

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%

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

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	negative		
		n=23 (%)	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

Genetic and protein biomarkers for isocyanate-induced asthma

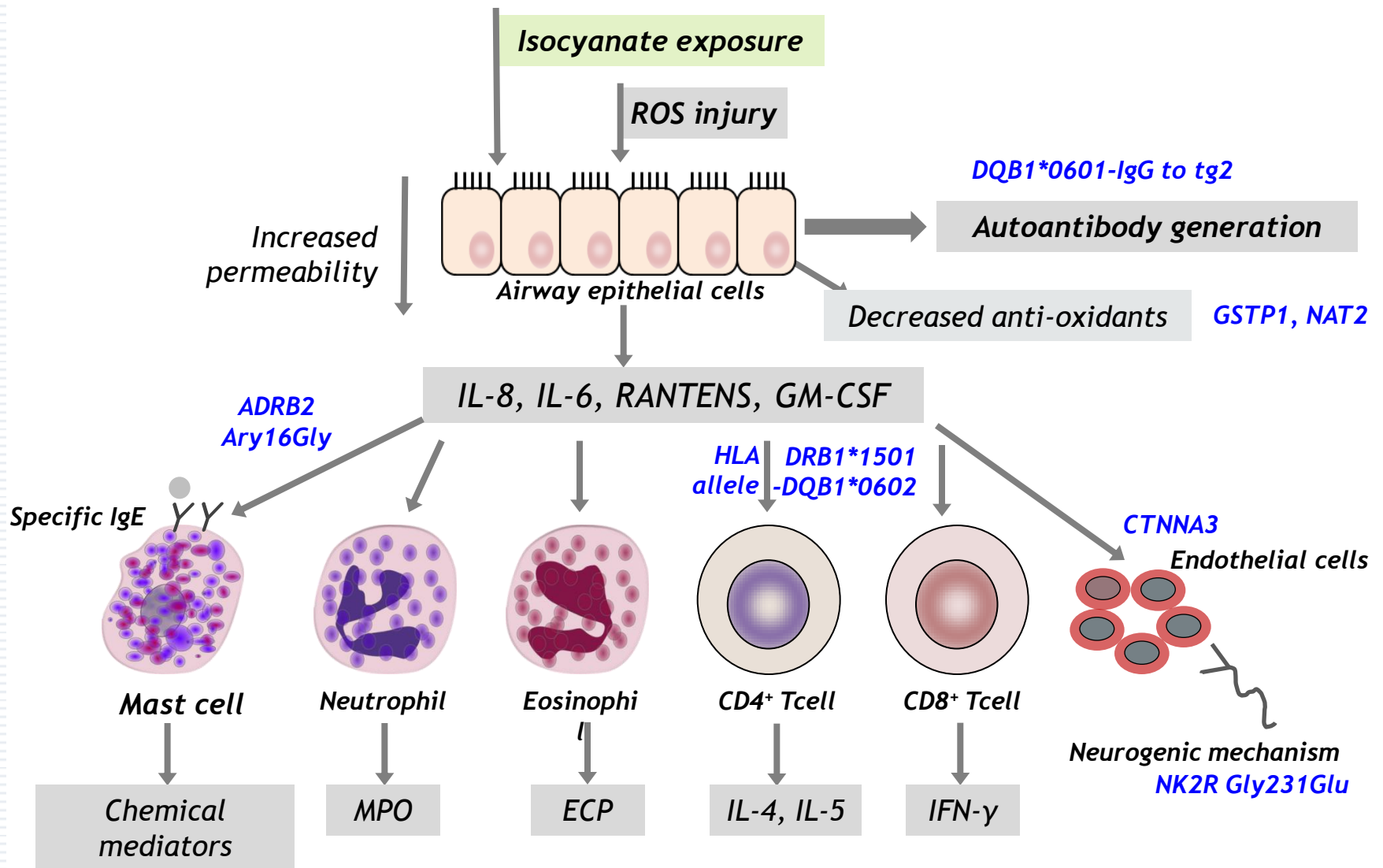
Gene	Full name	Genotype	Association	Population
Genetic biomarkers				
HLA	Human leukocyte antigen	DRB1*1501-DQB1*0602-DPB1*	Yes	Korean
HLA	Human leukocyte antigen	DQB1*0503	Yes	European
HLA	Human leukocyte antigen	DQB1 *05	Yes	Swedish
HLA	Human leukocyte antigen	DQB1*0501	No	European
CTNNA3	Catenin alpha 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

Protein biomarkers

Cutoffs	Sensitivity (%)	Specificity (%)	AUC (95%CI)	P value
Ferritin<69.84ng/ml	85.71	71.48	0.786	0.053
Transferrin>2.48ug/mL	71.43	51.02	0.612	0.4
Ferritin<69.84ng/ml and transferrin>2.48 ug/ml	71.43	85.71	0.786	0.02

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

Genetic effect on airway inflammation in TDI-OA



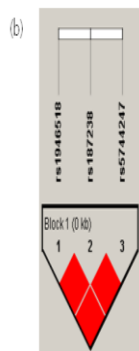
TLR4 polymorphism in bakers asthma

♣ **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

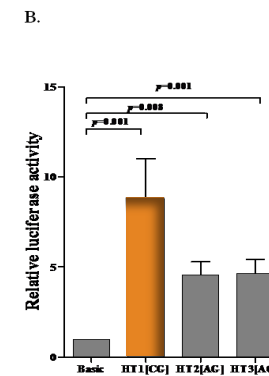
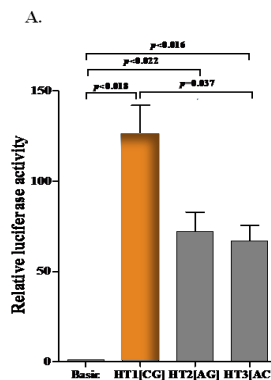
Effect of IL-18 gene polymorphisms on sensitization to wheat flour in bakery workers

	IL18_p3_137_ G>C			IL18_8685_ C>G		
	GG(%)	GC+CC (%)	p	CC(%)	CG+GG(%)	p
Atopy	38(35.8%)	89(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



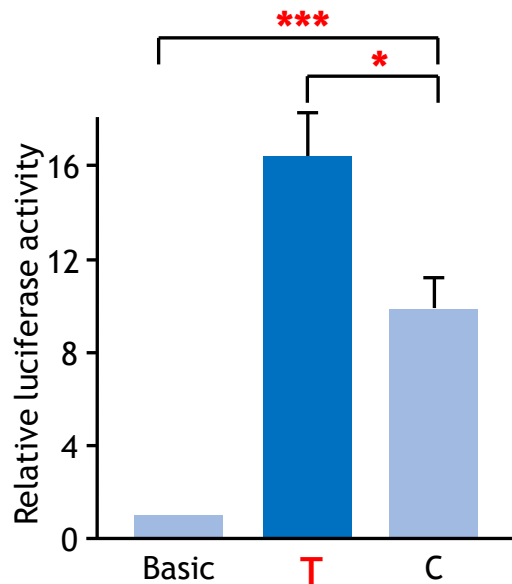
(c)

D ² /y ²	-607 A/C	-137 G/C	8685 C/G
-607 A/C		1/0.129	1/0.102
-137 G/C	1/0.129		1/0.569
8685 C/G	1/0.102	1/0.569	



Genetic risk factor for the IgE sensitization to cephalosporin in HCWs

Genes	Genotype	IgE sensitization to Cephalosporins		P value	Adjusted OR 95% CI
		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)		1.324~9.532
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

THANK YOU

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