Infection and Location: *gene* x environment interaction

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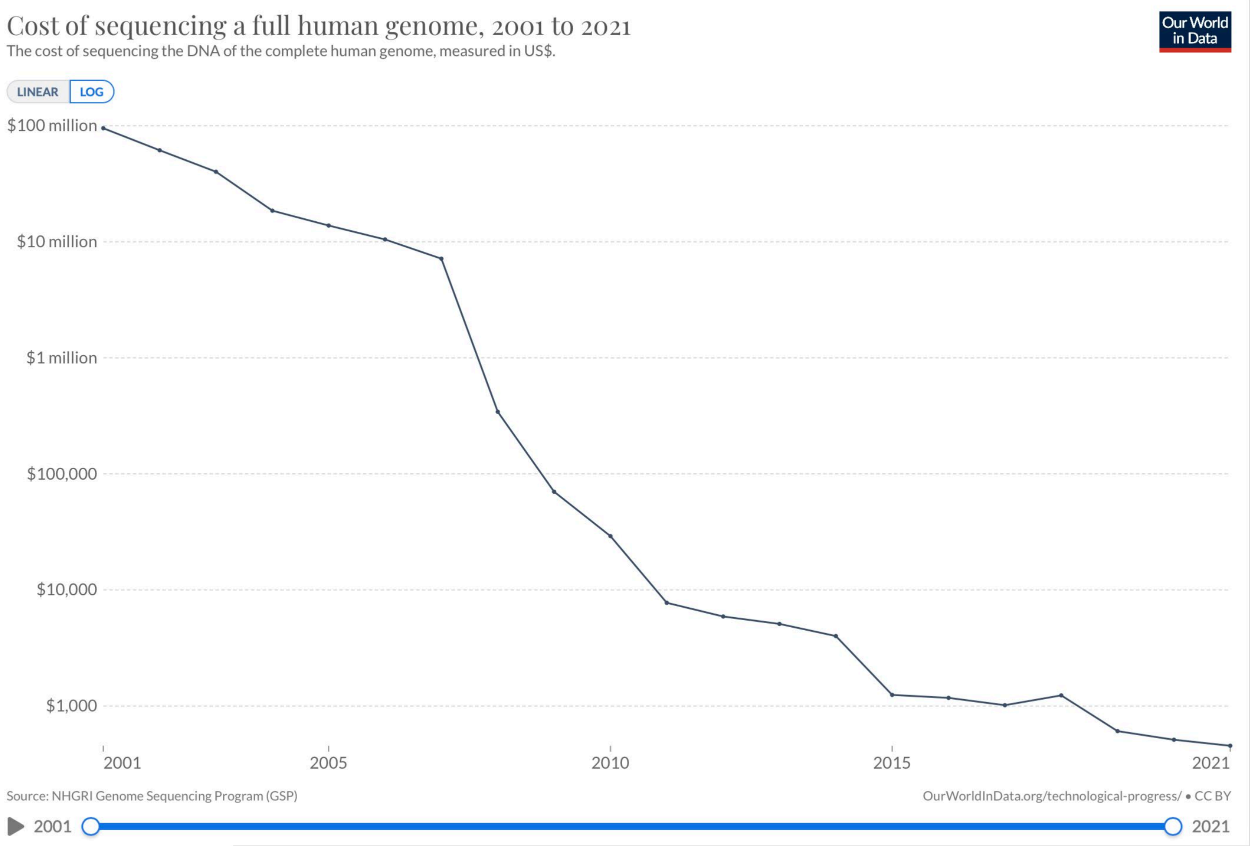
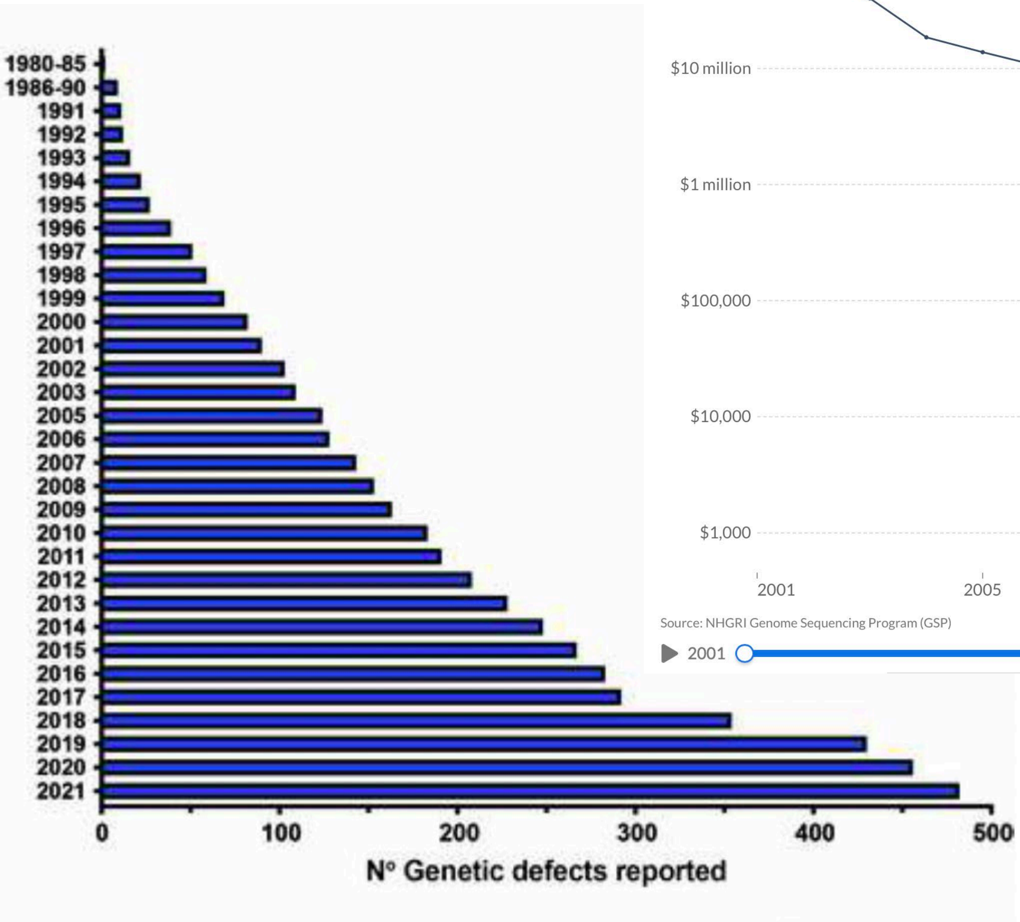


Cost of sequencing a full human genome, 2001 to 2021

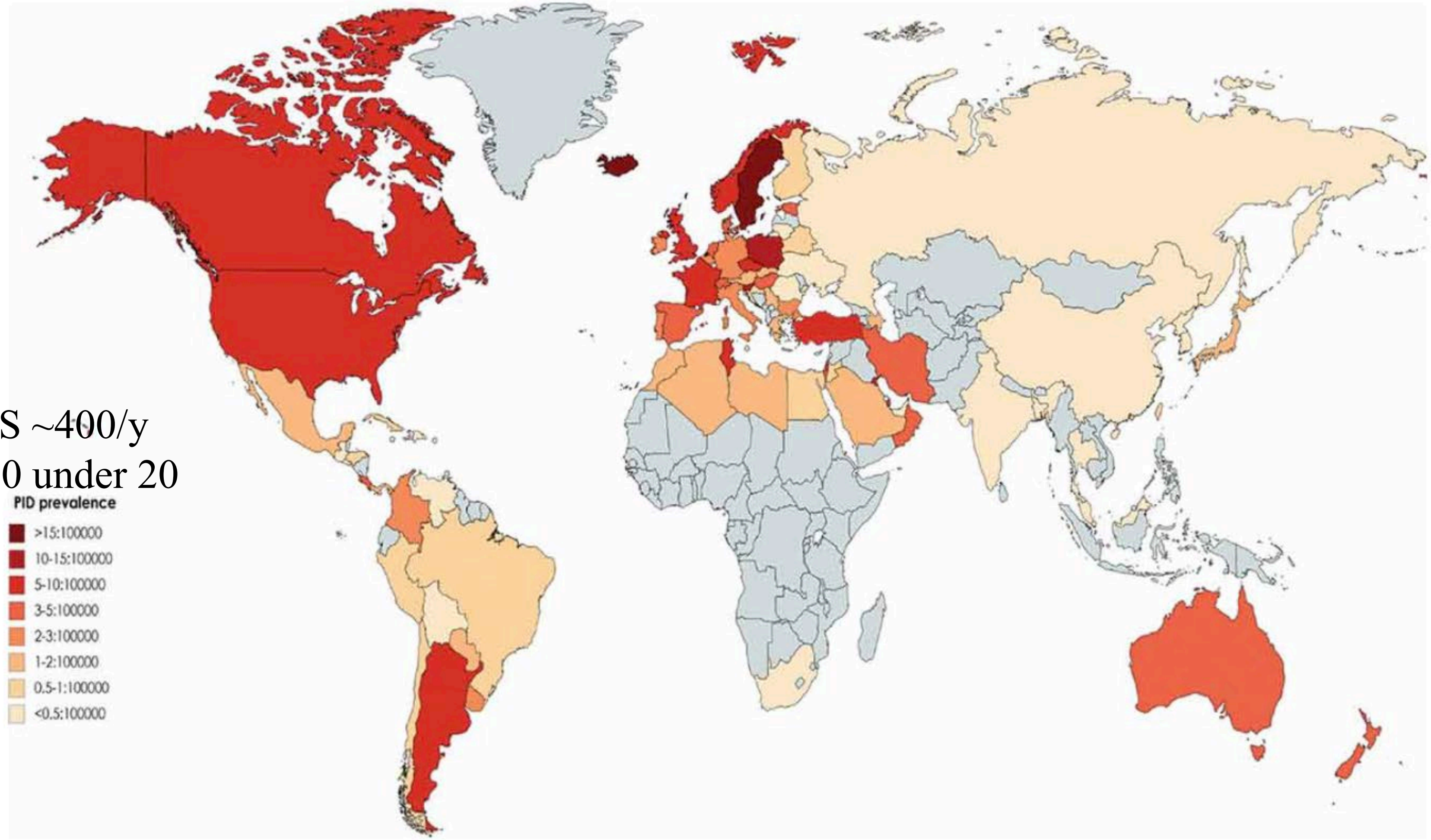
The cost of sequencing the DNA of the complete human genome, measured in US$.

Source: NHGRI Genome Sequencing Program (GSP)

OurWorldInData.org/technological-progress/ • CC BY



Prevalence of Primary Immune Deficiencies

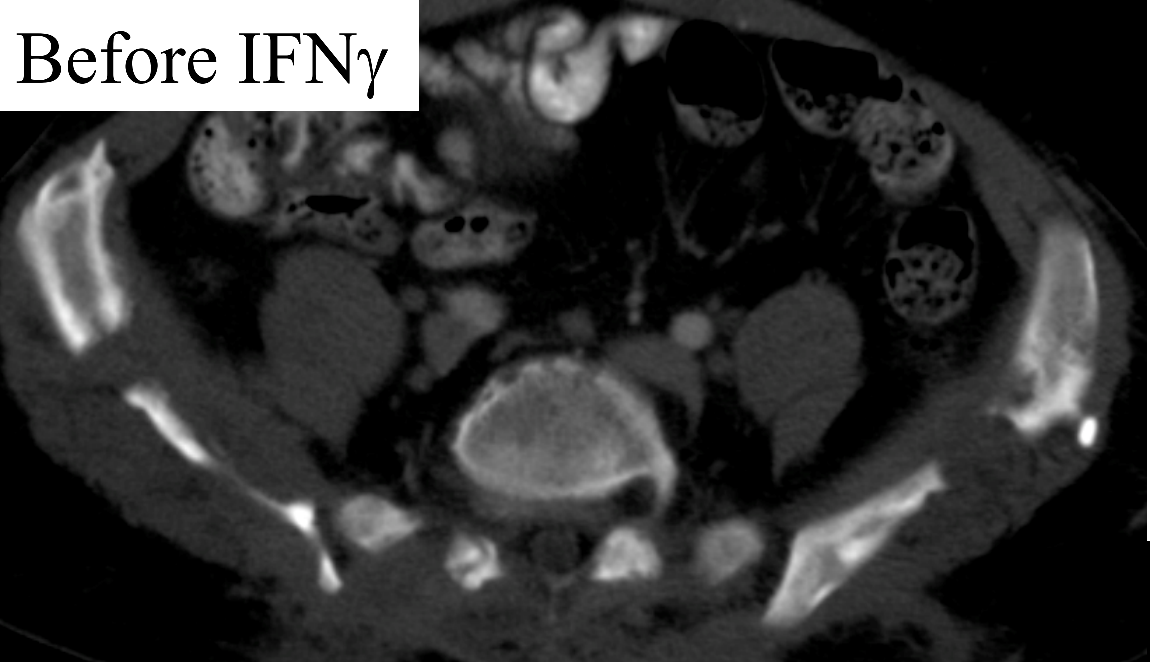


US ~400/y
8000 under 20

US PID 5-10/100,000 US TB 2.7/100,000

Abolhassani, EXPERT REVIEW OF CLINICAL IMMUNOLOGY2020, VOL. 16, NO. 7, 717-732


🟨 Areas in which coccidioidomycosis is endemic
🟧 Uncertain areas



Before IFNγ

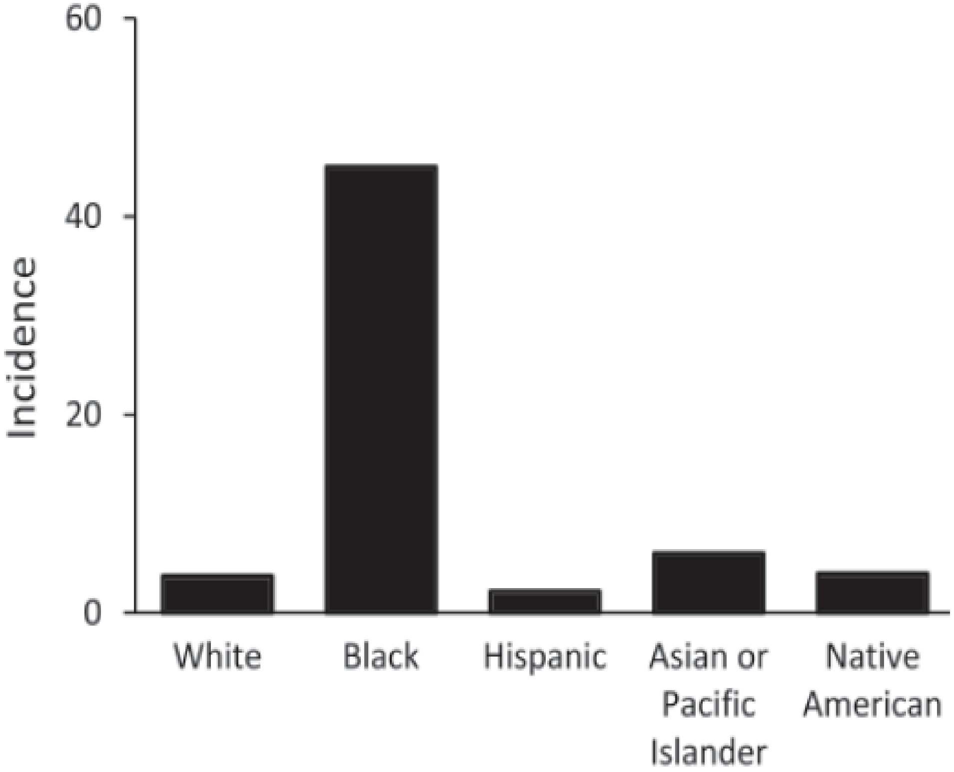
After IFNγ

Refractory Disseminated
Coccidioidomycosis
and Mycobacteriosis in Interferon-γ
Receptor 1 Deficiency

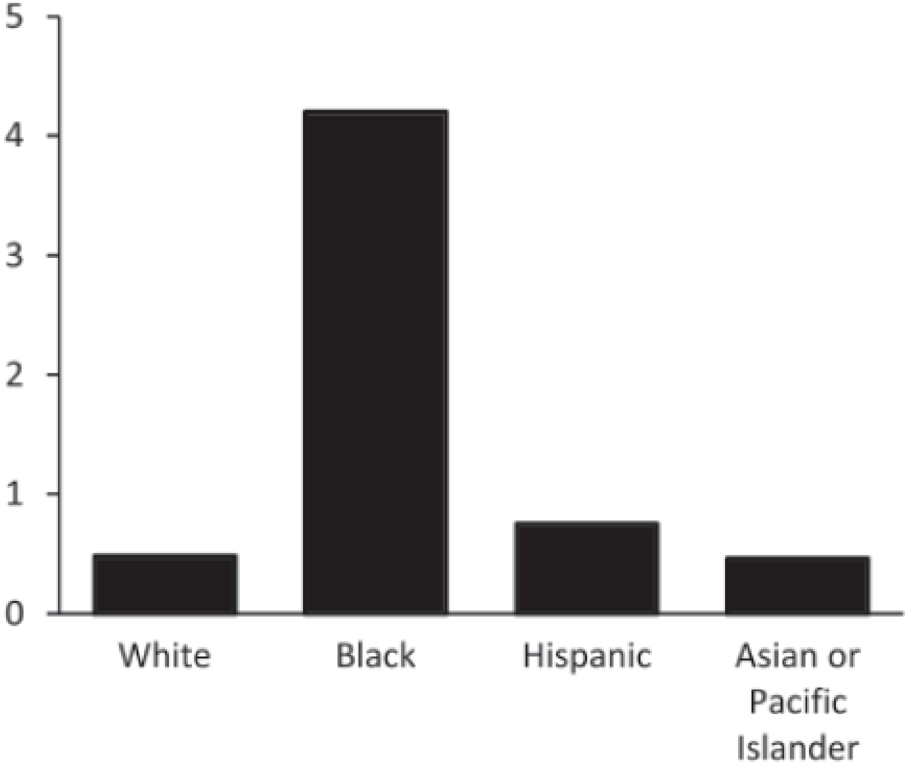
Clinical Infectious Diseases 2009; 49:e62–5

Disseminated Coccidioides Hospitalizations Rate/100,000 population

Arizona 2000-2009



California 2003-2008



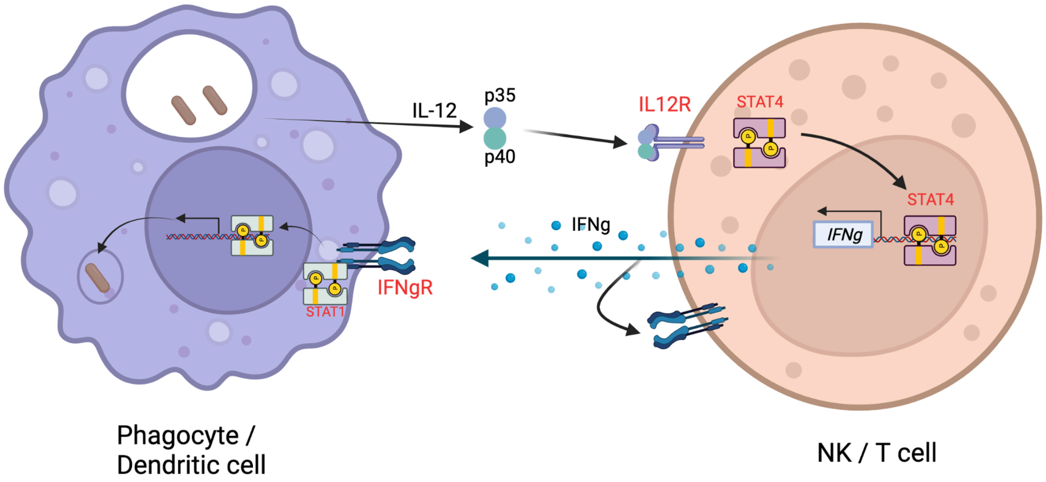
Seitz et al, Emerging Infectious Diseases September 2012

Risk Factors for Disseminated Coccidioidomycosis, United States

Pregnancy, HIV, immunosuppression
and

Targeted sequencing
STAT3 (2009)
IFNGR1 (2009)
IL12RB1 (2011)
STAT1 (2013)
IL12RB2 (2017)

IL12-IFNG pathway



Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 23, No. 2, February 2017

So the problem:

150,000 infections/y
50,000 cases
15,000 diagnosed

1000 DCM cases/year

only *8* have identified mutations
Ever?!

Whole Exome Sequencing for DCM

STAT3 p.R423* heterozygous fatal CNS disease

STAT3 p.R84* heterozygous prolonged CNS disease

	Not Hispanic	Hispanic
Asian	3F 1M	0
Black	2F 15M	0
White	11F 12M	6F 10M
Other	7M	1F

68 patients, 23 F and 45 M

Amy Hsu

Whole Exome Sequencing Usually Looks for Rare *Mendelian* Variants

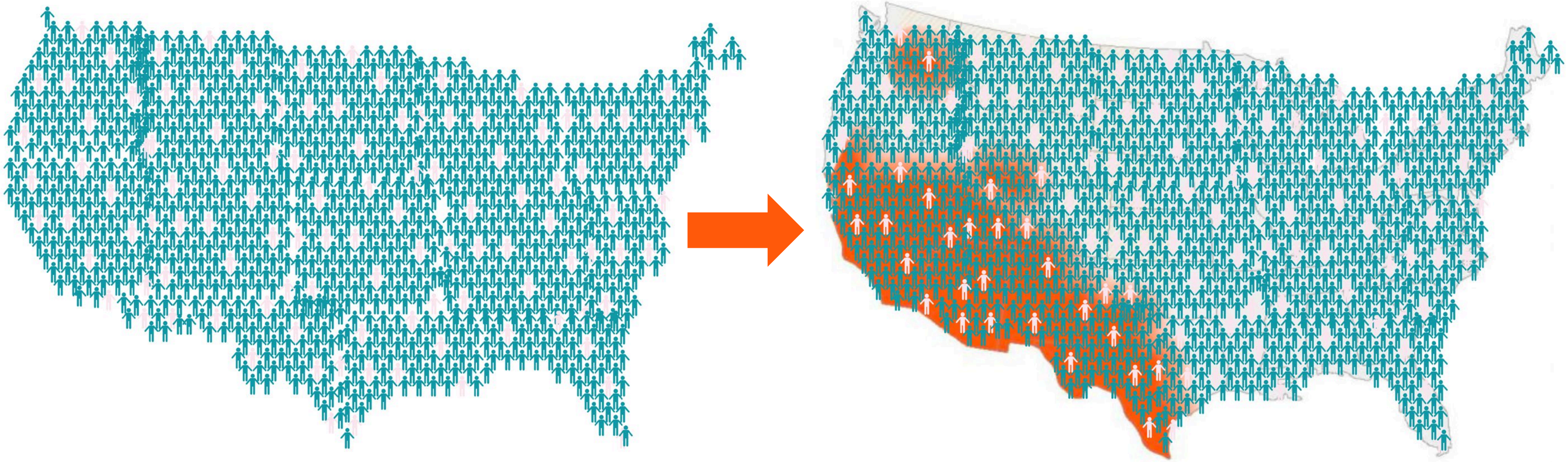
BUT, this is a virulent, geographically limited disease, and previously healthy people get it

So is RARE the right filter?

That is, common variants that have population effects would be rare by geography

Common variants found in healthy individuals

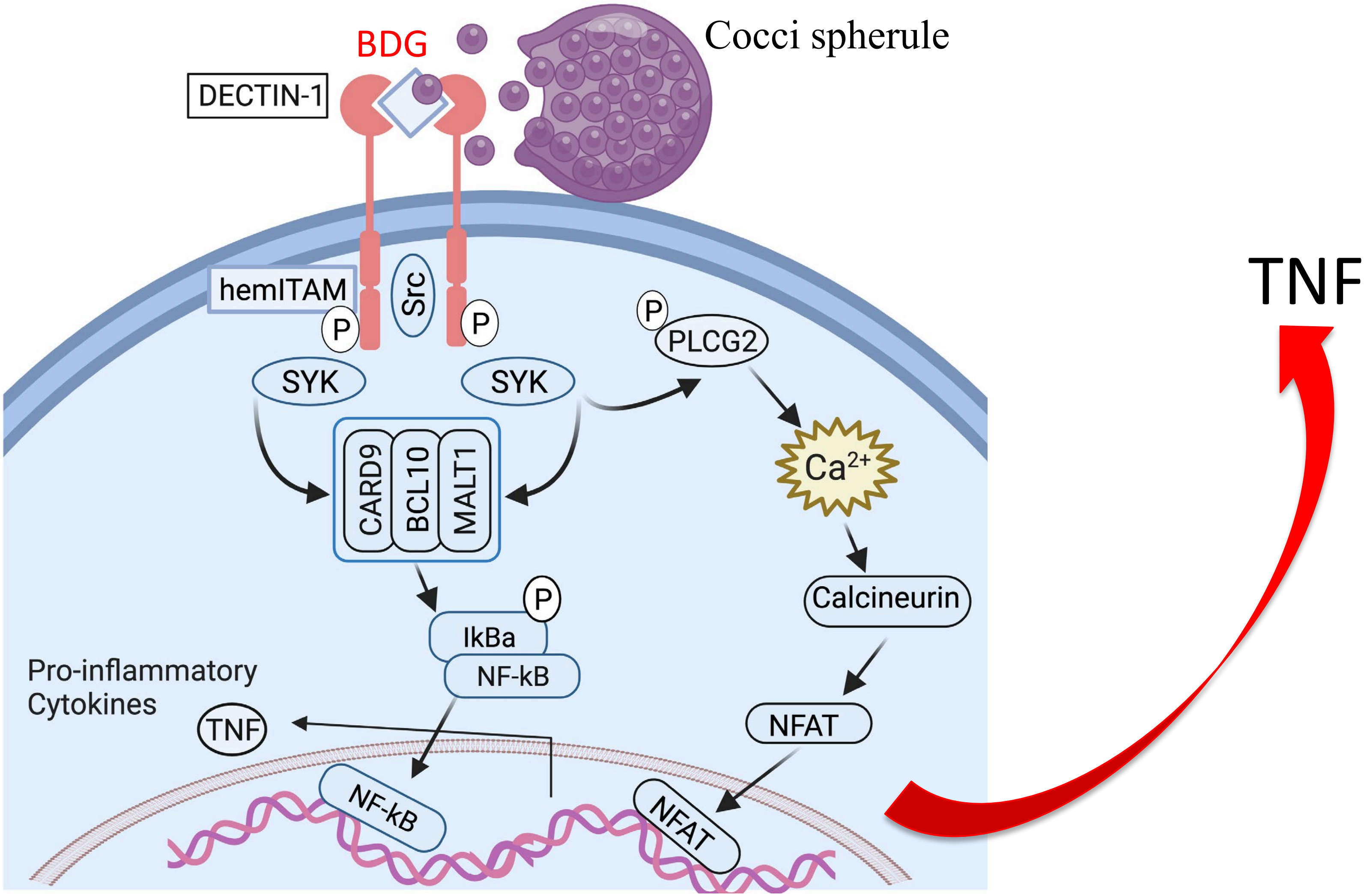
Manifest as disease in endemic areas



We already look for variants that only emerge in BMT or with immunomodulators

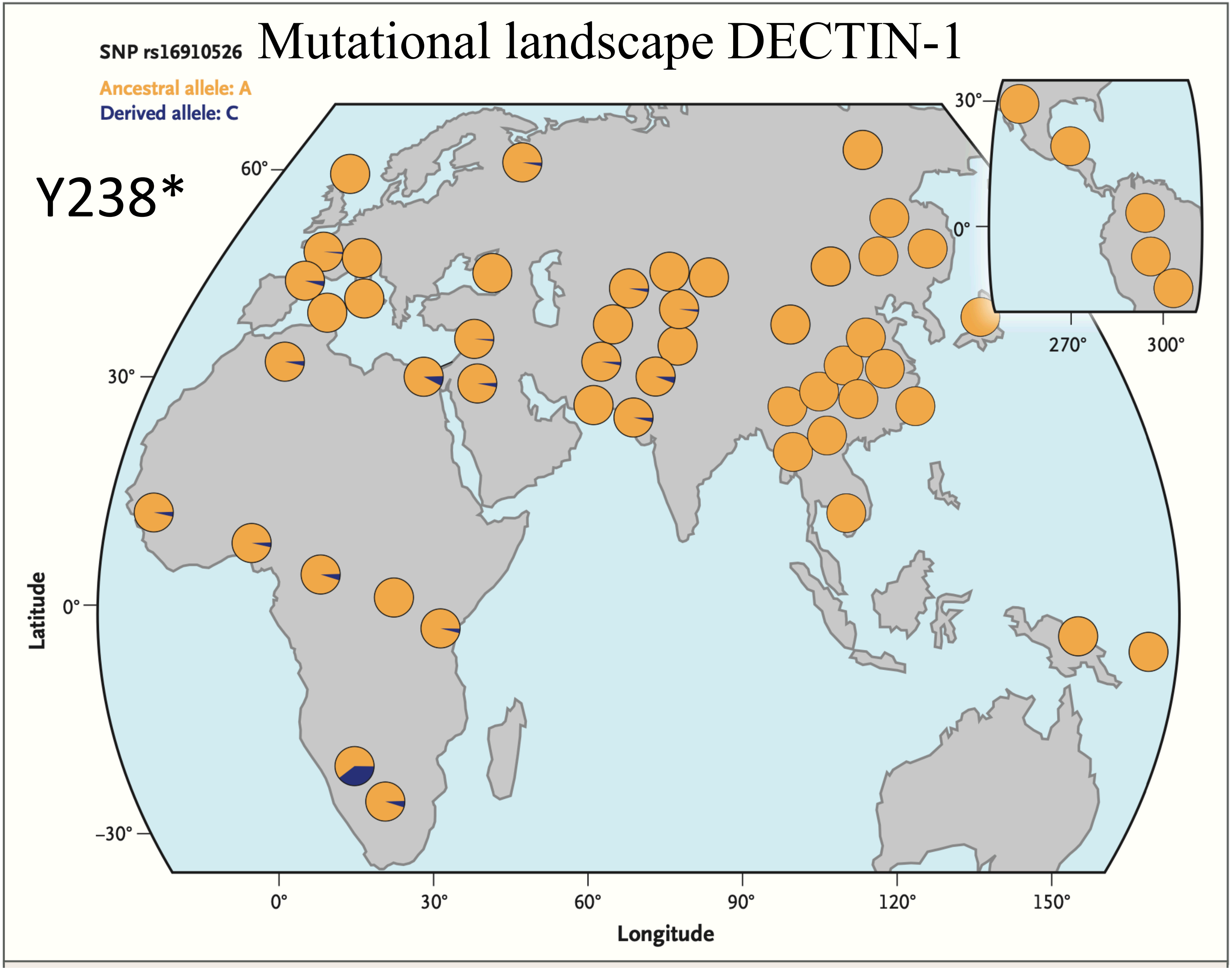
JCI Insight. 2022. https://doi.org/10.1172/jci.insight.159491.

Cellular DECTIN-1 binds fungal β-D-glucan (BDG)



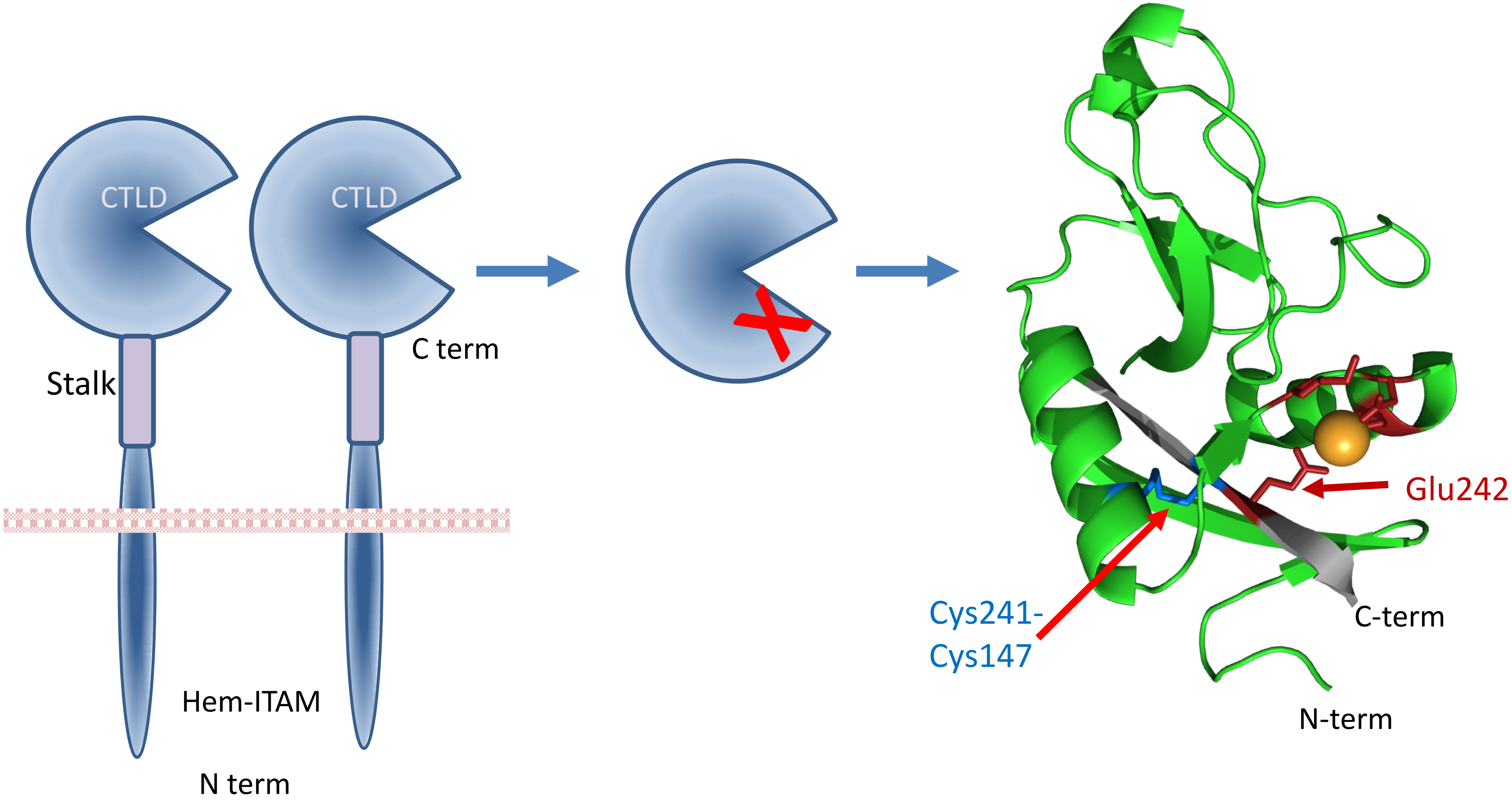
Mutational landscape DECTIN-1

Y238*



N Engl J Med 2009;361:17607

DECTIN-1 p.Y238* impairs β-glucan recognition



CLEC7A (DECTIN-1) p.Y238*

Homozygous

c.714T>G p.Y238*

3/68 DCM (4.41%)

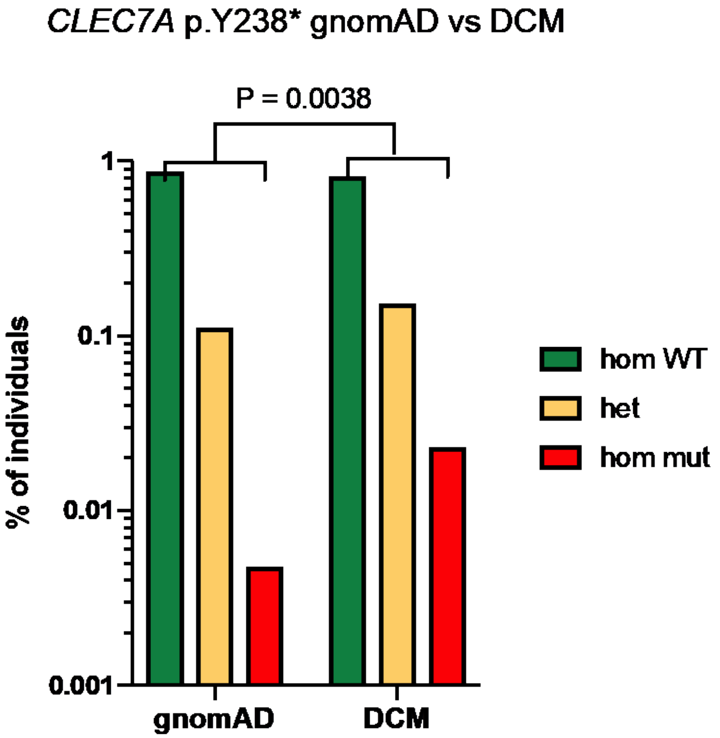
680/141265 gnomAD (0.48%)

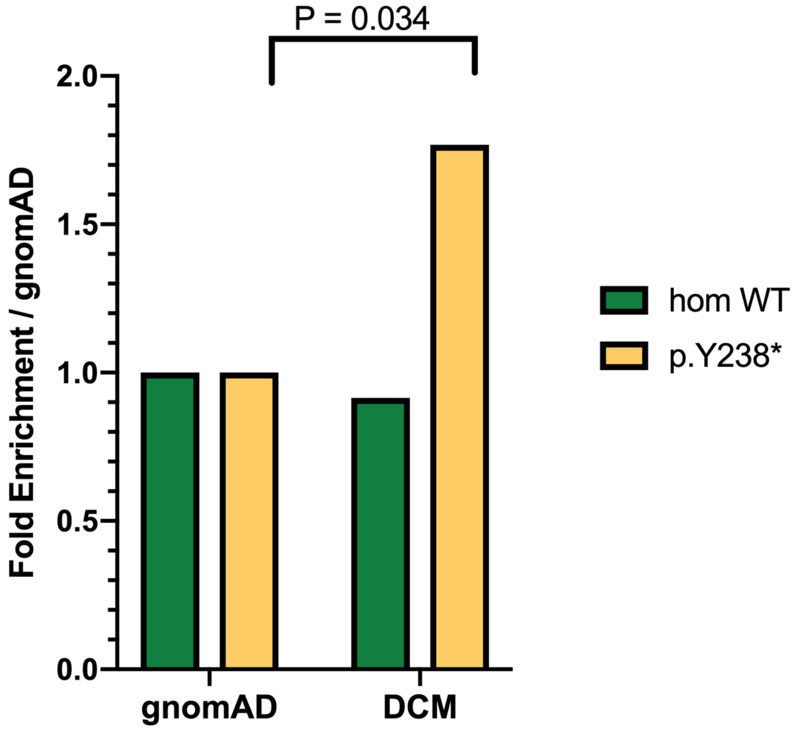
Homozygous AND Heterozygous

c.714T>G p.Y238*

14/68 DCM (20.6%)

16450/141265 gnomAD (11.6%)

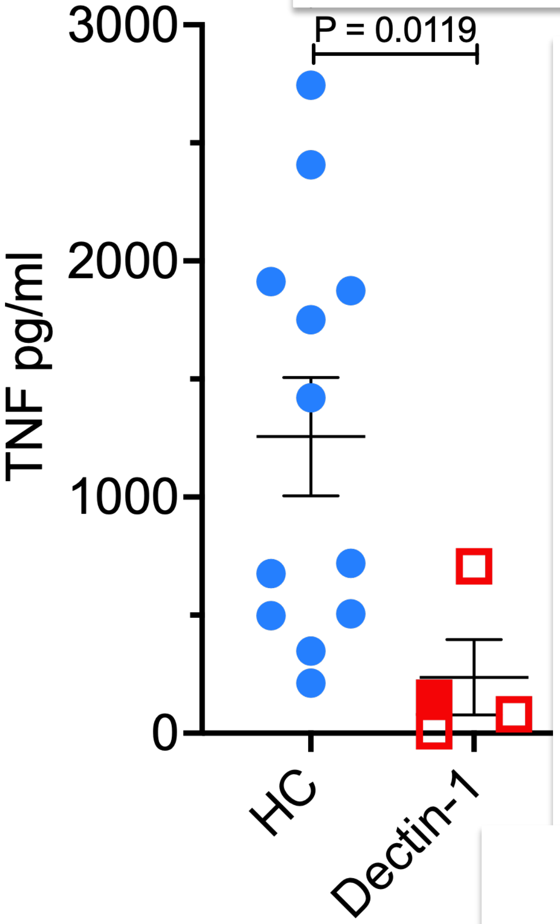




JCI Insight. 2022. https://doi.org/10.1172/jci.insight.159491.

DECTIN-1 Y238* blocks PBMC TNF Production to BDG

Stimulation Index

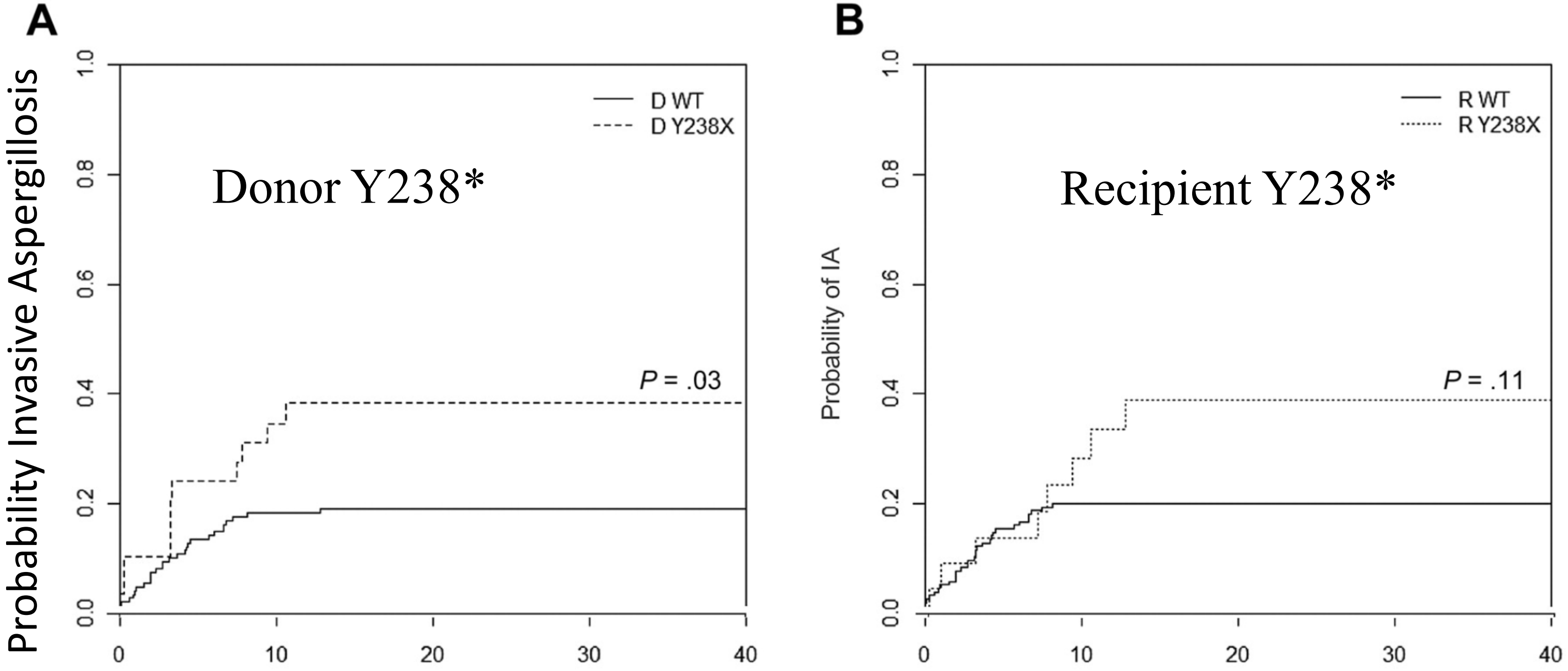


🟥 Homo

□ Het

Dominant effect

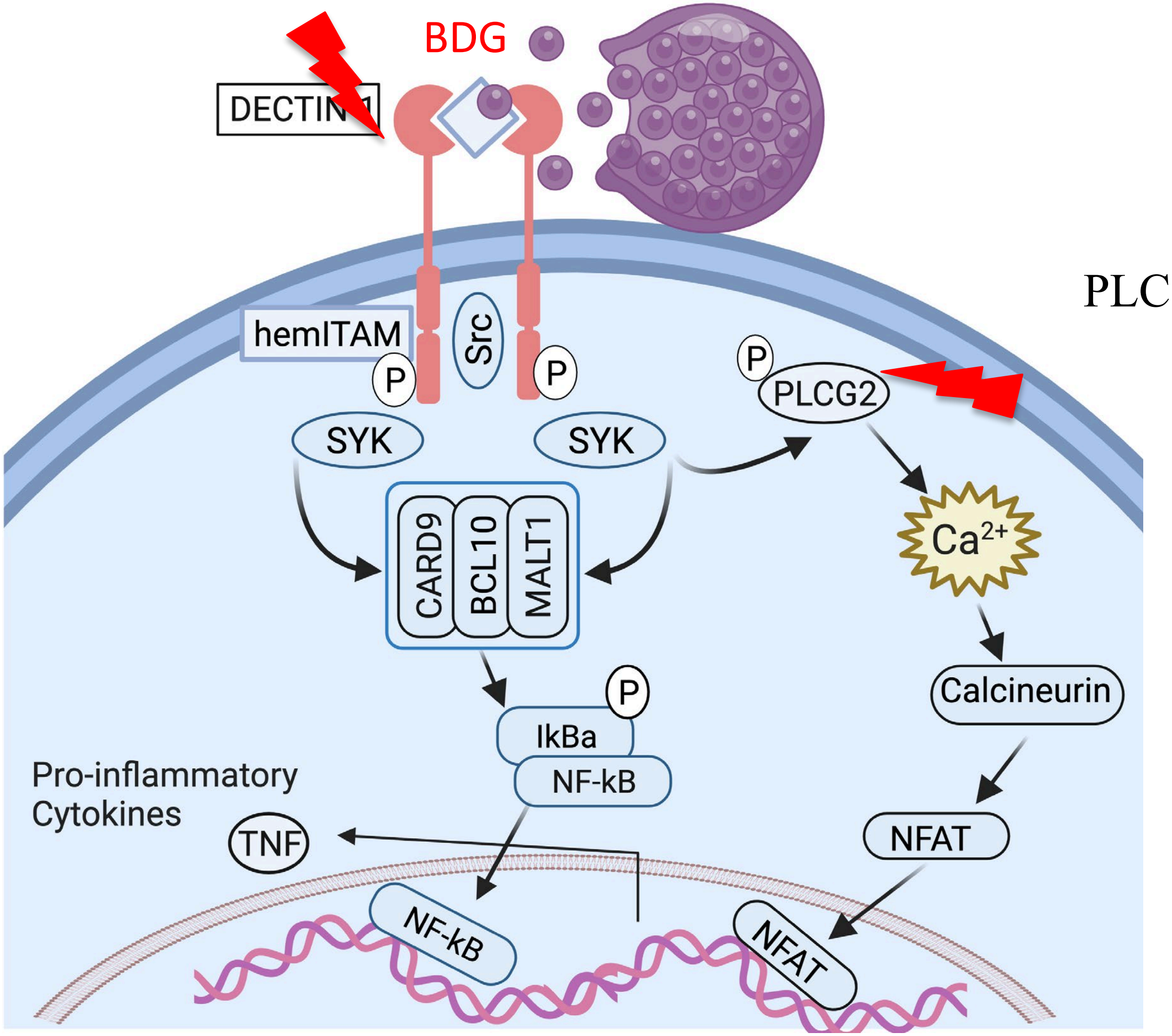
Invasive *Aspergillus* post bone marrow transplant



Both hematopoietic and somatic contributions

Cunha C et al. Blood. 2010;116:5394-402

Beyond DECTIN-1 signaling

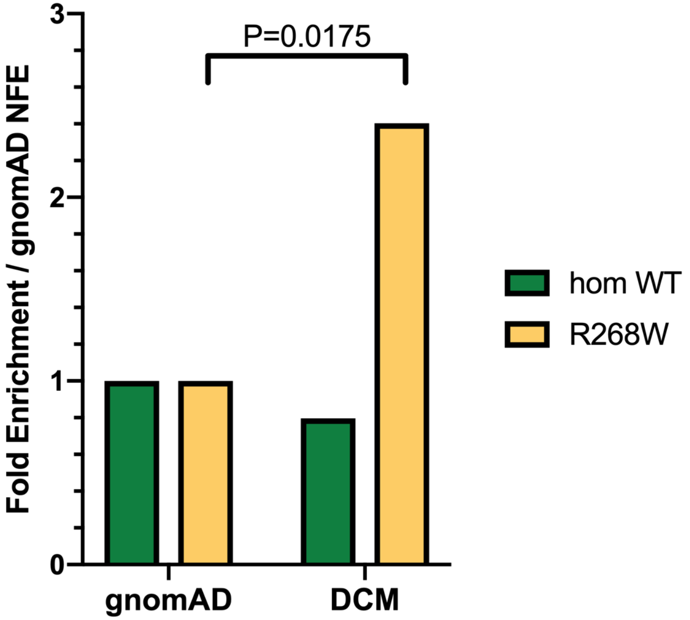


DECTIN-1

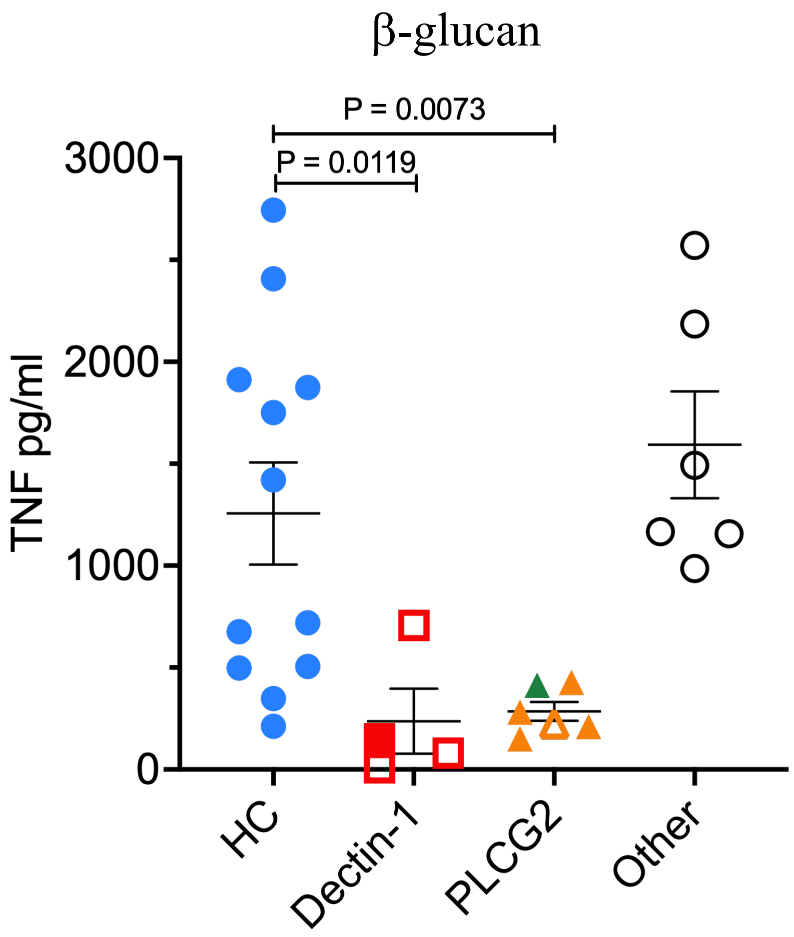
- p.Y238* (11 hets, 3 homozygotes)
- p.I223S (1 het)

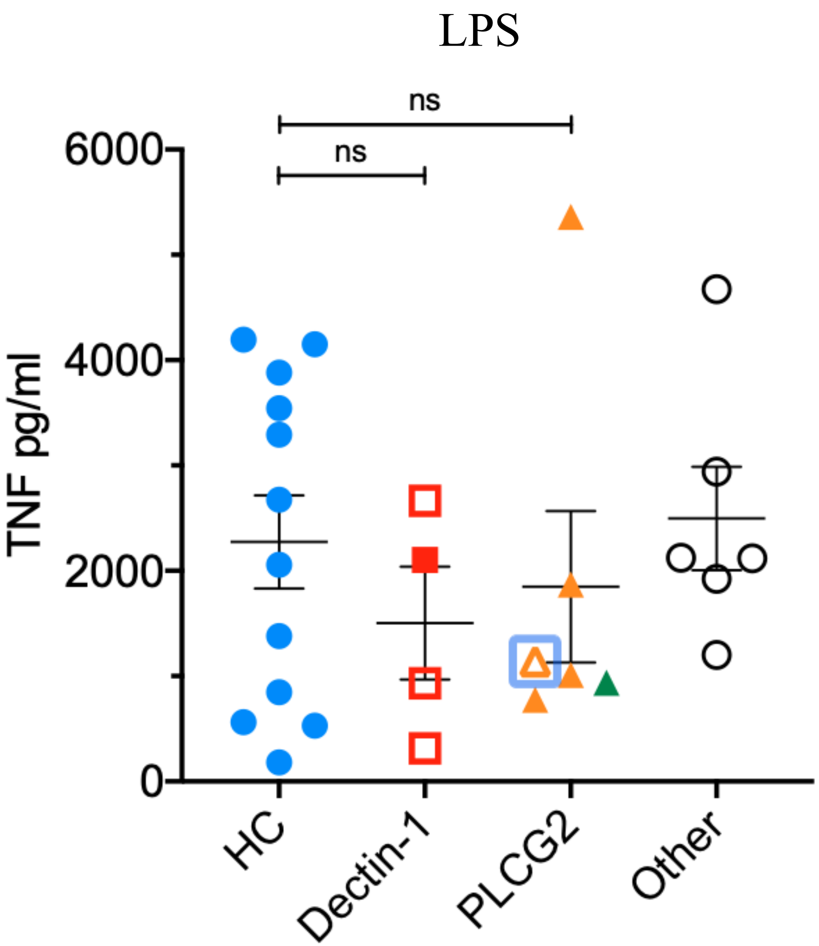
PLCG2

- p.R268W (associated with IBD)

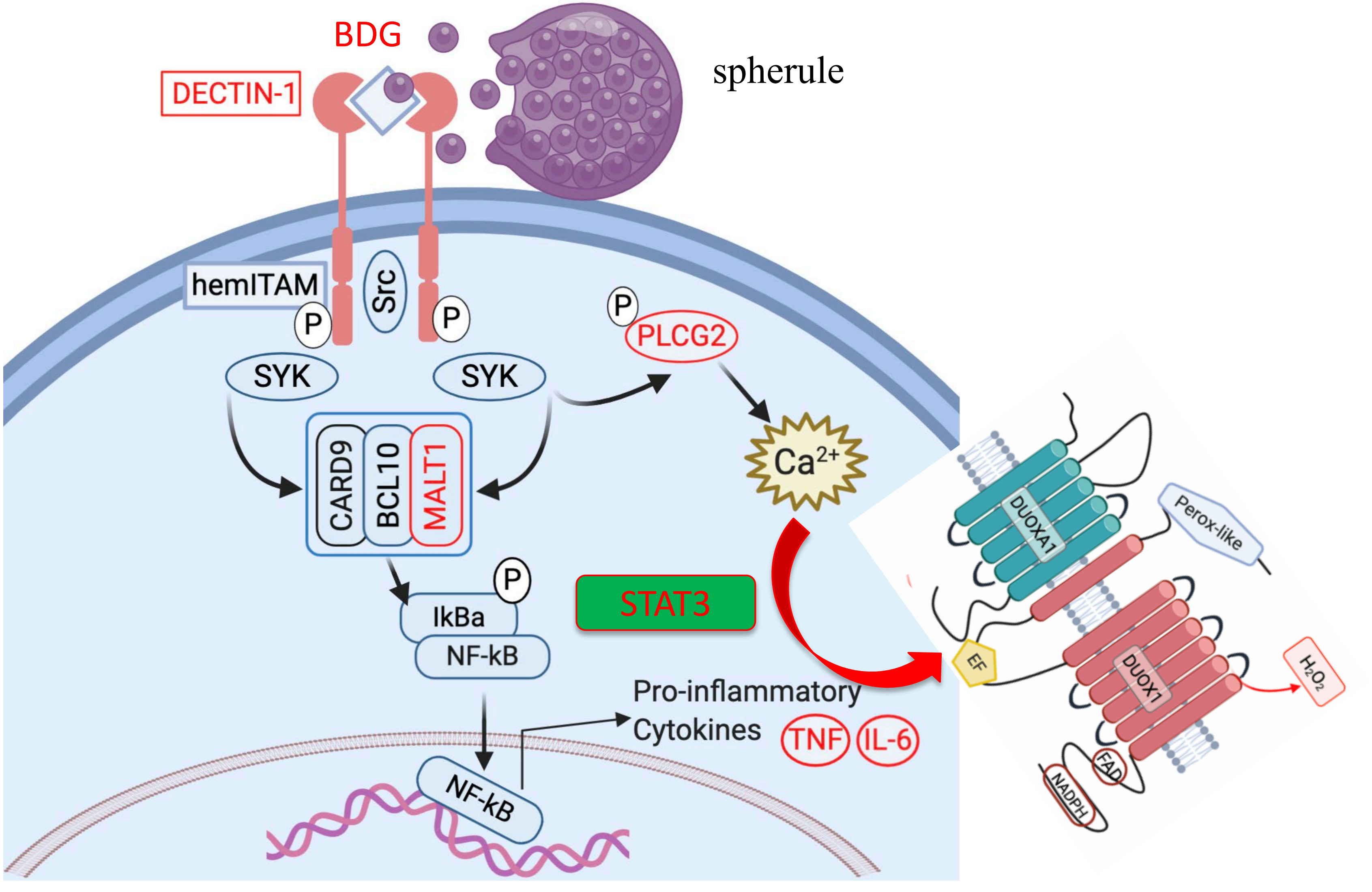


Decreased response to β-glucan, not LPS

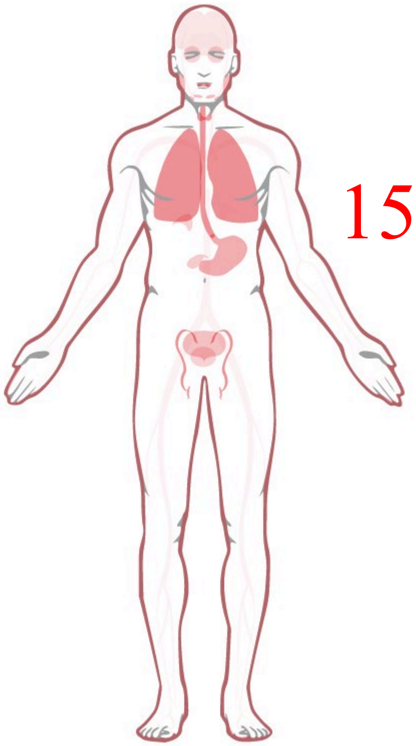




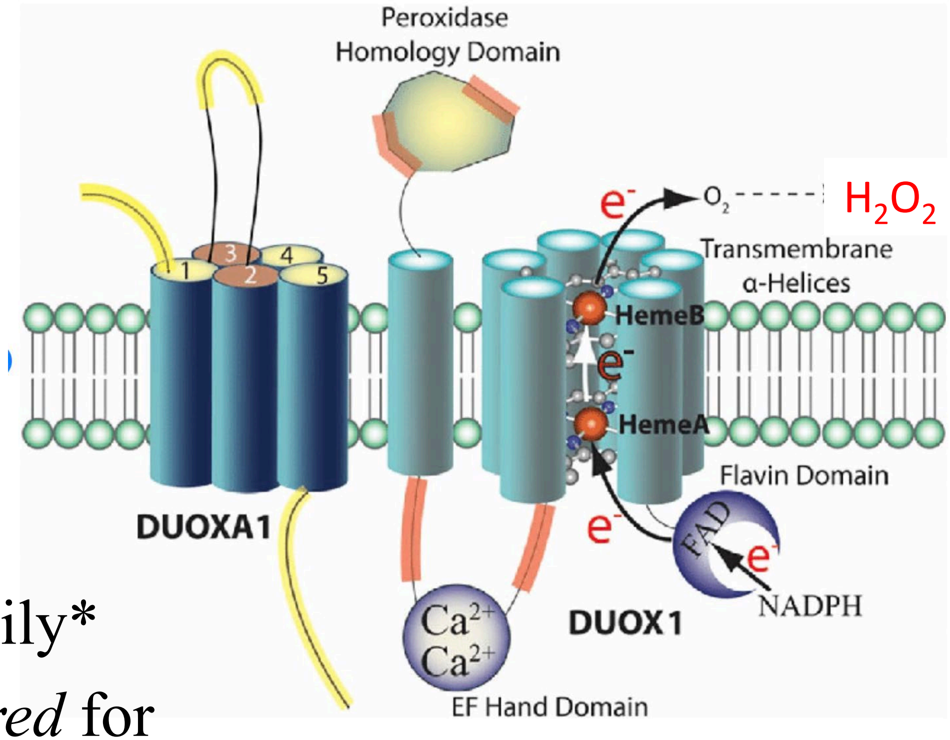
Beyond DECTIN-1 and PLCγ2 signaling?



DUOX1 and DUOXA1



15 patients have variants in DUOX1/DUOXA1



Expressed alveolar epithelium

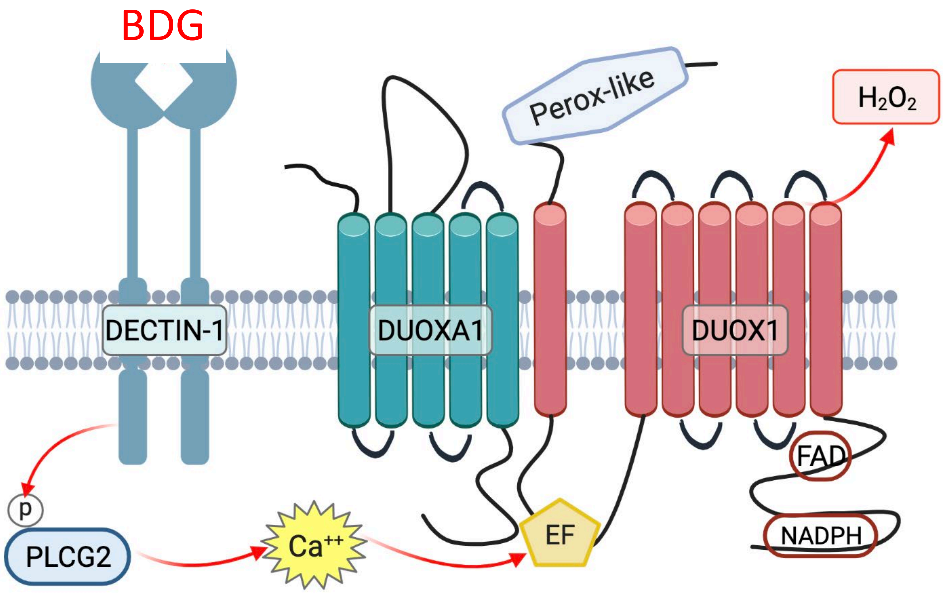
Member of NADPH oxidase family*

Heterodimeric assembly is *required* for expression

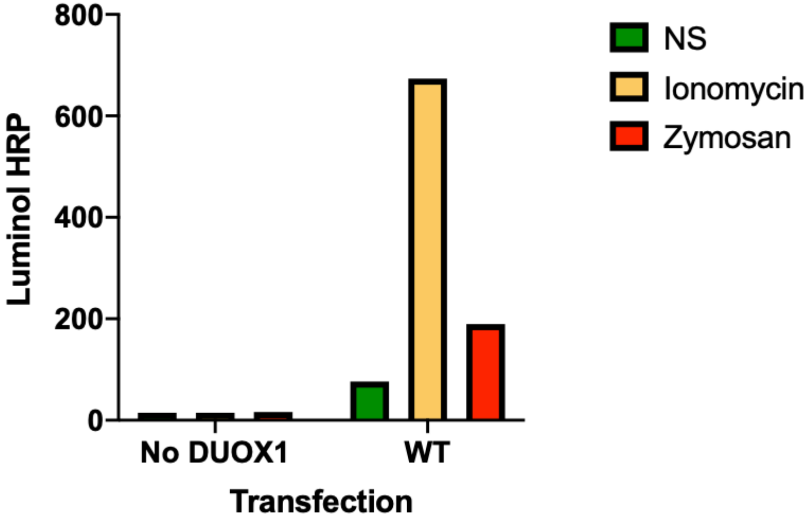
* CGD patients DO NOT get cocci

Little et al, 2017 Free Radical Biology and Medicine

DECTIN-1 drives DUOX1 H_2O_2



HEK cells transfected with DECTIN-1, PLCG2, DUOX1, DUOXA1



JCI Insight. 2022. https://doi.org/10.1172/jci.insight.159491.

Validation Cohorts

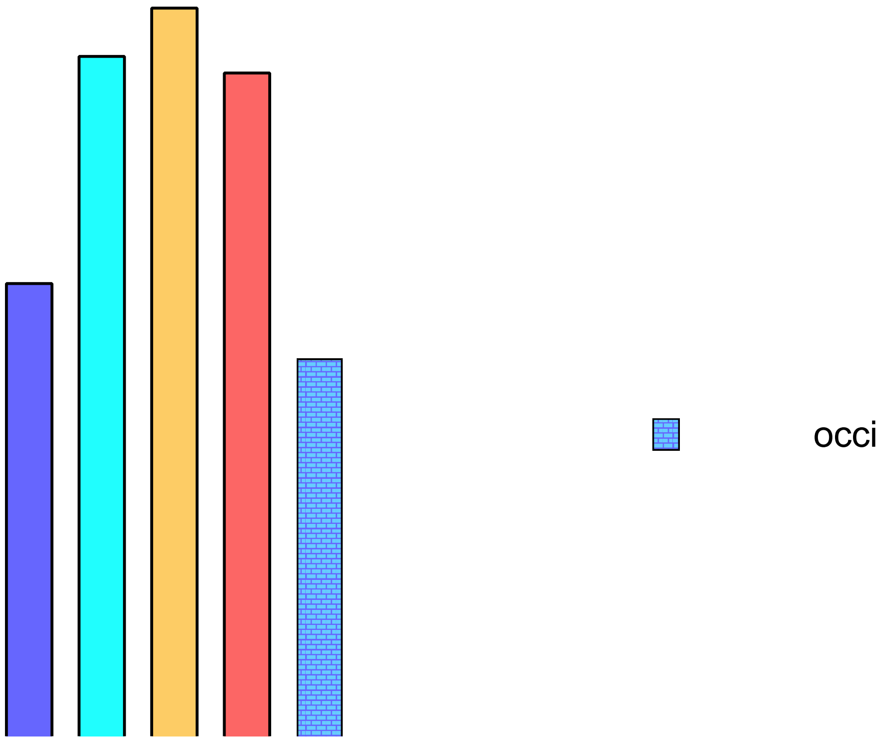
Primary pulmonary disease – NIH (n = 65)
George Thompson– UCD Coccidioidomycosis (n = 465)

- Primary pulmonary (n = 294) (no recurrence 2+ yrs after treatment)
- Chronic pulmonary (n = 59) (evidence of dx after > 1yr anti-fungals)
- Meningitis (n = 32)
- Non-meningitis DCM (n = 80)

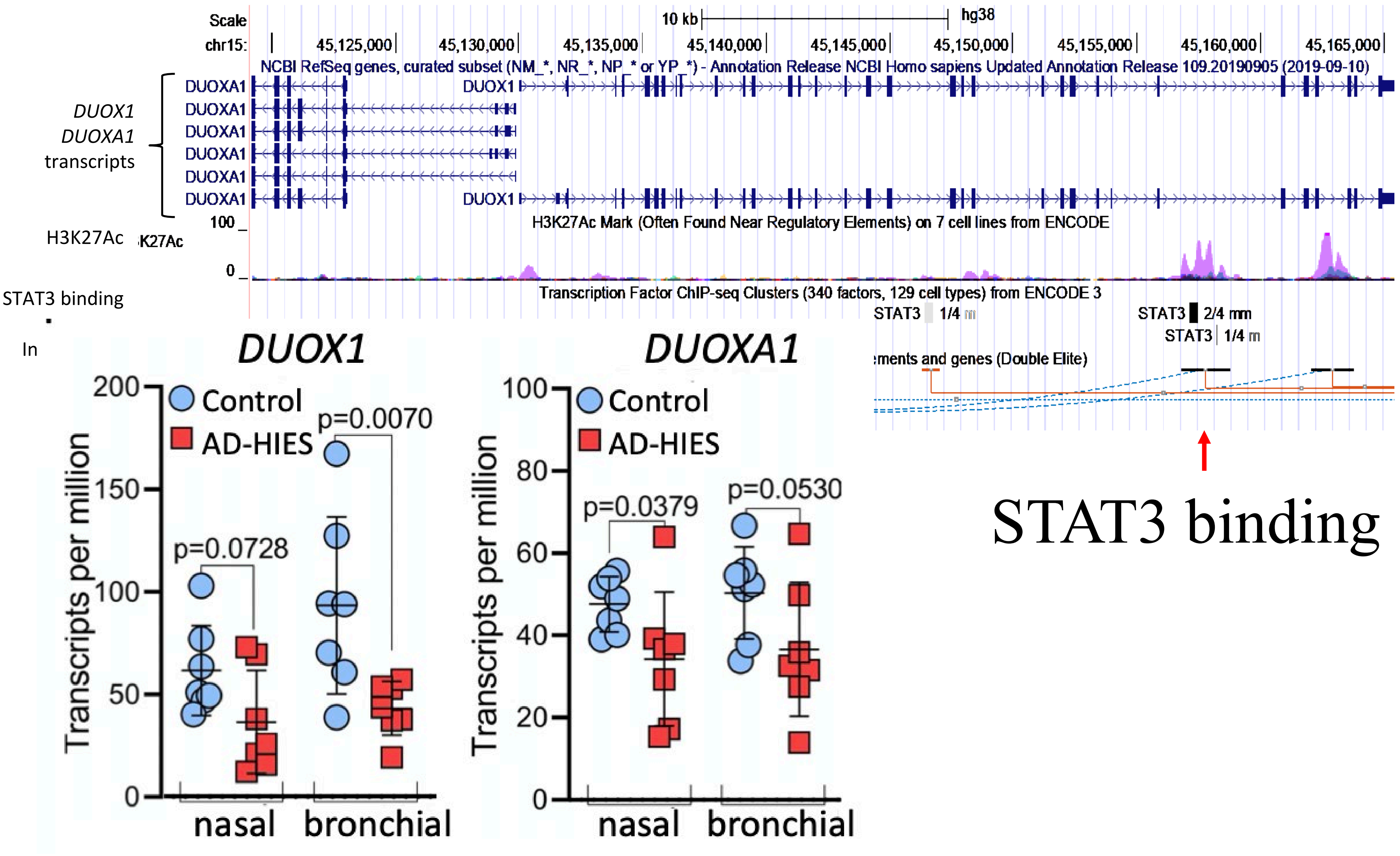
Healthy control cohort - 1000 Genomes (n = 2504)

Variant burden in severe disease

Validation NIH



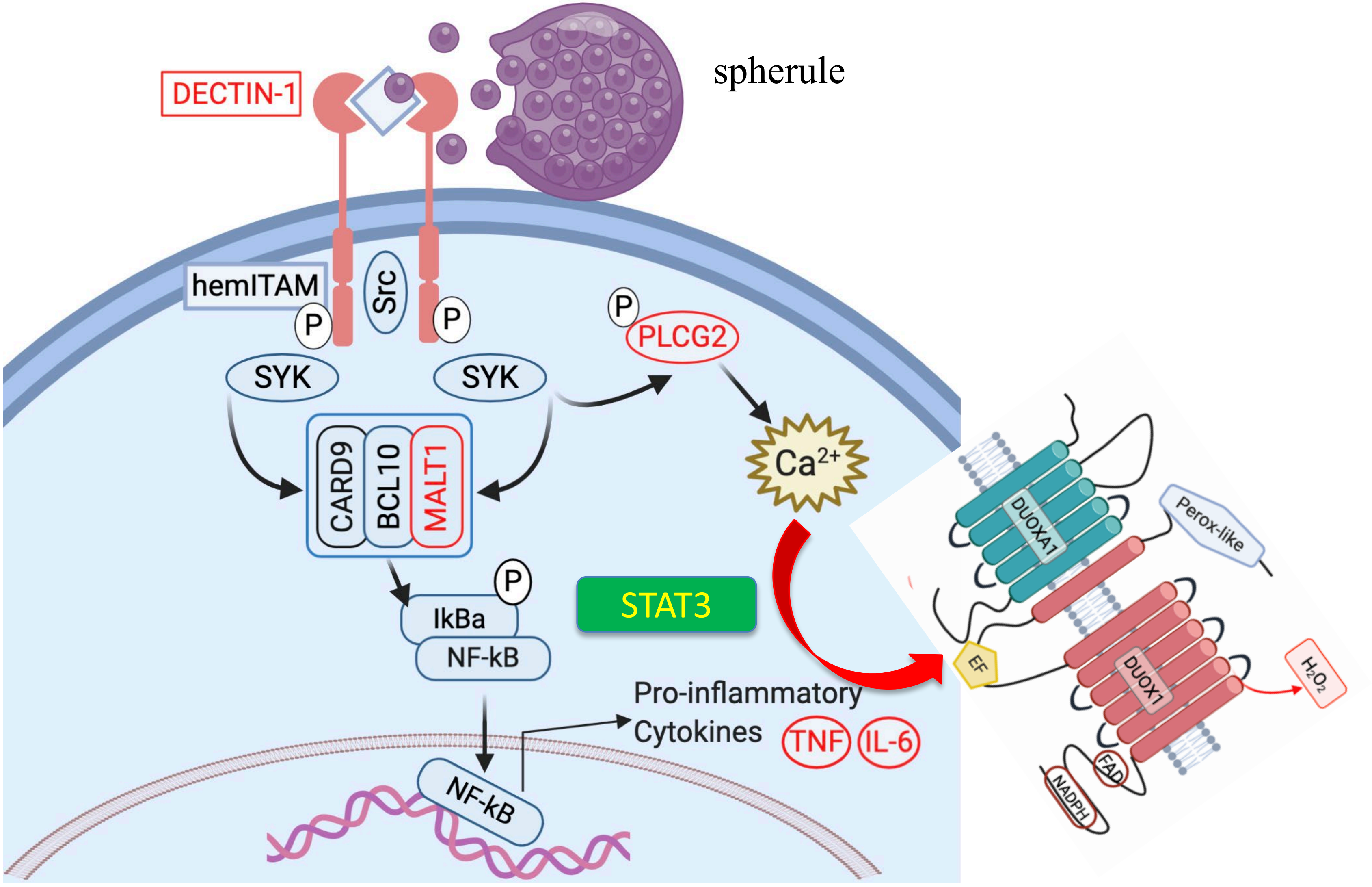
STAT3 binds in the DUOX1/DUOXA1 locus



STAT3 binding

Amy Hsu, Alex Freeman, Gang Chen, Rick Boucher

Functional Landscape of Early Control of *Coccidioides* (and it applies to other fungi as well!)



SUMMARY

Pt	54	79	80	69	71	91	50	52	57	67	84	29	39	45	60	61	77	36	33	63	70	72	73	86	48	41	65	25	40	22	35	37	42	66	76
STAT3	1	1																																	
CLEC7A			2	2	2	1	1	1	1	1	1	1	1	1	1																				
PLCG2			1	1		1	1	1								1,1	1,1	1	1	1	1	1	1	1											
MALT																									1										
DUOX1									1	1	1							1								1,1	1	1	1						
DUOXA1			1									1						1									1			1	1	1	1	1	1

Many relatively common variants in disseminated *Coccidioides*

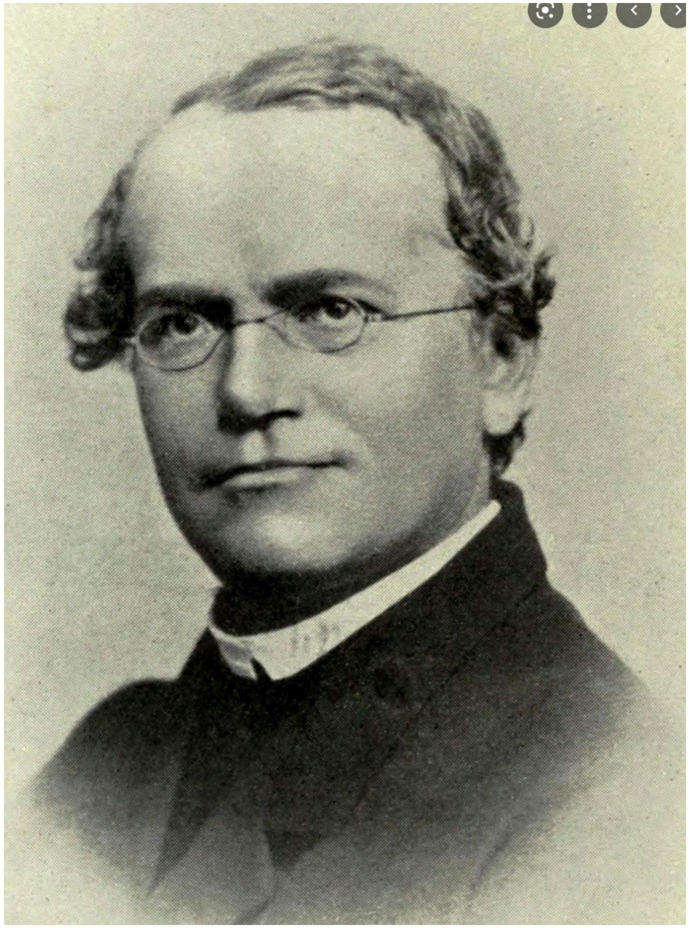
Affect early fungal sensing and antifungal response

TNF production unites some of them

Epithelial hydrogen peroxide appears important

JCI Insight. 2022. https://doi.org/10.1172/jci.insight.159491.

Mendel or Menzel?



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