Mechanistic Indicators of Childhood Asthma (MICA): A Systems Biology Approach for the Integration of Multifactorial Environmental Health Data

research&development

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Science Question

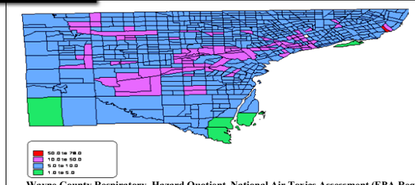
•Can biologically relevant air pollution species and sources (indoor, outdoor, traffic) support the analysis of MICA's genetic, biological and health data?
•Can genomic data viewed together with a spectrum of exposure, effects, clinical and susceptibility markers:
1) Increase the sensitivity needed to define exposure-response-effects relationships?
2) Provide mechanistic explanations as to varied asthmatic responses and susceptibility to environmental exposures?

Research Goals

•Identify biologically relevant air pollution species and sources for MICA through home monitoring, geospatial and exposure-related variables, such as proximity to various stationary and mobile sources
•Relate metrics and surrogates for traffic pollution to clinical markers of asthma allergy and inflammation
•Apply exposure, effect, clinical, and gene biomarkers to evaluate both overarching and specific studies along the source to health outcome paradigm
•Use blood and lung tissues from rodents to inform the blood gene expression analysis from the children's study.
•Identify panels of biomarkers from the array of MICA co variants for future application in large population studies by addressing their reliability, predictive value, sensitivity, specificity, affordability, applicability.
•Apply statistical and methodological approaches to help define asthma phenotypes and identify underlying mechanisms related to perturbation of gene networks related to environmental exposures and or genetic susceptibility.

Acknowledgments

We gratefully acknowledge our many collaborators: US EPA Region 5, NERL (RTP and Cincinnati), NHEERL (EPHD, ECD), Genomic and Chemistry Core, NIEHS, Michigan State University, Rutgers University , Harvard, University of North Carolina, Johns Hopkins, Mercy College, Integrated Laboratory Systems. Expression Analysis, Southwest Research Institute, RTI, Lab Corp, Henry Ford Health Systems and Westat

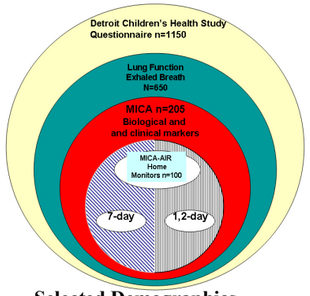


Wayne County Respiratory Hazard Quotient National Air Toxics Assessment (EPA Region 5 Jackie Nwai)

Why Detroit, Michigan ?

•Other major EPA initiatives DEARS (NHEERL) and DCHS (NHEERL) and NCEA (Near Roadway)
•Wayne county ranks in top 10 % of US counties with respect to criteria pollutants (person days exceeding 8-hr standard for ozone) and several air toxics chemicals

MICA provides biomarker and genomics component For the Detroit Children' s Health Study DCHS (L. Neas)

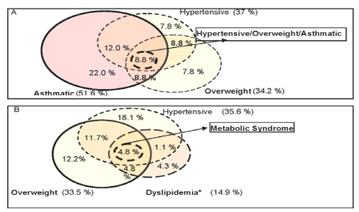


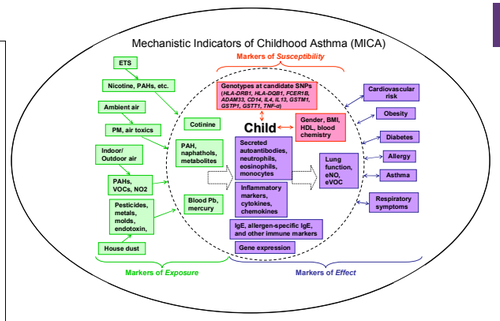
Selected Demographics

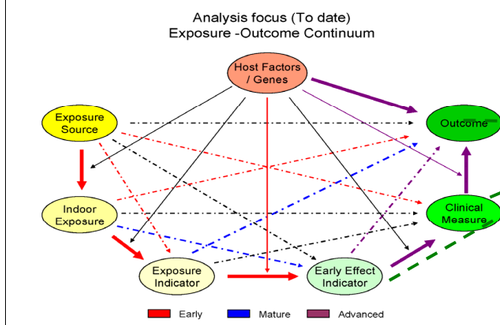
	N	Percent	Mean	SE	GeoMean	GeoStd
Male	205	58.0				
WhiteOnly	203	9.9				
BlackOnly	203	69.3				
OtherRace	203	6.9				
Asthma Diagnosis	195	52.3				
Age/Yrs	205		11.6	0.08		
SomePost High School	203	19.7				
=HighSchool	203	13.8				
<HighSchool	203	33.5				
Post College	203	32.5				
Weight/BMI						
Height	205		151.6	0.8		
Weight	205		52.7	1.3		
BMI	205		22.5	6.2	21.8	1.3
BMI< 25	205	66.3				
BMI25to30	205	22.9				
BMI>30 (obese)	205	10.7				
Cardiovascular						
MeanSys	203		110.2	0.8		
MeanDia	203		70.6	0.6		
Hypertensive Systolic	47	23.1	122.5	0.5		
Hypertensive Diastolic	52	25.6	81.4	0.7		
Selected lipids						
TotCholesterol	189		166.6	31.5	163.6	1.2
Triglycerides	189		83.9	38.2	76.9	1.5
HDL	189		54.4	12.8	52.8	1.4
LDL	189		95.0	28.4	90.7	1.4
TotCholesterol≥200	189	14.8				
Triglycerides≥150	189	7.9				
HDL<40	189	12.2				
LDL≥130	189	11.1				
Immunological Indicators						
Total serum IgE	196		94.8	5.1		
Food Screen allergen(+)	196	35.7				
Aeoallergen screen (+)	196	60.2				
Atopic Asthmatics	98	70.4				

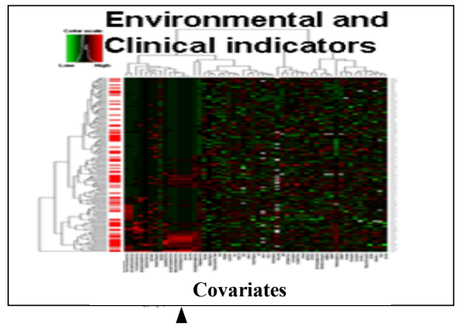
MICA more than an asthma study

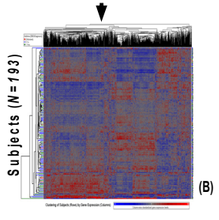
Health status (proportion) asthmatic, overweight, hypertensive, dyslipidemia

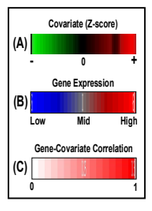




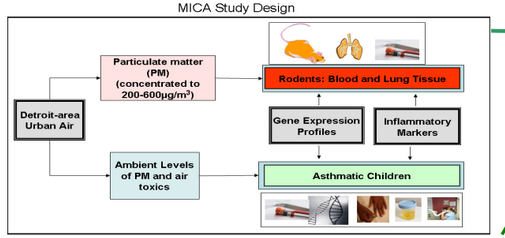


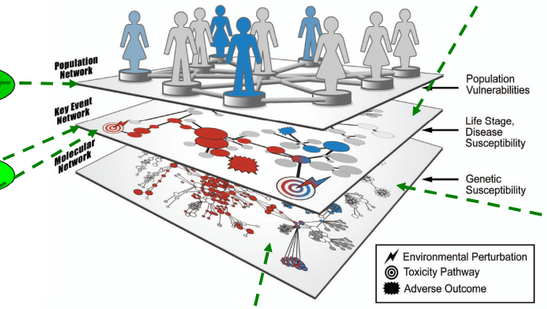


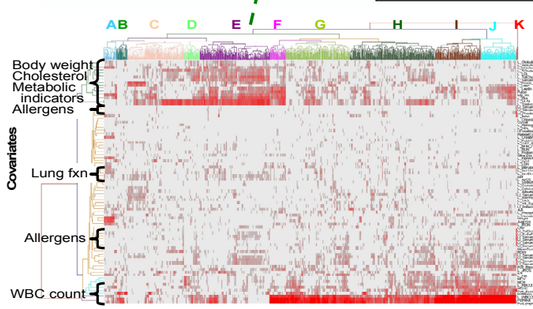




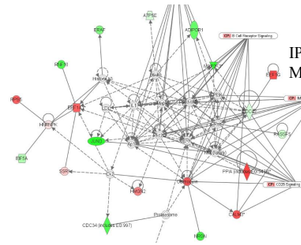
Approach



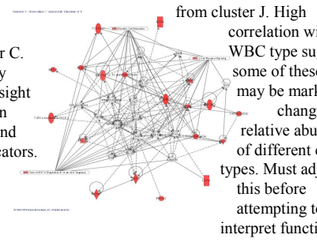




IPA network derived from cluster E. Central hubs suggest that this cluster may be linked to changes in the cytoskeletal structure in one or more cell types and that the processes may be regulated by NFkB.

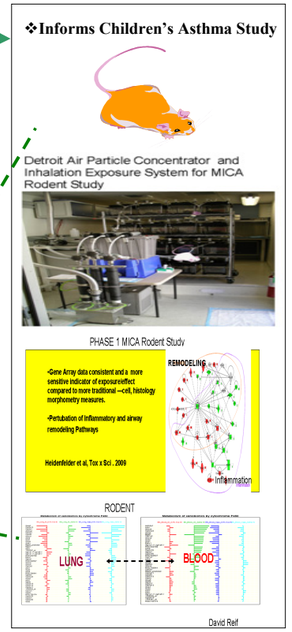


IPA network derived from cluster C. Makeup of central hub genes may provide mechanistic insight into the correlation seen between genes in this cluster and lipid and other metabolic indicators.



IPA network derived from cluster J. High correlation with WBC type suggests some of these genes may be markers for changes in relative abundance of different cell types. Must adjust for this before attempting to interpret function.

ANIMAL STUDY



Results/Conclusions

•Participant-based monitoring is a cost-effective approach to exposure assessment.
•Rodent gene expression data is both consistent and more sensitive than the more traditional morphometric, histological and phenotypic data.
•Clinical measurements and gene expression data provide unique insights into the mechanistic basis for asthma. Combining with exposure measures enhances understanding of the impact of environmental stressors.

Impact and Outcomes

•Environmental/gene markers and MICA's mechanism-based paradigm informs two significant EPA initiatives in the Detroit Area: Detroit Exposure Aerosol Research Study (DEARS) and the Detroit Children's Health Study DCHS).
•Source to outcome data can inform the National Children's Study and other large epidemiological studies.
•Global gene expression data is unbiased with regard to *a priori* assumptions on the mechanisms involved. This enhances the interpretation of mechanistic models built from the mechanism (or mode) of action.
•Leveraging both rodent (controlled exposures, blood & lung tissue) and human studies (relevance for risk assessment) help to better understand childhood asthma development.

Future Directions

•Identify impact of exposures on key pathways identified from the gene expression data
• Characterize the genetic variants that increase risk for childhood asthma.
•Estimate combined effects of different environmental exposures and genetic susceptibility in determining the likelihood of developing/exacerbating childhood asthma.
•Evaluate other endpoints of regulatory importance (i.e. hypertension, obesity, metabolic syndrome)

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