Effects of Germline Genetics on the TME

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Tumor Immune Microenvironment:
A Holistic Approach Workshop

April 21-22, 2022 • San Diego and Virtually

#SITCworkshop

sitc
Society for Immunotherapy of Cancer

OBJECTIVES OF THE TALK

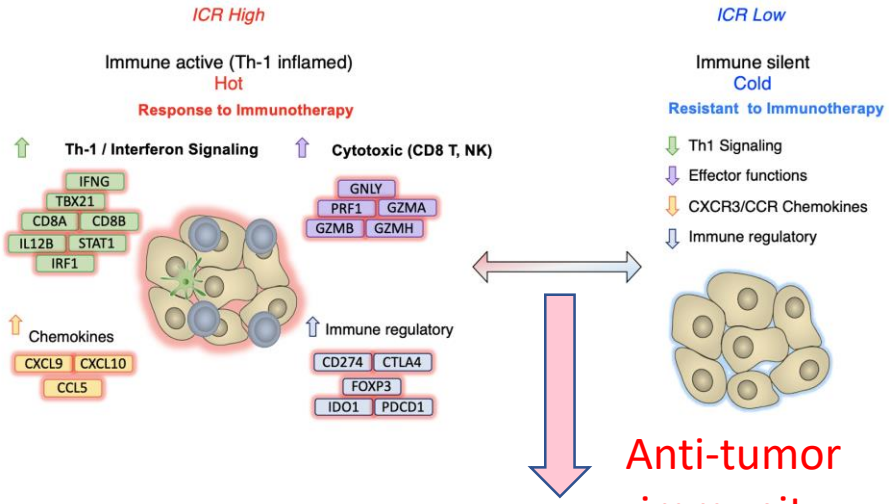
Present recent data regarding germline genetic contribution to cancer immunity

Discuss potential implications for precision medicine

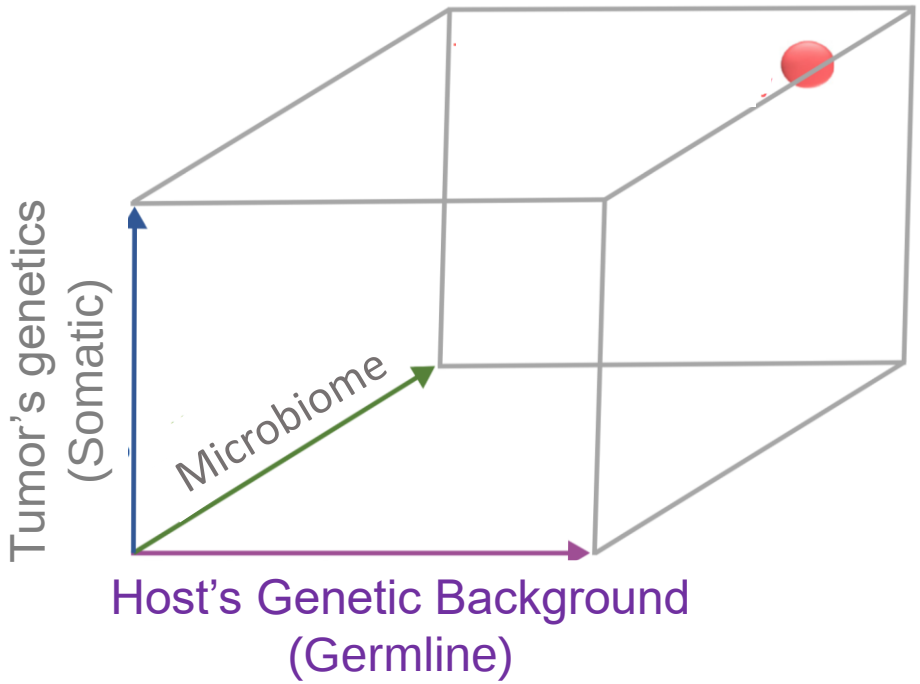
No competing interests to disclose

سدرة للطب
Sidra Medicine

Determinants of Immune Responsiveness



Anti-tumor immunity



SITC Cancer Immune Responsiveness (CIR) Taskorce 2019

Bedognetti *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:131
https://doi.org/10.1186/s40425-019-0602-4

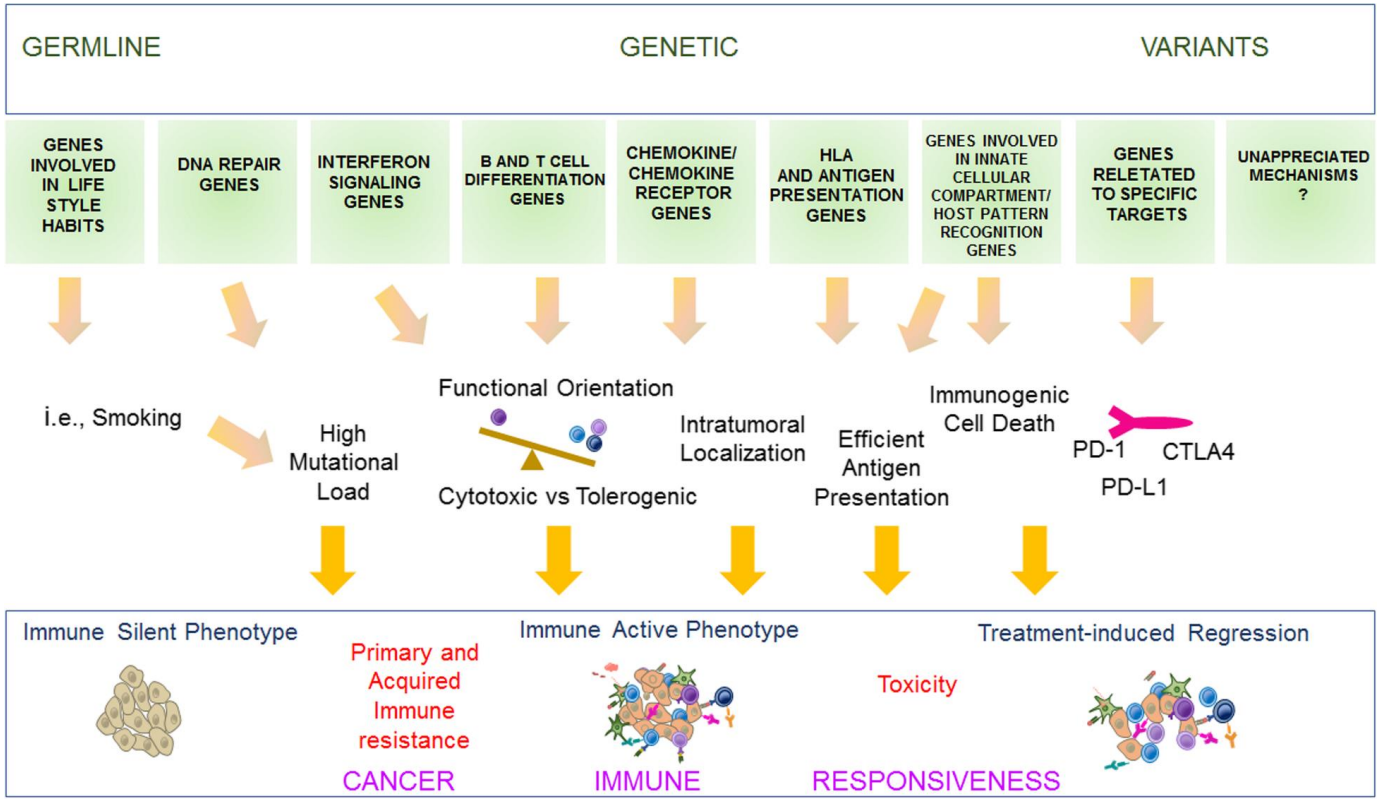
Journal for ImmunoTherapy of Cancer

REVIEW Open Access

Toward a comprehensive view of cancer immune responsiveness: a synopsis from the SITC workshop

Davide Bedognetti[1†], Michele Ceccarelli[2], Lorenzo Galluzzi[3,4,5], Rongze Lu[2†], Karolina Palucka[6], Josue Samayoa[2†], Stefani Spranger[7†], Sarah Warren[8†], Kwok-Kin Wong[9], Elad Ziv[10], Diego Chowell[11], Lisa M. Coussens[12], Daniel D. De Carvalho[13], David G. DeNardo[14], Jérôme Galon[15], Howard L. Kaufman[16], Tomas Kirchhoff[17], Michael T. Lotze[18], Jason J. Luke[19], Andy J. Minn[20], Katerina Politi[21], Leonard D. Shultz[22], Richard Simon[23], Vésteinn Thórsson[24], Joanne B. Weidhaas[25], Maria Libera Ascierto[26], Paolo Antonio Ascierto[27], James M. Barnes[2], Valentin Barsan[28], Praveen K. Bommareddy[29], Adrian Bot[30], Sarah E. Church[8], Gennaro Ciliberto[31], Andrea De Maria[32], Dobrin Draganov[33], Winson S. Ho[34], Heather M. McGee[35], Anne Monette[36], Joseph F. Murphy[37], Paola Nistico[31], Wungki Park[11], Maulik Patel[2], Michael Quigley[38], Laszlo Radvanyi[39], Harry Raftopoulos[40], Nils-Petter Rudqvist[3], Alexandra Snyder[41], Randy F. Sweis[19], Sara Valpione[42], Roberta Zappasodi[47,48], Lisa H. Butterfield[43], Mary L. Disis[44], Bernard A. Fox[45], Alessandra Cesano[8], Francesco M. Marincola[46*] and Society for Immunotherapy of Cancer (SITC) Cancer Immune Responsiveness Task Force and Working Groups

Determinants of Immune Responsiveness



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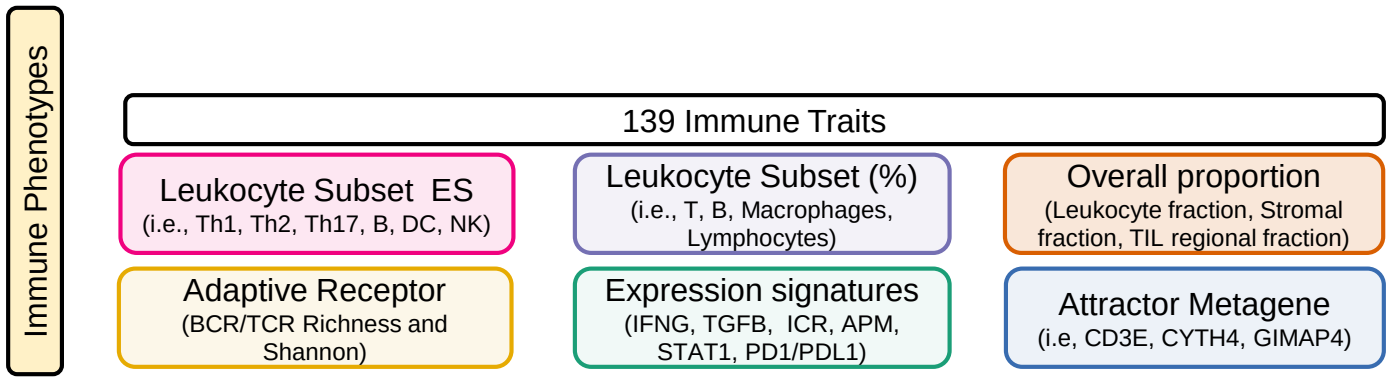
PanImmune Germline Working Group

Sayaman R*, Saad M*, Thorsson V, Hu D, Hendrickx W, Roelands J, Mokrab Y, Farshidfar F, Kirchhoff T, Sweis RS, Bathe OD, Porta-Pardo E, Campbell MJ, Stretch C, Hu D, Huntsman S, Graff RE, Syed N, Radvanyi L, Shelley S, Wolf D, Marincola FM, **Ceccarelli M**, Galon J, Ziv E#, Bedognetti D#

Aim: To define wether and how common and rare variants influence the functional orientation of the tumor immune microenviroment

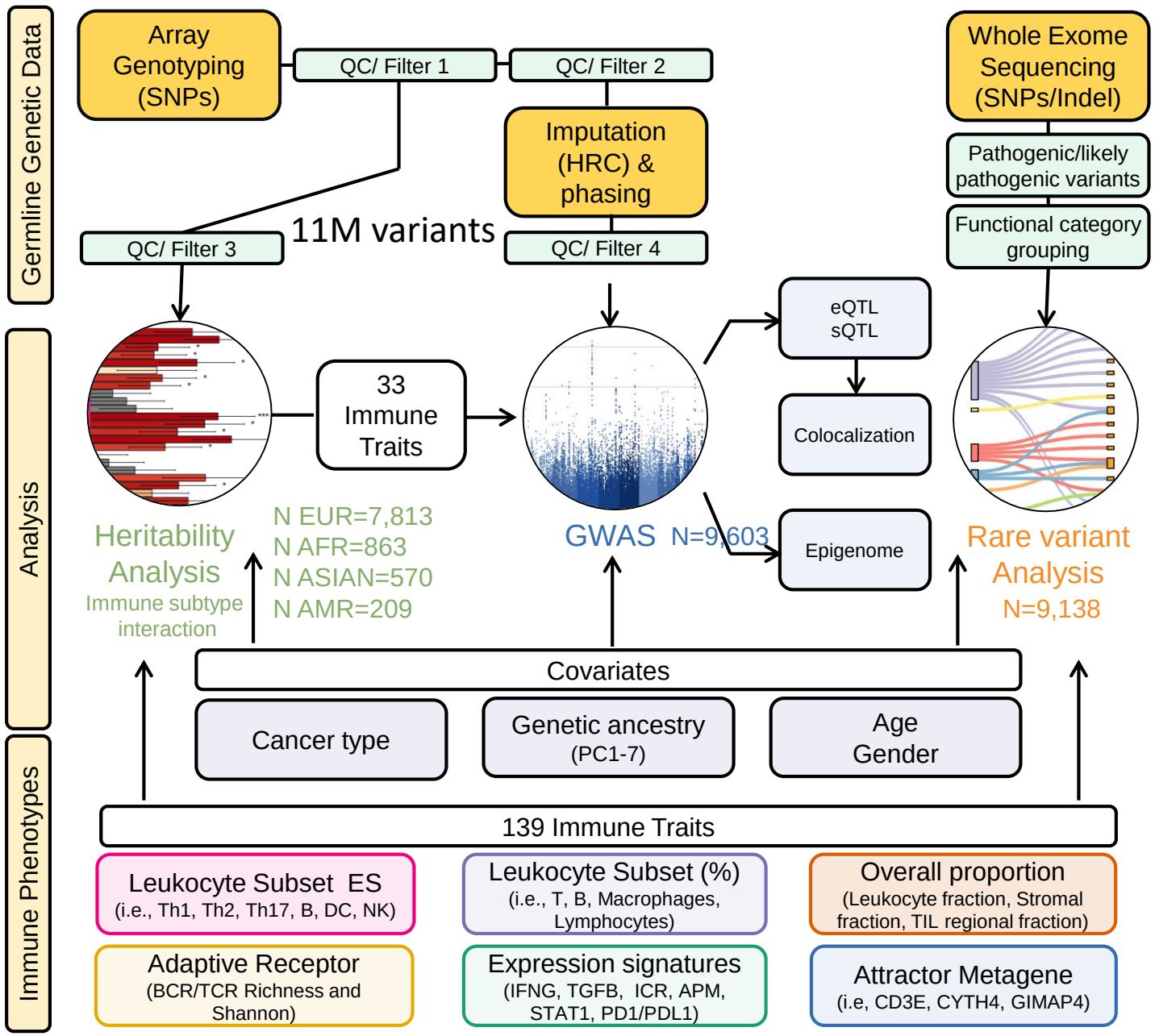
Sayaman et al, *Immunity 2021*

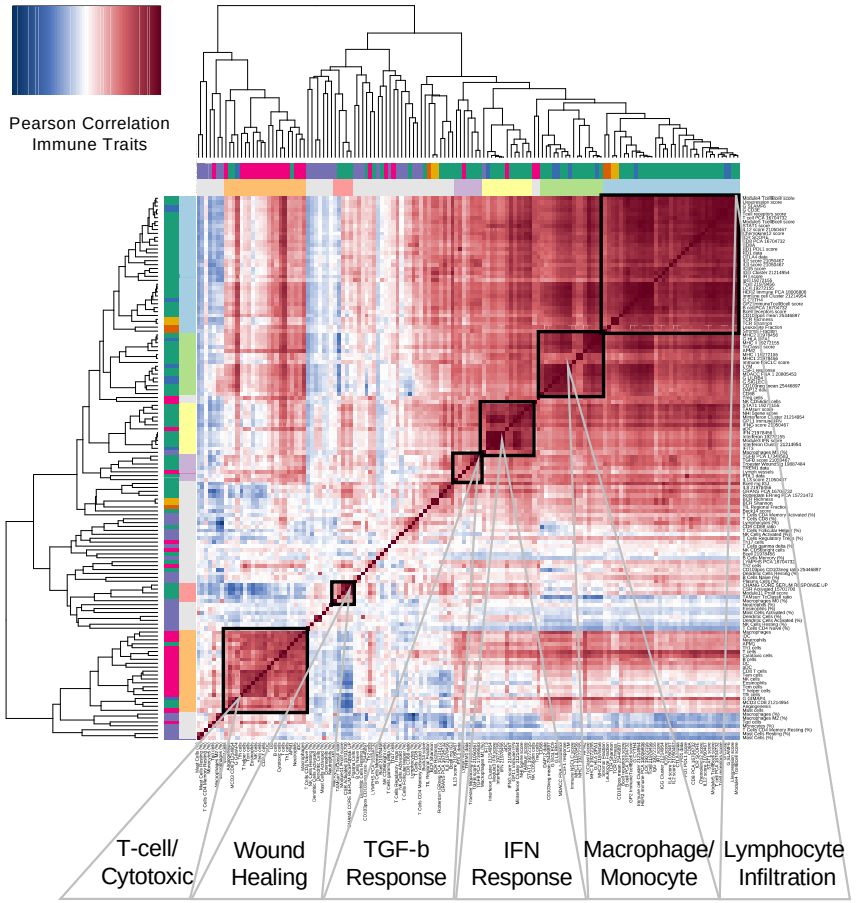
Immune traits



Sayaman et al, *Immunity 2021*

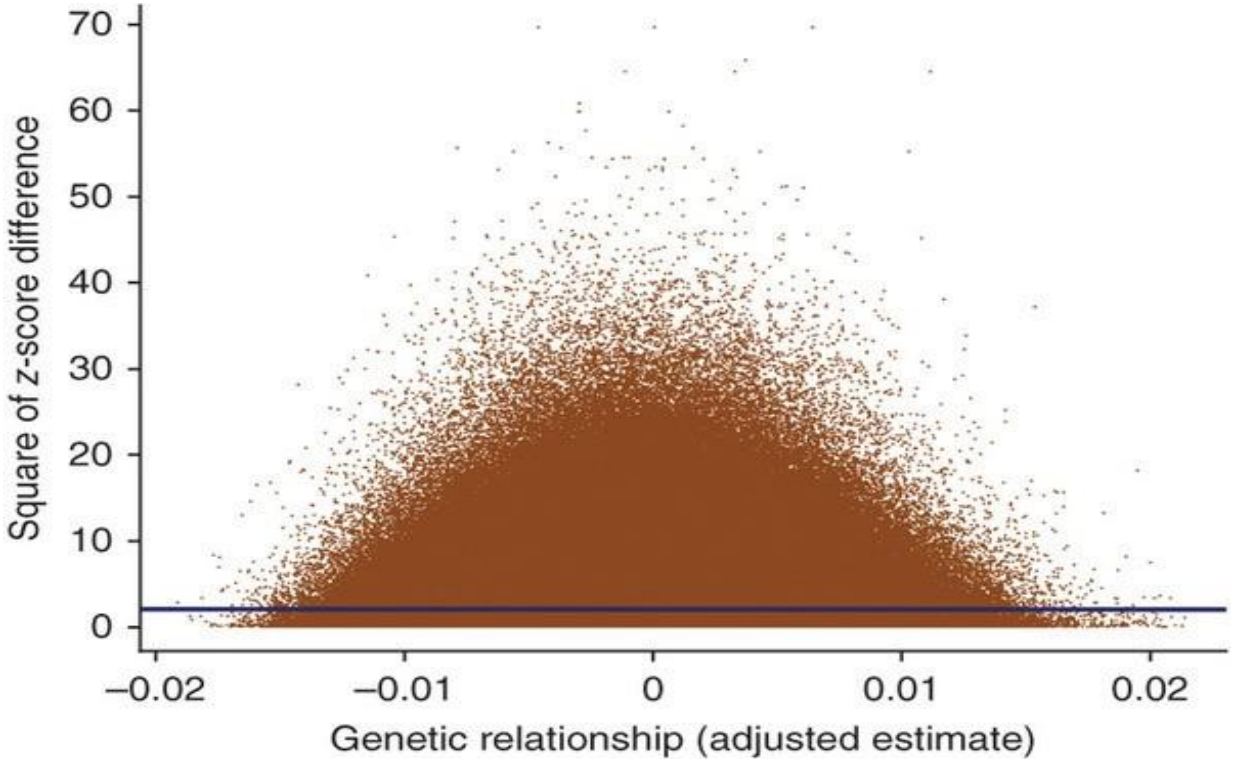
Discovery Approach





Sayaman et al, *Immunity 2021*

Heritability



Measure of the fraction of phenotypic variation contributed by genotypic variation

Heritability

Is the immune resonse against tumors heritable ?

To what degree germline genetic variants influence the diversity of anti-tumor immunity observed across patients?

Heritability

GCTA GREML approach which simultaneously models the effect of all genetic variants (MAF > 0.01) (Yang et al., 2010, 2011)

GREML calculates a genetic relatedness matrix (GRM) as a measure of the genetic similarity of unrelated individuals and compares it to the similarity of the measured immunological traits to calculate the total contribution of genotypic variance to overall phenotypic variance

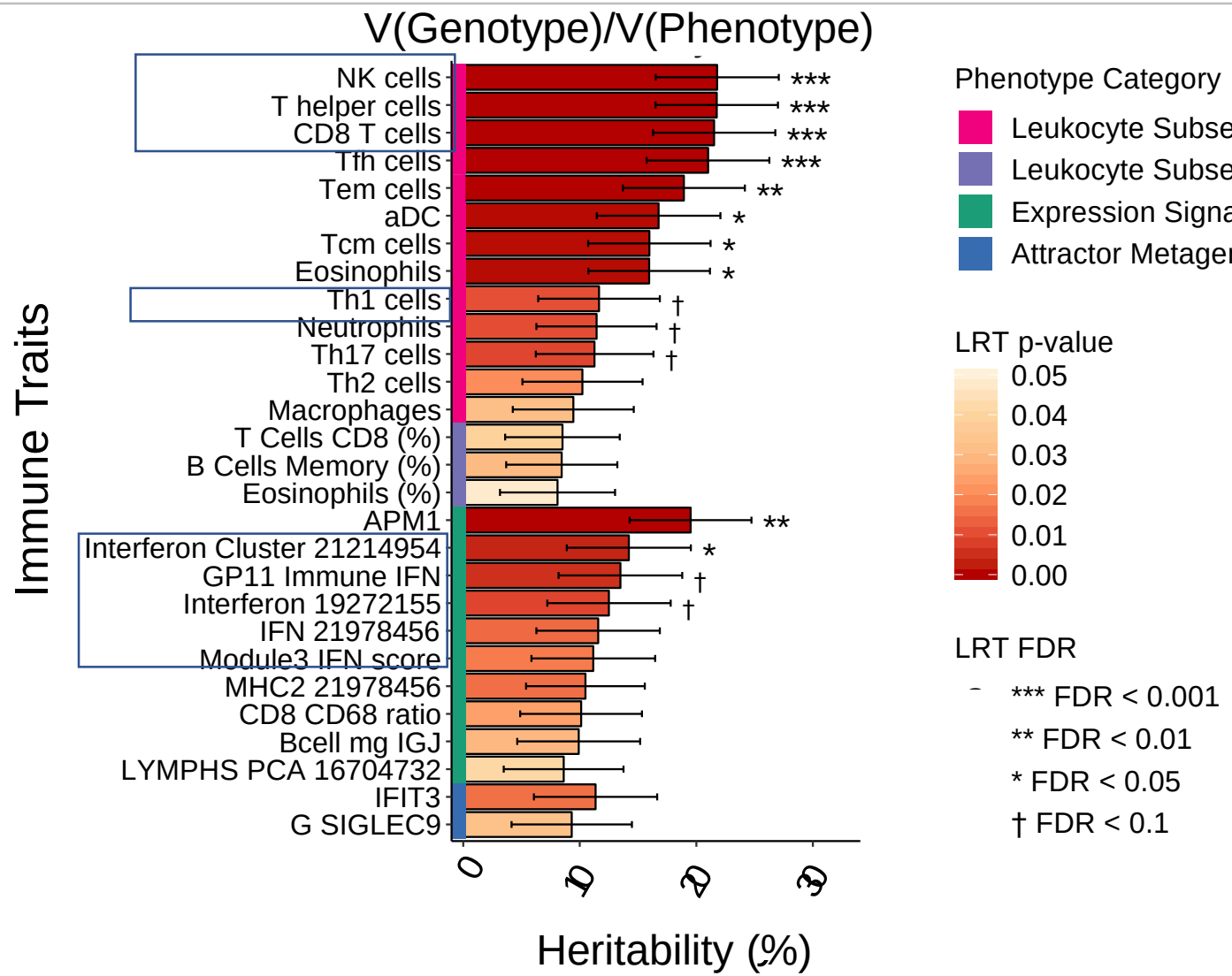
V(Genotype)/V(Phenotype) → % Heritability

(Requires large sample size, > 1000): Focus on EUR (N=7813)

Genome-wide heritability of immune traits

EUR
ANCESTRY
N =7,813

28 Heritable
Phenotypes



Sayaman et al, *Immunity 2021*

Main findings

- About 25% of the traits (33 of 139) were heritable
- The traits most strongly influenced by germline genetics include estimates of the abundance of cytotoxic T, NK, Tfh cells (heritability 20%), and IFN signaling (heritability 15%)
- These traits have been associated with favorable prognosis and/or responsiveness to immunotherapy

GWAS (on 33 Heritable Traits)

Which common germline variants associate with immune traits ?

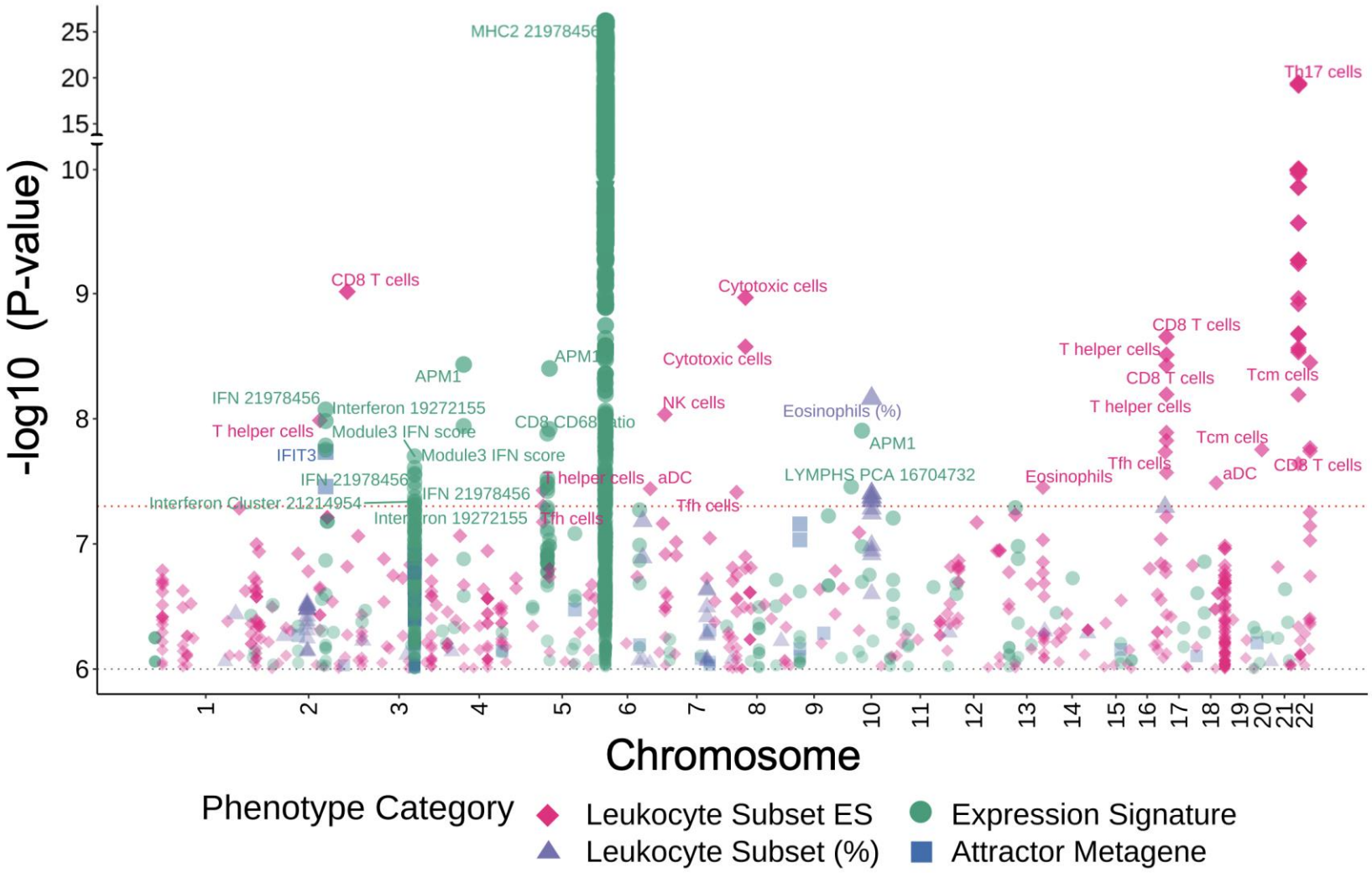
Genome-wide associations for variants affecting immune traits

21 Loci:

58 GW Significant associations (44 unique SNPs)

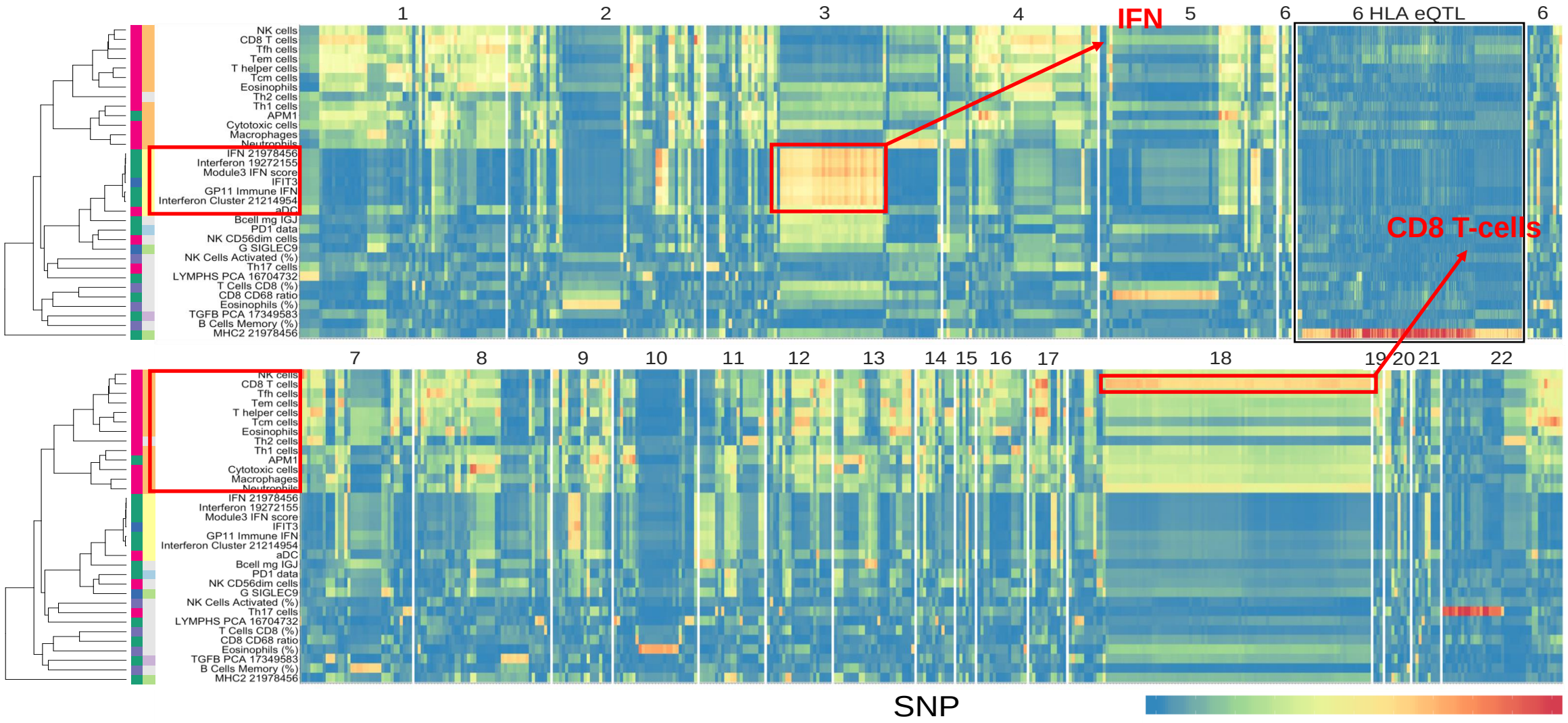
841 suggestive associations (667 unique SNPs)

(Excluding HLA and IL17RA loci)



Sayaman et al, *Immunity 2021*

Pleiotropy of the top GWAS associations across 33 immune traits



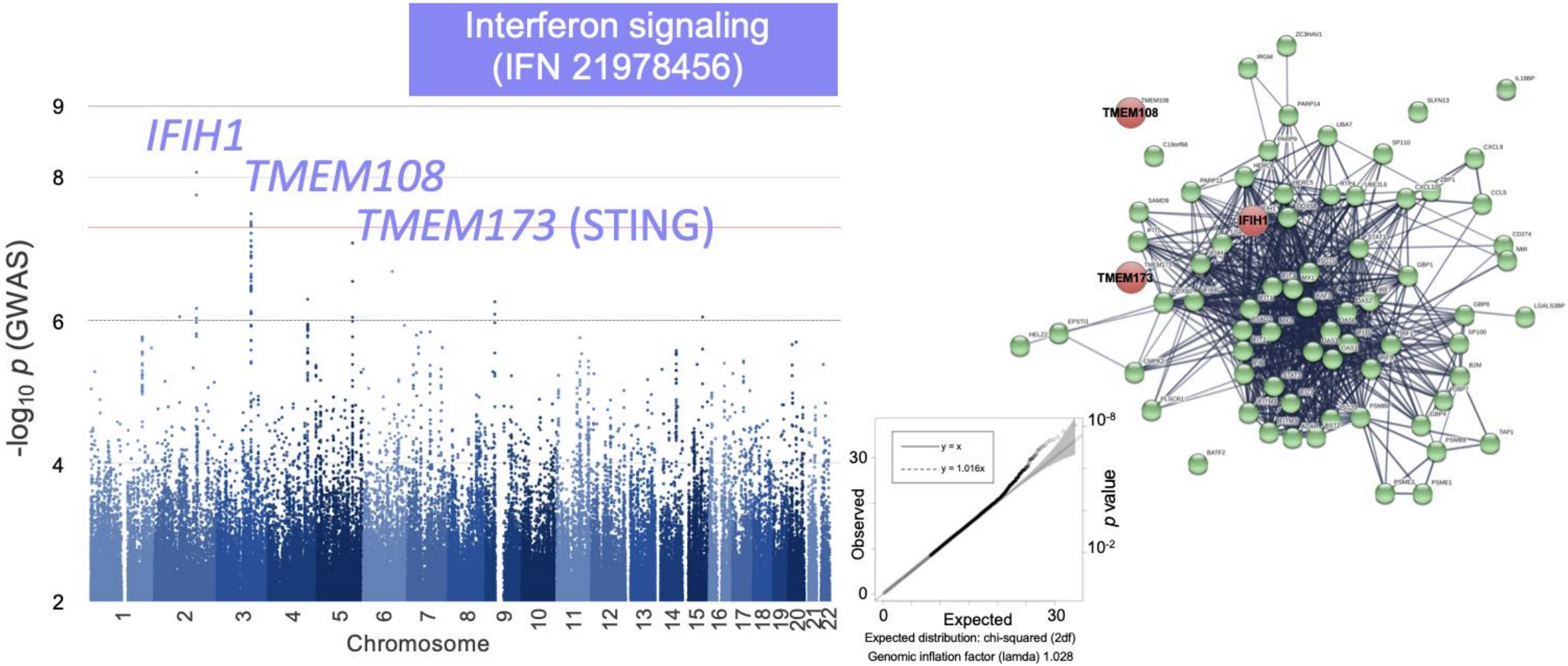
Immune Trait Category

- Leukocyte Subset ES
- Leukocyte Subset (%)
- Expression Signature
- Attractor Metagene

Immune Trait Module

- Lymphocyte Infiltration
- Macrophage/Monocyte
- IFN Response
- TGF-b Response
- T-cell/Cytotoxic
- Unassigned

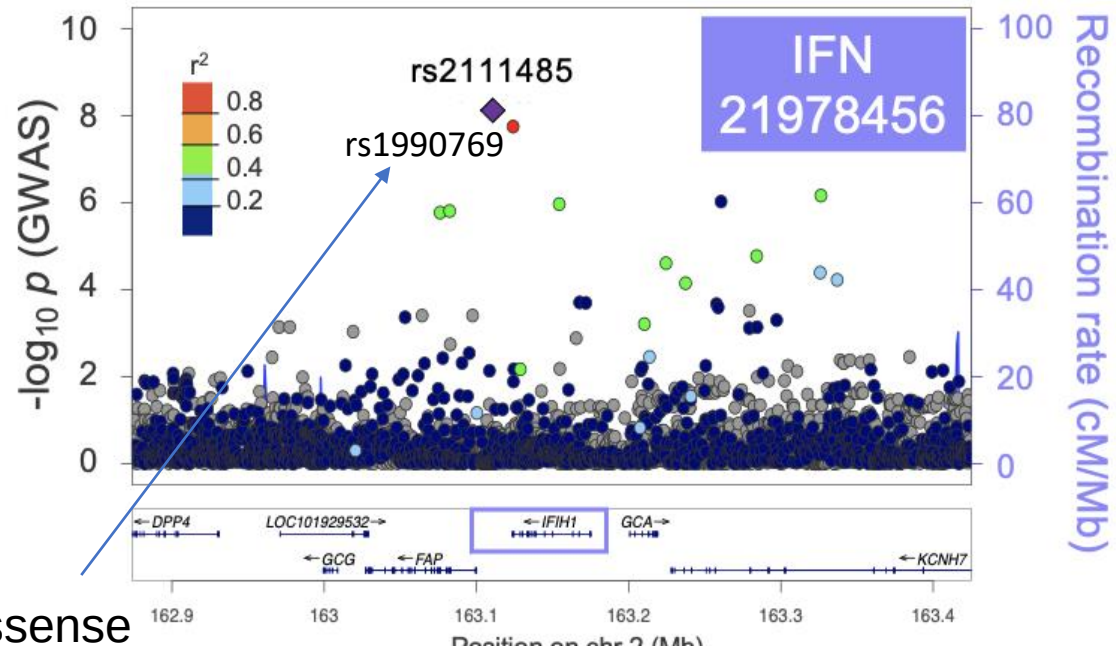
Interferon signaling



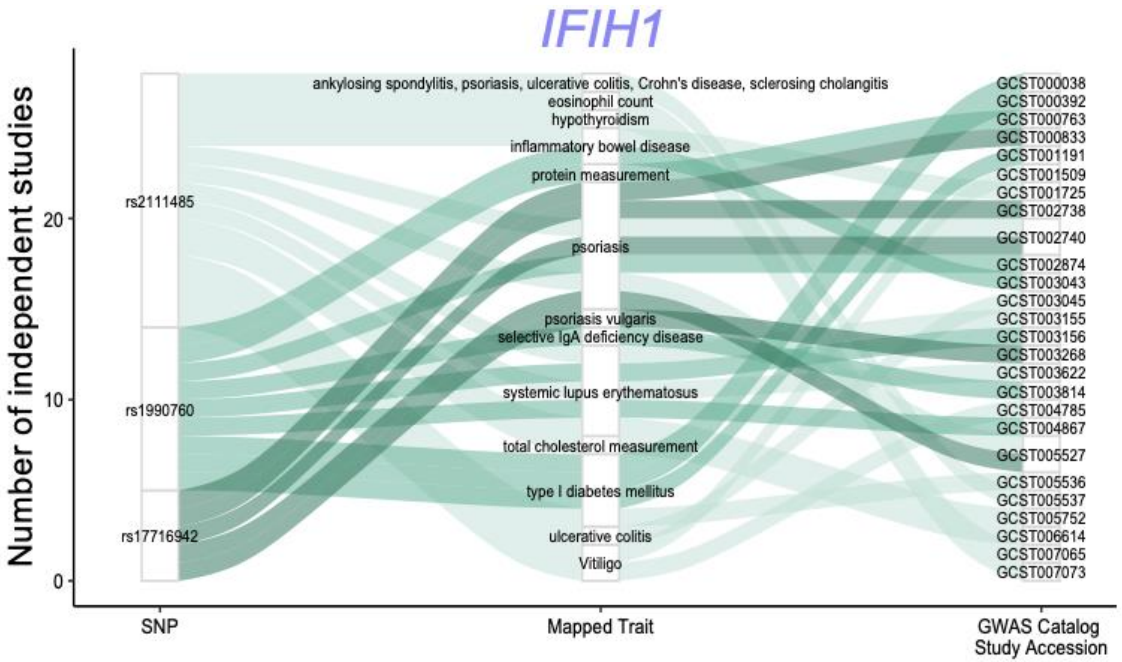
Sayaman et al, *Immunity 2021*

Interferon signaling - IFIH1

IFIH1: Interferon Induced With Helicase C Domain 1



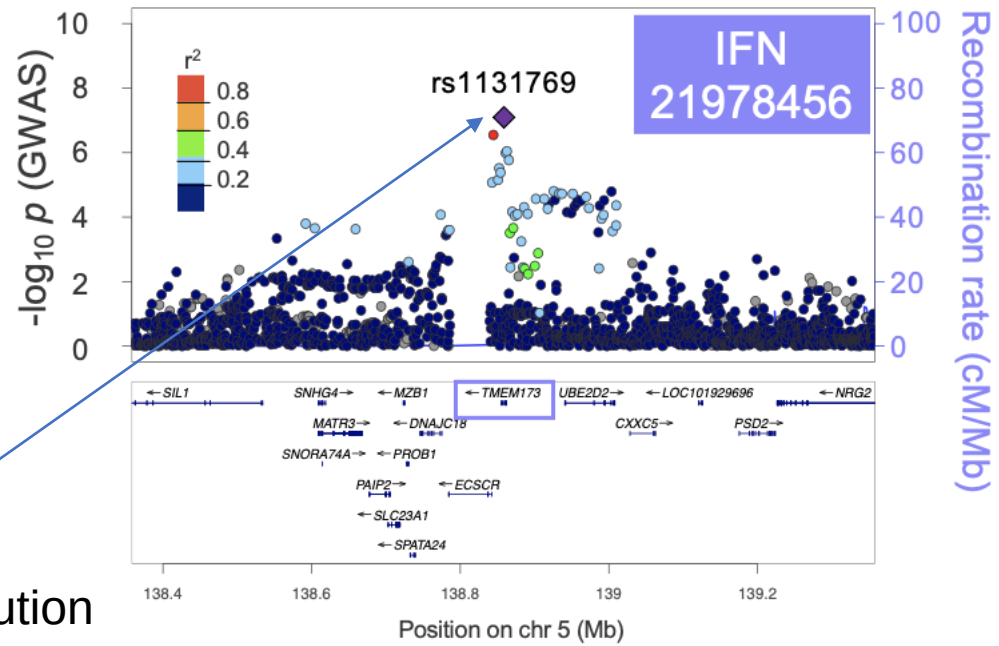
Missense



IFIH1
GWAS Studies in Aoutoimmune Diseases

Sayaman et al, *Immunity 2021*

Interferon signaling – TMEM173 (STING)



Missense

Arginin to Histidin Substitution

Sayaman et al, *Immunity 2021*

STING PATHWAY

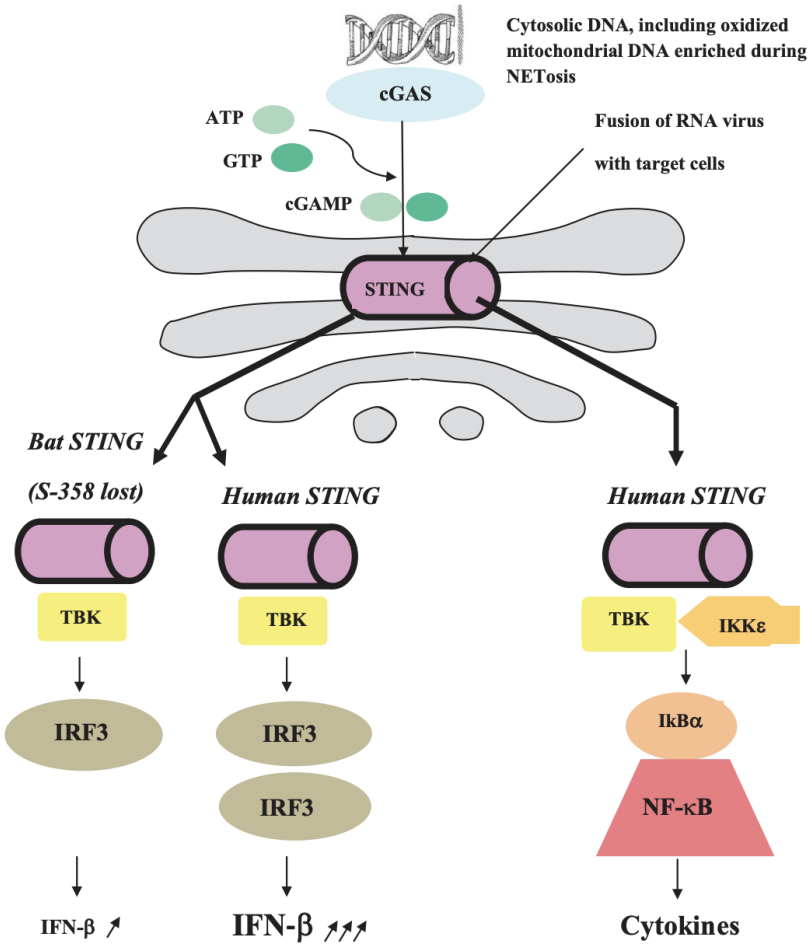
EBioMedicine
Published by THE LANCET

COMMENTARY | VOLUME 56, 102801, JUNE 01, 2020

COVID-19 as a STING disorder with delayed over-secretion of interferon-beta

Jean-Marie Berthelot • Frédéric Lioté

Open Access • Published: May 23, 2020 • DOI: https://doi.org/10.1016/j.ebiom.2020.102801 • Check for updates



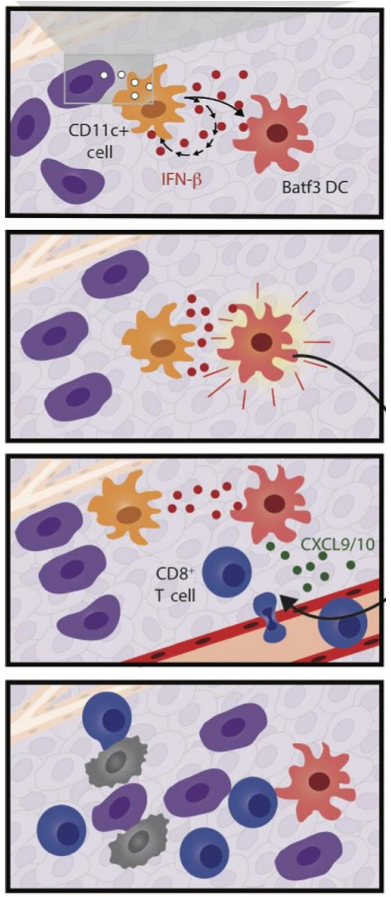
Received: 2 March 2019 | Accepted: 4 April 2019
DOI: 10.1111/imr.12765

INVITED REVIEW

WILEY Immunological Reviews

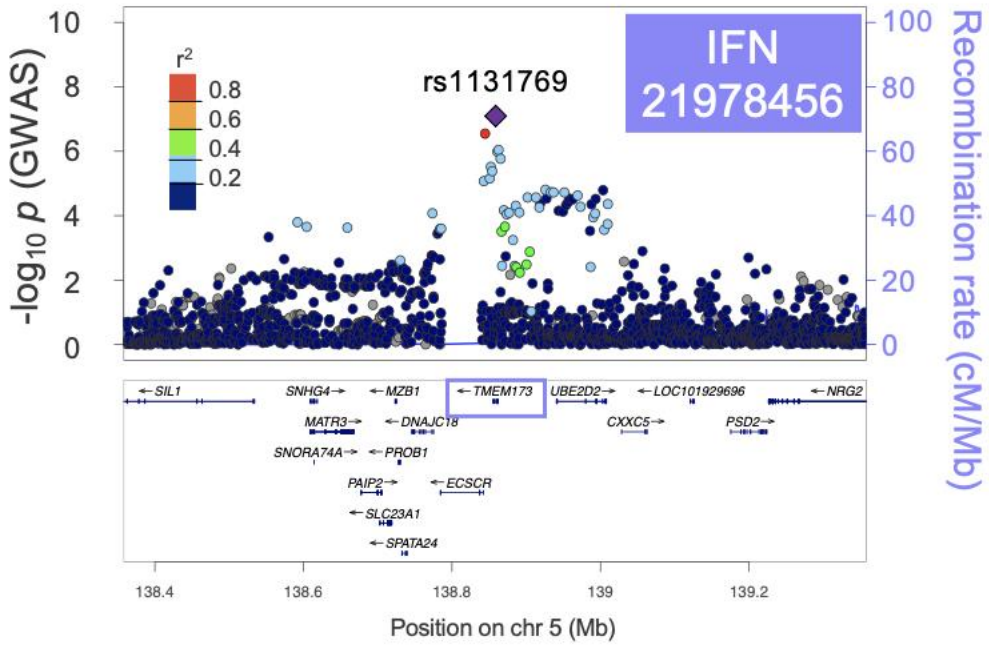
STING pathway agonism as a cancer therapeutic

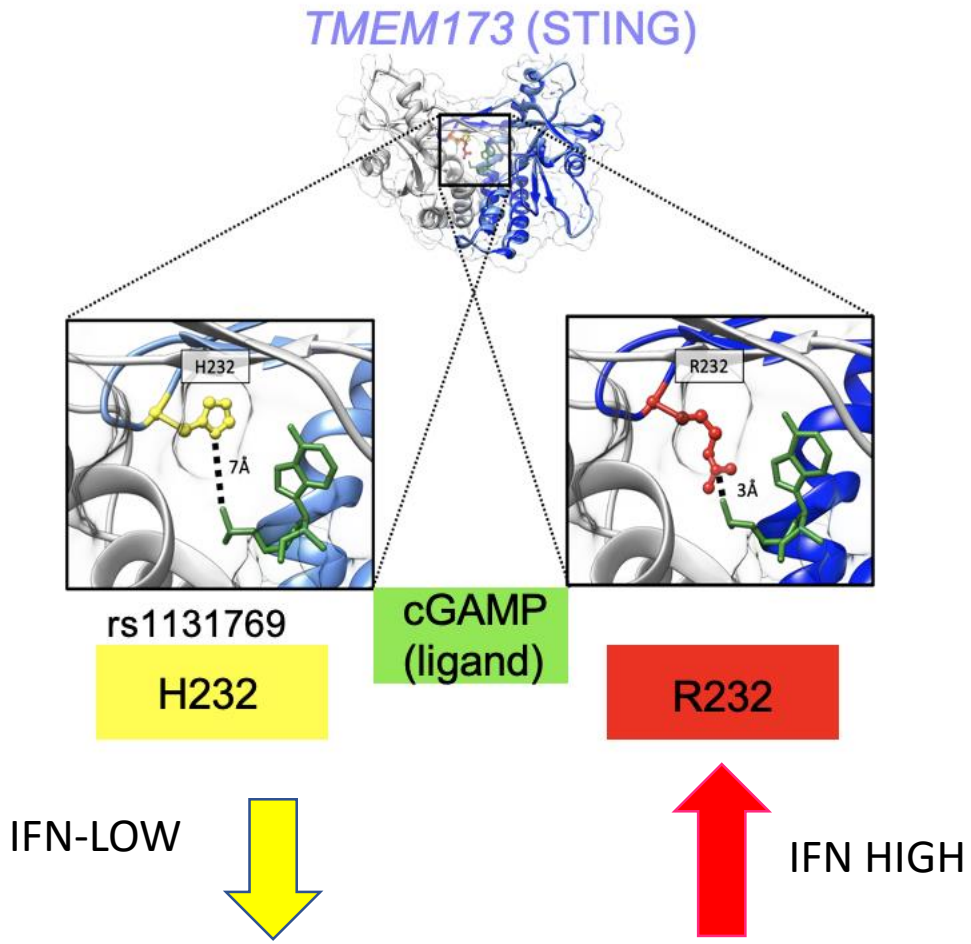
Blake A. Flood[1] | Emily F. Higgs[1] | Shuyin Li[1] | Jason J. Luke[2] | Thomas F. Gajewski[1,2]



Interferon signaling – TMEM173 (STING)

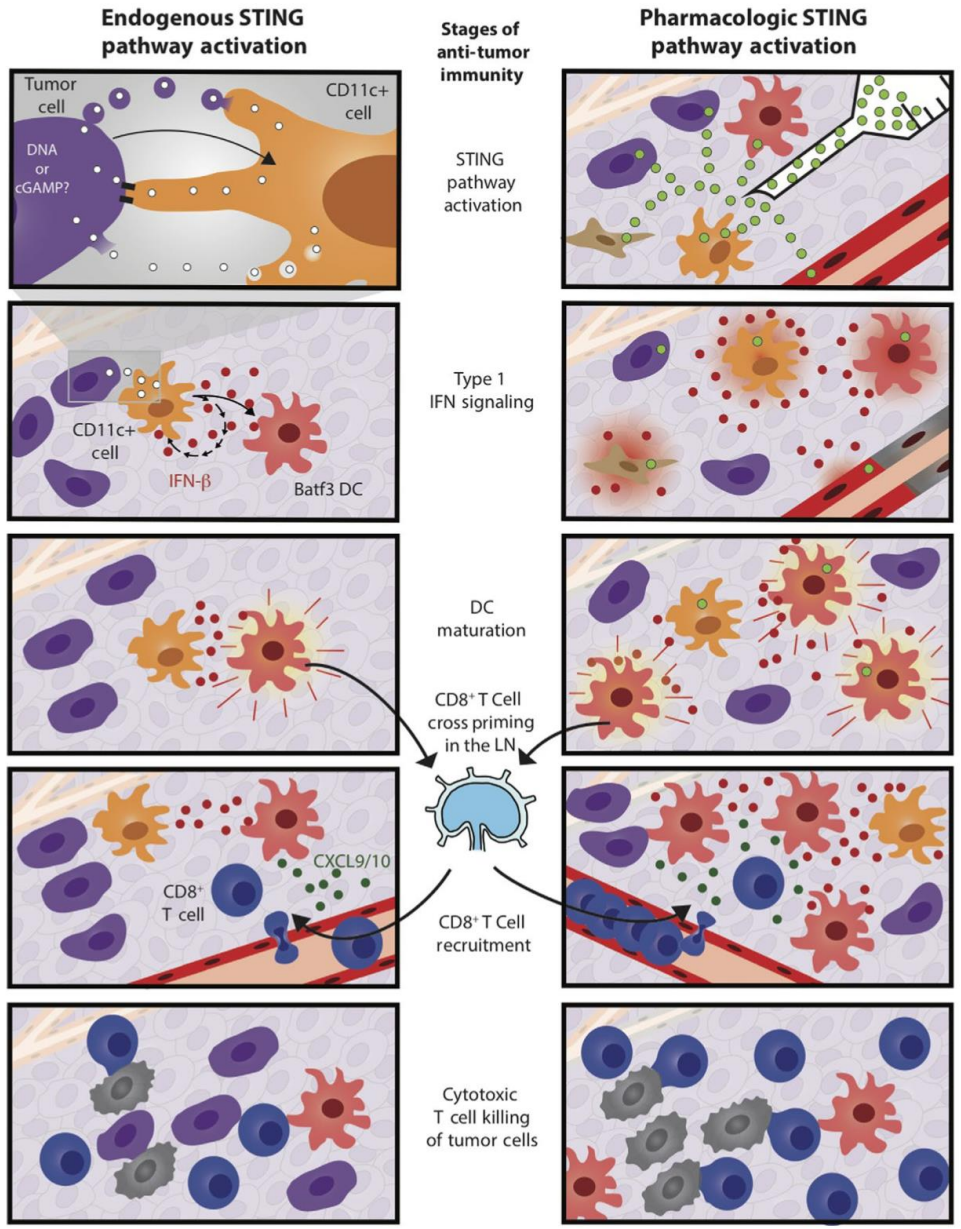
Arginin to Histidin Substitution

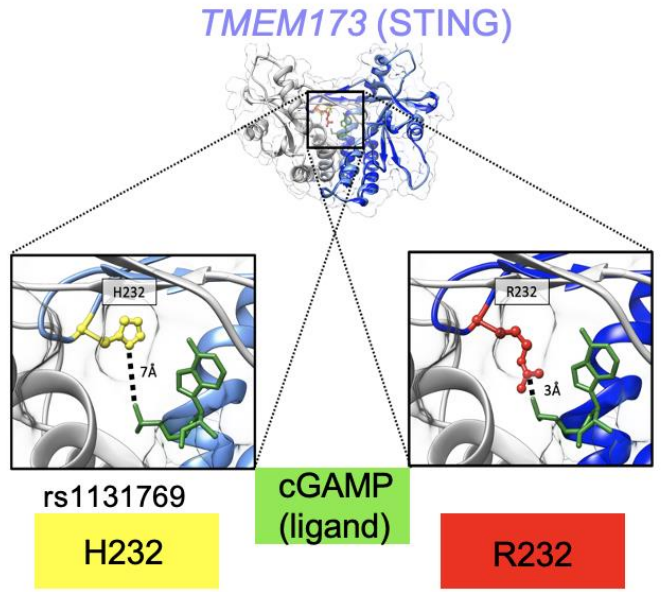




Sayaman et al, *Immunity 2021*

TARGETING STING





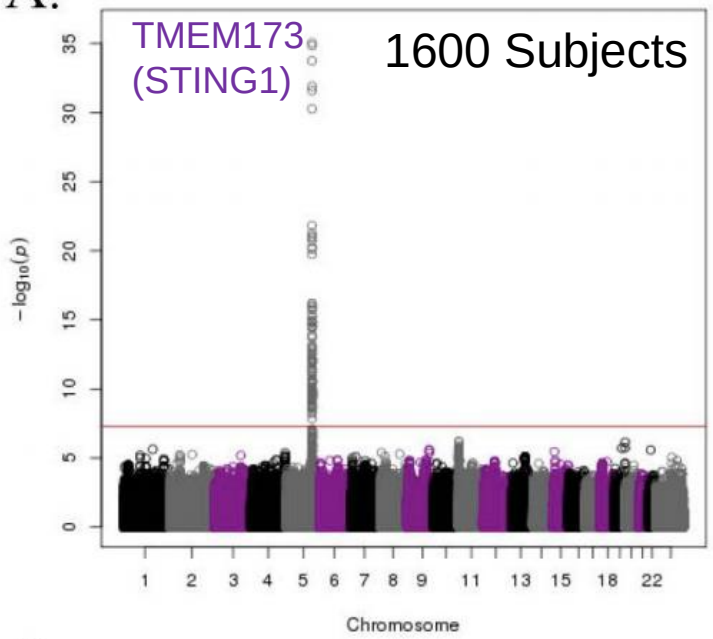
TMEM173 variants and anti-viral response

Frontiers Immunology 2021

Polymorphisms in STING affect human innate immune responses to poxviruses

Richard B. Kennedy, PhD[1*]; Iana H. Haralambieva, PhD[1]; Inna G. Ovsyannikova, PhD[1]; Emily A. Voigt, PhD[1]; Beth R. Larrabee[2]; Daniel J. Schaid, PhD[2]; Michael T. Zimmermann, PhD[3]; Ann L. Oberg, PhD[2]; Gregory A. Poland, MD[1]

A.

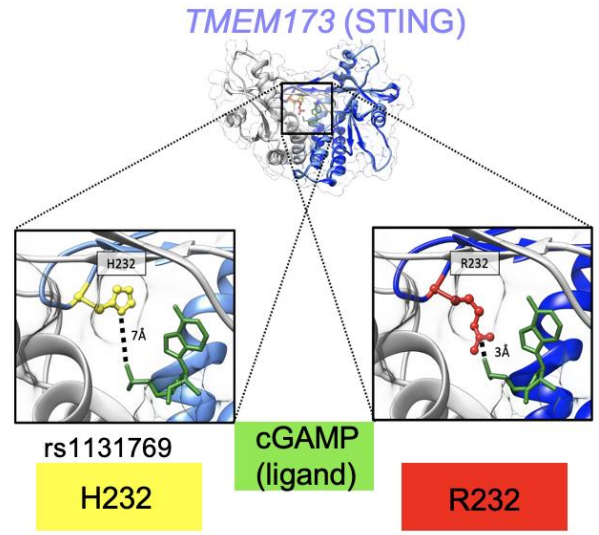


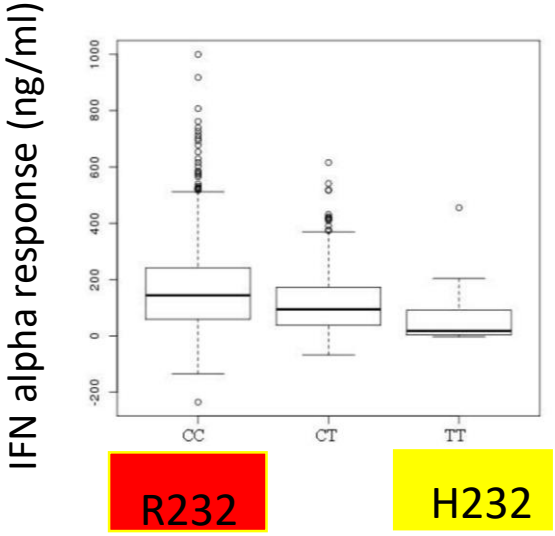
C

Table 1. Top SNPs significantly associated with vaccinia virus-specific IFNα secretion.

Table 1. Top SNPs significantly associated with vaccinia virus-specific IFNα secretion								
SNP	**Chromosome Location**	**Gene**	**SNP Function**	**Gene Location**	**p-value**	**Minor allele**	**Major allele**	**MAF**
rs7447927	138861146	TMEM173	protein-coding	synonymous	1.49E-36	C	G	34.7%
rs13166214	138862744	TMEM173	protein-coding	5'upstream	8.92E-36	A	G	35.3%
rs7444313	138865423	TMEM173	protein-coding	5'upstream	1.41E-35	G	A	34.5%
rs13181561	138850905	TMEM173	protein-coding	3'downstream	1.81E-34	G	A	30.0%
rs55792153	138854203	TMEM173	protein-coding	3'downstream	1.26E-32	A	C	34.2%
rs13153461	138852369	TMEM173	protein-coding	3'downstream	2.61E-32	G	A	31.4%
rs9716069	138842818	ECSCR	protein-coding	5'upstream	5.32E-31	T	A	31.3%
rs28419191	138844599	ECSCR	protein-coding	5'upstream	1.50E-22	T	C	13.2%
rs1131769	***138857919***	***TMEM173***	***protein-coding***	***missense***	**5.25E-22**	***T***	***C***	**14.0%**
rs11934037	138783832	RNU5B-4P	pseudo	3'downstream	8.99E-22	C	G	32.5%
rs36137978	138785565	ECSCR	protein-coding	5'upstream	1.13E-21	C	A	31.6%
rs10875554	138847652	ECSCR	protein-coding	5'upstream	1.99E-21	A	C	15.4%
rs6596479	138780599	RNU5B-4P	pseudo	5'upstream	5.63E-21	C	T	31.9%
rs7446197	138783734	RNU5B-4P	pseudo	3'downstream	7.51E-21	A	G	33.8%
rs10463977	138781765	RNU5B-4P	pseudo	5'upstream	1.80E-20	C	T	32.4%
rs2434576	138917674	UBE2D2	protein-coding	5'upstream	6.57E-17	G	A	30.8%
rs34530489	138873627	LOC642262	pseudo	gene	7.00E-17	G	A	31.4%
rs35779874	138869847	LOC642262	pseudo	5'upstream	1.11E-16	A	G	31.2%
rs7378724	138876953	LOC642262	pseudo	gene	1.13E-16	G	A	30.9%
rs78233829	**138857925**	**TMEM173**	**protein-coding**	**missense**	**3.16E-13**	**G**	**C**	**17.6%**
rs11554776	**138861078**	**TMEM173**	**protein-coding**	**missense**	**1.05E-12**	**T**	**C**	**16.5%**
rs7380824	**138856982**	**TMEM173**	**protein-coding**	**missense**	**1.25E-12**	**T**	**C**	**17.7%**

MAF: Minor allele frequency. Bold, italics – SNP studied in this report. Bold – SNPs in HAQ STING haplotype.





Colocalization: causal genes

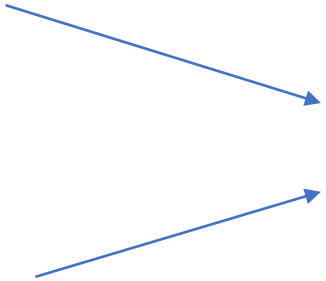
Non Protein Coding SNPs (>99% of the GW and suggestive associations)

Expression

eQTL in TCGA and GTEX

Splicing

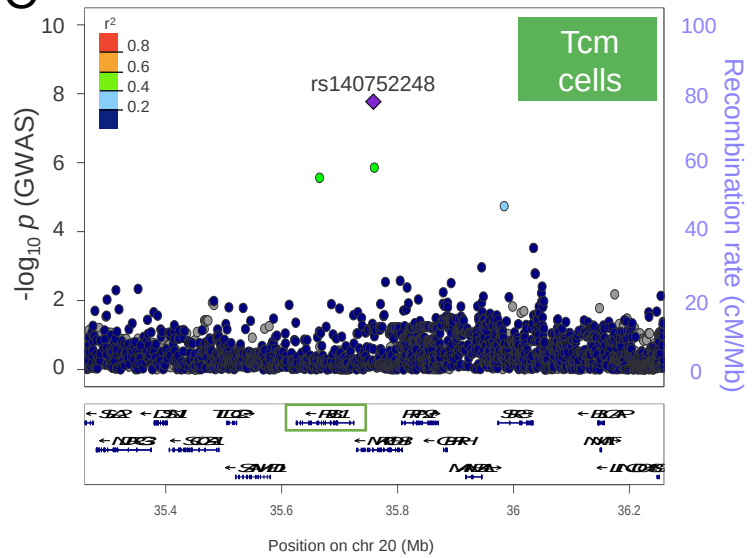
sQTL in TCGA and GTEX



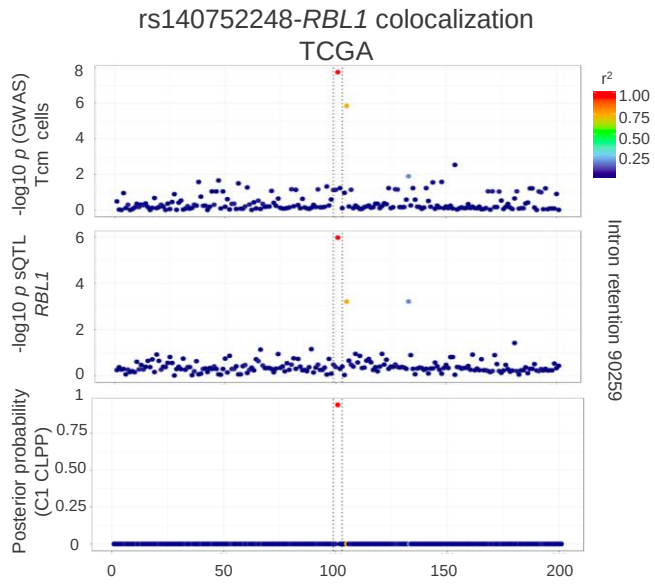
Colocalization

Colocalization: causal genes

C

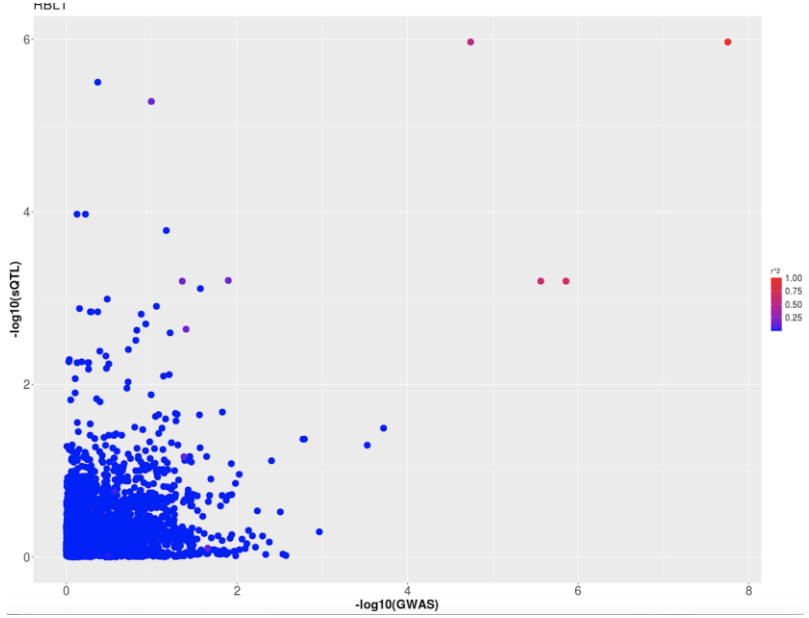


eCaviar



+/- 100 SNPS

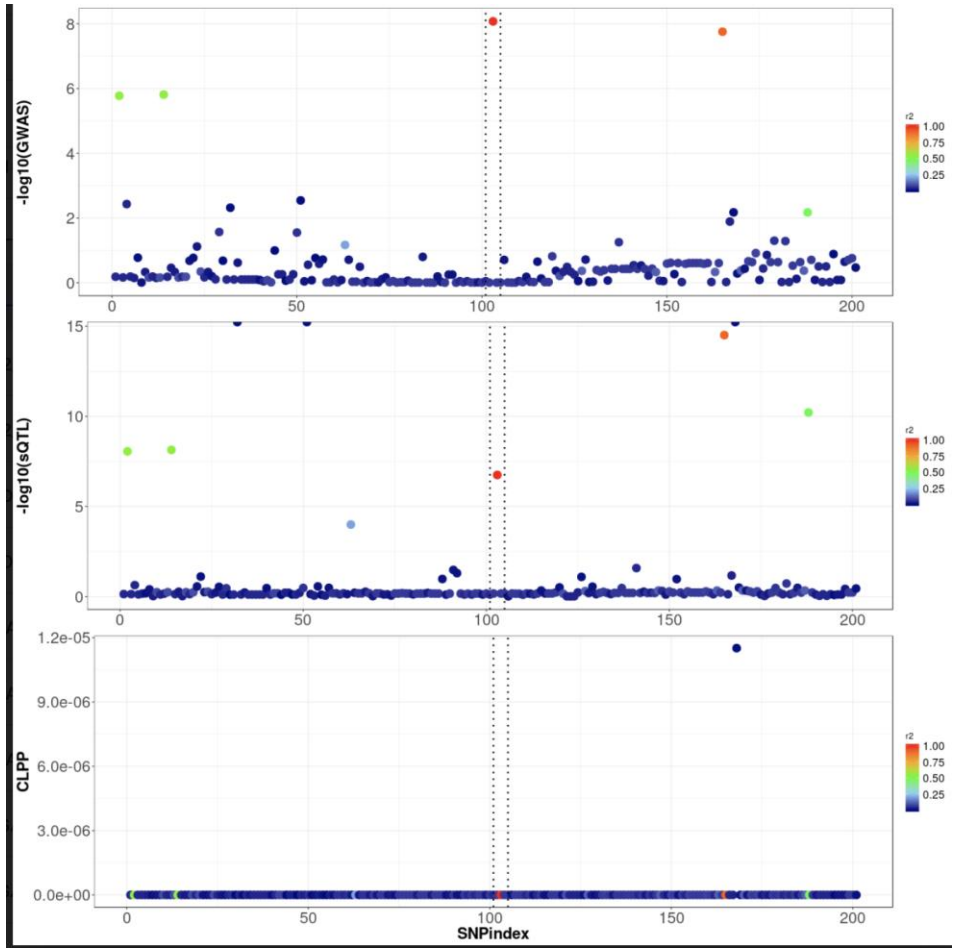
Expanded Region

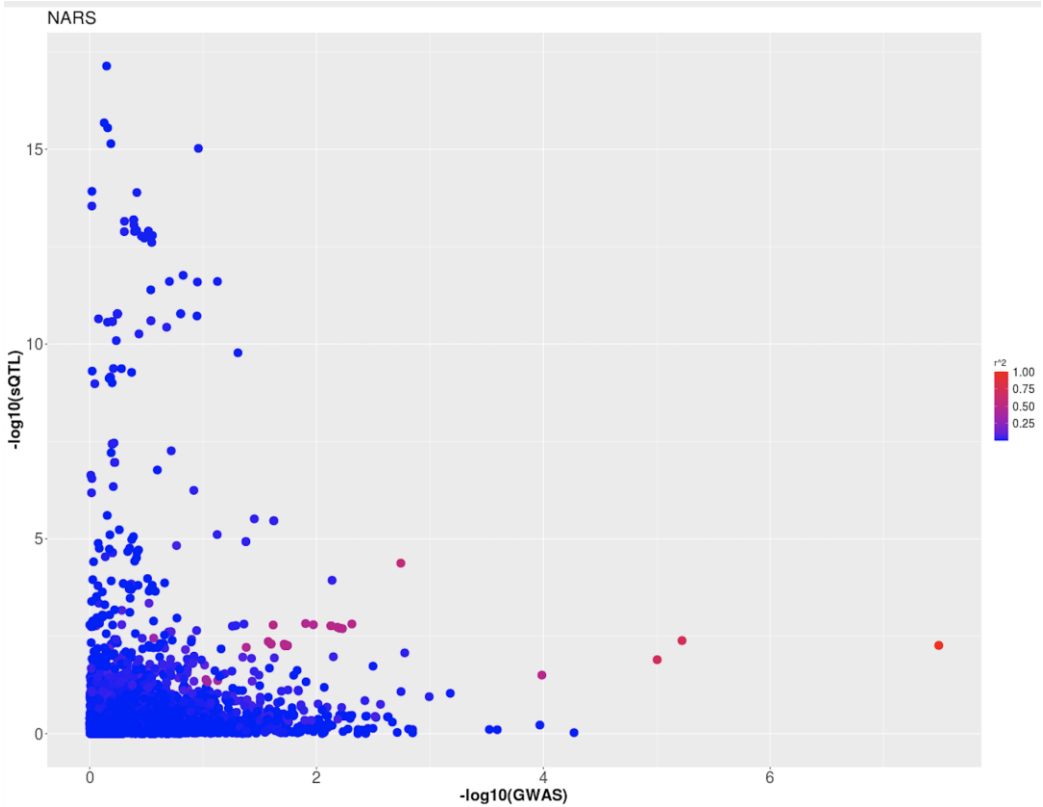


SNPs at +/- 500KB (for sQTL and 1MB for eQTL)

86 GW significant Hits Colocalized with a given gene
(31 confirmed by expanded region colocalization analysis)

Example of Negative Clocalization



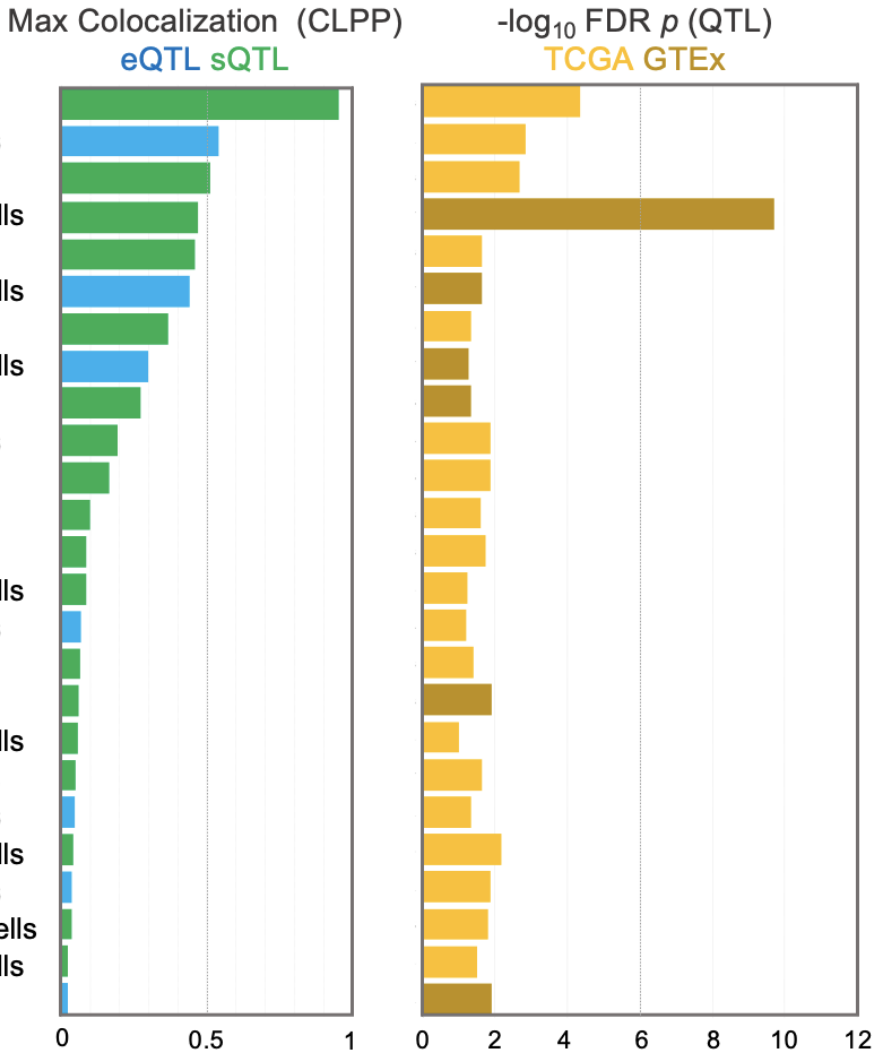


Colocalization: causal genes

86 GW significant colocalization (31 confirmed by expanded region colocalization analysis)

Genetic variants and candidate genes associated with T cell subset ES

Chr	Locus	SNP	Gene	Trait
20	21	rs140752248	*RBL1***	Tcm cells
22	23	rs572393792	*FBLN1*	CD8 T cells
20	21	rs140752248	*RPN2**	Tcm cells
17	19	rs112236917	*P2RX5*	T helper cells
20	21	rs140752248	*SRC*	Tcm cells
17	19	rs112236917	*P2RX1*	T helper cells
5	8	rs75108285	*DMGDH*	APM1
17	19	rs112236917	*RP11-235E17.6*	T helper cells
7	11	rs74347256	*AP5Z1**	NK cells
17	19	rs138156694	*ITGAE (CD103)*	CD8 T cells
22	23	rs73889576	*ARHGAP8*	Tcm cells
22	23	rs11914148	*PRR5*	Tcm cells
8	12	rs71510648	*INTS10**	Tfh cells
17	19	rs112262673	*ZZEF1***	T helper cells
17	19	rs138156694	*C17orf85**	CD8 T cells
22	23	rs11914148	*PARVG**	Tcm cells
8	12	rs71510648	*INTS10***	Tfh cells
17	19	rs112262673	*ATP2A3**	T helper cells
13	17	rs77280007	*ITGBL1**	Eosinophils
22	23	rs572393792	*NUP50**	CD8 T cells
2	1	rs79671915	*LYPD6B**	T helper cells
22	23	rs572393792	*PNPLA5*	CD8 T cells
8	13	rs16889186	*IDO1**	Cytotoxic cells
5	6	rs147730683	*CWC27*	T helper cells
17	18	rs12939291	*RP11-676J12.6*	Tfh cells



Rare Variant Analysis (Cancer Predisposition Genes)

Focused on well-annotated, germline pathogenic or likely pathogenic cancer predisposition variants as previously defined (allele frequency in 1000 Genomes and ExAC (release r0.3.1) < 0.05%) (Huang et al., Cell 2018).

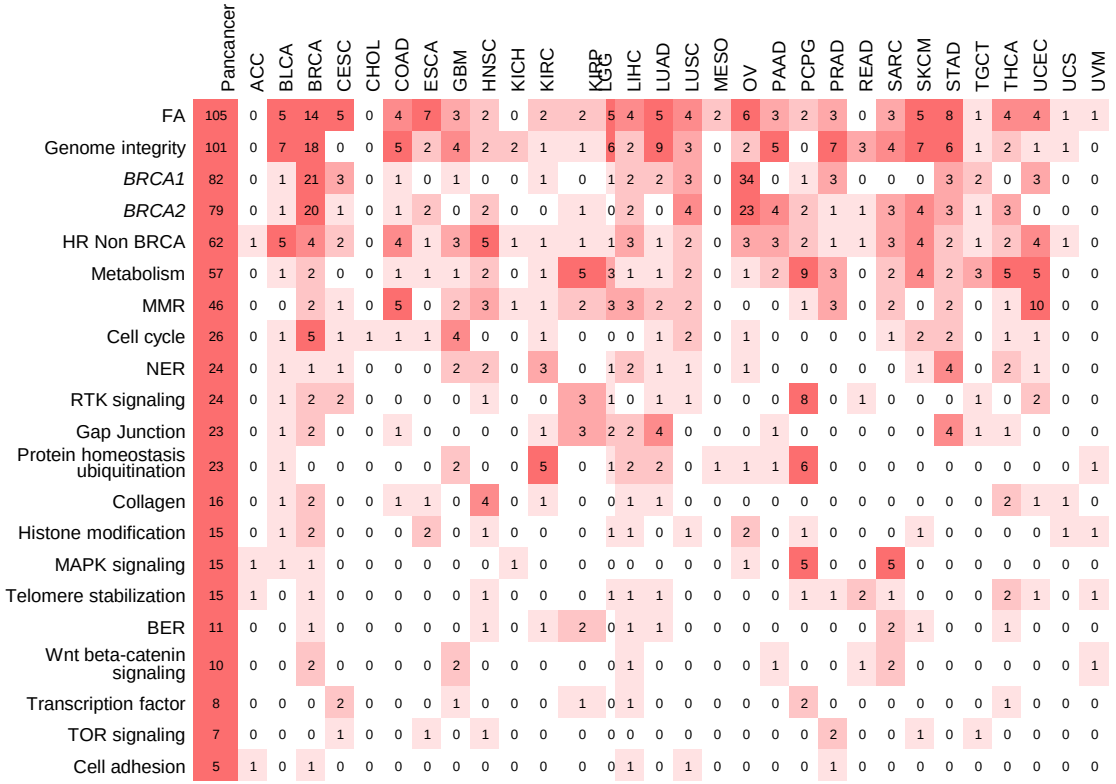
Exome files related to samples for which all the covariates (age, sex, cancer type, and PC1-7) and at least one immune trait was available were retained (N = 9,138).

832 pathogenic/likely pathogenic SNPs/Indels events with at least one copy of rare allele in the whole exome sequencing data, corresponding to 586 distinct pathogenic SNPs/Indels mapping to 99 genes.

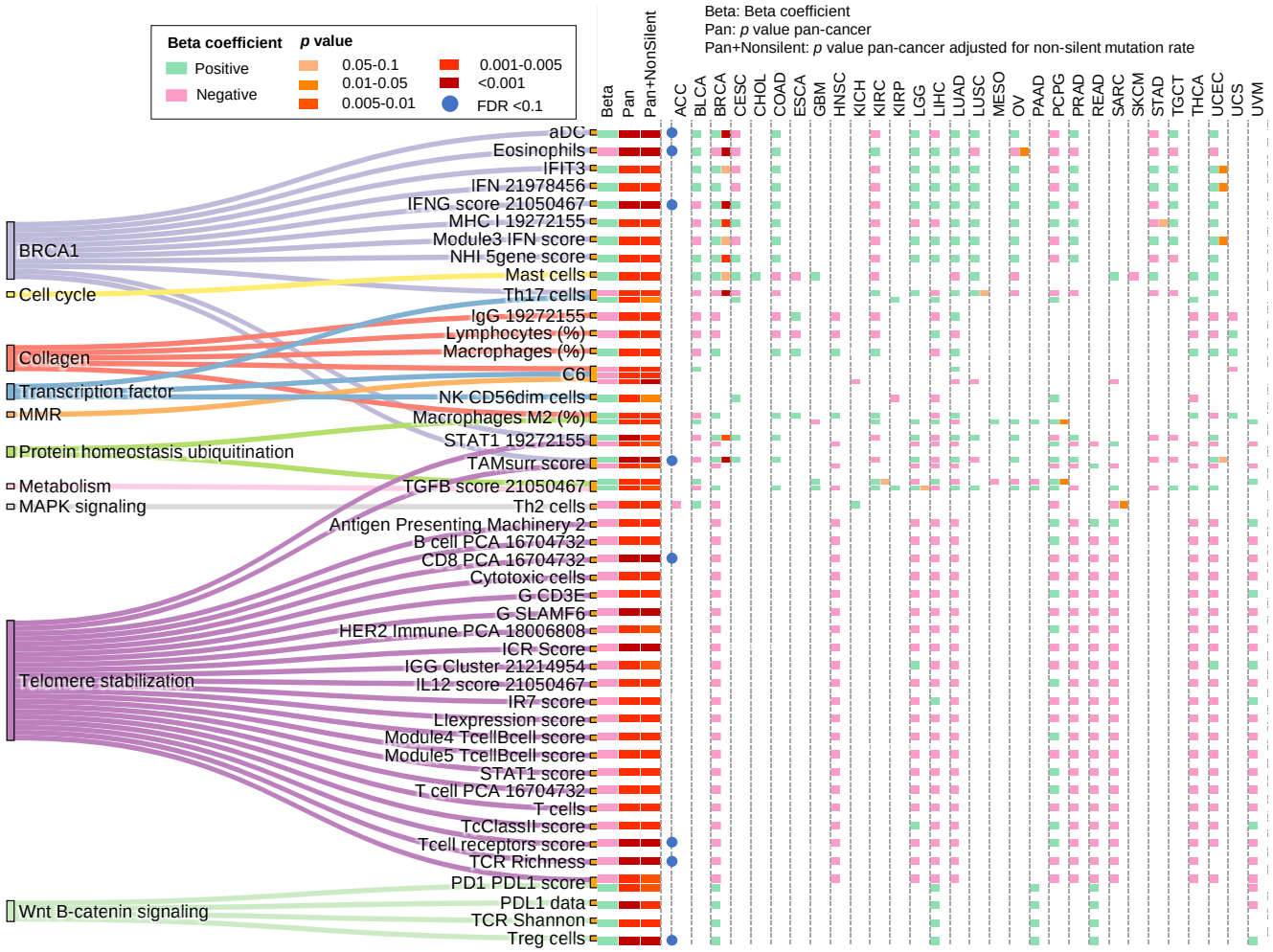
Rare Variant Analysis (Cancer Predisposition Genes)

Pathway burden analysis using selected pre-defined biological pathways: at least 5 events PanCancer (21 Genotypic Categories)

Pathway	Genes
BER (Base excision repair)	WRN, MUTYH
BRCA1	BRCA1
BRCA2	BRCA2
Cell adhesion	EPCAM, CDH1
Cell cycle	RB1, CDKN1B, CDKN2A, BUB1B, DOCK8
Collagen	COL7A1
FA (Fanconi anemia)	FANCE, FANCI, FANCC, FANCA, FANCG, FANCM, RAD51D, RAD51C, PALB2, BRIP1, ERCC4
Gap Junction	GJB2
Genome integrity	TP53, ATR, CHEK2, ATM
Histone modification	MEN1, PRDM9, JMJD1C
HR Non BRCA (Homologous recombination excluding BRCA1 and BRCA2)	POLH, BARD1, RAD50, NBN, BLM, RECQL4, RECQL
MAPK signaling	NF1
Metabolism	MTAP, HFE, FH, SDHD, SDHB, UROD, SDHA, FAH, EXT1, SDHC, GALNT3, EXT2
MMR (Mismatch repair)	MLH1, MSH2, MSH6, PMS2
NER (Nucleotide excision repair)	ERCC3, XPA, DDB2, POLD1, XPC, POLE
Protein homeostasis ubiquitination	CYLD, CBL, CTR9, BAP1, VHL
RTK signaling	MET, RET
Telomere stabilization	DKC1, POT1
TOR signaling	STK11, TSC2, TSC1
Transcription factor	MAX, HNF1A, PAX5, PHOX2B
Wnt B-catenin signaling	AXIN2, APC, PTCH1



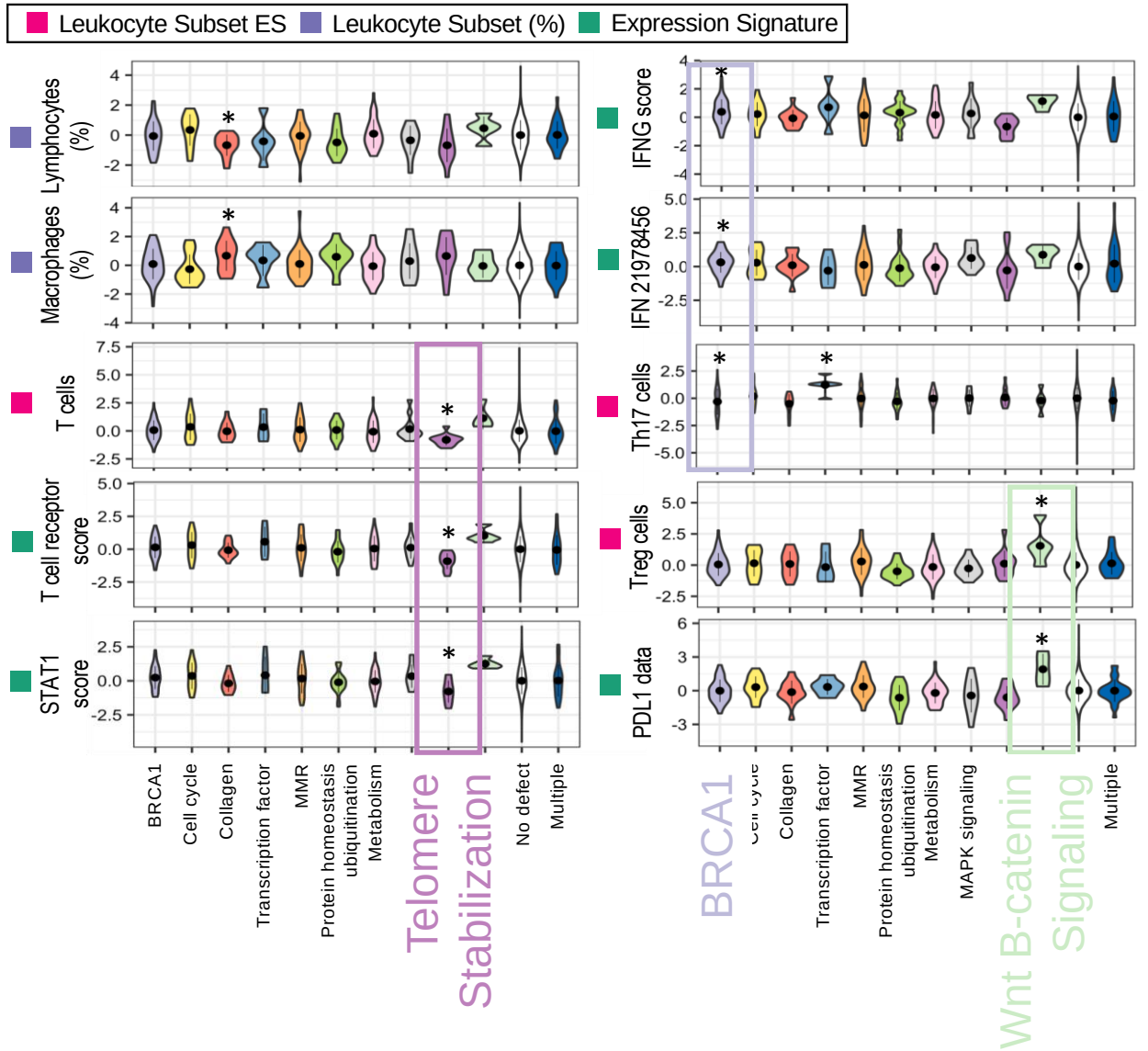
Rare Variant Analysis (Cancer Predisposition Genes)



10 Pathwat with p < 0.005

(3 with FDR < 0.1)

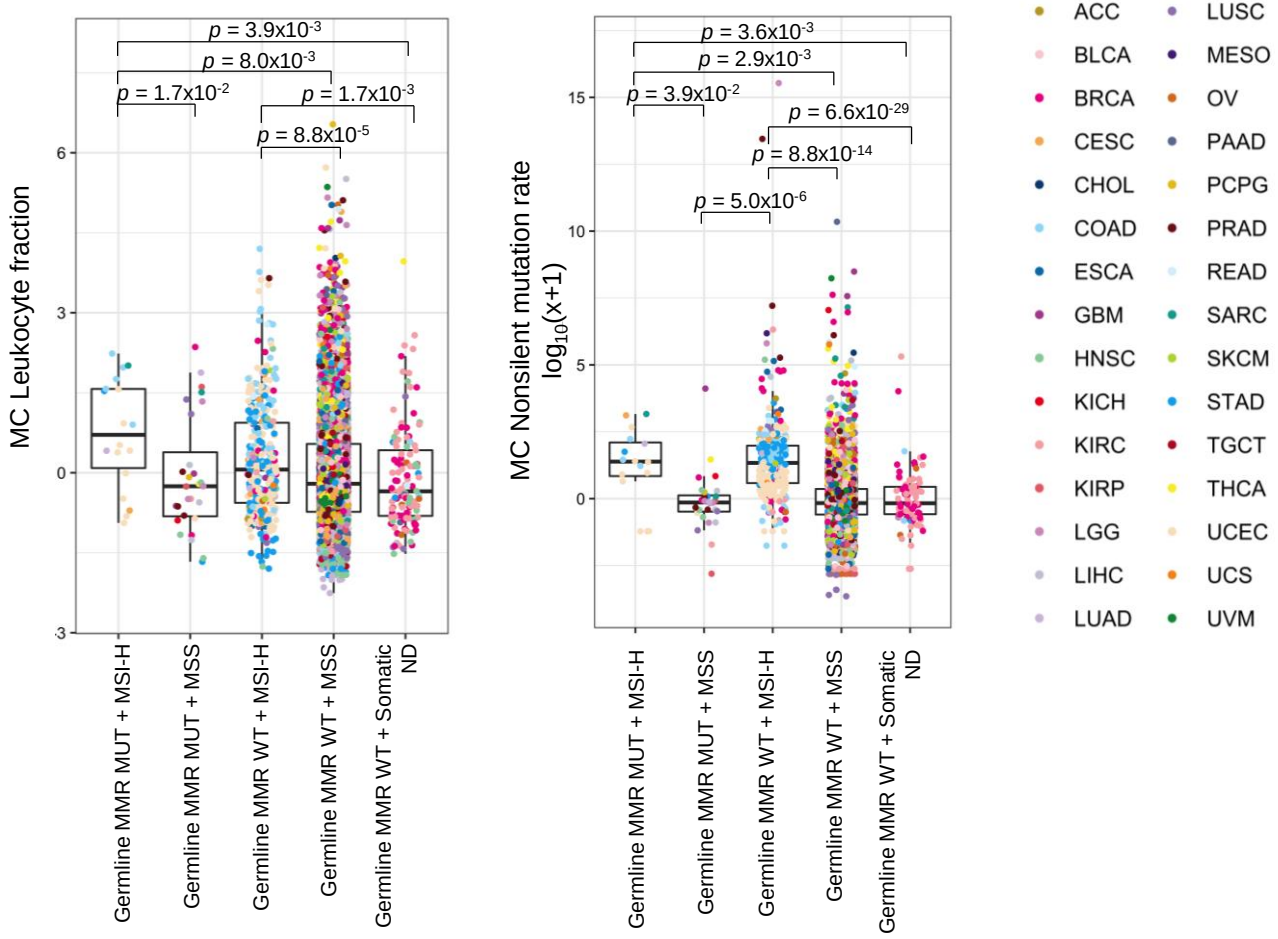
Rare Variant Analysis (Cancer Predisposition Genes)



Mismatch Repair Defect and Microsatellite Instability

MMR Germline Status	MSI Status	N Samples
MUT	MSI-H	18
MUT	MSS	28
WT	MSI-H	356
WT	MSS	8615
WT	NA	121

B



Take Home Messages

15–20% of intratumoral variation of interferon signaling and cytotoxic cells is heritable

Common variants of IFIH1, STING1, and TMEM108 affect cancer IFN signaling

Common variants of RBL1 are associated with differential T cell infiltration

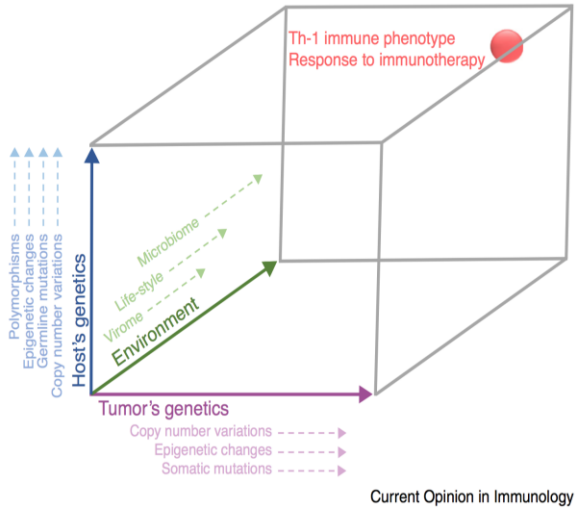
Rare cancer predisposition variants affect different immunomodulatory pathways

Potential Clinical Implications – Precision Medicine

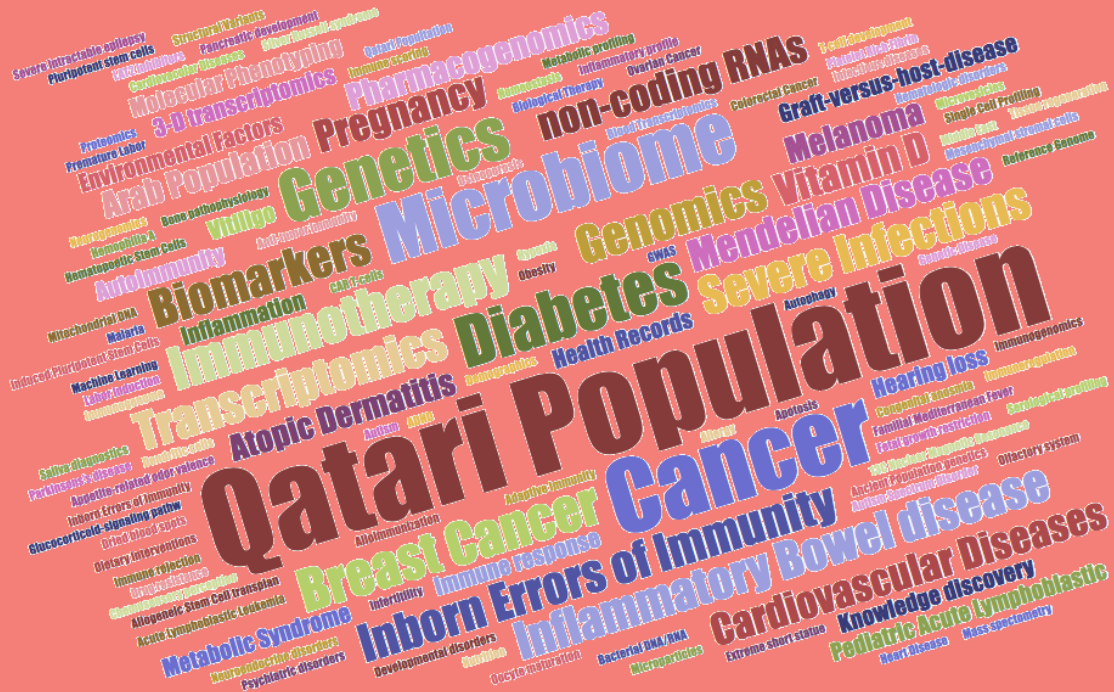
Checkpoint Inhibition (> 5000 patients needed for GWAS with 80% power)
Polygenic risk score
Patient stratification especially in the adjuvant context

Integration with other variables (tumor intrinsic features, microbiome, intratumoral immune signatures)

Multidimensional (HOST+TUMOR+MICROBIOME) predictor score



Thank You


Qatari Population
Cancer
Inborn Errors of Immunity
Inflammatory Bowel disease
Cardiovascular Diseases
Breast Cancer
Metabolic Syndrome
Transcriptomics
Immunotherapy
Microbiome
Genetics
Pharmacogenomics
non-coding RNAs
Pregnancy
Diabetes
Biomarkers
Genomics
Vitamin D
Melanoma
Graft-versus-host-disease
Mendelian Disease
Severe Infections
Hearing loss
Atopic Dermatitis
Health Records
Arab Population
Environmental Factors
Molecular Phenotyping
3-D transcriptomics
Autoimmunity
Inflammation
Knowledge discovery
Pediatric Acute Lymphoblastic