Update on Genetics of Rheumatoid Arthritis

RAIN Symposium
Omaha, Nebraska

April 26, 2024

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Disclosures

Grant/Research Support: BMS Investigator-Initiated Study

Outline

HSS

Background
1. Clinical Manifestations and Pathogenesis

Genetic Susceptibility
1. The HLA Region
2. Non-HLA Loci
3. Functional Genomics

Gene Curation

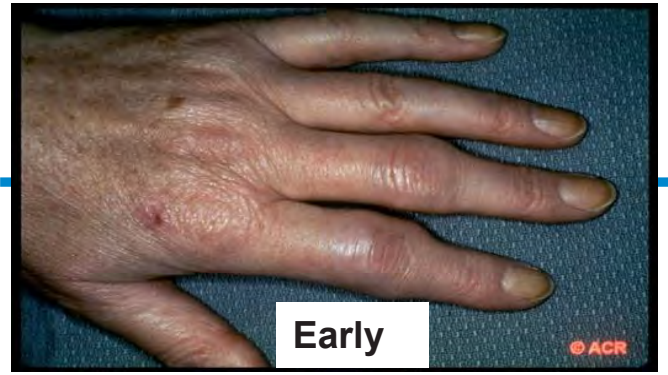
Mendelian Randomization

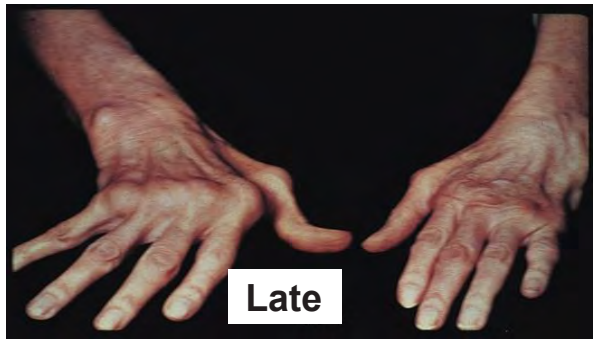
Somatic Mutations

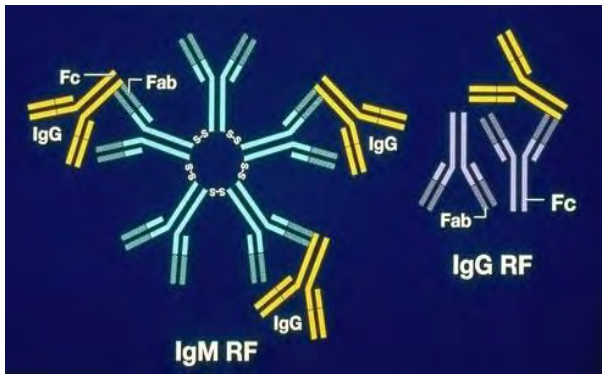
Pharmacogenetics

Rheumatoid Arthritis

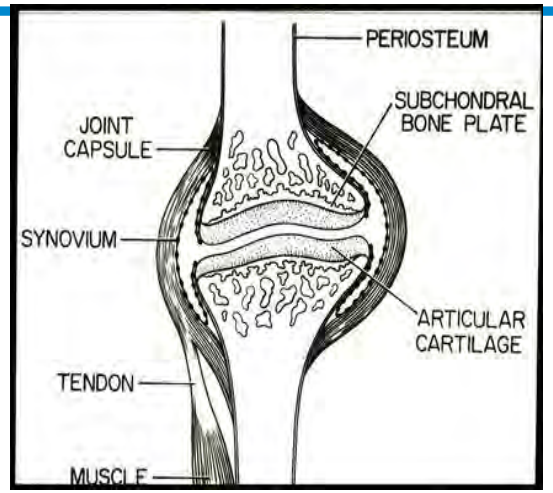
HSS HOSPITAL FOR SPECIAL SURGERY RHEUMATOLOGY



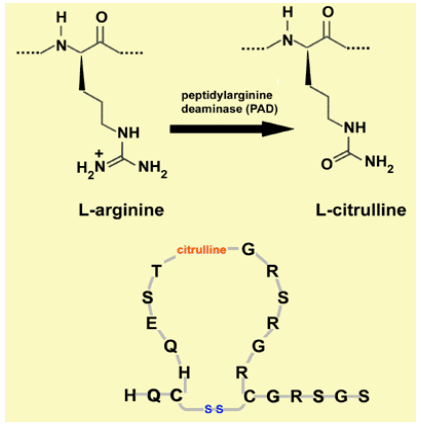




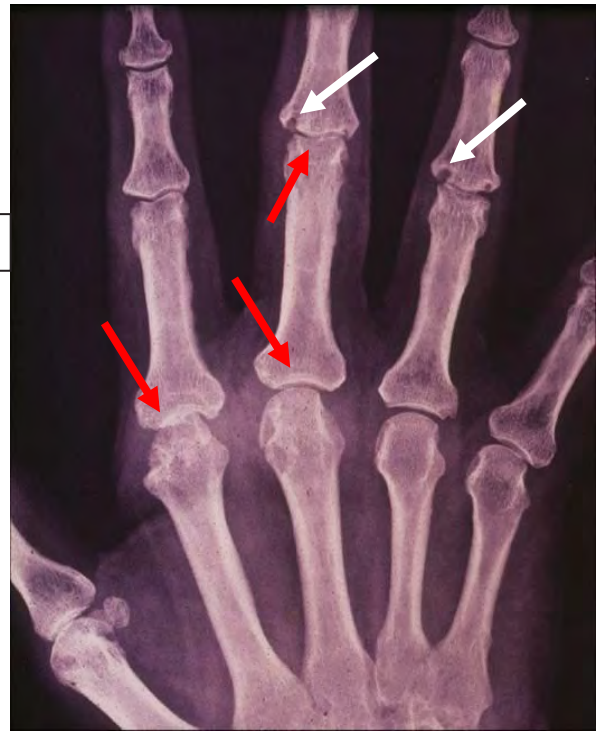
Autoantibodies



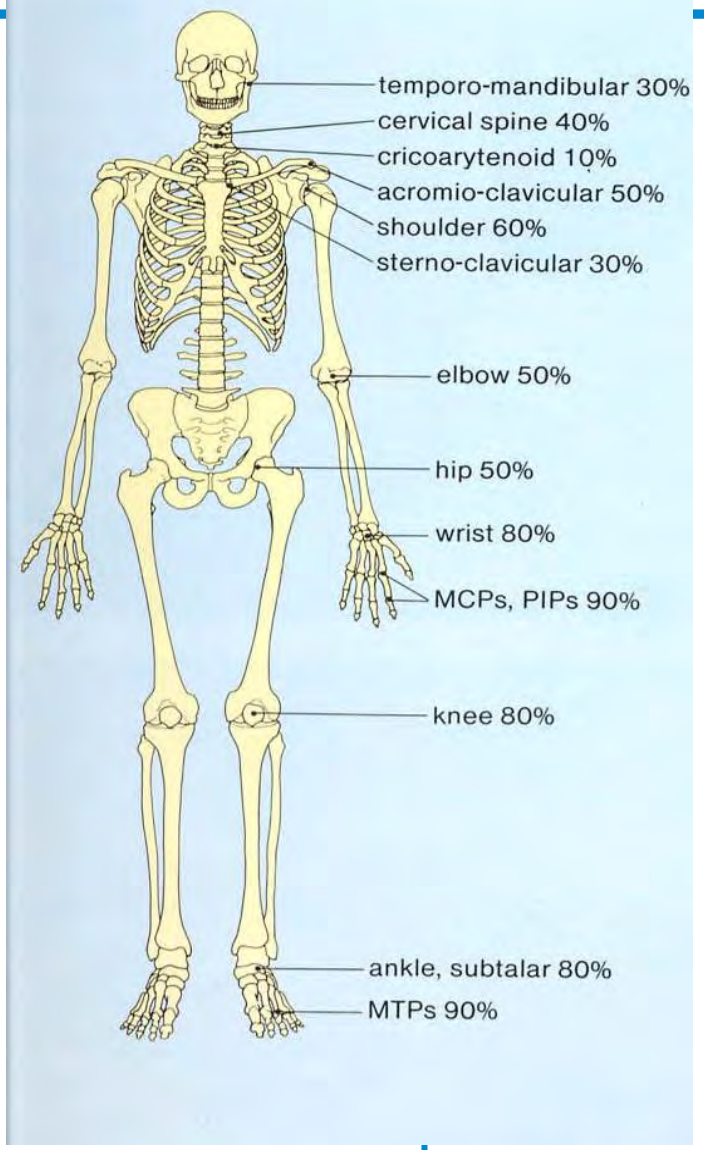
Synovium is the target tissue



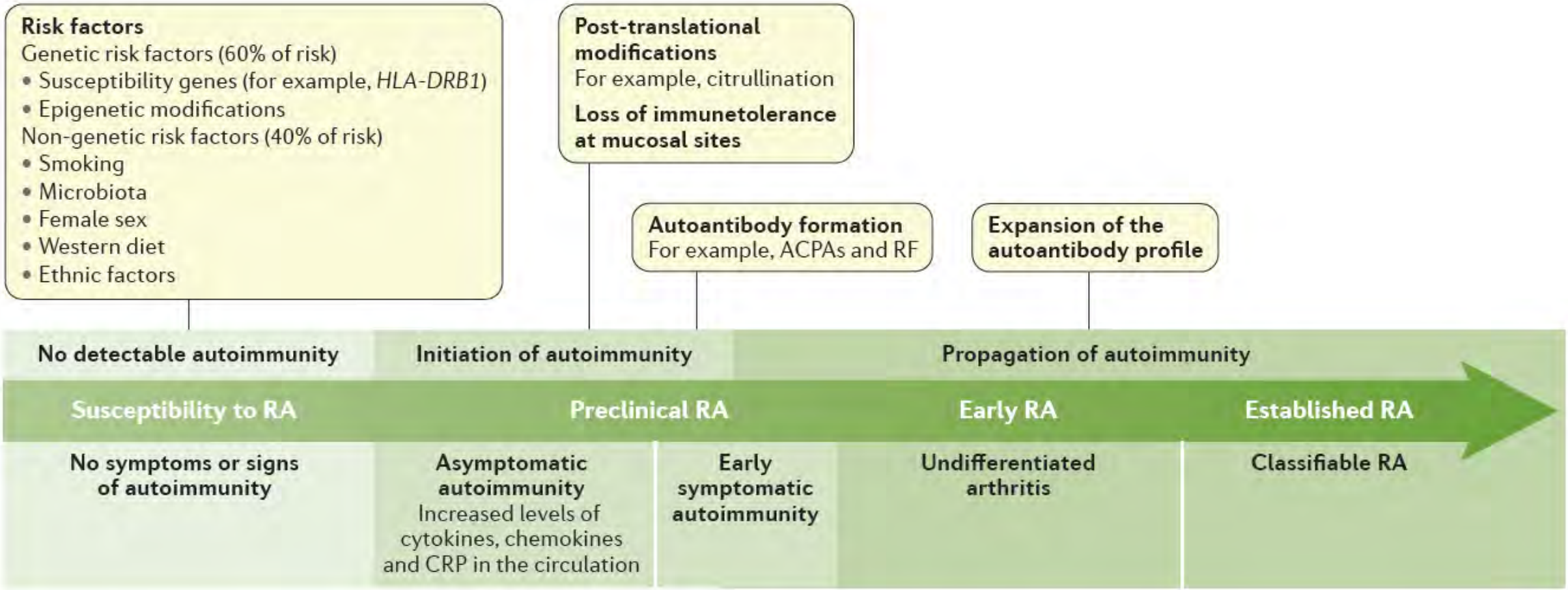
Erosions and Joint Space Narrowing



Target Joints

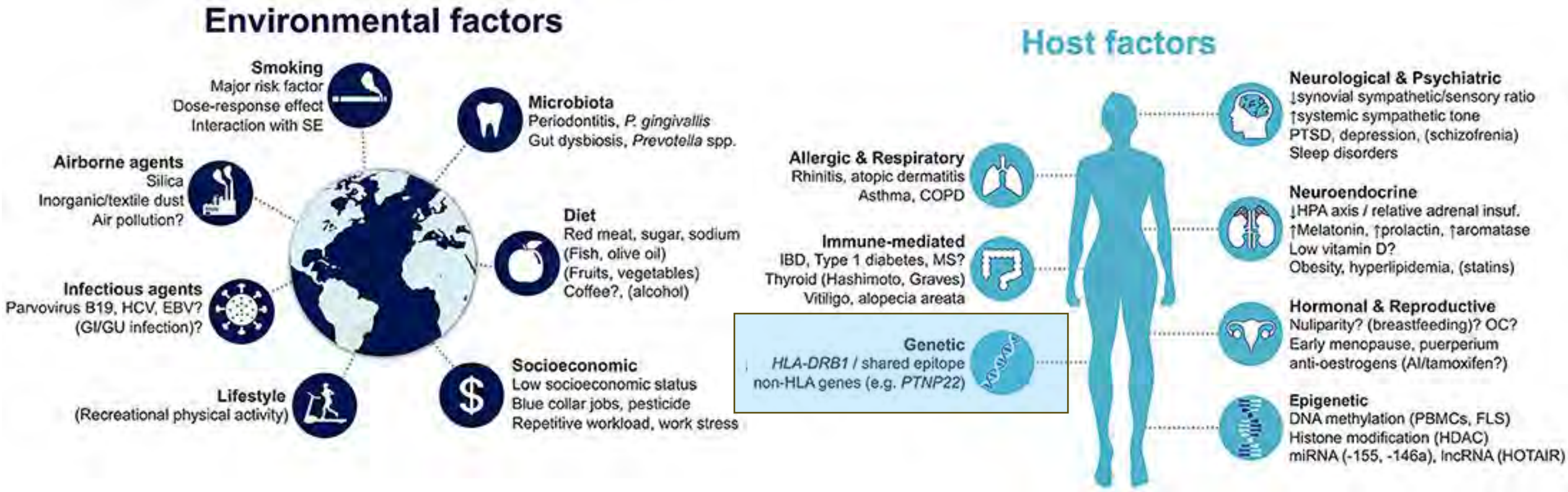


Development and Progression of RA



Smolen JS, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4:18001.

Risk Factors for Rheumatoid Arthritis



Romao VC and Fonseca JE. Etiology and Risk Factors for Rheumatoid Arthritis: A State-of-the-Art Review. Front Med (Lausanne). 2021 Nov 26;8:689698.

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Milestones in HLA Genetic Associations with RA

HLA-DRB1

- HLA Serologic Study
  - 80 white patients with erosive, RF+ RA
  - The B-cell alloantigen HLA-DRw4 occurred in 70% of 54 RA patients vs 28% of 68 normal controls ($P < 0.00001$)

Stasny P. NEJM 298:869, 1978

- Shared Epitope hypothesis

Gregersen PK et al. Arthritis Rheum. 30:1205, 1987

- Association of Shared Epitope with ACPA+ RA and Smoking

Klareskog L et al. Arthritis Rheum 54:38, 2006

- Importance of HLA-encoded amino acid residues

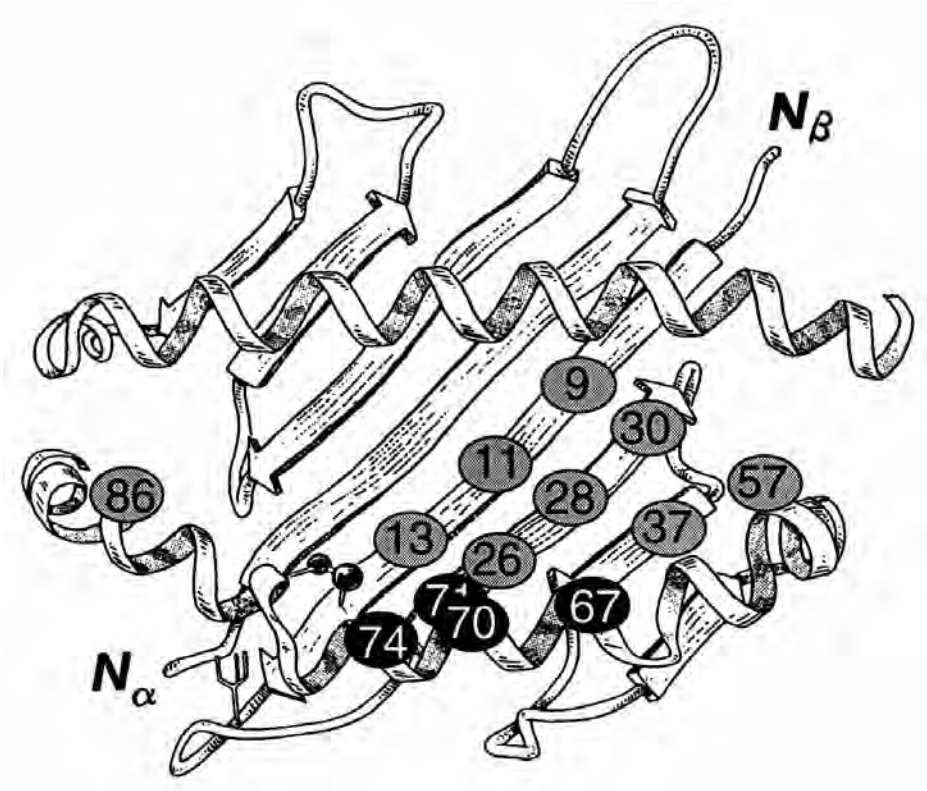
Raychaudhuri S et al. *Nat Genet*. 44:291 2012

HLA-DRB1 Shared Epitope in RA

Third Hypervariable Region Sequences of DRB1 Chains Associated With RA

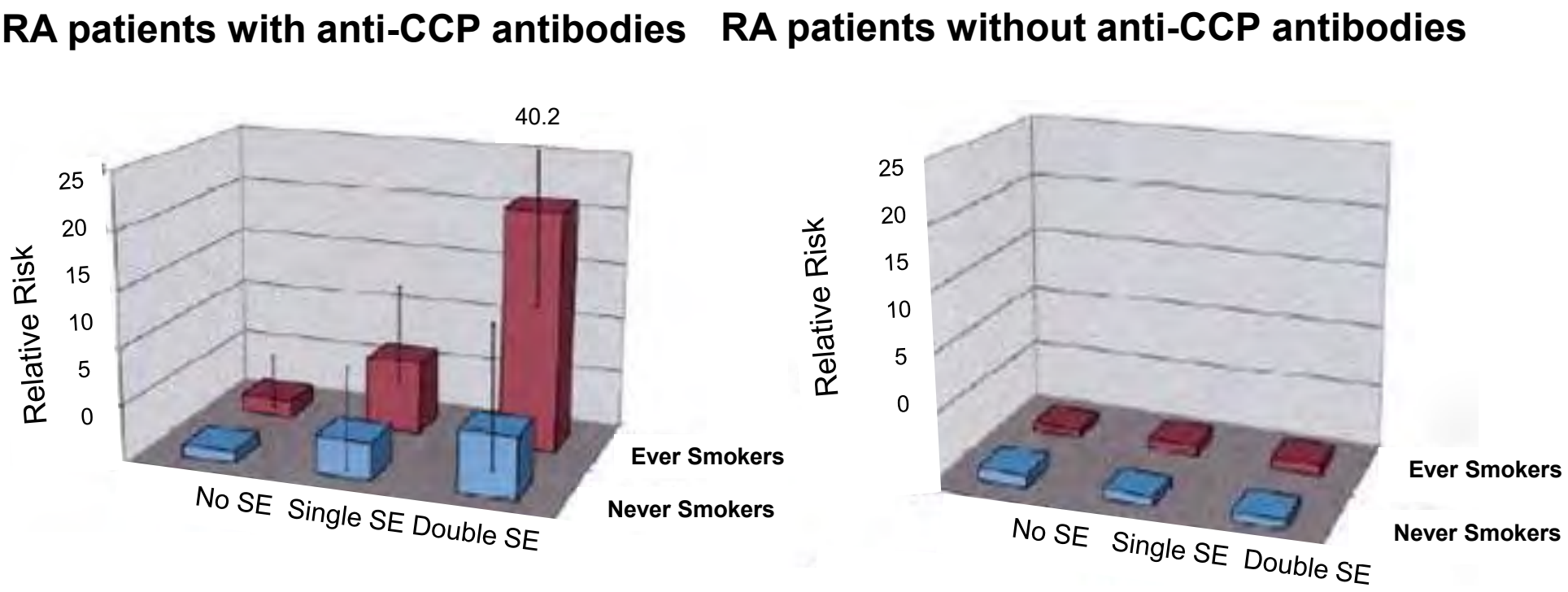
Collective Odds Ratio (OR) ~3.0; Population Freq ~0.35 (Caucasians)

	Amino Acid Position				
	70	71	72	73	74
DRB1*0401	**Q**	**K**	**R**	**A**	**A**
DRB1*0404	**-**	**R**	**-**	**-**	**-**
DRB1*0405	**-**	**R**	**-**	**-**	**-**
DRB1*0408	**-**	**R**	**-**	**-**	**-**
DRB1*0413	**-**	**-**	**-**	**-**	**-**
DRB1*0101	**-**	**R**	**-**	**-**	**-**
DRB1*0102	**-**	**R**	**-**	**-**	**-**
DRB1*1402	**-**	**R**	**-**	**-**	**-**
DRB1*1001	**R**	**R**	**-**	**-**	**-**



Gregersen PK, et al. *Arthritis Rheum.* 1987;30:1205.

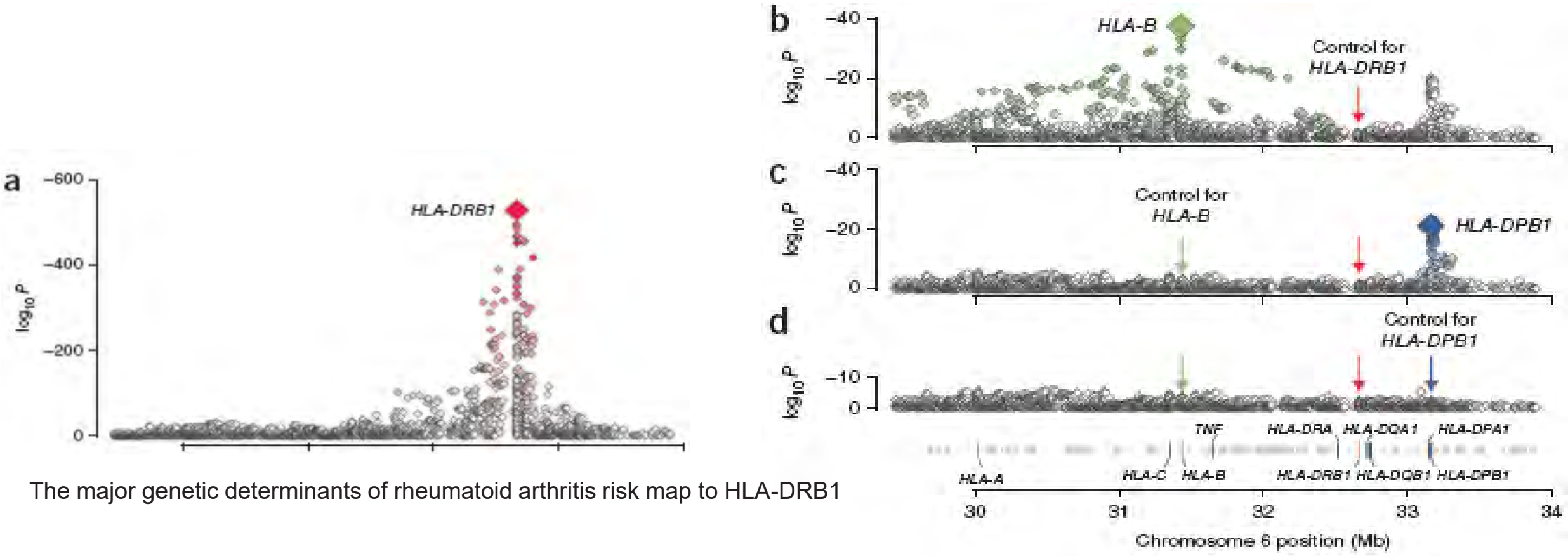
Relative Risk of Developing RA in Subjects Exposed to Different Combinations of Smoking and HLA–DR SE Alleles



Error bars represent 95% confidence intervals

Klareskog et al. *Arthritis Rheum* 54:38, 2006

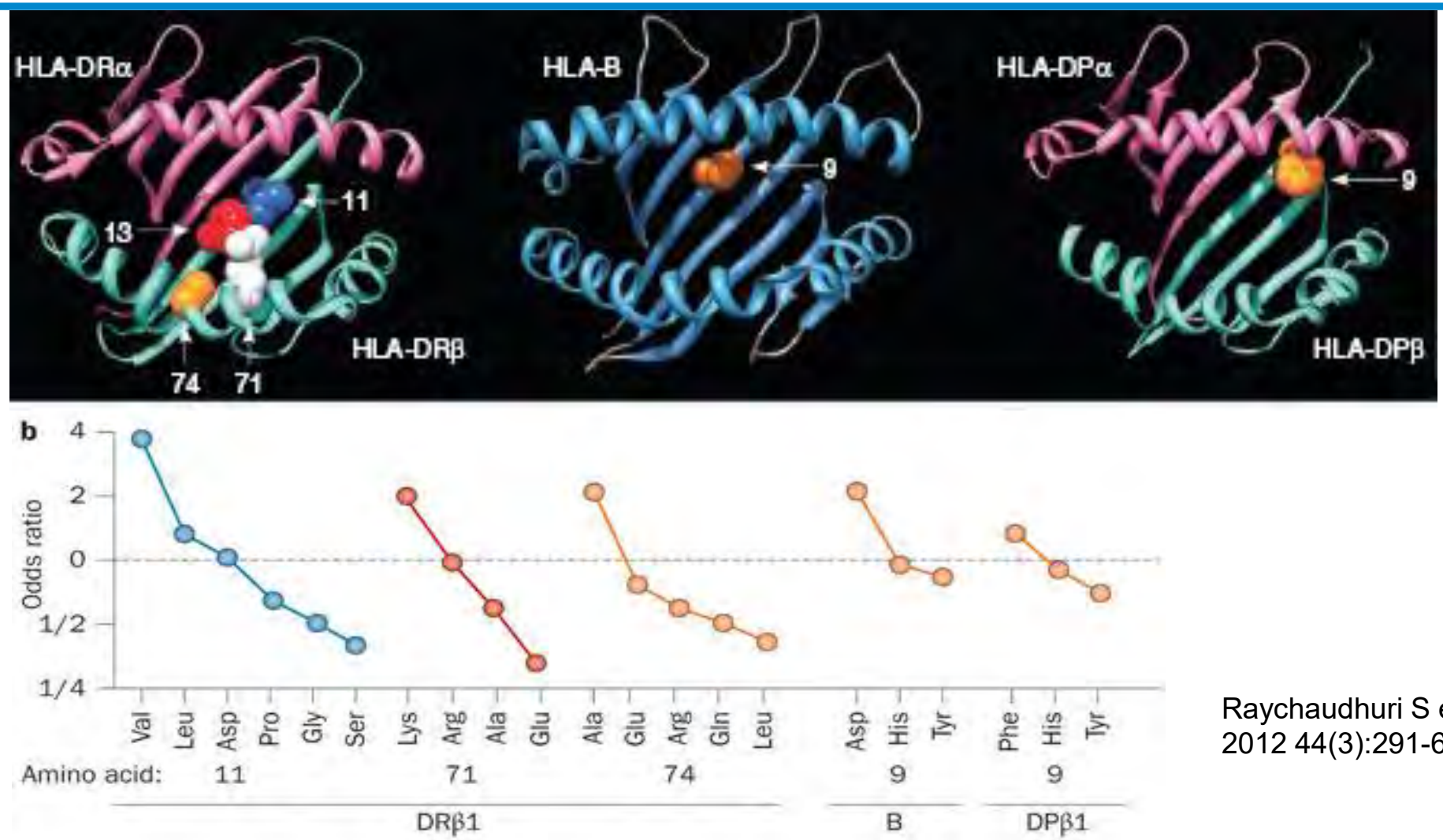
RA Associations within the MHC Region in European Ancestry



The major genetic determinants of rheumatoid arthritis risk map to HLA-DRB1

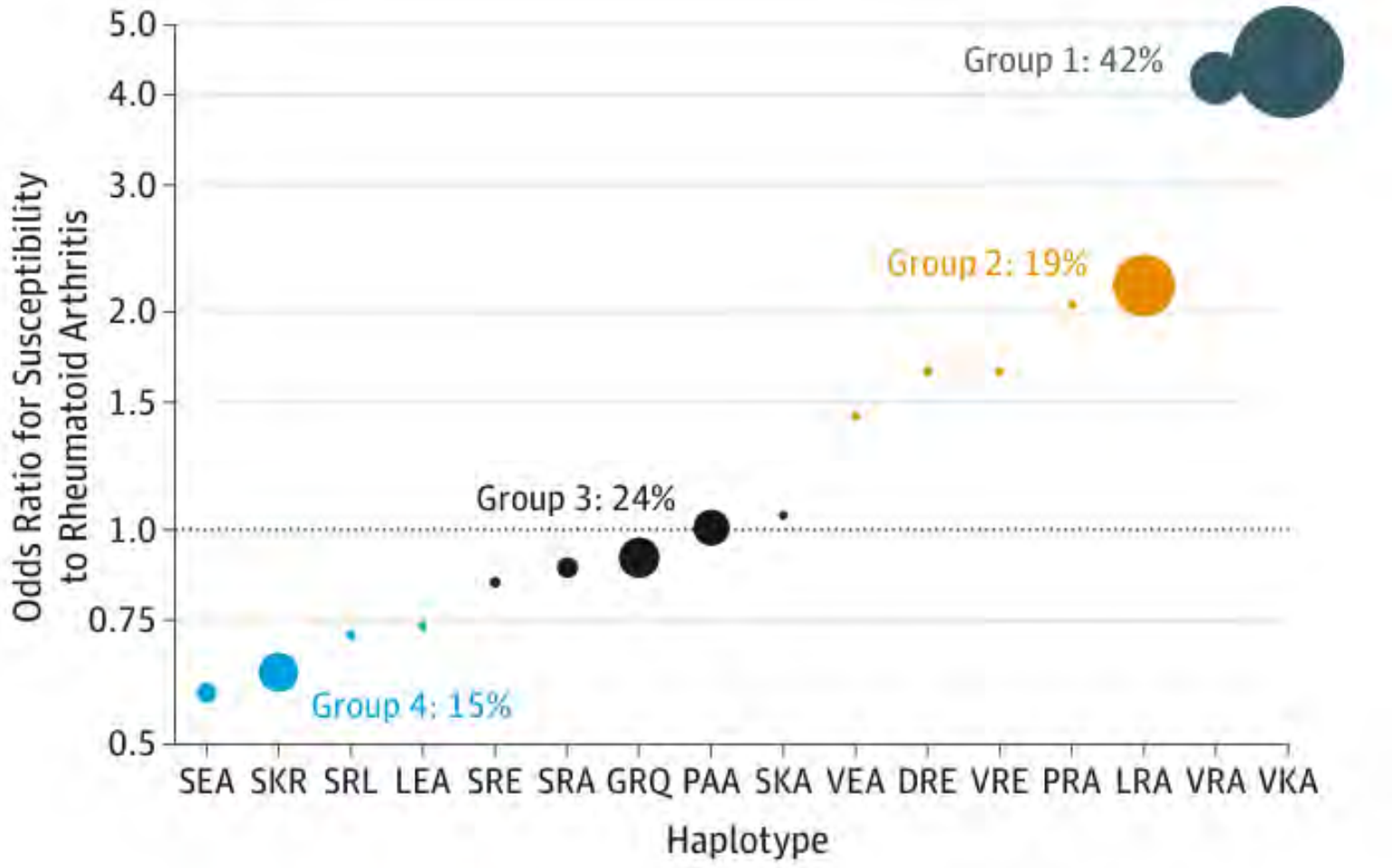
Raychaudhuri S et al. *Nat Genet*. 2012 44(3):291-6.

Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis



Raychaudhuri S et al. *Nat Genet*. 2012 44(3):291-6.

Haplotype Groups Defined at Amino Acid Positions 11, 71, and 74 of HLA-DRB1 Influence Susceptibility to RA

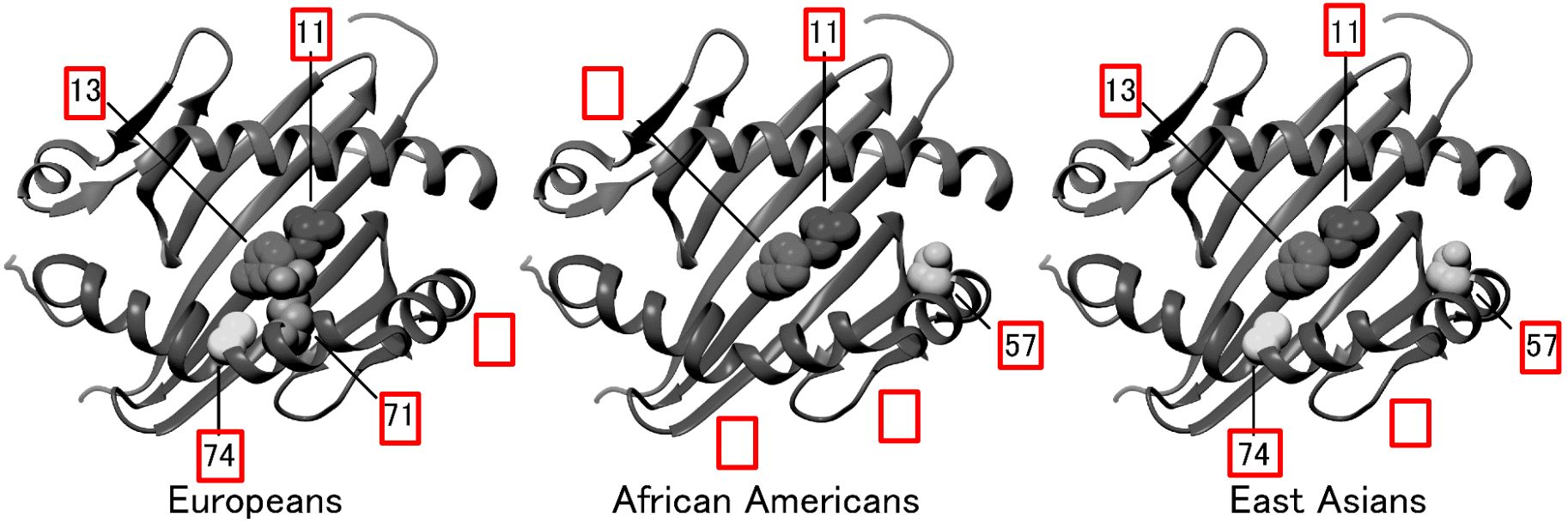


Viatte S. et al. JAMA.2015;313(16):1645-1656.

Differences in HLA-DRB1 Associations in African-Americans with RA compared to European Ancestry

- Amino acid position 11 accounted for nearly all variability explained by HLA–DRB1 (permutation P < 0.00001).
- Conditional analysis demonstrated that position 57 was also significant (permutation P < 0.05).
- The valine and aspartic acid residues at position 11 conferred the highest risk of RA in African Americans.
- Positions 71 and 74 were not associated with RA in African-Americans.
- Asp11 (OR=1 in Europeans) corresponds to the 4-digit classical allele *09:01, which is also a risk allele for RA in Koreans.

Reynolds RJ et al. Arthritis Rheumatol. 66, 3274–82 (2014)

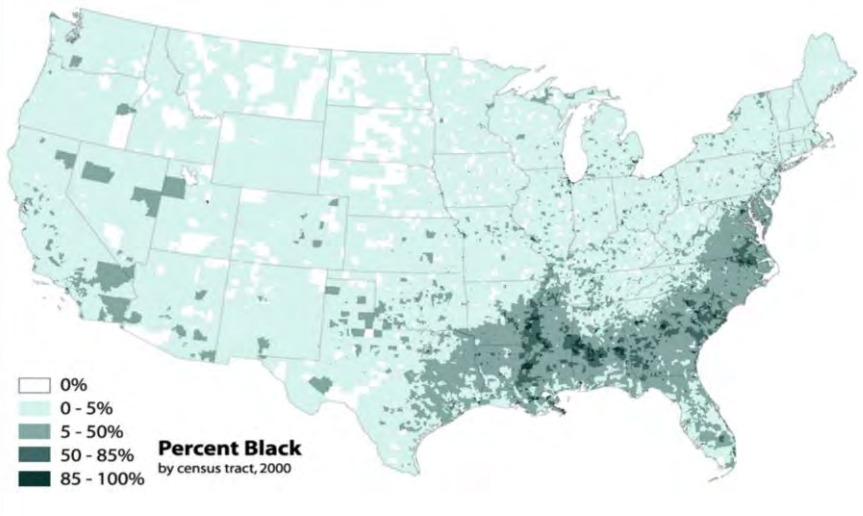


Okada Y, Rheum Dis Clinics NA, 2017 Aug; 43(3):481-487.

HLA-DRB1 Contributions to Genetic Susceptibility to RA in African Americans

HSS

CLEAR
Consortium for the Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis



- HLA-DRB1 alleles containing the SE are found in ~60-70% of European ancestry RA and ~40% of controls. The absolute contribution of HLA-DRB1 alleles containing the SE to RA in African-Americans appears to be less (42% vs. 25%) (p = 0.0004).

- Increased frequency of HLA-DRB1 RA risk alleles in African Americans is associated with higher admixture with European ancestry which may lead to higher susceptibility to RA when exposed to environmental triggers

Hughes LB, et al. Arthritis Rheum. 2008 Feb;58(2):349-58.

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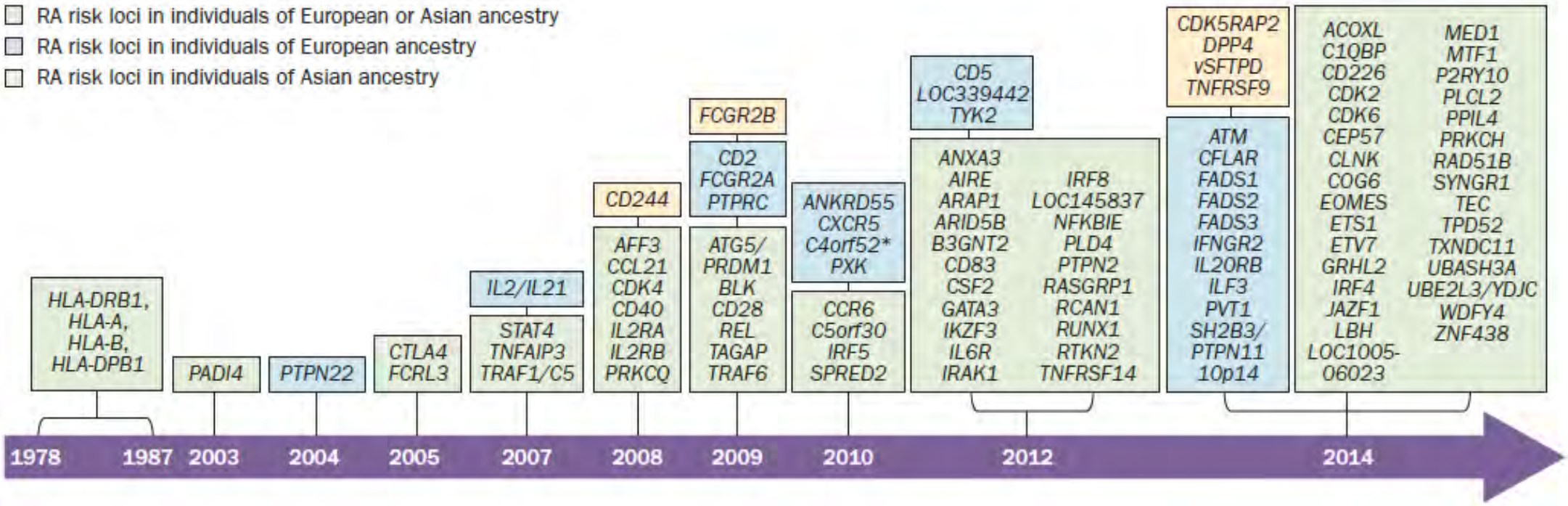
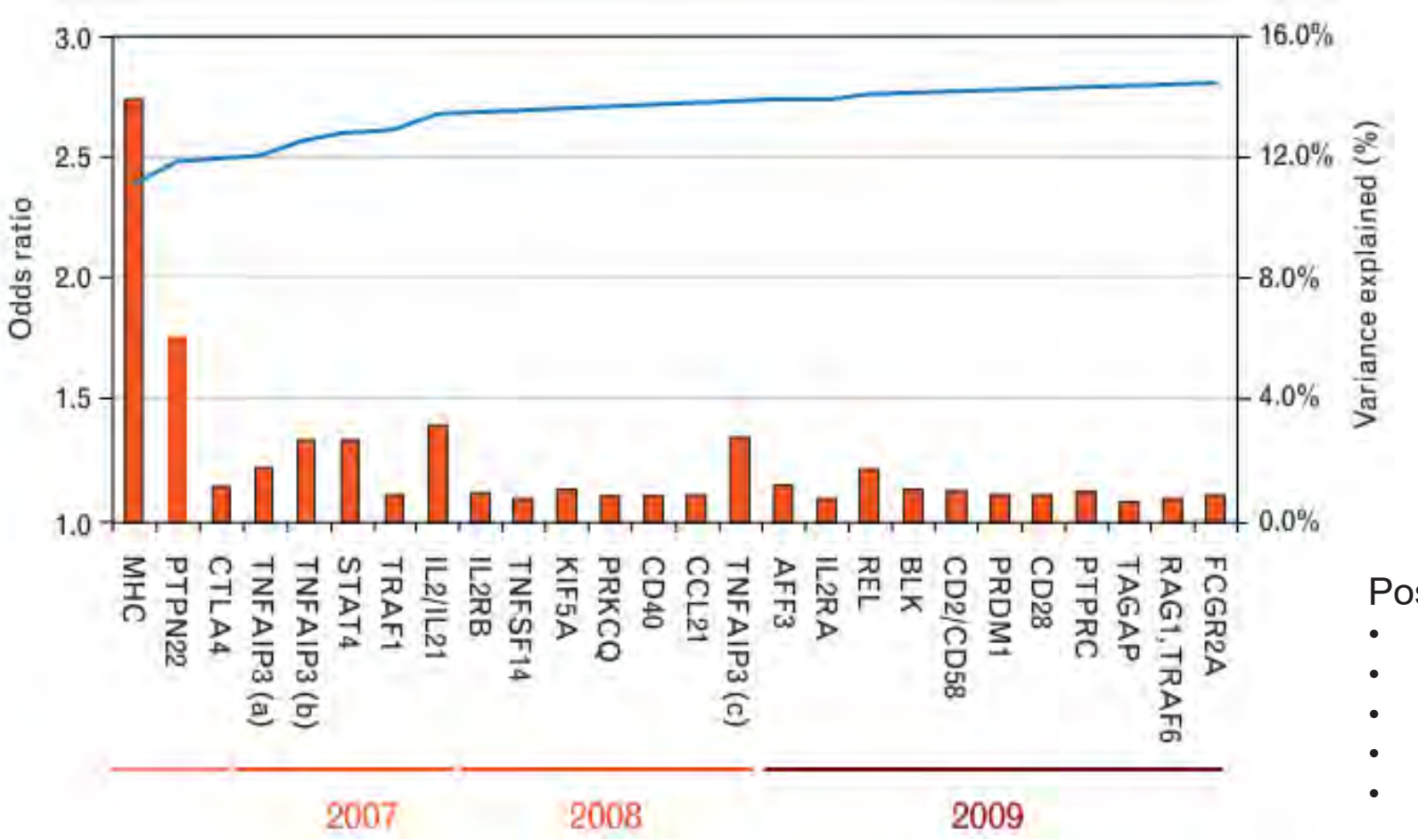
Historical Overview of RA Susceptibility Loci in Persons of European and Asian ancestry



Risk loci selected with a genome-wide significance threshold of $P < 5.0 \times 10\text{-}8$ are included. *Also known as *SMIM20*.

Yamamota K et al. Nat Rev Rheumatol. 2015 Jun;11(6):375-9.

Variance explained by Rheumatoid Arthritis Genetic Associations



Raychaudhuri S. Recent advances in the genetics of rheumatoid arthritis Current Opinion in Rheumatology 22(2):109-118, 2010

Personal Genomes:
The Case of the Missing Heritability

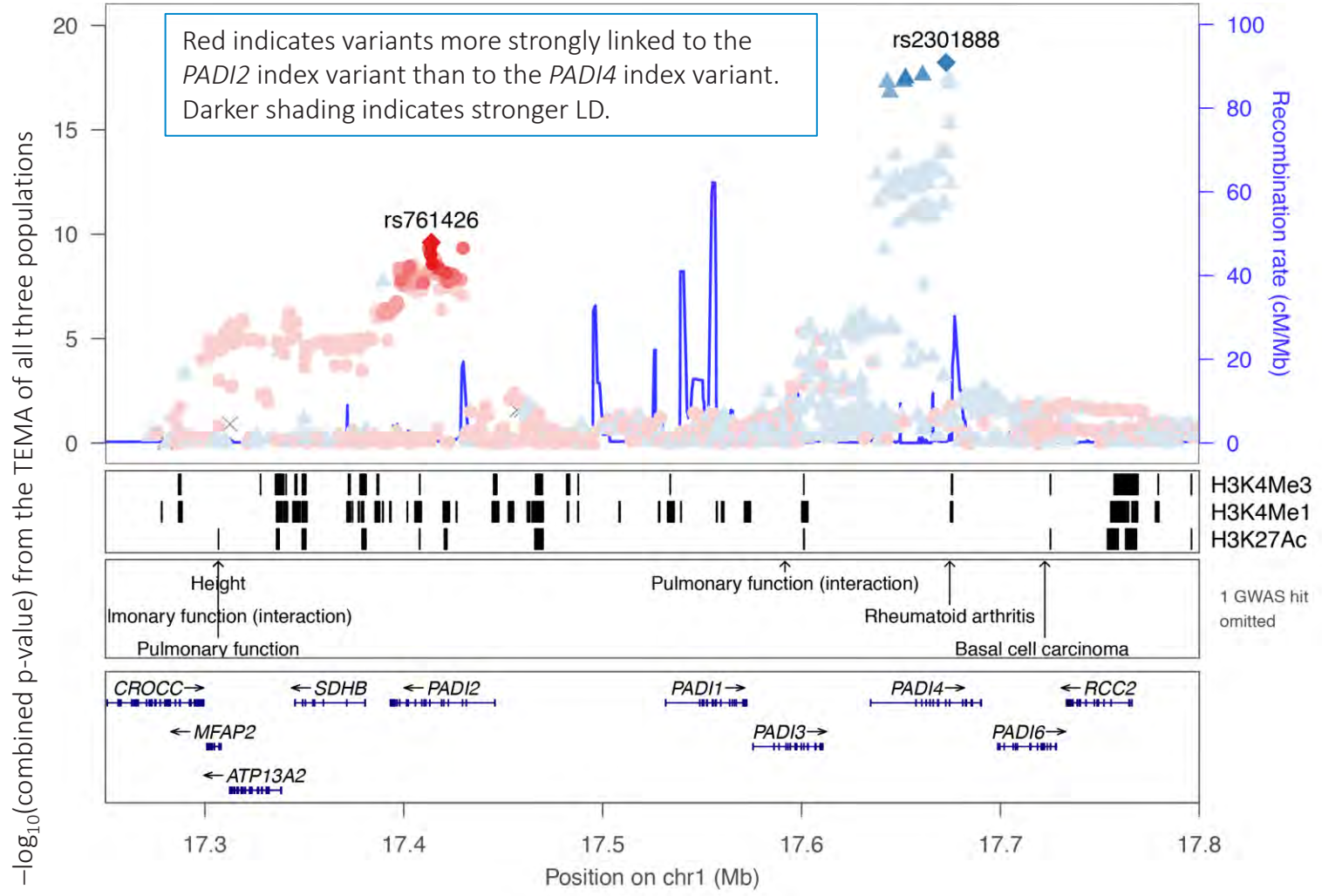
Maher BS. Nature 2008 456(7218):18-21

Possible Explanations:

- Genotyping technologies (not dense enough)
- Many loci with small effects contribute to phenotype
- Rare variants with larger effects
- Structural variants (indels)
- Interactions between many factors (gene x gene, gene x environment, etc.)

Genin E. Missing heritability of complex diseases: case solved? Human Genetics (2020) 139:103.

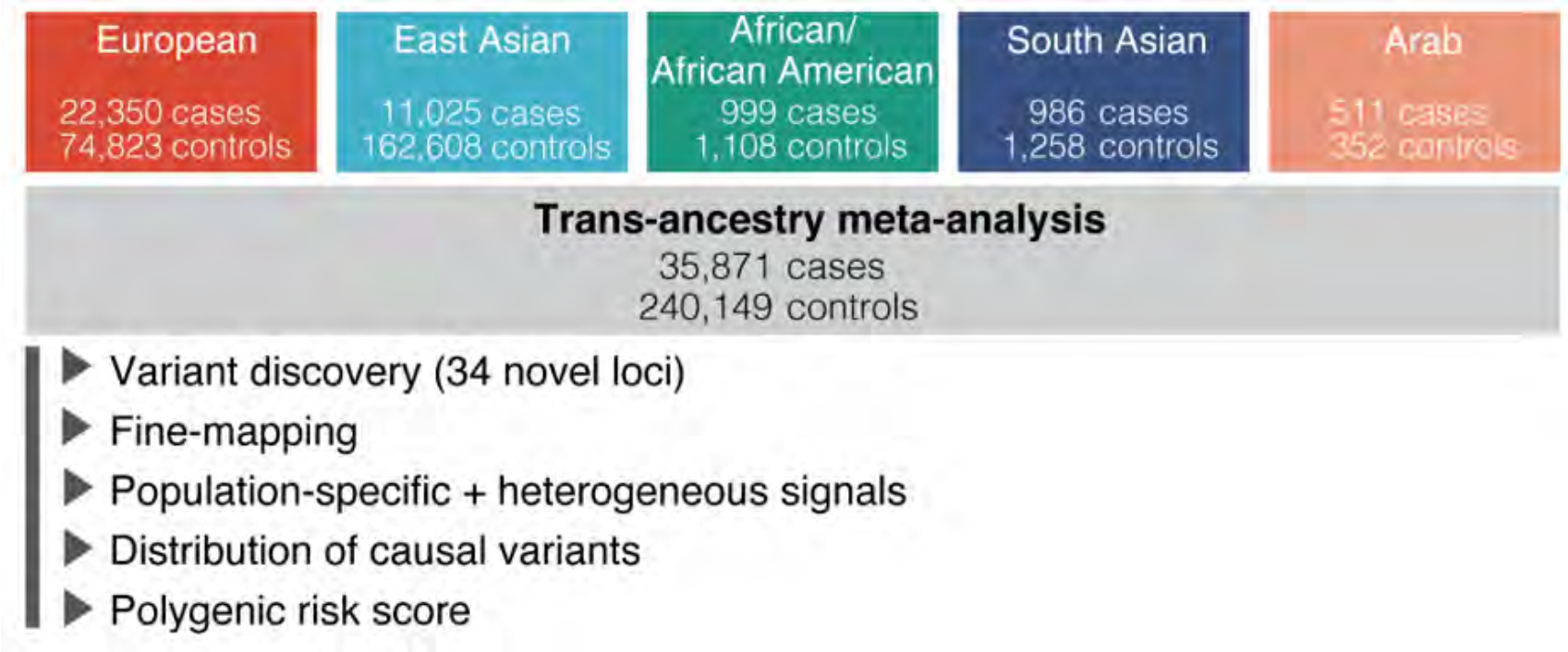
PADI4 and *PADI2* are Independently Associated with RA in African Americans



Laufer VA et al. Hum Mol Genet. 2019 Mar 1;28(5):858-874.

Diverse Ancestral Background and Study Design of a Trans-Ancestral Genome-wide Association Study

GWAS study design



Ishigaki K, . . ., Gregersen PK, Yamamoto K, Bridges SL Jr, Padyukov L, Martin J, Klareskog L, Okada Y, Raychaudhuri S. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in RA. *Nat Genet*. 2022 Nov;54(11):1640-1651.

Results of a Trans-Ancestral GWAS in RA

- Trans-ancestry meta-analysis of 276,020 samples of five ancestral groups identified 124 loci, of which 34 were novel; 25 had not been implicated in other autoimmune diseases.
- Candidate genes at the novel loci suggested essential roles of the immune system (e.g., TNIP2 and TNFRSF11A) and joint tissues (e.g., WISP1) in RA etiology.
- Trans-ancestry fine mapping identified putatively causal variants with biological insights (e.g., LEF1).
- There was insufficient power to discover new ancestry-specific variants in populations other than European or East Asians.
- Polygenic risk scores (PRS) based on trans-ancestry GWAS outperformed PRS based on single-ancestry GWAS.
- This study provides multiple insights into the etiology of RA and improves genetic predictability of RA.

Ishigaki K, . . ., Gregersen PK, Yamamoto K, Bridges SL Jr, Padyukov L, Martin J, Klareskog L, Okada Y, Raychaudhuri S. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in RA. *Nat Genet*. 2022 Nov;54(11):1640-1651.

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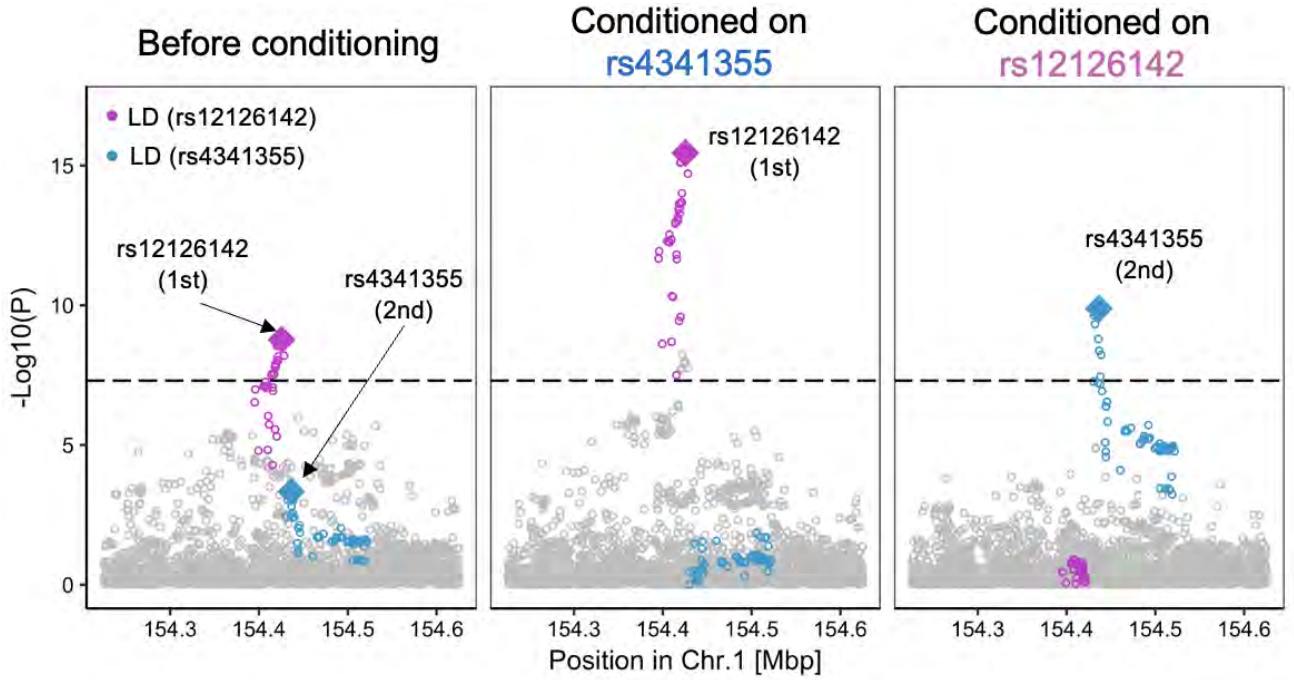
Splicing and Total Expression of IL6R Jointly Contribute to RA Risk

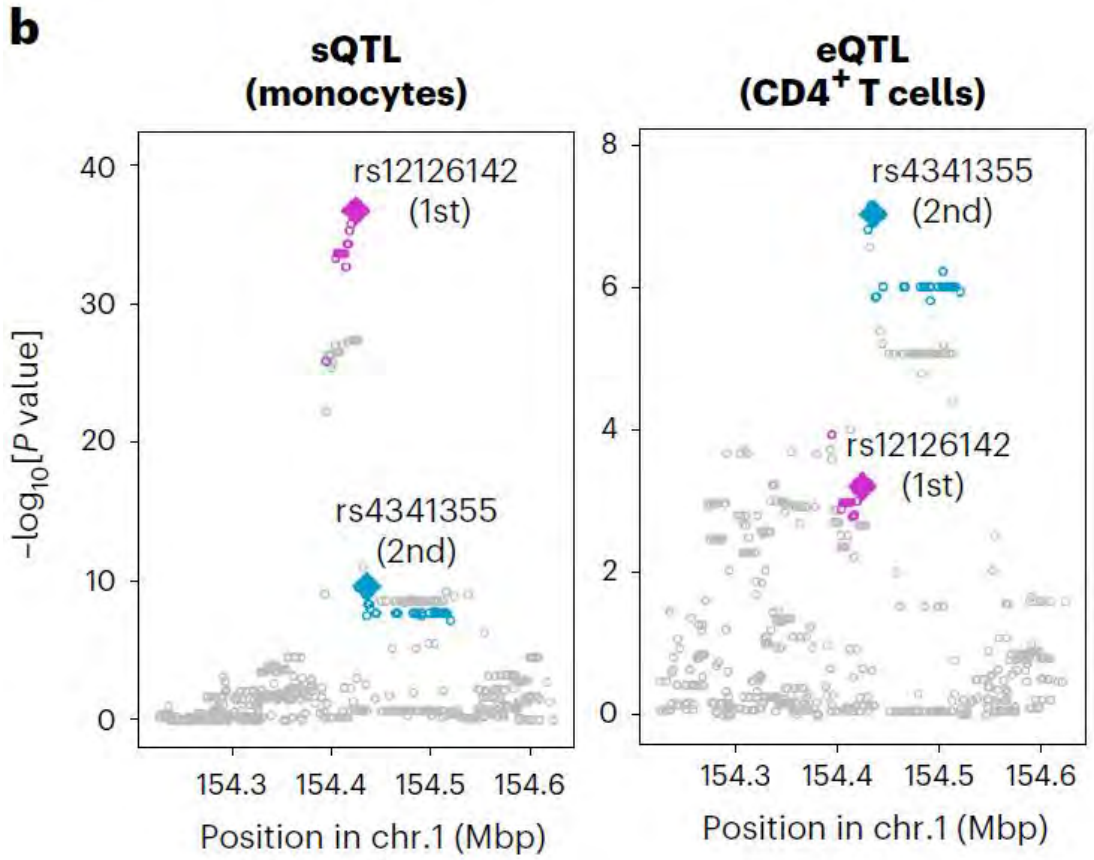
- In the *IL6R* locus, two lead variants are not correlated with each other, but are independently associated with RA in Europeans and East Asians.



The first lead variant (magenta) and the second lead variant (blue) mutually attenuate each other's signals (controlling the effect of the other increased their signals).

Ishigaki K, et al. *Nat Genet*. 2022 Nov;54(11):1640-1651.

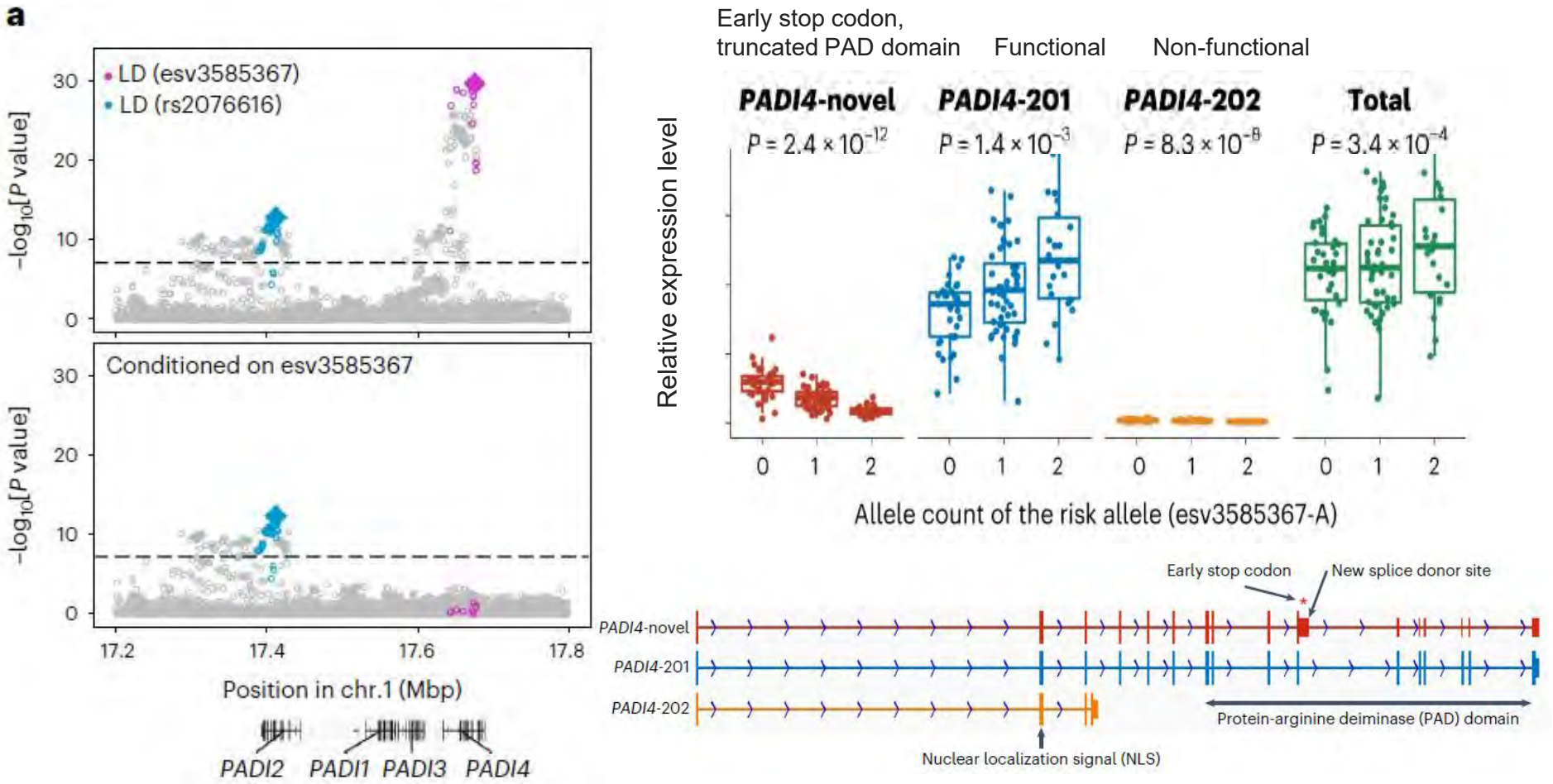
Splicing and Total Expression of IL6R Jointly Contribute to RA Risk



- Analysis of expression quantitative trait loci (eQTLs) and splicing quantitative trrait loci (sQTLs) in three immune cell types: CD4+ T cells, monocytes and neutrophils.
- Two SNPs likely affect *IL6R* transcripts via different mechanisms.
- Rs12126142 associates with a splice soluble form of IL6R in monocytes.
- Rs4341355 associates with expression of IL6R in CD4+ T cells

Ishigaki K, et al. *Nat Genet*. 2022 Nov;54(11):1640-1651.

Splicing of PADI4 contributes to RA risk



Ishigaki K et al. *Nat Genet*. 2022 Nov;54(11):1640-1651.

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See Report	Prefer
View	NM_000 (p.Arg25
View	NM_000 (p.Gly23
View	NM_000 (p.Arg21
View	NM_000 (p.Arg14
View	NM_000 (p.Val17

ACADVL [
ACVRL1
ADA
AKT
APC

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The NM_000022.4:c.532del (p.Val178*) variant in ADA creates a premature translational stop signal in exon 6 (of 12) and is expected to result in nonsense-mediated decay in a loss of function gene (PVS1). This variant was reported as homozygous in an infant with T-B- severe combined immunodeficiency (SCID) (PMID: 30290665) (PP4, PM3_Supporting). The highest population minor allele frequency for this variant in gnomAD v2.1.1 is 0.0001 (2/19948 alleles) in the East Asian population, which is lower than the ADA cutoff (gnomAD popmax filtering allele frequency <0.0001742). So PM2 is met. In summary, this variant meets the criteria to be classified as pathogenic for SCID. ACMG/AMP criteria applied, as specified by the ClinGen SCID-VCEP: PVS1, PP4, PM3_Supporting, PM2_Supporting (SCID VCEP specifications version 1.0).

Met criteria codes

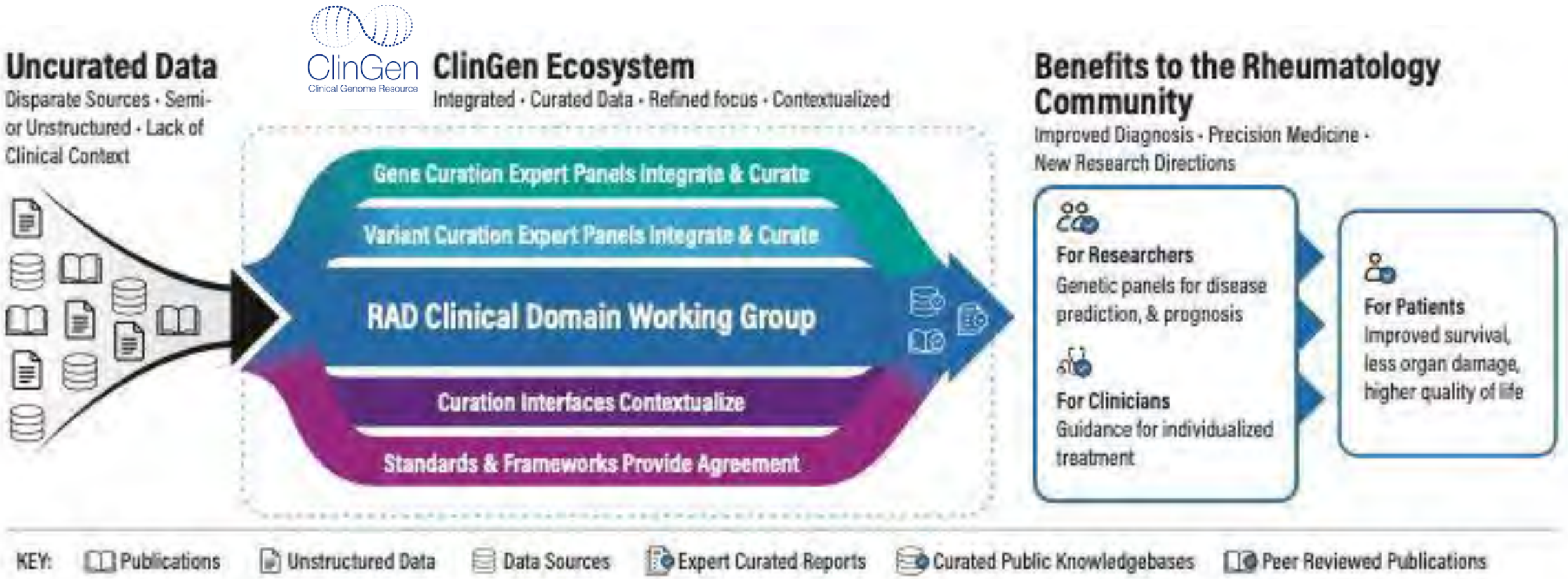
PVS1	✔	Nonsense variant occurring in exon 6 (of 12). NMD+ variant in a loss of function gene.
PP4	✔	Identified 1 homozygous proband with clinical diagnosis of SCID (T-B-)= 0.5p. A large SCID panel was tested, so it also meets PP4 specification for "SCID gene panel or exome/genome sequencing conducted (only applicable if genetic testing did not provide an alternative genetic explanation for SCID/Leaky SCID/Omenn syndrome phenotype)" = 0.5p. NK cells were not mentioned, but given the gene panel or exome/genome sequencing had ruled out alternative causes, we can apply T-B-NK- lymphocyte subset profile = 0.5p. Total 0.5p + 0.5p + 0.5p = 1.5 pts, PP4 is met.
PM2_Supporting	✔	Overall 2/282722 alleles in gnomAD v.2.1.1 (0.000007074). No homozygotes. https://gnomad.broadinstitute.org/variant/20-43252916-AC-A. The highest population minor allele frequency for this variant in gnomAD v2.1.1 is 0.0001 (2/19948 alleles) in the East Asian population, which is lower than the ADA cutoff (gnomAD popmax filtering allele frequency <0.0001742). So PM2 is met.
PM3_Supporting	✔	Homozygous in 1 proband meeting PP4 criteria. 1 homozygous occurrence is worth 0.5p which allows for PM3 at supporting level.

Approved on: 2024-01-16
Published on: 2024-01-16

Curating Genetic Associations with Rheumatic Autoimmune Diseases to Improve Patient Outcomes

HSS

The ClinGen Rheumatologic Autoimmune Diseases (RAD) Clinical Domain Working Group and its Activities



Bridges et al. Notes from the Field: Curating Genetic Associations with Rheumatologic Autoimmune Diseases to Improve Patient Outcomes. Arthritis Rheum, submitted.

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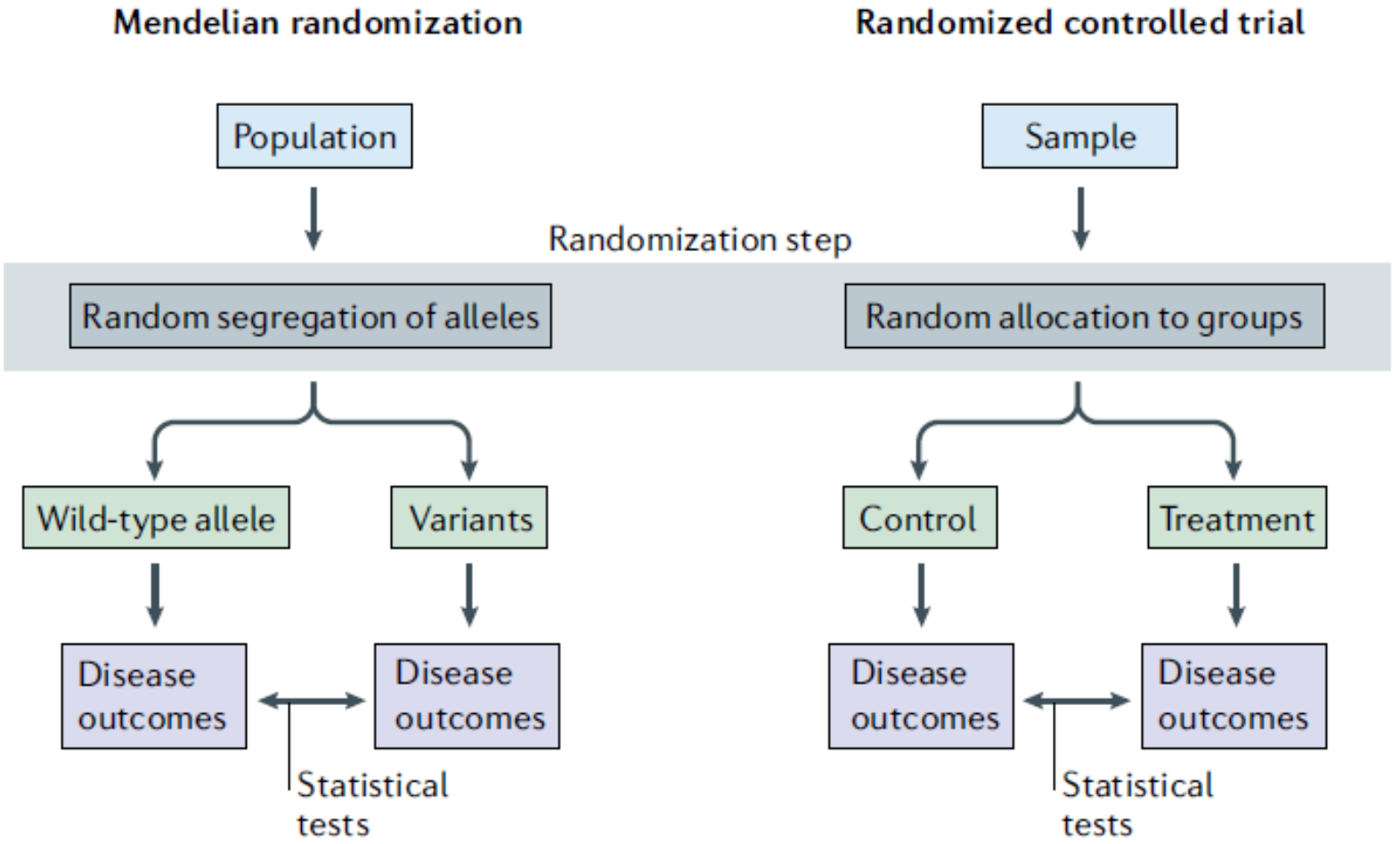
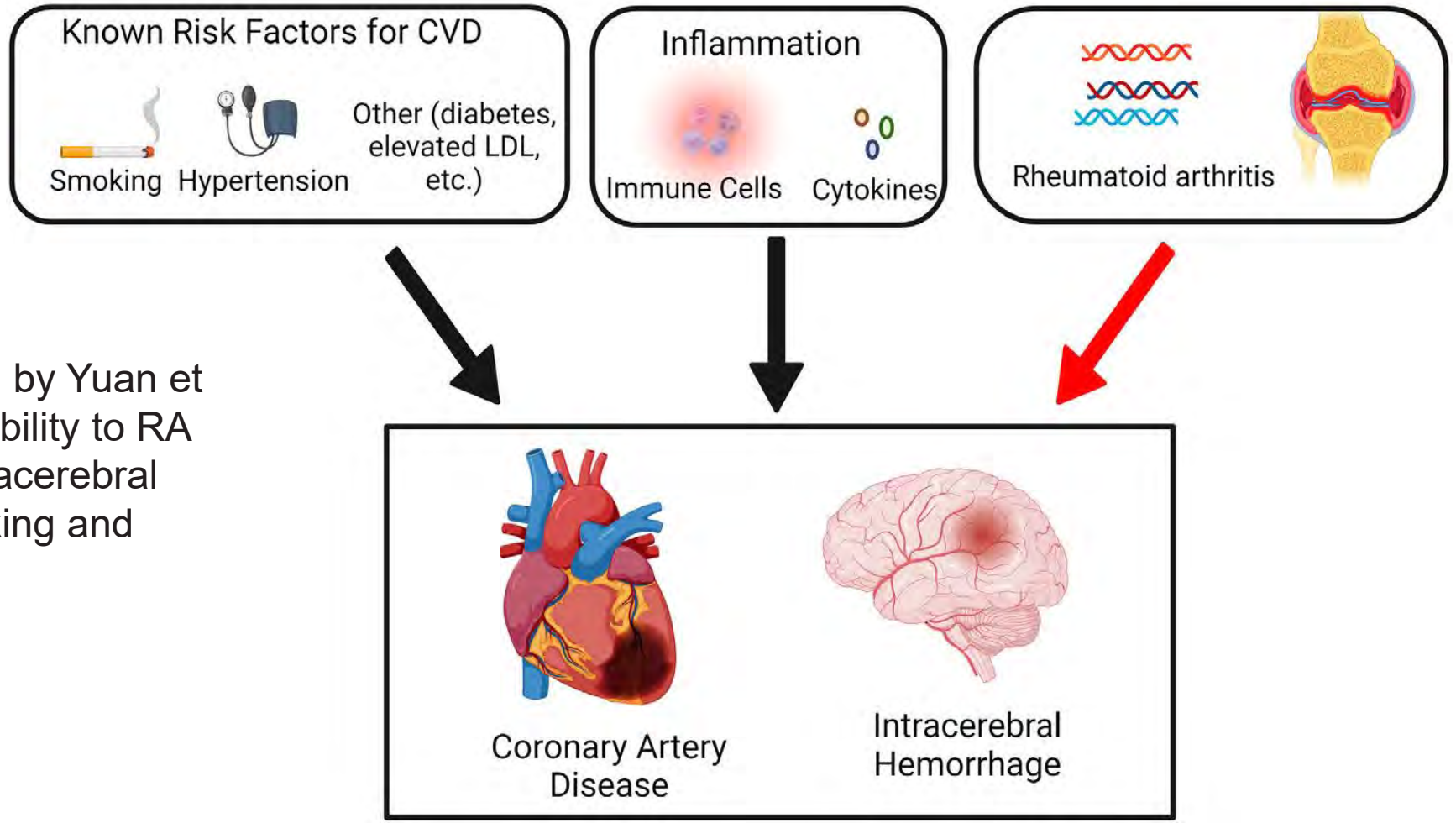
Mendelian Randomization: Comparison to Randomized Controlled Trials



Sanderson E, et al. Mendelian Randomization. Nat Rev Methods Primers. 2022 Feb 10;2:6.

Is RA a Causal Factor in Cardiovascular Disease?



Mendelian randomization analyses by Yuan et al provide evidence that genetic liability to RA is causally related to CAD and Intracerebral Hemorrhage, independent of smoking and other risk factors.

Yuan S, et al. Genetic liability to RA in relation to coronary artery disease and stroke risk. Arthritis Rheum 2022;74:1639.
Bridges SL, Jr., Niewold TB, Merriman TR. Editorial: Arthritis Rheum 2022 74(10), 1612–14.

Selected Mendelian Randomization Studies in RA

Condition	Findings
Age-related macular degeneration	Demonstrated a causal link between AMD and RA
Hashimoto's Thyroiditis	HT patients have elevated risk of RA, RA patients have increased risk of HT
Frailty	Credible evidence that RA is associated with higher risk of frailty
Smoking	Support for a causal association between smoking and increased risk of RA.
Alzheimer’s disease	No evidence of causal relationship
Educational Attainment	Potential inverse causative relationship between years of education and RA
Myasthenia Gravis	RA is a possible causal driver of MG risk
Atrial fibrillation	Causal association between RA and AF
Breast Cancer	No association
Valvular Heart Disease	Causality of genetically predicted IMIDs with the risk of developing into VHD
Cervical Cancer	Causal relationship between RA and the occurrence of cervical cancer
Colorectal Cancer	No association

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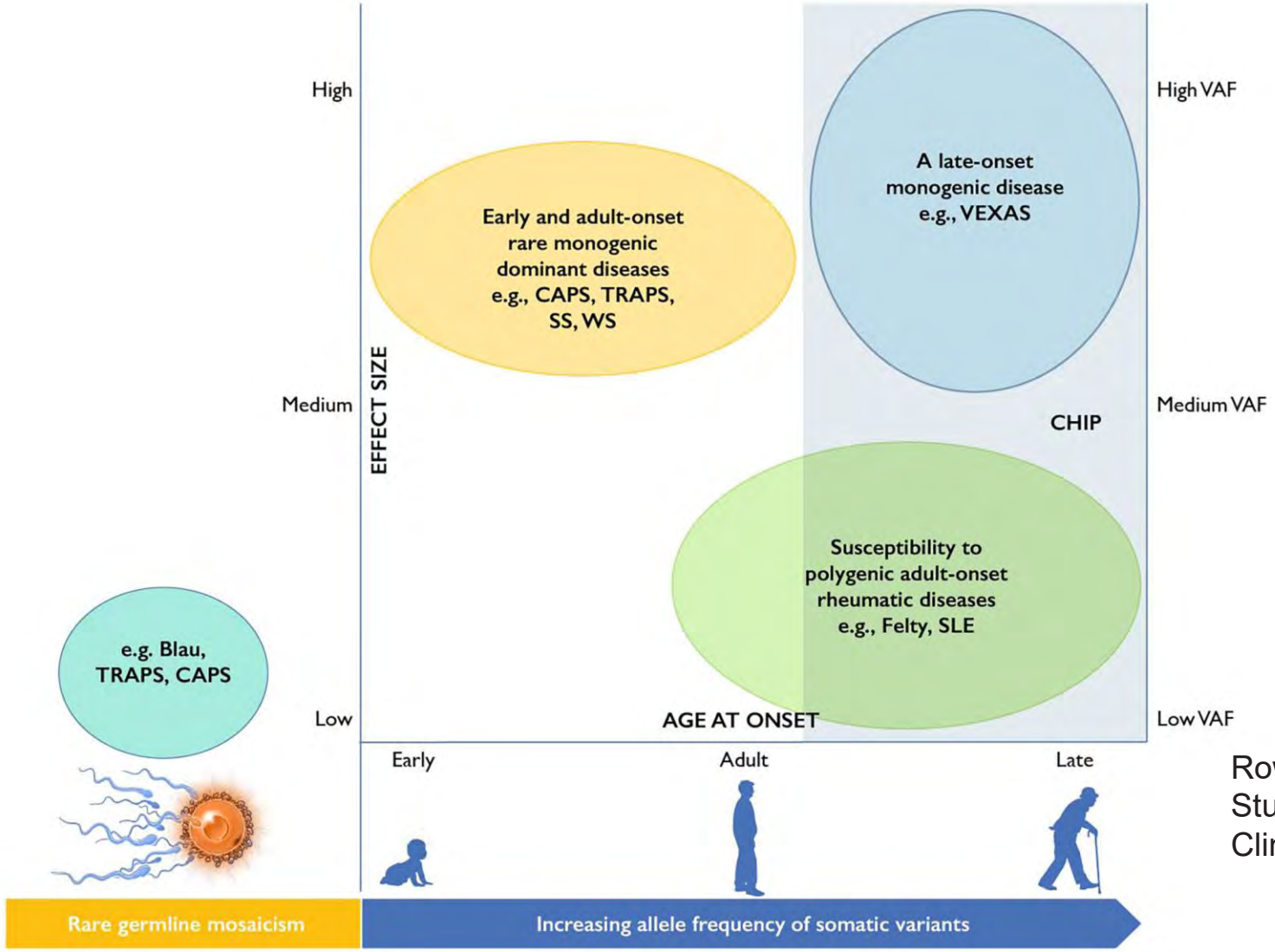
The Spectrum of Somatic Variants in Patients with Rheumatic Diseases Based on Their Effect Size, Age at Disease Onset, and Mutant Variant Allele Frequency



Rowczenio D, Aksentijevich I. Genetic Approaches to Study Rheumatic Diseases and Its Implications in Clinical Practice. Arthritis Rheum, online before print.

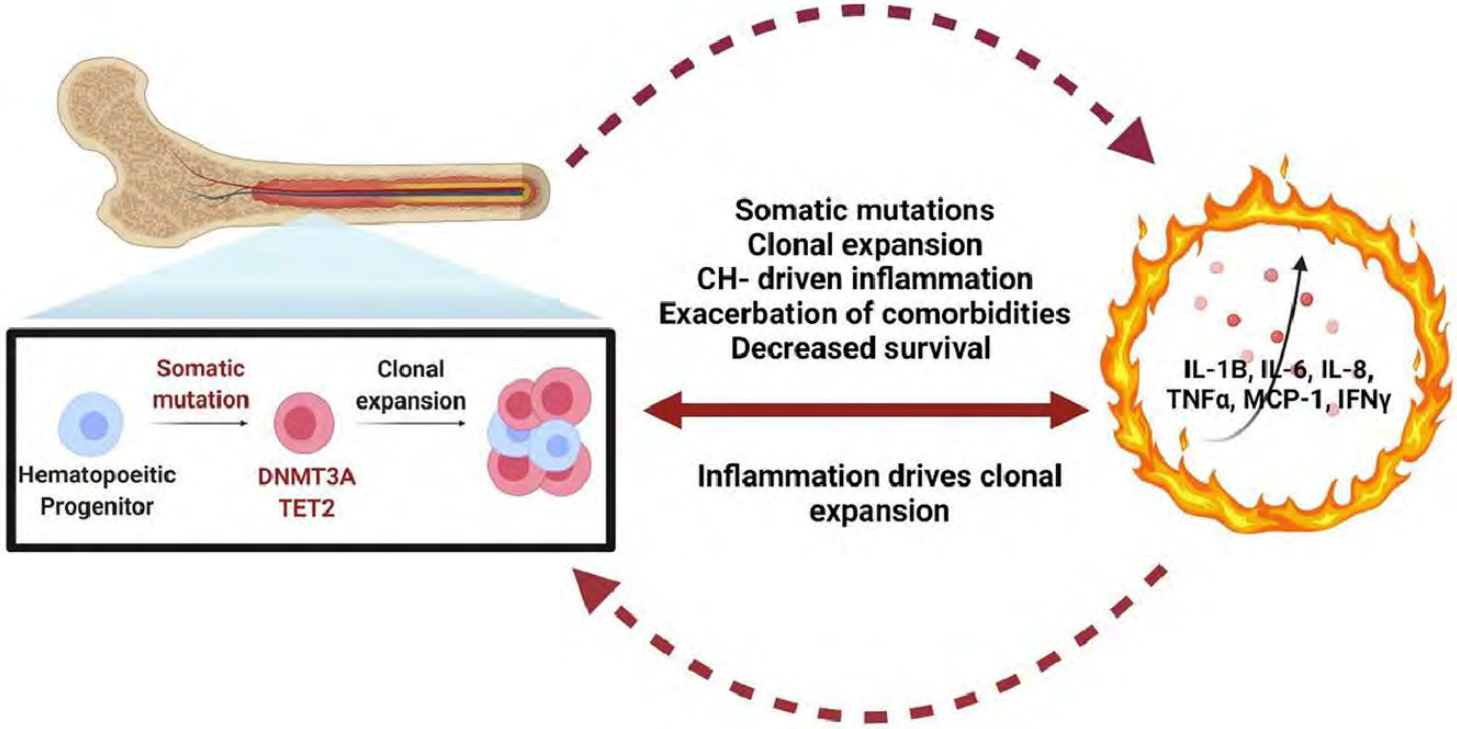
Inflammatory Diseases Associated with Somatic Mutations

Disease	Gene	Chr.	Mechanism
Autoimmunity			
ALPS	*FAS*	Chr10	LOF
RALD	*KRAS*	Chr12	GOF
	NRAS	Chr1	GOF
Felty syndrome	*STAT3*	Chr17	GOF
Autoinflammatory			
NLRP3-AID	*NLRP3*	Chr1	GOF
AIFEC	*NLRC4*	Chr2	GOF
TRAPS	*TNFRSF1A*	Chr12	GOF
Blau syndrome	*NOD2*	Chr16	GOF
SAVI	*TMEM173*	Chr5	GOF
VEXAS	*UBA1*	X	LOF
JAK1 GOF	*JAK1*	Chr1	GOF
MDS–Behçet's	N/A	Chr8	Trisomy
ECD	*BRAF*	Chr7	GOF

Sikora KA et al. Somatic mutations in rheumatological diseases: VEXAS syndrome and beyond. Rheumatology (Oxford). 2022 Aug; 61(8): 3149.

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

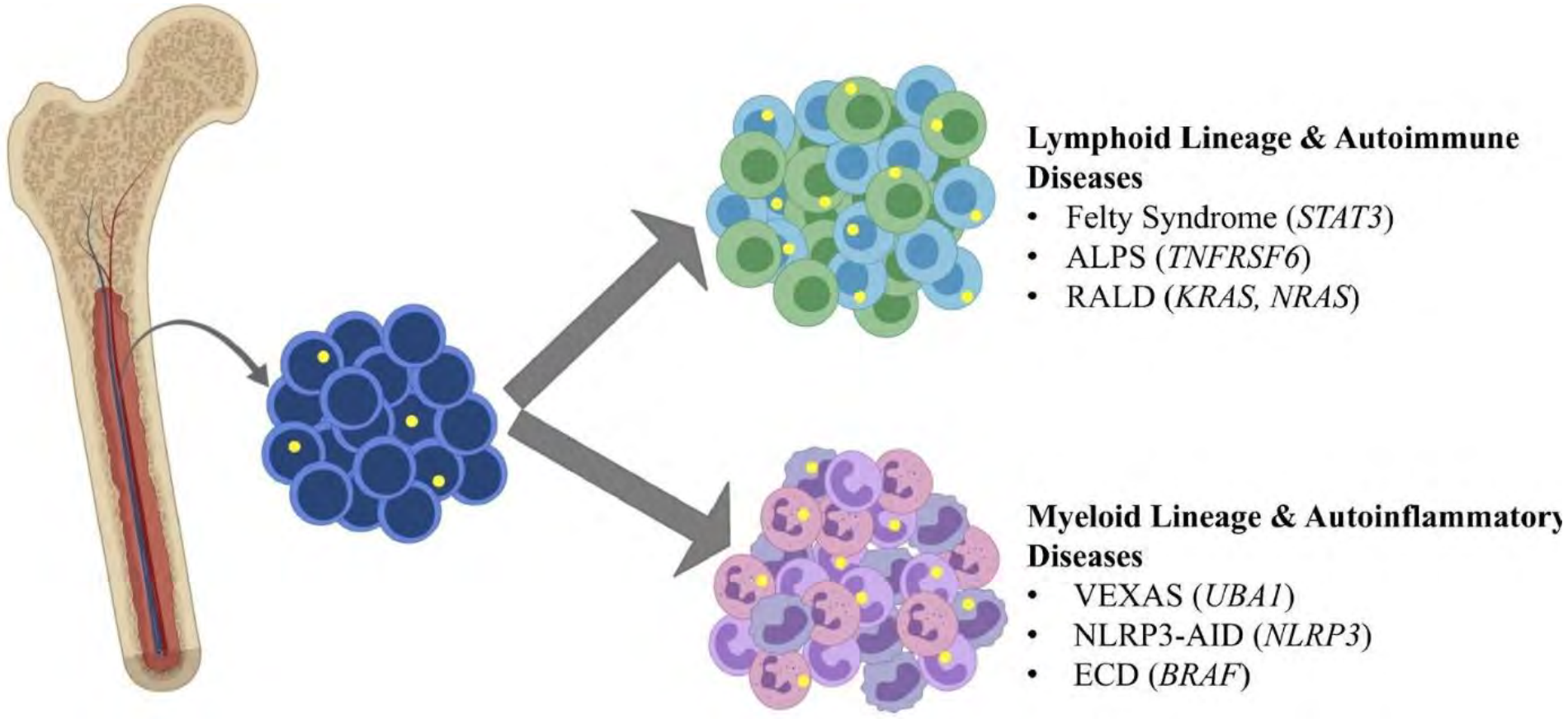
- Mutations in genes associated with myeloid neoplasms can be found in clonal populations of peripheral blood cells in some healthy people.
- CHIP is defined by somatic mutations in ≥ 1 gene usually with variant allele fraction ≥2% in blood) without cytopenia or clonal disorders.
- The most common genes are *DNMT3A*, *TET2*, *JAK2* and *ASXL1*.
- The prevalence of CHIP increases with age and is associated with independent risk for CVD and stroke.
- CHIP has been associated with RA, ANCA-associated vasculitis, SSc and GCA but whether it is driven by inflammation or directly contributes to inflammatory conditions is unknown.



Kusne Y et al. Clonal hematopoiesis and VEXAS syndrome: survival of the fittest clones? Semin Hematol 58(4)226. 2021

Sikora KA et al. Somatic mutations in rheumatological diseases: VEXAS syndrome and beyond. Rheumatology (Oxford). 2022 Aug; 61(8): 3149.

Somatic mutations in bone marrow become lineage restricted to myeloid or lymphoid cell populations



Sikora KA et al. Somatic mutations in rheumatological diseases: VEXAS syndrome and beyond. Rheumatology (Oxford). 2022 Aug; 61(8): 3149.

Outline

HSS

Background
1. Clinical Manifestations and Pathogenesis

Genetic Susceptibility
1. The HLA Region
2. Non-HLA Loci
3. Functional Genomics

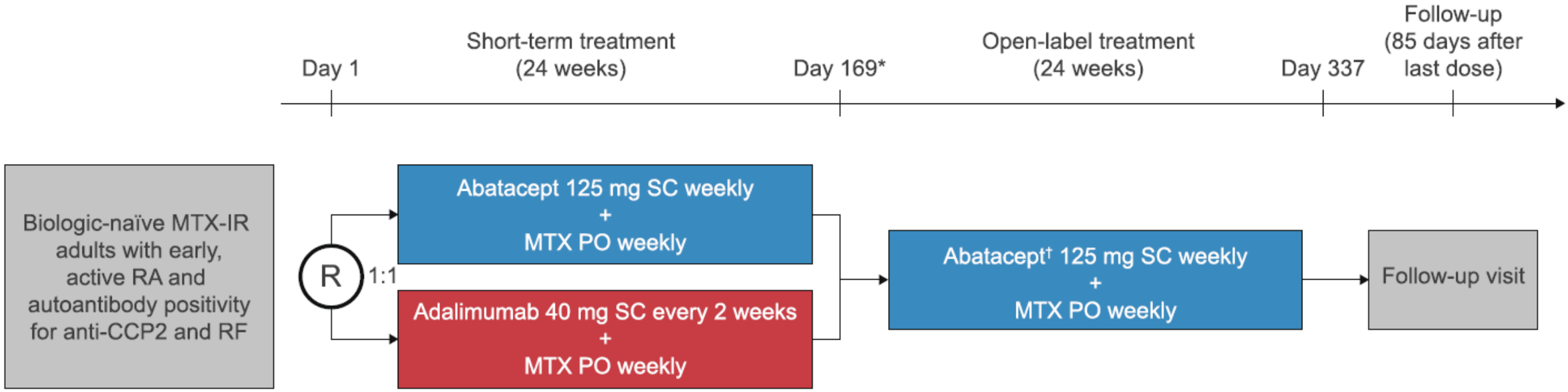
Gene Curation

Mendelian Randomization

Somatic Mutations

Pharmacogenetics

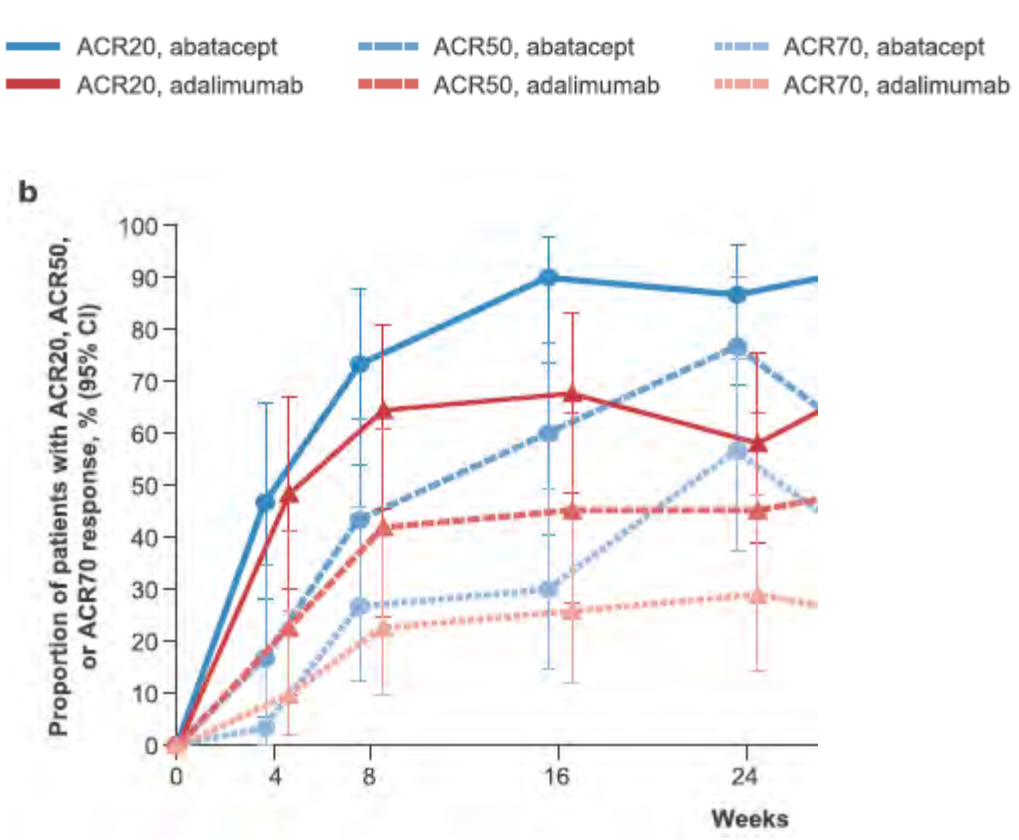
Study Design: Head-to-head, randomized, single-blind study of adalimumab vs abatacept in autoantibody-positive early RA

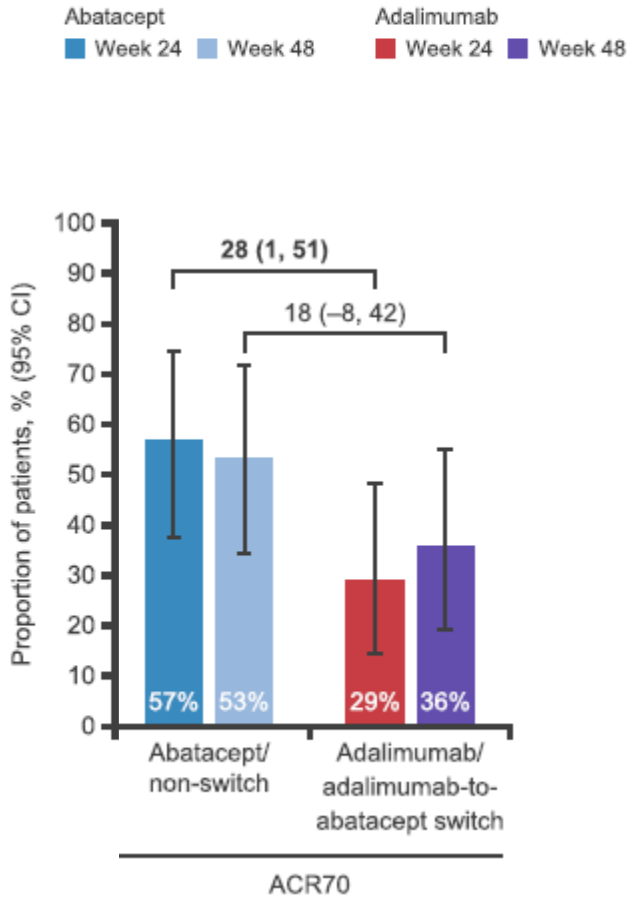


"Early AMPLE": Abatacept versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate

Rigby W, et al. Rigby et al. *Arthritis Research & Therapy* (2021) 23:245

Study Design: Head-to-head, randomized, single-blind study of adalimumab vs abatacept in autoantibody-positive early RA





Rigby W, et al. Rigby et al. *Arthritis Research & Therapy* (2021) 23:245

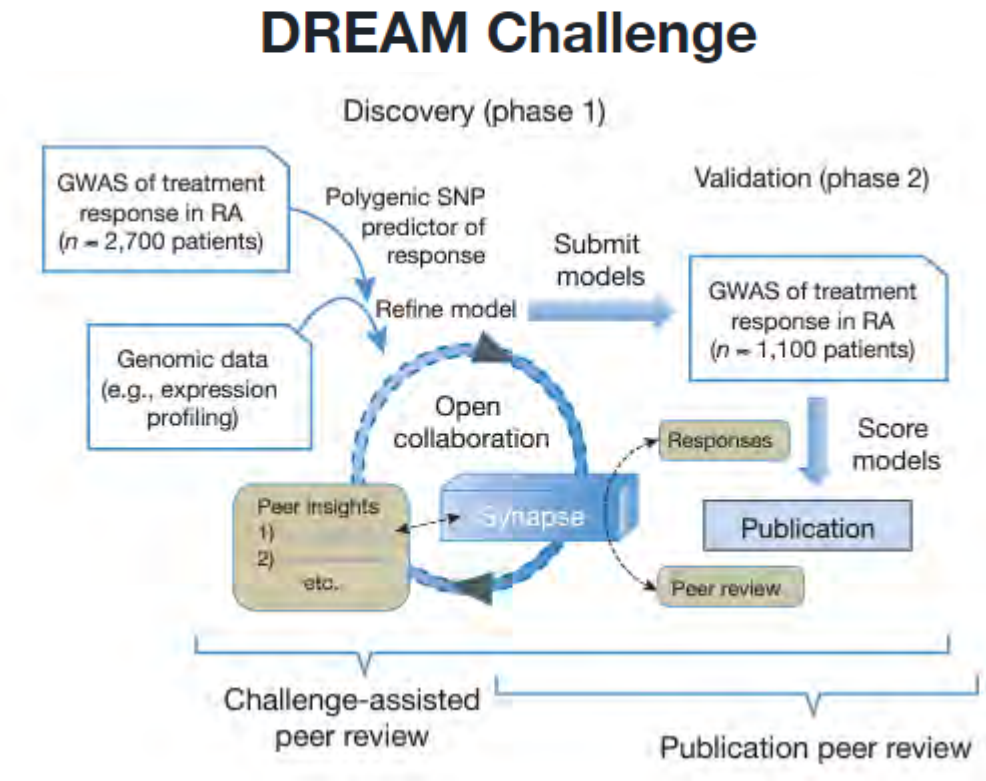
HLA-DRB1 Shared Epitope Dose Effect: RA Patients with 50% Clinical Response among Treatment Groups

	Double dose	*Single dose*	*None*	*p Value*
Methotrexate (%)	2/8 (25)	5/14 (36)	5/6 (83)	0.05
Sulphasalazine-hydroxychloroquine (%)	4/8 (50)	6/14 (43)	3/8 (38)	1.0
All three drugs (%)	5/5 (100)	12/13 (92)	7/8 (88)	1.0

*p Values are for dose effect of each treatment.

O'Dell JR et al. HLA-DRB1 typing in rheumatoid arthritis: Predicting response to specific treatments. Ann Rheum Dis. 1998 Apr;57(4):209-13.

Are There Genetic Predictors of Treatment Response to TNF Inhibitors in RA?



Plenge RM et al. Crowdsourcing genetic prediction of clinical utility in the RA Responder Challenge. Nat Genet. 2013 May;45(5):468-9.

DREAM Challenge Models Suggest SNPs Won't Improve Rheumatoid Arthritis Treatment Response Prediction

Aug 25, 2016 | Andrea Anderson

Premium

NEW YORK (GenomeWeb) – A project that brought together computational methods and modeling approaches from dozens of research groups suggests common SNP profiling is likely not the most promising avenue for unearthing markers for predicting treatment response in individuals with rheumatoid arthritis.

Researchers from more than 70 teams put forth modeling methods to evaluate the possibility of using SNP profiles to predict response to so-called anti-TNF treatments, which target the tumor necrosis factor-alpha inflammatory cytokine in individuals with rheumatoid arthritis.

Sieberts SK et al. Crowdsourced assessment of common genetic contribution to predicting anti-TNF treatment response in RA. Nat Commun. 2016 Aug 23:7:12460.

Summary

- Despite years of research, we still do not understand the mechanism by which HLA-DRB1 alleles predispose to RA.
- Multiple non-HLA genes contribute to RA susceptibility, likely through gene regulation and interactions between genes and environment.
- Functional Genomics has begun to shed light onto the role of PADI4 enzymes and the IL-6 Pathway in Susceptibility to RA,
- Gene Curation will hopefully help prioritize investigation of pathogenic variants to find better ways to treat patients.
- Newer genetic techniques are uncovering diseases associated with RA through genetics.
- Novel syndromes due to monogenic diseases or somatic mutations are being increasingly recognized.
- Pharmacogenetics may help to advance precision medicine in RA.

Questions?

HSS is nationally ranked No. 1 in orthopedics (for the 14th consecutive year) and No. 2 in rheumatology by *US News & World Report*. HSS has been top-ranked in orthopedics and rheumatology for 32 consecutive years