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Genetic susceptibility to Occupational asthma

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Topics today ...

LMW vs. HMW allergens

Isocyanate (TDI / MDI) vs. wheat flour

/ lab animals

/digestive enzymes in health professionals

1. HLA allele study

2. Candidate gene approach

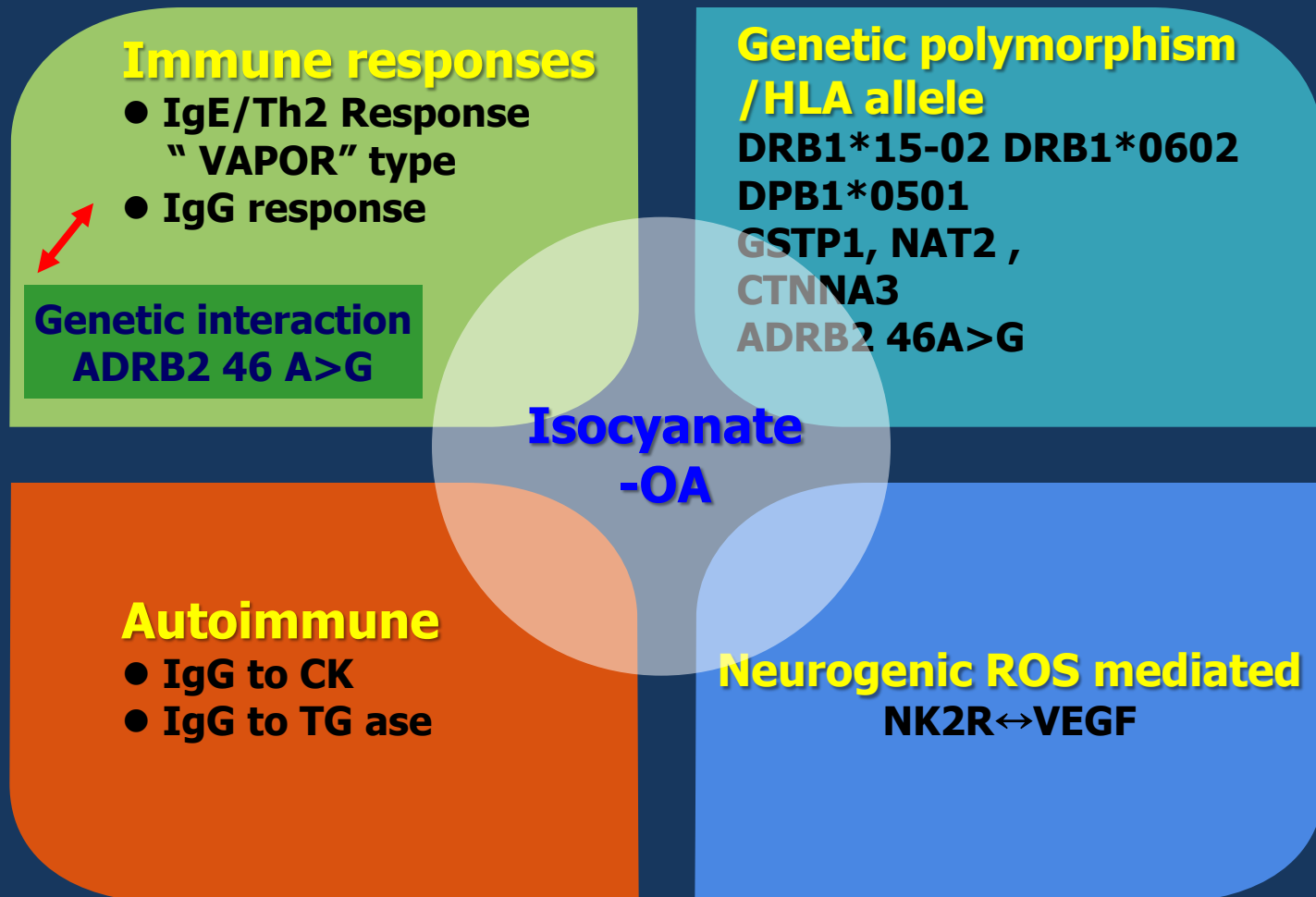
3. Genome wide association studies

4. Gene to environmental interaction

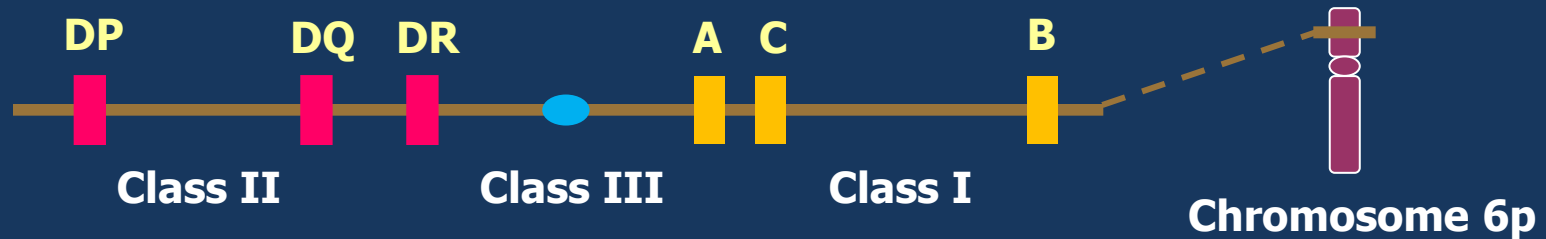
Occupational asthma : etiologies and risk factors

Agent	Finland	Canada, Quebec*	UK [†]	France [†]	South Africa [†]	Australia †	Belgium [†]	B2elgium *‡	Spain, Catalonia †	Korea*†
	1995- 2002	1995- 1999	1996- 2001	1996- 1999	1997- 1999	1997- 1999	2000- 2002	1998- 2002	2002	1992-2006
Flour, cereals	17%	24%	9%	22%	12%	2%	13%	31%	10%	1%
Isocyanates	2%	18%	13%	14%	20%	6%	17%	15%	16%	50%
Latex	<1%	10%	3%	7%	24%	3%	10%	23	7%	4%
Aldehydes	1%	na	4%	6%	1%	5%	1%	1%	2%	3%
Animals	24%	5%	5%	2%	1%	2%	4%	1%	4%	na
Wood dusts	3%	9%	6%	4%	Na	14%	3%	6%	8%	1%
Metals	1%	7%	4%	na	15%	7%	4%	4%	Na	9%

The pathogenic mechanisms of Isocyanate induced PA-complicated



Association of HLA genes with TDI-OA



- **DQB1*0503(Asp)↑ vs. DQB1*0501(Val)↓**

*Bignon et al. Am J Respir Crit Care Med 1994;149:71-75,
Balboni et al. Eur Respir J 1996;9:207-210*

- **DQA1*0104 and DQB1*0503↑ vs. DQA1*0101 and DQB1*0501↓**

Mapp et al. Clin Exp Allergy 2000;30:651-656

- **DRB1*15-DPB1*05 haplotype↑**

Kim SH and Park HS et al. Allergy 2006;61:891-894

- **DRB1*1501-DQB1*0602-DPB1*05010.001(OR=7.235)**

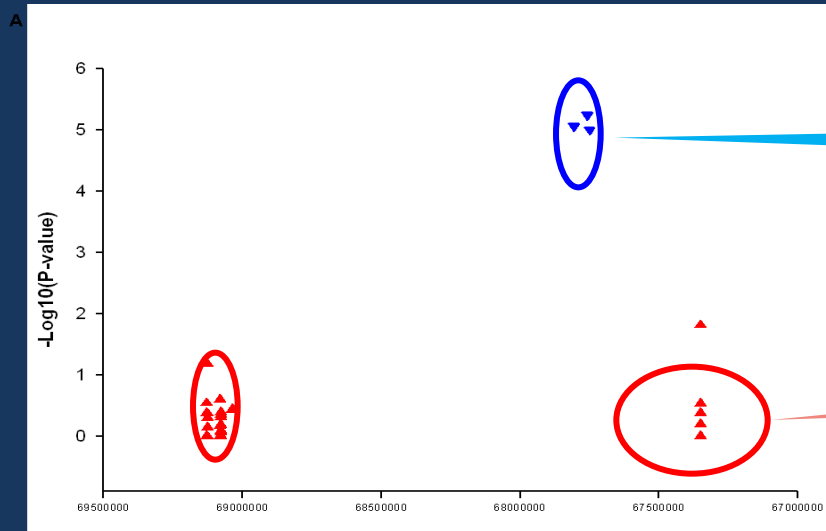
Choi JH and Park HS et al. Int Arch Allergy Immunol, 2008

Table . Genetic biomarkers for isocyanate-induced asthma

Gene	Full name	Genotype	Association	Population
Genetic biomarkers				
HLA	Human leukocyte antigen	DRB1*1501-DQB1*0602-DPB1*	Yes	Korean
HLA	Human leukocyte antigen	DQB1*0503	Yes	European
HLA	Human leukocyte antigen	DQB1 *05	Yes	Swedish
HLA	Human leukocyte antigen	DQB1*0501	No	European
CTNNA3	Catenin alpha 3, alpha-T catenin	HT2 [GG]	Yes	Korean
NK2R	Neurokinin2 receptor	7853G>A, 11424 G>A	Yes	Korean
NAT1	N-acetyltransferase	slow acetylator	Yes	Finnish
GSTP1	Glutathione transferase	105 Val	Yes	Swedish
NAT1	N-acetyltransferase	NAT1*10	Yes	Swedish
CCL5	Chemokine receptor	-403 AG+AA	Yes	Swedish

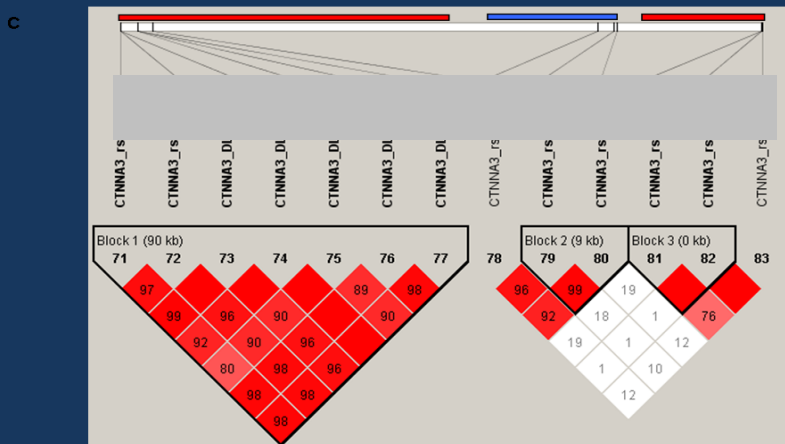
HLA; Human leukocyte antigen, CTNNA3; Catenin alpha 3, alpha-T catenin, NK2R; Neurokinin 2 receptor, NAT1; N-acetyl transferase, GSTP1; Glutathione transferase, CCL5; Chemokine receptor 5;AUC Area under curve

Genome wide scan using Affymetrix 500 k Gene chip in TDI-OA



SNPchip

Fine-mapping



⇒ **CTNNA3**

was associated with
the phenotype of
TDI-OA

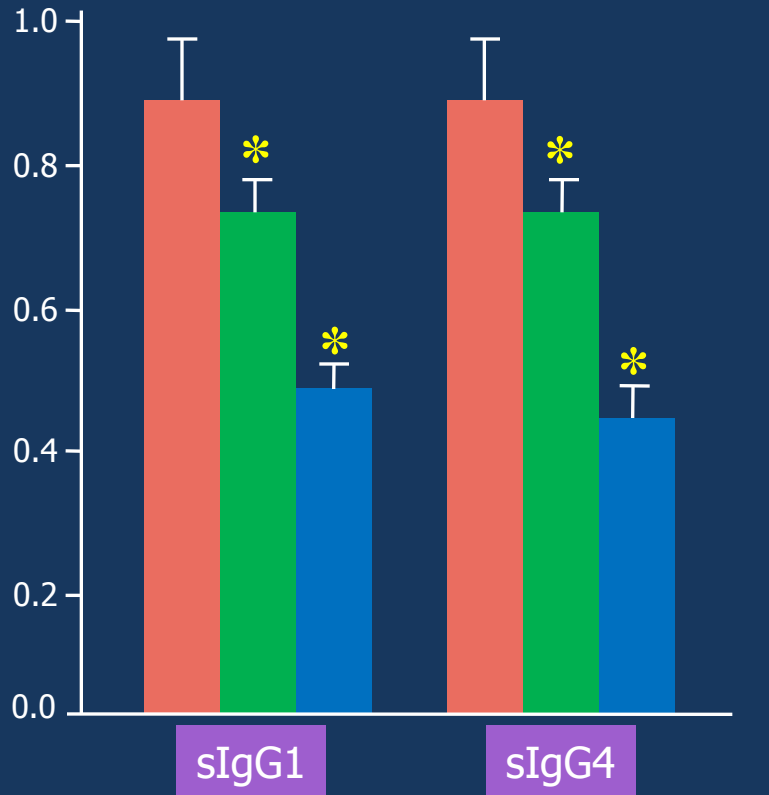
ADRB2 46 A>G polymorphism and **specific IgE** sensitization in TDI - exposed workers

Loci	Genotype /Haplotype	IgE to TDI-HSA		p-value*	OR (95% CI)
		positive n=23 (%)	negative n=117(%)		
46 A>G (Arg16Gly)	AA	11(47.8)	22(20.8)	0.013	14.95(1.77-126.01)
	AG	11(47.8)	55(51.9)	0.089	6.22(0.76-51.13)
	GG	1(4.3)	29(27.4)		R
252 G>A (Leu134Leu)	GG	12(52.2)	31(30.1)	0.045	8.87(1.05-74.93)
	AG	10(43.5)	51(49.5)	0.166	4.51(0.53-38.12)
	AA	1(4.3)	21(20.4)		R
523 C>A (Arg175Arg)	CC	13(56.5)	29(28.2)	0.021	12.33(1.45-104.74)
	AC	9(39.1)	51(49.5)	0.146	4.92(0.57-42.31)
	AA	1(4.3)	23(22.3)		R
ht1[TTACGC]	ht1/ht1	10(43.5)	20(18.7)	0.012	15.40(1.81-131.06)
	ht1/-	12(52.2)	57(53.3)	0.078	6.60(0.81-53.73)
	-/-	1(4.3)	30(28.0)		R
ht2[TTGCAA]	ht2/ht2	1(4.3)	18(16.8)	0.064	0.13(0.02-1.13)
	ht2/-	9(39.1)	55(51.4)	0.087	0.43(0.17-1.13)
	-/-	13(56.5)	34(31.8)		R

Baker's Asthma



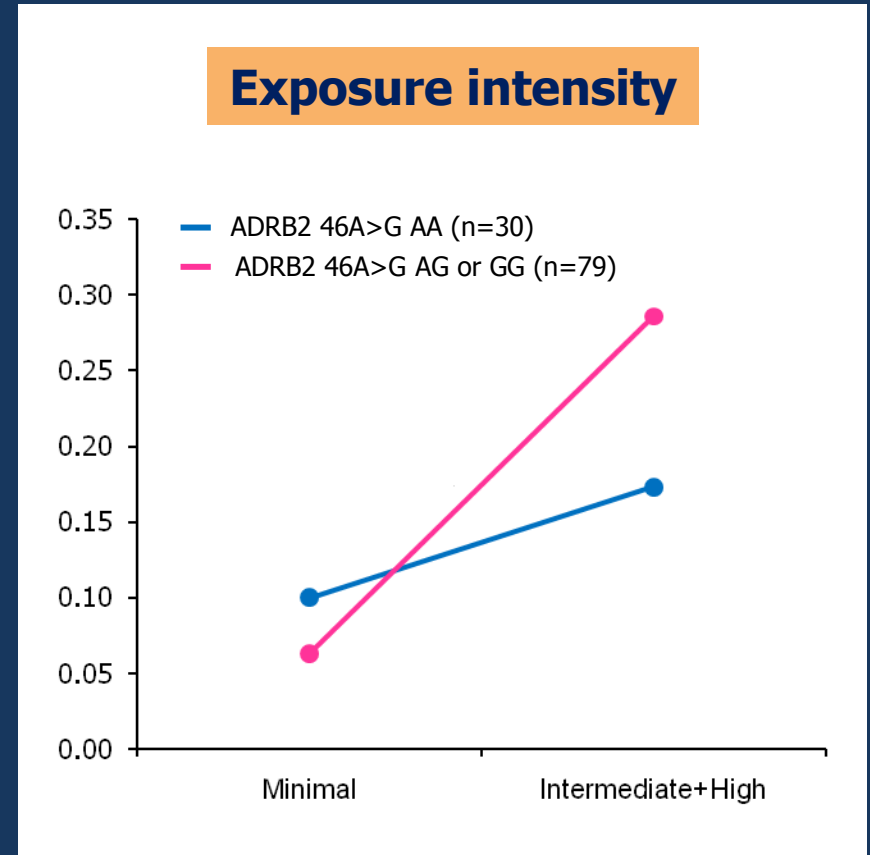
Serum specific IgG antibodies and ADRB2 interaction



Exposed workers with respiratory symptoms
Exposed workers without respiratory symptoms
non-exposed workers

* $p < 0.001$

Hur GY et al. Resp Med J, 102:545, 2008



Hur GY et al. Yonsei Med J, 52:488, 2010

Activated neutrophils in wheat exposed workers

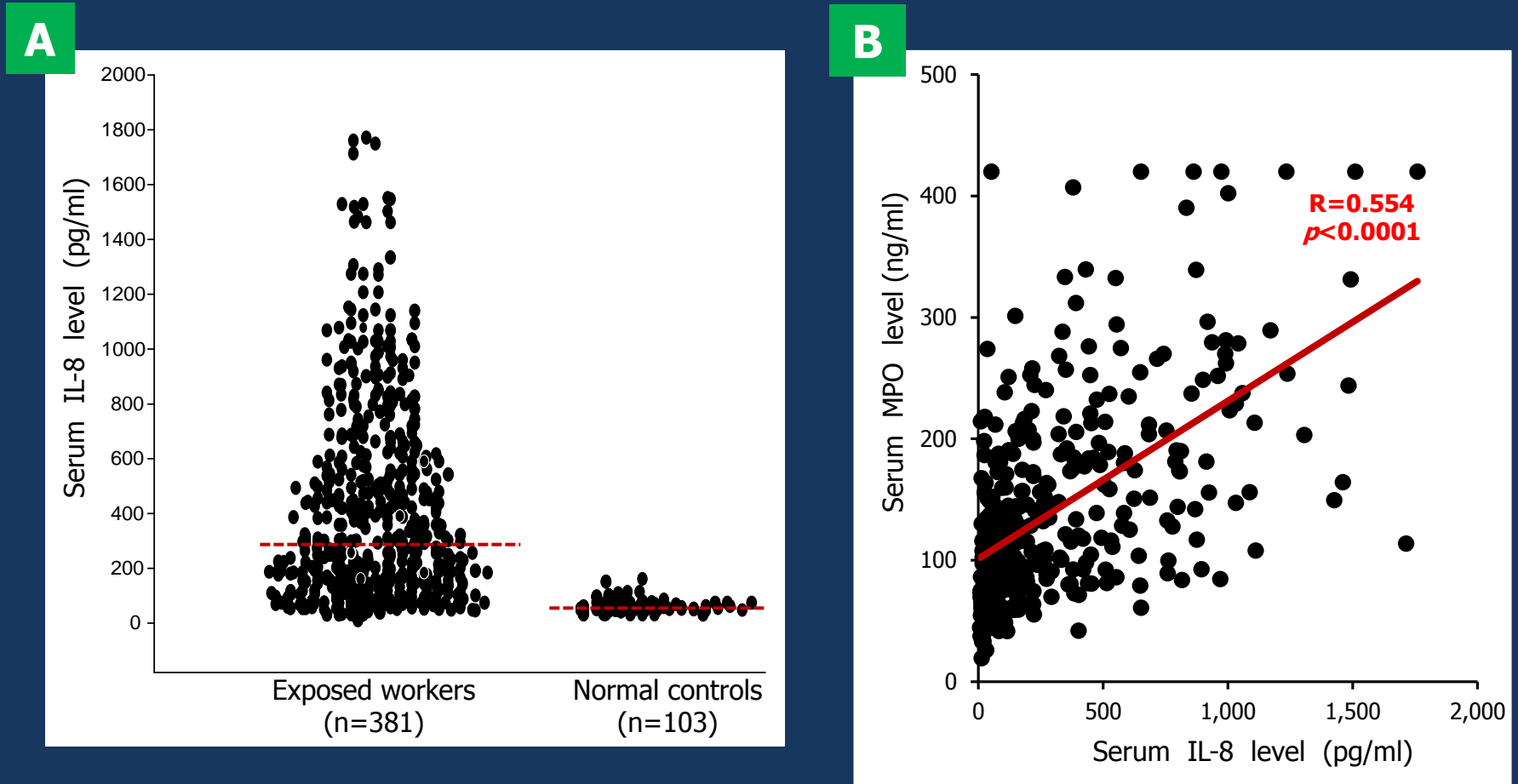


Fig. (A) Comparison of serum IL-8 level in the bakery workers and unexposed normal healthy controls. The mean value is indicated as horizontal line(---). (B) Correlation between the serum levels of MPO and IL-8 in the bakery workers.

TLR4 polymorphism in bakers asthma

 LPS → TLR4 → Neutrophil activation in wheat flour

	TLR4 -2026 A>G			TLR4 -1607 T>C		
	AA+AG (%)	GG (%)	<i>p</i>	TT+TC (%)	CC (%)	<i>p</i>
Work-related respiratory symptoms						
Upper	104 (32.5)	19(32.8)	1.000	108 (31.2)	11 (39.3)	0.402
Lower	52 (16.1)	2 (3.4)	0.007	54 (15.5)	0 (0)	0.021
Positive skin prick test to wheat flour						
	22 (7.0)	1 (1.8)	0.226	22 (6.5)	0 (0)	0.395
Specific IgE to wheat flour						
	20 (6.2)	5 (8.6)	0.562	21 (6.0)	3 (10.7)	0.408
IL-8 (pg/ml)*	299.15±19.92	283.74±46.03	0.754	297.92±18.85	286.92±52.60	0.872
MPO (ng/ml)*	141.61±4.68	129.23±8.02	0.284	284.70±22.35	311.73±28.70	0.458

Clinical features of occupational allergy in hospital personnel

High molecular weights

- Drugs: **digestive enzymes**
Porcine extracts, empynase,
Latex

Inhalation

- Occupational rhinitis
- Occupational asthma
- Allergic contact dermatitis
- Acute urticaria
- Anaphylaxis

Low molecular weights

- Antibiotics: **cephalosporin**, quinolone,
piperacillin
Cleaning and fixing agents

Skin

The pathogenic mechanisms

- Immediate (specific IgE) hypersensitivity reaction
- Delayed type hypersensitivity

Risk factor for IgE sensitization to digestive enzymes in HCWs

Digestives Allergy

- Specific IgE to digestives : OR 5.70 (1.919~16.923)
- SPT with digestives : OR 1.90 (0.865~4.179)

Asymptomatic
exposed workers

Work-related
Respiratory
symptoms

Occupational
Asthma
/ Rhinitis in HCW

- **ADRB2 46A>G AA [p=0.023, OR=1.694(1.077-2.666)]**
- **IL10-1082 A>G AG or GG [p=0.027, OR=2.251(1.2254.138)]**
 - **Total IgE, exposure intensity**

Perspectives

1

More efforts should be focused on developing **early diagnostic genetic markers** based on complicated pathogenic mechanisms of OA.

2

More efforts could be devoted for identifying **asymptomatic sensitizers** and **occupational rhinitis**, which are risk factors for OA.

3

We should set up a **surveillance system** to initiate the screening of OA patients using early diagnostic marker. If OA is suspected, we should refer the patients to a specialist to confirm OA.