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Oral Presentation 1



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Sensitization Pattern of Aeroallergens in Allergic Rhinitis within China

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Purpose: Optimization of skin prick test (SPT) panel was unmet need within China. Our aim was to investigate the pattern of aeroallergens sensitization in patients with allergic rhinitis (AR) and define the minimal battery of SPT allergens to identify a patient as sensitized.

Methods: In the patient-based study, 7148 self-reported AR patients in 28 provinces from 4 regions of main land China underwent standardized SPT with 21 common aeroallergens. Conditional approach allowed to determine the allergens selection. **Results:** 6350/7148 (88.8%) had at least one positive skin prick reaction. The prevalence of positive skin prick responses was 47.2% for Der f and 41.4% for Der p, respectively, which were the two most prevalent aeroallergens in mainland China. After standardization with regard to age and gender, the highest sensitization rates for house dust mites were observed in south China, whereas the three most prevalent aeroallergens were mugwort, ragweed and dandelion in north-west China. Higher sensitization rates of outdoor aeroallergens were observed in moderate-severe AR and persistent AR, whereas HDMs sensitization didn't present significant variations between different AR classifications. Higher sensitization rate and multiple sensitizations were associated with AR comorbidities. Overall, eight allergens allowed to identified more than 95% of sensitized subjects. However, differences were observed between regions, four allergens being sufficient for south China as opposed to eight for middle China.

Conclusion: Dust mites were the most prevalent allergens in patients with AR in China. There were significant differences in patterns of sensitizations between different geographic areas. Eight allergens allowed the identification of the majority of sensitized subjects.

Prevalence of Cockroach Sensitization among Children aged 2-11 Years Old from Batulao, Barangay Tatalon, Quezon City and its Association with Respiratory Allergies

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Allergic respiratory diseases are significant public health concern. Cockroaches, seen in both indoor and outdoor environments, are usually linked with respiratory allergies.

Purpose: To determine cockroach sensitization among children 2 to 11 years old from Batulao, Barangay Tatalon, Quezon City and its association with respiratory allergies.

Methods: Study Design: Cross sectional, analytic/Setting: Community/Patients/Participants: Children 2 to 11 years from Batulao, Barangay Tatalon, Quezon City without skin dermatoses at the site of allergy skin testing and have not used antihistamine within 72 hours before testing./Interventions: Allergy skin prick test using cockroach allergen (*Periplaneta americana*) positive and negative control was performed on the subject's volar arm. Net wheal diameter of 3-millimeter more than the negative control was considered positive. Association of cockroach sensitization with respiratory allergies will be determined based on the subject's clinical history.

Results: Ninety six (96) subjects were included in the study. The prevalence of cockroach sensitization was high at 67.70%, more common in 6 to 11 year age group. Gender was not a significant risk factor for cockroach sensitization as both sexes were affected equally. The mean age of onset of bronchial asthma and coexisting bronchial asthma and allergic rhinitis was earlier in subjects with cockroach sensitization, however, no association was observed in the mean age of onset of allergic rhinitis among subjects with cockroach sensitization and without cockroach sensitization. Further classifying respiratory allergies based on ARIA and GINA showed no significant difference among subjects with cockroach sensitization and without cockroach sensitization. Frequent hospital/clinic visits due to respiratory allergies were more common in subjects with cockroach sensitization.

Conclusion: There is a significant association between bronchial asthma, allergic rhinitis and coexisting bronchial asthma and allergic rhinitis with cockroach sensitization among children 2 to 11 years old from Batulao, Barangay Tatalon, Quezon City.

Clinical Implication of Sensitization Profiles of 9 House Dust Mite Component Allergens: Der f 1, Der f 2, Der f 10, Der f 11, Der f 13, Der f 14, Der f 30, and Der f Alt a 10

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Background: House dust mite (HDM) is composed of various component allergens. It can cause various diseases through lifetime; atopic dermatitis, asthma and allergic rhinitis. This diverse clinical entity suggests that various sensitization profiles can be present.

Objective: The aim of this study was to investigate the sensitization profiles of Korean HDM allergic patients. Sensitization patterns of major and minor component allergens are compared at respiratory (allergic rhinitis or asthma) and atopic dermatitis patients.

Methods: HDM allergic patients were enrolled at Severance Hospital in Seoul, Korea. IgE reactivity of 3 groups (allergic rhinitis/asthma, atopic dermatitis, and both) were analyzed using immunoblot after two-dimensional gel electrophoresis. In order to identify the proteins reactive with IgE antibodies, LC-coupled ESI-MS/MS analysis was carried out at ProteomeTech. Then, nine representative recombinant allergens (Der f 1, Der f 2, Der f 10, Der f 11 peptide fragment, Der f 13, Der f 14, Der f 30, Der f 32, and Der f Alt a 10) were produced. IgE reactivity of the component allergens were analyzed by ELISA and western blot method.

Results: In this study, sensitization profiles of 161 HDM-allergic patients were analyzed. Respiratory allergy group (asthma or allergic rhinitis) were mainly sensitized group 1 or group 2 allergens. However, patients who suffered from atopic dermatitis were poly-sensitized by major and minor HDM allergens, especially Der f 11 ($p=0.034$), Der f 13 ($p<0.001$), Der f 14 ($p<0.001$), Der f 32 ($p<0.001$). Among the allergen, Der f 14 is the prominent difference between the airway and cutaneous diseases by western blot and ELISA assay. In addition, there were 15 patients (9.3%) who neither sensitized to group 1 or 2 allergens.

Conclusions: Sensitization profiles of HDM are different between airway and cutaneous disease. Der f 14 sensitization is a main difference between respiratory allergy and atopic dermatitis patients.

Key Words: Allergen, Mite, Diagnosis

Vitamin D Levels in Patients with Allergic Rhinitis and Fungal Sensitisation and its Impact on Quality of Life

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Purpose: Vitamin D levels in patients with AR and fungal sensitisation as well as its impact on quality of life (QoL) is yet to be assessed.

Methods: The study comprised 203 consecutive patients with AR and 40 healthy volunteers. IRB approval and informed consent was obtained. AR was diagnosed as per the ARIA guidelines. All patients had positive SPT, normal spirometry without significant reversibility and also underwent CT-PNS to document CRS. Lund-Mackay scores (LMS) were calculated based on CT-PNS findings. Vitamin D level was estimated with ELISA readers. Based on SPT positivity for fungal allergens, patients were divided into: AR with fungal sensitisation (Group1) and AR without fungal sensitisation (Group2). Group 3 functioned as controls. Impact on QoL was assessed with Sinonasal Outcome Test 22 (SNOT-22),VAS and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

Results: Of the 203 patients recruited, fungal sensitisation was seen in 27 of them (Group1). Sensitisation to *Aspergillus* species was seen in 15/27 patients. *Aspergillus fumigatus* was the most common fungal species to which sensitisation was seen in 14/27 subjects. Serum vitamin D levels were significantly lower in Group 1 as compared to controls ($8.4+4.3$ v/s $26.5+20.9$; $P<0.0001$). Levels of vitamin D were significantly lower in patients in Group 1 as compared to Group 2 ($8.4+4.3$ v/s $15.6+10.5$; $P=0.0005$). Of the 27 patients, sinusitis was seen in 24 of them. The mean LMS in patients with sinusitis in Group 1 was significantly higher (Group 1: $7.78+5.5$ v/s Group 2: $5.9+3.8$; $P=0.04$). SNOT-22,VAS and RQLQ scores were higher in Group1, however difference was not significant.

Conclusions: Vitamin D levels were significantly lower in patients with AR and fungal sensitisation. Patients with fungal sensitisation and sinusitis had significantly higher LMS scores.

Wogonin induces eosinophil apoptosis by suppressing HIF-1alpha and survivin, and attenuates nasal polyp formation

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Background: Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) is an inflammatory sinonasal disorder characterized by eosinophilic inflammation and T-helper 2 (Th2) skewing. Accumulation of eosinophils in sinonasal mucosa is a major feature of CRSwNP. Persistent eosinophilic inflammation is related to prolonged survival of eosinophils as well as their accumulation in tissues. The aim of the study is to investigate the ability of the flavone wogonin to induce eosinophil apoptosis in vitro and attenuate eosinophilic CRSwNP in mice.

Material and methods: Double immunofluorescence, immunohistochemistry, flow cytometry, immunoblotting were done to evaluate hypoxia-inducible factor (HIF-1), survivin, and apoptotic markers in EoL-1 cells (human eosinophilic cell line) or sinonasal tissues from the patients with CRS with or without NPs. The effects of wogonin on nasal polygenesis were investigated in previously developed murine models.

Results: In sinonasal specimens from patients with CRS, HIF-1alpha and survivin was upregulated in eosinophils from patients with polyps compared with levels seen in patients without polyps. Under hypoxia, HIF-1alpha and survivin expression upregulated in EoL-1 cells. Wogonin decreases the expression of HIF-1alpha and down-regulated survivin in EoL-1 cells. Moreover, we found that survivin overexpression protected EoL-1 cells against apoptosis in response to wogonin. In fact, wogonin did not induce apoptosis in THP-1 and RPMI 2650 cells. Thus, wogonin could induce eosinophil apoptosis in a cell type-specific manner.

Conclusion: In summary, our findings suggest that wogonin could induce caspase-3 activation by suppressing HIF-1alpha and survivin expression in EoL-1. The mechanism of enhanced eosinophil survival in inflamed microenvironment need to be explored. Further studies in novel therapeutic options for CRSwNP that target eosinophil apoptosis are needed.

Key Words: Nasal polyp, Survivin, Wogonin

Wnt signaling and regulatory T cells in nasal polyp

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Background: The role of Wnt signaling is not clearly revealed in chronic rhinosinusitis with nasal polyp (NP). Recently, studies on interaction of Wnt signaling and T cells (or regulatory T cell, Treg) showed that Wnt signaling can modulate pro-inflammatory properties and modulate Treg. In this context, we sought to reveal the role of Wnt signaling and the association of Wnt signaling and Treg in human NP.

Methods: Patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) were enrolled. Turbinate or uncinata tissue were used as control. Immunohistochemistry (IHC), quantitative PCR and flow cytometry were used to analysis expressions of FOXP3, IL-17, beta-catenin, CD45RA, IL-10 in nasal tissue and single cells.

Results: Quantitative PCR showed that WNT3A, frizzled 1, frizzled 2 and frizzled 3 has increased in CRSwNP, showing increased Wnt signaling in NP. To confirm increased Wnt signaling, beta-catenin IHC were performed and beta-catenin positive cells were increased in CRSwNP. To reveal the change of Treg in NP, quantitative PCR and IHC of FoxP3 were performed and showed that Foxp3 were increased NP. Flowcytometry analysis showed that both CD45RA+FoxP3+ cells, which represent naive Treg which can be converted into suppressive Treg, and CD45RA-FoxP3+ Treg, which could be non-suppressive effector T cells, were increased in NP. In addition, IL-17+CD4+ effector T cells were also increased in NP. These flowcytometric findings suggests that proinflammatory effector cells were increased in NP rather than suppressive Treg, suggesting increased proinflammatory condition in NP. Mice treated with Wnt inhibitor showed decreased Treg in spleen, showing the effect of Wnt in Treg. And Wnt inhibitor decreased nasal polyp like lesion in mouse model of NP.

Conclusion: Wnt signaling were increased in NP and increased inflammatory effector cells may be associated with the increased Wnt signaling in terms of NP pathogenesis. Wnt signaling could be used as a target in CRS

Key Words: Nasal polyp, regulatory T cell, Wnt

Identification of *C11orf30-LRRC32* as Susceptibility Loci for House Dust Mite-sensitized Allergic Rhinitis in a Chinese Han Population

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Purpose: Sensitizations to house dust mite (HDM) species are among the most common causes of allergic rhinitis (AR) in China. The *C11orf30-LRRC32* locus appears to be important for more than two another allergic genotypes and immunologic diseases. In this study, we investigated the HDM-sensitized AR association signal from the *C11orf30-LRRC32* locus using fine-mapping and haplotype approach to characterize the genomic structure of *C11orf30-LRRC32* locus and to extract the predisposing genetic variants among a Chinese Han population.

Methods: A total of 400 HDM-sensitized AR patients and 326 control subjects were enrolled from allergy clinic and ward of Beijing TongRen Hospital. The selected 77 SNPs in the *C11orf30-LRRC32* locus were genotyped using iPLEX MassARRAY platform.

Results: Fine mapping of *C11orf30-LRRC32* region was performed and the simple SNP-phenotype association results are shown that three SNPs (rs11236817, rs12790184 and rs1892952) showed significant associations with HDM-sensitized AR. Rs11236817, approximately 21 kb downstream of *LRRC32*, showed the strongest associations. The frequency of A allele of rs11236817 was significantly higher in AR patients than control subjects (26.3% vs. 19.4%, $P = 0.002$, OR=1.48). The haplotype analysis identified three blocks (B10, B11 and B12) associated with HDM-sensitized AR ($P = 0.049$, 0.018 and 0.007). The first block (B10) comprised three SNPs (rs11236811, rs1941606 and rs10899243) and the strongest hit (rs11236817). Besides, the GG genotypes at rs11236817 were strongly associated with decreased total serum IgE levels as compared to those with the AA genotypes or the AG genotypes both in the patients group and in the control group.

Conclusion: The *C11orf30-LRRC32* locus is associated with house dust mite-sensitized allergic rhinitis in Chinese Han population.

Increased levels of human myeloperoxidase (MPO) and neutrophil lipocalin (HNL/NGAL) in childhood asthma

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Purpose: Myeloperoxidase (MPO) and human neutrophil lipocalin (HNL/NGAL) are stored in neutrophil granulocytes and secreted upon activation of the cells. They have been proposed to reflect the degree of inflammation in the airways.

Methods: Eighty six children with asthma and 59 control subjects were enrolled. Concentration of human MPO and HNL/NGAL were measured in sputum supernatants using ELISA. The characteristics of subjects include results of spirometry, methacholine challenge test and atopy.

Results: There was no difference in sputum neutrophil counts between asthma and control subjects. But sputum MPO and HNL/NGAL concentration were significantly higher in children with asthma than in control ($p=0.034$ and $p=0.001$, respectively), especially in children with moderate-to-severe persistent asthma. In asthma patients, sputum MPO and HNL/NGAL levels showed positive correlation with sputum neutrophil counts (MPO, $r=0.38$, $p=0.004$; HNL/NGAL, $r=0.595$, $p<0.001$) and they were positively correlated with each other ($r=0.610$, $p<0.001$). And sputum HNL/NGAL could reflect current pulmonary function, airway inflammation and limitation better than MPO in this study.

Conclusion: Airway neutrophilic inflammation plays an important role in pediatric asthma and its severity. Sputum MPO and HNL/NGAL reflecting neutrophil activation could be a good assessment for asthma severity in children.

Key Words: Asthma, children, neutrophil

Early-life cat or dog exposure is critical to develop childhood asthma and sensitization to cat or dog

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Introduction: High level of house dust samples including cat allergen in the first-year of life was inversely associated with recurrent wheezing at age 3 years in previous birth cohort study. However, little is known about the association between early-life pet exposure and allergic sensitization, and asthma, even though the population keeping indoor dogs and cats has increased recently in Korea. We investigated the rate of having dog or cat in house and whether it affects as risk factors for the development of childhood asthma.

Methods: The Panel Study of Korean Children (PSKC) study is a general population based birth cohort study which recruited 2,150 mother-baby dyads by using 2-step stratified random sampling at 2008. Among 1,577 children who followed at 2015, 642 children performed allergic evaluations including provocation test and skin prick test. Having cat or dog during infancy, current cat or dog holder, and the prevalence of asthma were evaluated by self-reported questionnaires and physician's medical records.

Results: During infancy, the rate of having dogs was 4.5%, and the rate of having cats was 0.5%. Of the 1563 subjects, 7.9% currently has at least a dog, 2.5% has at least a cat. The prevalence of physician diagnosed asthma was 8.1% in this cohort. Having dog or cat during infancy was associated with allergic sensitization to dog or cat (aOR 4.2, 95% CI 1.60-11.0), bronchial hyperresponsiveness(BHR) (PC20 < 8 mg/ml, aOR 3.09, 95% CI 1.28-7.43), the doctor diagnosed asthma (aOR 3.33, 95% CI 1.00-11.09), wheezing within 12 months (aOR 5.51, 95% CI 1.65-18.37) and current asthma (aOR 6.84, 95% CI 1.67-28.09). In contrast, currently having dog or cat during 12 months was not associated with allergic sensitization to dog or cat, BHR, wheezing within 12 months and current asthma.

Conclusion: Early-life exposure to cat or dog during infancy is critical to develop allergic sensitization to cat or dog, BHR and a asthma in children.

Key Words: Cat or dog, Early life, Asthma

Serum periostin levels and provocative challenges for diagnosis of asthma: exercise, methacholine, and mannitol

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Background: The aim of our present study was to explore the relationship between serum periostin levels and bronchial hyperresponsiveness (BHR) in asthmatic children.

Methods: We recruited all new asthma cases aged 6-15 years and all diagnoses were verified by the pulmonary function testing, and the methacholine bronchial provocation test (BPT). We excluded individuals with positive methacholine challenge for BHR from the groups without asthma. We measured the periostin levels in serum and performed exercise and mannitol BPTs.

Results: A total of 56 subjects were recruited and took part in this study. Of the 56 asthmatics with positive methacholine BPT results, 37 had positive exercise BPT results. Of the 37 subjects with positive exercise BPT results, 30 had positive mannitol BPT results. Of the 19 subjects with negative exercise BPT results, 10 had positive mannitol BPT results. Periostin levels were significantly correlated with both the maximum decreases in %FEV1 ($r=0.338$, $P=0.016$) and mannitol PD15 values ($R=-0.444$, $P<0.0001$). No significant correlations were found between serum periostin levels and methacholine PC20.

Conclusion: Serum periostin levels are significantly correlated with BHR induced by exercise and mannitol challenge rather than BHR induced by methacholine challenge in children with asthma.

Key Words: Periostin, Asthma, Bronchial hyperresponsiveness

Upper airway microbiome and functional metagenomic profiles in adult asthmatics: difference between young adults and elderly

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Background: Airway microbiota interacts with host immune system and influence respiratory diseases. Asthma presents distinct features according to age, but the role of airway microbiome in distinct features of adult asthma is unclear. We investigated the composition and functional profiles of upper airway microbiome from young adults and elderly patients with asthma to understand the role of microbiome. **Methods:** Thirty patients with asthma and 10 healthy controls of young adults (18-45yrs old), and 30 patients with asthma and 10 healthy controls of elderly (over 65yrs old) were enrolled for the study. Nasopharyngeal swab samples were collected from the subjects and microbiome composition were analyzed using 16S rRNA sequencing. In addition, functional metagenome profiles were analyzed using whole metagenome shotgun sequencing.

Results: Although the diversity of microbiota was not significantly different between adult and elderly, the composition of microbiota was different between two groups. The relative abundance of *Staphylococcus*, *Propionibacterium*, and Uncultured *Corynebacteriales* were higher in the adult group than those in elderly group ($P < 0.05$). In adult samples, the proportions of Proteobacteria phylum and Uncultured *Corynebacteriales* were higher in asthma group than those in control group ($P < 0.05$). In elderly samples, the proportion of *Moraxella* was higher in control group than that in asthma group. In addition, we found the difference of upper airway microbiota according age within the same adult or elderly group. The relative abundances of genes associated with biosynthesis of unsaturated fatty acids and cysteine/methionine metabolism were higher in asthma group than control group of adult samples ($P < 0.05$). These metabolism were related to the airway inflammation. However, the significantly different metabolic pathway genes of microbiome were not found in elderly group.

Conclusion: The upper airway microbiome was different according to age and asthma disease. The different functional genes of microbiome were related to the airway inflammation. These results can help to understand the role of airway microbiome in adult asthma, and can provide the potential biomarker and modulating target of microbiome.

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Key Words: Airway, Asthma, Microbiome

Changes of HDM-induced NLRP3 inflammasome activation in the lung of PI3K- δ knock out mice

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Phosphoinositide 3-kinase (PI3K)- δ -dependent Akt activation is associated with the pathogenesis of severe respiratory diseases partly through the induction of steroid resistance. However, the role of PI3K- δ isoform is still controversy in allergic inflammation. Moreover, many studies to define the role of PI3K- δ in inflammatory conditions have focused its action in immune/inflammatory cells. With trend a major pathobiological mechanism for asthma including severe form has shifted toward defects in epithelial innate immune responses to injury from typical Th2-biased adaptive immune responses, epithelial cells has resurfaced as one of immune effector cells. Therefore, in this study, we aimed to evaluate the role of PI3K- δ in induction and/or maintenance of HDM-induced allergic responses in the airway, focusing on activation of NLRP3 inflammasome, especially in bronchial epithelium. We used a murine model of HDM-induced asthma in wild type (WT) and PI3K- δ knock-out (KO) mice and also performed an in vitro study using primary cultured murine tracheal epithelial cells and human bronchial epithelial cells. We found that PI3K- δ inhibition decreased HDM-induced typical allergic asthmatic features and the activation of NLRP3 inflammasome in lung and primary cultured tracheal epithelial cells from mice. Interestingly, in LPS-stimulated airway epithelial cells, significant increased expression of PI3K- δ isoform was observed and the increases were markedly suppressed by inhibition or genetic blockade for PI3K- δ . This study indicates that HDM allergens activate NLRP3 inflammasome in the lung, specifically in airway epithelial cells through TLR4-PI3K- δ axis activation, highlighting the therapeutic potential of PI3K- δ targeting agents as well as the role of bronchial epithelial cells as an immune effector in allergic airway inflammation.

Key Words: PI3K- δ knock out mice, House dust mite, Inflammasome