Main Conclusions from Genetic Studies and Future Aspects:

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2011 Consensus Report

- Panel of 33 physicians (6 months)
- Conceptual Definition
  - “Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation”
- Pediatric and Adult EoE likely the same disease

2011 Updated Consensus Report

- Diagnostic Guideline
  - EoE is a clinico-pathologic disease
  - Clinically characterized by esophageal dysfunction
  - Pathologically 1 or more biopsies show eosinophil predominant inflammation (15+ eos in peak hpf)
  - Isolated to esophagus (need for other GI biopsies)
  - Other causes need to be excluded
  - EoE diagnosis made by clinicians
  - Rarely < 15 eos/hpf (if other path features are present)
Symptoms of EoE

EoE - Clinical manifestations

- Symptoms similar to those of GERD
- Histology does not respond to PPIs
- Age related differences in symptoms
- Symptoms may be intermittent
- Male > Female
- May progress to esophageal fibrosis and esophageal dysfunction if not managed appropriately.

<table>
<thead>
<tr>
<th>Age/Stage</th>
<th>Common Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>Food refusal, FTT, feeding intolerances/aversions</td>
</tr>
<tr>
<td>Children</td>
<td>Vomiting, dysphagia, abdominal pain, heartburn, regurgitation, feeding refusal/feeding aversions</td>
</tr>
<tr>
<td>Adult</td>
<td>Dysphagia, food impaction, heartburn, reflux</td>
</tr>
</tbody>
</table>

Furuta et al, Gastroenterology 2007
Spergel et al, J Pediatr Gastroenterol Nutr 2009

Types of Genetic Studies

- Candidate Gene
- Genomic Wide Association Studies

Genetics

- 3:1 male to female ratio
- Sibling recurrence risk of 80 (asthma-2)
- Predominant Caucasian
- Familial Recurrence in 7% of patients
Eotaxin-3

- Increased in EoE
- TGF-β1
- SMAD-2/3
- VCAM-1
- Decreases after topical CS
- Examined SNP variants in TGF-β1 promoter (−509)
- 20 EoE patients stratified
- 7 non-responders
- 13 responders

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TGF-β SNP Analysis


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Table 2: Patient genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonresponder</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Responder</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>
GWAS
Analysis on Illumina 550K BeadChip done at Center for Applied Genomic, The Children’s Hospital of Philadelphia, Univ. of Pennsylvania School of Medicine

<table>
<thead>
<tr>
<th></th>
<th>CCHMC</th>
<th>CHOP</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>181</td>
<td>170</td>
<td>2096</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>11.3 ± 10.4</td>
<td>7.8 ± 4.9</td>
<td>8.54 ± 5.65</td>
</tr>
<tr>
<td>Male</td>
<td>70%</td>
<td>75%</td>
<td>50.4%</td>
</tr>
<tr>
<td>Atopy</td>
<td>73%</td>
<td>72%</td>
<td></td>
</tr>
</tbody>
</table>

Eosinophils confirmed by biopsy with > 24 eos/hpf
Controls = all cases of PPI — CCHMC cohort only
All Patients were self-reported Caucasians

GWAS Analysis

TSLP-thymic stromal lymphopoietin
- IL-7-like cytokine
- Expressed in thymus and peripheral tissues
- Potent and maturation of dendritic cells
- Primes TH cells into TH2 cells
- TSLP is ↑ in lesional skin in AD and the asthmatic lung.
- In murine models, ↑ TSLP production from skin keratinocytes correlates ↑ the attracting chemokine production and epicutaneous sensitization
TSLP and WDR36 Expression

Risk Factors for EoE

<table>
<thead>
<tr>
<th>Gene</th>
<th>Loci</th>
<th>% in Normal</th>
<th>% in EoE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSLP</td>
<td>rs3806932</td>
<td>54</td>
<td>66</td>
<td>1e-9</td>
</tr>
<tr>
<td>TSLP-R</td>
<td>rs3806932</td>
<td>44</td>
<td>53</td>
<td>0.039</td>
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<tr>
<td>Eotaxin-3</td>
<td>rs1910209</td>
<td>3.6%</td>
<td>14.7%</td>
<td>0.010</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>rs1048496</td>
<td>0.02</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Other Genetic Risk Factors
- Dock 8
  - 2/11 pts in series
- IPEX
  - Case report of one patient with EoE
Other Genes

- Filaggrin
  - p=0.018 rs=61816761

TSLP Risk Factor

- Asthma
  - 1.1x10^-5 Celedron et al. Nature Genetics 2012

- Allergic Rhinitis
  - 5 x 10^-5 Ramasamy et al J Allergy Clin Immunol 2011

Updated GWAS on EoE

- 900 patients
- TSLP now 10^-11
- 2 new regions:
**Pathway analysis**
- Included all SNPs Pval < 0.001
- Top pathway
  - Inflammatory Disease, Respiratory Disease, Cell-To-Cell Signaling and Interaction
  - Connective Tissue Disorders
- Disease pathways:

**Collaborators**

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**TSLP and basophils in EoE**
- TSLP promotes matures basophil survival and new basophil population with TSLP-R

Siracusa et al, Nature 2011
**The role of basophils in EoE**

ST2/T1, also IL33 receptor, leads to basophil activation.

IL-33 leads to Eosinophil, TH2, mast cells and basophil activation.

Siracusa et al, Nature 2011
Future Aspects
- Genotype-Phenotype data
  - TSLP
  - TGF-Beta
- New molecular targets for therapy
  - Inflammatory pathway
  - Fibrosis pathway

Conclusion
- Multi-factorial Disease
- Male, Predominant
- TSLP strongest identified gene

If interested in sending samples, please contact me
  - Spergel@email.chop.edu