“Omics in Allergic Disease”

Program

Moderators:
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1. Welcome to the World Allergy Forum Symposium and Introduction to “Omics in Allergic Disease”
   Ruby Pawankar

2. Overview of Omics for: Protein Analysis in Lung Disease
   Allan Brasier, MD
   University of Texas Medical Branch
   Galveston, TX

3. Genomics in Allergic Disease
   Mayumi Tamari, MD PhD
   Genomu Ikagaku Kenkyu Center
   Yokohama-Shi, Kanagawa Japan

4. Proteomics in Asthma and Chronic Rhinosinustis
   Christian Scharf, PhD
   Greifswald University Medical School
   Greifswald, Germany

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About WAO

The World Allergy Organization (WAO) is an international alliance of 92 regional and national allergy, asthma and clinical immunology societies. Through collaboration with the Member Societies, WAO provides a wide range of educational and outreach programs, symposia and lectureships to allergists/immunologists around the globe and conducts initiatives relating to clinical practice, service provision, and physician training in order to better understand and address the challenges facing allergists/immunologists worldwide. WAO helps expand the knowledge, expertise and skills of young physicians establishing careers in allergy through Research Fellowships with international placements at renowned allergy centers.

Mission Of The World Allergy Organization

WAO’s mission is to be a global resource and advocate in the field of allergy, advancing excellence in clinical care through education, research and training as a world-wide alliance of allergy and clinical immunology societies.

WAO Meetings

World Allergy Congress™ (WAC)

WAO hosts the World Allergy Congress™ (WAC) — its main scientific meeting — biennially in different regions of the world. Please join us in Milan, Italy in 2013 and Seoul, South Korea in 2015.

WAO International Scientific Conference (WISC)

WAO International Scientific Conference (WISC) is a theme-based Scientific Conference alternating with and complementing WAO’s biennial scientific meeting, the World Allergy Congress (WAC). Please join us in Rio de Janeiro, Brazil in December 2014.

World Allergy Organization Journal

The World Allergy Organization Journal (WAO Journal) provides a global forum for the exchange of research and information on allergy, asthma, and clinical immunology. The journal supports this scientific interaction among members of the World Allergy Organization, an alliance of 92 societies worldwide, through publication of original research, clinical reviews, position papers, and epidemiological studies that contribute to current knowledge in patient care. Articles cover diagnosis, therapeutic options, crisis management, and treatment efficacy. Authors and reviewers represent all geographic regions, providing a truly global perspective. Published monthly online, with access on computers and mobile devices, the journal ensures the widest availability of practice-relevant science at the point of care. www.waojournal.org

WAO Online Resources

As a leading global online destination for allergy, asthma and clinical immunology the WAO website supports and enhances WAO educational activities and provides materials specifically designed for continued learning and reference.

Popular resources include:

• Specially commissioned educational synopses on major topics posted in the Allergic Diseases Resource Center
• Interactive case studies that challenge allergists to diagnose unusual cases
• Online learning programs including the Immunology Online Lecture Series, Asthma and Allergic Rhinitis Online Lecture Series, and the case-based interactive learning modules on Allergic Rhinitis as well as those with CME on Food Allergy and Drug Allergy
• An archive of webinars recorded at major meetings, and audio recordings of interviews with key opinion leaders around the world
• A special section, Defining the Specialty, which provides easy access to WAO publications and other resources that help to define the specialty of allergy and immunology including the WAO White Book on Allergy
• Disease-specific sections of the website including the Allergic Rhinitis Working Group, Small Airways Working Group, and HAE International Alliance.

The WAO website is HONcode certified. www.worldallergy.org
WAO Programs For Education, Research And Patient Care

World Allergy Forum® (WAF)
The World Allergy Forum® (WAF) program brings cutting edge symposia to major allergy meetings throughout the world. Developed by international expert advisory panels, the symposia provide up-to-the minute presentations on scientific and clinical developments in the field of allergic disease. WAF is the longest running educational program series sponsored by WAO and currently provides two or three placements a year with up to 1,000 attendees at each program. WAF is supported by an unrestricted educational grant from Novartis. View presentations for free at www.worldallergy.org/waf.

Emerging Societies Program (ESP)
In order to advance the WAO mission of supporting developments that will enable allergists to better serve patients now and in the future, the Emerging Societies Program (ESP) aims to disseminate information on and share experiences about new treatments for allergic disease and about new indications for available therapies. As a response to an area of need identified by ESP Delegates, the ESP has also started to offer World Allergy Training Schools (WATS) in various regions of the world. All ESP meetings and training schools are conducted with the help and support of WAO Member Societies and held in conjunction with a Member Society’s annual meeting and in partnership with the American College of Allergy, Asthma and Immunology (ACAAI). View all ESP activities at www.worldallergy.org/.

WAO Publications
WAO papers support and promote the specialty of allergy and help set standards for clinical practice and training. A full bibliography is available at www.worldallergy.org/publications/.

World Allergy Week
World Allergy Week is an annual initiative of the World Allergy Organization (WAO), together with its Member Societies, to raise awareness of allergic disease and related disorders and advocate for the provision of training and resources in the diagnosis, management, and prevention of these diseases and asthma, which are rising in prevalence around the world.

WAO established the initiative with the vision of bringing together multiple stakeholder groups including physicians, medical educators, patient advocates, policy makers, the general public, and health care authorities for an integrated approach to addressing the needs of patients who suffer from allergic diseases and asthma and those who provide care for them. Historically, WAO hosted “World Allergy Day,” in association with the biennial World Allergy Congress, beginning with the first event in July 2005. After recommendations from WAO Member Societies and other associates of WAO to expand the scope and timeline of World Allergy Day so as to facilitate wider participation around the world, the WAO Board of Directors approved the establishment of World Allergy Week in 2011.

There are many ways to get involved. Each year WAO receives stories, audio and video recordings, photographs and press releases from the many programs and activities that take place locally, nationally and regionally due to the innovative planning of participating individuals and organizations. Many of these reports are archived on this website.

WAO provides resources every year regarding the global theme for its Member Societies and information for everyone interested in World Allergy Week. Learn more at www.worldallergyweek.org.
WAO Member Societies

The World Allergy Organization (WAO), a world federation of allergy, asthma, and clinical immunology societies, consists of 89 Member Societies. All active members of dues-paying Member Societies are Individual Members of WAO.

Albanian Society of Allergology and Clinical Immunology
National Association for Private Algerian Allergists
American Academy of Allergy, Asthma and Immunology
American College of Allergy, Asthma and Immunology
Argentine Association of Allergy and Immunology
Argentine Society of Allergy and Immunopathology
Australasian Society of Clinical Immunology and Allergy
Austrian Society of Allergology and Immunology
Azerbaijan Society for Asthma, Allergy and Clinical Immunology
Bangladesh Society of Allergy and Immunology
Belgian Society for Allergy and Clinical Immunology
Brazilian Society of Allergy and Immunopathology
British Society for Allergy and Clinical Immunology
Bulgarian Society of Allergology
Canadian Society of Allergy and Clinical Immunology
Chilean Society of Allergy and Immunology
Chinese Society of Allergy and Immunology
Colombian Allergy, Asthma, and Immunology Association
Croatian Society of Allergology and Clinical Immunology
Cuban Society of Allergology
Czech Society of Allergology and Clinical Immunology
Danish Society of Allergology
Dutch Society of Allergology
Egyptian Society of Allergy and Clinical Immunology
Egyptian Society of Pediatric Allergy and Immunology
Finnish Society of Allergology and Clinical Immunology
French Society of Allergology
Georgian Association of Allergology and Clinical Immunology
German Society for Allergology and Clinical Immunology
Hellenic Society of Allergology and Clinical Immunology
Honduran Society of Allergy and Clinical Immunology
Hong Kong Institute of Allergy
Hungarian Society of Allergology and Clinical Immunology
Icelandic Society of Allergy and Immunology
Indian College of Allergy, Asthma and Applied Immunology (ICAAI)
Indonesian Society for Allergy and Immunology
Israel Association of Allergy and Clinical Immunology
Italian Association of Territorial and Hospital Allergists
Italian Society of Allergy and Clinical Immunology
Japanese Society of Allergology
Jordanian Society for Allergy and Clinical Immunology
Korean Academy of Allergy, Asthma and Clinical Immunology
Kuwait Society of Allergy and Clinical Immunology
Latvian Association of Allergists
Lebanese Society of Allergy and Immunology
Malaysian Society of Allergy and Immunology
Mexican College of Clinical Immunology and Allergy
Mexican College of Pediatricians in Allergy and Clinical Immunology
Mongolian Society of Allergology
Moroccan Society of Allergology and Clinical Immunology
Netherlands Society of Allergology
Norwegian Society of Allergology and Immunopathology
Panamanian Association of Allergology and Clinical Immunology
Paraguayan Society of Immunology and Allergy
Peruvian Society of Allergy and Immunology
Philippine Society of Allergy, Asthma and Immunology
Polish Society of Allergology
Portuguese Society of Allergy and Clinical Immunology
Romanian Society of Allergology and Clinical Immunology
Russian Association of Allergology and Clinical Immunology
Serbian Association of Allergologists and Clinical Immunologists
Allergy and Clinical Immunology Society (Singapore)
Slovenian Association for Allergology and Clinical Immunology
South African Society of Allergy
Spanish Society of Allergy and Clinical Immunology
Swiss Society for Allergy and Immunology
Allergy, Asthma and Immunology Society of Thailand
Turkish National Society of Allergy and Clinical Immunology
Ukrainian Association of Allergologists and Clinical Immunologists
Uruguayan Society of Allergology
Venezuelan Society of Allergy and Immunology
Vietnamese Society of Allergy, Asthma and Clinical Immunology
Zimbabwe Allergy Society

Associate Member Societies

Allergy Society of Kenya
Belarus Association of Allergology & Clinical Immunology
Ecuadorian Society of Allergy, Asthma, and Immunology
Indian Academy of Allergy
Iranian Society of Asthma and Allergy
Moldavian Society of Allergology and Immunology
Swedish Association for Allergology
Taiwan Academy of Pediatric Allergy Asthma Immunology
Tunisian Society of Respiratory Diseases and Allergology

Regional Organizations

Asian Pacific Association of Allergy, Asthma and Clinical Immunology
Asian Pacific Association of Pediatric Allergy, Respiratory and Immunology
Commonwealth of Independent States Society of Immunology and Allergology

Affiliate Organizations

British Society for Immunology
GA2LEN (Global Allergy and Asthma European Network)
International Association of Asthmology
International Primary Care Respiratory Group
Southern European Allergy Societies

Apply for your National Allergy Society to become a WAO Member Society at www.worldallergy.org/wao_societies/apply.php.
25 June 2013

Dear Colleagues,

A warm welcome to the forty-fourth symposium in the World Allergy Forum (WAF) series: Omics in Allergic Disease. Recognizing the importance of molecular profiling through the application of ‘omics’, the World Allergy Organization (WAO) is delighted to co-host this symposium with EAACI at the 2013 EAACI-WAO World Allergy and Asthma Congress in Milan, Italy. WAO is proud to announce that the year 2013 marks the 16th anniversary of the WAF and we are grateful to EAACI for co-hosting this symposium annually. Since 1997, WAF has flourished and become the longest continuing educational program of World Allergy Organization (WAO).

Great advances have been made in the understanding, diagnosis and treatment of allergic diseases but with the phenotypic heterogeneity, the search for specific biomarkers is still an unresolved field. In addition, genetic variability between individuals suggest that interactions between genes, proteins and the environment contribute to differences in human phenotype, maintenance of health and susceptibility to disease. During the last decade, genomic, transcriptomic, epigenomic, metabolomic, microbiomic, and proteomic (‘omics) profiling have been applied to further our understanding of molecular pathogenesis of heterogeneous disease, and to develop personalized or stratified strategies for improving disease management. Molecular profiling through the application of ‘omics should lead to sensitive, specific and non-invasive methods linked to causative pathways for early diagnosis. Pathway analysis will also facilitate the prediction of response to therapy and outcome, as well as they identify novel therapeutic targets close to disease pathogenesis. In this symposium on ‘omics in Allergic Disease’, Allan Brasier will overview the rapidly evolving field of proteomics as it applies to the study of lung disease. Mayumi Tamari will review the genomics of allergic disease focusing on the GWAS of asthma and atopic dermatitis and Christian Scharf will discuss proteomics in asthma and chronic rhinosinusitis.

The WAO Board hopes that you enjoy today’s program with its wealth of information which can be used in your everyday clinical practice. If you would like to access the faculty materials after the session they will be available at: http://www.worldallergy.org/educational_programs/world_allergy_forum/

WAO gratefully acknowledges the unrestricted educational grant from Novartis that supports educations programs such as this conjoint program at the 2013 EAACI-WAO World Allergy and Asthma Congress.

With best regards,

Symposium Chairs

Ruby Pawankar, MD, PhD, FAAAAI
President
World Allergy Organization

Cezmi Akdis, MD, PhD
President
European Academy of Allergy and Clinical Immunology
This talk will overview the rapidly evolving field of proteomics as it applies to the study of lung disease. I will overview proteomics techniques that can be used for understanding responses of lung cells to viral interactions, a field known as functional proteomics. I will illustrate the use of subcellular fractionation, 2DE-peptide mass fingerprinting, stable isotope labeling by amino acids in culture (SILAC) and discuss considerations in the design of proteomics analysis of lung disorders. The complexity and challenges of biomarker discovery in lung disease will be discussed and illustrated with a platform recently developed at the UTMB Proteomics Center. Finally, I will introduce new advances in quantitative proteomics using selected reaction monitoring (SRM), a mass spectrometric technique for quantifying targeted proteins. The SRM will be illustrated by its application to measure the activation state of the innate pathway in airway cells. The ability to profile proteins in airway fluids now enables clinical researchers to identify subtle differences in the pathophysiology of airway disease at a level of precision that is not otherwise possible. Protein profiling has the promise to revolutionize the field of medicine because it identifies robust objective features associated with disease phenotypes. I will discuss status and challenges in the application of personalized medicine in airway inflammatory disease.
Introduction to OMICs:
Proteomics of Airway Diseases

Allan R. Brasier, MD
Nelda C and HJ Lutcher Stark Distinguished Chair in Endocrinology
Director, Institute for Translational Sciences
Director, Sealy Center for Molecular Medicine
University of Texas Medical Branch, Galveston, TX USA
Email: arbrasier@utmb.edu

Disclosure

Disclosure (funding):
- UTMB CTSA (UL1TR000071 and KL2RR025875, PI Brasier)
- NIAID PO1 Signalling in Airway Inflammation (2P01AI062885, Brasier, Garofalo)
- NHLBI Proteomics Center grant: “Proteomics Technologies for Airways Inflammation” (NIH-NIAID-DMD-08-18, Kurosky, Brasier)
Conflicts: none

Educational objectives:
- Describe considerations for proteomics-based study of airway disease
- Describe approaches for personalized medicine in asthma

Overview

Introduction
Functional Proteomics
  2DE-MS using “mass fingerprints”
  SILAC
  Post-translational modifications: S-nitrosylation (SNO)
Biomarker Discovery Strategies
Quantitative Proteomics
  Selected Reaction Monitoring
Applications to Personalized Medicine
Strategies and applications of proteomics to airway inflammation

Proteomics is an emerging field that seeks to study proteins and their functions at a global level.

Two applications in airway disease
- Functional proteomics: cell/organism response to perturbation
- Biomarkers: quantification of fluids in disease

Functional proteomics of virus-cell interactions: 2DE-mass fingerprint

Identification (p value) → MALDI-TOF MS → Database search → Picking/inspinization → Spot detection → 2DE gel

Functional proteomics-viral-epithelial interactions

Zhang, J Virol. 78: 11461, 2004
Nuclear cytoskeleton as target for RSV induced oxidative damage

Effect of RSV Infection on Differential Antioxidant Protein Expression by 2-DE in Mouse BAL

Antioxidant protein
1cys peroxiredoxin
Catalase
GPX1
GST mu1
GST mu2
GST omega 1
Peroxiredoxin 6
PRDX2
SOD1
Thioredoxin

The biomarker development pipeline

<table>
<thead>
<tr>
<th>Step</th>
<th>requirements/platform</th>
<th>No. analytes</th>
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<tbody>
<tr>
<td>Discovery</td>
<td>Semi-quantitative/low</td>
<td>1000s</td>
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<tr>
<td></td>
<td>Assays/assays</td>
<td></td>
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<td></td>
<td>LC-MS/MS-2DE</td>
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<tr>
<td>Qualification</td>
<td>Quantitative/high</td>
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<tr>
<td></td>
<td>throughput</td>
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<tr>
<td>Verification</td>
<td>NSD-Multiplex</td>
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<tr>
<td>Validation/Assay</td>
<td>Analytical precision</td>
<td>4-10</td>
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<tr>
<td>Development</td>
<td>Development</td>
<td></td>
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<tr>
<td>Clinical application</td>
<td>Analytical precision</td>
<td>4-10</td>
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Considerations in sampling airway cells/fluids

<table>
<thead>
<tr>
<th>Sampling Method</th>
<th>Probe/Concentration</th>
<th>Potential Applications</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Bronchoalveolar Lavage</td>
<td>0–3 h, 1–3 days</td>
<td>Plasma proteins abundant, cell types: macrophages (60%), lymphocytes (20%)</td>
<td>Cytokine network analysis, discovery proteomics</td>
</tr>
<tr>
<td>Induced sputum</td>
<td>Macrophages, lymphocytes, neutrophils</td>
<td>Focused proteomics, DNA, RNA</td>
<td>Sputum process to rescue upper airway contamination</td>
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<tr>
<td>Bronchial Brush biopsy</td>
<td>Cells, macrophages, neutrophils</td>
<td>Elaborate cell analysis, tissue banking</td>
<td>Invasive, no serial sampling difficult</td>
</tr>
<tr>
<td>Extrathoracic samples</td>
<td>Neutrophils, macrophages, lymphocytes</td>
<td>Focused proteomics, DNA, RNA</td>
<td>Rarely available, limited samples needed</td>
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Challenges of the Plasma proteome

- Classical Plasma Proteins
- Tissue Leakage
- Cell Secreted

Biofluids Analysis Platform

Unique challenges for candidate biomarker discovery:
- High-abundance proteins limit the assayable dynamic range and absorb low-abundance proteins/peptides requiring denaturation before depletion
- Numerous endogenous proteases can generate misleading peptide abundances that must be differentiated from authentic candidate peptide biomarkers
- Pre-quantification strategy must ensure minimal protein/peptide losses
- Isotopics must be established, and denaturant removed to prevent protein modifications (e.g., carbamylation)
- Proteins and peptides must be separated and diluted to minimize the chance of re-association
- Complex mixtures require decreased complexity with precise (reproducible) inoculation to permit accurate differential comparisons
Conclusions

Proteomics approaches need to be carefully selected based on considerations of sample abundance, sample complexity, accuracy of quantification, and...

Functional proteomics in viral epithelial interactions has provided key concepts in disruption of cellular function, including oxidant defense.

Protein patterns in BAL are associated with distinct intermediate phenotypes.

New quantitative approaches for proteomic profiling opens paths for personalized medicine.

This approach holds promise for identifying subgroups and making therapy more efficient and reducing morbidity.

Acknowledgements

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<tr>
<th>Brasier Lab</th>
<th>NHLBI Proteomics Center/NIAID</th>
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<tr>
<td>Bing Tian, PhD</td>
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<td>NIH SAR</td>
<td>NHLBI Proteomics Center</td>
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<td>W. Busse, MD</td>
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<td>Mario Castro, MD</td>
<td>UTMB CTSA</td>
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<td>Gene Bleecker, MD</td>
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Genomics in Allergic Disease

Mayumi Tamari, MD PhD
Genomu Ikagaku Kenkyu Center
Yokohama-shi, Kanagawa Japan

Background: Allergic diseases are common inflammatory diseases caused by interaction of genetic and environmental factors. A large number of genetic studies have been conducted to determine the genetic components of allergic disease and to discover the cellular pathways underlying them.

Method: GWASs have accelerated biomedical research to discover the genes and cellular pathways underlying disease in an unbiased and hypothesis-free manner. We conducted genome-wide association studies (GWASs) of asthma and atopic dermatitis in the Japanese population.

Results: We identified a total of five susceptibility loci of adult asthma: the major histocompatibility complex (MHC) on 6p21, TSLP-WDR36 on 5q22, an USP38-GAB1 locus on 4q31, a locus on 10p14 and a gene-rich region on 12q13. We observed the most significant association with adult asthma at rs404860 in the MHC region, which is close to rs2070600, a SNP previously reported for association with FEV1/FVC in GWAS for lung function.

We also identified eight new susceptibility loci of atopic dermatitis with genome-wide significance: IL1RL1-IL18R1-IL18RAP, the MHC region, OR10A3-NLRP10, GLB1, CCDC80, CARD11, ZNF365 AND CYP24A1-PFDN4. We also replicated the associations of the FLG, C11orf30, TMEM232-SLC25A46, TNFRSF6B-ZGPAT, OVOL1, ACTL9 and KIF3A-IL13 loci that were previously reported in GWAS of European and Chinese individuals and meta-analysis of GWAS for atopic dermatitis.

Conclusion: Candidate genes in the susceptibility loci suggest roles for epithelial barrier functions, innate-adaptive immunity, IL-1 family signaling, regulatory T cells and the vitamin D pathway in the pathogenesis of allergic diseases. Interestingly, the IL1RL1, TSLP, HLA, IL13, and C11orf30 regions are overlapping susceptibility loci among atopic dermatitis and asthma. Although a more complete collection of associated genes and pathways is needed, biologic insights revealed by GWASs improve our understanding of the pathophysiology of human allergic diseases. Further cross-disciplinary studies combining genetics, proteomics, bioinformatics, immunology, epidemiology, and clinical allergology are necessary for translation of research into clinical practice. These studies will help to protect humans from developing allergic diseases and provide molecular targets for therapeutic intervention.
Abstract

Background: Allergic diseases are common inflammatory diseases caused by the interaction of genetic and environmental factors. A large number of genetic studies have been conducted to determine the genetic components of allergic diseases and to discover the cellular pathways underlying them.

Methods: GWAS have accelerated biomedical research to discover the genes and cellular pathways underlying disease in an unbiased and hypothesis-free manner. We conducted genome-wide association studies (GWASs) of asthma and atopic dermatitis in the Japanese population.

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Genomics in Allergic Diseases

- Genomic variation
- Genome-wide association study

Methods

BioBank Japan project

- GWAS for adult asthma in the Japanese population
- GWAS for atopic dermatitis in the Japanese population
The genome—Blueprint of life
The human genome contains around 3 billion base pairs
Inherited from our mother and father

Genetic polymorphisms
Humans were known to carry a heterozygous site roughly every 1300 bases

SNPs cause individual characters
In Medical Field
Disease susceptibility
Disease severity
Drug response & side effects

Linkage disequilibrium, HapMaps and SNP chips
Progress in the study of genetic variation

The discovery of the haplotype structure of the human genome
Genetic variants in a region are tightly correlated in structures called haplotypes, reflecting LD and separated by hotspots of recombination
A limited set of ~500,000-1,000,000 SNPs could capture ~90% of the genetic variation in the population

The development of genotyping arrays (SNP chips)
SNP chips now assay up to ~2 million variants simultaneously

Genome-wide association study (GWAS)
A better understanding of the complexity of the diseases
GWAS has begun to reveal underlying cellular pathways and, in some cases, already pointed to new therapeutic approaches

Millions of genetic variants are read using SNP arrays
It is important to correct for occurrence of false positives

Statistical strength of an association
X-axis; the –log of the association P value for each SNP
X-axis; genomic coordinates
Candidate locus
Genome-wide significance level
Cochrane-Armitage trend test

Genome-wide significance level ($\alpha = 0.05, 0.05/1,000,000 = 5 \times 10^{-8}$)
To avoid the multiple testing problems for 1,000,000 SNPs
The BioBank Japan Project on the implementation of personalized medicine (2003~)
Project Leader: Prof. Yusuke Nakamura  
Dr. Michiaki Kubo
The project aims for construction of basic information for personalized medicine
For the collection of genomic DNA, serum and clinical information from 300,000 cases diagnosed with any of 47 diseases by a collaboration network of 66 hospitals in all areas of Japan
Supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT)
The RIKEN Center for Integrative Medical Sciences (IMS) functions as a core research organization for the project

GWAS of Adult Asthma
GWAS Cases (n=1532) RIKEN samples  
Illumina HumanHap610-Quad  
Controls (n=3304) BioBank Universal Control 6
Illumina HumanHap550v3

GWAS for lung function
Three GWASs for lung function, using cross-sectional spirometric measurements in healthy individuals
Genome-wide association study identifies five loci associated with lung function. (in Europe) Nat Genet. 2010 Jan;42(1):36-44
FEV1: Forced expiratory volume in 1 sec.  
FVC: Forced vital capacity  
FEV1/FVC ratio (FEV1%)  
A decreased FEV1/FVC is a characteristic of obstructive diseases  
Asthma  
COPD (Chronic bronchitis/Emphysema)
1. Association results and LD map of the MHC region

GWAS for adult asthma in Japanese
rs2070600
rs9273349
rs2079300
rs9192563


Association results and LD map of the MHC region

GWAS for adult asthma in Japanese
rs2070600
rs9273349
rs2079300
rs9192563


**Large scale GWAS for bronchial asthma**

Tight collaboration between PAMPs and DAMPs is needed to start an immune response to allergens

- **DAMP** Damage-associated molecular patterns
- **PAMP** Pathogen-associated molecular patterns

**Danger signals** (smoking, air pollution, allergen protease, respiratory infections)

**Allergen**

**Japanese Adult asthma**

**European Meta-analysis**

**Dendritic cell**

**IL1RL1, IL33**

**HLA, GAB1/USP38**

**GATA3**

**IKZF4**

**TSLP**

**IL13**

**collaborative genetic studies using very large population samples have provided valuable insights into the pathophysiology of asthma**

**GWAS of Atopic Dermatitis**


**Hallmarks of atopic dermatitis**

- a chronic, relapsing form of skin inflammation
- a disturbance of epidermal-barrier function
- IgE-mediated sensitization to food and environmental allergens

**Three GWASs of AD**

- **European populations**
  - A total of 7 loci have been identified
  - Chinese Han populations
    - Sun LG. et al. Genome-wide association study identifies two new susceptibility loci for atopic dermatitis in the Chinese Han population. Nat genet. 43. 690-694 (2011)
  - Meta-analysis of European populations

**GWAS of atopic dermatitis in the Japanese population**

- **GWAS** Platform: Illumina HumanOmniExpress
- **606,164 SNPs** BioBank Japan
  - 1,472 cases (with atopic dermatitis)
  - 7,971 controls (without allergic diseases)

To identify susceptibility genes for atopic dermatitis

**Validation study** Invader or Taqman

- **87 Tag SNPs/1635SNPs** Trend test $P < 1.0 \times 10^{-4}$
  - BioBank Japan & RIKEN samples
    - 1,856 cases (with Atopic dermatitis)
    - 7,021 controls (without allergic diseases)

A total of 8 new loci were associated with atopic dermatitis at genome-side significant levels
A total of 8 New Loci 
GWAS of Atopic Dermatitis
Hirota T. et al., Nature genetics 2012;44:1222-6

GWAS
IL1RL1-IL18R1-IL18RAP
MHC
OR10A3-NLRP10
GWAS & Validation study
GLB1
ZNF365
GWAS
C3DC80
CARD11
CYP24A1-PFDN4

GWAS & Validation study 
Genome-Wide Association Studies for Atopic Dermatitis In the Japanese Population

2q12
IL1RL1/IL18R1/IL18RAP
IL1RL1 (IL-33 receptor) IL33 promotes Th2 immune response

3p21.33
GBL1/CCR4
CCR4 encodes a Th2-associated chemokine receptor for CCL22 and TARC

3q13.2
CCDC80
CCDC80 involves in the induction of C/EBPα and PPARγ

6p21.3
The MHC region
The MHC region contains a number of genes related to immune system

7p22
CARD11 (CARMA1)
CARMA1 has a critical role in the regulation of the Th2 cytokine production

10q21.2
ZNF365/EGR2
EGR2 encodes a T-cell anergy-associated transcription factor

11p15.4
OR10A3/NLRP10
NLRP10 is essential to initiate adaptive immunity by dendritic cells

20q13
CYP24A1/PFDN4
CYP24A1 degradates 1,25-OH vitamin D3

Chinese
1p21.3
FLG


European
5q11.1
TMEM232/SLC25A46

20q13.3
TNFRSF6B/ZG PAT

Paternoster L. et al. Nat genet. 44. 187-192 (2011)

Japanese
2q12
IL1RL1/IL18R1/IL18RAP

Hirota T. et al. Nat genet. 44. 1222-1226 (2012)

Genome-Wide Association Studies for Atopic Dermatitis

European
5q31
KIF3A/IL4/IL13

Paternoster L. et al. Nat genet. 44. 187-192 (2011)

Japanese
3p21.33
GBL1/CCR4

Hirota T. et al. Nat genet. 44. 1222-1226 (2012)

Atopic dermatitis
• Skin barrier dysfunction
• Chronic inflammation
• Sensitization to antigens

Skin barrier
• Immune responses
• Regulatory T cells
• Vitamin D pathway
### Overlapping loci identified by GWAS

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Locus</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>2q12</td>
<td>IL1RL1/IL18R1/IL18RAP</td>
<td>Asthma, Atopic dermatitis, Eosinophil count</td>
</tr>
<tr>
<td>5q22</td>
<td>TSLP/WDR36</td>
<td>Asthma, Eosinophilic esophagitis</td>
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<tr>
<td>5q31</td>
<td>KIF3A/IL4/IL13</td>
<td>Asthma, Atopic dermatitis, Total IgE</td>
</tr>
<tr>
<td>6p21.3</td>
<td>the MHC region</td>
<td>Asthma, Total IgE</td>
</tr>
<tr>
<td>11q13.5</td>
<td>C11orf30/LRRC32(GARP)</td>
<td>Asthma, Atopic dermatitis, Allergic rhinitis</td>
</tr>
</tbody>
</table>

### Roles of genes identified by GWAS of allergic diseases in innate immune cells

Basophils play a role in the protective immunity to helminth infections and the critical APCs for driving Th2 cell differentiation.

Group 2 innate lymphoid cells play a role in the protective immunity to helminth infections, wound healing and allergic diseases.

#### References


Proteomics in Asthma and Chronic Rhinosinusitis

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Notes