

Genetic and environmental factors in the etiology of occupational asthma



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Prevalent causes of occupational asthma

Agent	Finland	Canada	UK	France	South Africa	Australia	Belgium	Belgium	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%
Persulphates	2%	na	na	6%	na	na	4%	2%	12%	na
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%

Vandenplas O, Allergy Asthma Immunol Res. 2011;3:157-67

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)**
Park HS et al. Int Arch Allergy Immunol, 2008

Occupational asthma : Genetic risk factors

Agent	No. of subjects with OA	Gene	Strength of association*
Anhydride acids	30 IgE+	HLA-DR3	OR 6.0
Trimellitic anhydride	11 IgE+	HLA-DR3	OR 16.0
Anhydride acids	52 IgE+	HLA-DQ5 HLA-DQB1*0501 HLA-DR1	OR 4.3 (1.7-11.0) OR 3.0 (1.2-7.4) OR 3.0 (1.2-11.0)
Platinum salts	44 SPT+	HLA-DR3 HLA-DR6	OR 2.3 (1.0-5.6) OR 0.4 (0.2-0.8)
Red cedar	56 SIC+	HLA-DQB1*0302 HLA-DQB1*0603 HLA-DQB1*0501 HLA-DRB1*0401-DQB1*0302 HLA-DRB1*0101-DQB1*0501	OR 4.9 (1.3-18.6) OR 2.9 (1.0-8.2) OR 0.3 (0.1-0.8) OR 10.3 OR 0.3

Vandenplas O, Allergy Asthma Immunol Res. 2011;3:157-67

Serum specific IgE and IgG to vapor type of TDI-HSA conjugate

Specific antibody	TDI-OA (n=66)	Asymptomatic exposed workers (n=167)	Allergic Asthma (n=64)	Unexposed healthy controls (n=113)	p value
Specific IgG to TDI-HSA					
Liquid	11 (16.7%)	9 (5.3%)	0	3 (2.7%)	<0.0001
↑ Vapor-80%V	20 (30.8%)	16 (9.6%)	1 (1.6%)	2 (1.8%)	<0.0001
Specific IgE to TDI-HSA					
Liquid	5 (7.6%)	1 (0.6%)	0	4 (3.5%)	0.02
↑ Vapor-80%V	29 (43.9%)	7 (4.2%)	0	1 (0.9%)	<0.0001

Ye YM and Park HS, J Allergy Clin Immunol. 2006

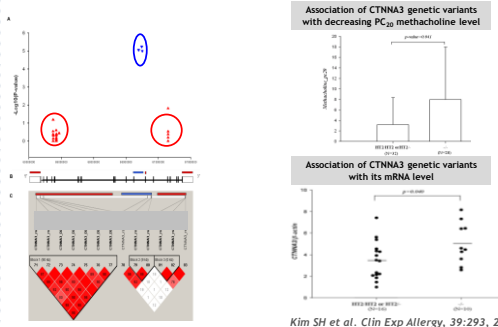
ADR2 46 A>G polymorphism and specific IgE sensitization in TDI - exposed workers

Loci	Genotype /Haplotype	IgE to TDI-HSA		p-value*	OR (95% CI)
		positive	negative		
		n=23 (5)	n=117(5)		
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 (Leu154Leu)	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

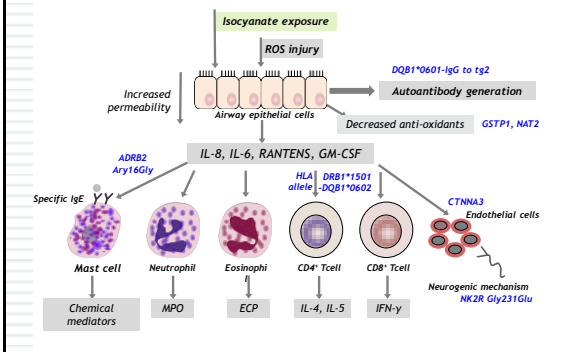
Ye YM et al. AAIR 2:260, 2010

GWAS study in TDI-OA

CTNNA3 was associated with the phenotype of TDI-OA



Genetic effect on airway inflammation in TDI-OA



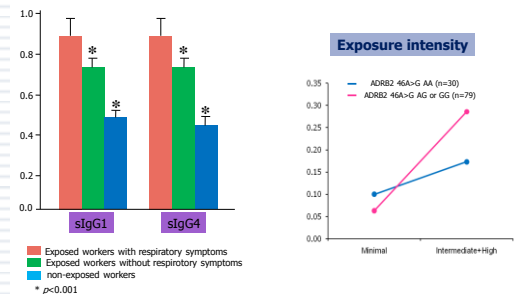
IgE mediate mechanism in baker's asthma

Association of clinical parameters with the skin prick test results and specific IgE antibodies to wheat flour.

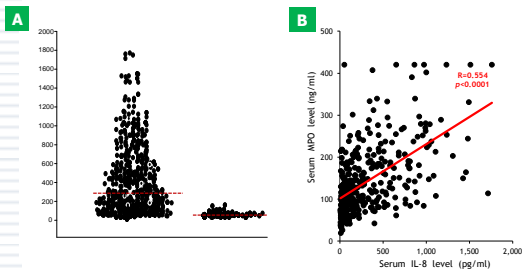
	Skin prick test		Specific IgE	
	Positive	P	Positive	P
Presence of work-related symptoms	15/67	<0.001	13/65	0.060
lower respiratory symptoms	10/53	<0.01	13/52	<0.01
Atopy	21/134	<0.001	14/131	<0.05
Highly exposed group	20/142	0.412	13/142	0.447
Smoking	7/59	0.125	8/57	0.590
Other exposed allergens				
House dust mite	17/108	<0.005	10/105	0.171
Rye	11/12	<0.001	8/12	<0.001
Yeast	2/15	0.357	2/14	0.237
Storage mite	4/18	0.052	1/17	1.000

Hur GY et al. Resp Med. 2008

Serum specific IgG antibodies and ADRB2 interaction



Activated neutrophils in wheat exposed workers



Cho HJ et al. Ann Allergy Asthma Immunol, 107:57, 2011

TLR4 polymorphism in bakers asthma

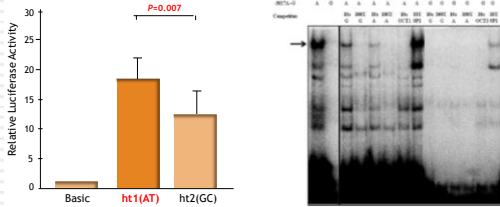
♣ LPS → TLR4 → Neutrophil activation in wheat flour

	TLR4 -2026 A>G			TLR4 -1607 T>C		
	AA>AG (%)	GG (%)	p	TT>TC (%)	CC (%)	p
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

Cho HJ et al. Ann Allergy Asthma Immunol, 107:57, 2011

TLR4 polymorphism and bakers' asthma

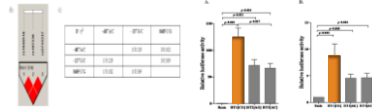
In vitro promoter activity and EMSA findings



Cho HJ et al. *Ann Allergy Asthma Immunol*, 107:57, 2011

Effect of IL-18 gene polymorphisms on sensitization to wheat flour in bakery workers

	IL18_p3_137_G>C			IL18_8685_C>G		
	GG(%)	GC+CC (%)	p	CC(%)	CG+GG(%)	p
Atopy	38(35.8%)	69(34.2%)	0.768	48(36.9%)	79(33.3%)	0.489
Total IgE (kU/L)	4.3±1.4	4.5±1.6	0.333	4.5±1.5	4.4±1.4	0.488
WRS						
Upper(+)	89(32)	32(34.8)	0.624	40(30.5%)	82(33.9%)	0.51
Lower(+)	35(12.6)	15(16.3)	0.366	20(15.3%)	31(12.8%)	0.51
Positive skin prick test to wheat flour	11(4)	12(13)	0.002	9(6.9%)	14(5.9%)	0.693
Specific IgE to wheat flour	14(5)	9(9.8)	0.102	8(6.1%)	16(6.6%)	0.85
IL-18 (pg/ml)*	5.5±0.4	5.5±0.4	0.159	5.6±0.4	5.5±0.4	0.081



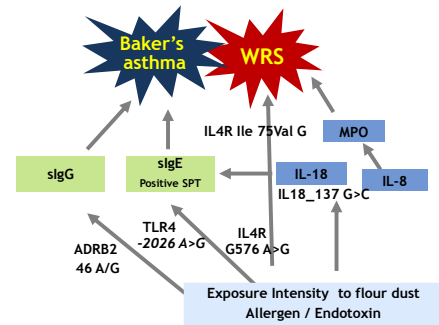
Kim SH et al. *J Kor Med Sci*, 2012

IL4Ra polymorphism in baker's asthma

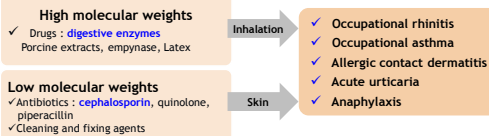
	IL-4Ra Ile75Val A>G			IL-4Ra G576A A>G		
	AA	AG+GG	P	AA	AG+GG	P
Age	34.99±8.02/69	35.02±7.71/300	0.973	34.9±7.8	35.5±7.7	0.545
Gender (male)	39(56.5%)	167(55.7%)	0.897	148(54.2%)	56(60.2%)	0.314
working period (yrs)	3.91±3.37/68	3.96±3.51/292	0.905	3.8±3.4	4.3±3.7	0.282
smoking status	16(57.1%)	64(61.0%)	0.714	56(57.7%)	23(67.6%)	0.309
Work-related respiratory Sx						
lower (+)	2(2.9%)	48(16%)	0.004	34(12.5%)	17(18.3%)	0.161
Atopy	21(31.4%)	105(35.7%)	0.407	101(37.8%)	25(26.9%)	0.057
Log total IgE	4.54±1.67/69	4.36±1.42/299	0.361	4.5±1.4	4.1±1.5	0.052
SPT to wheat flour (+)	2(2.9%)	21(7.1%)	0.195	22(8.2%)	1(1.1%)	0.015
Specific IgE to wheat flour (+)	4(5.8%)	20(6.7%)	0.792	19(7%)	5(5.4%)	0.594

Hur GY et al. *submitted*, 2012

Genetic mechanisms of baker's asthma



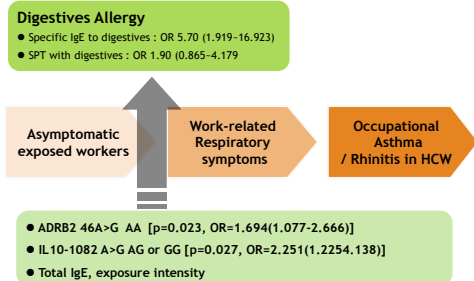
Clinical features of occupational allergy in hospital personnel



The pathogenic mechanisms

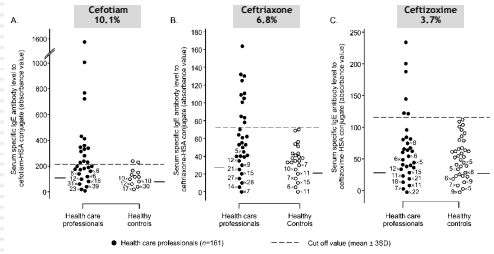
- Immediate (specific IgE) hypersensitivity reaction
- Delayed type hypersensitivity

Genetic risk factor for IgE sensitization to digestive enzymes



Ye YM et al. *Int Arch Allergy Immunol*, 153:193, 2010

The IgE sensitization to cephalosporins in HCWs via skin or inhalation route : 17.1 %

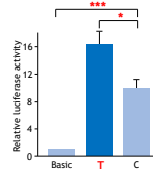


153 exposed subjects HCWs and 143 unexposed healthy controls (NC) in a single university hospital. Serum specific IgE to cephalosporin-HSA conjugate was measured by ELISA.

Kim JE et al, Allergy Asthma Immunol Res. 2012

Genetic risk factor for the IgE sensitization to cephalosporin in HCWs

Genes	Genotype	IgE sensitization to Cephalosporins		P value	Adjusted OR
		Positive	Negative		
FCER1B -109 T>C	TT	15/23(65.2)	28/80(35)	0.012	3.553
	CT or CC	8(34.8)	52(65)		
FCER1B q1 237 A>G	AA	23/25(92)	53/79(67.1)	NS	
	AG or GG	2(8)	26(32.9)		



Increased transcriptional activity of FcεR1B on mast cells in HCWs carrying T allele

→ Enhance IgE sensitization in exposed workers

Nam YH et al. J Kor Med Sci, 2012

Conclusion

1 Several susceptible genetic risk factors including HLA alleles and SNPs could be genetic markers for OA

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

THANK YOU

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