

Environment-wide Association Studies (EWAS) for a more complete view of disease risk

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About me...





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environmental exposure informatics



environment + genome = health

Complex disease is a function of genes and environment...



... and we're exposed to many environmental factors...

and lack *methods* and *data* to comprehensively and systematically connect the environment with disease.



... and the case is different with genetics (e.g., genomics)!

over 1,400 Genome-wide Association Studies (GWAS)

NHGRI GWAS Catalog https://www.genome.gov/ type 2 diabetes heart disease

obesity

kidney disease



autism

asthma

Alzheimer's

arthritis

cancer

preterm birth

...but, much disease risk may be due to differences in **environment**^{1,2,3}.

Willett WC, Science. (2002)
 Lichtenstein P., NEJM. (2000)
 Lindorff et al., PNAS. (2009)

... but we lack a search engine to discover new **exposures** in disease. (see: **GWAS**!)

Big Environmental Exposure: Human *Exposome*¹ Project to "E"WAS?



Rappaport S, Smith M. Science (2010)
 Patel CJ, Ioannidis JPA. JAMA (2014)



... but there is no "microarray" for environmental exposure...

In lieu of an *exposome* chip: National Health and Nutrition Examination Survey¹



since the 1960s: 50 years! now biannual: 1999 onwards 10,000 participants per survey

hundreds of exposure measures

many clinical measures & health assessments



I <u>http://www.cdc.gov/nchs/nhanes.htm</u>

NHANES ascertains >300 exposures in serum and urine!





Nutrients and Vitamins e.g., vitamin D, carotenes Infectious Agents

e.g., hepatitis, HIV, Staph. aureus



Plastics and consumables e.g., phthalates, bisphenol A



Pesticides and pollutants e.g., atrazine; cadmium; hydrocarbons



Physical Activity e.g., steps

Environmental exposures are associated with **Type 2 Diabetes**?

EWAS in Type 2 Diabetes visualized in a *Manhattan Plot*



EWAS has had utility in searching for exposures in disease

A Nutrient-Wide Association Study on Blood Pressure

Ioanna Tzoulaki, PhD;* Chirag J. Patel, PhD;* Tomonori Okamura, MD, PhD; Queenie Chan, PhD; Ian J. Brown, PhD; Katsuyuki Miura, MD, PhD; Hirotsugu Ueshima, MD, PhD; Liancheng Zhao, MD; Linda Van Horn, PhD; Martha L. Daviglus, MD, PhD; Jeremiah Stamler, MD; Atul J. Butte, MD, PhD; John P.A. Ioannidis, MD, DSc; Paul Elliott, MB BS, PhD

Circulation, 2012

Systematic evaluation of environmental factors: persistent pollutants and nutrients correlated with serum lipid levels

Chirag J Patel,^{1,2} Mark R Cullen,³ John PA Ioannidis^{4,5,6} and Atul J Butte^{1,2}*

IJE, 2012

Systematic evaluation of environmental and behavioural factors associated with all-cause mortality in the United States National Health and Nutrition Examination Survey

Chirag J Patel,¹ David H Rehkopf,² John T Leppert,³ Walter M Bortz,⁴ Mark R Cullen,² Glenn M Chertow⁴ and John PA Ioannidis¹*

IJE, 2013

EWAS and searching for **GxE** in disease:

EWAS-identified exposures + **GWAS-identified** SNPs = *greater* risk for disease?

Screening all possible **EWAS-GWAS** interactions: OR for **rs13266634** (*SLC30A8*) stratified by E +30-40% vs. no E



Adjusted for race, sex, BMI, age

Patel CJ, et al. Human Genetics. 2013

Studying the Elusive Environment in Large Scale

VIEWPOINT

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It is possible that more than 50% of complex disease risk is attributed to differences in an individual's environment.¹ Air pollution, smoking, and diet are documented environmental factors affecting health, yet these factors are but a fraction of the "exposome," the totality of the exposure load occurring throughout a person's lifetime.¹ Investigating one or a handful of exposures at a time has led to a highly fragmented literature of epidemiologic associations. Much of that literature is not reproducible, and selective reporting may be a major reason for the lack of reproducibility. A new model is required to discover environmental exposures associated with disease while mitigating possibilities of selective reporting.

To remedy the lack of reproducibility and concerns of validity, multiple personal exposures can be assessed simultaneously in terms of their association with a condition or disease of interest; the strongest associations can then be tentatively validated in independent data sets (eg, as done in references 2 and 3).^{2,3} The main advantages of this process include the ability to search the list of exposures and adjust for multiplicity systematically and report all the probed associations instead of only the most

the EWAS vantage point, intervening on β -carotene (Figure, D) seems a futile exercise given its complex rela-

A Serum cotinine 37 Total correlations





However, eventually for most environmental correlates, there may be unsurpassable difficulty establishing potential causal inferences based on observational

JAMA, 2014

- evaluate new 'omics technologies
 new informatics methods
- Iongitudinal and linkable health data

i2b2?

ENVIRONMENT-WIDE ASSOCIATION STUDY (EWAS) FOR TYPE 2 DIABETES IN THE MARSHFIELD PERSONALIZED MEDICINE RESEARCH PROJECT BIOBANK

PhenX: Alcohol 30Day Frequency PhenX: Smoking At Home DHQ: Caffeine(mg) Activity: Leisure Index Activity: Sports Index PhenX: Exposure Smoke Childhood Hours PhenX: House Gas Powered Device Storage PhenX: Energy Level PhenX: Former Smoker Quantity 1Day PhenX: Exposure Smoke Adulthood Work PhenX: House Farm Use PhenX: Dwelling Type PhenX: Leisure Time Activity PhenX: Former Smoker More 1stHour PhenX: Former Smoker 1stSmoke Time PhenX: Exposure Smoke Adulthood Home PhenX: Alcohol Withdrawal Hallucination PhenX: Mania Increased Sex PhenX: Building Residence Age PhenX: Weekend Sun Hours Last Decade PhenX: Air Conditioning Stop Month PhenX: Weekday Sun Hours Last Decade PhenX: Lifetime Use PhenX: Alcohol Use Liver Disease PhenX: Former Smoker Quantity 1DayA PhenX: Exposure Smoke Present Time Hours PhenX: Tanning Booth Ever PhenX: Mania Impatient PhenX: Depression Number Weeks PhenX: Exposure Smoke Adulthood Home Hours PhenX: Sunlamp Times Estimate DHQ: Carbohydrate (g)



Hall et al, Proc Symp Biocomputing (2013)

314 self-report **E** (PhenX toolkit) ~2000 cases and controls T2D via eMERGE algorithm

https://www.phenxtoolkit.org/

Searching for maternal exposures associated with preterm birth Mothers in **NHANES** and **attending Stanford Clinics**



Screened 253 exposures in >100 mothers (NHANES)

Bruce Ling Andy Hu Ting Yang Atul Butte





Tuesday, July 15, 14

Searching for maternal exposures associated with preterm birth: Mothers in **NHANES** and attending **Stanford Clinics**



les°

16 moms with preterms21 moms with normal births

collected urine during gestation

identified via EHR

Patel CJ, et al. Reprod Tox 2013

Location, location, location: Exposure assessment via geolocation of patients





(latitude, longitude)

Income/SES Air pollution (e.g., PM 2.5) "Green space" Climate

John Brownstein

EWAS can enable a *comprehensive view* of exposures in disease by studying the environment...



Understanding the role of the **exposome** will lead to a more precise medicine.



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