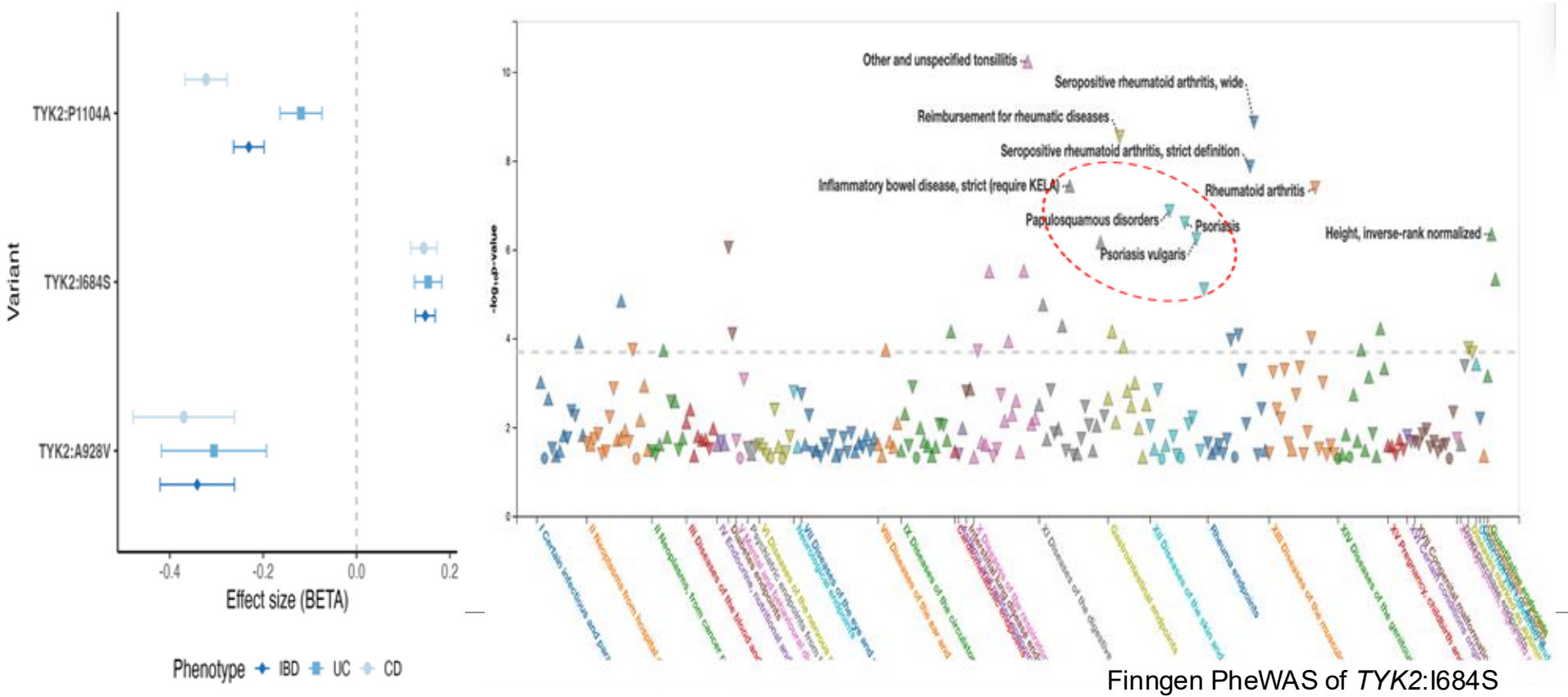
Unpublished data: IIBDGC
courtesy of Mark Daly

TYK2:I684S increases risk for IBD and other gastrointestinal/digestive/respiratory disease endpoints



Finngen PheWAS of *TYK2*:I684S

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE

ORIGINAL ARTICLE

Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis

Arthritis&Rheumatology

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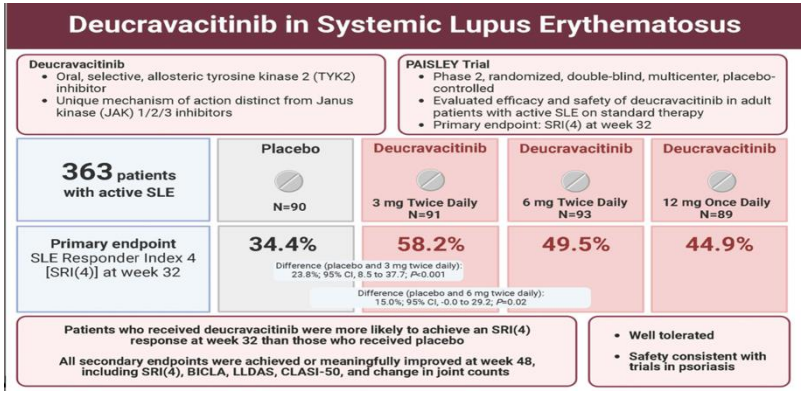
Deucravacitinib, a Tyrosine Kinase 2 Inhibitor, in Systemic Lupus Erythematosus: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial

Journal of Crohn's and Colitis, 2025, **19(5)**, jjaf080
https://doi.org/10.1093/ecco-jcc/jjaf080
Advance access publication 13 May 2025
Original Article

JCC JOURNAL OF CROHN'S AND COLITIS | OXFORD

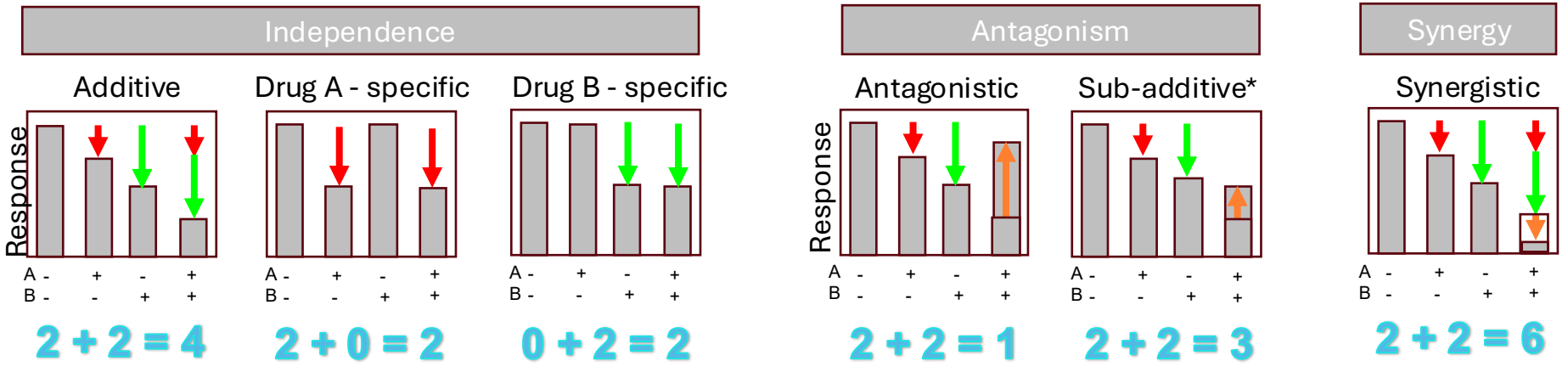
Deucravacitinib in patients with inflammatory bowel disease: 12-week efficacy and safety results from 3 randomized phase 2 studies in Crohn's disease and ulcerative colitis



5. Conclusions

Deucravacitinib at multiple doses did not demonstrate significant clinical benefit versus placebo in patients with moderately to severely active CD or UC. Deucravacitinib was safe and well tolerated.

Future – Combination Therapies – The Search for Synergy



*Sub-additive is a special case of antagonistic where the combo is at least as strong as the strongest single effect

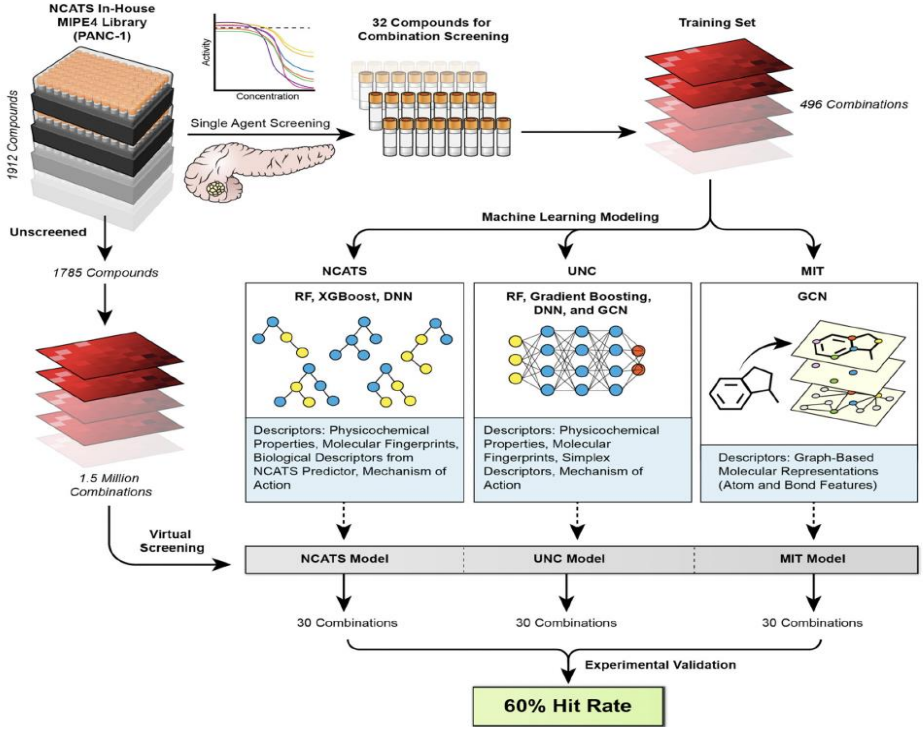
Future – Combination Therapies – The Search for Synergy

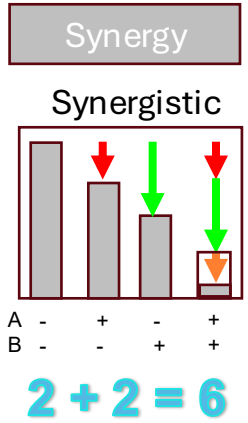
nature communications

Article

https://doi.org/10.1038/s41467-025-56818-6

AI-driven discovery of synergistic drug combinations against pancreatic cancer





Pourmousa et al, Nature Communications 2025

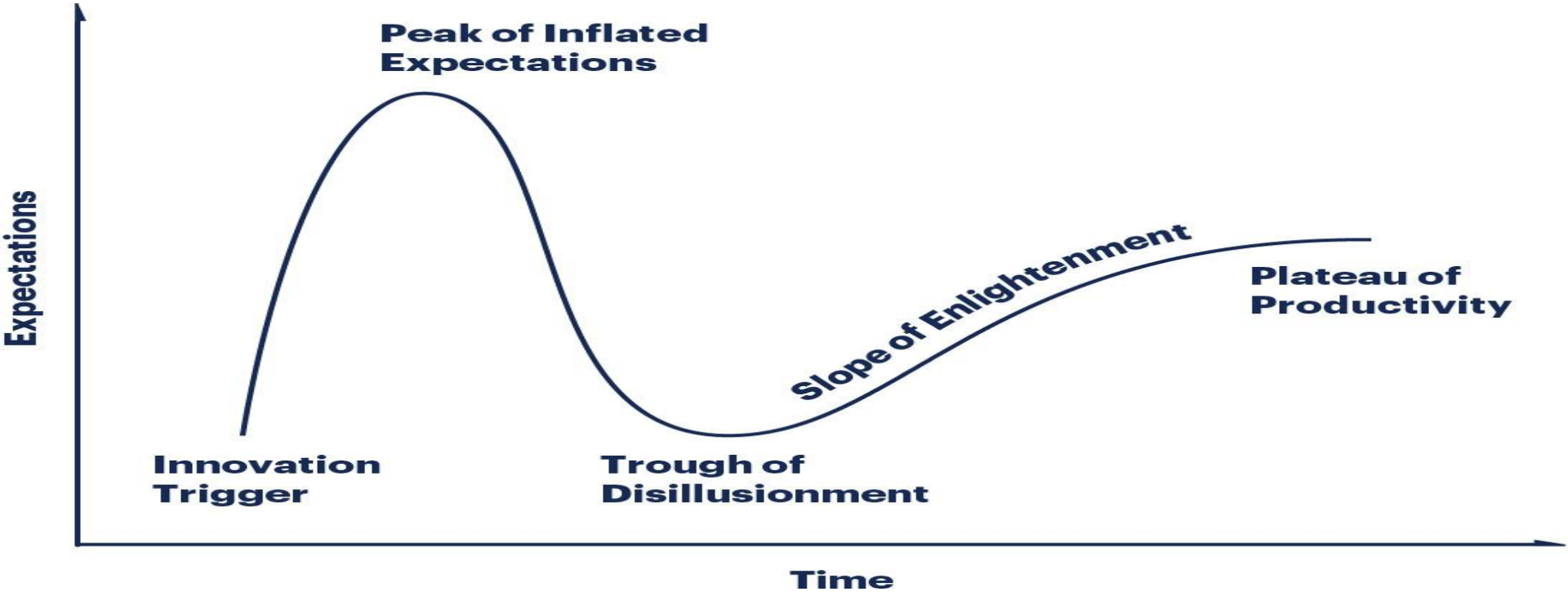
AI and Drug Development Beyond Target Identification

Pipeline of drug development	Target identification	Drug discovery	Preclinical studies (animal)	Clinical trials (human)	Approval/launch	Post-market surveillance
Main tasks	New target 	Discovery of active compounds (hits/leads) Lead optimization for drug candidates CMC	Biomarker discovery DMPK evaluation Safety evaluation Pharmacodynamics evaluation Medication scheme		New drug 	Evaluating or monitoring - Therapeutic efficacy - Side effect - Drug stability - Medication plan Failure analysis Counterfeit analysis
AI-powered applications	• Multi-omics data analysis • Biological network construction and analysis • Literature and real-word data mining • Knowledge graph construction • Target validation	• Virtual screening • Prediction of ligand–receptor interaction • Molecular generation • ADMET prediction • Lead optimization • Synthesis route planning • Automated synthesis	• Diagnostic, predictive and prognostic biomarkers • Pharmacometrics property prediction • Clinical trial success prediction • Prediction of drug side effects • Digital Twins in clinical trial design • Drug repurposing • Regulatory approval support		• Personalized efficacy assessment • Personalizing patient care • Early detection of safety issues • Automated adverse event reporting • Continuous safety monitoring • Drug benefit–risk assessment • Enhancing pharmacovigilance compliance	

Cedars Sinai

Zhang et al, Nature Medicine 2025

Summary and Conclusions



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