Colloque "Rein et Obésité"
Académie de Médecine
Paris, 9 Mars 2016

Les gènes de l'obésité

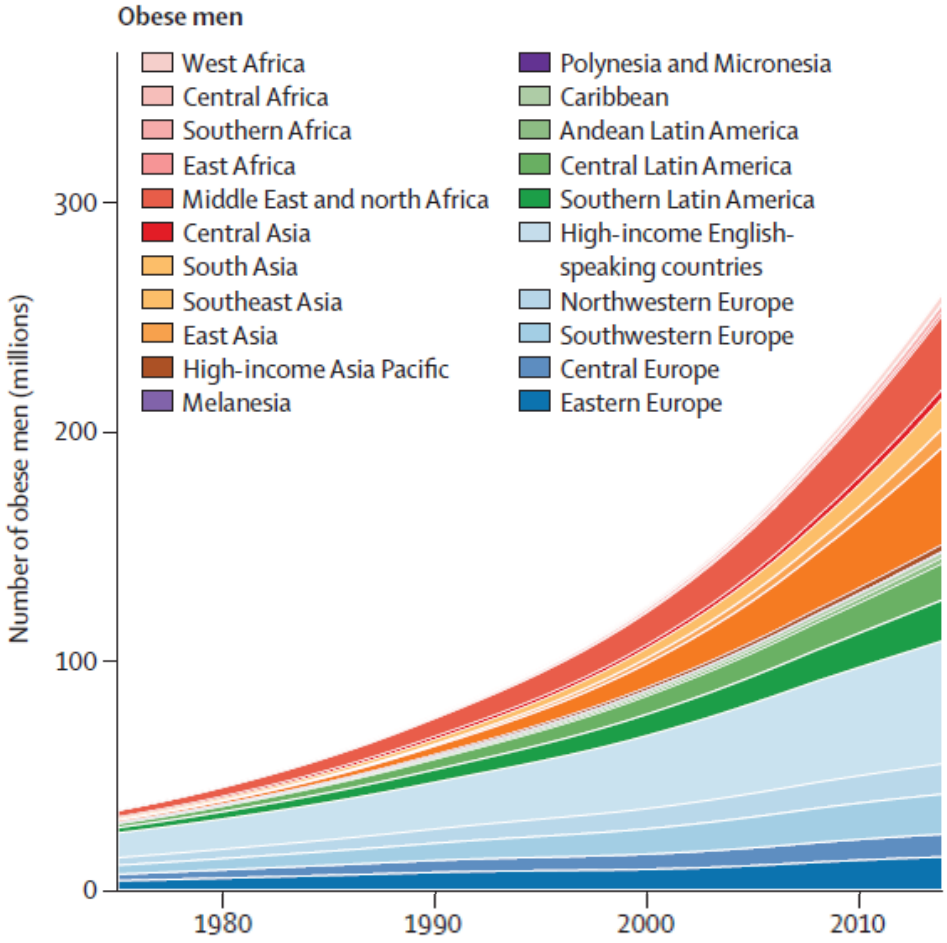
Dr Amélie Bonnefond

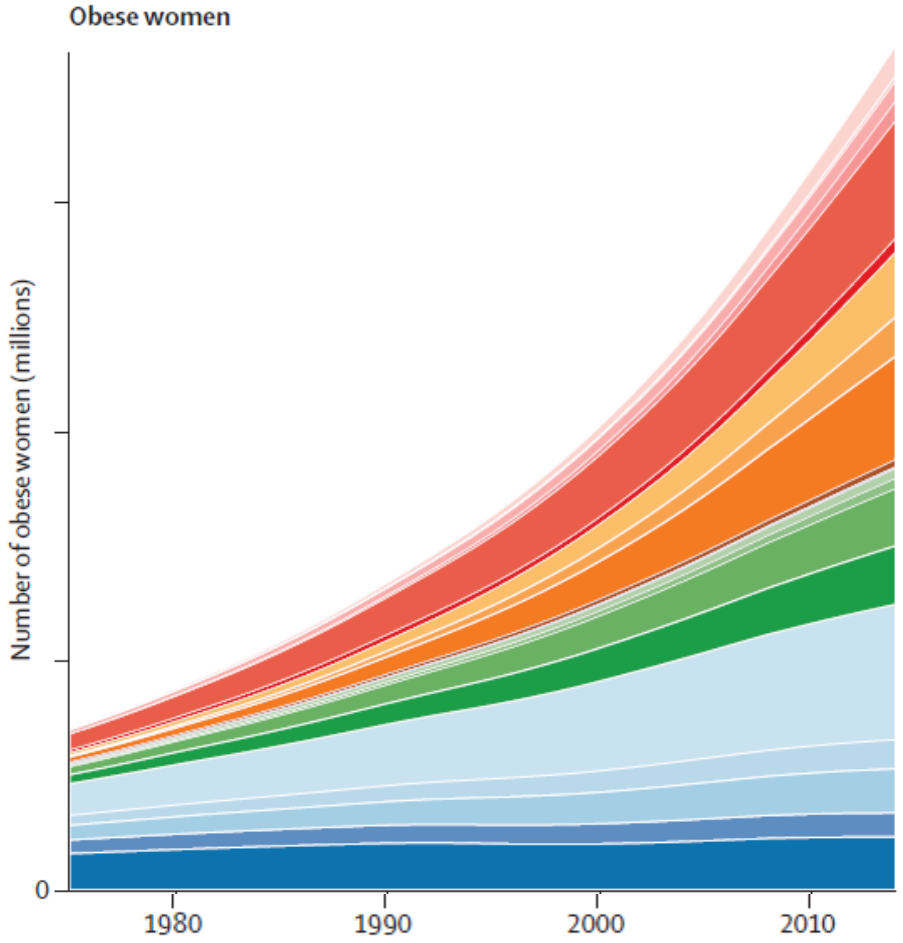
E.g.i.d. European Genomic Institute for Diabetes
Institut Pasteur de Lille
cnrs dépasser les frontières
Université de Lille 2 DROIT ET SANTÉ
Inserm

The global epidemic of obesity

Lancet 2016; 387: 1377–96

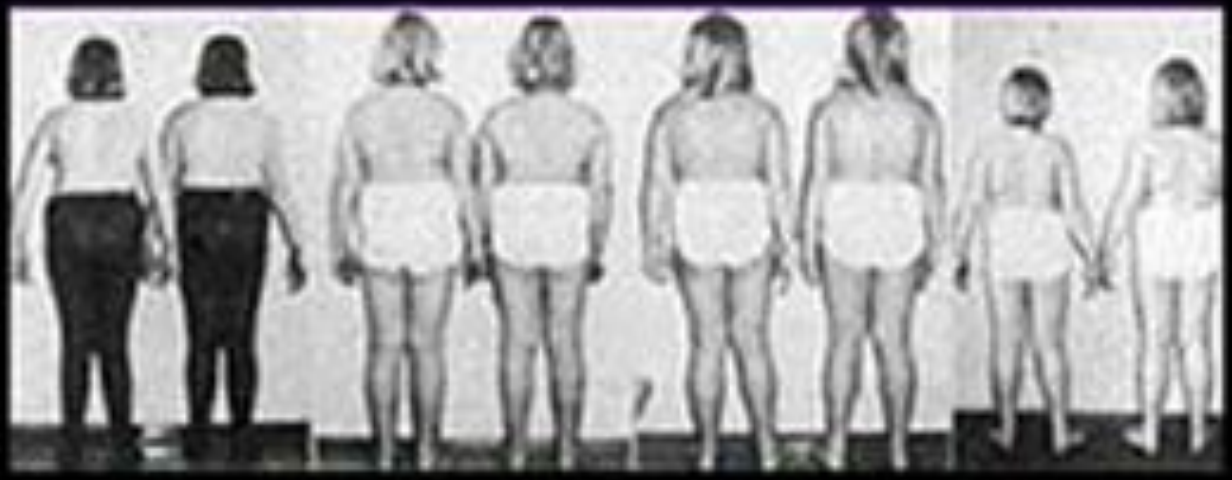
Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants





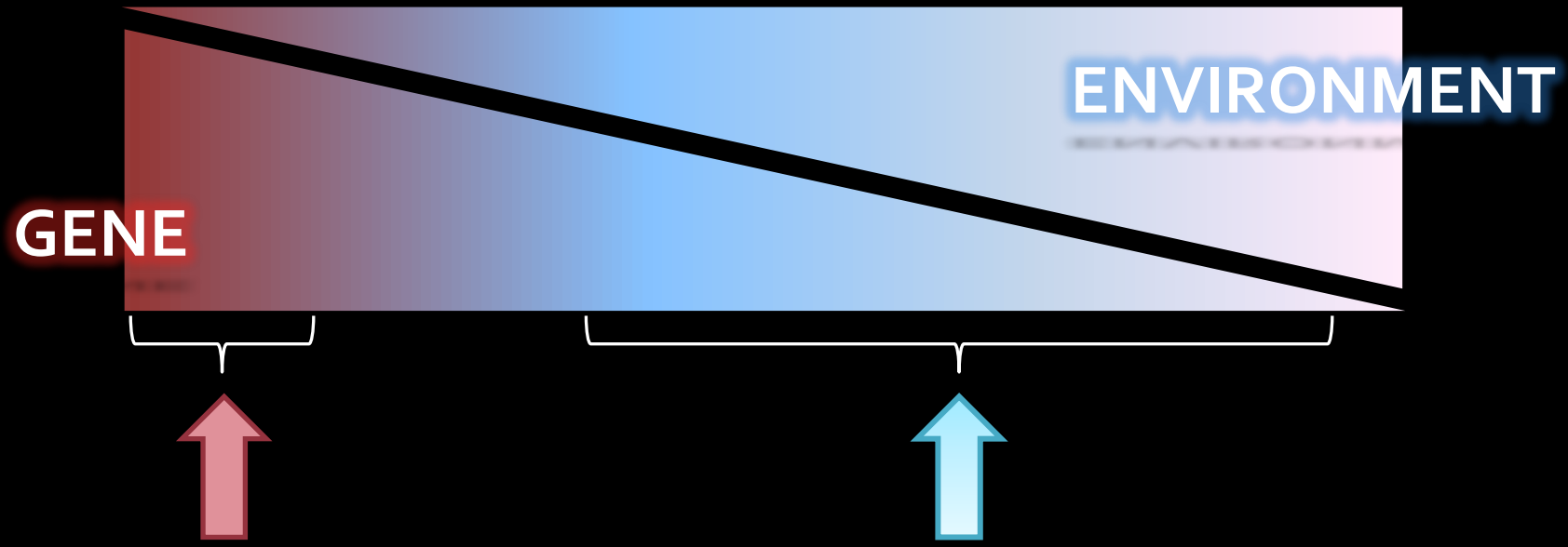
Obesity is a genetic disorder

Identical Twins



Fraternal Twins

Heterogeneity of the genetics of obesity

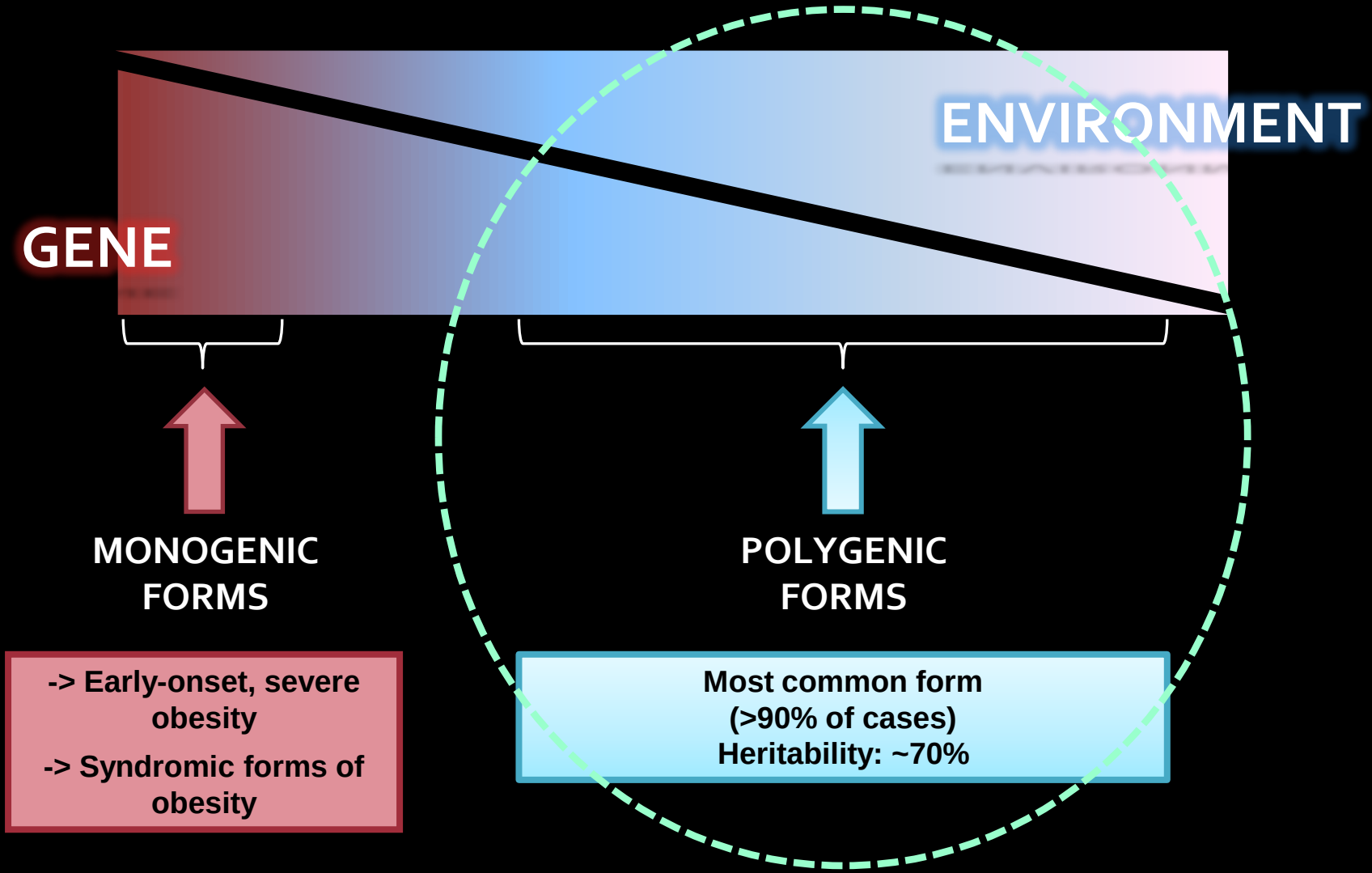


-> Early-onset, severe obesity

-> Syndromic forms of obesity

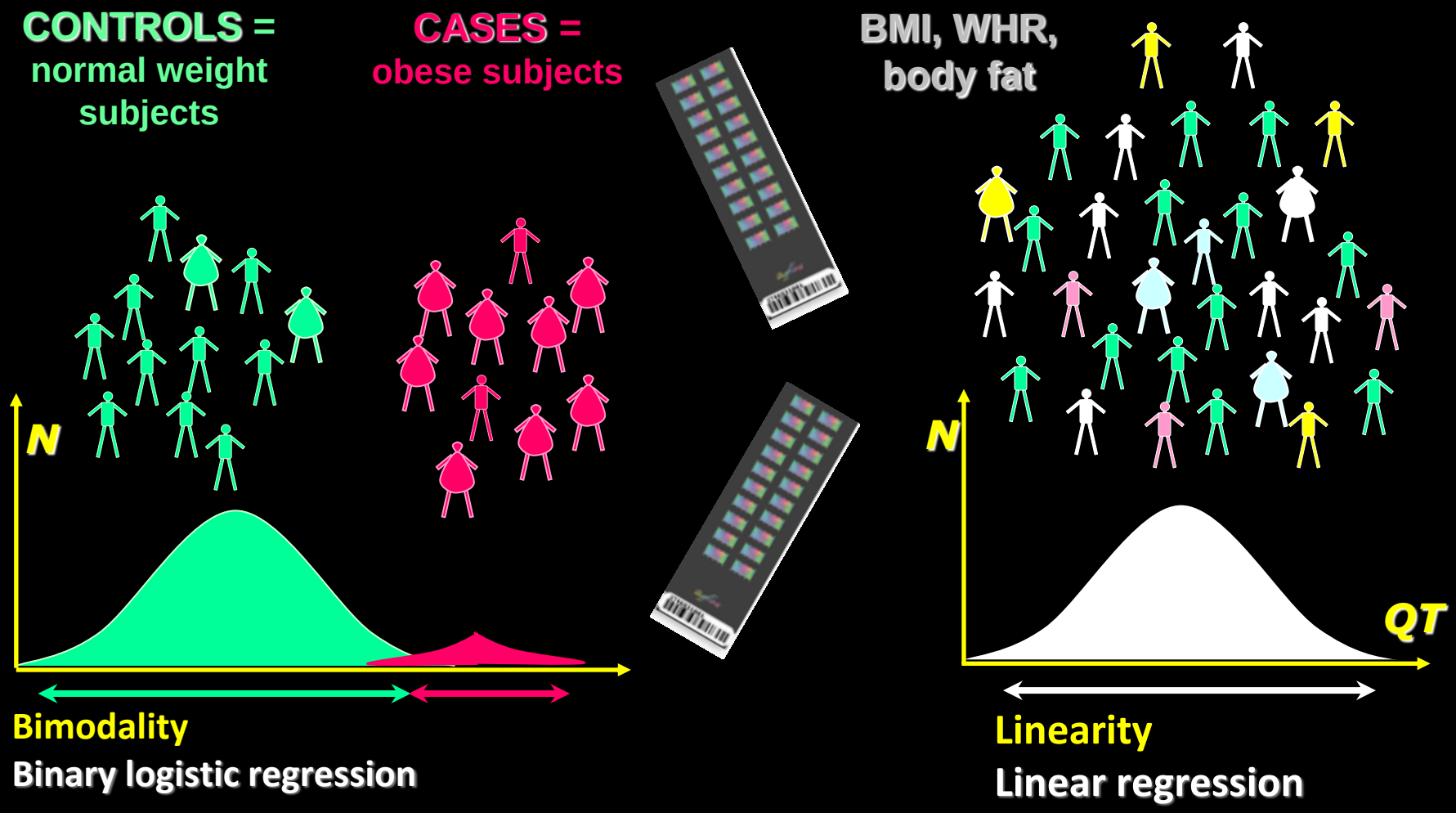
Most common form
(>90% of cases)
Heritability: ~70%

Heterogeneity of the genetics of obesity

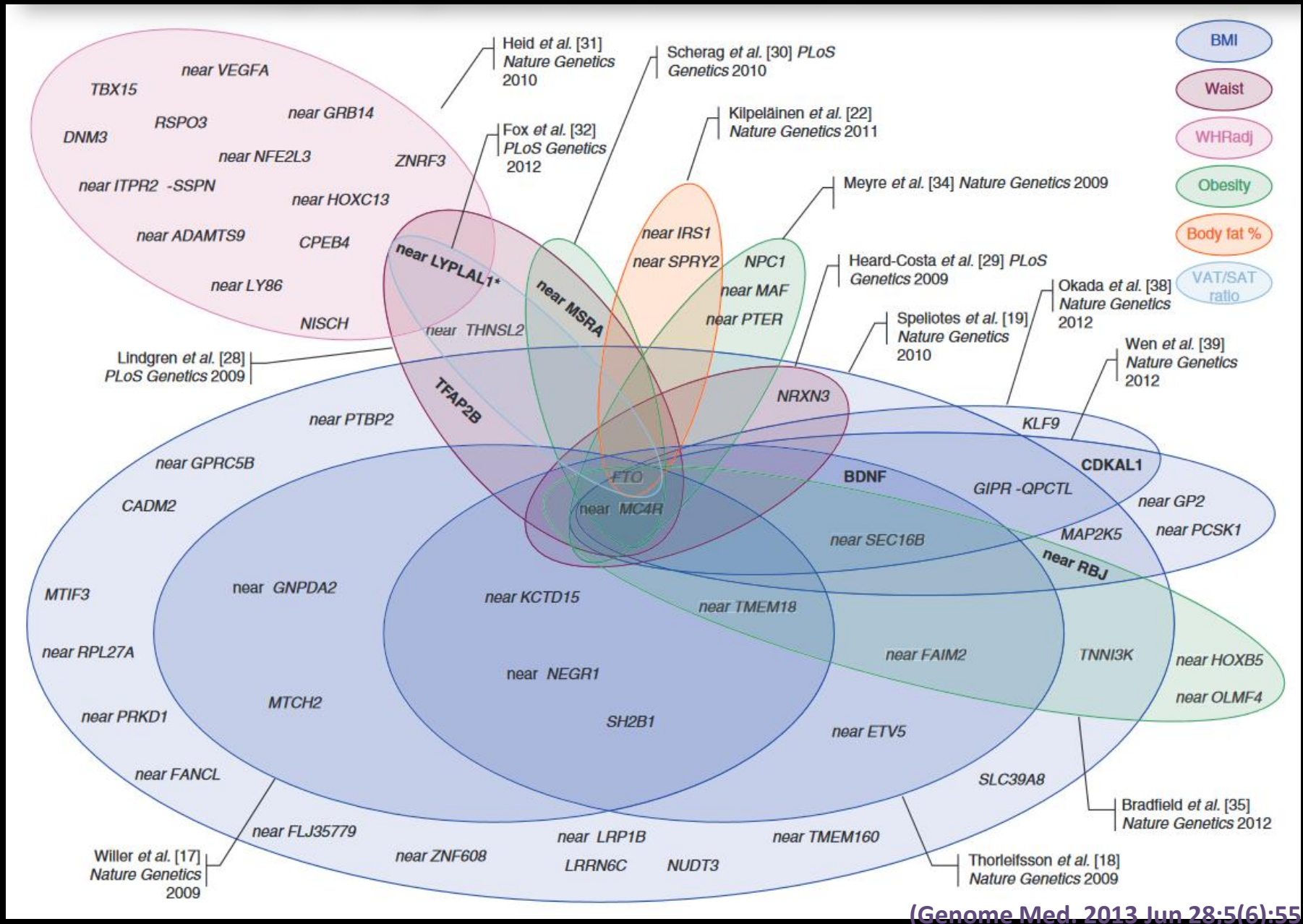


Legacy of genome-wide association studies (GWAS)

-> GWAS: Hypothesis of 'Common Disease, Frequent Variants'



Legacy of genome-wide association studies (GWAS)



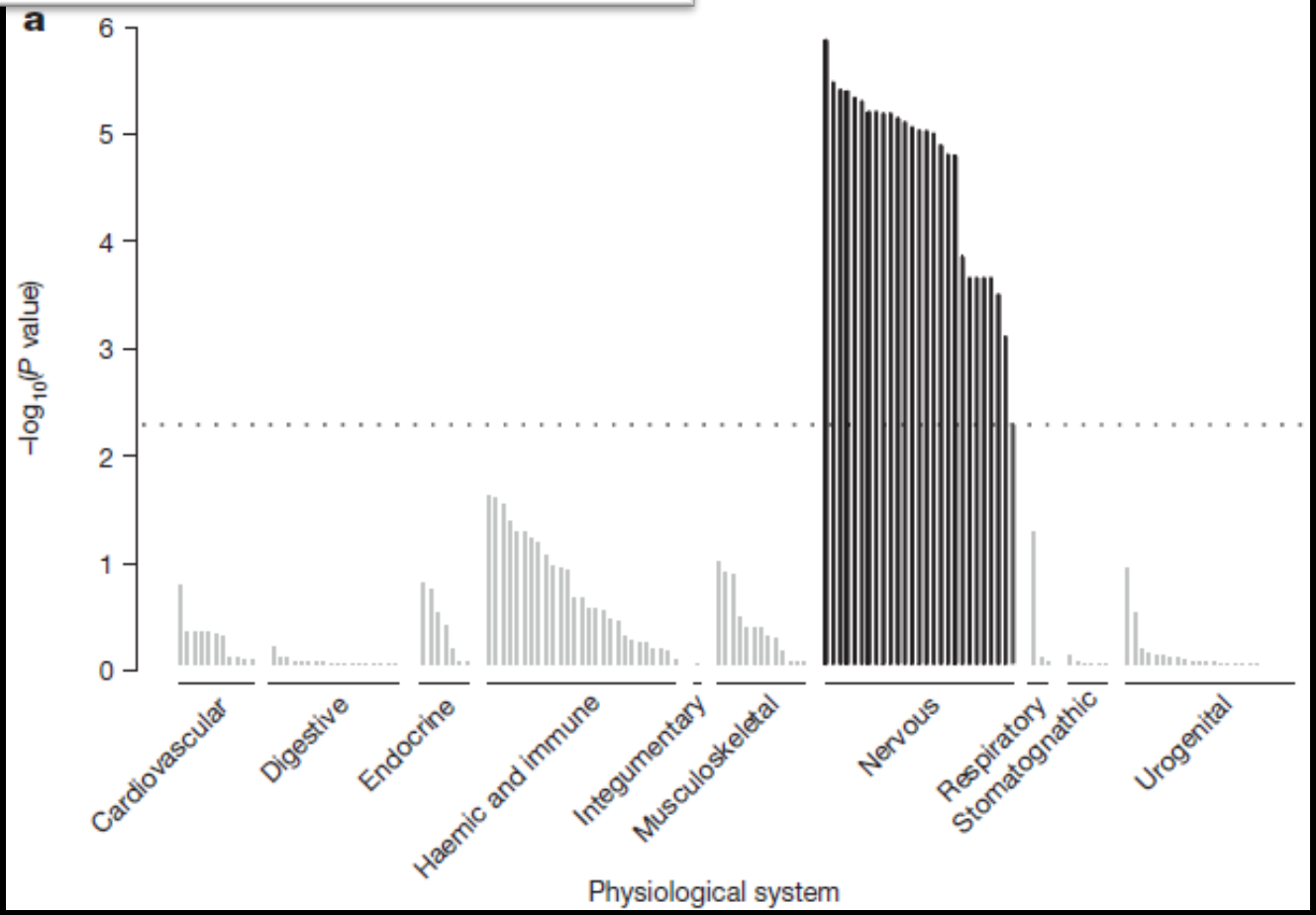
(Genome Med. 2013 Jun 28;5(6):55)

Legacy of genome-wide association studies (GWAS)

ARTICLE

doi:10.1038/nature14177

Genetic studies of body mass index yield new insights for obesity biology



Expression of obesity-associated genes

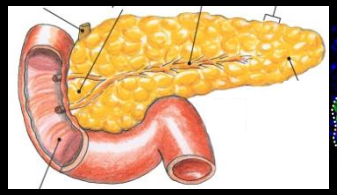
Whole brain
Substantia nigra
Hypothalamus
Pituitary gland
Dorsal root ganglion
Insula
Caudate Nucleus
Hippocampus
Frontal lobe

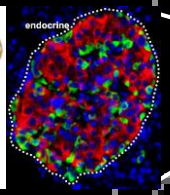
Heart

Lung

Liver

Whole pancreas
Exocrine pancreas
Islet
FACS-sorted beta-cell
LCM beta-cell
EndoC-βH1





Kidney

Colon

Small intestine

Adipose tissue / pre-adipocyte /
mature adipocyte

Skeletal muscle

STXBP6
HHIP
HIP1
ETV5
MAP2K5
NPTX2
ADCY3
KCTD15
NPC1
PARK2
GPRC5B
GRID1
NTRK2
PTCD
NUDT3
ERBB4
CADM2
LRP1B
UBE2E3
GRP
SBK1
RPTOR
SH2B1
PMS2P11
TRIM66
BDNF
MC4R
NEGR1
DNAJC27
FAIM2
FANCL
AGBL4
CADM1
RMST
KLHL32
RALYL
KCNMA1
PTBP2
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DMXL2
ELAVL4
HS6ST3
PCSK1
LINGO2
RABEP1
NAV1
PACS1
GALNT10
GNPDA2
PRKD1
FOXO3
TNKS
CDKAL1
ZC3H4
CCDC171
POC5
SDCCAG8
SCARB2
HSD17B12
ZZZ3
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FUBP1
NT5C2
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HNF4G
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QPCTL
CLIP1
GBE1
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TDRG1
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NLRC3
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TFAP2B
MTCH2
TOMM40
SEC16B
TCF7L2
LEPR
TLR4
ADCY9
ATP2A1
RARB
TNNI3K
C6orf106
MAF
INO80E
KAT8
CTNNBL1
NFE2L3
GLRX4
HIF1AN
FHIT
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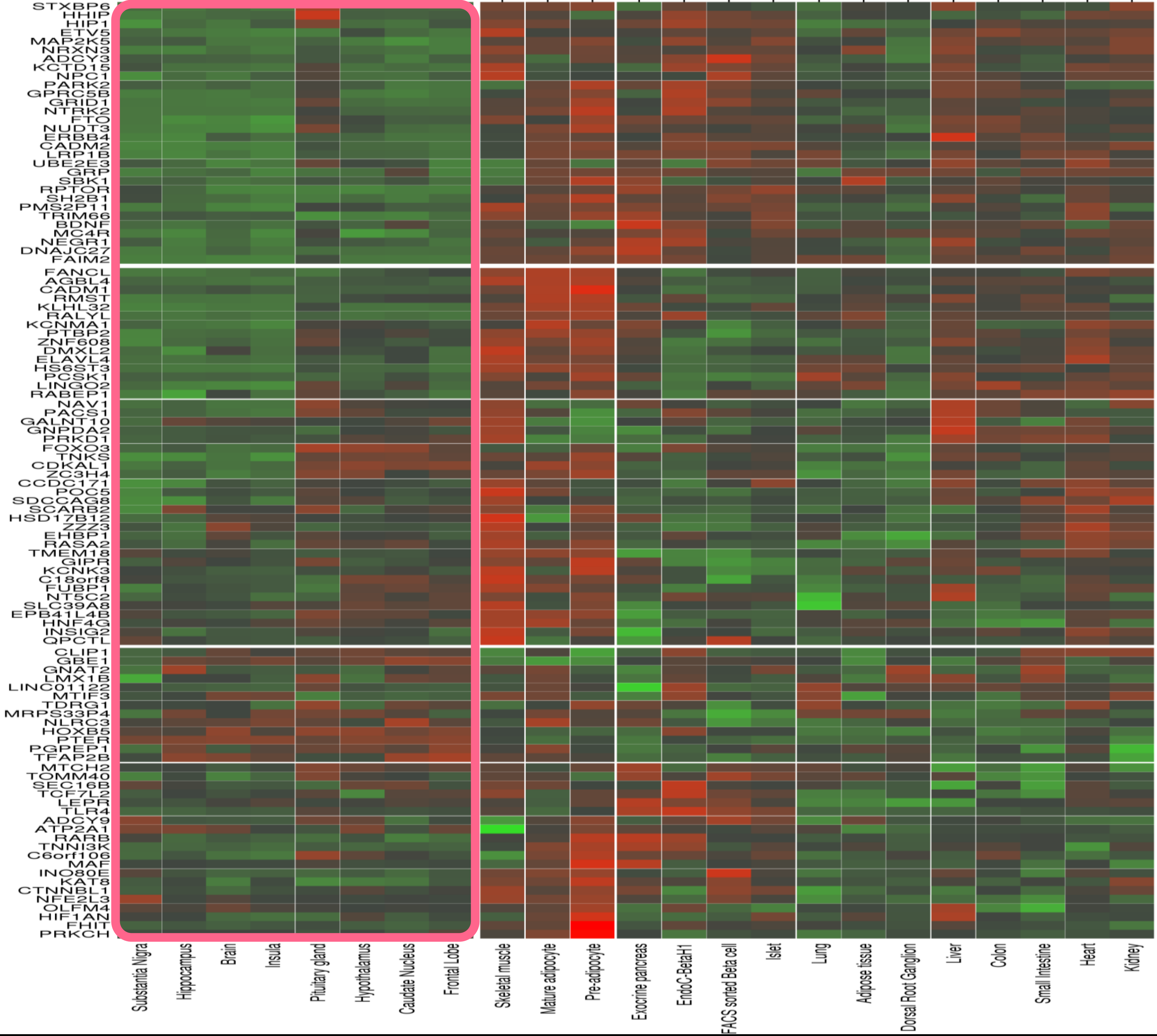
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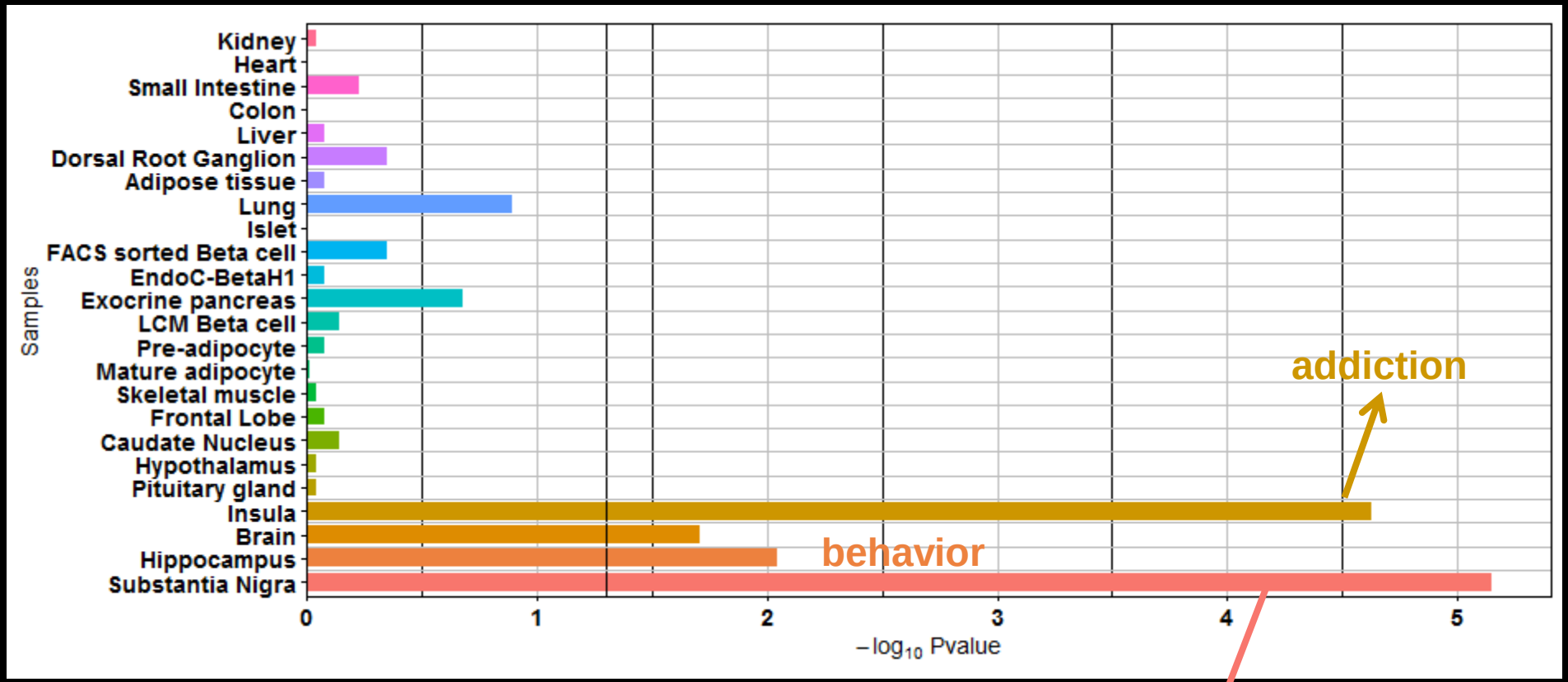

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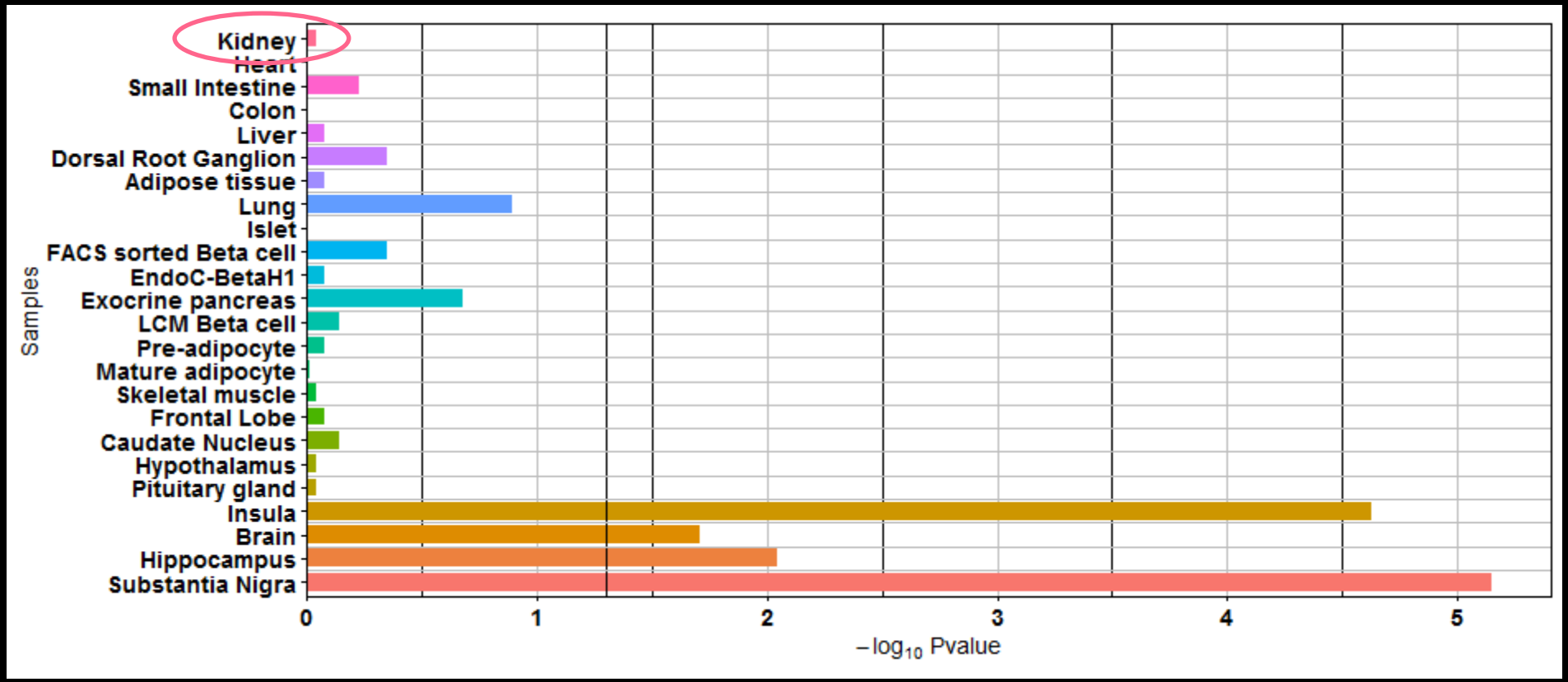

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Obesity-related GRS and diabetic kidney disease

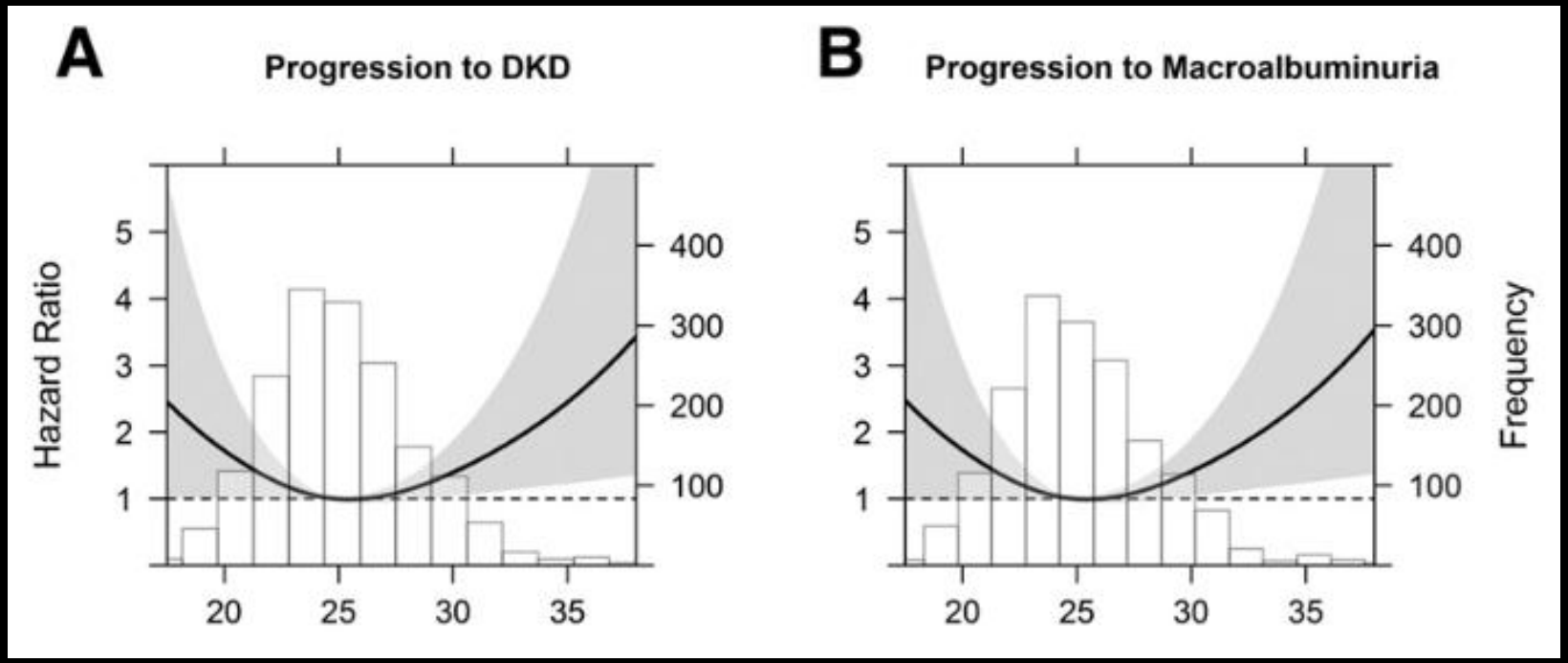
Jennifer N. Todd,[1,2] Emma H. Dahlström,[3,4,5] Rany M. Salem,[1,2,6] Niina Sandholm,[3,4,5] Carol Forsblom,[3,4] the FinnDiane Study Group, Amy J. McKnight,[7] Alexander P. Maxwell,[7,8] Eoin Brennan,[9] Denise Sadlier,[10] Catherine Godson,[9] Per-Henrik Groop,[3,4] Joel N. Hirschhorn,[1,2,6] and Jose C. Florez[6,11,12]

Genetic Evidence for a Causal Role of Obesity in Diabetic Kidney Disease

Diabetes 2015;64:4238–4246 | DOI: 10.2337/db15-0254

"Obesity has been posited as an independent risk factor for both diabetic and nondiabetic renal disease.

However, epidemiologic studies have produced conflicting results, and establishing causality from observational data is difficult."



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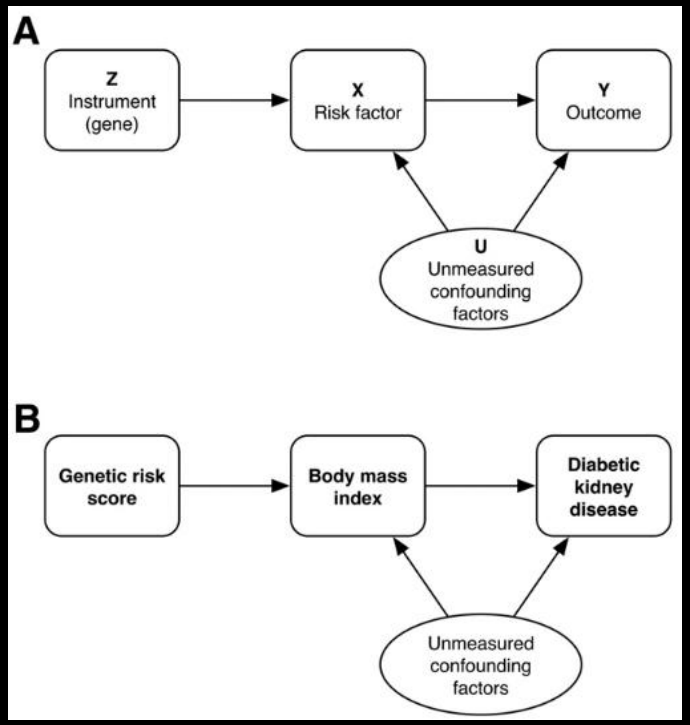
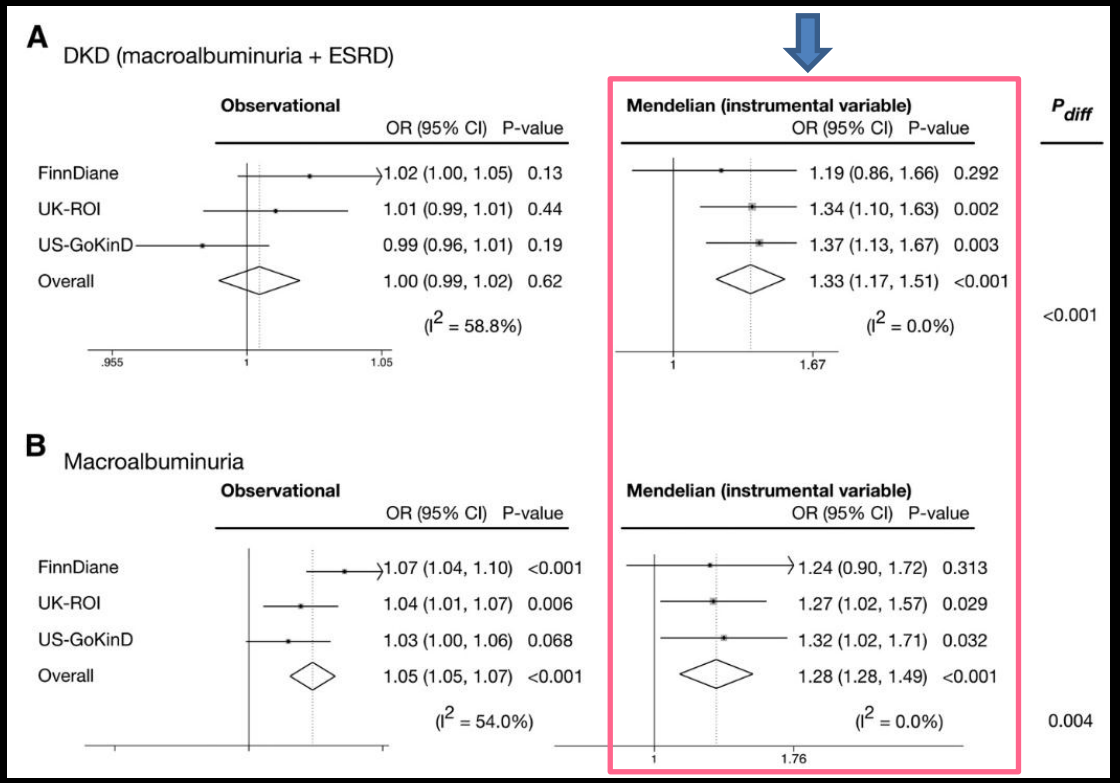
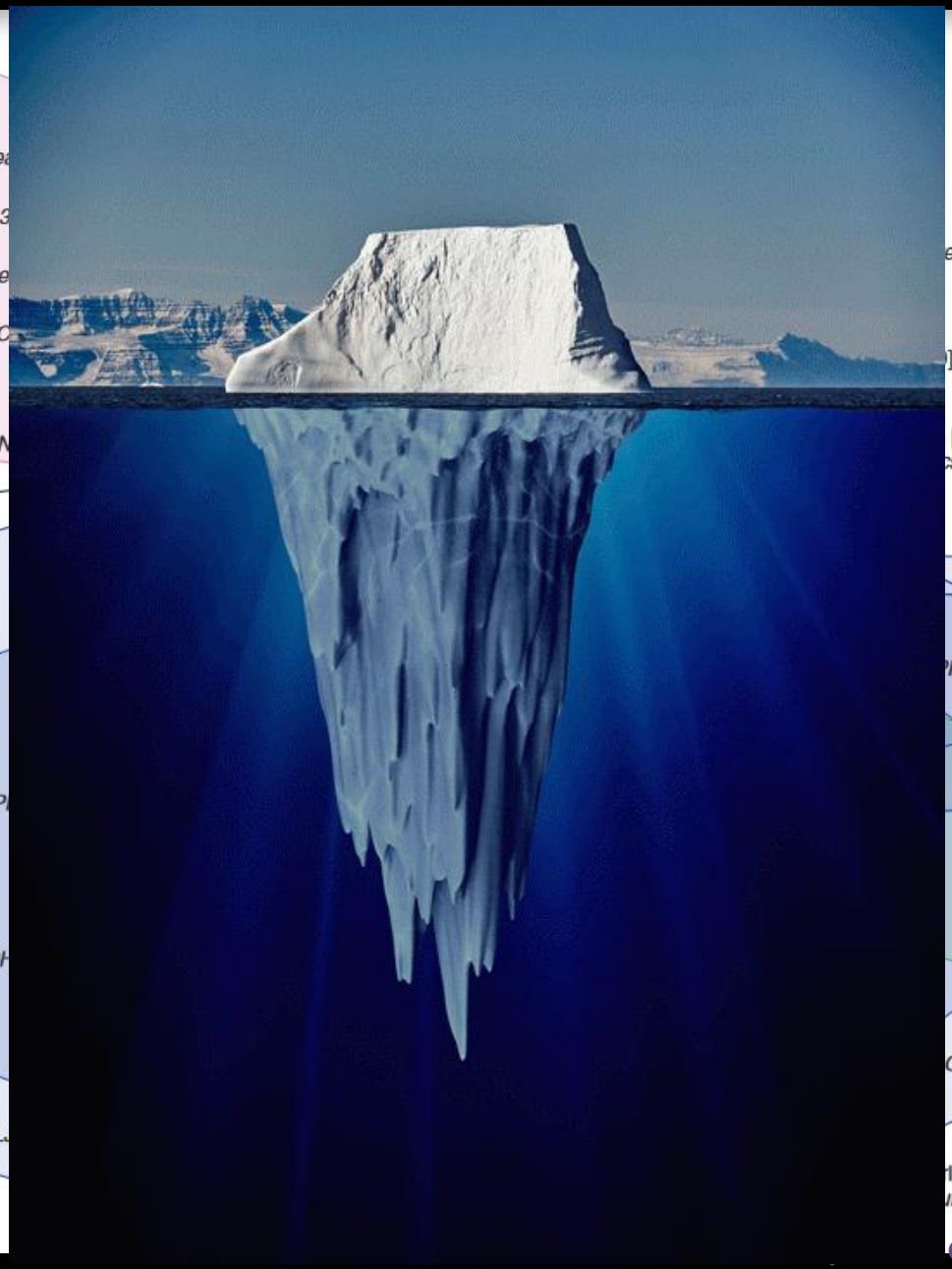
In 6,049 subjects with type 1 diabetes, they used a genetic risk score (GRS) including 32 validated BMI loci

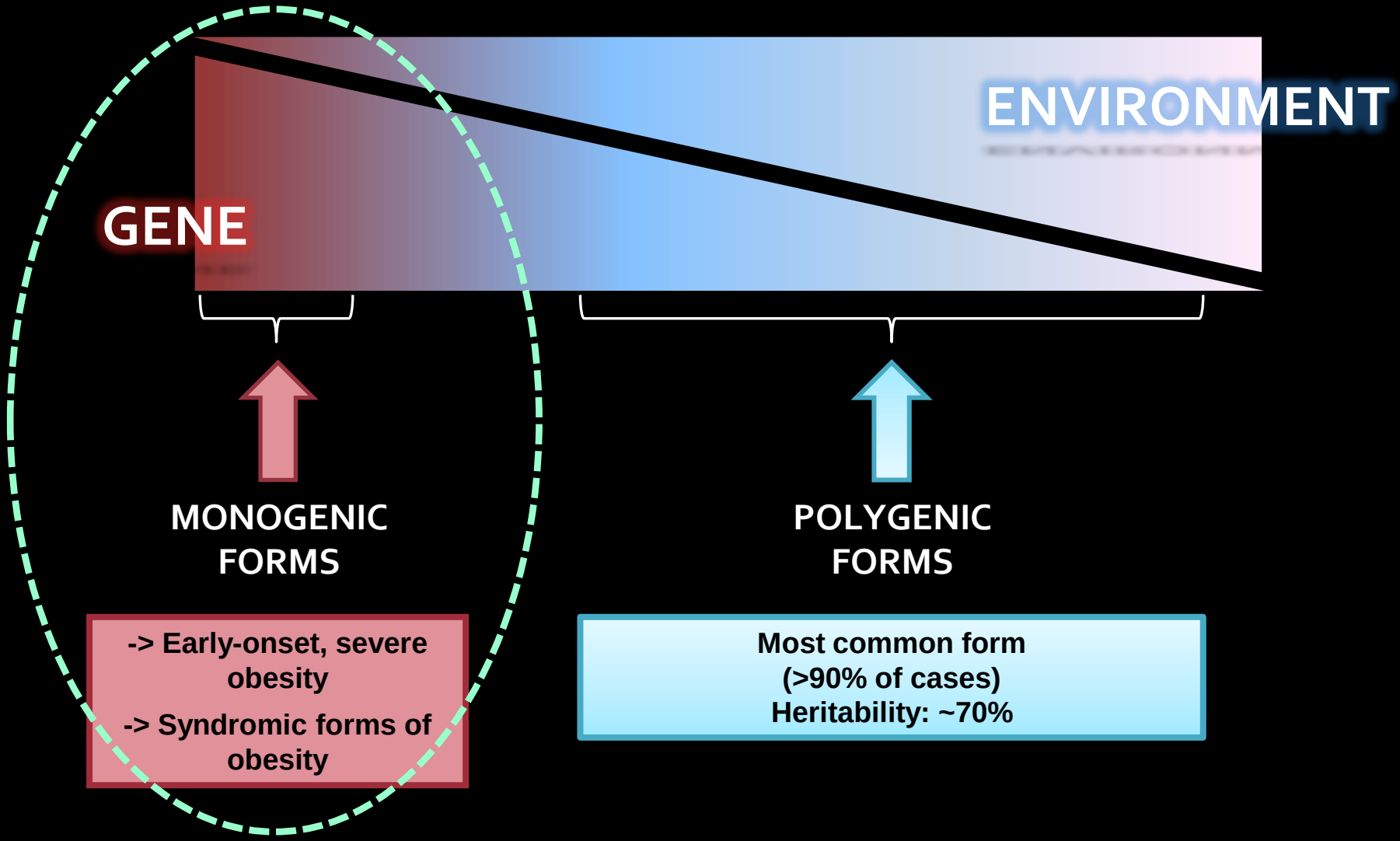




Legacy of genome-wide association studies (GWAS)

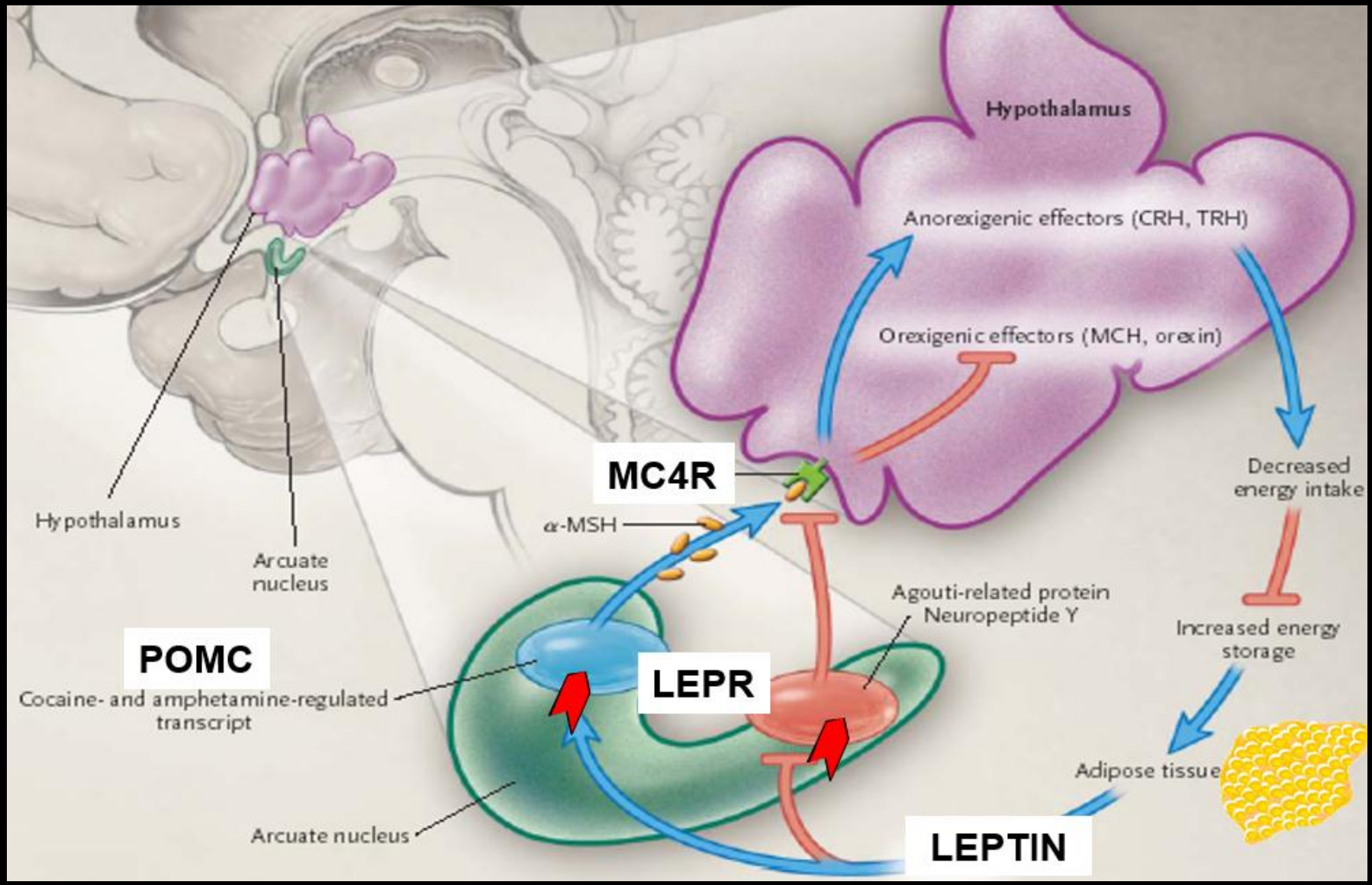


Heterogeneity of the genetics of obesity



Genes involved in non-syndromic monogenic obesity

⇒ **A central role of the Hypothalamus and of the Leptin-melanocortin pathway in the regulation of food intake**



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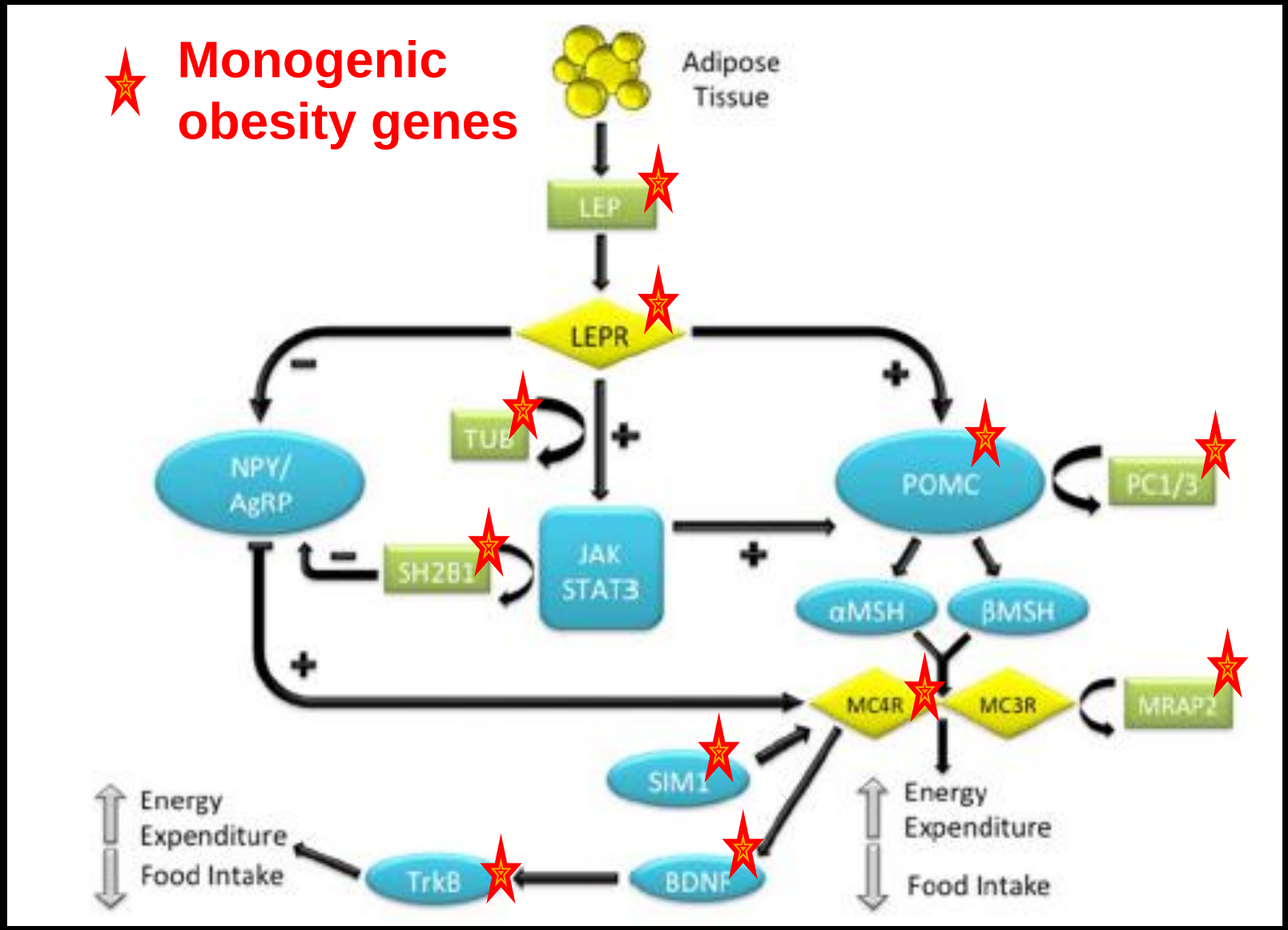
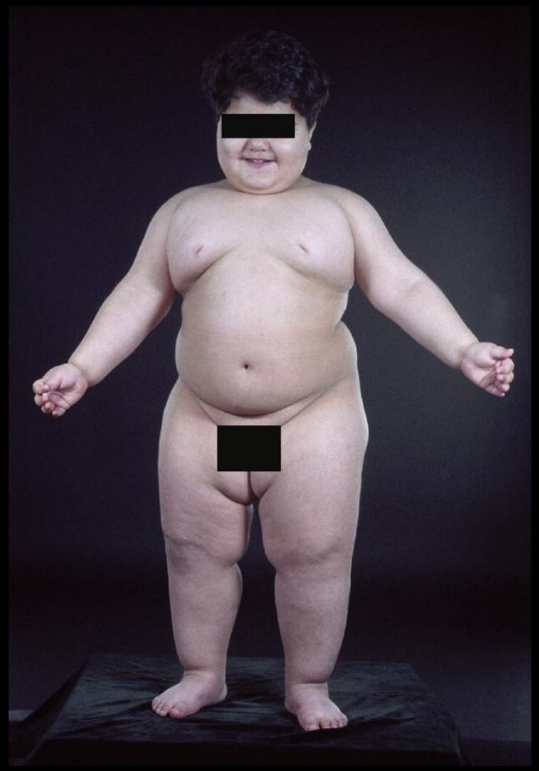


Genes involved in monogenic obesity – *LEP*



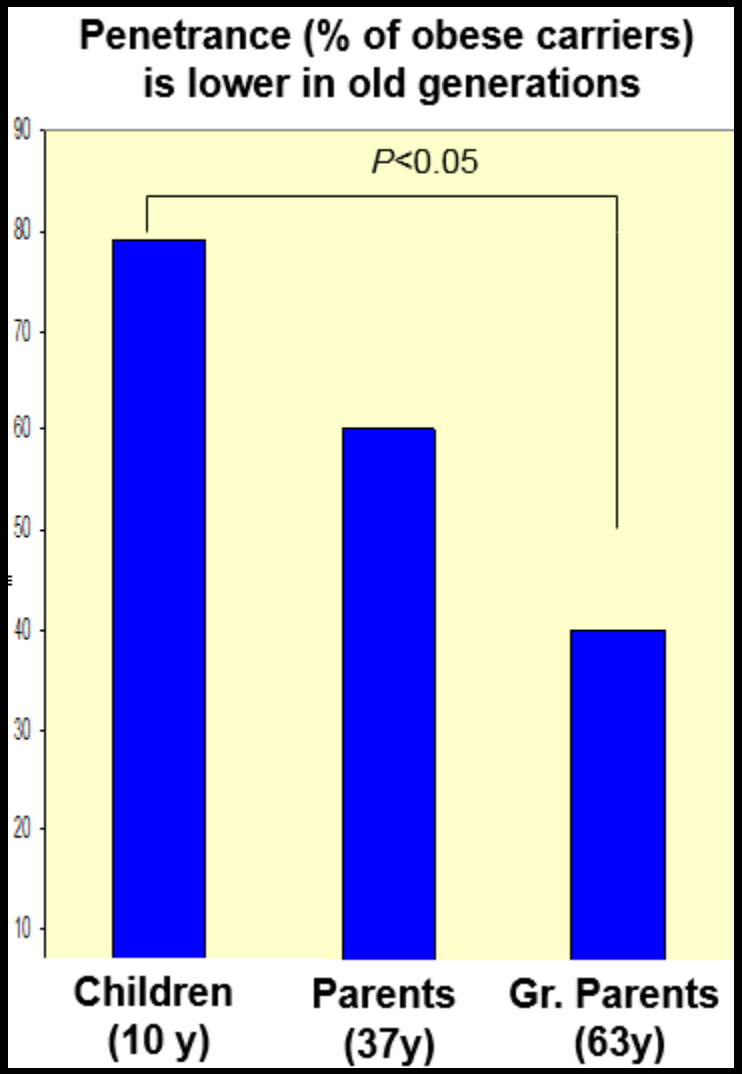
Child B **before** leptin
(wt = 42kg at 3yrs)

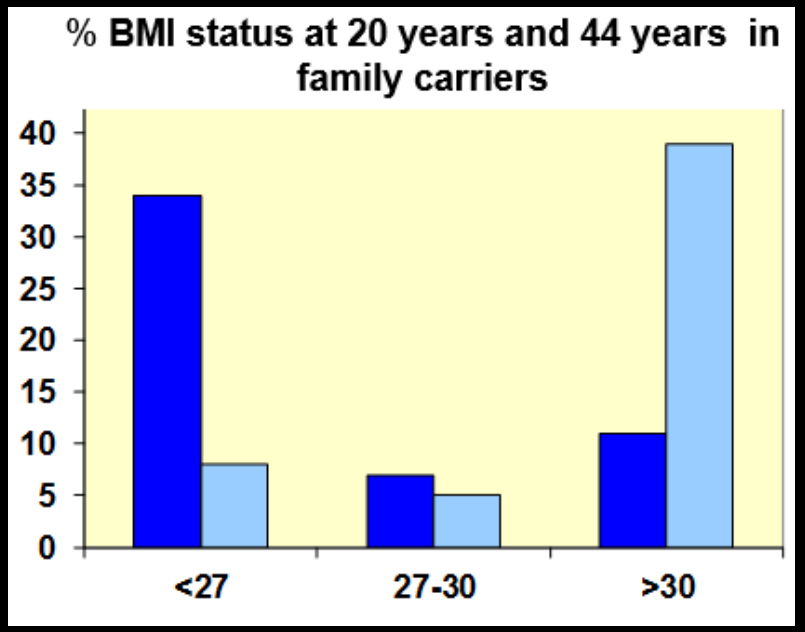
Child B **after** leptin
(wt = 32kg at 7yrs)

=> Child with genetic deficiency of leptin can be “cured” by recombinant leptin

Genes involved in monogenic obesity – *MC4R*

In Europe, the penetrance of *MC4R* mutations is generation- and age-dependent (Stutzmann et al. Diabetes 2008)





- 21st century children carrying *MC4R* mutations have 80% risk to be obese.
- Only 10% of their parents carriers were obese when young but currently 40% are obese

Genes involved in monogenic obesity – *MC4R*

Original Article
PEDIATRIC OBESITY

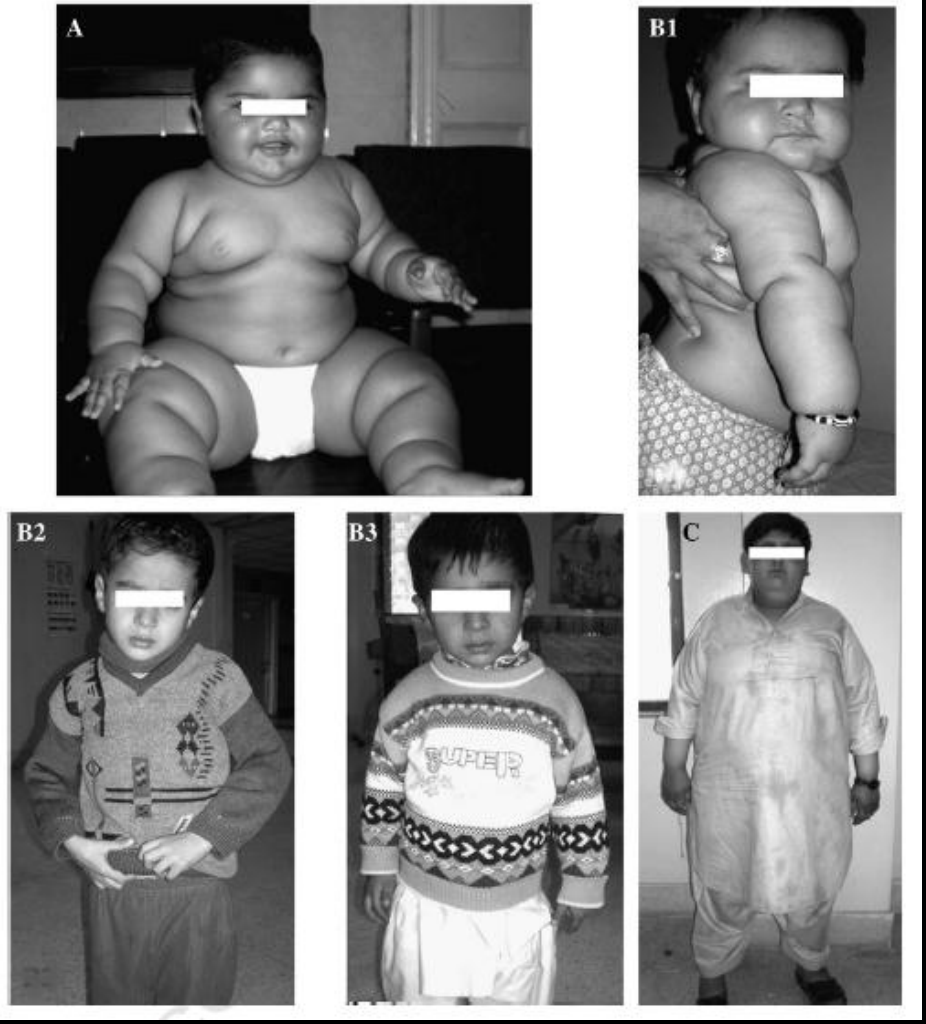
Obesity

Genetic Variants in *LEP*, *LEPR*, and *MC4R* Explain 30% of Severe Obesity in Children from a Consanguineous Population

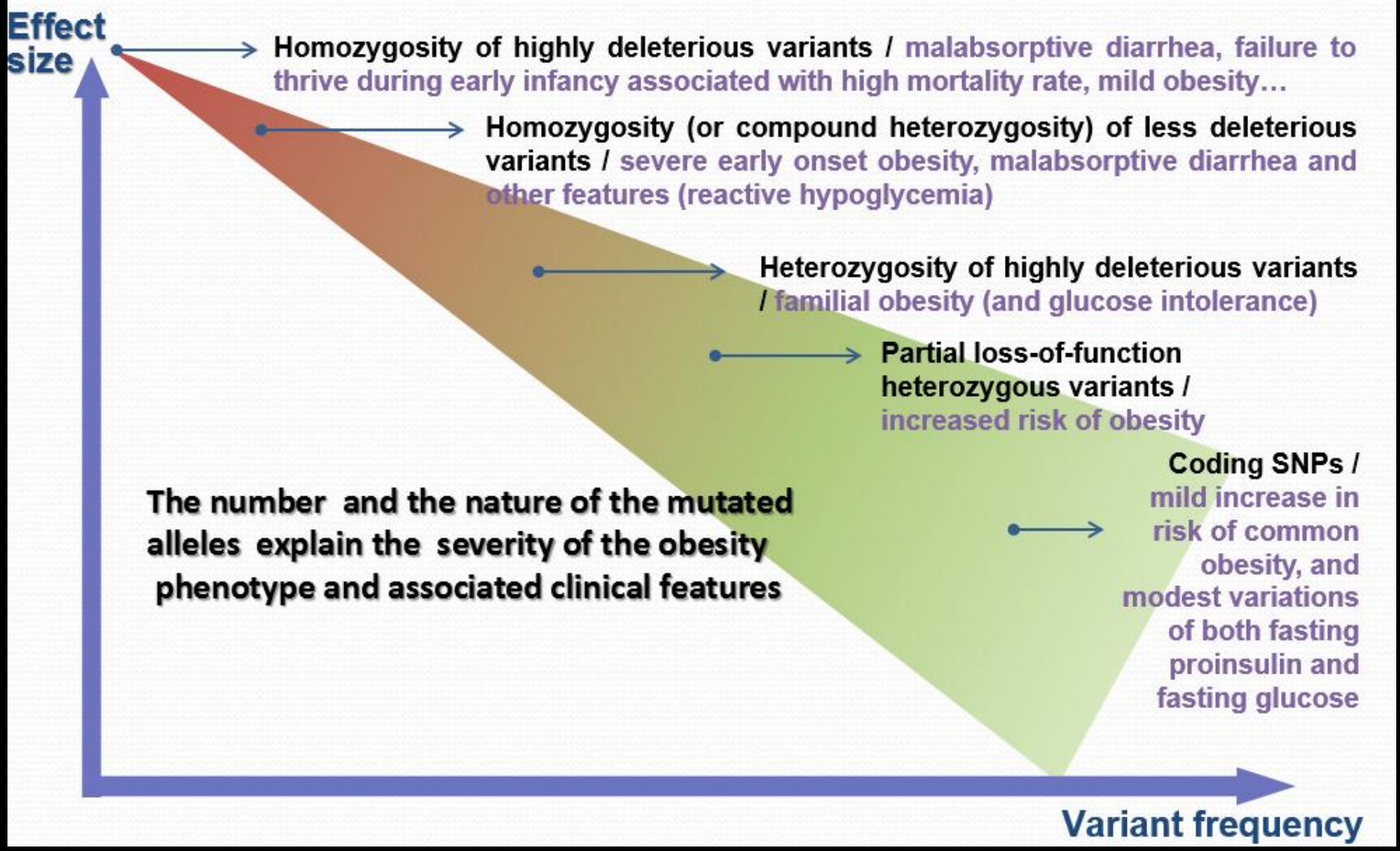
Sadia Saeed[1], Amélie Bonnefond[2,3,4], Jaida Manzoor[5], Faiza Shabir[6], Hina Ayesha[7], Julien Phil Emmanuelle Durand[2,3,4], Hutokshi Crouch[1], Olivier Sand[2,3,4], Muhammad Ali[8], Taeed Butt[9], Ahs Mario Falchi[1], Muhammad Arslan[6,10], and Philippe Froguel[1,2,3,4]

All obese children are from consanguinous families and are <u>homozygous</u> for these mutations

<u>Heterozygous</u> *MC4R* carrier parents are <u>NOT</u> obese which shows the key role of the permissive environment in the mutation penetrance



Wide spectrum of phenotypes related to *PCSK1* variants



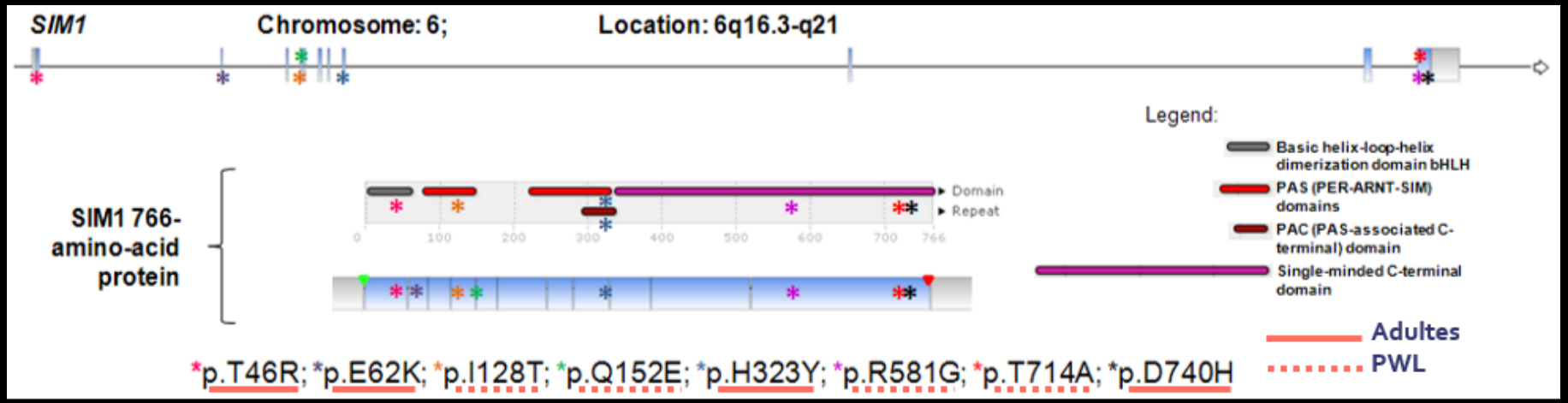
Genes involved in monogenic obesity – *SIM1*

Brief report

Loss-of-function mutations in *SIM1* contribute to obesity and Prader-Willi–like features

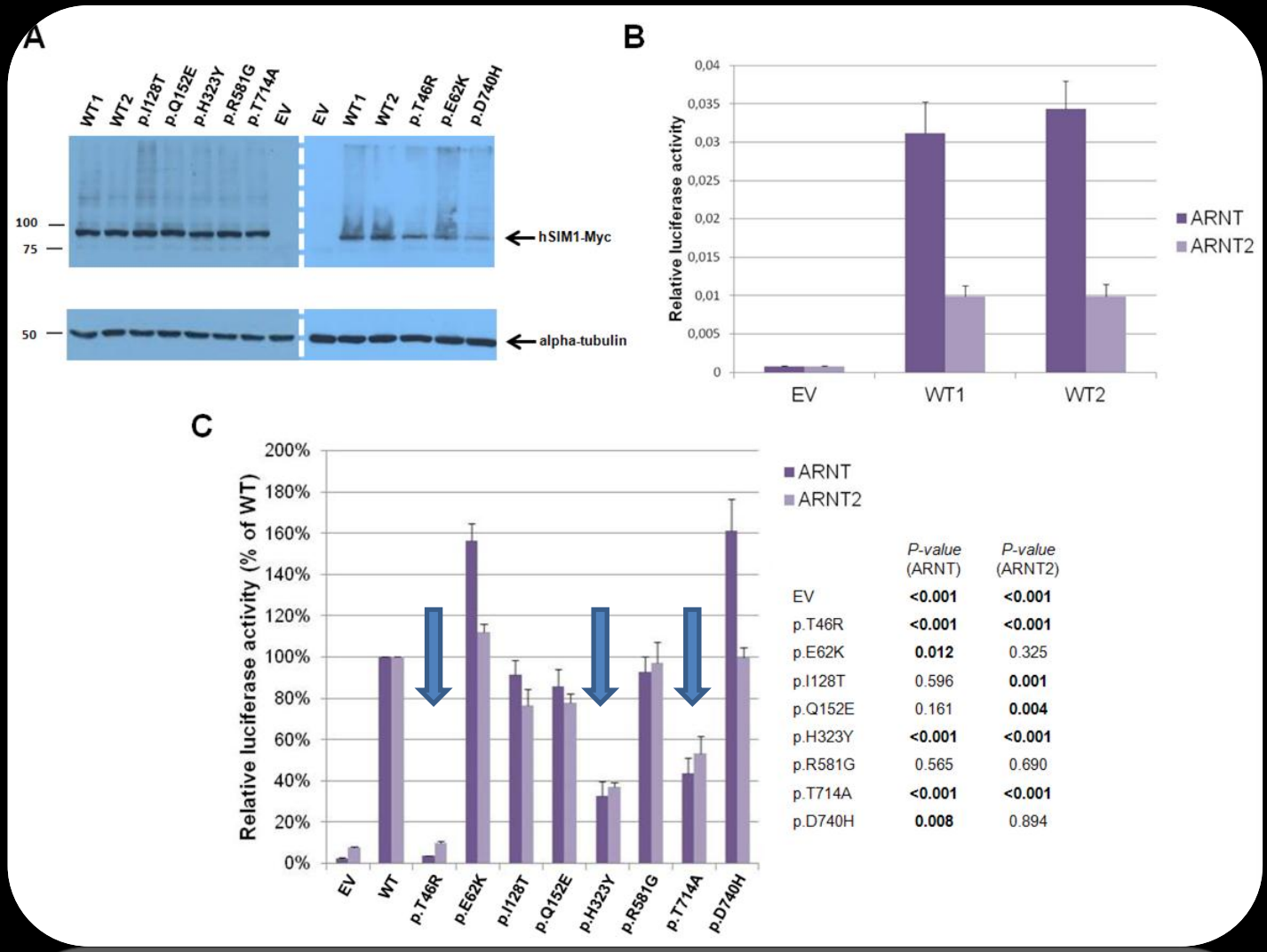
Amélie Bonnefond,[1,2,3] Anne Raimondo,[4] Fanny Stutzmann,[1,2,3] Maya Ghoussaini,[1,2,3,5] Shwetha Ramachandrappa,[6] David C. Bersten,[4] Emmanuelle Durand,[1,2,3] Vincent Vatin,[1,2,3] Beverley Balkau,[7,8] Olivier Lantieri,[9] Violeta Raverdy,[1,3,10] François Pattou,[1,3,10,11] Wim Van Hul,[12] Luc Van Gaal,[13] Daniel J. Peet,[4] Jacques Weill,[14] Jennifer L. Miller,[15] Fritz Horber,[16,17] Anthony P. Goldstone,[15,18] Daniel J. Driscoll,[15] John B. Bruning,[4] David Meyre,[1,2,3,19] Murray L. Whitelaw,[4] and Philippe Froguel[1,2,3,20]

=> In 44 children with severe obesity and PWL, 198 children with severe obesity, 568 adults with morbid obesity and 383 controls



OR=21; *P*=9.3×10^{-4}

Genes involved in monogenic obesity – *SIM1*



	P-value (ARNT)	*P*-value (ARNT2)
EV	**<0.001**	**<0.001**
p.T46R	**<0.001**	**<0.001**
p.E62K	**0.012**	0.325
p.I128T	0.596	**0.001**
p.Q152E	0.161	**0.004**
p.H323Y	**<0.001**	**<0.001**
p.R581G	0.565	0.690
p.T714A	**<0.001**	**<0.001**
p.D740H	**0.008**	0.894

T46R/ H323Y/ T714A
OR=28
***P*=5.6×10^{-3}**

Others
***P*=0.158**

Genes involved in monogenic obesity – *SIM1*

T46R/H323Y/T714A

- Adults with morbid obesity (*N*=9)
- Overweight adult (*N*=1)
- Adults or children with severe obesity and PWL (*N*=4) :
  - Developmental delay
  - Intellectual disability
  - Behavioural problems
  - Facial dysmorphism
  - No hypotonia no hypogonadism

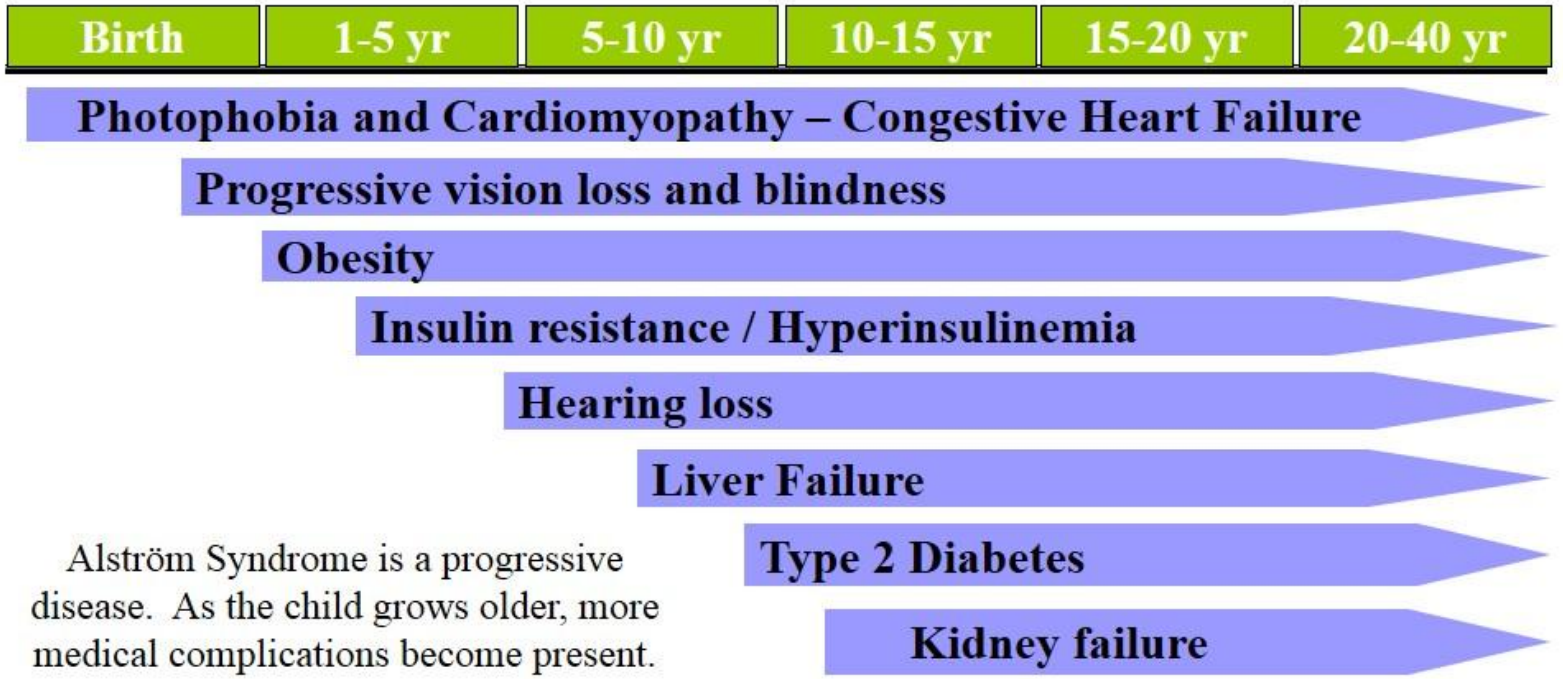
CONCLUSIONS:

- Incomplete penetrance… environment (cf *MC4R*)? Epigenetics? Modifiers?
- All *SIM1* mutations are not functional… problems in the molecular diagnostic

Renal failure and monogenic (syndromic) obesity

Alström Syndrome and Bardet-Biedl syndrome

Alström Syndrome Typical Disease Progression

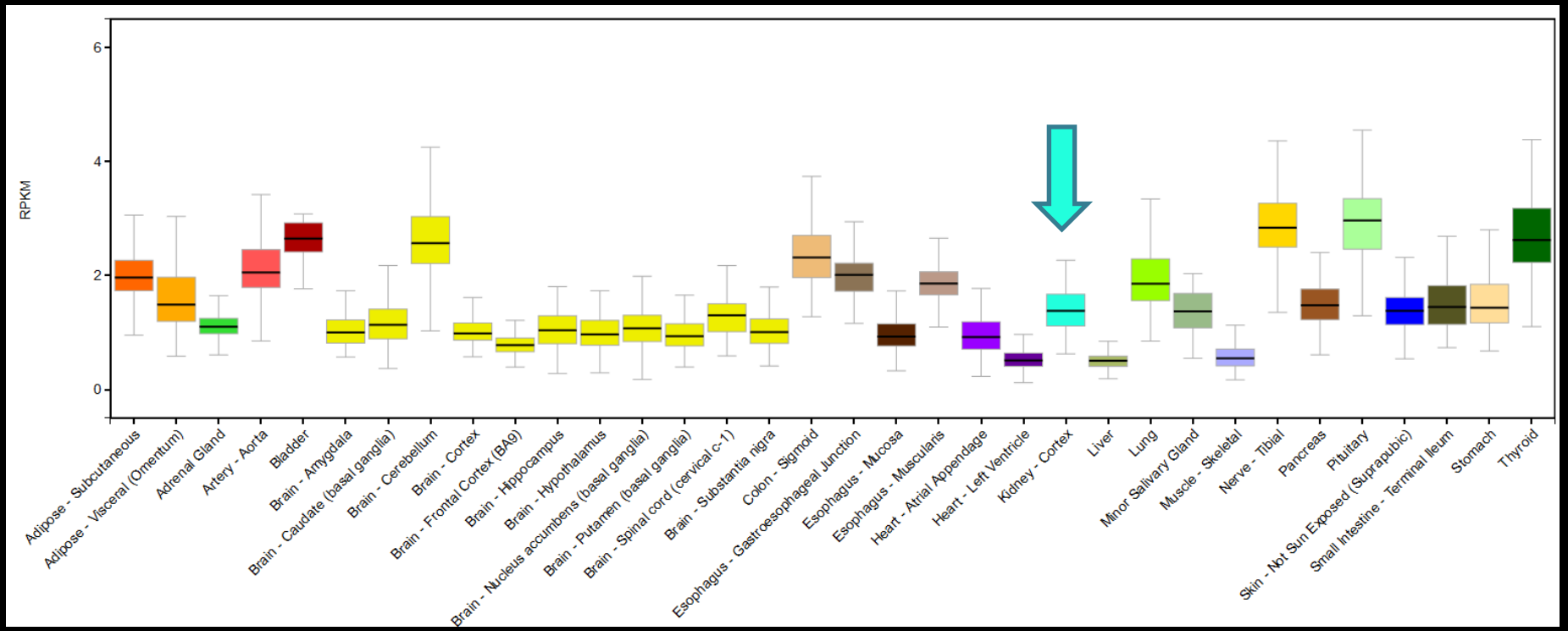


Alström Syndrome is a progressive disease. As the child grows older, more medical complications become present.

Most children are lost in their late teens and early twenties due to these medical complications.

Renal failure and monogenic (syndromic) obesity

Alström Syndrome: due to recessive mutations in *ALMS1*



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PLoS GENETICS

A Role for Alström Syndrome Protein, Alms1, in Kidney Ciliogenesis and Cellular Quiescence

Guochun Li[1], Raquel Vega[1], Keats Nelms[2], Nicholas Gekakis[1], Christopher Goodnow[3,4], Peter McNamara[5¤], Hua Wu[6], Nancy A. Hong[5], Richard Glynne[1*]

Renal failure and monogenic (syndromic) obesity

Bardet-Biedl syndrome

PRIMARY FEATURES	
Rod-cone dystrophy	93%
Post-axial polydactyly	69%
Truncal obesity	72%
Hypogonadism	98%
Renal anomalies	24% (only 52% of patients had undergone renal examination)
SECONDARY FEATURES	
Speech disorder/delay	54%
Developmental delay	50%
Behaviour	33%
Ataxia/imbalance	40%
Diabetes mellitus	6%
Congenital heart defects	7%
Liver disease	NA
Hearing loss	21%
Facial features	NA
Hirschprung disease	NA
Situs inversus	NA
Polyuria/polydipsia	NA
Dental crowding	NA
Anosmia	60%

Renal failure and monogenic (syndromic) obesity

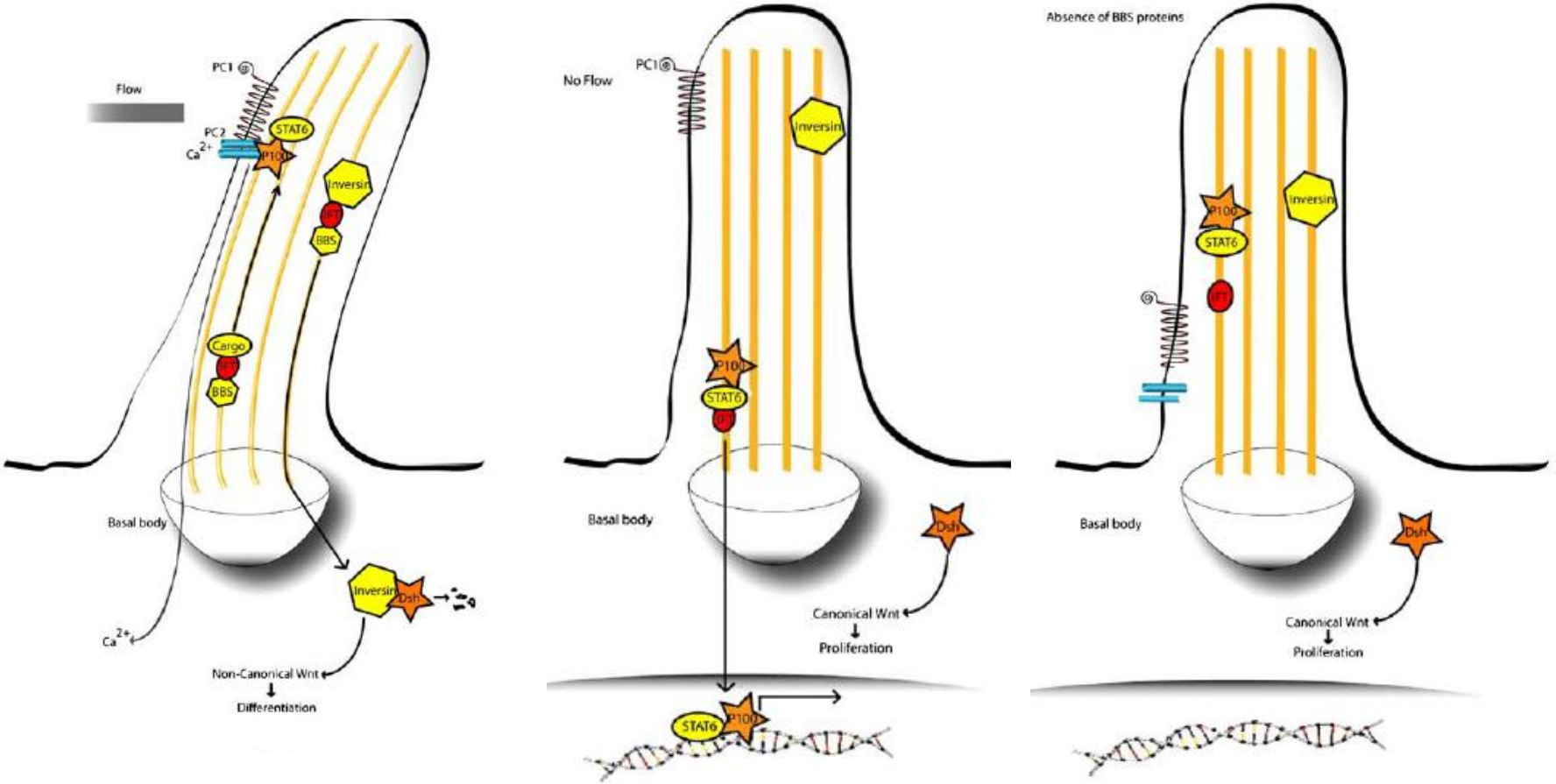
Bardet-Biedl syndrome

Table 2 BBS genes identified so far (*IFT* intraflagellar transport)

Gene	Method of discovery	Chromosomal location	Cellular localisaiton	Domains	Putative function
BBS1	Linkage analysis	11q13	Basal body/cilium	None	Cilia function
BBS2	Positional cloning	16q21	Basal body/cilium	None	Cilia function/ flagellum formation
BBS3/ARL6	Linkage analysis	3p12-q13	Basal body/cilium	GTP-binding	Vesicle trafficking
BBS4	Positional cloning	15q23	Pericentriolar/basal body	TPR/PilF	Microtubule transport
BBS5	Comparative genomics	2q31	Basal body/cilium	DM16 DUF1448	Cilia function/ flagellum formation
BBS6/MKKS	Mutation analysis	20p12	Basal body/cilium	TCP1 chaperonin	Cilia function/ flagellum formation
BBS7	Similarity to BBS2	4q32	Basal body/cilium	TPR/PilF	IFT particle assembly
BBS8/TTC8	Similarity to BBS4	14q31	Basal body/cilium	TPR/PilF	IFT particle assembly
BBS9/B1	Homozygosity mapping with SNP arrays	7p14.3	Unknown	COG1361 membrane biogenesis	Unknown—expressed in bone cells
BBS10	SNP arrays	12q21.2	Unknown	TCP1 chaperonin	Unknown
BBS11/ TRIM32	SNP arrays	9q31-34.1	Unknown	RING WD40 NHL Barmotin B-Box	E3 ubiquitin ligase
BBS12	SNP arrays	4q27	Unknown		Type II chaperonin

Renal failure and monogenic (syndromic) obesity

Bardet-Biedl syndrome

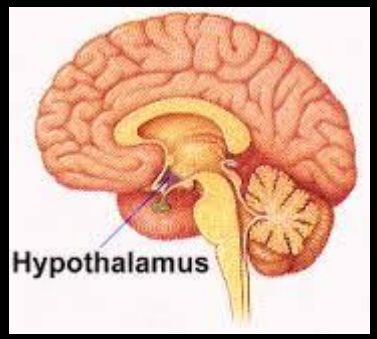


Putative pathomechanism for renal cystic hyperplasia in BBS

Take-home message

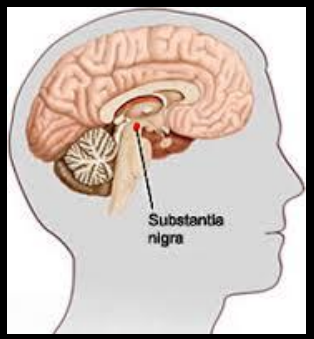
Obésité monogénique

FAIM



Obésité polygénique

SATISFAC-TION/ ADDICTION



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