FROM MOLECULE TO PATIENT

Predicting immune-mediated adverse drug reactions and emerging immunogenetic discoveries

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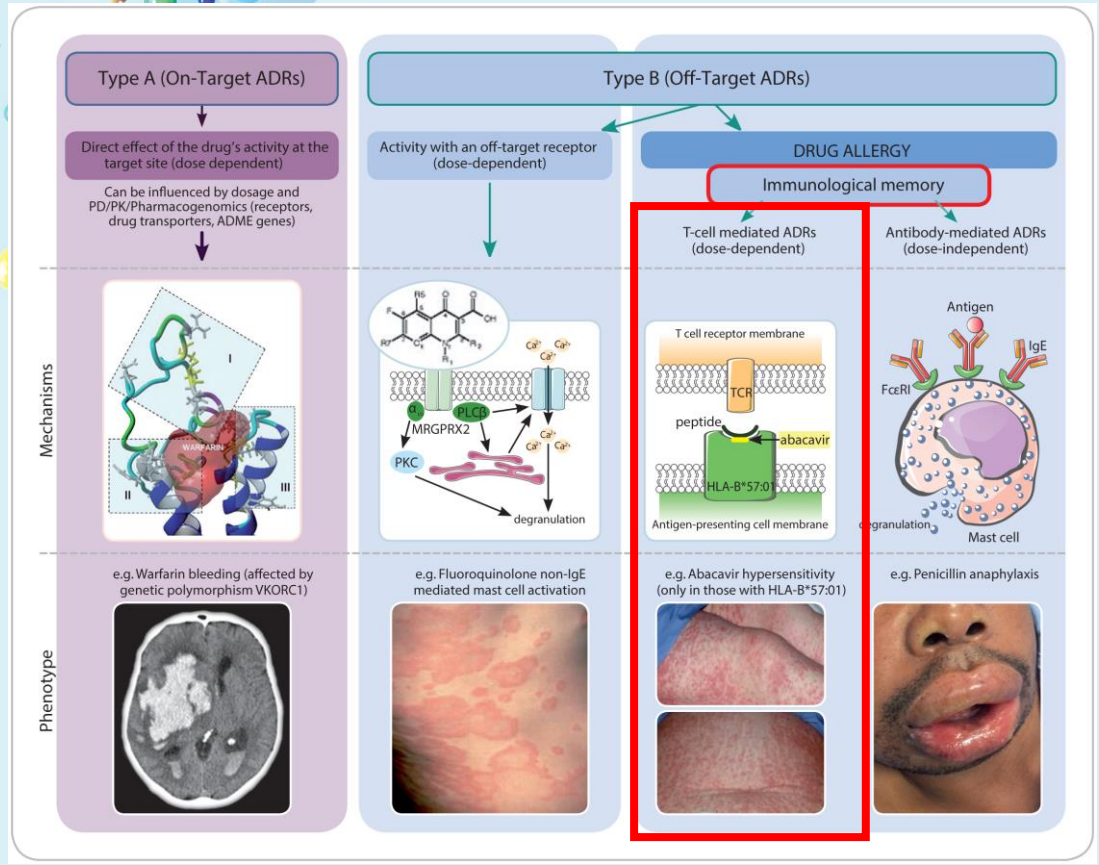
University of Arizona

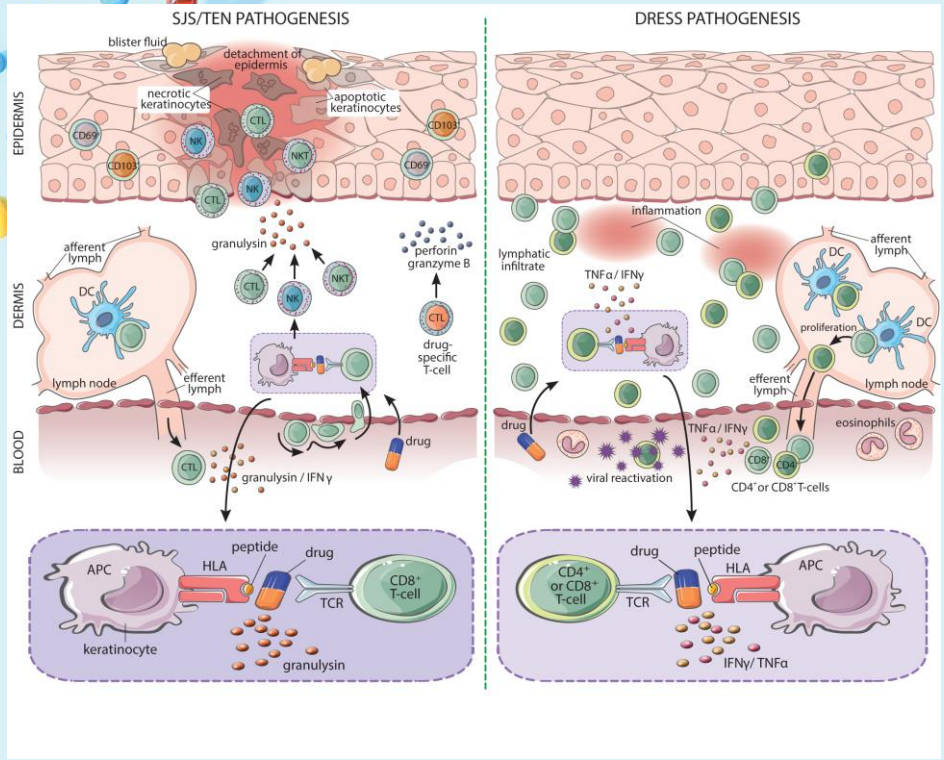
Immune-mediated adverse drug reactions



- ADRs a major health problem
  - 6-7% hospitalizations
  - 100,000 deaths/year in US
  - Primary cause of drug withdrawal from market
  - 20% of ADRs are immune-mediated with often greater health care cost
- Type 1 (Type A)
  - Dose dependent, "predictable"
  - Related to drug's pharmacological action
- Type 2 (Type B - idiosyncratic)
  - "unpredictable"
  - inappropriate immuno-allergic reaction

Karnes et al. *Annual Review of Pharmacology and Toxicology.* 2019
Pavlos et al. Annu Rev Med 66:439-54

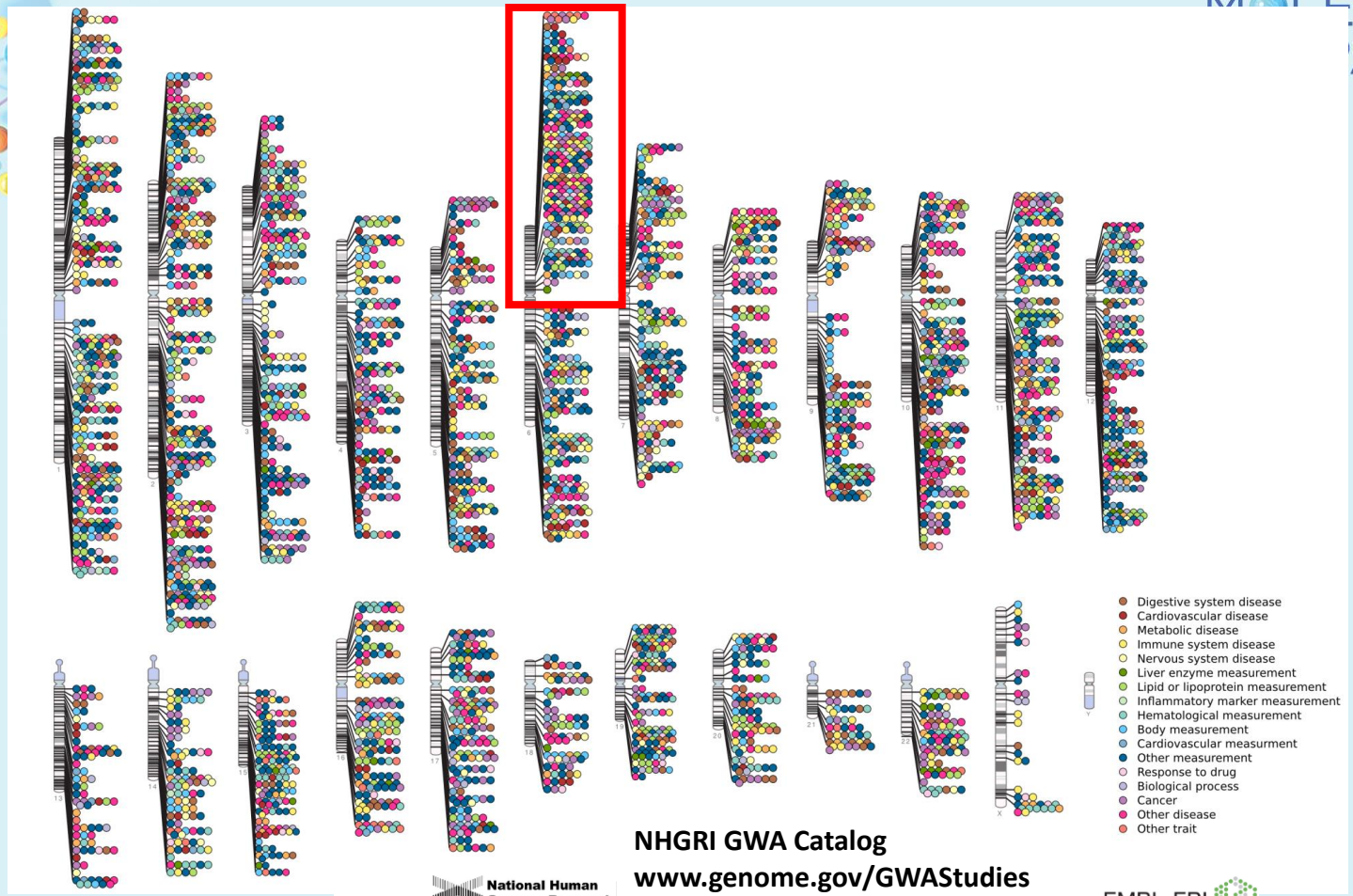
Severe immune-mediated adverse drug reactions



- Types of serious reactions:
  - usually delayed, T cell-mediated
  - Stevens-Johnson syndrome (SJS)
  - Toxic epidermal necrosis (TEN)
  - Drug induced liver injury (DILI)
  - Hypersensitivity syndromes (HSS)
- SJS/TEN
  - Mortality rate up to 50%
  - No treatment guideline, highlighting lack of evidence-based treatment
- HLA alleles can be used to predict severe IM-ADRs to certain anti-epileptics, antibiotics, HAART, and other drugs

Karnes et al. *Annual Review of Pharmacology and Toxicology.* 2019

Published Genome-Wide Associations through 12/2013
Published GWA at p≤5X10^{-8} for 17 trait categories



NHGRI GWA Catalog
www.genome.gov/GWAStudies

National Human Genome Research Institute

EMBL-EBI

Key HLA-associated IM-ADRs

FROM MOLECULE TO PATIENT

Drug (references)	*HLA* allele	Adverse reaction	Prevalence of ADR	Carriage rate (%) of *HLA* allele[a]	OR	NPV (population)	PPV (population)	NNT
Abacavir (46, 47, 110, 137)	*B*57:01*	Hypersensitivity reaction	8% of population (3% true, 2–7% false positive HSR)	5–8 (European) <1 (Sub-Saharan African) <1 (Southeast Asian) 2–3 (African American)	960	100%	55%	13
Allopurinol (58, 129, 138–145)	*B*58:01*	SJS/TEN; DRESS/DIHS	1–4/1,000	1–6 (European) 10 (Sub-Saharan African) 10–15 (Southeast/South Asian) 4 (African American)	580	100% (Han Chinese)	3% (Han Chinese)	250
Carbamazepine (50, 109, 117–120, 146–151)	*B*15:02*	SJS/TEN	<1–6/1,000	<0.1 (European) 10–15 (Southeast Asian) <1 (African)	>1,000	100% (Southeast Asian)	2–8%	1,000
Carbamazepine (54, 56, 112, 122, 152, 153)	*A*31:01*	DRESS/DIHS	0.05%	≤6 (European) <1 (Sub-Saharan African)	57.6	99.9%	0.89%	3,334
Dapsone (67)	*B*13:01*	DRESS/DIHS	1–4/100	0 (European) 2–30 (Southeast Asian)	20	99.8%	7.8%	84
Flucloxacillin (43)	*B*57:01*	Drug-induced liver injury	8.5/100,000	5–8 (European) <1 (Sub-Saharan African) <1 (Southeast Asian) 2–3 (African American)	81	99.9%	0.12%	13,819
Methimazole/ carbimazole (32, 65, 154)	*B*38:02*	Agranulocytosis	Unknown	5–15 (China, Taiwan) <1 (European) <1 (African)	266–753	99.9%	7–30%	211–238
	*B*27:05*			4–8 (European) <2 (China) <1 (Africa)				
Nevirapine (4, 155)	*C*04:01*	DRESS	Unknown	15–30 (average prevalence across races)	3–7	95–97%	5–27%	Variable
Oxcarbazepine (156–158)	*B*15:02*	SJS/TEN	Unknown	<0.1 (European) 10–15 (Southeast Asian) <1 African	27.9	99.9% (Han Chinese)	0.73% (Han Chinese)	>5,000

Karnes et al. *Annual Review of Pharmacology and Toxicology.* 2019

CPIC guidelines for IM-ADRs

FROM MOLECULE TO PATIENT

Table 2 Recommended therapeutic use of abacavir in relation to *HLA-B* genotype

Genotype	Implications for phenotypic measures	Recommendations for abacavir	Classification of recommendations[a]
Noncarrier of *HLA-B*57:01*	Low or reduced risk of abacavir hypersensitivity	Use abacavir per standard dosing guidelines	Strong
Carrier of *HLA-B*57:01*	Significantly increased risk of abacavir hypersensitivity	Abacavir is not recommended	Strong

HLA-B, human leukocyte antigen B.

[a]Rating scheme described in **Supplementary Data** online.

Table 2 Recommended therapeutic use of allopurinol by *HLA-B* genotype

Genotype	Implications for phenotypic measures	Recommendations for allopurinol	Classification of recommendations[a]
Noncarrier of *HLA-B*5801* (*X/*X)[b]	Low or reduced risk of allopurinol-induced SCAR	Use allopurinol per standard dosing guidelines	Strong
Carrier of *HLA-B*5801* (*HLA-B*5801/*X,[b] *HLA-B*5801/HLA-B*5801*)	Significantly increased risk of allopurinol-induced SCAR	Allopurinol is contraindicated	Strong

HLA-B, human leukocyte antigen-B; SCAR, severe cutaneous adverse reaction.

[a]Rating scheme described in **Supplementary Table S4** online. [b]*HLA-B* genotype other than *HLA-B*5801* is indicated by *X.

Table 2 Recommendations for carbamazepine therapy based on *HLA-B* and *HLA-A* genotypes

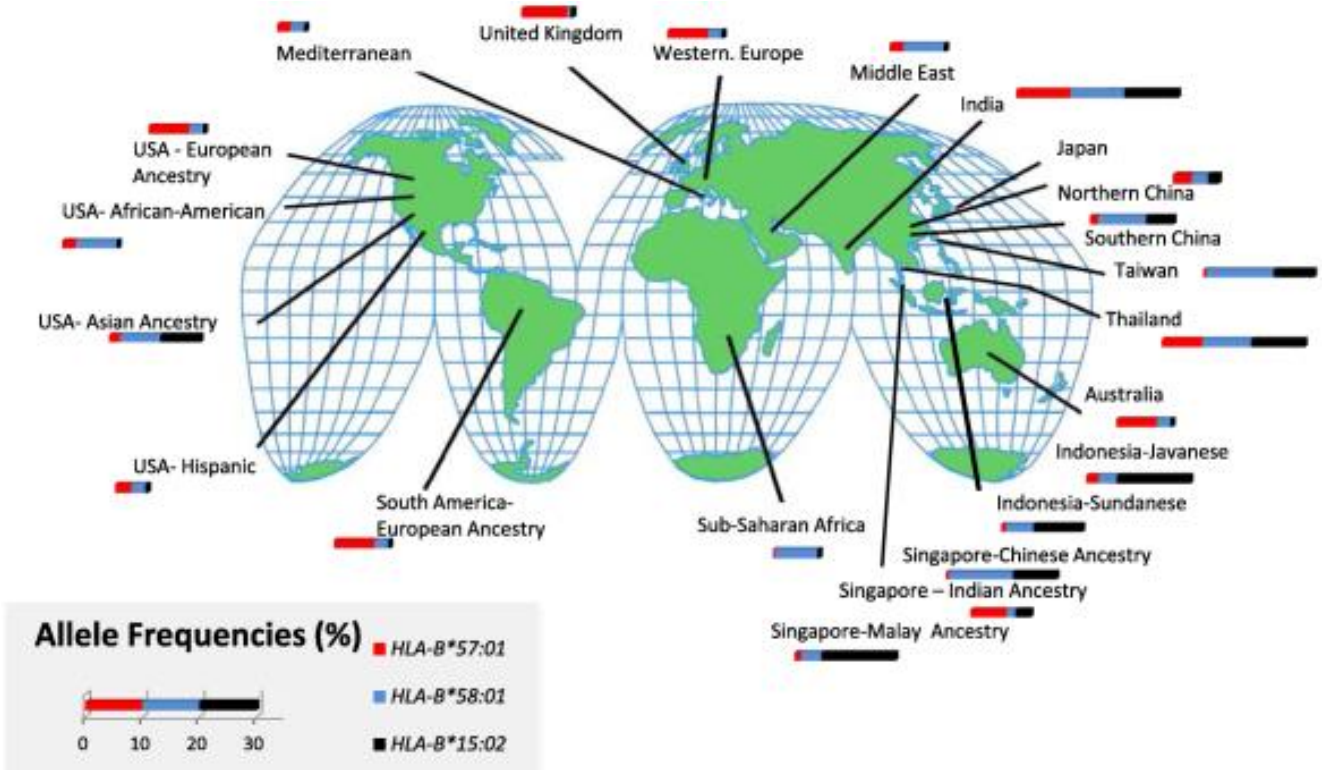
Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative and *HLA-A*31:01* negative	Normal risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	Use carbamazepine per standard dosing guidelines.[b]	Strong	N/A
*HLA-B*15:02* negative)1 positive	Greater risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	If patient is carbamazepine-naïve and alternative agents are available, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent.

Table 2 Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype

	*HLA-B*15:02* carrier			*HLA-B*15:02* noncarrier		
Phenotype/ genotype	Implication	Therapeutic recommendation	Classification of recommendation[a]	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C9 extensive metabolizer	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Normal phenytoin metabolism	Initiate therapy with recommended maintenance dosed	Strong
CYP2C9 intermediate metabolizer	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 25% reduction of recommended starting maintenance dose.[d] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response	Moderate
CYP2C9 poor metabolizer	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin naive,[b] do not use phenytoin/ fosphenytoin[c]	Strong	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 50% reduction of recommended starting maintenance dose.[d] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response	Strong

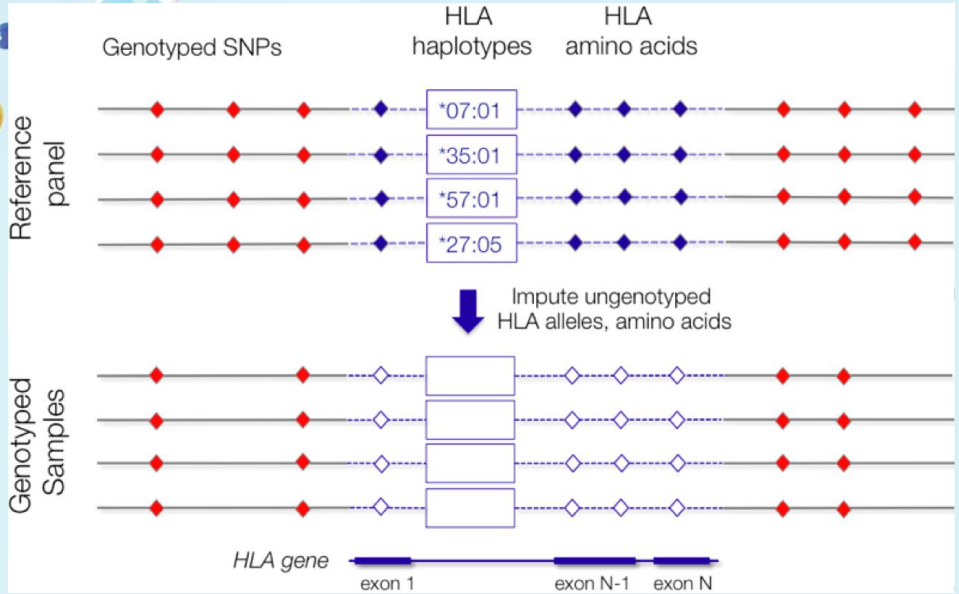
Martin et al. Clin Pharm Ther (2012)
Phillips et al. Clin Pharm Ther (2018)
Caudle et al. Clin Pharm Ther (2014)
Hershfield et al. Clin Pharm Ther (2013)
Saito et al. Clin Pharm Ther (2015)
https://cpicpgx.org/guidelines/

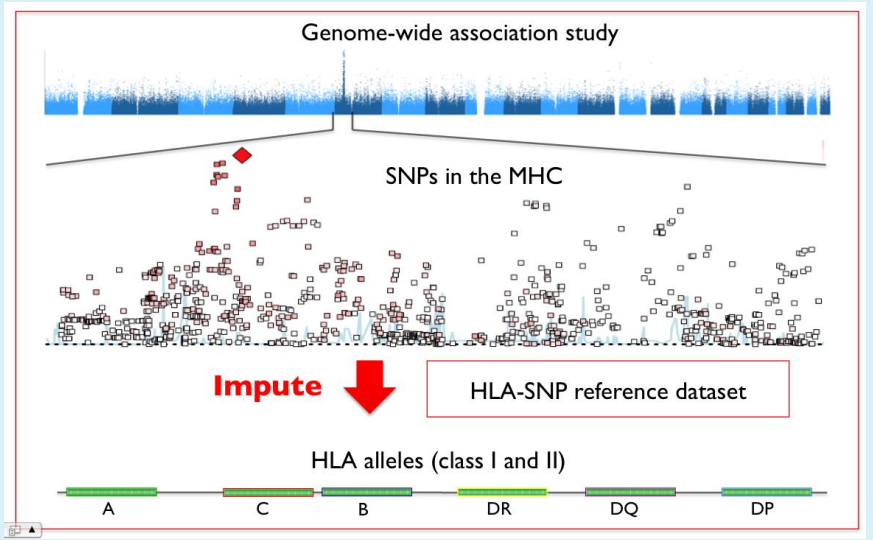
Research Directions in Genetic Predispositions to Stevens–Johnson Syndrome / Toxic Epidermal Necrolysis



Clinical Pharmacology & Therapeutics
Volume 103, Issue 3, pages 390-394, 6 NOV 2017 DOI: 10.1002/cpt.890
http://onlinelibrary.wiley.com/doi/10.1002/cpt.890/full#cpt890-fig-0001

HLA Imputation using GWAS data



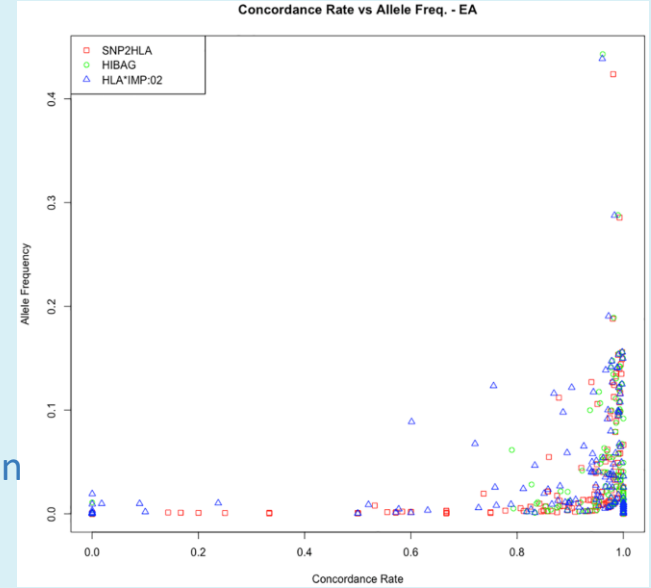


software.broadinstitute.org

		European Americans		African Americans	
Allele	**Imputation Program**	**Concordance Rate**	**Call Rate**	**Concordance Rate**	**Call Rate**
HLA-A	SNP2HLA	0.983	0.999	0.969	0.995
	HLA*IMP:02	0.963	0.997	0.675	0.855
	HIBAG	0.986	0.996	0.960	0.796
HLA-B	SNP2HLA	0.969	1.00	0.884	1.00
	HLA*IMP:02	0.952	0.979	0.423	0.752
	HIBAG	0.978	0.967	0.953	0.403
HLA-C	SNP2HLA	0.987	1.00	0.884	1.00
	HLA*IMP:02	0.984	0.994	0.792	0.741
	HIBAG	0.987	0.992	0.957	0.619
HLA-DPB1	SNP2HLA	0.957	1.00	0.945	1.00
	HLA*IMP:02	0.829	0.987	0.567	0.708
	HIBAG	0.957	0.975	0.834	0.475
HLA-DQB1	SNP2HLA	0.988	1.00	0.907	1.00
	HLA*IMP:02	0.983	0.993	0.845	0.761
	HIBAG	0.988	0.990	0.904	0.654
HLA-DRB1	SNP2HLA	0.964	1.00	0.920	1.00
	HLA*IMP:02	0.924	0.961	0.414	0.791
	HIBAG	0.959	0.946	0.946	0.557

Concordance and call rates generated from imputed alleles with posterior probability>0.50 versus sequenced alleles after combining data for HumanOmni1-QUAD and HumanOmni5-QUAD platforms by HLA locus and race/ethnicity.

doi:10.1371/journal.pone.0172444.t002

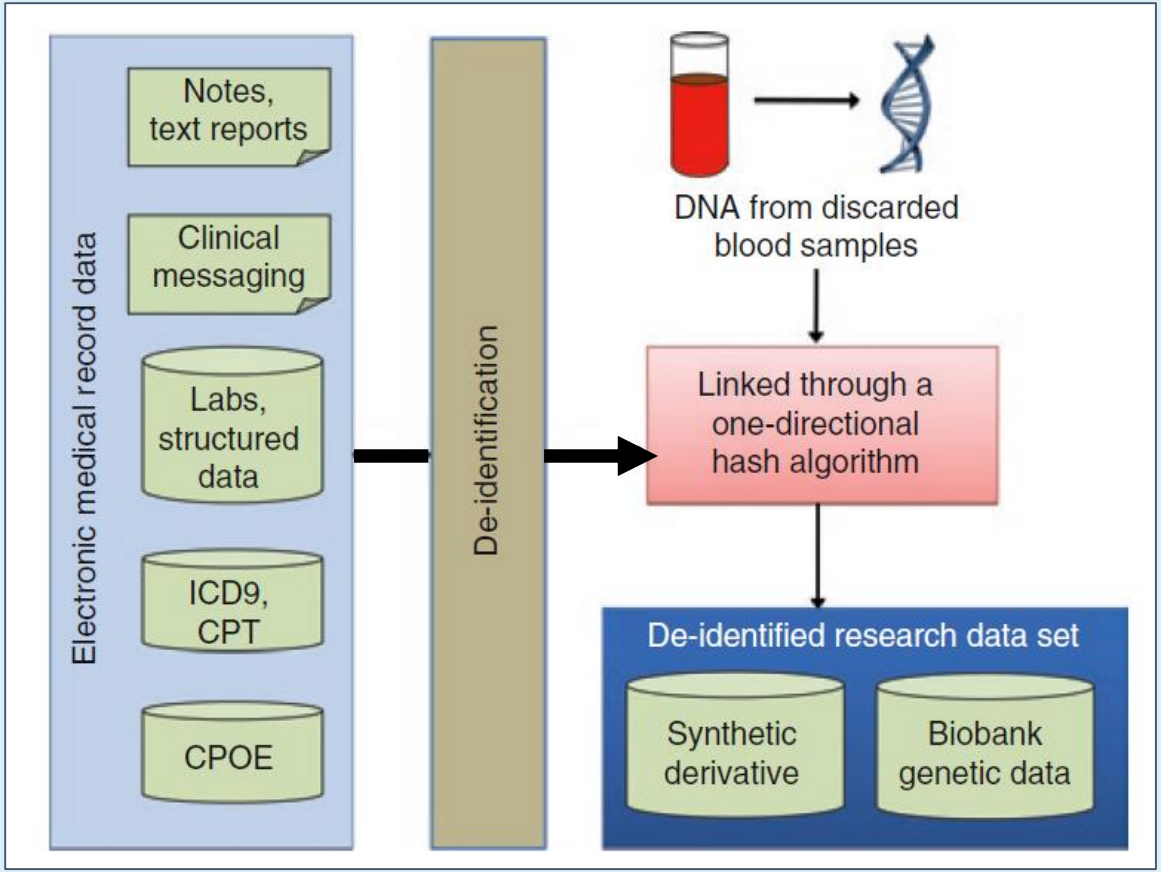


- Comparison of HLA imputation programs to sequenced HLA alleles in 3,265 samples
- Overall concordance rates similar in Whites
  - 0.975 (SNP2HLA)
  - 0.939 (HLA*IMP:02)
  - 0.976 (HIBAG)
- Accuracy decreases with African ancestry, decreasing allele frequency, lower genomic coverage, limited reference panels

Karnes et al. *Plos One.* 2017

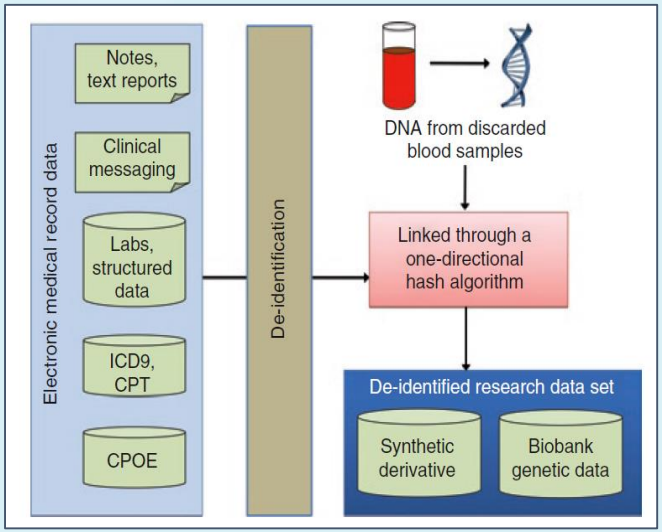
Vanderbilt BioVU

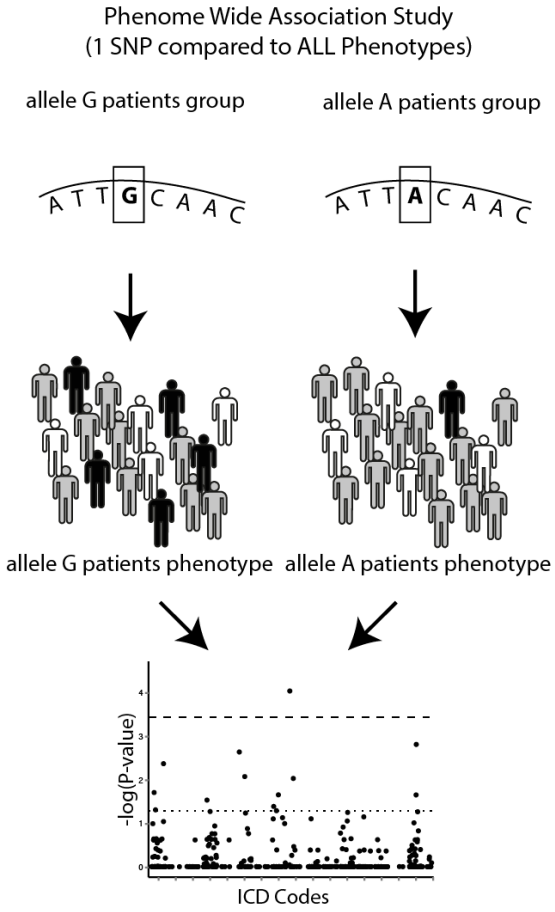
FROM MOLECULE TO PATIENT



Phenome-wide association studies (PheWAS)

EHR resources such as BioVU





PheWAS of HLA Variation

FROM MOLECULE TO PATIENT

- Imputed HLA genomic variation from European ancestry individuals
  - 29,712 patients from BioVU
- Genotyped on the HumanExome BeadChip
  - 2,061 HLA tag SNPs
- Tested association with 1,545 phenotypes
- Data for four and two digit HLA alleles and amino acid changing variants

Karnes et al. *Science Translational Medicine.* 2017

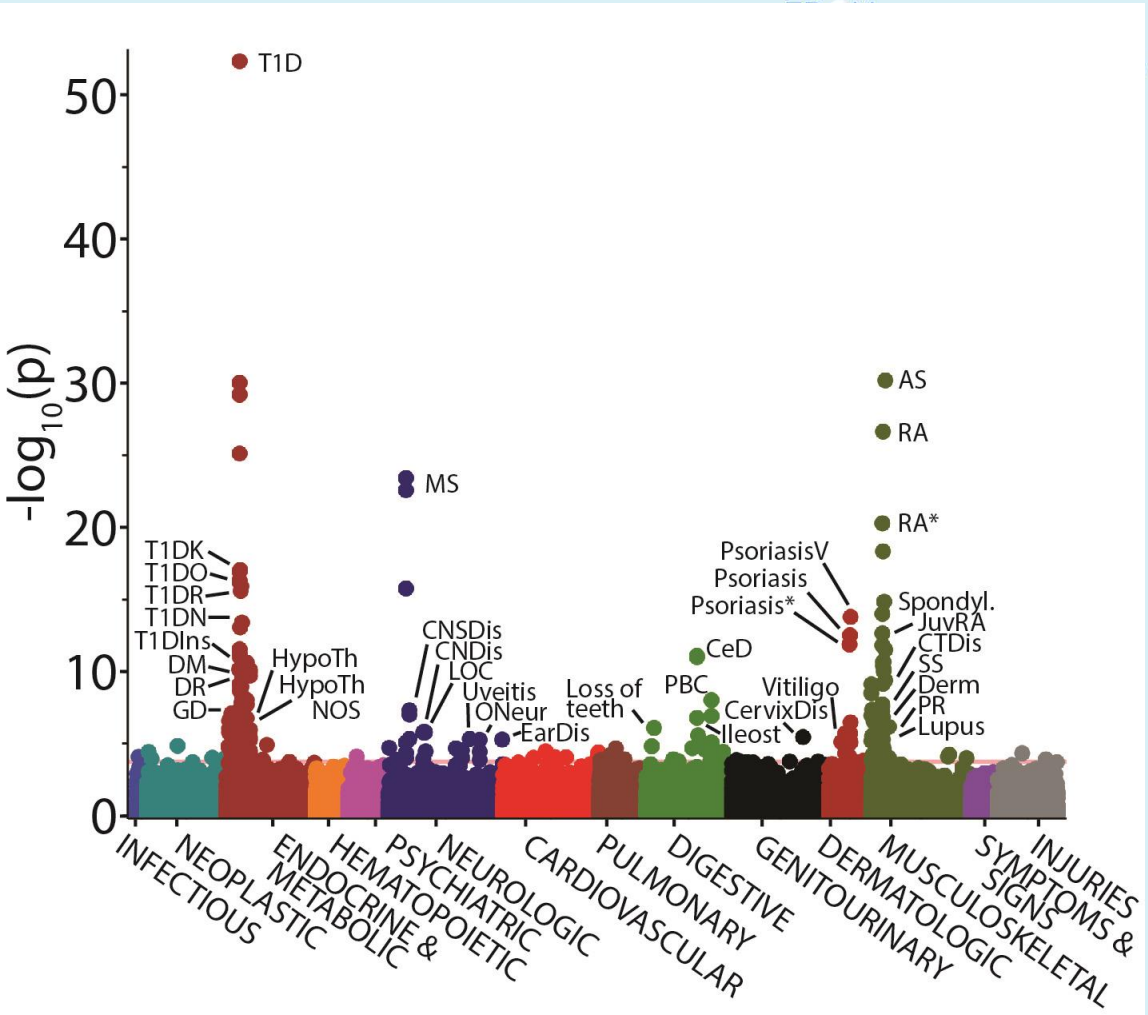
HLA PheWAS Results

FROM MOLECULE TO PATIENT

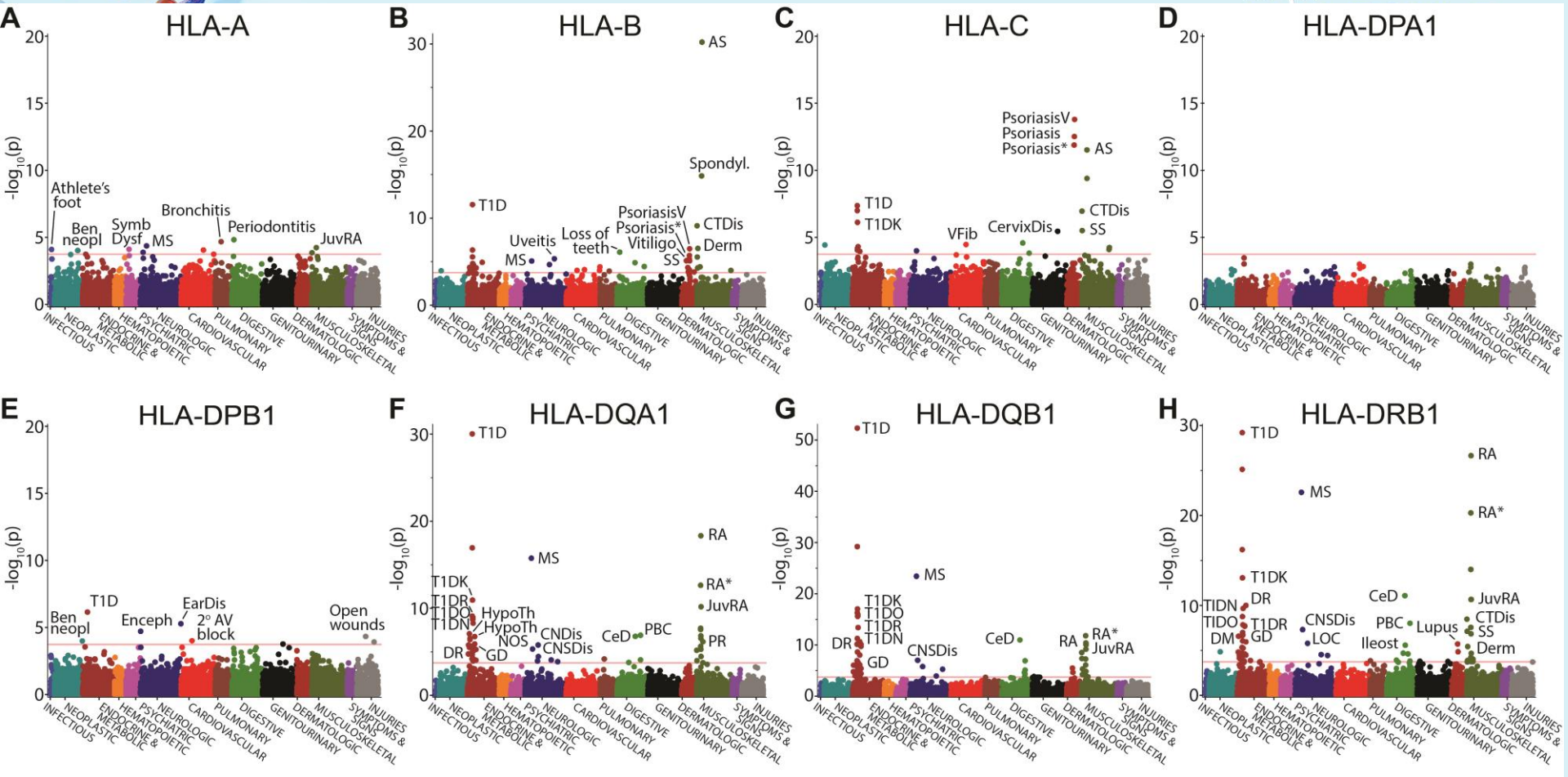
- 66 four-digit HLA allele-phenotype associations significant in both discovery and replication cohorts
  - Strongest *HLA-DQB1*03:02* and type 1 diabetes (odds ratio 4.31[3.57-5.19], $p=4.50 \times 10^{-53}$)
- 62 two-digit HLA allele-phenotype associations significant
  - *HLA-DQA1*01* and T1D (OR 0.32 (0.26-0.39), $p=8.19 \times 10^{-32}$).
- 1223 significant associations amino acid changing variants
  - T1D and an alanine/valine substitution at position 57 of *HLA-DQB1* (OR 0.20 [0.17-0.25], $p=2.6 \times 10^{-60}$)
- Data replicate many known phenotypic associations
  - Primarily autoimmune diseases
- Provide comprehensive, publicly-available catalog of clinical phenotypes associated HLA variation

Karnes et al. *Science Translational Medicine.* 2017

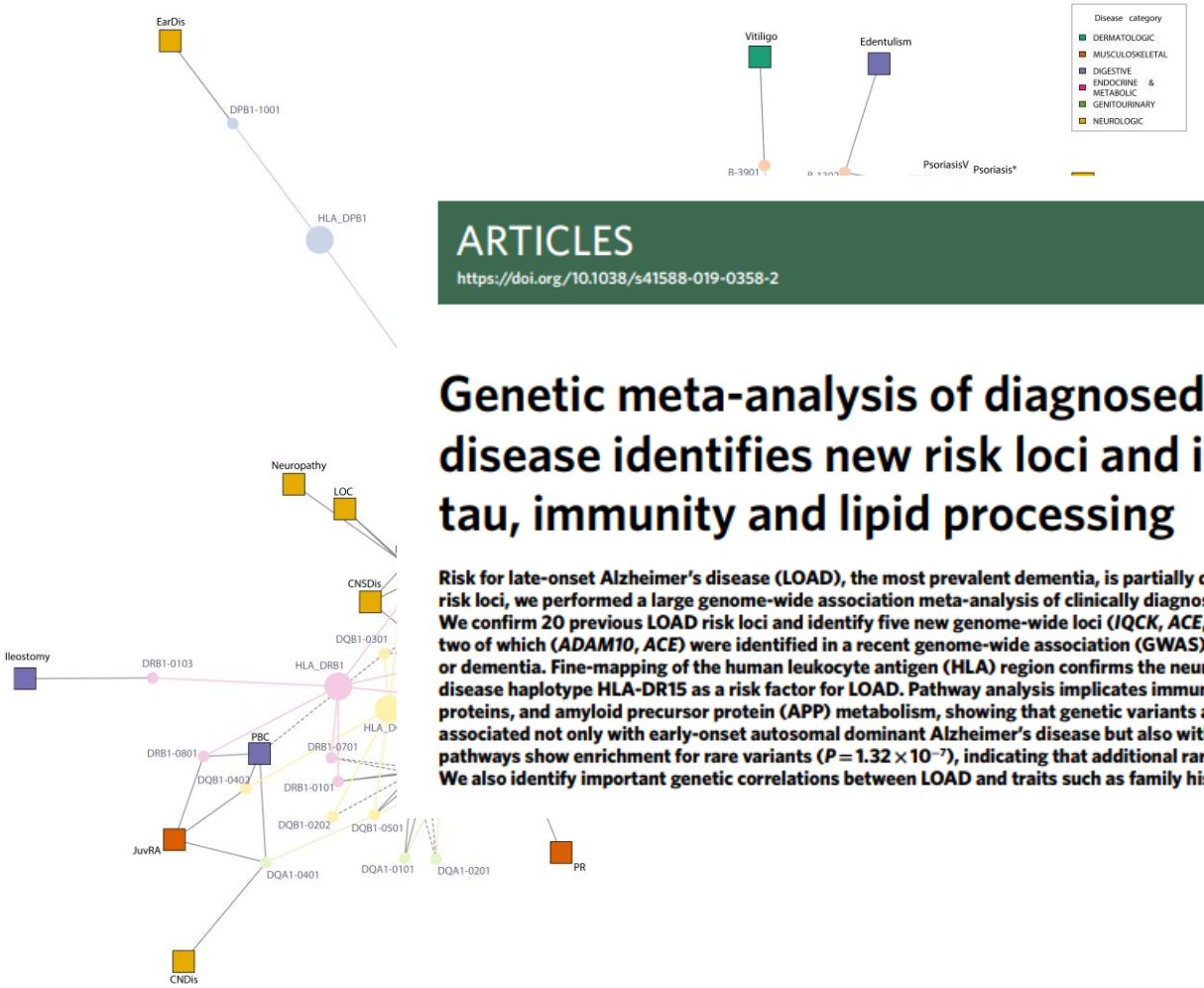
PheWAS plot of four digit HLA allele associations



Karnes et al. *Science Translational Medicine.* 2017



Karnes et al. *Science Translational Medicine.* 2017



ARTICLES
https://doi.org/10.1038/s41588-019-0358-2
nature genetics

Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing

Risk for late-onset Alzheimer's disease (LOAD), the most prevalent dementia, is partially driven by genetics. To identify LOAD risk loci, we performed a large genome-wide association meta-analysis of clinically diagnosed LOAD (94,437 individuals). We confirm 20 previous LOAD risk loci and identify five new genome-wide loci (*IQCK*, *ACE*, *ADAM10*, *ADAMTS1*, and *WWOX*), two of which (*ADAM10*, *ACE*) were identified in a recent genome-wide association (GWAS)-by-familial-proxy of Alzheimer's or dementia. Fine-mapping of the human leukocyte antigen (HLA) region confirms the neurological and immune-mediated disease haplotype HLA-DR15 as a risk factor for LOAD. Pathway analysis implicates immunity, lipid metabolism, tau binding proteins, and amyloid precursor protein (APP) metabolism, showing that genetic variants affecting APP and Aβ processing are associated not only with early-onset autosomal dominant Alzheimer's disease but also with LOAD. Analyses of risk genes and pathways show enrichment for rare variants ($P = 1.32 \times 10^{-7}$), indicating that additional rare variants remain to be identified. We also identify important genetic correlations between LOAD and traits such as family history of dementia and education.

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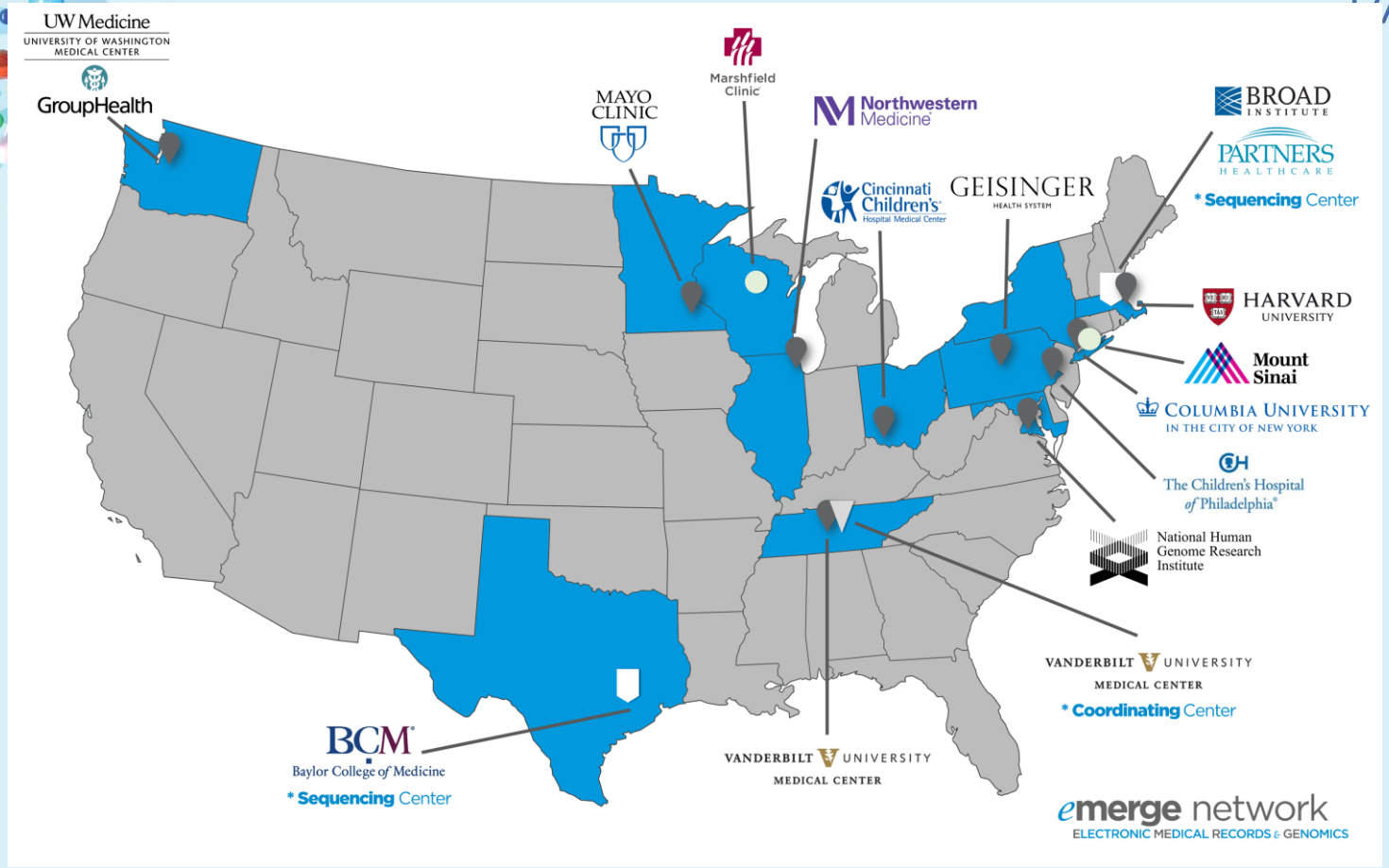
Karnes et al. *Science Translational Medicine.* 2017

Nat Genet. 2019 Mar;51(3):414-430

Electronic Medical Records & Genomics (eMERGE) Network

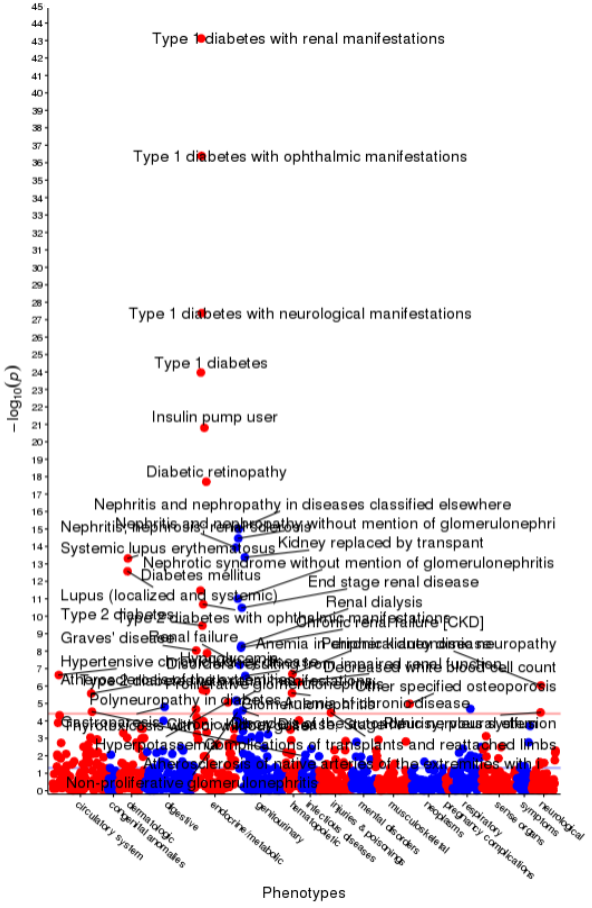


HLA PheWAS in eMERGE

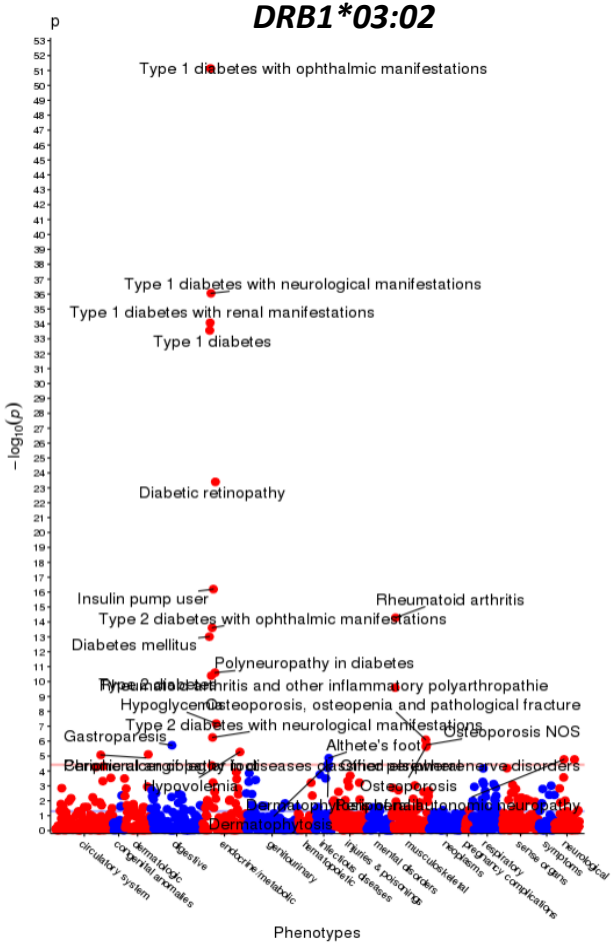
Gene	Alleles
HLA-A	40
HLA-B	92
HLA-C	31
HLA-DPB1	27
HLA-DQA1	16
HLA-DQB1	20
HLA-DRB1	50
Total	276

- PheWAS performed in 83,717 individuals with EMR data
  - Adjusted for gender, site, PC, and PC2
  - ~500,000 regressions in total
- 1,338 PheWAS Codes greater than 500 Cases
- 531 Significant PheWAS Codes
- lowest p-value: 7.3×10^{-52} for T1D with ophthalmic manifestations
- Led by Dr. Ian Byrell Stanaway, UW and Dr. Vivek Naranbhai, Massachusetts General Hospital, Harvard

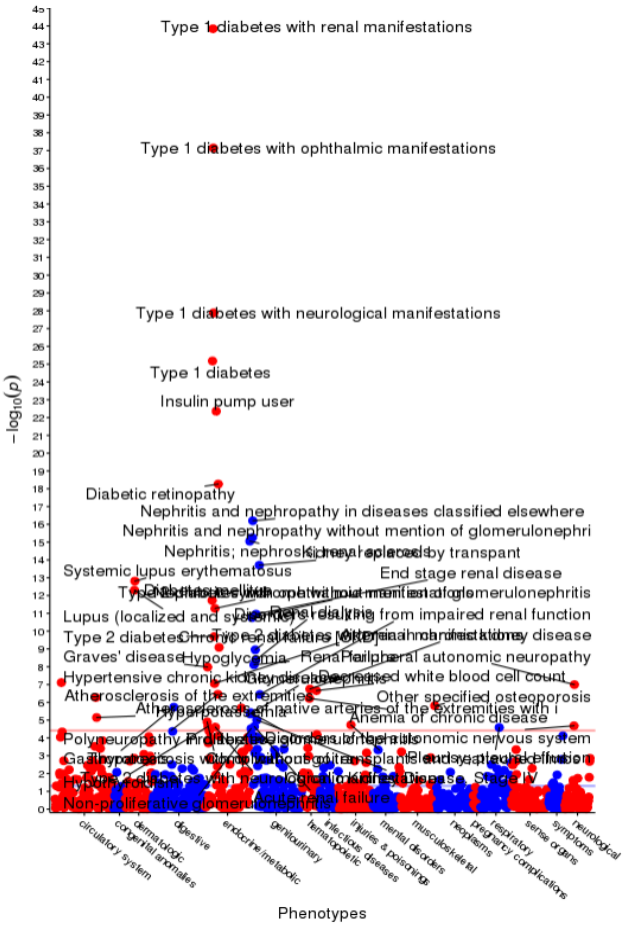
DRB1*03:01

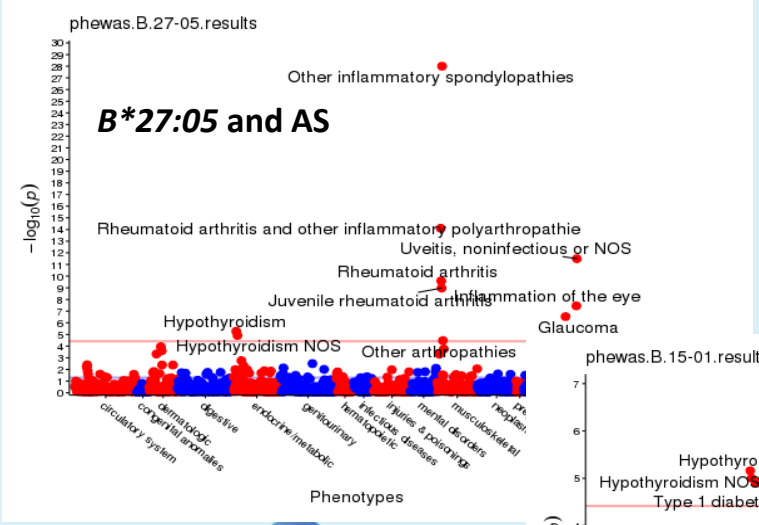


DRB1*03:02

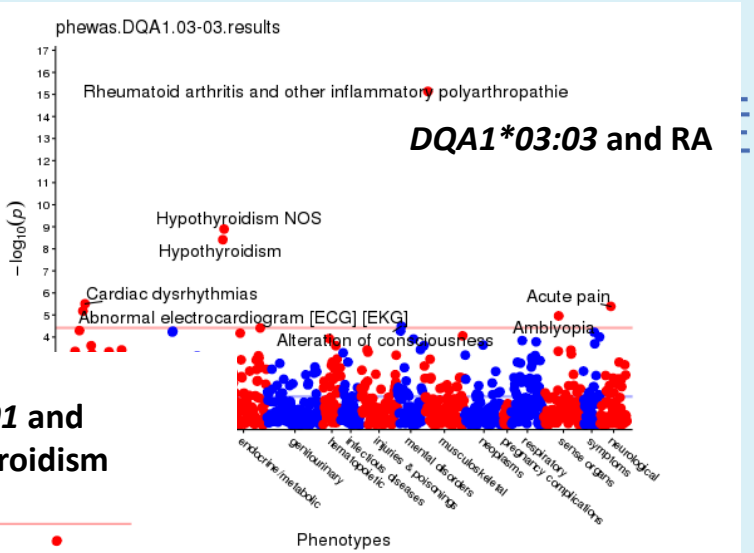


DQA1*05:01

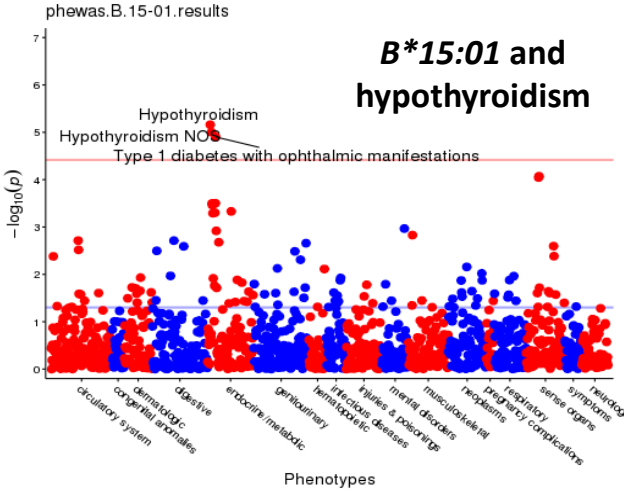




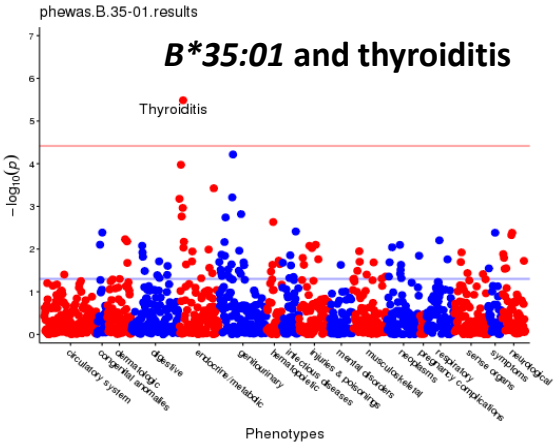
B*27:05 **and AS**



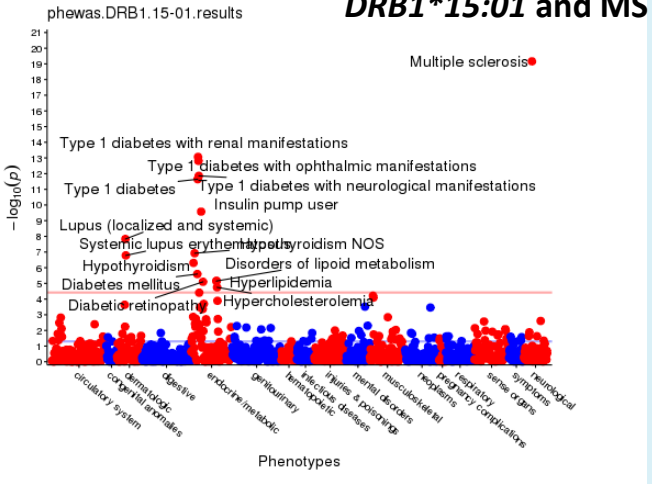
DQA1*03:03 **and RA**



B*15:01 **and hypothyroidism**



B*35:01 **and thyroiditis**



DRB1*15:01 **and MS**

Race and Ethnicity in eMERGE Network

FROM MOLECULE TO PATIENT

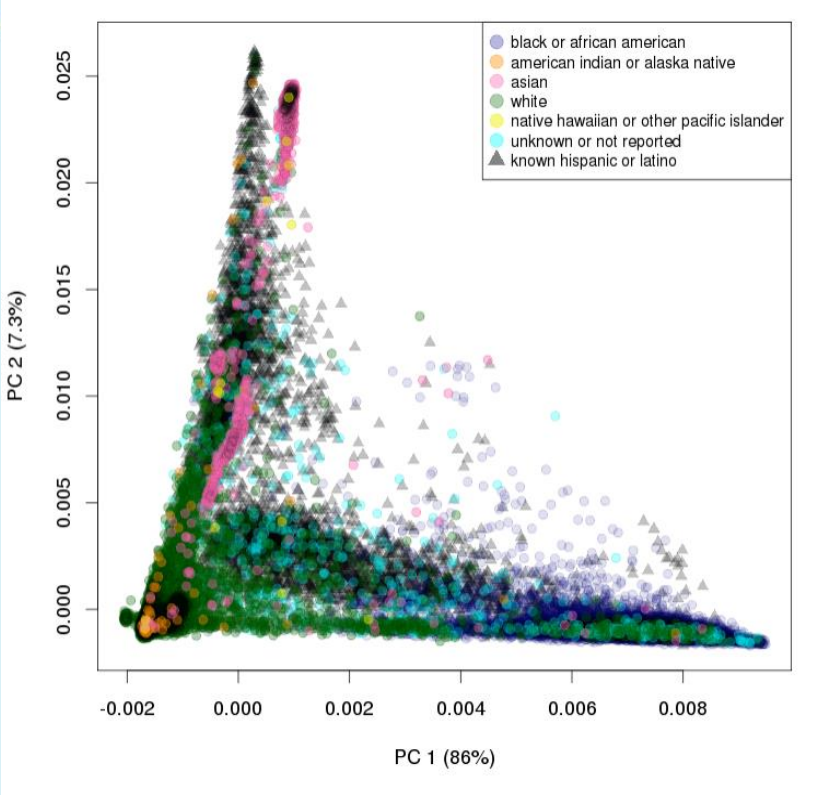
TABLE 1 Number of unique participant eMERGE IDs and reported demographics

Medical center	Participants	Arrays Batches	Gender Male	Gender Female	African/ Black	American Indian	Asian	White	Pacific Islander	Hispanic/ Latino	Unknown
Boston Children's	1,019	1	596	423	66	2	21	676	0	125	129
CCHMC	5,717	12	3,262	2,455	601	5	67	4,673	5	143	223
CHOP	10,465	21	5,630	4,835	4,666	7	161	4,890	3	321	417
Columbia	2,065	2	1,058	1,007	179	6	77	619	2	448	734
Geisinger	3,111	1	1,638	1,473	9	2	0	3,085	0	13	2
Harvard	10,095	3	4,626	5,469	509	0	172	8,579	0	474	361
Kaiser/GHC/UW	3,316	3	1,428	1,888	109	12	89	2,922	6	69	109
Marshfield Clinic	4,756	5	1,878	2,878	2	3	12	4,690	0	14	35
Mayo Clinic	10,256	16	5,193	5,063	23	18	21	8,810	0	1,043	341
Mt. Sinai	6,255	4	2,555	3,700	4,046	33	3	679	0	1,297	197
Northwestern	4,848	2	817	4,031	598	0	0	4,207	0	36	7
Vanderbilt	21,814	10	9,868	11,946	3,854	16	102	17,313	0	211	318
Total	83,717		38,549	45,168	14,662	104	725	61,143	16	4,194	2,873

Note. eMERGE: Electronic Medical Records and Genomics.

Stanaway IB, ... Crosslin DR. Genet Epidemiol. 2018 Oct 8.

HLA PheWAS in African Americans

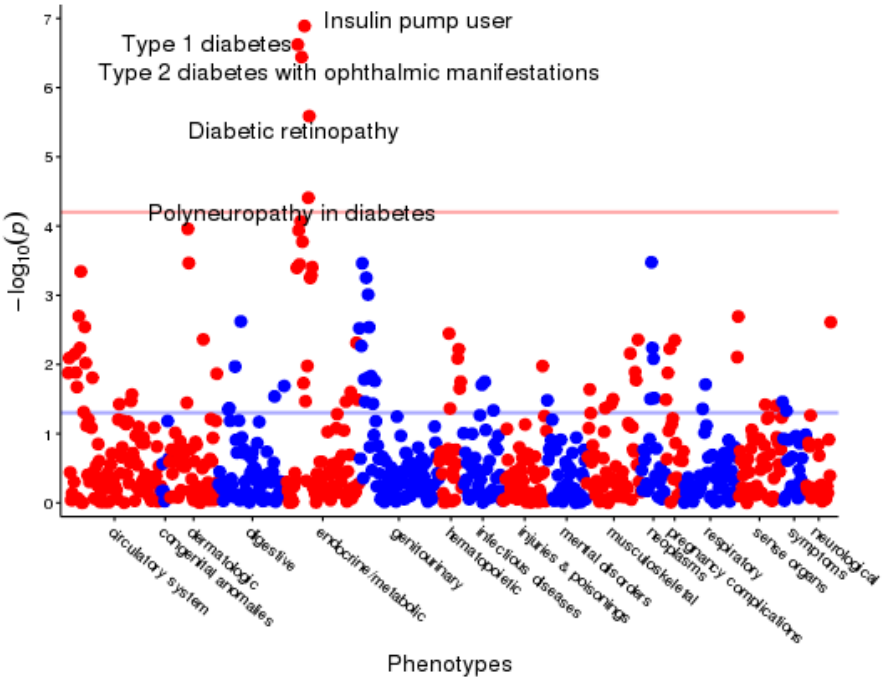


- 14,662 African Americans
- 820 PheWAS codes greater than 200 cases in African Americans
- 120 HLA alleles MAF >= 0.01
- 820 x 120 = 98,400 tests

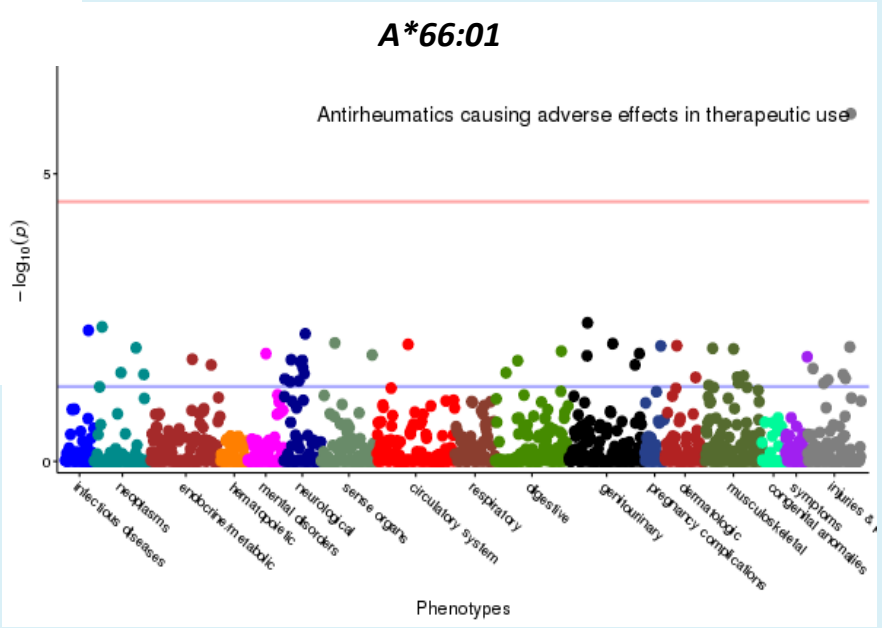
- Significant Phecodes:
  - African 167
  - Asian 19
  - European 754
- Significant Regressions:
  - African 236
  - Asian 21
  - European 4480

FROM MOLECULE TO PATIENT

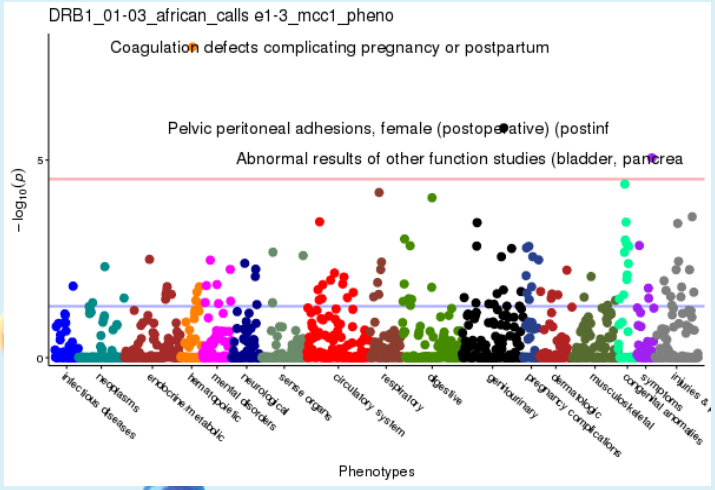
*DQA1*05:01*

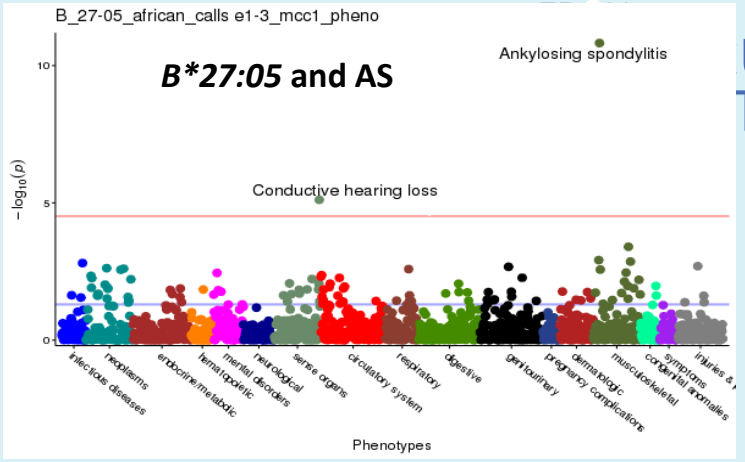


*A*66:01*

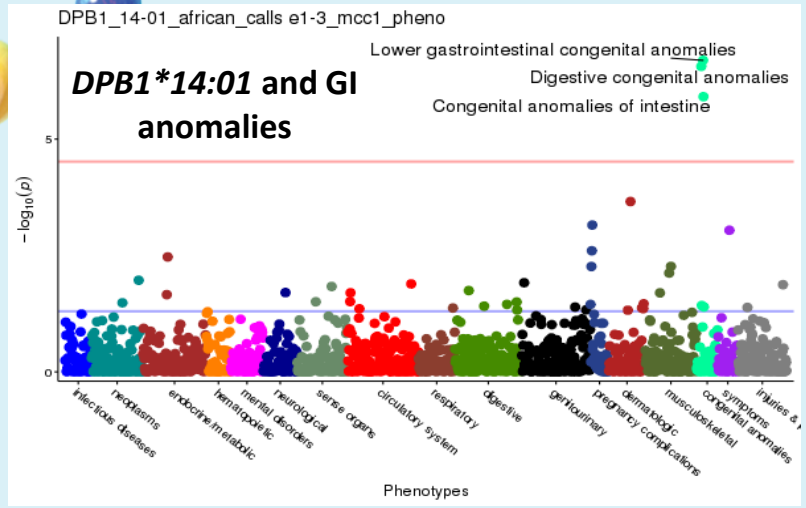


*DRB1*01:03* and coagulation defects in pregnancy

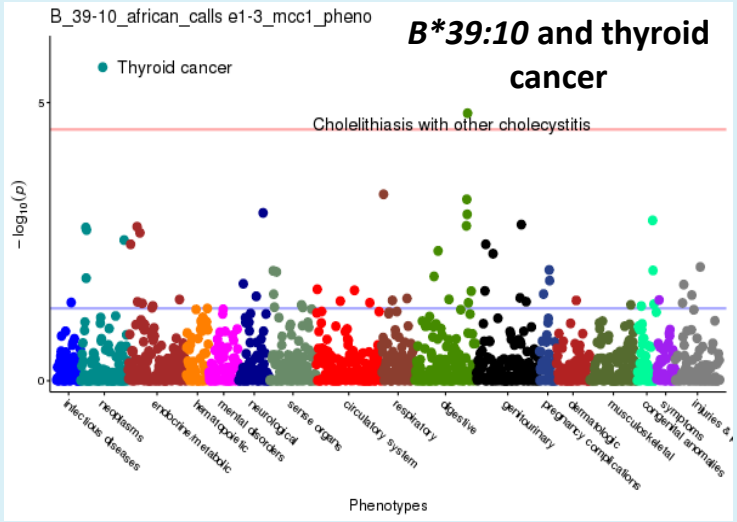




*B*27:05* and AS



*DPB1*14:01* and GI anomalies



*B*39:10* and thyroid cancer

PNAS

Sex bias in MHC I-associated shaping of the adaptive immune system

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HLA associations, T cell receptor (TCR) repertoire bias, and sex bias have independently been shown for many diseases. While some immunological differences between the sexes have been described, they do not fully explain bias in men toward many infections/cancers, and toward women in autoimmunity. Next-generation TCR variable beta chain (TCRBV) immunosequencing of 824 individuals was evaluated in a multiparametric analysis including HLA-A -B/MHC class I background, TCRBV usage, sex, age, ethnicity, and TCRBV selection/expansion dynamics. We found that HLA-associated shaping of TCRBV usage differed between the sexes. Furthermore, certain TCRBVs were selected and expanded in unison. Correlations between these TCRBV relationships and biochemical similarities in HLA-binding positions were different in CD8 T cells of patients with autoimmune diseases (multiple sclerosis and rheumatoid arthritis) compared with healthy controls. Within patients, men showed higher TCRBV relationship Spearman's rhos in relation to HLA-binding position similarities compared with women. In line with this, CD8 T cells of men with autoimmune diseases also showed higher degrees of TCRBV perturbation compared with women. Concerted selection and expansion of CD8 T cells in patients with autoimmune diseases, but especially in men, appears to be less dependent on high HLA-binding similarity than in CD4 T cells. These findings are consistent with studies attributing autoimmunity to processes of epitope spreading and expansion of low-avidity T cell clones and may have further implications for the interpretation of pathogenic mechanisms of infectious and autoimmune diseases with known HLA associations.

TCR binding amino acids of MHC molecules specifically influence the binding to and usage of TCR variable alpha (TCRAV) and TCRBV chains (19), and that the presence of specific TCR rearrangements is an indication of the HLA background of the host and also of previous exposure to pathogens (20). Dysregulation in the TCR–antigen–MHC complex can lead to autoimmunity (21) in the case of uncontrolled immune cell expansion or cross-reactivity between foreign and autoantigens. Hypoexpansions or low TCR avidity might lead to susceptibility to infections. Additionally, to combat tumor-associated immune system suppression, cancer patients can now be treated with T cell-relevant immune checkpoint inhibitors such as blockade of CTLA-4 (22) or PD-1 (23).

Most immune system dysfunctions show strong sex bias: men are more susceptible to many infectious diseases and cancers of nonreproductive organs, whereas autoimmune diseases are much more common in women (24, 25). Even in psychological disorders such as major depression (26) and in neurodegenerative diseases such as Alzheimer's, recent studies have shown immune system involvement (27) and sex bias (28). Many studies have been conducted concerning either sex (25), HLA (29, 30), or TCR (31) associations with diseases. However, even though some sex differences in immune regulation have been reported (25, 32), it is still not completely clear why this bias exists. Multiparametric analysis of the influence of sex on HLA-mediated shaping of the TCR repertoire has been hindered by

PheWAS: sex bias of HLA associations

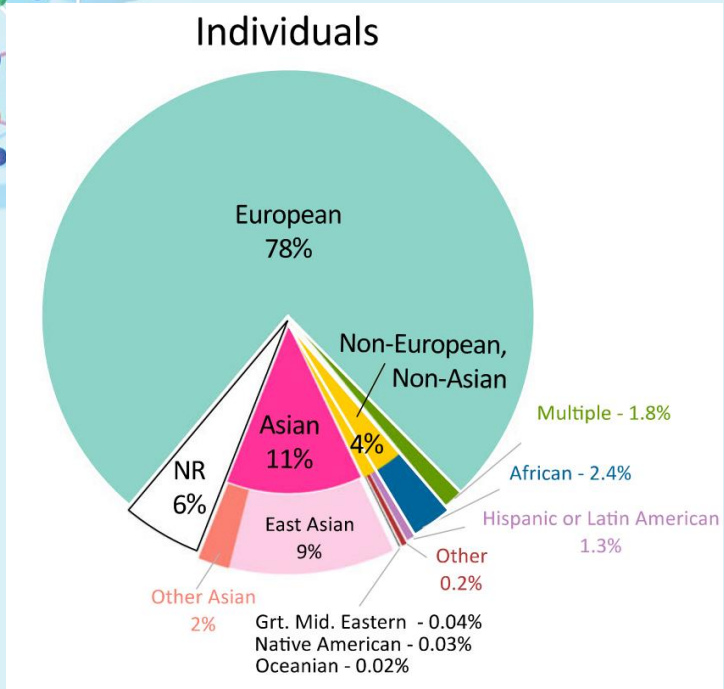
FROM MOLECULE TO PATIENT

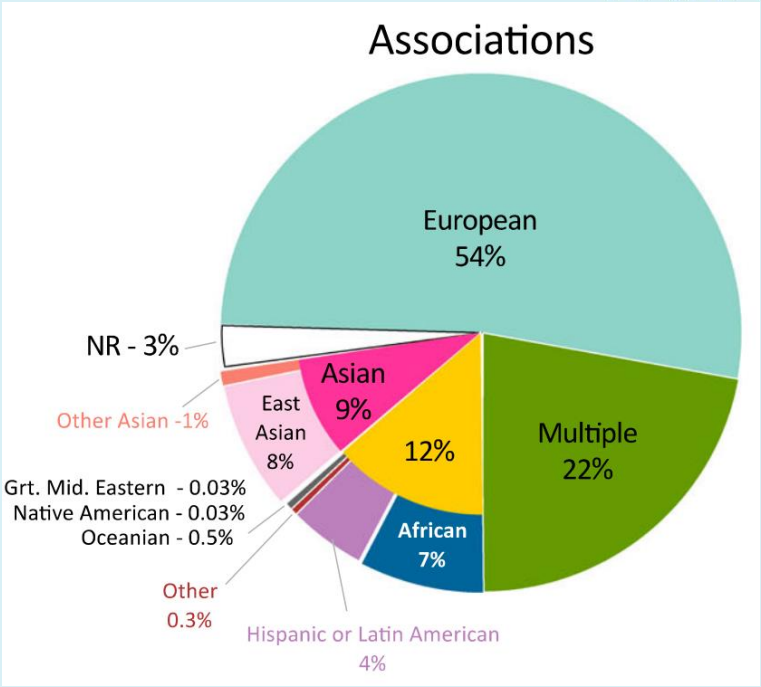
		All		Females		Males		Interaction
HLA Allele	**Phenotype**	**cases**	**controls**	**OR**	**P**	**OR**	**P**	**P**
*B*2705*	Other inflammatory spondylopathies	223	23,403	1.60	0.082	8.12	3.4E-21	3.2E-06
*DPB1*0301*	Senile dementia	224	23,111	0.79	0.311	2.86	5.9E-06	1.0E-04
*C*0702*	Vitamin deficiency	1,966	21,062	1.04	0.572	0.67	8.3E-05	2.4E-04
*B*0702*	Vitamin deficiency	1,966	21,062	1.02	0.818	0.66	8.4E-05	4.6E-04
*DQB1*0301*	Congenital anomalies of urinary system	433	26,979	1.81	9.5E-05	0.88	0.364	5.6E-04
*DRB1*0401*	Noninfectious gastroenteritis	814	20,452	1.03	0.789	0.54	6.6E-05	9.9E-04
*DQB1*0301*	Genitourinary congenital anomalies	657	26,979	1.71	7.4E-05	1.00	0.966	1.7E-03
*C*0602*	Psoriasis	369	22,973	2.98	7.7E-14	1.44	0.049	2.0E-03
*B*4002*	Benign neoplasm of colon	1,719	24,588	0.70	0.258	2.13	5.3E-05	2.4E-03
*DQB1*0202*	Respiratory abnormalities	1,006	20,833	1.65	5.5E-06	1.03	0.822	2.7E-03
*C*0602*	Psoriasis and related disorders	384	22,973	2.84	3.9E-13	1.42	0.054	2.8E-03
*B*1401*	Chronic liver disease and cirrhosis	1,173	22,347	2.43	1.9E-05	0.79	0.459	3.5E-03
*A*1101*	Cardiac arrest	136	17,561	3.76	3.9E-05	0.98	0.957	3.6E-03
*DQA1*0102*	Rosacea	322	24,376	1.13	0.399	2.18	8.4E-05	5.9E-03

Major Challenges for HLA association

- Power
  - Low prevalence of IM-ADRs
  - For discovery and replication
  - Need for clinical networks to drive research and guidelines
- Phenotyping
  - Syndromes may mimic IM-ADRs
  - Electronic medical records
- Influence of race and ethnicity in IM-ADRs
  - Availability of reference populations
  - Disparate frequency of alleles between race groups
  - Disparate allelic associations between race groups

Distribution of ancestry in the GWAS catalogue

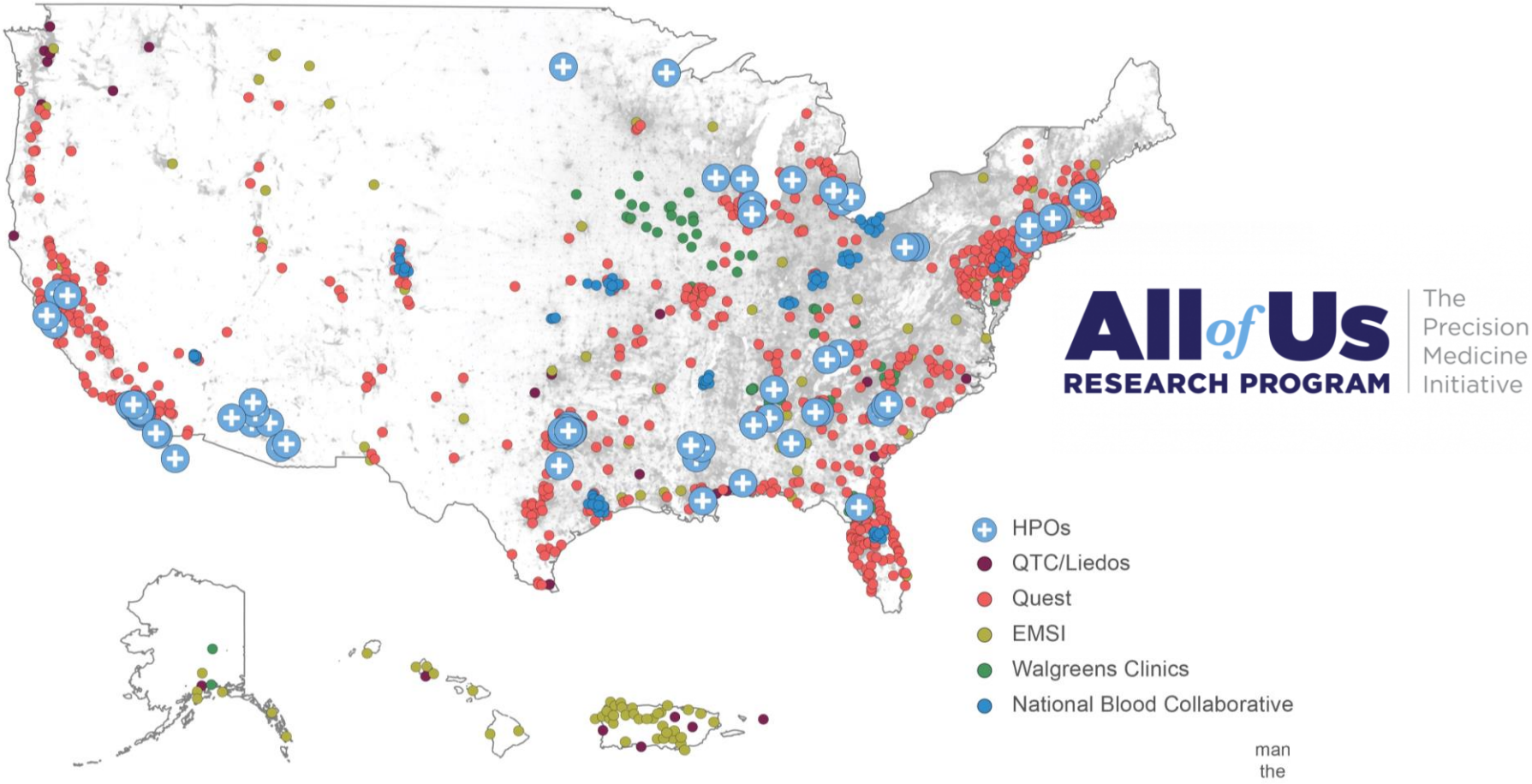




- Disproportionate contribution of associations from African and Hispanic/Latin American categories compared to percentage of individuals

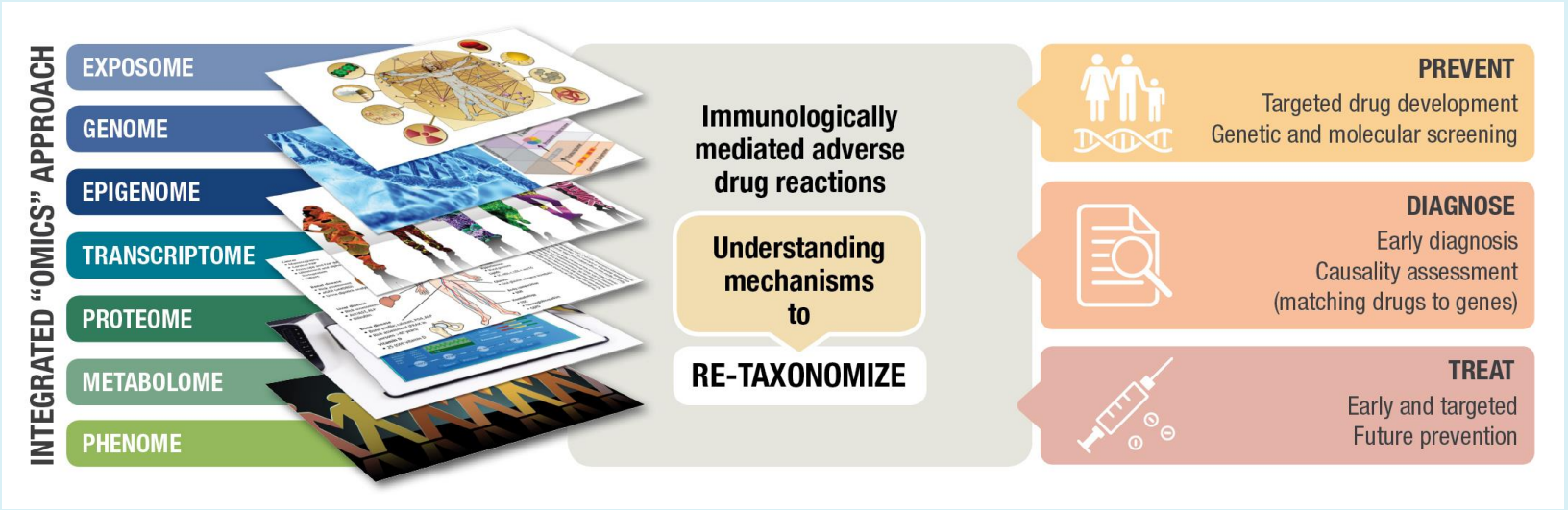
Morales et al. Genome Biology (2018)

Current and planned in-person enrollment centers (over the course of enrollment)



Future Directions

- KIR, TCR, BCR, HLA expression
  - Interaction of immunogenomic variation
- Assessment of Pleiotropy in PheWAS
- IPSC testing for patient-specific drug hypersensitivity



Karnes et al. *Annual Review of Pharmacology and Toxicology.* 2019

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- Jonathan Moseley, Vanderbilt University
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- Andrew Glazer, PhD, Vanderbilt University

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NIH National Heart, Lung, and Blood Institute

accp American College of Clinical Pharmacy

NIH National Human Genome Research Institute