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The innate immune defence: role in infections and significant ethnic genetic differences

Aarhus April 18 2013

Innate immune system

- First line of defense
- Fast but non-specific response (Hours)
- Germline-encoded proteins
- Complement system
- Effector cells: Macrophages
  Dendritic cells
  Neutrophils
  Natural Killer cells

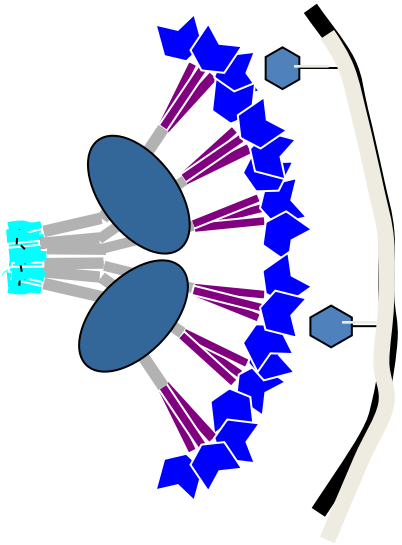
Esben Axelgaard

Adaptive immune system

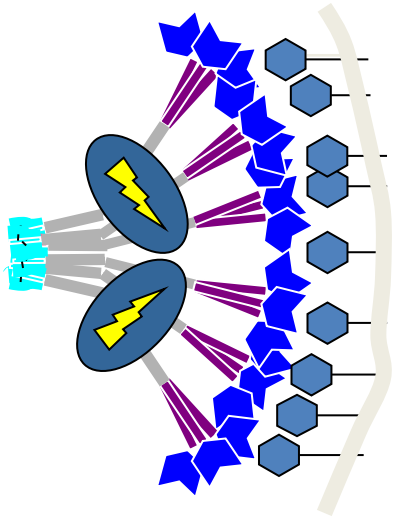
- Second line of defense
- Slow but highly specific response (Days)
- Somatic hypermutation and V(D)J recombination
- B-cells (Plasma cells)
- T-cells (Helper or cytotoxic)
- Immunological memory

Esben Axelgaard

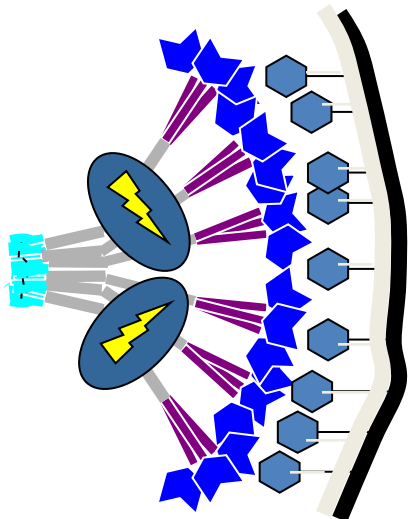
MBL and ficolins are pattern recognizing molecules, PRMs, binding to pathogen associated molecular patterns PAMPs



Normal "self"
low density of recognized carbohydrates



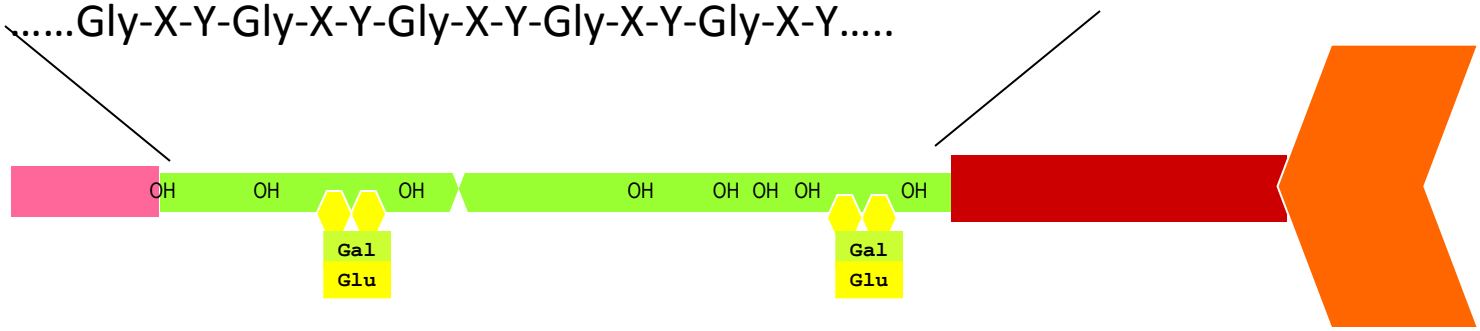
Microbial surface
high density of recognized carbohydrates



Altered self", e.g. Ischemic cells, apoptotic cells, cancer cells

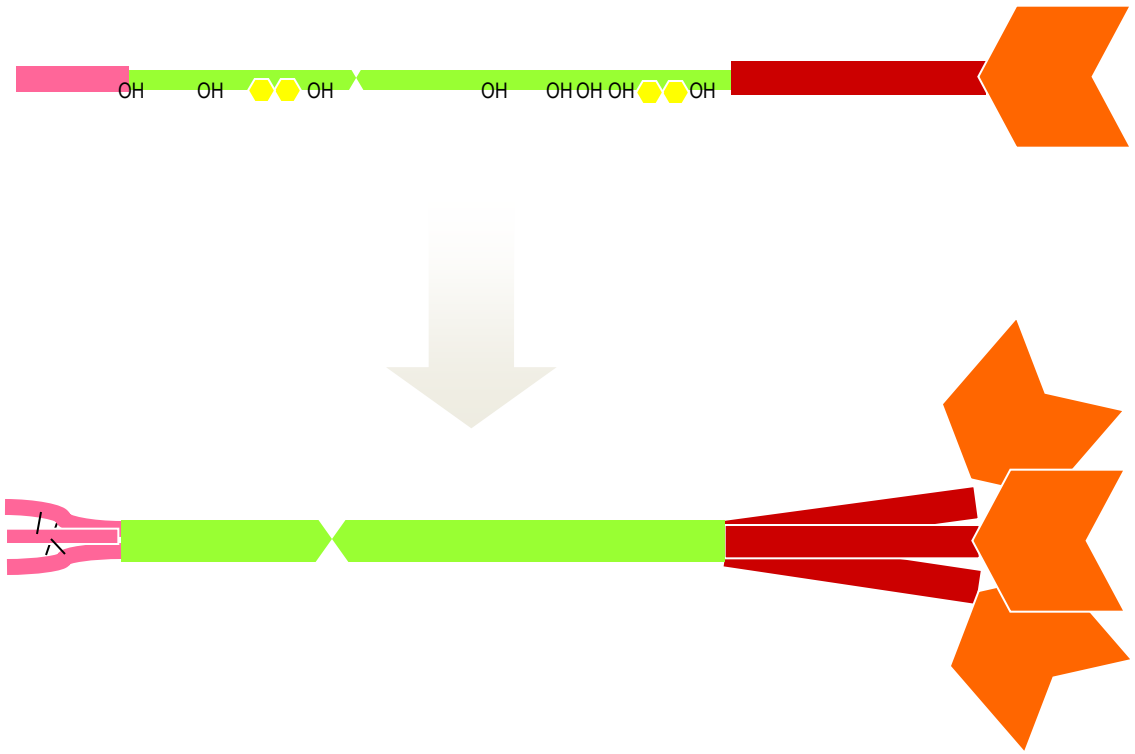
Pattern recognition collagens

Polypeptide chain contains short N-terminal end followed by a collagen-like region followed by a recognition domain.



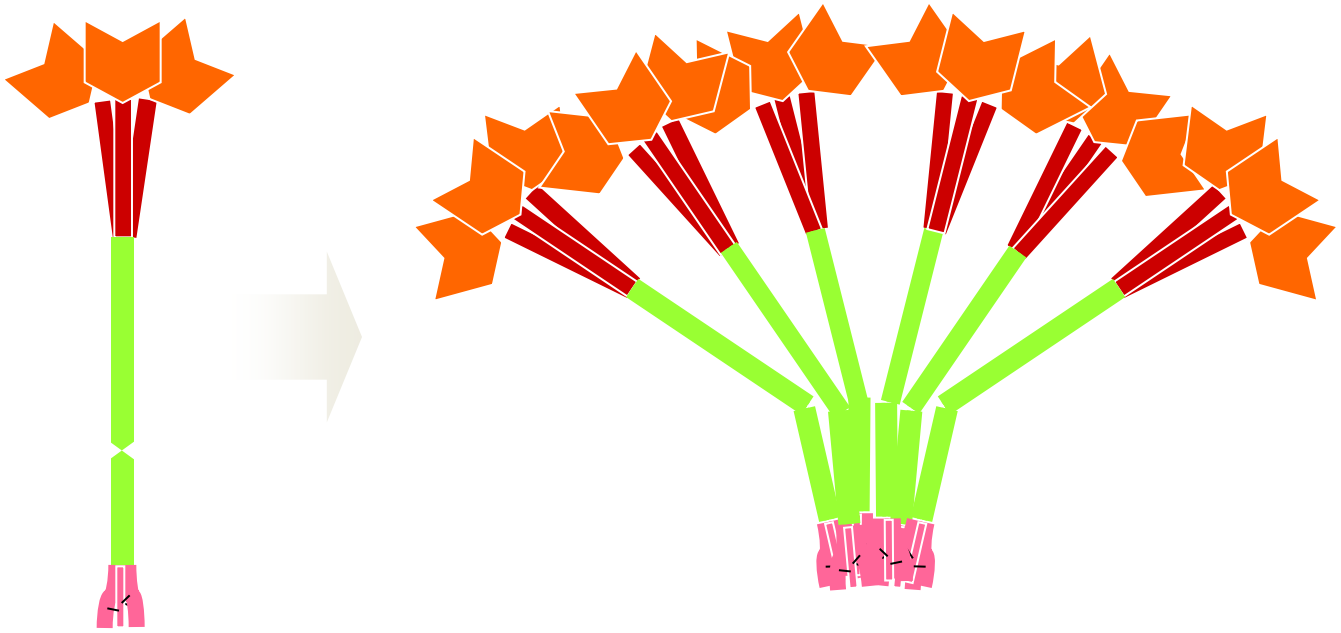
Pattern recognition collagens assembly

Formation of structural unit from polypeptide

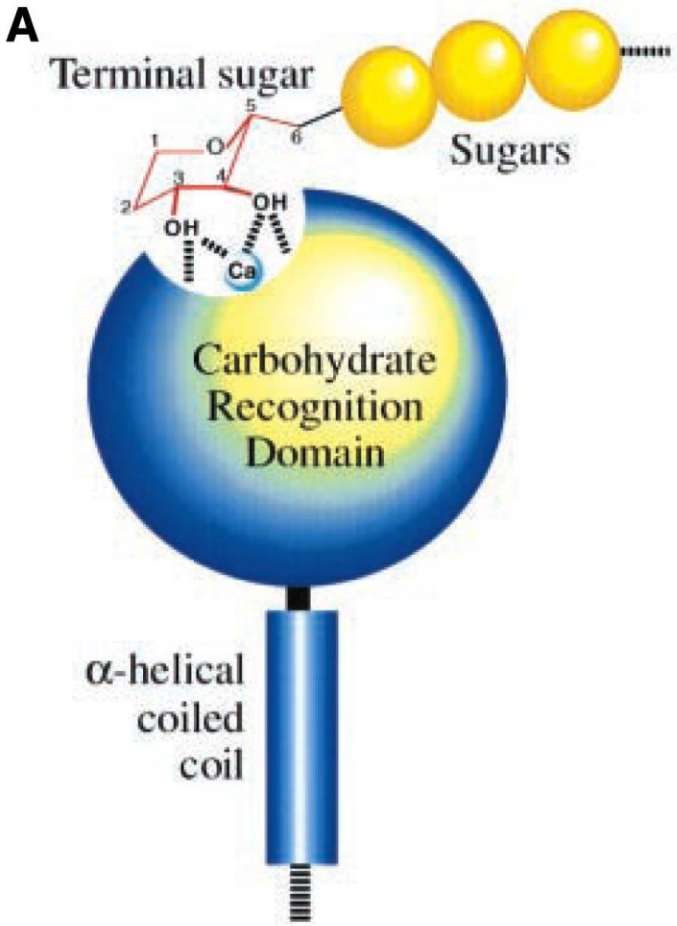


Pattern recognition collagens assembly

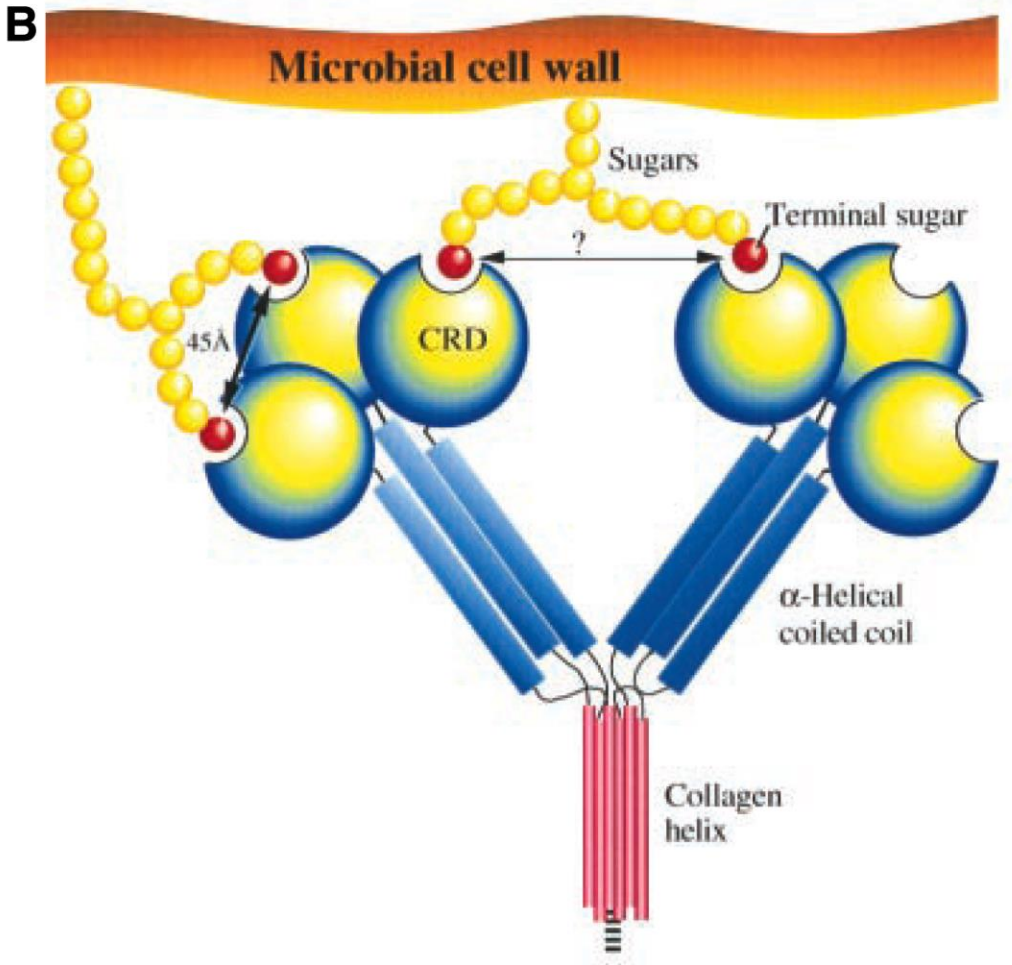
Association of structural unit to oligomers



Oligomer (3-6 structural units)



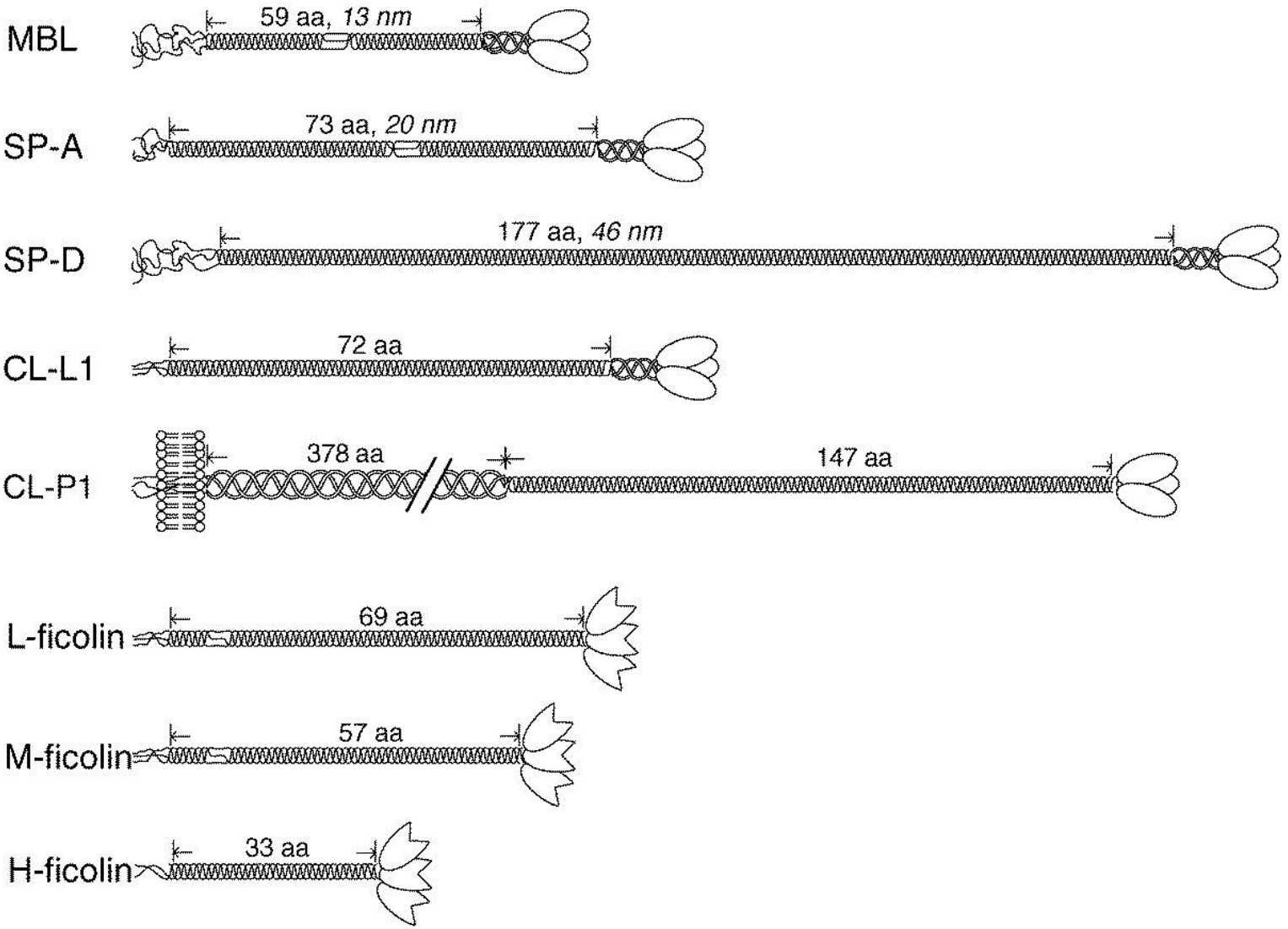
Low affinity binding



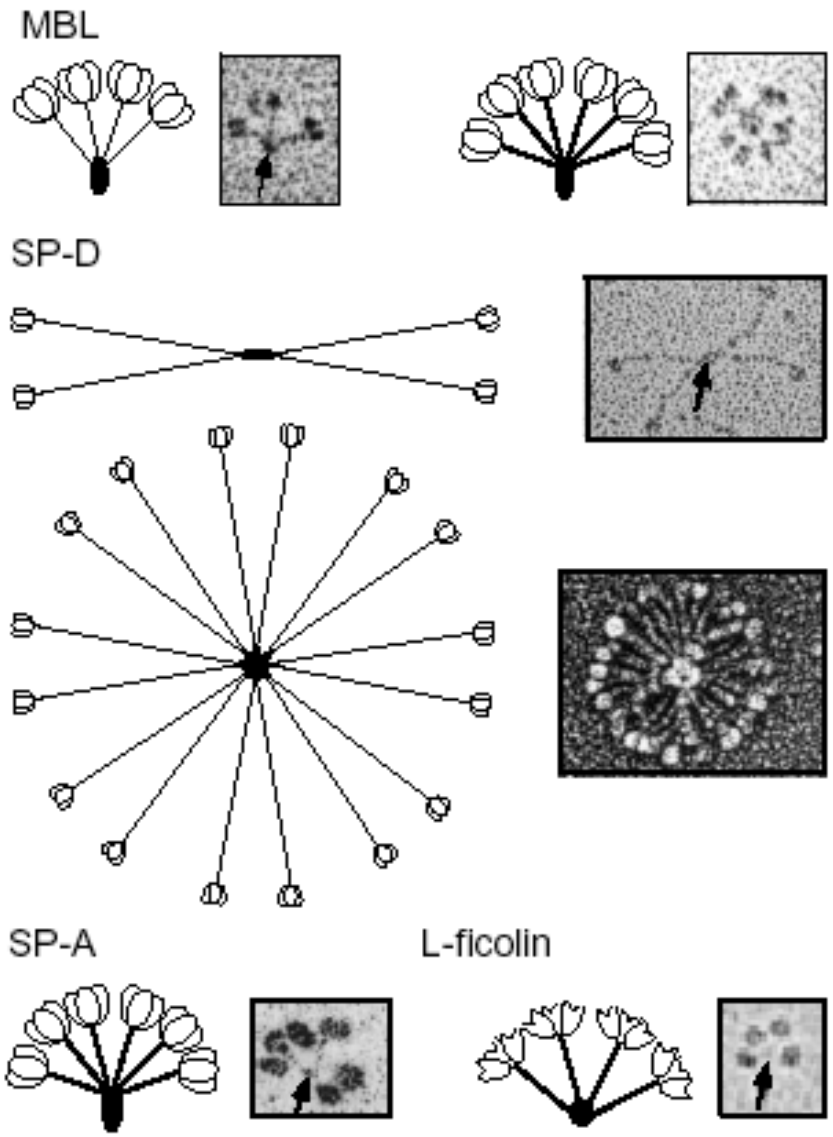
High avidity binding

Jules A. Hoffmann,[1]* Fotis C. Kafatos,[2] Charles A. Janeway Jr.,[3] R. A. B. Ezekowitz[4]
SCIENCE VOL 284 21 MAY 1999

Subunit structures of human collectins and ficolins



Holmskov, Thiel, Jensenius 2003 Annual review of immunology 21, 547-578



Holmskov, Thiel & Jensenius. Collectins and Ficolins: Humoral Lectins of the Innate Immune Defense. Annu Rev Immunol. 2003;21:547-78

MBL has broad recognition

- **Bacteria**
  - gram negative
  - gram positive
  - Mycobacteria
  - Clamydia
- **Yeast/fungi**
  - Candida sp
  - Aspergillus sp
  - Saccharomyces sp
- **Parasites**
  - Leishmania
  - Trypanosomes
  - Schitzomas
- **Viruses**
  - influenza
  - RSV
  - HSV
  - HIV

Miller ME, Seals J, Kaye R and Levitsky LC
University of Philadelphia

A Familial, Plasma-associated Defect of Phagocytosis
A New Cause of Recurrent Bacterial Infection

The Lancet, July 13 1968

3 month infants with:
Diarrhoea and severe eczema
Defective yeast opsonization –
corrected by weekly plasma infusions

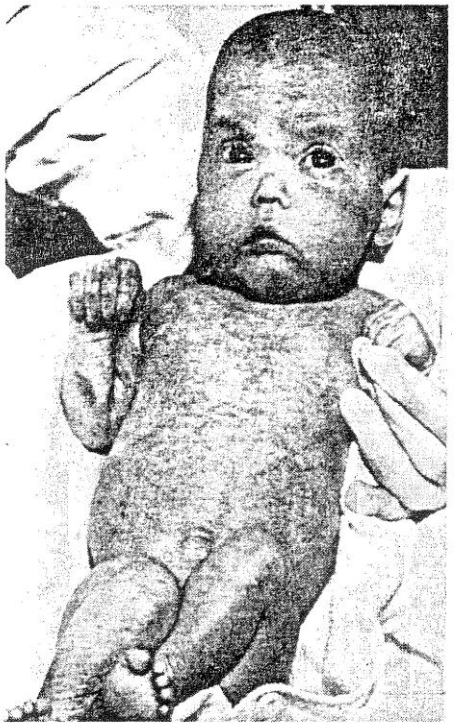
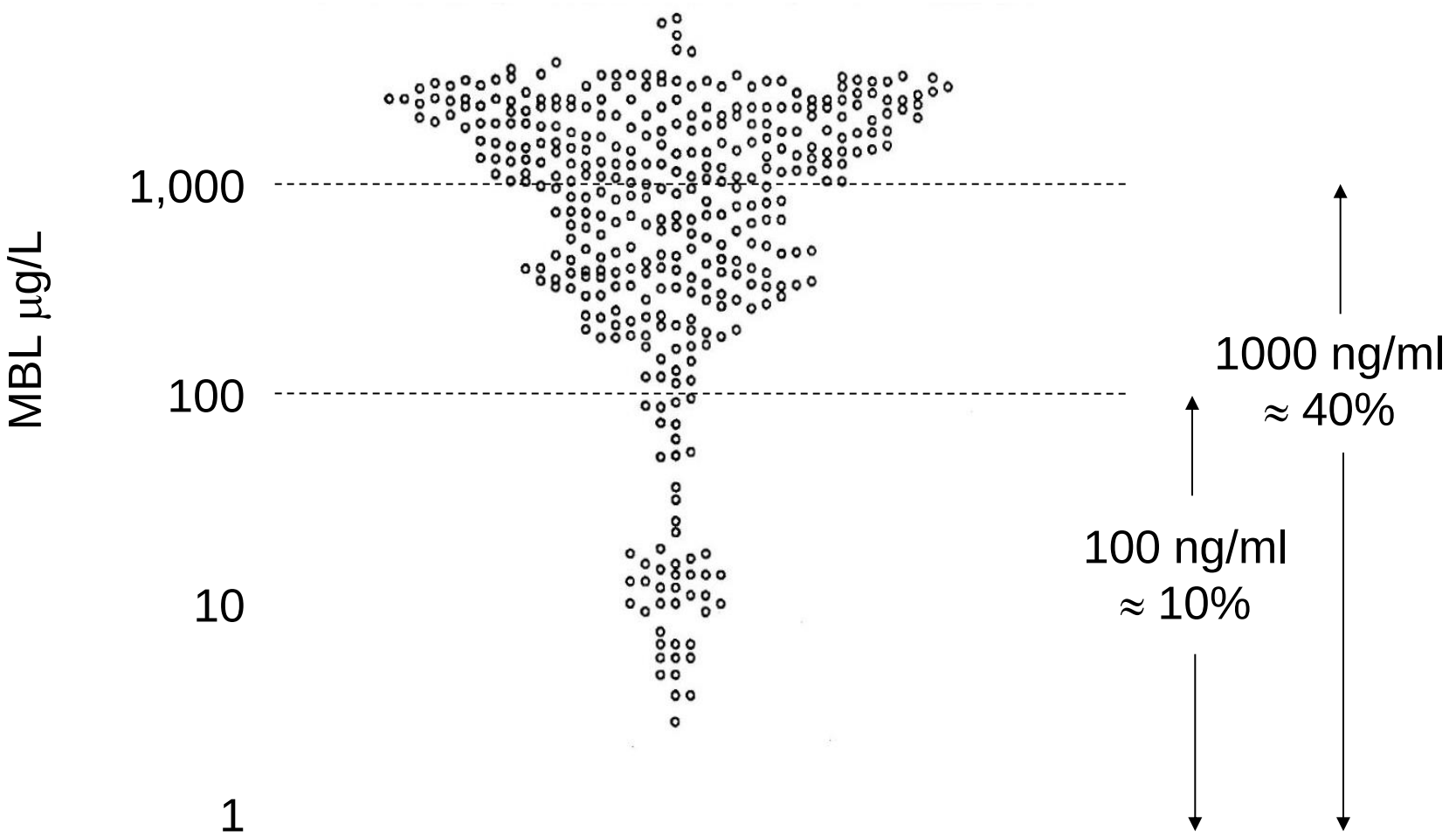


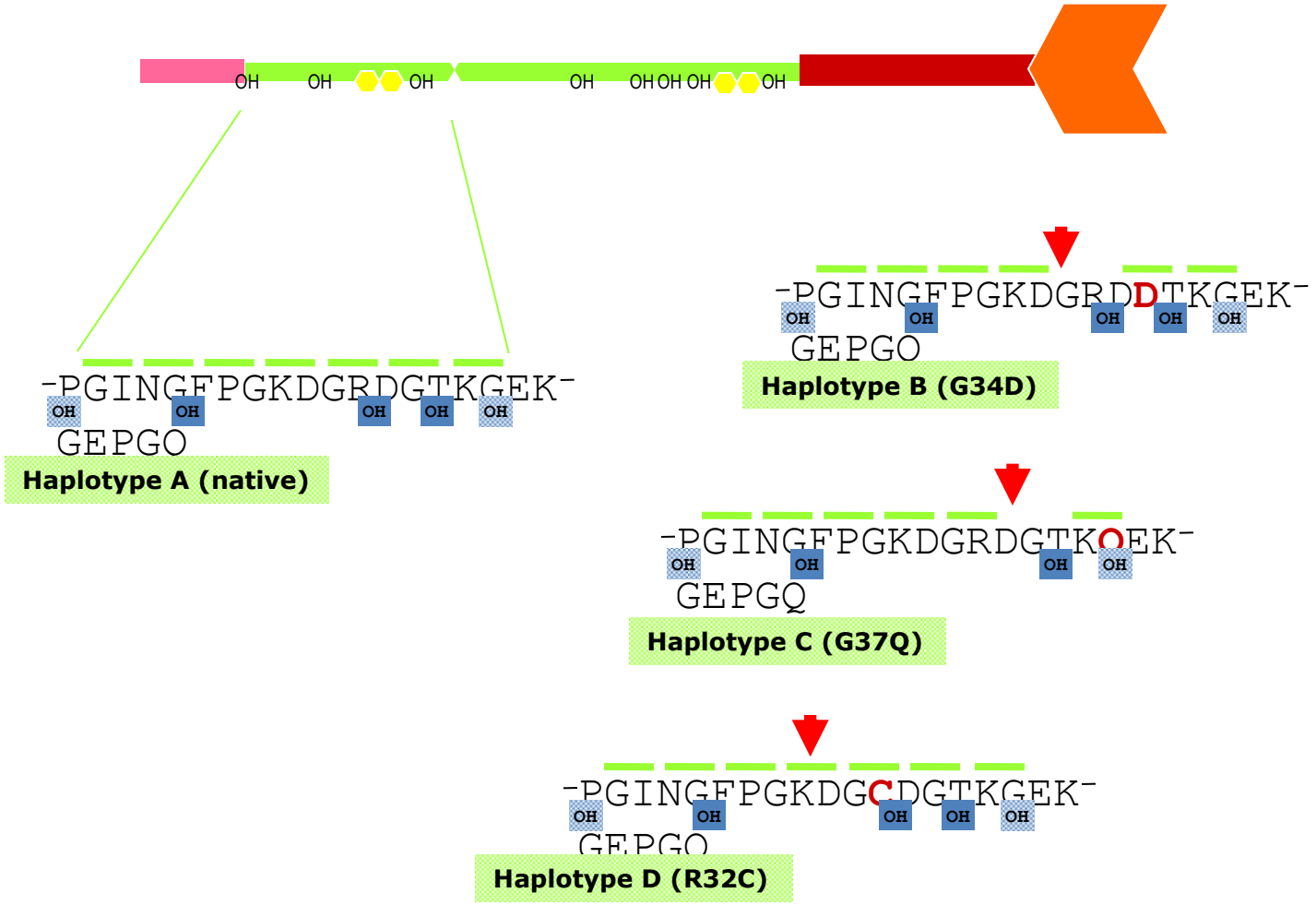
Fig. 1—Appearance of child shortly after admission.

MBL levels in 374 normal plasmas

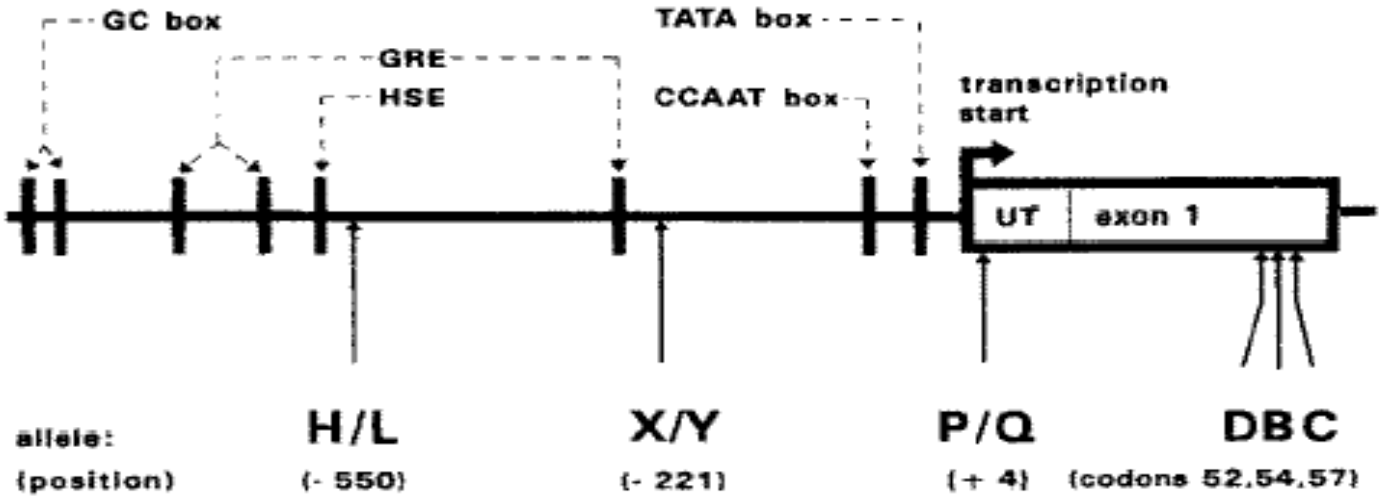


MBL Haplotypes

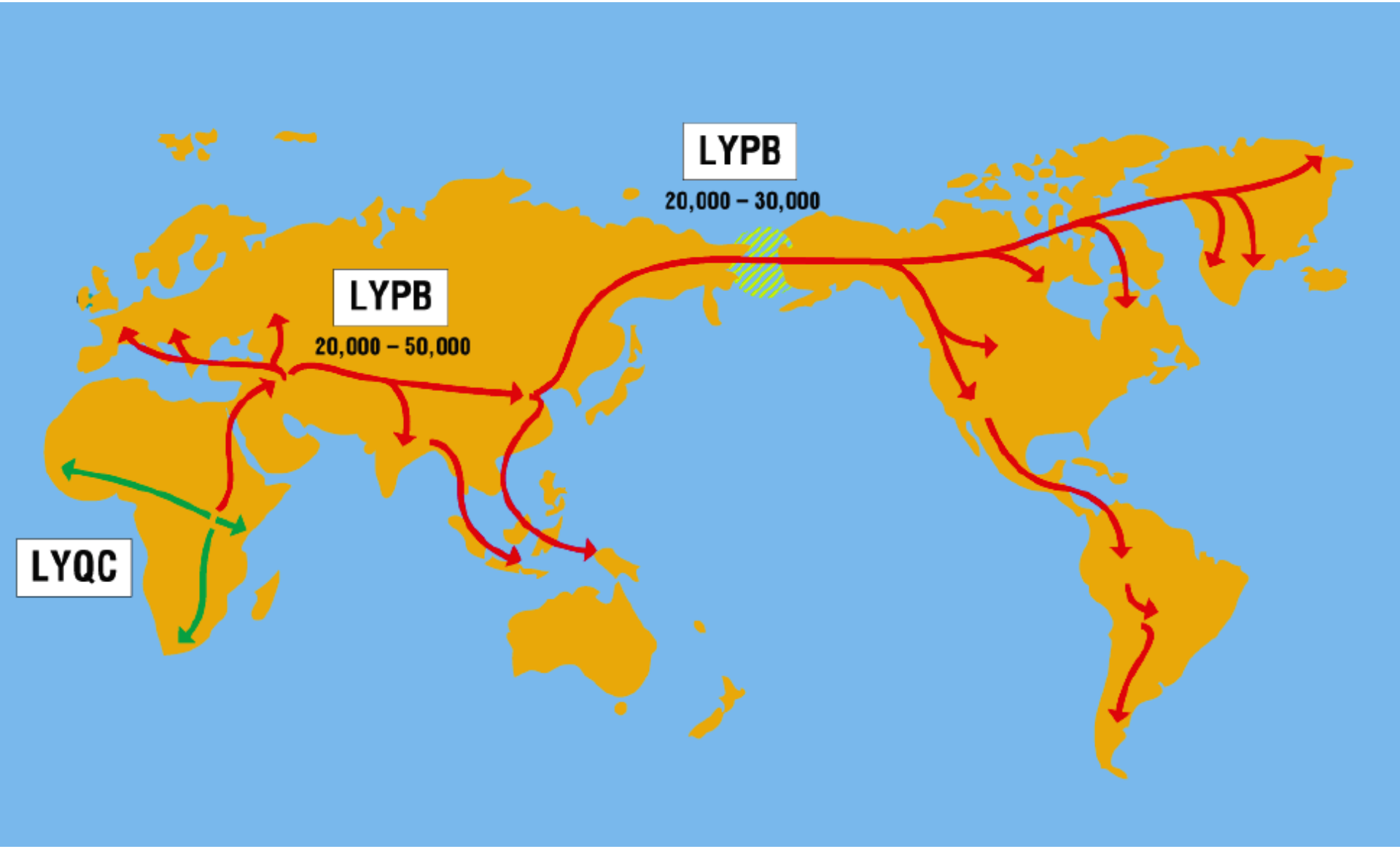
Structural mutations



MBL alleles

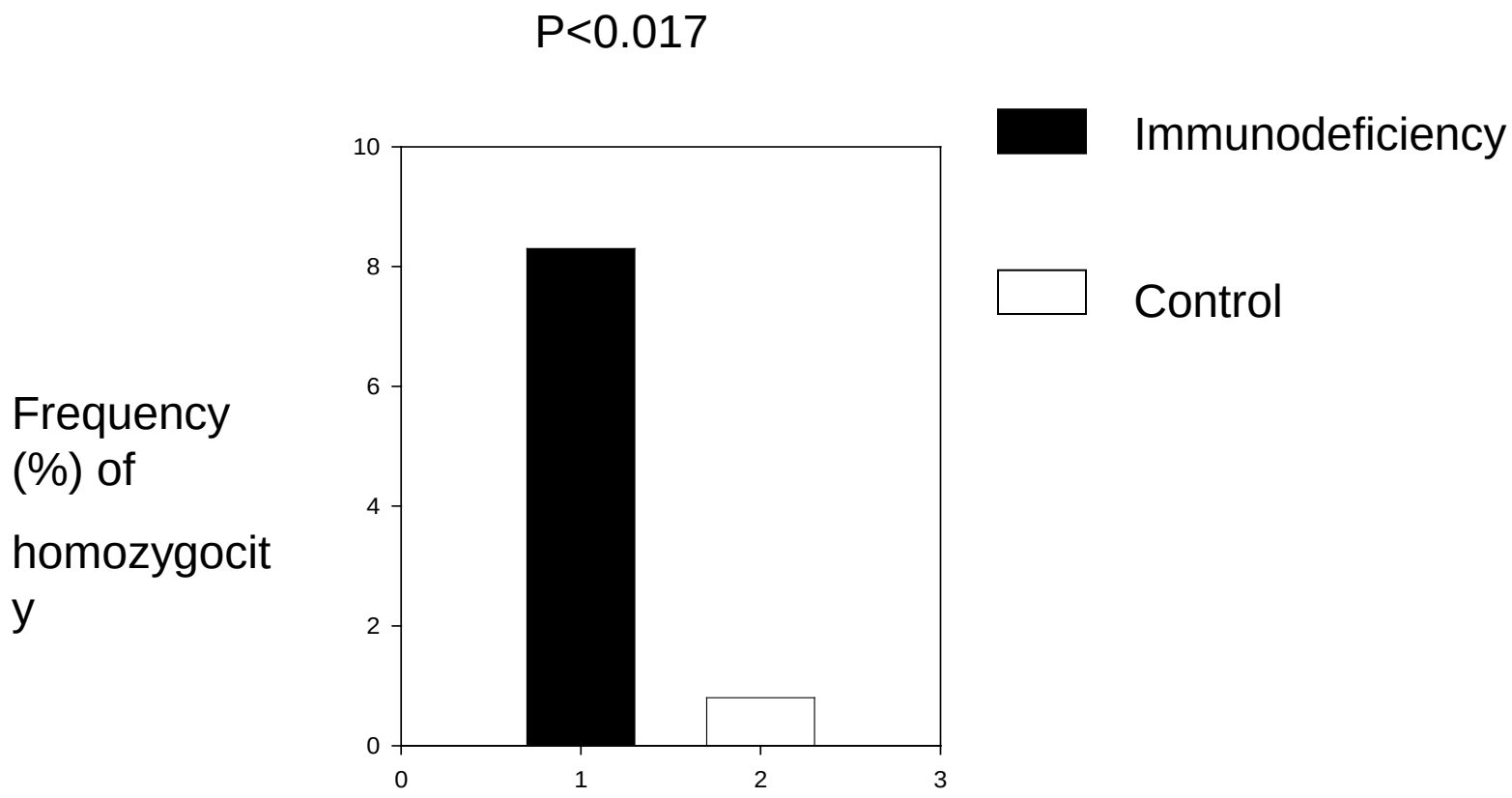


Madsen et al, JI, 155, 3013, 1995



World map of MBL allotypes by Mac W. Turner

Frequency of homozygocity of mutant alleles in children with suspected immunodeficiency



Garred, Madsen, Hofmann, Svejgaard - Increased frequency of homozygosity of abnormal mannan-binding-protein alleles in patients with suspected immunodeficiency. The Lancet 1995;346:941–943.

Mannose-Binding Lectin in Severe Acute Respiratory Syndrome Coronavirus Infection

W. K. Eddie Ip,[1,a] Kwok Hung Chan,[2] Helen K. W. Law,[1] Gloria H. W. Tso,[1] Eric K. P. Kong,[1] Wilfred H. S. Wong,[1] Yuk Fai To,[1] Raymond W. H. Yung,[3] Eudora Y. Chow,[4] Ka Leung Au,[5] Eric Y. T. Chan,[6] Wilina Lim,[7] Jens C. Jensenius,[8] Malcolm W. Turner,[9] J. S. Malik Peiris,[2] and Yu Lung Lau[1]

569 patients with SARS and 1188 control subjects

Higher frequency of MBL deficiency haplotypes in patients with SARS than in control subjects.

Serum levels of MBL were significantly lower in patients with SARS than in control subjects.

No association between *MBL* genotypes and mortality related to SARS.

MBL bound SARS-CoV and enhanced complement deposition.

MBL inhibited the infectivity of SARS-CoV in fetal rhesus kidney cells..

Journal of Infectious Diseases 2005; 191:1697–704

Haurum, J., Thiel, S., Jones, I.M., Fischer, P., Laursen, S.B., Jensenius, J.C.:
Complement activation upon binding of mannan-binding protein to HIV envelope glycoproteins.
AIDS 7, 1307-1313, 1993.

Nielsen, S.L., Andersen, P.L., Koch, C., Jensenius, J.C., Thiel, S.:
The level of the serum opsonin, Mannan-binding protein in HIV-1 antibody positive patients.
Clin. exp. Immunol. 100, 219-222, 1995.

Mannan-Binding Lectin Deficiency is Associated with Unexplained Recurrent Miscarriage

O. B. CHRISTIANSEN*, D. C. KILPATRICK†, V. SOUTER†, K. VARMING‡, S. THIEL§ & J. C. JENSENIUS§

Scand. J. Immunol. **49**, 193–196, 1999

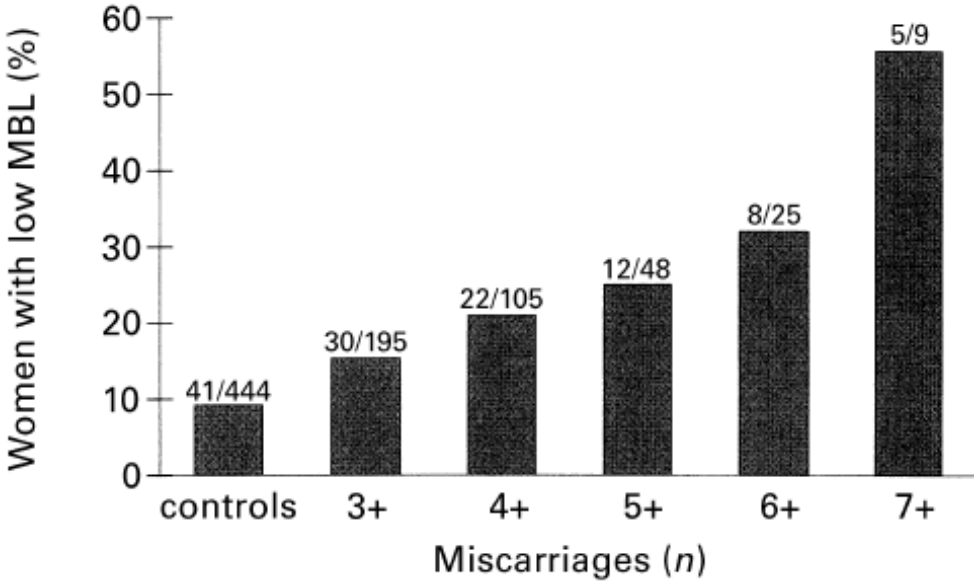


Fig. 2. Frequency of serum MBL level < 50 ng/ml by number of previous miscarriages in Danish and Scottish women with recurrent miscarriages and in controls. The figures on top of the columns

MBL KO mice

MBL DKO mice are double knock-out mice: MBL-$A^{-/-}$ MBL-$C^{-/-}$

- MBL KO mice are susceptible to *S.aureus* Infection
  (Shi et al. J. Exp. Med. 199:1379 2004)

- MBL KO mice are susceptible to HSV-2 infection
  (Gadjeva et al. Clin Exp Immunol. 138:134 2004)

- MBL KO mice fail to clear apoptotic cells, but do not show signs of autoimmune disease
  (Stuart et al. J Immunol. 174:3220 2005)

- MBL KO mice are protected from ischemia/reperfusion injuries (kidneys, gastrointestinal, heart)
  (Moller-Kristensen et al Scand. J. Immun 61:426 2005,
  Hart et al J. Immunol 174: 6373 2005,
  Walsh et al J. Immunol 175; 541 2005)

The complement system

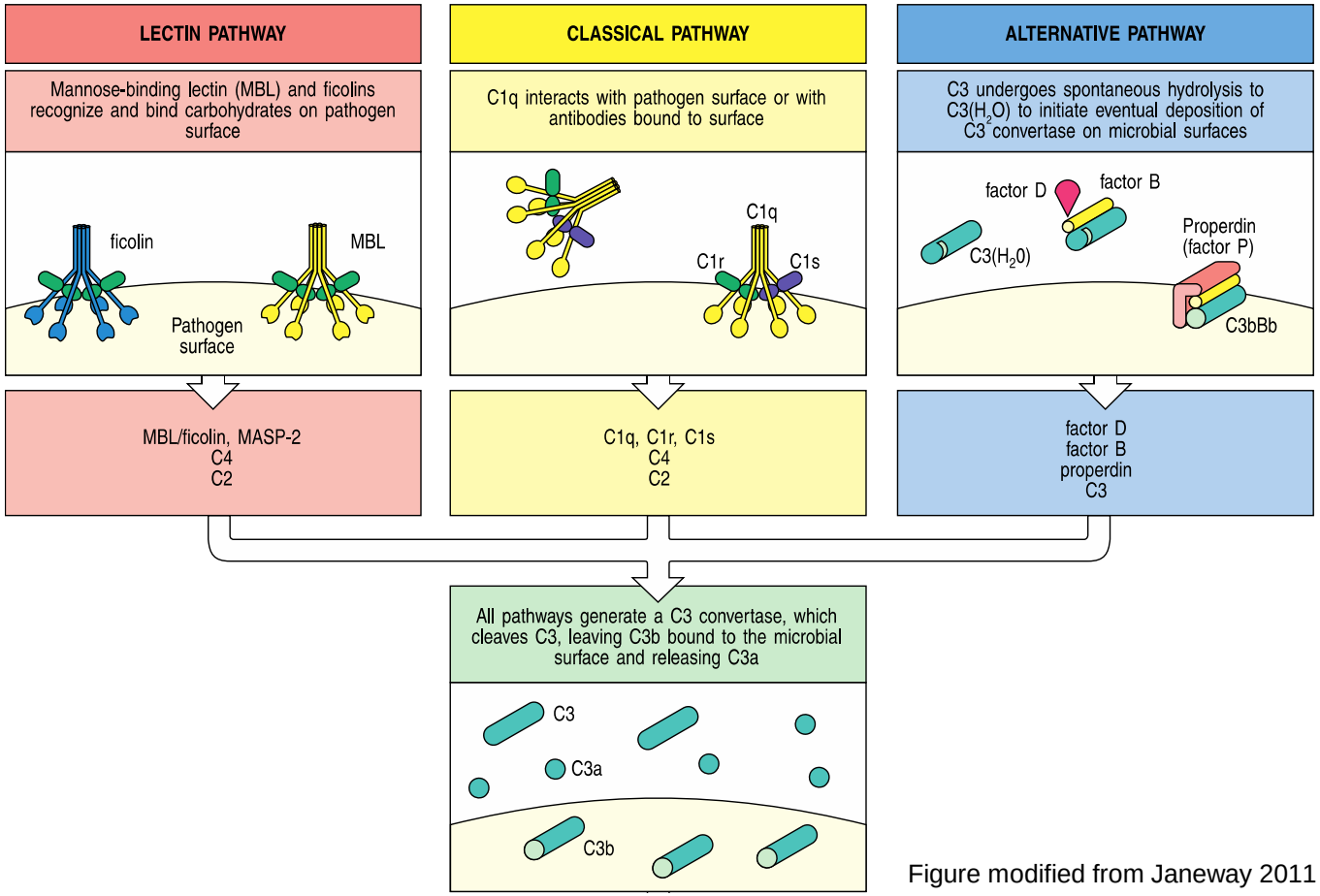
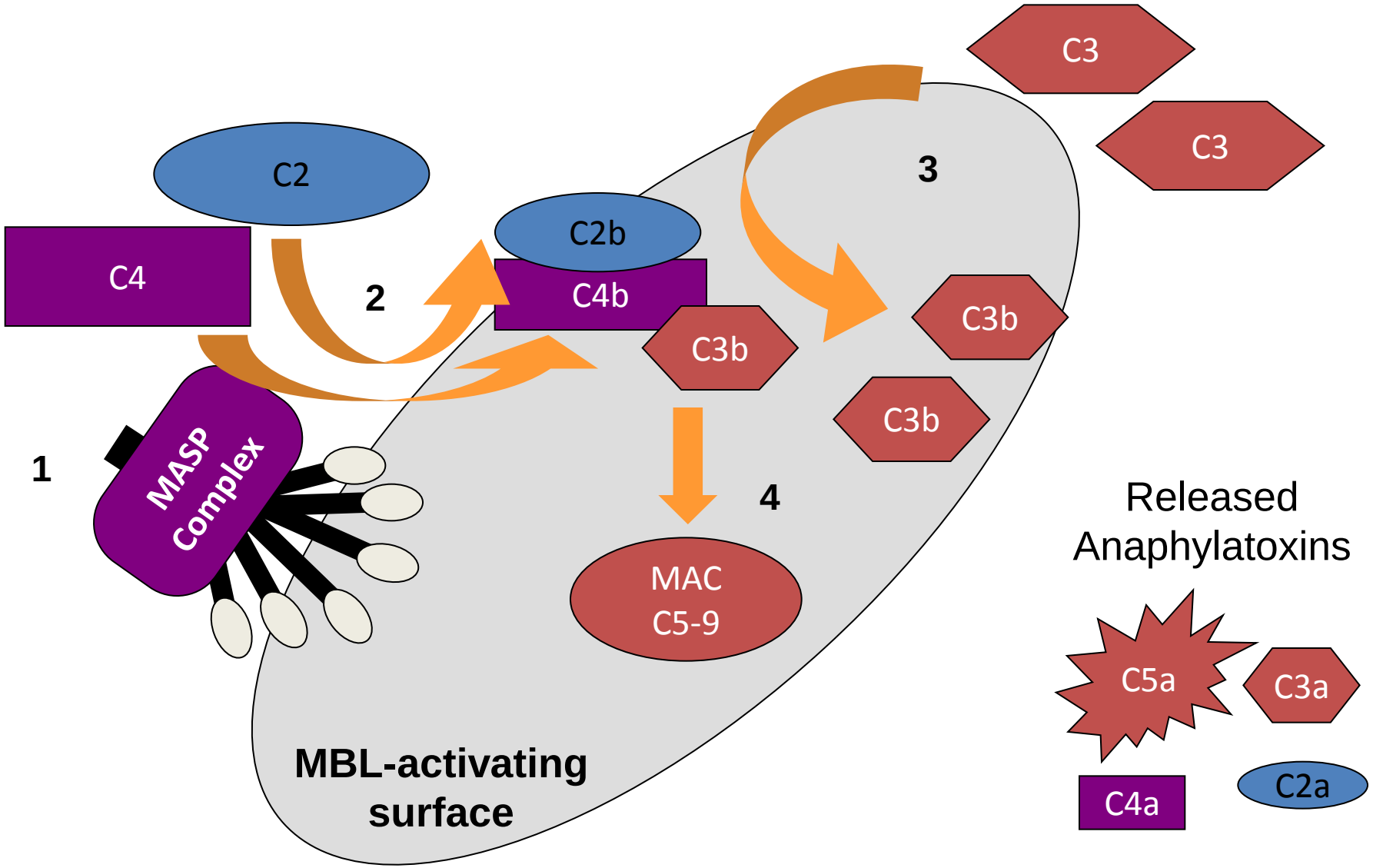
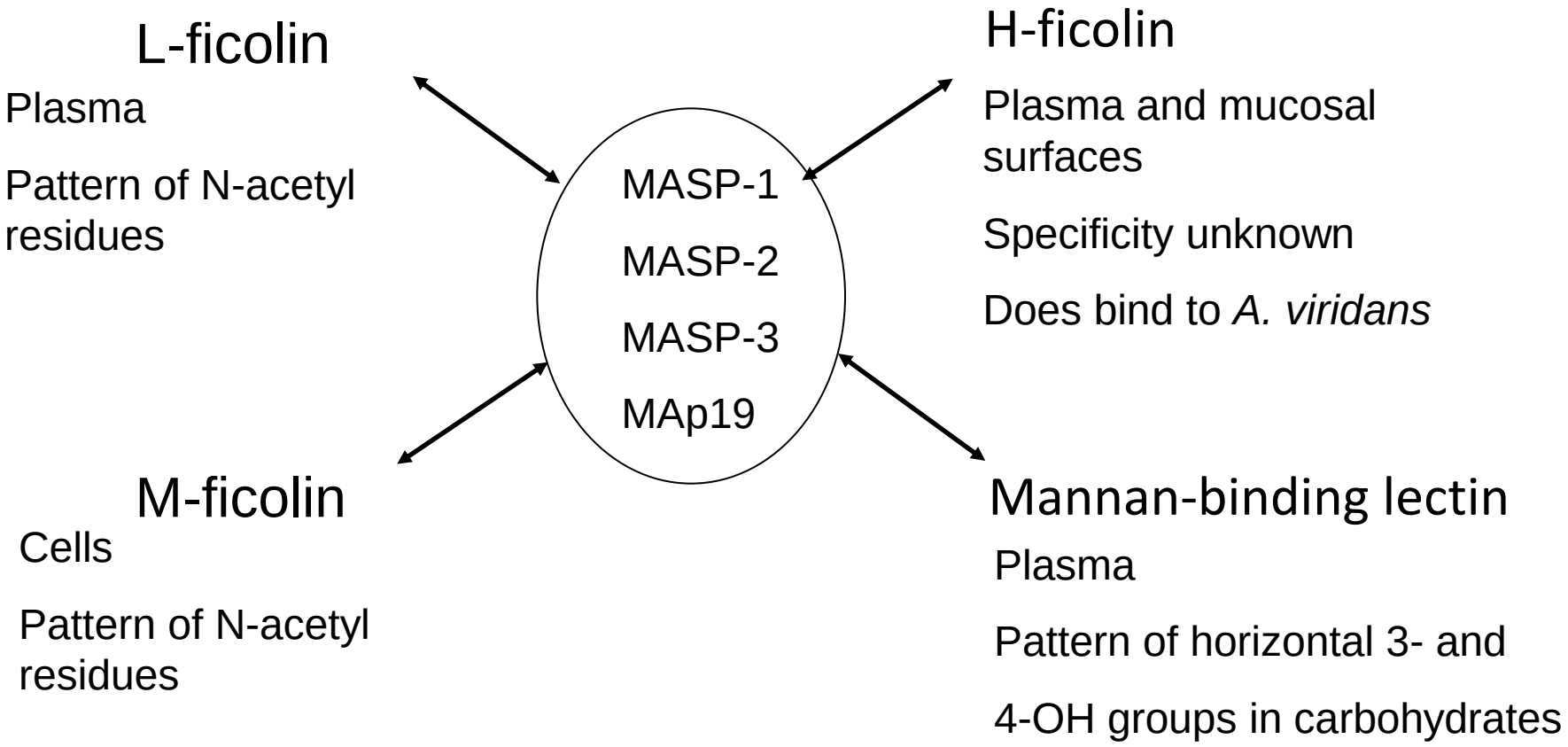


Figure modified from Janeway 2011

Initiation of complement activation via MBL



MASPs are associated with more than MBL



Collectin subunit structure

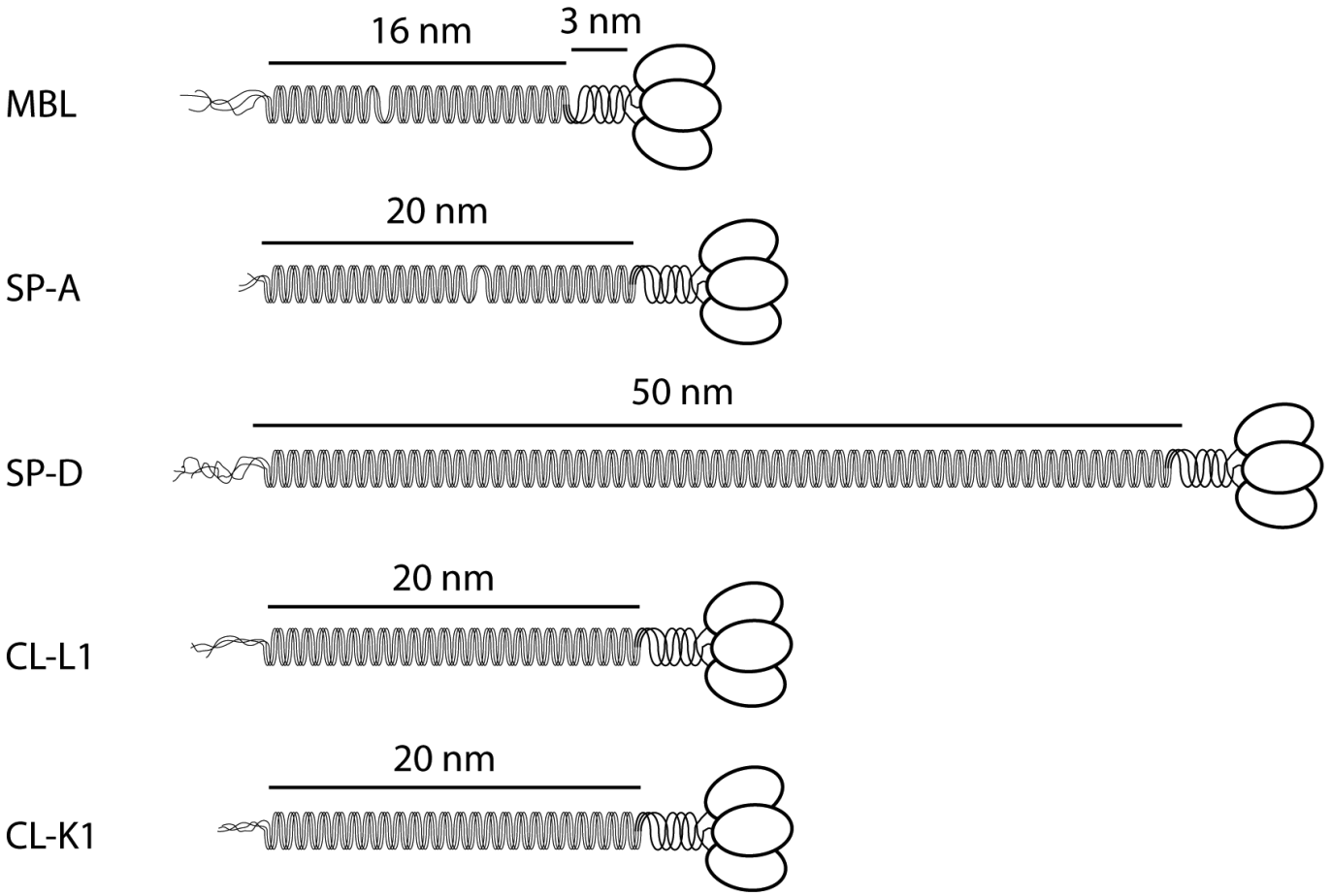
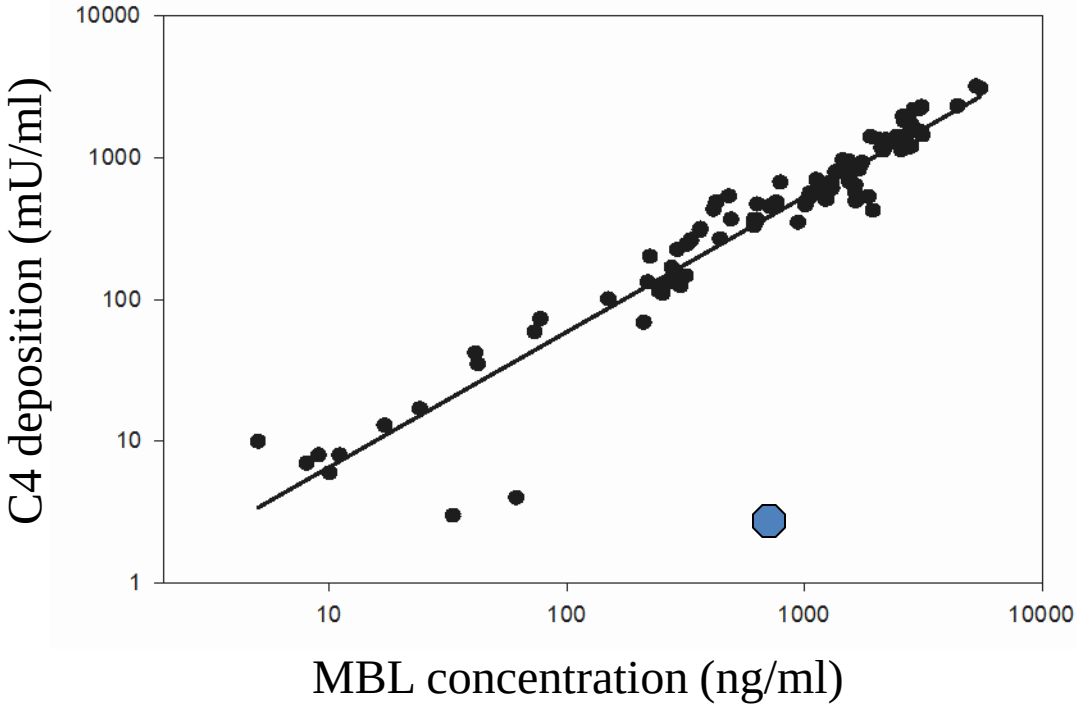


Figure modified from Søren Degn, 2010 by Esben Axelgaard

C4 Activity in 100 Sera from Healthy Individuals and from one suspected immunodeficient patient



Inherited Deficiency of Mannan-BindingLectin–Associated Serine Protease-2

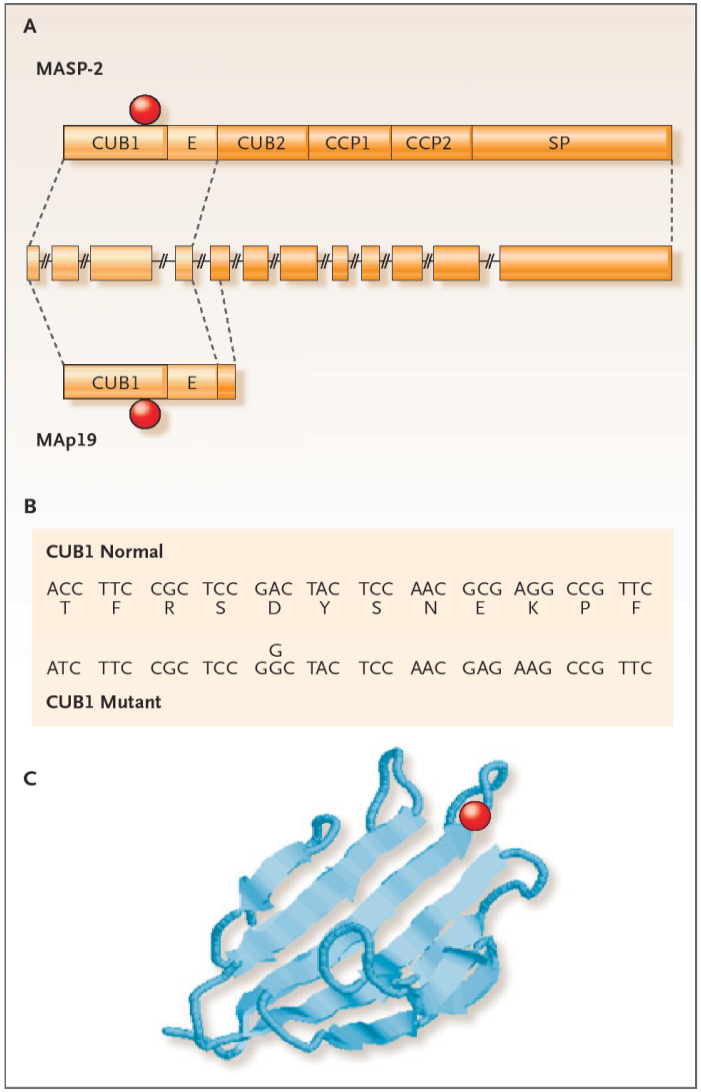
Stengaard-Pedersen, Thiel, Gadjeva, Møller-Kristensen, Sørensen, Jensen, Sjöholm, Fugger, and Jensenius N Engl J Med 2003;349:554-60.

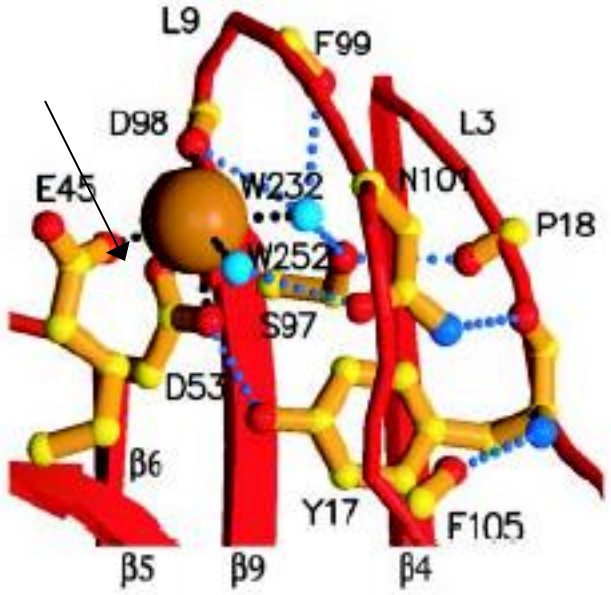
Patient Outline

A male, now 26 years old, essentially healthy until 23 years of age when a diagnosis of ulcerative colitis was made. In 1996 he developed erythema multiforme bullosum. Severe pneumococcal pneumonia was documented at least three times between 1995 and 1997; one of the infections with septicemia.

- Complement C1q ↓
- Complement C4 ↓
- Complement C3 ↓
- C3dg fragment ↑
- Classical Pathway Function ↓
- Alternative Pathway Function ↓
- Anti-C1q Antibodies ↑

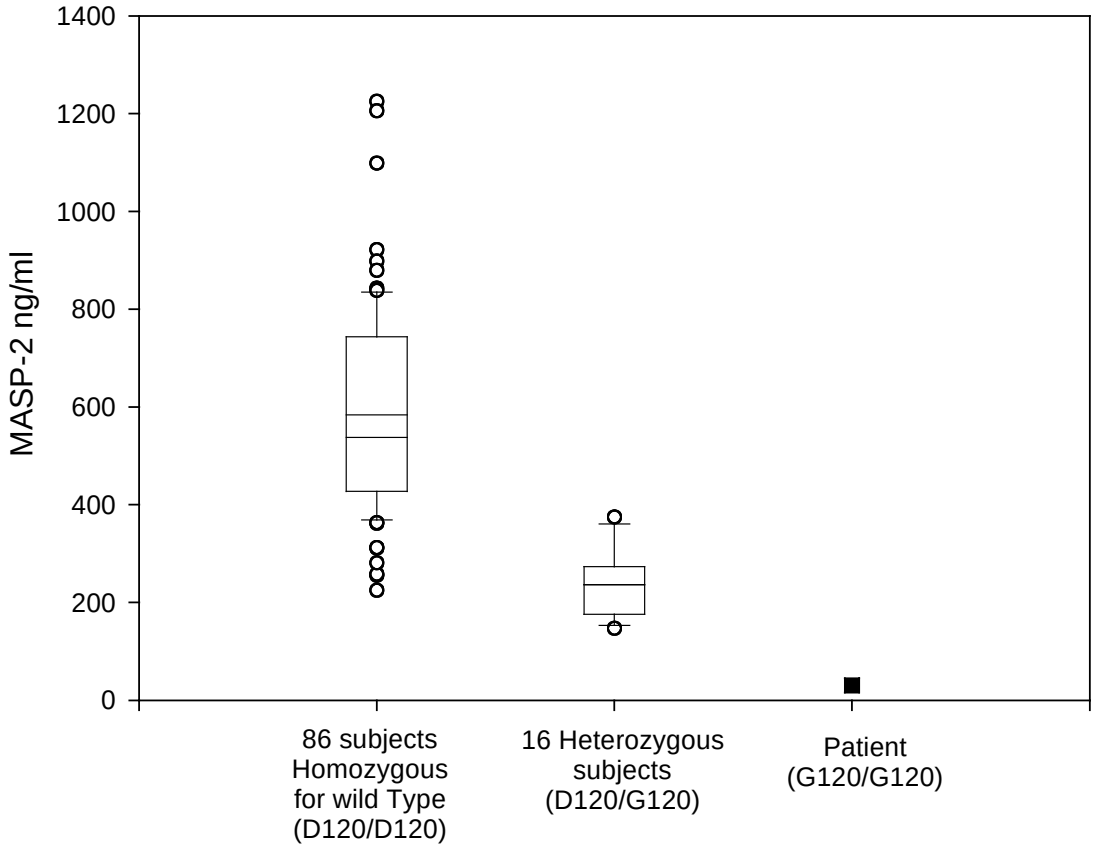
Mutation in MASP-2/MAp19 gene in CUB1 domain





Stengaard-Pedersen, Thiel , Gadjeva, Moller-Kristensen, Sorensen, Jensen, Sjoholm, Fugger, Jensenius.
N Engl J Med. 349:554-60 (2003).

MASP-2 levels in plasma

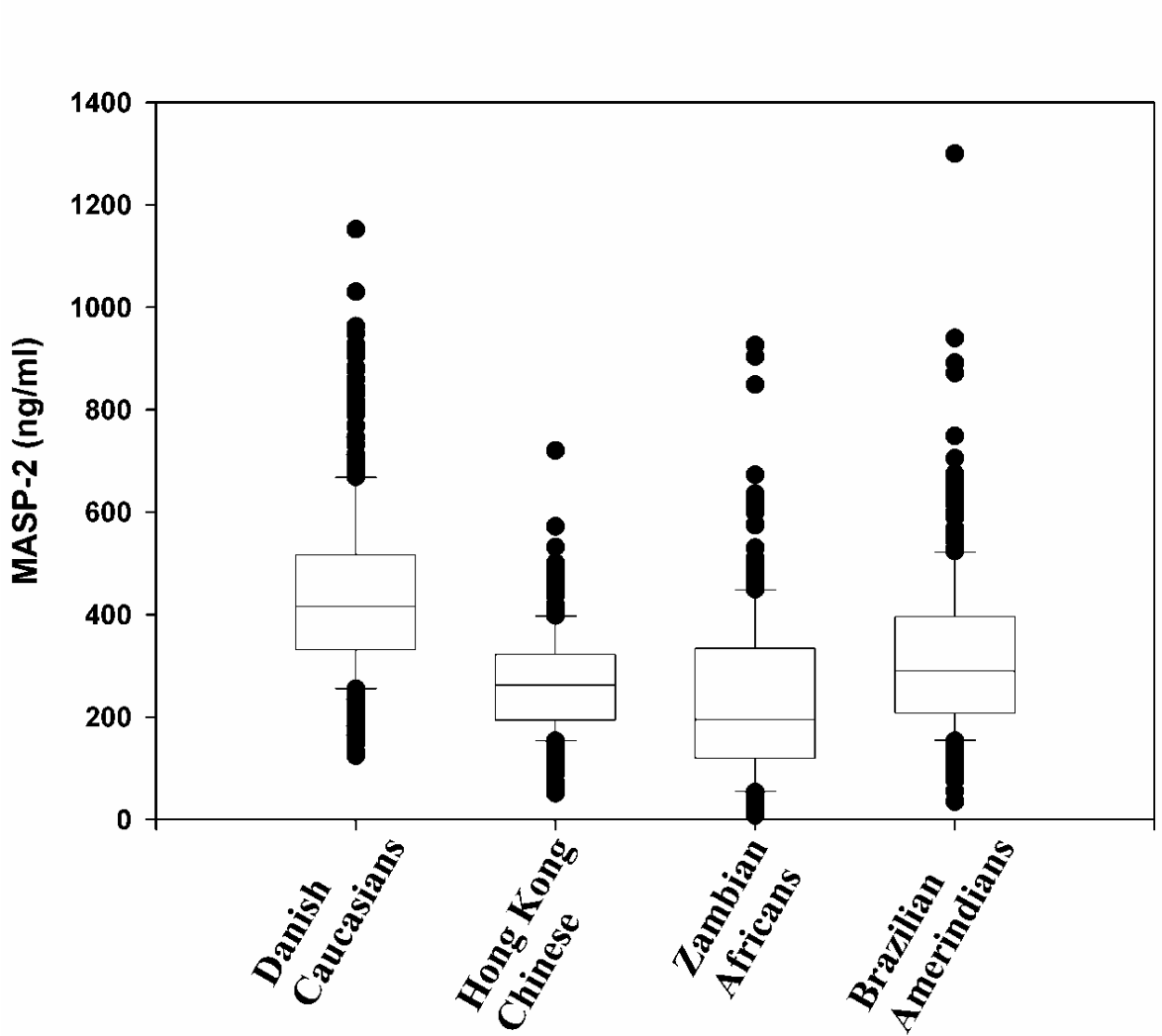


Inherited Deficiency of Mannan-Binding Lectin–Associated Serine Protease-2

Stengaard-Pedersen, Thiel, Gadjeva, Møller-Kristensen, Sørensen, Jensen, Sjöholm, Fugger, and Jensenius

The MASP-2 levels in different ethnic populations

Caucasian Danes (n = 350), Hong Kong Chinese (n = 200), African Zambians (n = 194) and Amerindian Brazilians (n =324).



A tandem duplication in MASP-2 in Asian samples – not seen in other populations.

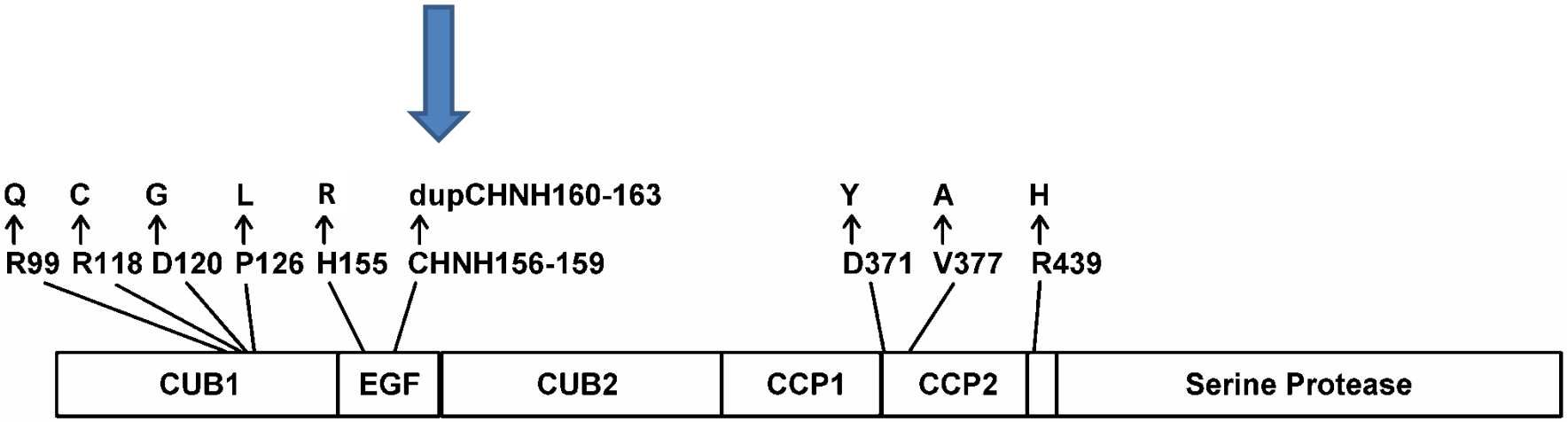


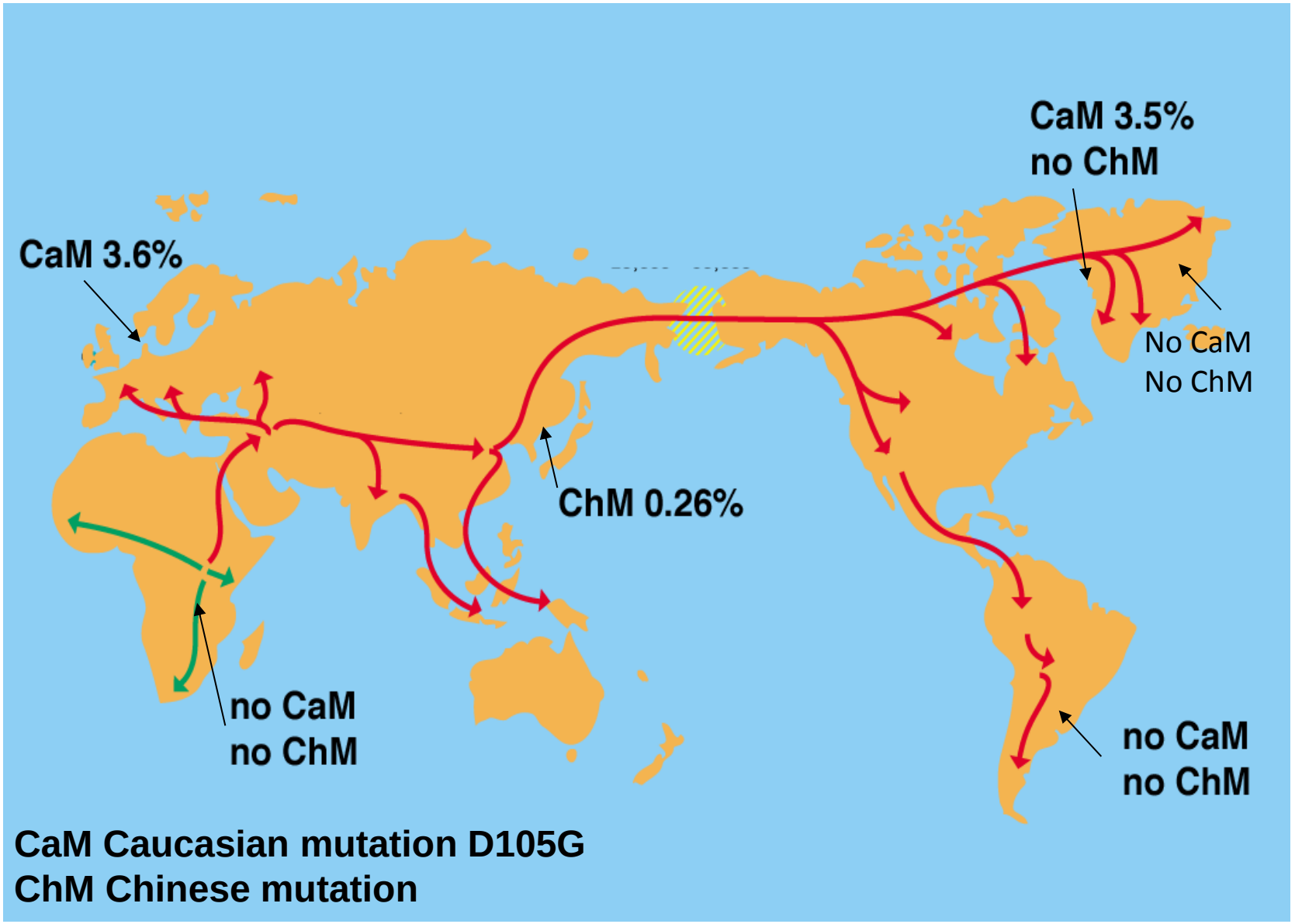
Table 2 The frequency of MASP2 alleles in different populations

		Africans Zambia N = 194	*Chinese Hong Kong N = 573*	*Caucasians Denmark N = 350*	*Inuits West Greenland N = 41*	*Inuits East Greenland N = 96*	*Amerindians Brazil N = 324*
Allele	Genotype						
p.R99Q c.296G > A	c.296 GG	163 (G = 91.8%)[a]	ND[b]	349 (G = 99.9%)	41 (G = 100%)	96 (G = 100%)	322 (G = 99.7%)
	c.296 AG	30 (A = 8.2%)		1 (A = 0.14%)	0	0	2 (A = 0.3%)
	c.296 AA	1		0	0	0	0
p.R118C c.352 C > T	c.352 CC	194 (C = 100%)	ND	350 (C = 100%)	41 C = 100%)	96 (C = 100%)	324 (C = 100%)
	c.352 CT	0		0	0	0	0
	c.352 TT	0		0	0	0	0
p.D120G c.359A > G	c.359 AA	194 (A = 100%)	573 (A = 100%)	323 (A = 96.1%)	38 (A = 96.3%)	96 (A = 100%)	324 (A = 100%)
	c.359 AG	0	0	27 (G = 3.9%)	3 (G = 3.7%)	0	0
	c.359 GG	0	0	0	0	0	0
p.P126L c.377C > T	c.377 CC	138 (C = 84%)	573 (C = 100%)	350 (C = 100%)	41 (C = 100%)	96 (C = 100%)	320 (C = 98.8%)
	c.377 CT	50 (T = 16%)	0	0	0	0	4 (T = 1.2%)
	c.377 TT	6	0	0	0	0	0
p.156_159 dupCHNH	cons/cons[c]	194 (cons = 100%)	570 (cons = 99.7%)	350 (cons = 100%)	41 (cons = 100%)	96 (cons = 100%)	324 (100%)
c.466_477 dupTGCCACAACCAC	dup/cons	0	3 (dup = 0.26%)	0	0	0	0
	dup/dup	0	0	0	0	0	0
p.V377A c.1130T > C	c.1130 TT	137 (T = 83.2%)	ND	343 (T = 99%)	41 (T = 100%)	82 (T = 92.7%)	298 (T = 95.8%)
	c.1130 TC	49 (C = 16.8%)		7 (C = 1.0%)	0	14 (C = 7.3%)	25 (C = 4.2%)
	c.1130 CC	8		0	0	0	1

[a]The gene frequencies are given in brackets.
[b]Due to lack of DNA from the Chinese some polymorphisms were not determined. These are indicated with ND (not done).
[c]'Cons' means consensus sequence and 'dup' means the presence of the duplication.

Deficiency of mannan-binding lectin associated serine protease-2 due to missense polymorphisms

S Thiel[1], R Steffensen[2], IJ Christensen[3], WK Ip[4], YL Lau[4], IJM Reason[5], H Eiberg[6], M Gadjeva[1], M Ruseva[1] and JC Jensenius[1]


CaM 3.5%
no ChM
CaM 3.6%
No CaM
No ChM
ChM 0.26%
no CaM
no ChM
no CaM
no ChM
CaM Caucasian mutation D105G
ChM Chinese mutation

Acute respiratory tract infections and mannose-binding lectin insufficiency during early childhood.

Anders Koch, Melbye M, Sørensen P, Homøe P, Madsen HO, Mølbak K, Hansen CH, Andersen LH, Hahn GW, Garred P.

JAMA. 2001 Mar 14;285(10):1316-21.

Population-based, prospective, cohort study conducted in Sisimiut, Greenland.

Risk of ARI, based on medical history and clinical examination, compared by MBL genotype, determined from blood samples based on presence of structural and promoter alleles.

The data suggest that genetic factors such as MBL insufficiency play an important role in host defense, particularly during the vulnerable period of childhood from age 6 through 17 months, when the adaptive immune system is immature

M-ficolin reflects disease activity and predicts remission in early rheumatoid arthritis

Christian Gytz Ammitzbøll, Steffen Thiel, Jens Christian Jensenius, Torkell Ellingsen,
Kim Hørslev-Peterse, Merete L. Hetland, Peter Junker, Niels Steen Krogh Jan Pødenphant, Mikkel Østergaard, Kristian Stengaard-Pedersen.
accepted for publication

Stengaard-Pedersen K, Nielsen

Non-synonymous polymorphisms in the FCN1 gene determine ligand-binding ability and serum levels of M-ficolin.

Ammitzbøll CG, Kjær TR, Steffensen R, Stengaard-Pedersen K, Nielsen HJ, Thiel S, Bøgsted M, Jensenius JC.
PLoS One. 2012;7(11). Epub 2012 Nov 28.

Mannose-binding lectin deficiency is associated with myocardial infarction: the HUNT2 study in Norway.

Vengen IT, Madsen HO, Garred P, Platou C, Vatten L, Videm V.
PLoS One. 2012;7(7): Epub 2012 Jul 27.

Congenital H-ficolin deficiency in premature infants with severe necrotising enterocolitis (NEC).

Schlapbach LJ, Thiel S, Kessler U, Ammann RA, Aebi C, Jensenius JC.
Gut. 2011 Oct;60(10):1438-9.. Epub 2010 Oct 22.

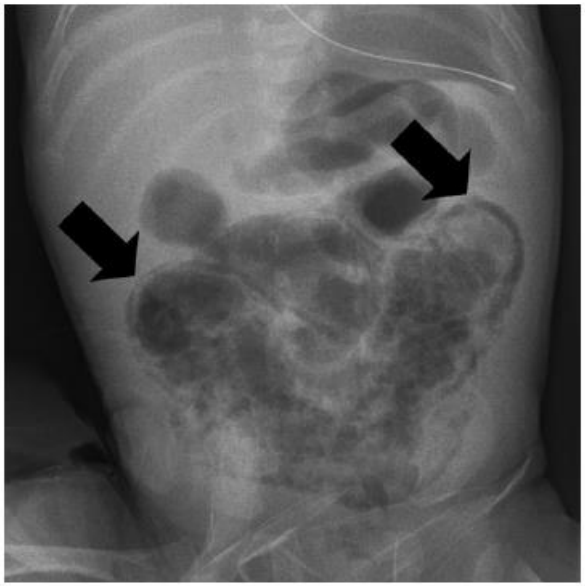


Figure 1 Abdominal X-ray picture showing extensive pneumatosis intestinalis (arrows) in the H-ficolin-deficient patient at onset of necrotising enterocolitis.

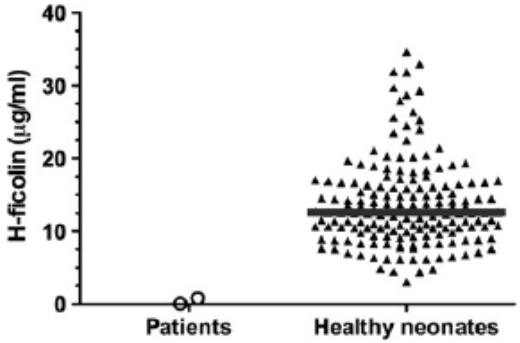


Figure 2 Concentrations of H-ficolin in cord blood of the two patients with necrotising enterocolitis and H-ficolin deficiency and in 169 healthy neonates. H-ficolin was determined by TRIFMA as described by Krarup *et al*. (*Infect Immun* 2005;73:1052–60).

2 NEC patients out of 32 were H-ficolin deficient and homozygous For deficiency-causing mutation

Gene frequency of deficiency causing mutation = 1%
Frequency of homozygocity = 1/10,000