Subphenotyping Asthma to Uncover Novel Genes

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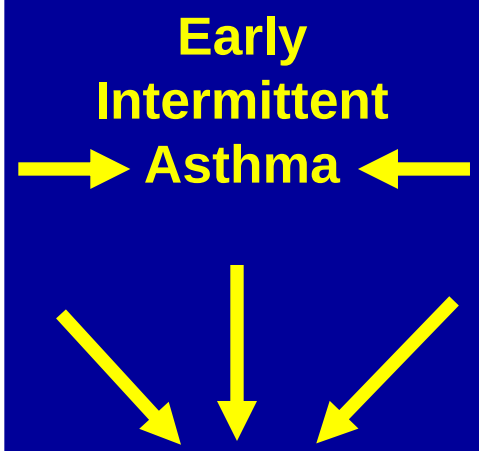
Gene-Environment Interactions in Susceptibility and Severity of Asthma

Genetics

Susceptibility:
Associated Phenotypes:
(atopy, BHR)
Expression and Progression:
Severity,
Pharmacogenetics



Environment /Epigenetics

Prenatal influences (prematurity), allergens, respiratory infections, tobacco smoke, air pollutants, diet, lung development etc.

Chronic Persistent Progressive
(reversible and irreversible changes in lung structure and function)
Disease Heterogeneity & Severity

Translational Research and Personalized Medicine in Asthma

- Team Science that integrates disease heterogeneity (phenomics), genomics, functional biology and individualized therapeutics

- These approaches are critically important to the effective development of “biologic” therapies for asthma and allergic diseases

Examples of (Personalized) Approaches

- **Disease heterogeneity and asthma severity phenotypes**
- *Genome-wide Studies of Susceptibility and Severity*
- *Pulmonary function and asthma severity*
- *Early onset Th2 phenotypes and severity*

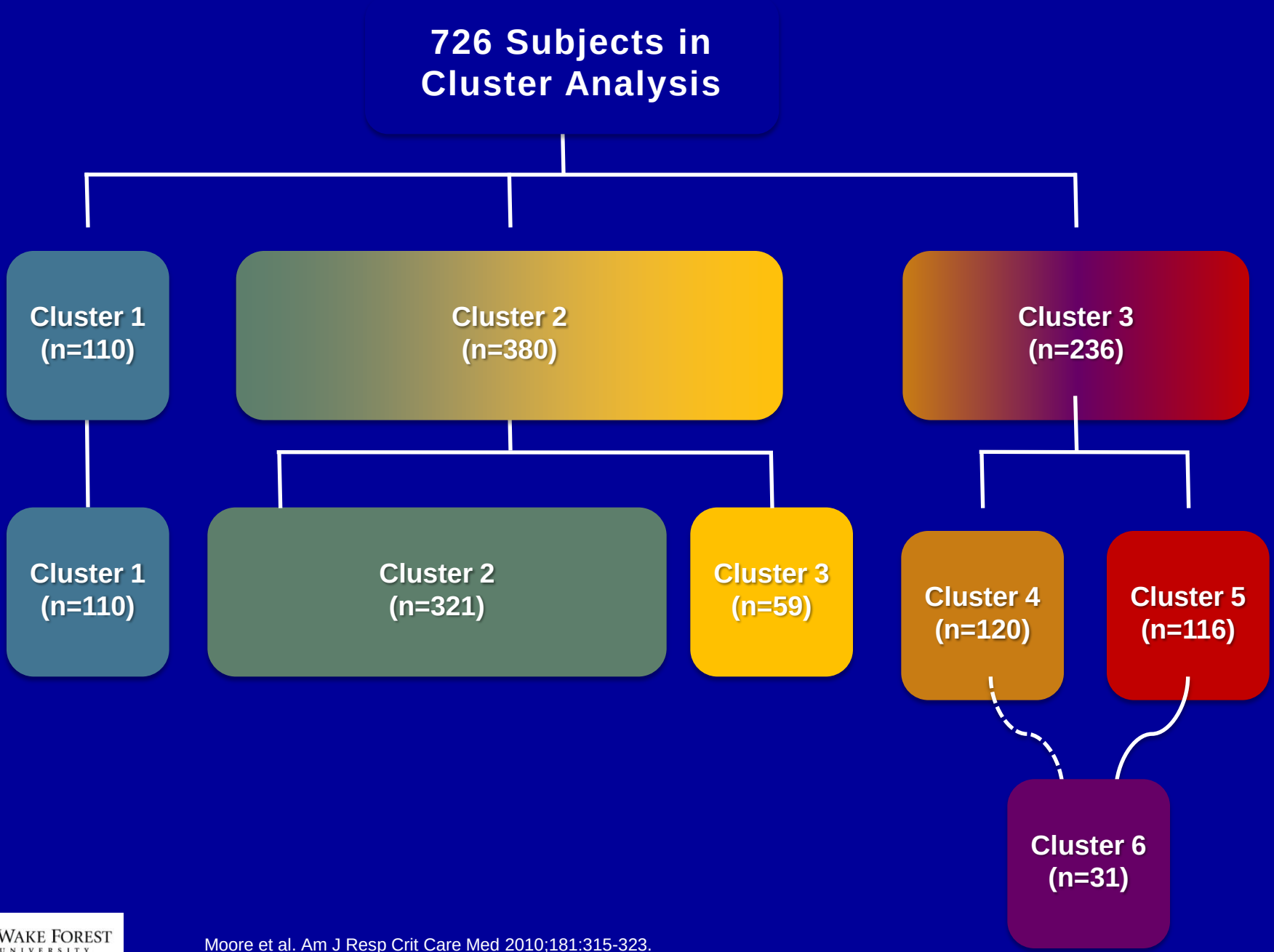
Recent Approaches Classifying Asthma Severity

- "Hypothesis Based": (Age of Onset, Allergic, Eosinophilic, Exacerbations etc)

- **"Model Free": Cluster Approaches**

  - Haldar et al AJRCCM (2008)

  - SARP NHLBI – Moore et al AJRCCM (2010)



Moore et al. Am J Resp Crit Care Med 2010;181:315-323.

Asthma Cluster Analysis: 5 Clusters

1 Mild Allergic Asthma	Early onset asthma (EOA); Normal lung function; atopic <= 2 Controller (medication use); Minimal Health Care Utilization (HCU): decreased sputum eosinophils (Eos)
2 Mild-Moderate Allergic Asthma	Most common cluster; EOA; Borderline normal FEV1 but reverses to normal; Atopic; <= 2 Controllers; Very low HCU, but some oral steroid bursts (OCS); (decreased EOS)
3 More Severe Older Onset Asthma	Older; Late onset(LOA); higher BMI; Less atopic; Moderately low FEV1 with some reversibility; Higher dos ICS; > 3 Controllers, but despite this more OCS bursts (increased sputum EOS)
4 Severe Variable Allergic Asthma	EOA; 53%; Severely decreased FEV1, but very reversible to near normal; Atopic OCS; "Variable" with need for frequent OCS; High beta agonist use; HCU and global symptoms(GS): (increased EOS)
5 Severe Fixed Airflow Asthma ("COPD similarities")	Older; (longest duration); 63% female; Less atopic; Severely decreased FEV1 less reversibility; On OCS; higher BMI; more GERD.HTN; High HCU, Beta use & GSS; (increased PMN, EOS)

Moore et al. Am J Resp Crit Care Med 2010;181:315-323.

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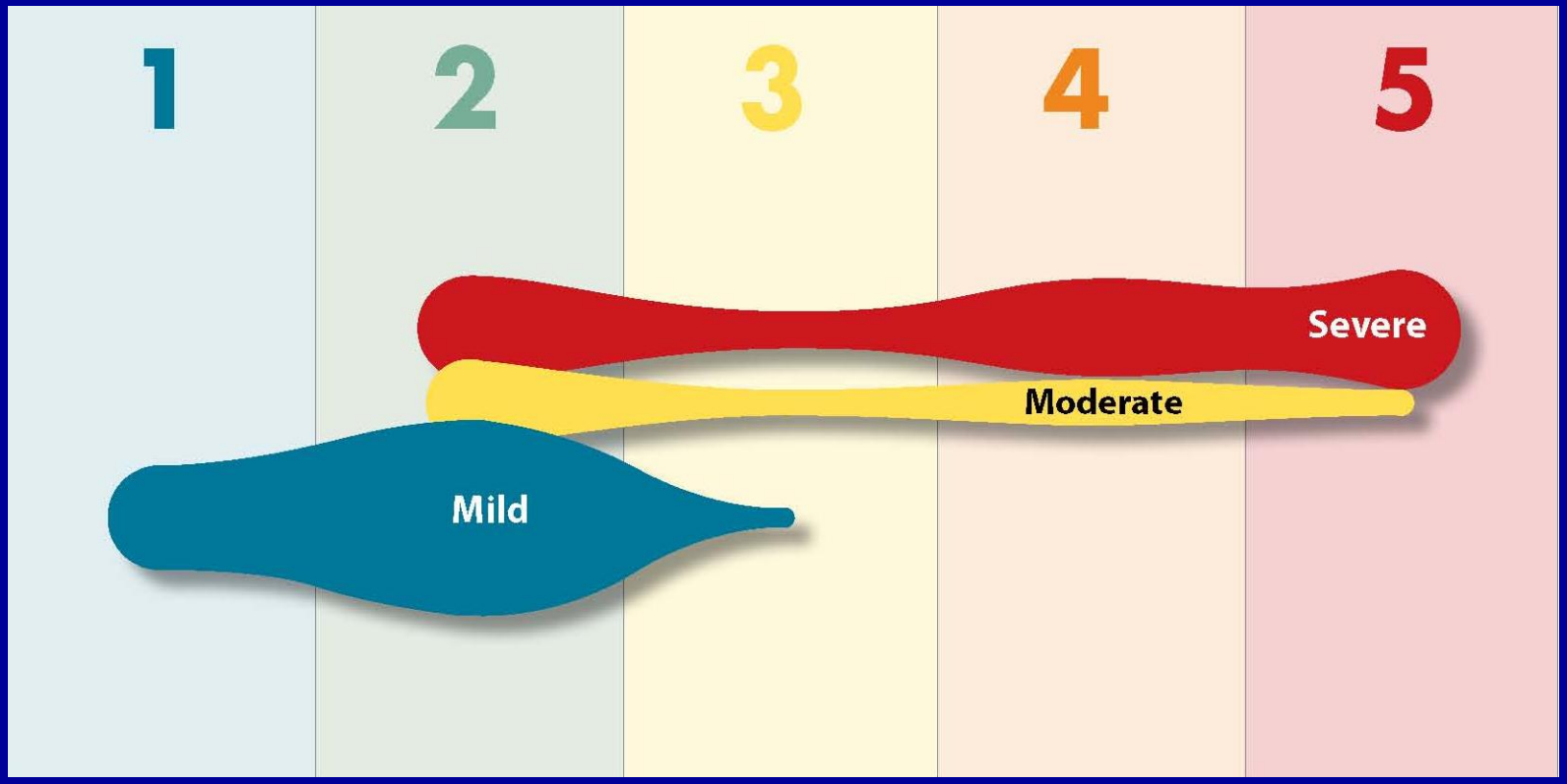
Relationship of Guideline Asthma Severity Classification and Cluster Assignment (Clusters 1-5)



Moore et al. Am J Resp Crit Care Med 2010;181:315-323.

Important Questions About the Cluster Analyses

Do these phenotypic subgroups have different genetic or molecular phenotypes (biomarkers)?

Do these subgroups respond the same or differently to current and future (biologic) therapeutic regimens?

What are the implications of overlapping phenotypes with COPD in nonsmoking asthma?

Examples of Stratified (Personalized) Approaches

- *Disease heterogeneity and asthma phenotypes*
- ***Genome-wide Studies of Susceptibility and Severity***
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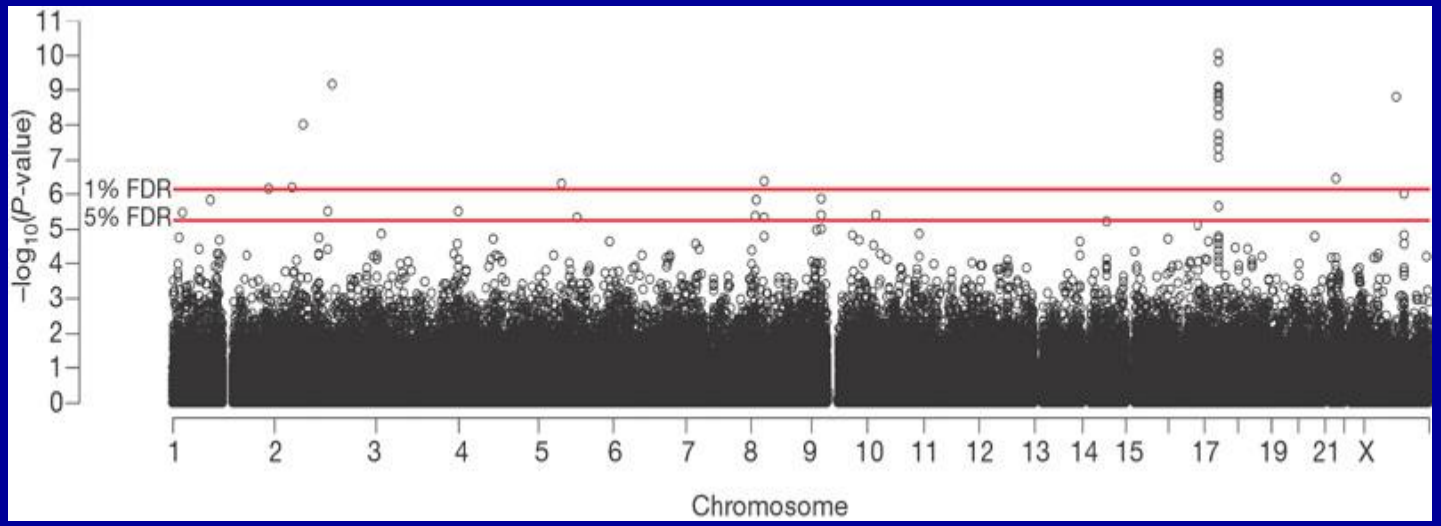
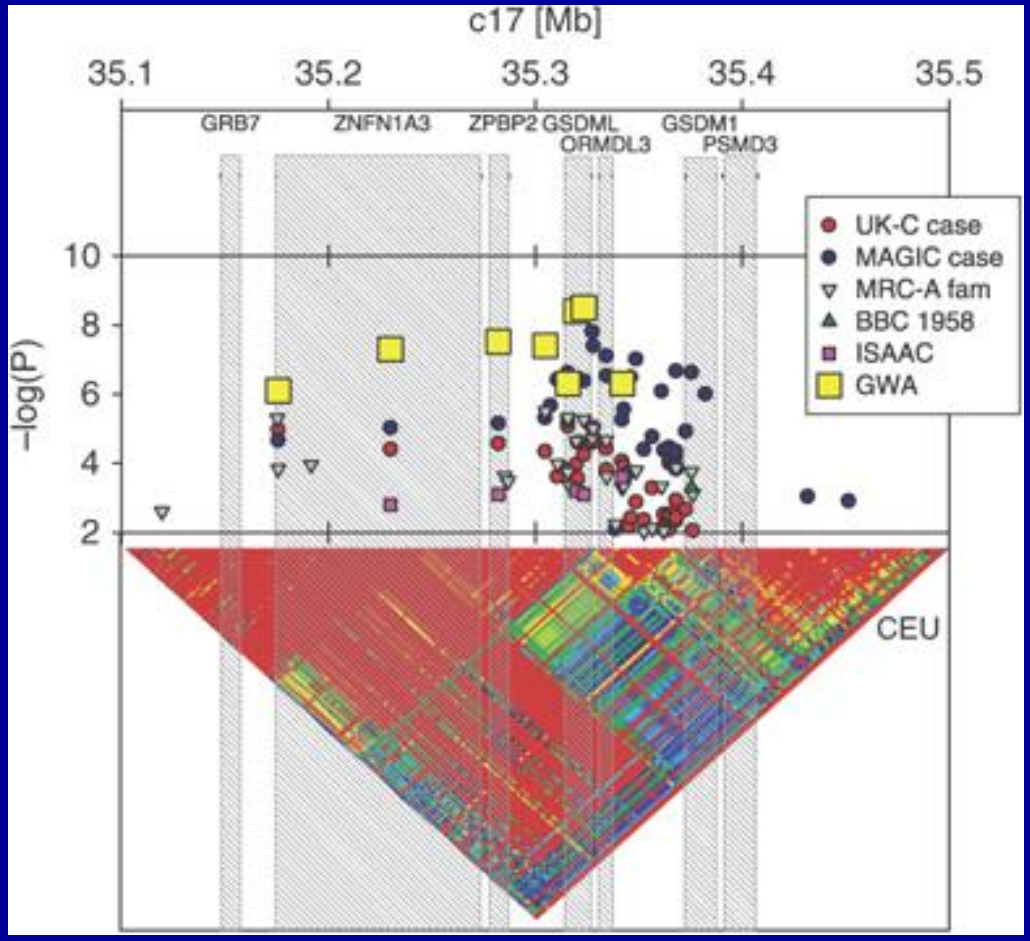
Genome Wide Association in Asthma

- Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma



Moffatt et al Nature 2007

Guilt By Association



Wjst M. 2008 Clin and Exp Allergy 338:1579-81.

Comments

- **Discovered novel asthma gene: *ORMDL3***

- **Disease susceptibility versus severity**
  - What is the question*?* *Childhood asthma susceptability*

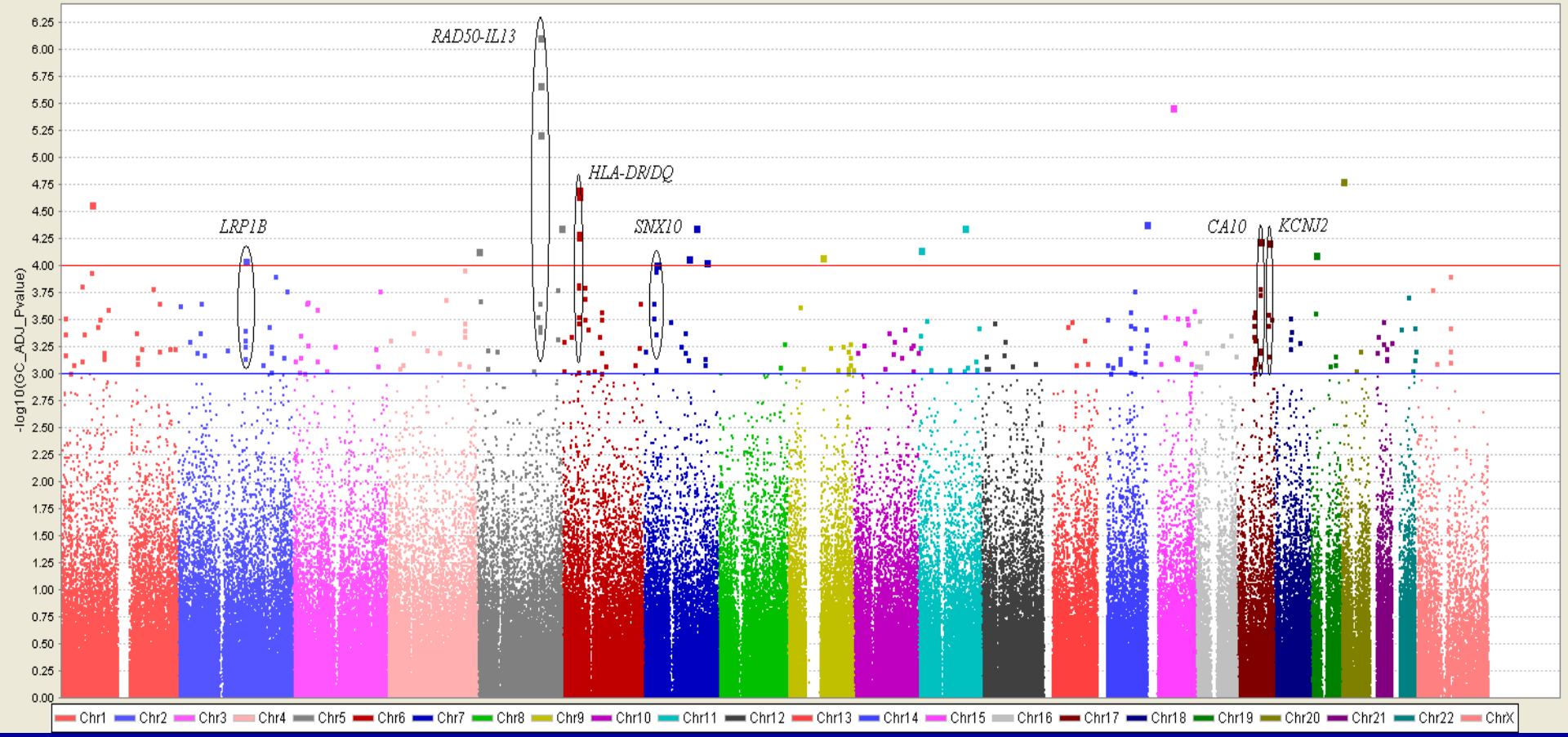
- **Importance of phenotype**
  ***- Qualitative (asthma diagnosis)*,not quantitative?**

- **Role of linkage disequilibrium**
  - European white population with LD extending across genes

Genome-Wide Association Study of Asthma identifies RAD50-IL13 and HLA-DR/DQ regions: TENOR (Difficult to Treat Asthma)

Li et al. JACI 2010

TENOR sings a high C



Li X et al. JACI, 2010

Comments

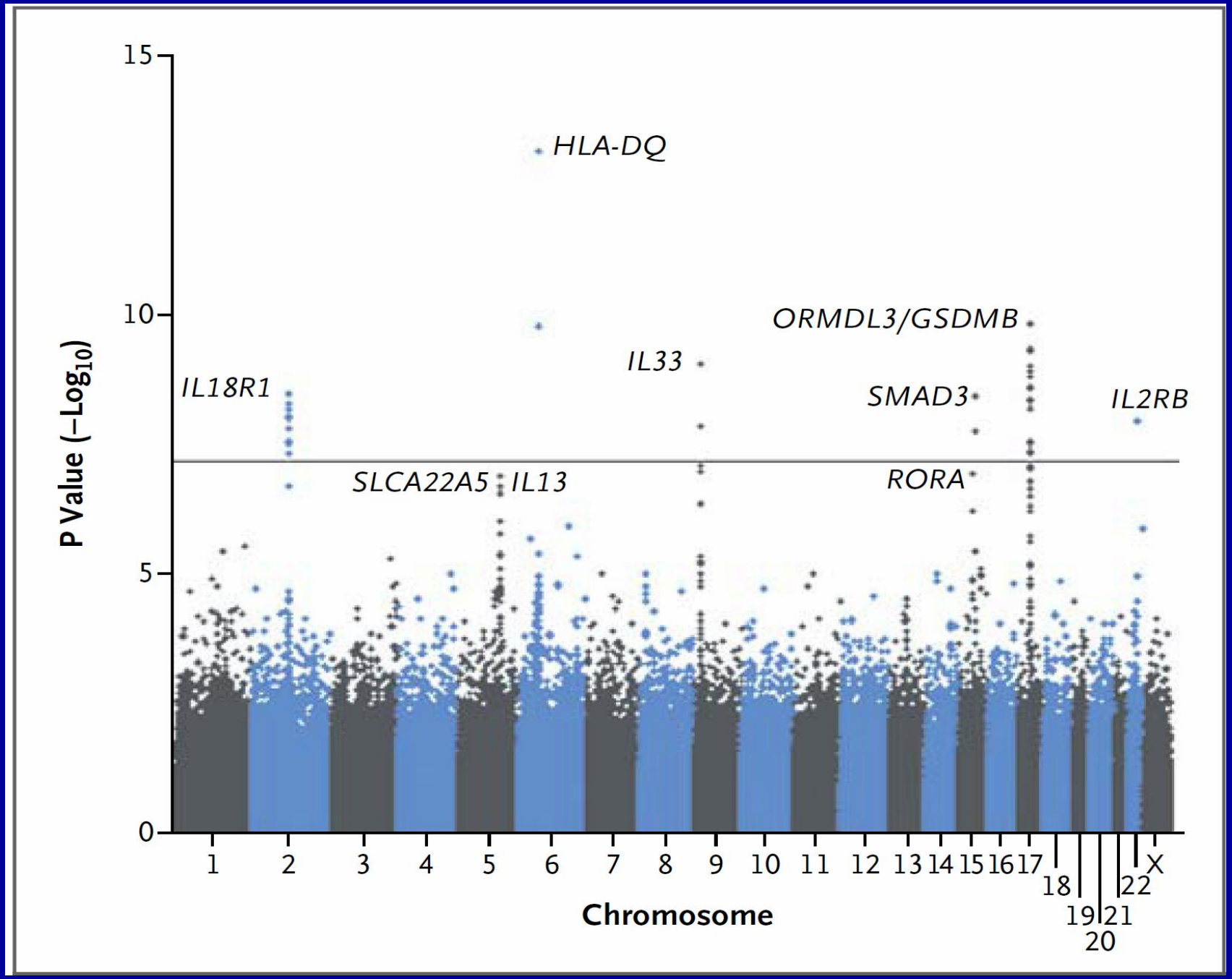
- **GWAS and replication studies**
  - **Relatively small study**
  - **How important is replication?** ***Identified well known biologic candidate genes***
- **Disease susceptibility versus severity**

  Susceptibility to developing asthma or susceptibility to developing severe asthma?
- **Importance of phenotype**
  - ***Qualitative: well phenotyped subjects with asthma***
  - ***used non-phenotyped controls***

A Large-Scale, Consortium-Based Genomewide Association Study of Asthma

Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, von Mutius E, Farrall M, Path FRC, Lathrop M, Cookson W.

N Engl J Med 2010; 363:1211-1221



Moffatt MF, et al. N Engl J Med. 2010; 363:1211-21

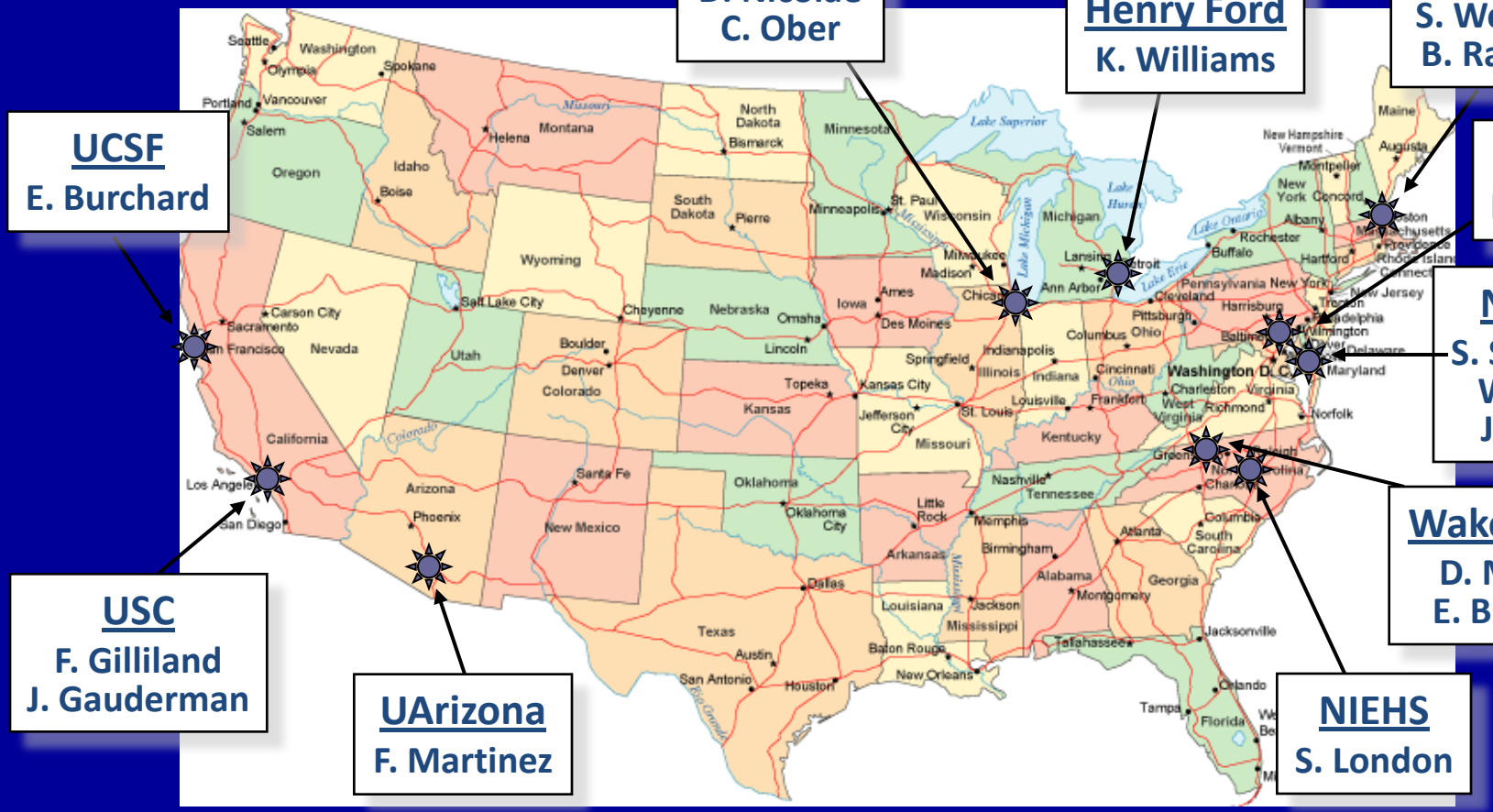
The EVE Consortium

A Collaboration to Identify Asthma Genes In Ethnically Diverse Populations

RC2 HL101651 (C. Ober, D. Nicolae, Co-Pis)

Torgerson et al Nature Genetics 2011

The EVE Consortium



Summary of Asthma GWAS Results

- 7-10 asthma susceptibility loci identified
  - Most are pan-racial; *PYHIN1* is ethnic/race-specific
  - Most were prior candidates (e.g., *TSLP*, *IL33*, *IL1RL1/IL18R1*); some novel (e.g., *ORMDL3/GSDML*, *PYHIN1*)
  - Small effect sizes (odds ratios ≅1.2-1.3)
  - Accounts for little of the total genetic risk for asthma
- Robust associations with *TSLP*, *IL33*, *IL1RL1* suggest a central role for innate immune-mediated allergic sensitization in asthma

.Torgeson et al Nature Genetics 2011

Comments

- **GWAS and replication studies**
  - ***Two very large studies of multiple populations***
  - ***Multiple replicated "asthma" genes***

- **Disease susceptibility versus severity**
  Asthma susceptibility with little specific phenotypes

- **Importance of phenotype**
  - **Qualitative, quantitative? What are the appropriate comparisons across large genetic studies? (feasability)**

Examples of Stratified (Personalized) Approaches

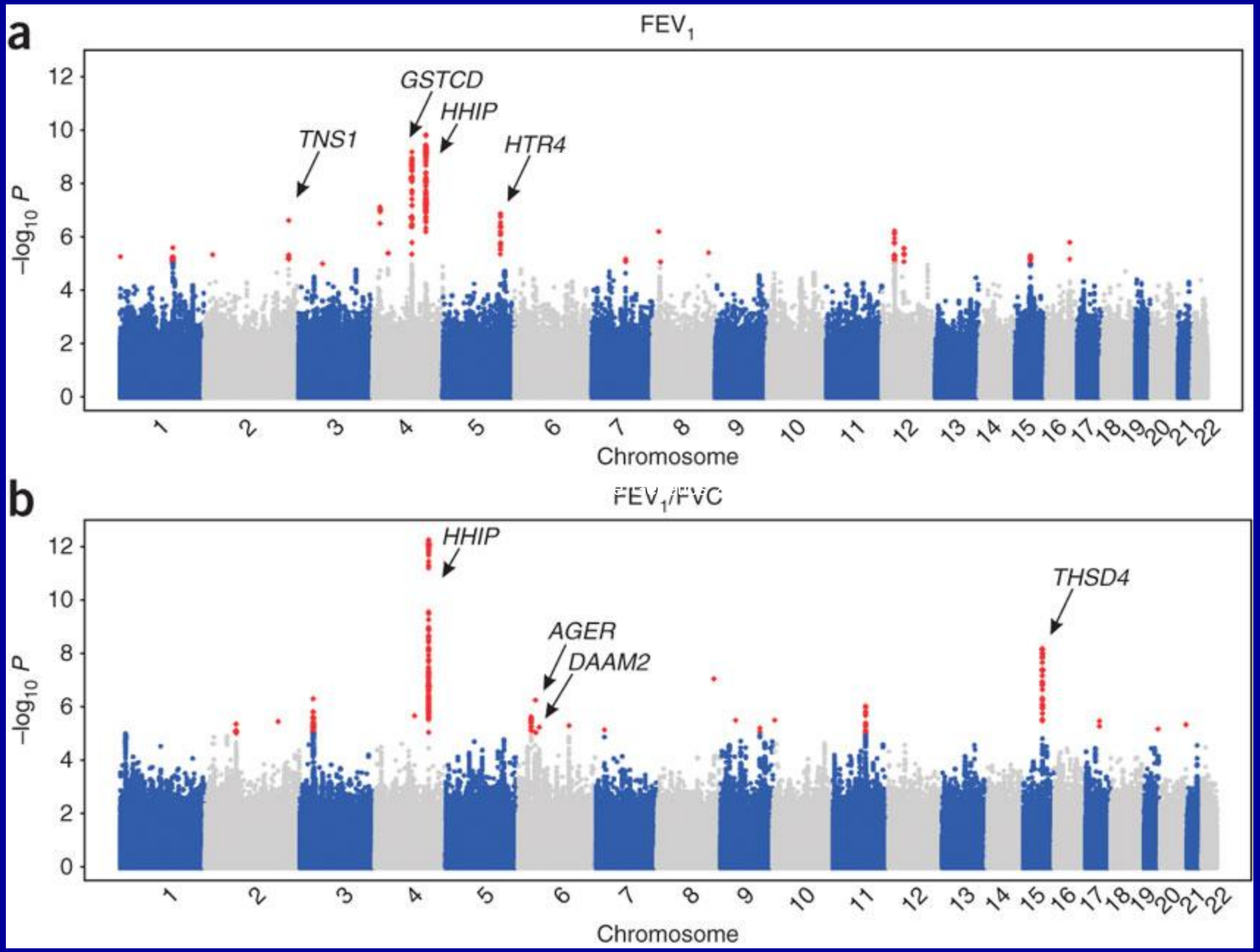
- *Disease heterogeneity and asthma phenotypes*
- *Genome-wide Studies of Susceptibility and Severity*
- ***Pulmonary function and asthma severity***
- *Early onset Th2 phenotypes and severity*

Meta-analyses of Genome-wide Association Studies Identify Multiple Loci Associated With Pulmonary Function

Hancock, et al. Nature Genetics 2010; 42:14-6

Genome-Wide Association Study Identifies Five Loci Associated with Lung Function

Repapi, et al. Nature Genetics 2010; 42:36-44



Repapi E, et al. Nature Genetics 2010; 42:36-44

Chromosome 4q: HHIP

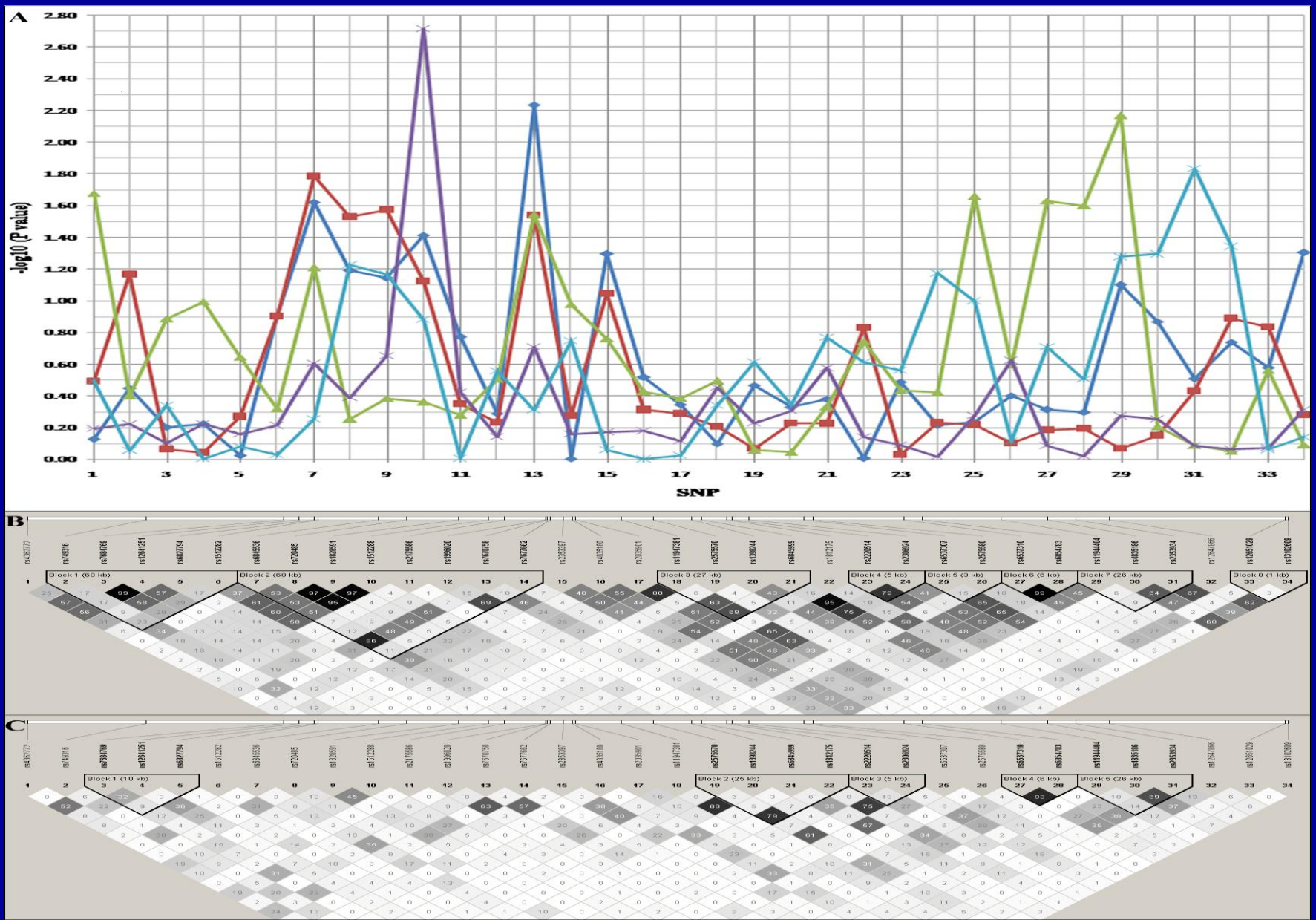
- Hedgehog interacting protein

- Hedgehop signaling pathway is important in early lung development

- Previously reported in GWAS of height: HHIP

Li et al, JACI 2011

Association/LD plot of *HHIP* region with ppFEV$_1$ in Five populations



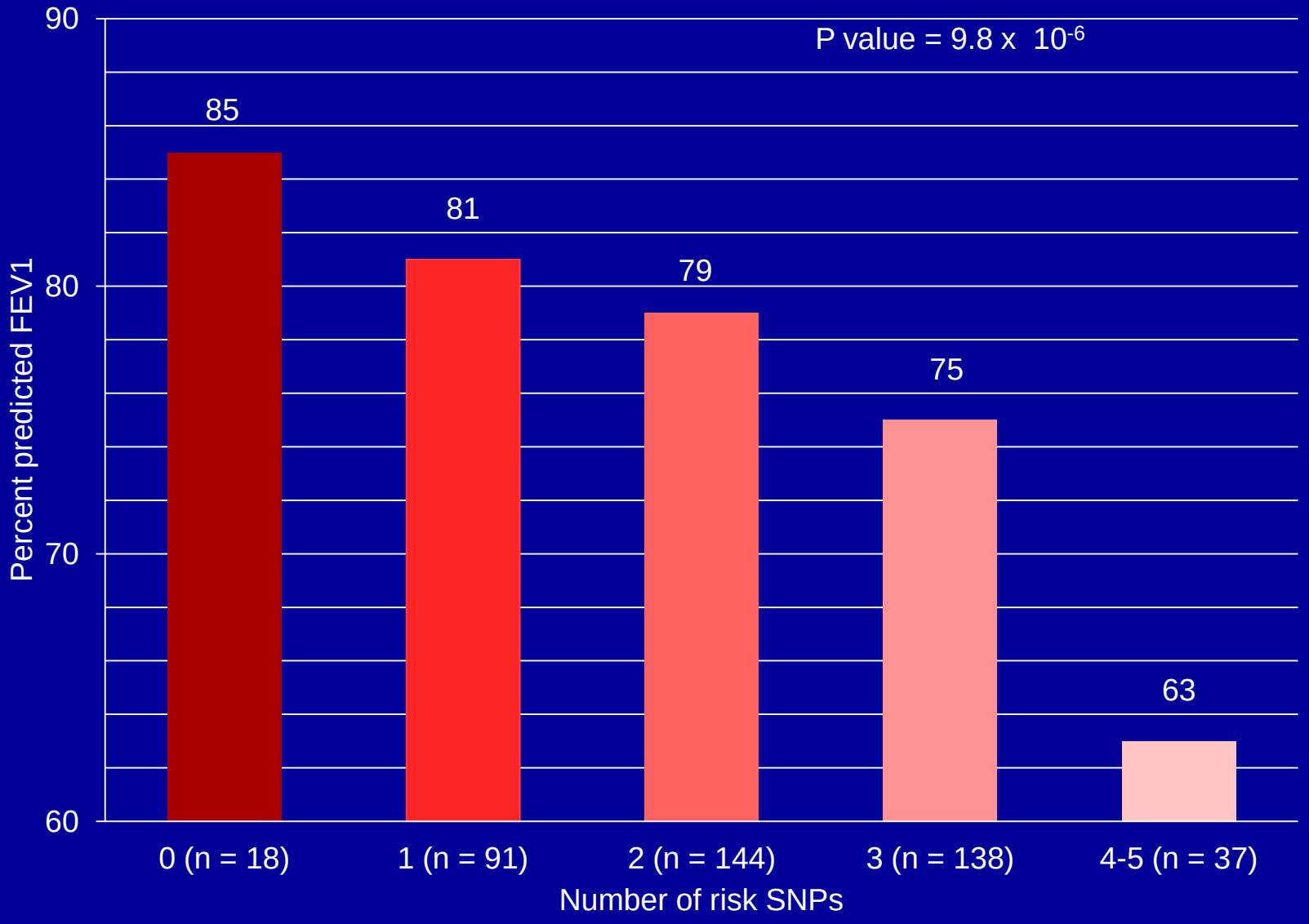
HHIP and levels of FEV1: Importance

- African-Americans: 252 ml lower with each copy of minor allele
- Non-Hispanic whites: 85 ml lower with each copy of minor allele

Genes Associated with Lung Function in Asthma

- *HHIP*
- *FAM13A*
- *PTCH1*
- *PID1*
- *NOTCH4*

SARP: Joint analysis of 5 SNPs: *HHIP, PTCH1,FAM13A, PID1, NOTCH4*



Li, X, et al JACI 2011

Comments

- **Disease susceptibility versus severity**

  Lung function and asthma severity severity

- **Importance of phenotype**

  - Qualitative, *quantitative?*

- **Role of linkage disequilibrium**

  - How do we identify the casual variant? *Very different LD structure in African-Americans provided insight across SNPs that were genotyped*

- **Data mining after completing your GWAS**

  - Analyze candidate genes and pathways : *Lung function genes identified in the general population*

Lung Function: Summary

- **Will this additive genetic approach be useful to identify patients with at risk for severe asthma in early life with the potential for specific/early therapeutics interventions?**

- ***Additional studies are needed for replication and longitudinal outcomes***

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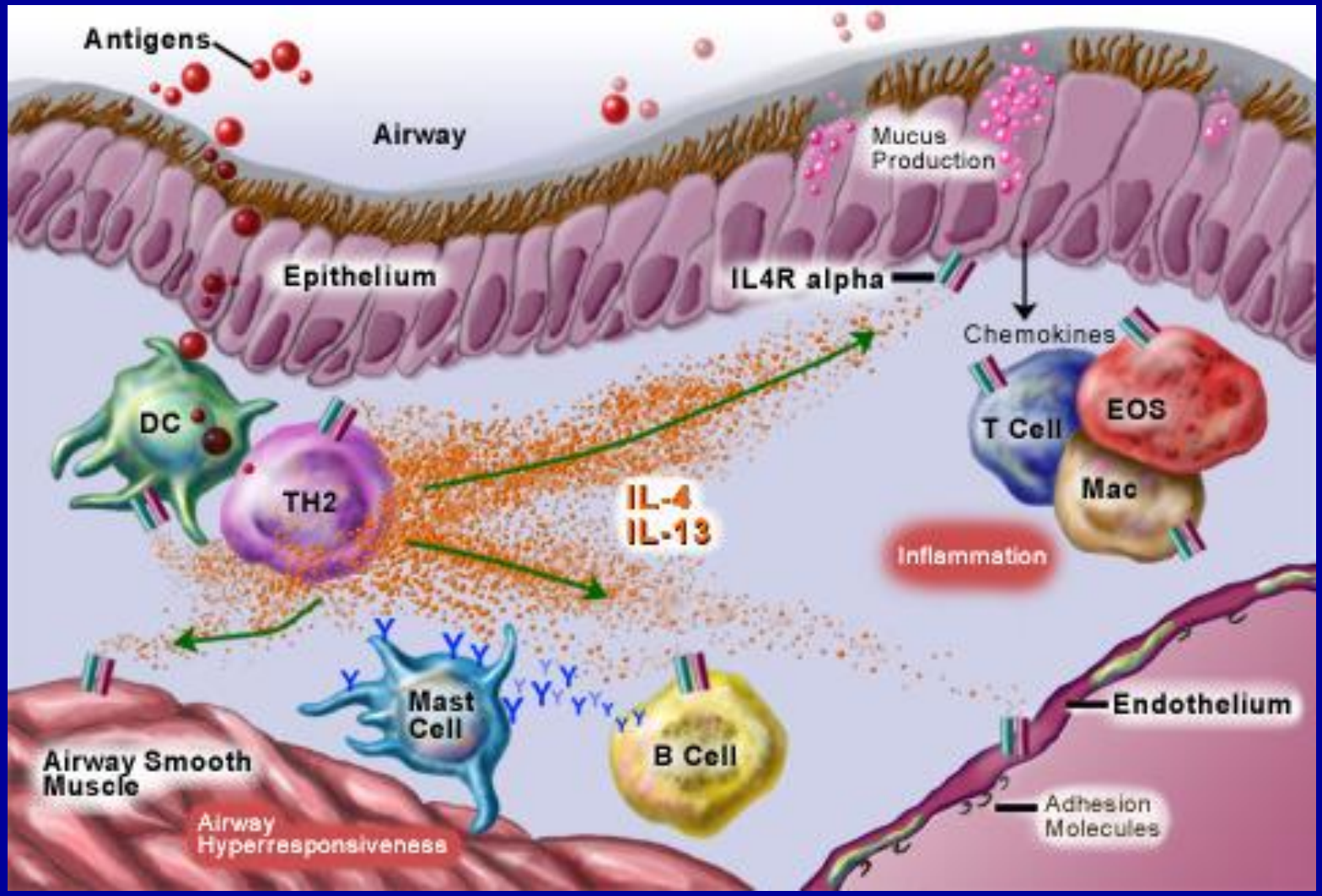
T helper 2 (Th2) Pathway in Asthma



Rational Therapeutic Targeting in Patients with Relevant IL4/IL13 Pathway Variation

D Vercelli 2011 ATS

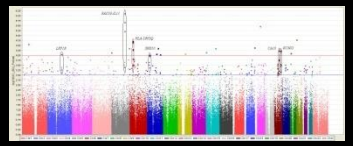
Genetic Approaches in Asthma: Future Directions

Susceptibility/Severity: Pattern of SNPs in a group of candidate genes may be useful to predict disease susceptibility and/or asthma heterogeneity and severity

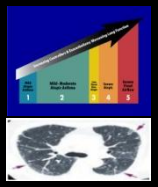
Therapy: SNPs in specific genes that regulate important biologic pathways may predict responses therapeutic approaches (eg, IL-13/IL-4R, IL6/IL6r etc)

Genomic Approaches in Asthma

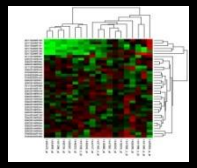
Genome Wide (GWAS)



COMPREHENSIVE PHENOTYPE

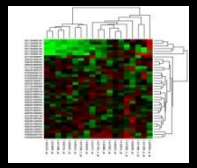


EXPRESSION DATA



Epithelial cells

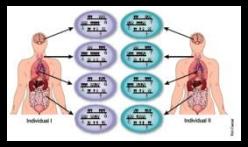
EXPRESSION DATA



BAL cells (Macrophages)

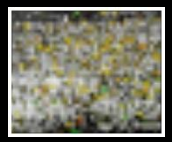
SEVERITY and SUSCEPTIBILITY LOCI

EPIGENETICS



Gene Expression Profiles

EXPRESSION DATA

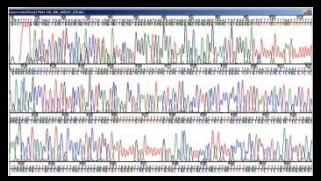


Inflammatory Signatures

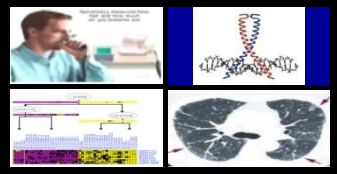
GENOMIC ANALYSIS and SYSTEMS BIOLOGY

Proteinomics Metabalomics

Deep Sequencing



NEW MOLECULAR PHENOTYPES & TARGETS



Advantages of Personalized Medicine: Everyone Can Win

- **Patients:** Identify the right drug for the right patient at the right time with improved compliance and better outcomes
- **Physicians:** More choices and more specific therapies
- **Government/Payers:** Better outcome driven return on investments
- **Regulators:** Increased confidence to approve earlier (licensing)
- **Pharma:** Better investment strategies for novel therapies

Acknowledgements

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Genomics and Proteomic Approaches to Complex Heart, Lung, Blood & Sleep Disorders

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