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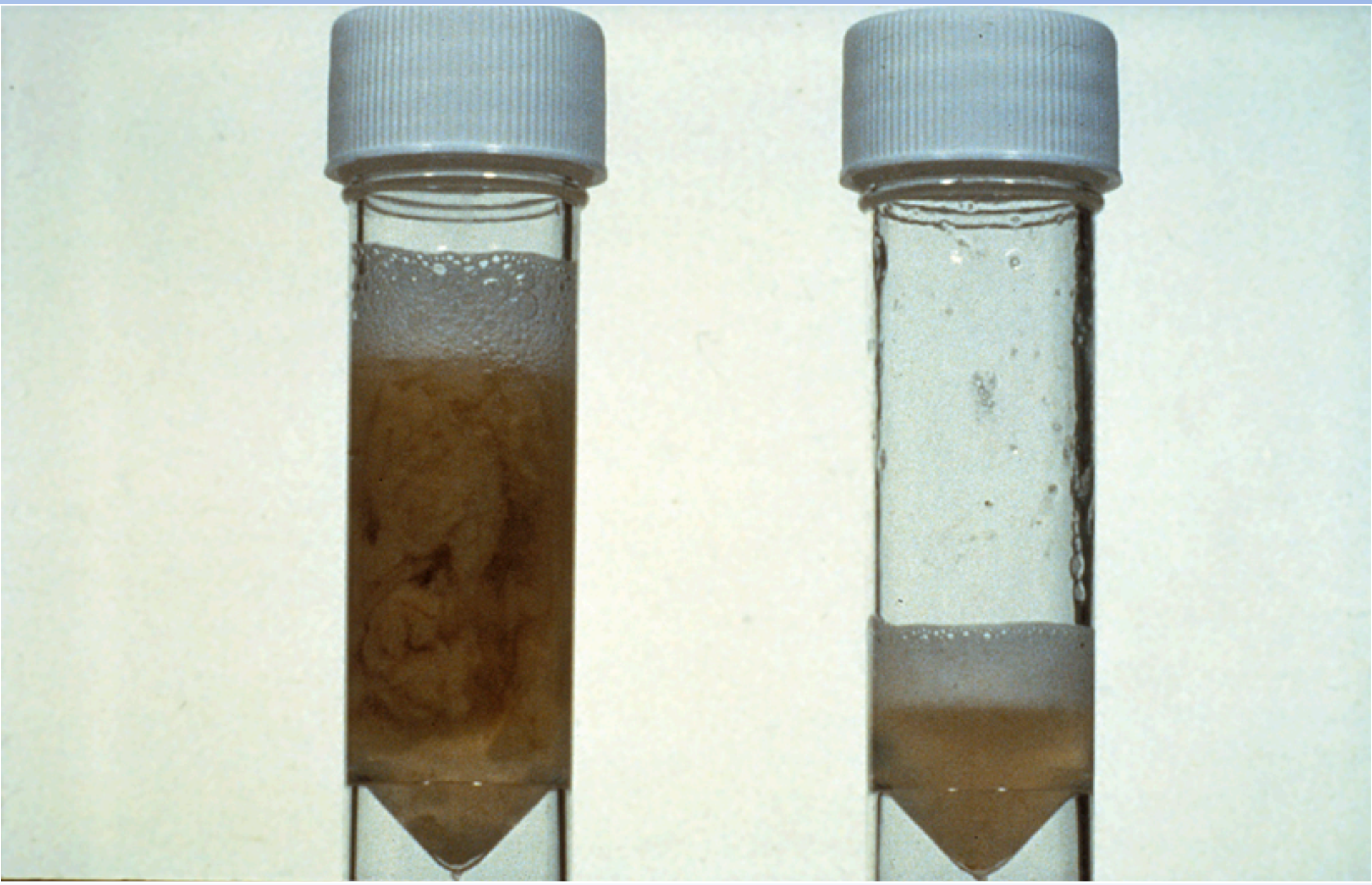
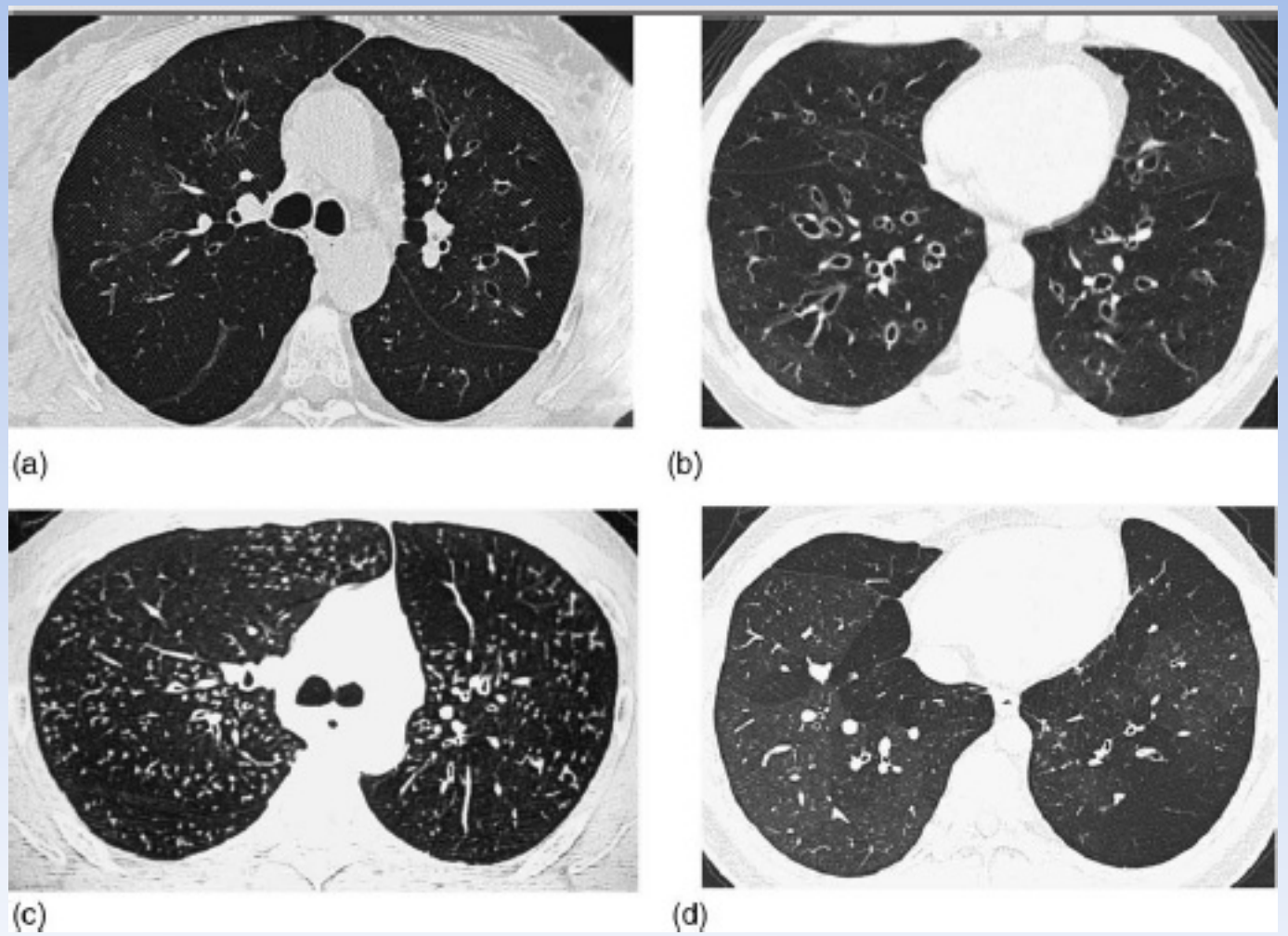
Immune regulation in idiopathic bronchiectasis

Bronchiectasis

- Irreversible, abnormal dilatation of one or more bronchi, with chronic airway inflammation. Associated chronic cough, sputum production, recurrent chest infections, airflow obstruction, and malaise
- Prevalence: Australian Aborigines & Alaskan Native children 14/1000; & 1/1,000,000 Finnish children
- Pathological endpoint with many underlying causes

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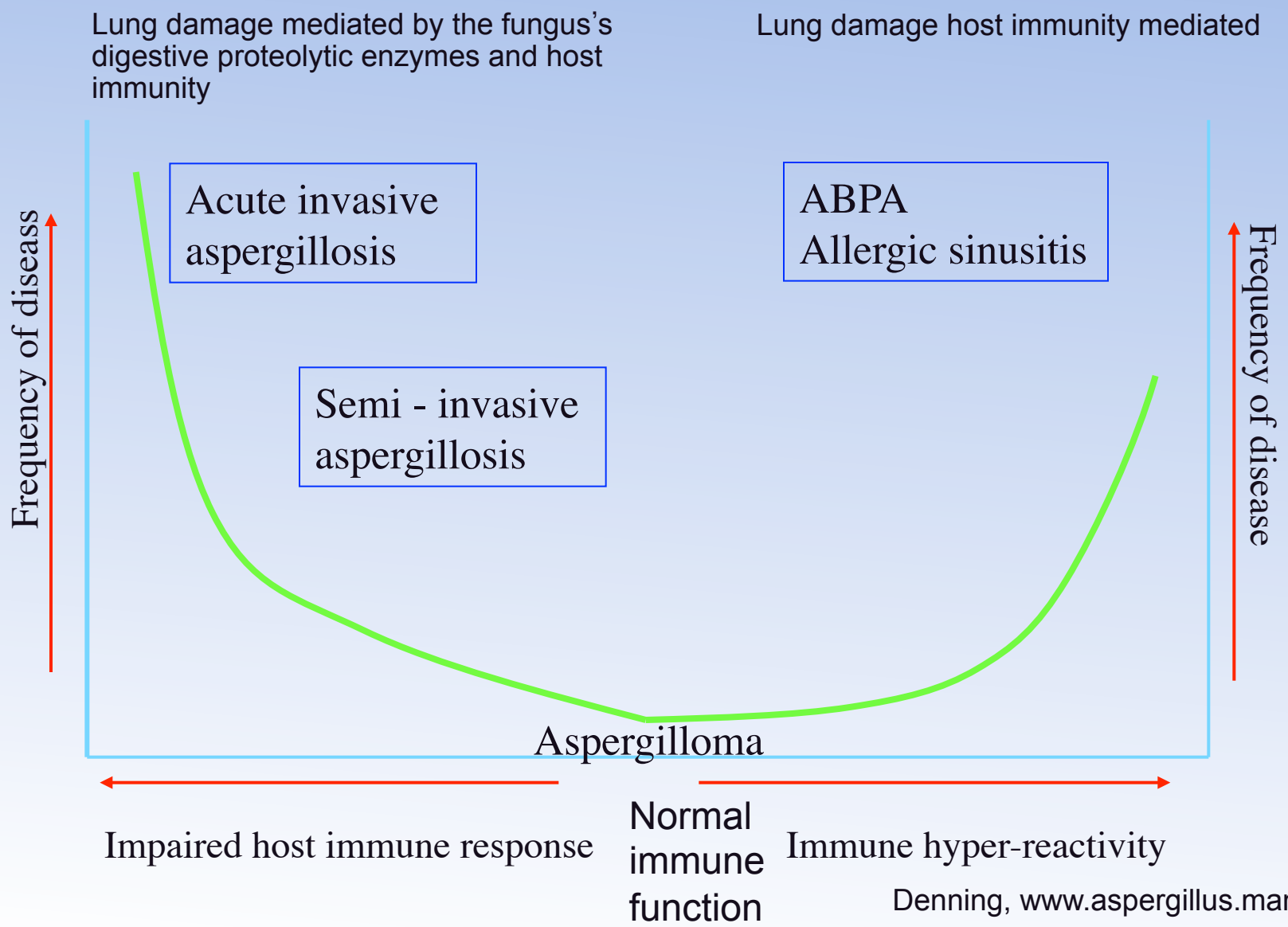
Causes and associations of bronchiectasis

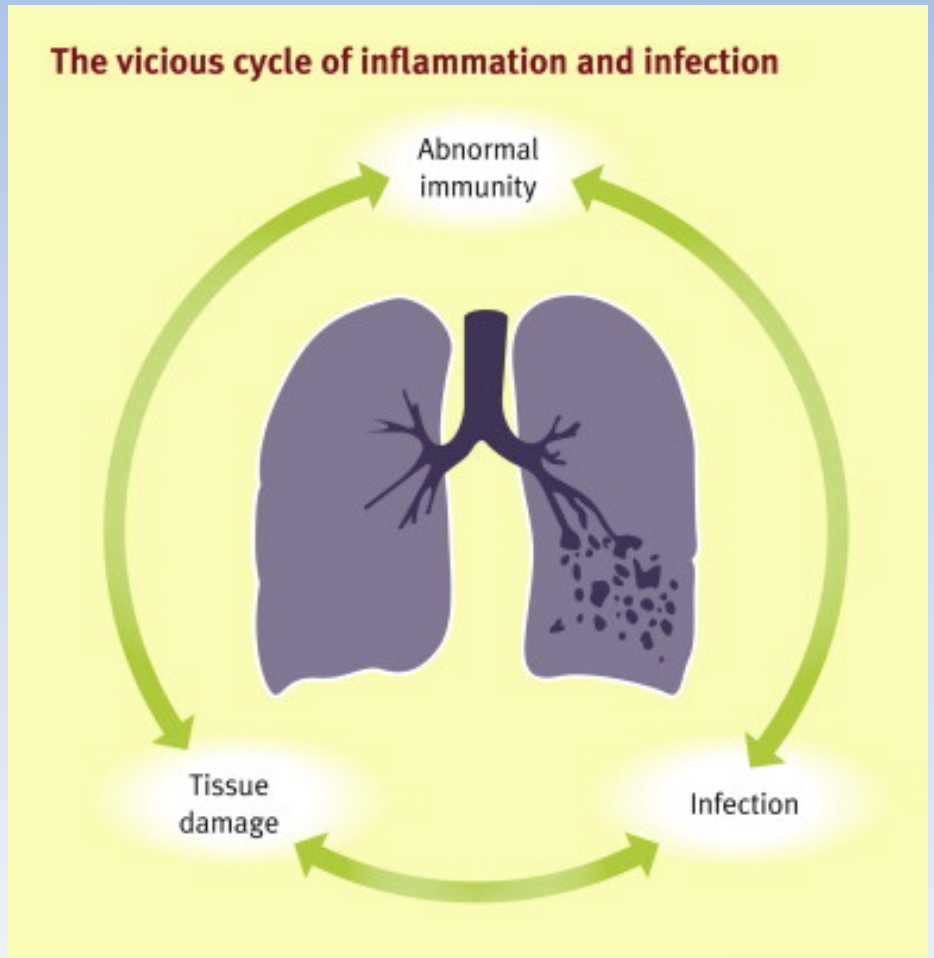
	Papworth (n=150)	Brompton (n=165)
• Idiopathic	53	26
• Postinfectious	29	34
• Humoral immunodeficiency	8	7
• Allergic bronchopulmonary aspergillosis ABPA	7	8
• Aspiration/GI reflux	4	1
• Rheumatoid arthritis	3	2
• Youngs Syndrome	3	3
• Cystic Fibrosis	3	1
• Ciliary dysfunction	1.5	10
• Ulcerative colitis	<1	3
• Panbronchiolitis	<1	2
• Congenital	<1	-
• Yellow nail syndrome	-	2

[Pasteur et al, Am J Respir Crit Care Med 2000; 162:1277 & Shoemark et al, Resp Med 2007; 101:1163]

Aspergillus lung disease & the host immune response



Denning, www.aspergillus.man.ac.uk



Boyton RJ. (2008). **Bronchiectasis.** Medicine. 36:315-320.

Growing evidence from clinical data and genetic studies that there is dysregulated immune function in bronchiectasis

Altered susceptibility to specific pathogens

Dysregulated inflammatory response

Evidence for dysregulated immunity in bronchiectasis

- Increased susceptibility to infection - bacterial, non-tuberculous mycobacterial (NTM), and aspergillus-related lung disease
- Associated with autoimmune disease such as inflammatory bowel disease, ulcerative colitis
- Neutrophils are markedly raised, as predicted from high local levels IL-8
- Associated with immune deficiency syndromes such as TAP deficiency syndrome

Bronchiectasis associated with increased susceptibility to specific pathogens

Haemophilus influenzae
Haemophilus parainfluenzae
Pseudomonas aeruginosa

Streptococcus pneumoniae
Moraxella catarrhalis
Staphylocccus aureus
Stenotrophomonas maltophilia
Gram-negative enterobacter

- Non-tuberculosis mycobacteria
  - *M. avium complex (MAC)*
  - *M. kansasii*
  - *M. chelonae*
  - *M. fortuitum*
  - *M. malmoense*
  - *M. xenopi*
- Aspergillus-related disease

Non-tuberculous mycobacteria (NTM) in bronchiectasis

- NTM are ubiquitous environmental organisms
- Prevalence of NTM in patients with bronchiectasis is 2%
- *Mycobacterium avium complex* (MAC) is the most frequent NTM isolated in bronchiectasis
- *Pseudomonas aeruginosa* and *Staphylococcus aureus* are frequently co-cultured
- NTM may be associated with progressive lung damage
  - HRCT thorax (progressive bronchiectasis, new nodules, new/progression of cavities, consolidation)
- A mutation in the interferon-gamma-receptor gene linked to susceptibility to mycobacterial infection

[Newport et al N Engl J Med 1996; 335:1941] [Wickremasinghe M et al. Thorax 2005; 60:1045]

Nontuberculous mycobacterial (NTM) disease and aspergillus-related lung disease in bronchiectasis

- Positive *Aspergillus* serology/radiology more prevalent in bronchiectasis complicated by NTM

Independent variable	Simple regression OR (95% CI) p value	Multiple regression* OR (95% CI) p value
NTM lung disease Y/N	7.01 (2.3-21.1) 0.0005	5.1 (1.5-17.0) 0.008
FEV1 L	0.25 (0.10-0.64) 0.003	0.34 (0.13-0.89) 0.028

*multiple logistic regression model with *aspergillus*-related lung disease as the binary dependent variable and NTM lung disease, age and FEV1 as independent variables.

[Kunst H et al Eur Resp J 2006; 28:352]

Interferon-γ therapy beneficial in two patients with progressive chronic pulmonary aspergillosis

- Semi-invasive aspergillosis not responding to conventional anti-fungal therapy
- Impaired interferon-γ production

	Controls	Case 1	Case 2
	IFN-γ $pgmL^{-1}$		
PHA	11759 ± 6122 (3613-19989)	1000	2239
PHA + IL-12	41201 ± 19957 (9307-65875)	15500	14252
	TNF-γ $pgmL^{-1}$		
LPS	1097 ± 596 (493-1942)	2087	2629
LPS + IFN-γ	3837 ± 1767 (303-7317)	10166	8199

- Adjunctive sc interferon-γ therapy (50mgm^{-2}) associated with significant clinical improvement

[Kelleher P et al Eur Resp J 2006; 27:1307]

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Bronchiectasis associated with autoimmune disease

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Relapsing polychondritis
- Inflammatory bowel disease - Ulcerative colitis and Crohn's disease

Gene polymorphisms in bronchiectasis associated with ulcerative colitis

IFNγ (+874)AA genotype associated with 5.6-fold increased susceptibility to bronchiectasis associated with UC

- IFNγ (+874T/A) - functional gene polymorphism.
  Associated with susceptibility to mycobacterial infection
- Individuals homozygous for IFNγ (+874)A 3.75-fold increased risk of mycobacterial infection
- High IFNγ production associated with +874T allele.
- TT genotype never seen in individuals with bronchiectasis associated with UC [Boyton et al.Tissue Antigens 2006; 68: 325]

Gene polymorphisms in bronchiectasis associated with ulcerative colitis

CXCR-1 (+2607)GC genotype associated with 8.3-fold increased susceptibility to bronchiectasis associated with UC

- CXCR-1 (+2607 G/C) -AA substitution from serine to threonine at residue of CXCR-1 critical for ligand binding - alters binding of IL-8 to CXCR-1
- Airway inflammation in bronchiectasis characterised by increased IL-8
- IL-8 binds CXCR-1 receptor expressed on neutrophils, T and natural killer (NK) cells and promotes neutrophil trafficking to the lung

[Boyton et al.Tissue Antigens 2006; 68: 325]

Gene polymorphisms in bronchiectasis associated with ulcerative colitis

UC attributed to T cell induced mucosal inflammation, loss of control of mucosal inflammation by regulatory T cells and strong upregulation of CXCR-1 receptors in mucosal epithelium

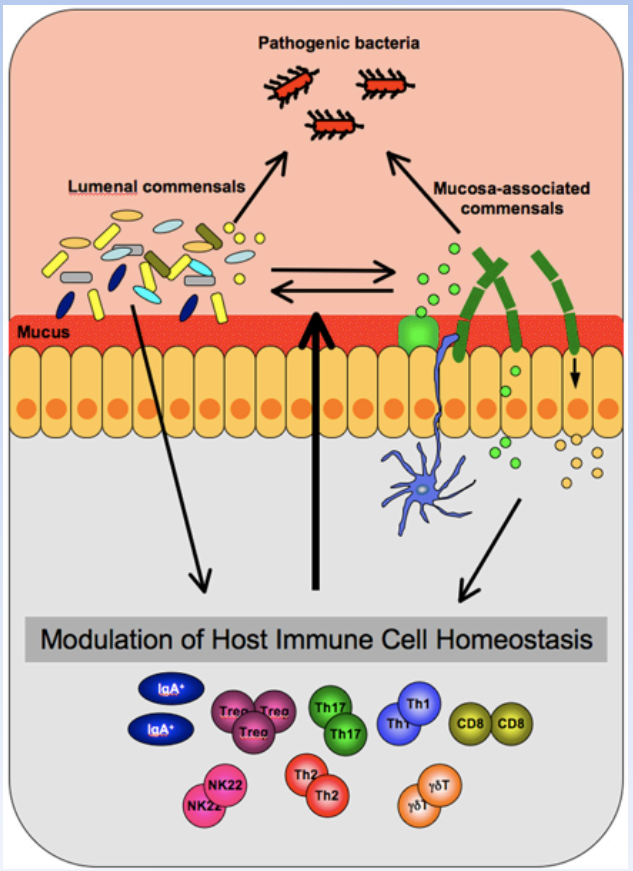
CXCR-1 (+2607)GC and IFNγ (+874)AA genotype associated with 56-fold increased susceptibility to bronchiectasis associated with UC (OR = 56; CI 5.4-582.9, P<0.0003)

Implicates a common aetiological link through autoimmune mechanisms between UC and steroid responsive bronchiectasis

[Boyton et al.Tissue Antigens 2006; 68: 325]

Modulation of T cell homeostasis and mucosal immune responses by signals from commensal bacteria

Th17:Treg balance



Ivanov I et al Curr Opin Micribiol 2011, 14: 106

Bronchiectasis associated with HLA-DR1, DQ5 implicates a role for adaptive immunity

Idiopathic bronchiectasis associated with
HLA-DRB1*01 DQA1*01/DQB1*05
(OR 2.19, 95%CI 1.15-4.16, p=0.0152)

May operate through influencing susceptibility to specific pathogens or self reactivity

[Boyton et al.Clin Exp Immunol 2008]

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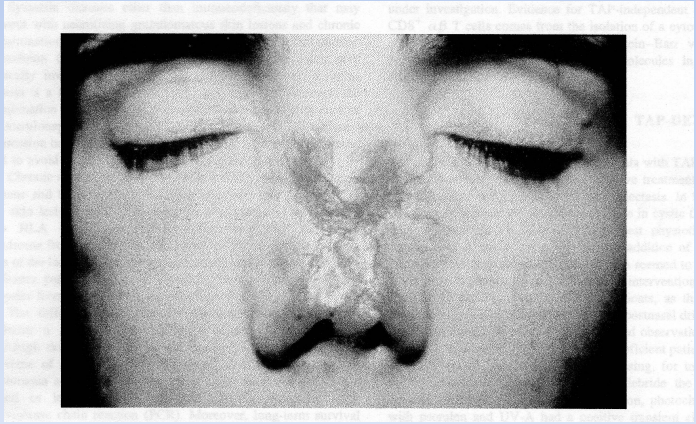
Bronchiectasis is a clincial feature of TAP deficiency syndrome

Table 1. Clinical manifestations in 10 patients with TAP deficiency syndrome

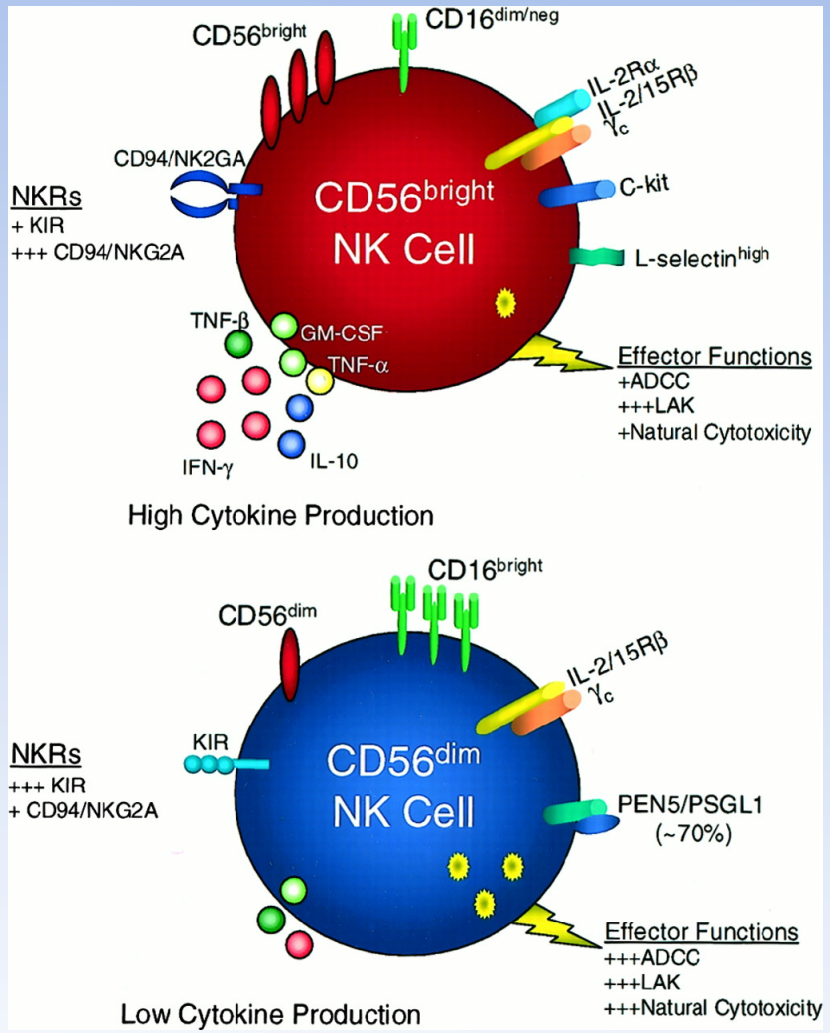
Ear/nose/throat (10/10):
Chronic sinusitis
Nasal disease (discharge, polyps, septum ulcers)
Postnasal drip syndrome
Otitis media
Mastoiditis
Erosion/destruction of facial tissues around the nose
Lungs (8/10):
Chronic spastic bronchitis
Recurrent bacterial pneumonia
Bronchiectasis
Skin (7/10):
Necrotizing granulomatous skin lesions (7/7):
Brownish nodular or plaque-like dermal infiltration, on extremities and midface, often ulceration and scar formation; often asymmetrical
Leucocytoclastic vasculitis (2/7):*
Symmetrical purpura on arms and legs
Nervous system (2/10):
Cerebral abscess
Encephalomyelitis
Gastrointestinal tract (2/10):
Chronic gastritis
Pseudomembranous colitis
Other organs (2/10):
Non-erosive symmetrical polyarthritis (2/10)*
Retinal vasculitis (1/10)

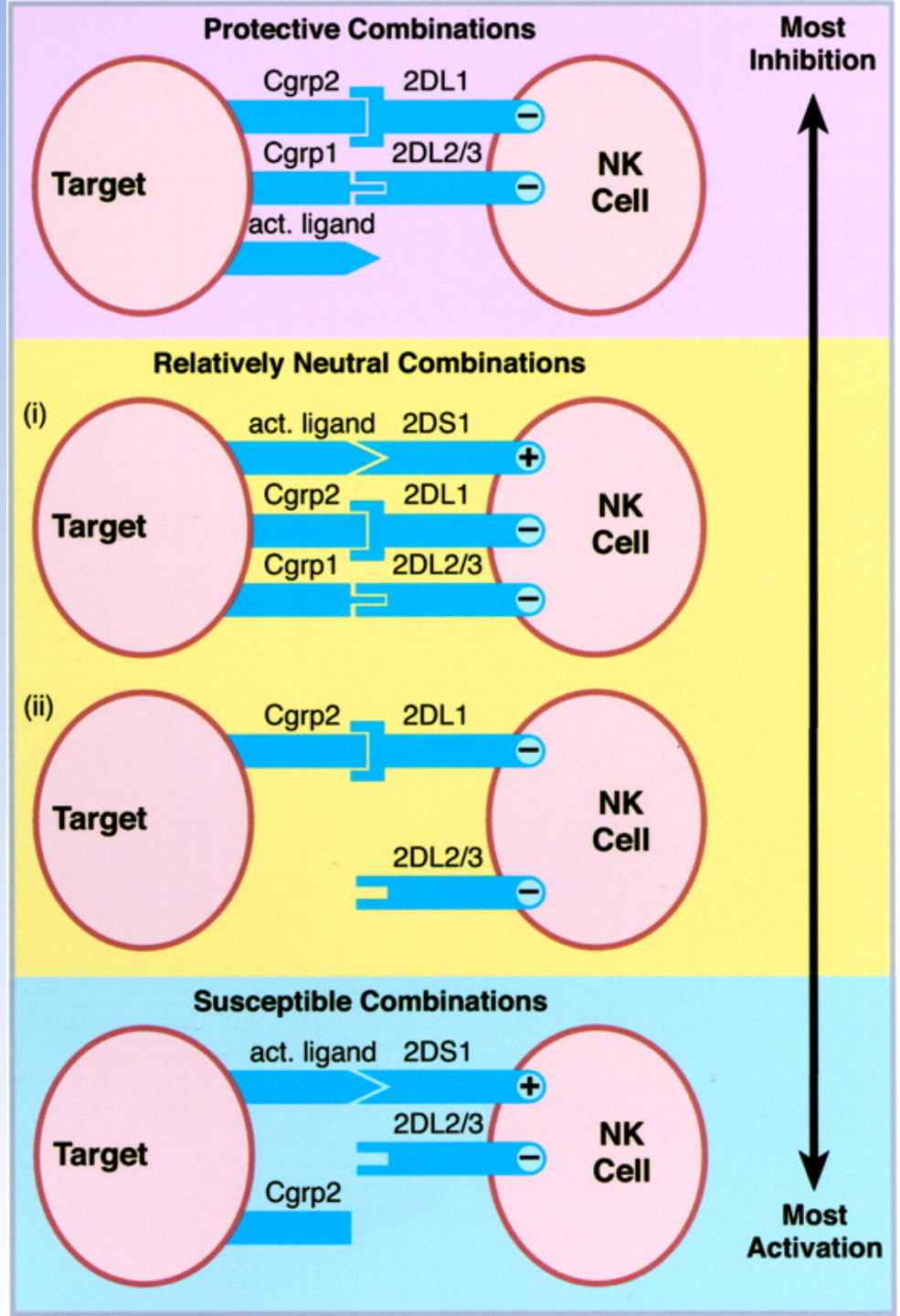


Families with HLA class I deficiencies resulting from mutations in the ***T***ransporter associated with ***A***ntigen ***P***rocessing gene 2 (TAP-2), leading to a complex syndrome that includes familial bronchiectasis.
[review by Enzo Cerundolo, Clin. Exp Immunol. 121, 173]

NK cell activation

- A tug-of-war between between activatory and inhibitory ligand-receptor interactions between NK cell and target cell
- Several such pairings - one group is the interaction between HLA-C molecules and KIRs (killer immunoglobulin-like receptors)
- Different HLA-C alleles interact with different KIRS - Asn/Lys at position 80
- Some KIRS have short cytoplasmic tails, the 2DS family, and give an activatory signal to the cell, while others, the 2DL family, have long cytoplasmic tails and give an inhibitory signal
- Different individual carry different numbers of KIR genes
- Each KIR locus is highly polymorphic
- Within an individual, KIR expression varies between clones





Mary Carrington, 2005

HLA-C group 1 / group 2 motifs and their corresponding HLA-C alleles and KIR receptors

HLA-C	Amino Acid position-80	Corresponding HLA-C Alleles	Corresponding KIR
Group 1	Asn	Cw*01 (02, 03) Cw*03 (02, 03, 041) Cw*07 (01, 02, 03, 04, 05, 06) Cw*08 (01, 02, 03) Cw*12 (021, 022, 03, 06) Cw*14 (002, 03) Cw*16 (01, 03, 041)	2DL2, 2DL3, 2DS2
Group 2	Lys	Cw*02 (021, 022, 023, 024) Cw*04 (01) Cw*05 (01) Cw*06 (02) Cw*07 (07) Cw*12 (041, 042, 05) Cw*15 (02, 03, 04, 051, 052) Cw*16 (02) Cw*17 (01, 02) Cw*18 (01, 02)	2DL1, 2DS1

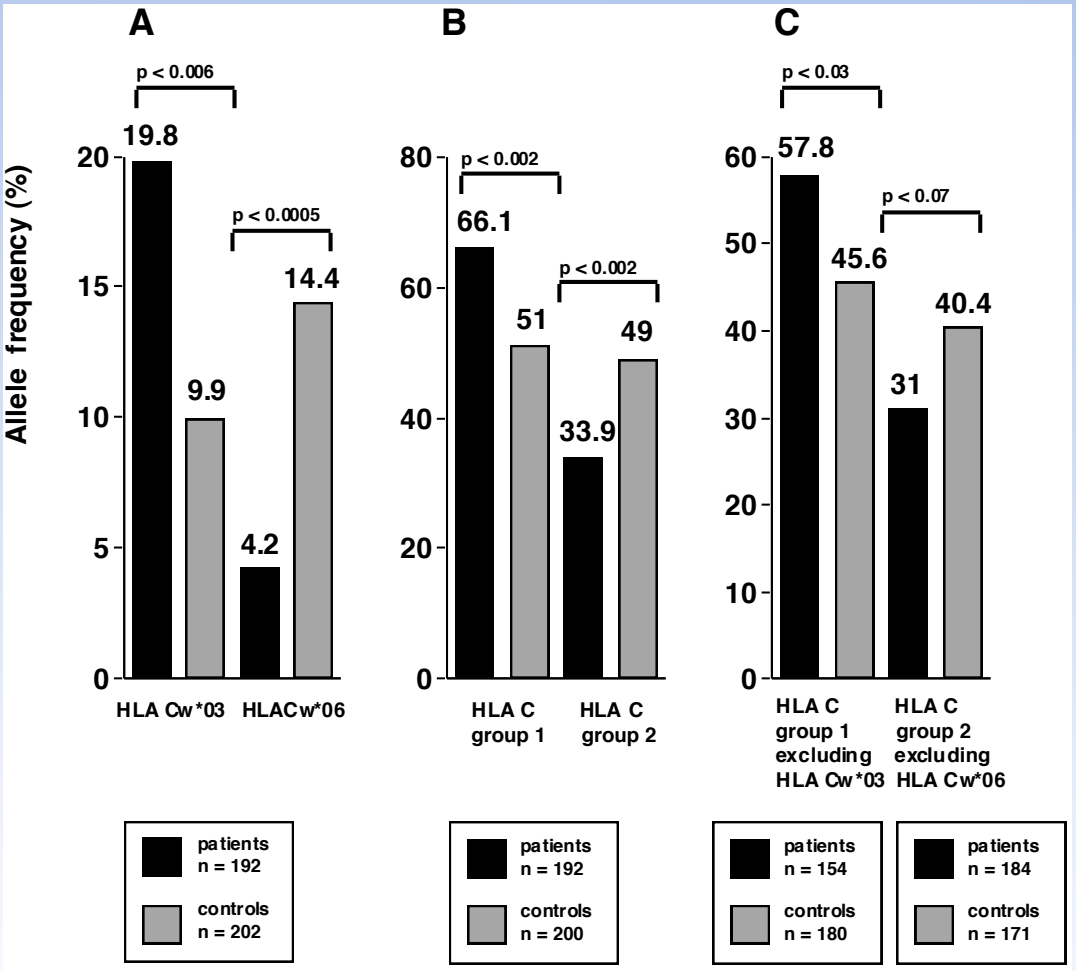
HLA Cw*03 allele increased frequency in idiopathic bronchiectasis

HLA-C allele		Bronchiectasis (n = 92), n (%)	Control Subjects (n = 98), n (%)	Odds Ratio	(OR)95% CI	p value
HLA-Cw*						
01	Cw*0102-04	9 (4.9)	5 (2.6)	1.96	(0.65 - 6.00)	0.23
02	Cw*0202-05	8 (4.3)	17 (8.7)	0.48	(0.20 – 1.14)	0.09
03	**Cw*0302-06/09/10-14**	**36 (19.0)**	**19 (9.7)**	**2.27**	**(1.25-4.12)**	**0.006***
04	Cw*0401/03-09N	24 (13.0)	25 (12.8)	1.03	(0.56-1.87)	0.93
05	Cw*0501/03/04	21 (11.4)	23 (11.7)	0.97	(0.52-1.82)	0.92
06	**Cw*0602-07**	**8 (4.3)**	**29 (14.8)**	**0.26**	**(0.12-0.59)**	**0.0005****
07	Cw*0701-15	55 (29.9)	56 (28.6)	1.07	(0.68-1.66)	0.78
08	Cw*0801-09	8 (4.3)	7 (3.6)	1.23	(0.44-3.45)	0.70
12	Cw*1202-08	2 (1.1)	2 (1.0)	1.07	(0.15-7.65)	0.95
13	Cw*1301	0 (0.0)	0 (0.0)	ND	ND	ND
14	Cw*1402-05	2 (1.1)	1 (0.5)	2.14	(0.19-23.83)	0.53
15	Cw*1502-10	4 (2.2)	4 (2.0)	1.07	(0.26-4.32)	0.93
16	Cw*1601/02/041	7 (3.8)	8 (4.1)	0.93	(0.33-2.62)	0.89
17	Cw*1701-03	0 (0.0)	0 (0.0)	ND	ND	ND
18	Cw*1801/02	0 (0.0)	0 (0.0)	ND	ND	ND

*** p (corrected) <0.01. **p (corrected) <0.001. n = number of individuals studied.**

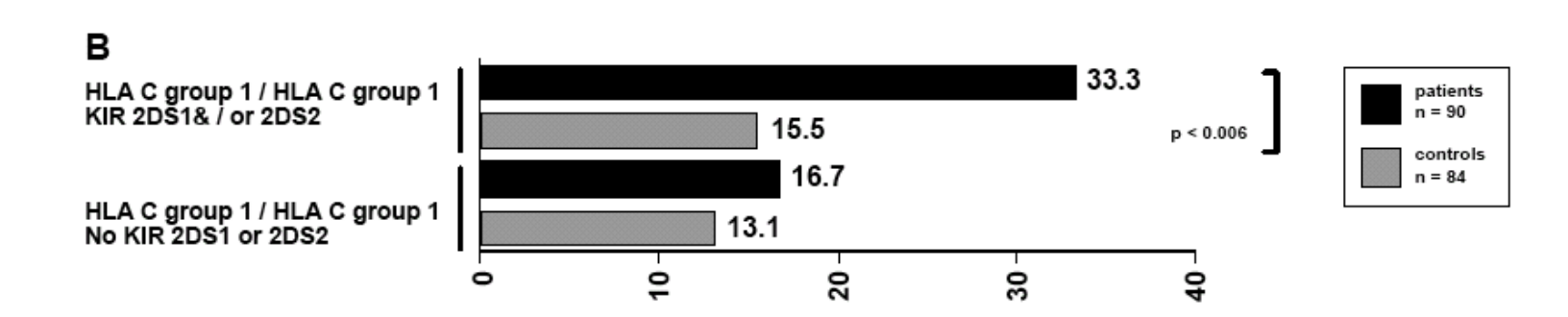
[Boyton et al Am J Respir Crit Care Med 2006; 173: 327]

Increased HLA-C group 1 homozygosity in idiopathic bronchiectasis



[Boyton et al Am J Respir Crit Care Med 2006; 173: 327]

HLA-C Group 1 homozygosity plus stimulatory KIRs associated with susceptibility to idiopathic bronchiectasis



[Boyton et al Am J Respir Crit Care Med 2006; 173: 327]

Relationship between HLA-C and KIR haplotype in idiopathic bronchiectasis

HLA - Cw*03 - 2.3-fold

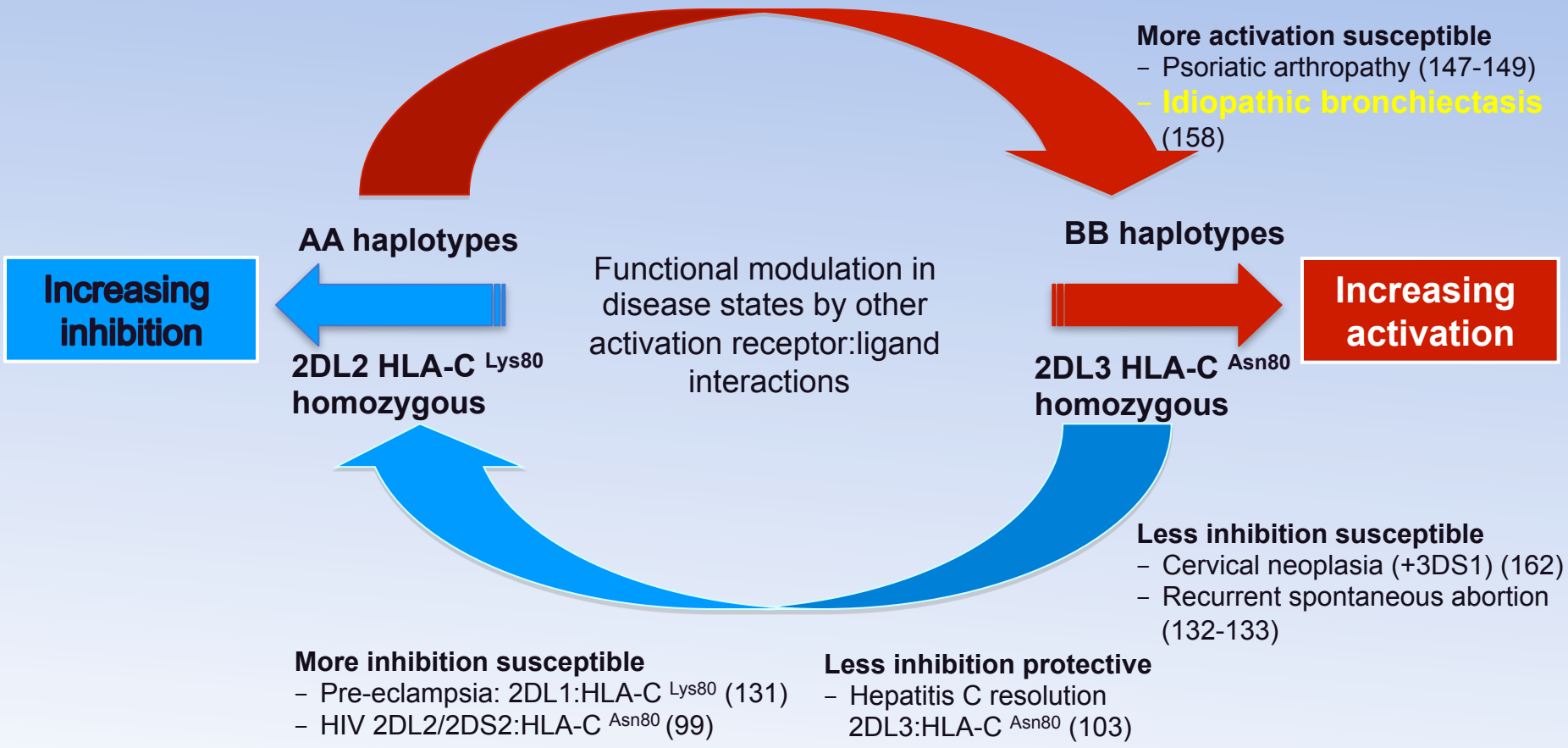
HLA - Cw*06 - 0.3-fold

Group 1 motif homozygosity

Group 1 motif homozygosity plus stimulatory KIRs

Group 1/2 motif heterozygosity plus stimulatory KIRS

[Boyton et al Am J Respir Crit Care Med 2006; 173: 327]



[Carrington M et al Immunological Reviews 2006; 214: 186]

Human leucocyte antigen (HLA) & killer immunoglobulin-like receptor (KIR) disease associations

Table 1. Human leucocyte antigen (HLA) and killer immunoglobulin-like receptor (KIR) disease associations.

Disease	KIR / HLA association	Observation	References
Infection			
CMV	> 1 activating KIR in donor	Reduced risk of CMV reactivation in recipient following bone marrow transplantation	[63]
HCV	2DL3/2DL3 - HLA-C1/C1	Resolution of infection	[51]
	3DS1 - HLA-Bw4	Resolution of infection	
	3DS1 - HLA-B-Bw4 80I	Protection against the development of hepatocellular carcinoma	[64]
HIV-1	3DS1 - HLA-Bw4 80I	Delays progression to AIDS	[43]
	3DL1 - HLA-B*57alleles that contain Bw4 80I	Delays progression to AIDS	[65]
Plasmodium falciparum	3DL2*002	High NK cell response to *P. falciparum*-infected RBC	[66]
Idiopathic bronchiectasis	HLA-Cw*03	Susceptibility	[53]
	HLA-Cw*06	Protection	
	2DS1 and/or 2DS2 - HLA-C1/C1	Susceptibility	
Autoimmunity			
Behçet's disease	Altered 3DL1 expression	Associated with severe eye disease	[67]
IDDM	2DS2 - HLA-C1	Susceptibility	[61]
	Decrease in inhibitory KIR-HLA genotype combinations	Susceptibility	[60]
Psoriatic arthritis	2DS1/2DS2; HLA-Cw group homozygosity	Susceptibility	[68,38]
Rheumatoid vasculitis	2DS2; HLA-Cw*03	Susceptibility	[59]
Scleroderma	2DS2+ /2DL2–	Susceptibility	[58]
Spondylarthritides	3DL2 expression increased	May contribute to disease pathology	[62]
Acute coronary syndromes	*De novo* expression of 2DS2/DAP12 in CD4+ T cells	T cells acquire cytolytic capability that can bypass TCR triggering	[69]
Cancer			
Malignant melanoma	2DL2/2DL3; HLA-C1	Susceptibility	[70]
Cervical cancer	3DS1/absence of HLA-C2 and/or HLA-Bw4	Susceptibility	[71]
	Genotype 10 (2DL1/2/3/4, 3DL1/2/3, 2DS4	Susceptibility	[72]
	2DL5*002	Protection	
Nasopharyngeal carcinoma	EBV seropositive individuals with ≥ 5 activating KIR	Susceptibility	[73]
Leukaemia	2DL2	Susceptibility	[74]
	AB1 (AML) and AB9 (CML) KIR		
	3DL1/3DL1 +Bw4 (CLL)	Susceptibility	[75]
	3DL1/3DL1 – Bw4 (CLL)	Protection	[75]
	2DL2/2DL3 +Cw1 (myeloid leukaemia)	Susceptibility	
	2DL3/2DL3 +Cw1 (myeloid leukaemia)	Protection	[76]
Cutaneous T cell lymphoma	Expression of 3DL2 on malignant cells	May contribute to disease pathology	[77]
Reproduction			
Pre-eclampsia	Maternal AA KIR genotype; fetus HLA-C2	Susceptibility	[78]
Recurrent spontaneous abortion	Mothers lacking inhibitory KIRs with specificity for fetal HLA-Cw alleles	Susceptibility	[79]

AML: acute myeloid leukaemia; CML: chronic myeloid leukemia; CLL: chronic lymphoid leukaemia; CMV: cytomegalovirus; IDDM: insulin-dependent diabetes mellitus; NK: natural killer; RBC: red blood cells.

[Boyton R et al. Clin Exp Immunol 2007; 149:1]

Genetic studies implicate altered regulation of natural killer (NK) cells in idiopathic bronchiectasis

- HLA-Cw*03 and HLA-C group 1 homozygosity associated with idiopathic bronchiectasis
- Analysis of relationship between HLA-C and KIR genes suggest a shift to activated NK cell activity

[Boyton et al Am J Respir Crit Care Med 2006; 173: 327]

Regulaton of immunity in bronchiectasis - summary

Evidence for dysregulated adaptive and innate immunity in idiopathic bronchiectasis

- HLA-Cw*03 and HLA-C group 1 homozygosity association implicates NK cell activation
- HLA class II association with HLA-DR1, DQ5 haplotype implicates adaptive immunity
- Bronchiectasis in the context of impaired HLA-class I expression (TAP deficiency syndrome) implicates altered NK cell and/or $\gamma\delta$ cell activation
- Clinical association with autoimmune diseases suggests a possible role for poorly regulated adaptive immunity
- Clinical association with UC post colectomy may indicate a role for altered immune regulation after a change in the microbiome
- Increased susceptibility to chronic bacterial, NTM, and aspergillus related lung infection and chronic lung remodelling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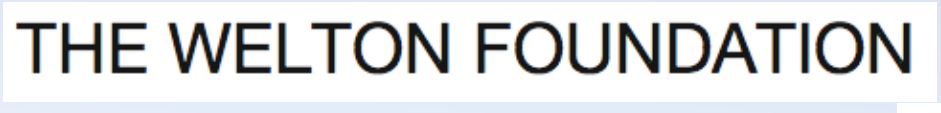
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