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Germline Genetic Contributions to Immune Landscape

Questions

1) How can germline variants influence cancer immune responsiveness and toxicity ?

2) What is the rationale to support the role of germline variants on cancer immune responsiveness (response to immunotherapy, development of spontaneous anti-tumor immune response) ?

3) Which level of evidence is available supporting the existence of a relationship between germline variants and cancer immune responsiveness ?

4) What are the potential clinical implications of “immune” germline variant identification ?

5) Which approach should be prioritize to answer the “germline” question?

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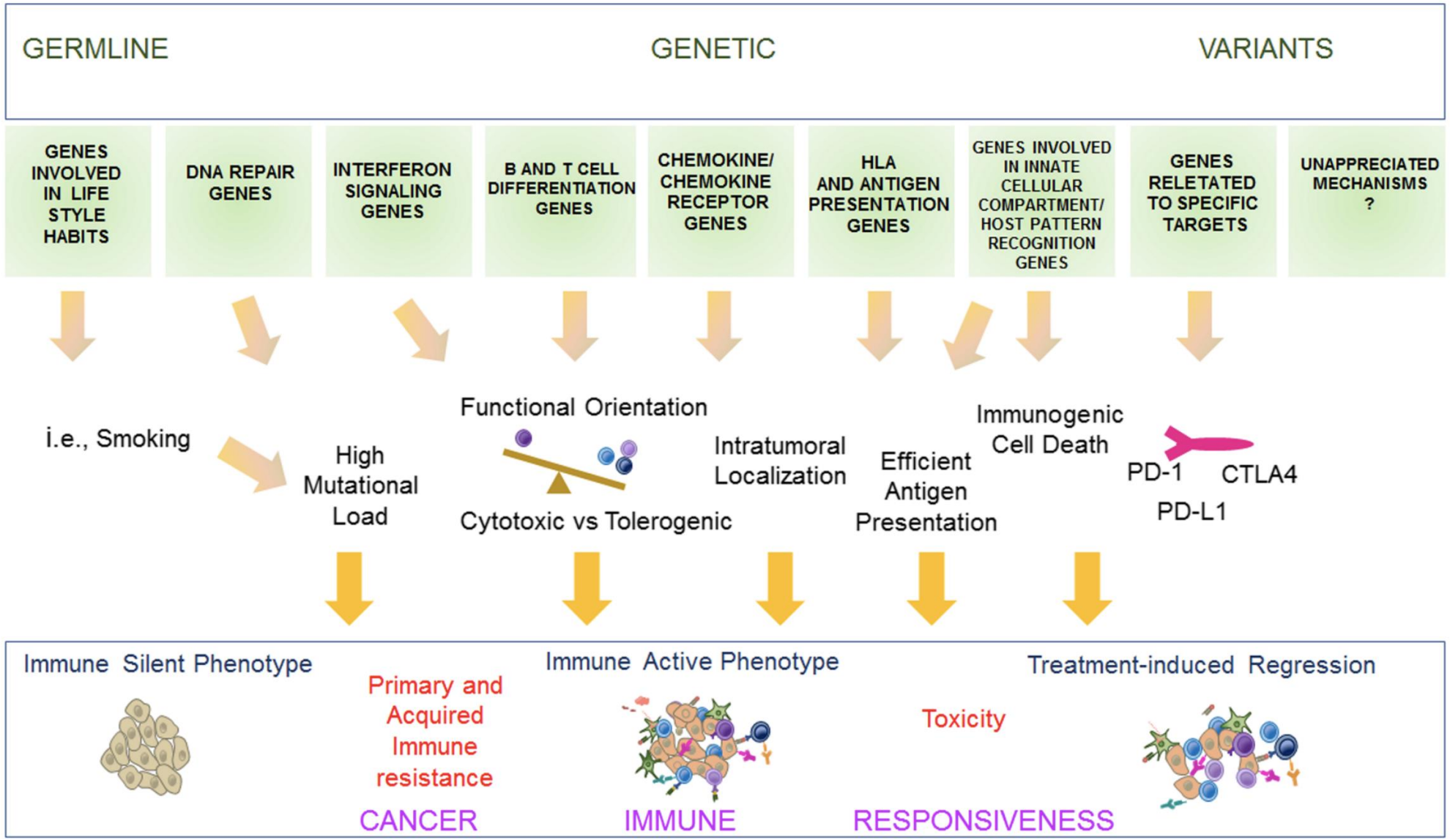

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Bedognetti D et al (on behalf of Cancer Immune Responsiveness Taskforce), JITC 2019

(2A) What is the rationale to support the role of germline variants on cancer immune responsiveness ?

GWAS studies have identified about a hundred loci associated with the development of autoimmune diseases.

Deleterious mutations in immune genes (including CTLA4) have been associated with the onset severe auto-immune diseases.

HLA polymorphisms have been consistently associated with susceptibility to leukemia and virally induced tumors such as head and neck, cervical, and nasopharyngeal cancer. – how they will respond to treatment?

Associations between killer cell immunoglobulin–like receptor (KIR) polymorphisms and cancer susceptibility have been reported with some conflicting results, particularly in leukemia and lymphoma.

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(2B) What is the rationale to support the role of germline variants on cancer immune responsiveness ?

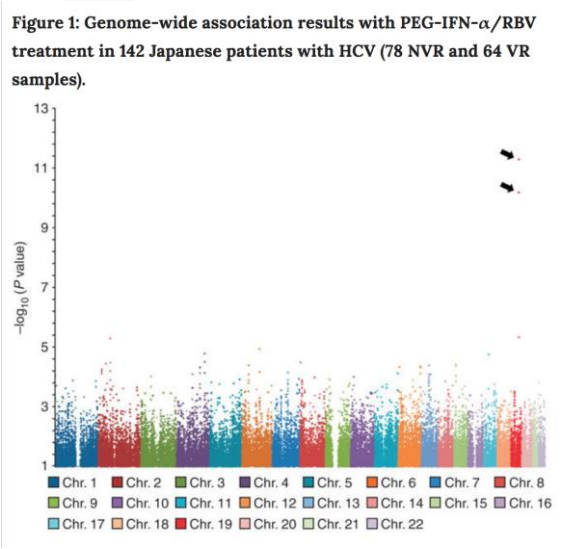
Polymorphisms of IL28 (Interferon lambda) have been strongly associated with response to IFN-alpha treatment in HCV patients (Ge, Narure 2009 N=1600; Tanaka, Nat Gen, 2009, N=315, Suppiah, Nat Gen, 2009. N=260) – GWAS

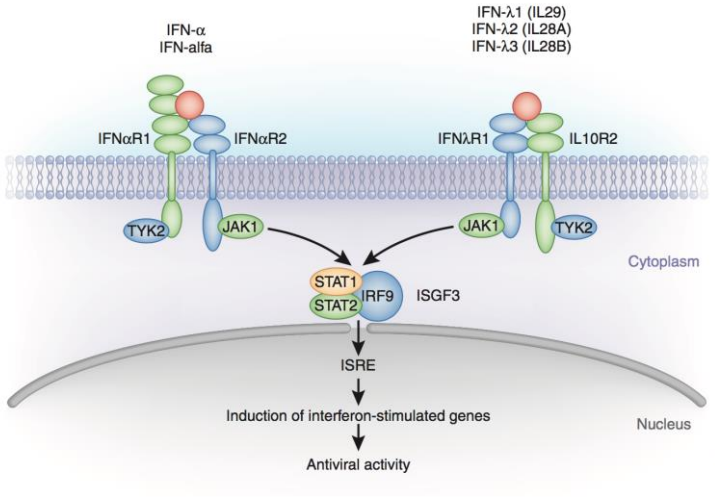
Interferon-alfa, interferon-λ and hepatitis C

Thomas R O'Brien

Three new studies report genetic variants near *IL28B*, which encodes interferon-λ3 (interleukin 28B), are associated with response to treatment of chronic hepatitis C virus infection with interferon-alfa/ribavirin combination therapy. This renews interest in how interferons suppress viremia and could lead to improved clinical decisions for chronic HCV infection treatment based on individual genotype.

O'Brien Nat Gen 2009





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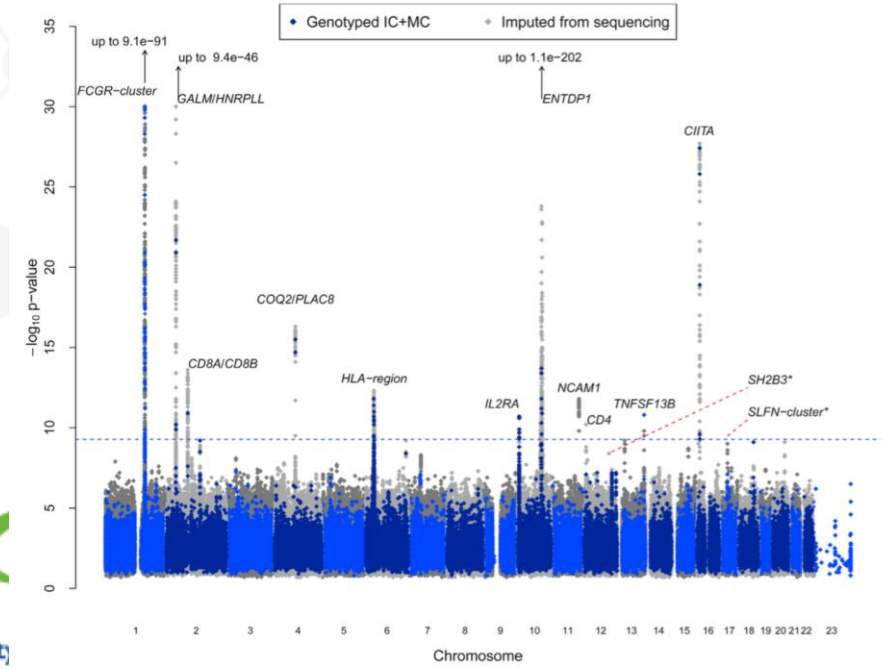
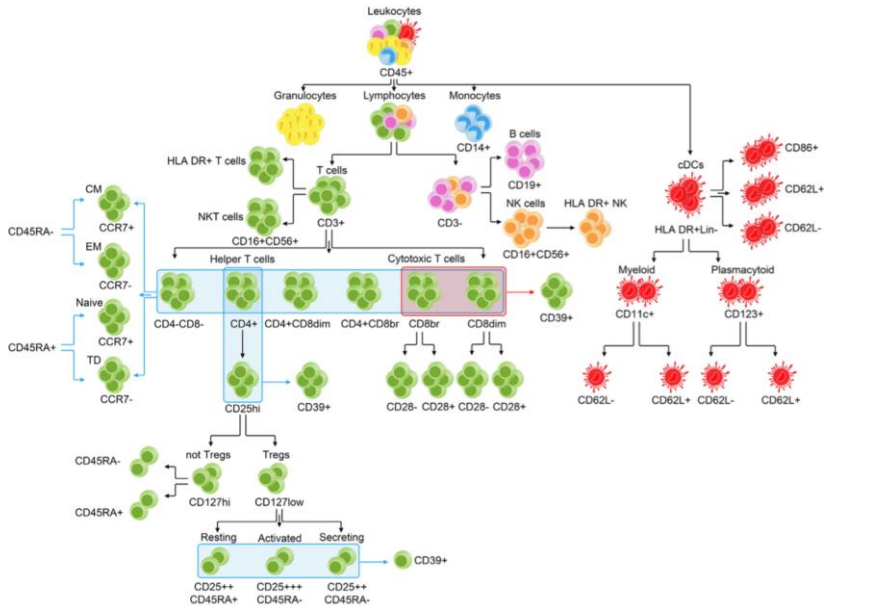
(2C) What is the rationale to support the role of germline variants on cancer immune responsiveness ?

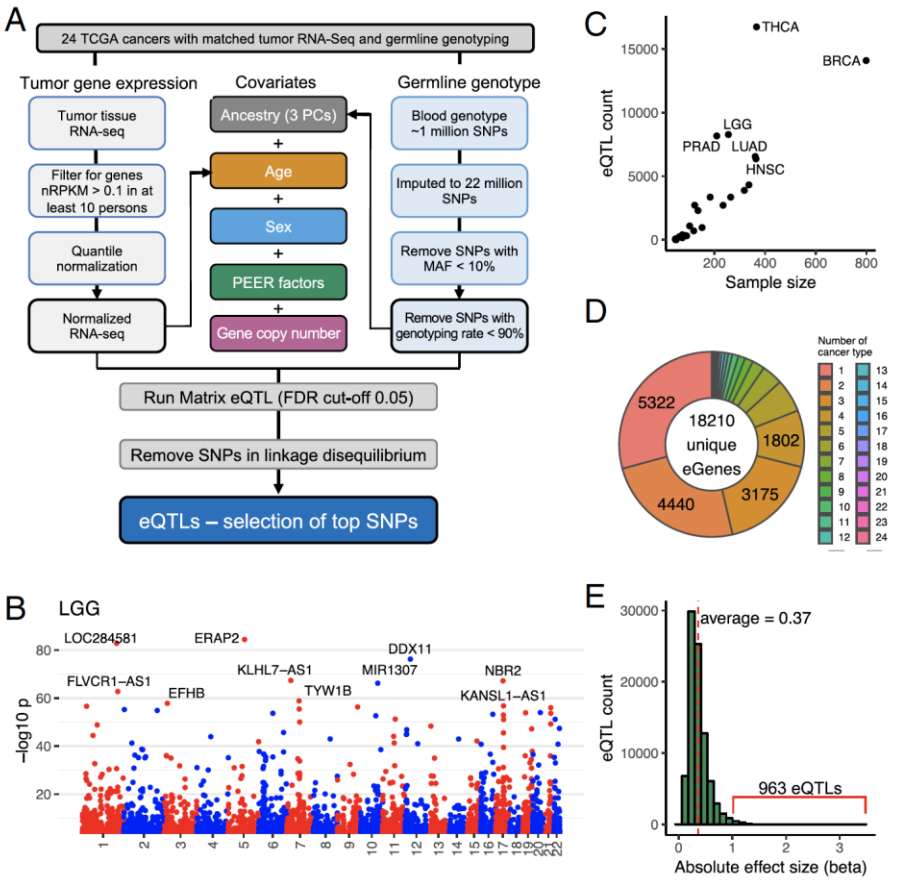
Polymorphisms of immune-related genes influence the fraction of lymphocyte populations in the peripheral blood (Orru, Cell, 2013, N=1600) - GWAS





(2C) What is the rationale to support the role of germline variants on cancer immune responsiveness ?

eQtl of immune genes have been correlated with cancer prognosis
Vogelsang and Kirchoff, CCR, 2016
Lim YW, PNAS, 2018



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3A) Which level of evidence is available supporting the existence of a relationship between germline variants and cancer immune responsiveness ?

N	Method	Setting	Gene	Results	Reference
139	PCR	Met Melanoma, chemo-immunotherapy	CCR5	Association with survival	Ugurel, CII, 2007
272	HAL Typing PCR	Met Melanoma, IL-2	HLAs	No association with response; association with toxicity	Marincola, JIETI, 1995
142	Target seq	Met Melanoma, adoptive therapy	CCR5	Association with response	Bedognetti, BJC, 2013
142	Target seq	Met Melanoma, adoptive therapy	IRF5	Association with Response	Uccellini, JTM, 2013
152	Target seq	Met Melanoma, anti-CTLA4	CTLA4	Association with response	Breunis, J Imminotherapy, 2008
55	Target seq	Met Melanoma, anti-CTLA4	CTLA4	No Association	Hamid, J Trans Med, 2011
14	Target seq	Met Melanoma, anti-CTLA4	CTLA4	Association with response	Queirolo, Canc Inv, 2013
286	Target seq	Resected Melanoma, adjuvant IFN-a	CTLA4	No association with survival	Gogas, JTM, 2010
286	Target seq	Melanoma, adjuvant IFN-a	HLAs	Association with survival and PFS	Gogas, Cancer 2010 Wang Plos One, 2012

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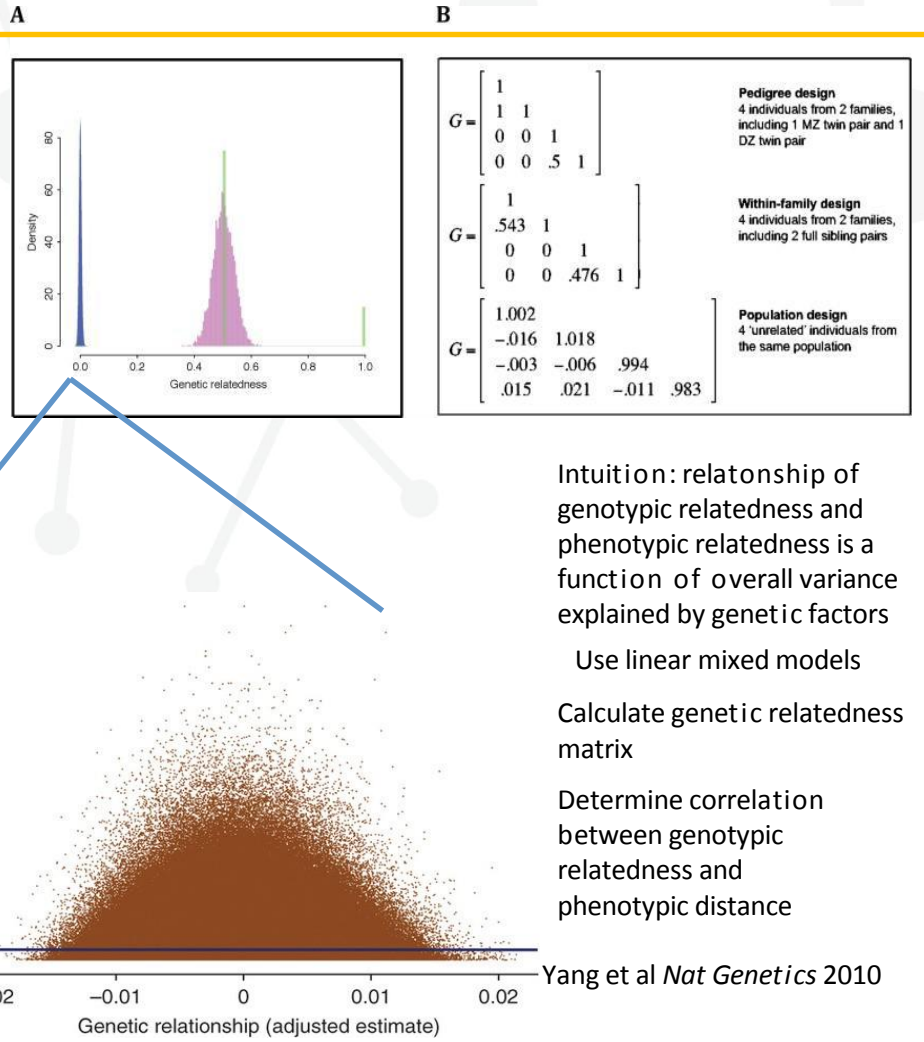
3B) Heritability from GWAS Data



Intuition: relatonship of genotypic relatedness and phenotypic relatedness is a function of overall variance explained by genetic factors

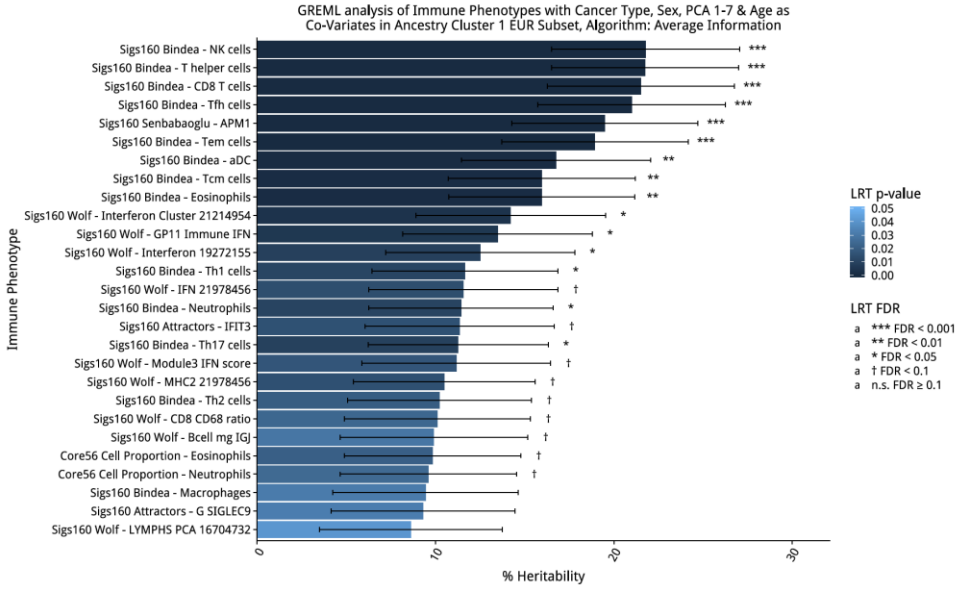
Use linear mixed models

Calculate genetic relatedness matrix

Determine correlation between genotypic relatedness and phenotypic distance

Yang et al *Nat Genetics* 2010

Heritability of Immune Phenotypes



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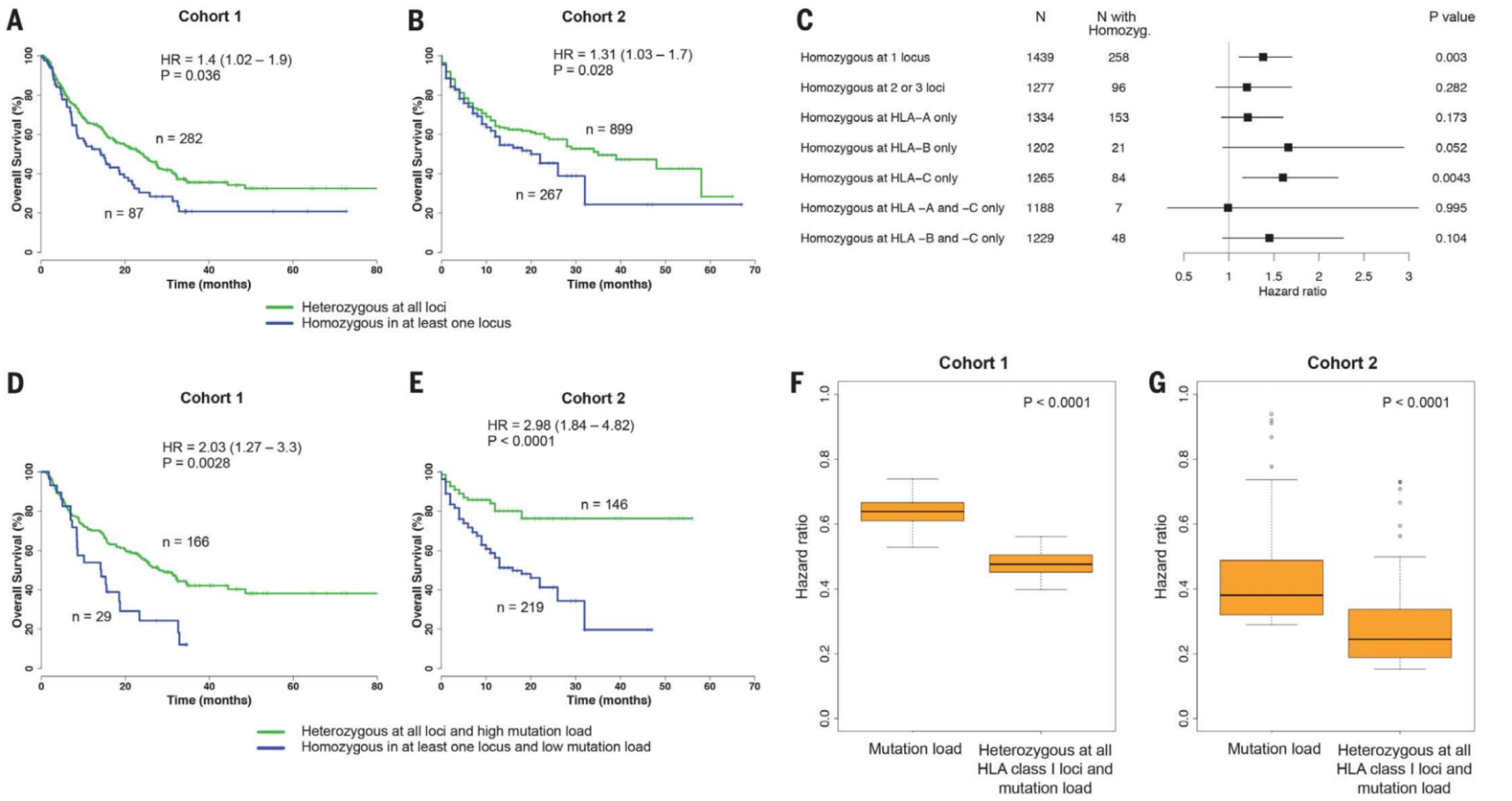
(3C) Which germline variants have been associated with cancer immune responsiveness ? HLA



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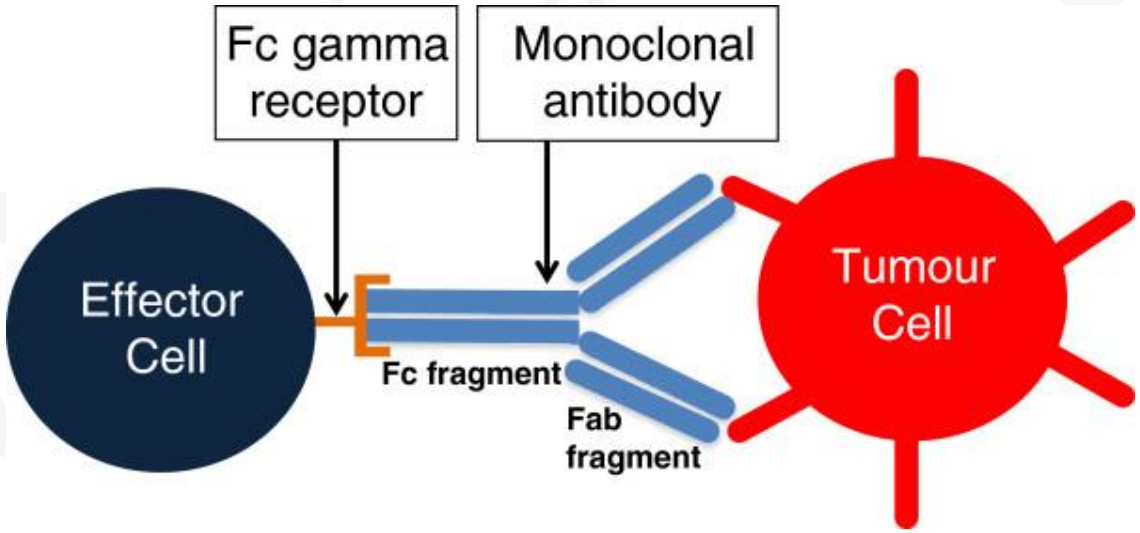
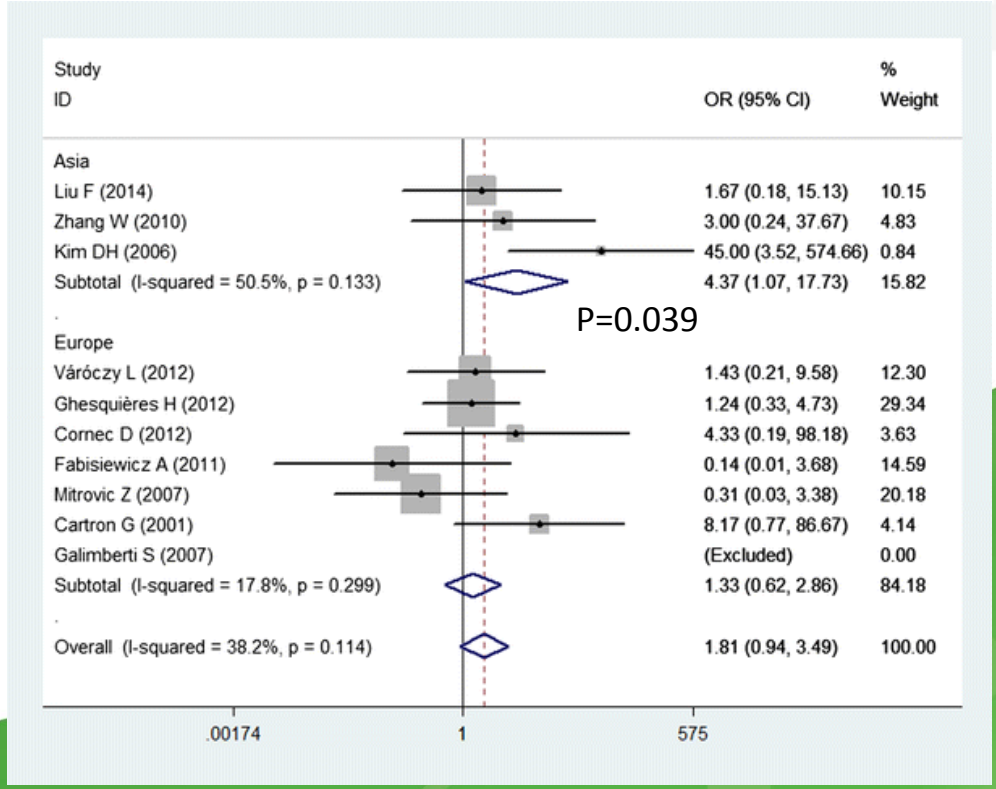
Chowell et al, Science 2018

(3D) Which germline variants have been associated with cancer immune responsiveness ? FCR

Polymorphisms of the FC receptor have been associated with responsiveness to mAB (trastuzumab and rituximab), although, not consistently with outcome (> 15 studies assessing specifically FC polymorphisms and response to trastuzumab or rituxumab).



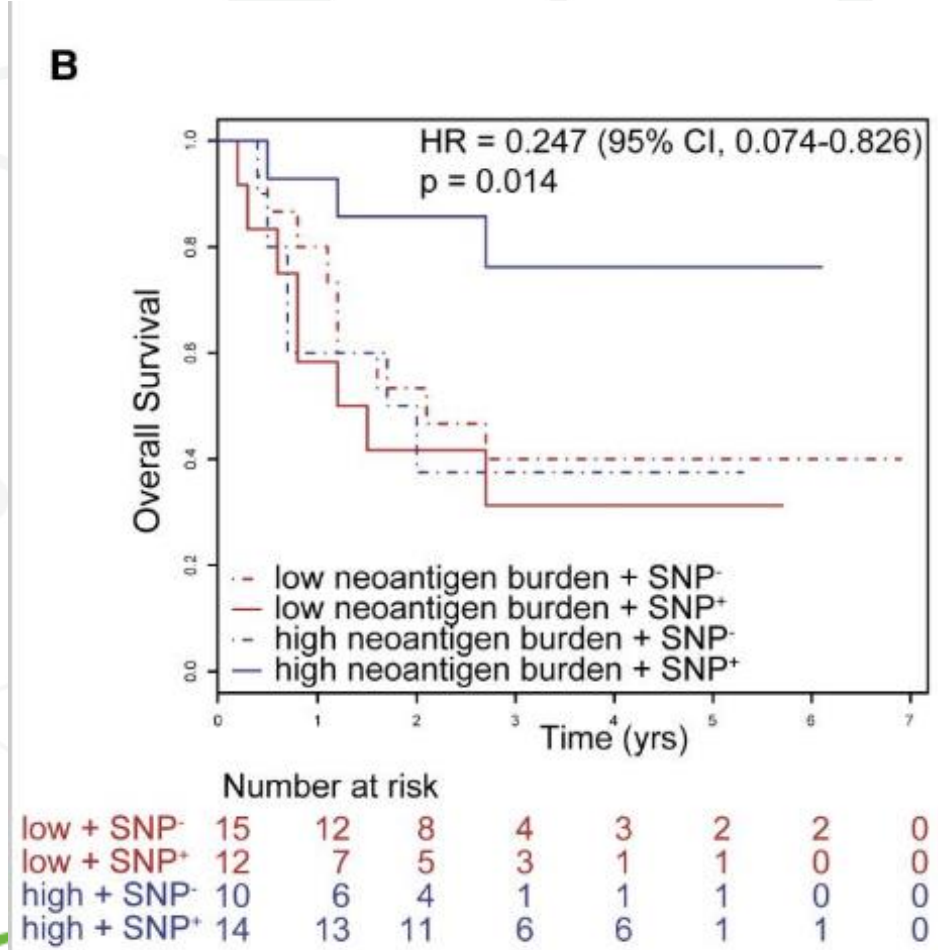


Liu, Ann Hem, 201016

Mellor, J Hemat Onc, 2010

Tamura, Ann Onc, 2010

(3E) Which germline variants have been associated with cancer immune responsiveness ? FCR



Fc-gamma high-affinity CD16a-V158F SNP

Arce Vargas, Cancer Cell 2018

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Autoimmune risk loci associate with efficacy to immune therapy

SNPs	Reported Genes	Autoimmune disease	Anti-CTLA4 (N Controls=78, N Cases=135) (N total=213)		Anti-PD1 (N Controls=88, N Cases=81) (N total=169)		Combined therapy (N Controls=33, N Cases=10) (N total=43)	
			OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
rs10488631	TNPO3, IRF5	Lupus, RA, systemic sclerosis	----------	-------	----------	-------	31.19(1.62-597.9)	0.02
rs17388568	IL2, ADAD1, IL21	Allergy, colitis, T1D	----------	------	0.26(0.12-0.53)	0.0002	----------	---------
rs1893217	PTPN2	Celiac disease, IBD, RA, T1D	2.79(1.36-5.73)	0.005	----------	------	6.95(1.06-45.26)	0.04
rs2111485	FAP, IFIH1	Colitis, IBD, lupus, vitilago	----------	-------	----------	------	0.21(0.04-0.98)	0.04
rs2187668	HLA-DQA1	Celiac disease, colitis, lupus	----------	-----	2.14(1.06-4.31)	0.03	----------	----------
rs2476601	PHTF1, PTPN22	Lupus, RA, T1D, vitiligo	3.17(1.02-9.85)	0.04	0.36(0.09-1.48)	0.16	----------	----------
rs6679677	PHTF1, PTPN22	Lupus, RA, T1D, vitiligo	2.95(1.14-7.60)	0.02	----------	-------	----------	----------

cer > 900 patients analyzed

- Logistic regression comparing non-responders as controls and responders as cases
- OR<1 therapy resistance, OR>1 – therapy sensitivity

Autoimmune risk loci associate with anti-CTLA4 toxicity

SNP	Gene	AID	NMISS	OR	L95	U95	P
rs3024493	IL10	Colitis, IBD, lupus	78/103	3.67	1.516	8.885	**0.00003942**
rs3024505	IL19, IL10	colitis, IBD, lupus, T1D	63/111	3.609	1.399	9.309	**0.000794**
rs11203203	UBASH3A	Celiac, rheumatoid arthritis, T1D, Vitiligo	67/109	2.301	1.007	5.255	0.04802
rs2187668	HLA-DQA1	Celiac, colitis, lupus	70/113	2.268	0.781	6.585	0.1322

Genetic variants in interleukin-related pathways associate with immune response and toxicity across treatments

Kirchoff

4) What are the potential clinical implications of “immune” germline variant identification ?

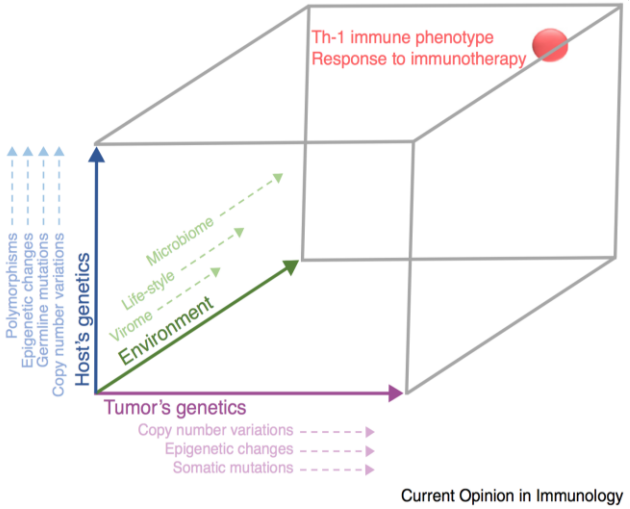
Mechanistic vs biomarkers

Patient selection (large effect on a minority of patients (rare variants/hereditary cancer), small effect on a majority of patients, large effect in the majority of patients might be possible in the context of pharmacokinetic studies)

Polygenic risk score computation.

Patient stratification in clinical trial especially in the adjuvant context or for maintenance in patients with CR.

Integration with other variables (tumor intrinsic features, microbiome, intratumoral immune signatures) + Multidimensional (HOST+TUMOR+MICROBIOME) predictor score



Treatment-specific variants.

Therapeutic implementations

(e.g., epitope design according to HLA type; discovery of novel target, drug-class selection)

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5) How can we implement the study of host genetic diversity to identify novel biomarkers of responsiveness or toxicity to cancer immunotherapy?

Platforms: WGS (low pass 1-3 X), WES?, **genotyping**, off-target reads

1) Population based (UK Biobank, CPTP Canada)
2) Investigator-based consortia
3) Government-industry partnership (PACT)
4) Exploitation of existing data (i.e., ICGR, unaligned reads from exome or target

Dataset (potential available database need to be catalogued; ---ICGC-ARGO)

Collaborative efforts possibly supported by SITC (sample of data sharing) ?

Immunoscore-like consortium?

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END

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Take-home message

Recent findings suggest that germline variants might shape intra-tumoral immune response, and influence responsiveness and toxicity to immunotherapy.

Current large cancer databases are useful resources to explore the relationship between individuals' genetic background and intra-tumoral immune response but lack information on treatment outcome, especially on immunotherapeutic agents.

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Take-home message

It is critical to establish dedicated large collaborative consortia or networks collecting harmonized clinicopathological information, which represents a major roadblock in the systematic exploration of the germline component in IO.

Germline information should be integrated with phenotypic information such as somatic alterations, epigenetic and transcriptional features to increase prediction accuracy. Analytic integrative pipelines need to be implemented for deciphering causal associations and for prioritizing putative functional variants and pathways.

Once identified, genetic germline biomarkers might be used to increase treatment outcome, adverse event prediction and to define novel therapeutic strategies.

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