Immunity and genetics as health determinants

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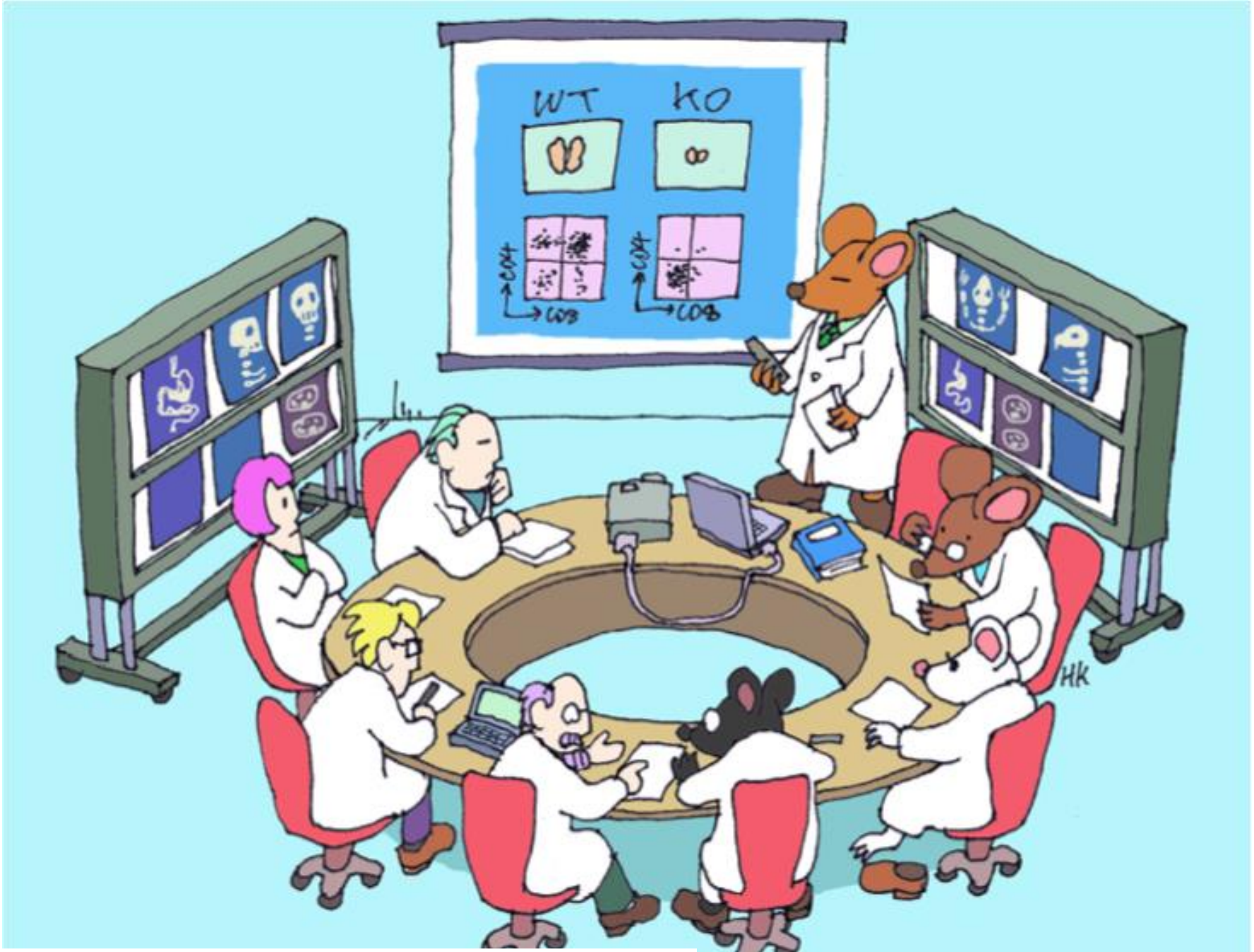
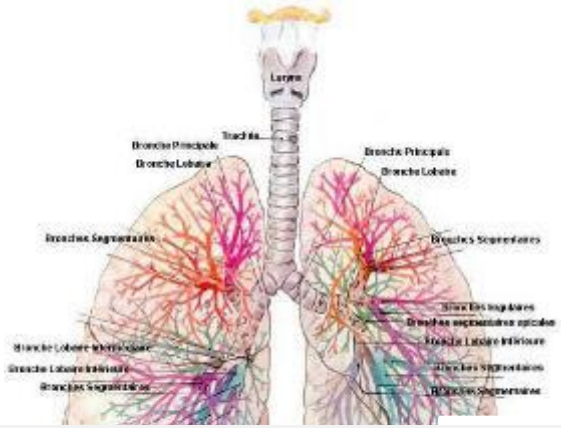


The Imagine Institute at work !

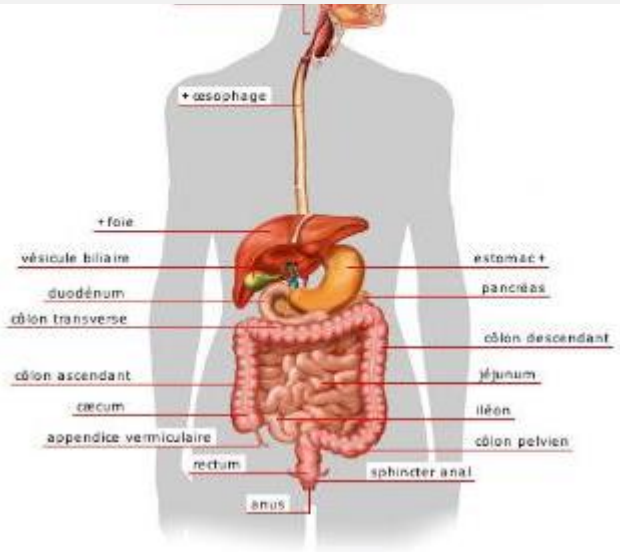
Illustrated by Prof. Hiroshi Kawamoto@Kyoto Univ.

The immense challenges of our immune system



Respiratory tract (Rt)
140 m²
lower resp.tract is
usually kept « clean »

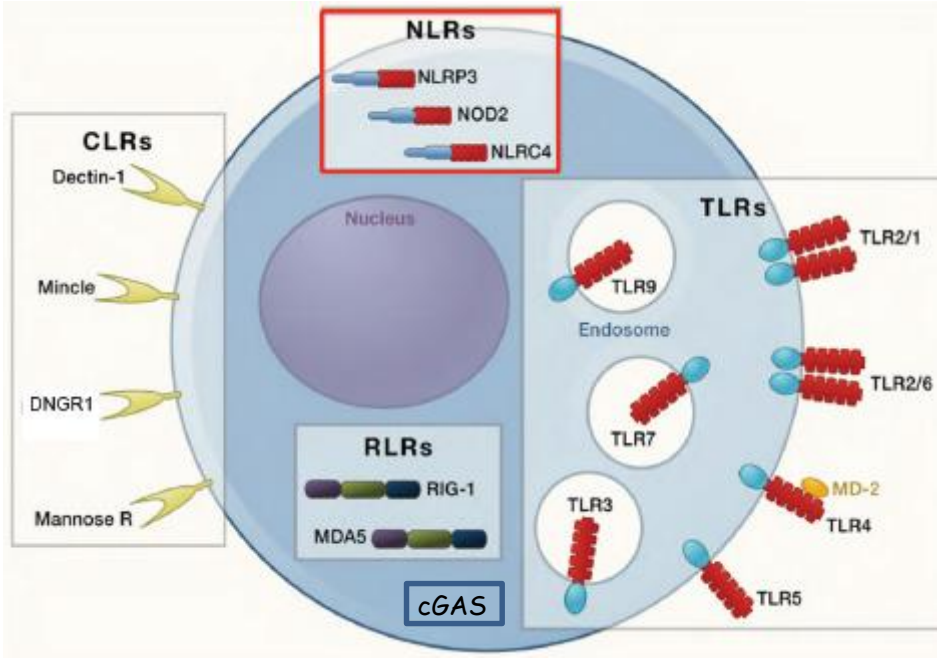
to fight pathogenic microbes
to trade off with commensals
to « ignore » self

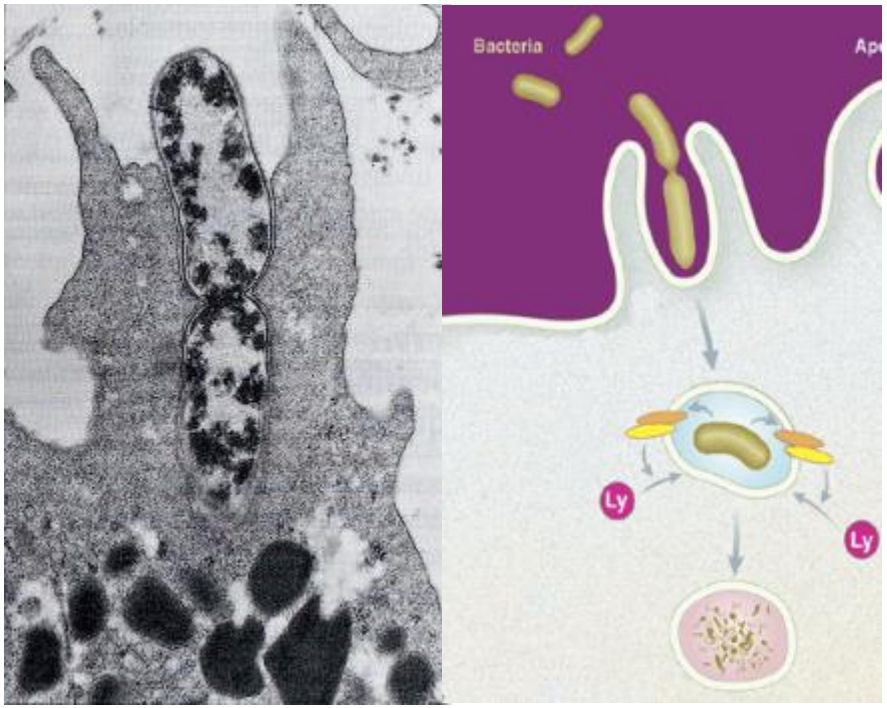


Gut 300 m²

3x10¹³ bacteria ≥1000 species
≥ 1x10¹⁵ virus
fungi,
parasites…

Innate Immunity



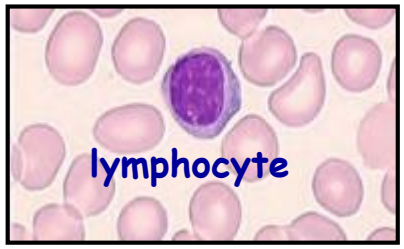


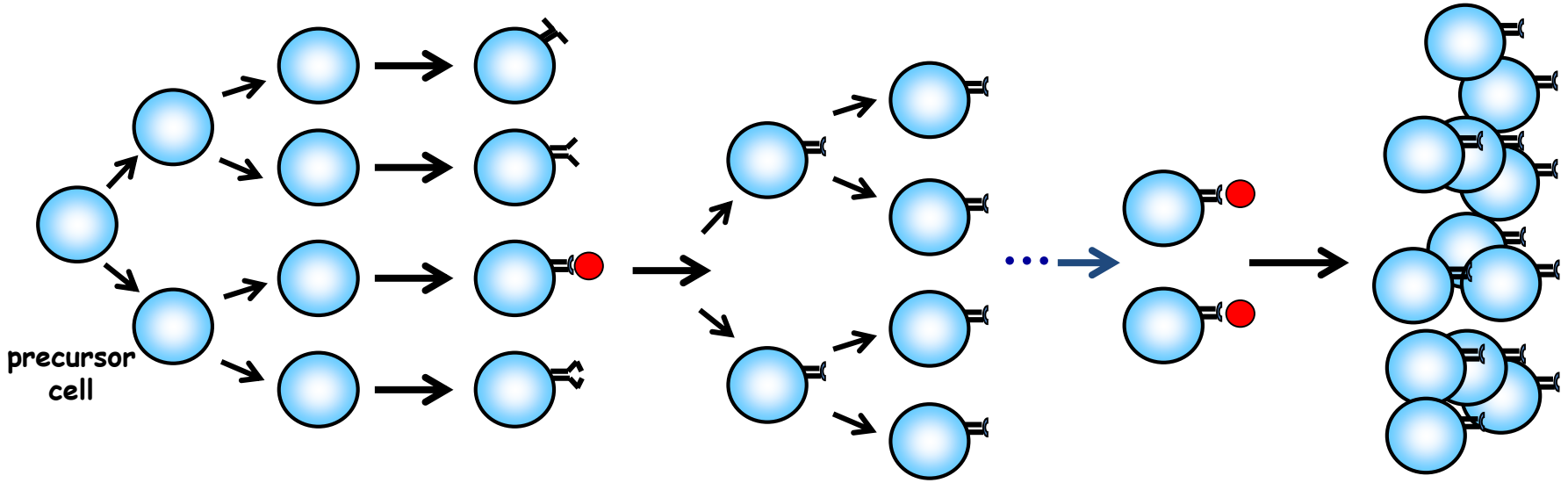
Surface and intracellular receptors binding to microbial products (or endogeneous « danger » molecules)
Rapid immune response

Phagocytosis et microbicidy

phagocytic cells

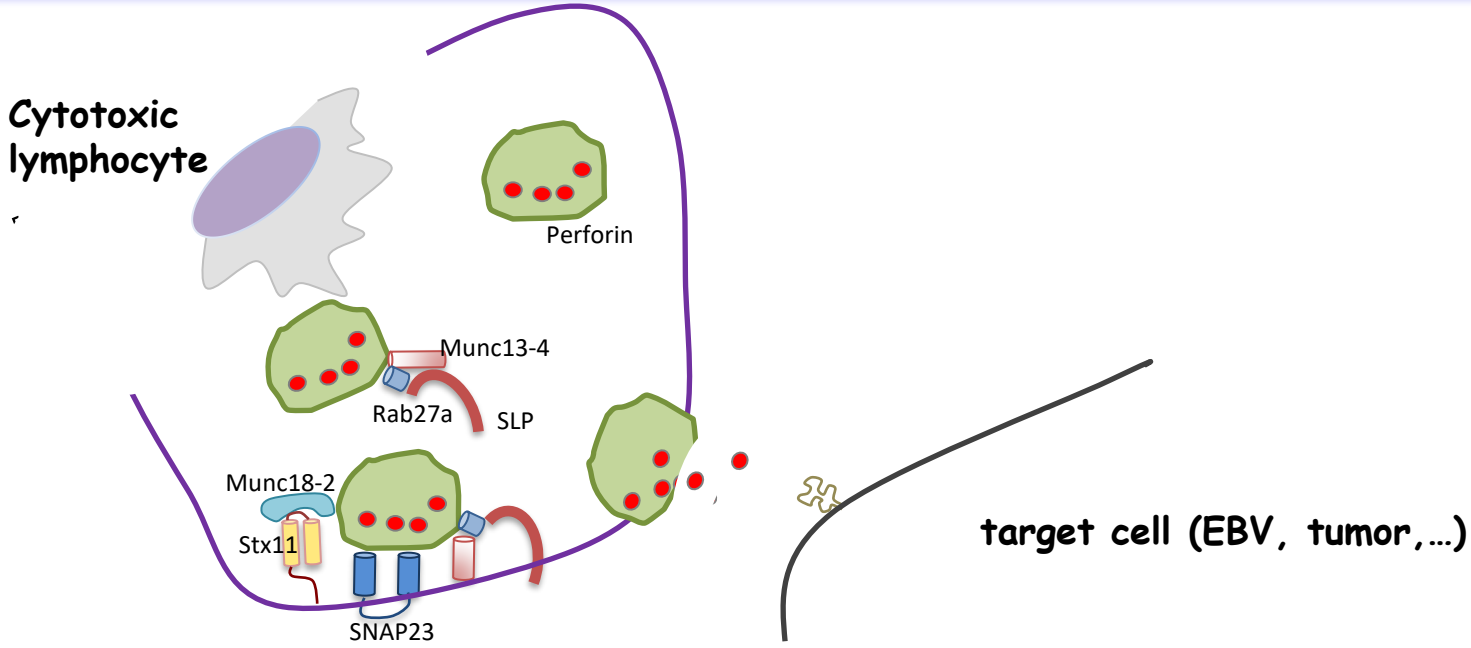
Adaptive immunity



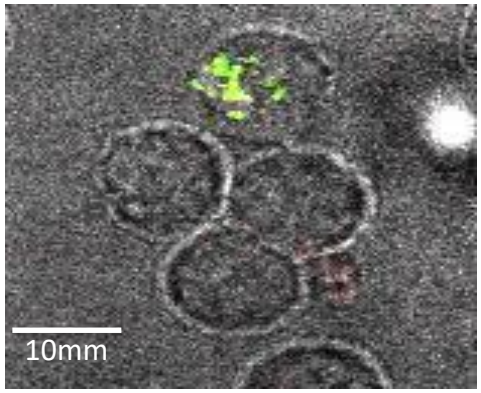


Dual system: T+B

An example of efector function: cell killing

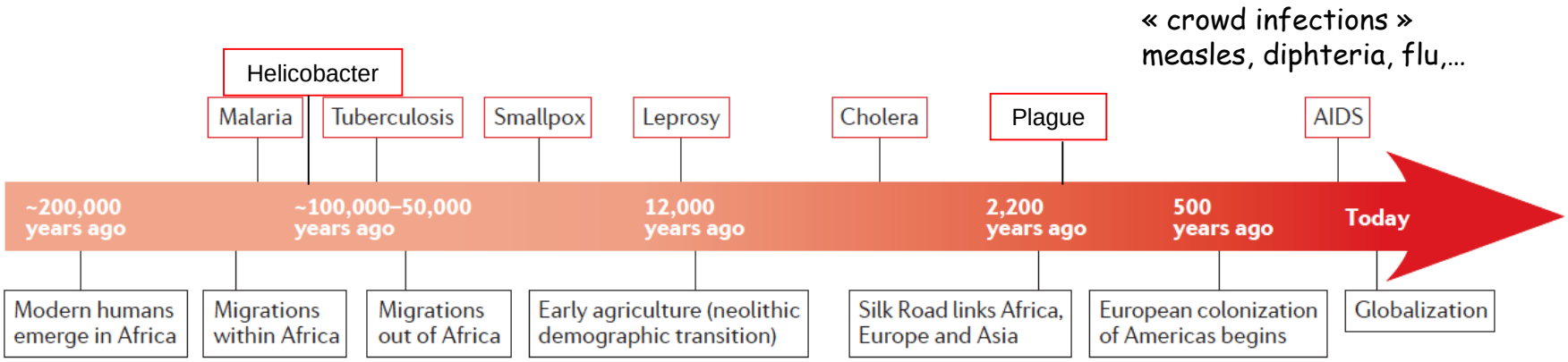


WT CTL



Efficient but toxic process !!

Coevolution of men and microbes in changing environments

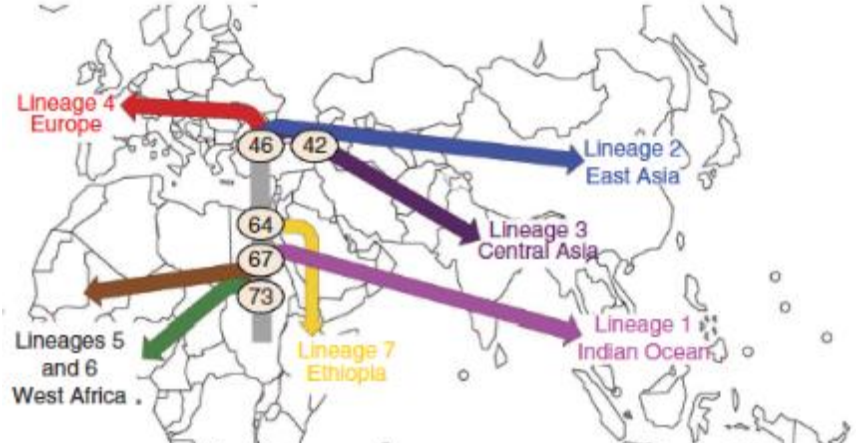


Adapted from E.K. Karlsson et al, Nature Reviews Genetics, 2014

considerable selective pressure on the immune system,.. and conversely on microbes !

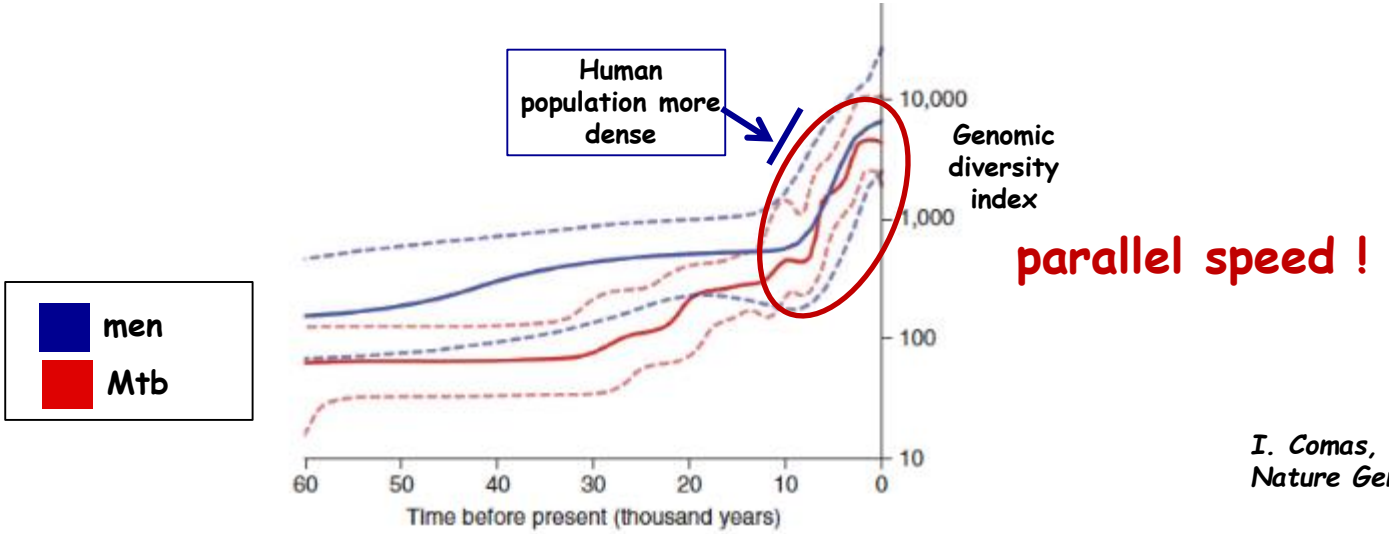
An example of coevolution: tuberculosis

Phylogenetic tree of *Mtb* (259 strains)



kyears

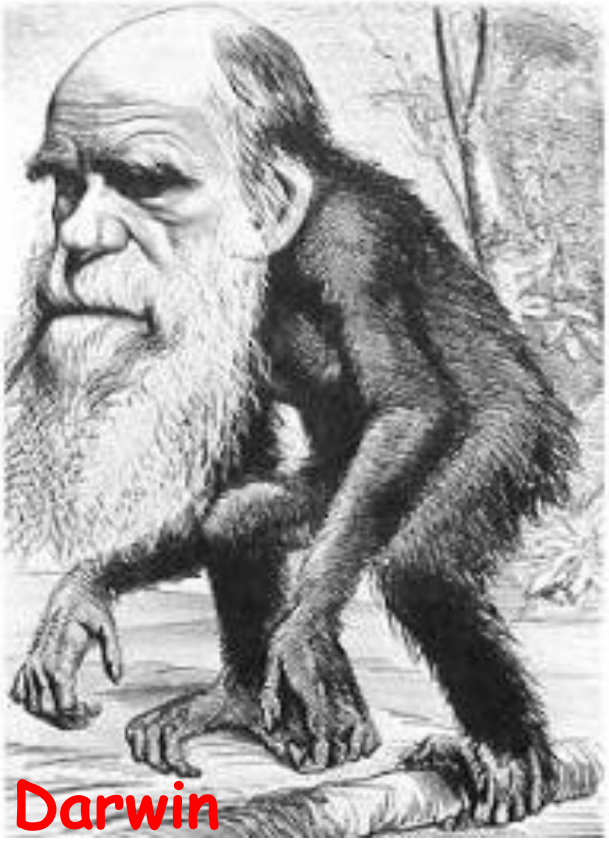
Men won by 9 to 1 !
(but $1x10^9$ died in 200 years)



parallel speed !

I. Comas, Nature Genetics 2013

Evolution of our genome



Mutations/admixing/

selection

approximately 2 000 genes

involved in immune responses

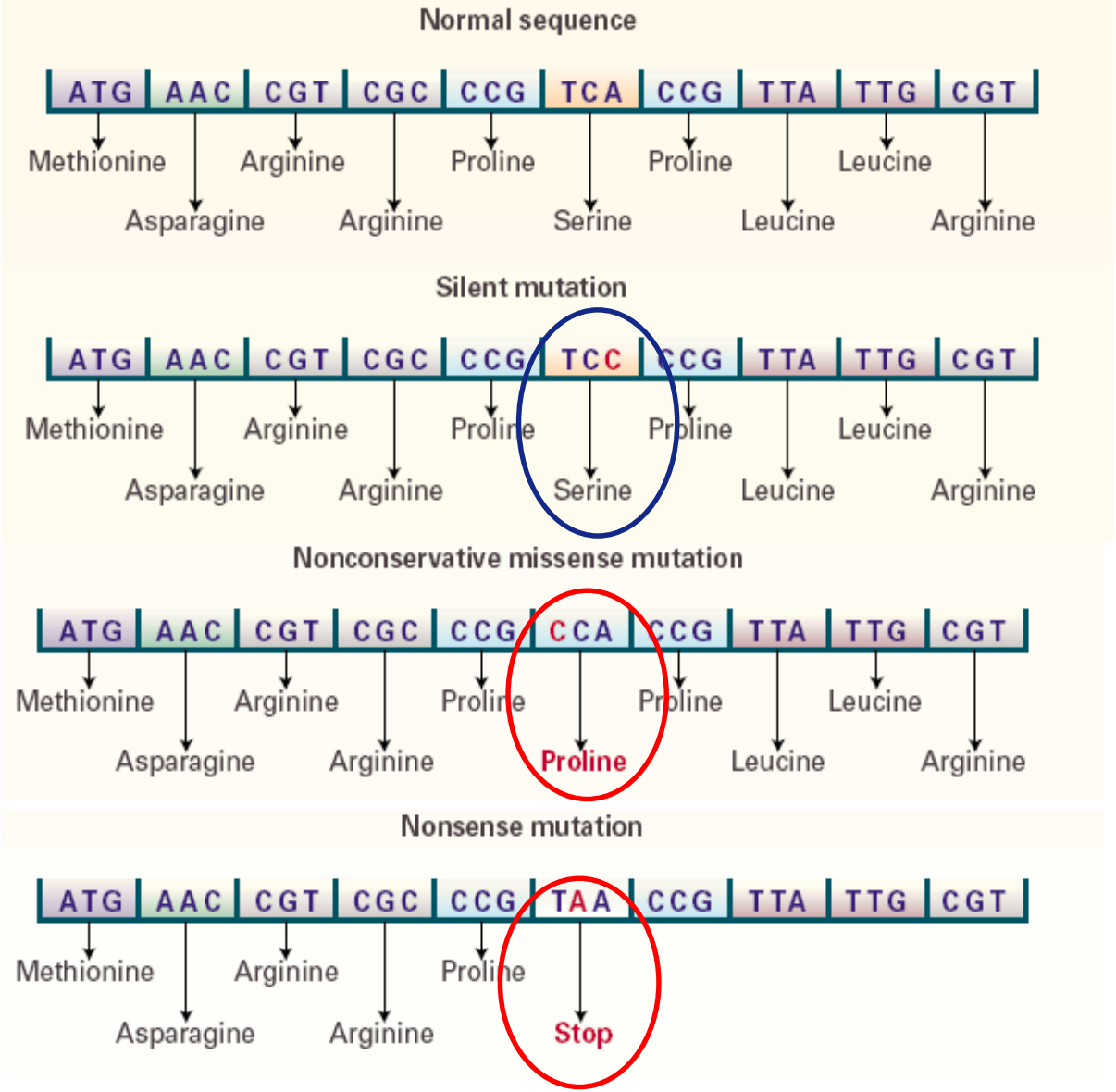
(9% of our genes)

Mutations

DNA sequence

4 « letters » code

aminoacids



Occurrence of germ line mutations are not so rare !!

***De novo* mutations observed with parental origin assigned**

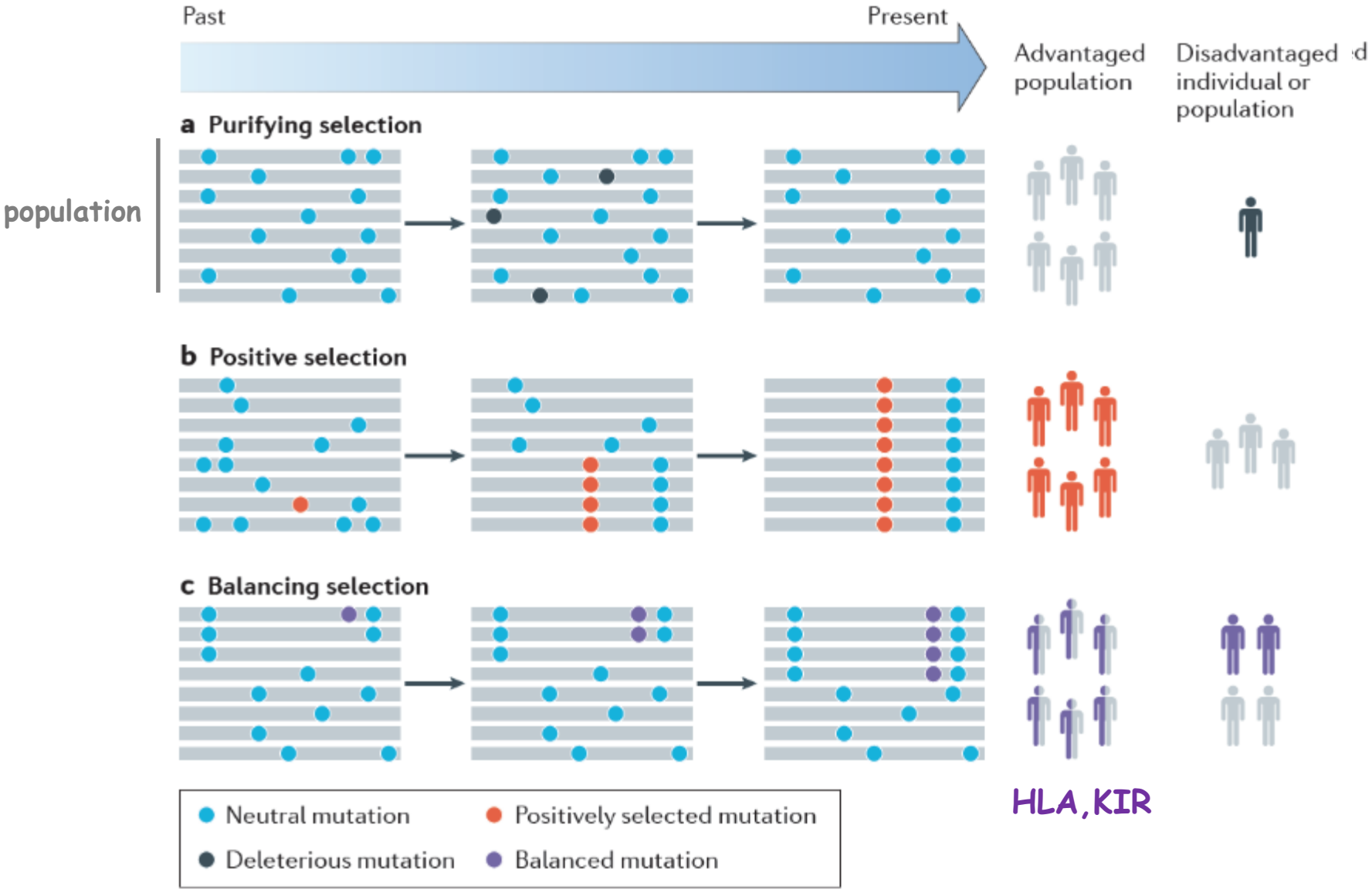
			Number of *de novo* mutations in proband		
	Father's age (yr)	Mother's age (yr)	Paternal chromosome	Maternal chromosome	Combined
Trio 1	21.8	19.3	39	9	48
Trio 2	22.7	19.8	43	10	53
Trio 3	25.0	22.1	51	11	62
Trio 4	36.2	32.2	53	26	79
Trio 5	40.0	39.1	91	15	106
Mean	29.1	26.5	55.4	14.2	69.6
s.d.	8.4	8.8	20.7	7.0	23.5
Variance	70.2	77.0	428.8	48.7	555.3

1.2 mutation/1x10^8 nucleotides/generation

10% potentially deleterious, or beneficial, ..or both !

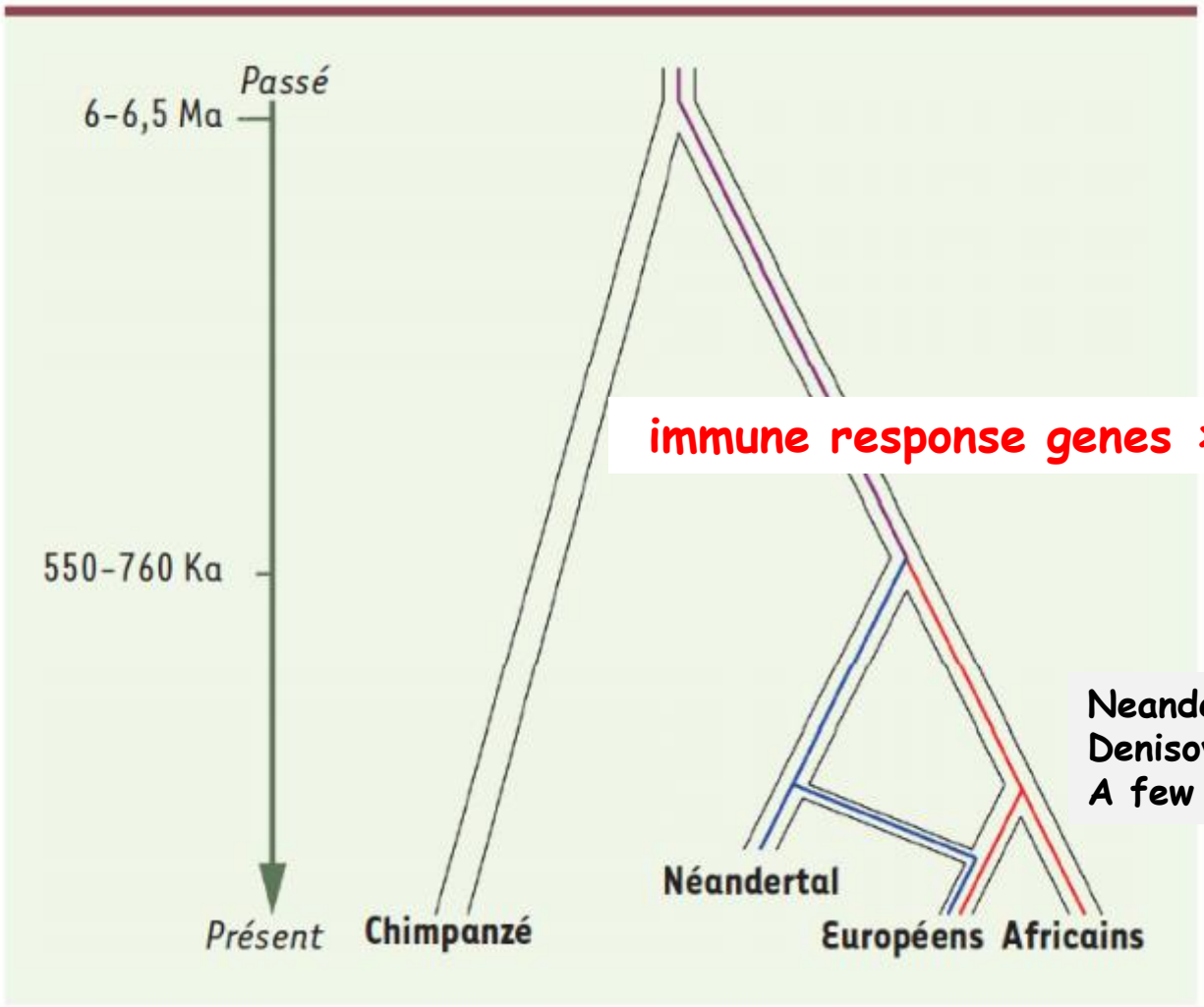
A. Kong et al, Nature 2012

Selection events



adapted from L. Quintana-Murci et al, Nat. Rev. Immunol, 2013

Admixture with "archaic hominins", a way to genome diversification



immune response genes > rest of the genome !

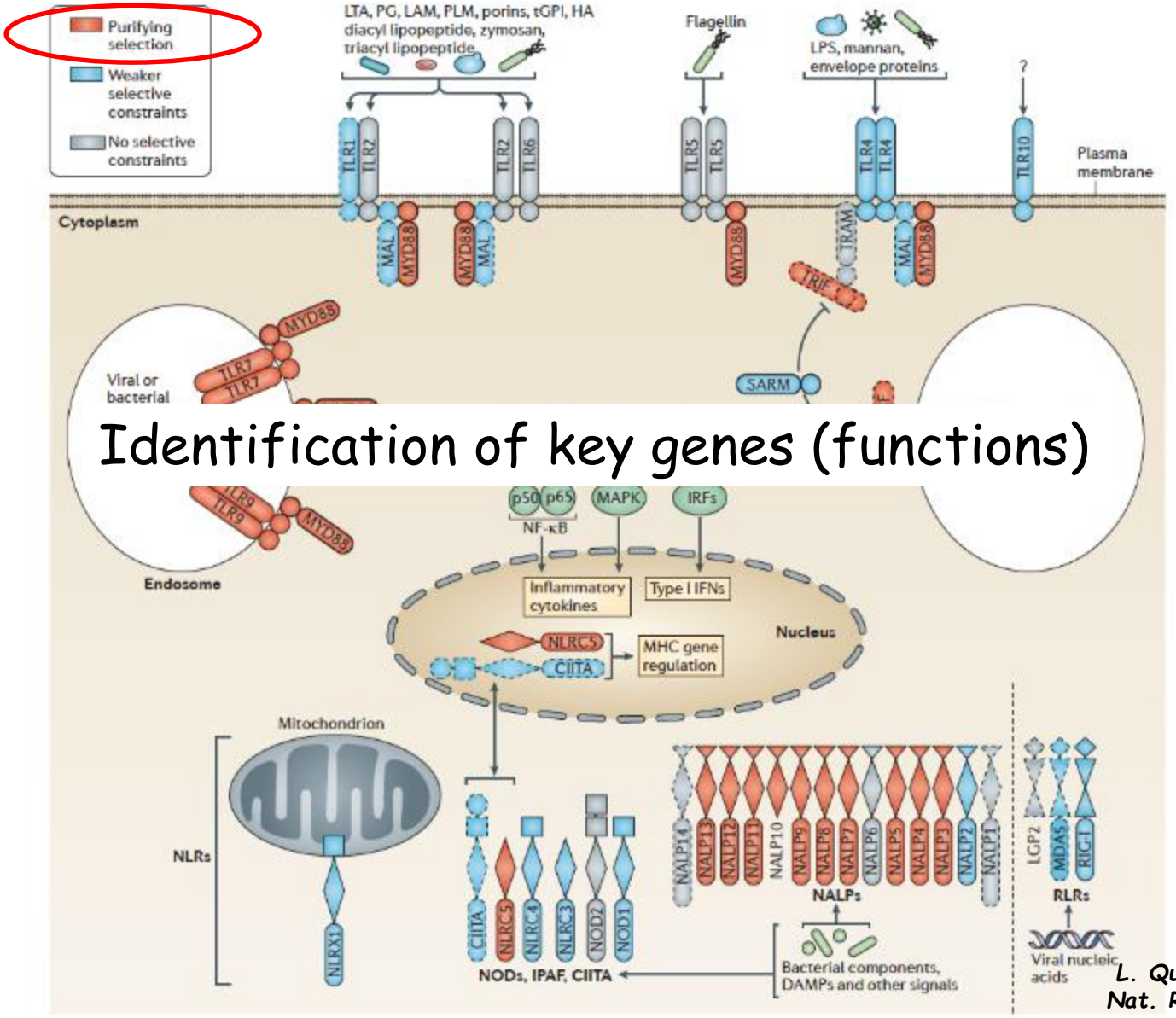
Neandertal in Europe: 50 kyears ago
Denisova in Asia
A few % of our genome

Adapted fromM. Deschamps et al, 2016

Selection events

Adapted fromL. Quintana-Murci et al, Nat. Rev. Immunol, 2013

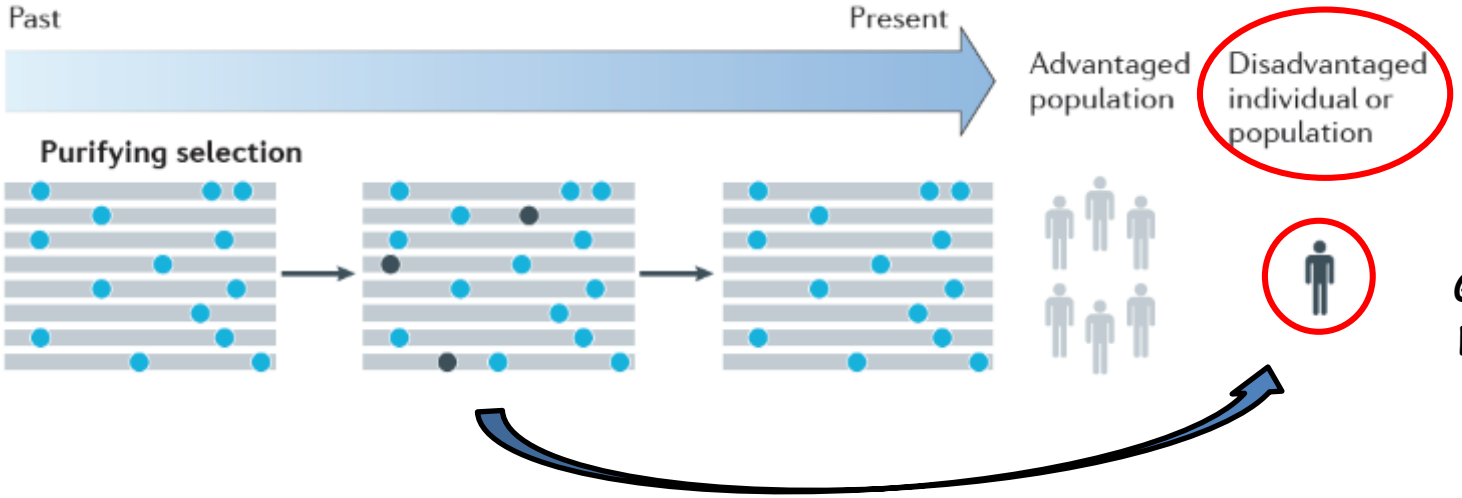
Negative selection of innate immunity genes



Identification of key genes (functions)

L. Quintana-Murci et al, Nat. Rev. Immunol, 2013

Selection, evolution…. and inherited diseases

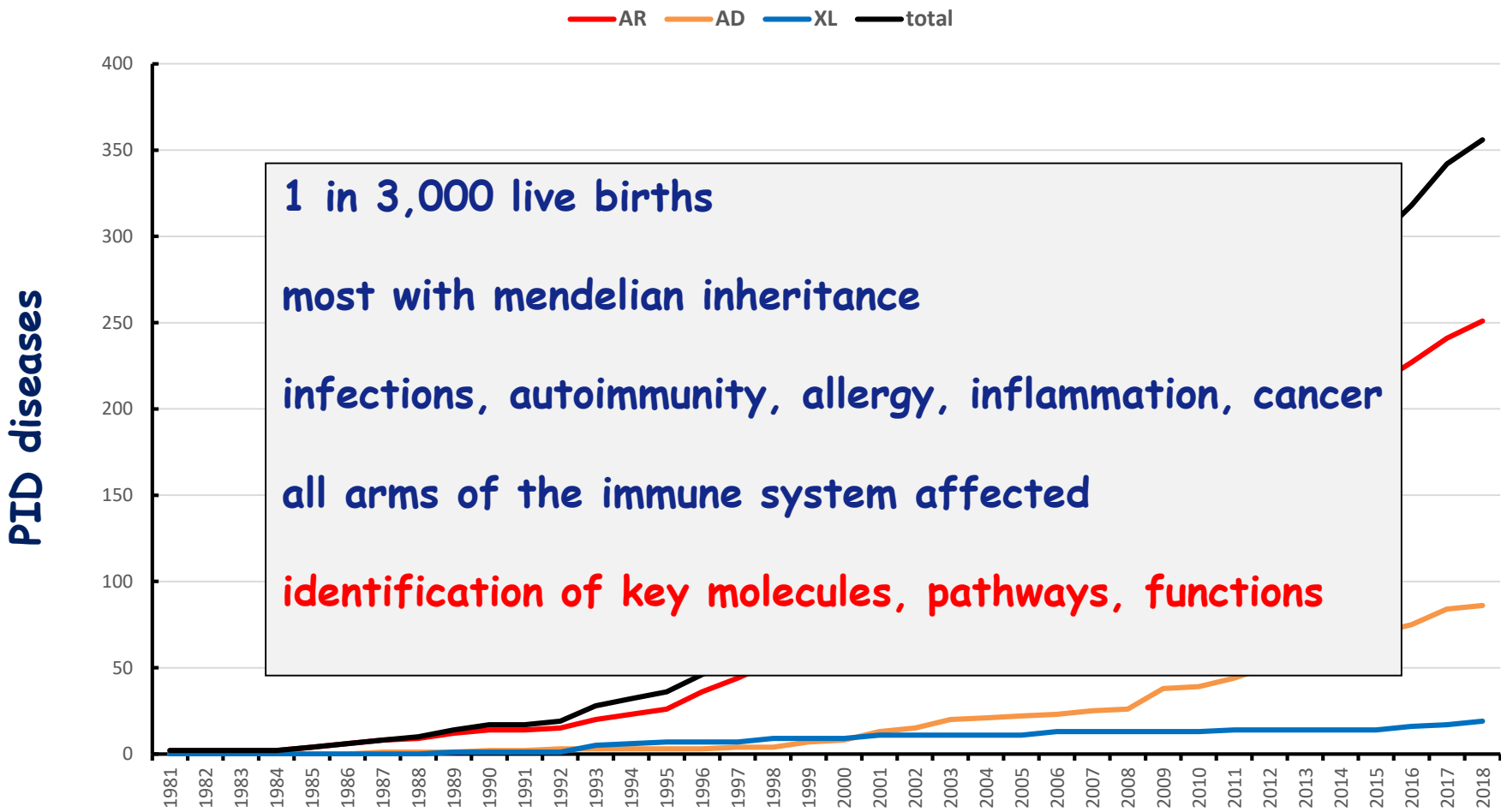


Inherited monogenic diseases

↓

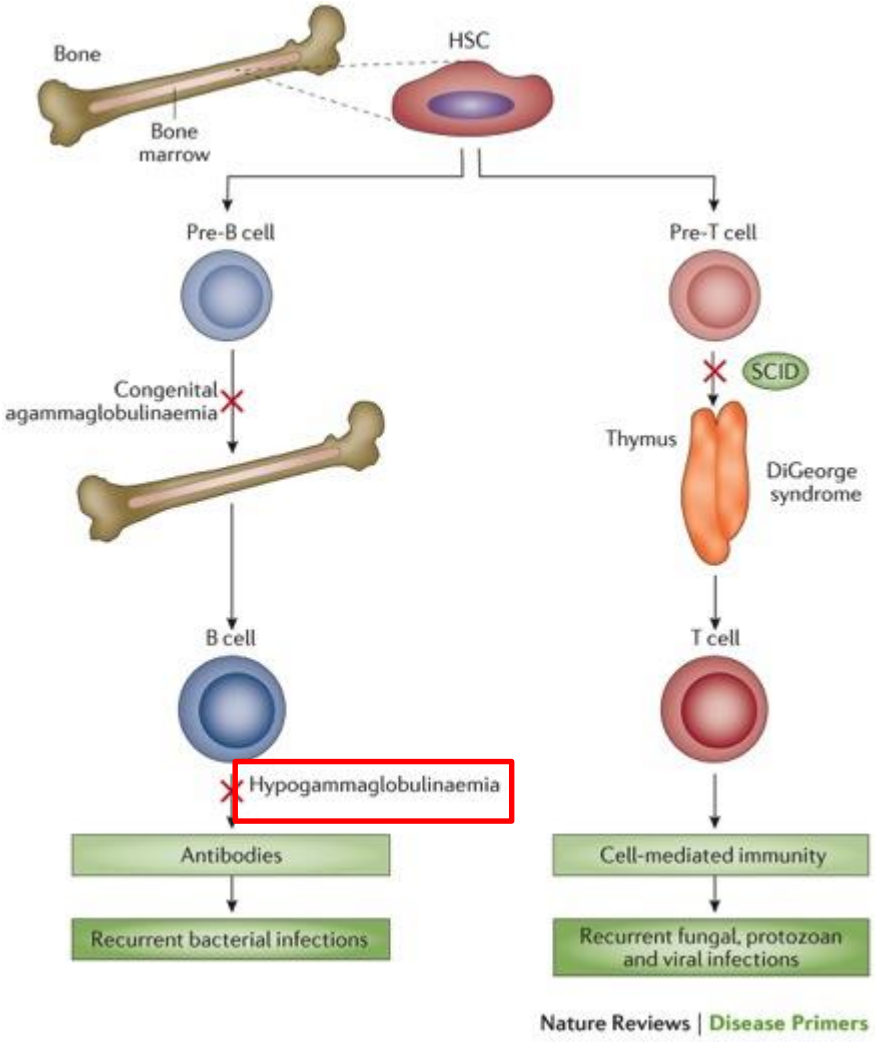
Genetic identification of key products involved in immune responses

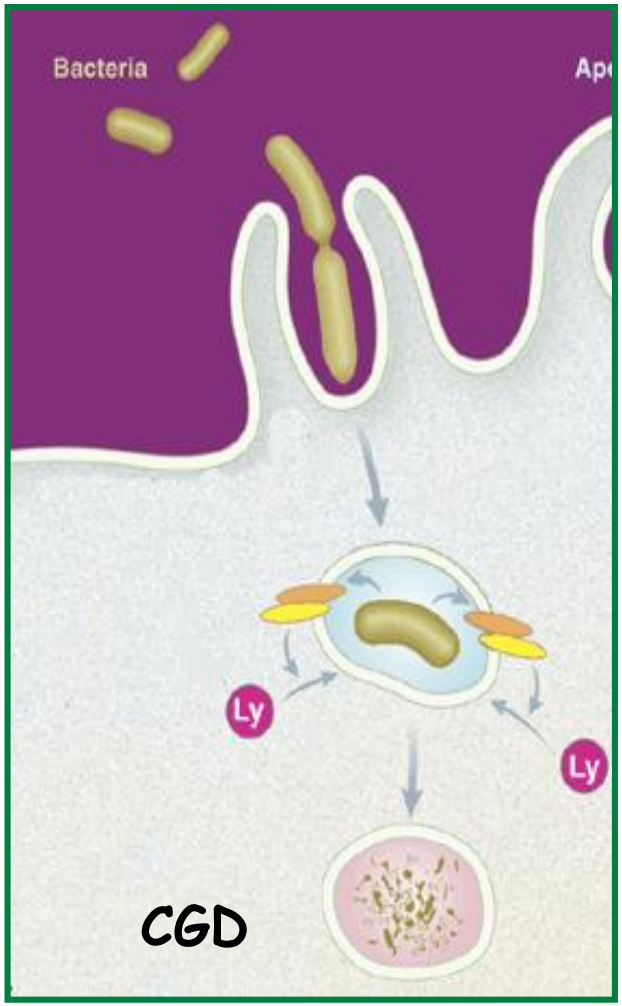
Monogenic inherited disorders of the immune system



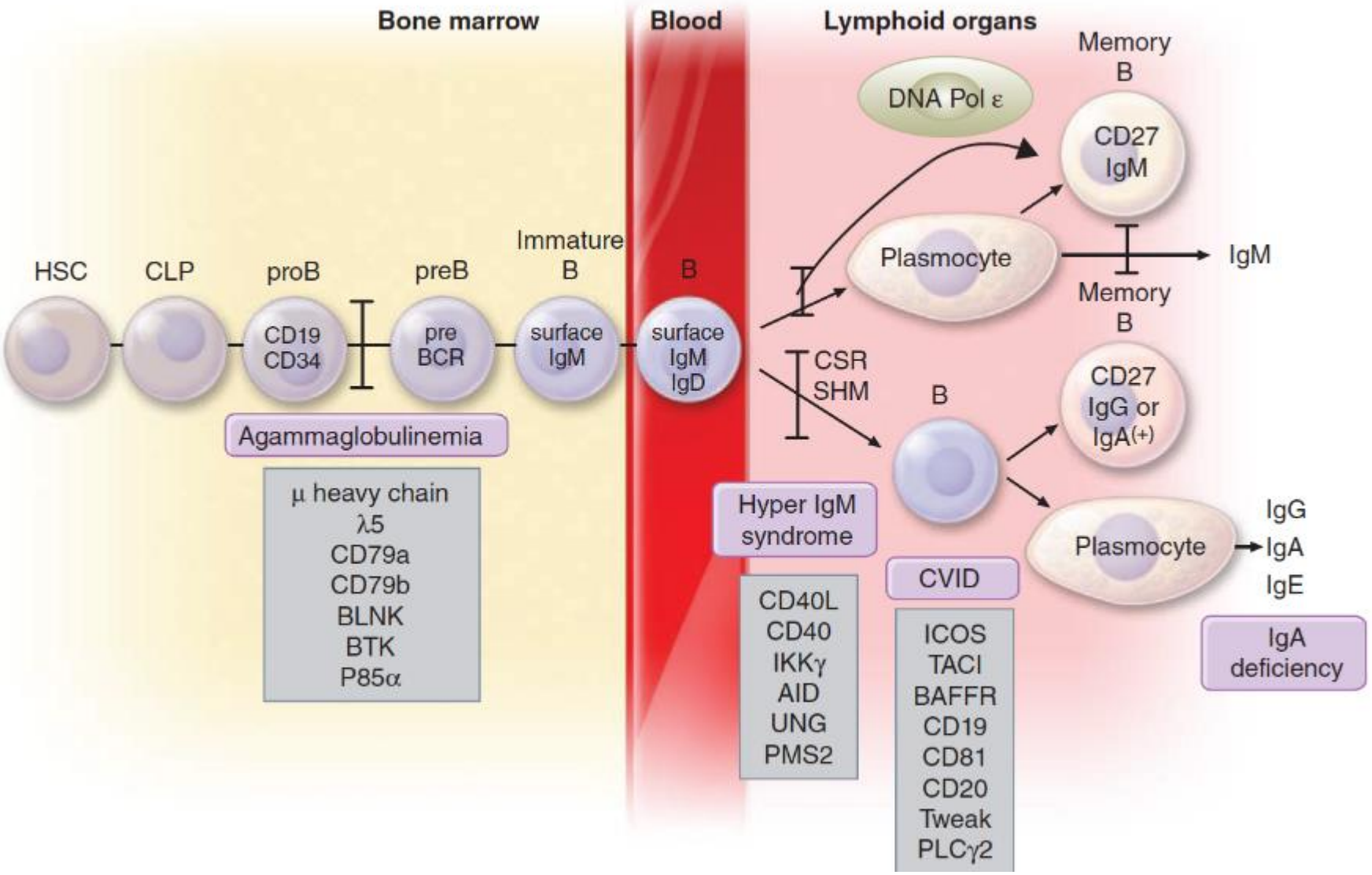
C. Picard

PID in 1980 !

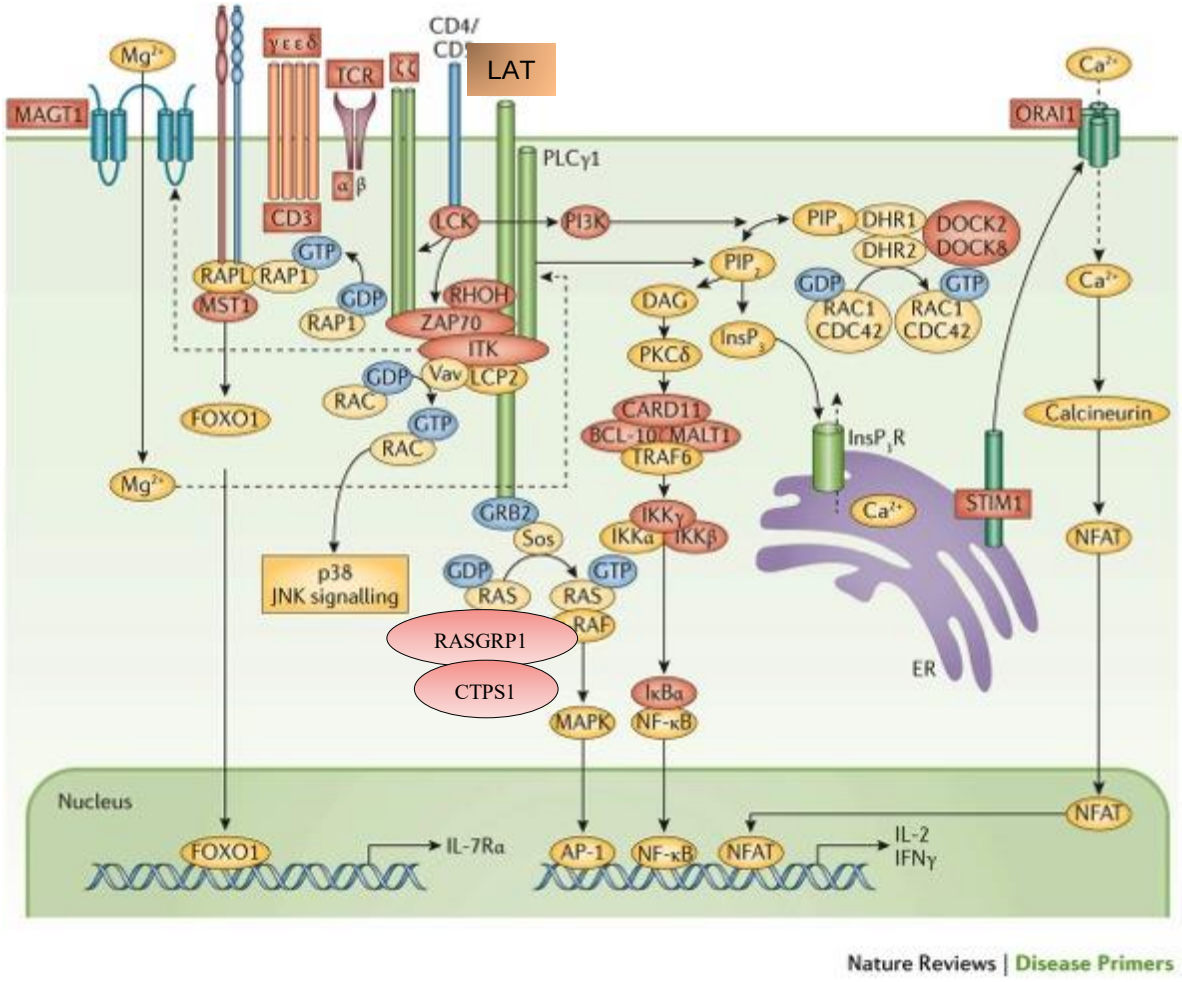

Bone
Bone marrow
HSC
Pre-B cell
Pre-T cell
Congenital agammaglobulinaemia
SCID
Thymus
DiGeorge syndrome
B cell
T cell
Hypogammaglobulinaemia
Antibodies
Cell-mediated immunity
Recurrent bacterial infections
Recurrent fungal, protozoan and viral infections
Nature Reviews | Disease Primers


Bacteria
Ly
Ly
CGD

Antibody deficiency in 2019



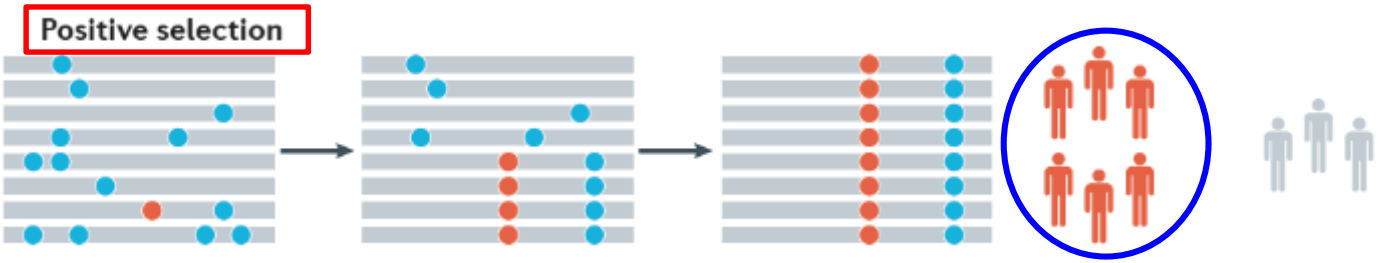
Deficiency of T cell activation and downstream signaling



Nature Reviews | Disease Primers

Identified genetic defects causing T cell ID

Selection, evolution….



Adaptation to nutrition environment

Neutral mutation Positively selected mutation

Adapted from L. Quintana-Murci et al, Nat. Rev. Immunol, 2013

Example of adaptation by convergent (recurrent) evolution

- Mutations in the promoter of the lactase gene that appeared:
  - 8-9000 years ago in Europe
  - 7000 years ago Africa (south of Sahara)

- → persistence in adults of lactase gene expression enabling milk lactose digestion

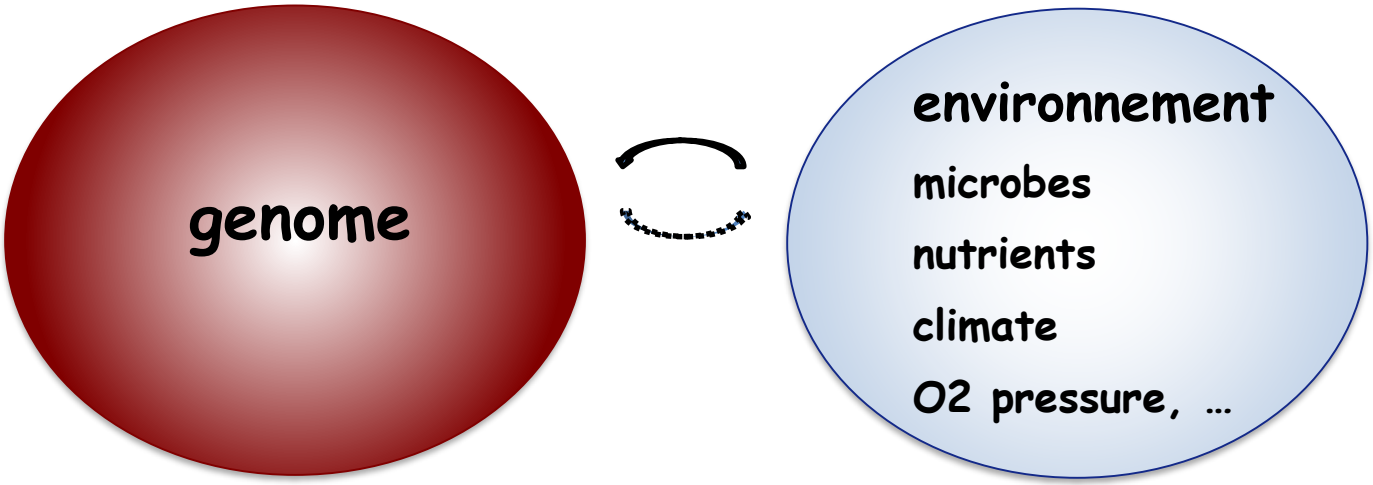
Setting of transition from gather/hunters to farmers

Selection, evolution…. desadaptation

Adaptation to nutrition environment
resistance to a pathogen..
Increased risk of immunopathology
in modern times !!

Adapted from L. Quintana-Murci et al, Nat. Rev. Immunol, 2013

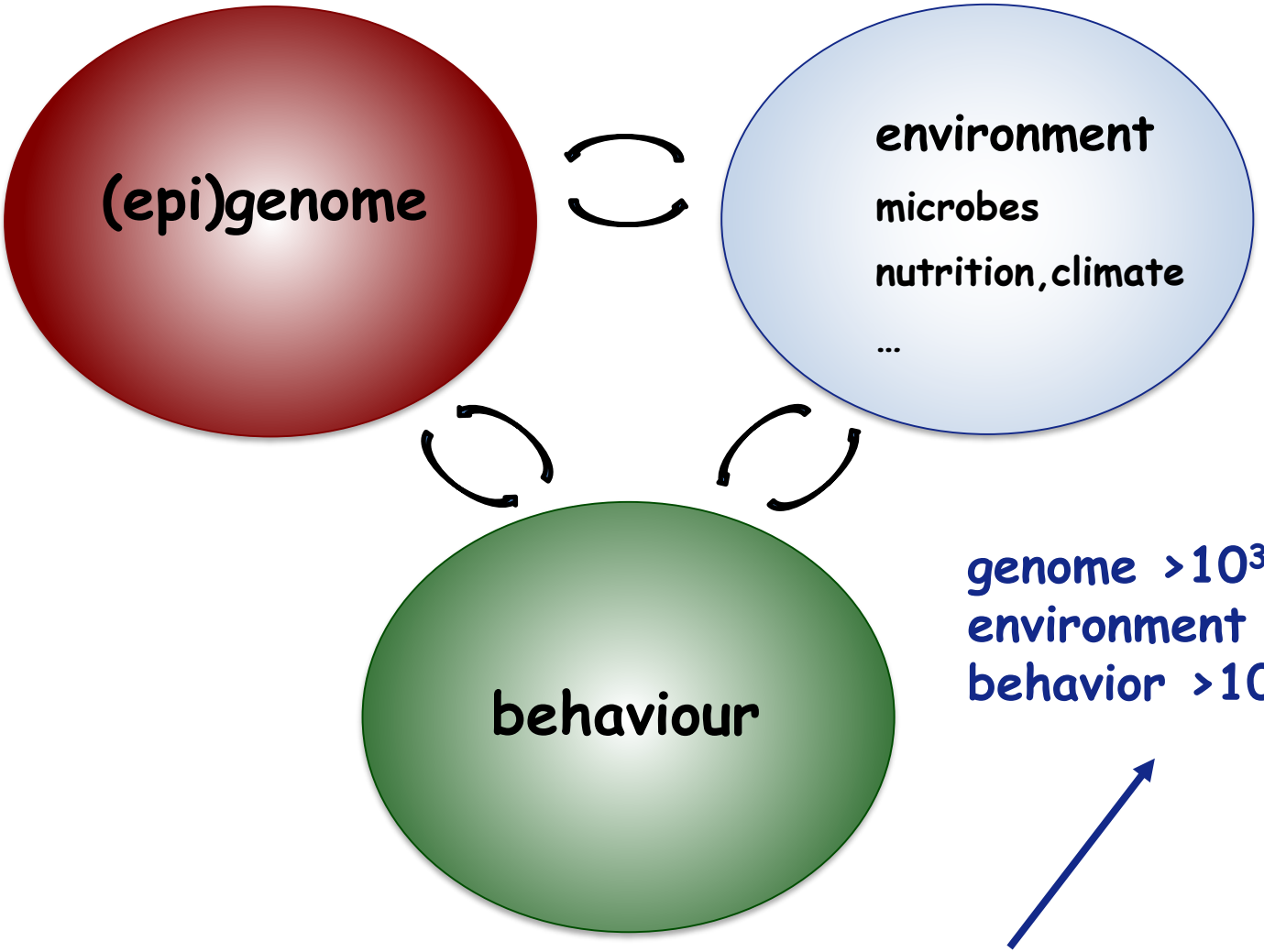
Selection and consequences



- Alleles conferring resistance to trypanosomiasis (*APOL1*) at risk for progressive kidney failure (E. Pays)

- Malaria and sickle cel disease (*HBB*),
  Malaria and deficiency in G6PD (anemia)
  Protection of red cells against productive infection

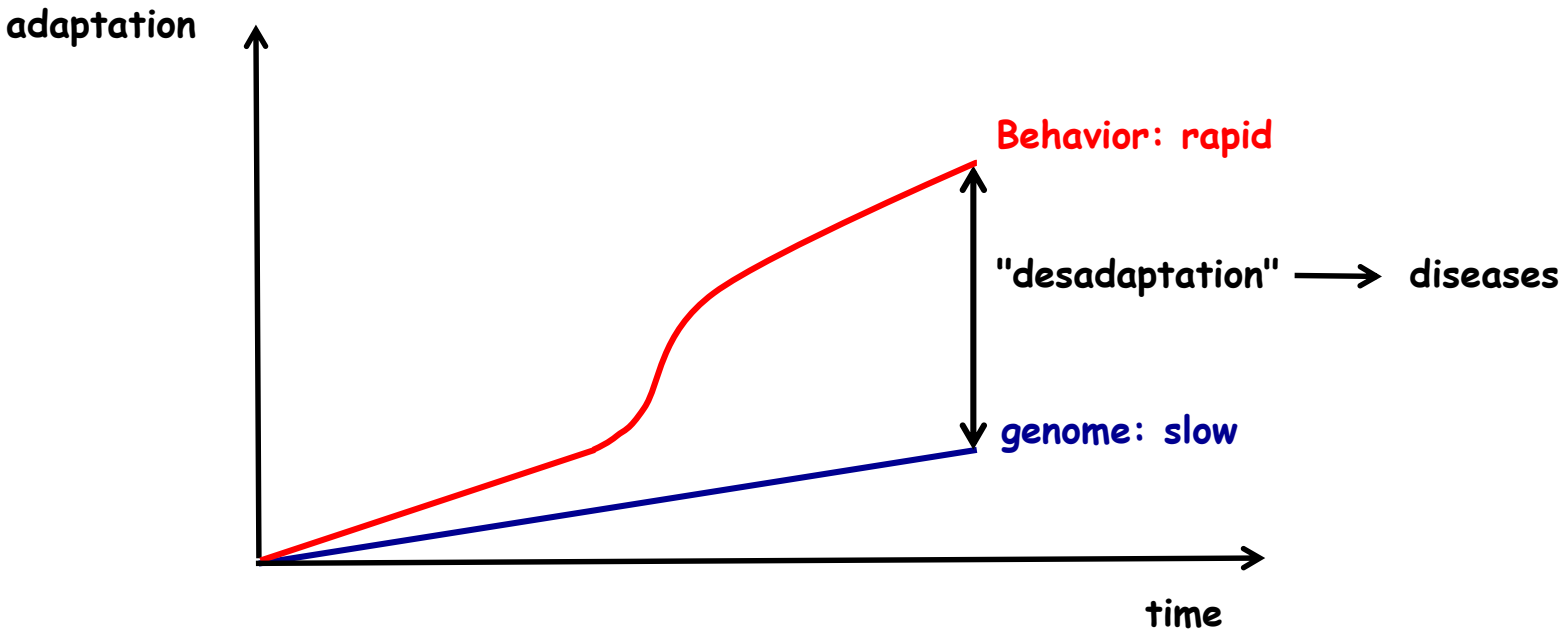
Health is the end result of a compromise



genome >10^3 years
environment >10^1 y.
behavior >10^0 y.

3 dependent variables with an asynchronous evolution

Consequences: asynchronous evolution/adaptation

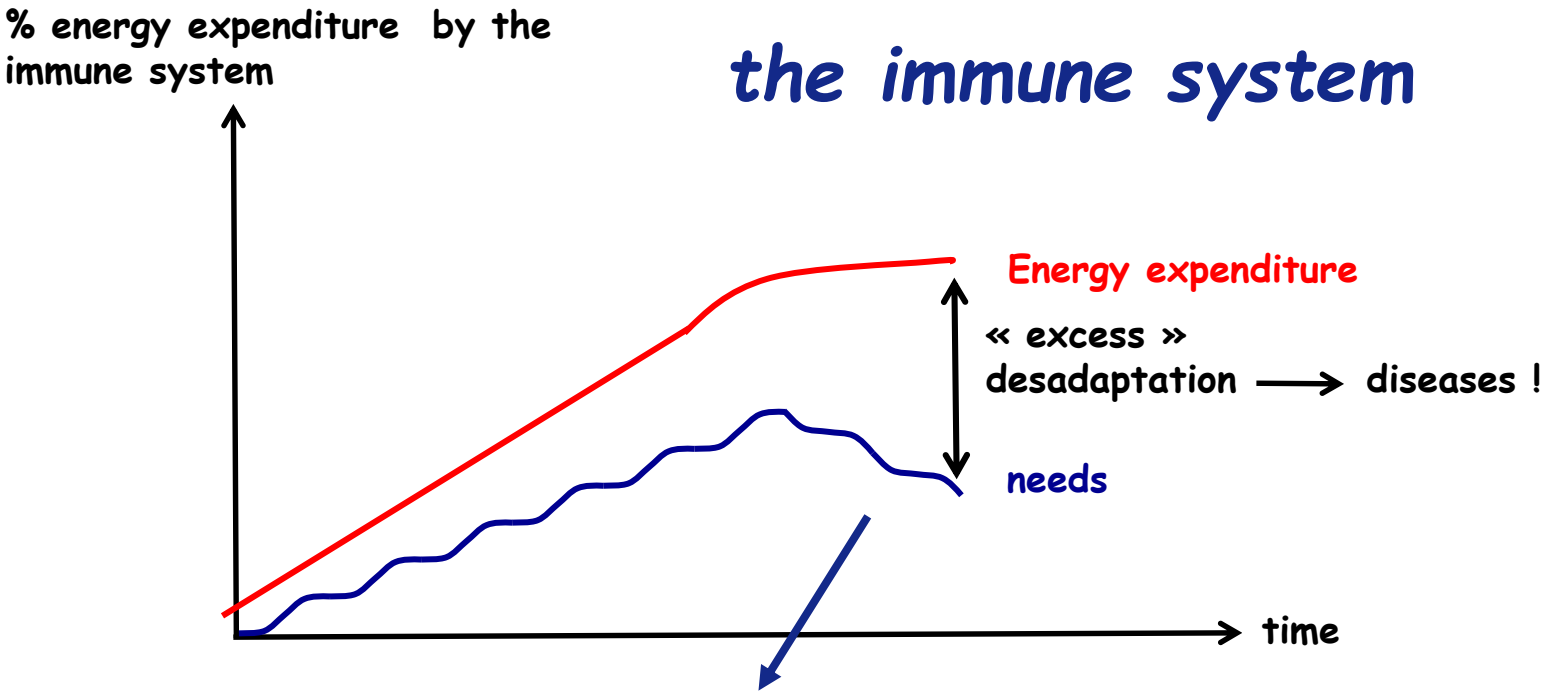


Exemples:

nutrition: type II diabetes, obesity

immune system: allergy, autoimmunity and inflammation

Asynchronous evolution/adaptation



Pathogen-induced pressure reduced (western style countries)

Increase in the frequency of allergy, autoimmune and inflammatory disorders

Autoimmune diseases

- 80 diseases
  systèmic (lupus, dermatomyositis)
  or organ-specific (diabetes, thyroïditis)

- 7-10 % of the population (Europe, North America)

- Increased frequency with age (exceptions)

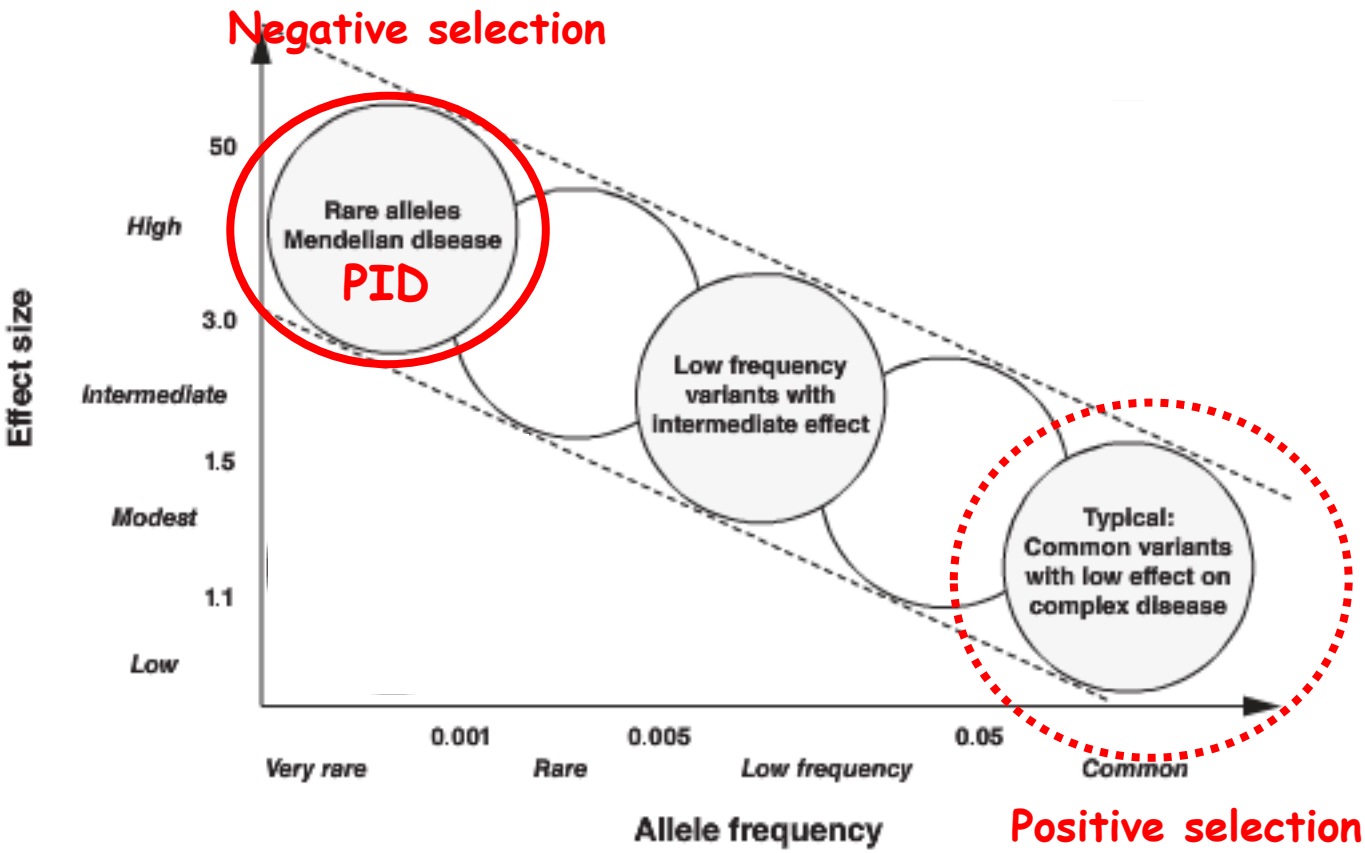
- T lymphocyte–dependent (diabetes) and/or
  B lymphocyte–dependent (hemolytic anemia, lupus,…)

- Multifactorial – genetics, environment

Prevalence and heritability of autoimmune diseases

	Prevalence (Europe /10^3)	Concordance Monozygotic twins (%)	Sibling risk (%)
Lupus	0.5	11-40	2
Crohn's disease	1	20-50	1.2
Type I Diabetes	≥ 2	13-47	6
Psoriasis	5	35-64	17
Multiple sclerosis	1	6-30	10
Rheumatoid arthritis	2	0-20	8

Genetics and immune diseases



Evolution ans temporal desadaptation

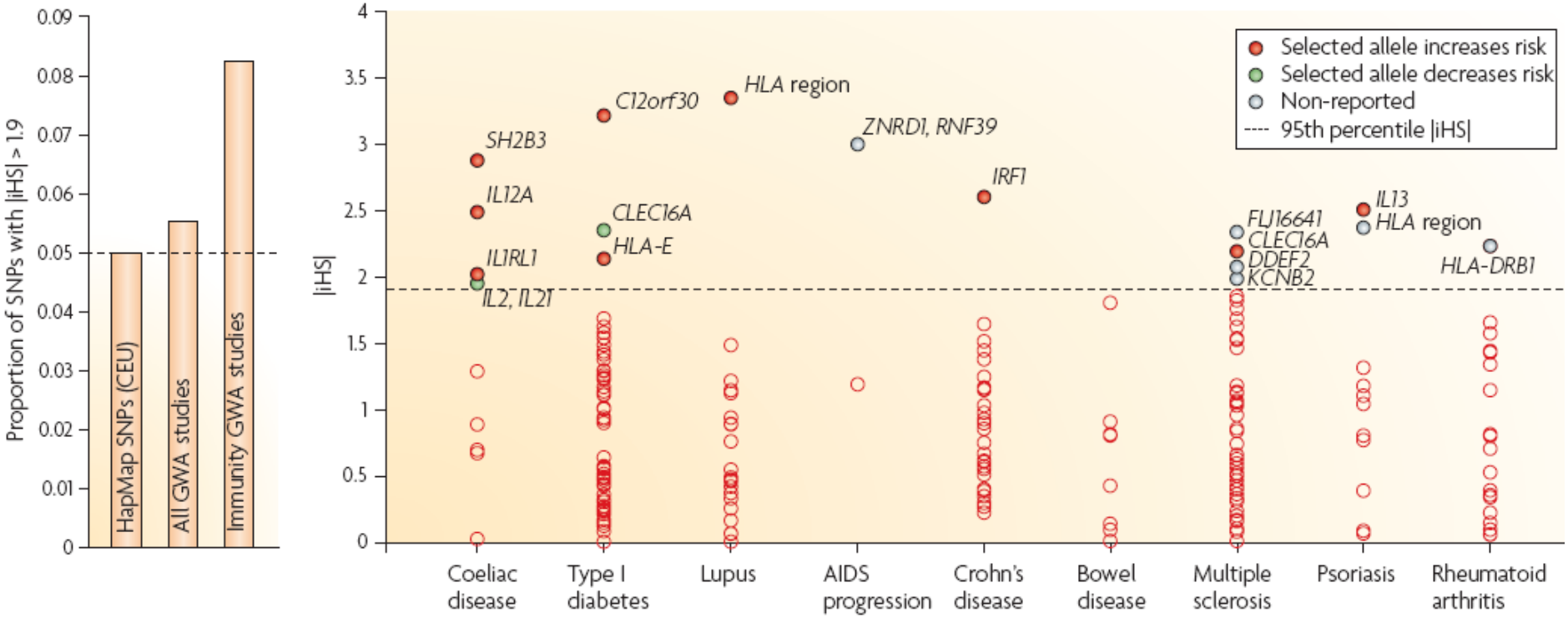
Selection by resistance to microbes
(myobacteria,hepatitis C virus ,invasive bacterias…)
of genome variants associated with an increased risk of autoimmune diseases or allergy

Examples :

MDA 5	psoriasis
NALP1	Addison, type I diabetes, vitiligo
DEFB1	asthma
HLA DQ	cœliac disease: gluten intolerance

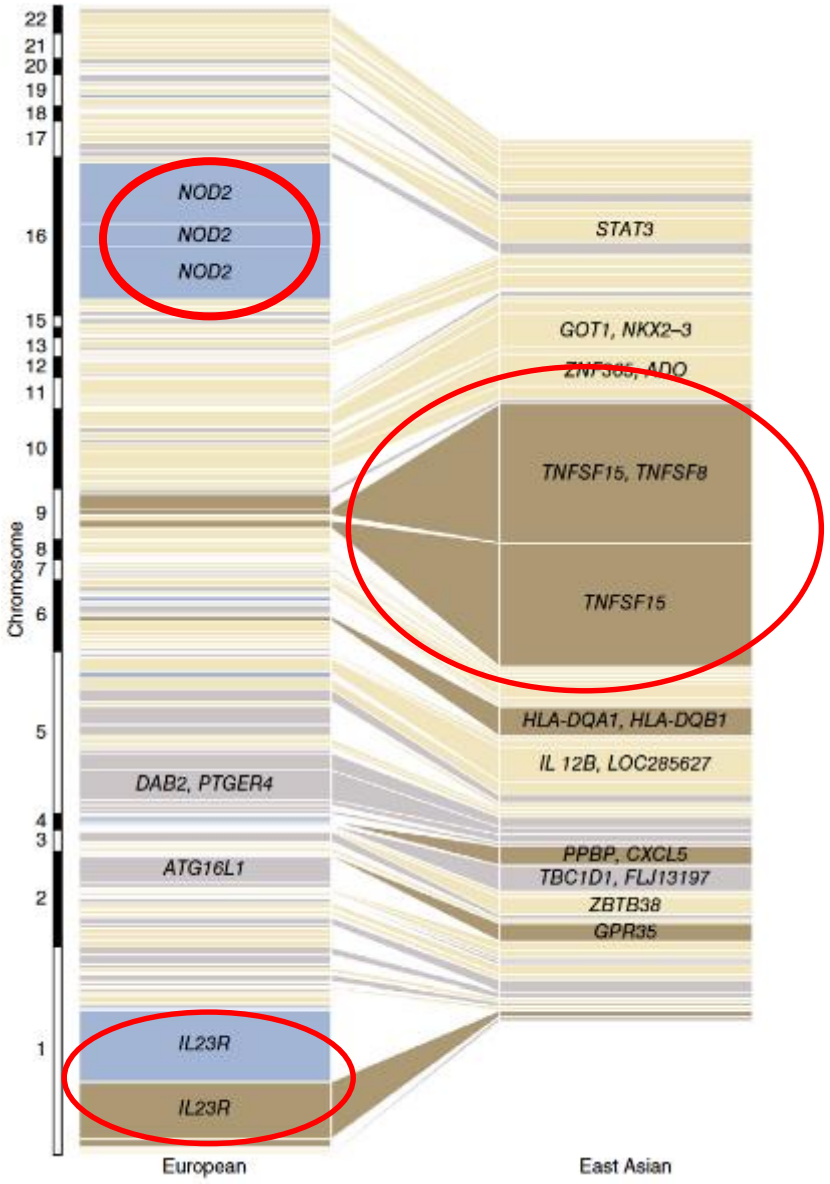
(emerged with agriculture 10,000 years ago)

Genetic variants selected during evolution associated with autoimmunity



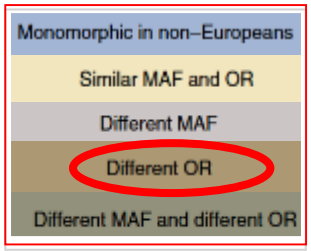
LB Barreiro et al
Nature Reviews Genetics, 2010

Geograhical variations in susceptibilty: Crohn's disease



→ **A likelly effect of gene environment interaction**

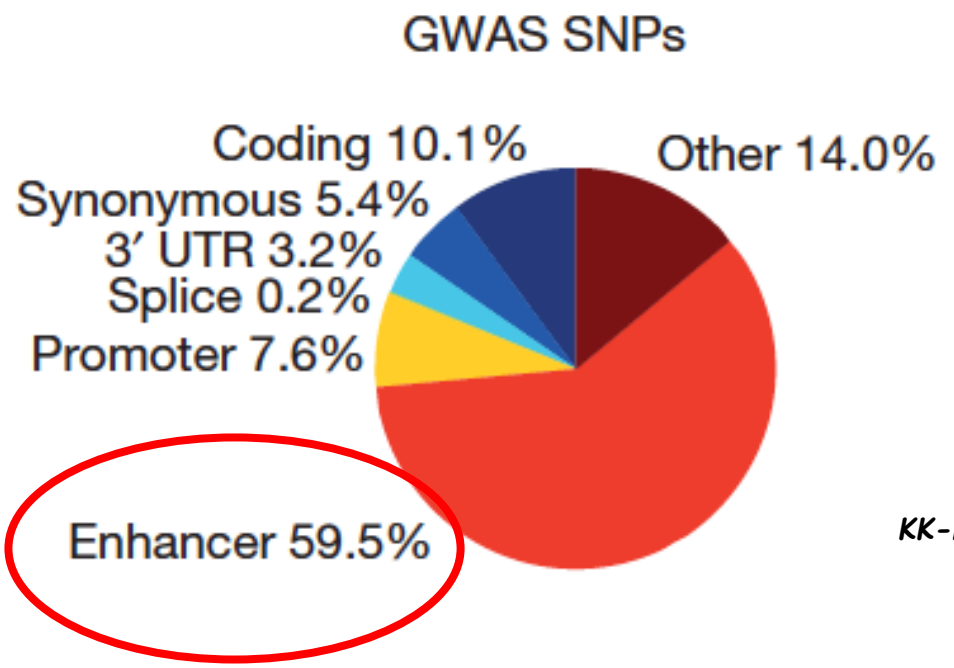
Distinct maladaptation !



OR = relative risk
MAF = allele frequency

JZ Liu et al, Nature Genetics 2015

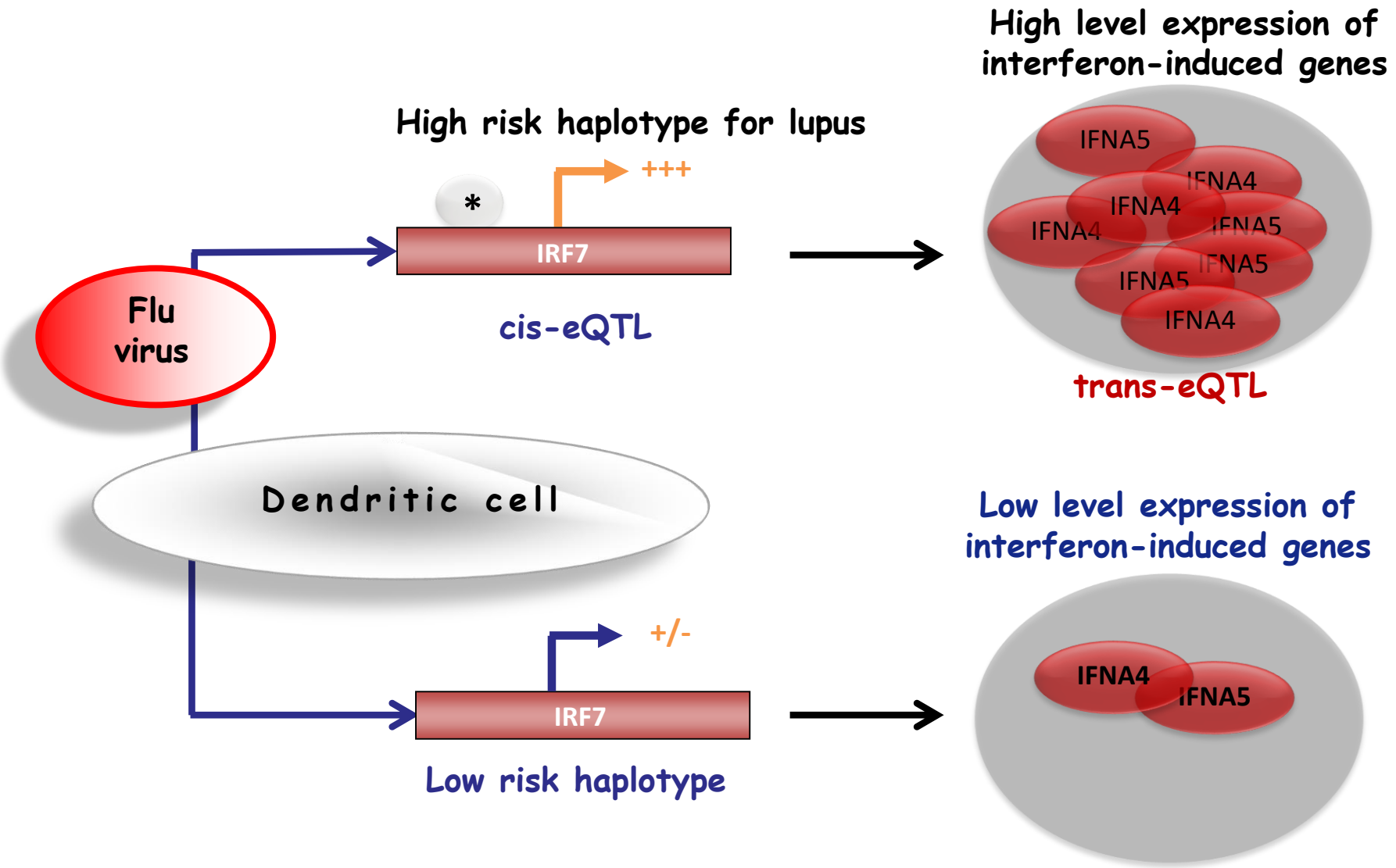
Variants associated with immunopathology are regulatory in most cases



KK-H Farth et al, Nature 2015

- 90 % non coding
- 60 % in enhancers at work in immune cells « cis and trans eQTLs » → variation in gene (protein rexpression)

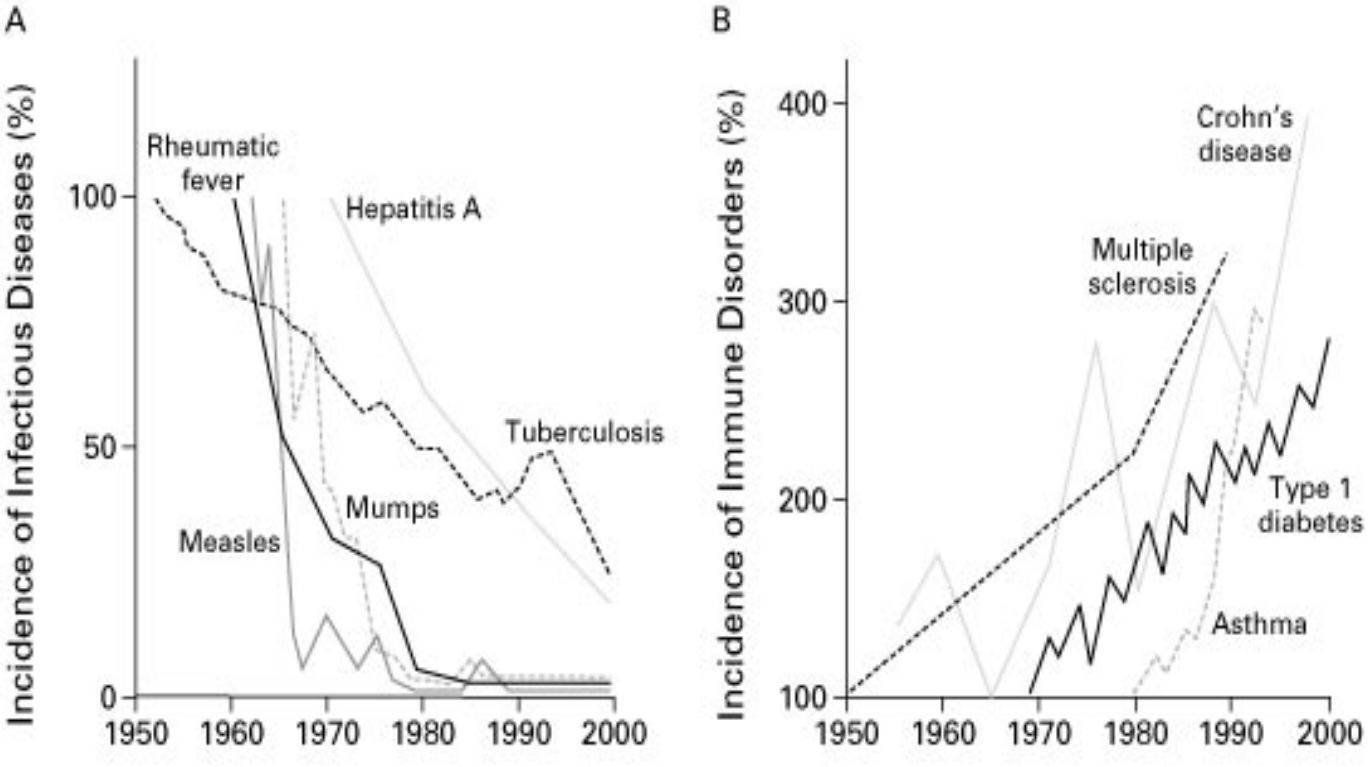
Genetic variation, immune response and diseases



* variant at risk of lupus

Adapted from PK Gregersen, Science 2014

Evolution in the frequency of infectious diseases and immunopathological diseases

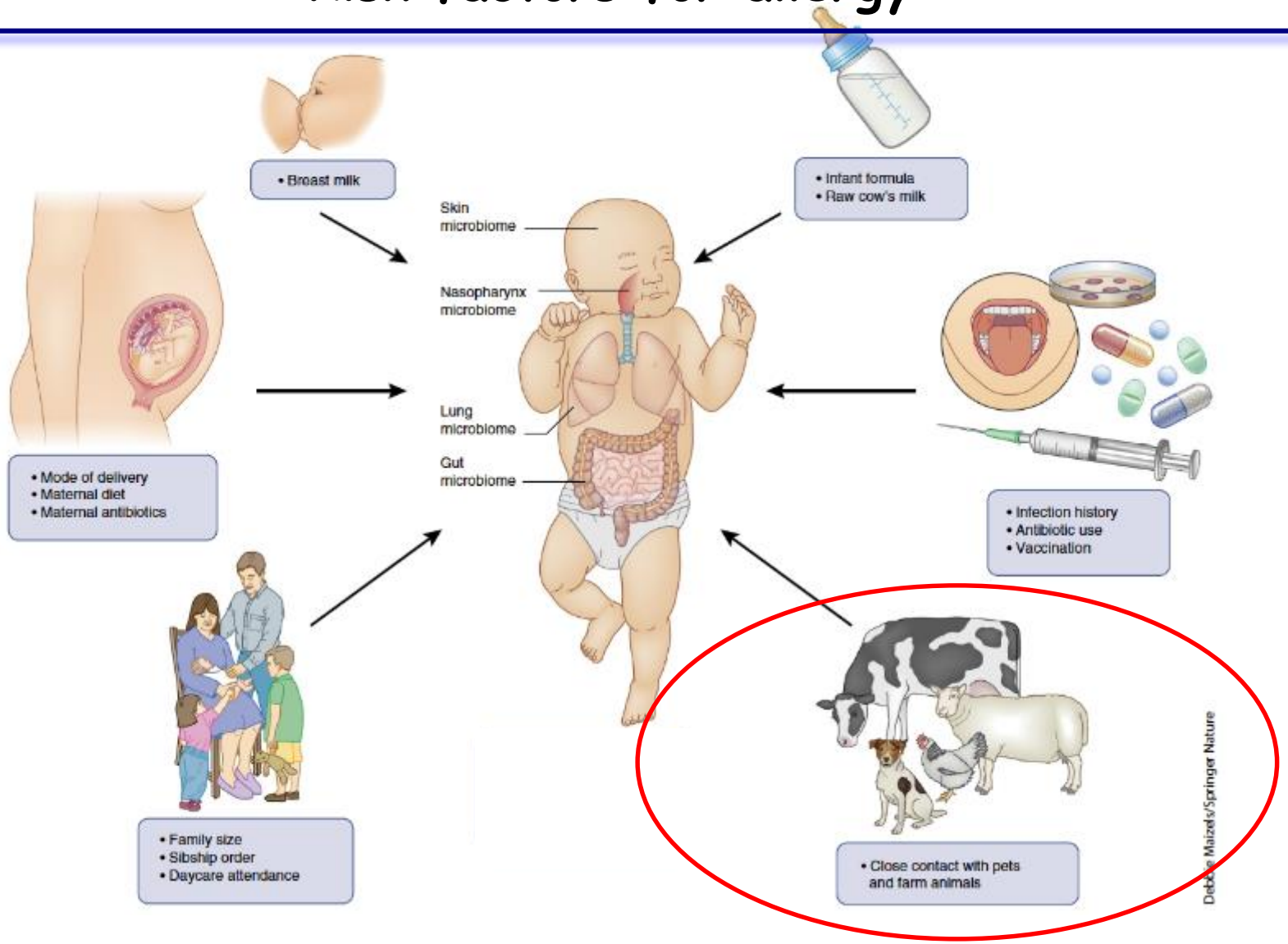


7 to 10 % of population with autoimmune disases

The hygiene hypothesis

Bach JF, 2002

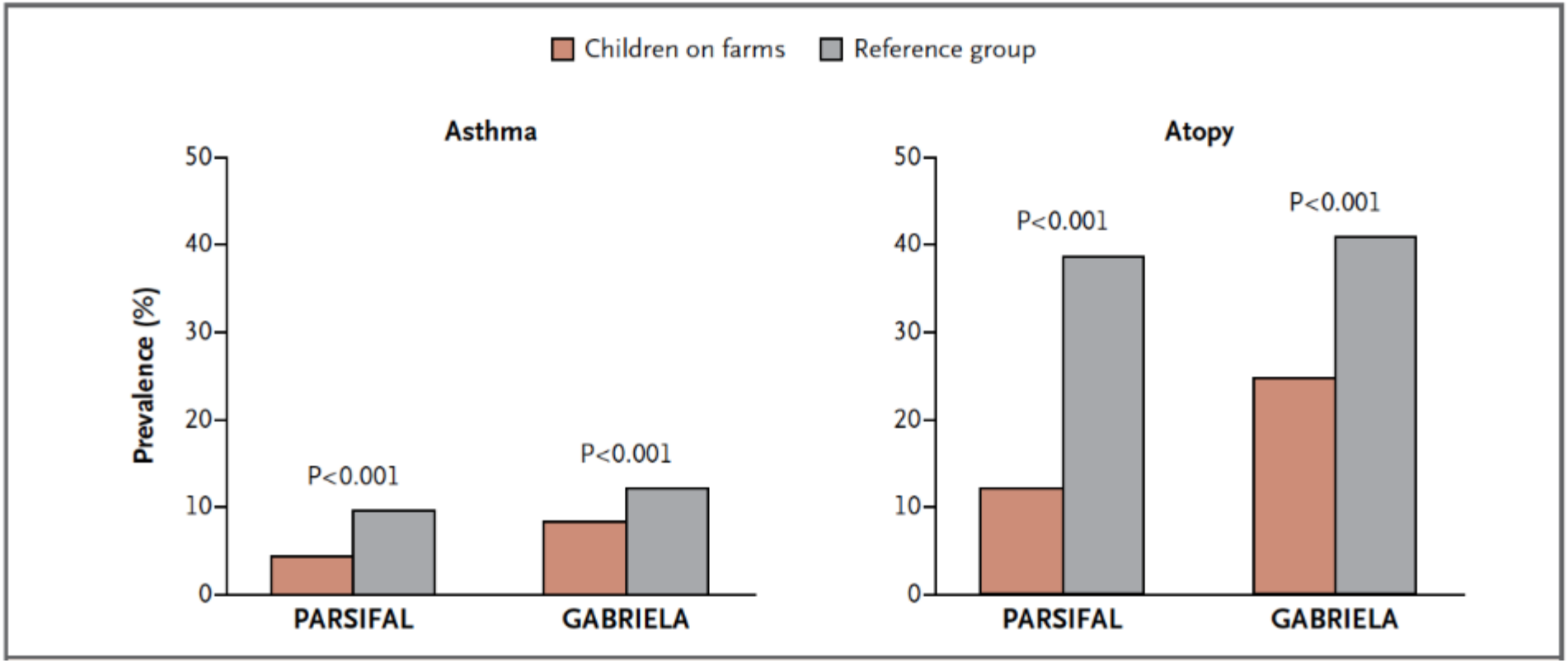
Mechanism(s) ?
Risk factors for allergy



Mostly determined during early childhood !

B N Lambrecht & H. Hammad
Nature Immunology 2017

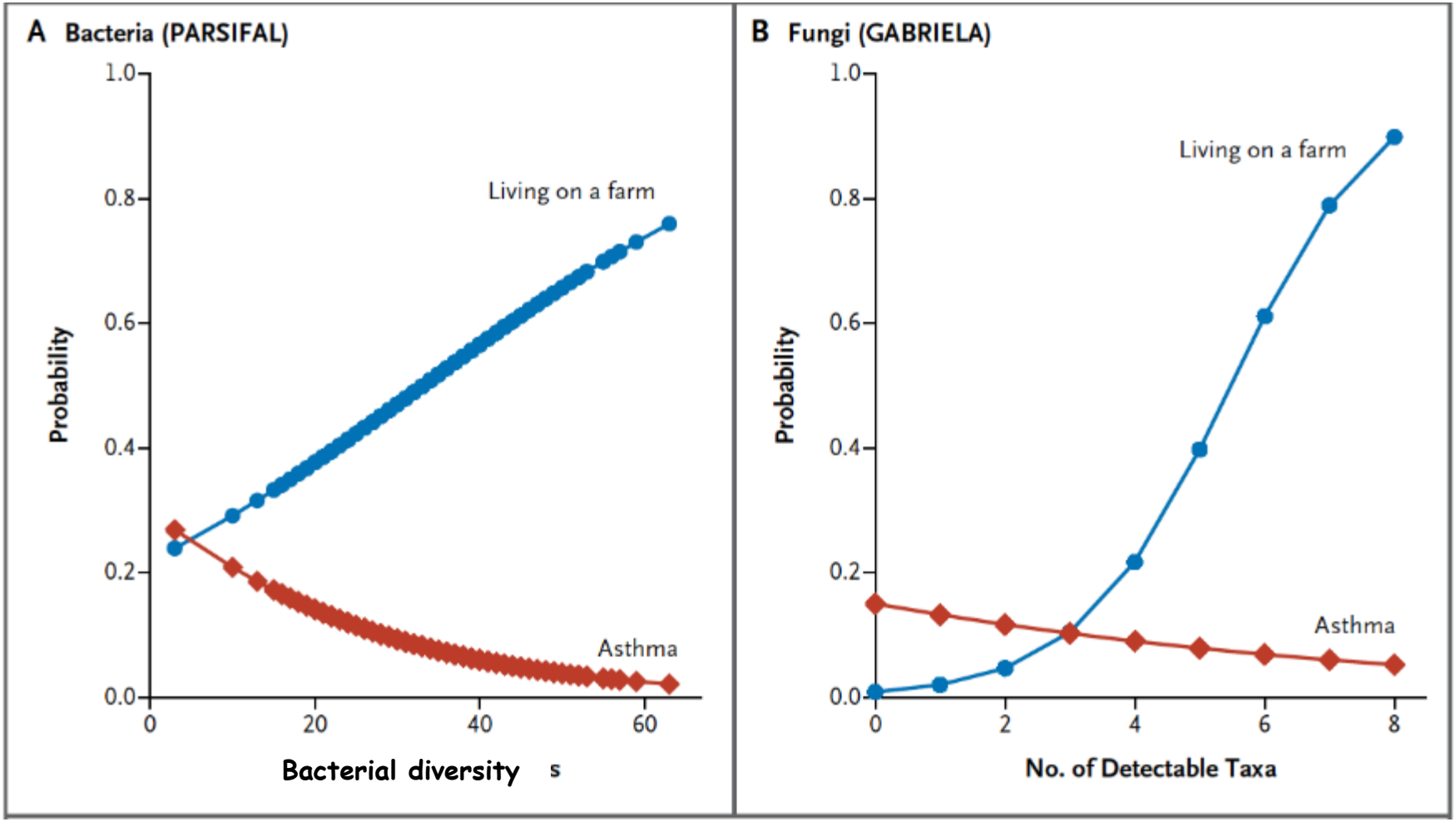
Astma and atopy prevalence in children raised in farms



Cohorts of 6843 (PARSIFAL) et 9668 children (GABRIELA) (Germany/Switzerland)

MJ Ege et al, NEJM 2011

Microbial exposure and risk of asthma



Détection of microbes in dust of children living rooms

MJ Ege et al, NEJM 2011

Microbial diversity inversely correlated with asthma occurrence

Animals in farms are protective !

Comparison of 2 environments :

1. Farms with animals (Amish)
2. Industrialized farm (Hutterite)

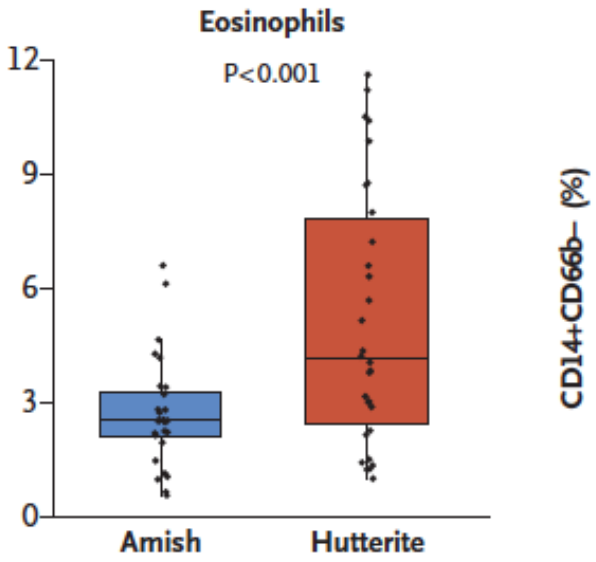
Amish and Hutterite are closely related populations

(%)	Amish	Hutterite
prevalence of asthma	5.2	21.3
Allergic Sensitization	7.2	33.3

Table 1. Demographic and Clinical Characteristics of the Study Populations.*

Characteristic	Amish (N=30)	Hutterite (N=30)
Age (yr)		
Median	11	12
Range	8–14	7–14
Girls (no.)	10	10
Sibships (no.)	15	14
Children with asthma (no.)	0	6
Positivity for allergen-specific IgE (no.)		
>0.7 kUA/liter	5	9
>3.5 kUA/liter	2	9
Serum IgE (kU/liter)		
Median	21	64
Interquartile range	10–57	15–288

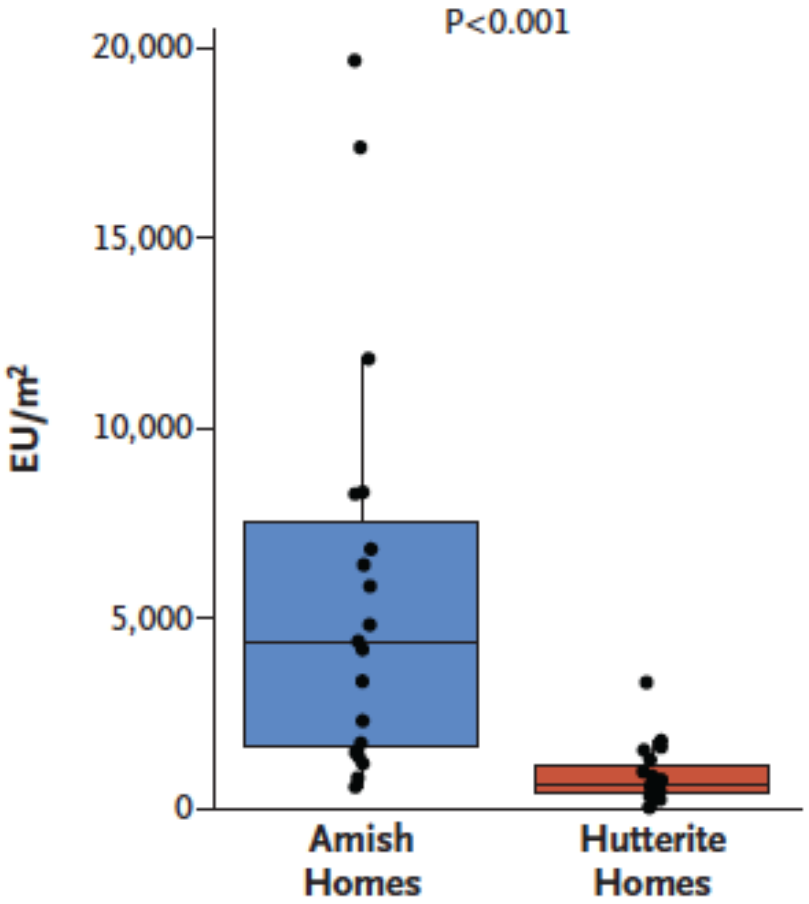
* UA denotes allergen-specific unit.



MM Stein et al, NEJM 2016

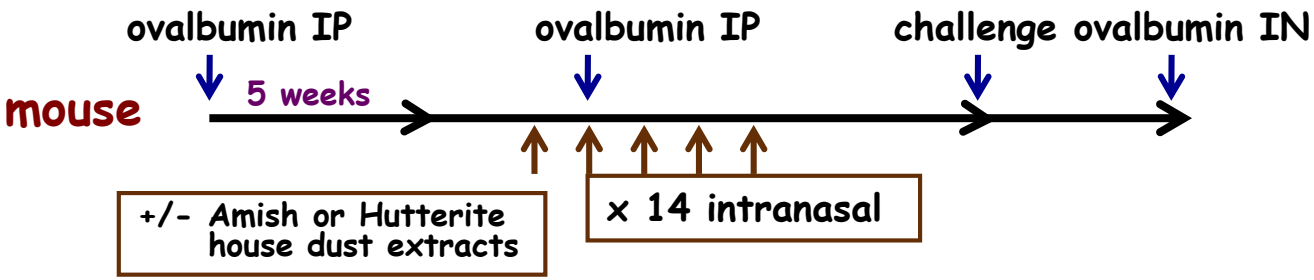
A role for microbial endotoxins ?

Detection of endotoxins in house dust

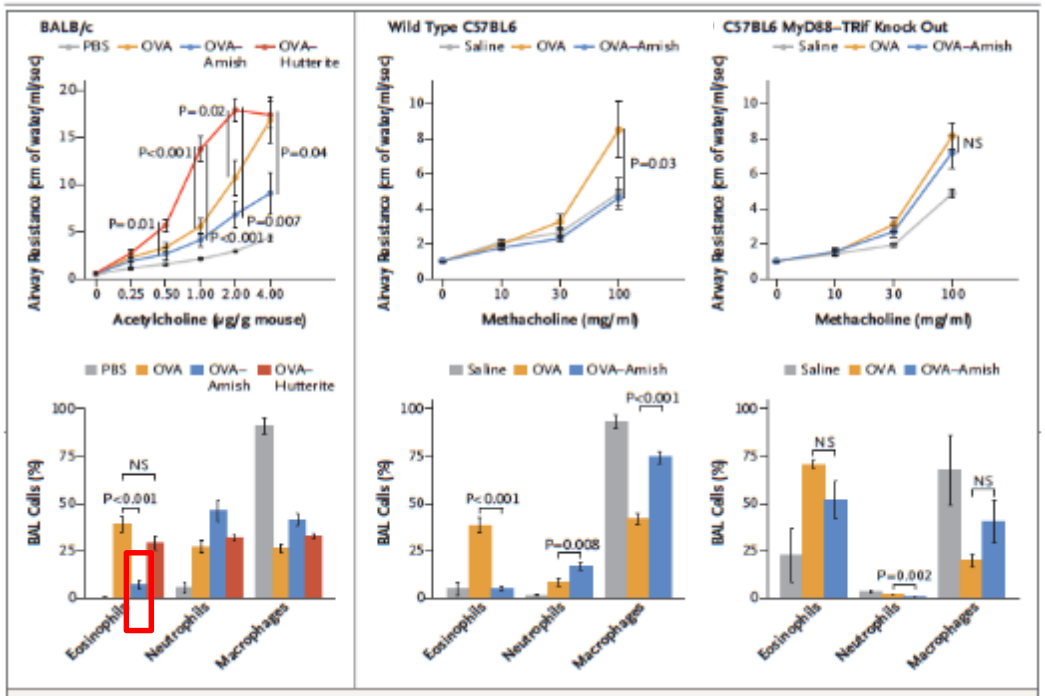


MM Stein et al, NEJM 2016

Experimental evidence



MM Stein et al, NEJM 2016

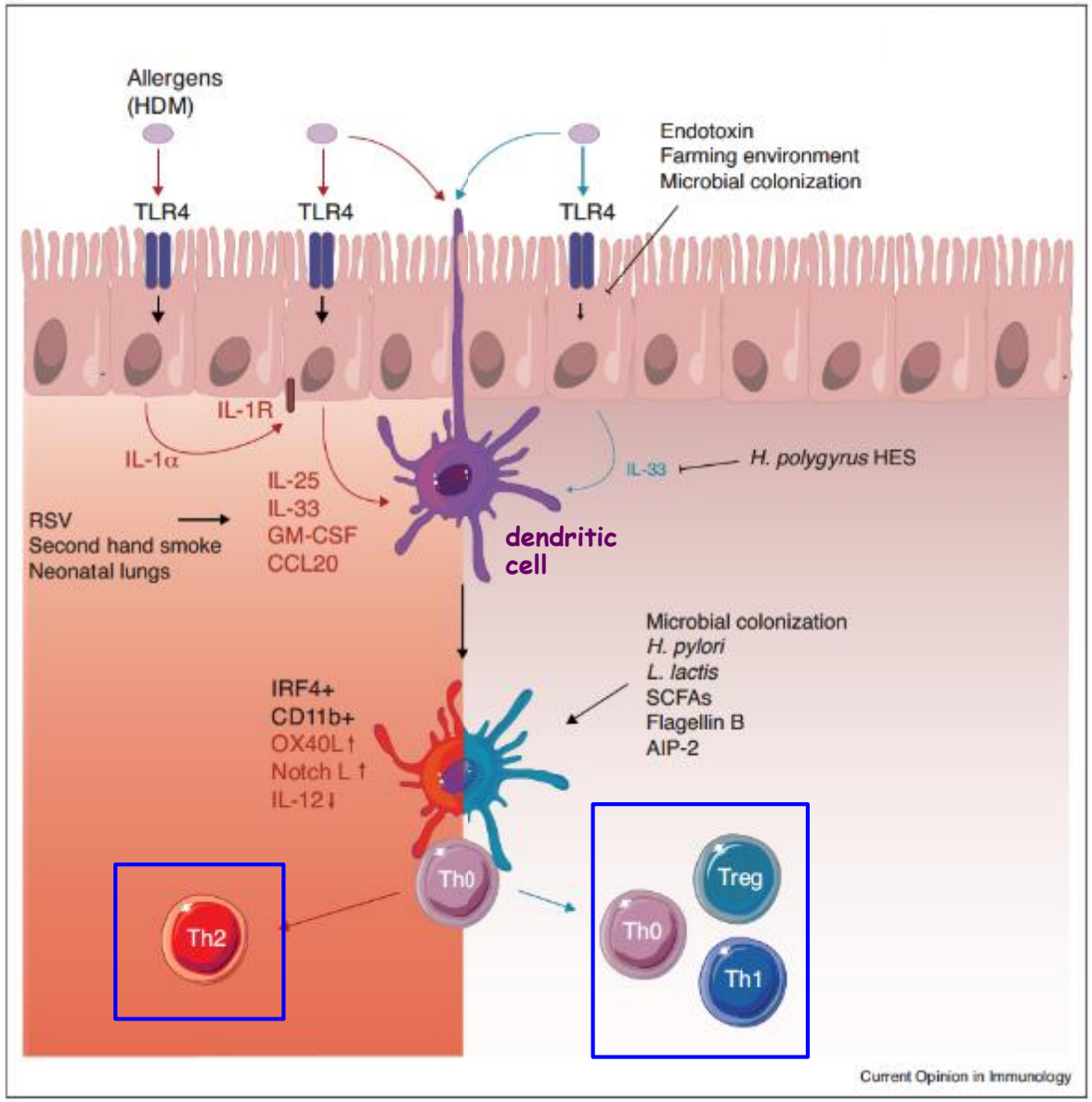


Airway resistance

Cells in broncho-alveolar lavage

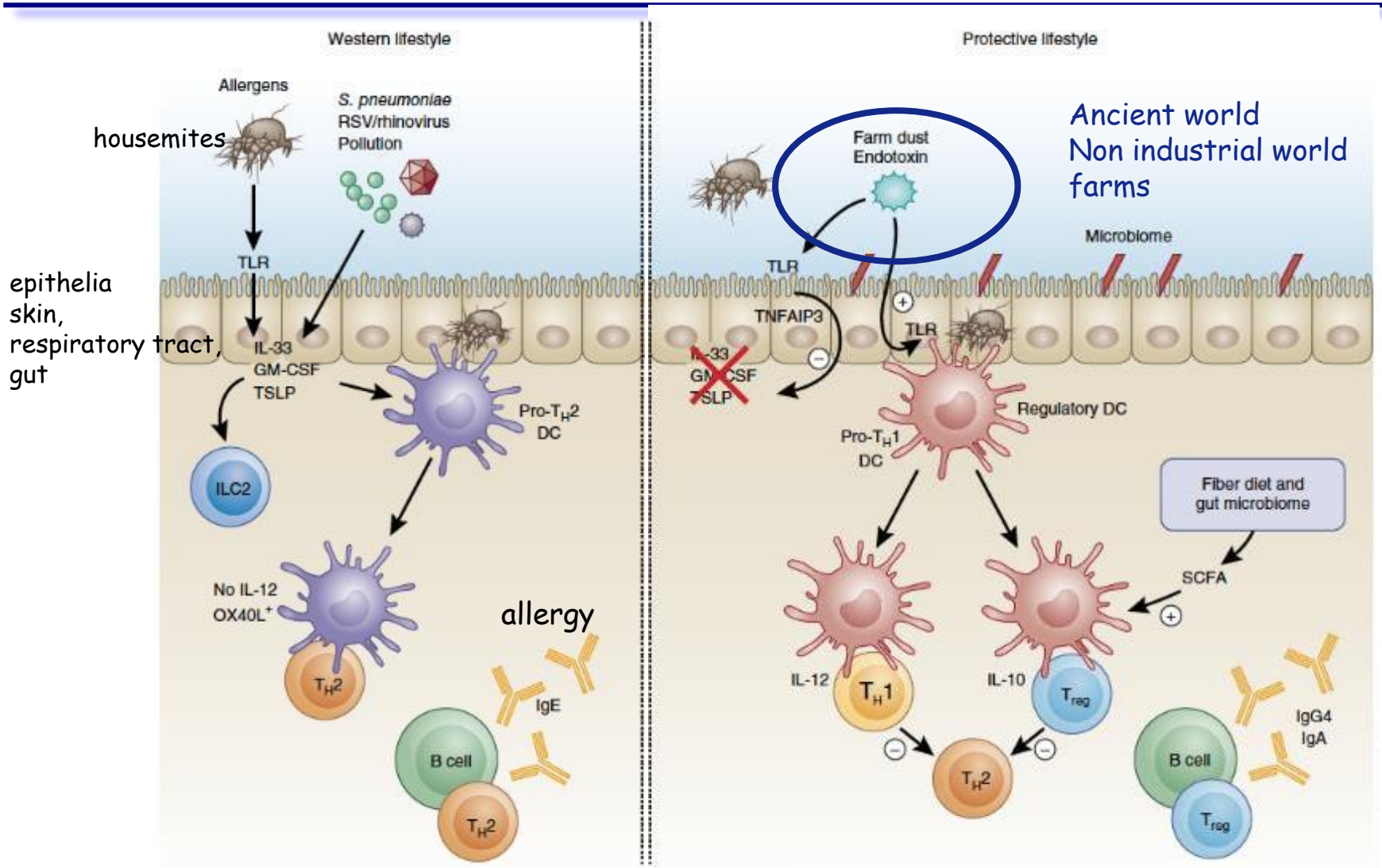
→ Amish house dust is protective !

Possible mechanism



E Haspeslagh et al, COI 2019

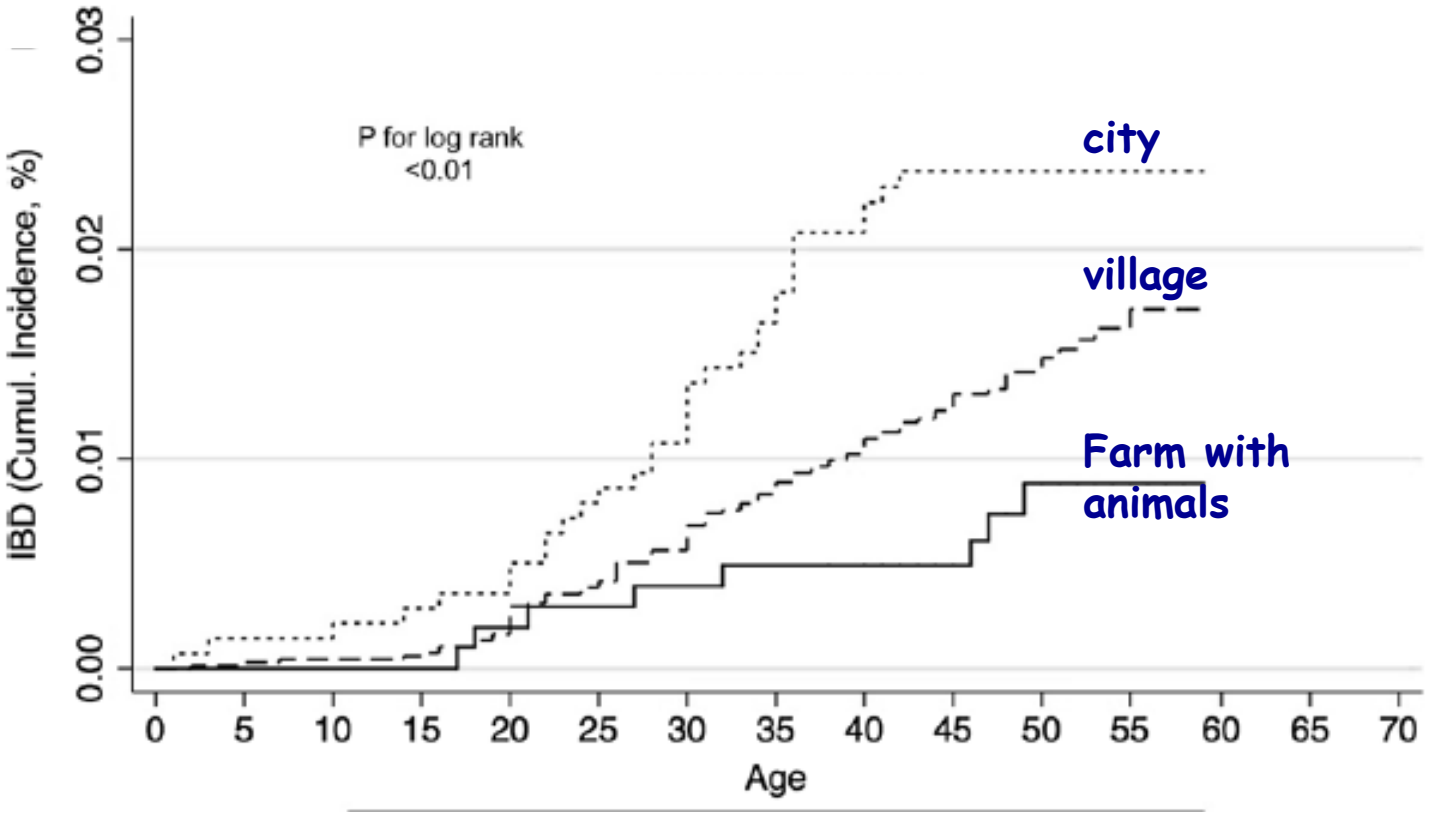
Farms environment may recapitulate ancient environment to which our immune system is better (genetically) adapted



Programmed system poised to produce IgE
Immunity against parasites !

B.N. Lambrecht & H. Hammad
Nature Immunology 2017

Effect on the risk of inflammatory bowel disease

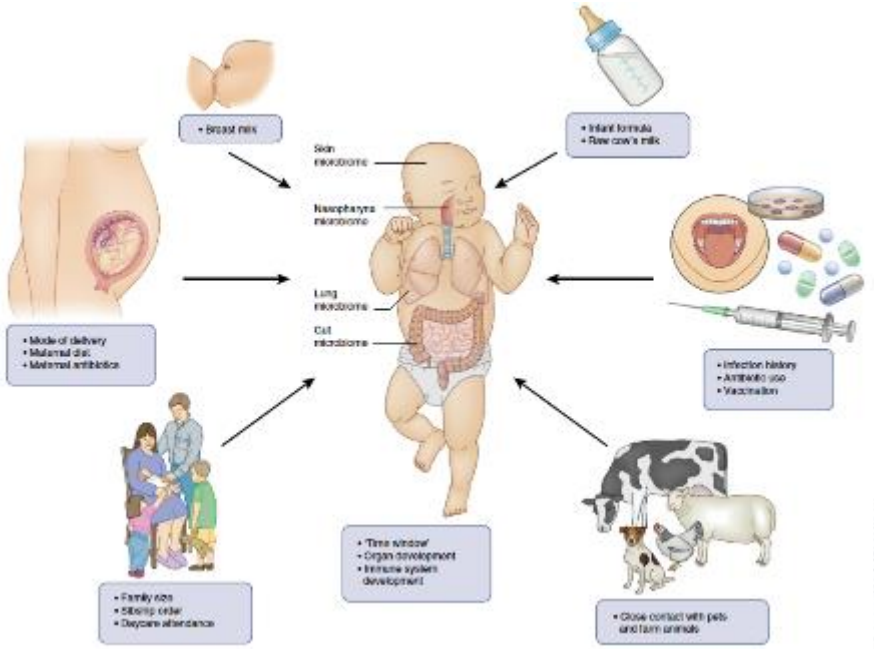


S Timm et al,
Eur J Epidemiol 2014

Conclusions

- Our health is in part determined by consequences of genetic adaptation events (selection) that occurred a long time ago, in a naturel environnement much different from ours

- Science may provide knowledge to at least in part compensate our relative inadaptation to the present environnement…



Implications

- Are there selection factors to anticipate ?
  a role for cancer, cardiovascular diseases ? no ! (late onset)
  environment ??
  new infectious agents ?

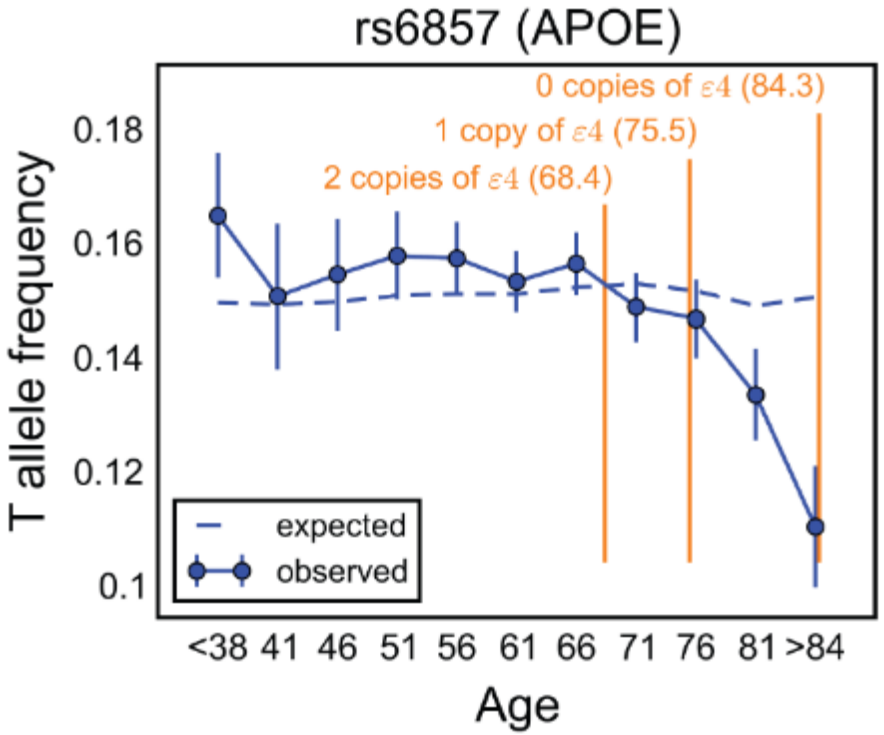
- Does modern medicine prevent any selection/evolution ?

- If yes, is there a risk to accumulate deleterious germ-line mutations ?

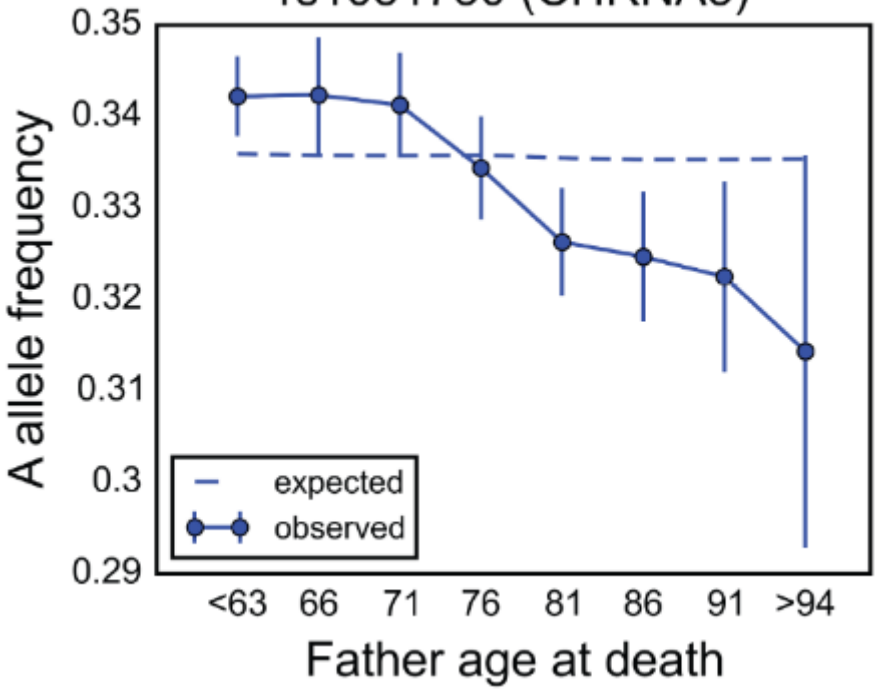
- Socioeconomic determinants are likely to play a much more important role

Selection still at work at the individual level*

Alzheimer disease



Tobacco (nicotin receptor)



EH Mostafavi et al, Plos Biology 2017

Reduction in allele frequency: negative selection !

**age related, post reproduction*