Asthma & Allergy
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Health Outcomes
"It feels like something was standing on my chest." Madison, age 7 yr

Asthma

- One term, many etiologies
Asthma & Allergy Phenotypes & Endotypes

- asthmas
- comorbidities
- confounding factors
  - age of observation
  - sex
  - many others
- quantitative measures
  - lung function
  - serum IgE
  - skin prick testing
Comorbidities

Asthma
Atopic dermatitis / eczema
Allergic rhinitis / hayfever
(Food allergy)
Immunology of Asthma & Allergy

- Adaptive immune system polarized to Th2 & Th17 responses
  - Appropriate for extracellular pathogens
  - Inappropriate >>> allergens
Complex genetic disease

• familial inheritance

• environmental modifiers
Asthma & Allergy
Early studies

• **Candidate genes**
  - single genes

• **Positional candidate genes**
  - linkage in families

• **Modest replication**

• **Few functional mutations**

• **Limited effect size**
Genome-wide association studies

- Single nucleotide polymorphism (SNP)
- Array-based technology
- Unbiased
- Case-control design

![Image of DNA sequencing and array technology]
GWAS Results

First hit: 17q21 ORMDL3/GSDML genes
Genome-wide significance (~30)
Replications (none universal)

GWAS meta-analyses

- modest replication
- minimal effect size

"Missing heritability"

Moffatt et al, NEJM 2010
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Epigenetics

Epi: Ancient Greek (ἐπί) on, upon, outside, outside of, before

- Cell differentiation
- Genomic imprinting
- X chromosome inactivation
- Gene expression
DNA methylation

Gene regulation
- Gene silencing
- Repetitive elements
- Oncogenes
- Viral DNA inserts
- Cell-specific gene expression

Arrays with genome-wide coverage (>850,000 DNA-M)
- Automated processing

Direct exposure vs. transgenerational epigenetic inheritance

Modified by environmental exposures
- Prenatal smoke exposure
  - Decreased ISRE gene promoter methylation
  - Increased TLR4 expression
  - Increased atopic dermatitis risk (Wang et al. 2013)

Hypomethylation transcription
- CpGs
  - Present globally
  - Concentrated CpG islands

Hypermethylation silencing
Arrays with genome-wide coverage (>850,000 DNA-M)

automated processing
hypomethylation
transcription
hypermethylation
silencing
CpGs
- present globally
- concentrated CpG islands
Gene regulation

- Gene silencing
- Repetitive elements
- Oncogenes
- Viral DNA inserts
- Cell-specific gene expression
Modified by environmental exposures

Prenatal smoke exposure
- decreased TSLP gene promoter methylation
- increased TSLP expression
- increased atopic dermatitis risk (Wang et al 2013)
Direct exposure vs transgenerational epigenetic inheritance

Epigenetic marks erased
- after fertilization
- primordial germ cells
- some cells evade erasure

Mother - 1st generation
Fetus - 2nd generation
Reproductive cells - 3rd generation
Asthma risk ratio associates with IL4R & increases as SNP methylation level increases

Genotype (rs 3024685)
- CC
- CT
Reference TT

IL4R gene: 13 SNPs genotyped, shown is rs3024685
IL4R gene region contains 12 CpG sites, shown is cg09791102

Soto-Ramirez et al, 2013
Risk ratio of eczema associated with Filagrin (FLG) gene variants increased as DNA-M increased

Ziyab et al., JEADV, 2012
Epigenetic therapies

- Inhibition of DNA-M at *IFNG* locus by 5Aza restores Th1/Th2 balance & decreases development of experimental asthma in mice

(Brand et al, 2012)
• Link between genes & environment
• Missing heritability

Future goals:
• Inhibit DNA-M associated with allergic inflammation
• Leave global methylation unaltered

• Understand how environmental exposures impact epigenetics
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