Genetics and Environment in Asthma

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PI SAPALDIA Cohort & Biobank
Gene-environment interactions in asthma

- why
Epidemiology of asthma
Papi A et al. Lancet 2017; Dec 19

affects around 334 million people worldwide

causes disability, impaired quality of life and premature deaths

prevalence of self-reported, doctor-diagnosed adult asthma
  Global 4·3% - Australia 21·0% - China 0·2%

prevalence stable or decreasing in many developed countries, but increasing rapidly in low-income countries
The prevalence of asthma and allergic disease in immigrants is
• lower than in host country population, but converges over time
• higher in second than first generation immigrants, and increases with length of residence in the host country

findings consistent across populations, host countries, age groups

suggests strong influence of the environment over the life course – related to Western and urban environment
Modifiable risks - poorly understood

**Randomization** of exposures often not possible

**Small effects**

**Measurement error**
- exposure
  - spatial and temporal variation
  - long latency – unknown windows of susceptibility
  - mixture effects – correlation of hazards
- phenotype/endotype
  - childhood vs. adult asthma
  - allergic vs. non-allergic asthma
  - persistent vs. non-persistent asthma
- ...

**Confounding Susceptibility**

challenging causal inference
Mendelian Randomization
Is BMI causally associated with asthma?

Randomized Controlled Trial
- Random assignment into treatment groups
  - Weight-loss Intervention → BMI lower
  - Control → BMI higher

Mendelian Randomization
- Random allocation of genetic variants
  - Obesity-protecting genotype → BMI lower → lower asthma incidence
  - Obesity-predisposing genotype → BMI higher → higher asthma incidence

lower asthma incidence  higher asthma incidence
classic
lower asthma incidence  higher asthma incidence
Mendelian Randomization
towards causal understanding of BMI in asthma
Biomarkers and biological understanding

most exposures are not genetically determined

*air pollution, passive smoking, chemicals*

- Mendelian Randomization is not a solution

- the next best option for causal inference

apply biomarkers towards mechanistic understanding
Gene-Environment interactions in asthma

- which genes, which environment
10 years of genomewide association studies in asthma

Vicente CT. Clinical & Translational Immunology (2017) 6, e165

good replication

small effects

rare variants unlikely to improve ~2.5% heritability
Clinical utility of asthma GWAS findings

Novel drug targets

associations with IL6R gene variants raise the question on tocilizumab (TCZ; humanized antibody against IL6R) as asthma treatment

Mechanistic understanding

associations with polymorphisms for *IL33, IL1RL1/IL18R1, HLA-DQ, SMAD3*, and *IL2RB9* and the locus on chromosome 17q21 including the genes *ZPBP2, GSDMB,* and *ORMDL3* implicate abnormalities in epithelial barrier function and innate and adaptive immune responses as contributing to asthma
GWAS meta-analysis of asthma in Puerto Ricans
Yan et al. Eur Resp J 2017; 49(5)

Puerto Ricans highest asthma rates in the US
17q21 variants strongest signals – equivalent to other ethnic groups
environmental differences matter more than genetics
Relevant exposures for asthma GEI studies
Bonnelykke/Ober J Allergy Clin Immunol 2017;137:667

Early-life exposures in childhood-onset asthma
- maternal asthma is still the most significant predictor
- growing up on a farm in central Europe protective
- viral respiratory tract infections
- intrauterine smoke exposure
- maternal diet during pregnancy

Inhalant exposures in adult-onset asthma
- occupational
- air pollution

Candidate gene-environment interactions (GEI)
Agnostic genome-wide interactions (GWIS)
Multiancestry random-effect meta-analysis of asthma risk
Demenais F et al. Nature Genetics 2018;50:42

candidate gene of interest

17q12-21
A decade of research on the 17q12-21 asthma locus
Stein MM J Allergy Clin Immunol. 2018 Jan 4

- major genetic risk locus for childhood-onset asthma & allergies
- physiologic function remains elusive
  - locus harbors the co-expressed genes ORMDL3 and GSDMB
  - ORMDL3 SNPs – decreased sphingolipid synthesis –relevant to immune signalling, vascular tone, inflammation,…
- 17q12-21 SNPs may affect asthma risk through the expression of different genes and in different tissues
Early wheeze effects on asthma at age 6 depend on 17q12-21 SNPs the PASTURE study
Loss G et al. AJRCCM 2016;193:889

A

- No wheeze in year 1
- >= 1 wheeze episode

B

- No wheeze in year 1
- >= 1 wheeze episode

C

- No wheeze in year 1
- >= 1 wheeze episode

P < 0.001 for interaction of SNP and wheeze

rs8076131

rs7216389

rs2290400
Animal shed exposure protects against early wheeze among carriers of 17q12-21 at-risk genotype asthma
GWIS childhood asthma and farming exposure

Key messages

- A genome-wide interaction analysis revealed several novel interaction candidate genes for asthma and atopy in a farming environment.
- In turn, the top SNPs of a meta-analysis for childhood asthma did not interact with farming.
- Previously published interactions with farming-related exposures for asthma and atopy were not replicated.

need for very large sample size

need for harmonized exposure in meta-analyses
GWIS early life environmental tobacco smoke exposure and childhood asthma
Scholtens S et al. J Allergy Clin Immunol 2014;133:885

**TABLE I.** Results of the GWIS of *in utero* tobacco smoke exposure and childhood-onset asthma

<table>
<thead>
<tr>
<th>Ch</th>
<th>SNP</th>
<th>Closest gene*</th>
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GWIS ever tobacco smoking  
adult-onset asthma  
Vonk et al. PLoS One 2017

SNP 5011804 located between KRAS and RPL39P27

never smokers  
ever smokers
GWIS air pollution in childhood asthma
Gref A et al. AJRCCM 2017;195:1373

<table>
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<tr>
<th>Chr</th>
<th>SNP</th>
<th>MAF</th>
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<th>Discovery GWIS Meta-analysis: BAMSE, GINplus/LISAp:lus, PIAMA (n = 1,534)</th>
<th>Look-up</th>
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<td>Interaction P Value*</td>
<td>Stratification by Genotype OR (95% CI)</td>
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<td>AA: 1.68 (0.85–3.29)</td>
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Direction of interactions not all consistent across studies
Gene expression in lung tissue, by B4GALT5 genotype
Gref A et al. AJRCCM 2017;195:1373
### NO$_2$ exposure at birth & peripheral blood gene expression at age 16

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<th>Chr</th>
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Mechanistic evidence from air pollution GWIS
Gref A et al. AJRCCM 2017;195:1373

**B4GALT4**

glycosphingolipid pathway

as is ORMDL3/GSDMB at 17q12-21
Cell models for targeted GEI selection
agnostic in cells – candidate GEI in humans
Ober C. Annals ATS 2016;13:S1

SNPs in common disease GWAS enriched for regulatory variants

relevant cell models of gene-environment interactions

*response expression QTLs; response methylation QTLs*

*genotype-specific transcriptional/epigenetic response to exposures*

targeted GEI in humans
Asthma research in the post GWAS era
About EXPOsOMICS

The exposome concept refers to the totality of environmental exposures from conception onwards, and is a novel approach to studying the role of the environment in human disease.
Air pollution & asthma incidence in adults
Jacquemin et al EHP 2015; Young MT et al. AJRCCM 2015

ESCAPE: 23’704 non-asthmatics; 1’257 incident asthmatics over 10 yrs
What are **causal** and mechanisms **mediating** health effects of traffic-related exposures?

**The Vehicular Traffic and Obesity/Metabolic Syndrome Pathway**

- **Exposure (Diesel Exhaust; PM, SOx,)**
- **Perceived Safety**
- **Noise**
- **Vibration**
- **Stress**
- **Systemic Inflammation**
- **Endocrine Disruption:**
  - Hypothalamic Pituitary Sexual Axis
  - Metabolic Sensors NRs
  - Glucose dysregulation
  - Insulin resistance
- **e.g. Bisphenol A, Diethylstilbestrol, Phthalates, Organotins, Perfluorooctanoic acid (PFOA)...**
- **Obesity/Metabolic Syndrome**
  - Diabetes, Hypertension, Cardio-respiratory disease, Cancer, Depression, etc..
- **Caloric Intake**
- **Sleep Disruption**
- **Cortisol Dysregulation**

**Figure 1**

*Jarrett M et al. Environmental Health 2014*
Meet-in-the-Middle Concept
Vineis P et al. Environmental Molecular Molecular Mutagenesis 2013

Prospective Study

risk-predictive biomarkers associated with exposure
risk-predictive biomarkers associated with disease

exposure
intermediate biomarkers of effect
disease
Perturbation of metabolic pathways mediates the association of air pollutants with asthma and cardiovascular diseases

A Jeong/N Probst-Hensch and Exposomics consortium

Metabolites
Agilent UHPLC-QTOF-MS system

Air Pollution
MWAS

Asthma
MWAS

CVD
MWAS

Adult-onset Asthma
SAPALDIA Cohort

CVD
EPIC Cohort

Regression analysis

Air Pollution calibrated by personal exposure measurement
Asthma phenome – Investigate endotypes

Papi A et al Lancet 2017, Dec 19
Systems epidemiology
- beyond single exposure
& single disease associations
Public Health relevant causal pathways
interlinking the «urban» exposome and phenome

- Urban exposome
  - Physical act.
  - Obesity
  - Noise
  - Air pollution
  - Chemicals

- Urban phenome
  - Respiratory diseases
  - Cardiovascular diseases
  - Diabetes
  - Cognitive function

- Psycho-social stressors
  - Systemic inflammation
  - Insulin resistance
  - Hypothalamus-pituitary-adrenal axis

Mechanisms
Overlap of asthma GWAS signals with autoimmune and inflammatory diseases

Demenais F et al. Nature Genetics 2018;50:42

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Number of GWAS-catalog association signals</th>
<th>Number of SNPs associated with asthma at $P_{\text{random}} \leq 10^{-4}$ in the multiancestry meta-analysis</th>
<th>$P$ value for overlap</th>
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<td>Cardiovascular</td>
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<td>$7.8 \times 10^{-42}$</td>
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<td>Body size and morphology</td>
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<td>Immune/autoimmune</td>
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<td>$1.4 \times 10^{-8}$</td>
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<tr>
<td>Blood</td>
<td>594</td>
<td>10</td>
<td>$1.3 \times 10^{-19}$</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>114</td>
<td>5</td>
<td>$1.5 \times 10^{-12}$</td>
</tr>
<tr>
<td>Cancer</td>
<td>417</td>
<td>7</td>
<td>$4.0 \times 10^{-14}$</td>
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<tr>
<td>Endocrine system</td>
<td>276</td>
<td>2</td>
<td>$4.0 \times 10^{-4}$</td>
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<tr>
<td>Digestive system</td>
<td>347</td>
<td>16</td>
<td>$1.4 \times 10^{-37}$</td>
</tr>
<tr>
<td>Eyes</td>
<td>177</td>
<td>2</td>
<td>$2.0 \times 10^{-4}$</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>85</td>
<td>2</td>
<td>$3.6 \times 10^{-5}$</td>
</tr>
<tr>
<td>Infectious disease/infection</td>
<td>104</td>
<td>2</td>
<td>$5.3 \times 10^{-5}$</td>
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<tr>
<td>Urinary system</td>
<td>144</td>
<td>1</td>
<td>$1.5 \times 10^{-2}$</td>
</tr>
<tr>
<td>Alcohol, smoking, and illicit substances</td>
<td>30</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>132</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
What associations – What mechanisms
Patel C Pac Sym Biocomput 2015; Sun YV Advances in Genetics 2016

Meet-in-the-Middle Concept – Prospective Biosampling
Vineis Environmental Molecular Mutagenesis 2013

mixtures → cross –omics perturbations → sub-phenotypes co-morbidities
SAPALDIA - Exposome*Genome to Phenome Data
The only Swiss-wide citizen biobank to date: N=6000

not personally modifiable exposures

effect modification/ life style

functional parameters

diseases/ death

25 years of follow-up

Quality of life

lung function Bronchial reagibility

Cardiovasc. parameters:
- BP
- HRV
- PWV
- CIMT

parameters of aging

Respiratory Diseases
• COPD
• Asthma
• Lung cancer

Cardiovascular Diseases
• Ischemic HD
• Heart failure

Diabetes

Other Chronic Diseases

Health & social service use

mortality

- genetics
- gender
- noise exposure
- air pollution
- green space
- socioeconomic status

- blood markers
- smoking
- nutrition
- physical activity
- occupation
- obesity
- reproductive/hormonal factors
- early life expo
- social network
Acknowledgement

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Swiss Health Study Team
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