Overview

- Common, complex diseases are characterized by health disparities, not limited to socioeconomic disparities, but including race and ethnicity.
- Is there a genetic basis for these disparities (i.e., asthma)?
- If yes, what is the evolutionary basis for selection of variants that confer risk to a common disease?
- Is the basis for this selection rooted in adaptations in the innate and adaptive immune response?
The worldwide prevalence of asthma


The prevalence of common diseases is higher among African Americans

<table>
<thead>
<tr>
<th>Disease</th>
<th>African American</th>
<th>European American</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN (45-64 yrs)</td>
<td>344.7 (per 1,000)</td>
<td>207.8 (per 1,000)</td>
</tr>
<tr>
<td>CHD (death)</td>
<td>140.4 (per 100,000)</td>
<td>102.1 (per 100,000)</td>
</tr>
<tr>
<td>Diabetes (45-64yrs)</td>
<td>121.4 (per 1,000)</td>
<td>55.8 (per 1,000)</td>
</tr>
<tr>
<td>Asthma (children)</td>
<td>8.9%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

The impact of ethnicity on disease severity

Annual mortality rates for asthma stratified by race and year, US, 1979-1995

CDC, 2000

* Unstable rates, number of deaths less than one per 100,000.
Health Disparities in Common, Complex Diseases: a Role for Genetics?  
Prof. Kathleen C. Barnes

"Are genetic differences between populations likely to have a role in health status...?"

- Causes of health disparities likely derive from differences in:
  - Social marginalization
  - Environmental exposures
  - Socioeconomic status
  - Access to health care
  - Education
  - Diet
  - Culture
  - Discrimination

Definition of complex traits

- Genetically heterogeneous
  - Many distinct genes, or groups of genes, lead to similar clinical phenotypes
Health Disparities in Common, Complex Diseases: a Role for Genetics?
Prof. Kathleen C. Barnes

Monogenic disease
CFTR gene \(\xrightarrow{\text{Mutation}}\) Cystic fibrosis

Complex disease
Gene 2 \(\longrightarrow\) Gene 3
Gene 1 \(\longrightarrow\) Gene 4
Environmental factor 1 \(\longrightarrow\) Environmental factor 2
Ethnicity \(\longrightarrow\) Age \(\longrightarrow\) SES

Asthma

Adapted from Whittaker, PA, Current Opinion in Chemical Biology, 2001, 5: 352-359

Concordance for atopic disease in twins

<table>
<thead>
<tr>
<th>Authors</th>
<th>PA values</th>
<th>MZ</th>
<th>DZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaich and Ostertag, 1936</td>
<td>&lt;0.05</td>
<td>0.88</td>
<td>0.63</td>
</tr>
<tr>
<td>Harvald and Hauge, 1956</td>
<td>&lt;0.01</td>
<td>0.50</td>
<td>0.09</td>
</tr>
<tr>
<td>Gedda and Teodor, 1962</td>
<td>NS</td>
<td>0.61</td>
<td>0.49</td>
</tr>
<tr>
<td>Parrot and Sandalle, 1962</td>
<td>NS</td>
<td>0.05</td>
<td>0.44</td>
</tr>
<tr>
<td>Miliari and Comparotti, 1970</td>
<td>&lt;0.01</td>
<td>0.78</td>
<td>0.25</td>
</tr>
<tr>
<td>Charpin and Arnoud, 1971</td>
<td>&lt;0.01</td>
<td>0.86</td>
<td>0.35</td>
</tr>
<tr>
<td>Edfores-Lubs, 1971</td>
<td>&lt;0.01</td>
<td>0.25</td>
<td>0.16</td>
</tr>
<tr>
<td>Wuthrich, et al, 1981</td>
<td>&lt;0.05</td>
<td>0.56</td>
<td>0.20</td>
</tr>
<tr>
<td>Bonini, et al, 1983</td>
<td>NS</td>
<td>0.50</td>
<td>0.35</td>
</tr>
<tr>
<td>Hopp, et al, 1984</td>
<td>NS</td>
<td>0.36</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Genes associated with asthma/atopy phenotypes

<table>
<thead>
<tr>
<th>Number of genes</th>
<th>10th genes total</th>
<th>15th genes total</th>
<th>25 solid genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies with positive associations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allergic response genes</th>
<th>1 study only: replication failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host defense (innate immunity) genes</td>
<td></td>
</tr>
<tr>
<td>HLA associations</td>
<td></td>
</tr>
</tbody>
</table>

Genes by positional cloning

Ober and Hoffjan, 2006, Genes and Immunity

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Concordance for atopic disease in twins

<table>
<thead>
<tr>
<th>Authors</th>
<th>MZ</th>
<th>DZ</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spoel and Oster, 1936</td>
<td>0.88</td>
<td>0.63</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Horvath and Haage, 1956</td>
<td>0.57</td>
<td>0.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gedda and Tedoni, 1962</td>
<td>0.61</td>
<td>0.49</td>
<td>NS</td>
</tr>
<tr>
<td>Parrot and Saindelle, 1962</td>
<td>0.55</td>
<td>0.44</td>
<td>NS</td>
</tr>
<tr>
<td>Milani and Comparetti, 1970</td>
<td>0.78</td>
<td>0.25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Charpin and Arnaud, 1971</td>
<td>0.86</td>
<td>0.35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Edfors-Lax, 1971</td>
<td>0.90</td>
<td>0.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wuthrich, et al, 1981</td>
<td>0.56</td>
<td>0.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Bonini, et al, 1983</td>
<td>0.50</td>
<td>0.35</td>
<td>NS</td>
</tr>
<tr>
<td>Hopp, et al, 1984</td>
<td>0.48</td>
<td>0.20</td>
<td>NS</td>
</tr>
</tbody>
</table>

Definition of complex traits

- Genetically heterogeneous
  - Many distinct genes, or groups of genes, lead to similar clinical phenotypes

- Multifactorial
  - Disease expression is influenced by interactions between multiple major and minor genes, and is modulated by interacting non-genetic factors (e.g., degree of allergen exposure)

Relative influence on trait development

Health Disparities in Common, Complex Diseases: a Role for Genetics?
Prof. Kathleen C. Barnes

Components of total variance in specific serum IgE levels against HDM and timothy grass (RAST index)

- Environment
  - Additive genetic
  - Common family environment
  - Common sibling environment
- Genes
  - 34%
- Non-familial environmental

Components: 4.23 (0.57) for EC, 0.25 (0.34) for CE, 1.36 (0.46) for CS

Phenotypes:
- Type A
  - Phenotype 1
  - Phenotype 2
  - Phenotype 3
- Type B
  - Phenotype 4
  - Phenotype 5
  - Phenotype 6
- Type I
  - Phenotype 7
  - Phenotype 8
  - Phenotype 9
- Type II
  - Phenotype 10
  - Phenotype 11
  - Phenotype 12

The association between Dermatophagoides mites and the increasing prevalence of asthma in village communities within the Papua New Guinea highlands

"...Allergy to house dust mites appears to be a significant feature in the disease pathogenesis, and it is likely that this is associated with modifications to traditional lifestyles by the recent introduction of blankets and changes in sleeping habits that promote a more fertile environment for growth and multiplication of mites"
Health Disparities in Common, Complex Diseases: a Role for Genetics?
Prof. Kathleen C. Barnes

Achoo! Must be the roaches!

Environment or ethnicity?

Skin test sensitization to American cockroach in adolescents with asthma, deriving from the highest and lowest income quartiles according to ethnicity (African American vs. European American)

† p < 0.0001, compared to European American

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a Role for Genetics? 
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Health and the human condition

- Until last ~400-500 years, lived in primarily hunting/gathering systems in non-city-state communities in West Africa
- Recent admixture with European and Aboriginal populations
- Exposure to extracellular and intracellular parasites continued in endemic regions, often removed from these environments;
- During past 11,000 yrs, Europeans traded hunting/gathering for domestication of plants and animals, sedentism and urbanization
- Profound changes in microbial environment
- Prevalence of 'crowd' infections; Epidemics of smallpox, plague, measles, TB
- High mortality rates associated with pathogens exerted strong selective pressures?
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Immune pathways

Sepsis
Helminths
Malaria

Bacteria, viruses
Host defense

Schistosomiasis
TH1
Host defense
Atopic response

TH2
Environmental antigens
Asthma

Genes and environment

Environment

Developing countries
Large family size
Rural homes, livestock
Intestinal microflora - variable, transient
Low antibiotic usage
High helminth burden
Poor sanitation, high oro-faecal burden

Westernized countries
Small family size
Affluent, urban homes
Intestinal microflora - stable
High antibiotic usage
Low or absent helminth burden
Good sanitation, low oro-faecal burden

Non-allergic
Allergic disorders (asthma, eczema, rhinitis)


Gene environment interaction at work in farming families

Health Disparities in Common, Complex Diseases: a Role for Genetics?
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Ascertained by probands selected for asthma
~850 subjects (125 nuclear and extended pedigrees)
African descent
High geometric mean total IgE (>1,000 ng/mL)
High dust mite allergen exposure

Barbados study

<table>
<thead>
<tr>
<th>Site in home</th>
<th>Park et al., 2001 (Boston)</th>
<th>Braun-Fahrländer et al., 2002 (Bavaria)</th>
<th>Michel et al., 1996 (Belgium)</th>
<th>Douwes et al., 1991 (Dutch)</th>
<th>Barbados (unpubl.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitchen</td>
<td>225–30,025</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>N = 245</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living room composite</td>
<td>50–17,825</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>2,649–155,468</td>
</tr>
<tr>
<td>N = 245</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(21,060)</td>
</tr>
<tr>
<td>Bedroom mattress</td>
<td>200–6,425</td>
<td>5,453–157,208</td>
<td>5–5,000</td>
<td>16,157</td>
<td></td>
</tr>
<tr>
<td>N = 26</td>
<td>N = 319</td>
<td>N = 69</td>
<td></td>
<td></td>
<td>2,447–105,368</td>
</tr>
<tr>
<td>N = 92</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(19,667)</td>
</tr>
<tr>
<td>Bedroom composite/ floor</td>
<td>50–19,025</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>N = 323</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall level for house</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

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CD14 is a major player in innate immunity

- Primary ligand for the LPS binding complex
- Necessary for an inflammatory response to endotoxin exposure (animal models)

*CD14* is a major player in innate immunity

- Primary ligand for the LPS binding complex
- Necessary for an inflammatory response to endotoxin exposure (animal models)

T allele exhibits ↑d transcriptional activity

-167 167TTAAGGCCCCCTGCCTGAA -146

- TT genotype confers:
  - High sCD14
  - Low tIgE

60 C/T variant
with allergic disease
Sp1/Sp2 >> Sp3

Family-based association test (FBAT) for the CD14 (-260) T variant and asthma-associated traits (129 Afro-Caribbean families)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>FBAT Z-score</th>
<th>Adjusted for ST*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma (yes/no)</td>
<td>-2.444</td>
<td>0.0145</td>
</tr>
<tr>
<td>Age asthma severity</td>
<td>-2.615</td>
<td>0.0089</td>
</tr>
<tr>
<td>tIgE</td>
<td>-0.848</td>
<td>-</td>
</tr>
<tr>
<td>+ST (yes/no)</td>
<td>-1.021</td>
<td>-</td>
</tr>
<tr>
<td>sCD14</td>
<td>-1.606</td>
<td>-</td>
</tr>
</tbody>
</table>

*Values for ST*: Tested for 16 common aeroallergens

Age-adjusted ORs and 95% CIs for CD14 (C-260T) genotype and asthma, stratified by high vs. low HDE load:

<table>
<thead>
<tr>
<th>CD14-260 genotype</th>
<th>Low HDE (N = 332)</th>
<th>High HDE (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC (N = 182)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>CT (N = 205)</td>
<td>1.0</td>
<td>0.77 (0.27-2.23)</td>
</tr>
<tr>
<td>TT (N = 56)</td>
<td>0.84 (0.39-1.82)</td>
<td>11.66 (1.03-31.7)</td>
</tr>
</tbody>
</table>

* Defined according to a living room composite endotoxin load ≥ (high) or < (low) 44,000 EU/m³

TT homozygotes have ↓ asthma severity score


Frequency of the CD14 -260 C/T genotypes:

<table>
<thead>
<tr>
<th>Study</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
<th>p(r)</th>
<th>q(f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tucson study (Baldini, et al., 1999)</td>
<td>0.29</td>
<td>0.49</td>
<td>0.22</td>
<td>0.54</td>
<td>0.46</td>
</tr>
<tr>
<td>German study* (Sengler, et al., 2003)</td>
<td>0.27</td>
<td>0.51</td>
<td>0.21</td>
<td>0.54</td>
<td>0.46</td>
</tr>
<tr>
<td>Dutch study (Koppelman, et al., 2001)</td>
<td>0.20</td>
<td>0.54</td>
<td>0.26</td>
<td>0.47</td>
<td>0.53</td>
</tr>
<tr>
<td>Baltimore African Americans Asthma probands</td>
<td>0.54</td>
<td>0.41</td>
<td>0.06</td>
<td>0.74</td>
<td>0.26</td>
</tr>
<tr>
<td>Unrelated normal controls</td>
<td>0.47</td>
<td>0.40</td>
<td>0.04</td>
<td>0.73</td>
<td>0.29</td>
</tr>
<tr>
<td>Barbados African Caribbean Asthmatics</td>
<td>0.47</td>
<td>0.47</td>
<td>0.06</td>
<td>0.71</td>
<td>0.29</td>
</tr>
<tr>
<td>Nonasthmatics</td>
<td>0.44</td>
<td>0.45</td>
<td>0.11</td>
<td>0.67</td>
<td>0.34</td>
</tr>
<tr>
<td>ALI/sepsis (African American)</td>
<td>0.42</td>
<td>0.42</td>
<td>0.16</td>
<td>0.63</td>
<td>0.28</td>
</tr>
</tbody>
</table>

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Survival curves of African American ALI patients compared to European American ALI patients

Survival curves of European American ALI patients according to CD14 (-260) C>T genotype

Frequency of the CD14 -260 C/T genotypes

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Amino acid sequence alignments of different tropomyosins

- Bla g 7 and Per a 7 have 97% sequence identity
- Per a 7 has 80% identity and 88% similarity with Der p 10 and Der f 10
- Per a 7 has substantial homology to helminthic tropomyosins from S. mansoni (72%), S. japonicum (72%), Onchocerca volvulus (70%), Caenorhabditis elegans (71%), and Brugia pahangi (67%)

Barnes, et al., unpublished data
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Frequency distributions of log [total IgE (ng/ml)] among Amish and Barbadian subjects

Subjects

0 1 2 3 4 5 6

Log [total serum IgE (ng/mL)]

Barnes, K. C., 2006, JACI, Feb., 117(2) 243-54, 255-6


Ascaris infection, schistosomiasis
Ascaris infection
Schistosomiasis
Leishmaniasis, schistosomiasis*
Schistosomiasis, leishmaniasis, malaria

*Murine

Barnes, et al., Current Opinion in Allergy and Immunology, 2005, Oct., 5 (5): 379-85

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Allelic variants associated with both allergic disease and parasitic diseases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>A220G</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>IFN-γ receptor 1 (IFNγR1)</td>
<td>G2803A</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Interleukin-4 (IL-4)</td>
<td>C-590T</td>
<td>Leishmaniasis, schistosomiasis</td>
</tr>
<tr>
<td>Interleukin-13 (IL-13)</td>
<td>Arg-105G &gt; C</td>
<td>Onchocerciasis</td>
</tr>
<tr>
<td>β2-adrenoreceptor (ADRB2)</td>
<td>Arg586G &gt; A</td>
<td>Ascariasis</td>
</tr>
<tr>
<td>Signal transducer and activator of transcription (STAT6)</td>
<td>G4219A</td>
<td>Ascariasis</td>
</tr>
</tbody>
</table>

*‘At risk’ alleles underscored


Identifying genes with ‘global’ effects: common variant/multiple disease hypothesis

‘Common variant, common disease’ hypothesis

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Genetic association database


'Common variants/multiple disease' hypothesis

- Common alleles contributing to a given disease under a certain combination of interacting genes and environmental conditions may act in other genetic backgrounds influenced by other environmental factors.
- Different, possibly related clinical outcomes


Pathogens and host counter-adaptations: "antagonistic pleiotropy"

- Alleles that are effective against one pathogen might be ineffective against another pathogen, or for some other function.

In the absence of the Duffy receptor, protection id called

K. C. Barnes

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**Frequencies of Duffy positive genotype**

<table>
<thead>
<tr>
<th>Population</th>
<th>FY-NUL*1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africans</td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>0%</td>
</tr>
<tr>
<td>C. Afr. Rep.</td>
<td>0%</td>
</tr>
<tr>
<td>Europeans</td>
<td></td>
</tr>
<tr>
<td>England</td>
<td>100%</td>
</tr>
<tr>
<td>African Americans</td>
<td></td>
</tr>
<tr>
<td>New York</td>
<td>21%</td>
</tr>
<tr>
<td>Baltimore</td>
<td>14%</td>
</tr>
<tr>
<td>Caribbean</td>
<td></td>
</tr>
<tr>
<td>Barbados</td>
<td>21%</td>
</tr>
<tr>
<td>Jamaica</td>
<td>7%</td>
</tr>
<tr>
<td>African Americans</td>
<td></td>
</tr>
<tr>
<td>New York</td>
<td>21%</td>
</tr>
<tr>
<td>Baltimore</td>
<td>14%</td>
</tr>
<tr>
<td>Caribbean</td>
<td></td>
</tr>
<tr>
<td>Barbados</td>
<td>21%</td>
</tr>
<tr>
<td>Jamaica</td>
<td>7%</td>
</tr>
<tr>
<td>White Americans</td>
<td></td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>98%</td>
</tr>
<tr>
<td>Detroit</td>
<td>99%</td>
</tr>
</tbody>
</table>

*Parra, et al., 1998; Nickel, et al., 1999*

---

**Duffy antigen/receptor for chemokines (DARC)**

- Point mutation in the DARC promoter (T-46C) selectively abolishes the DARC expression on erythrocytes ⇒ "Duffy-negative" phenotype (Fy(a-b-))
- Expressed by subsets of endothelial as well as erythroid cells
- Binds with high affinity to chemokines of both the CXC and CC classes, which promote the formation of acute and chronic inflammatory infiltrates, respectively
- Functions as a regulatory 'sink' for chemokines

Could the lack of expression of DARC result in sustained levels of chemokines and promote features of CC chemokine-mediated allergic inflammation?

---

**Family-based association test (FBAT) for DARC CC genotype* and asthma-associated phenotypes**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
<th>Z-Score</th>
<th>FBAT P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma (yes/no)</td>
<td>LT</td>
<td>2.058</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>1.055</td>
<td>0.294</td>
</tr>
<tr>
<td>Asthma severity</td>
<td>LT</td>
<td>-2.241</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>0.684</td>
<td>0.494</td>
</tr>
<tr>
<td>Total IgE</td>
<td>LT</td>
<td>-2.201</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>0.790</td>
<td>0.429</td>
</tr>
</tbody>
</table>

*Fy(a-b-): N=129 African Caribbean families*

Vergara, et al., in preparation
Summary

- Common (chronic) diseases are complex traits resulting from a mix of major and minor effect genes and a host of environmental factors.
- Genetic diversity for host susceptibility has resulted largely from pathogen/host counter-adaptations, leading to a greater appreciation of these host responses that may improve our understanding of disease pathology and prioritize candidate genes for complex diseases.
- Consideration for genes that represent a shared genetic component between distinctly different clinical conditions: common variant/multiple disease hypotheses.
- Differences in allelic frequencies in susceptibility genes could account for disparities observed between ethnic groups.

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