Host genetics and immune responses

Paul Thomas

MHC molecules are compartments for holding peptide antigen

- MHC molecules are cell surface receptors that contain a peptide-binding cleft
- Small protein pieces (8-20 aa long, depending on the MHC molecule)
- First identified as transplant compatibility antigens (more on this later)

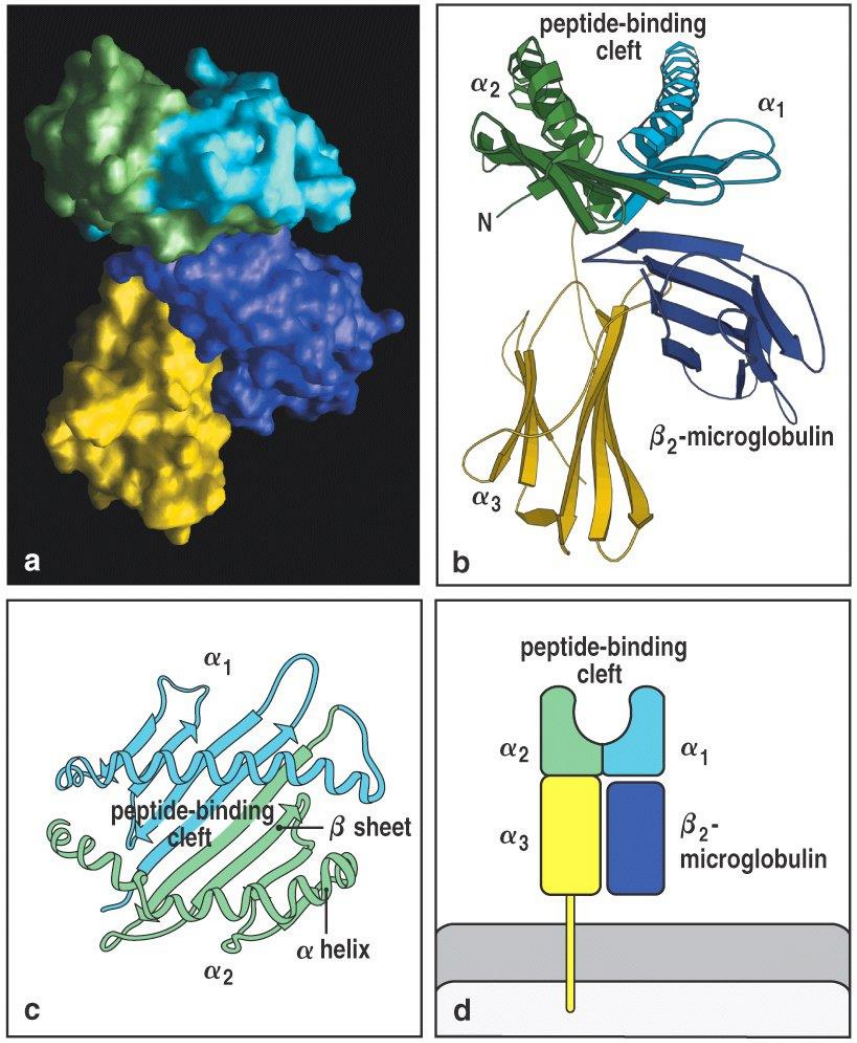


Figure 3-20 Immunobiology, 6/e. (© Garland Science 2005)

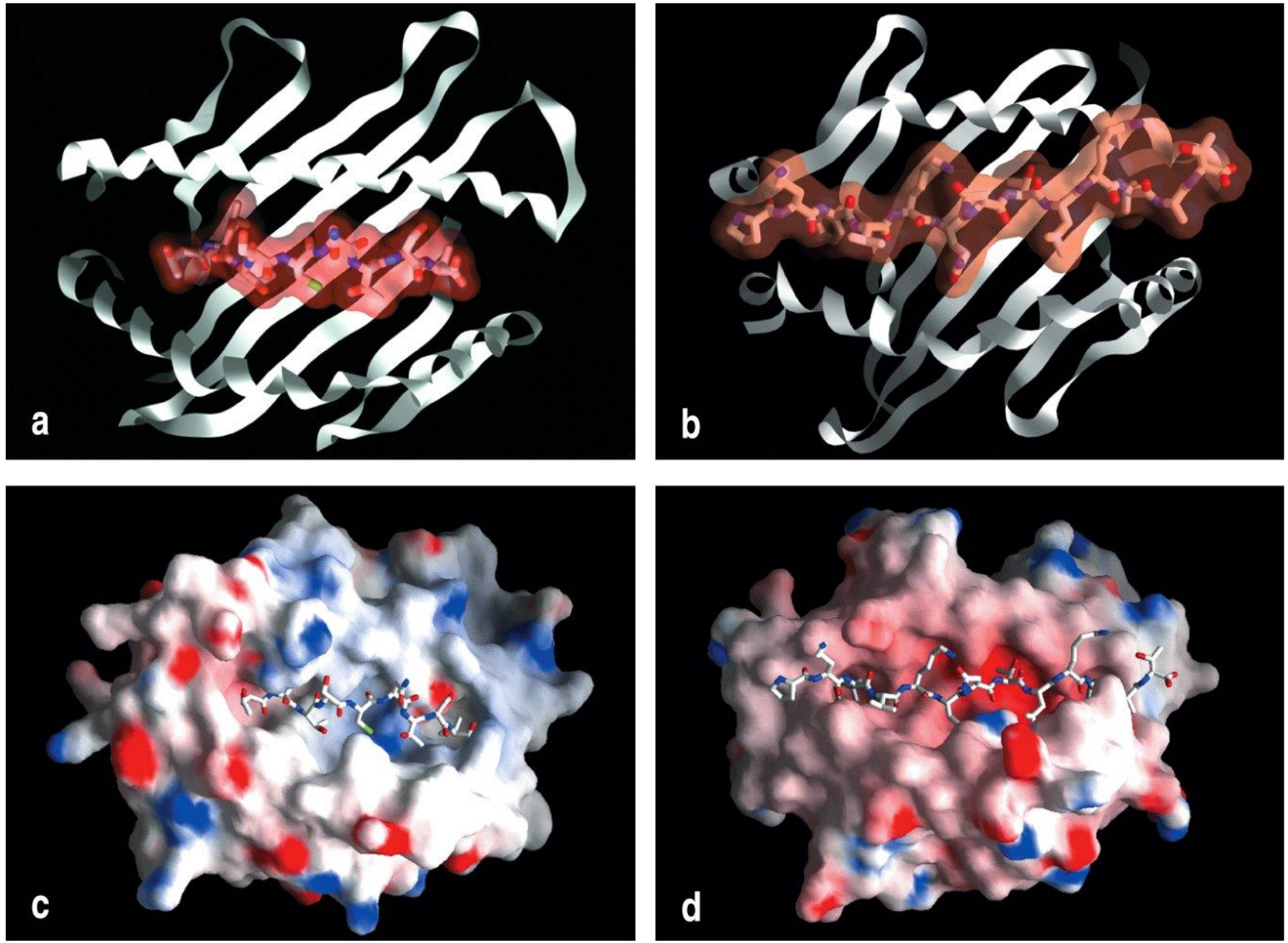


Figure 3-22 Immunobiology, 6/e. (© Garland Science 2005)

T cell Lineages Determine MHC Restriction

- CD4 and CD8 molecules both expressed during development—whether a T cell becomes CD4 or CD8 positive in maturity is dependent on the "restriction" of its TCR—whether it preferentially interacts with Major Histocompatibility Complex I (MHCI) or MHCII molecules

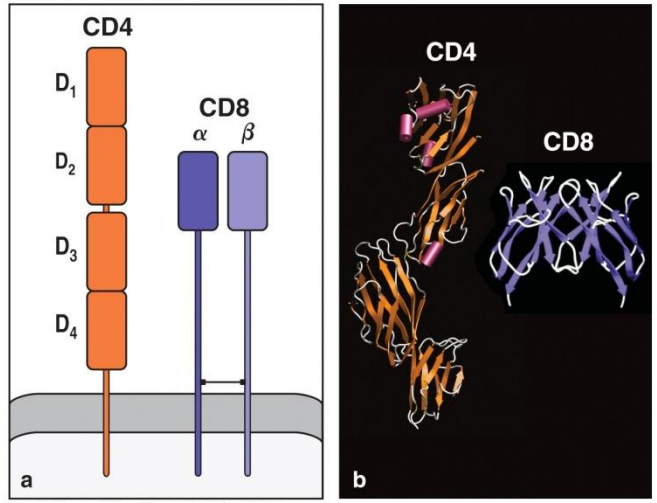


Figure 3-15 Immunobiology, 6/e. (© Garland Science 2005)

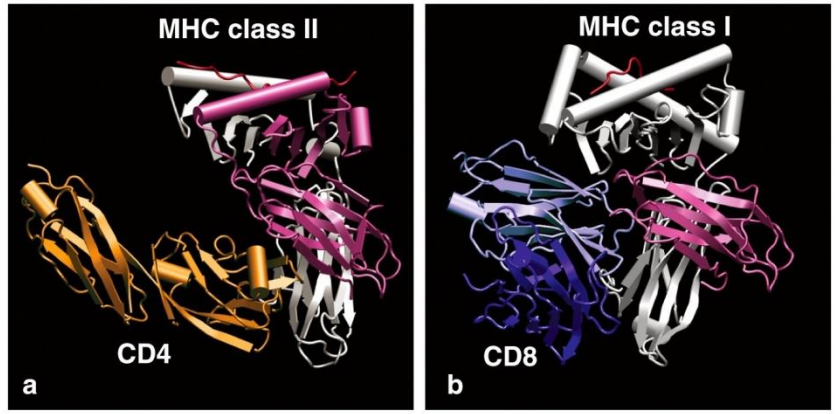


Figure 3-16 Immunobiology, 6/e. (© Garland Science 2005)

Thymus Selection Restricts MHC recognition and removes autoreactive cells

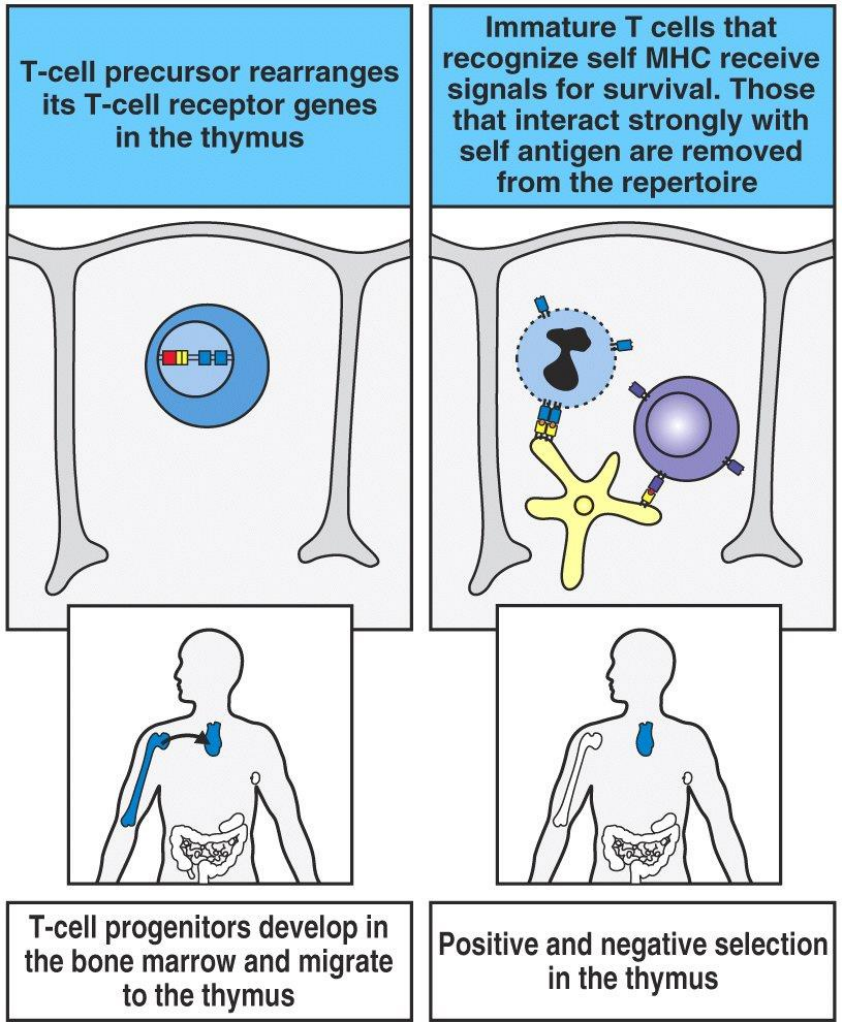


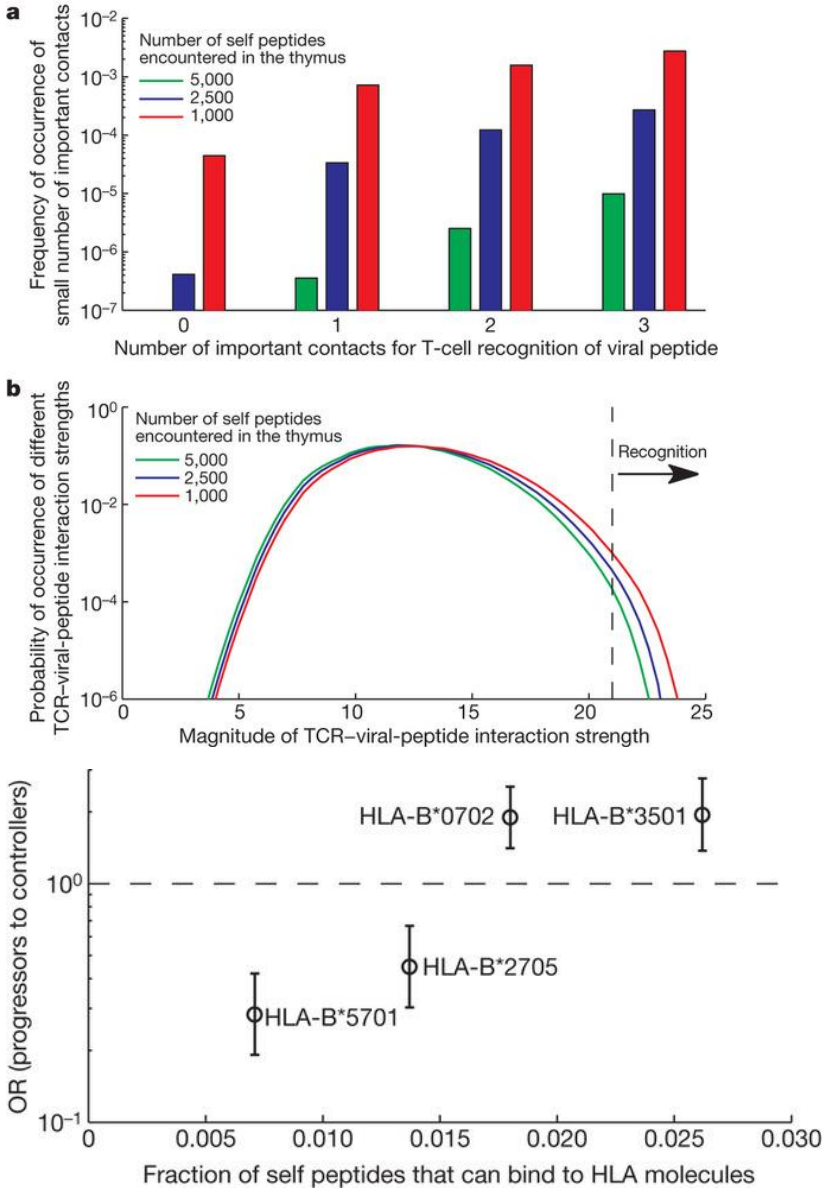
Figure 7-2 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Recent Reports Relating MHC Haplotype to HIV control

Nature 465, 350–354 (20 May 2010) Effects of thymic selection of the T-cell repertoire on HLA class I-associated control of HIV infection

Andrej Košmrlj, Elizabeth L. Read, Ying Qi, Todd M. Allen, Marcus Altfeld, Steven G. Deeks, Florencia Pereyra, Mary Carrington, Bruce D. Walker & Arup K. Chakraborty

- Relating the breadth of the TCR repertoire (how many different T cell receptors does the body make?) to the MHC haplotype (the more self peptides available for negative selection, the narrower (and less “cross-reactive” the TCR repertoire)
- Less cross-reactive TCR repertoires are then associated with poor control



Genetic studies of influenza susceptibility in mice

Protective effect on survival after IAV infection

ACE2, ADAP, ANXA1, ARNTL, ASC, ASK1, AXL, BIRC3, C3, C3, C5, CASP1[3], CBFB, CCR5[2], CD34, CSF2[2], CSF2RA, CSF2RB, CXCL4, DNAJC3, DUOX2, EIF2KA2[2], FADD, FB, FBWX7, FGF2, FHL2, GALNT3, HCFC2, HO, IFITM3, IFNAR1[6], IFNLR1, IGHM, ITGB6, IKBKE, IL1R1[3], IL28RA, IL36G[2], IL6[4], IL6R, IRAK3, IRF3, IRF5, IRF7, ISG15, LCAD, LGALGS1, LTA, MINDIN, MVP, NCR1, NOD2[2], NRAS, TP53, PIK3CG, PRPN, PYCARD, RAG2[2], RIPK2, SERPINB1, SERPINE1, SFPTA1, SOCS5, SPRED2, STAT1[2], STAT2, TNFRSF18, TNFSF9, TPL2, TNFRSF18, TNFSF10, TREML4, TGFBRII, UBE1L, ZBP1, ZMPSTE24

Negative effect on survival after IAV infection

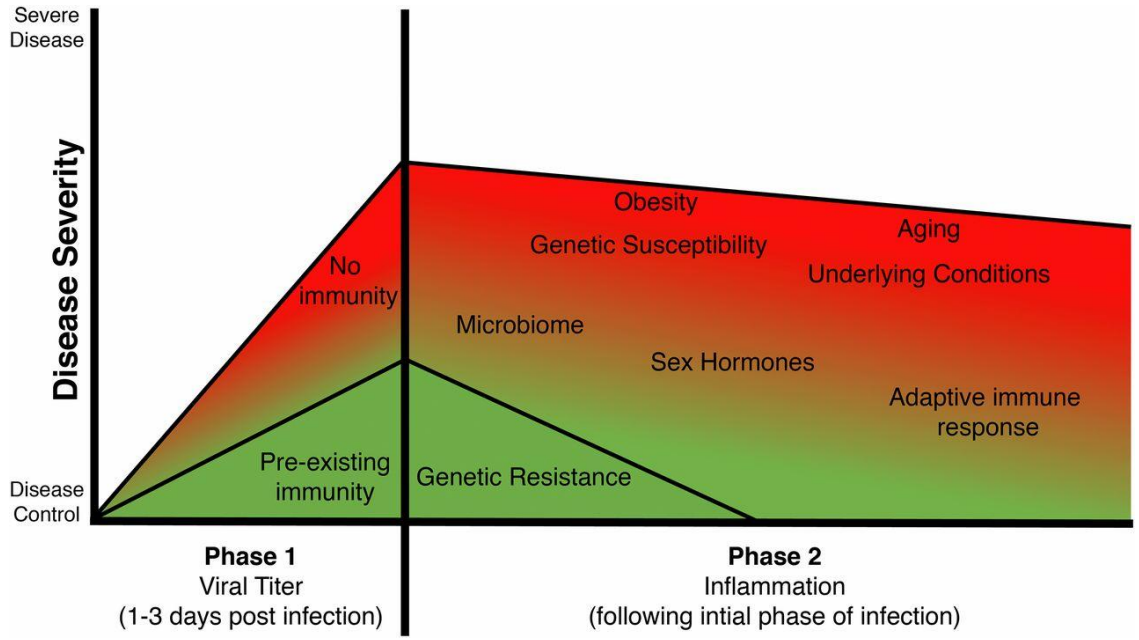
A20[2], ADORA1, ATG14, ATG5, ATG7, CARD9, CLEC5A, COX2, DUSP10, EPG5, FMRP, IFI35, IL10, IL15[2], IPO7[4,*], IL1RL2, IRGM1, LGALS3, NOS2[2], P2XR7, PAR1, PLA2G10, PLG, PTAFR, PTGES, RB1CC1, TMPRSS2[2], TRIM29

Conflicting effect on survival after IAV infection

AIM2[2], CCR2[4], IL17[3], MYD88[6], NLPR3[3], OPN[2], PAR2[2], RIPK3[3], TLR3[3], TLR4[2]

No effect on survival after IAV infection

ADAMTS5, ATG16L1, BCL2A1, CD73, COX1, CXCL14, CXCR2, CXCR3, DDX58, FAP, FCER1G, IFIT1, IgA, IFNG[2], IL18, IL1RL1, IL21R, IRG1, LGR4, LST1, MAVS[2], MLK3, MLKL, NLRC4, NLRC5, NLRX1, P50, PAD4, PLAUR, DDX58, RSAD2, SAP, SOCS4, ST6GAL1, THEMIS2, TRIF[2], TRIM56, UNC93B1



J Immunol January 15, 2019, 202 (2) 341-350; DOI: https://doi.org/10.4049/jimmunol.1801010

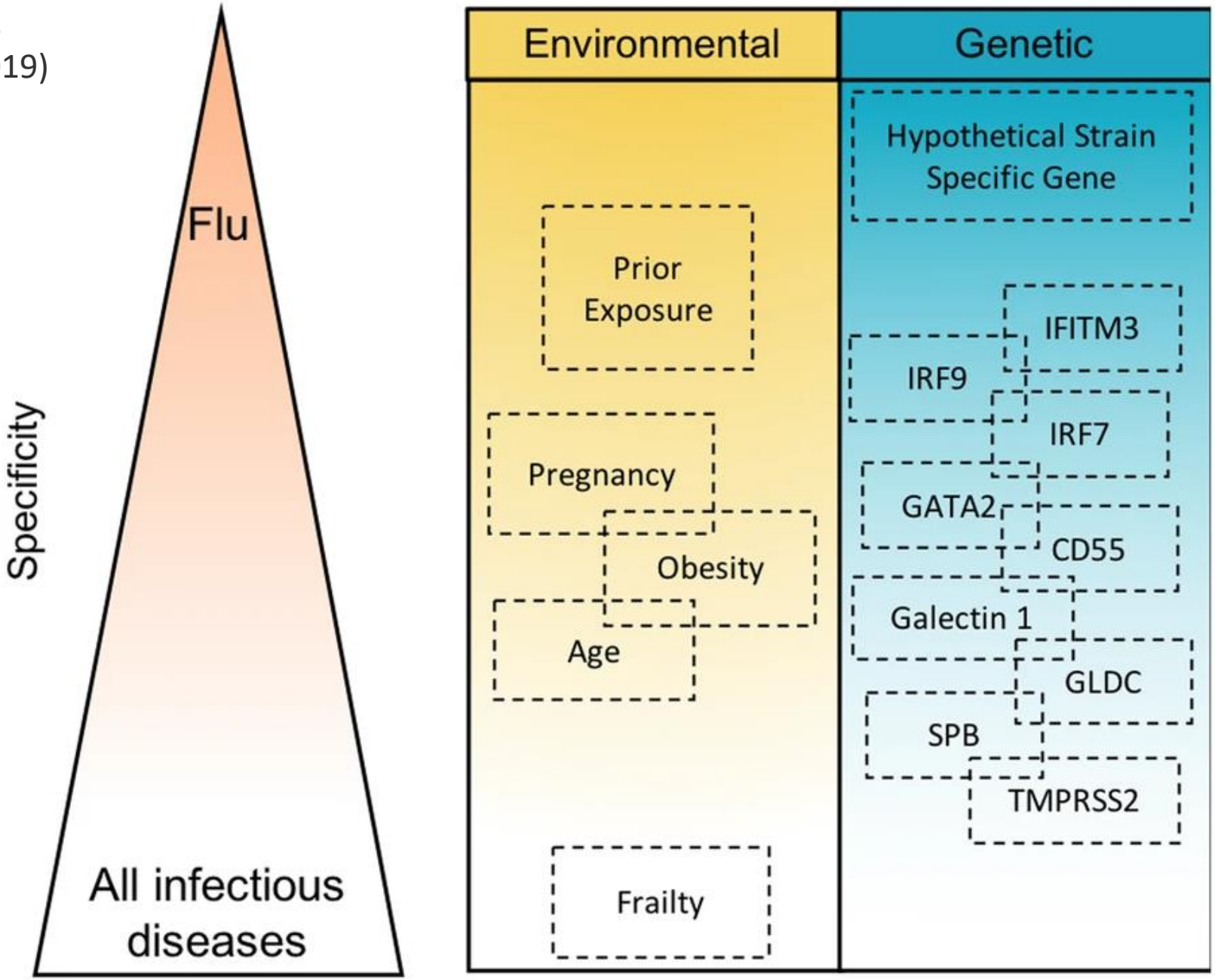
Table 1 Three categories of IEIs underlying severe infectious diseases

Characteristics	Primary immunodeficiencies[a]	Mendelian infections[b]	Monogenic infections[c]
Number of patients	Known (intermediate)	Known (small)	Unknown (large?)
Familial cases	Common	Common	Rare (sporadic)
Penetrance	High or complete	High or complete	Low
Age at onset	Children ≫ adults	Children > adults	Children or adults
Number of infectious agents	High	Single (or a few)	Single
Number of infectious episodes	High (acute or chronic)	Low or high	Low
Infectious diseases	Often rare, opportunistic	Rare, idiopathic	Common
Immunological abnormalities	Before gene discovery	After gene discovery	After gene discovery
Cell types involved	Leukocytes	Leukocytes or other cell types (e.g., keratinocytes and *CIB1*)	Leukocytes or other cell types (e.g., cortical neurons and *TLR3*)
Other clinical phenotypes	Common (autoimmunity, allergy, autoinflammation, cancer, others)	Rare (syndromic forms)	Very rare
Examples	AR SCID and variations in *RAG1* XR agammaglobulinemia and *BTK* AD congenital neutropenia	AR EV and variations in *CIB1* XR EBV disease and *SAP* AD MSMD and *IFNGR1*	AR severe influenza pneumonitis and variations in *IRF7* XR invasive pneumococcal disease and *NEMO* AD HSE and *TLR3*

[a]Primary immunodeficiencies comprise more than 400 monogenic IEIs disrupting host defense against various infectious agents. They are also associated with overt immunological abnormalities. They typically display high or complete immunological and clinical penetrance.
[b]Mendelian infections are five monogenic IEIs that disrupt host defense against one or a few infectious agents. The infections were idiopathic until the discovery of disease-causing genes led to the recognition of immunological abnormalities. Their clinical penetrance is high or complete.
[c]Monogenic infections comprise at least 10 monogenic IEIs that disrupt host defense against one or a few infectious agents. These infections also typically remained idiopathic until the discovery of disease-causing genes. Their penetrance is low (hence their mode of inheritance in parentheses), accounting for these infections being typically sporadic, as opposed to familial. Importantly, variations at a given locus can underlie the three types of phenotypes, as neatly illustrated by variations at the *NEMO* locus (148, 150).
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EBV, Epstein–Barr virus; EV, epidermodysplasia verruciformis; HSE, herpes simplex encephalitis; IEI, inborn error of immunity; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency; XR, X-linked recessive.

. 2020 Apr 14. doi: 10.1146/annurev-pathol-031920-101429. Online ahead of print.

Critical Care **volume 23**,
Article number: 303 (2019)



Conceptual visualisation of variation in specificity of host susceptibility factors. Factors predicted to confer more specific susceptibility to influenza are placed higher in the diagram

Gene	Gene name	Function	SNP	Reference
Entry factors/cell membrane				
IFITM3	Interferon-induced transmembrane protein 3	Antiviral	rs12252-C	[64,65,66]
			rs34481144-A	[67]
CD55	Complement decay-accelerating factor precursor 55	Inhibition of complement activation	rs2564978 T/T	[71, 72]
TMPRSS2	Transmembrane protease, serine 2	Serine protease	rs2070788 GG	[73,74,75,76]
GLDC	Glycine decarboxylase	Component of the glycine cleavage system	rs1755609-G	[80]
LGALS1	Galectin-1	Cell-cell interactions	rs4820294	[82]
			rs2899292	[82]
			rs4820294	[82]
ST3GAL1 (*)	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	Transfer of sialic acids to galactose-containing substrates	rs113350588	[90]
			rs1048479	[90]
TNFA (*)	Tumour necrosis factor alpha	Inflammation and immune signalling	rs361525-A	[91]
TLR3 (*)	Toll-like Receptor 3	Pathogen recognition	rs5743313-CT	[92]
			rs5743313-CC	[72]
Surfactant proteins				
SP-A2 (*)	Pulmonary-surfactant associated protein A2	Pathogen binding and immune signalling	rs1965708-C	[89]
			rs1059046-A	[89]
SP-B	Pulmonary-surfactant associated protein B	Pathogen binding and immune signalling	rs1130866	[77]
Interleukins				
IL1A (*)	Interleukin 1 alpha	Inflammation and immune signalling	rs17561-T	[84]
IL1B (*)	Interleukin 1 beta	Inflammation and immune signalling	rs1143627-C	[84]
			rs16944-AG	[85]
			rs3136558-TC	[85]
IL28B	Interleukin 28 b, IFN-λ 3	Immunomodulation	rs8099917-TT	[86]
IL17 (*)	Interleukin 17	Inflammation and immune signalling	rs2275913 (GG and AG)	[87]
IL6 (*)	Interleukin 6	Inflammation and immune signalling	rs1818879-(GA and GG)	[85, 88]

Gene: gene symbol. Gene name: gene name and alternate name. Function: summary function of gene product. SNP: SNPs associated with host susceptibility to influenza A associated with gene. (*) represents genes not addressed in the text

Published: 18 January 2012

Rare and common variants: twenty arguments

Greg Gibson

Nature Reviews Genetics **13**, 135–145(2012) | Cite this article

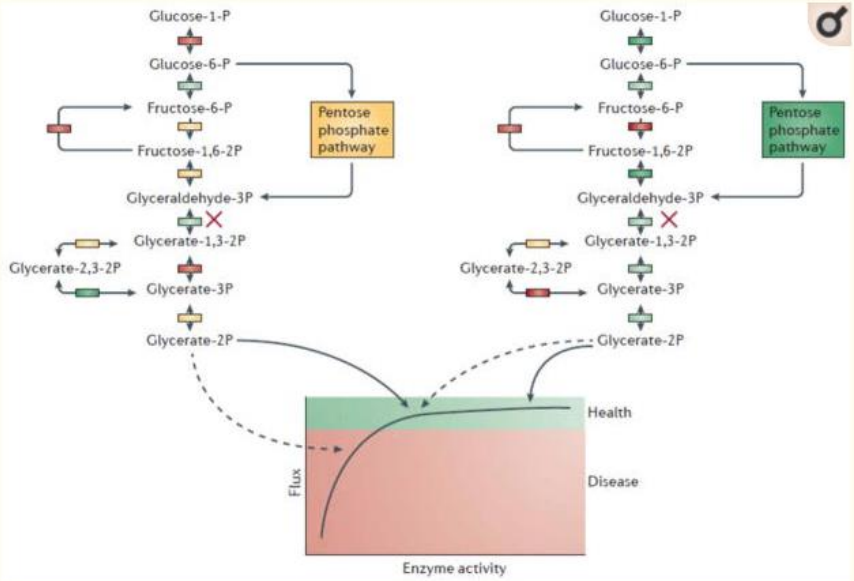


Figure 4

Joint effects of rare and common variants

A straight forward reconciliation of the effects of rare and common variants supposes that pervasive common variation influences the expression and activity of genes in pathways, establishing the background liability to disease that is then further modified by rare variants with larger effects. In this hypothetical example of central metabolism, standing variation results in some individuals having lower flux than others (left versus right; colored boxes imply enzyme activity differences from low, red, to high, green), but according to standard biochemical theory[130], systems evolve such that most variation is accommodated within the healthy range. The impact of a rare variant that knocks out one copy of the enzyme indicated with the cross is conditional on this liability, pushing the individual on the left beyond the disease threshold, while the individual on the right can accommodate the mutation given higher activity elsewhere in glycolysis.

Table 1

The 20 Arguments

For Rare Alleles
Evolutionary theory predicts that disease alleles should be rare.
Empirical population genetic data shows that deleterious variants are rare.
Rare copy number variants contribute to several complex psychological disorders.
Many rare familial disorders are due to rare alleles of large effect.
Synthetic associations may explain common variant effects.
Con Rare Alleles
Simulation of GWAS is not consistent with rare variant explanations.
GWAS associations are consistent across populations.
Sibling recurrence rates are greater than postulated rare variant effect sizes.
Epidemiological transitions cannot be attributed to rare variants.
Rare variants do not obviously have additive effects.
For Common Alleles
GWAS has successfully identified thousands of common variants.
Model organism research supports common variant contributions to complex phenotypes.
Variation in endophenotypes is almost certainly due to common variants.
The infinitesimal model is standard quantitative genetic theory.
Common variants collectively capture the majority of the genetic variance in GWAS.
Con Common Alleles
What accounts for the missing heritability?
Demographic phenomena suggest more than a simple common variant model.
The QTL paradox.
Absence of blending inheritance.
Very few common variants for disease have been functionally validated.