



# Pourquoi tombe-t-on malade?

Jean-Pierre Hugot

Hôpital Robert Debré, Paris

[Jean-pierre.hugot@aphp.fr](mailto:Jean-pierre.hugot@aphp.fr)

# I Les causes des maladies : découvertes et limites actuelles

# drépanocytose

## NORMAL $\beta$ -GLOBIN

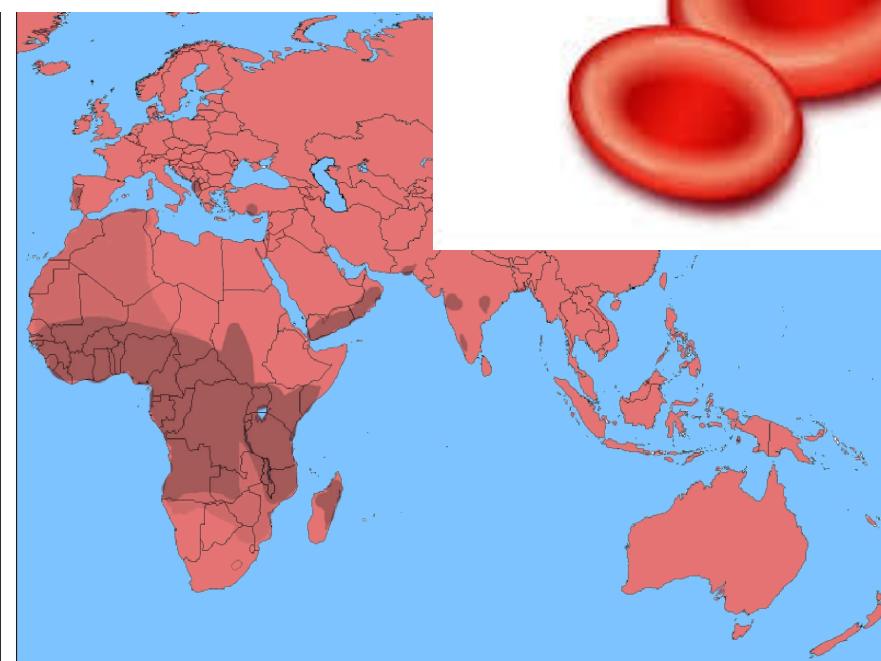
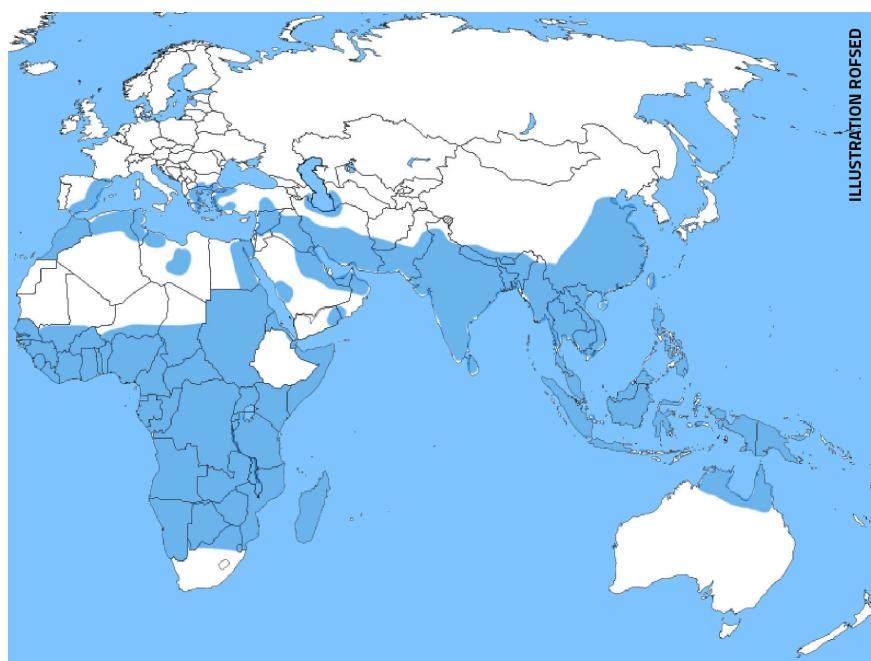
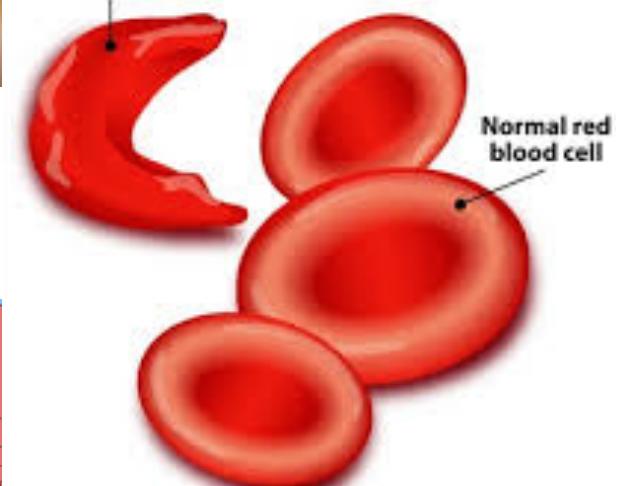
DNA.....	TGA	GGA	CTC	CTC.....
mRNA.....	ACU	CCU	GAG	GAG.....
Amino acid.....	thr	pro	glu	glu.....

## MUTANT $\beta$ -GLOBIN

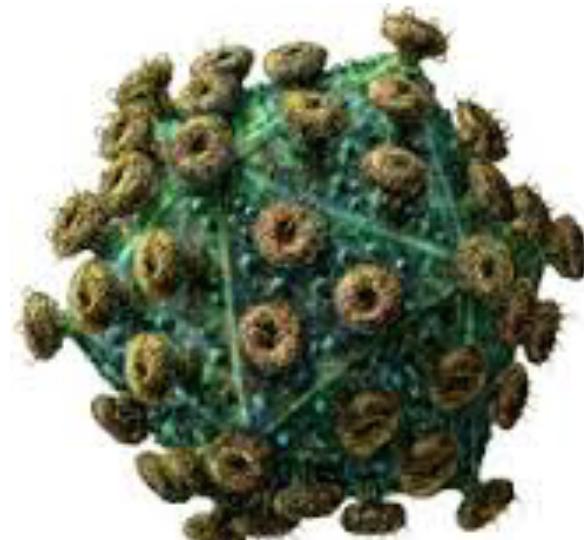
DNA.....	TGA	GGA	CAC	CTC.....
mRNA.....	ACU	CCU	GUG	CTC.....
Amino acid.....	thr	pro	val	glu.....



Sickle cell



HIV



## Spectrum of HIV Complications

### Malignancy

### Nervous System

- Cognitive function
- Neuropathy

### GI

- Diarrhea

### Endocrine

- Vitamin D deficiency
- Thyroid disease
- Diabetes

### Reproductive

- Hypogonadism

### Metabolic

- Hyperlipidemia
- Lactic acidosis

### Pulmonary

### Cardiovascular

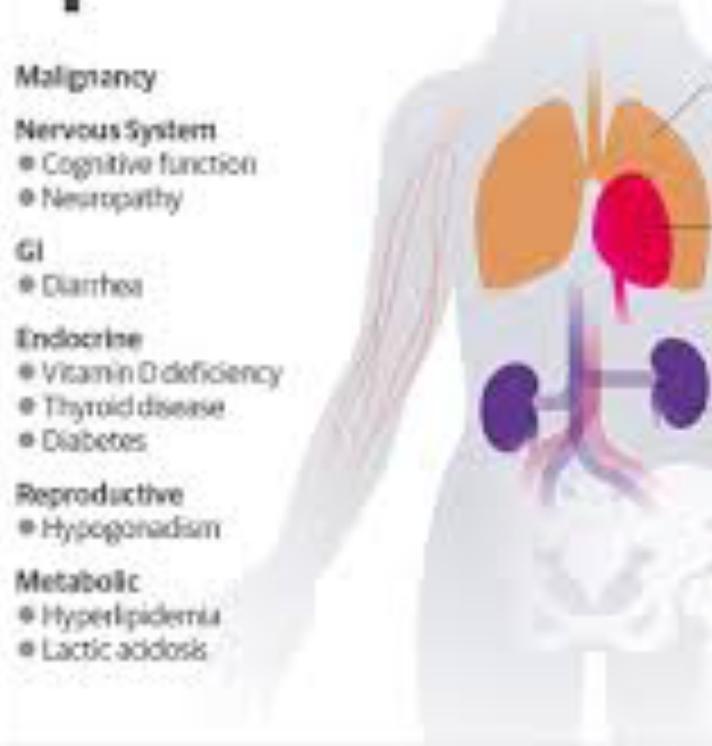
- Hypertension
- Atherosclerosis
- Vascular disease

### Renal

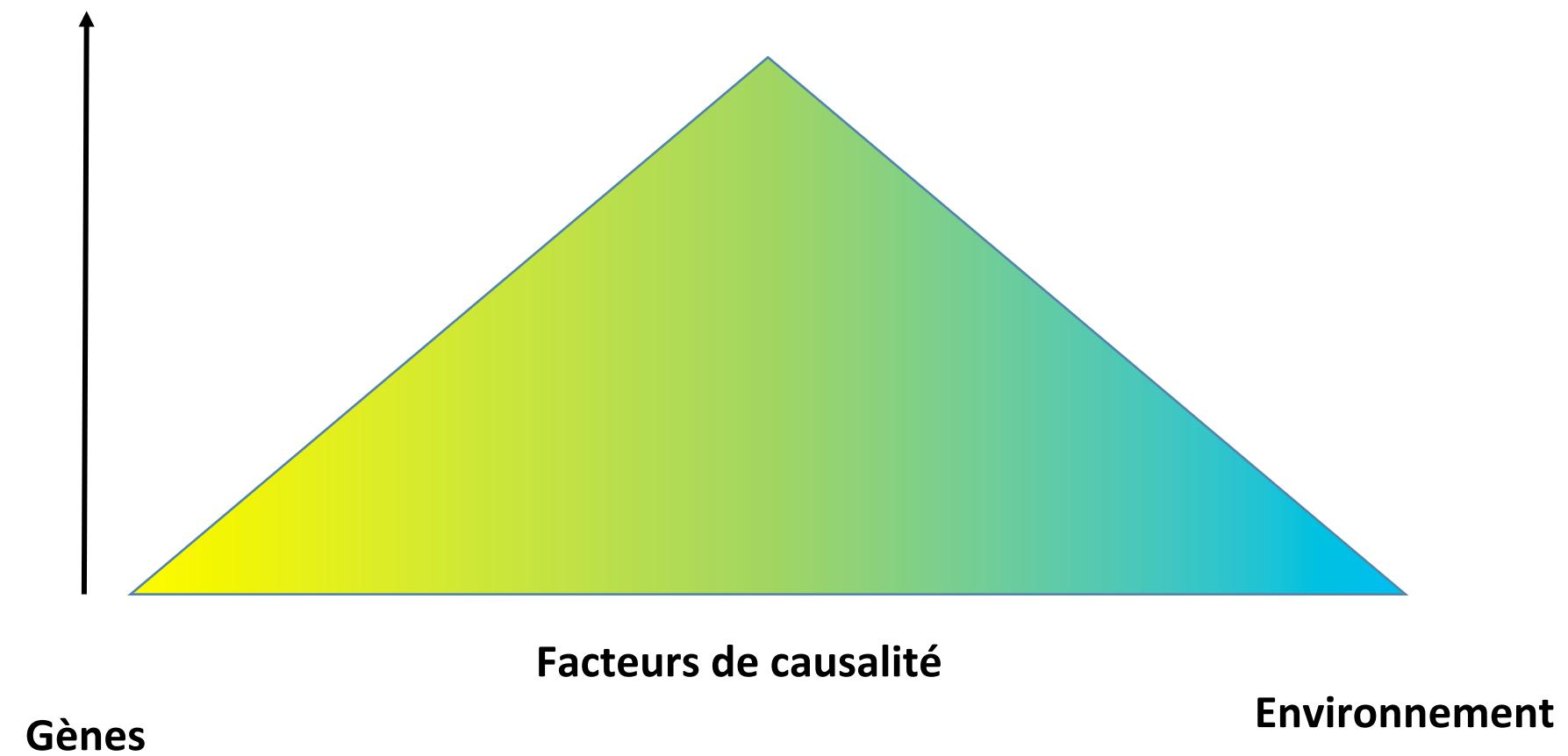
- Renal insufficiency

### Skeletal/Muscle

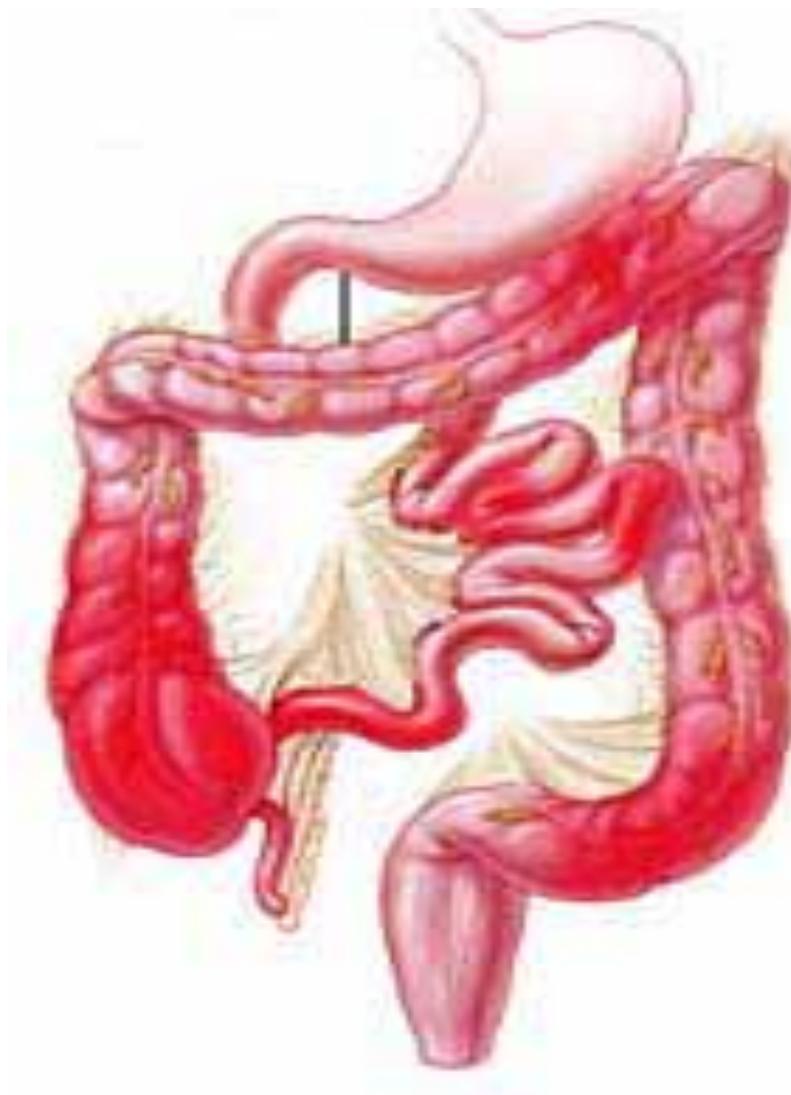
- Osteoporosis/pena
- Fractures
- Myopathy
- Sarcopenia



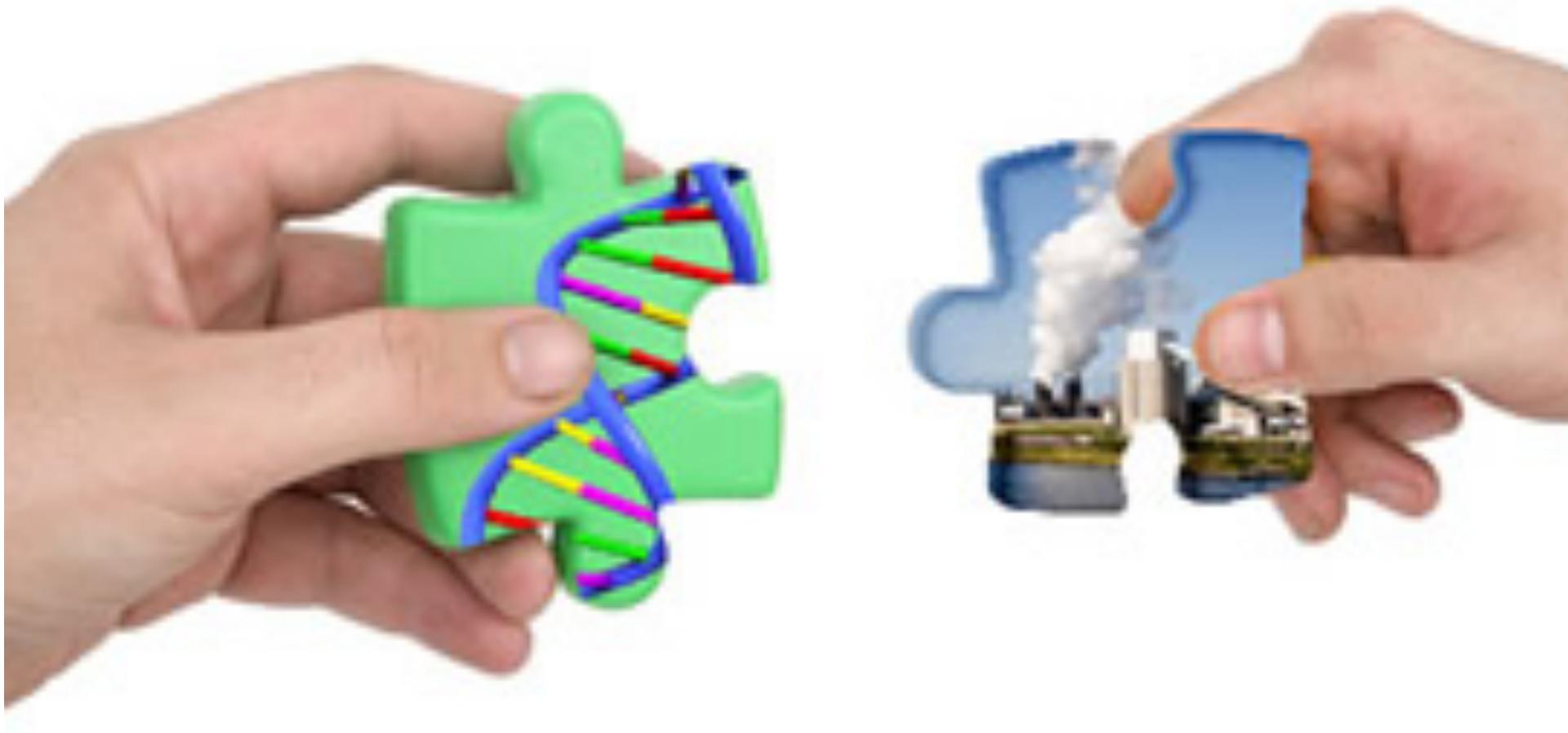
**Nb de malades**



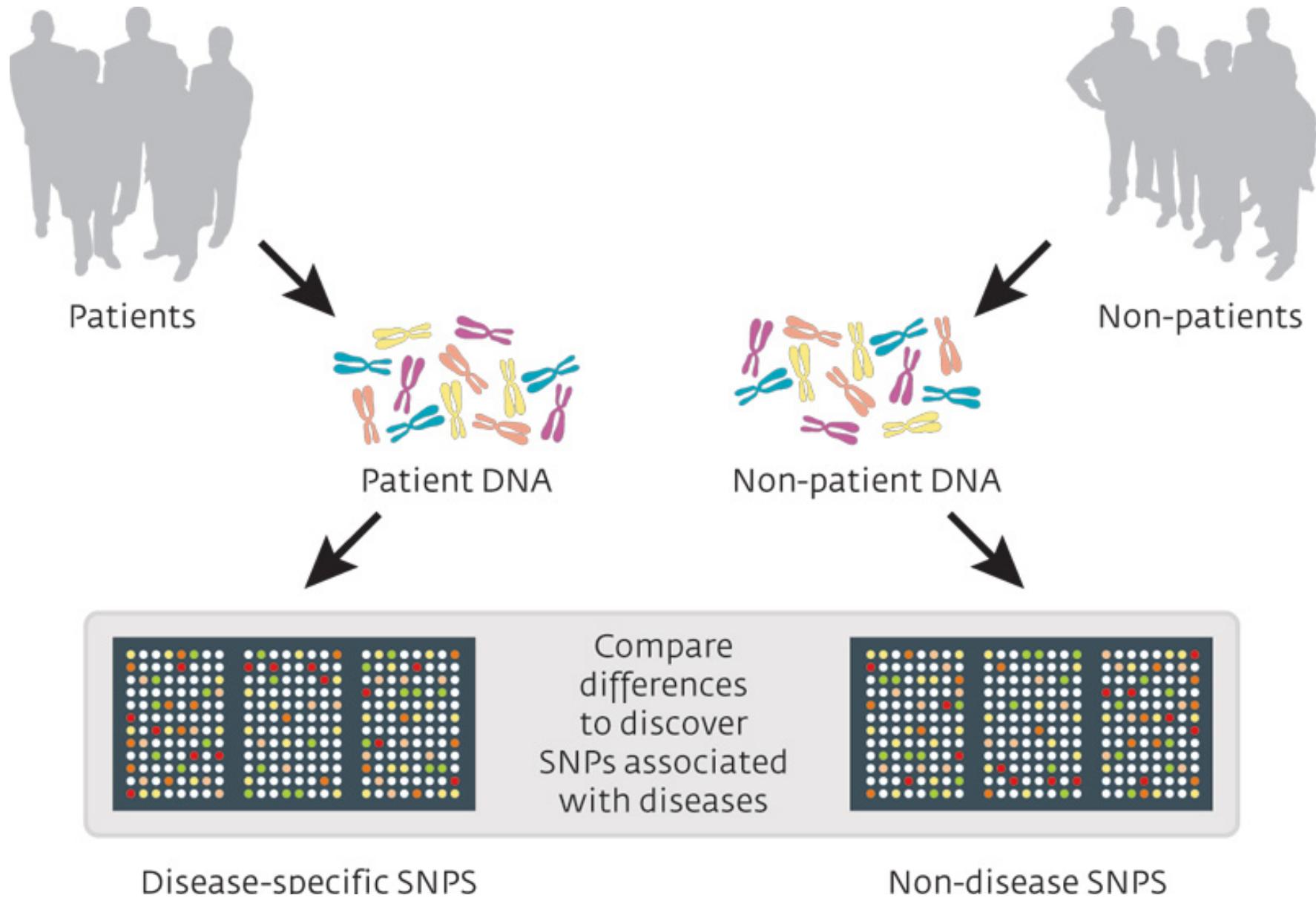
# Maladie de Crohn

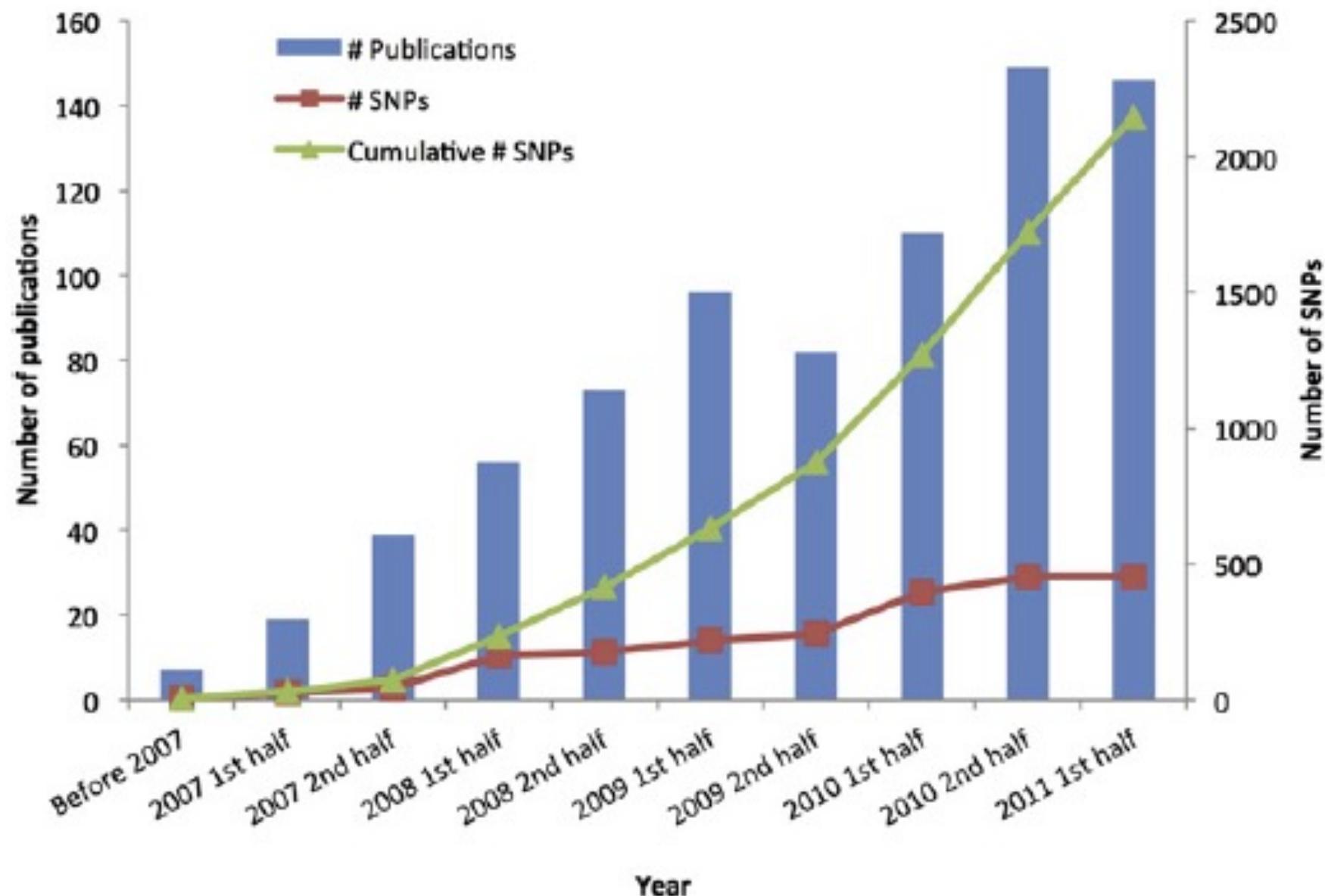


Maladie = Gene x Environnement



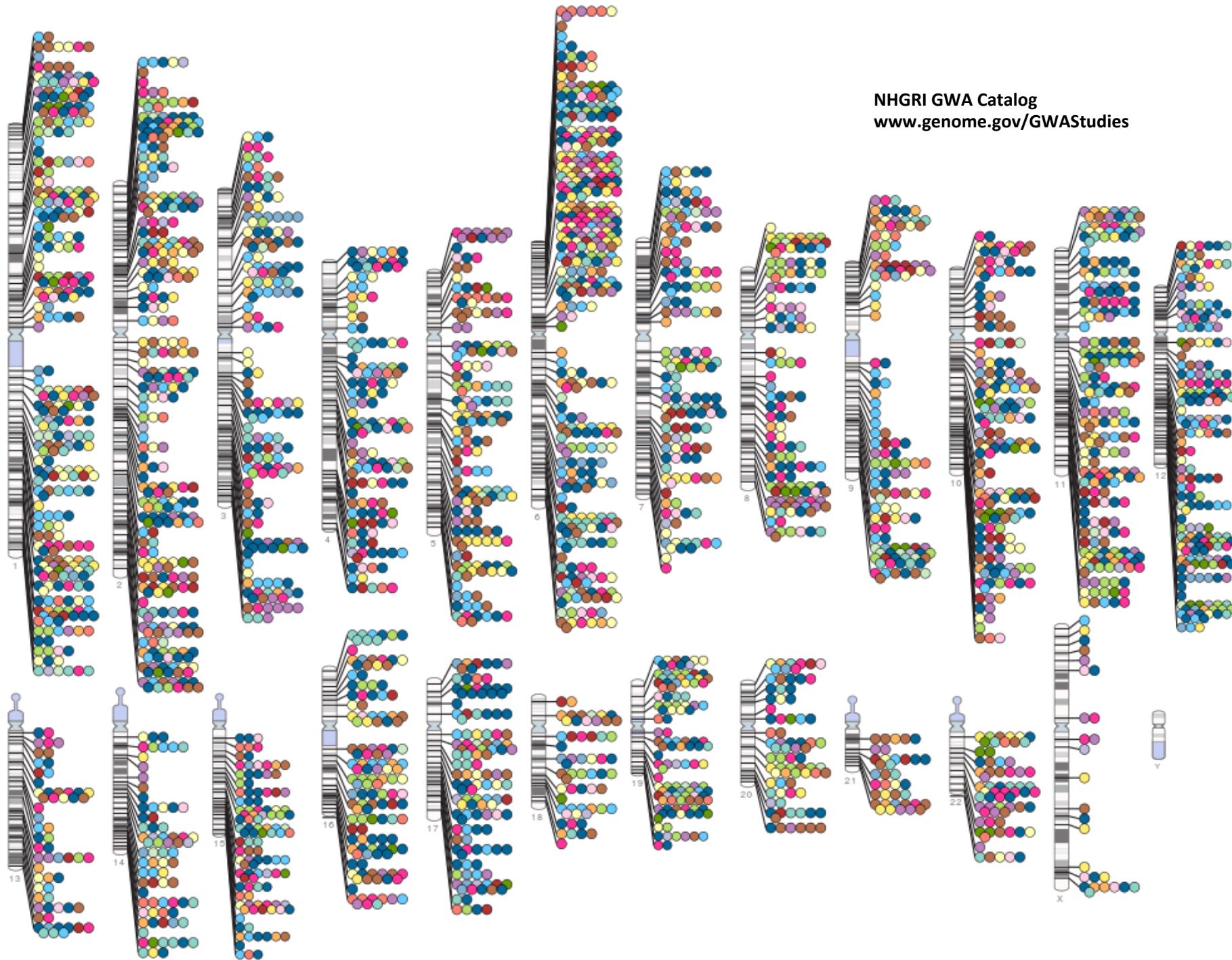
# Genome wide association studies

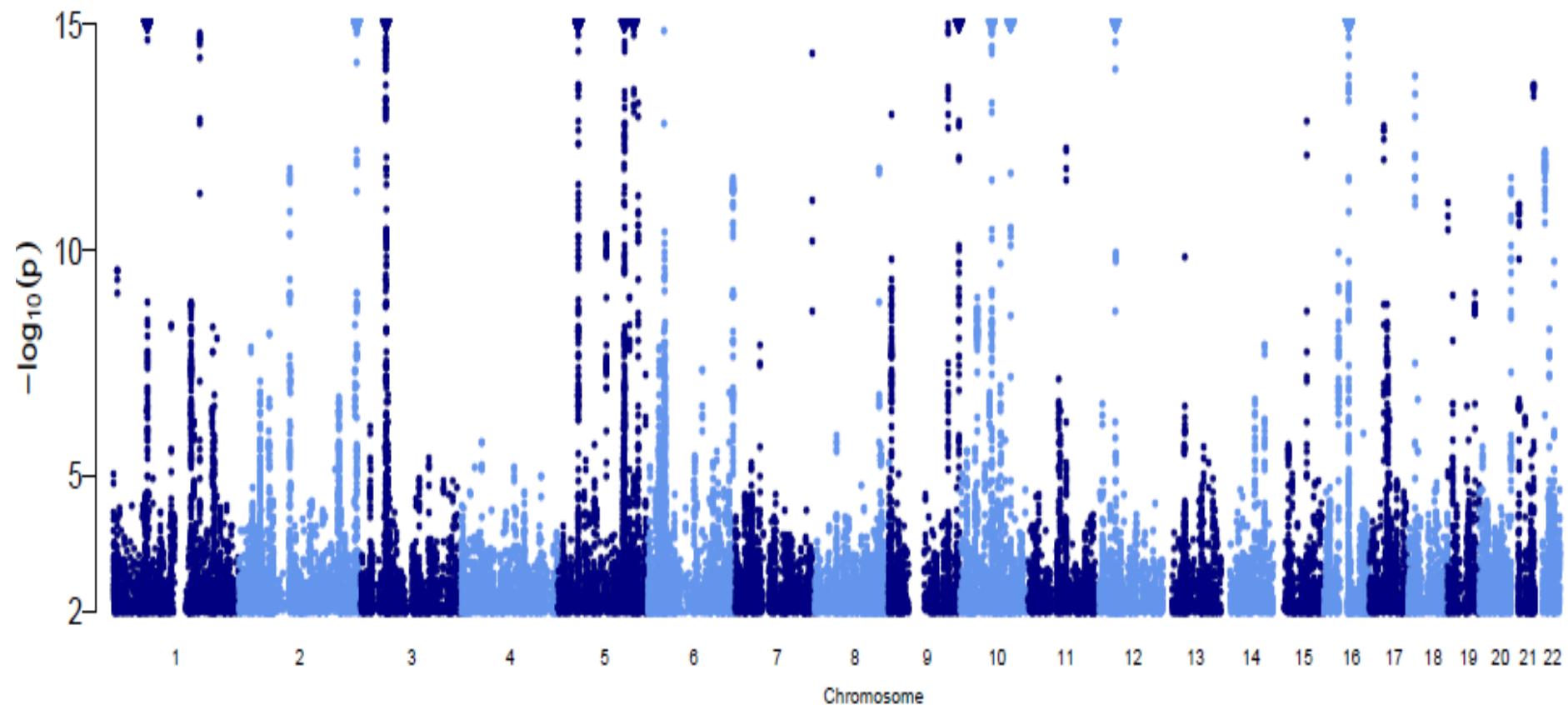




Vischner 2012

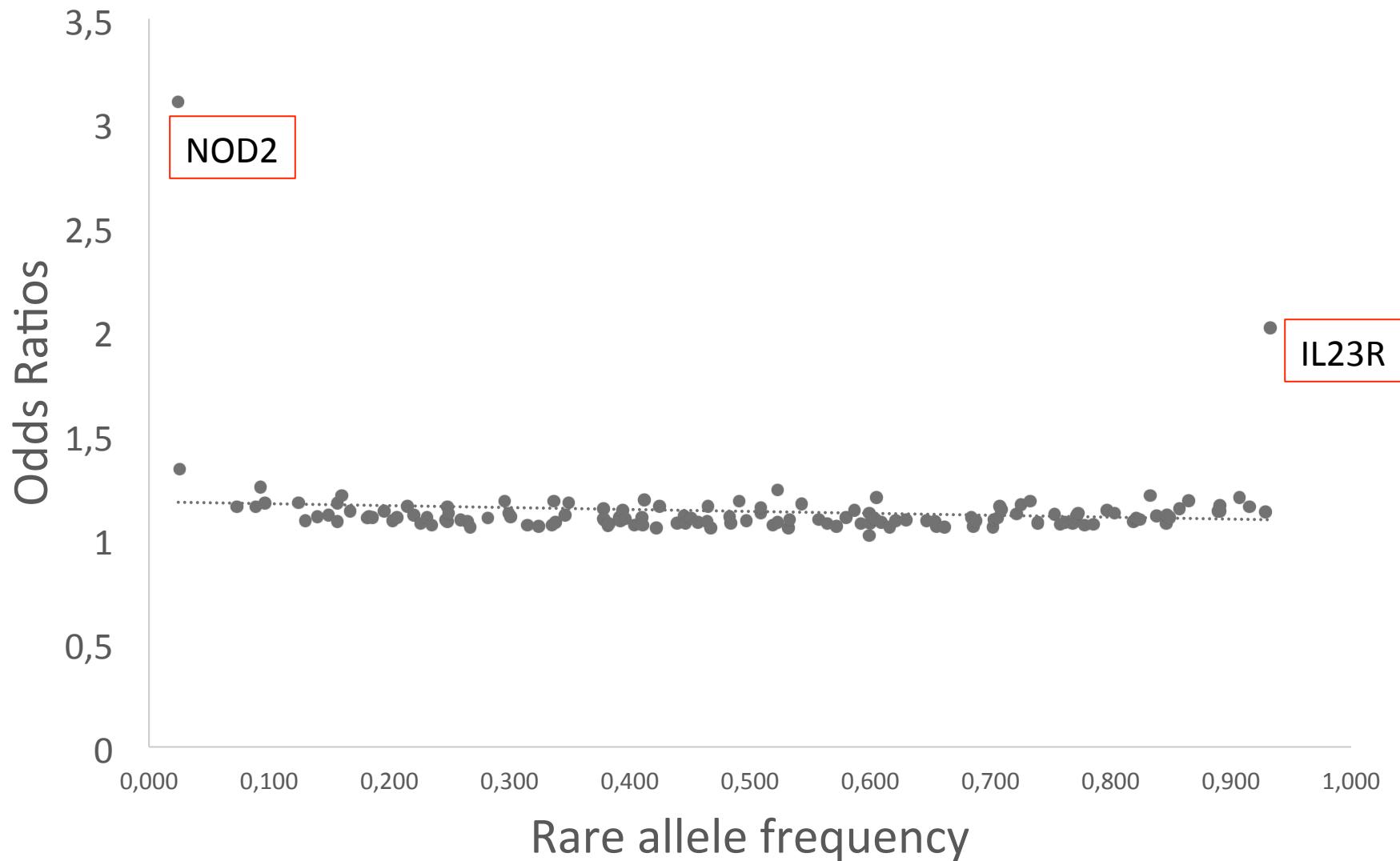
NHGRI GWA Catalog  
[www.genome.gov/GWASStudies](http://www.genome.gov/GWASStudies)



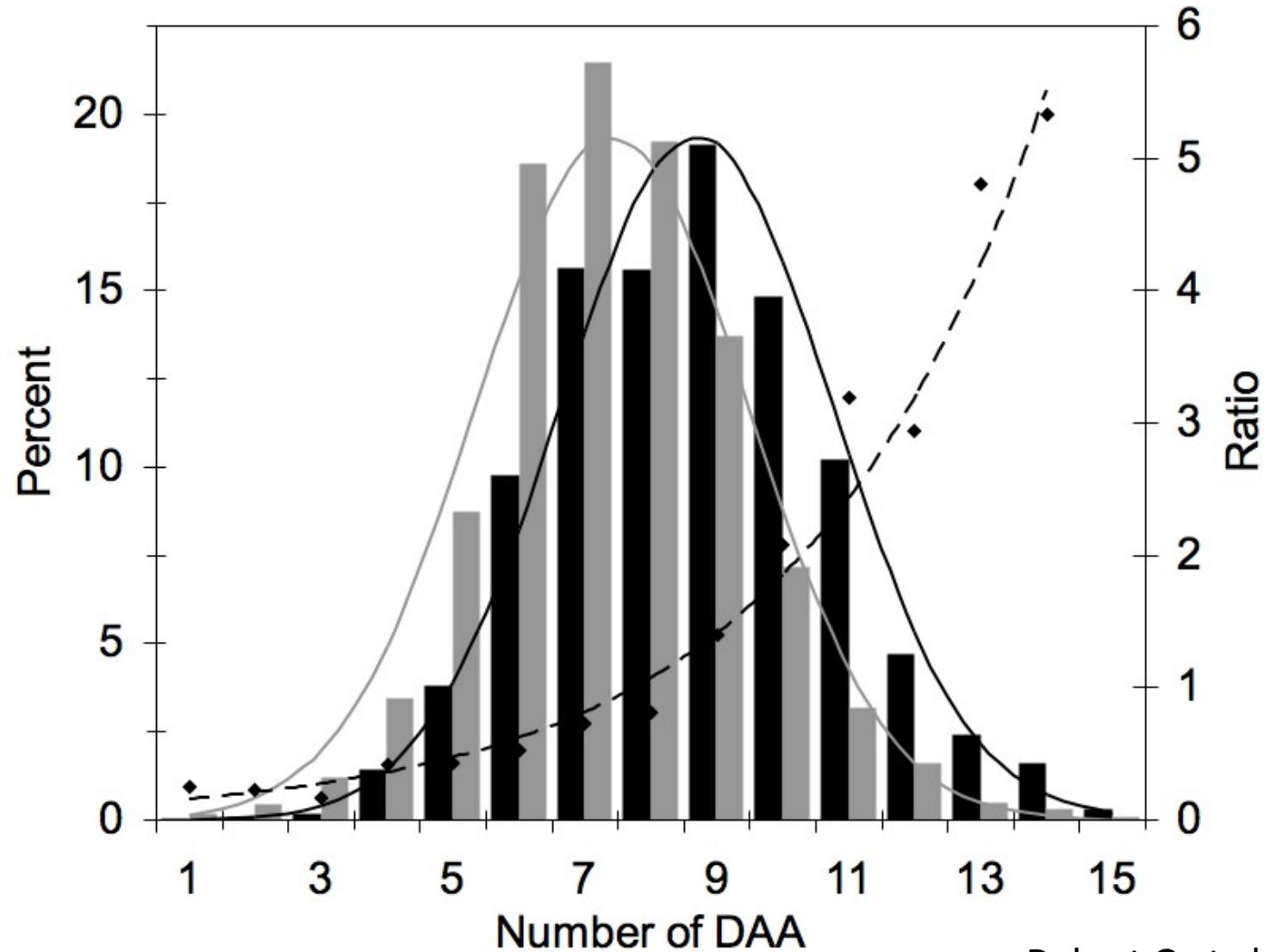


Franke et al. Nature genet 2010  
Jostins et al. Nature 2012

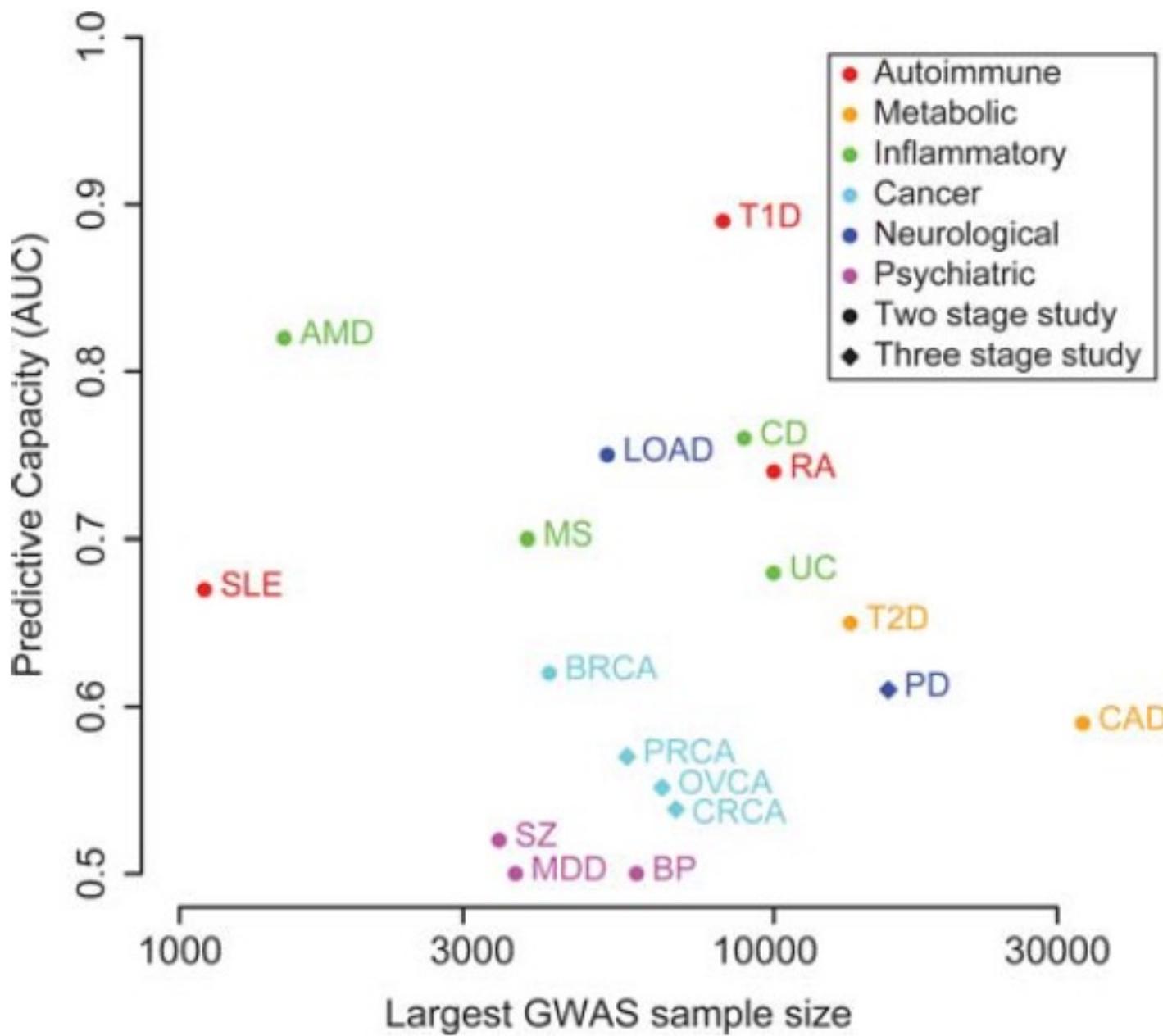
# Fréquence et effet des variations génétiques associées à la maladie de Crohn



# Valeur prédictive de la génétique



Debret G et al. Non publié



Jostins 2011

# Etude en Nouvelle Zélande

- Antécédents familiaux (MC: 3.06, RCH: 2.52)
- Tabac (MC:1.99, RCH:0.67),
- Haut niveau socio-économique (MC et RCH,  $P < 0.001$ )
- Urbain (MC,  $P < 0.01$ ).
- Etre migrant (RCH: 1.40)
- Avoir un jardin potager (MC : 0.52, RCH : 0.65)
- Avoir été allaité (MC : 0.55, RCH : 0.71)
- Appendicectomie, adénoïdectomie, mononucléose infectieuse, asthme : MC.

# Mode de vie et maladie de Crohn

## Une liste à la Prévert.....

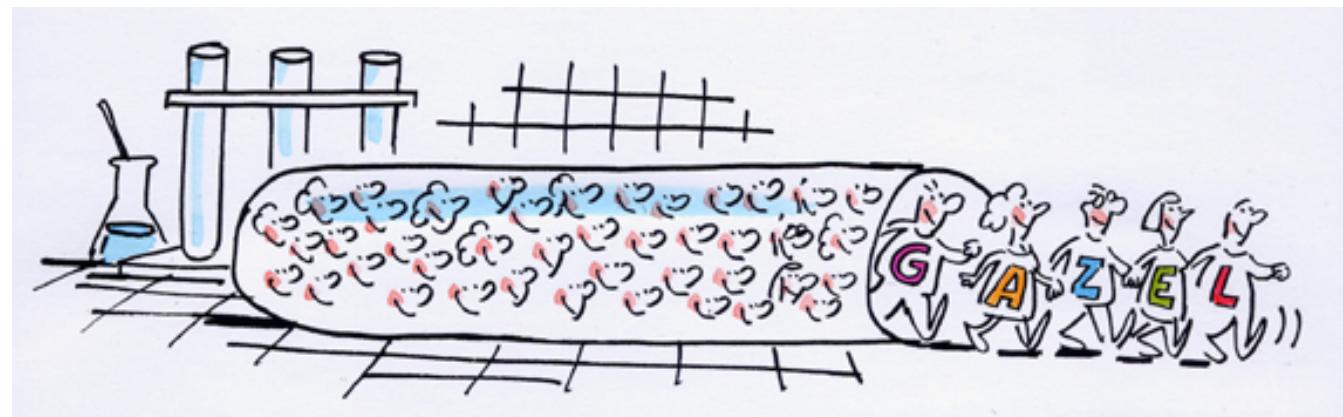
- Sucres raffinés
- Fast-food et Cola
- Microparticules
- Pate dentifrice
- Chewing-Gum
- Margarine
- Fibres
- Levure de boulanger
- Alcool
- Café
- Corn-flakes
- Emulsifiants
- Pathogènes opportunistes

- Mode de vie urbain
- Haut niveau économique
- Eau chaude
- Refrigération
- Infections Périnatales
- Infections dans l'enfance
- Antibiotiques
- Adenoïdectomie
- Atopie
- Allaitement
- Jardin Potager
- Aluminium
- Eau ferrugineuse
- Baignades en rivière
- Ensoleillement
- Evènements de vie
- Contraceptifs
- Tabac

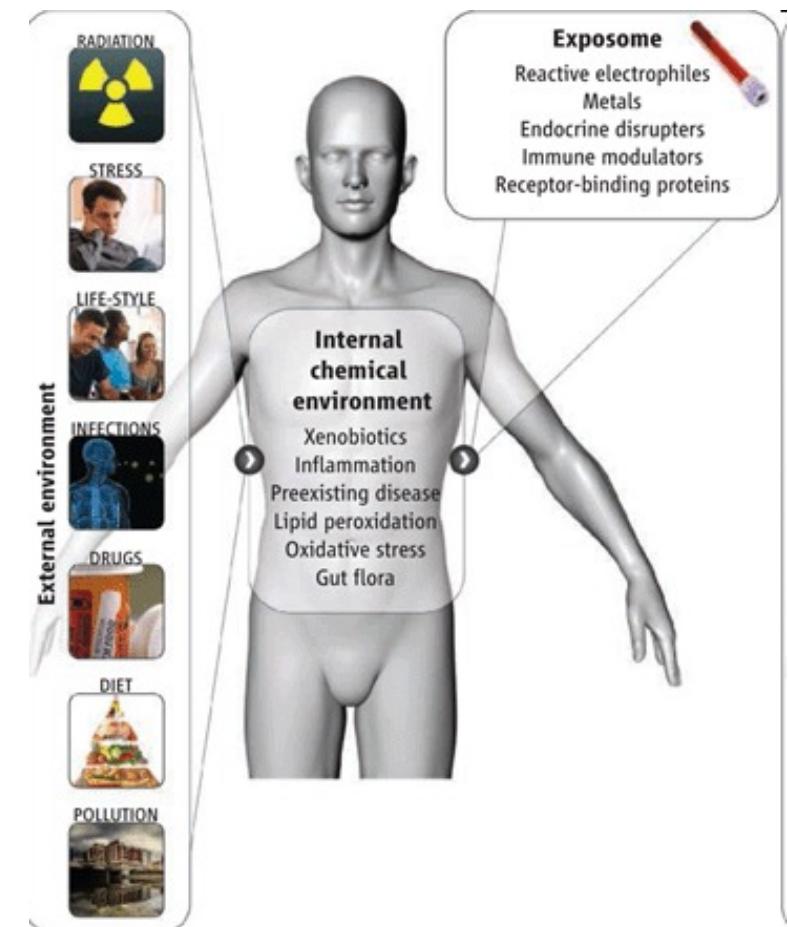
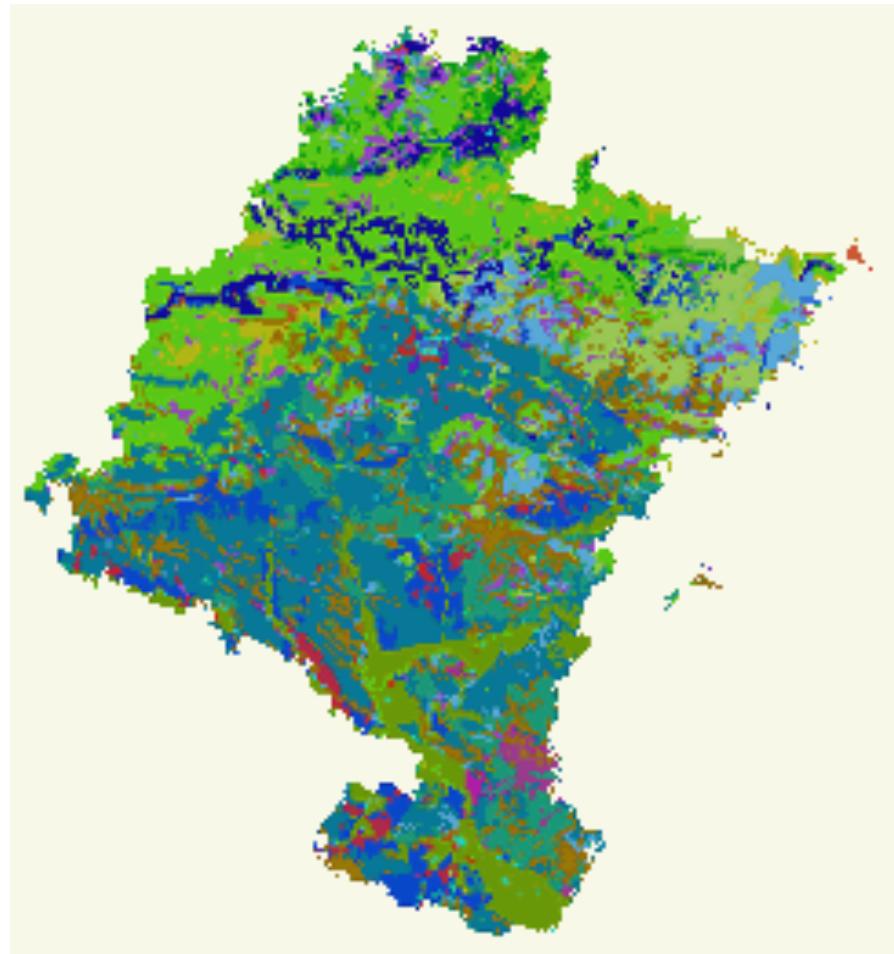
# Grandes cohortes

## Cohorte Framingham

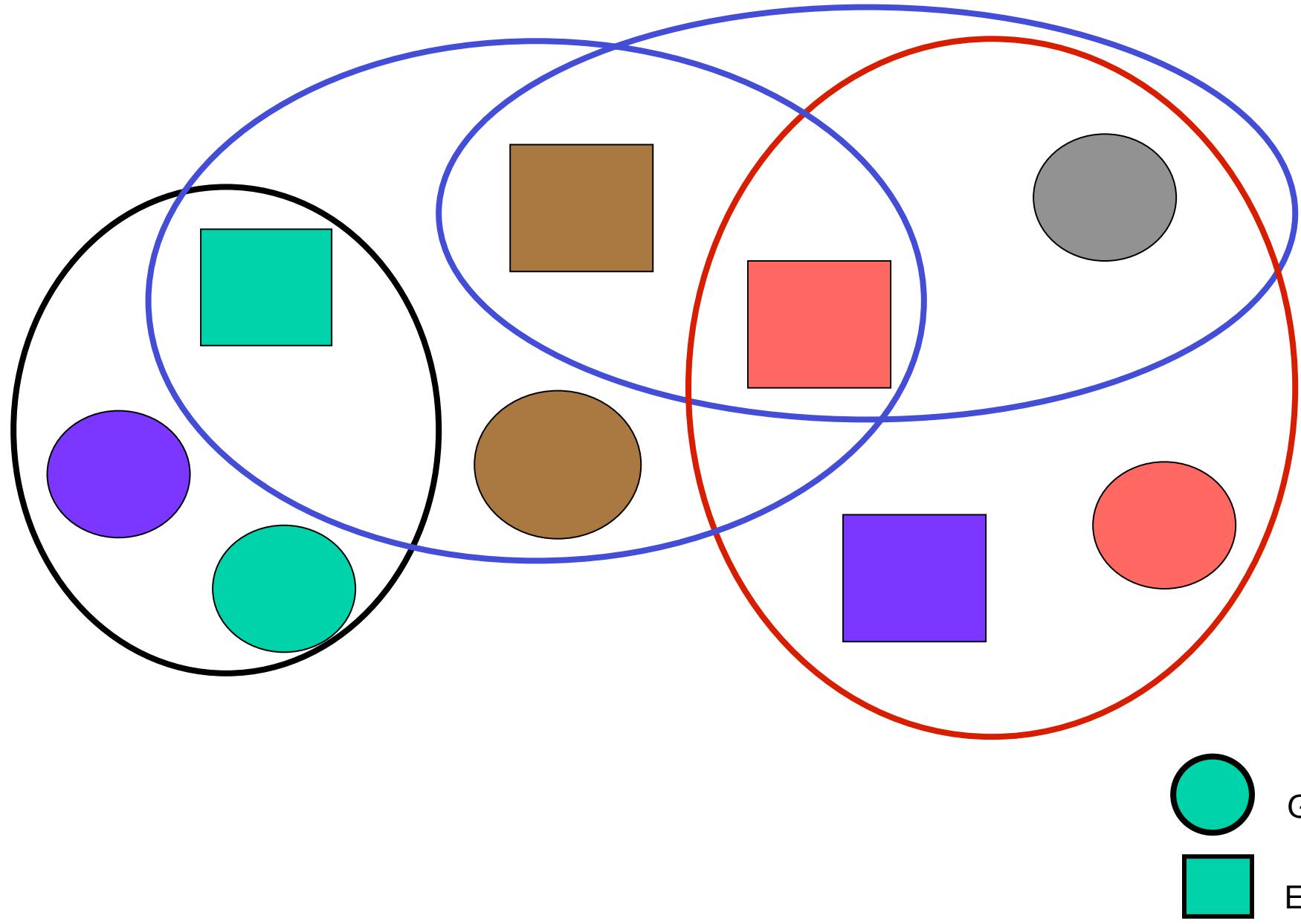
- Ville de Framingham, Massachusetts (USA)
- 5200 habitants sains, suivis depuis 1948 sur plus de 5 décennies
- Récolte de nombreuses caractéristiques d'intérêt (« facteurs de risques ») pour l'étude d'une ou de plusieurs maladies

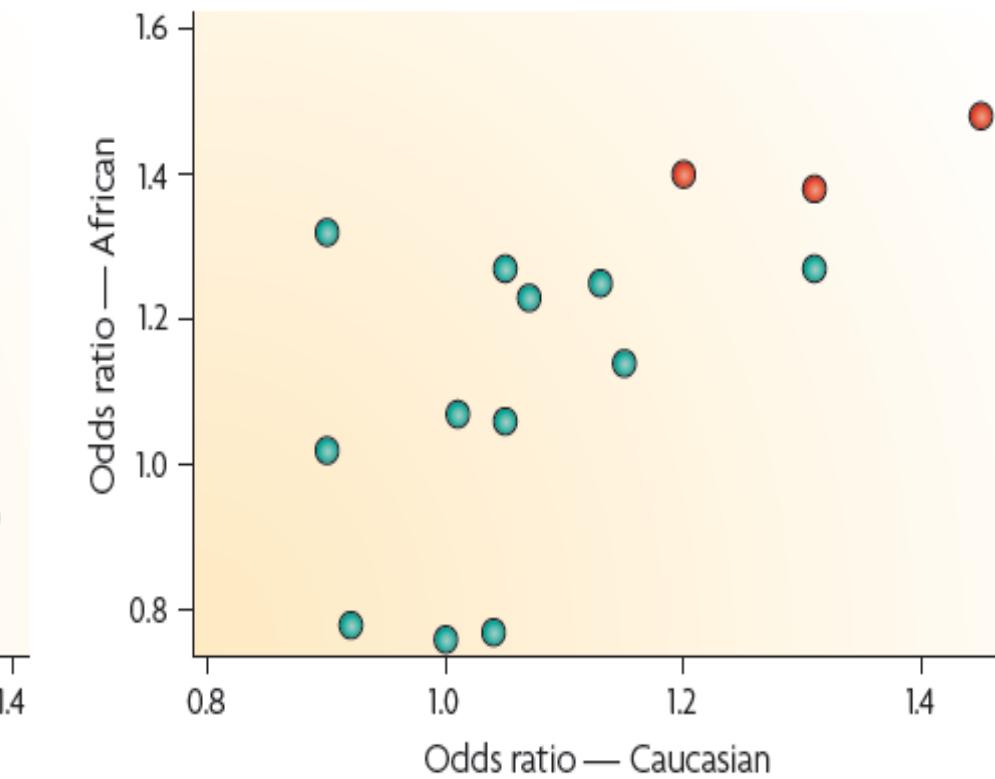
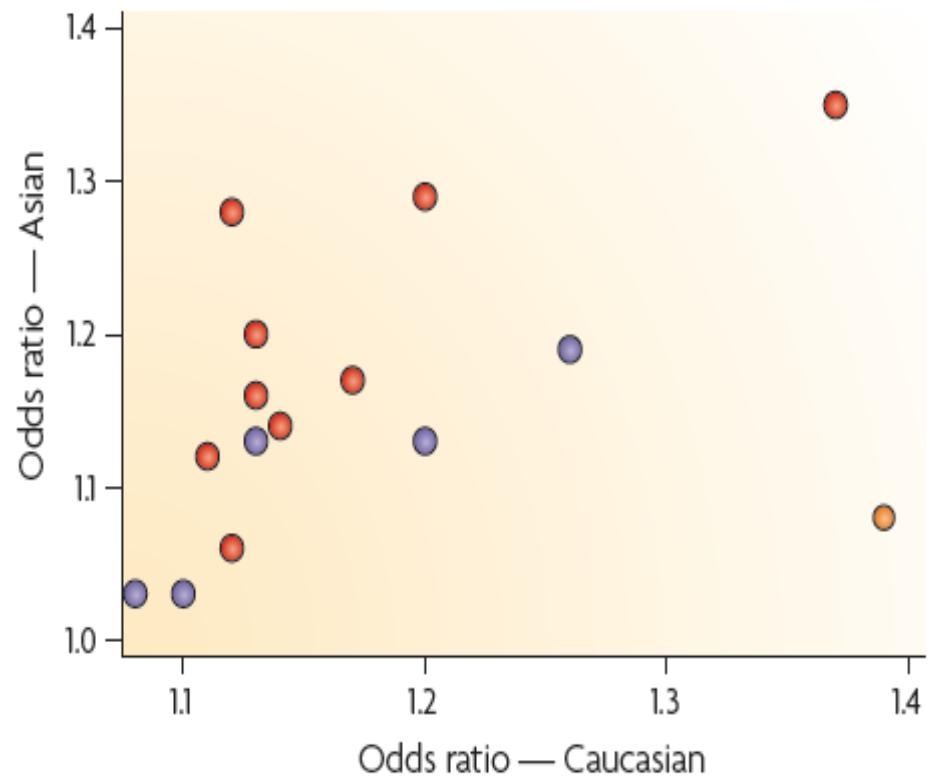


# EXPOSOME



Rappaport 2011





● Type 2 diabetes   ● Breast cancer   ● Atrial fibrillation   ● Obesity

Ioannidis 2009

# II Modélisation théorique

Jean-Marc Victor<sup>1#</sup>, Gaëlle Debret<sup>1</sup>, Annick Lesne<sup>1,2</sup>,  
Leigh Pascoe<sup>3</sup>, Pascal Carrivain<sup>1</sup>, Gilles Wainrib<sup>4,5</sup>, Jean-  
Pierre Hugot<sup>5,6,7#</sup>

1) *Laboratoire de Physique Théorique de la Matière Condensée (LPTMC) UMR 7600 CNRS & Université Pierre et Marie Curie-Paris 6, France.*

2) *Institut des Hautes Études Scientifiques, Bures-sur-Yvette, France.*

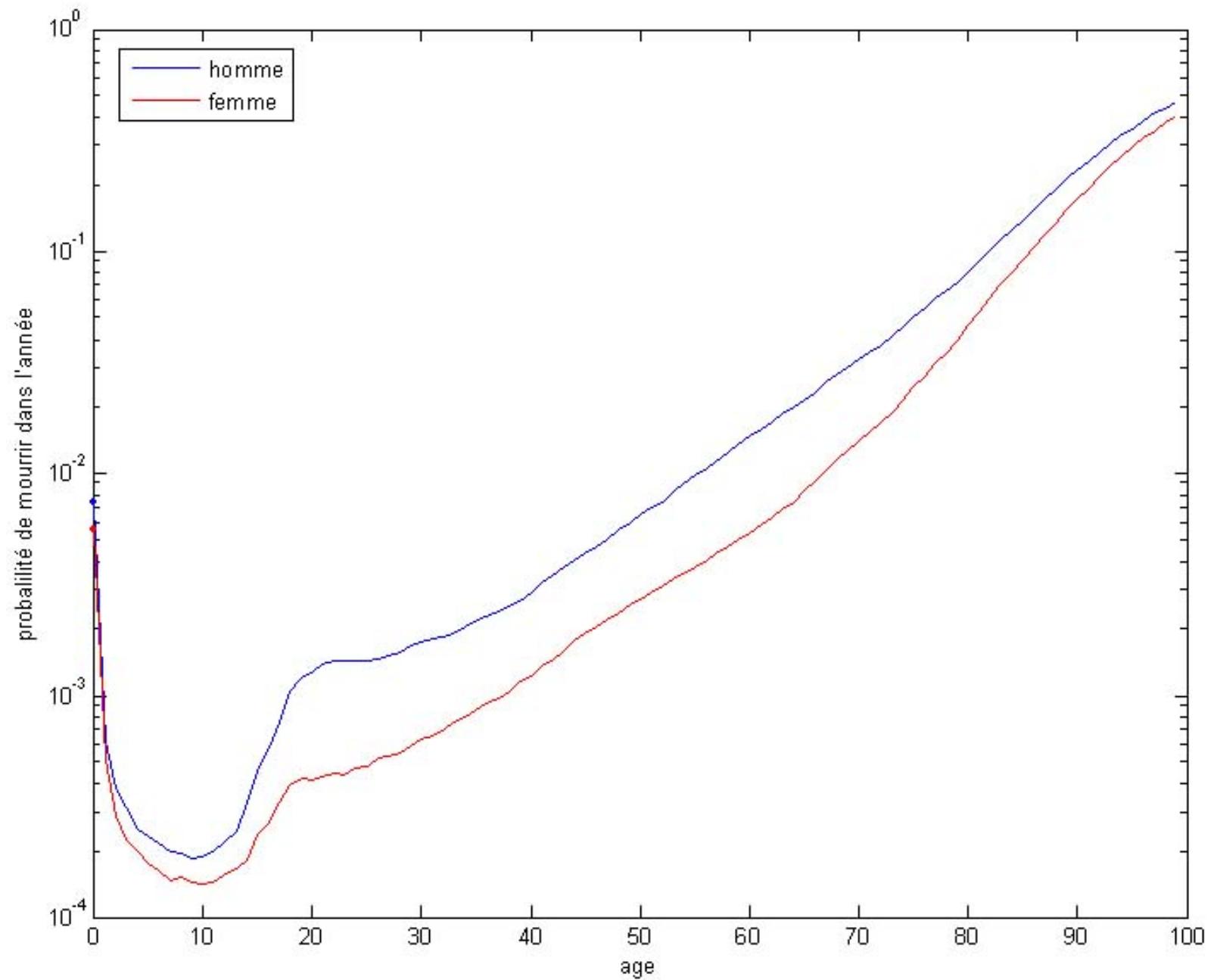
3) *Fondation Jean Dausset (CEPH), Paris, France.*

4) *ENS ,rue d'Ulm, 75005 Paris*

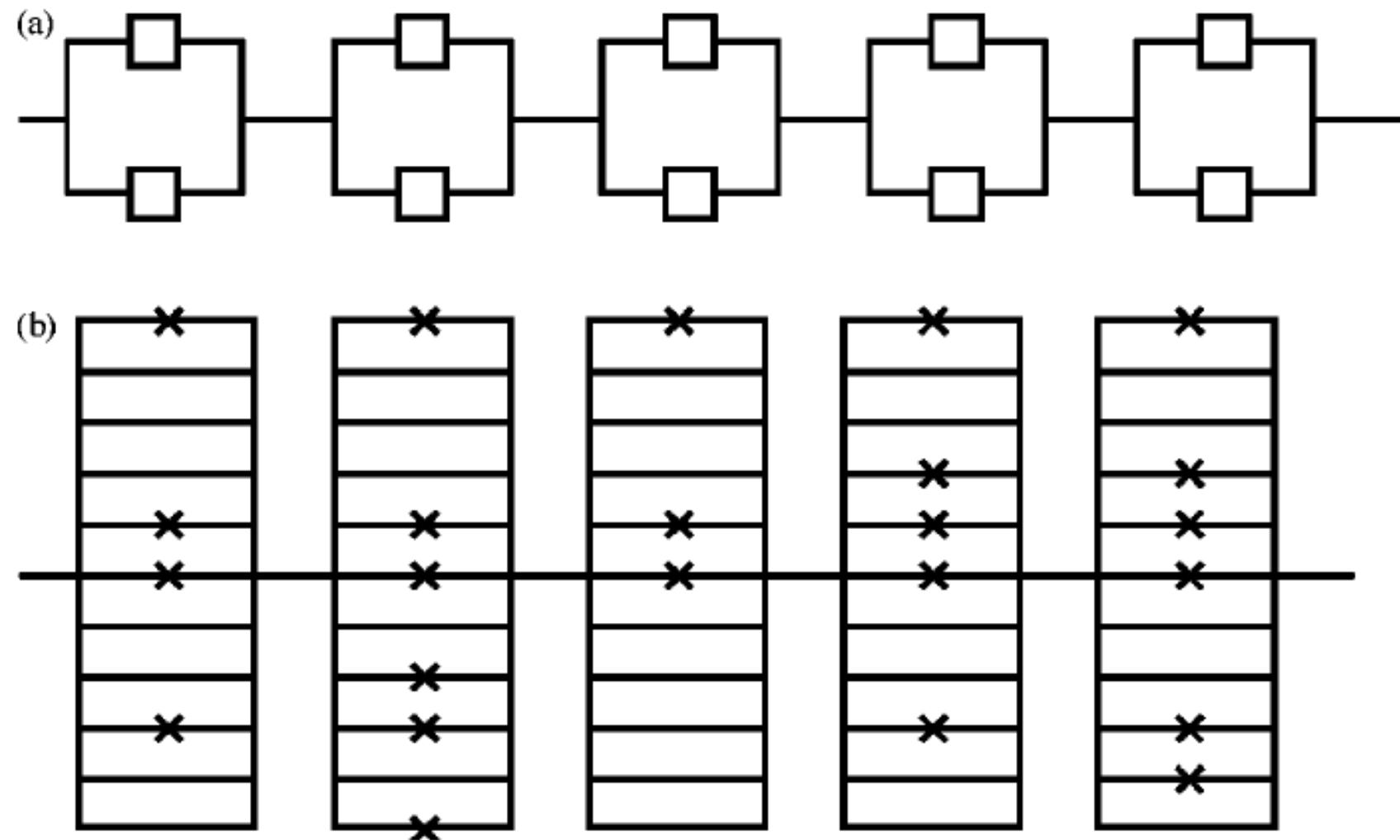
5) *Labex inflamex, Université Paris-Diderot Sorbonne Paris-Cité, Paris, France*

6) *Assistance Publique Hôpitaux de Paris, Hôpital Robert Debré, Paris, France.*

7) *UMR 1149, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France*

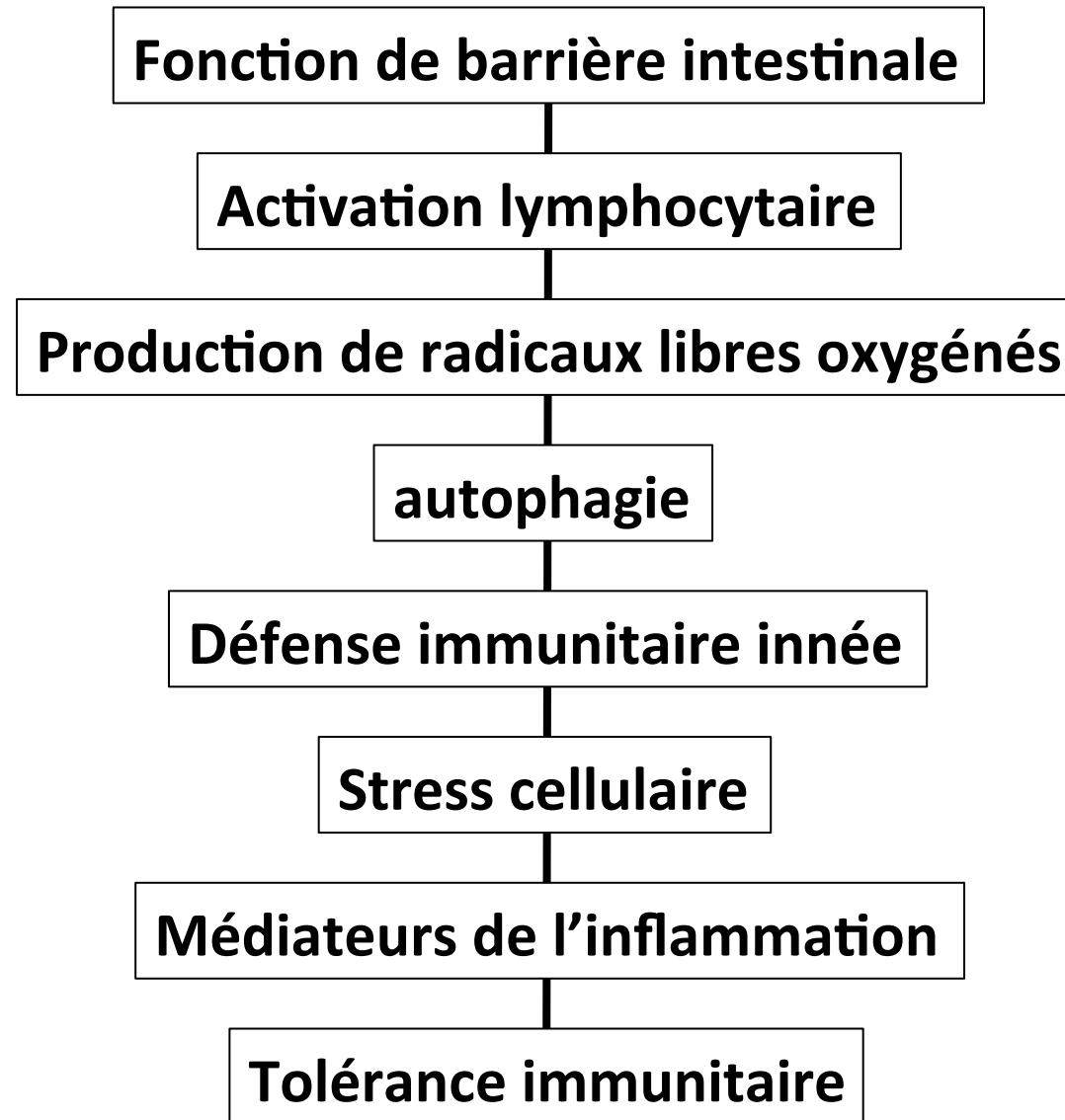


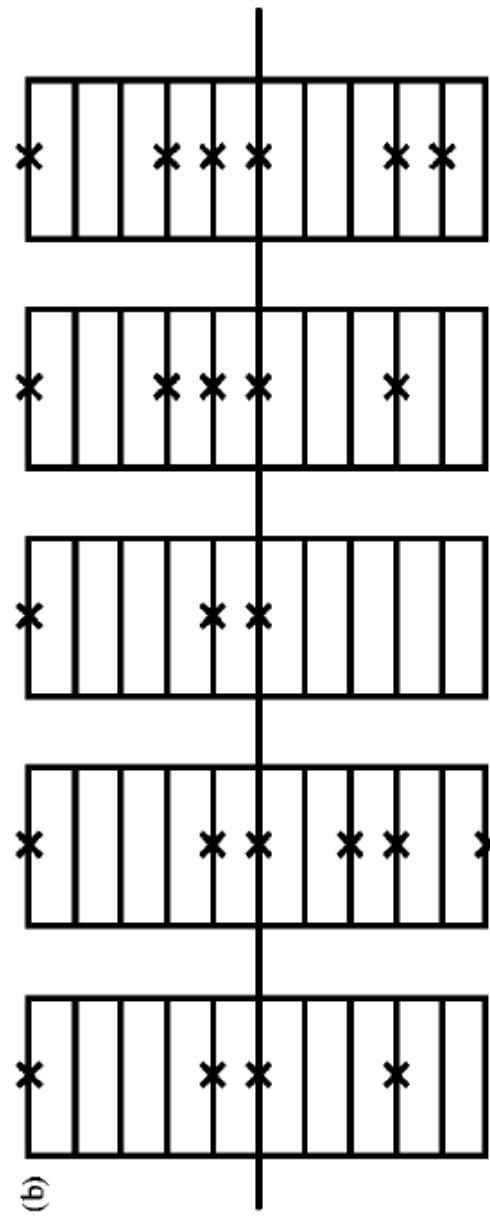
# Modèle de fiabilité

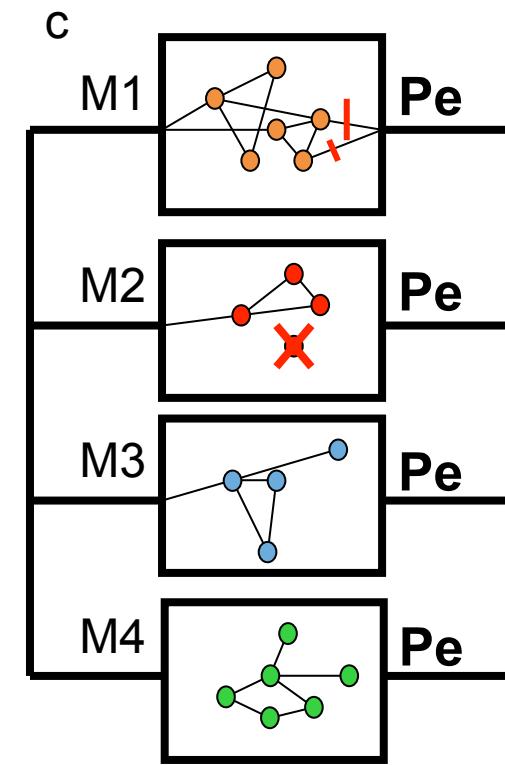
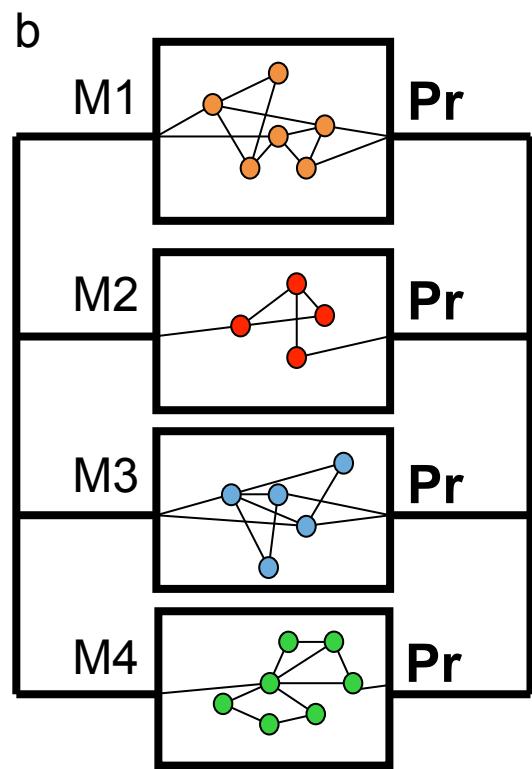
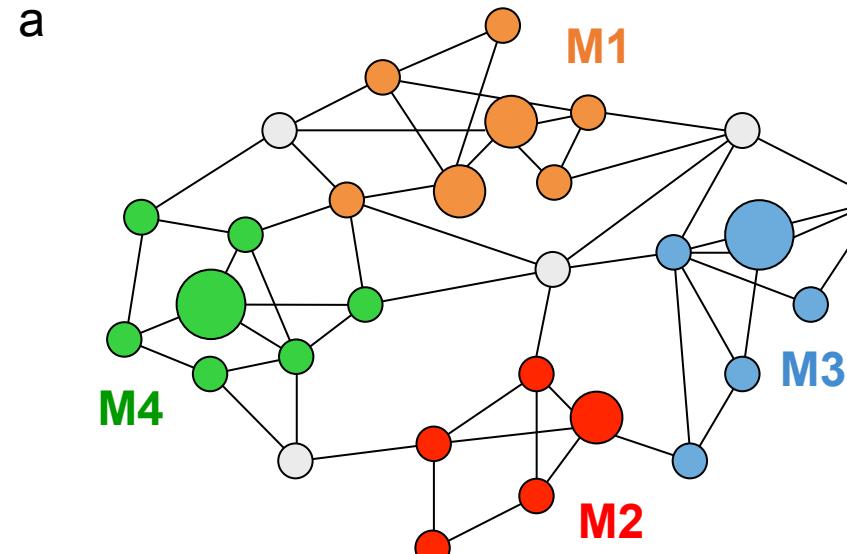


Gavrilov 2001

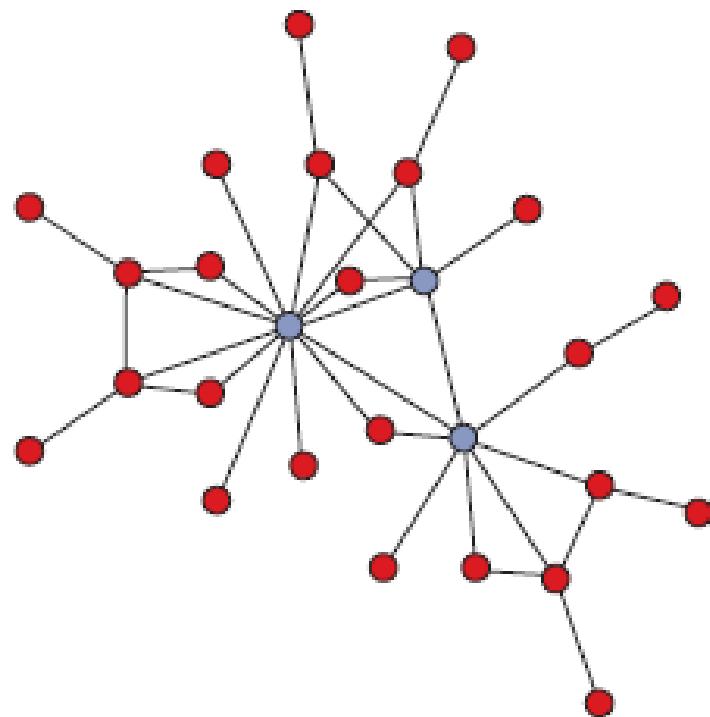
intracellular logistics interferon response **tolerance** carbohydrate metabolism  
barrier function chemotaxis solute carrier  
iron metabolism dendritic cell plasticity polarized secretion microtubules/centrosome  
miRNA/lincRNA exocytosis DNA methylation  
inflammation mediators negative regulators of immunity  
solute transport adenosine  
inflammasome fibrogenesis lymphocyte activation  
restitution IL-23-IL-23R DNA/RNA binding antimicrobial peptides  
actin cytoskeleton IgA/B<sub>reg</sub> cells phagocytosis Paneth cells  
T<sub>H</sub>17/T<sub>reg</sub> cells GPCR signalling ROS ER stress  
Gr1<sup>+</sup>Ly6Chigh/Gr1<sup>-</sup>Ly6C<sup>low</sup> autophagy hypoxia pathogen sensing  
antigen presentation lipid metabolism goblet cells/mucin  
stress response signature NF-κB activation/inhibition  
mycobacteria restriction factors



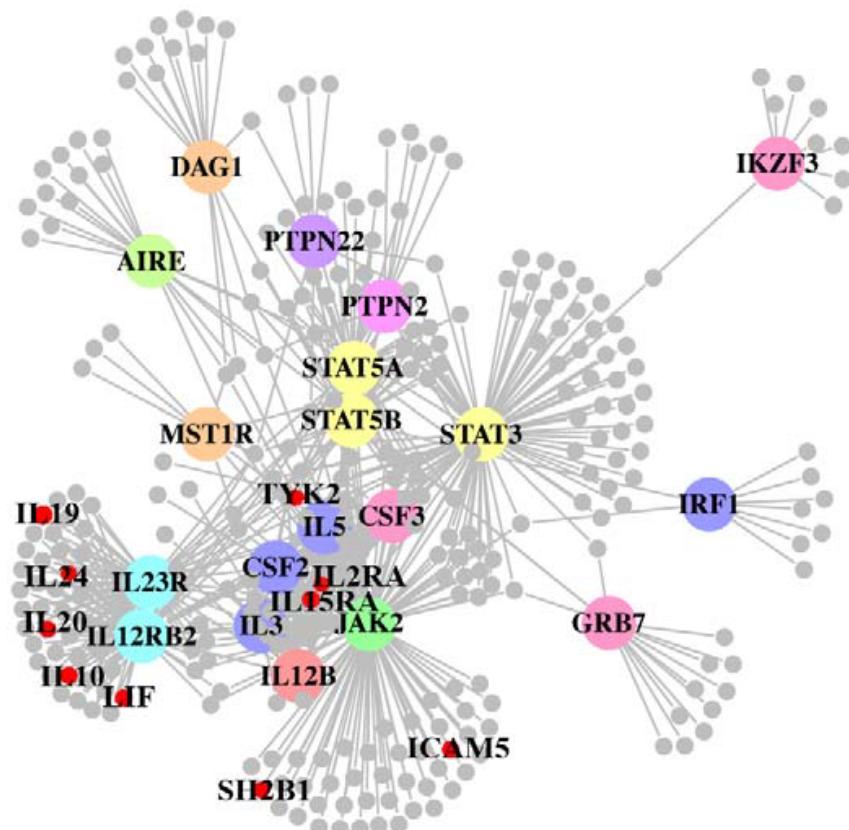




# Réseaux biologiques scale-free

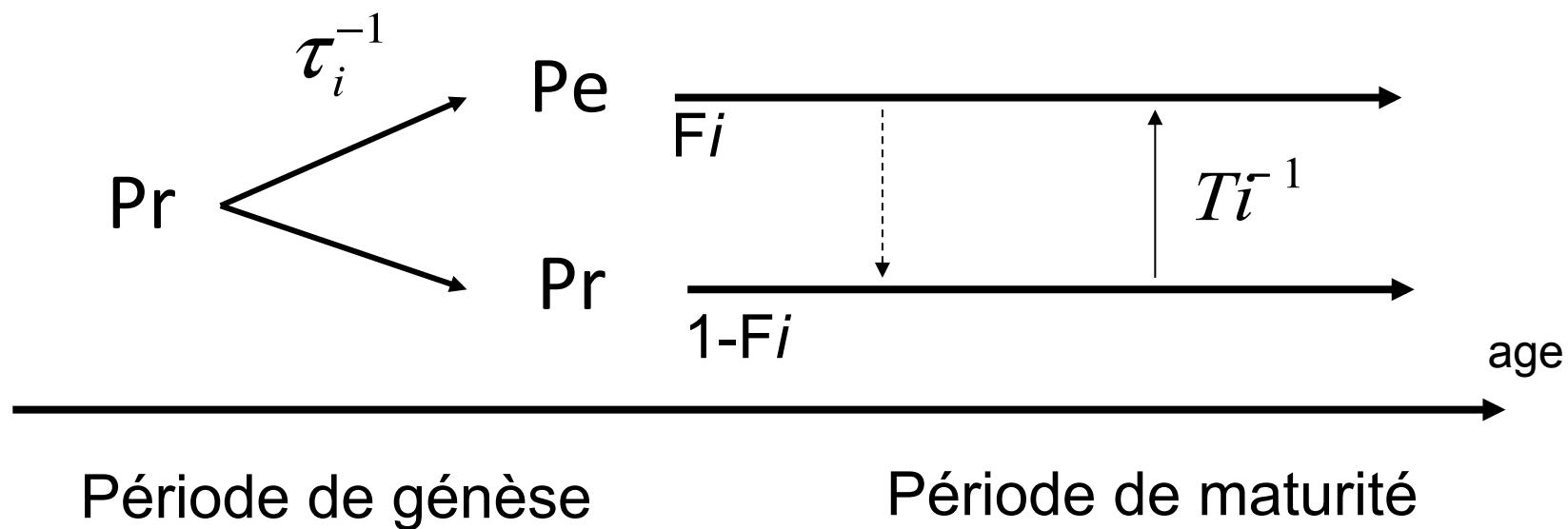


Barabasi 2012

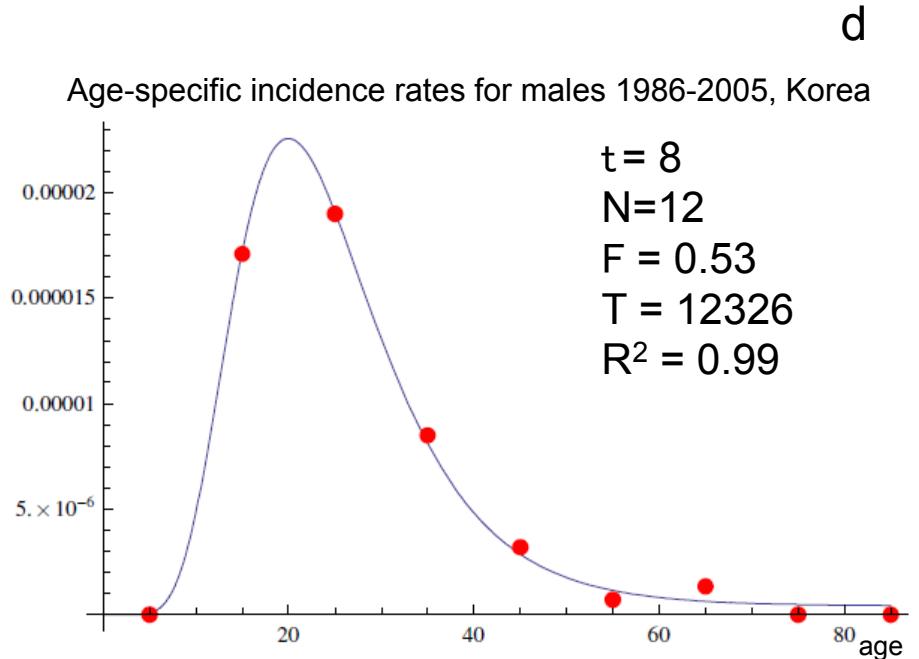
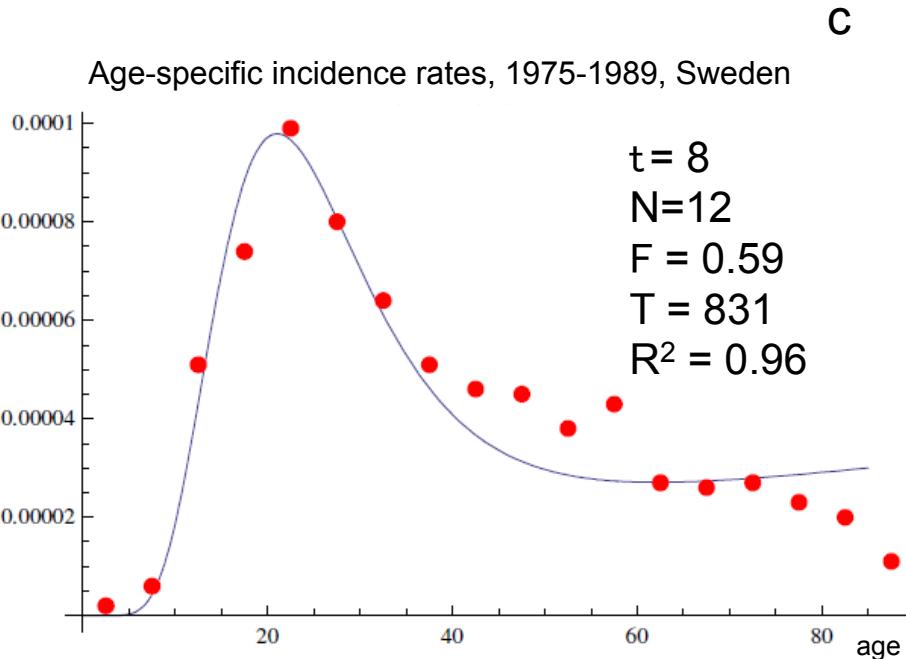
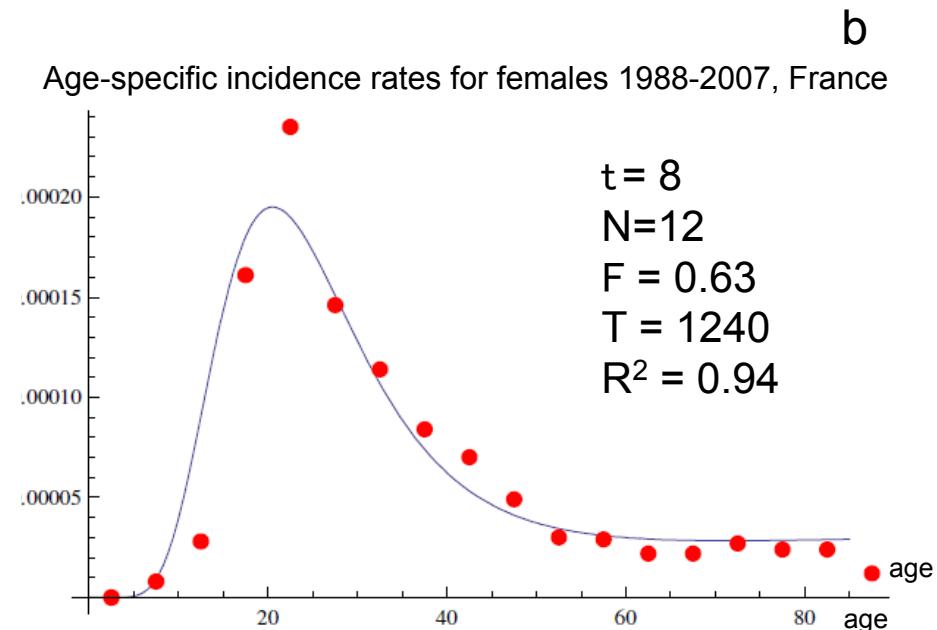
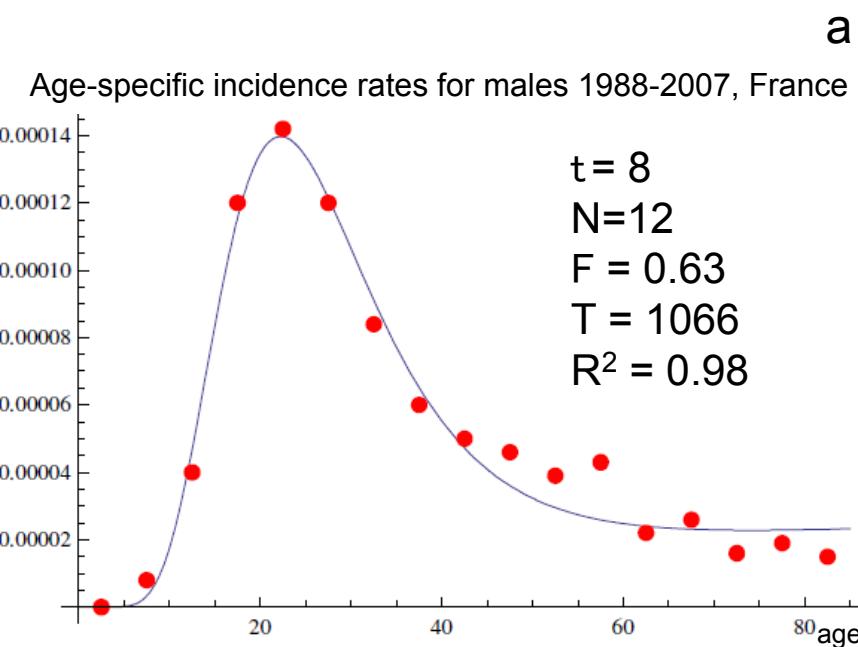


Rossin 2011

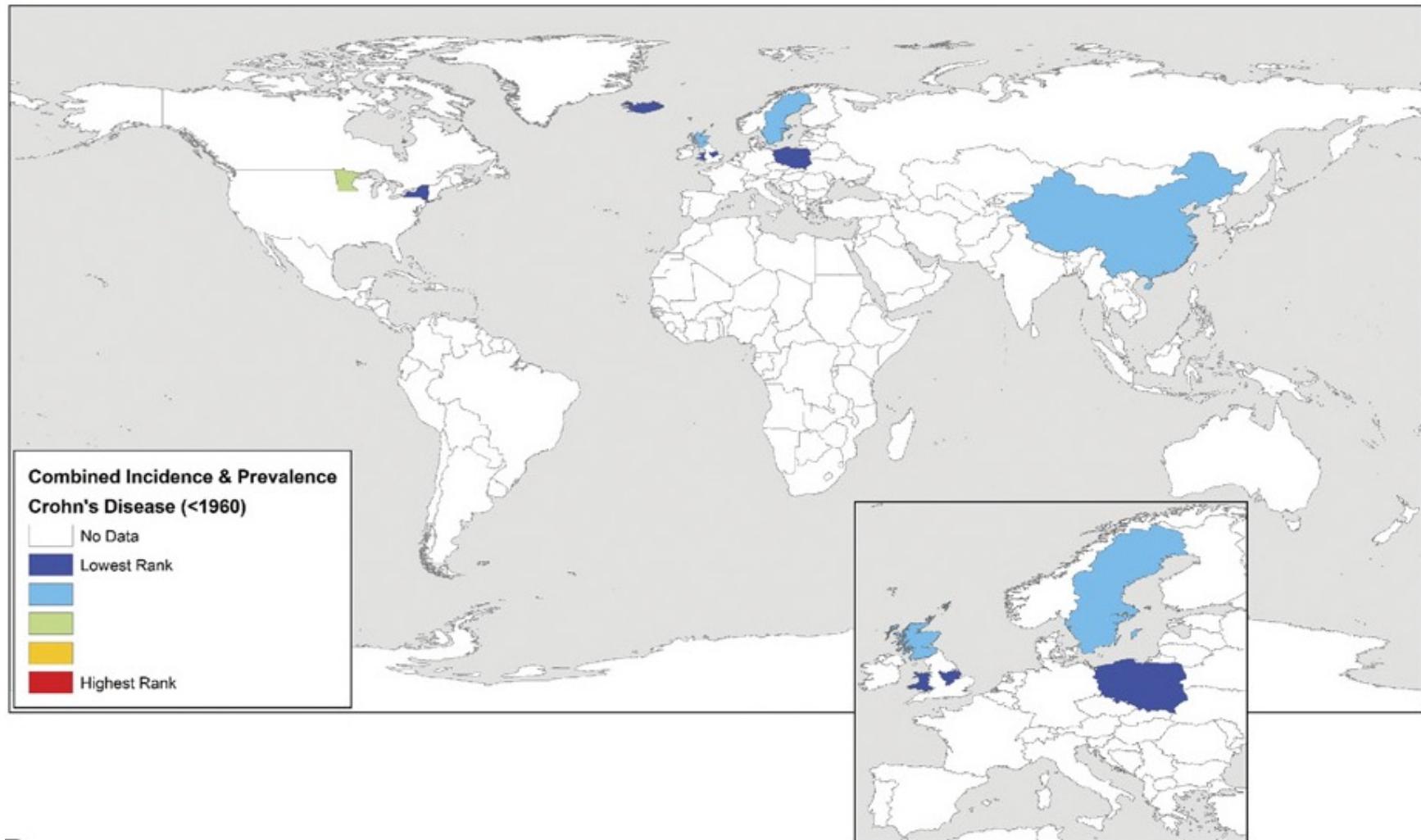
# Modèle de vieillissement des modules



$F_i$  est la propension à développer une maladie de Crohn.

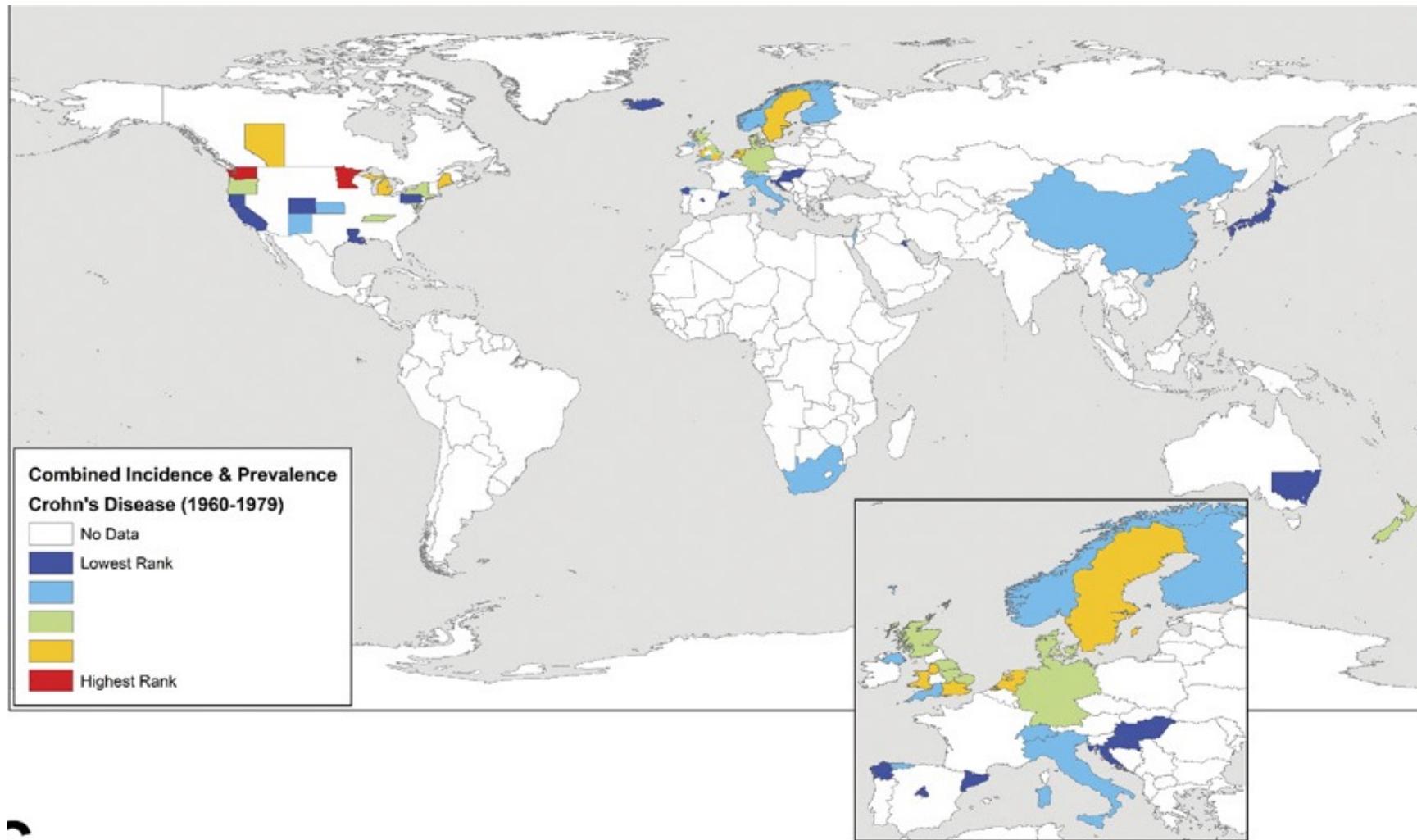


# Crohn avant 1960



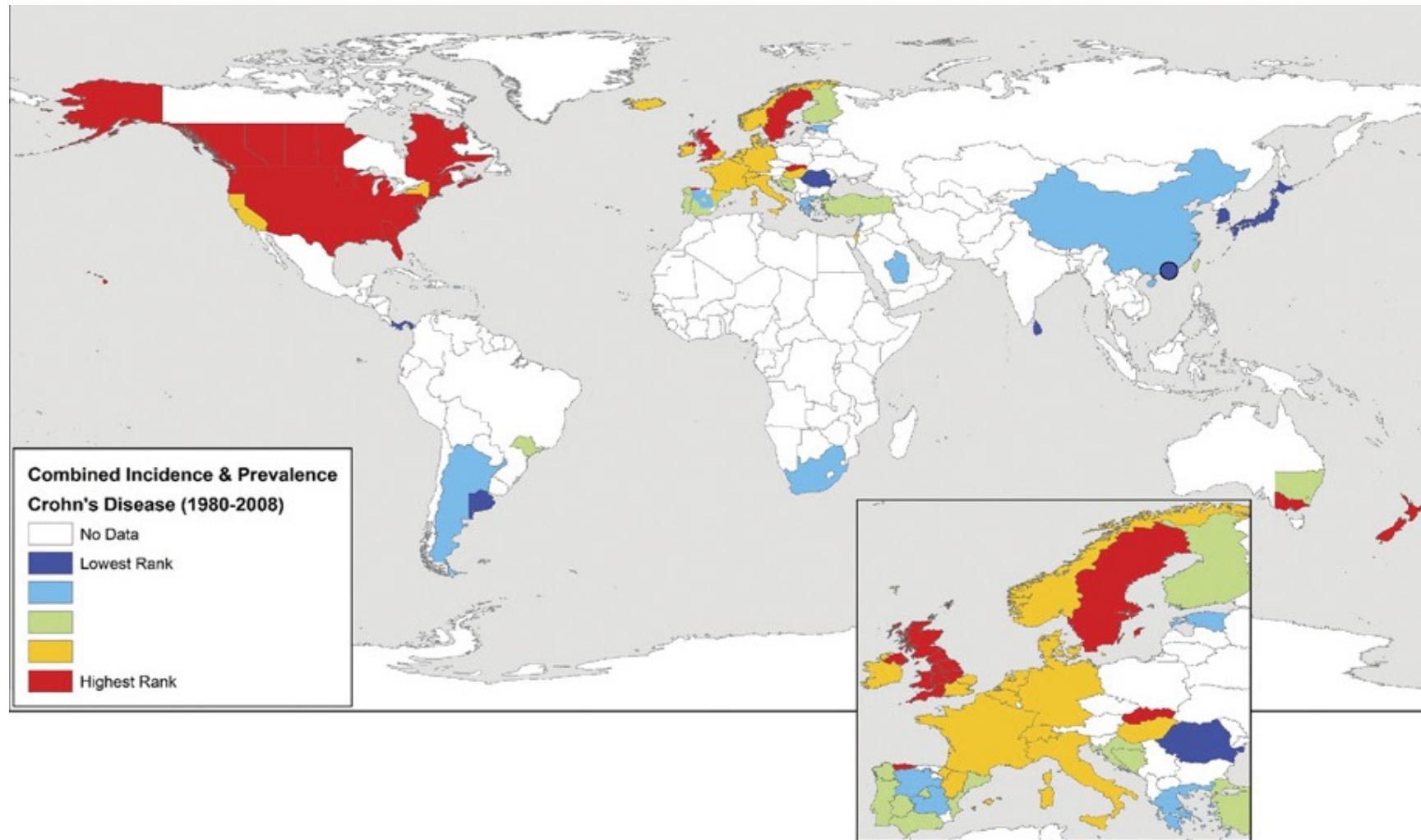
Molodecky 2012

# Crohn 1960-79



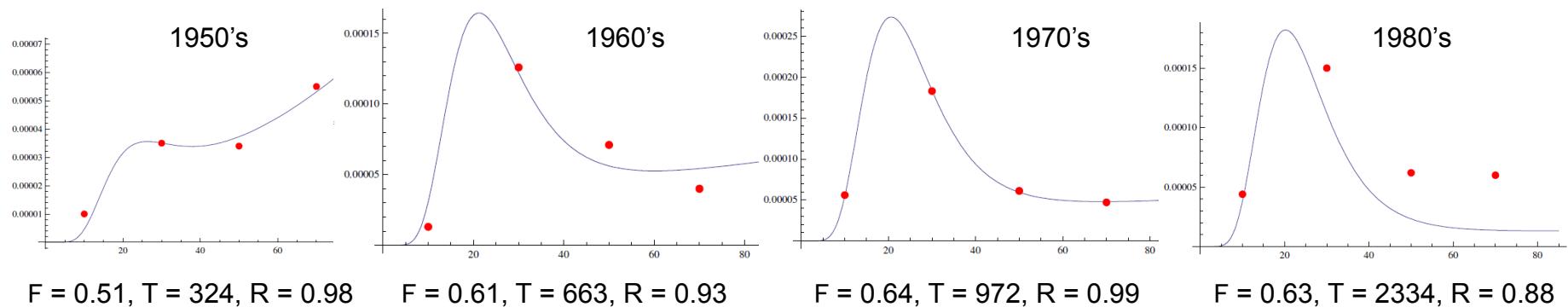
Molodecky 2012

# Crohn 1980-2008

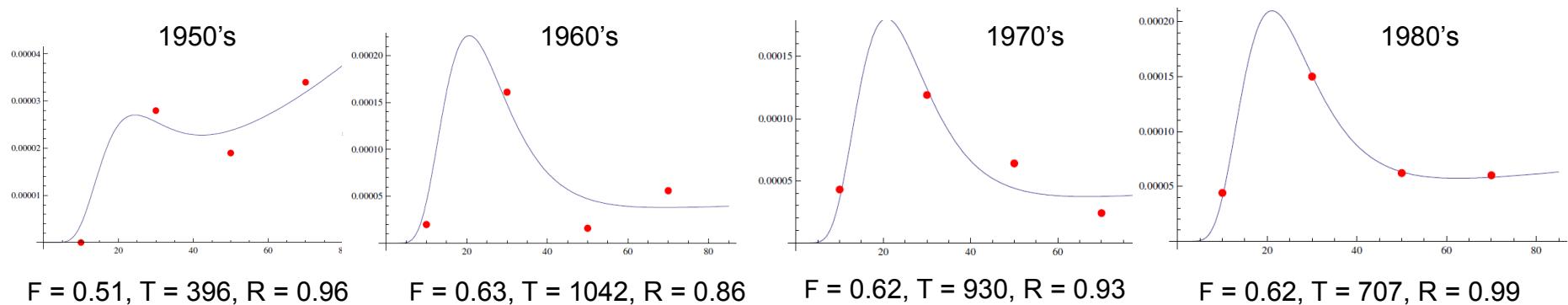


Molodecky 2012

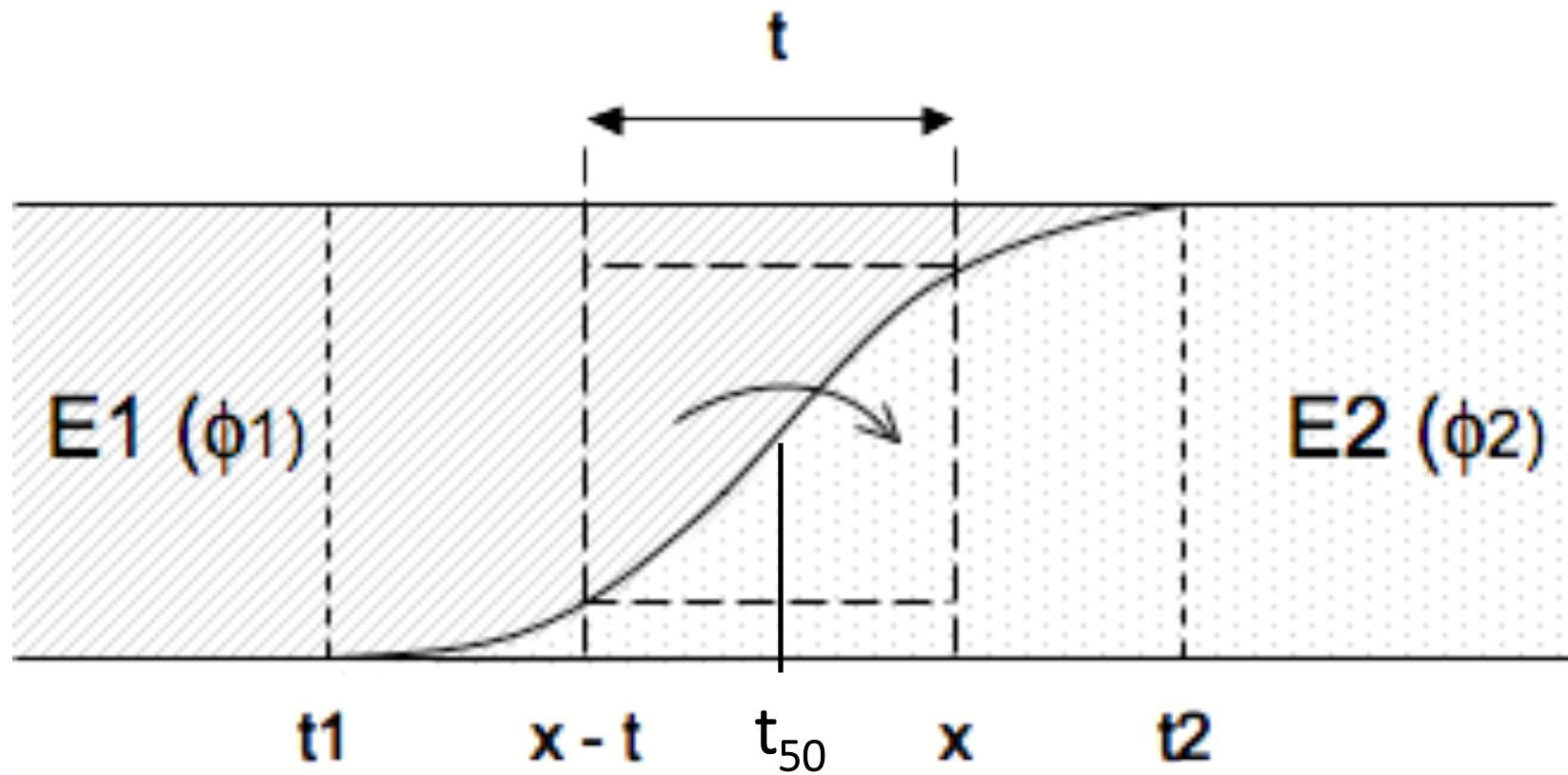
### a. Females

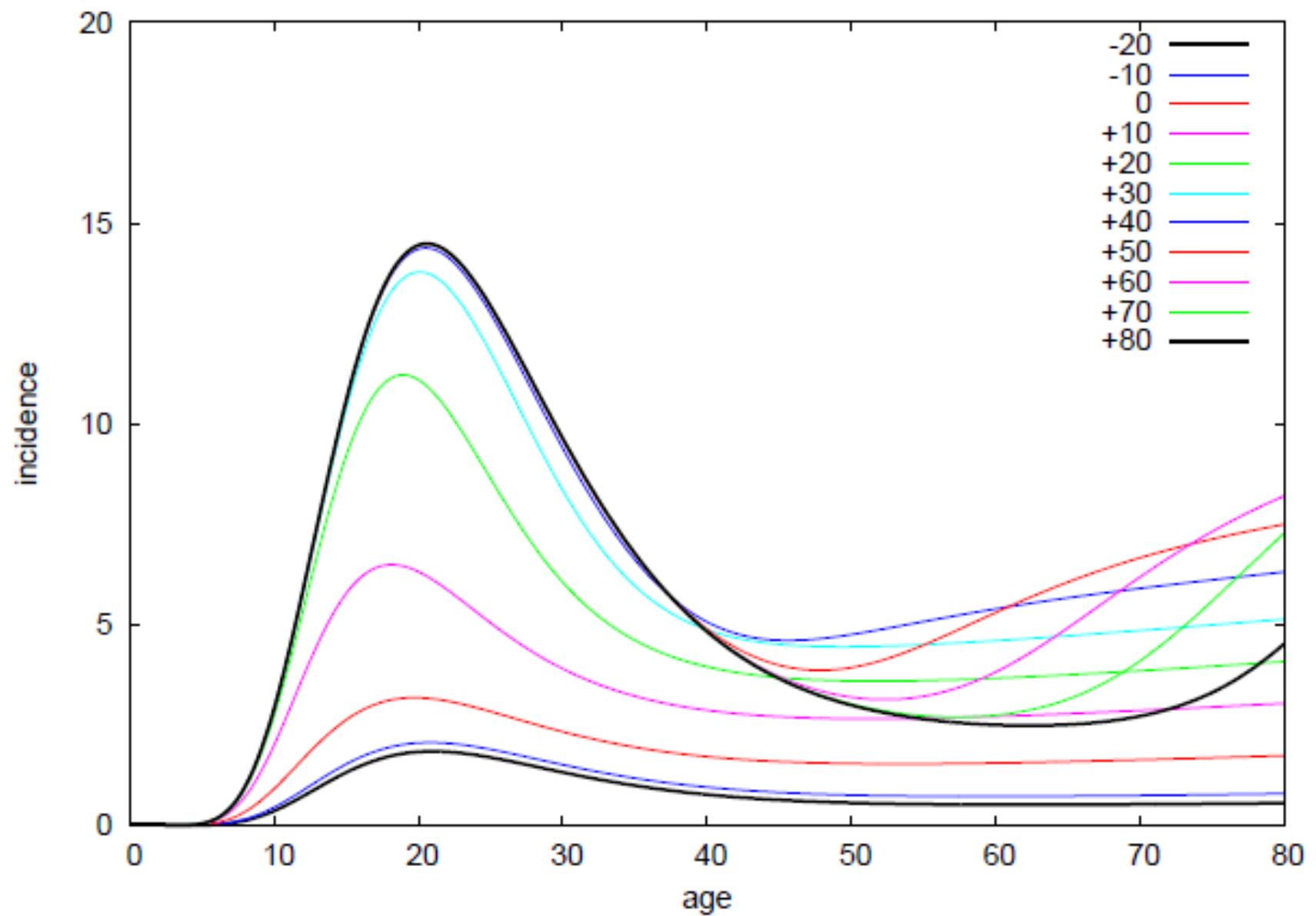


### b. Males

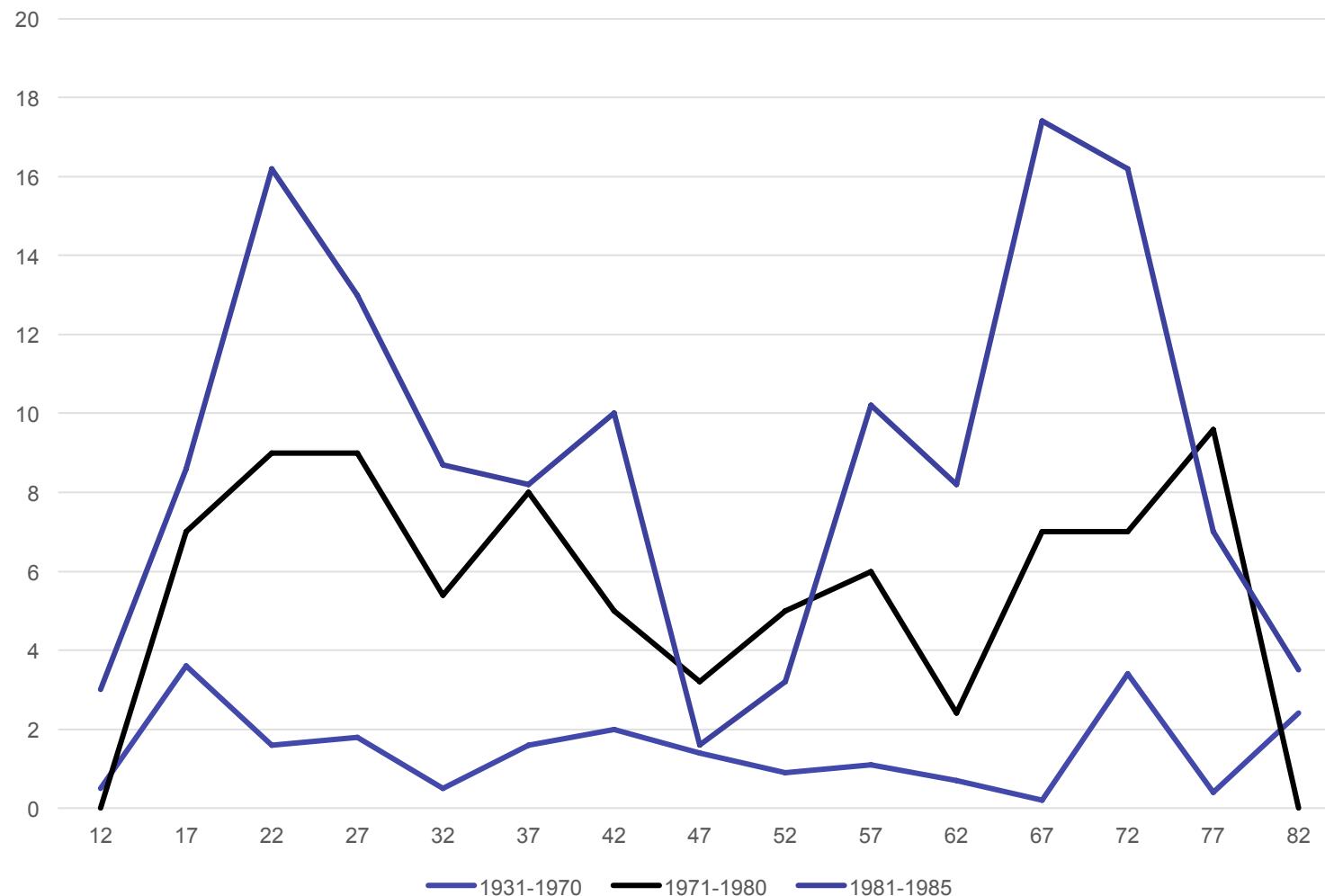


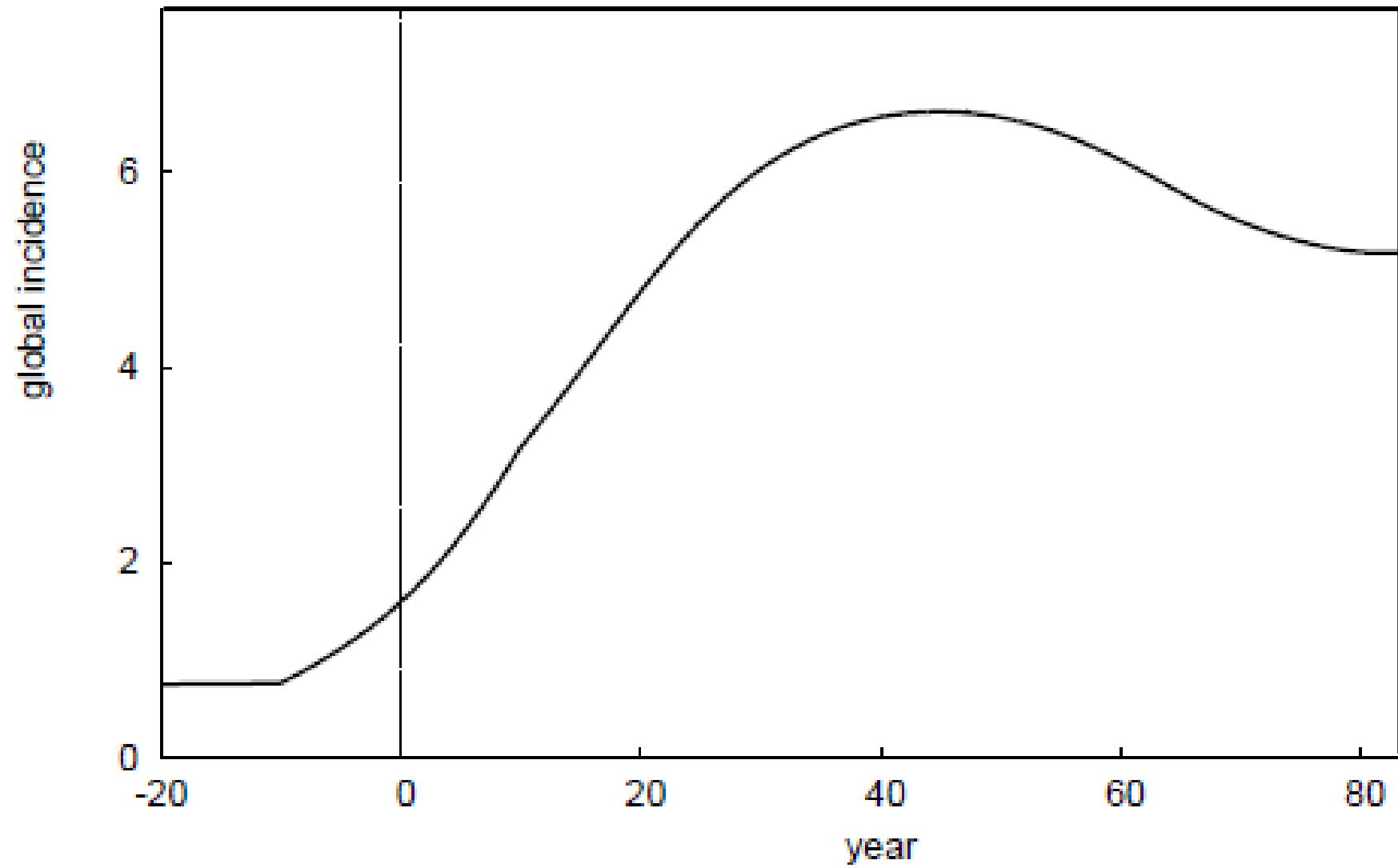
## Modeling the environmental transition





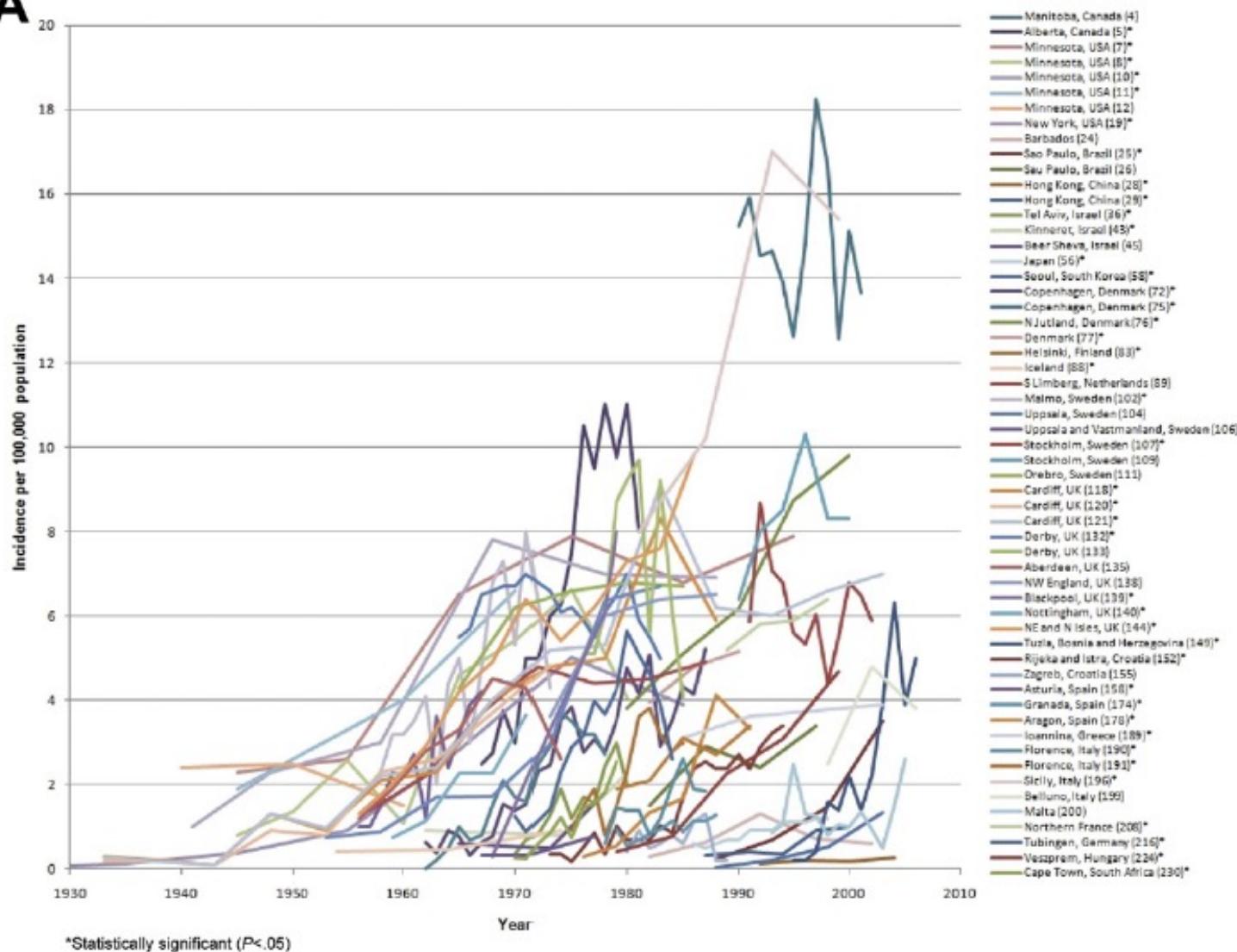
## Crohn Incidence by decade in Cardiff



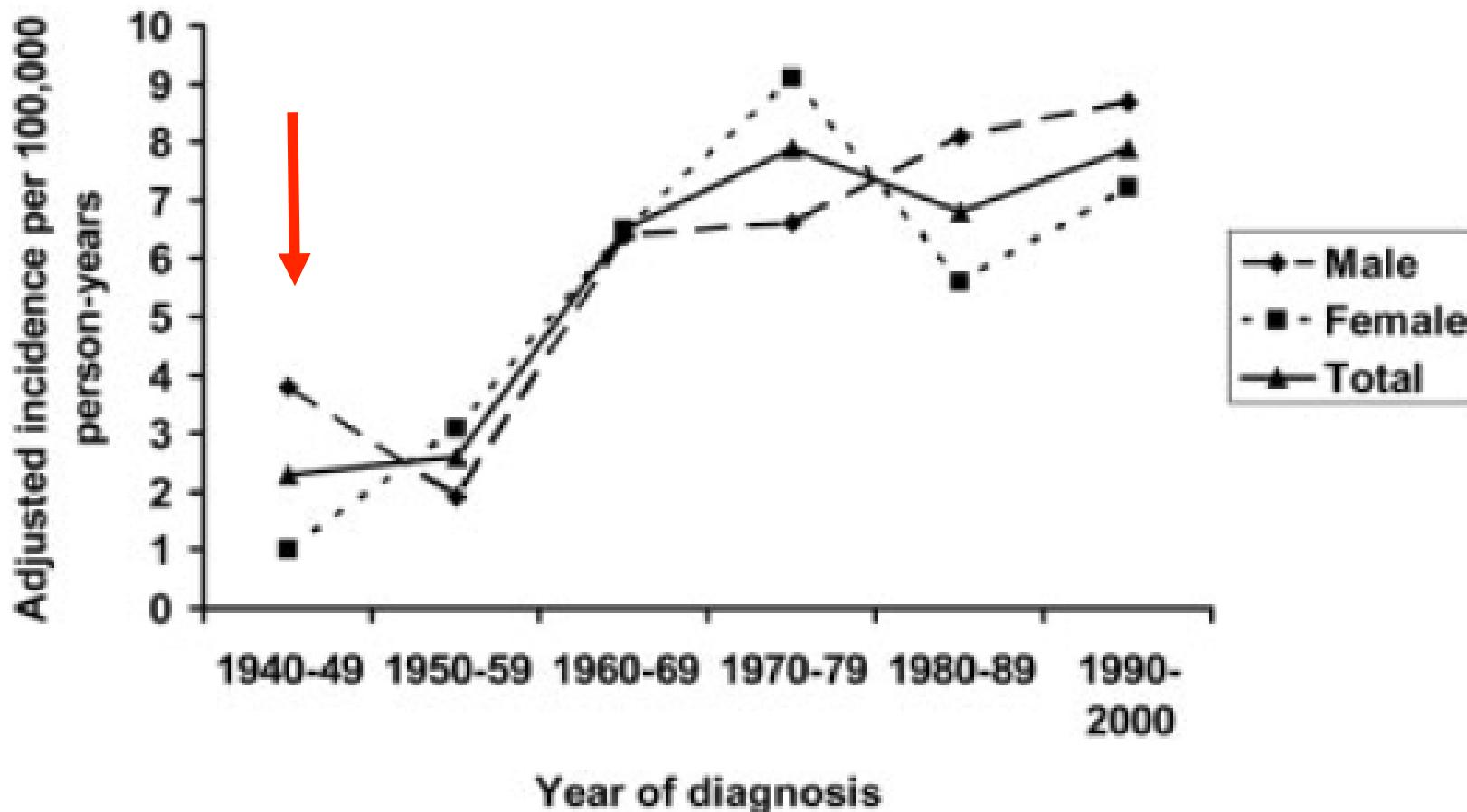


Revue des courbes d'incidence globale évolution séculaire.  
L'allure des courbes est en faveur d'une augmentation d'incidence sur une trentaine d'années le plus souvent avec un pic puis une décroissance modérée.

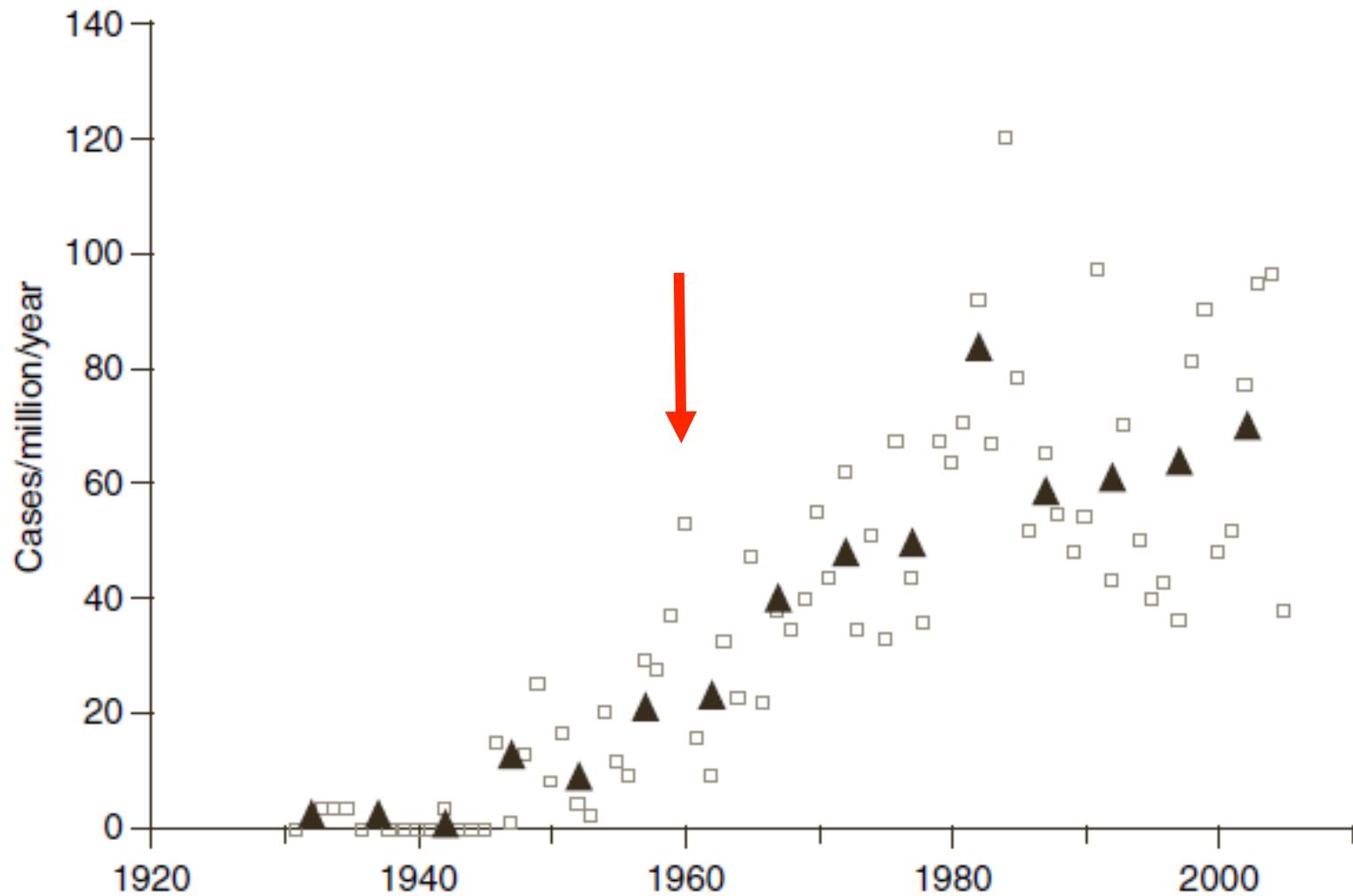
**A**



Olmsted county Minnesota.



## Crohn Disease Incidence in Cardiff



Cardiff incidence globale. Triangle: moyenne sur 5 ans.

## Hypothesis

# Crohn's disease: the cold chain hypothesis

Jean-Pierre Hugot, Corinne Alberti, Dominique Berrebi, Edouard Bingen, Jean-Pierre Cézard

Crohn's disease is the result of an abnormal immune response of the gut mucosa triggered by one or more environmental risk factors in people with predisposing gene variations, including CARD15 mutations. Epidemiological data allow assessment of familial environmental risk factors related to western lifestyle, diet, bacteria, and domestic hygiene. All findings point to refrigeration as a potential risk factor for Crohn's disease. Furthermore, cold-chain development paralleled the outbreak of Crohn's disease during the 20th century. The cold chain hypothesis suggests that psychrotrophic bacteria such as *Yersinia* spp and *Listeria* spp contribute to the disease. These bacteria have been identified in Crohn's disease lesions and we discuss their pathogenic properties with respect to our knowledge of the disease. From a molecular perspective, we postulate that the disease is a result of a defect in host recognition by pathogenic bacterial components that usually escape the immune response (eg, Yop molecules), which results in an excessive host response to these bacteria.

Lancet 2003; 362 : 2012-15.

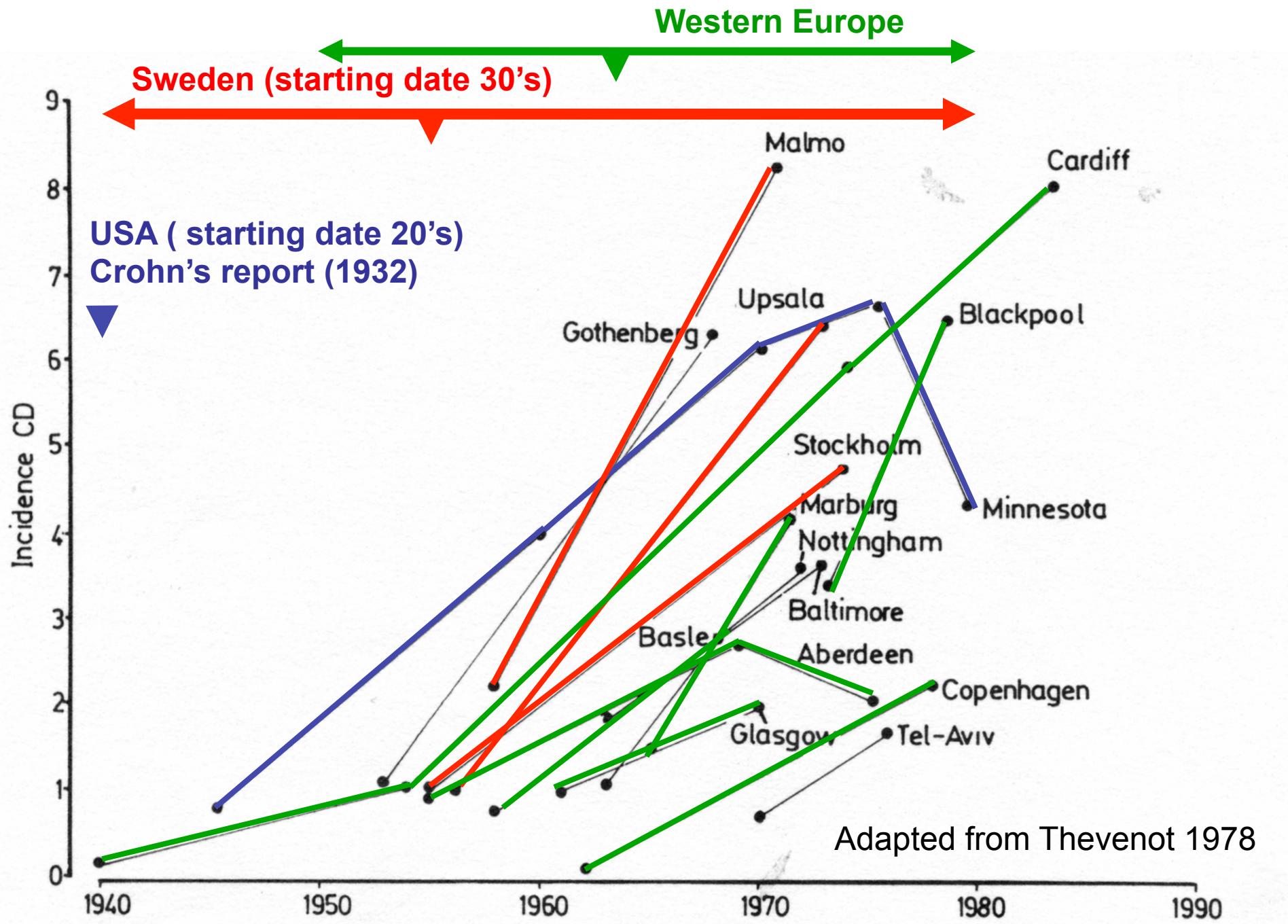
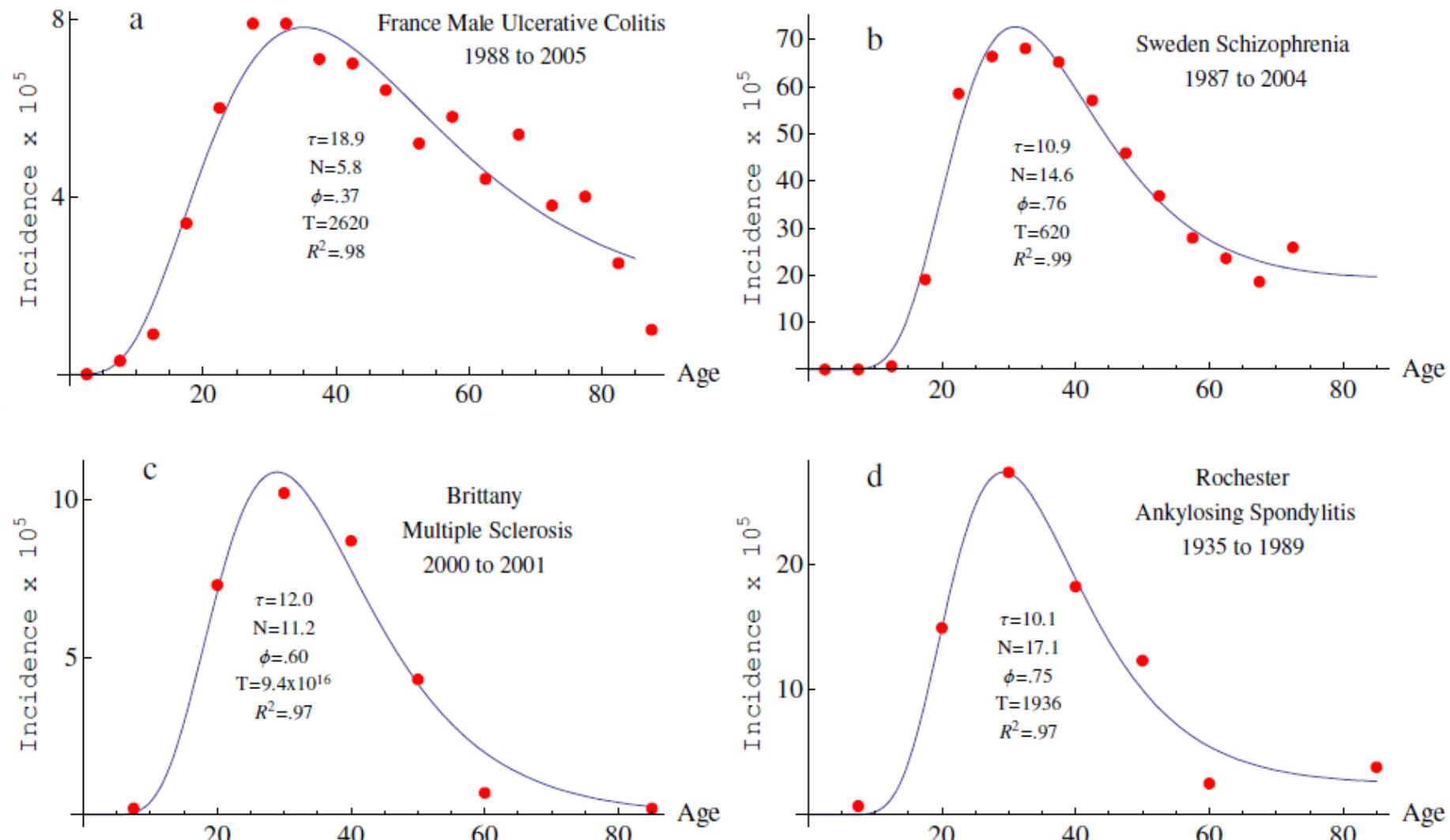
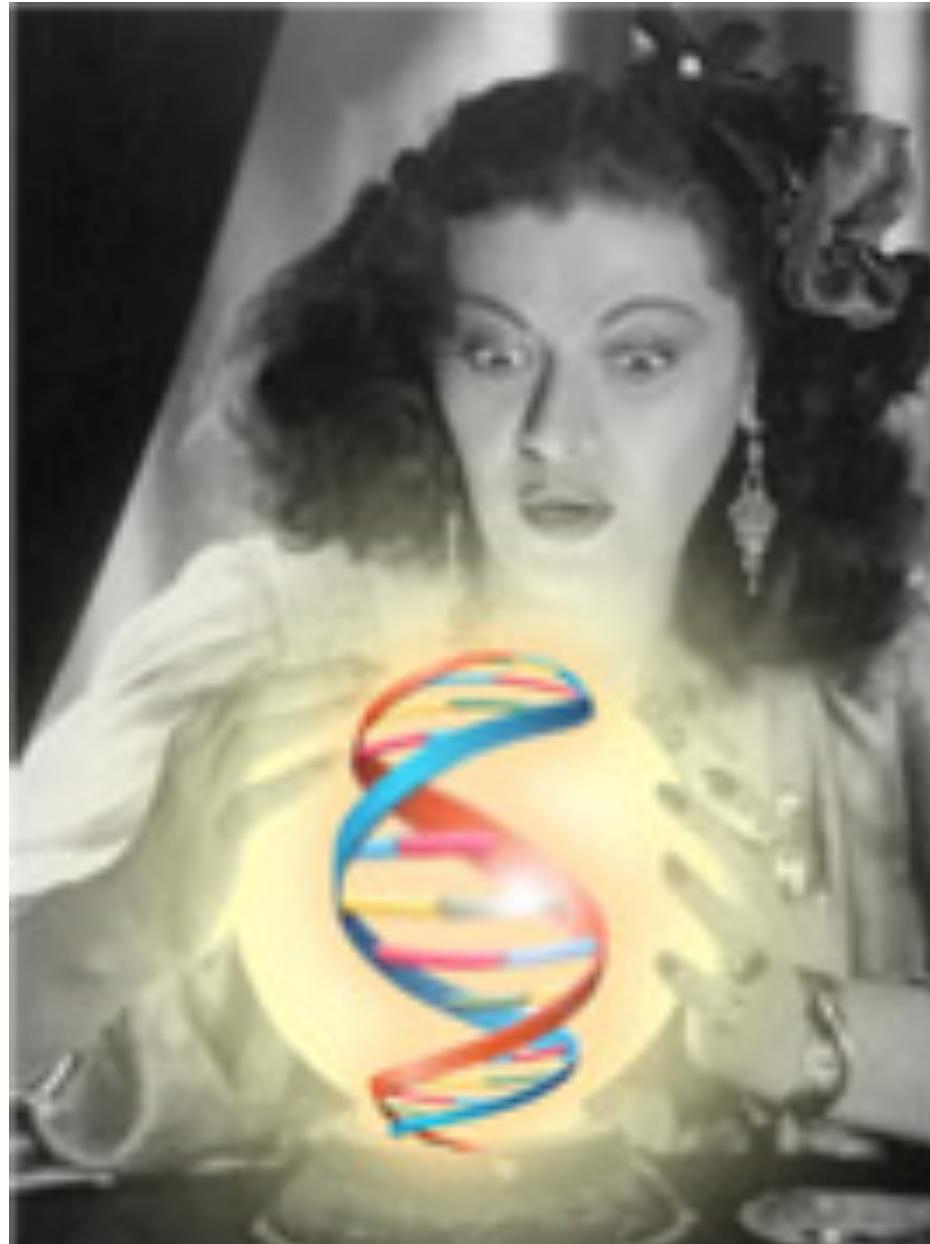
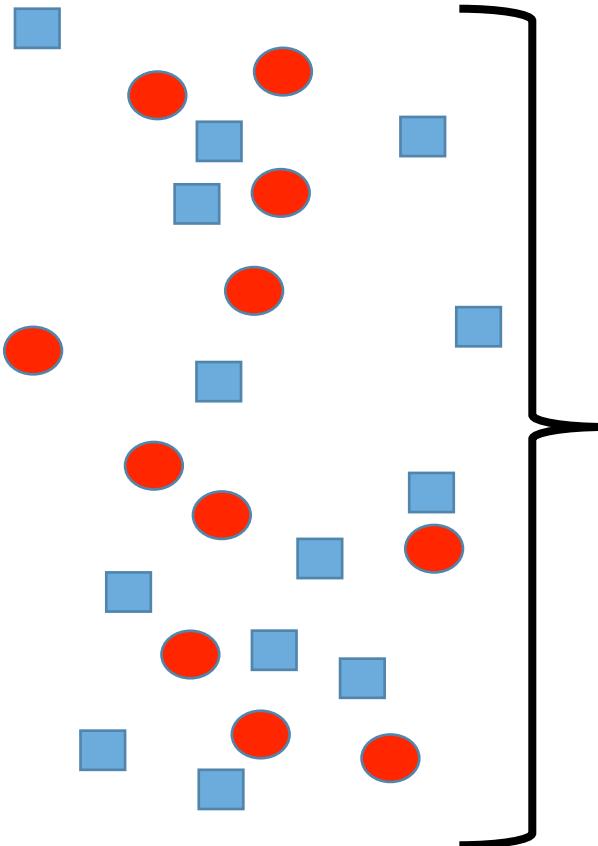


Figure 4

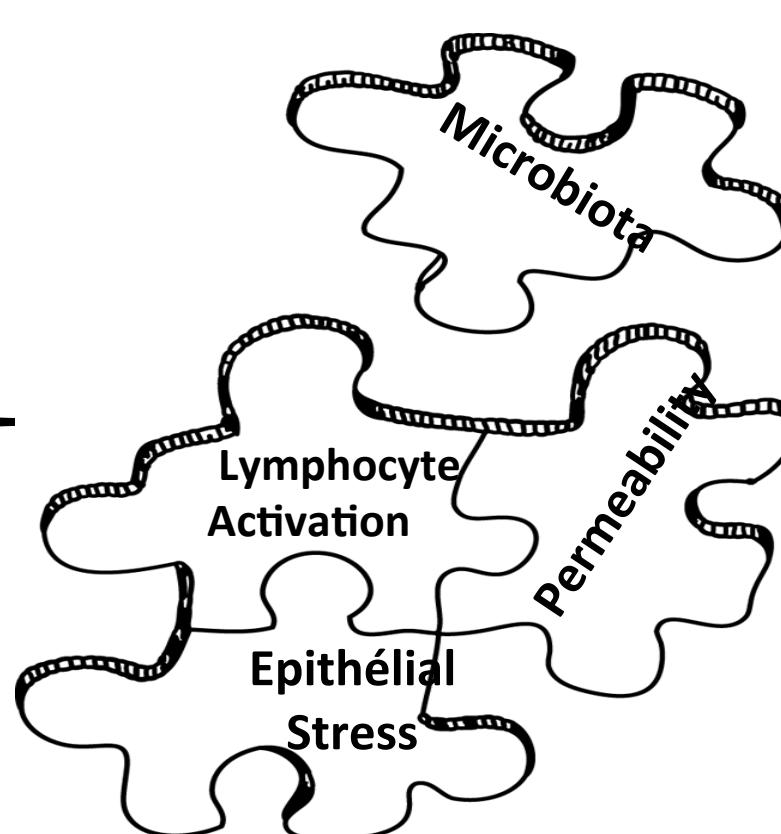




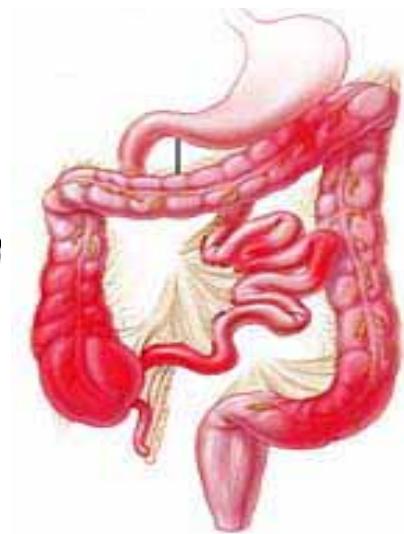
# Médecine prédictive



Multiples causes distales  
probabilistes



Quelques causes proximales  
déterministes



Maladie





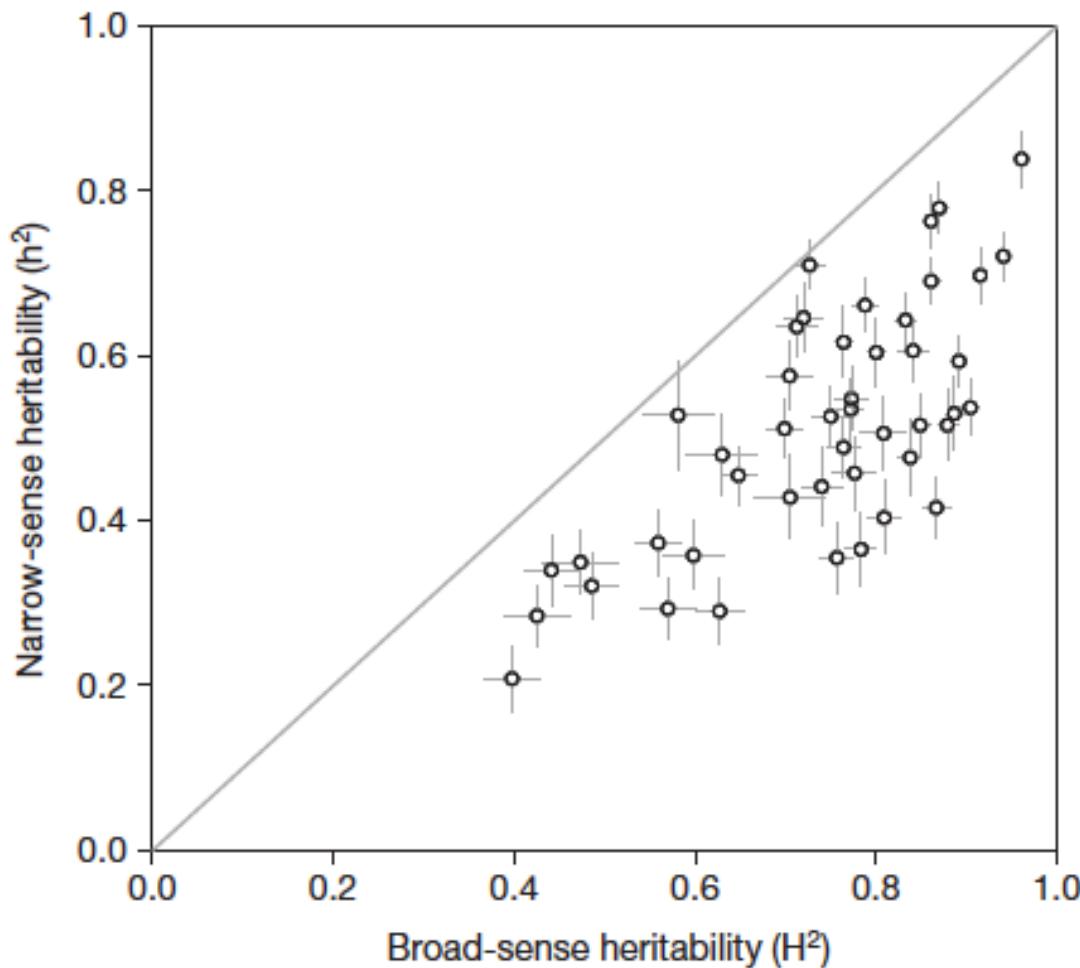


# **Genome, epigenome and RNA sequences of monozygotic twins discordant for multiple sclerosis**

Sergio E. Baranzini<sup>1</sup>, Joann Mudge<sup>2</sup>, Jennifer C. van Velkinburgh<sup>2</sup>, Pouya Khankhanian<sup>1</sup>, Irina Khrebtukova<sup>3</sup>, Neil A. Miller<sup>2</sup>, Lu Zhang<sup>3</sup>, Andrew D. Farmer<sup>2</sup>, Callum J. Bell<sup>2</sup>, Ryan W. Kim<sup>2</sup>, Gregory D. May<sup>2</sup>, Jimmy E. Woodward<sup>2</sup>, Stacy J. Caillier<sup>1</sup>, Joseph P. McElroy<sup>1</sup>, Refujia Gomez<sup>1</sup>, Marcelo J. Pando<sup>4</sup>, Leonda E. Clendenen<sup>2</sup>, Elena E. Ganusova<sup>2</sup>, Faye D. Schilkey<sup>2</sup>, Thiruvarangan Ramaraj<sup>2</sup>, Omar A. Khan<sup>5</sup>, Jim J. Huntley<sup>3</sup>, Shujun Luo<sup>3</sup>, Pui-yan Kwok<sup>6,7</sup>, Thomas D. Wu<sup>8</sup>, Gary P. Schroth<sup>3</sup>, Jorge R. Oksenberg<sup>1,7</sup>, Stephen L. Hauser<sup>1,7</sup> & Stephen F. Kingsmore<sup>2</sup>

« In the first systematic effort to estimate sequence variation among monozygotic cotwins, we did not find evidence for genetic, epigenetic or transcriptome differences that explained disease discordance. »

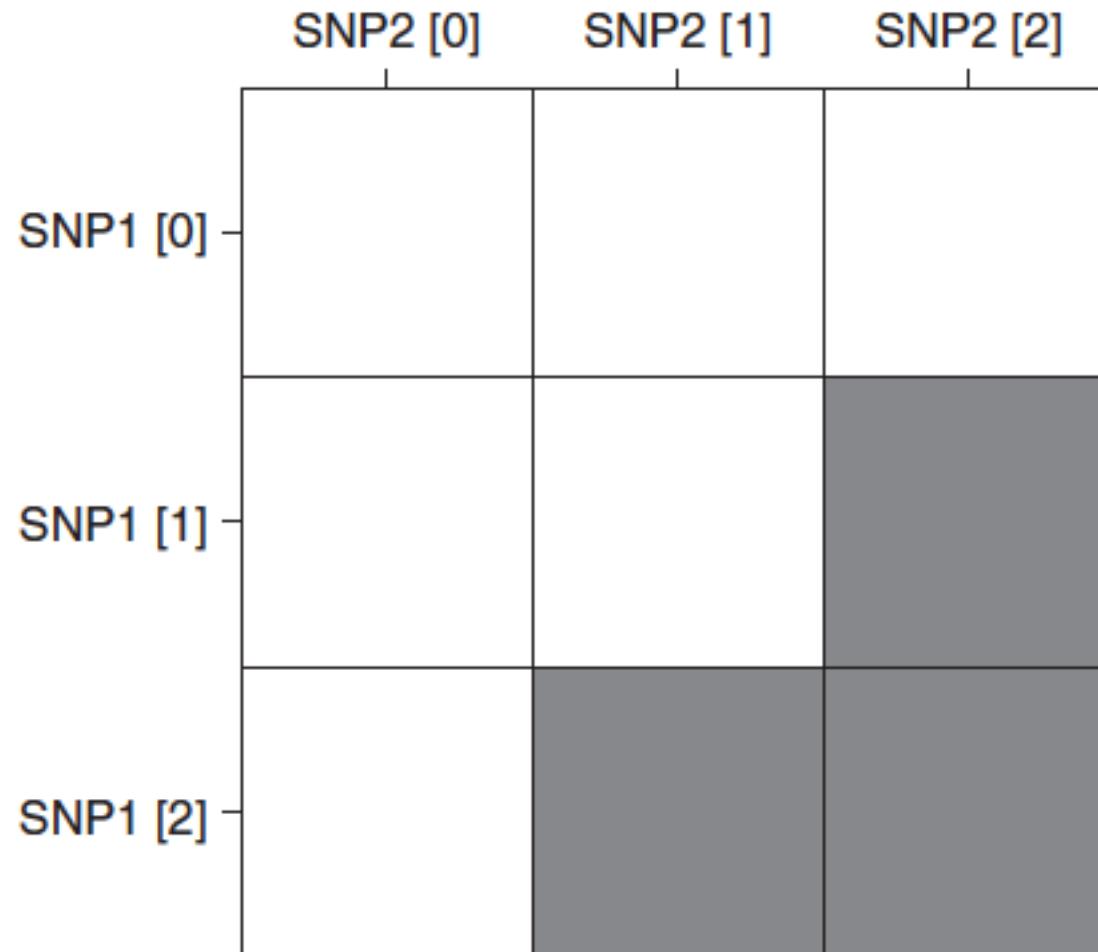
Epistasie chez la levure : 0 à 0.5 (moyenne 0.3) de l'héritabilité est due à l'épistasie



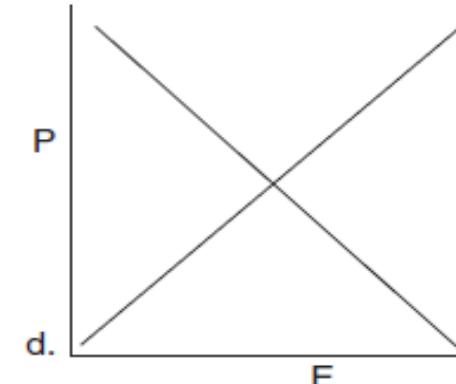
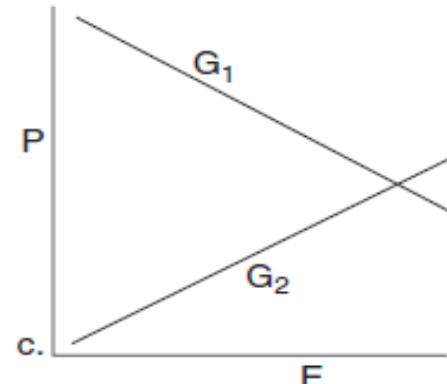
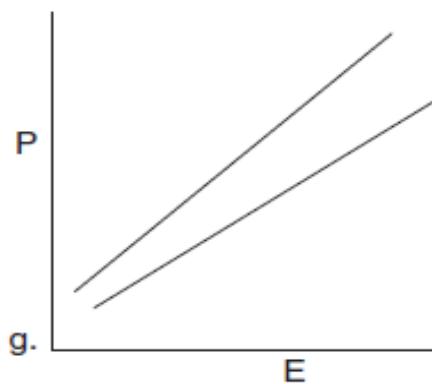
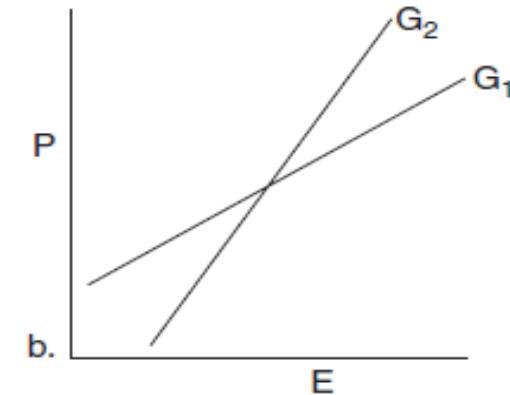
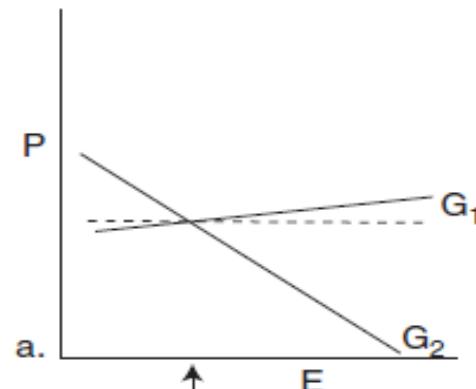
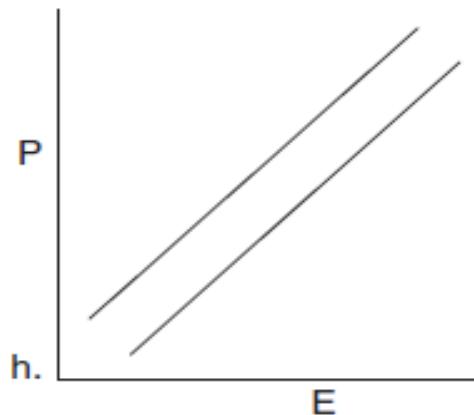
**Figure 1 | Heritability for 46 yeast traits.** The narrow-sense heritability ( $h^2$ ) for each trait is plotted against the broad-sense heritability ( $H^2$ ). Error bars show  $\pm$  s.e. in heritability estimates. The diagonal line represents  $h^2 = H^2$  and is shown as a visual guide.

Bloom 2013

# Régression logistique



## Gene-environment interaction: the reaction norme

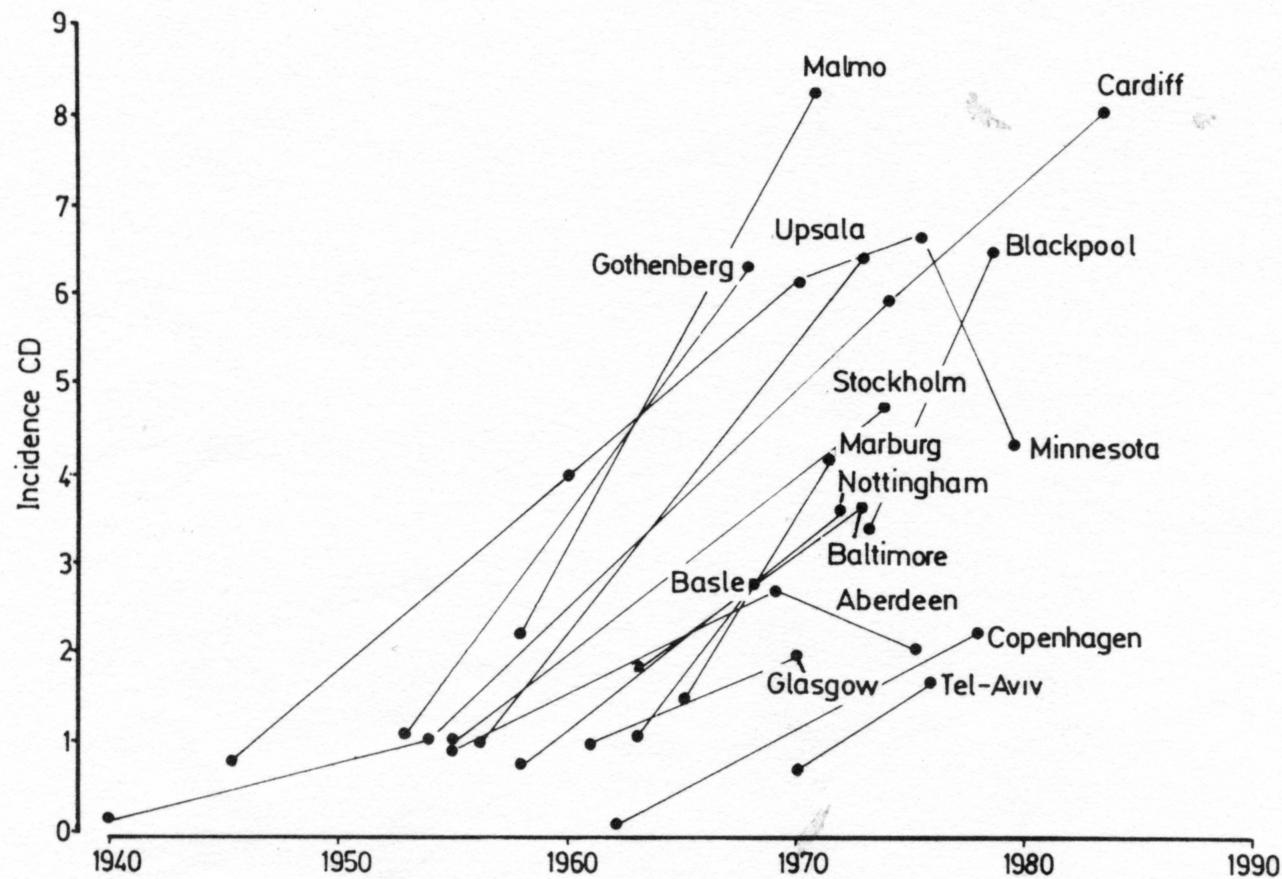


Lewontin 1974

# Génétique des maladies

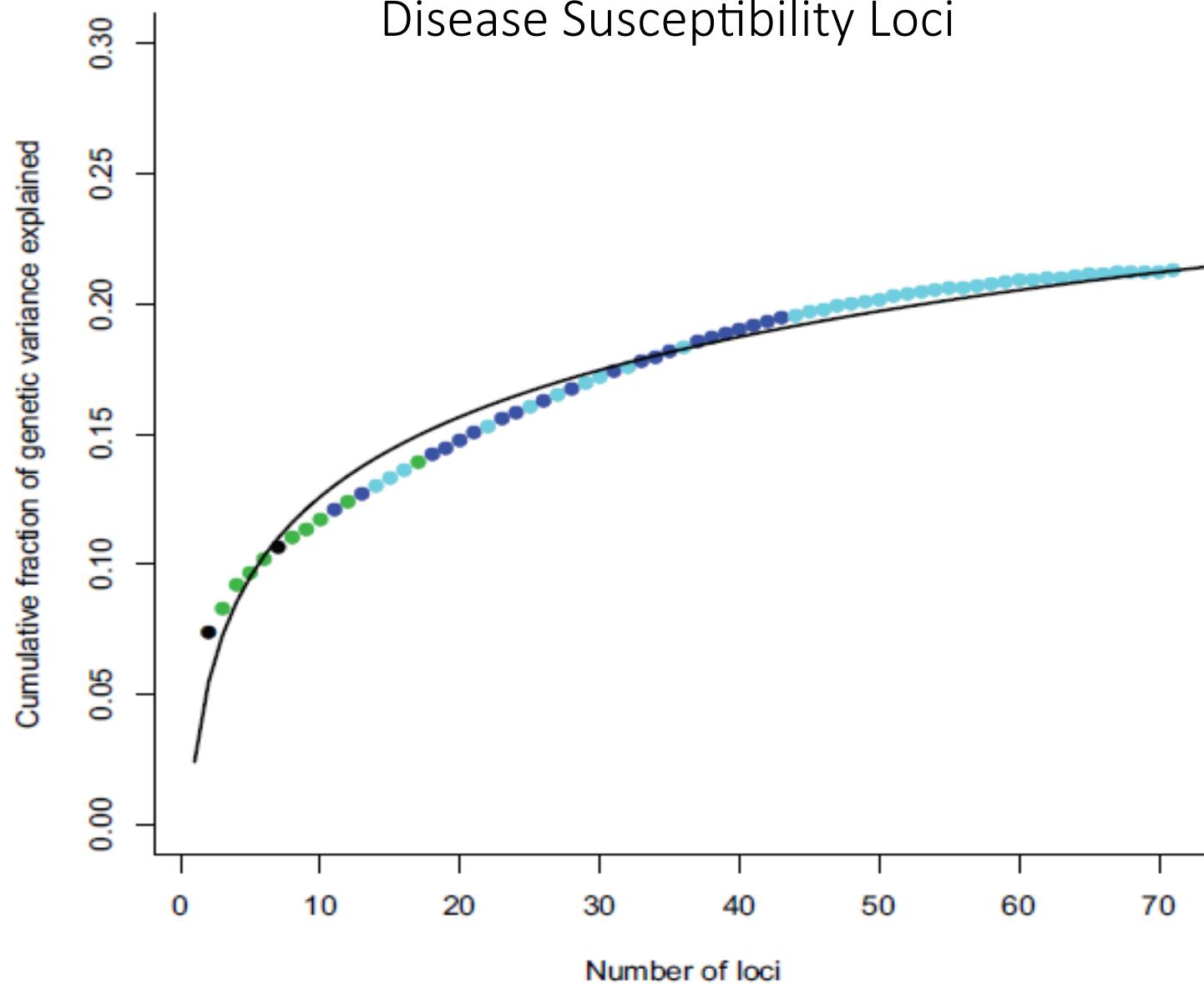
	Monogénique	Complexé
Maladie	Rare	Fréquente
Environnement	Non	Oui
Nb de gènes	1	Beaucoup
Variants	rares	Toutes fréquences
Effet sur la protéine	Structure	Quantité
Risque associé	infini	<2
Caractère explicatif	fort	faible

# Le risque de la modernité



From Rose JDR et al. Gut 1988

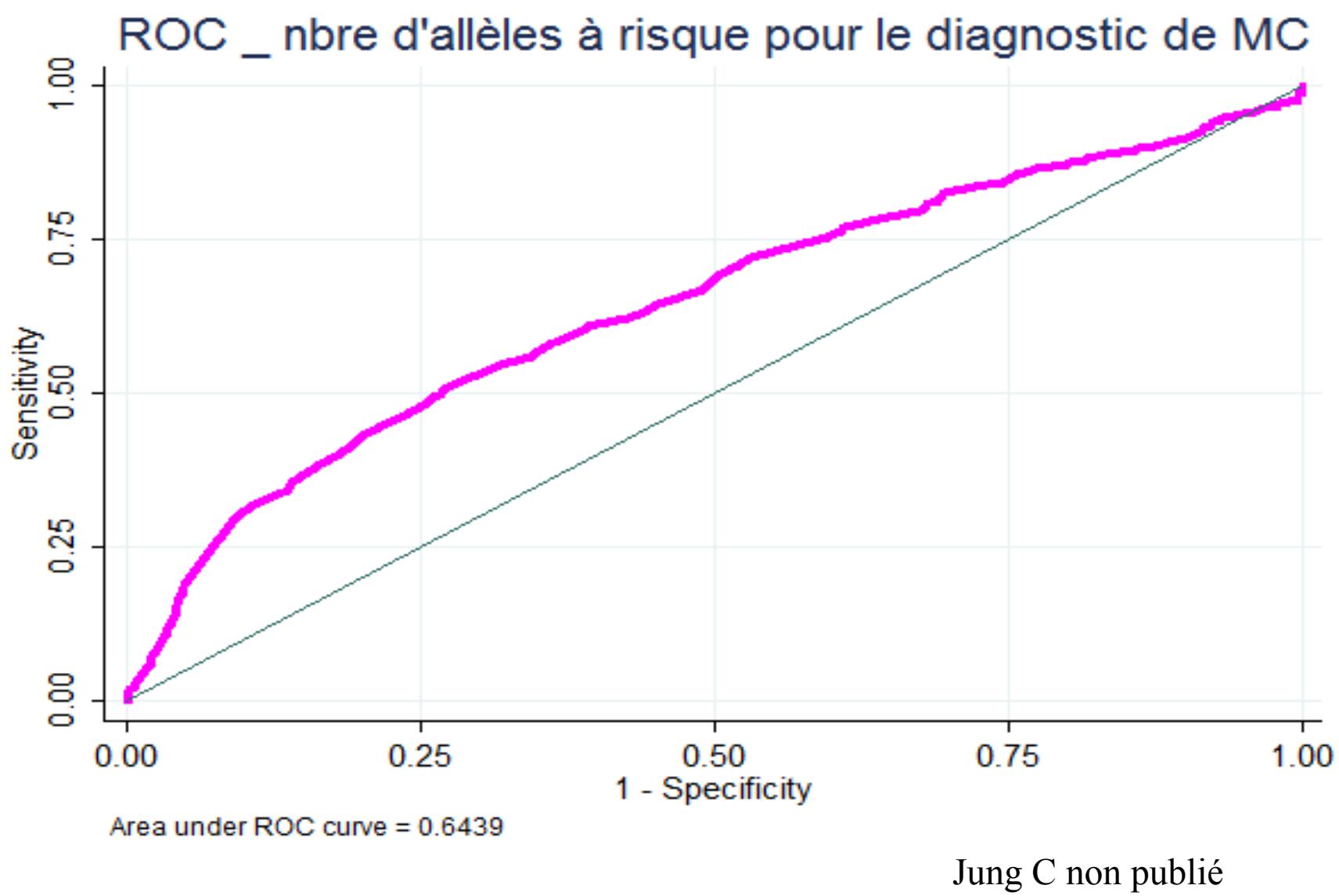
# Meta-Analysis Increases to 71 the Tally of Confirmed Crohn's Disease Susceptibility Loci



Franke et al. Nature Genet 2010

# Où est l'héritabilité manquante?

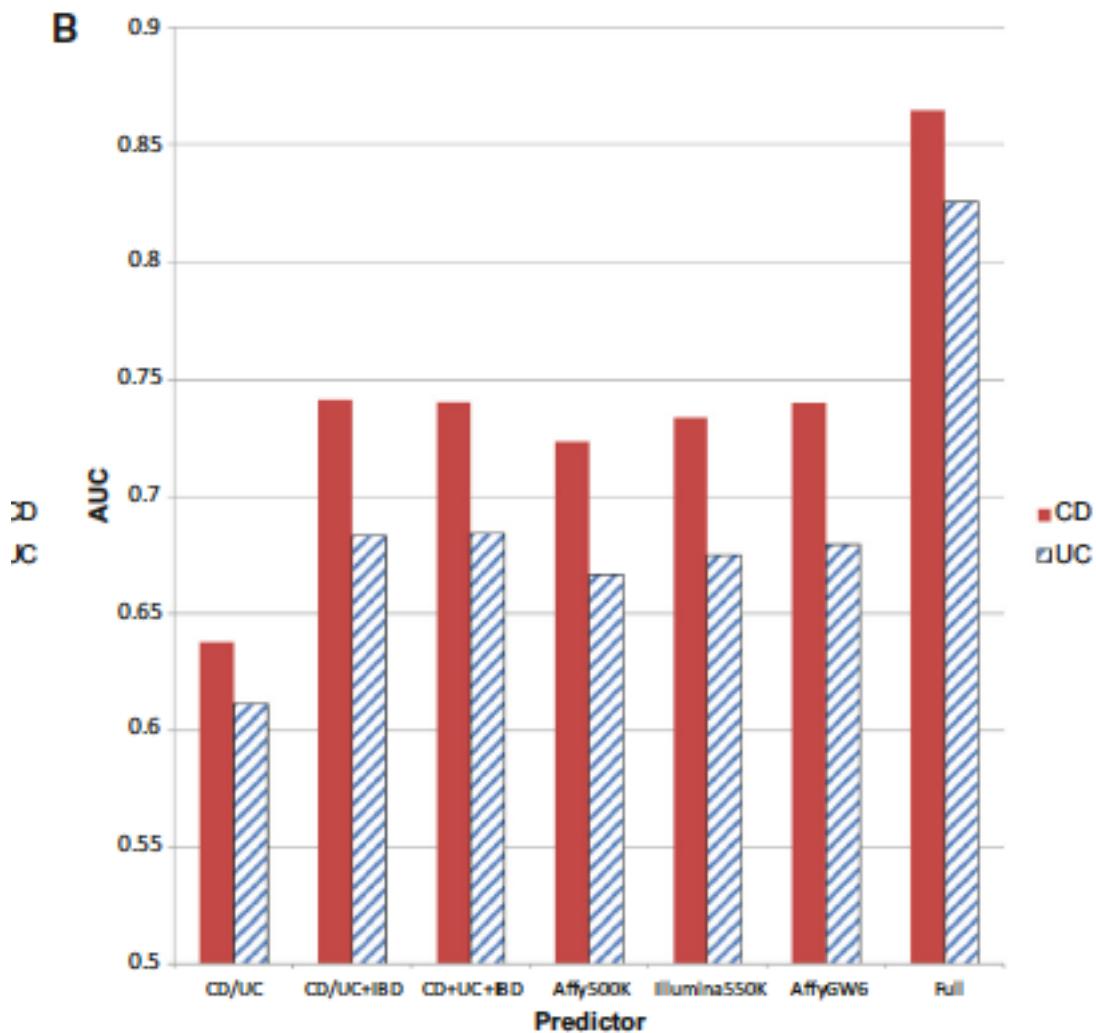
- Dans des variants non testés ?
- Dans tous les gènes du génome ?
- Dans des interactions gène/gène ou gène/environnement ?
- Dans une erreur de calcul de l'héritabilité ?



**Table 5** Interaction analysis for *NOD2*, IBD5, *DLG5*, *IL23R* and *ATG16L1*

Interaction	p Value	OR (95% CI)
<b>Two-way interaction</b>		
IBD5 × <i>DLG5</i>	0.67	0.86 (0.43 to 1.71)
IBD5 × <i>ATG16L1</i>	0.58	1.15 (0.70 to 1.88)
IBD5 × <i>NOD2</i>	<b>0.02</b>	0.53 (0.31 to 0.92)
IBD5 × <i>IL23R</i>	0.34	0.68 (0.31 to 1.51)
<i>DLG5</i> × <i>ATG16L1</i>	0.77	0.88 (0.36 to 2.15)
<i>DLG5</i> × <i>NOD2</i>	<b>0.01</b>	3.02 (1.29 to 7.08)
<i>DLG5</i> × <i>IL23R</i>	0.09	2.71 (0.85 to 8.62)
<i>ATG16L1</i> × <i>NOD2</i>	0.06	0.51 (0.26 to 1.03)
<i>ATG16L1</i> × <i>IL23R</i>	0.74	0.85 (0.32 to 2.25)
<i>NOD2</i> × <i>IL23R</i>	0.77	1.15 (0.45 to 2.89)
<b>Three-way interaction</b>		
IBD5 × <i>DLG5</i> × <i>ATG16L1</i>	0.72	1.08 (0.71 to 1.63)
IBD5 × <i>DLG5</i> × <i>NOD2</i>	0.17	0.70 (0.42 to 1.17)
IBD5 × <i>DLG5</i> × <i>IL23R</i>	0.84	0.95 (0.56 to 1.60)
IBD5 × <i>ATG16L1</i> × <i>NOD2</i>	0.46	0.59 (0.35 to 0.99)
IBD5 × <i>NOD2</i> × <i>IL23R</i>	<b>0.02</b>	0.54 (0.32 to 0.92)
IBD5 × <i>ATG16L1</i> × <i>IL23R</i>	0.69	0.92 (0.59 to 1.41)
<i>DLG5</i> × <i>ATG16L1</i> × <i>NOD2</i>	0.62	0.86 (0.48 to 1.55)
<i>DLG5</i> × <i>ATG16L1</i> × <i>IL23R</i>	0.72	1.12 (0.60 to 2.10)
<i>ATG16L1</i> × <i>NOD2</i> × <i>IL23R</i>	0.22	0.69 (0.38 to 1.25)
<b>Four-way interaction</b>		
IBD5 × <i>DLG5</i> × <i>ATG16L1</i> × <i>NOD2</i>	0.16	0.69 (0.41 to 1.15)
IBD5 × <i>DLG5</i> × <i>ATG16L1</i> × <i>IL23R</i>	0.83	1.04 (0.71 to 1.53)
IBD5 × <i>DLG5</i> × <i>NOD2</i> × <i>IL23R</i>	0.22	0.73 (0.44 to 1.21)
IBD5 × <i>ATG16L1</i> × <i>NOD2</i> × <i>IL23R</i>	0.59	0.61 (0.36 to 1.02)
<i>DLG5</i> × <i>ATG16L1</i> × <i>NOD2</i> × <i>IL23R</i>	0.82	0.94 (0.54 to 1.62)
<b>Five-way interaction</b>		
IBD5 × <i>DLG5</i> × <i>ATG16L1</i> × <i>NOD2</i> × <i>IL23R</i>	0.74	0.74 (0.44 to 1.23)

Weersma 2009

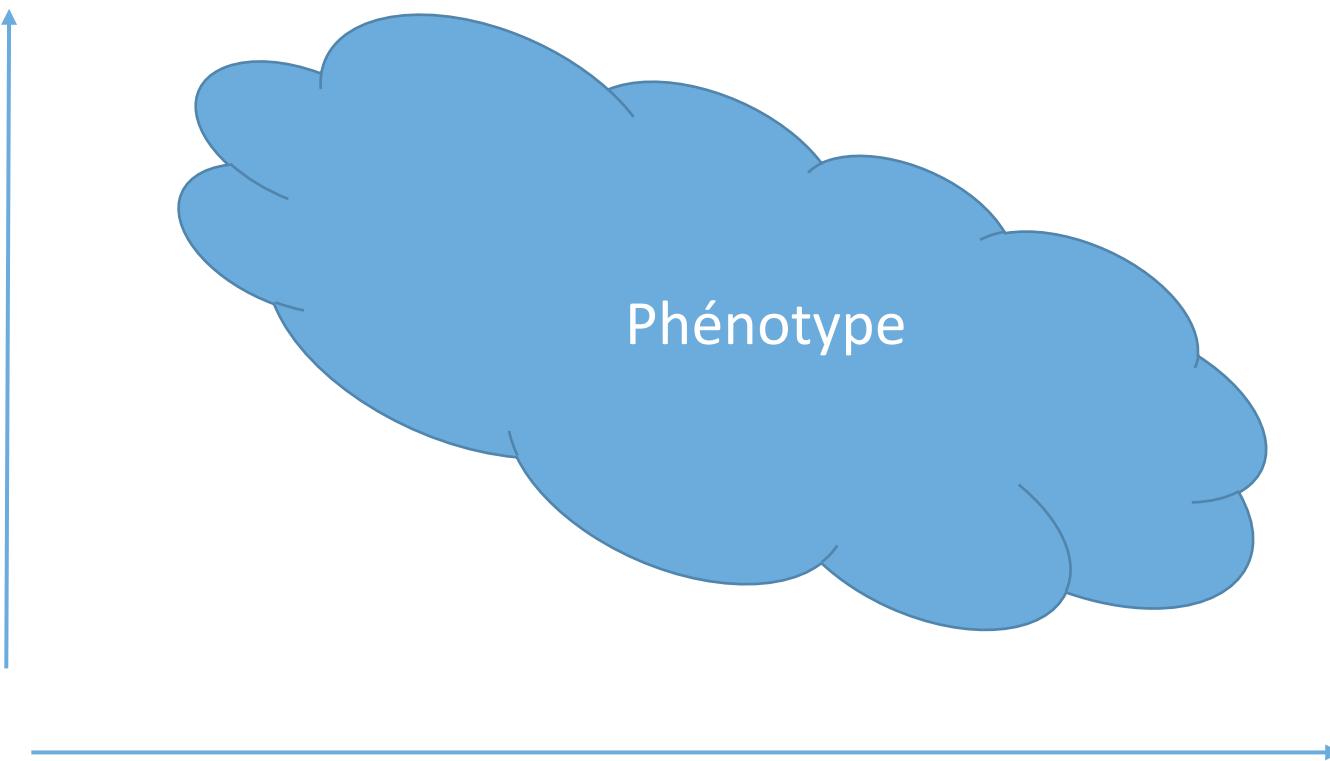


Wei 2013

Wei 2013

(B) UC/CD: AUCs were achieved by using only the 30 CD-specific loci or the 23 UC-specific loci; UC/CD + IBD: AUCs were achieved by using the UC or CD loci plus the 110 IBD loci; UC + CD + IBD: AUCs were achieved by using all the 163 IBD loci; Affy500K: AUCs were achieved by using the 1,201/724 CD/UC Immunochip SNPs that are also typed on the Affymetrix 500K chip; Illumina550K: AUCs were achieved by using 1,728/1,142 CD/UC Immunochip SNPs that are also typed on the Illumina 550K chip; AffyGW6: AUCs were achieved by using 1,933/1,204 CD/UC Immunochip SNPs that are also typed on Affymetrix Genome-Wide SNP Array 6.0 chip; full: AUCs were achieved by using all Immunochip SNPs.

Génétique



Environnement