



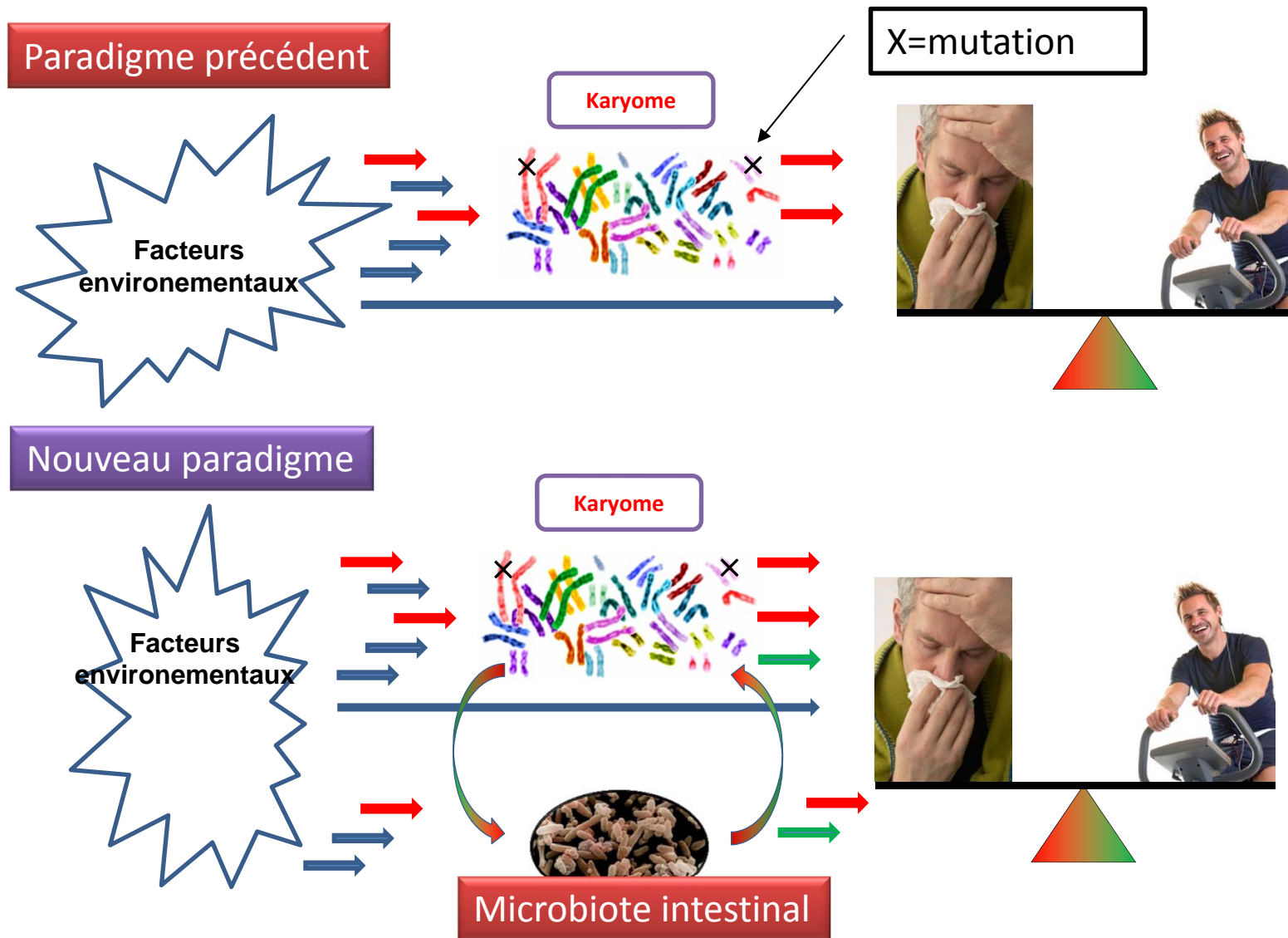
Microbiote intestinal et santé humaine : Accent sur les maladies métaboliques

Pr. Karine Clément, MD, PhD
Institute of Cardiometabolism and Nutrition (ICAN)
Pitié-Salpêtrière Hospital,
INSERM, Université Pierre et Marie-Curie
Paris

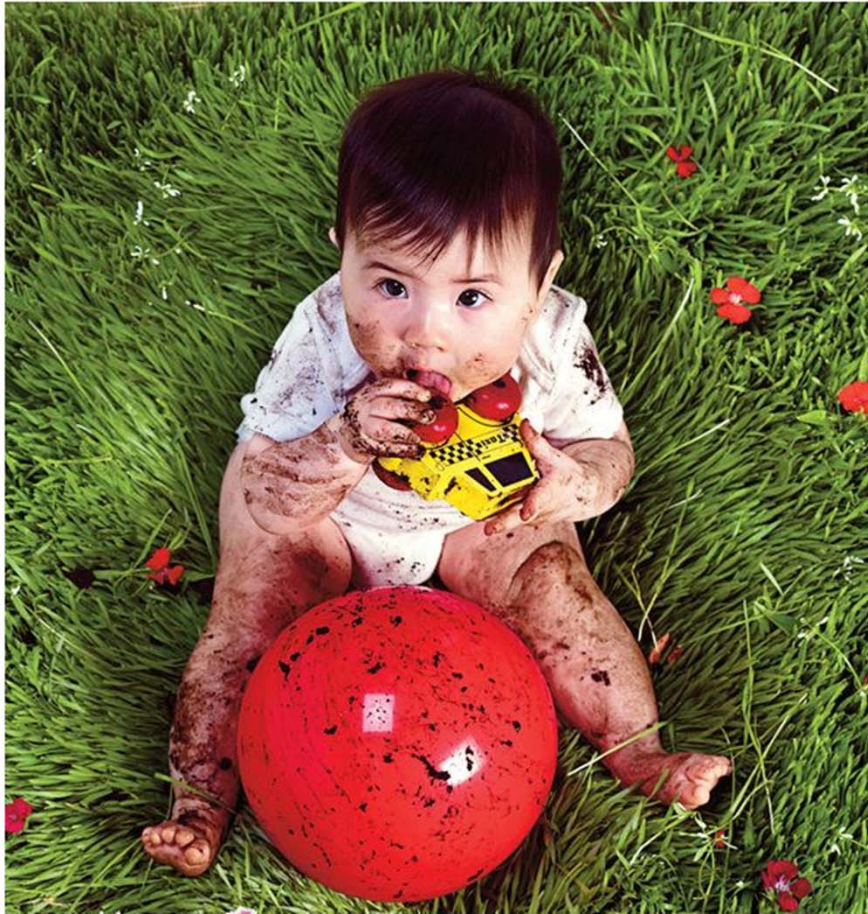
Karine.clement@psl.aphp.fr



November 2013

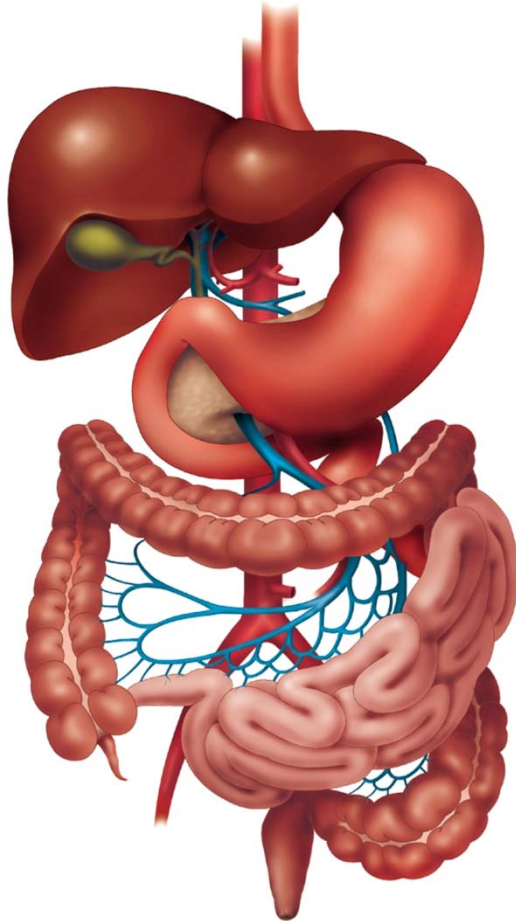


Some of My Best Friends Are Germs



By MICHAEL POLLAN
Published: May 15, 2013





Le microbiote : un atout

- Défense – antagonisme bactérien
- Initiation de l'immunité mucoale
- Péristasis
- Métabolisme des carcinogènes alimentaires
- Synthèses des vitamines (B et K)
- Nutriments épithéliales (*e.g.* SCFAs)
- Conversion des promédicaments
- Utilisation des « indigestibles » ($(CH_2O)_n$)

Le microbiote : un problème

- Procarcinogènes → carcinogènes
- Opportunisme - Translocation
- Ingrédient essentiel pour l'IBD
- Impliqué dans l'obésité, le syndrome métabolique et le cancer colorectal

Fibromyalgie



IBD



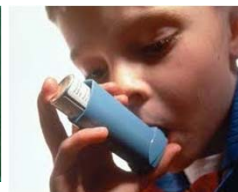
Cancer du colon



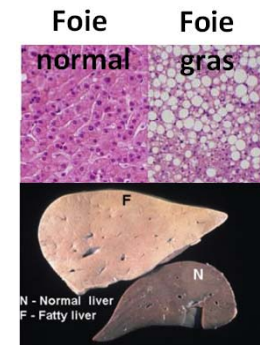
L'idée sous-tendant l'intégration du microbiote intestinale dans la biologie de l'hôte est de comprendre comment il maintient la bonne santé et initie ou maintient certaines maladies



Maladie atopique



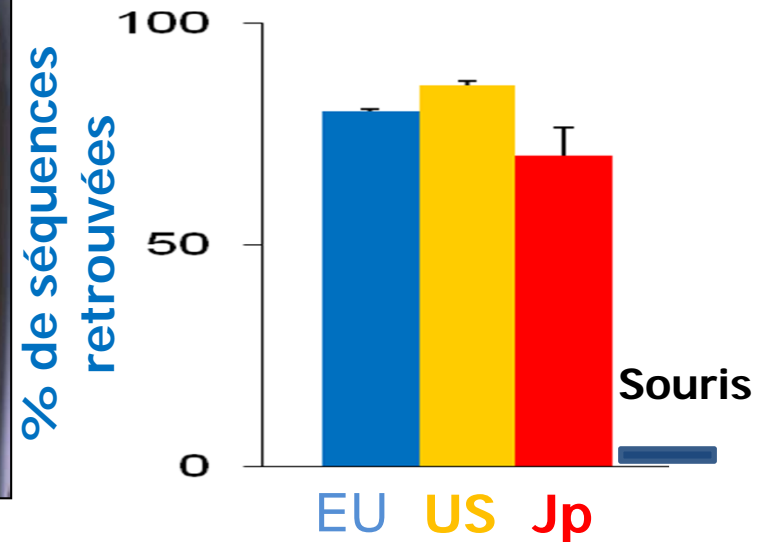
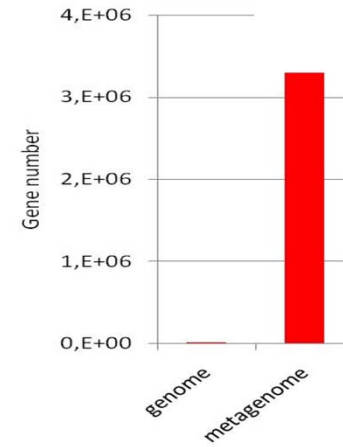
Calculs rénaux



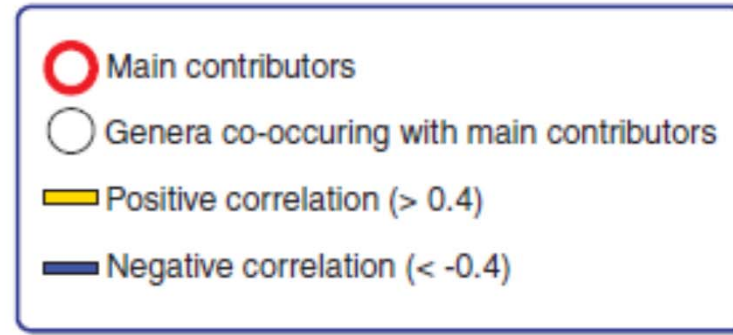
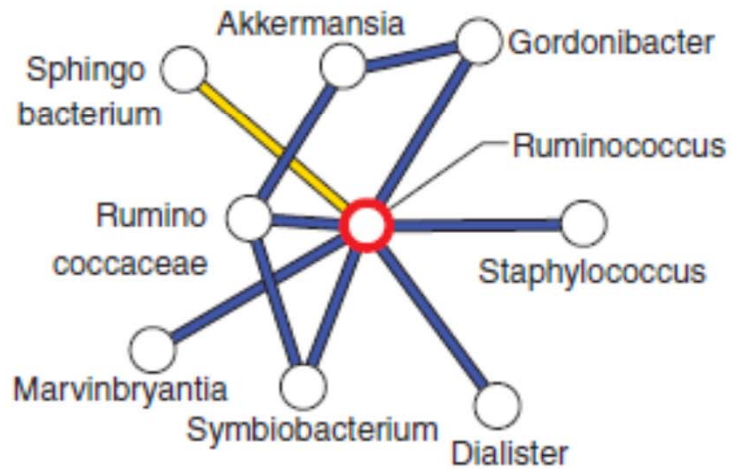
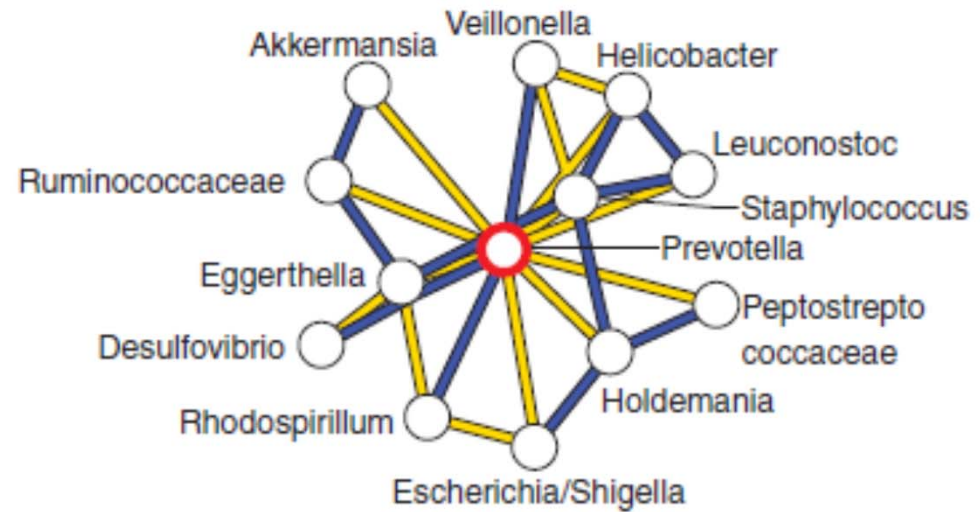
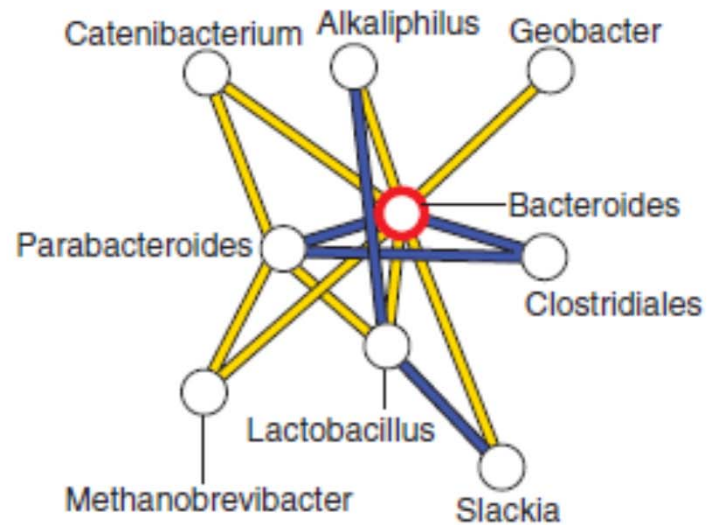
NASH

3.3 millions de gènes bactériens : 150 fois le génome humain

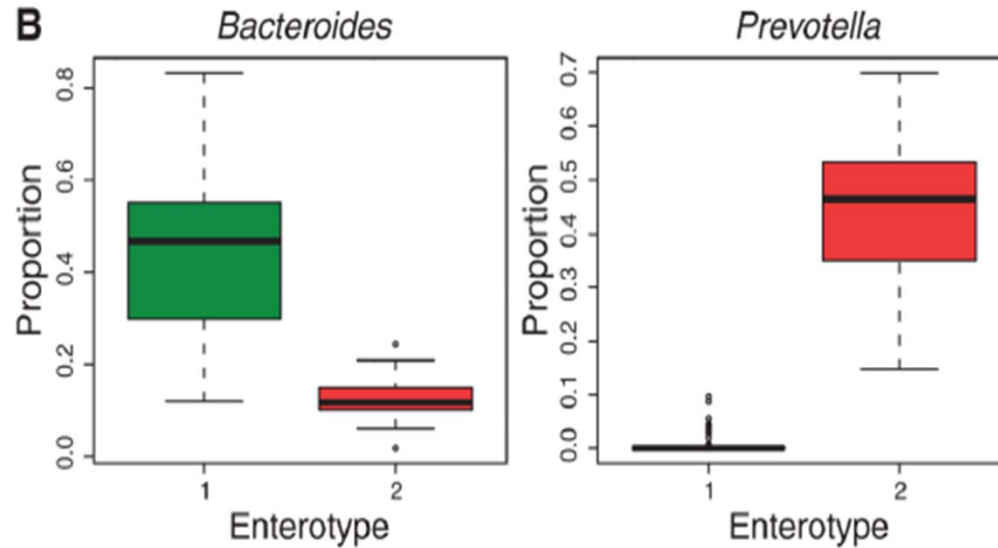
85% des gènes abondant d'une cohorte de 124 européens
représentent bien des individus américains et japonais



Merci à Dusko Ehrlich

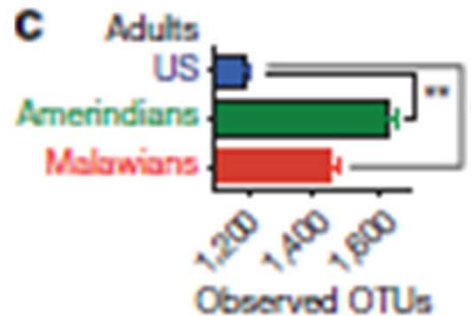
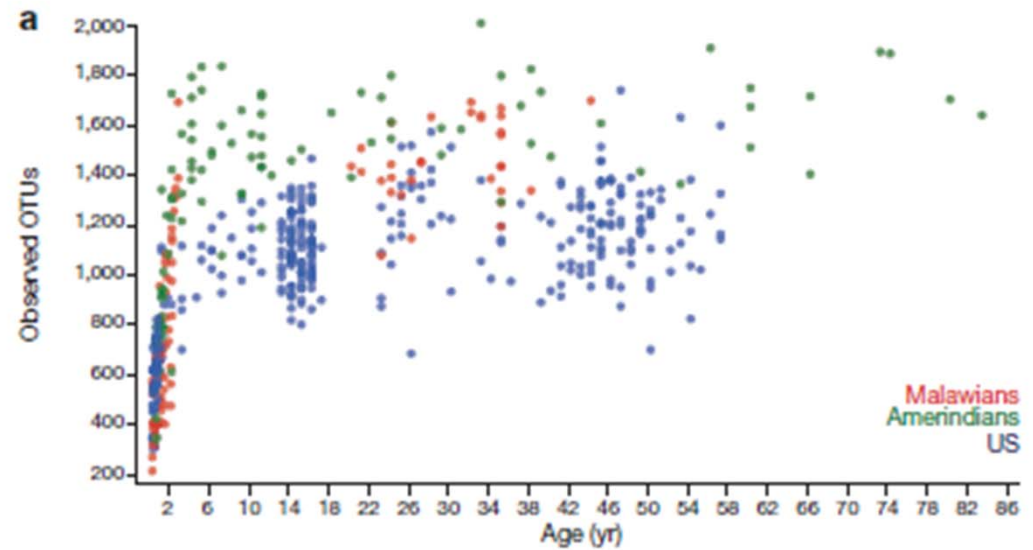
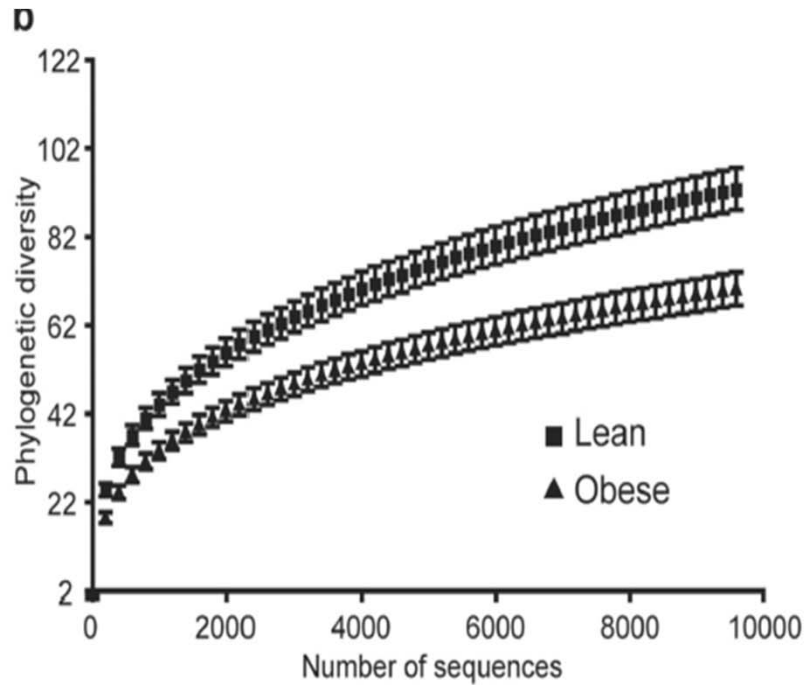


↓
Gras animal



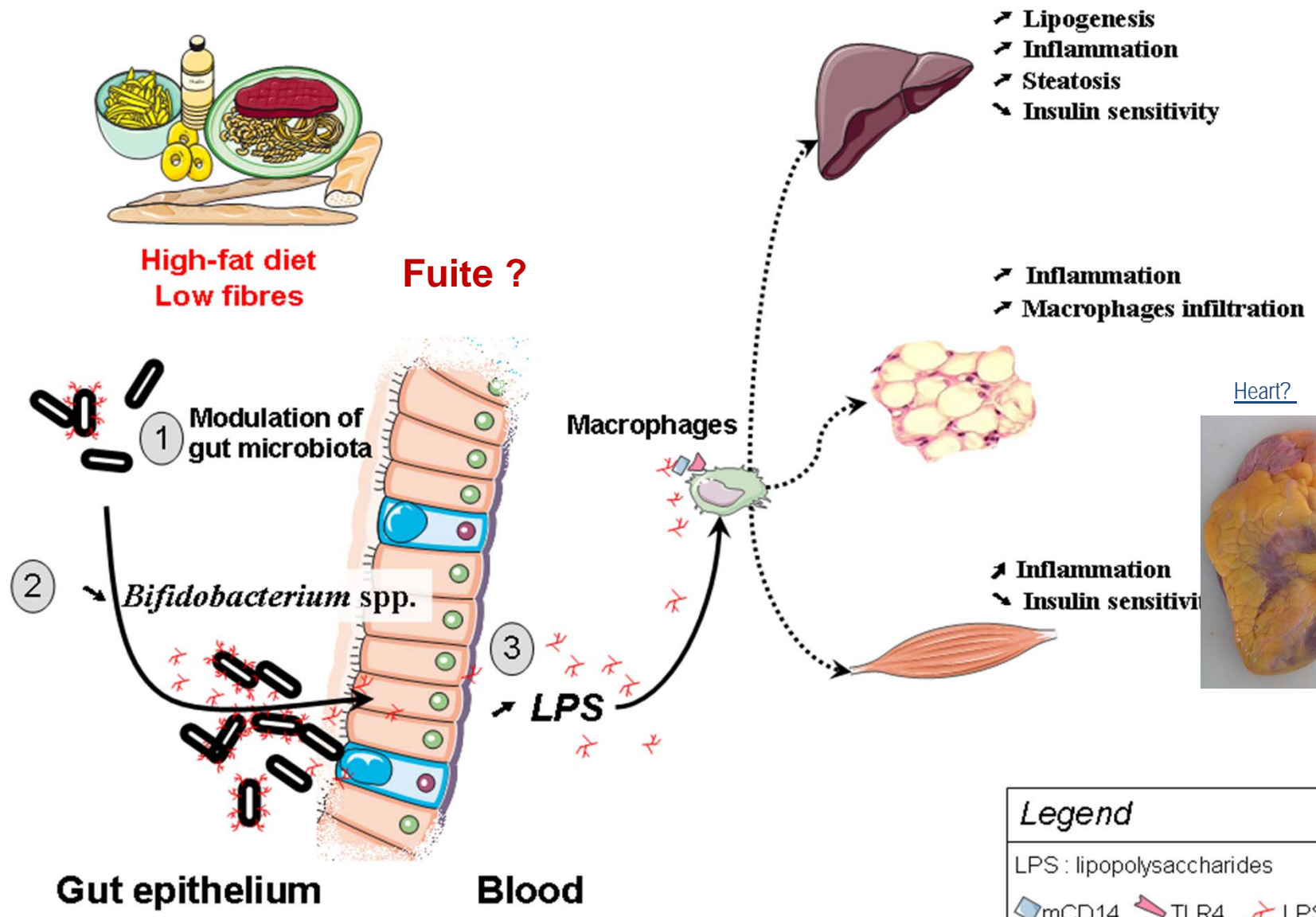
↓
Carbohydrates





326 sujets ages de 0 à 17 ans
(Malawian, Amerindiens et 178 US),
plus
202 adultes ages de 18 à 70 ans (31
Malawians, 35 Amerindiens et 136 US).

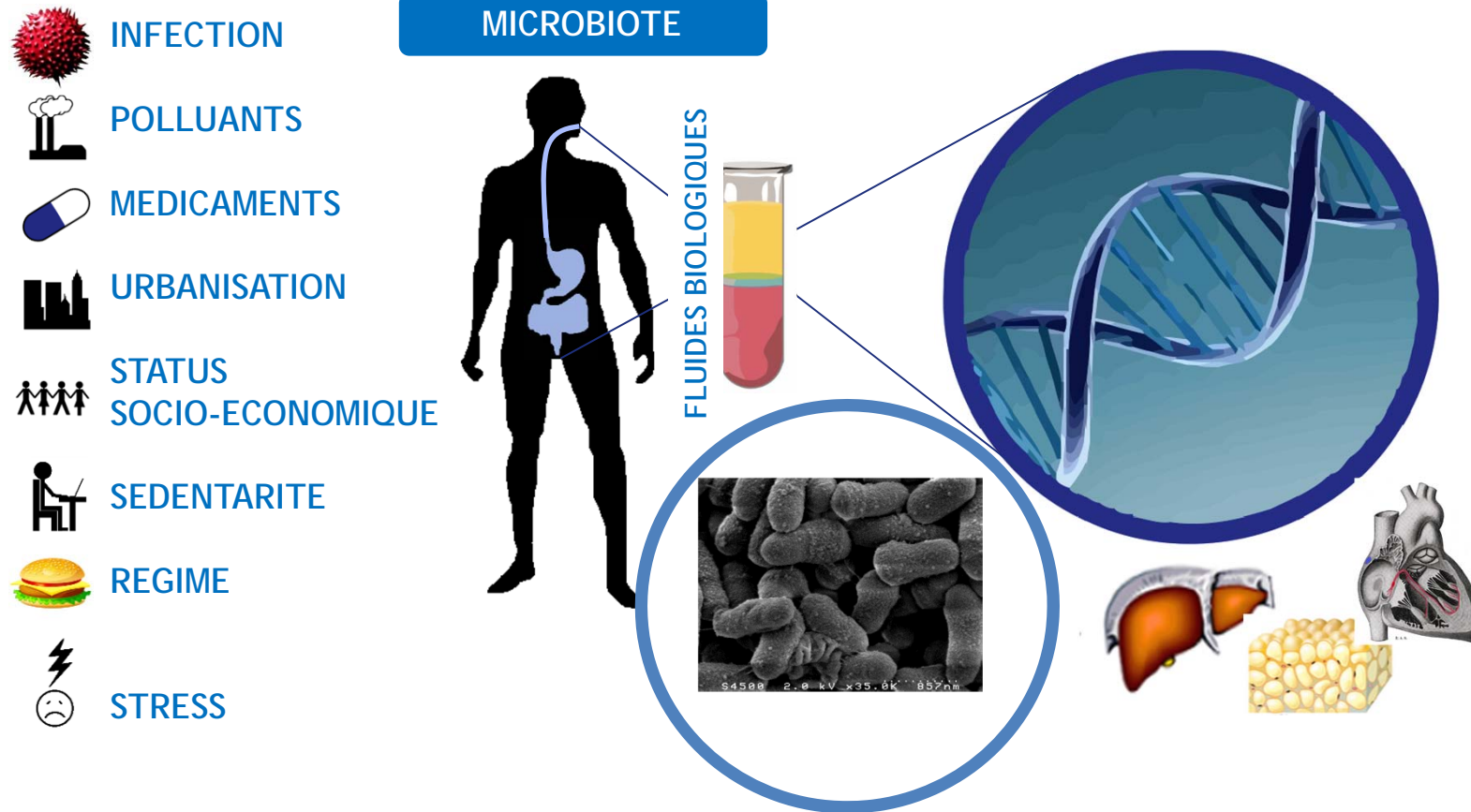
Turnbaugh *et al.* Nature 2009
Yatsunenko *et al.* Nature 2012



Cani P.D. *et al. Diabetes* 2007, Cani P.D. *et al. Diabetologia* 2007, Tsukumo *et al. Diabetes* 2007, Cani P.D. *et al. Diabetes* 2008, Kim *et al. Circ. Res.* 2007

FACTEURS ENVIRONNEMENTAUX ET SOCIÉTAUX

GENETIQUE et EPIGENETIQUE



Study participants are recruited from the population-based Inter99 study of 6,784 Danes (age 30-60 years)



1999

- Anthropometric measurements
- Biochemistry
- Oral glucose tolerance test
- Health questionnaire
- Food frequency questionnaire

2004

- Anthropometric measurements
- Biochemistry
- Oral glucose tolerance test
- Health questionnaire
- Food frequency questionnaire

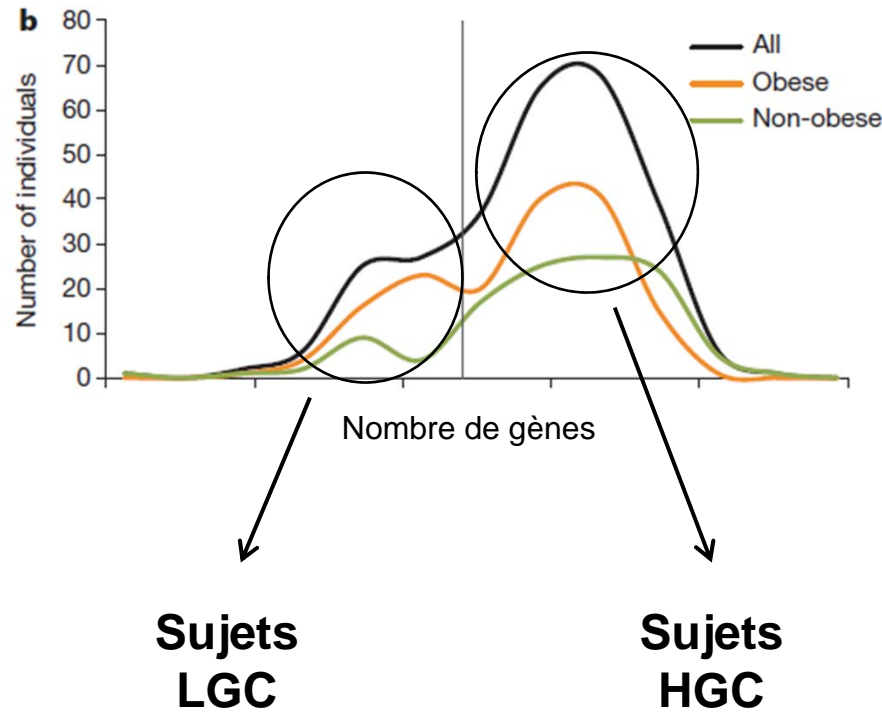
2009+

- Anthropometric measurements
- Blood biochemistry
- DEXA scan
- Health questionnaire
- Food frequency questionnaire
- **Faeces sample**
- Saliva sample

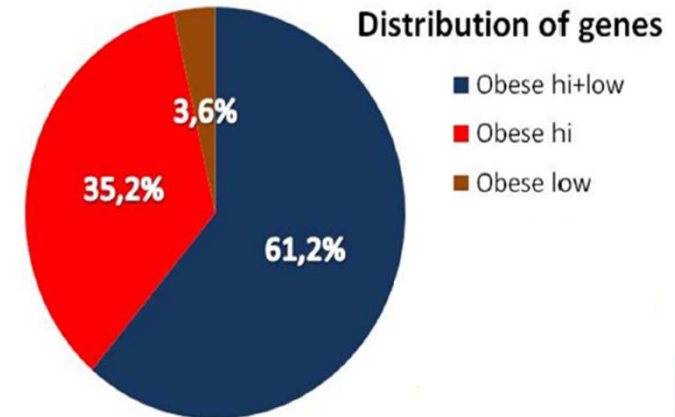
292 individus non diabétiques
(123 minces, 169 obèses)

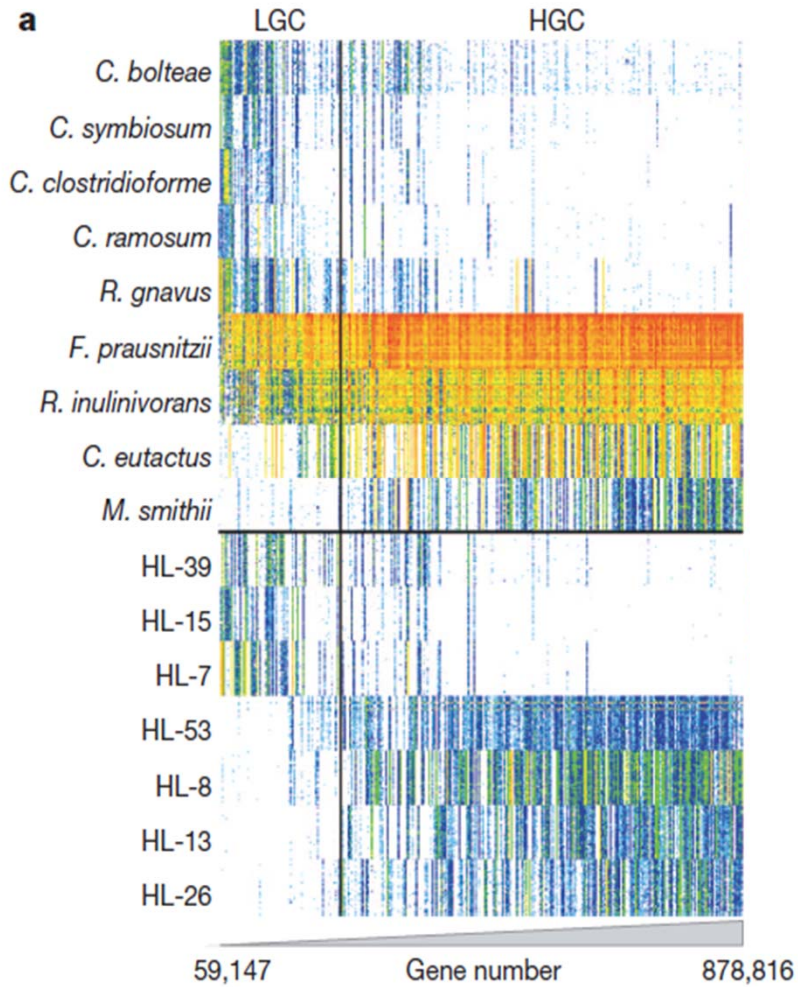
Richesse génétique : nombre de gènes bactériens distincts d'un sujet

Le Chatelier *et al.*, Nature, 2013

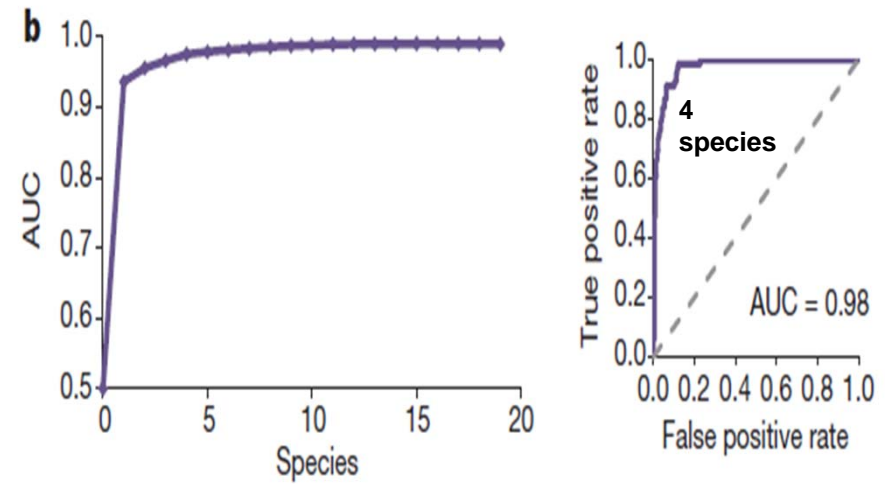


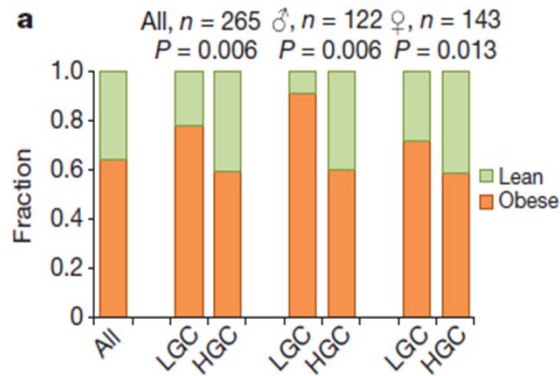
Sean Kennedy, Ecole NGS
INRA, Lyon, January 2012





Meilleur AUC pour la prédiction des groupes





Plus d'obèses dans le groupe LGC

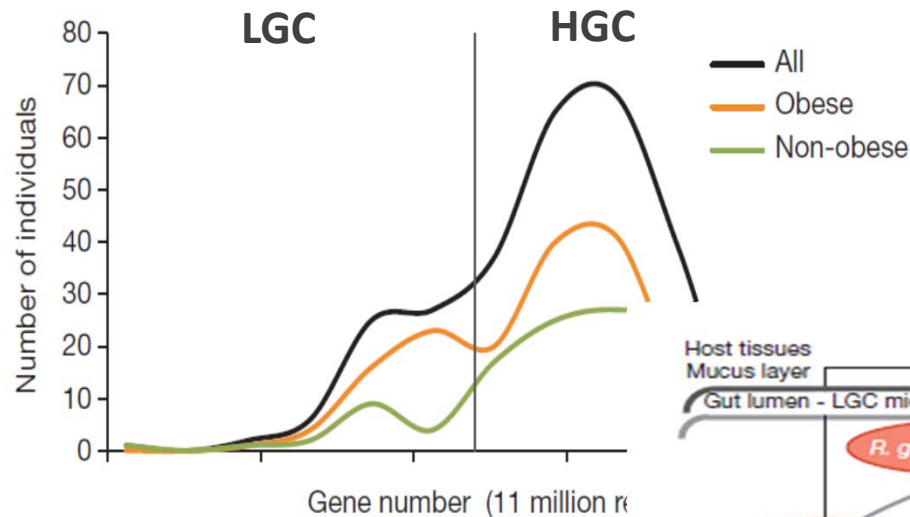
Table 1 | Characteristics of 292 participants stratified by low and high gene counts

	LGC	HGC	LGC versus HGC		Gene count	
			<i>P</i>	<i>q</i>	<i>P</i>	<i>q</i>
<i>N</i> (men/women)	68 (23/45)	224 (113/111)			277 (133/144)*	
Age (years)	55 (50–62)	57 (50–61)	0.86	0.89	0.81	0.84
BMI (kg m^{-2})	32 (29–34)	30 (23–33)	0.035	0.059	0.11	0.18
Weight (kg)	95 (75–103)	86 (71–102)	0.019	0.037	0.12	0.18
Whole body fat (%)	37 (29–42)	31 (25–39)	0.0069	0.022	0.0024	0.014
S-insulin (pmol l^{-1})	50 (35–91)	44 (26–66)	0.0095	0.023	0.0052	0.018
HOMA-IR	1.9 (1.2–3.3)	1.6 (0.9–2.6)	0.012	0.027	0.0059	0.018
P-triglycerides (mmol l^{-1})	1.32 (0.97–1.76)	1.15 (0.82–1.57)	0.0014	0.013	0.00073	0.0062
P-free fatty acids (mmol l^{-1})	0.55 (0.39–0.70)	0.48 (0.35–0.60)	0.014	0.029	0.00042	0.0062
P-ALT (U l^{-1})	20 (14–30)	19 (15–26)	0.22	0.31	0.029	0.06
S-leptin ($\mu\text{g l}^{-1}$)	17.0 (6.7–32.6)	8.3 (3.4–26.4)	0.0036	0.019	0.00058	0.0062
S-adiponectin (mg l^{-1})	7.5 (5.5–12.0)	9.6 (6.7–13.7)	0.006	0.022	0.016	0.026
B-leucocytes (10^9l^{-1})	6.4 (5.2–7.8)	5.6 (4.8–6.9)	0.0021	0.014	0.0026	0.014
B-lymphocytes (10^9l^{-1})	2.1 (1.6–2.3)	1.8 (1.5–2.1)	0.00082	0.012	0.0037	0.015
P-hsCRP (mg l^{-1})	2.3 (1.1–5.7)	1.4 (0.6–2.7)	0.00088	0.012	0.0038	0.015
S-FIAF ($\mu\text{g l}^{-1}$)	88 (72–120)	78 (60–101)	0.0047	0.021	0.0088	0.023

Descriptive data are reported as median and interquartile range. To test for differences between the HGC and LGC group, a linear model adjusting for age and sex (*P*) was applied. In the analysis of plasma triglycerides, treatment for lipid lowering medications was added as a covariate to the linear model. Benjamini-Hochberg method was used for multiple testing corrections setting the FDR at 10% (*q*). A similar model was applied to test for associations with gene counts. The P-, S- and B- prefixes denote plasma, serum and blood. ALT, alanin aminotransferase; HOMA-IR, homeostatic model assessment of insulin resistance.

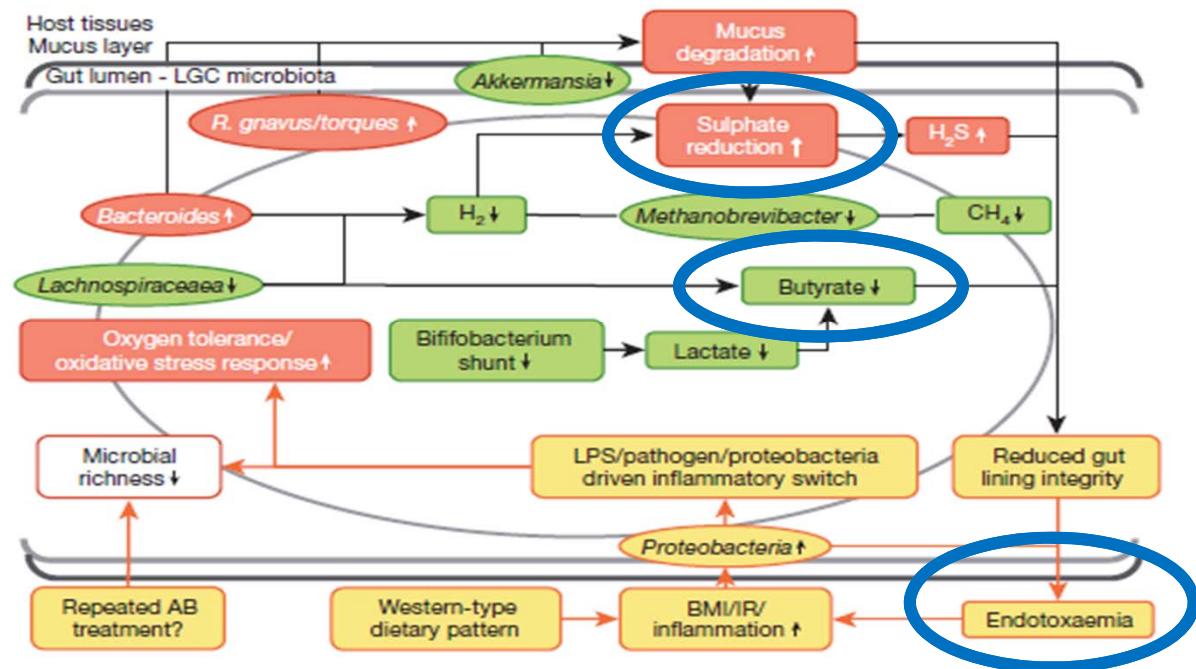
**n* = 277 owing to downsizing of the reads to 11 million.

Plus de déséquilibres métaboliques dans le groupe LGC que dans le groupe HGC : un risque accru de diabète de type 2 et de maladies cardiovasculaires ?



◆ Sujets LGC sont plus souvent obèses que les sujets HGC

◆ Bactéries des patients LGC sont plutôt pro-inflammatoires



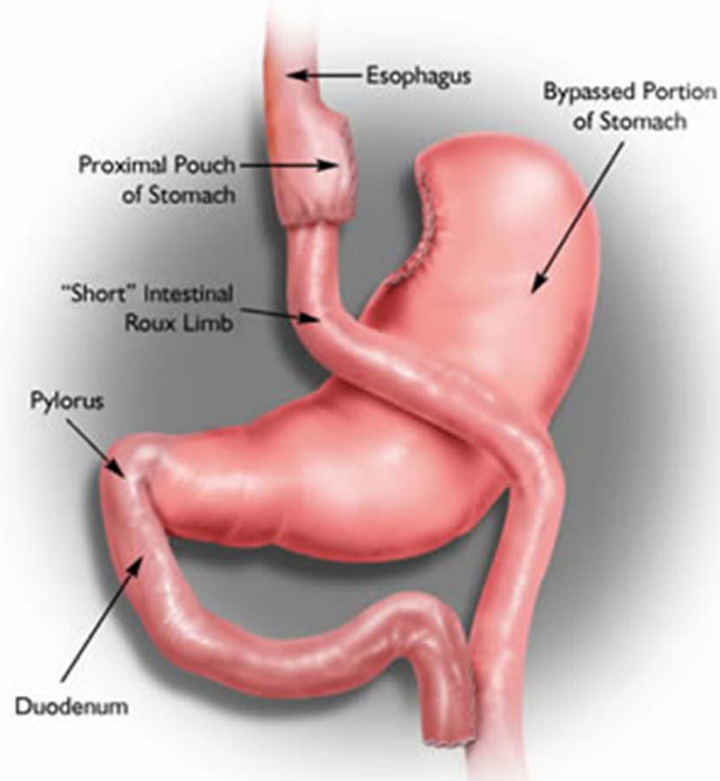
Le Chatelier *et al.* Nature 2013

➤ Il existe des différences entre le microbiote intestinal des minces et celui des obèses



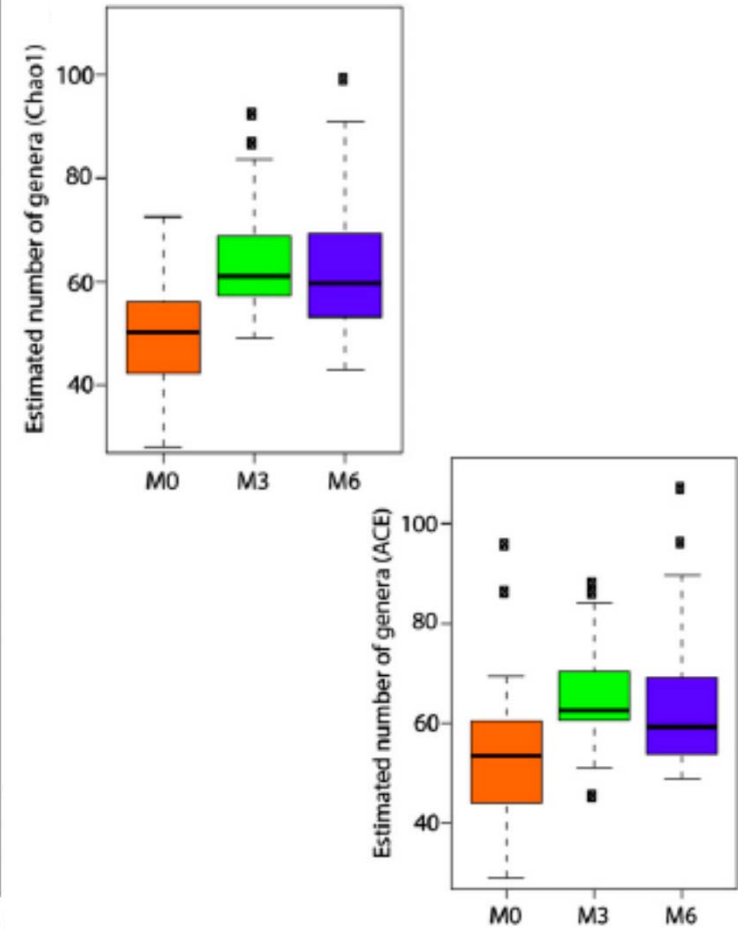
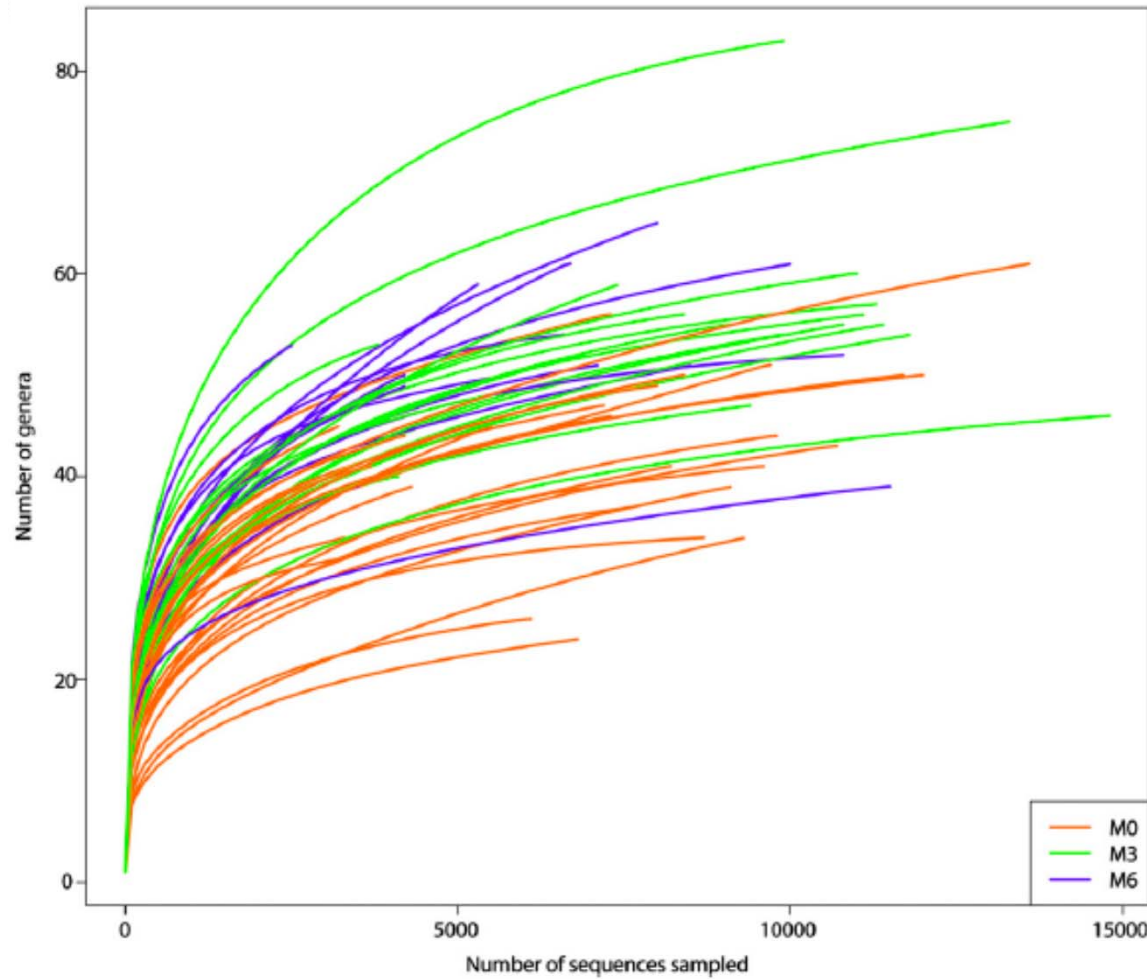
Sujets obèses (30)

0, 1, 3, 6 mois



Chirurgie bariatrique

- ◆ Evaluation du régime
- ◆ Analyse par *microarray* du tissu adipeux sous-cutané
- ◆ Pyrosequençage



Kong *et al.* Am J Clin Nutr 2013

➤ Chirurgie bariatrique augmente la richesse du microbiote intestinal

MicroObese / ANR

49 subjects

Energy-restricted diet
(1200-1500 kcal)

Body weight
maintaining diet

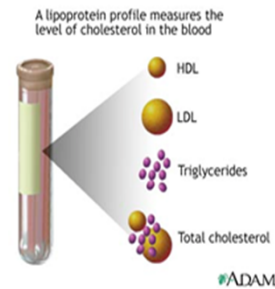
0wk

6wks

12wks



Diet



Phenotype

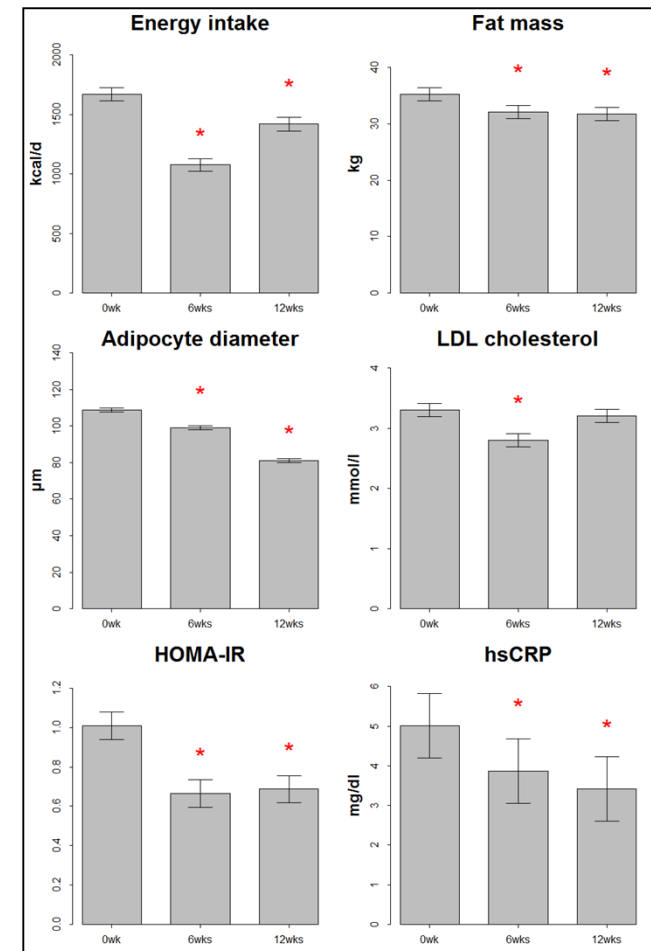


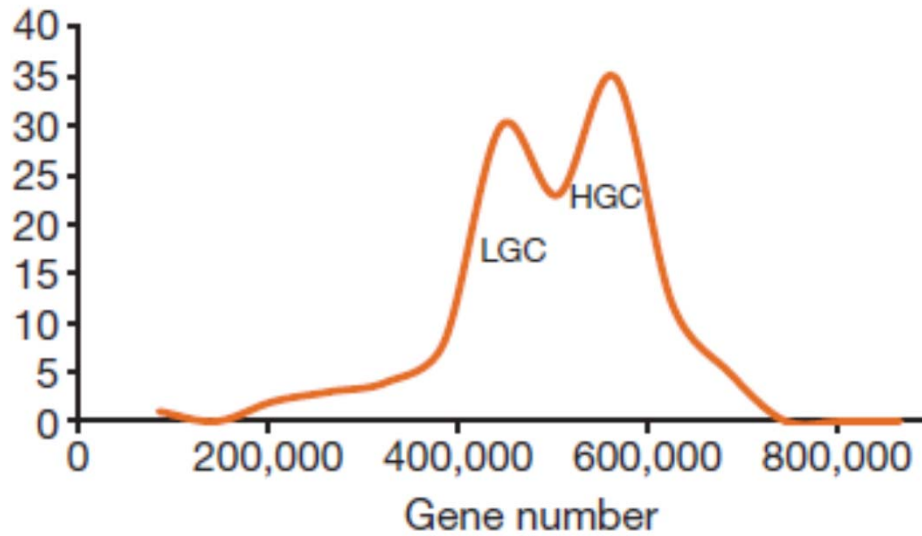
Gut flora*

* SOLiD™ reads were mapped on a 3.3 million genes catalog [1]

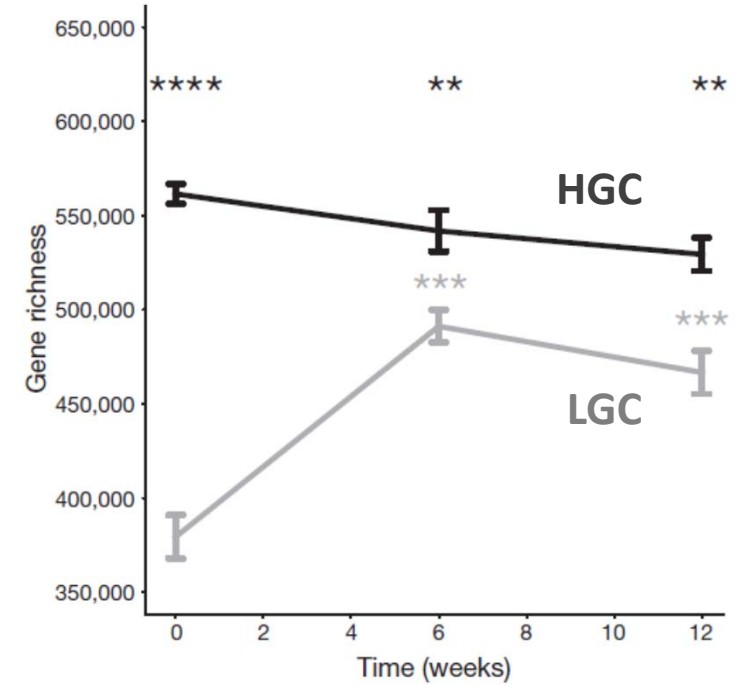
[1] Qin J. et al., g. Nature, 464 7285:59-65, 2010.

Obèses ou patients en sur-poids
Régime : riche en fibres et
protéines avec peu de
carbohydrates



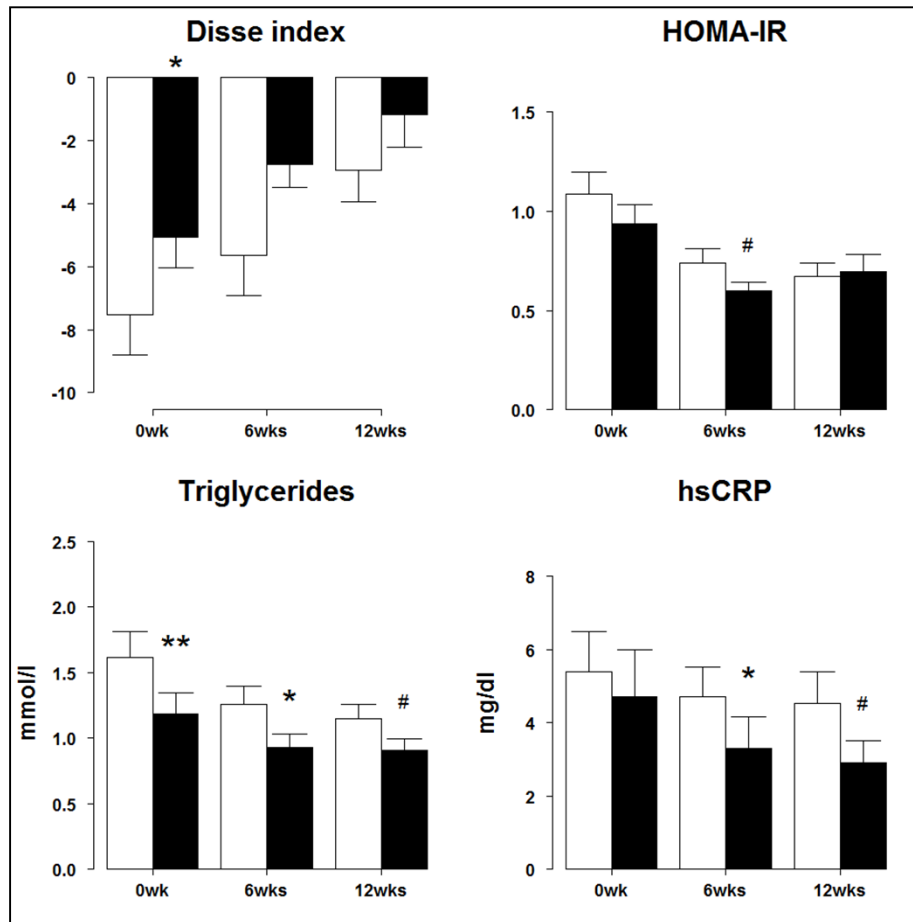


Cotillard *et al.* Nature 2013



➤ Un régime **augmente aussi la richesse génétique**

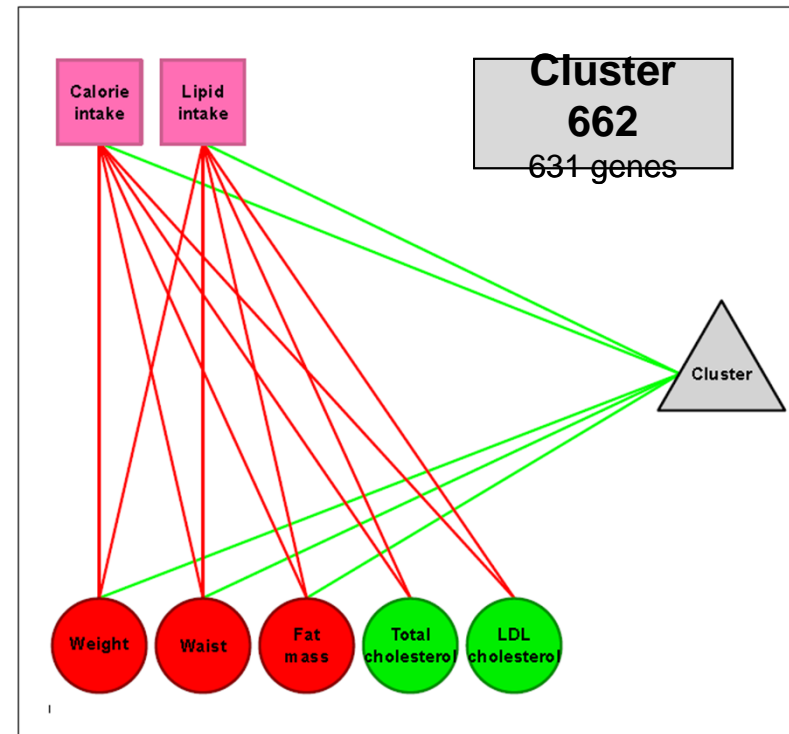
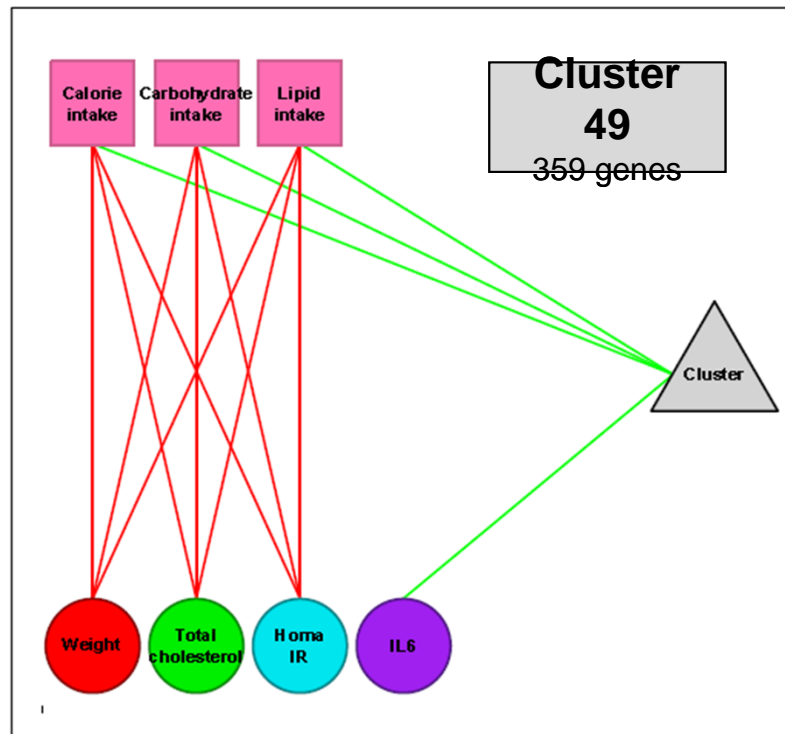
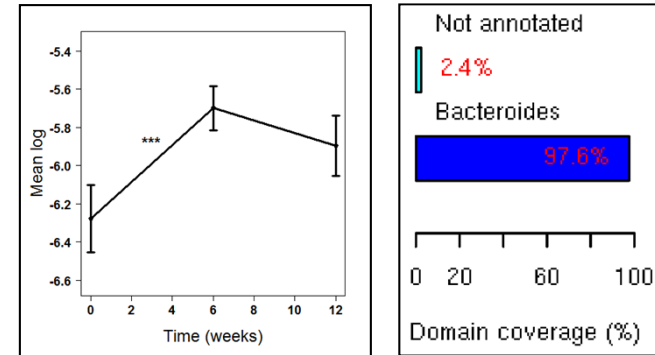
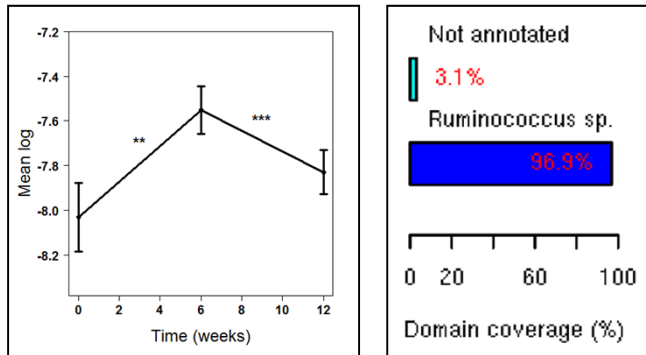
- Dys-métabolisme plus prononcé et une tendance vers une inflammation bas-grade plus forte chez les sujets LGC



□ Sujets LGC
■ Sujets HGC

#: p-value<0.1, *: p-value<0.05, **: p-value<0.01 by Mann-Whitney tests.
“Disse index” est calculé en combinant les valeurs lipides et insuline.

Focus on two specific gene clusters

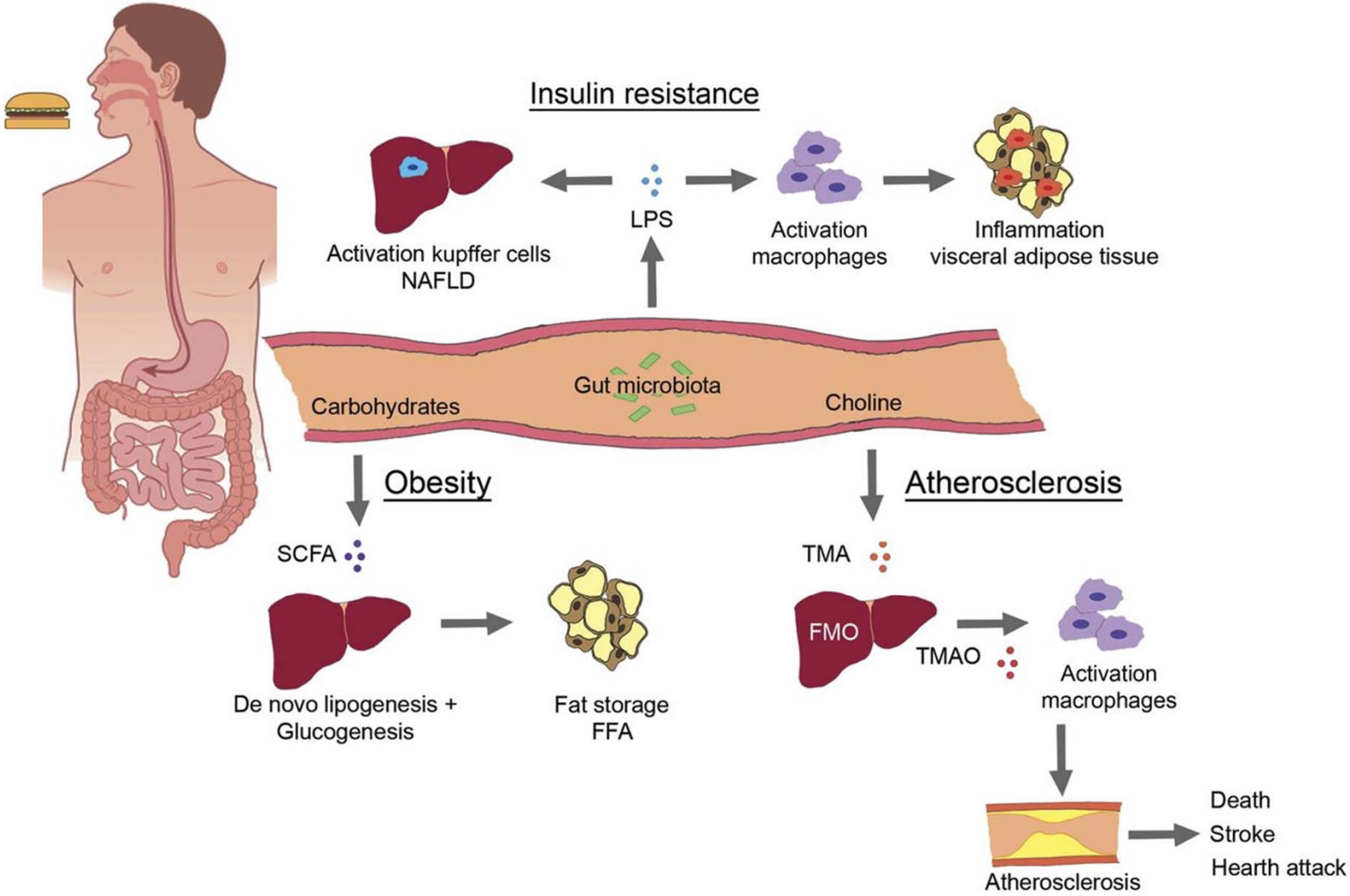


Associations with bioclinical/environmental factors

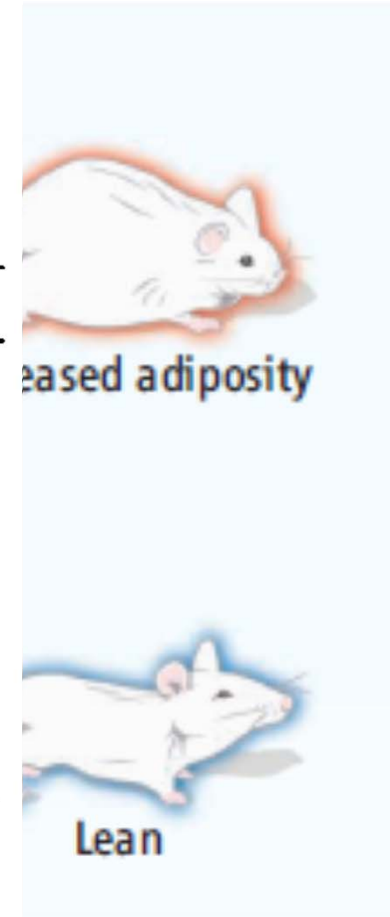
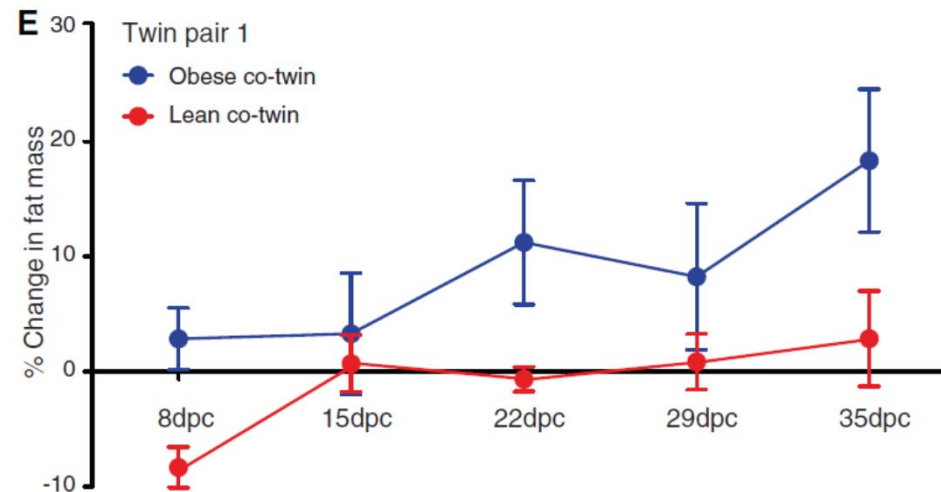
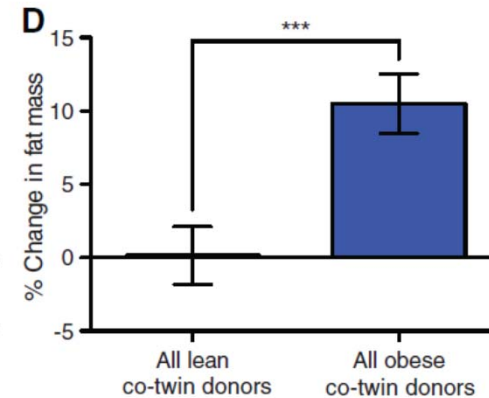
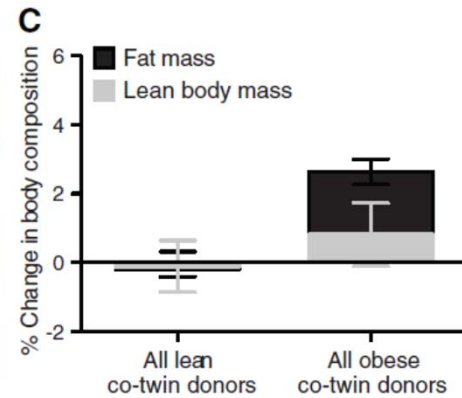
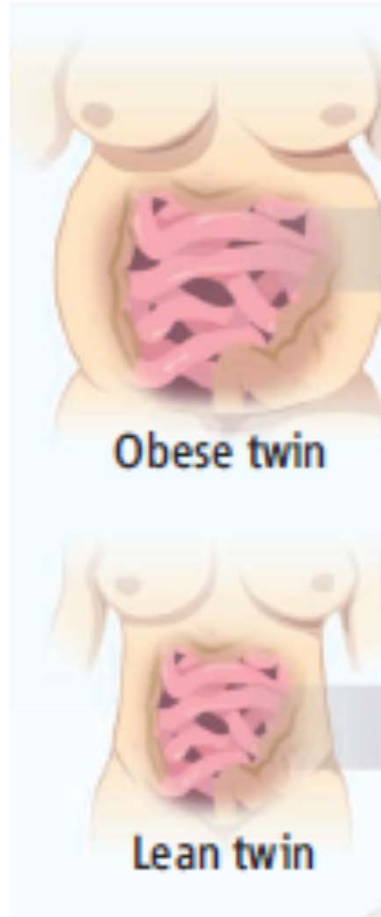
Are relations between bioclinical variables and bacterial gene clusters dependent on food intake? [linear mixed models]

	Number of relations for the 16 clusters	Number of food-dependent relations	Percentage of food-dependent relations
Body composition	15	5	33
Glucose metabolism	15	4	27
Lipid metabolism	19	16	84
Inflammation	2	0	0
All	51	25	49

Three major pathways via which intestinal microbiota can alter human cardio-metabolism.



Vinjé S et al. Eur Heart J 2013;eurheartj.eht467



Ridaura *et al.* Science 2013

➤ Le microbiote intestinal pourrait être une cause de l'obésité

- Importance du microbiote
- Role de la diversité?
- Biomarqueurs/prédicteurs
- Causalité / quels bactéries => intérêt des modèles animaux
- Comment la moduler?



**Aurelie
Cotillard**



Edi Prifti



**Salwa
Rizkalla**



**Jean-Daniel
Zucker**



**LingChun
Kong**



**Christine
Poitou**



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