Genomics- Hope or Hype?

Marc S. Williams, MD, FAAP, FACMG
Director Intermountain Healthcare
Clinical Genetics Institute
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April in Genetics

April 23, 1953 Watson and Crick published structure of DNA

April 25, 2003 Publication of Human Genome Sequence (declared DNA day)

Why Asthma Genomics?

Objectives

- What is genomics
- How may genomics impact medicine and public health
- What is known about genetic factors and asthma
- How does the genome interact with the environment
- Future questions

Definitions

Genetics-The branch of biology that deals with heredity, especially the mechanisms of hereditary transmission and the variation of inherited characteristics among similar or related organisms.

Genomics-The study of genes and their function. Genomics aims to understand the structure of the genome, including the mapping genes and sequencing the DNA. Genomics examines the molecular mechanisms and the interplay of genetic and environmental factors in disease.

Human Genome Project

Genome Project Nano-lecture (24 Seconds)

Human Genome Project: Biology's Moonshot. Fifteen years, six countries, twenty centers. Three billion dollars, three billion letters. One dollar per letter—such a deal!

Twenty-three chromosomes. Supposed to contain 100,000 genes. Turns out to only have 30,000 genes—or maybe 25,000. But it could be 40,000—check back with us next year.

Said to have the answer to everything, absolutely everything. Diabetes, Asthma, Cancer, Evolution, Populations, Migrations, Life, Death, Taxes. Even the Boston Red Sox.

The only problem is: there's no index.

Genome Project Nano-lecture (7 Words)

Genome: Bought the book, hard to read.

Eric Lander IgNobel® Prize Nano-lecture

10/2/2003

What does this mean for medicine?

History of Medicine (abridged)

- 2000 BC Here, eat this root
- 1000 BC That root is heathen, say this prayer
- 1850 AD Prayer is superstition, drink this potion
- 1940 AD That potion is snake oil, swallow this pill
- 1990 AD That pill has a narrow therapeutic window and low efficacy; take this biologically engineered drug
- 2000 AD That drug is artificial; here eat this root

2010 AD I want to study your genotype before prescribing anything.

Human Genome Project

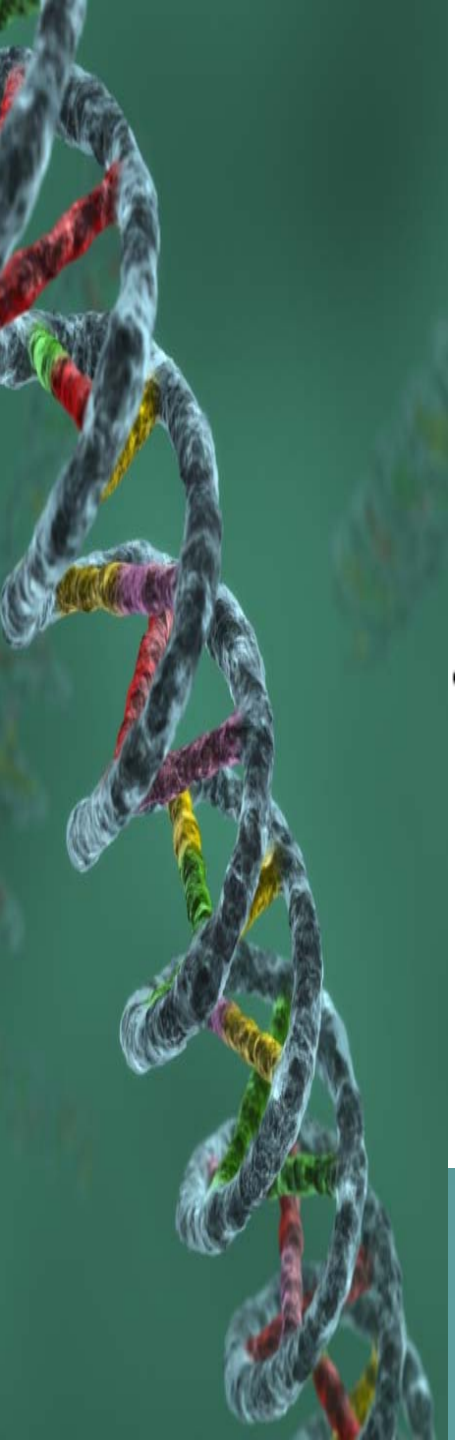
- ~30,000 genes
- 3.7 proteins per gene
- 1/1000 base pair difference
- 3 billion base pairs
- Differ at 3 million places!!
- “Junk DNA”

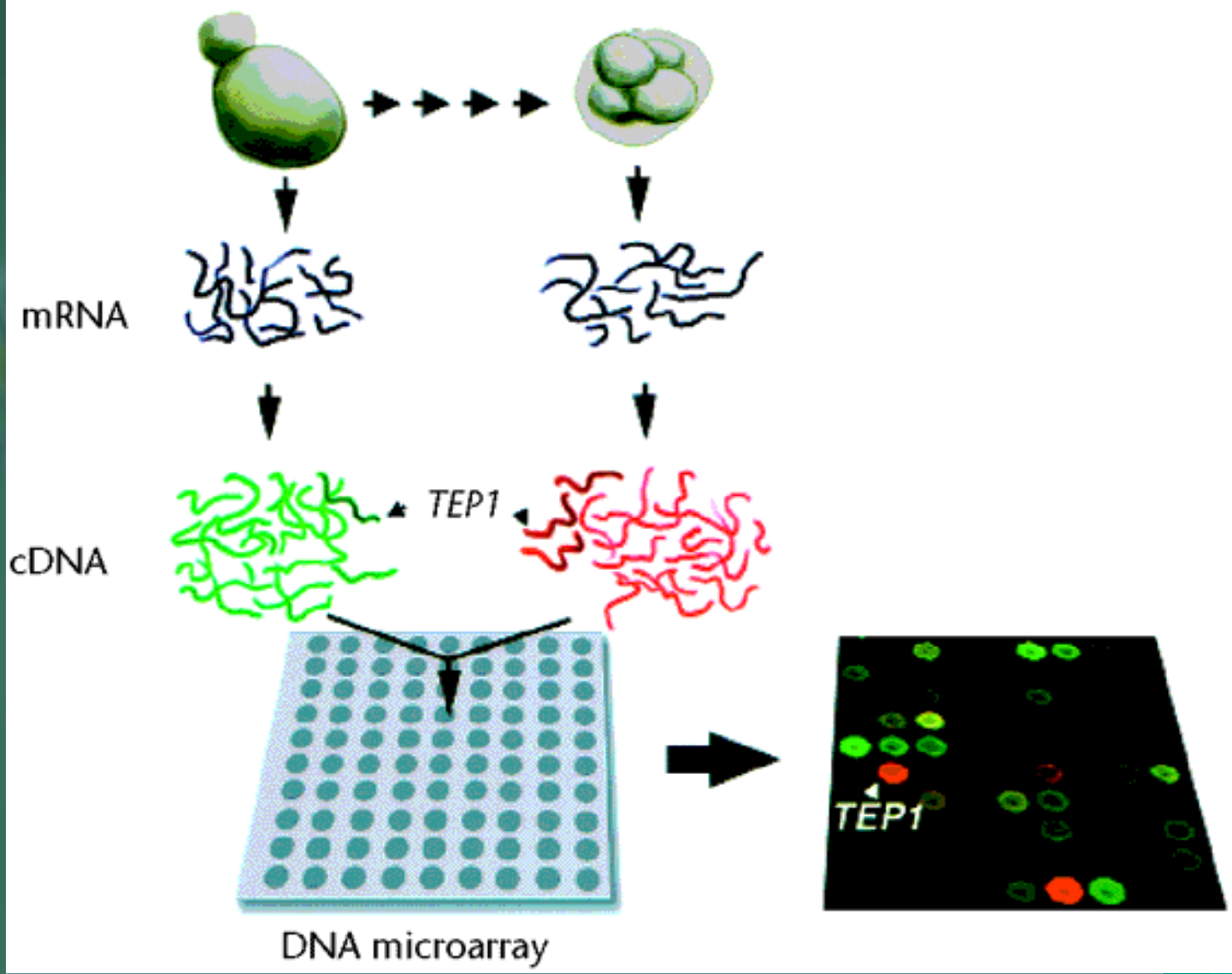
Single Nucleotide Polymorphism

A single nucleotide polymorphism (SNP) can be defined as a single base pair site in the human genome that is different from person to person.

Hypothesis

Patterns of polymorphisms predict predisposition to disease




mRNA
cDNA
TEP1
TEP1
DNA microarray


a
ALPH
ELU
CDC15
SPO
HT
D
C
DX
b
c
d
e
f
g

Generic prevention

vs.

Personalized prevention

Generic therapy

vs.

Personalized therapy

Benefits

- More effective therapy
- Safer therapy
- More cost-effective therapy
- Decreased pharmaceutical utilization?
- Innovative therapies

Limitations/Risks

- Availability of information
- Availability of new technology
- Predictive accuracy
- Preparation of provider system
- Adoption of new technology
- Consumer demand/direct to consumer
- Cost implications

Economics of Genomic Medicine

- Decrease costs
  - Preventive measures
  - Earlier interventions
  - More effective interventions
- Increase costs
  - Treatments for the untreatable
  - Longevity
  - Pharmacy
  - Gene therapy and stem cell therapy


1/3
©SEGA

What Is Asthma

- Asthma Triad
  - Bronchial hyperresponsiveness
  - Increased mucous production in airway
  - Edema of airway epithelial cells
- Asthma is a disorder of inflammation!!
- Treatment must control bronchospasm (rescue) and inflammation (controller)

Is Asthma Genetic?

- Twin studies estimate heritability at 36-79%
- Three times more likely to have asthma if mother has asthma
- Seven times more likely if mother and father have asthma
- 20 chromosomal regions linked to asthma (4 in >1 study)

Is Asthma Environmental?

- Prevalence of asthma increasing faster than can be explained by genetics
- Proposed factors
  - Air pollution
  - Allergens
  - Early infection

Genes and Environment

GENES

ENVIRONMENT

Lead

HIV/AIDS

Asthma

Diabetes

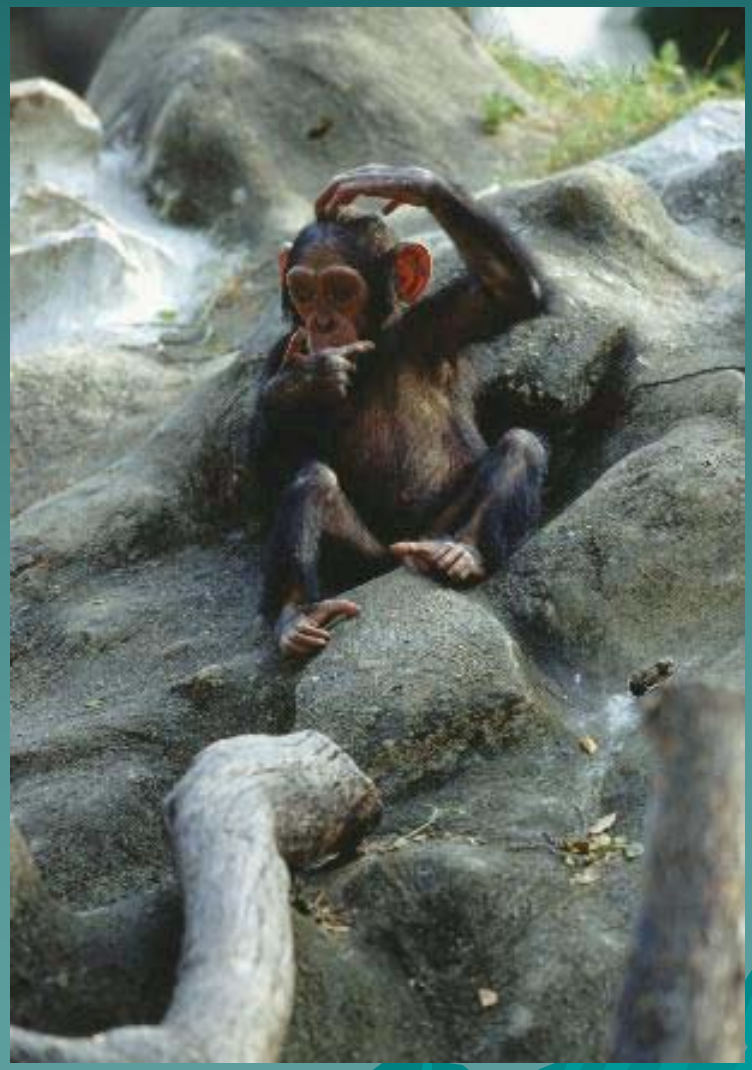
Cancer

Phenylketonuria

Cystic Fibrosis

Tay-Sachs

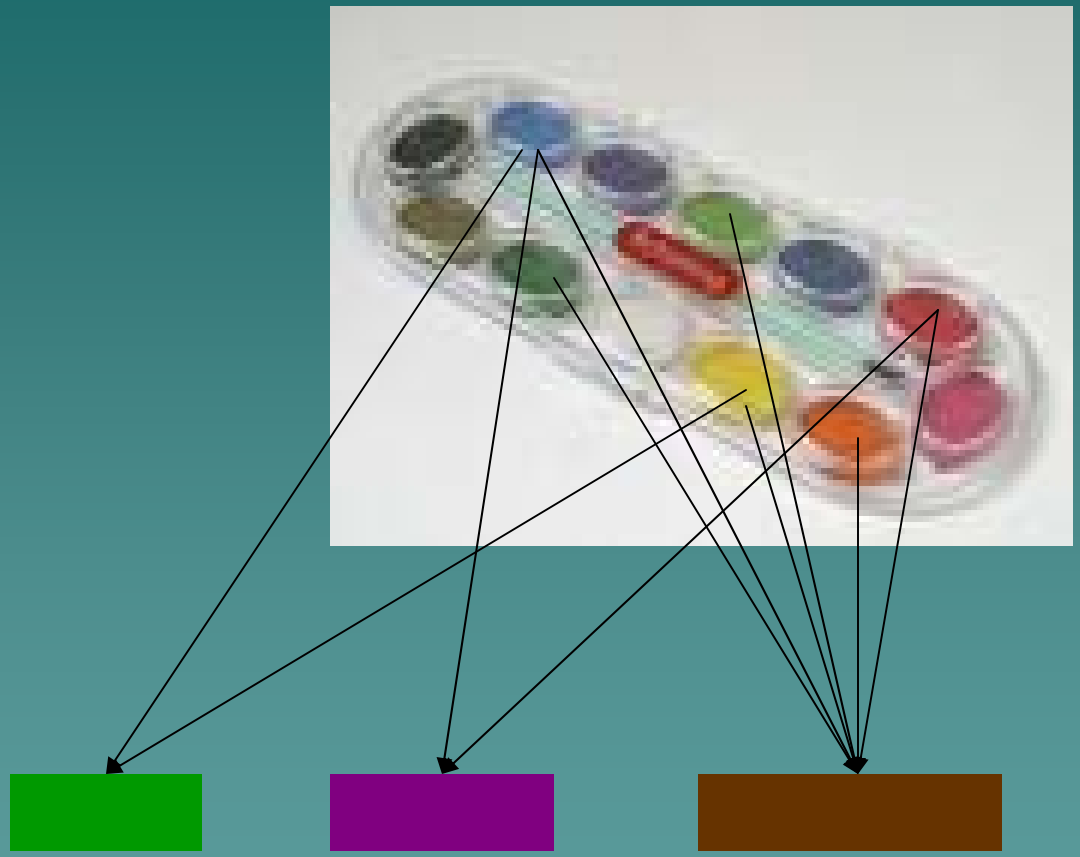
How do we sort it all out?



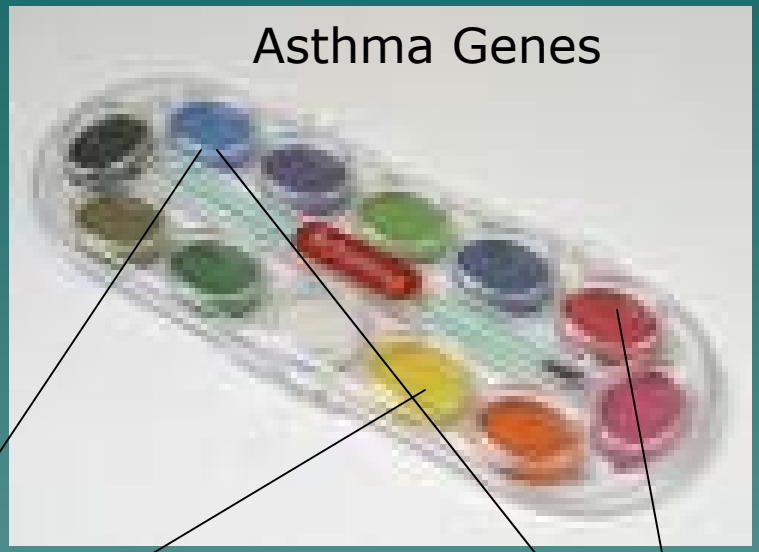
Asthma (pre-2003)

- How is asthma (a trait) inherited?
- How does a family history of asthma increase risk for a patient?
- Techniques include family studies, twin studies, adoption studies to sort out heritability and environmental effect
- Linkage studies
  - Hampered by definition of ‘phenotype’

Phenotype



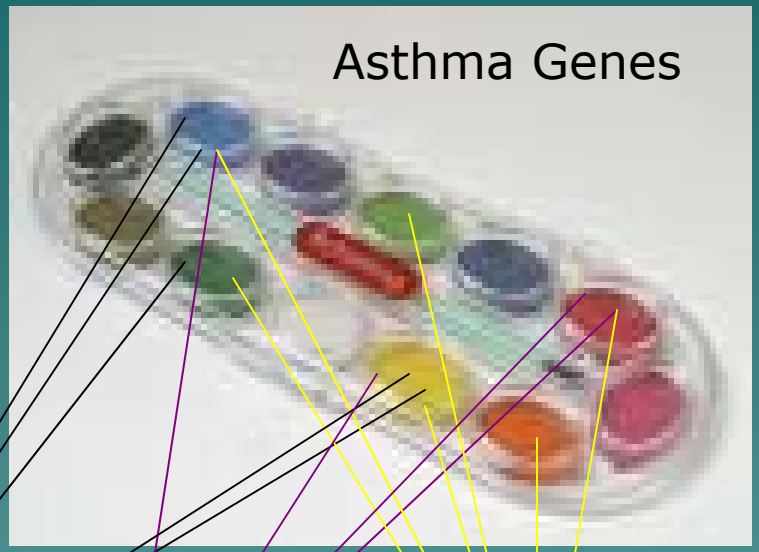
Phenotype



Cold-induced asthma

Exercise-induced asthma

Phenotype



Asthma

Asthma

Asthma

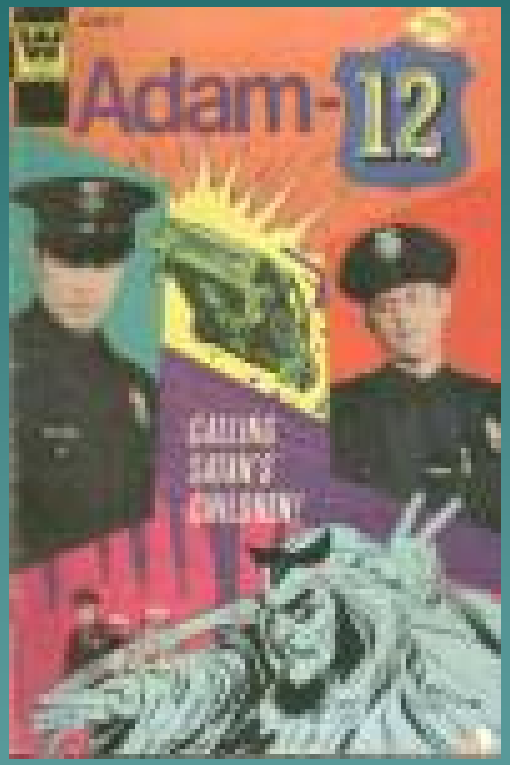
Asthma (post-2003)

- Identify all genes that contribute to asthma trait (phenotype)
  - Association studies
- Study all gene-gene and gene-environment interactions
- Identify different ‘phenotypes’
  - Environmental response (exercise, cold)
  - Drug response

Combined Approach

- Start with conventional mapping/linkage analysis
- Use genomic approaches (such as SNPs) to rapidly identify candidate genes
- Define role of candidate gene
- Assess for appropriateness as treatment target

First Success
ADAM33



First Success *ADAM33*

- Locus on 20p13 identified on genome-wide screen of 460 Caucasian families
- Association increased when phenotype was tightened to focus on airway hyperresponsiveness
- Fine mapping with SNPs identified *ADAM33*
- *ADAM33* expressed in lung (bronchial smooth muscle and fibroblasts) and lymph nodes
- Other ADAM proteins interact with inflammatory cytokines

First Success
ADAM33

- Conclusions
  - *ADAM33* is an excellent candidate gene for asthma susceptibility
  - Represents a great target for drug development

First Success? *ADAM33*

- Linkage to 20p13 not seen in previous genome-wide screens
- Two cohorts were used in study and may not have been independent (favoring spurious results)
- Other methodologic concerns
- No functional data on role of gene variants reported

First Success? *ADAM33*

- Subsequently, three other groups have been unable to reproduce the study results, although some association in certain populations was seen
- Role of *ADAM33* in asthma unclear

Problems with Association

- Failure to replicate association studies very common
- Reasons
  - False association in study
  - Insufficient power
  - Population admixture
  - Heterogeneity of genetic and phenotypic factors
  - Environmental factors

Other Genes

- *PHF11*
  - Associated with IgE levels
  - Identified in multiple studies of atopic individuals
  - Association with asthma less impressive
  - Function of gene unknown
  - Two other genes in the region also possible candidates

Other Genes

- *DPP10*
  - Located adjacent to Interleukin-1 gene cluster
  - IL-1 variants known to be associated with asthma
  - Identified variant in promoter of gene, which could affect expression
  - No other convincing data at present

Gene-Environment Interaction?

- *CD14*
  - Plays a role in innate immune system response
  - Relationship between polymorphisms and IgE levels
  - Linkage strengthened if population stratified by exposure to cigarette smoke in infancy
- *TLR4*
  - Toll-like receptor 4
  - Signal similar to that seen in ILR
  - Association found between exposure to endotoxin in house dust and asthma

Where Are We?

Where Are We?

Table 1. Asthma related genes and their location

Description	Gene	Chromosome	Genomic location from p-ter
1	2	3	4
Early growth response protein 1	*EGR-1*	1p34	45.5
Prostaglandin E receptor 3	*PTGER3*	1p31	71
Chloride channel calcium activated family member 1	*CLCA1*	1p31	86
Vascular cell adhesion protein 1 precursor	*V-CAM 1*	1p21	100.9
Glutathione-S-transferase	*GSTM1*	1p13	109.9
Adenosine A3 receptor	*A3AR; ADORA3*	1p13	111.7
Adenosine A1 receptor	*A1AR; ADORA1*	1q32	199.8
Transforming growth factor beta 2 precursor	*TGF-β-2*	1q41	214.9
Interleukin-1 receptor	*IL-1R1*	2q11	102.2
High affinity interleukin-8 receptor A	*IL-8RA; CXCR1*	2q35	218.9
Interleukin-1 receptor antagonist protein precursor	*IL-1RN*	2q13	113.6
Interleukin-1 alpha precursor	*IL-1α*	2q13	113.2
Interleukin-1 beta precursor	*IL-1β*	2q13	113.3
Dipeptidylpeptidase 10 isoform 1	*DPP10*	2q14	114.9
C-C chemokine receptor type 1	*CCR1*	3p21	46.2
Interleukin-8 precursor	*IL-8*	4q13	75.0
Aminopeptidase A	*APA*	4q25	111.8
Interleukin-5 precursor	*IL-5*	5q23	131.9
Interleukin-4 precursor	*IL-4*	5q23	132
Interleukin-13 precursor	*IL-13*	5q23	132
Interleukin-9 precursor	*IL-9*	5q31	135
Monocyte differentiation antigen CD14 precursor	*CD14*	5q31	140
Serine protease inhibitor Kazal-type 5 precursor	*SPINK5*	5q32	147.4
Beta-2 adrenergic receptor	*ADRB2*	5q32	148.2
Plasma glutathione peroxidase precursor	*GPX3*	5q33	150.4
SH2 domain-containing leucocyte protein	*SLP-2 LCP2*	5q35	169.6
Lymphocyte cytosolic protein 2	*SLP-76*	5q35	169.6
HLA class I histocompatibility antigen – alpha chain G precursor	*HLA G*	6p21	30
Major histocompatibility complex – class II – DR beta 1	*HLA-DRB1*	6p21	32.7
Tumor necrosis factor precursor	*TNF-α*	6p21	37.1
Pim-1 oncogene	*PIM1*	6p21	37.2
Peroxisome assembly factor-2	*PAF-2*	6p21	43
Arginase I	*ARG1*	6p23	131.9
Superoxide dismutase 2 mitochondrial	*SOD2*	6q25	160.1
Interleukin-6	*IL-6*	7p15	22.5
G-protein-coupled receptor for asthma susceptibility	*GPRA*	7p14	34.3
T cell receptor gamma	*TCRG*	7p14	38
Epidermal growth factor receptor precursor	*EGFR*	7p11	59.9
Plasminogen activator inhibitor-1 precursor	*PAI-1 o SERPINE1*	7q22	100.4
Nitric-oxide synthase – endothelial	*eNOS; NOS3*	7q36	150.1
Peroxisome assembly factor-1	*PAF-1*	8q21	78.1
Prostaglandin E synthase	*PTGES*	9q34	129.6
Mucin 2	*MUC2*	11p15	
Prostaglandin D2 receptor DP	*PTGDR*	11q	51.8
High affinity immunoglobulin epsilon receptor beta-subunit	*FcεRI*	11q12.1	59.6
Glutathione-S-transferase	*GSTP1*	11q	67.1
Early activation antigen CD69	*CD69*	12p13	9.8
Vitamin D3 receptor	*VDR*	12q13	46.5
Signal transducer and activator of transcription 6	*STAT6*	12q13	55.8
Interleukin-1 receptor-associated kinase 3	*IRAK3*	12q14	64.9
Interleukin-22 precursor	*IL-22*	12q15	66.9
Interferon gamma precursor	*IFNG*	12q15	68.8
Kit ligand precursor	*KITLG*	12q21	87.4
Nuclear transcription factor Y subunit beta	*NF-YB; CCAAT-binding transcription factor subunit A*	12q23	103
Nitric-oxide synthase type I	*nNOS; NOS1*	12q24	116.9
SET domain bifurcated 2	*SETDB2*	13q14	48.9
PHD finger protein 11	*PHF11*	13q14	49
Regulator of chromosome condensation	*RCBTB1*	13q14	49
Regulator of chromosome condensation	*RCC1; RCBTB1*	13q14	49
Prostaglandin E receptor 2	*PTGER2*	14q22	51.9
Arginase II	*ARG2*	14q24	67.2
Alpha-1-antichymotrypsin precursor	*AACT*	14q32	94.1
Extracellular signal-regulated kinase 3	*ERK-3*	15q21	50.1
Arachidonate 15-lipoxygenase	*ALOX15*	17p13	4.5
Nitric oxide synthase - inducible	*iNOS; NOS2*	17q11	23.1
Small inducible cytokine A2 precursor	*CCL2;MCP-1*	17q12	29.6
Small inducible cytokine A7 precursor	*CCL7;MCP-3*	17q12	29.6
Squamous cell carcinoma antigen 1	*SCCA-1 SerpinB4*	18q21	59.5
Low affinity immunoglobulin epsilon Fc receptor	*Fc-ε-RII; CD23*	19p13	7.7
Intercellular adhesion molecule-1 precursor	*ICAM-1*	19p13	10.2
Prostaglandin E receptor 1	*PTGER1*	19q13	14.4
Transforming growth factor beta 1 precursor	*TGF-β-1*	19q13	46.5
Disintegrin and metalloproteinase domain 33	*ADAM33*	20p13	3.6
Superoxide dismutase [Cu-Zn]	*SOD1*	21q22	32.0
Prostaglandin-E(2) 9-reductase	*CBR1*	21q22	36.4
Glutathione-S-transferase	*GSTT1*	22q11	22.7
Tissue inhibitor of metalloproteinase 1	*TIMP1*	Xq11	47.2
Synaptobrevin-like protein 1	*SYBL1*	Xq28	154.7
Signal transducer CD24 precursor	*CD24*	Yq11	19.5
Synaptobrevin-like protein 1	*SYBL1*	Yq12	57.6

Chromosome and genomic locations have been extracted from the Ensembl Genome Browser – Ensembl v27 (http://www.ensembl.org/). Genes were arbitrarily ordered by location from chromosome 1 to the sex chromosomes.

From Malerba and Pignatti J Appl Genet 46:93-104, 2005

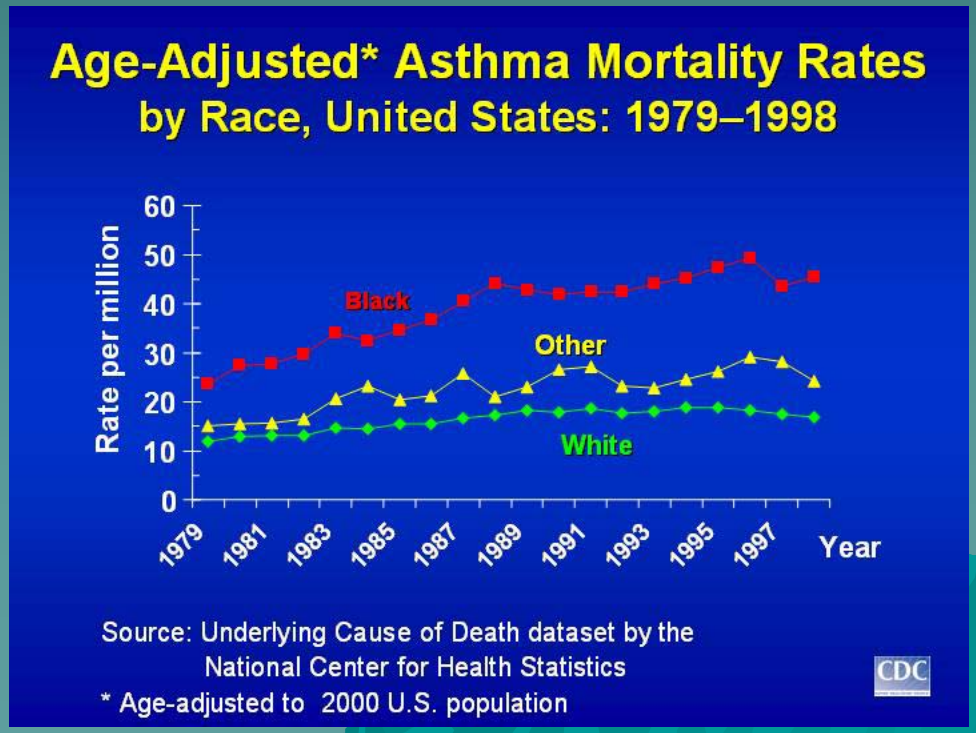
Where Are We Going?

Future Research in Asthma NHLBI Working Group 2004

- 4 priorities and 2 initiatives
- Priority 4-Genetics/Gene-Environment interactions, Pharmacogenetics
  - To identify all relevant susceptible variants in environment-specific and population-specific contexts
  - To characterize the function of susceptible genetic variants
  - To incorporate genetics information into the clinical management of asthma

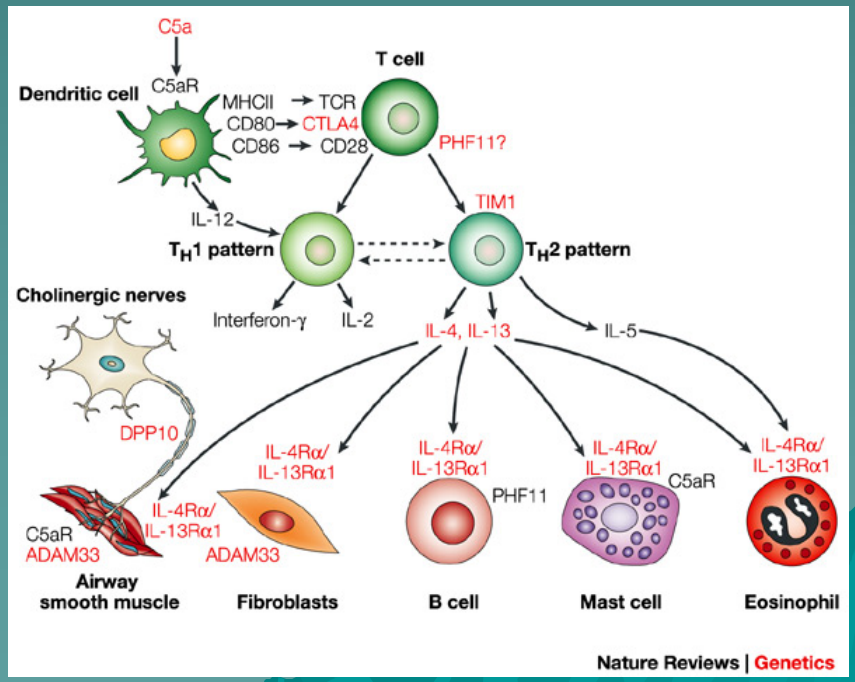
Population Differences

- Ethnic differences
- Understand genomic variation that underlies difference



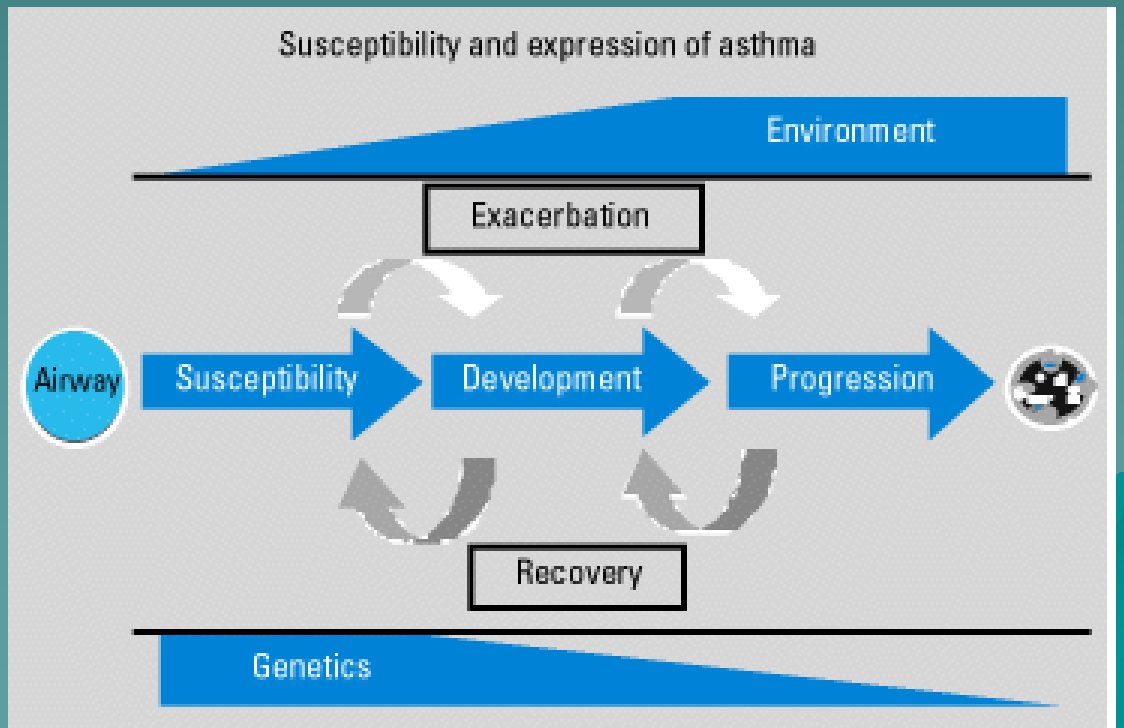
Genomic Approaches

- Refine asthma phenotypes
- More robust association studies
- Identify relevant pathways



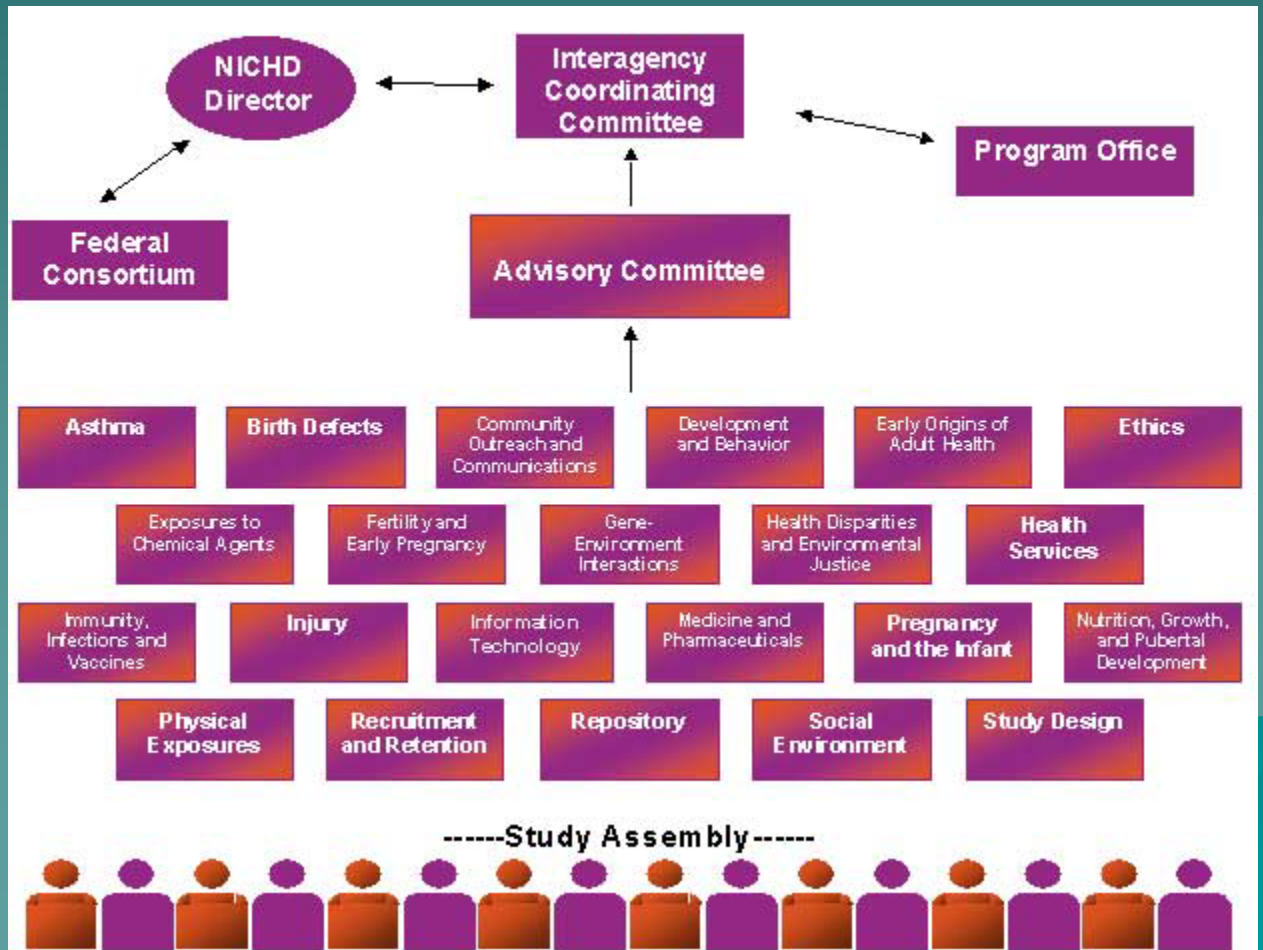
Gene-Environment Interactions

- Define how environment affects gene regulation
- Can this effect by modified?



Gene-Environment Interactions

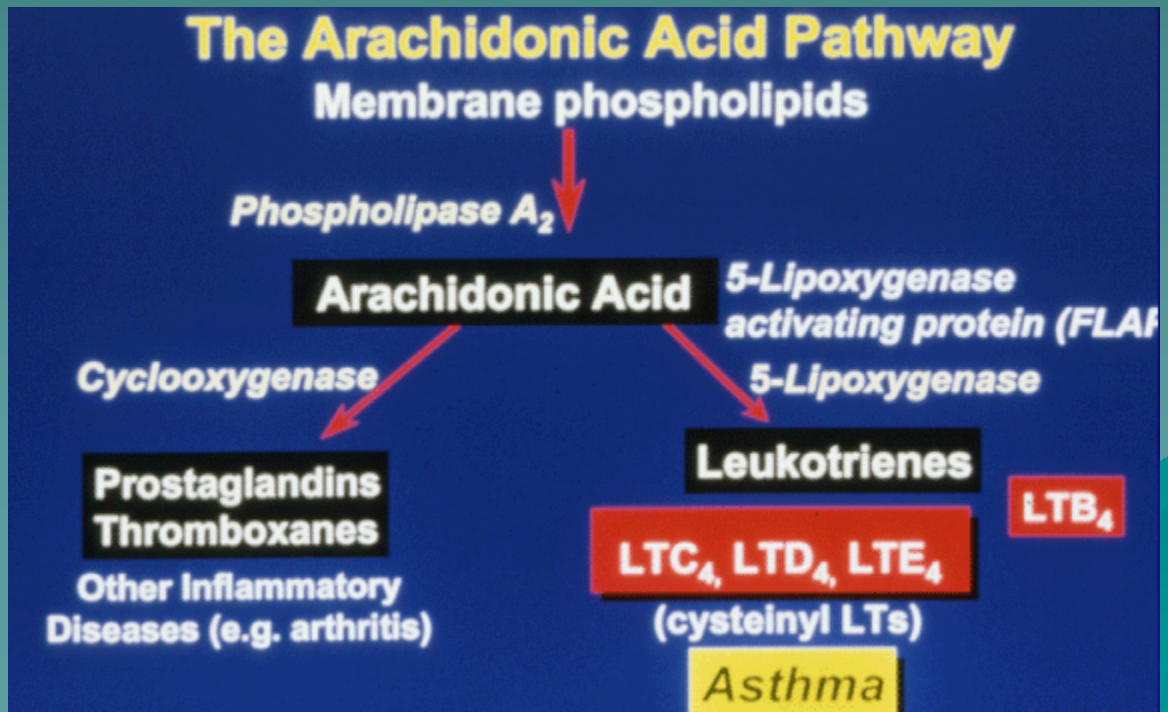
- National Children's Study



Pharmacogenomics

Differential response to drugs

- Response to β-agonists
- Response to Leukotriene receptor antagonists



Asthma Genomics Hope or Hype?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