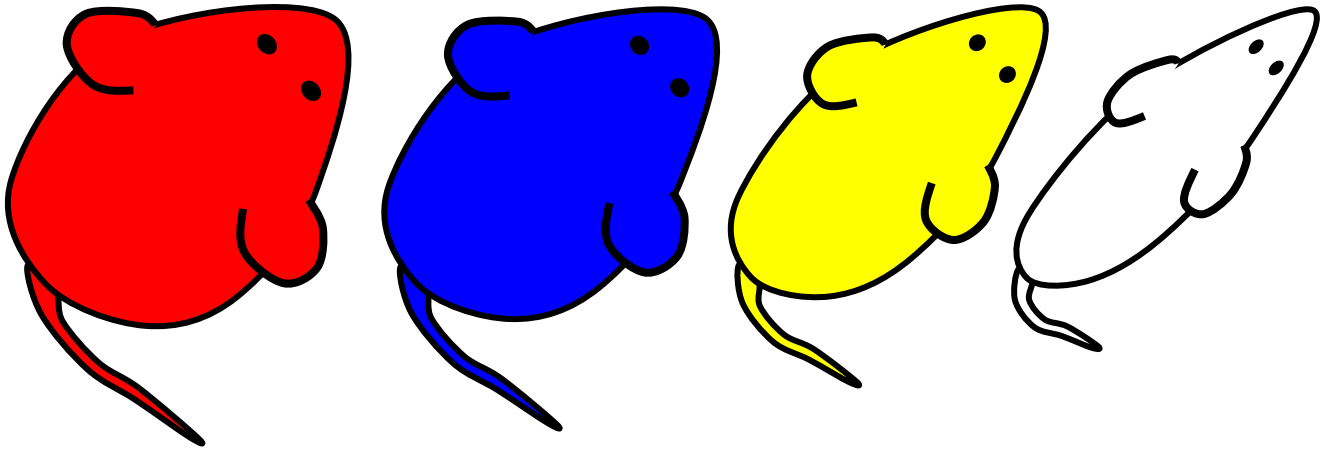
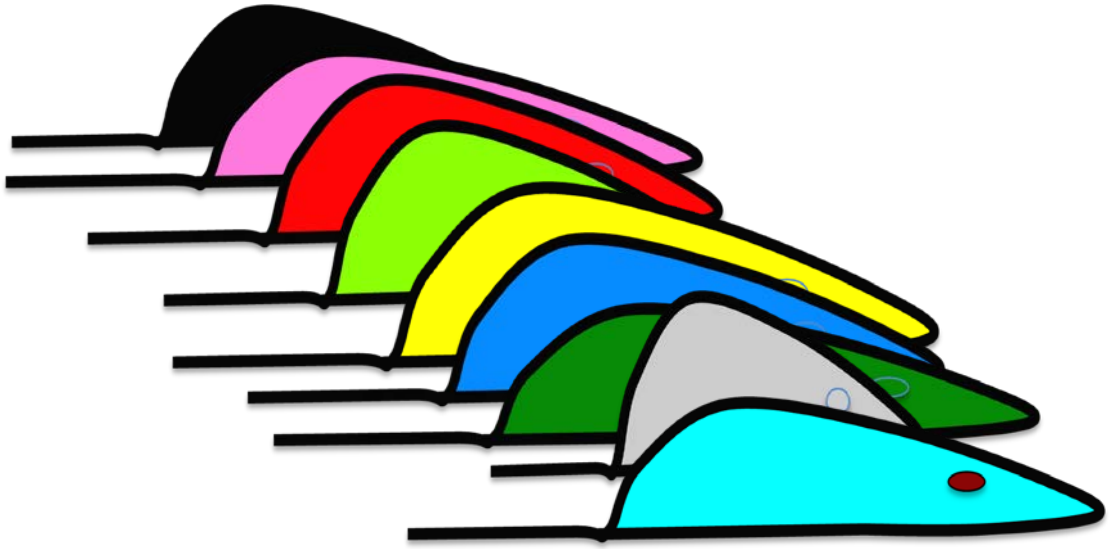
The Hybrid Mouse Diversity Panel:
A Resource for Systems Genetics

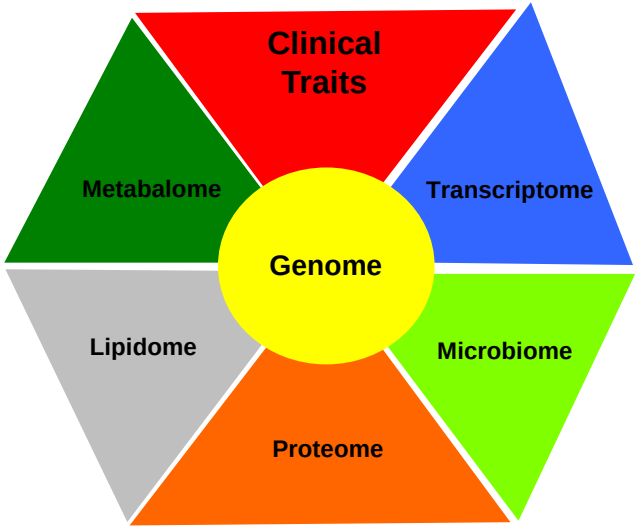


Brian W. Parks
University of California, Los Angeles

The Hybrid Mouse Diversity Panel (HMDP)

- Over 100 fully genotyped genetically unique inbred mice
- Large diversity in clinically-relevant parameters
- Ability to perform **systems genetics** analysis across multiple scales of biology
- Understand biological parameters as they work under natural genetic variation





High-Resolution Association Mapping

Linkage

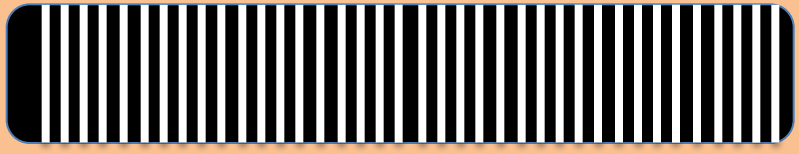
Resolution: 20-80mb

Genes: 1000s

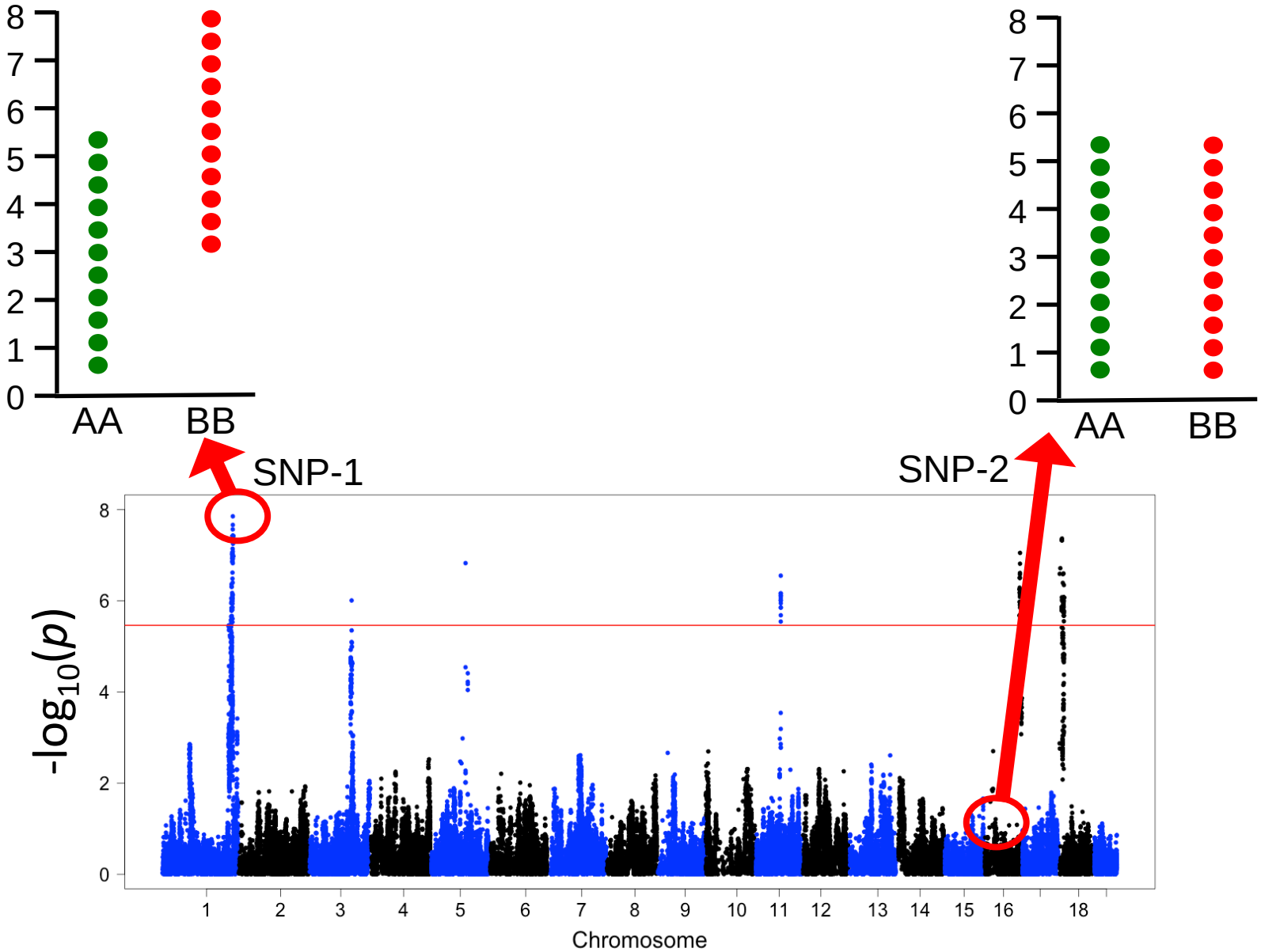
Association

Resolution: 0.5-5mb

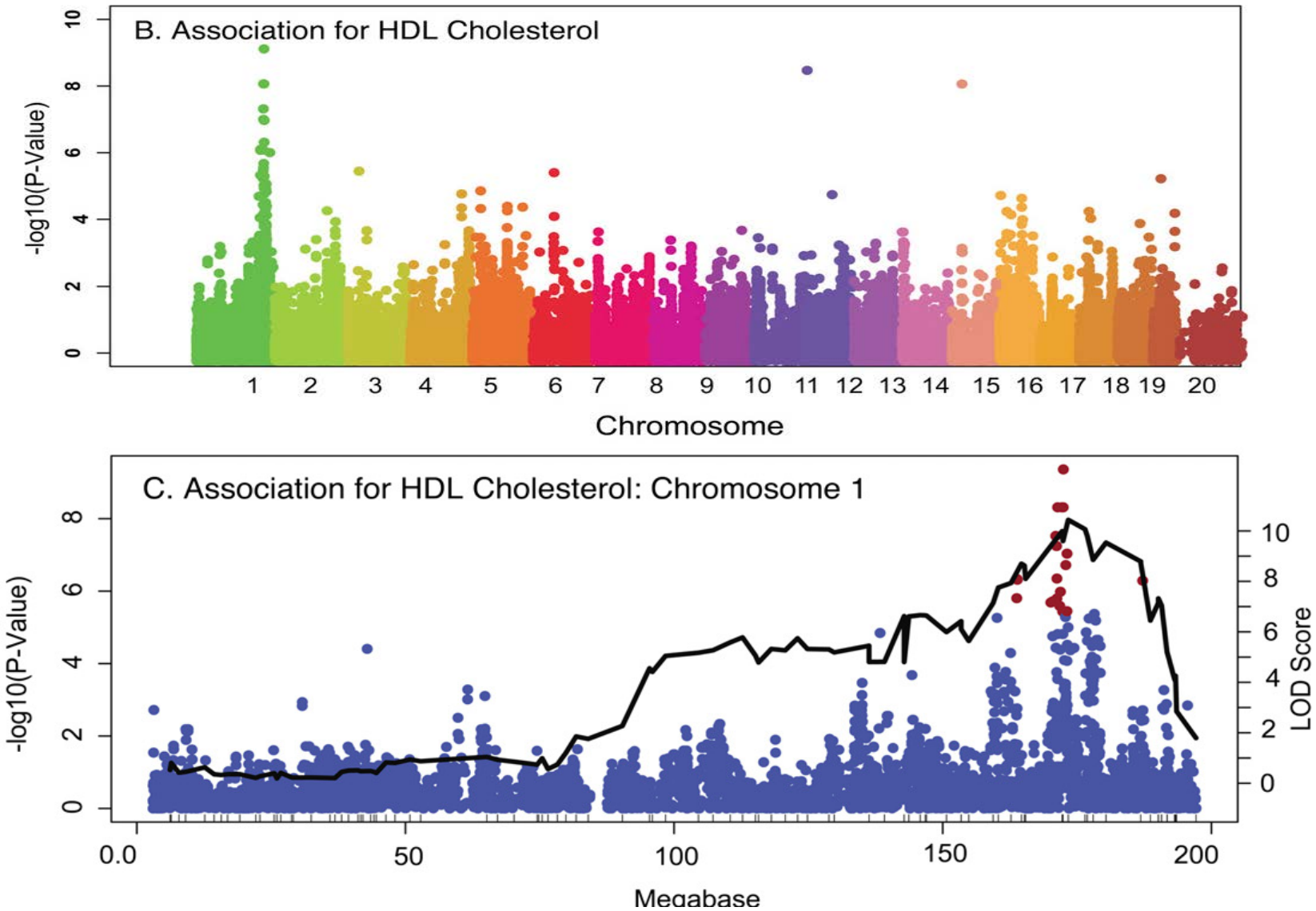
Genes: 1-60



Genome-Wide Association Studies

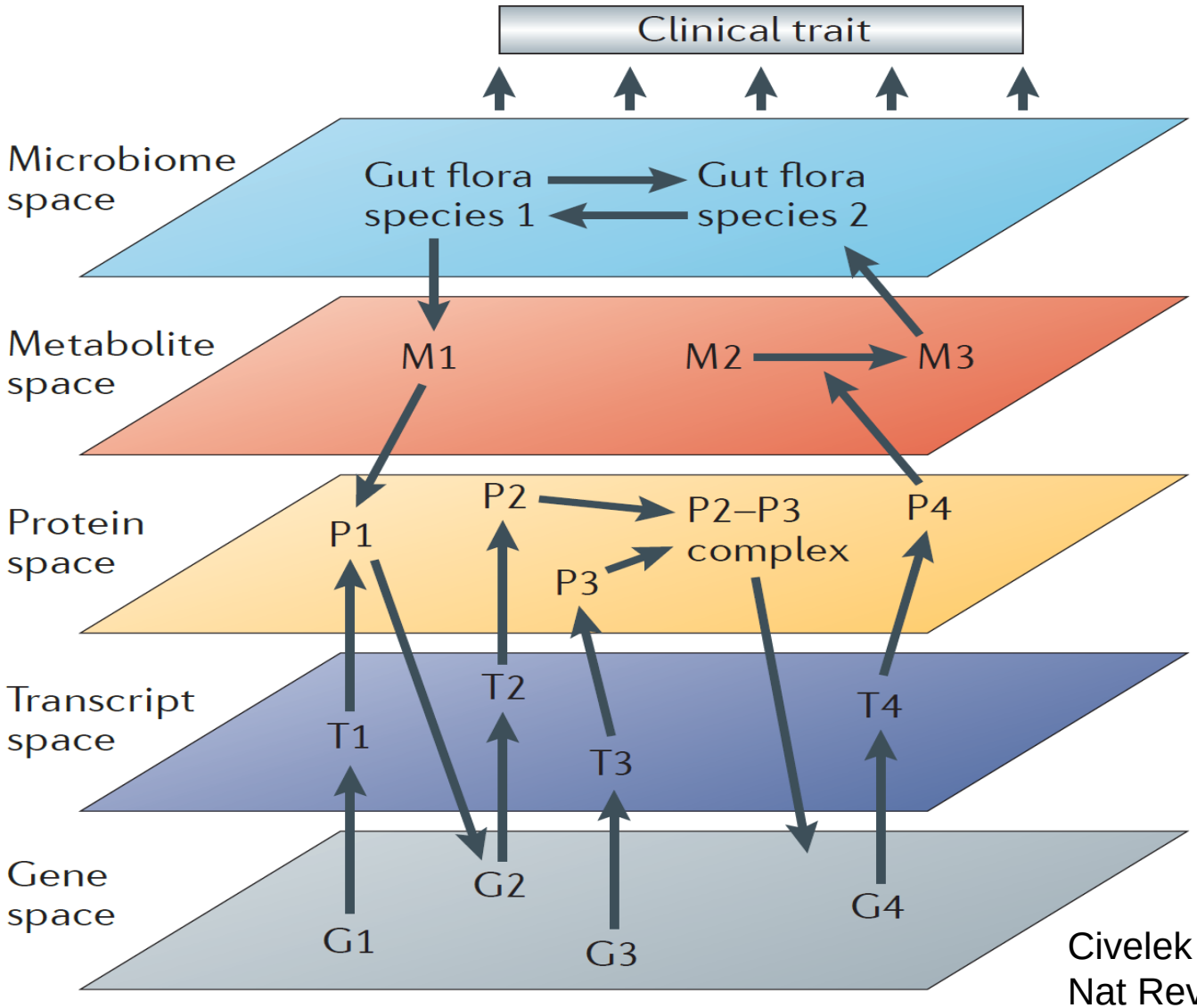


HMDP GWAS: HDL Cholesterol



Bennett, B. *et al.* Genome Res. 2010

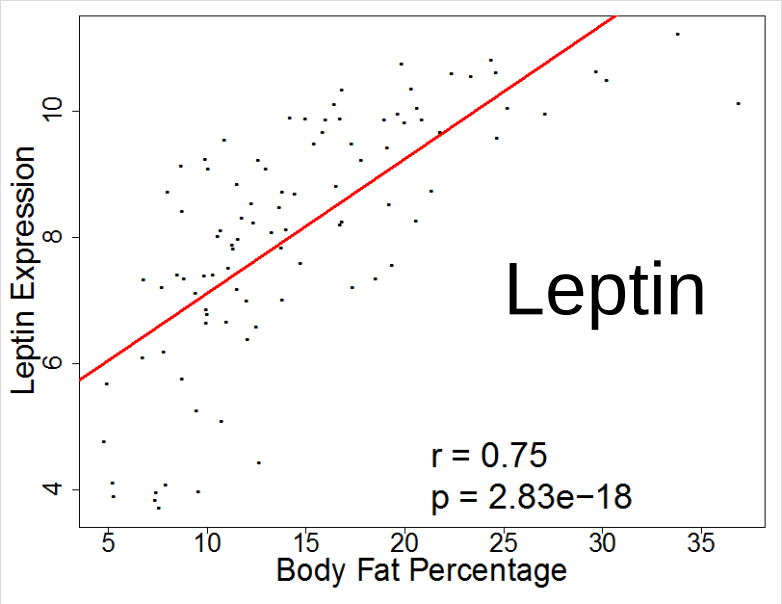
Using Systems Genetics to Identify Genes and Determine Pathways



Civelek M and Lusis AJ, Nat Rev Genetics. 2014

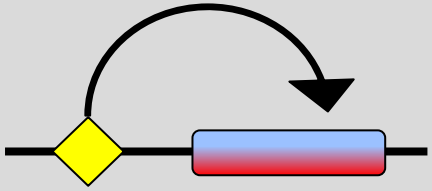
Systems Genetics: Integration of Genome-wide Gene Expression Data

Correlation

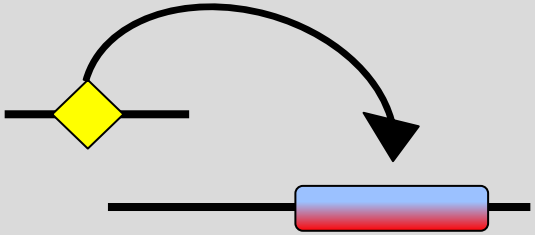


Identify *cis* and *trans* expression QTL (eQTL)

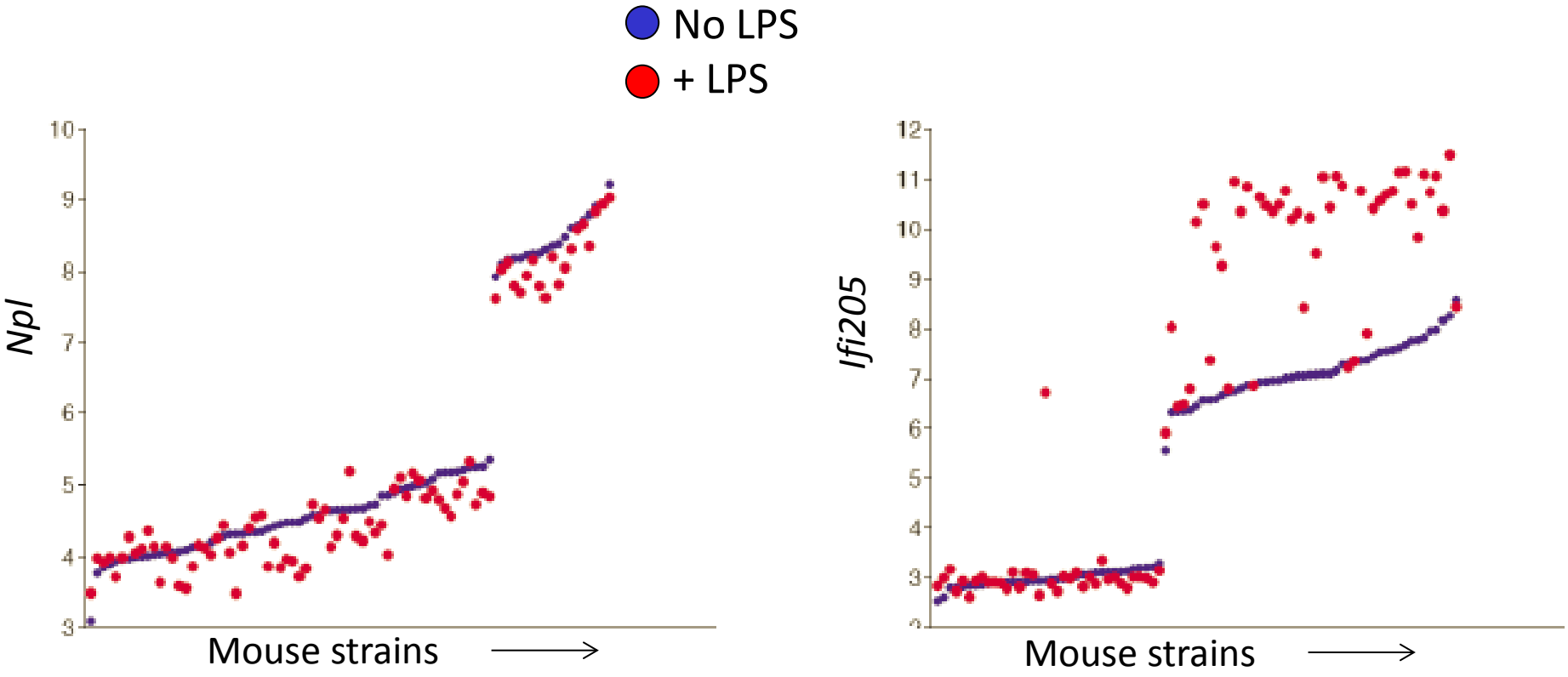
Cis- (Local) acting variant



Trans- acting variant

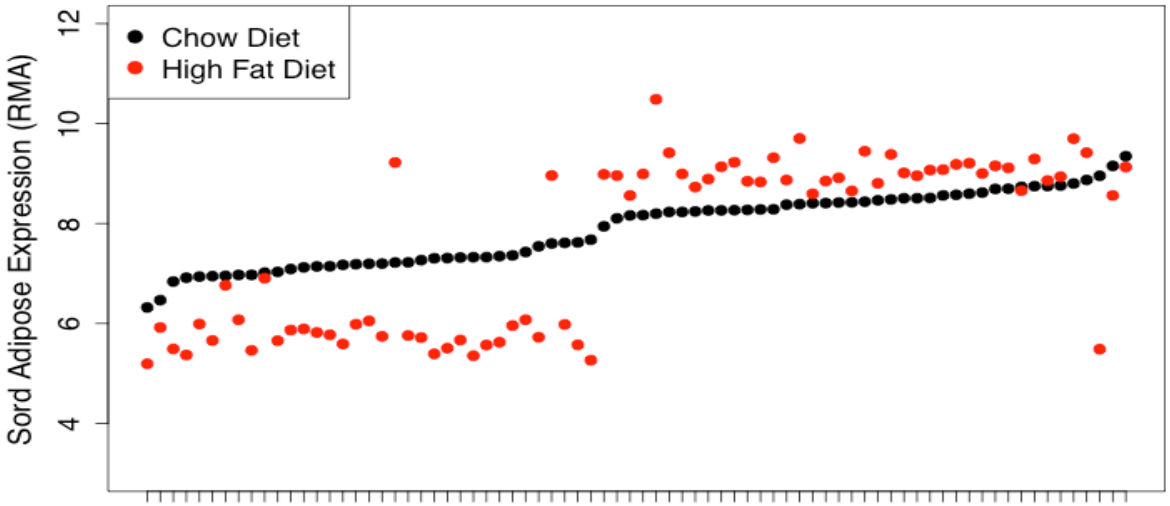


Genetics of Gene Expression:
Gene X Environment Interactions

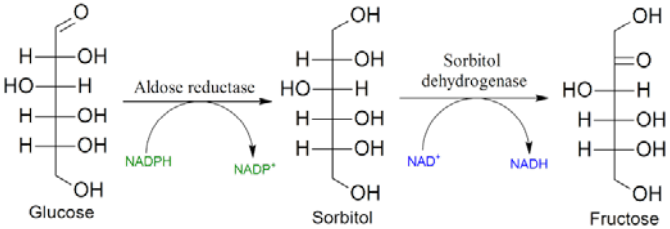


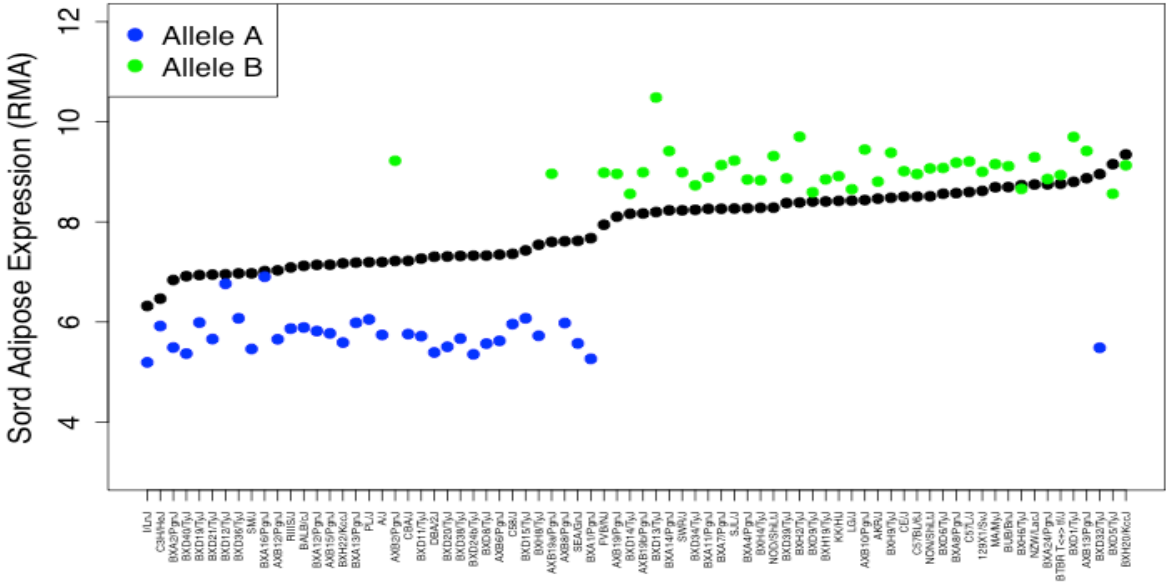
Orozco *et. al. Cell* 2012

Genetics of Gene Expression:
Gene X Diet Interactions



Sorbitol dehydrogenase is part of the polyol pathway that plays an important role in diabetic complications





cis-acting eQTL mediating gene-by-diet interaction

HMDP: *Gene Identification and Validation*

Bone Mineral Density (*Asxl2*) → Farber *et.al. Plos Genetics*. 2011

Obesity (*Cbr1*) → Parks *et.al. Cell Metabolism.* 2013

Insulin Resistance (*Agpat5*) → Parks *et.al. Cell Metabolism.* 2015

Cardiac Fibrosis (*Abcc6*) → Rau *et.al. Circ Cardiovasc Genet.* 2015

Inflammatory Gene Expression (*2310061C15Rik*) → Orozco *et.al. Cell* 2012

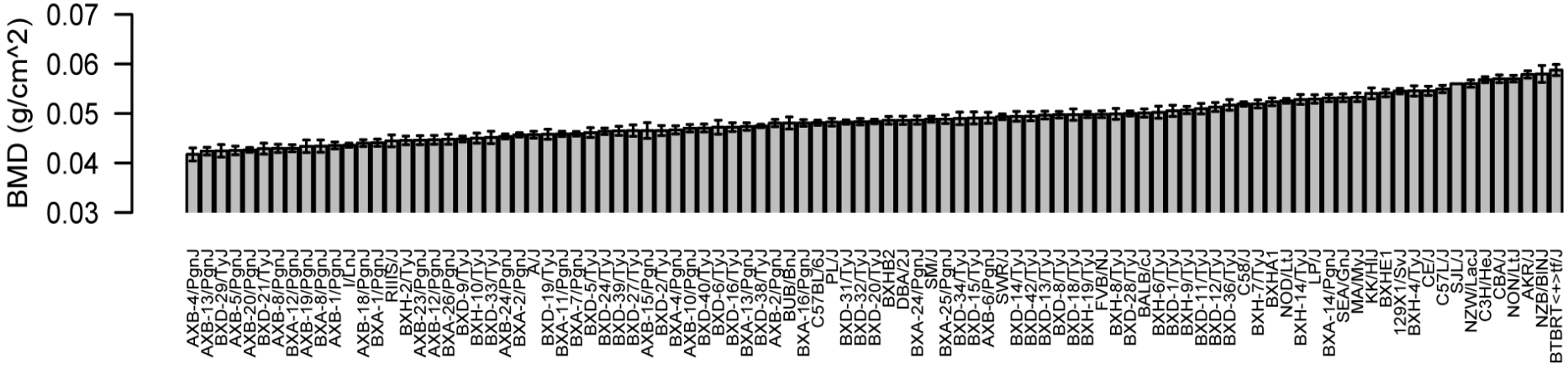
DNA methylation (*Mttr*) → Orozco *et.al. Cell Metabolism (Accepted)*

Network Integration

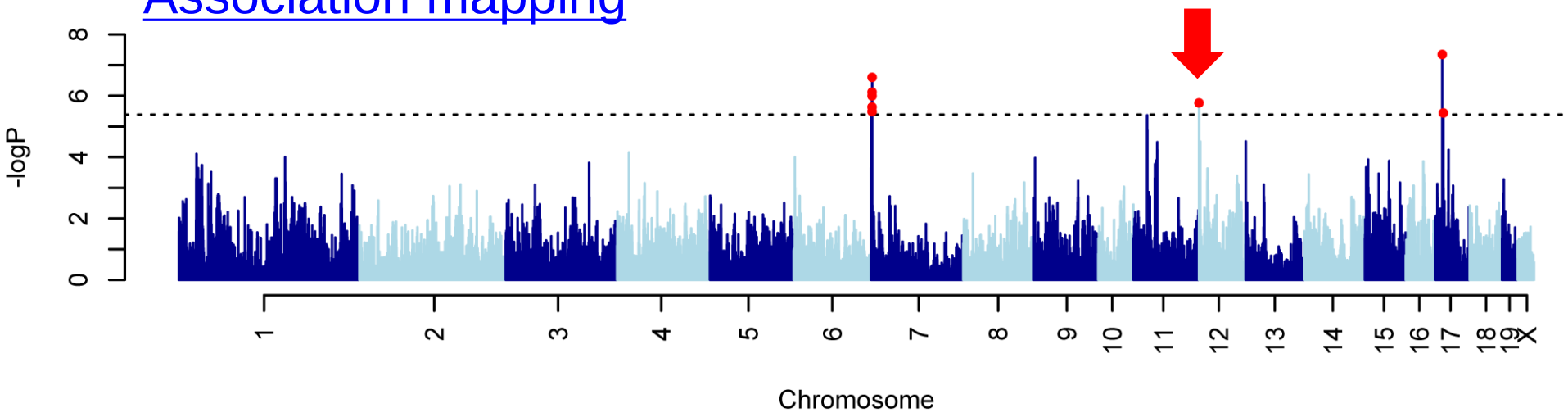
Osteoblast Lineage (*Maged1 and Pard6g*) → Farber *et.al. Plos Genetics* 2012

GWAS: Bone Mineral Density (BMD)

Trait distribution

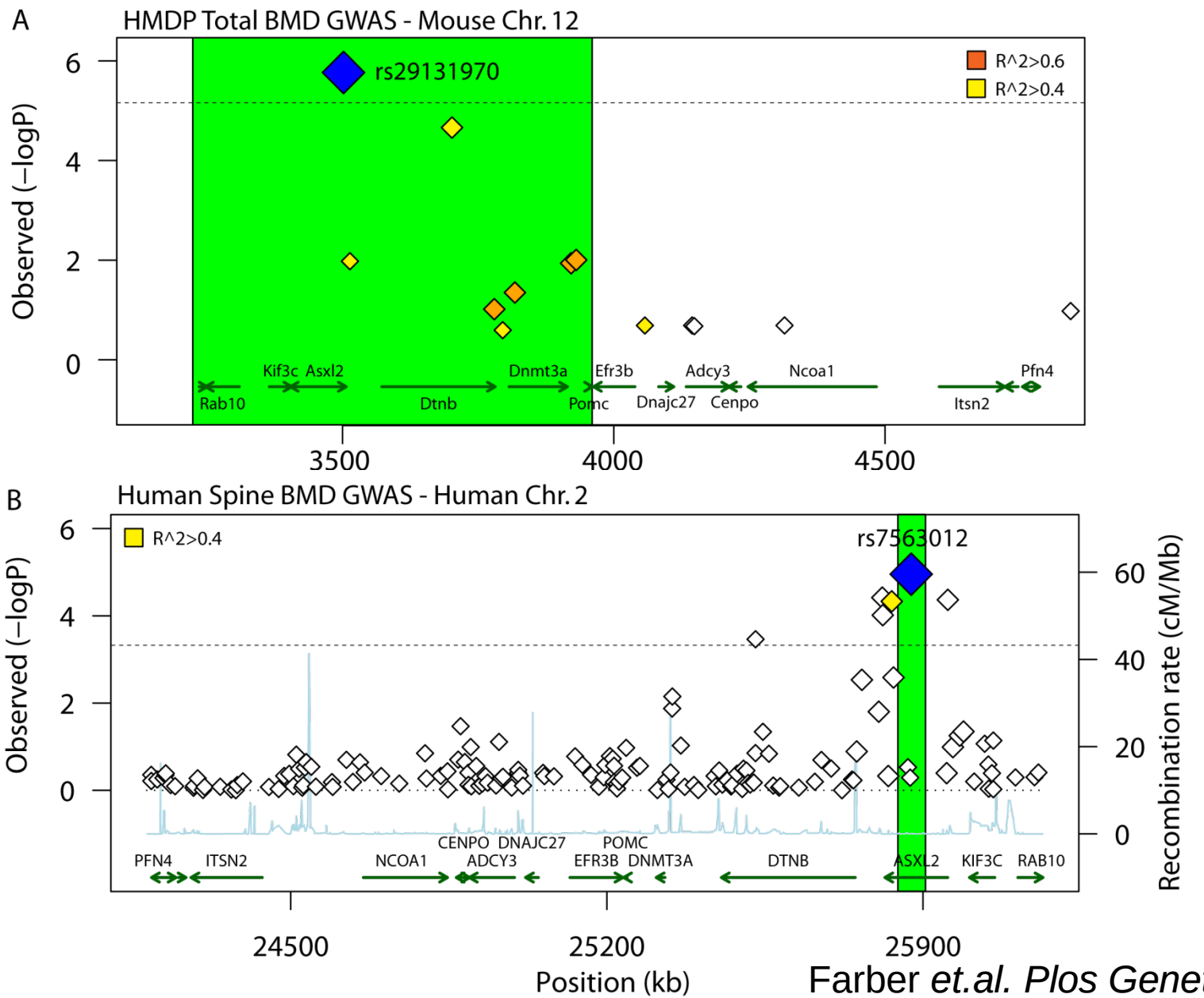


Association mapping



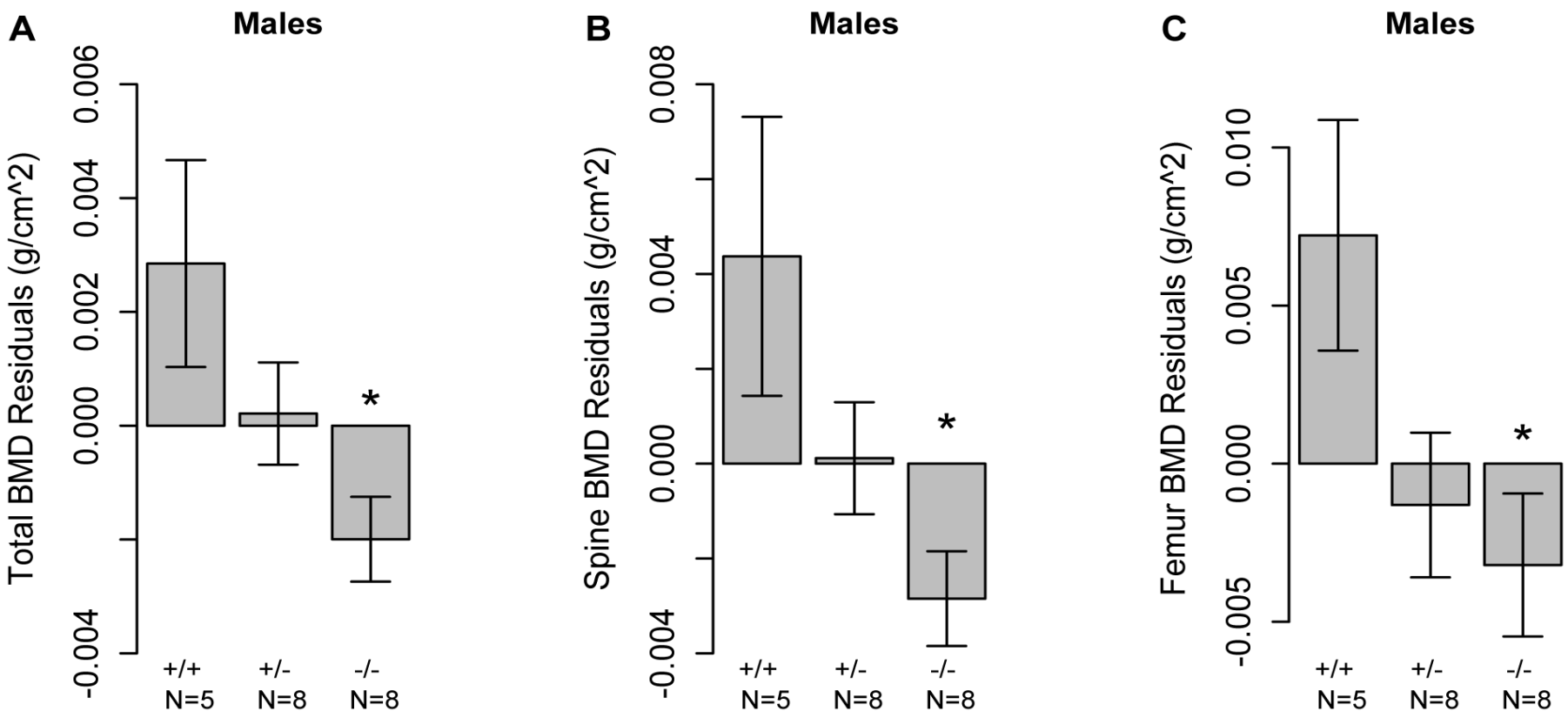
Farber *et.al. Plos Genetics.* 2011

GWAS: Bone Mineral Density (BMD)

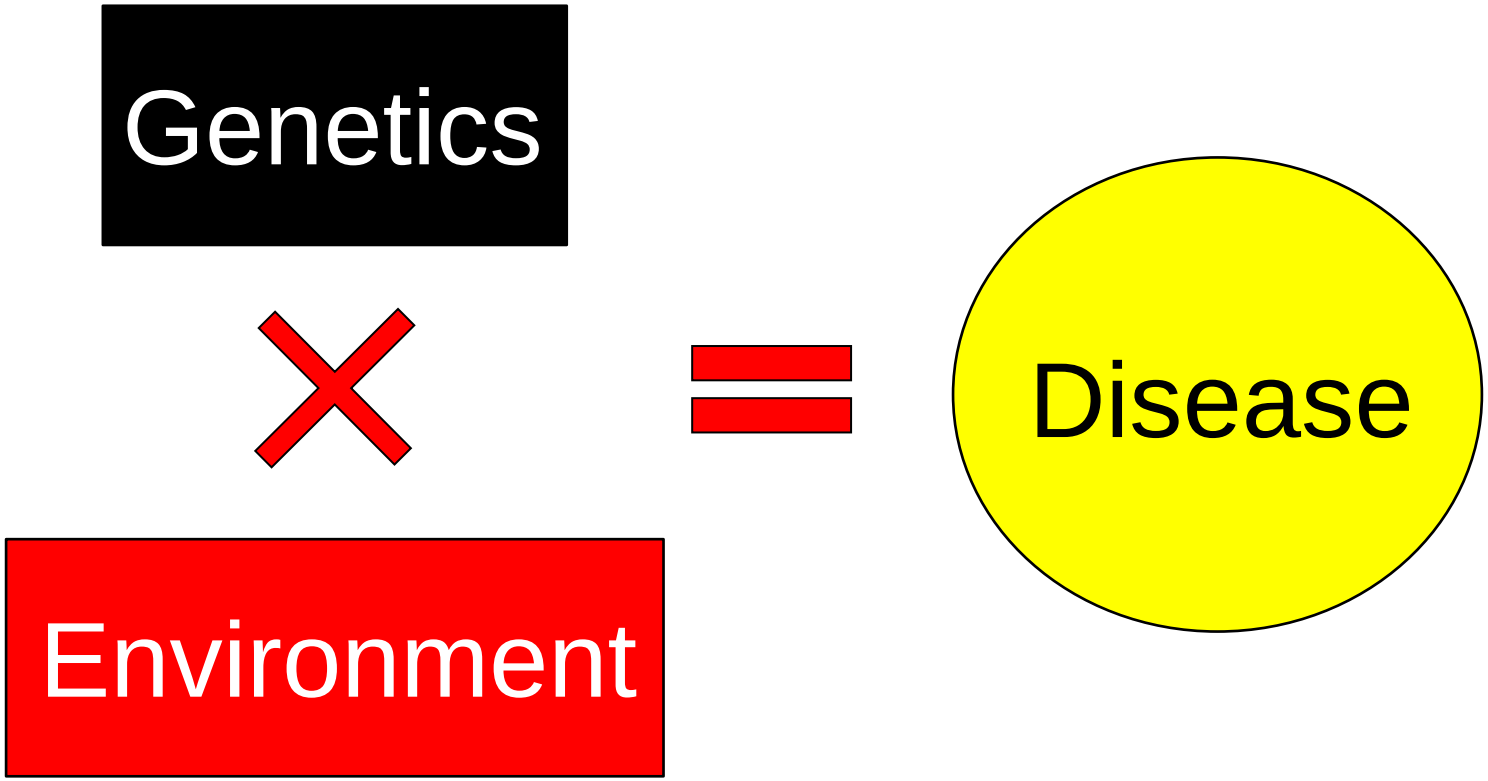


Farber *et.al. Plos Genetics.* 2011

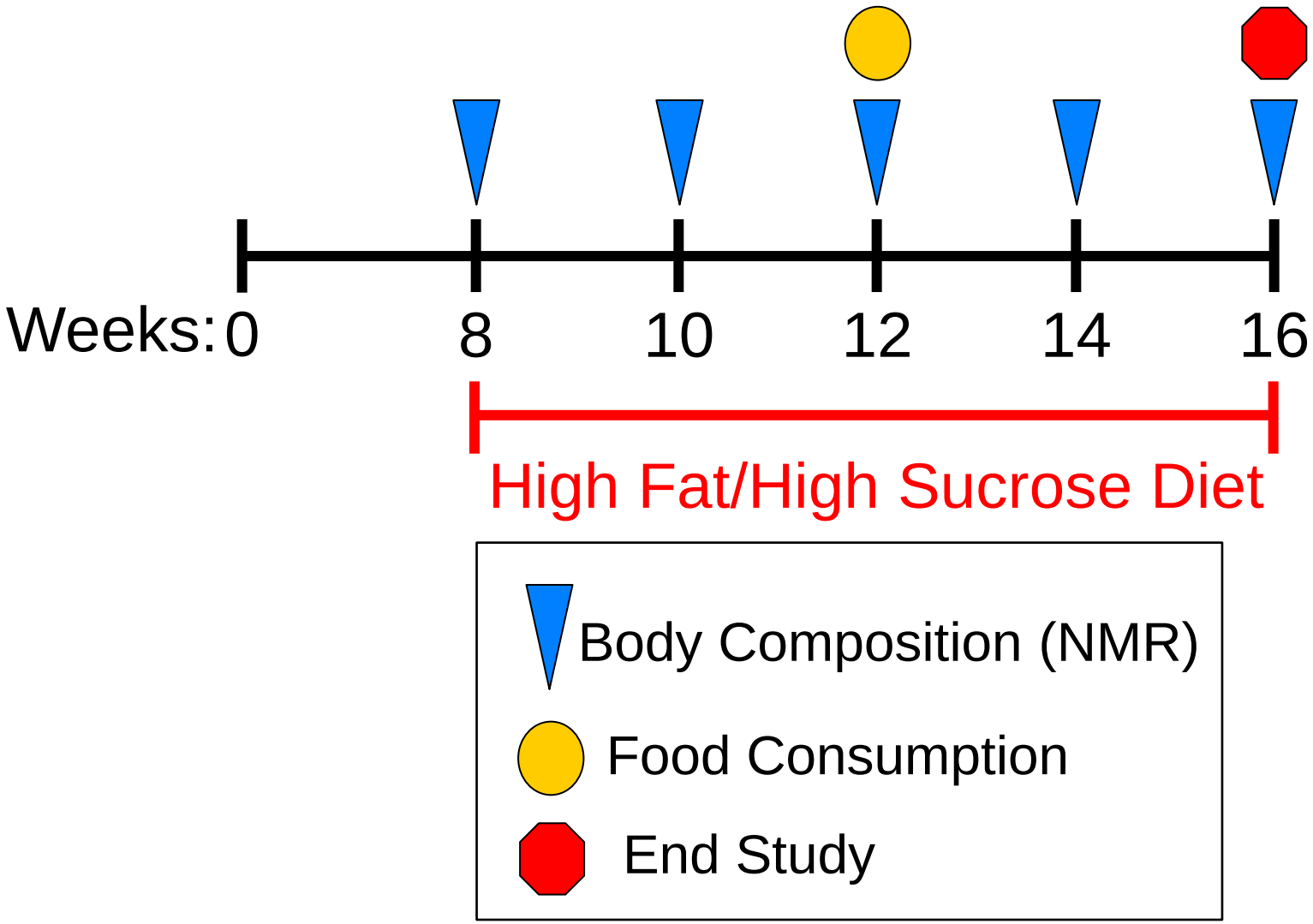
Validation: Asxl2 Deletion Decreases Bone Mineral Density



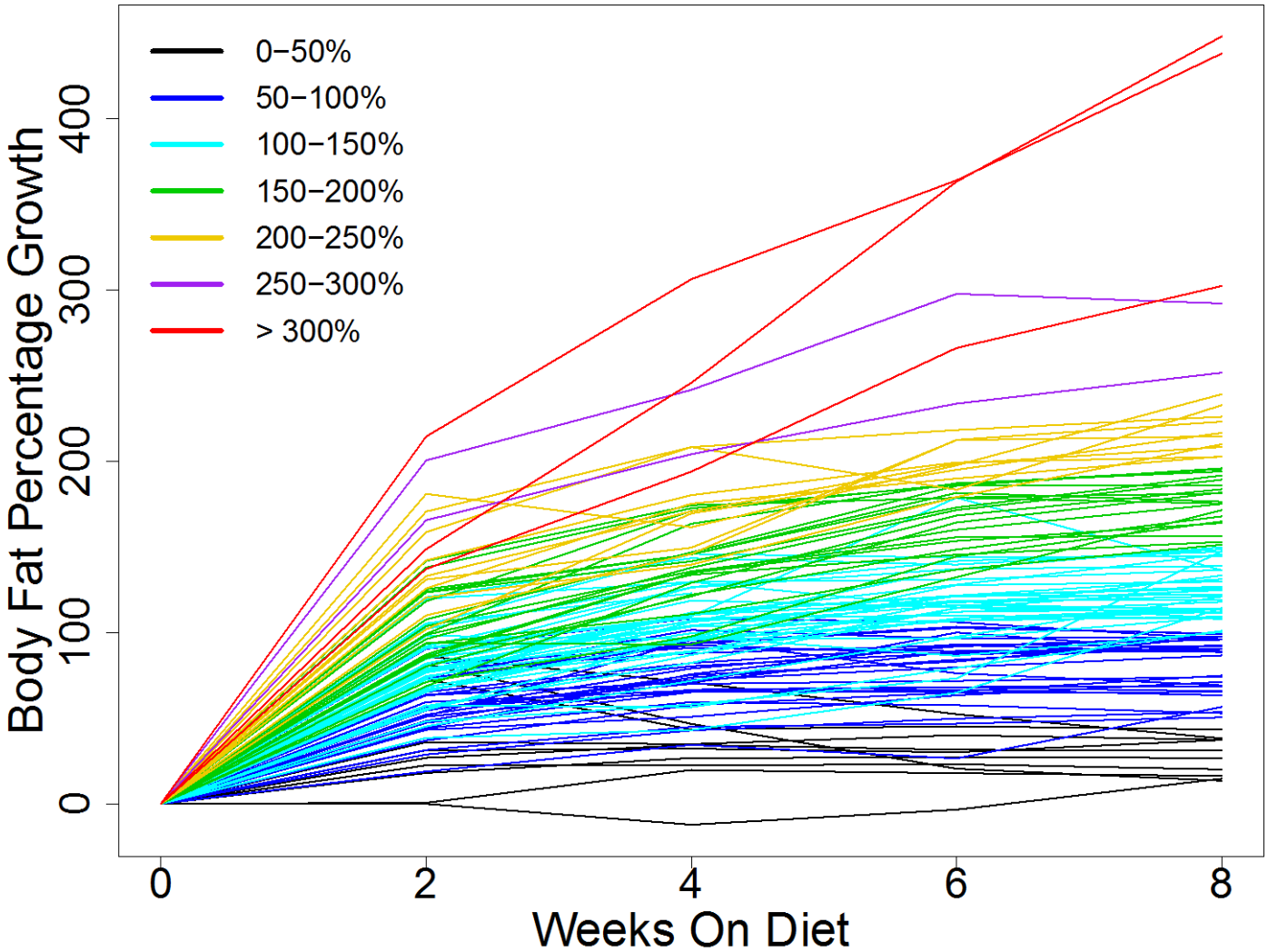
Farber *et.al. Plos Genetics.* 2011


Genetics
Environment
Disease

HMDP Obesity and Metabolic Syndrome Project: Study Design

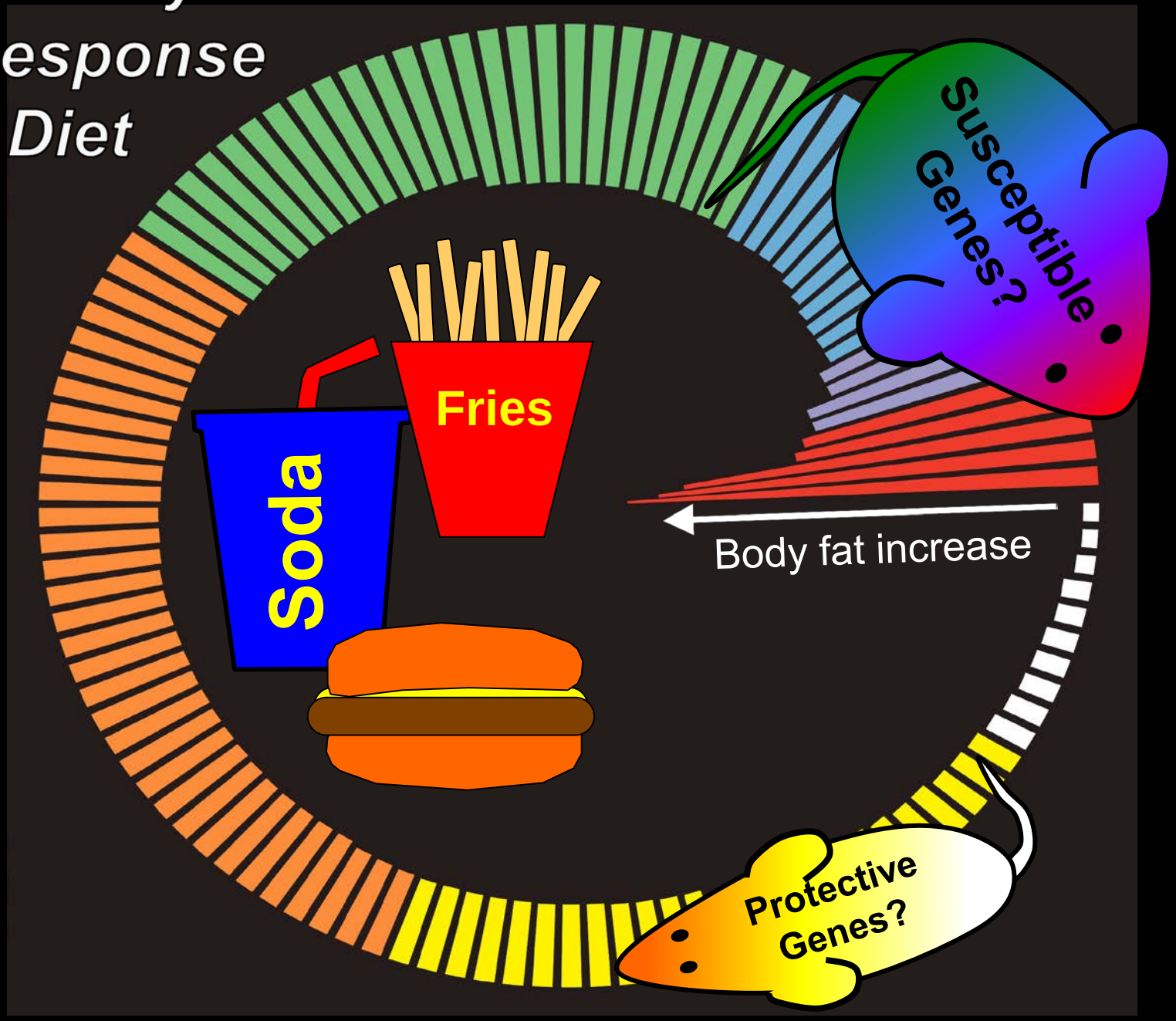


Large Variation in Response to Diet

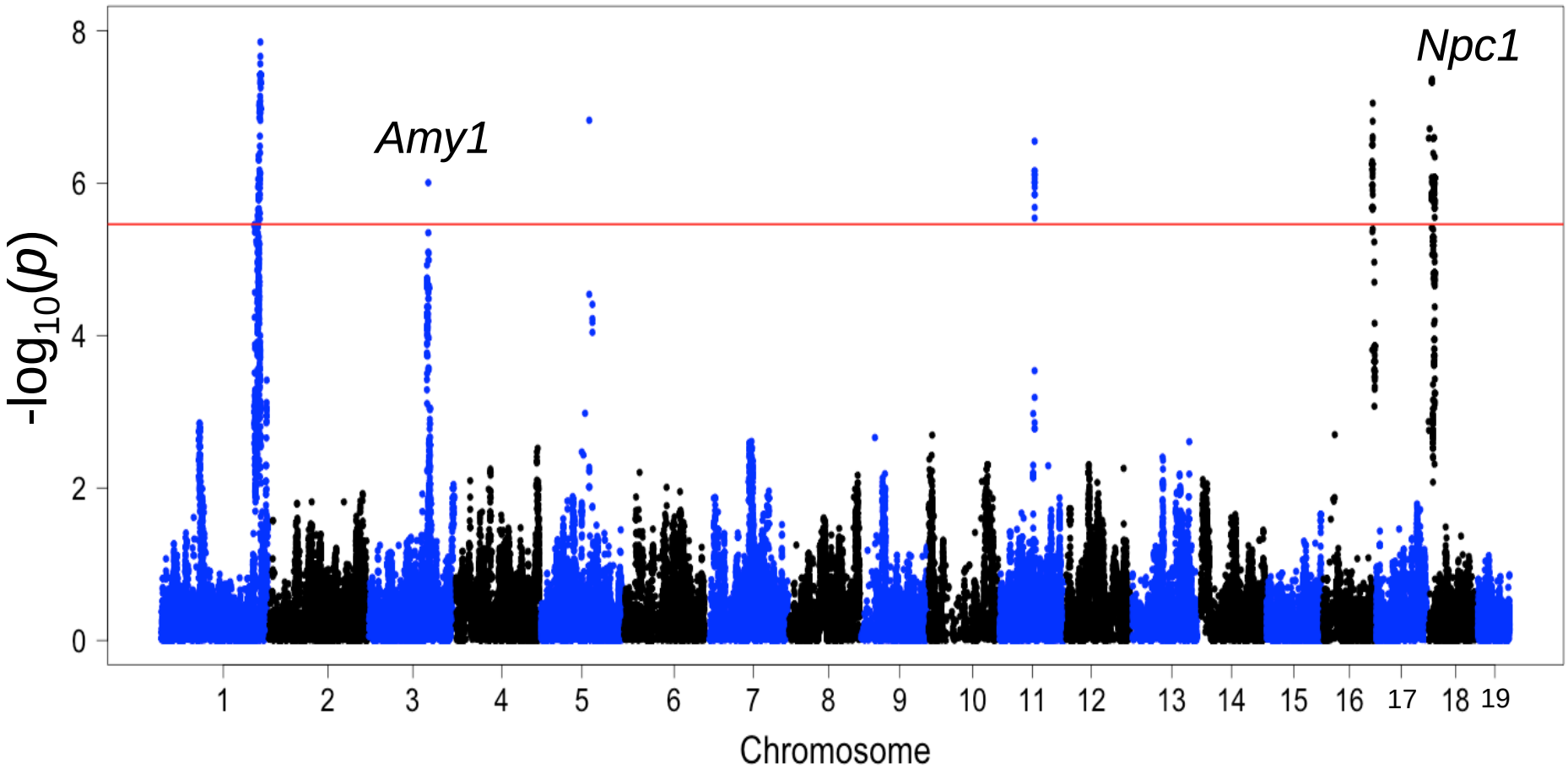


Parks BW, et. al. *Cell Metabolism.* 2013 Jan 8;17(1):141-52

Genetic Analysis With Response to Diet



GWAS For Response To Diet



Parks BW, *et. al. Cell Metabolism.* 2013

NPC1 and AMY1: Identified In Human Studies

Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations

David Meyre[1], Jérôme Delplanque[1], Jean-Claude Chèvre[1],

Nature Genetics **41**, 157 - 159 (2009)

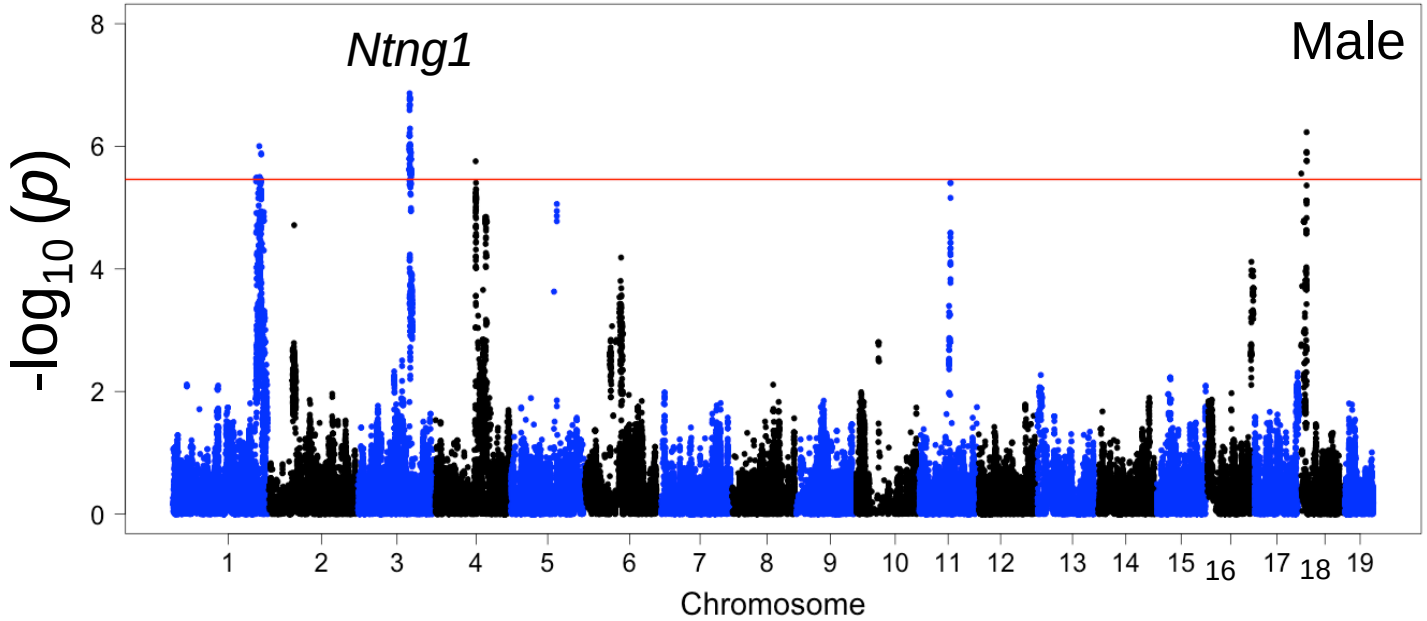
We analyzed genome-wide association data from 1,380 Europeans with early-onset and morbid adult obesity and 1,416 age-matched normal-weight controls. Thirty-eight markers showing strong association were further evaluated in 14,186 European subjects. In addition to ***FTO*** and ***MC4R***, we detected significant association of obesity with three new risk loci in ***NPC1*** (endosomal/lysosomal Niemann-Pick C1 gene, $P = 2.9 \times 10^{-7}$), near ***MAF*** (encoding the transcription factor c-MAF, $P = 3.8 \times 10^{-13}$) and near ***PTER*** (phosphotriesterase-related gene, $P = 2.1 \times 10^{-7}$).

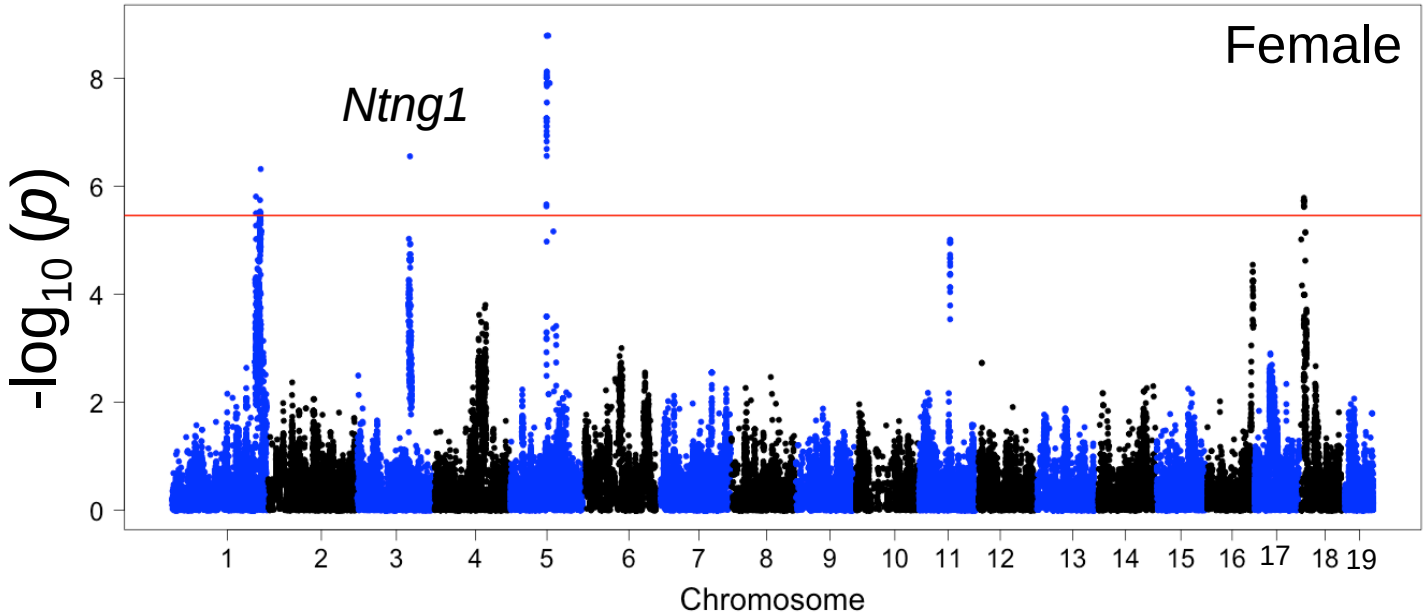
Low copy number of the salivary amylase gene predisposes to obesity

Mario Falchi[1,39,40], Julia Sarah El-Sayed Moustafa[1,39], Petros Takousis[1], Francesco Pesce[1,2], Amélie Bonnefond[3–6], Johanna C Andersson-Assarsson[1,7,8], Peter H Sudmant[9], Rajkumar Dorajoo[1,10], Mashael Nedham Al-Shafai[1,11], Leonardo Bottolo[12], Erdal Ozdemir[1], Hon-Cheong So[13], Robert W Davies[14], Alexandre Patrice[6,15,16], Robert Dent[17], Massimo Mangino[18], Pirro G Hysi[18], Aurélie Dechaume[3,4,6], Marlène Huyvaert[3,4,6], Jane Skinner[19], Marie Pigeyre[4,6,15,16], Robert Caiazzo[4,6,15,16], Violeta Raverdy[6,15,16], Emmanuel Vaillant[3,4,6], Sarah Field[20], Beverley Balkau[21,22], Michel Marre[23,24], Sophie Visvikis-Siest[25], Jacques Weill[26], Odile Poulain-Godefroy[3,4,6], Peter Jacobson[7,8], Lars Sjostrom[7,8], Christopher J Hammond[18], Panos Deloukas[20,27,28], Pak Chung Sham[13], Ruth McPherson[29,30], Jeannette Lee[31], E Shyong Tai[31–33], Robert Sladek[34–36], Lena M S Carlsson[7,8], Andrew Walley[1,37], Evan E Eichler[9,38], Francois Pattou[4,6,15,16], Timothy D Spector[18,40] & Philippe Froguel[1,3–6,40]

Nature Genetics. 2014 May;46(5):492-7

The First GWAS for Food Intake?





NTNG1 Identified in Human GWAS for Anorexia

ORIGINAL ARTICLE

A genome-wide association study on common SNPs and rare CNVs in anorexia nervosa

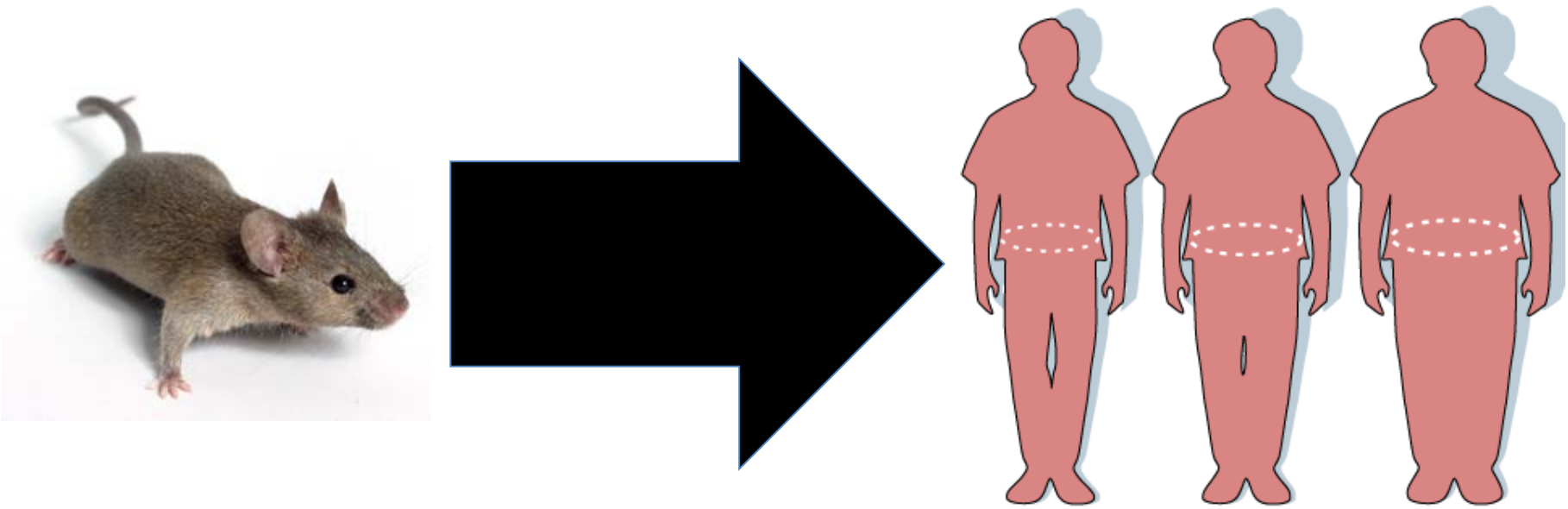
K Wang[1], H Zhang[1], CS Bloss[2], V Duvvuri[3], W Kaye[3], NJ Schork[2,4], W Berrettini[5], H Hakonarson[1,6], and the Price Foundation Collaborative Group[7]

Table 1 The list of SNP markers that are most significantly associated with AN ($P < 1 \times 10^{-5}$)

Index SNP[a]	*Locus*	*Closest gene*	*SNP-gene distance*	*MAF (case)*	*MAF (control)*	P-*value*	# *additional SNP*[b]
rs6959888	7q21.13	*ZNF804B*	0	0.15	0.11	1.63E-06	0
rs17725255	20p11.23	*CSBP2BP*	39396	0.14	0.11	1.72E-06	0
rs10494067	1p13.3	*NTNG1*	0	0.03	0.06	5.83E-06	0
rs2383378	14q12	*AKAP6*	0	0.35	0.41	6.41E-06	2
rs410644	5q14.1	*SSBP2*	40462	0.41	0.47	6.74E-06	2
rs4479806	5p14.1	*CDH9*	156926	0.06	0.10	7.79E-06	0
rs957788	13q33.3	*FAM155A*	0	0.37	0.31	8.11E-06	4
rs830998	2q31.1	*LRP2*	0	0.23	0.19	8.68E-06	3
rs6782029	3p25.3	*VGLL4*	0	0.19	0.24	9.04E-06	0
rs512089	9p21.3	*ELAVL2*	47984	0.28	0.24	9.85E-06	1
rs3808986	11q24.3	*APLP2*	29217	0.05	0.08	9.92E-06	0

Molecular Psychiatry **16**, 949-959 (2011)

Relevance to Humans?



Farber *et.al. Plos Genetics.* 2011

Parks *et.al. Cell Metabolism.* 2013

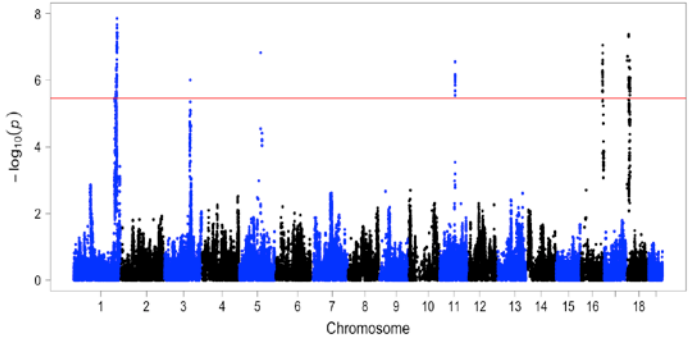
Systems Genetics: Pathway Discovery

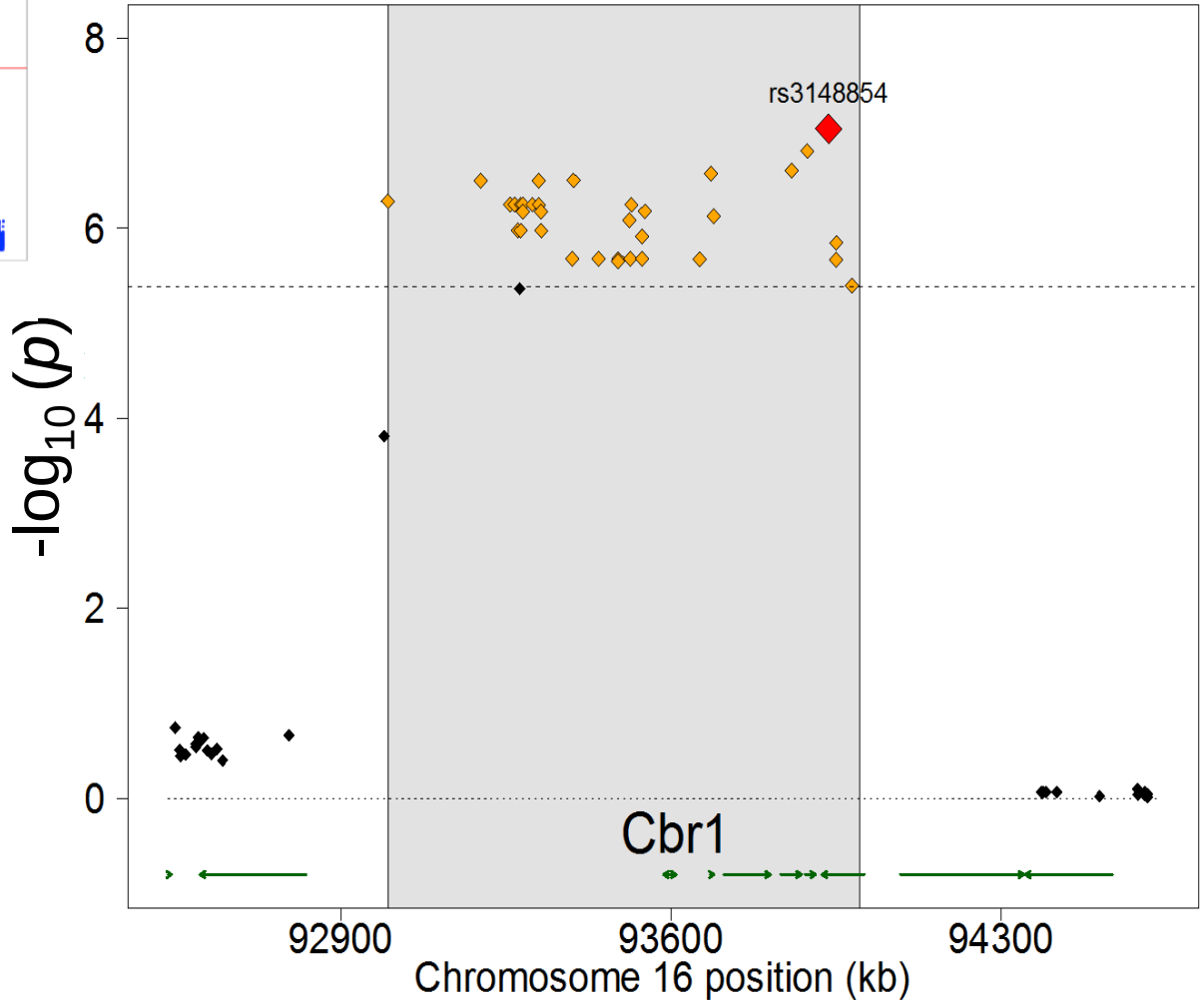
HMDP

Gene Identification

Biological Pathway

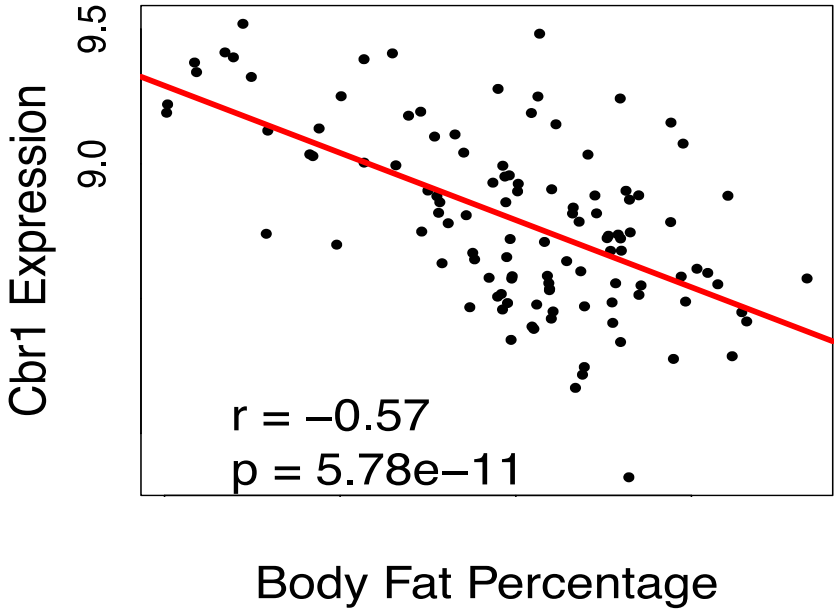
Chromosome 16 Locus For Body Fat Response To Diet

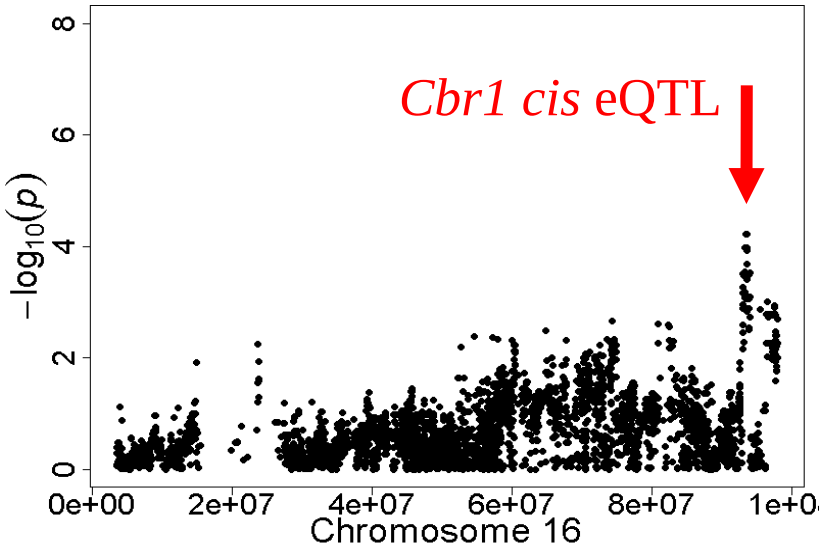




Parks BW, et. al. *Cell Metabolism.* 2013

Systems Genetics: Integration of Gene Expression





Adipose Tissue From High-Fat/High-Sucrose Fed Male Mice

Parks BW, et. al. *Cell Metabolism.* 2013

What is Cbr1?

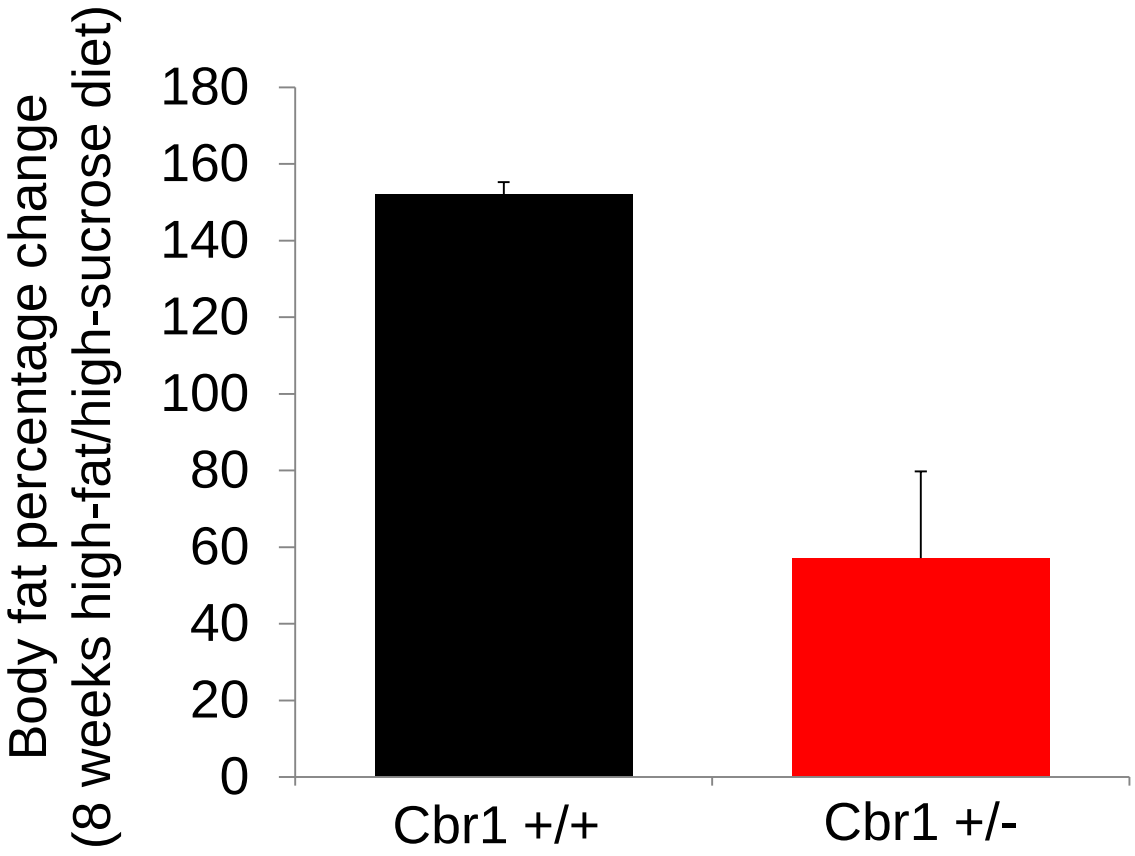
Carbonyl Reductase 1

NADPH-dependent reductase with broad substrate specificity.

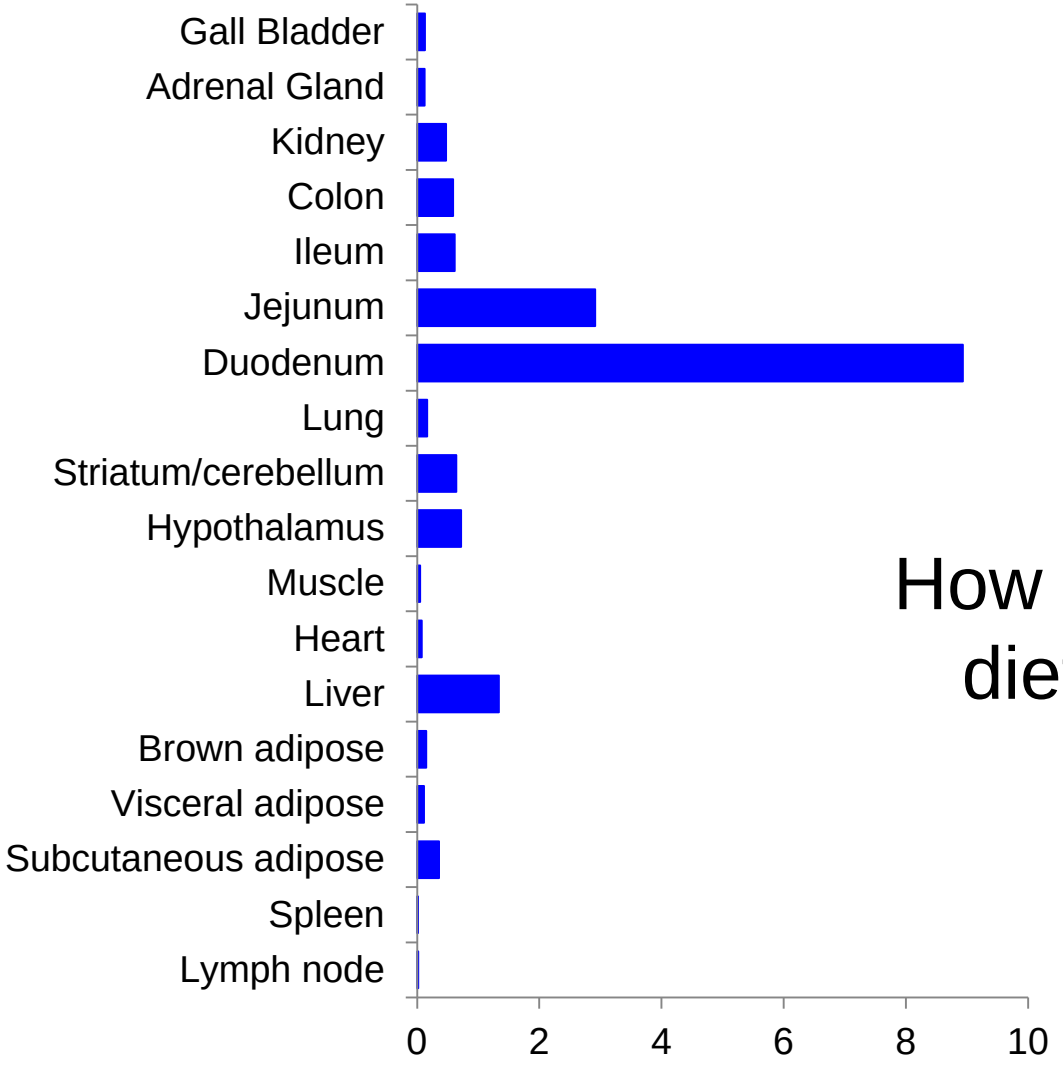
Catalyzes the reduction of a wide variety of carbonyl compounds including quinones, prostaglandins, plus various xenobiotics.

Never before studied in obesity and metabolism

Validation of Cbr1

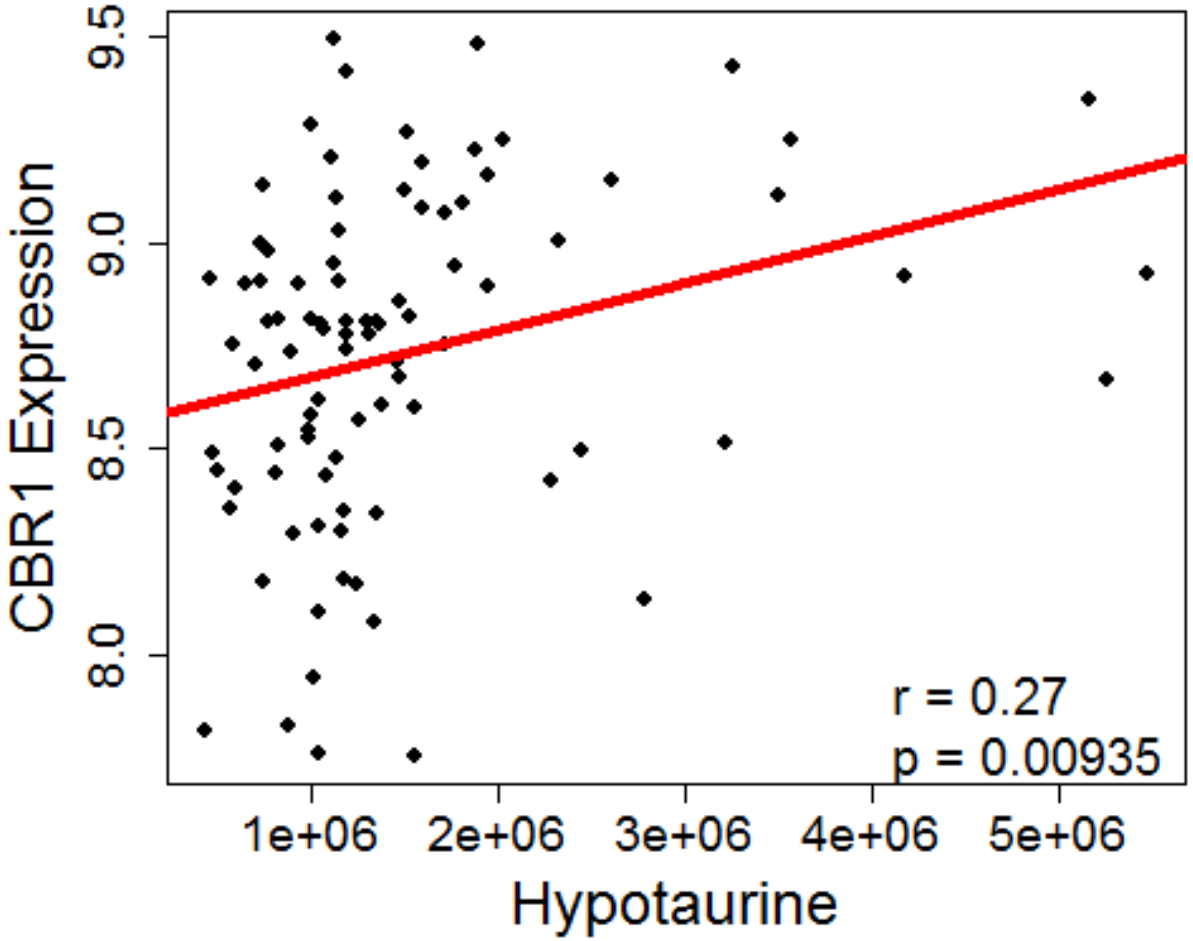


Cbr1 Expressed in Multiple Relevant Tissues

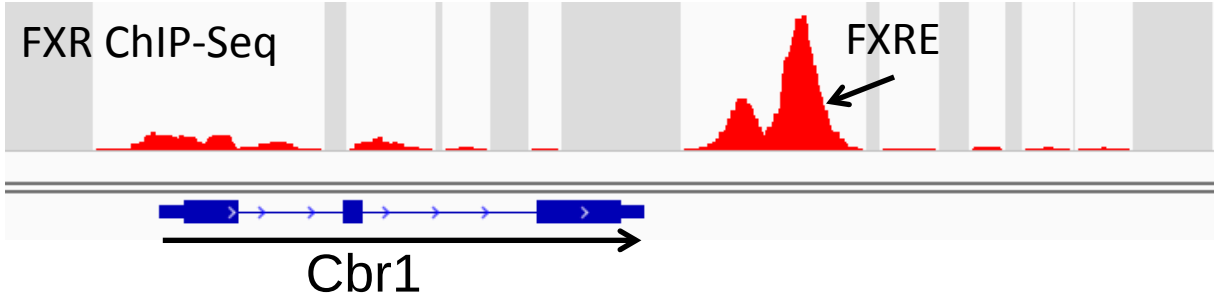


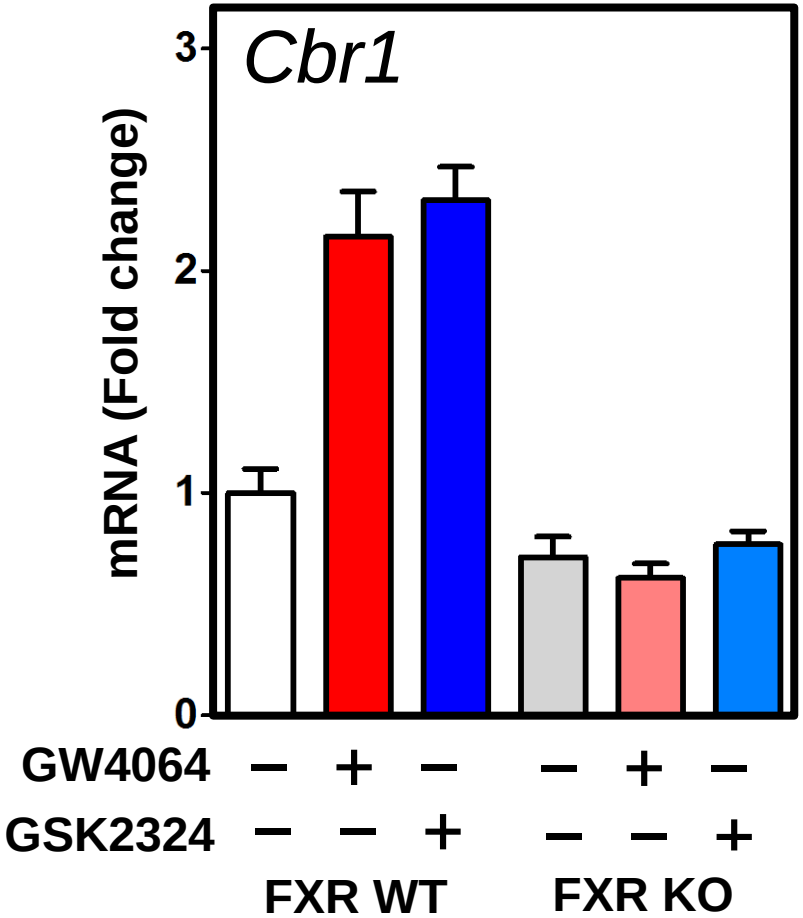
How is Cbr1 controlling dietary responses?

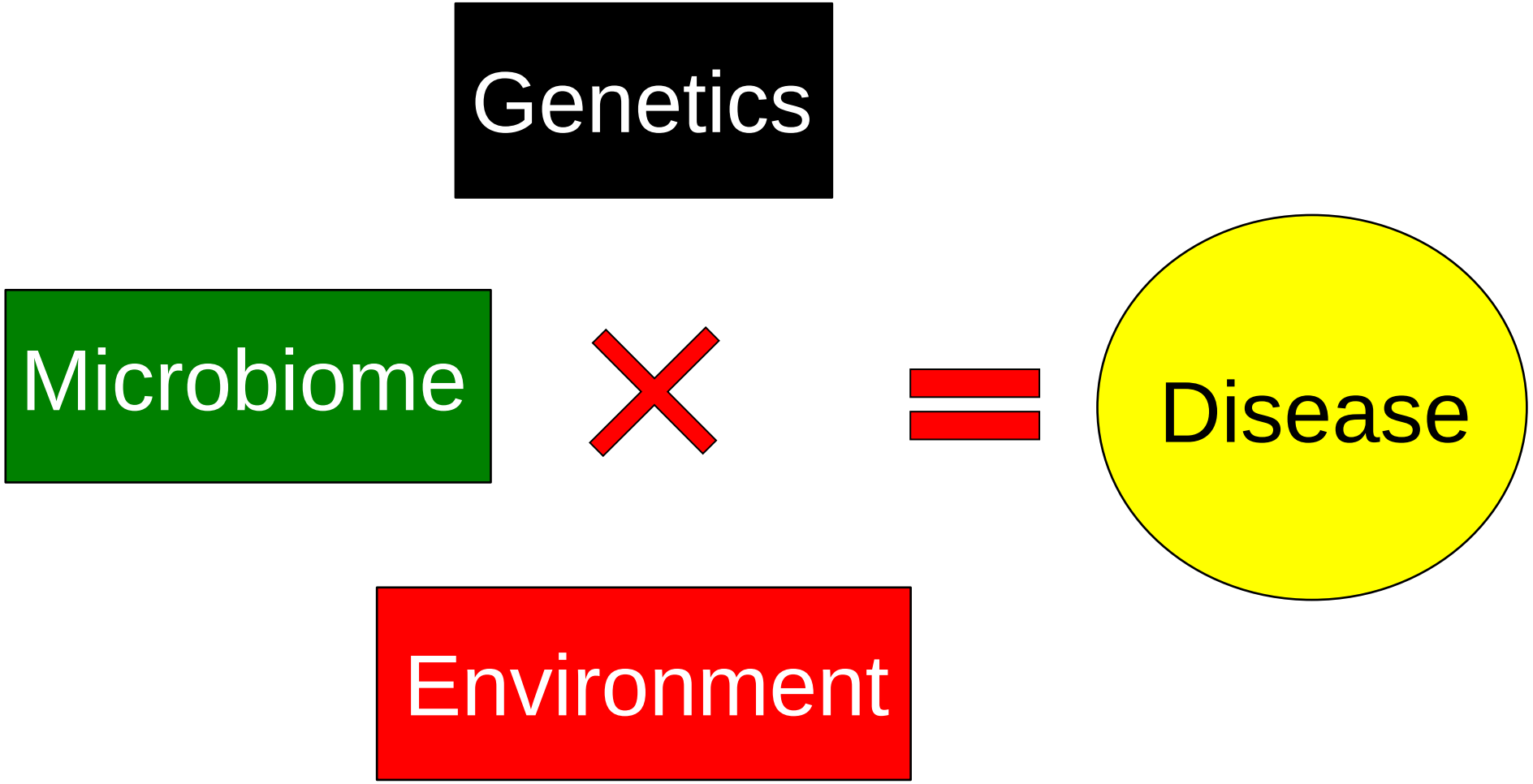
Cbr1 expression in liver correlates with hypo-taurine (conjugated to Bile Acids)



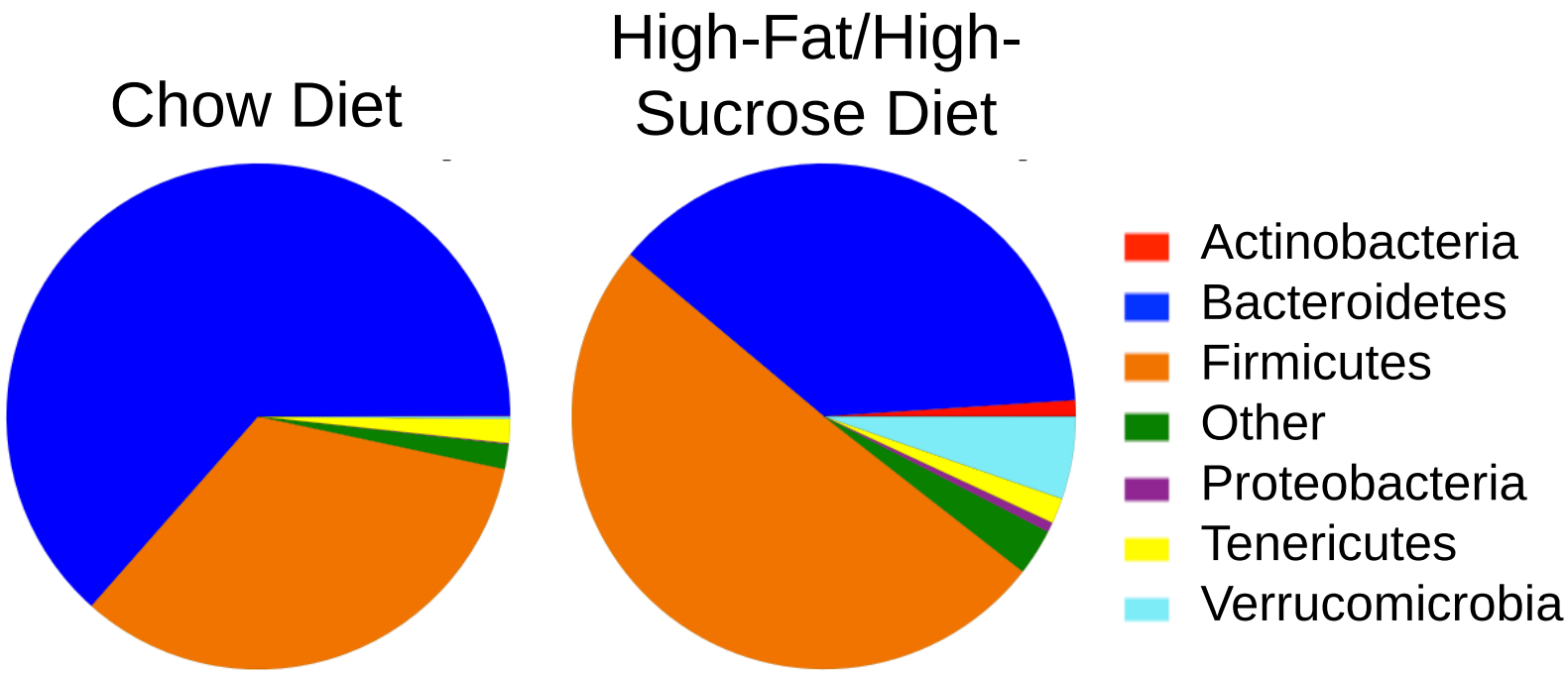
Cbr1 is a direct FXR target gene





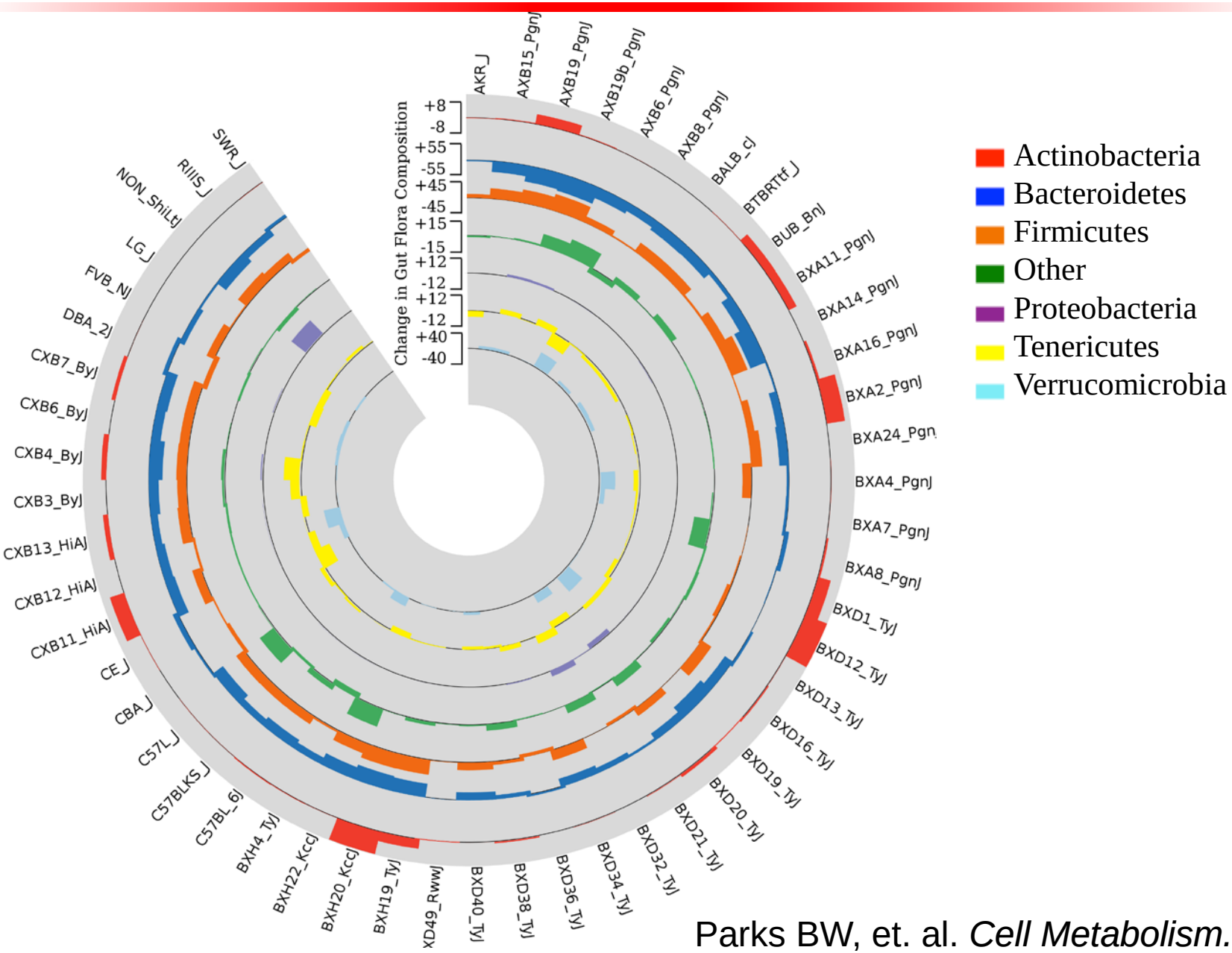

Genetics
Microbiome
Environment
Disease

Dramatic Shift in Gut Microbiota



Parks BW, et. al. *Cell Metabolism.* 2013

Strain-Specific Shift in Gut Microbiota

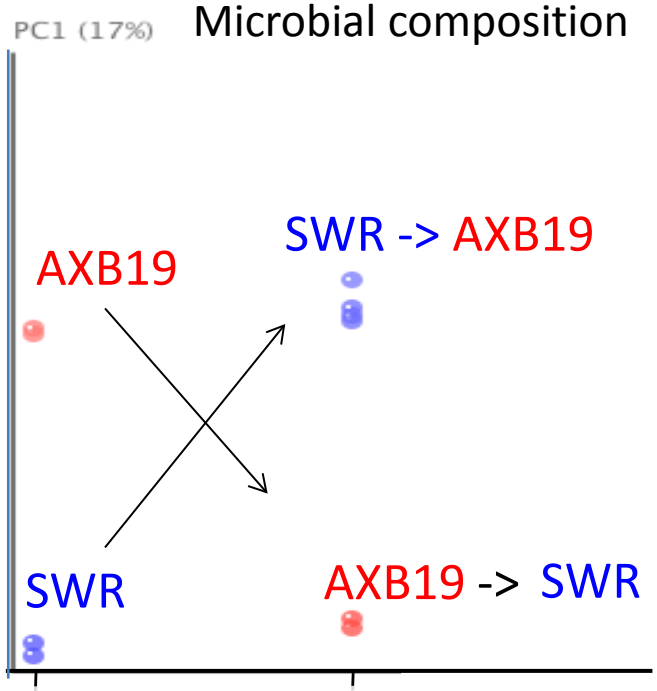


Parks BW, et. al. *Cell Metabolism.* 2013

Cross-fostering Microbial Communities

Cross-fostering pups

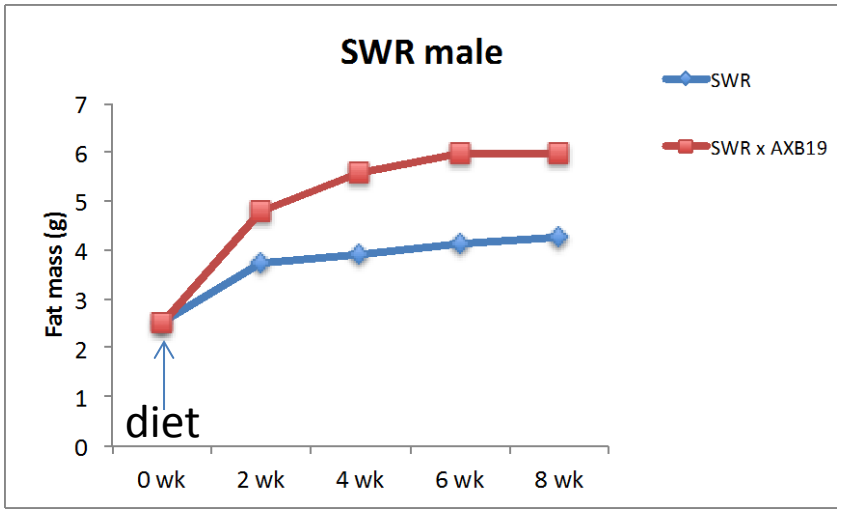
Microbial composition



Parents

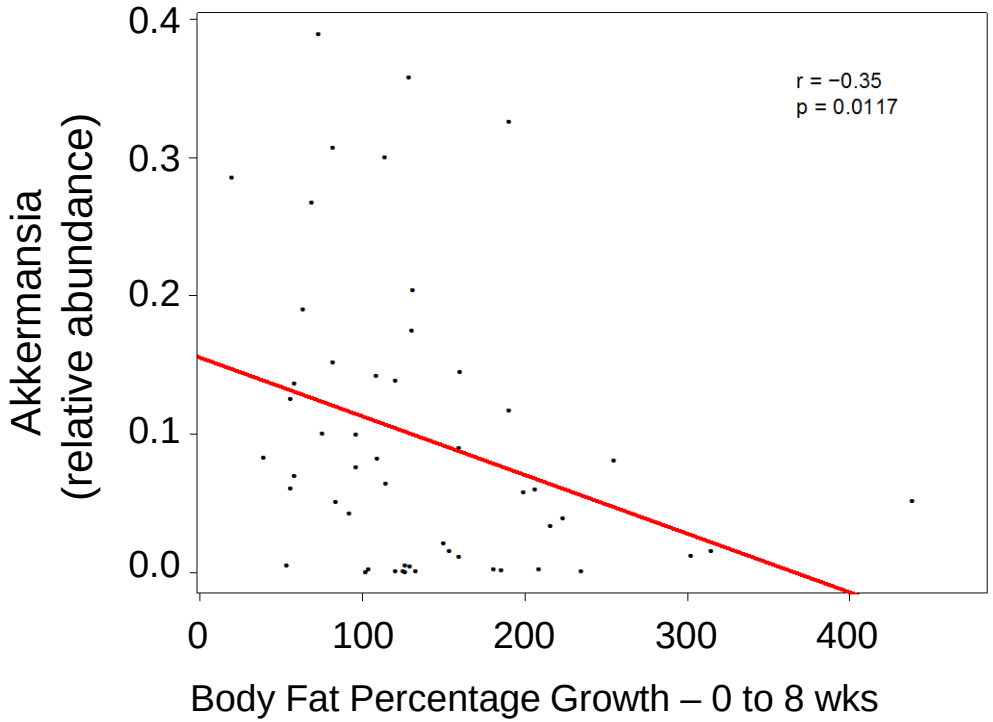
Cross fostered pups
4 wks after weaning

SWR → AXB19



Elin Org (Unpublished)

Akkermansia Relationship to Obesity



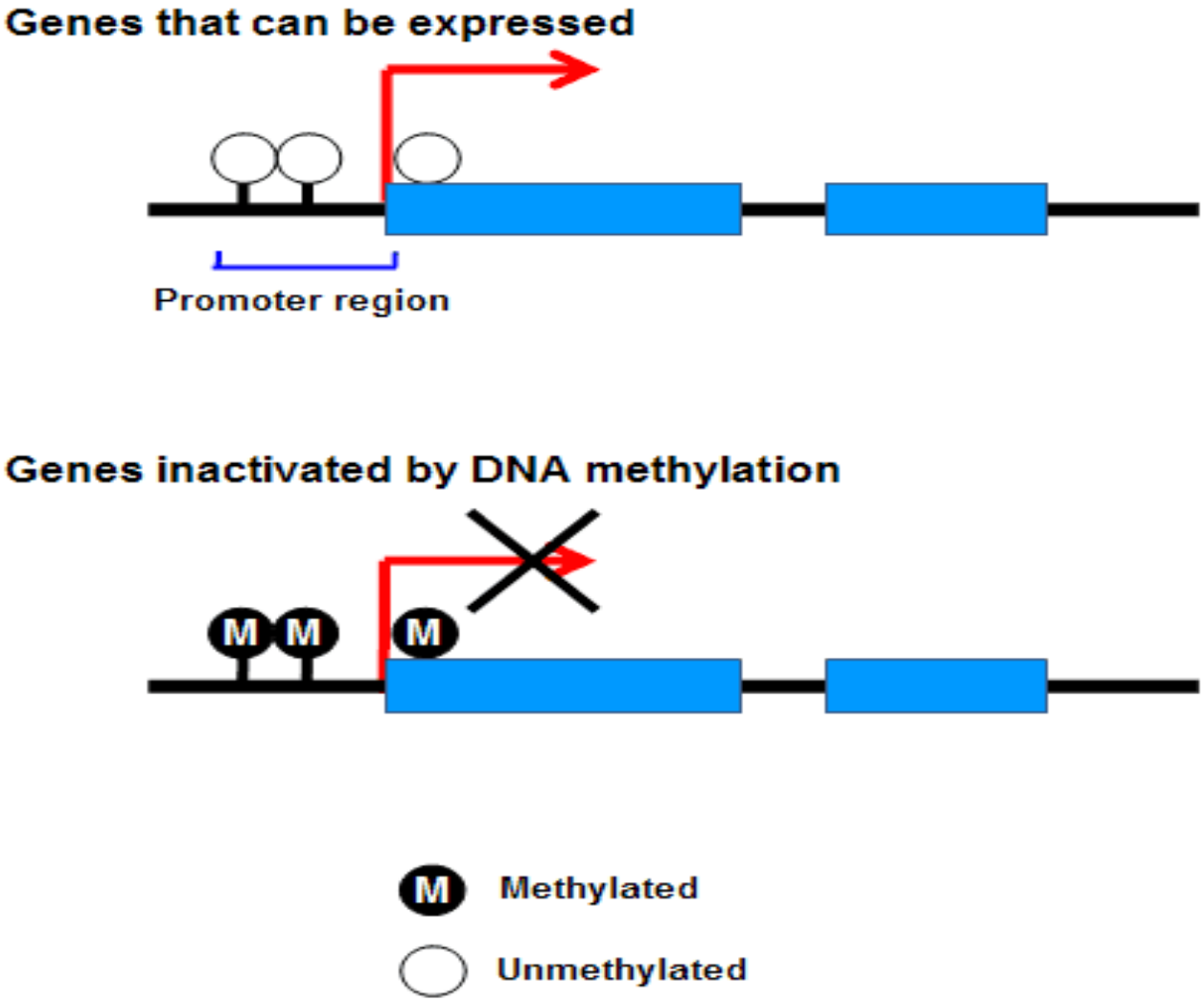
Parks BW, et. al. *Cell Metabolism.* 2013

Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity

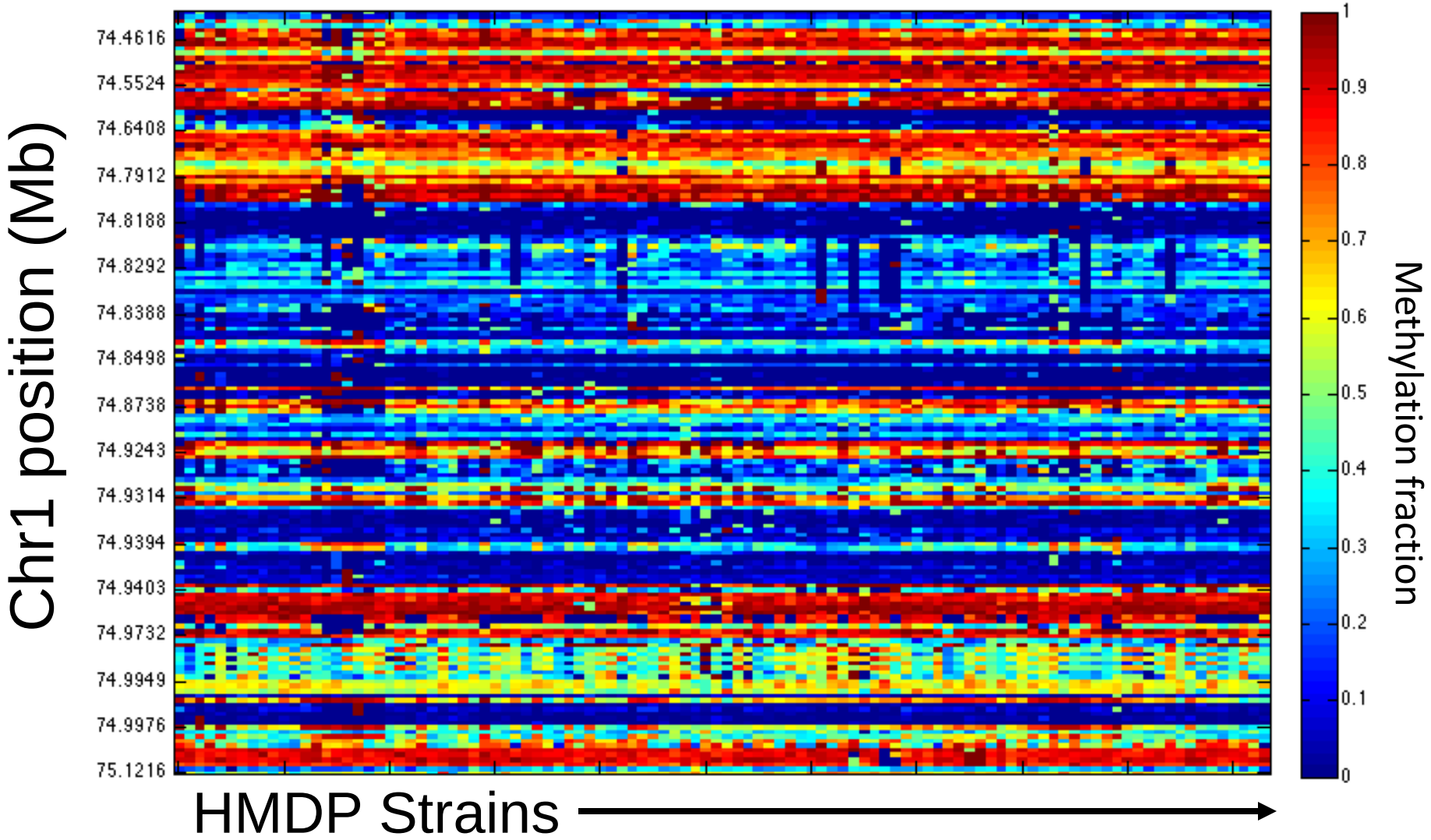
Amandine Everard[a], Clara Belzer[b], Lucie Geurts[a], Janneke P. Ouwerkerk[b], Céline Druart[a], Laure B. Bindels[a], Yves Guiot[c], Muriel Derrien[b], Giulio G. Muccioli[d], Nathalie M. Delzenne[a], Willem M. de Vos[b,e], and Patrice D. Cani[a,1]

9066–9071 | PNAS | May 28, 2013 | vol. 110 | no. 22

Epigenetics: DNA Methylation



DNA Methylation on Chromosome 1 in Liver



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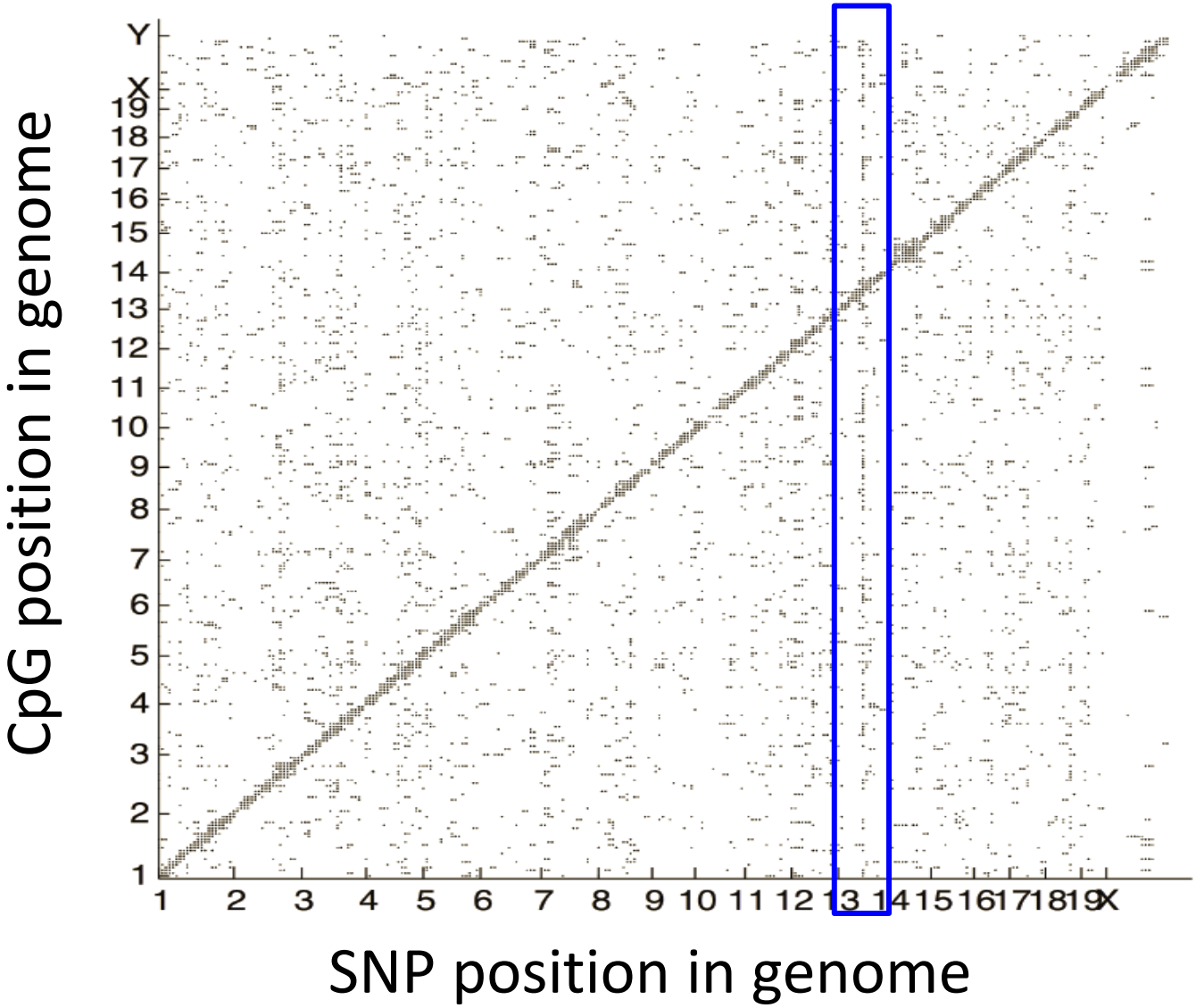
Genetic Control of DNA Methylation



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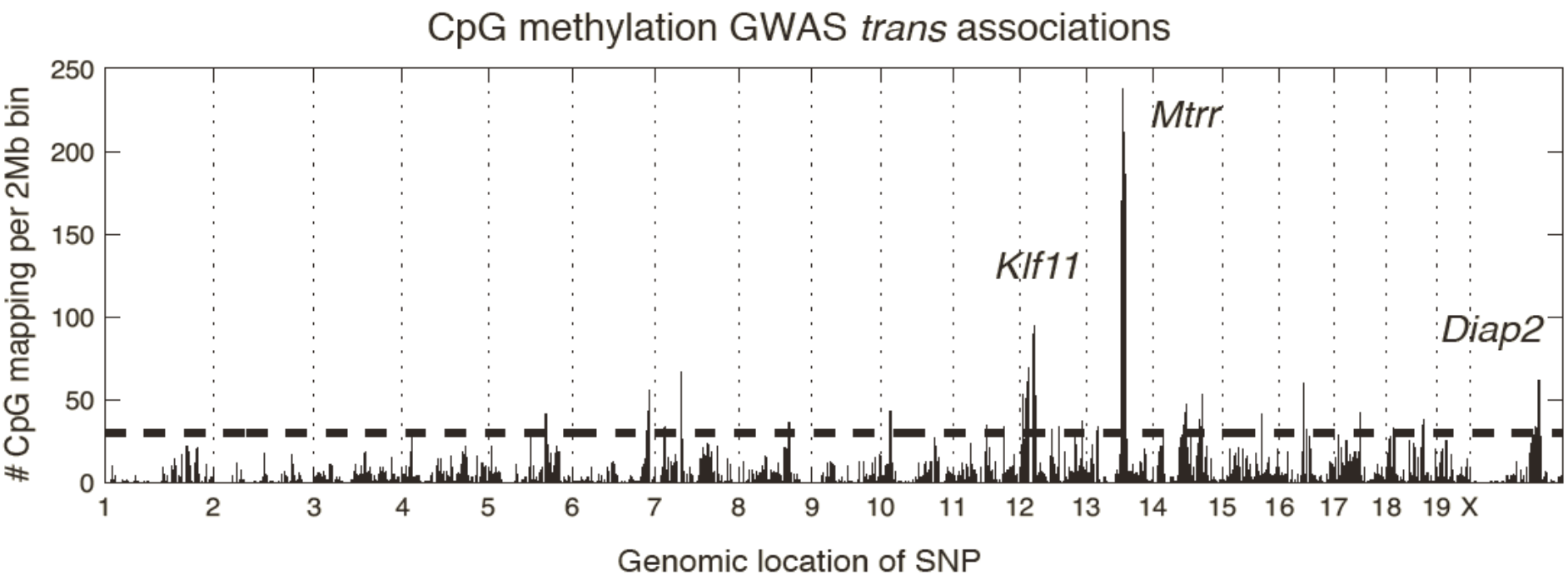
Trans Regulation of Methylation in Liver



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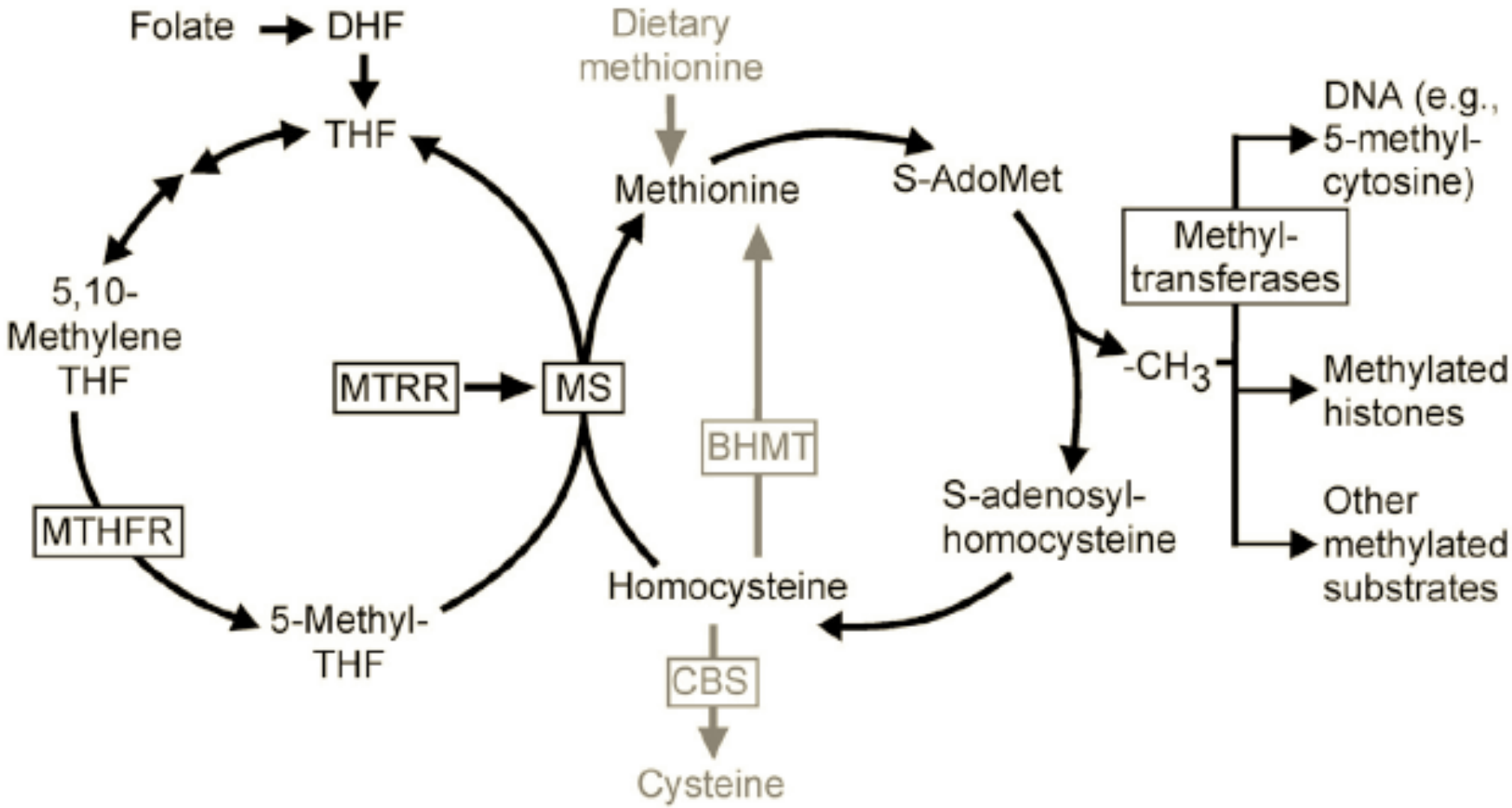
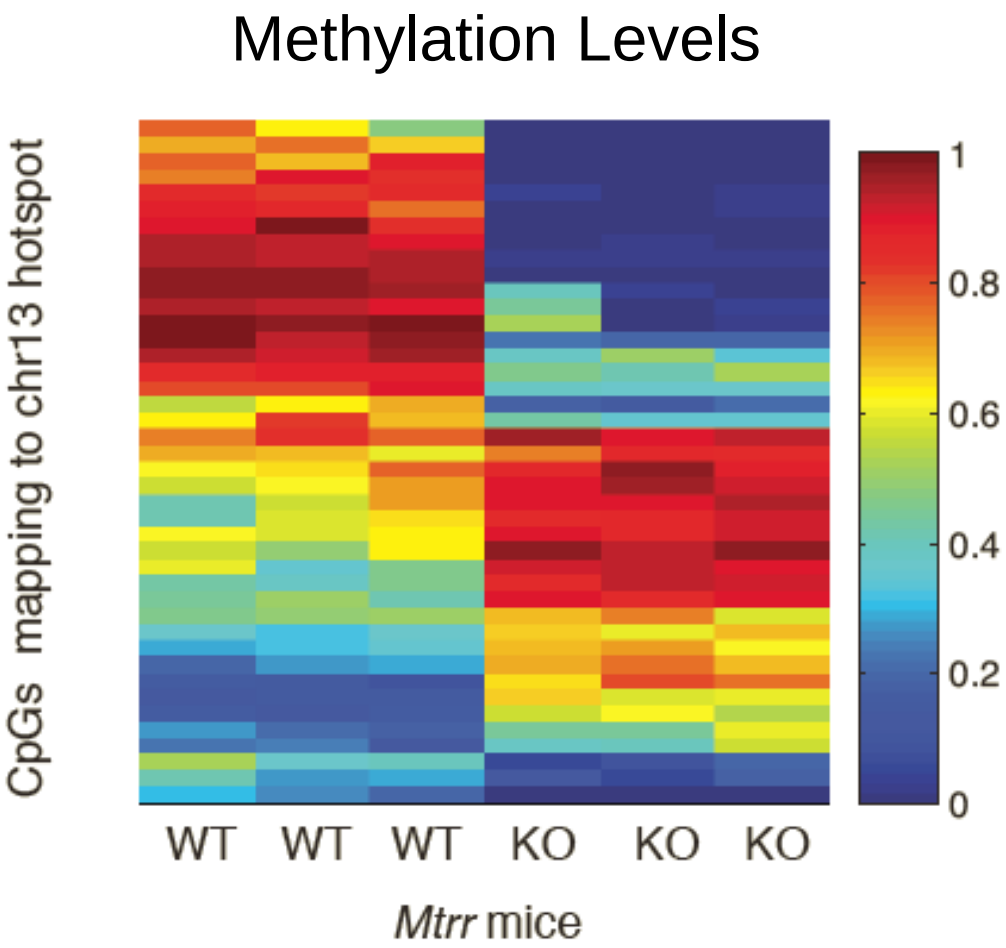
Methionine Synthase Reductase (Mtrr) and Generation of Methyl Groups



Padmanabhan *et al. Cell.* 2013

Mtrr KO Mice Have Altered Methylation at Hotspot Sites



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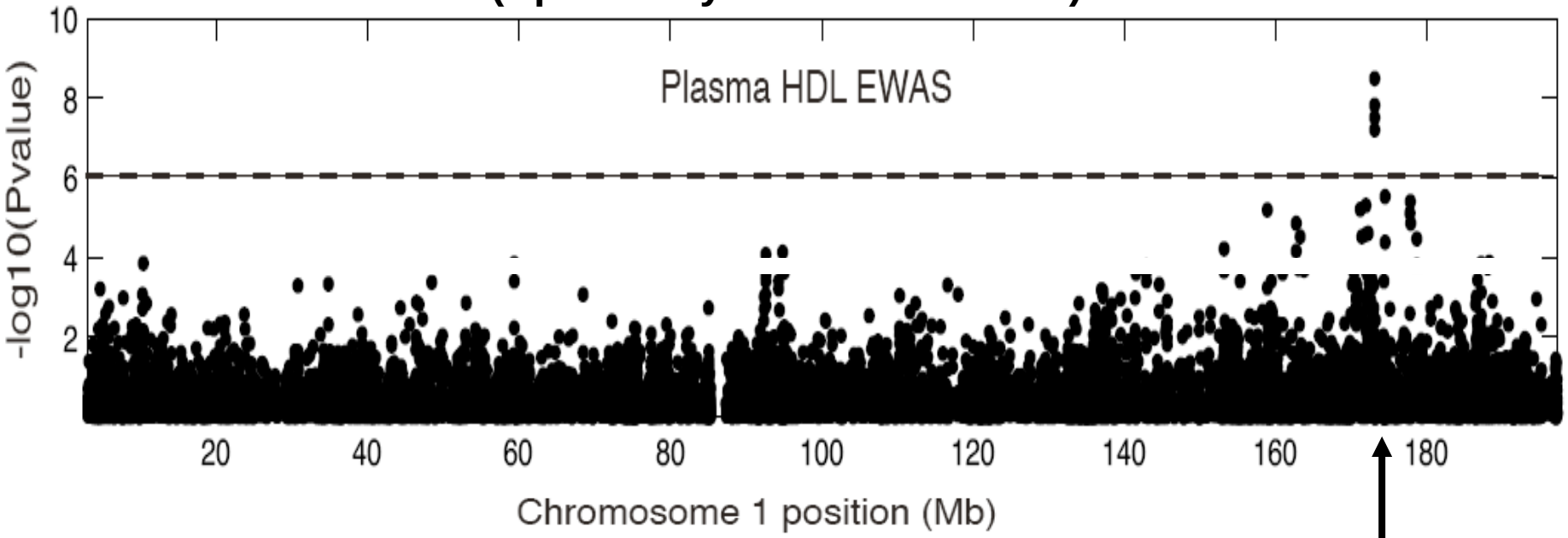
Epigenome-wide Association Study (EWAS) Identifies HDL locus on Chromosome 1

Plasma HDL EWAS (CpG methylation association)



Apoa2 gene

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Overview

Hybrid Mouse Diversity Panel (HMDP)

Gene Identification/validation: *Asxl2* (Bone Mineral Density), *Cbr1* (Gene X Diet), *Agpat5* (Insulin Resistance), ***Dusp7* (Insulin Resistance)**

Pathway Discovery: *Cbr1* (Gene X Diet) → Bile Acids

Integration: Transcriptomics, Microbiome, Epigenetics

EWAS: Using variation in epigenetics for association mapping

Poster by Marcus Seldin: "***Systems genetics approach uncovers Dusp7 as a novel phosphatase regulating skeletal muscle insulin signaling.*** "

Hybrid Mouse Diversity Panel: Ongoing Projects

Diabetic complications (Jake Lusis, Rich Davis, NIH grant)
Heart failure (Yibin Wang, Jake Lusis, NIH grant)
Atherosclerosis (Jake Lusis, Eleazer Eskin, NIH grant)
DNA methylation (Matteo Pelligrini, NIH grant)
Asthma (Hooman Allayee, USC, NIH grant)
Gene-by-diet interactions in obesity (Jake Lusis, Eskin, NIH grant)
Osteoporosis (Charles Farber, U. Virginia, NIH grant)
Deafness (Rick Friedman, House Ear Inst., NIH grant)
Gum disease (Flavia Pirih, Sotirios Tetradis, grant submitted)
Hepatotoxicity (Simon Beaven, grant in preparation)
Addictive behavior (David Jentsch, NIH grant)
Vascular injury (Renee LeBoeuf, U. Wash., NIH grant)
Conditioned frea (Des Smith, NIH grant)
Gut flora (Tom Drake, grant in preparation)
Arrhythmia (Jim Weiss, grant submitted)
Mineral metabolism (Chris Vulpe, UC Berkeley, NIH grant)
Jaw shape (Sotirios Tetradis, grant in preparation)

HMDP: Gene X Environment Projects

- Jake Lusis, UCLA: diet-metabolic disorders
- Frank Gilliland, USC: air pollution – asthma
- Chris Vulpe, UC Berkeley: metals-metabolic traits
- David Jentsch, UCLA: drugs-addictive behavior
- Rick Friedman, USC: noise-deafness
- Yibin Wang, UCLA: adrenergic stimulation-heart failure
- Karen Reue, UCLA: statins-myopathy

HMDP: Advantages and Disadvantages

Advantages

Mice freeily available (JAX)

High Quality Genotypes (Mouse Diversity Array)

Inbred mice → Repeated Measures

Lots of variation in all traits measured

Results can be integrated across studies

Building database of results

Disadvantages

Low Power → Only 100-150 strains

Commitment → Long term project

Cost

Genetic Drift

Acknowledgements

Aldons 'Jake' Lusis

HMDP

Brian Bennett (UNC)
Charles Farber (UVA)
Luz Orozco (UCLA)

Lab

Elizabeth Nam
Margarete Mehrabian
Simon Hui
Frode Norheim
Hannah Qi
Zhiqiang Zhou
Elin Org
Marcus Seldin
Mete Civelek
Calvin Pan

UCLA Computer Science

Eleazar Eskin

Jackson Laboratories

Gary Churchill

Bristol Myers Squibb

Isis Pharmaceuticals

Microbiome

Elin Org
Rob Knight (Colorado)

Funding

K99/R00 Pathway to Independence Award

National Institutes of Health

A toolbox for dissecting complex traits