Allergy and Immunology

RESEARCH AND TRAINING DETAILS

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CLINICAL ACTIVITIES AND TRAINING

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Research Highlights
Cincinnati Children's Inaugural Member of the Food Allergy Research & Education Clinical Network

The Food Allergy Research & Education (FARE) Clinical Network is an initiative that aims to accelerate the development of drugs for patients with food allergies, as well as improve the quality of care for this serious illness. Cincinnati Children's became a FARE Center of Excellence and an inaugural member of the FARE Clinical Network in large part through divisional efforts and the Food Allergy Program of the Division of Allergy and Immunology.

Excellence of Division Trainees and Junior Faculty

The Division of Allergy and Immunology is proud of the excellence of its undergraduate, graduate, postdoctoral, and clinical trainees and junior investigators. Several have been recognized for their achievements throughout the year. Rahul D'Mello, a MD, PhD, student in the Rothenberg Lab, won first place at the 2015 Graduate Student Research Forum poster competition at the University of Cincinnati College of Medicine. Nurit Azouz, a research fellow in the Rothenberg Lab, won the first prize at the 2015 Annual Scientific Symposium of the Digestive Health Center. Masashi Yukawa, a postdoctoral fellow in the Barski Lab, and his mentor, Artem Barski, PhD, were awarded a Careers in Immunology Fellowship award by the American Association of Immunologists (AAI). Ting Wen, PhD, a research instructor in the division, won the first place for 2014 Outstanding Poster Presentation at the 2014 Ohio River Valley Cytometry Association meeting and was awarded a Digestive Health Center Pilot and Feasibility Award and a 2015 APFED HOPE Pilot Grant for his research investigating esophageal lymphocytes in eosinophilic esophagitis. Assistant professor Patricia C. Fulkerson, MD, PhD, was awarded a 2015 Young Physician-Scientist Award by the American Society for Clinical Investigation Council and a Trustee Award by the Trustee Award & Procter Scholar (TAPS) Program at Cincinnati Children's.

Clinical Director Contributes to Peanut Desensitization Study

Our division and center has been one of the top enrolling centers in the multi-center peanut desensitization study using the Viaskin patch. This important clinical research could not have been accomplished without the dedicated efforts and expertise of our clinical research team, led by our division’s director of clinical services, Amal H. Assa’ad, MD, and the support of the division and the individuals and families who entered the study. DBV technologies, the sponsor of the study, announced in a press release that the primary endpoint for this phase IIb clinical trial has been met. The division has conducted four clinical trials with two methods of desensitization, one oral and one by a patch applied to the skin. Both studies yielded data supporting a high rate of success and captured national and international attention.

Research Director Receives Mentoring Achievement and Research Awards

Our division's director of research, Simon P. Hogan, PhD, was recognized for his dedicated efforts with the Mentoring Achievement Award in the Fourth Annual Faculty Awards by Cincinnati Children's. (Watch the video). His excellence in mentoring is coupled to his merit in research and collaboration. He was awarded a 2015 FARE Investigator in Food Allergy Award, a Mid-Career Investigator Award from Food Allergy Research & Education (FARE), that will support Hogan in identifying the key proteins and cells that cause the blood vessel fluid leak leading to severe anaphylaxis triggered by foods. Furthermore, divisional collaborators Hogan and Yui-Hsi Wang, PhD, and national collaborator Rodney Newberry, MD, (Washington University in St. Louis) were awarded a multi-principal investigator R01 grant from the National Institute of Allergy and Infectious Diseases (NIAID) for their project investigating goblet cell antigen passages in food allergy.

Furthering Data Analysis of Next-Generation Sequencing to Facilitate Research

Assistant professor Artem Barski, PhD, and Andrey Kartashov, MS, have developed a user-friendly, integrated platform for analyzing the “big data” derived from genome and epigenome sequencing, which was recently described in Genome Biology. The recent proliferation of next-generation sequencing (NGS)–based methods for analysis of gene expression, chromatin structure and protein–DNA interactions has opened new horizons for molecular biology. However, the sheer volume of the data obtained from sequencing requires computational data analysis, and the bioinformatic and programming expertise required for this analysis is usually absent in typical biomedical laboratories, resulting in data
inaccessibility or delays in applying modern sequencing-based technologies to pressing questions in basic and health-related research. Barski and Kartashov collaboratively developed a new approach and platform, called “BioWardrobe”, to facilitate the analysis and utilization of both newly generated and publically available datasets. More than twenty labs at Cincinnati Children’s currently use BioWardrobe, including the Barski Lab, Fulkerson Lab, Grimes Lab, Hogan Lab, Namekawa Lab, Rothenberg Lab, and Singh Lab, as well as national colleagues at New York University School of Medicine (Cuddapah Lab) and Cedars-Sinai (Berman Lab). Primary research using the BioWardrobe platform has recently been published in several journals, including Developmental Cell and Mucosal Immunology, and more are forthcoming. Barski and Kartashov intend to continue to improve BioWardrobe using an Innovative Core Facility grant provided by the University of Cincinnati’s Center for Clinical and Translational Science and Training (CSTST) and employing BioWardrobe in their own research on epigenetic regulation in the immune system (e.g. Cincinnati Children’s 2015 Trustee Award to Barski, "Epigenetic Suppression of IL4 Expression in T Cells") and collaborative projects with other investigators. The work to develop BioWardrobe was supported in part by the Cincinnati Children’s Research Foundation, NHLBI NIH Career Transition Award (K22 HL098691 to Artem Barski) and the Center for Clinical and Translational Science and Training (CSTST) Innovative Core Facility grant (NIH/NCRR Institutional Clinical and Translational Science Award, 8UL1TR000077-06). (Read the press release.)

Cincinnati Children’s Receives NIH Grant To Lead Multicenter Consortium on Eosinophilic Disorders

Cincinnati Children’s has received a five-year, $6.25 million grant from the National Institutes of Health to lead a consortium of organizations from around the country that will conduct clinical research into eosinophilic gastrointestinal disorders and train investigators in how to conduct clinical research—the Consortium of Eosinophilic Gastrointestinal Disease Researchers CEGIR. This NIH grant (U54AI117804) is believed to be the first to establish a network focusing on the three distinct diseases of eosinophilic esophagitis, eosinophilic gastritis and eosinophilic colitis and is funded by the Office of Rare Diseases Research, which is part of the NIH’s National Center for Advancing Translational Sciences, as part of the Rare Disease Research Network and is funded by the NIAID, NIDDK and NCATS at the NIH. CEGIR will further research and clinical expertise, train clinical investigators, pilot clinical research projects and provide access to information related to eosinophilic disorders for basic and clinical researchers, physicians, patients and the lay public. Marc Rothenberg, MD, PhD, director of the Division of Allergy and Immunology and the Cincinnati Center for Eosinophilic Disorders at Cincinnati Children’s, is the principal investigator. To coincide with Rare Disease Day® 2015, CEGIR launched a new Patient Contact Registry for Rare Eosinophilic Gastrointestinal Diseases. (Read the press release)

Environment Plays Bigger Role than Genetics in Food Allergic Disease Eosinophilic Esophagitis

In an international collaboration involving multiple institutions and led by Marc Rothenberg, MD, PhD, director of the Division of Allergy and Immunology and the Cincinnati Center for Eosinophilic Disorders, researchers at Cincinnati Children’s quantified the risk associated with genes and environment on familial clustering of eosinophilic esophagitis (EoE). The researchers constructed and examined patient family pedigrees of patients with EoE and their first-degree relatives (nuclear family analysis) and of patients with EoE and their identical or fraternal twin/triplets (twin analysis). Using these two distinct analyses, they determined that 2.4% of siblings and 1.8% of first-degree relatives of patients with EoE also had EoE. This study, published in the Journal of Allergy and Clinical Immunology and first authored by Eileen S. Alexander, PhD, MS, BSN, RN, is the first EoE heritability study to analyze twins. This is a necessary step in separating the contribution of genetics from environment. It also identified a few environmental risk factors, including food allergies, high twin birth-weight difference, and self-reported penicillin allergy.

Anti–Interleukin 13 may have Clinical Utility in Treating Eosinophilic Esophagitis

Marc Rothenberg, MD, PhD, Ting Wen, PhD, and national and international researchers of eosinophilic disorders have
translated their pre-clinical findings by demonstrating that a humanized antibody against interleukin 13 (IL-13), called QAX576, is effective for the emerging food allergic disorder eosinophilic esophagitis (EoE). As reported in the *Journal of Allergy and Clinical Immunology* in 2015, adult patients received intravenous QAX576 or placebo every four weeks for three doses and were then followed for six months. The responder rate was 12.5% (90% confidence limit, 1% to 43%) with placebo, compared to 40.0% (90% confidence limit, 22% to 61%) with QAX576. Esophageal eosinophil counts decreased by 60% with QAX576 versus an increase of 23% with placebo, and the decrease was sustained up to six months. There was a trend for improved symptoms, particularly dysphagia. QAX576 improved expression of EoE-relevant esophageal transcripts, including eotaxin-3, peristin, and markers of mast cells and barrier function, for up to six months after treatment. The investigators found that QAX576 was well tolerated. Thus, this study provides proof-of-principle to support a long-standing theory of the Cincinnati Center for Eosinophilic Disorders—that anti–IL-13 may have clinical utility for the treatment of EoE and may have a persistent effect. The potential for persistent effect is especially promising as disease usually recurs after cessation of steroid or dietary treatment, the current standards of care for treatment of EoE.

**High-dose Fluticasone Effective Against Eosinophilic Esophagitis**

In another finding for eosinophilic esophagitis (EoE), the results of a clinical trial led by Marc Rothenberg, MD, PhD, director of the Division of Allergy and Immunology and the Cincinnati Center for Eosinophilic Disorders, and published in *Gastroenterology* showed that high doses of the corticosteroid fluticasone propionate halted the inflammation of eosinophilic esophagitis (EoE) in a number of people. The disease of some trial participants did not respond to fluticasone, however, even after six months of high-dose treatments, providing evidence that certain people have EoE that is steroid resistant. By analyzing gene expression in esophageal tissues, the scientists identified a cluster of genes that may help predict steroid responsiveness. The study was funded by a grant from the NIAID at the NIH. (Read the press release.)

**Parent-reported Symptoms Gauge Pathogenic Features of the Food Allergic Disease Eosinophilic Esophagitis in Children**

Researchers have identified that parent-reported responses to a questionnaire called the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS® v2.0) correspond to clinical and biologic features of eosinophilic esophagitis (EoE) – a severe and often painful food allergy that renders children unable to eat a wide variety of foods. This study, published online in *Journal of Allergy and Clinical Immunology*, was led by researchers at Cincinnati Children’s, including Marc Rothenberg, MD, PhD, director of the Division of Allergy and Immunology and the Cincinnati Center for Eosinophilic Disorders. The current focus for evaluating treatment for eosinophilic esophagitis involves looking at changes in the tissues and cells of the esophagus. However, to improve both clinical outcomes and patients’ quality of life, there is a need to objectively measure and consider both patients’ symptoms and how they feel, according to the research team. The authors of this study recruited pediatric patients with eosinophilic esophagitis. The PEESS® v2.0 questionnaire measured symptoms and their impact. On the basis of a previous study, the authors grouped these questions into four categories that represent the major symptom types observed in eosinophilic esophagitis—dysphagia, gastrointestinal reflux disease, nausea/vomiting, and pain. The study demonstrated that these four PEESS® v2.0 symptom categories were meaningful and that each corresponded with clinical symptoms of eosinophilic esophagitis. With the PEESS® v2.0 categories, researchers can better track disease activity in clinical settings, and this instrument can be used to test the impact and benefit of new therapies. The categories will also aid diet intervention and drug trials. Long term, this work may help identify the biologic pathways to target for intervention. The investigators are now working to get this questionnaire approved by the FDA. (Read the press release.)

**Significant Publications**

Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin*
Proton pump inhibitor (PPI)-responsive esophageal eosinophilia (PPI-REE) presents with similar clinical features to eosinophilic esophagitis (EoE) and is clinically, endoscopically and histologically indistinguishable from EoE. Whether PPI-REE reflects a GERD phenotype or shares an antigen-driven, T helper type 2–associated allergic pathogenesis similar to EoE was previously unknown. This transcriptomic study provides convincing evidence that PPI-REE is an EoE sub-entity with significant molecular overlap with EoE but that PPI therapy reverses nearly the entire allergic inflammatory transcriptome in PPI-REE. These expression data will inform about disease classification, molecular etiology and management strategies for patients with significant esophageal eosinophilia.


Although most prior research on eosinophilic gastrointestinal disorders has focused on eosinophilic esophagitis, partially because it has well-defined consensus diagnostic criteria, this recent investigation advances the understanding of eosinophilic gastritis through much-needed characterization of the fundamental molecular, histopathologic and clinical features of eosinophilic gastritis (EG). More specifically, the authors found that gastric tissue of patients with EG had a shared pattern of gene expression (EG transcriptome), as well as common cellular features including increased proliferating cells, mast cells, and FOXP3+ T cells. In addition, patients with EG frequently had blood eosinophilia and extra-gastric gastrointestinal eosinophilia. A clinical advance in this study was the determination that blood eosinophil levels correlate with the degree of tissue eosinophilia, raising hope for the value of this as a non-invasive biomarker. These findings will not only benefit clinical diagnosis and care but also serve as a platform for further research of this rare disorder.


This murine study provides mechanistic evidence that components of the innate and adaptive immune system, type 2 innate lymphoid cells (ILC2s) and acquired CD4-positive type 2 helper T cells, respectively, work cooperatively to exacerbate allergic airway disease in response to recurring antigen exposures. As these cells' roles in antigen-driven exacerbation of chronic murine allergic airway disease was previously understudied, these findings advance our insights into the underlying cellular molecular processes that drive allergic airway diseases such as asthma.


This investigation identifies an autocrine cytokine loop, involving CCL3 and CCR1, that is capable of sustaining eosinophil differentiation in the absence of interleukin 5 (IL-5) after a brief, initial IL-5 exposure. As IL-5 is known as a critical regulator of eosinophilia, this finding contributes greatly to elucidating prior suggestive evidence that IL-5 neutralization (e.g., anti–IL-5 clinical trials) is not sufficient to completely counteract eosinophilia in disease contexts and provides insights that will be of research and clinical utility.


Using whole-exome sequencing technology, Andrew W. Lindsley, MD, PhD, and colleagues identified a novel NFKB2 mutation in a pediatric patient with common variable immune deficiency (CVID) and the mutation-associated phenotype of impaired antibody production and T cell proliferation. Though dysregulated NFKB2 signaling has
previously been shown to cause humoral immune deficiency, the patient’s phenotype of combined immune deficiency with alopecia universalis and impaired T-cell antigen responses highlights a new role for NFKB2-mediated regulation of T cell activity.

Division Publications


42. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J


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**Faculty, Staff, and Trainees**

**Faculty Members**

**Marc E. Rothenberg, MD, PhD,** Professor  
*Leadership* Director, Division of Allergy and Immunology; Director, Cincinnati Center for Eosinophilic Disorders  
*Research Interests* Elucidating mechanisms, genetics, and novel therapies for allergic diseases with a focus on eosinophilic esophagitis.

**J. Pablo Abonia, MD,** Associate Professor  
*Research Interests* Investigates eosinophilic esophagitis (EoE) & focuses on informatics analysis of medical records related to eosinophilic gastrointestinal disease (EGID). In this capacity, he investigates the phenotypic subtypes of disease associated with EoE & EGID.

**Amal H. Assa’ad, MD,** Professor  
*Leadership* Clinical Director  
*Research Interests* Investigates food allergy (natural history of IgE-mediated food allergy, diagnostic tools, association with cardiovascular morbidity) and conducts clinical trials of novel therapies for atopic disorders (food allergy, eosinophilic disorders, asthma).

**Artem Barski, PhD,** Assistant Professor  
*Research Interests* Investigates chromatin biology and epigenomic and transcriptional regulation of immune responses and develops bioinformatic tools for epigenomic transcriptomic data analysis.

**Sheharyar Durrani, MD,** Assistant Professor  
*Research Interests* Implementing mobile health technology into the care of difficult-to-treat pediatric asthma.

**Thomas J. Fischer, MD,** Adjunct  
*Research Interests* Focuses on healthcare systems / economics (with special reference to pediatric allergy and immunology).

**Patricia C. Fulkerson, MD, PhD,** Assistant Professor  
*Research Interests* Researches the biology of the eosinophil-lineage committed progenitor (EoP). Aiming to identify novel therapeutic targets to block eosinophil production for the treatment of patients with eosinophilic disorders.

**Simon P. Hogan, PhD,** Associate Professor  
*Leadership* Research Director  
*Research Interests* Studies allergies, food allergies, eosinophil biology and gastrointestinal inflammation.

**Michelle B. Lierl, MD,** Adjunct  
*Research Interests* Investigates the role of basidiomycete and myxomycete fungal spores as aeroallergens, conducts allergen component testing for food allergies and participates in food allergy research to desensitize
patients to food allergens (e.g. peanut).

Andrew W. Lindsley, MD, PhD, Instructor
Research Interests Role of sphingolipids in the pulmonary inflammatory response, especially in asthma and during viral infections; Humoral immunity with a special interest in terminal B cell differentiation.

Santa J. Ono, PhD, Professor
Research Interests Focuses on the transcriptional regulation in the human immune system, mechanisms of mast cell-dependent inflammation on the ocular surface and the immune component of age-related macular degeneration.

Kimberly A. Risma, MD, PhD, Assistant Professor
Leadership Director, Allergy and Immunology Division Fellowship Program
Research Interests Develops novel diagnostic/therapeutic approaches to improve outcomes for children with hemophagocytic lymphohistiocytosis, an inflammatory disease caused by genetic defects in the cytotoxic pathways of natural killer cells and cytotoxic T lymphocytes

Yui-Hsi Wang, PhD, Assistant Professor
Research Interests Investigating how inflammatory mediators regulate the function of adaptive CD4+ T-helper cells and innate effector cells in order to understand whether the interplay between these cells contributes to allergic responses in the airway and gut.

Ting Wen, PhD, Instructor
Research Interests Molecular, cellular, and genetic pathogenesis of eosinophilic esophagitis, and its associated sub-entities, such as PPI-REE.

Nives Zimmermann, MD, Adjunct
Research Interests Focuses on deciphering the mechanisms of eosinophilia and eosinophil survival and death in allergic inflammation and asthma.

Joint Appointment Faculty Members

Alexandra H. Filipovich, MD, Professor (Hematology/Oncology Diagnostic Laboratory)
Research Interests Primary immunodeficiencies; BMT for primary immunodeficiencies; hemophagocytic lymphocytosis; post-BMT immune reconstruction.

Kenneth M. Kaufman, PhD, Professor (Division and Center for Autoimmune Genomics and Etiology)
Research Interests Focuses on understanding genetic disease mechanisms using high density SNP arrays and Next-Generation DNA sequencing technology.

Gurjit Khurana Hershey, MD, PhD, Professor (Asthma Research)
Research Interests Integrating clinical, translational and basic research to identify genetic & environmental factors that promote asthma, delineate the mechanisms underlying their contributions and develop new strategies for asthma prevention, management and treatment

Clinical Staff Members
- Benjamin P. Davis, MD, Staff Physician
- Harpinder K. Kalra, MD, Staff Physician

Trainees
- Michael Goodman, MD, PGY-6, Washington University, St. Louis, MO
- David Morris, MD, PGY-6, Wright State University, Detroit, MI
- Leilanie Perez-Ramerez, MD, PGY-6, University of Puerto Rico School of Medicine, San Juan, Puerto Rico
- Cecilia Nguyen, MD, PGY-5, Children's Mercy, Kansas City, KS
- Kari Brown, MD, PGY-4, Vanderbilt University, Nashville, TN
- Nurit P. Azouz, PhD, Tel Aviv University, Tel Aviv, Israel
- Carine Bouffi, PhD, University of Montpellier, Montpellier, France
- Benjamin P. Davis, MD, University of Iowa, Des Moines, IA
- Adrianne E. Hontz, PhD, University of Kansas Medical Center, Kansas City, KS
- Jeffrey Rymer, MS, University of Tennessee, Knoxville, TN
- Simone Vanoni, PhD, Paracelsus Medizinische Privatuniversität, Salzburg, Austria
- Masashi Yukawa, PhD, University of Tokyo, Tokyo, Japan
- Rahul D'Mello, BS, Johns Hopkins University, Baltimore, MD
- Bo Liu, BS, Tsinghua University, Beijing, China
- Jared B. Travers, BS, University of Cincinnati, Cincinnati, OH
- Netali Ben-Baruch Morgenstern, MS, Tel Aviv University, Tel Aviv, Israel

## Grants, Contracts, and Industry Agreements

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Immunobiology of Peanut Allergy and its Treatment: A Prototype
National Institutes of Health (Mount Sinai Medical Center)
U19 AI066738 7/1/2010-6/30/2015 $341,329

Consortium of Eosinophilic Gastrointestinal Disease Researchers
National Institutes of Health
U54 AI117804 8/15/2014-7/31/2019 $974,834
Abonia, P Pilot Core $135,281
Fulkerson, P Trainee award $16,025

Comparative Efficacy of Therapies for Eosinophilic Esophagitis
Patient-Centered Outcome Research Institute
SC14-1403-11593 1/1/2015-12/31/2017 $793,565

Expression and Function of Paired Immunoglobulin-Like Receptor B in Eosinophils
US-Israel Binational Science Foundation
2011244 10/1/2012-9/30/2016 $5,217

Epithelial Genes in Allergic Inflammation - Project 2
National Institutes of Health
U19 AI070235 9/01/2011-8/31/2016 $258,478

Wen, T
Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Diseases - Pilot & Feasibility
National Institutes of Health
P30 DK078392 6/1/2012-5/31/2017 $46,750

Zimmermann, N
Molecular Mechanism of Eosinophil Cell Death
National Institutes of Health
R21 AI103853 8/9/2013-7/31/2015 $150,000

Current Year Direct $4,000,764

Industry Contracts
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A gene called CAPN14 has been identified as a novel genetic component in epithelial tissue in the esophagus, and the gene’s interaction with the immune hormones thymic stromal lymphopoietin (TSLP) and interleukin 13 (IL-13) may explain why some patients develop eosinophilic esophagitis (EoE), a hard-to-treat food allergy marked by chronic inflammation of the esophagus.

In effect, EoE turns out to develop from interplay of a patient’s underlying genetic susceptibility to allergies and a tissue-specific process dictated by the molecular aspects of the CAPN14 gene, according to Marc Rothenberg, MD, PhD, Director of the Cincinnati Center for Eosinophilic Disorders and the Division of Allergy and Immunology. Rothenberg, and colleagues in the Divisions of Gastroenterology, Hepatology and Nutrition; Human Genetics; and the Center for the Genetics Autoimmune Etiology, probed millions of genetic variants in nearly 1,000 people with EoE and 9,000 people without EoE.

They found several genetic linkages, with the strongest associations being at the CAPN14 and TSLP loci. The study was published online July 13, 2014, in the journal *Nature Genetics*.

EoE is triggered by allergic sensitivity to certain foods and an accumulation of eosinophils, specialized immune cells, in the esophagus. Rothenberg and his team found that CAPN14, which encodes the enzyme calpain 14 in the esophagus, is dramatically upregulated when epithelial cells in the esophagus are exposed to IL-13, a known molecular activator of EoE. The CAPN14 gene is part of the esophageal disease process of EoE.

CAPN14’s upregulation, Rothenberg’s team noted, occurs in an epigenetic “hot spot” that encodes for an EoE-associated genetic variant that regulates the binding of transcription factors to the upstream region of the CAPN14 gene.

This new finding “is a breakthrough for this condition and gives us a new way to develop therapeutic strategies by modifying the expression of calpain 14 and its activity,” Rothenberg says. “Our results are immediately applicable to EoE and have broader implications for understanding eosinophilic disorders, as well as allergies, in general.”
This Manhattan plot (above) shows P values obtained from genome-wide association analysis of data from 736 subjects with EoE and 9,246 controls having 1,468,075 genetic variants. Genome-wide significance is indicated with the red dotted line, and suggestive significance marked with a solid blue line. Subsequent charts show genetic association of variants at the 2p23, 5q22, 8p23, and 15q13 loci with EoE risk. P values of the genetic association analysis of genotyped and imputed variants are plotted against the genomic positions of each genotyped (blue) and imputed (red) SNPs on the x axis on chromosomes 2, 5, 8, and 15. Genes in the region are shown above. The black lines indicate the recombination rates in cM per Mb using subjects of European ancestry from the 1,000 Genomes Project.