NASEM
Committee for the Assessment of NIH Research on Autoimmune Diseases

Autoimmune Disease Research Supported by Intramural NIEHS

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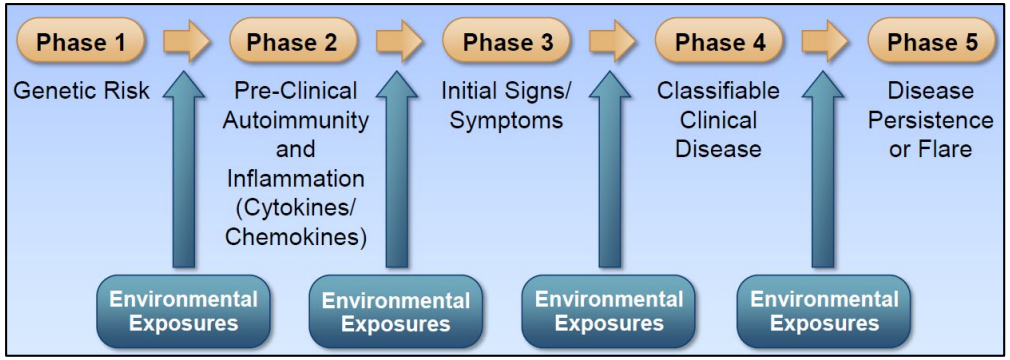
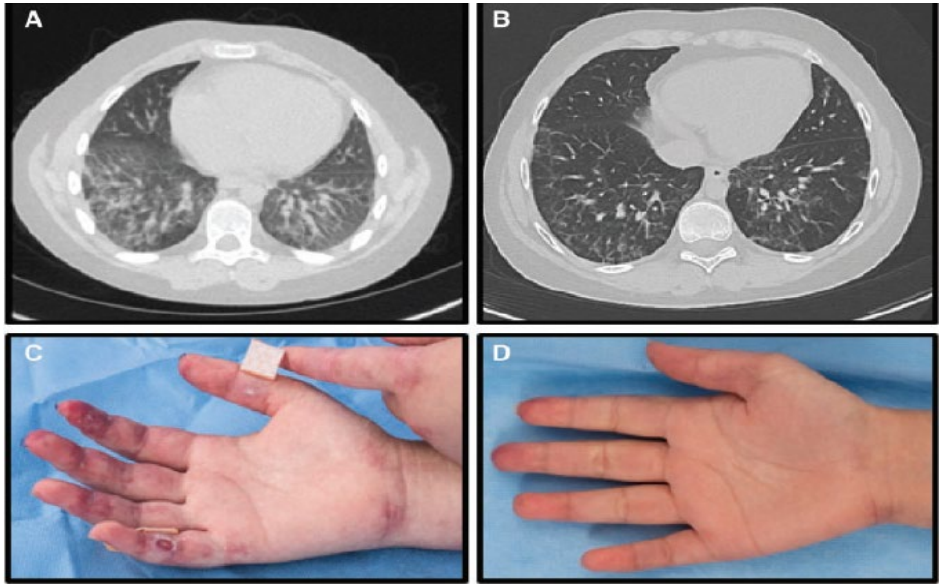
National Institute of Environmental Health Sciences NIEHS

- The **Mission** of NIEHS is to discover how the environment affects people, in order to promote healthier lives
- The **Vision** of the NIEHS is to provide global leadership for innovative research that improves public health by preventing disease and disability
- Main campus in Research Triangle Park, NC is where most basic and epidemiologic research is conducted
- The Clinical Research Unit (CRU) is the NIEHS clinical research center in NC
- Environmental Autoimmunity Group (EAG) in the Clinical Research Branch is located in the NIH Clinical Center, Bethesda, MD and is focused on systemic autoimmune diseases

NIEHS and Autoimmune Disease Research Overview

- Basic, epidemiologic, translational and clinical research, including observational and mechanistic studies and clinical trials
- Lifespan approach including pediatric and adult disease
- Genetic and environmental risk factors
- Disease activity and damage assessment
- Classification and disease improvement criteria
- Immune parameters
- Mechanisms of disease





Juvenile myositis improvement after JAK inhibition

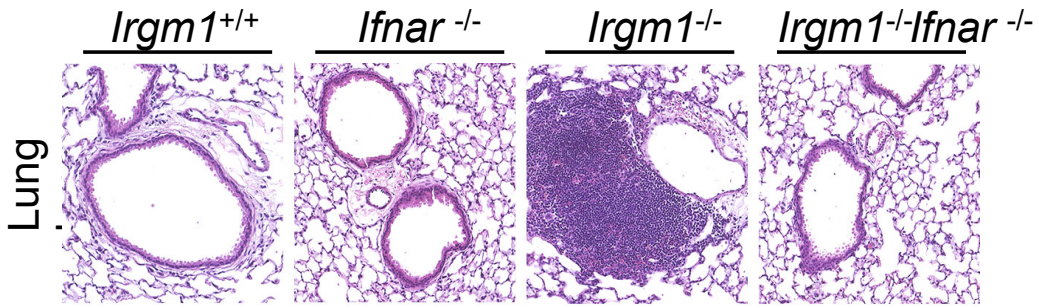
Miller et al. 2018 Nature Rev Rheum; Rider et al. 2018 Nature Rev Rheum; Parks et al. 2020 Arthritis Care Res; Sabbagh et al. 2019 Brain

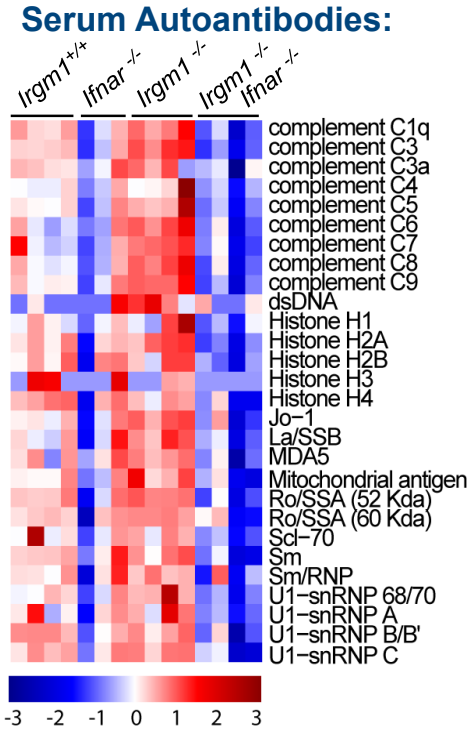
NIEHS Intramural Process for Reviewing Funding and Research for Investigators and Changes in Autoimmune Disease Funding

- The **NIEHS Scientific Director** determines Principal Investigator resources based on comparisons with similar programs, productivity, and Board of Scientific Counselor (BSC) reviews
- The **BSC review** evaluates a research program's objectives, accomplishments, innovation, relevance to the NIEHS mission, and overall quality and impact. The review includes an evaluation of both the Laboratory/Branch leadership and the research performed by independent investigators
- Over the past two decades, **autoimmune disease research has been enhanced** in NIEHS DIR, with several branches now working on autoimmune disease
  - With the retirement of Dr. Fred Miller from the EAG, which is now overseen by Dr. Lisa Rider, EAG resources have been decreased to align with similar programs in other institutes

Immunity, Inflammation and Disease Laboratory (IIDL) Autoimmune Disease Basic Research Accomplishments

- Polymorphisms in *IRGM* and other autophagy genes have been associated with autoimmune disease.
- Michael Fessler (Chief, IIDL) and colleagues recently reported that mice null for the homologous gene *Irgm1* develop a Sjogren's Syndrome-like presentation that is driven by excess type I interferon.
- *Irgm1* deficiency was found to impair mitophagy, leading to mtDNA-dependent activation of the dsDNA receptor cGAS and induction of interferon.
- Defective autophagic clearance of mtDNA may be an under-recognized cause of autoimmunity.

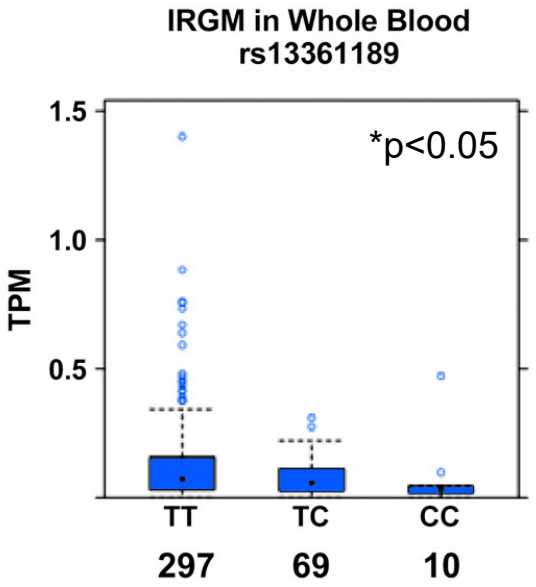




Rai P et al. 2021 Nature Immunology

Immunity, Inflammation and Disease Laboratory (IIDL) Autoimmune Disease Basic Research Accomplishments

- Environmental Polymorphisms Registry provides a unique resource for studies of the interaction of genetic and environmental determinants of human health.
  - ~20,000 participants have contributed biological samples (blood, DNA, other materials), and disease and exposure data that support wide range of research
- Using the NIEHS EPR, Michael Fessler (Chief, IIDL) and colleagues recently found a specific IRGM SNP (rs13361189) increases risk for Crohn's disease.
  - Subjects with the risk allele had reduced *IRGM* and increased *TNF* mRNA in whole blood.
  - ~60 subjects with varying genotypes at this *IRGM* locus have been seen at NIEHS CRU for immunophenotyping,multicolor flow cytometry of leukocytes, and *ex vivo* stimulation of whole blood with TLR ligands



- **Future plans:**
  - Cross of Irgm1-/- mice with innate immune receptor knockout mouse lines
  - Determine immune pathway responsible for lymphoid aggregates (BALT) in lung
  - Mass cytometry (CyTOF) of PBMC markers from subjects with different *IRGM* genotypes to profile activation status of immune system.

Ajayi T et al. 2019 Am J Physiol Gastrointest Liver Physiol

Epidemiology Branch Autoimmune Disease Research

Environmental Risk Factors for Autoimmune Diseases – Population-based and Occupational Cohort Studies

Agricultural Health Study (www.aghealth.nih.gov)

- ~89,000 licensed pesticide applicators (mostly farmers) and their spouses, followed over 25 years for cancer and chronic diseases via surveys and record linkage (mortality, cancer, end stage kidney disease, Medicare data); Long-standing collaboration with the NCI
- Subcohort with biological and environmental samples examined for autoimmunity
  - Specific pesticides and other agricultural exposures associated with risk of *systemic autoimmune diseases*: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), thyroid diseases
  - Specific pesticides linked to thyroid dysfunction, antinuclear antibodies (ANA)
  - Ongoing research includes updated exposure data, increased sample size for specific outcomes, and additional autoimmune disease outcomes
    - RA/SLE/SS, cutaneous lupus, myositis, scleroderma, psoriasis, inflammatory bowel disease, multiple sclerosis

Parks et al. 2019 Occup Environ Med; Shrestha et al. 2018 and 2019 Occup Environ Med; Parks et al. 2018 Am J Epidemiol; Meyer A et al 2017 Envi Health Persp

Epidemiology Branch Autoimmune Disease Research

Environmental Risk Factors for Autoimmune Diseases – Population-based and Occupational Cohort Studies

The Sister Study (www.sisterstudy.niehs.nih.gov)

- 50,884 breast-cancer free women ages 35-74 at enrollment (2003-2009) with a sister who had breast cancer, followed for breast cancer and other health outcomes
  - Early life risk factors for adult-onset RA and SLE, including childhood residential pesticide use and maternal and childhood farming and pesticides
  - Ongoing research on breast cancer risk in relation to autoimmune diseases
  - Ongoing research on risk factors for incident RA, SLE, thyroid diseases

The Gulf Long-term Follow-up (GuLF) Study (www.gulfstudy.niehs.nih.gov)

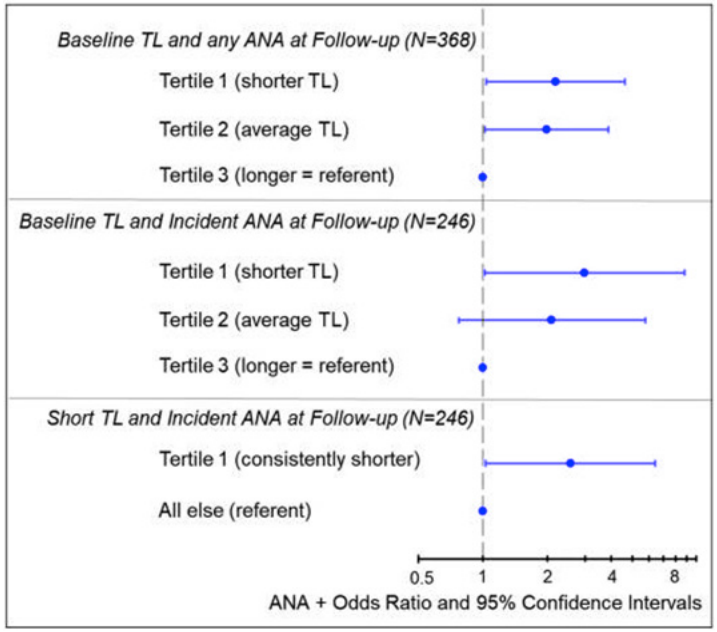
- 32,000 participants who worked on response and cleanup or trained and were not hired following the 2010 Deepwater Horizon oil spill disaster; followed since 2011 via questionnaires, home visits, and clinical exams
  - Ongoing research on altered immune response following exposure to oil spill chemicals- will include autoimmunity

Parks et al. 2019 Occup Environ Med; Shrestha et al. 2018 and 2019 Occup Environ Med; Parks et al. 2018 Am J Epidemiol; Meyer A et al 2017 Envi Health Persp

Epidemiology Branch Autoimmune Disease Research

Rates and Factors Associated with Pre-Clinical Autoimmunity

- Antinuclear antibodies (ANA) in farmers and associations with pesticides in a sub-sample of the **AHS** (collaboration with NCI)
- Risk factors for ANA in older adults in the **Baltimore Longitudinal Study on Aging** (collaboration with NIA)
  - Leukocyte telomere length (immune aging)
  - Multimorbidity, vitamin D deficiency
  - Ongoing research on incidence of ANA



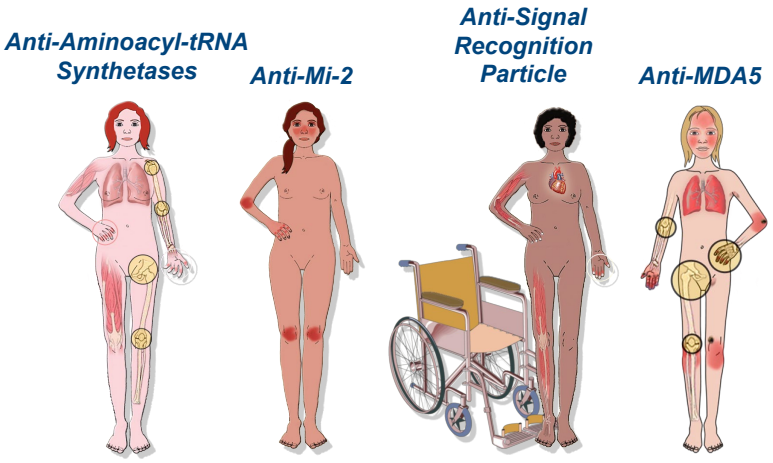
- Factors associated with ANA in a representative sample of the US population, the **National Health and Nutrition Examination Survey** (collaboration with Environmental Autoimmunity Group)
  - Vitamin D deficiency and ANA in middle age and older adults
  - Ongoing research in adolescents and young adults studying markers of the hygiene hypothesis (infections and asthma), other phenols, parabens (found in sunscreen and personal care products)

Meier et al. 2019 J Autoimmun; Parks et al. 2019 Front Immunol; Meier et al. 2016 Cancer Epidemiol Biomarkers Prev

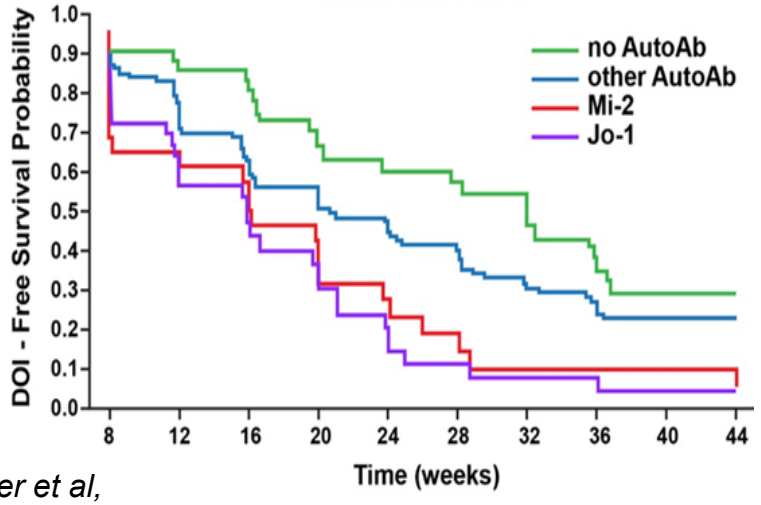
Environmental Autoimmunity Group (EAG) Focuses on Autoimmune Muscle Disease (Myositis)

- Developed largest databases and sample repositories in the world, with >1800 clinically well-characterized patients and leading many national/ international collaborations
- Defined mutually exclusive and stable phenotypes, allowing for more precise characterization of risk factors, pathogenesis and outcomes
- Developed and validated ACR/EULAR myositis classification criteria
- IMACS Group developed ACR/EULAR myositis response criteria and other disease activity/damage measures
- Discovered some refractory patients respond to rituximab and JAK inhibitors

Myositis Antibody Phenotypes

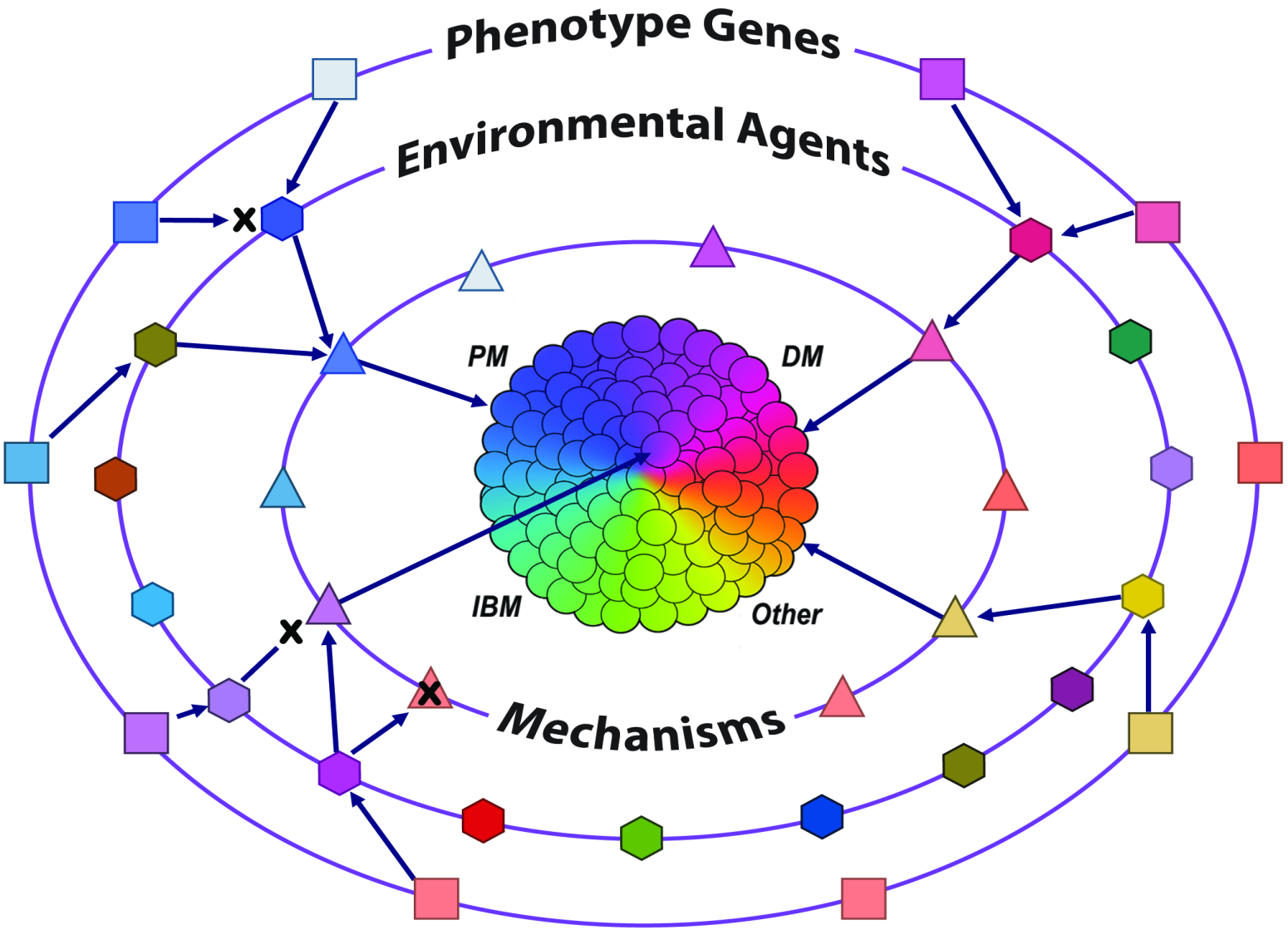


Rituximab Responses by Autoantibody



Rider and Nistala 2016 J Int Med; Lundberg et al, 2017 Ann Rheum Dis; Rider et al, 2107 Ann Rheum Dis; Sabbagh et al. 2019 Brain; Oddis et al. 2013 Arth Rheum

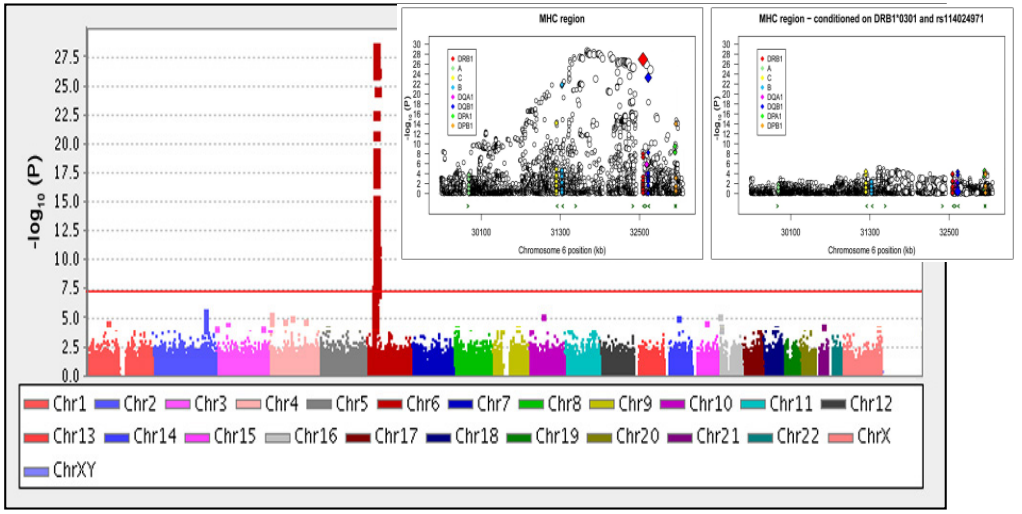
Defining Risk Factors and Mechanisms for Autoimmune Disease Phenotypes



Miller 2021 Nature Rev Rheum, In press

Identified Genetic Risk Factors for Myositis

- The HLA 8.1 ancestral haplotype is the major risk factor for myositis
- Other genes associated with autoimmune diseases are additional risk factors for certain phenotypes
- HLA risk factors for some myositis autoantibodies are protective for others

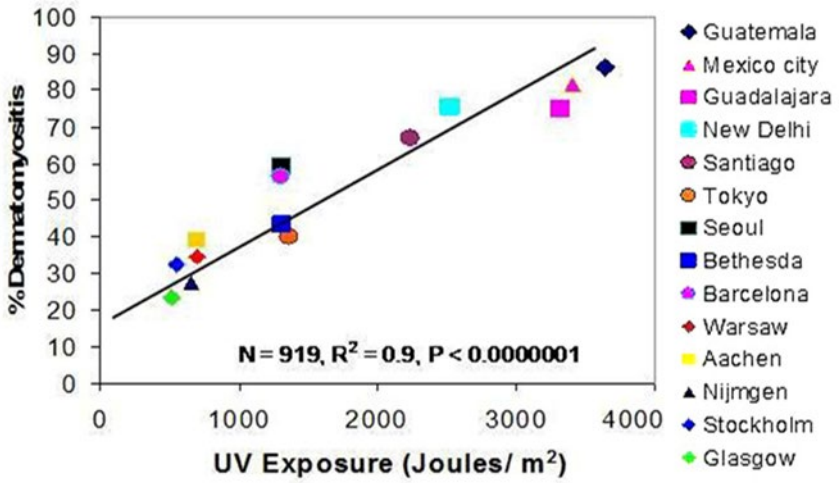


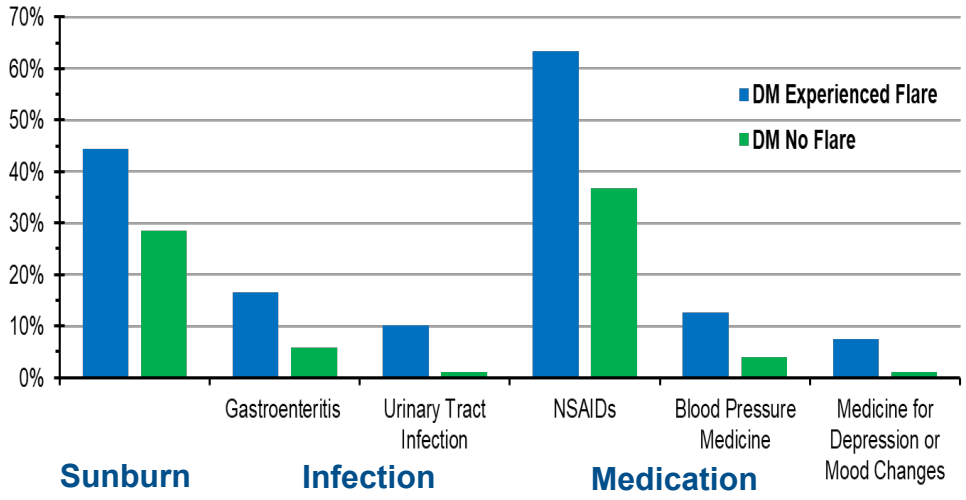
Gene: Name	Protein Function	Phenotype*	SNP Disease Associations*
PTPN22: Protein tyrosine phosphatase	Non-receptor type 22 alters the responsiveness of T and B cell receptors and TCR signaling	PM	RA, JIA, SLE, SSc, ATD, T1D
STAT4: Signal transducer and activator of transcription 4	Required for Th1 cell development and IFN-γ production	PM	RA, JIA, SLE
PLCL1: Phospholipase C-like 1	Cell signaling	DM/JDM	SLE
GSDMB: Gasdermin B	Promotes pyroptosis, inflammatory programmed cell death	DM/JDM	RA, T1D, IBD, MS
BLK: B lymphoid tyrosine kinase	Involved in B cell receptor signaling and B cell development	DM/JDM	RA, SLE
CCL21: Chemokine (C-C motif) ligand 21	Involved in dendritic cell and T cell migration and proliferation and type I IFN signature generation	DM/JDM	RA, Sjogren's

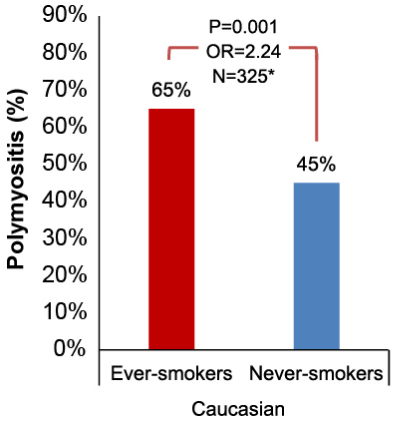
Miller 2018 Nature Rev Rheum; Rothwell 2019 Ann Rheum Dis; Miller 2015 Genes Immun; Acosta-Herrera 2019 Ann Rheum Dis

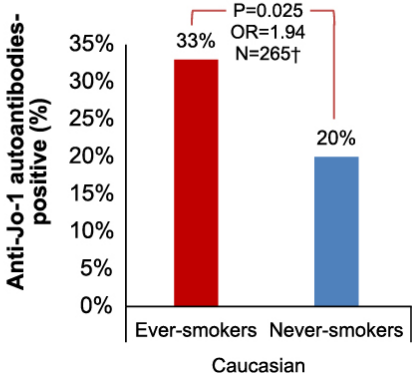
EAG Key Findings – Environmental Risks for Myositis

- UV radiation is a risk factor for DM and DM autoantibodies in children and adults, in U.S. and globally
- Smoking is a risk factor for PM and anti-Jo-1 autoantibodies. HLA DRB1*03 further increases risk
- Sunburn, urinary tract infections and gastroenteritis, and medications are risk factors for JDM/DM disease flares





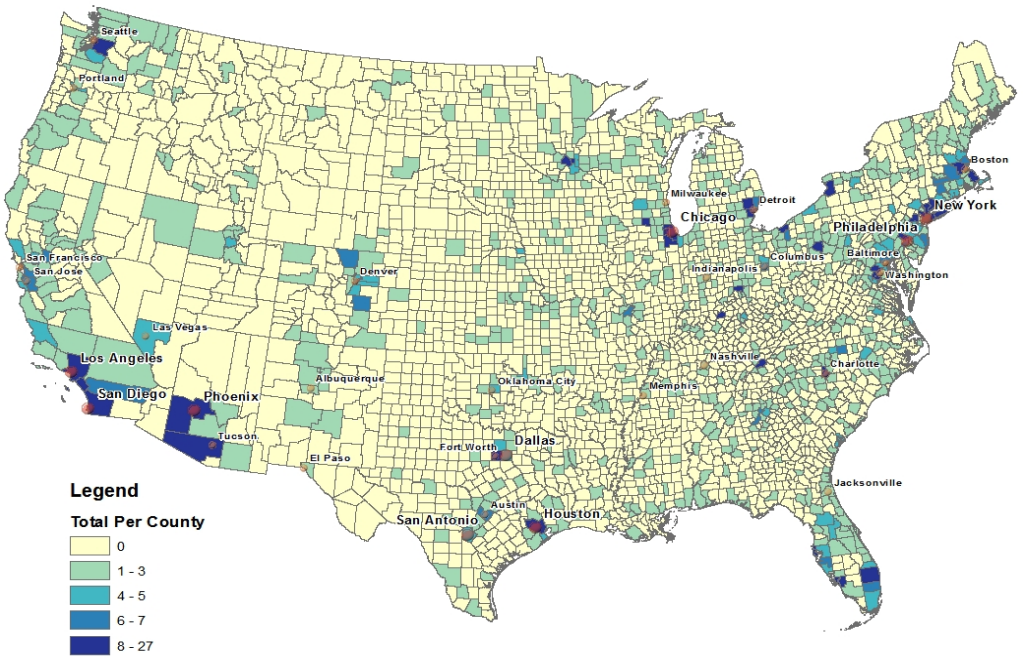




Miller et al. 2018 Nature Rev Rheum; Schiffenbauer et al. 2018 Sem Arthr Rheum; Mamyrova et al 2017 Rheum

EAG Ongoing Studies of Myositis and other Systemic Autoimmune Diseases

- Defining novel genetic and environmental risk factors, GXE interactions
  - Twin Sibling Systemic AIDs, MYORISK (ARS+), Military
- Detailed assessments for phenotyping, disease activity/ damage assessment, imaging, and biomarker studies
- Assessing novel therapies for calcinosis, DM

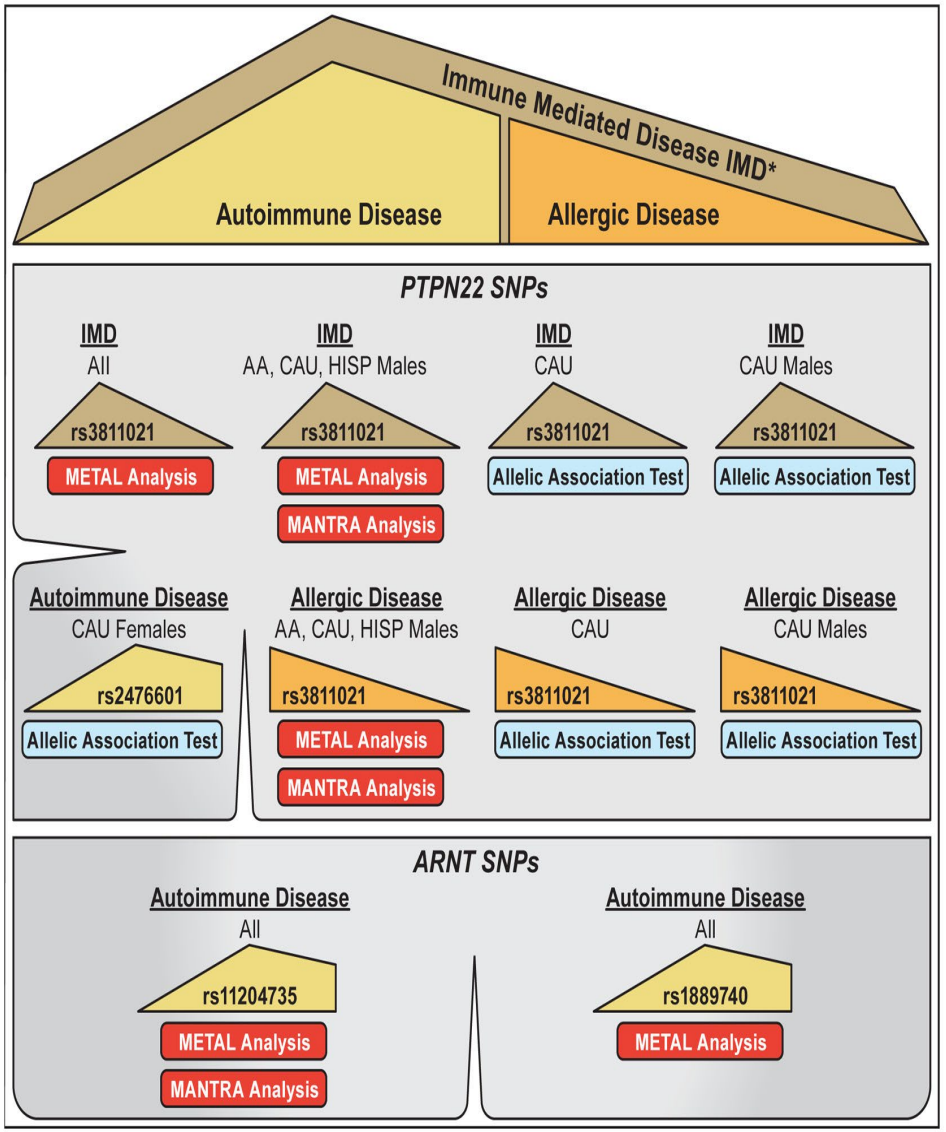


- Established a National Myositis Patient Registry, MYOVISION
  - 1800 patients with DM, PM, IBM, JDM
  - QoL significantly impaired vs. normative population and RA
  - Personal UVR (job exposure in men, hobbies in women) is risk for DM
  - Questionnaire on myositis features, medications, job/hobby exposures, infections, medications – examining exposure risks for phenotypes
  - Partnered with The Myositis Association, CCHMC; initial funding CDC

Feldon et al, 2018 Arthr Care Res.; Parks et al, 2020 Arthr Care Res.

Environmental Polymorphisms Registry (EPR) Autoimmune Disease Projects

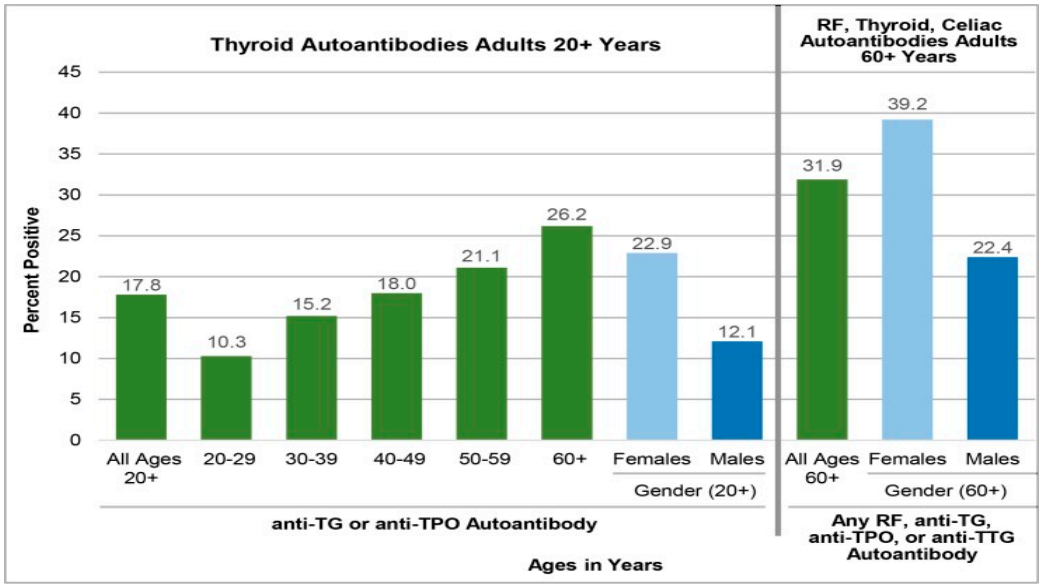
- EPR provides a unique resource for studies clarifying the interaction of genetic and environmental determinants of human health.
- ~20,000 participants have contributed biological samples (blood, DNA, other materials), as well as disease and exposure data that support a wide range of research questions.
  - Whole genome sequencing completed on ~5000 participants.
- Immune-mediated diseases, including autoimmune, allergic and asthmatic conditions, were found to have similar *PTPN22* SNP risk factors, and novel *ARNT* SNPs in autoimmune diseases.
  - These are being investigated for additional genetic and environmental risk factors and GXE interactions.

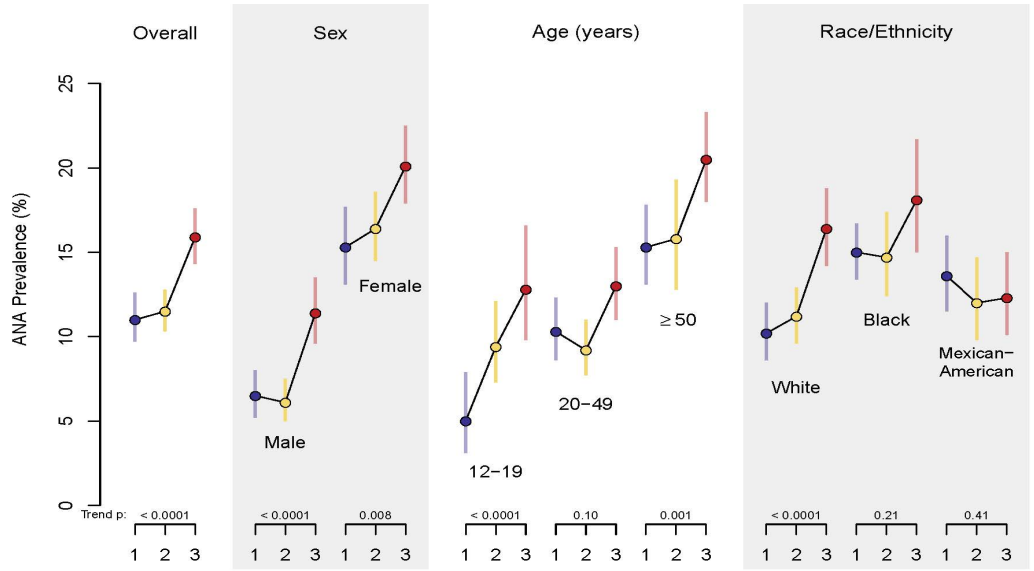


Schurman et al. 2019 J Autoimmunity

NIEHS Intramural Recent Findings in Autoimmunity: High and Increasing Prevalence

- Using U.S. population – representative data from NHANES, Dr. Fred Miller and associates identified overall autoantibody prevalences increased significantly with age and 32% of adults 60+ years of age had at least one of four autoantibodies: rheumatoid factor, anti-thyroglobulin, anti-thyroperoxidase, or anti-tissue transglutaminase.
- ANA prevalence increased from 11% to 16% in the U.S. over the last several decades, and especially in men, adolescents, older adults, and non-Hispanic whites.





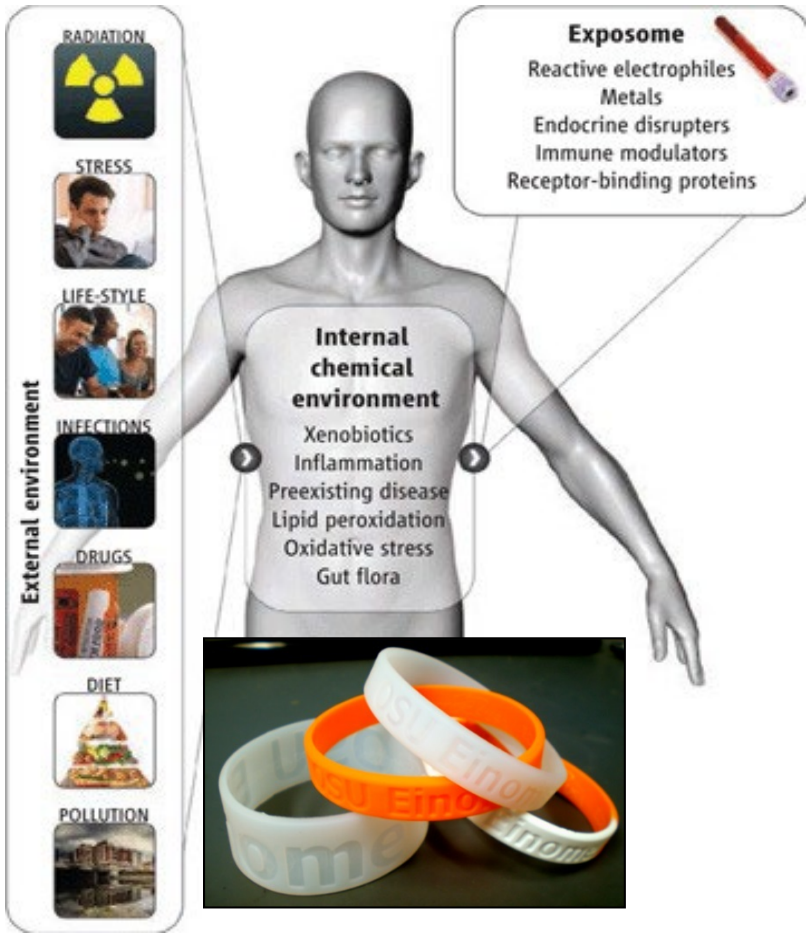
Dillon et al. 2020 PLoS One; Dinse et al. 2020 Arthr Rheum

Possible Approaches to Enhance Understanding of Risks and Prevention of Autoimmune Diseases

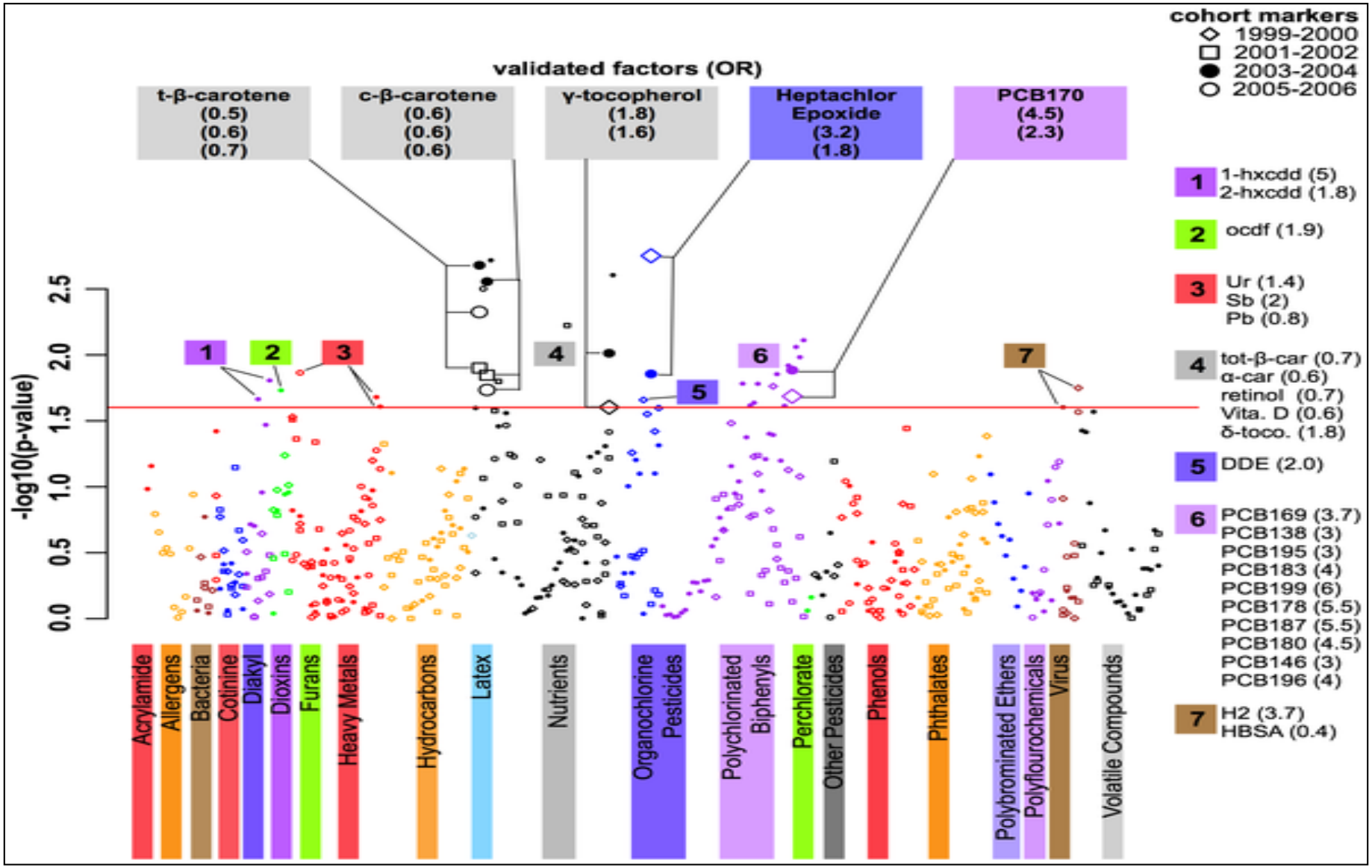
- Foster multidisciplinary consortia among basic and clinical researchers to optimally utilize databases, registries, specimen repositories, animal models
- Include autoimmunity as an outcome of large NIH cohort and registry studies
- Create a National Autoimmunity Disease Registry
- Detailed prospective clinical, environmental and molecular assessments of high-risk populations (high exposure settings, multi-case families)
  - Include patients before disease onset to define pre-disease progression mechanisms, and also over the lifespan
- Integrate clinical/immunologic/molecular deep phenotyping and environmental exposure studies within future genetic and environmental investigations
- Validate standardized environmental exposure assessments and biomarkers
  - Increase environmental sensors – geographically distributed in target areas
  - Enhanced Geographic Information Systems – new modeling and mapping tools
  - Wearable real-time personal sensors
  - Exposome and Environment-wide Association Studies (EWAS)

The Exposome and Environmental Wide Association Studies (EWAS)

- Exposome – A new paradigm to assess how a lifetime of exposures, from conception onwards, contribute to human health and disease
- EWAS – Method to assess many environmental exposures simultaneously
- Multi-omics integration – metabolomics, transcriptomics, proteomics, genomics
- Assay wearable silicone wrist bands
- Estrogenic activity – monitor the effect of multiple endocrine disruptors
- Immune modulators → cytokines and chemokines
- Measure metals, hormones, antibodies to pathogens and xenobiotics, and proteins released by cells in response to stress
- Detect changes to lymphocyte gene expression or chemical modifications of DNA (methylation, acetylation) after exposures

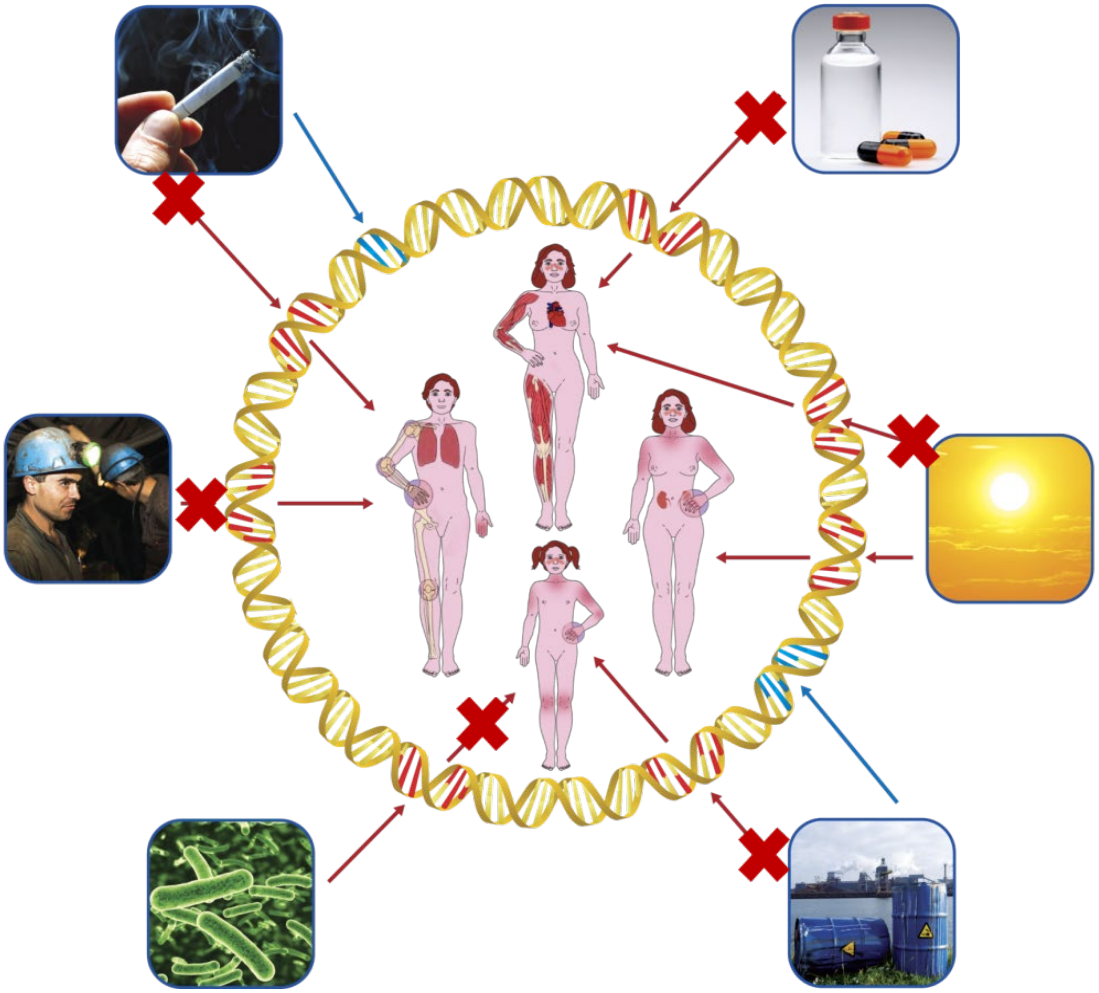


Manhattan Plot Style Graphic Showing an NHANES Environment-wide Association Study (EWAS) with T2D



Patel er al. 2010 PLoS ONE

Possible Outcomes of Enhanced Studies of Autoimmune Disease



New approaches and technologies to carefully define autoimmune disease phenotypes and identify environmental and genetic risk/protective factors may lead to new disease pathways, better treatments, and possibly enable future prevention

NIEHS Links for More Information

- NIEHS website https://www.niehs.nih.gov/
- NIEHS Strategic Plan 2018-2023 https://www.niehs.nih.gov/about/strategicplan/index.cfm
- NIEHS Intramural Research Division https://www.niehs.nih.gov/research/atniehs/dir/index.cfm
  - Immunity, Inflammation, and Disease Laboratory https://www.niehs.nih.gov/research/atniehs/labs/iidl/index.cfm
  - Epidemiology Branch https://www.niehs.nih.gov/research/atniehs/labs/epi/index.cfm
  - Clinical Research Branch https://www.niehs.nih.gov/research/atniehs/labs/crb/index.cfm
    - Clinical Research Unit https://www.niehs.nih.gov/research/clinical/durham/index.cfm
    - Environmental Polymorphisms Registry https://dnaregistry.niehs.nih.gov/
    - Environmental Autoimmunity Group https://www.niehs.nih.gov/research/atniehs/labs/crb/pi/ea/index.cfm