Leveraging the Genetics of *Racially Mixed* Children to Advance Precision Medicine

*Esteban González Burchard, M.D., M.P.H.*
United States 2015

- White: 81.7%
- Latino: 17.3%
- African American: 12.8%
- Asian: 3.9%
- American Indian and Alaska Native: 1.2%
- Multiracial: 1.0%
- Native Hawaiian and Other Pacific Islander: 0.2%

U.S. Population, 2015. 318.7M
SAMPLING BIAS
Most genome-wide association studies have been of people of European descent.

96% European descent

4% Non-European descent
NIH-Funded Pulmonary Publications 1993-2013

95% of study populations are of European origin

Publications including minority participants (%)

Year of publication

Burchard et al. AJRCCM 2015;191:514-21
Lung research survey highlights lack of minority subjects in many biomedical studies
Making Precision Medicine

Socially Precise
What is asthma?

- Tightening of Airways
- Airway Remodeling
- Thick Mucous Production
- Acute and Chronic
  - Wheezing
  - Coughing
  - Shortness of Breath
Most Disparate Common Disease

- Asthma
- Coronary heart disease
- Childhood obesity
- Type 2 diabetes
- COPD
- Adult obesity

Oh et al. *AJRCCM* (2016)
Asthma Affects ~334M Globally

**Prevalence**

- **Mexican American**: 10%
- **Caucasian**: 13%
- **African American**: 16%
- **Puerto Rican**: 26%

**Mortality**

- **Mexican American**: 11.3
- **Caucasian**: 15.0
- **African American**: 40.8
- **Puerto Rican**: 40.9


Asthma Affects ~334M Globally

Genetics vs. Environment?

Mortality

- Mexican American: 11.3
- Caucasian: 15.0
- African American: 40.8
- Puerto Rican: 40.9

Recruited > 10,000 minority participants
GALA & SAGE STUDIES
Local, national, international

1998 - present
Genomic
Clinical
Behavioral
Socio-demographic
Built environment
Geographic
Racially Mixed Populations

Rich resource for study of complex diseases
Ancestry of Latinos & African Americans

African Native American European

Admixed
Can We Leverage *Genetic Ancestry* to Scientific Advantage?
African Americans & Multiple Sclerosis
African Americans & Multiple Sclerosis

Disease Gene

European Marker
NAM ancestry: lower IgE levels in Latinos (6p21)

AFR ancestry: protective for asthma in Mexicans (6q15)
NAM ancestry increases asthma risk in Puerto Ricans (8q12)

NAM ancestry: lower BrCA risk in Latinas (6q25)
Locus Specific Ancestry

- NAM ancestry: lower IgE levels in Latinos (6p21)
- AFR ancestry protective for asthma in Mexicans (6q15)
- NAM ancestry: lower BrCA risk in Latinas (6q25)
Measuring Bronchodilator Response

Exhalation

Bronchodilator Response $\Delta FEV_1$

Flow (L/s)

Inspiration

FEV1

FVC
Ethnicity & Drug Response

% Reversibility in FEV\textsubscript{1} after albuterol

- Puerto Ricans (≤ 16 years old)
- Mexicans (≤ 16 years old)
- Puerto Ricans (> 16 years old)
- Mexicans (> 16 years old)

Mean ± S.E.

\( p = 0.0002 \)

\( p = 0.0003 \)
Children with Moderate-to-Severe Asthma

Drug response (Delta FEV%)

- Puerto Ricans
- African Americans
- Mexicans

Good drug response

Naqvi, M, J. of Asthma, 2007
Black Box Warning

“In African Americans, asthma-related deaths occurred at a higher rate in patients treated with Salmeterol than those treated with placebo (..relative risk: 7.26..)…”
Whole genome sequencing study on bronchodilator response in minority children

UCSF Asthma Collaboratory
Whole genome sequencing

1,500 minority children

Albuterol response
4.1 – 5.3 million variants/sample

66 million loci jointly called in 1484 samples
(PASS FILTER)
BDR Association

\[ \text{BDR} = \text{Variants} + \text{Age} + \text{Sex} + \text{BMI} + \text{Global Ancestry} \]

**Individual effects**
- PLINK
- Common variants
  - MAF > 1%
- Logistic regression

**Combined effects**
- SKAT-O
- Rare variants
- Group variants by sliding windows
Cosmopolitan, Common Variants

CTNND2/DNAH5 (Intergenic) 
\( p=3.91\times10^{-8}, \ OR=1.62 \)

\( p=5\times10^{-8} \)
**Ethnic-specific Rare Variants, Combined Effects**

**Puerto Ricans**
- chr7 FOXK1

**African Americans**
- chr1 NEGR1

**Mexican**
- chr2 FHL2, KCNS3

SKAT-O, 5kb sliding window, step of 500 bp
Ancestry-specific BDR Association

Native American Ancestry (Puerto Ricans)

Chr1
- CD2
- CD58
- SLC22A15
- VANGL1
Top BDR Genes & Clinical Traits

Lung capacity
COPD

Corticosteroids / BDR

Airway hyper-responsiveness

T-cell stimulation

**DNAH5**

**FOXX1**
**SLC22A15**

**FHL2**
**KCNS3**
**VANGL1**

**CD2**
**CD58**
BDR WGS Summary

• Racial differences in Drug Response

• WGS = novel, ethnic-specific associations
  – Impossible to identify with array data alone
Team Science

UCSF

Angel Mak
Marquitta White
Zachary Szpiech
Sam Oh
Ryan Hernandez
Noah Zaitlen
Dara Torgerson
Donglei Hu
Scott Huntsman
Celeste Eng
Sandra Salazar
Asthma Collaboratory

Soren Germer
Karen Bunting
Robert Darnell
NYGC team

NIH
National Heart, Lung, and Blood Institute

TOPMed