FACTORS INFLUENCING PEDIATRIC ASTHMA

4/5/17
COMMUNITY-BASED INITIATIVE

- Chronic, intermittent
- Sometimes lifelong
- Often adequately controlled
- But often with serious morbidity/mortality
- Sometimes triggered by external environment
- Often worsened by tobacco smoke, air pollution
- More likely in families
COMMUNITY-BASED INITIATIVE

- Rae O’Leary, RRT, RN
- Respiratory Therapist
- Dr. James Wallace, PEDS Pulmonologist, Sanford
- Developed intensive educational program for children with asthma
- Not a controlled trial
- Dr. Amy Elliot solicited ideas for CRCAIH
CASE/CONTROL STUDY

- 108 CHILDREN BETWEEN 6 AND 17 YO WITH A DIAGNOSIS OF ASTHMA
- EACH MATCHED WITH 2 CHILDREN WITHOUT ASTHMA
- AIR ENVIRONMENT TESTS
- BLOOD TESTS FOR ALLERGIES, INFLAMMATION
- DNA TESTING
RANDOMIZED TRIAL

- Intensive Education to improve control (BREATHE), N=104
  - Systematic follow-up for intervention arm, open access to asthma educator
  - “Usual Care” for control arm, written asthma education materials at enrollment
  - Outcome measure is Emergency Room visits related to asthma
- DSMB committee established (infrequent in tribal research)
- No statistically significant effect seen; but those with intensive education slightly less likely to visit ER.
  - Fewer ER visits among controls
  - Slightly fewer recruited and 4 declined RCT participation
IMMUNE MEASURES

**hsCRP**

- Sensitivity to all tested individual allergens: mold, cat/dog, mite, cockroach was greater among cases compared with controls

**IgE**
IMMUNE MEASURES

Specific Sensitization

<table>
<thead>
<tr>
<th></th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOLD</td>
<td></td>
</tr>
<tr>
<td>CAT</td>
<td></td>
</tr>
<tr>
<td>COCKROACH</td>
<td></td>
</tr>
<tr>
<td>MITE</td>
<td></td>
</tr>
<tr>
<td>DOG</td>
<td></td>
</tr>
</tbody>
</table>

Axis Title

Case | Control
## PREVALENCE OF GENETIC VARIANTS

<table>
<thead>
<tr>
<th>dbSNP ID</th>
<th>Chromosome Band</th>
<th>Nearest Gene</th>
<th>Annotation</th>
<th>Alleles (major/minor)</th>
<th>Minor allele frequency*</th>
<th>95% CI</th>
<th>H-W p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2305480</td>
<td>17q21</td>
<td>GSDMB</td>
<td>missense</td>
<td>G/A</td>
<td>35.0%</td>
<td>31.2 - 38.7</td>
<td>0.674</td>
</tr>
<tr>
<td>rs7216389</td>
<td>17q21</td>
<td>GSDMB</td>
<td>intronic</td>
<td>T/C</td>
<td>39.6%</td>
<td>35.8 - 43.4</td>
<td>0.872</td>
</tr>
<tr>
<td>rs8076131</td>
<td>17q21</td>
<td>ORMDL3</td>
<td>intronic</td>
<td>A/G</td>
<td>34.4%</td>
<td>30.7 - 38.2</td>
<td>0.512</td>
</tr>
<tr>
<td>rs4795405</td>
<td>17q21</td>
<td>LRRC3C</td>
<td>intronic</td>
<td>C/T</td>
<td>37.9%</td>
<td>34.1 - 41.7</td>
<td>0.792</td>
</tr>
<tr>
<td>rs9303277</td>
<td>17q21</td>
<td>IKZF3</td>
<td>intronic</td>
<td>C/T</td>
<td>39.0%</td>
<td>35.1 - 42.9</td>
<td>0.705</td>
</tr>
<tr>
<td>rs1558641</td>
<td>2q11.2</td>
<td>IL1R1</td>
<td>5’ upstream</td>
<td>G/A</td>
<td>4.6%</td>
<td>3.0 – 6.3</td>
<td>0.088</td>
</tr>
<tr>
<td>rs10056340</td>
<td>5q21</td>
<td>SLC25A46-TSLP</td>
<td>intergenic</td>
<td>T/G</td>
<td>16.5%</td>
<td>13.6 – 19.3</td>
<td>0.317</td>
</tr>
<tr>
<td>rs6871536</td>
<td>5q31</td>
<td>RAD50</td>
<td>intronic</td>
<td>T/C</td>
<td>15.2%</td>
<td>12.4 – 18.0</td>
<td>0.596</td>
</tr>
<tr>
<td>rs928413</td>
<td>9q21</td>
<td>IL33</td>
<td>5’ upstream</td>
<td>A/G</td>
<td>8.4%</td>
<td>6.2 – 10.5</td>
<td>0.541</td>
</tr>
<tr>
<td>rs2155219</td>
<td>11q13.4</td>
<td>EMSY-LRRC32</td>
<td>intergenic</td>
<td>G/T</td>
<td>47.3%</td>
<td>43.4 – 51.2</td>
<td>0.781</td>
</tr>
</tbody>
</table>
PREVALENCE OF GENETIC VARIANTS
# EFFECTS OF GENETIC VARIANTS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.909</td>
<td>0.833 - 0.992</td>
<td>0.033</td>
</tr>
<tr>
<td>Body-mass index (BMI) Kg/m²</td>
<td>3.219</td>
<td>1.204 - 8.610</td>
<td>0.020</td>
</tr>
<tr>
<td>&gt; one specific antibody over detection limit</td>
<td>3.889</td>
<td>2.370 - 6.381</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Above 3 covariates plus genetic variants

| rs2305480, 17q21, A allele | Additive | 0.635 | 0.434 - 0.927 | 0.019 |
| rs7216389, 17q21, C allele | Additive | 0.681 | 0.472 - 0.982 | 0.040 |
| rs8076131, 17q21, G allele | Additive | 0.668 | 0.459 - 0.971 | 0.035 |
| rs4795405, 17q21, T allele | Additive | 0.680 | 0.469 - 0.985 | 0.041 |
| rs9303277, 17q21, T allele | Additive | 0.648 | 0.447 - 0.940 | 0.022 |
| rs1558641, 2q11.2, A allele | Additive | 1.044 | 0.457 - 2.386 | 0.918 |
| rs10056340, 5q21, G allele | Additive | 2.020 | 1.283 - 3.180 | 0.002 |
| rs6871536, 5q31, C allele | Additive | 0.968 | 0.591 - 1.585 | 0.896 |
| rs928413, 9q21, G allele  | Additive | 1.187 | 0.634 - 2.222 | 0.592 |
| rs2155219, 11q13.4, T allele | Additive | 1.206 | 0.842 - 1.729 | 0.306 |
1 SNP from 5q21 locus genotyped all participants

- rs10056340
  - Intergenic, between *SLC25A46* and *TSLP*
- *SLC25A46*
  - solute carrier family 25 member 46
  - promotes mitochondrial fission and prevents hyperfilamentous mitochondria
- *TSLP*
  - thymic stromal lymphopoetin
  - promotes T helper, type 2 (TH2) response seen in asthma and other inflammatory diseases
GENES AT 17q21

- 5 SNPs from 17q21 locus genotyped all participants
  - rs7216389, GSDMB gene, "gasdermin B", intronic
    - Regulation of apoptosis in epithelial cells
  - rs2305480, GSDMB gene, coding, missense
  - rs8076131, ORMDL3 gene, intronic
    - "sphingolipid biosynthesis regulator 3"
      - possible role in Ca++ signaling, lymphocyte activation
  - rs4795405, LRRRC3C gene, intronic
    - immune modulator
  - rs9303277, IKZF3 gene, intronic
    - transcription factor regulating lymphocyte development
Calcium-Sensing Receptor

CaSR gene on chromosome 3, not tested in present study
Calcilytics: e.g. NPS89636, used in osteoporosis treatment

ASTHMA
Calcium-sensing receptor antagonists abrogate airway hyperresponsiveness and inflammation in allergic asthma


Sci. Transl. Med. DOI: 10.1126/scitranslmed.aaa0282
3/1/16, NIMHD approves Joe Yracheta’s training grant for ancillary study of immune factors among FIPA participants

- leveraging:
  - Joe’s extensive knowledge of genetics
  - MBIRI’s MagPix instrument
  - repository of FIPA samples

Congratulations Joe!

Thanks NIMHD and CRCAIH!
TRANSLATIONAL EFFORTS

• Completed or in process, 2017
  – PRESENTATION OF FINDINGS TO THE LOCAL MEDICAL STAFF, 9/22/15
  – REVIEW AND APPROVAL OF MANUSCRIPTS BY TRIBAL GOVERNMENT
  – PRESENTATION AT AAIP, 7/31/15
  – PARTICIPATION IN CRST RESEARCH CONF, 4/10/15, 3/24/16
  – ENGAGEMENT WITH INMED, HIGH SCHOOL AND SUMMER ENRICHMENT PROGRAMS
  – STUDENT POSTER PRESENTATIONS:
    • INBRE, Grand Forks, ND, 10/23/15
    • CCCC, Fort Totten, ND, 4/1/16
Genetics Demonstrations at tribal colleges and schools
- Willing students collect their own DNA
- Test their ability to taste a specific substance (PTC)
- Test their DNA for the variant that allows tasting of PTC
- Expected correlation between genotype and phenotype?
- Ethics and potential career/business opportunities in genetics
- Pre and Post survey to evaluate attitude and knowledge about genetics (knowledge post test)

One tribal college and ~20 INMED students in 2014
INMED, Duluth CAIMH, Sanford Research, TMCC, 2015
- 57 students participated

NDSU, 2016, SURP program, 6 students
Immune measures

Genetic effects
- under review at Annals of allergy, Asthma and Immunology
- Lead: Best, LG

Indoor air quality
- Lead: Yracheta, Joseph

Pulmonary function testing
- Lead: O’Leary, Rae

Social determinants of health
- Lead: Kinghorn, Breanna

Recruitment and Retention
- Lead: O’Leary, Rae
STUDENT RESEARCHERS

- Obtain informed consent from participants
- Collect samples, analyze DNA
- Research literature, manuscript prep
- Teach other students about their experience
- Total of 37 SRAs involved with program to date
  - 21 Completing BS or greater in nursing, social work, secondary science education, physical therapy
  - 1 Physician Assistant
  - 1 Medical School Student, 2\textsuperscript{nd} YEAR
- First lab tech, 2004, pending PhD in Epidemiology at U. Minn
NEW INITIATIVES

• Minority Supplement to Strong Heart Study (Dakota Center) for Kaytlin Lawrence
  – 2nd year Medical Lab Tech at University of Mary
  – Previously worked as summer intern for MBIRI
  – extending recruitment of SHS participants to investigate pre-eclampsia
  – Obtaining additional instrumentation (thermocycler) through SPHERE, Precision Medicine grant at Stanford University
REAL TIME ANALYSIS

- “Regular” PCR = run reaction, then analyze to see how much DNA was produced
- “Real-Time” PCR = run reaction and watch in “Real Time” how much DNA is produced cycle by cycle
NETWORKING

- Laboratory and student research assistants at Turtle Mountain Community College
- Univ. North Dakota, INBRE
- Sanford Research, CRCAIH
- Stanford University, SAIL Study
- Stanford University, Precision Medicine (SPHERE) grant
- Strong Heart Study, NHLBI
- YouTube “Red Talks”, NCAI
Acknowledgements

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  – Ms Rae O’Leary, Mr. Joe Yracheta, Kendra Enright, Terilynn Half Red
• Cheyenne River Sioux Tribe
• Cheyenne River Sioux Tribal Health Department
• Turtle Mountain Community College
• Indian Health Service, especially the Eagle Butte IHS Hospital and Staff
• The CRCAIH grant and Sanford Research
• The North Dakota INBRE program
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