Role of Respiratory Infections in Childhood Asthma

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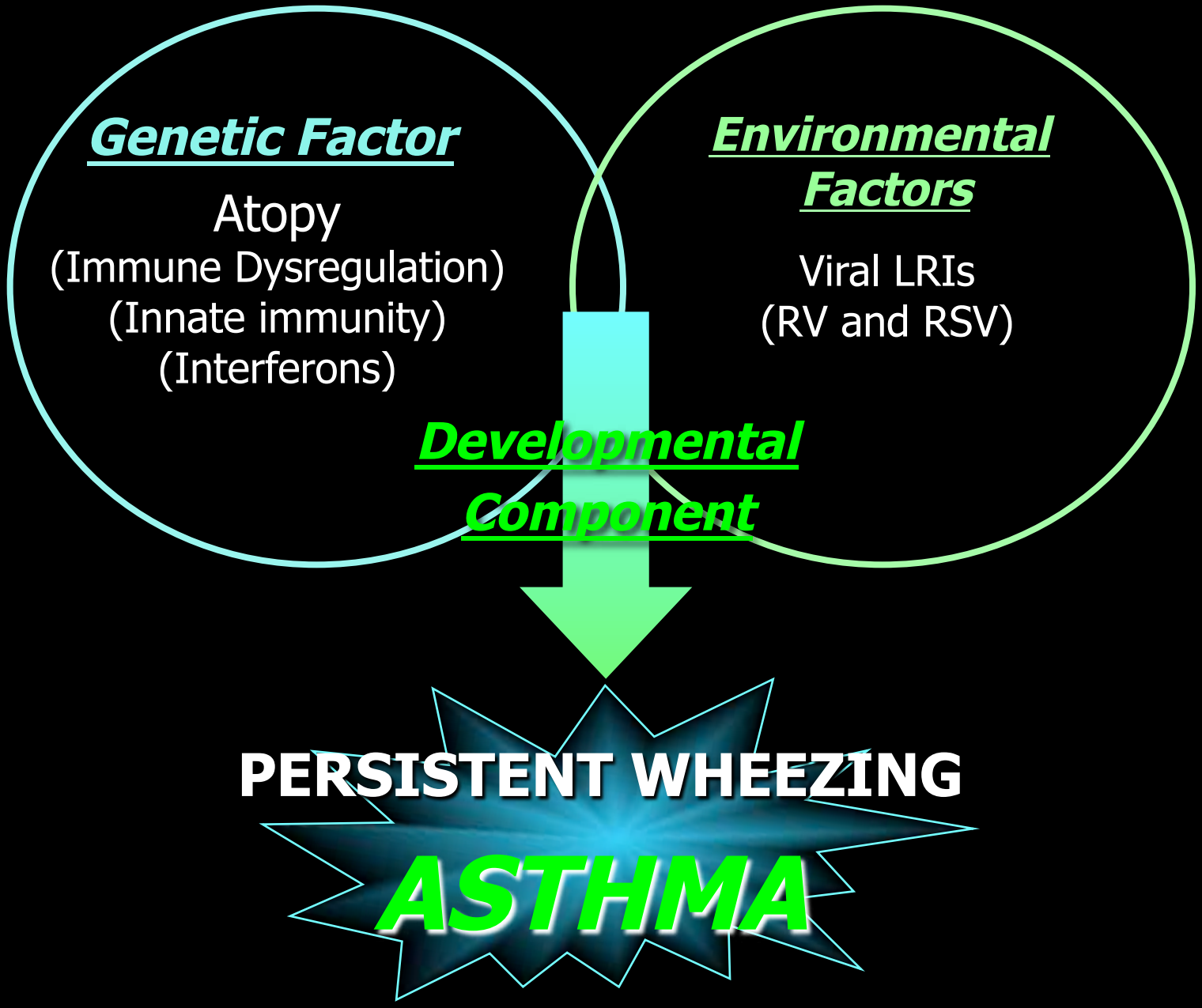
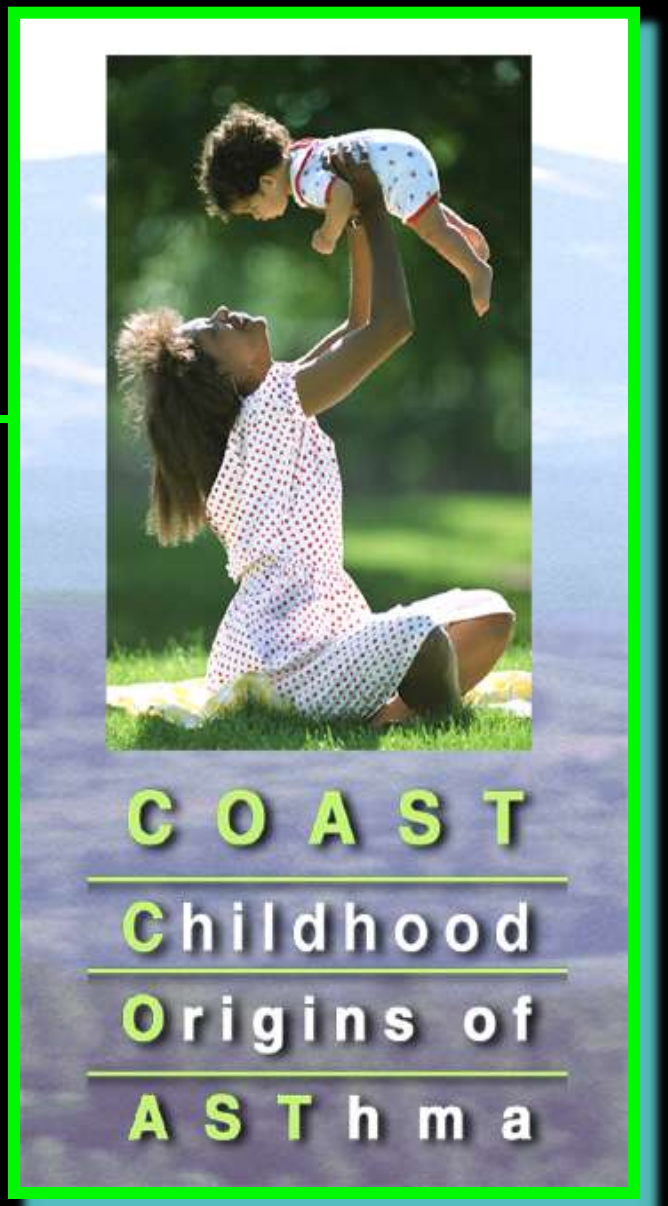

Genetic Factor
Atopy
(Immune Dysregulation)
(Innate immunity)
(Interferons)
Environmental Factors
Viral LRIs
(RV and RSV)
Developmental Component
PERSISTENT WHEEZING
ASTHMA



COAST

Childhood Origins of ASThma

A prospective study in a high risk cohort designed to evaluate the interactions among age, patterns of immune dysfunction, and virus infections with respect to the subsequent development of asthma and allergic diseases

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Co-Is: Jim Gern, MD
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Ron Gangnon, PhD
Wai-Ming Lee, PhD
Kathy Roberg, RN, MS

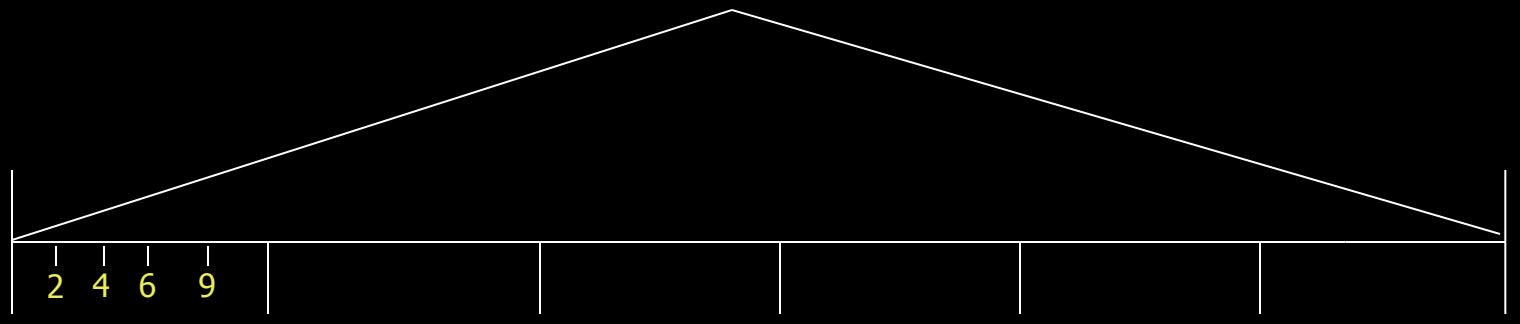
Funded by the NHLBI

Research Design and Methods

- Target enrollment: 300 families
- At least one parent with allergies or asthma
- Prospective (developmental) evaluation of
  - Immune system
    - Child (annually from birth) and parent
    - Cytokine response profiles; antigen-specific IgE
  - Respiratory infections (nasal aspirates)
  - Wheezing phenotypes (questionnaires)
  - Airway physiological evaluation (ages 4-7 yrs)
    - Impulse oscillometry, spirometry, eNO, meth. challenge
  - Environmental evaluation (diet, allergens, pets)
  - Genotype evaluation
- Minimum 12-14 year follow-up

COAST Evaluations

Nasal lavage specimens collected
at symptomatic illnesses



Nasal Washes collected at
"Well Child Visits"

Persistent
Wheezing
Evaluation

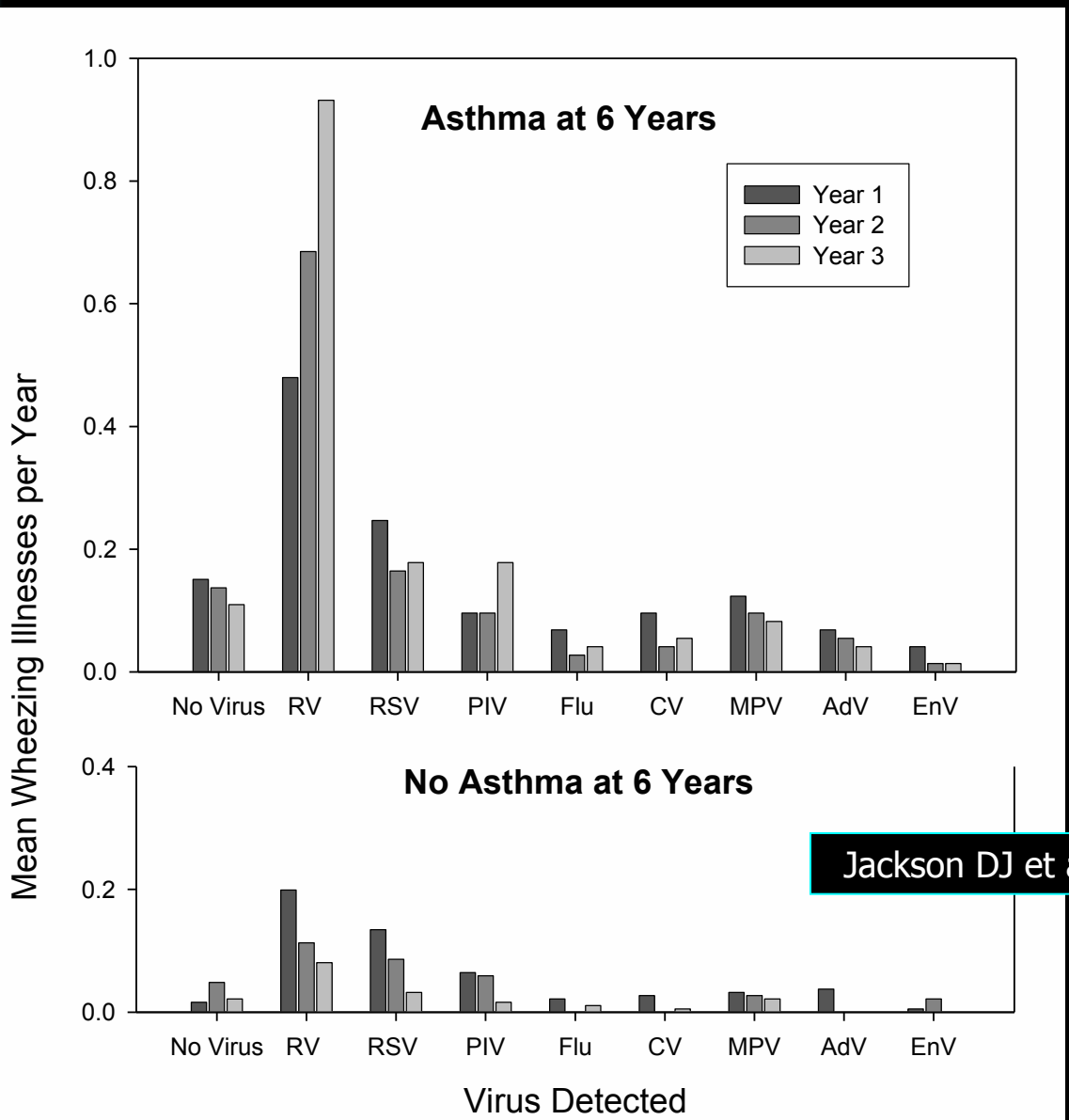
[JACI 116:571, 2005]

Asthma Evaluation
[AJRCCM 178:667, 2008]

Timing, severity & etiology of respiratory
illnesses determined throughout childhood

What viral infections in early life are associated with the development of asthma at age 6 years?

Etiology of Wheezing Illnesses in Early Childhood

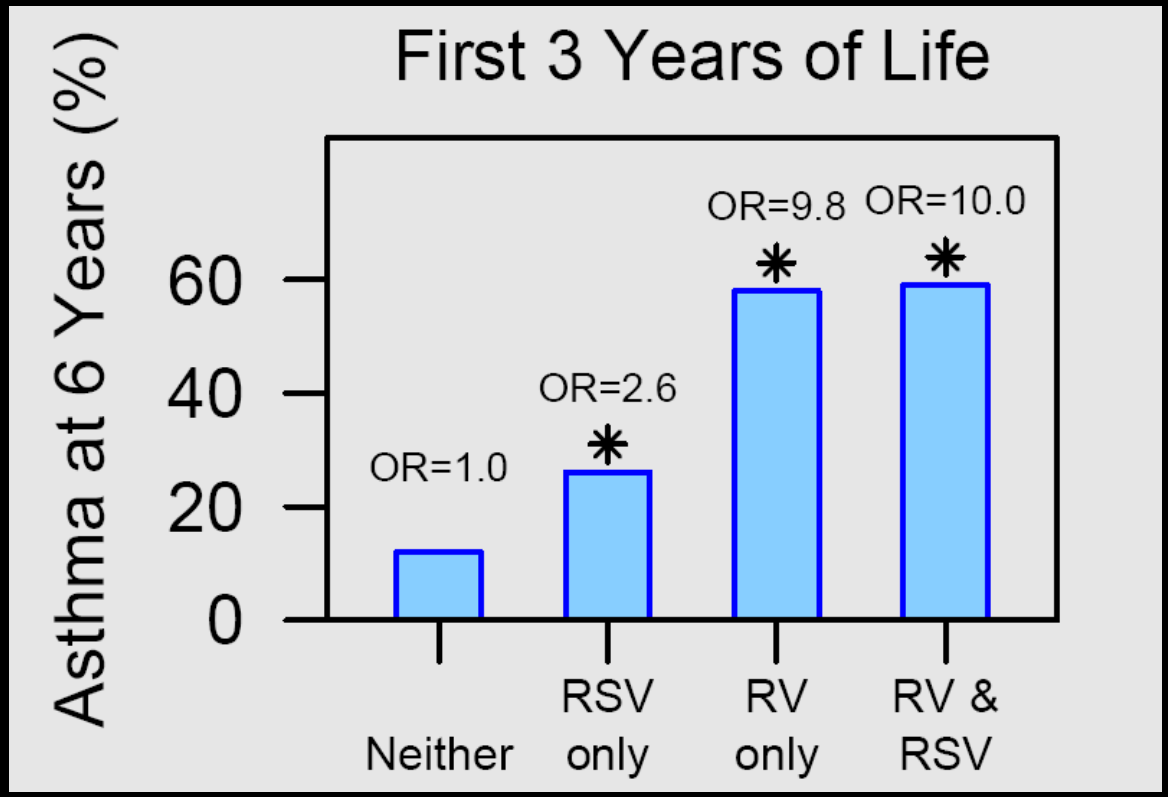


RV Rhinovirus
RSV Respiratory syncytial virus
PIV Parainfluenza
Flu Influenza
CV Coronavirus
MPV Metapneumovirus
AdV Adenovirus
EnV Enterovirus

Jackson DJ et al. AJRCCM, 178:667, 2008

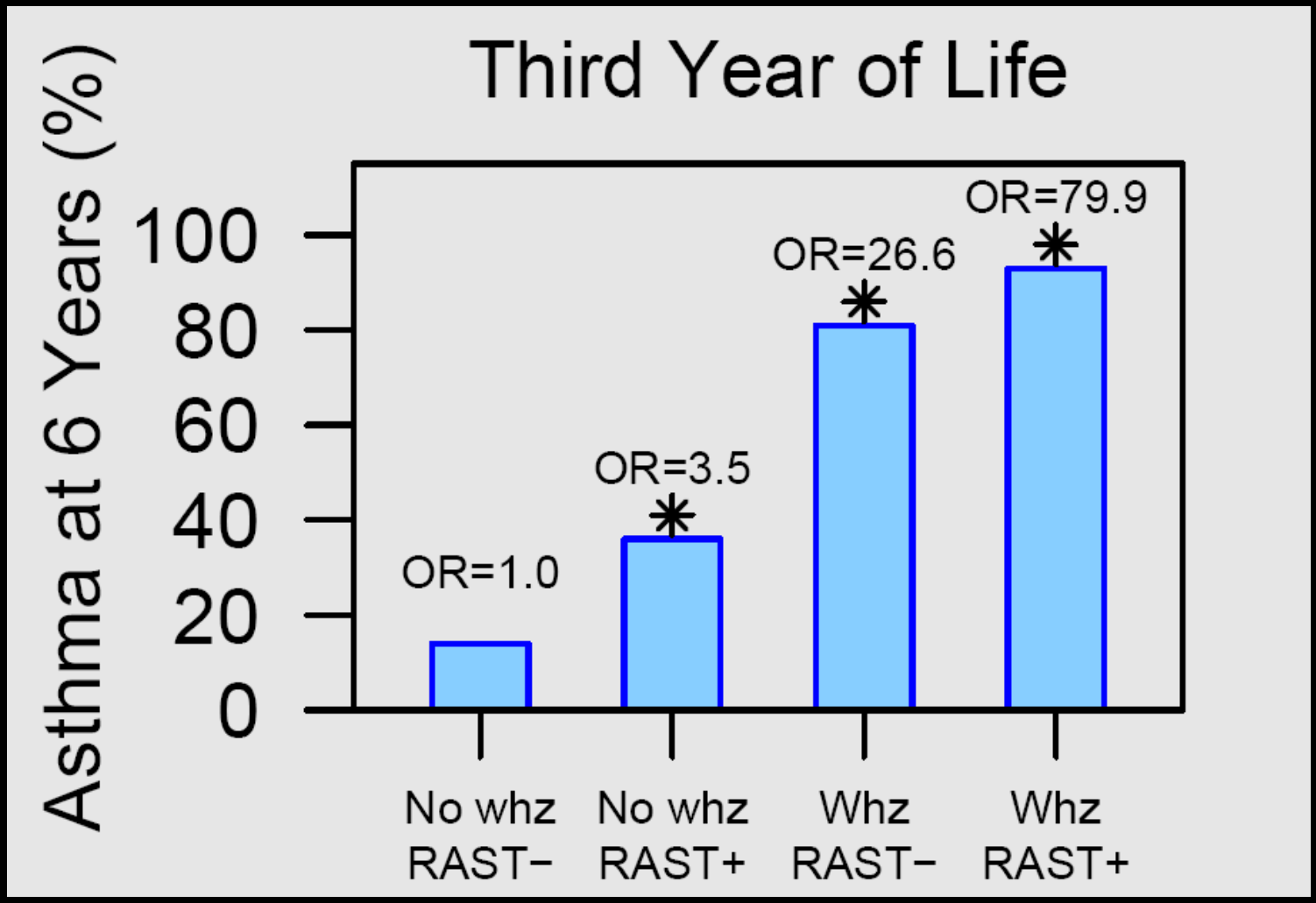
Did RV or RSV wheezing illnesses during years 1-3 impact the risk of asthma at age 6?

RV Wheezing vs. RSV Wheezing in First 3 Years and Asthma at Age 6 Years



Jackson DJ et al. AJRCCM, 178:667, 2008

RV Wheezing & Allergic Sensitization in Year 3 and Asthma at Age 6 Years

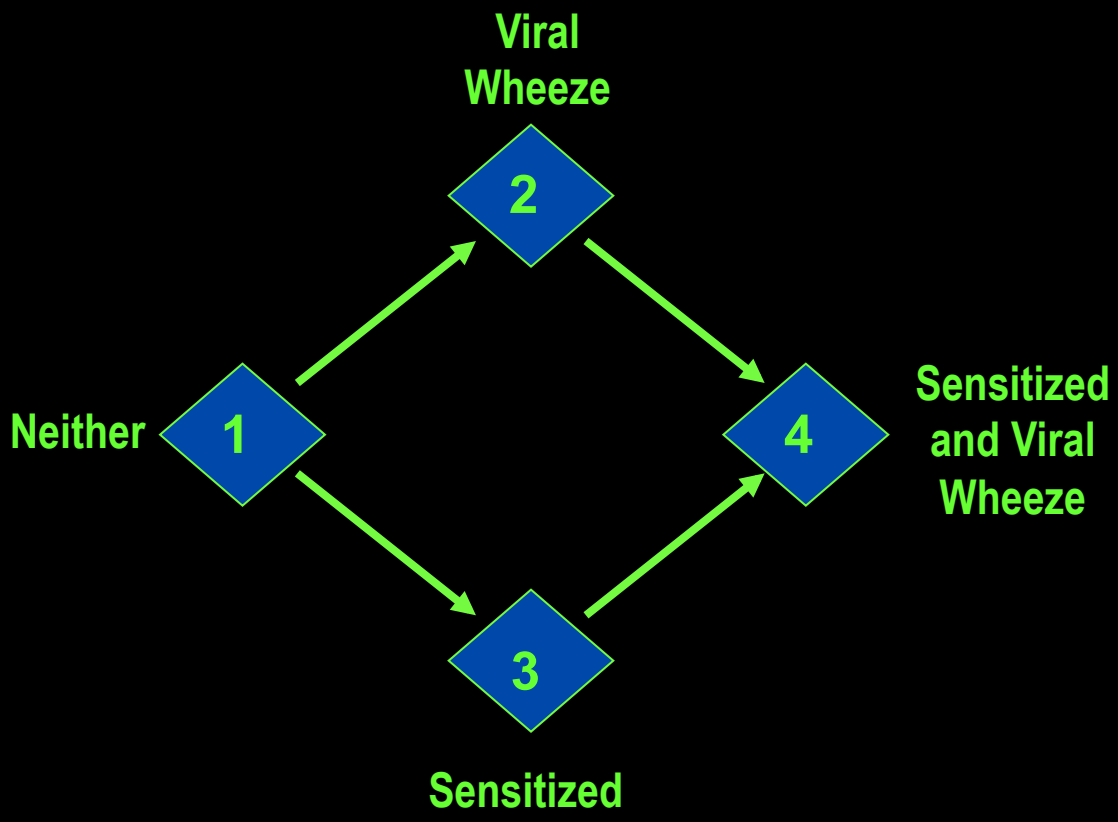


Jackson DJ et al. AJRCCM, 178:667, 2008

Which comes first?

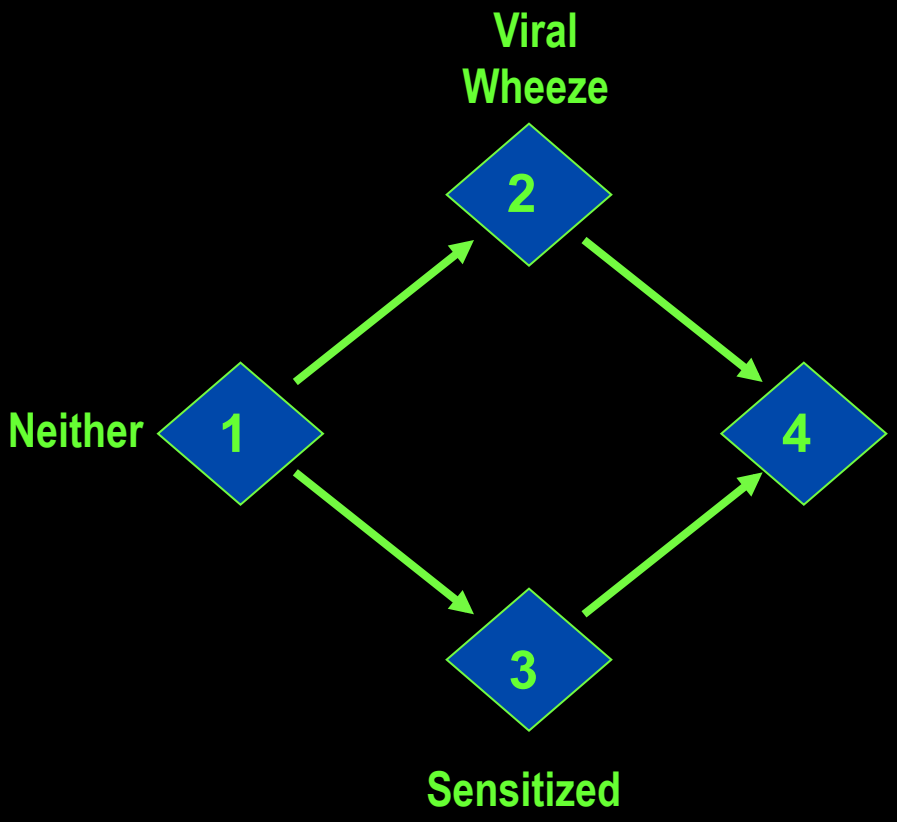
Allergic sensitization or wheezing illnesses?

Does sensitization lead to viral wheezing, or does viral wheezing lead to sensitization?



Jackson et al. AJRCCM 185:281, 2012

Does sensitization lead to viral wheezing, or does viral wheezing lead to sensitization?



If viral wheeze causes sensitization:

$2 \rightarrow 4 > 1 \rightarrow 3$

If sensitization causes viral wheeze:

$3 \rightarrow 4 > 1 \rightarrow 2$

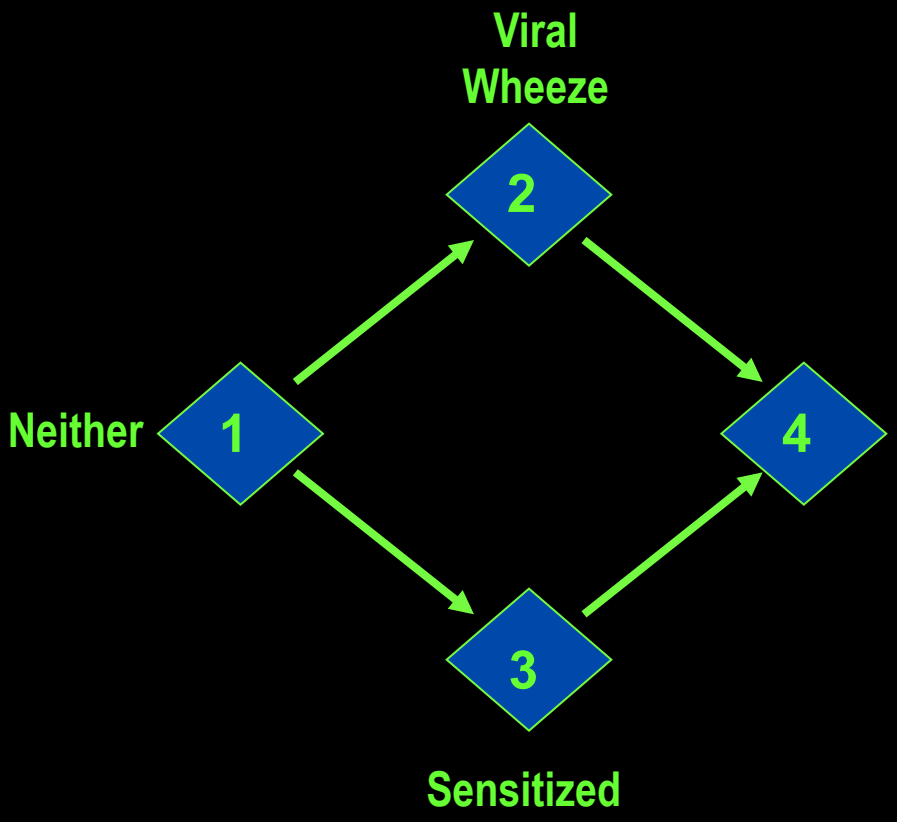
No causality:

$2 \rightarrow 4 = 1 \rightarrow 3$

$3 \rightarrow 4 = 1 \rightarrow 2$

Jackson et al. AJRCCM 185:281, 2012

Sensitization Leads to Viral Wheeze
(the reverse does not appear to be true)

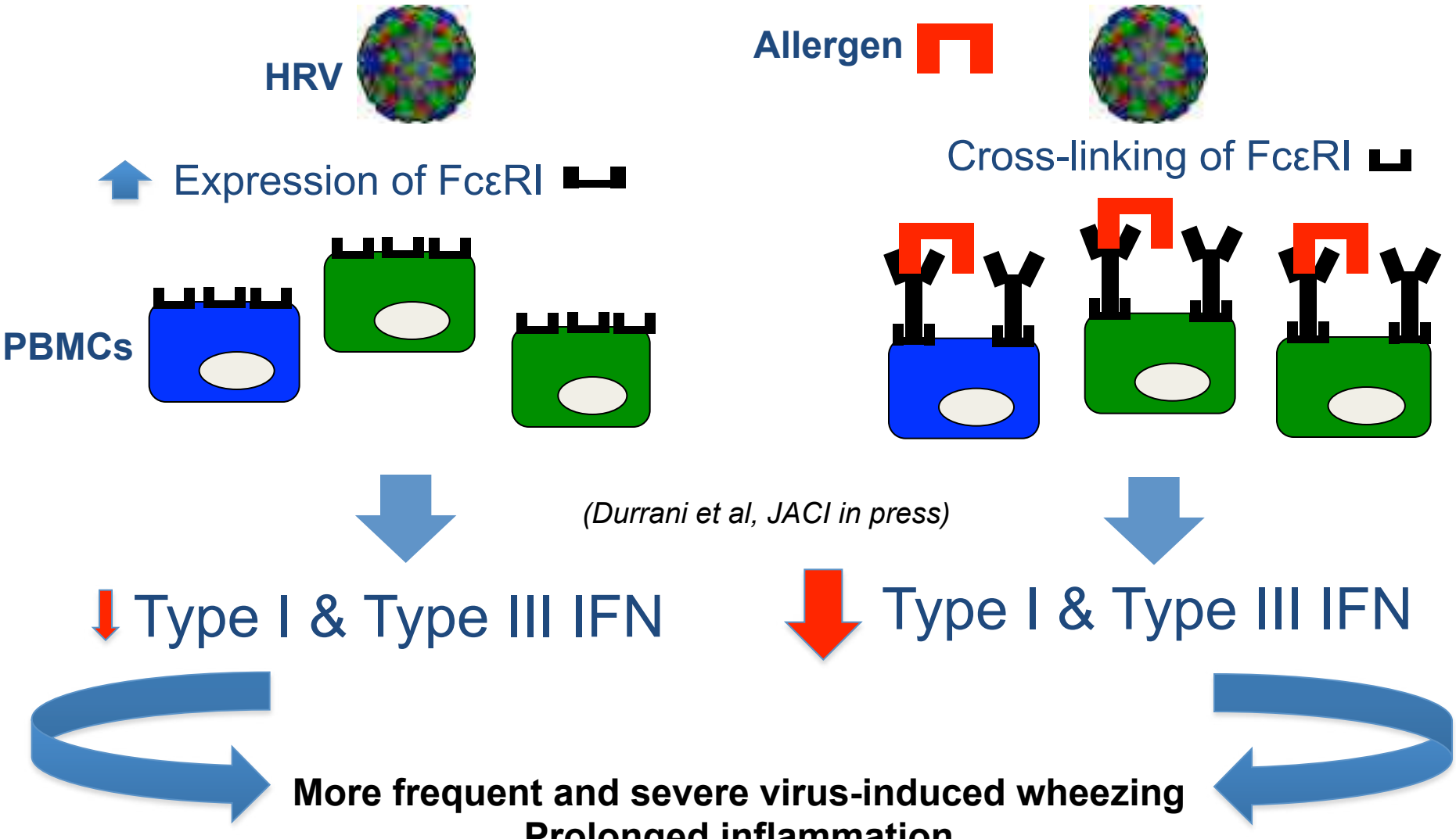


Virus	Ratio $\frac{3\rightarrow4}{1\rightarrow2}$	Ratio $\frac{2\rightarrow4}{1\rightarrow3}$
Any	1.9* (1.2, 3.1)	0.75 (0.49, 1.1)
HRV	2.4* (1.4, 4.3)	0.69 (0.41, 1.2)
RSV	1.6 (0.9, 2.9)	0.8 (0.52, 1.3)

Jackson et al. AJRCCM 185:281, 2012

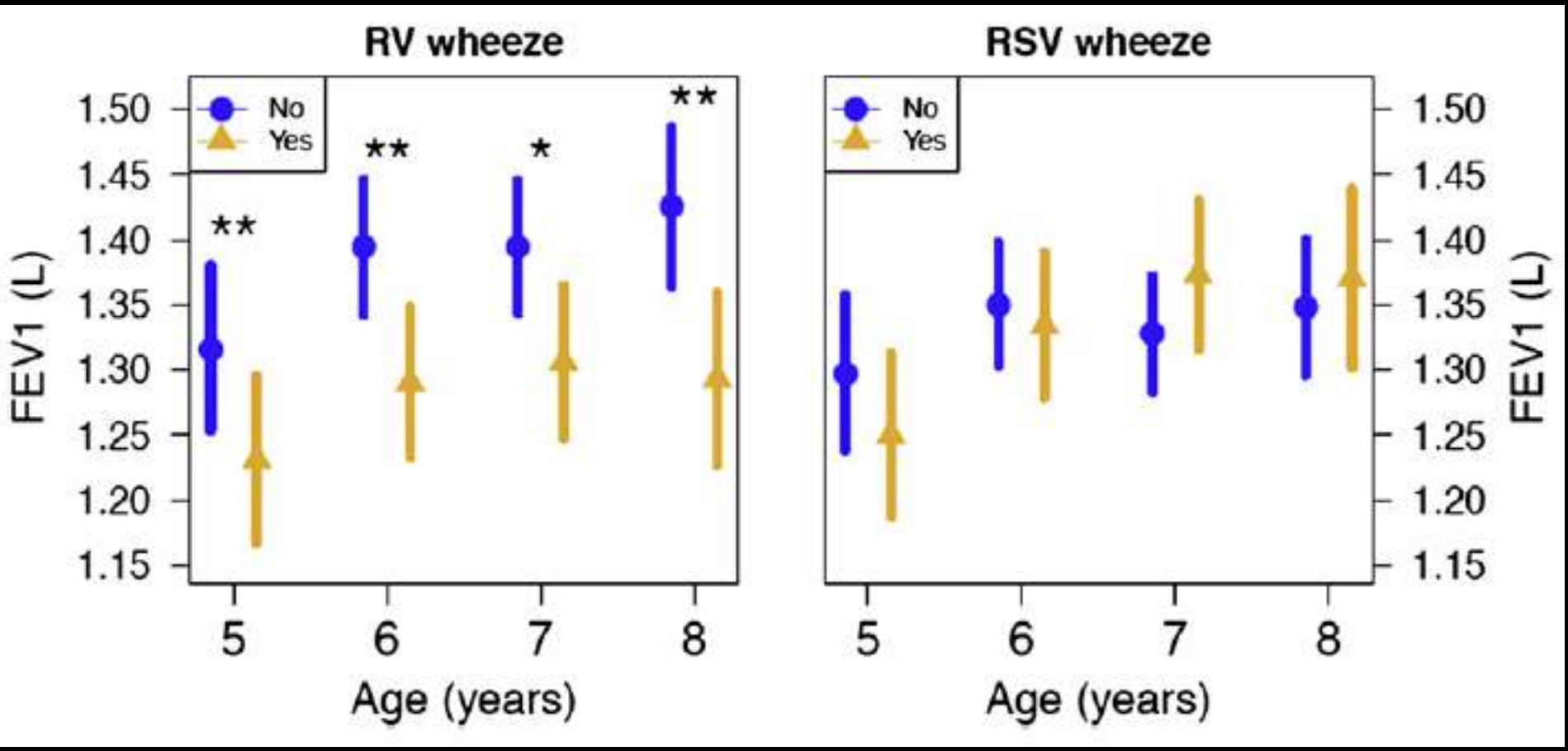
How does allergic sensitization alter the host response to viral respiratory infections?

Hypothesis: Allergy Inhibits Innate Immune Responses Through FcεRI



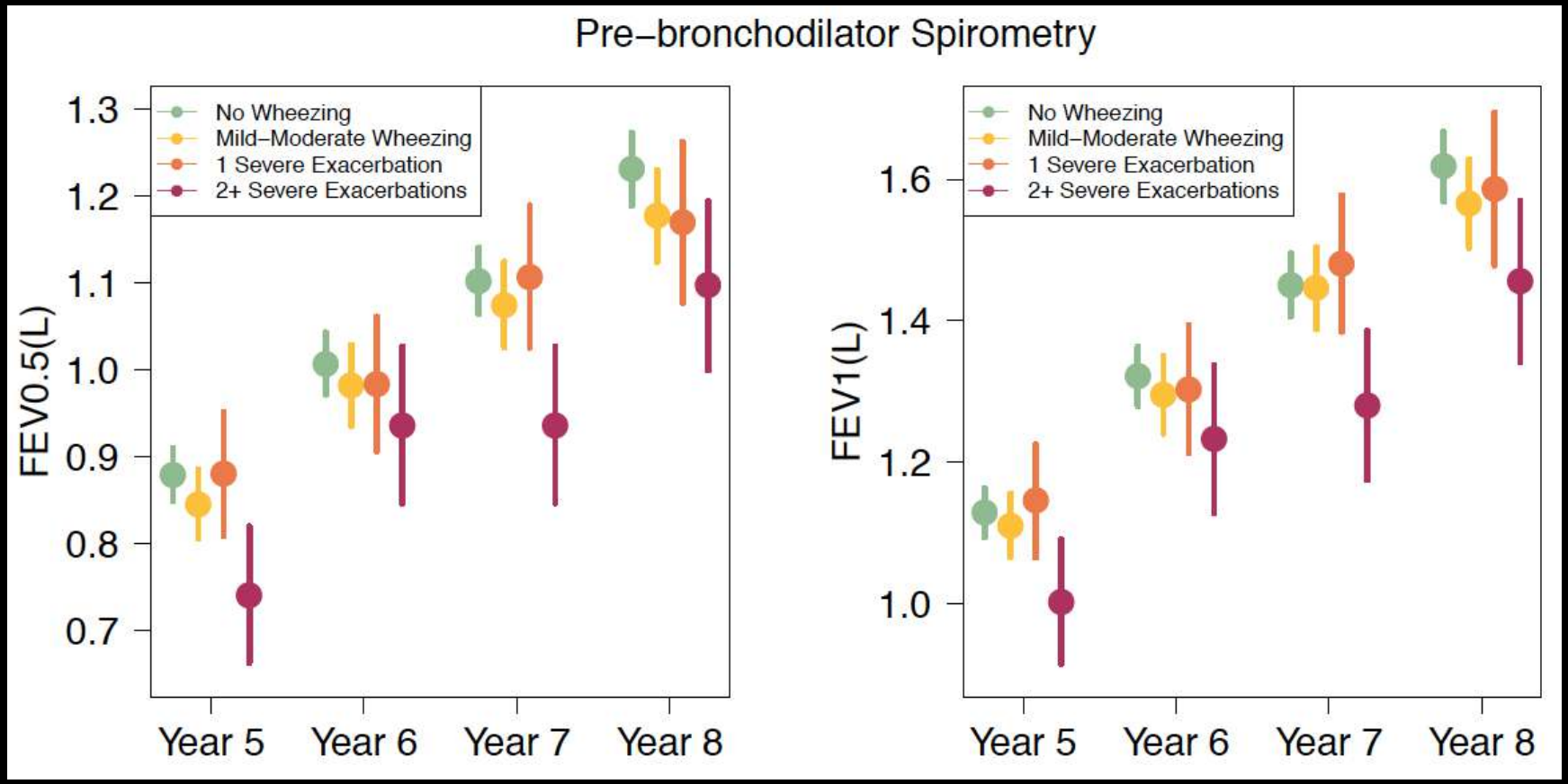
Do wheezing RV infections in early life influence subsequent lung function?

Influence of Viral Etiology for Wheezing on Lung Function



Guilbert T et al. JACI 128:532, 2011

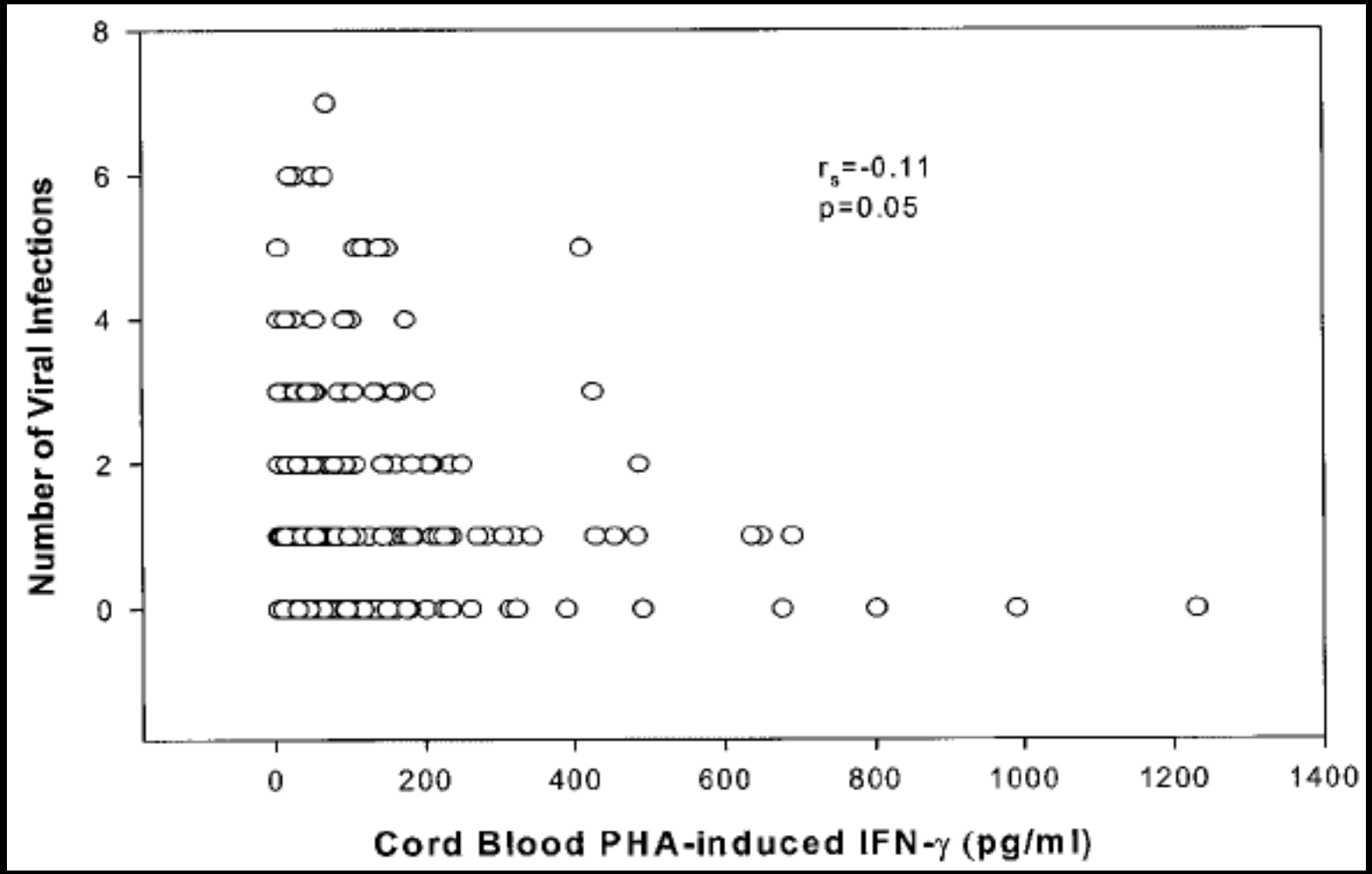
Effects of Asthma Exacerbation Severity on Lung Function



O'Brian A. et al. JACI 129:1162, 2012

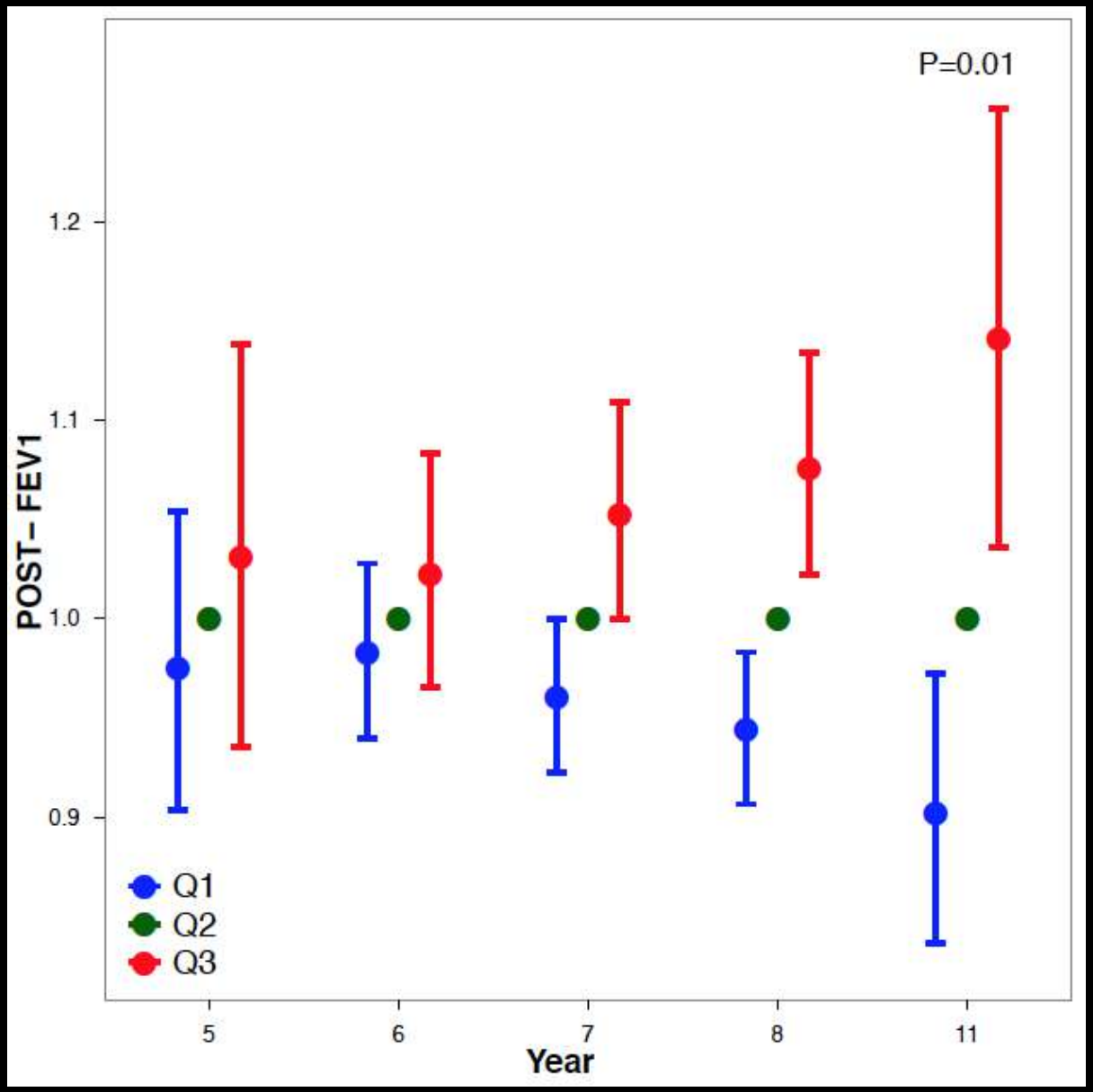
Innate immune development, viral respiratory tract illnesses, and loss of lung function in childhood

Innate Immune Responses and Frequency of Viral Infections during Infancy



Copenhaver C et al. AJRCCM 170:175, 2004

Cord Blood Innate Interferon-γ Responses and Loss of Lung Function



Mechanisms

Do wheezing RV infections in early life *cause* asthma?

Host Factors

↓ antiviral responses

↓ lung function

Genetic polymorphisms

Asthma

Abnormal Host

Mechanisms

- Airway epithelial cells[1]
  - Normal: apoptosis
  - Asthma: viral replication
- Immune dysregulation[1-4]
  - Altered innate immune responses
    - Type 1-3 interferons (α, β, γ, λ)
  - Fc ε R1 numbers and bridging on antigen-presenting cells[4]
- Genetic polymorphisms[5]
  - CD14_159 and Toll 3 receptors

1. Contoli M et al. Nat Med 12:1023, 2006
2. Wark PA et al. J Exp Med 201:937, 2005
3. Copenhaver CC et al. AJRCCM 170:175, 2004
4. Gill M et al. JI 184:5999, 2010
5. Hewson CA et al. J Virol 79:12273, 2005
6. Martin AC et al. AJRCCM 173:617, 2006

Normal Host

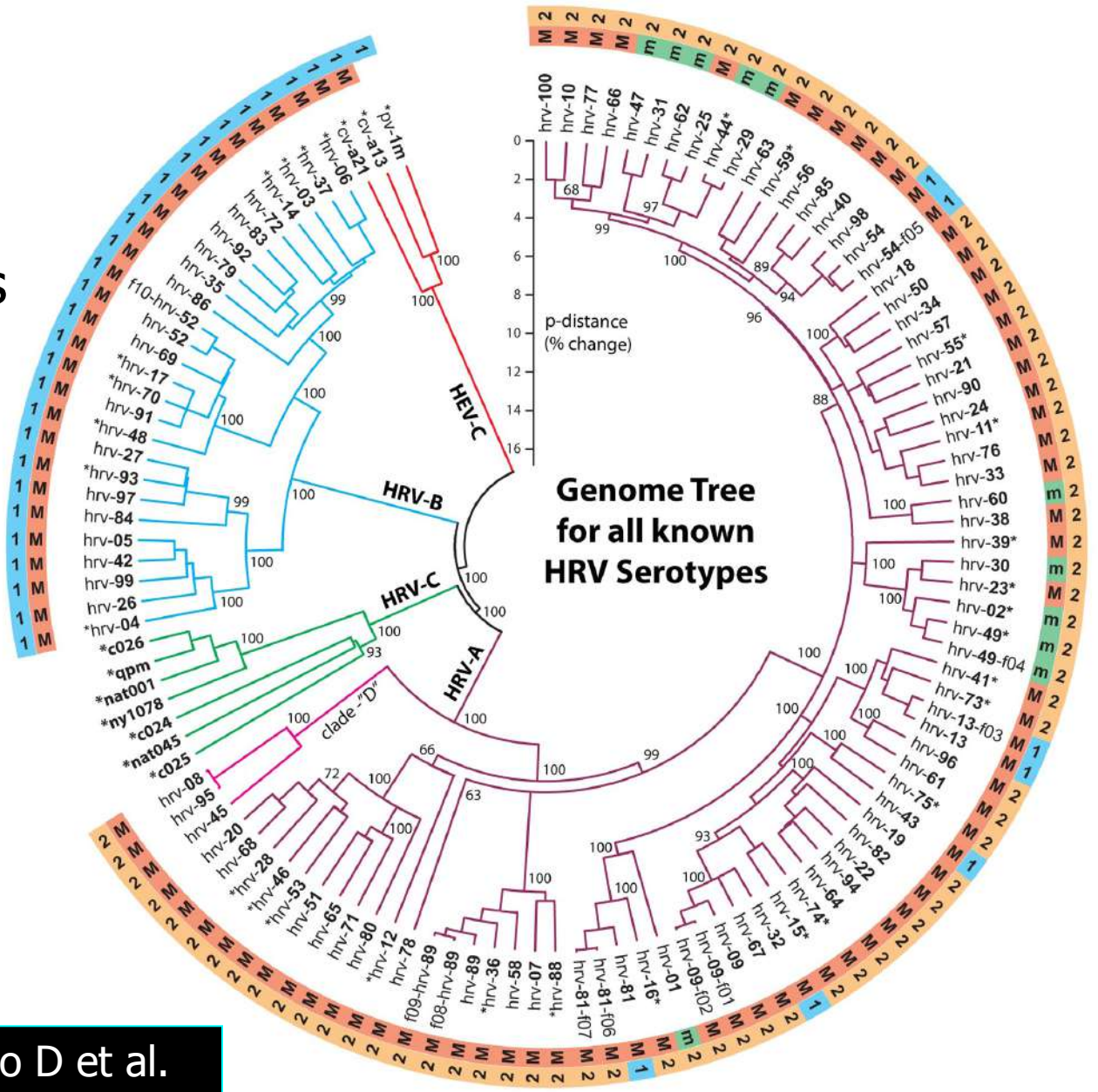
Asthma

Virus Factors

Lung/Airway damage

Virulent strains?

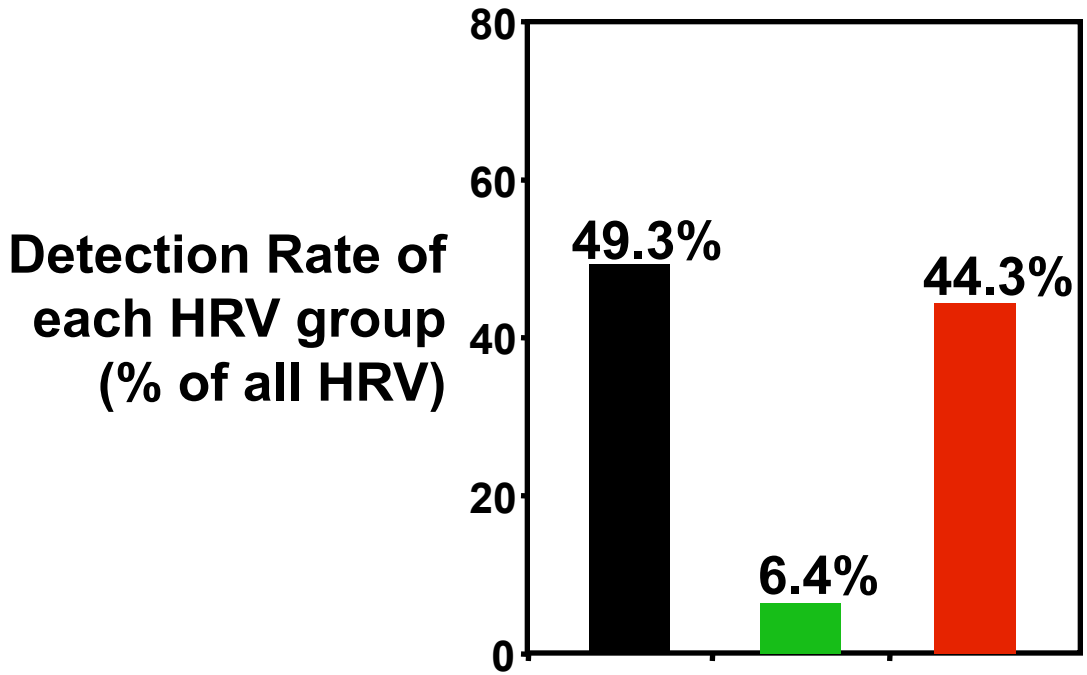
Sequencing and Analyses of All Known Human Rhinovirus Genomes Reveals Structure and Evolution



Palmenberg A and Spiro D et al.
Science 2009;324:55-59

HRVA & HRVC are similarly common in infants. Together, they account for 94% of HRV infections.

456 HRV were typed in 451 HRV-positive samples



	HRVA	HRVB	HRVC	
# of Isolate	225	29	202	Total=456
# of strain	45	8	35	Total=88

HRV Strain Virulence

HRV-C and Asthma Exacerbations

- Prospective population-based surveillance[1]

  Nashville TN and Rochester NY

  1052 children age <5 yrs hospitalized with ARI or fever

  HRV-C vs. HRV-A:

  - ↑ discharge diagnosis of asthma (55% vs 36%, *P* = .022)

- ED Asthma Study (2-16 y/o)[2]

  Perth, Australia

  HRV C detected in 59% of children:

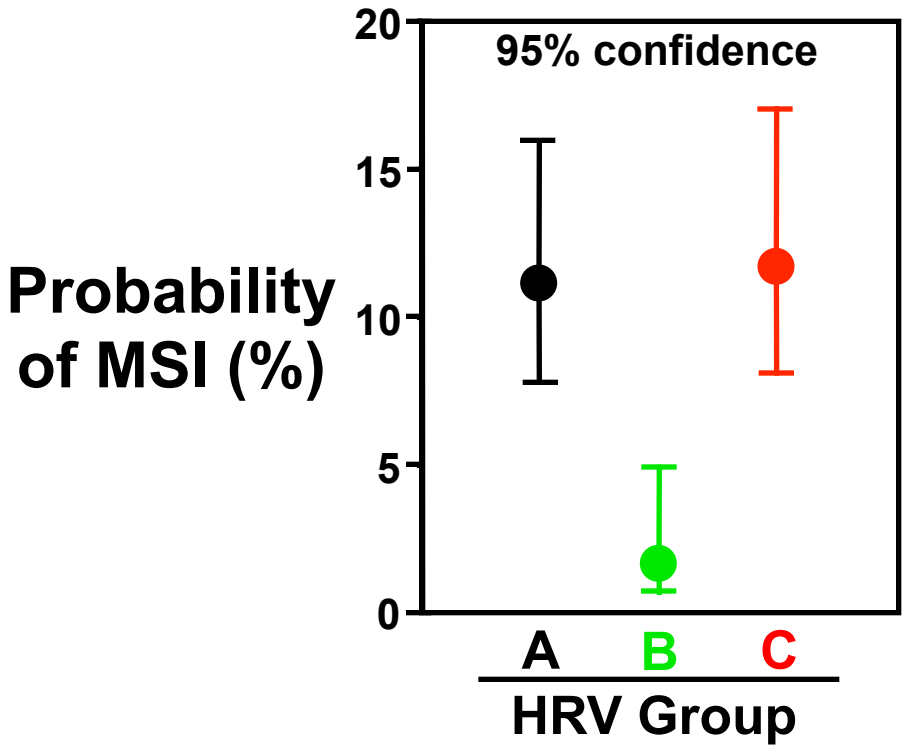
  - ↑ severity in HRV C vs. A or B

1 Miller EK et al. JACI 2009
2 Bizzintino J et al. ERJ 2011

The probability of inducing MSI is similar for HRVA & HRVC infections that is significantly higher than that of HRVB

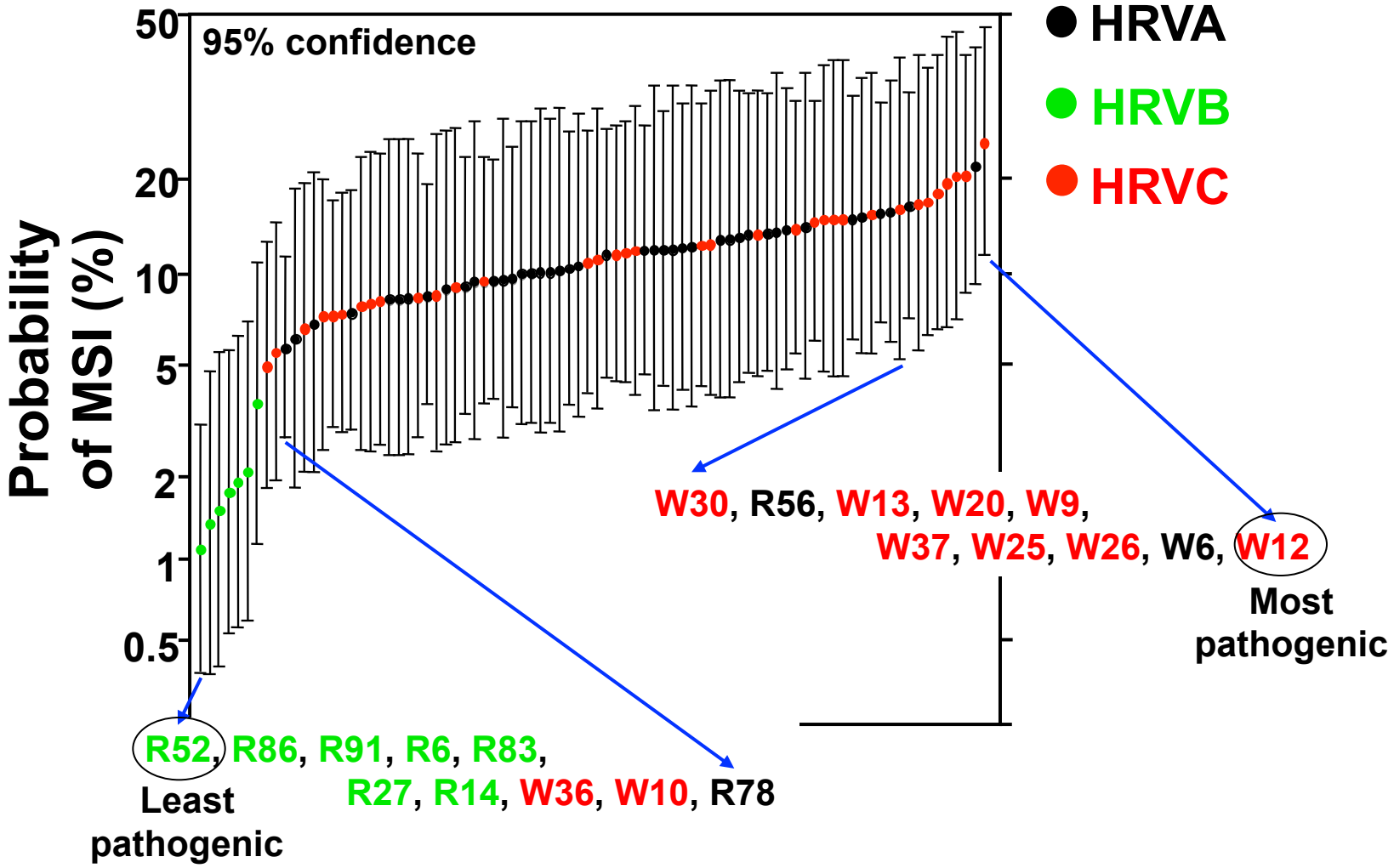
367 HRV only infection

MSI = Moderate-Severe Illness



Probability of inducing MSI varied with HRV strain

84 serotypes/strains (367 HRV only infections)



Gene by environment interactions

GWAS and 17q21

- Two large meta-analyses of asthma GWAS have recently provided strong evidence for involvement of specific genes in asthma risk: GABRIEL and EVE

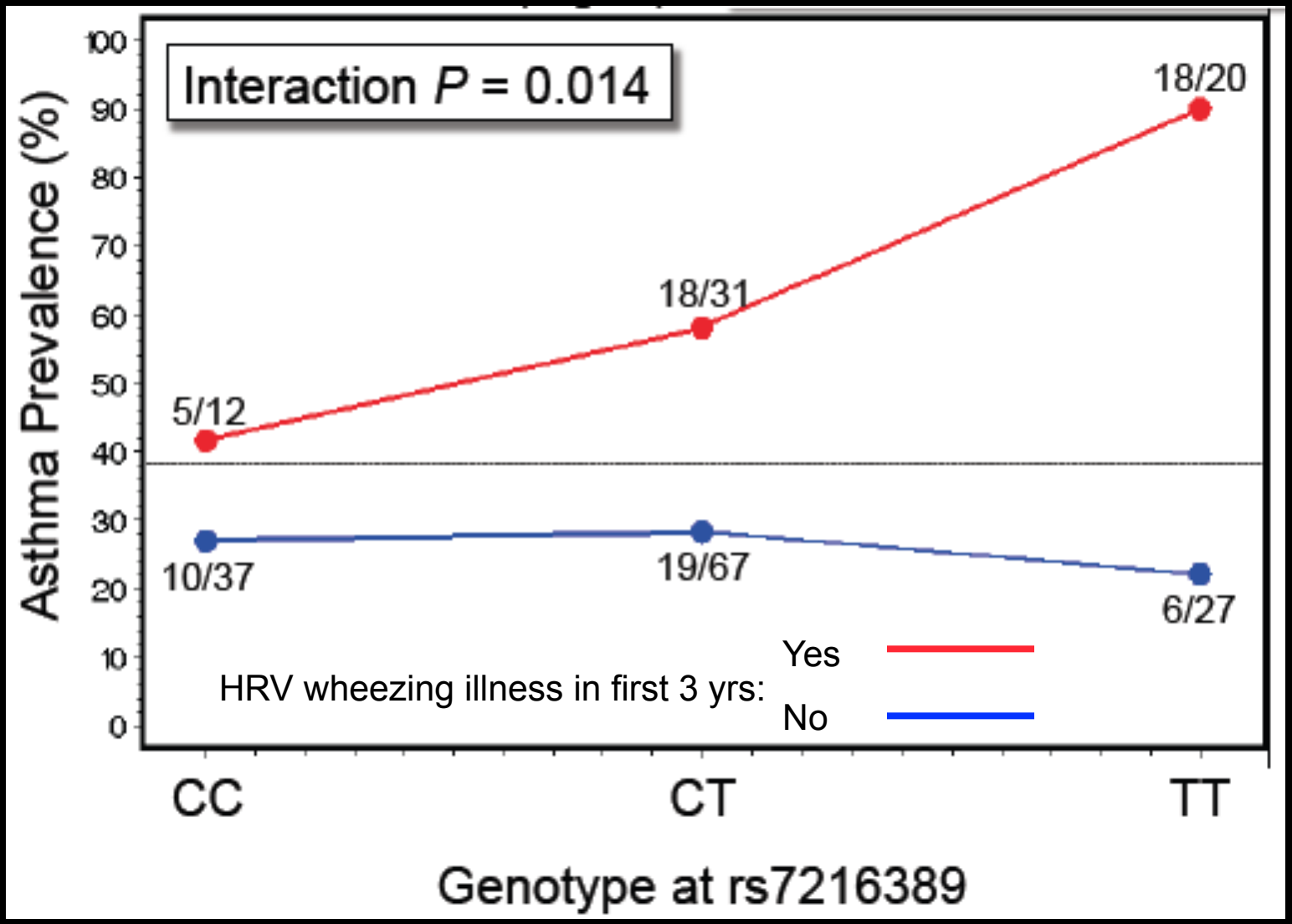
- Variation at a locus spanning five genes on chromosome 17q21, including the *ORMDL3* gene yielded the most significant association

- The 17q21 locus is the most replicated asthma locus and represents the *most significant genetic risk factor for childhood asthma* known to date

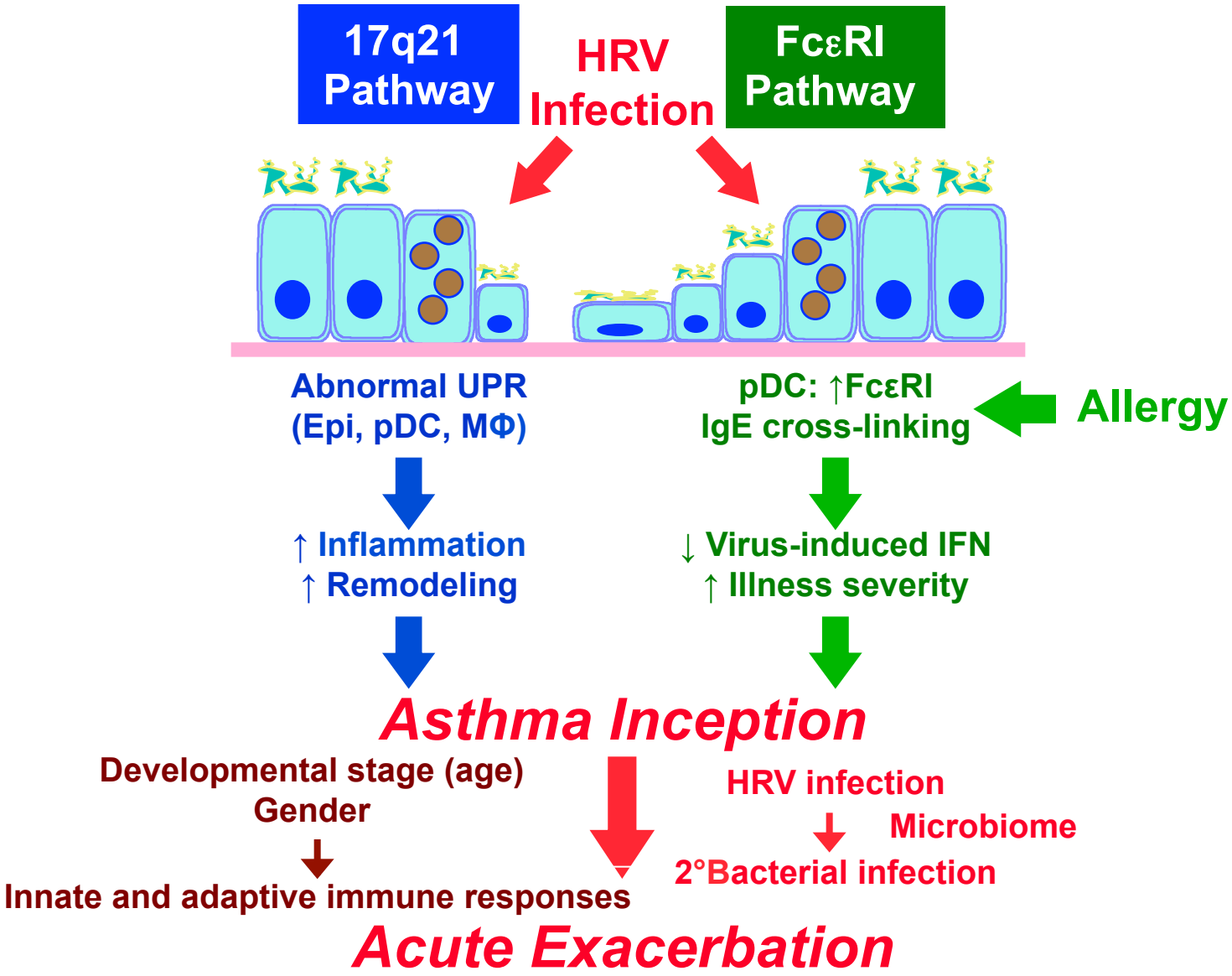
17q21 Genotype and HRV Wheezing Illnesses

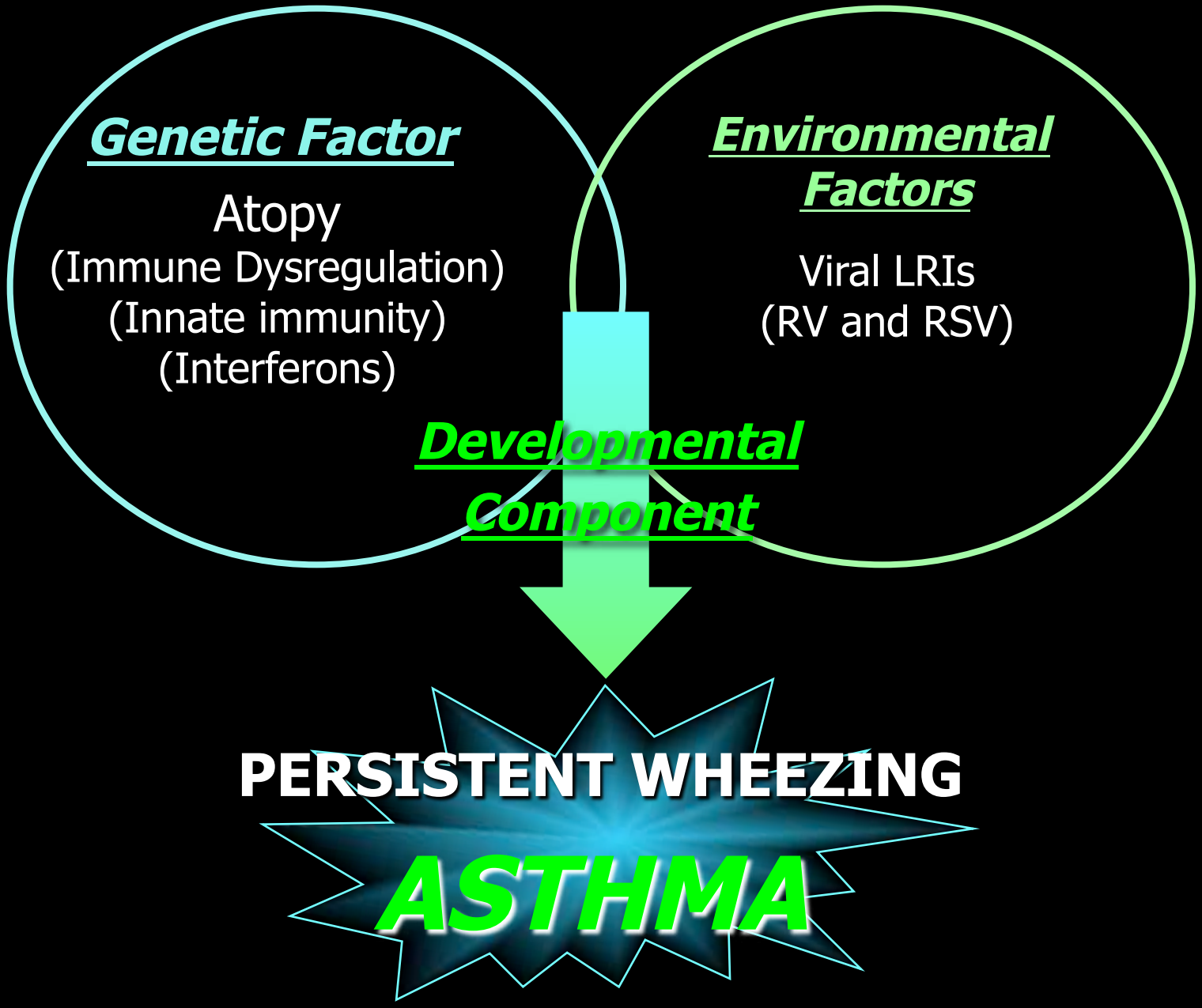
- COAST studies of asthma candidate genes revealed significant associations between genotypes at the 17q21 asthma-susceptibility locus (rs7216389) and:
  - Asthma (p=0.0059)
  - The number of moderate-to-severe wheezing illnesses with human rhinovirus infection (HRV wheezing illness) in the first 3 years of life (p=0.00070)
  - Not with allergic sensitization (p=0.69) or with respiratory syncytial virus (RSV) wheezing illness (p=0.26)

Gene by Environment Interactions



This SNP is located in an intron of GSDML and is an eQTL for both ORMDL3 and GSDML.


17q21 Pathway
HRV Infection
FcεRI Pathway
Abnormal UPR (Epi, pDC, MΦ)
pDC: ↑FcεRI IgE cross-linking
Allergy
↑ Inflammation ↑ Remodeling
↓ Virus-induced IFN ↑ Illness severity
Asthma Inception
Developmental stage (age) Gender
Innate and adaptive immune responses
HRV infection
Microbiome
2°Bacterial infection
Acute Exacerbation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