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GENETICS OF OBESITY

Sandro Loche

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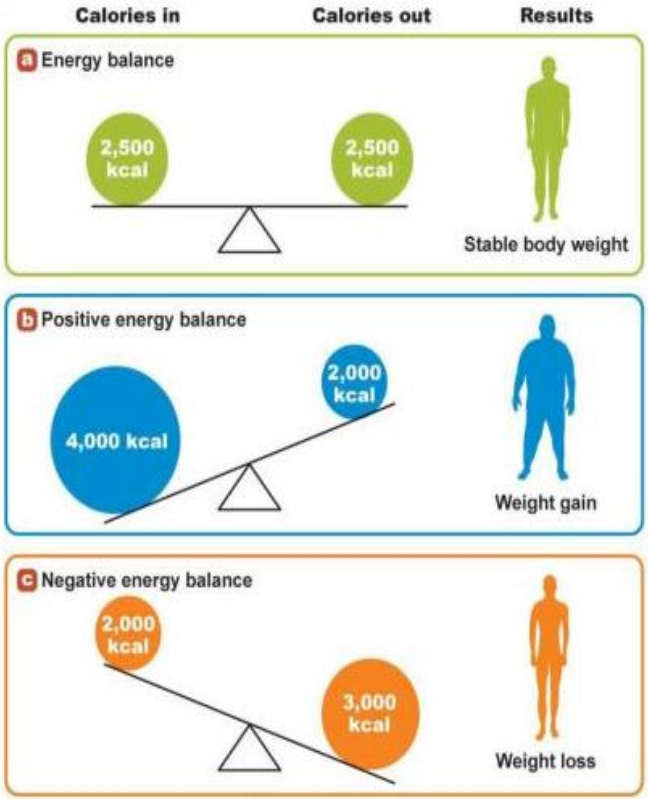
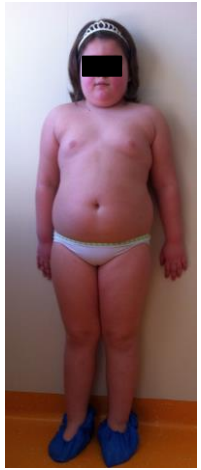
Ospedale Pediatrico Microcitemico "A. Cao"
AO Brotzu, Cagliari

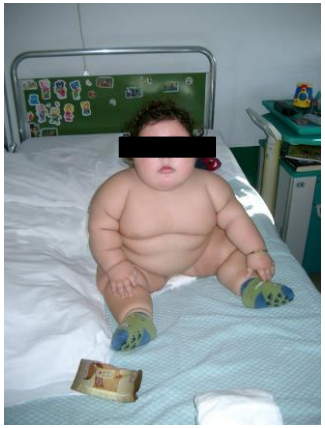
DISCLOSURES

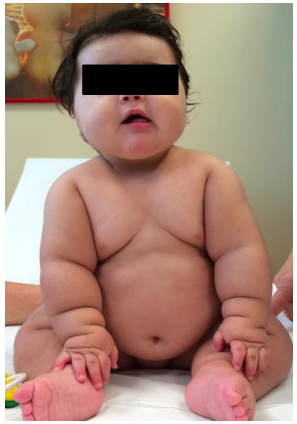
No relevant financial information to disclose

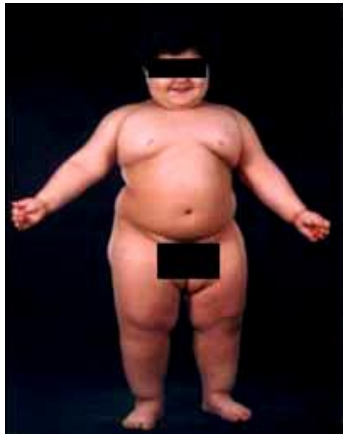
THE CONCEPT OF ENERGY BALANCE











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THE GENETIC CONTRIBUTION TO OBESITY

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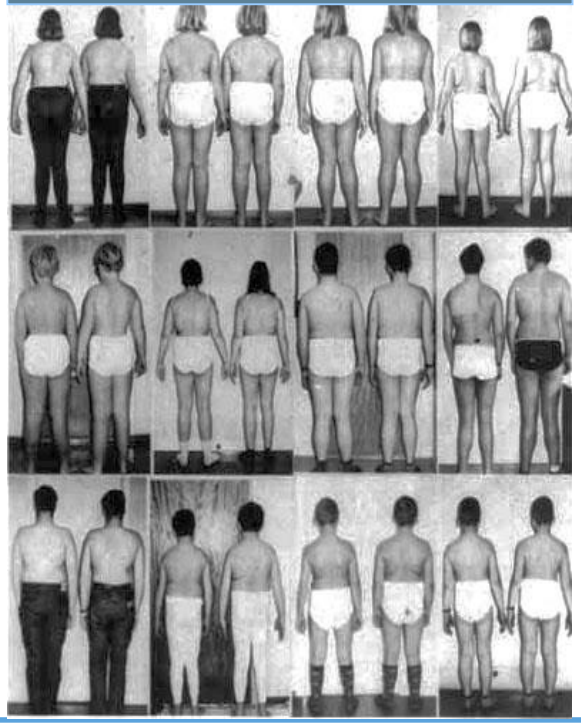
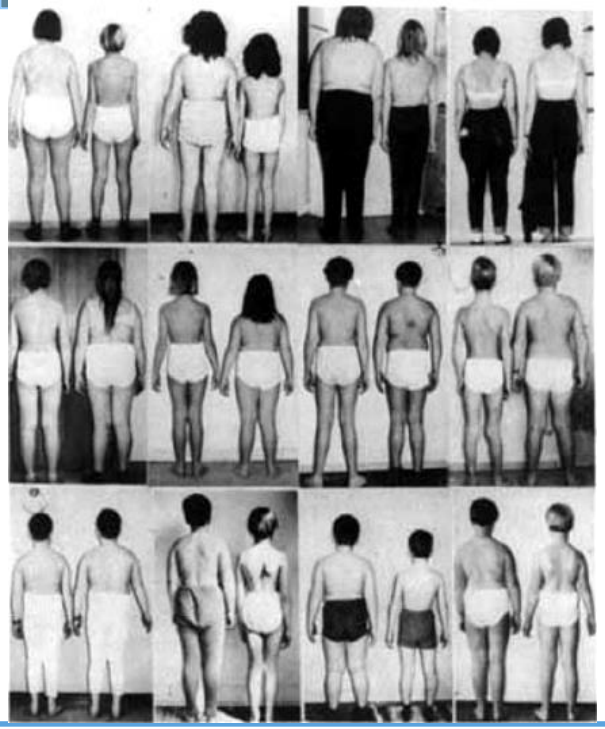
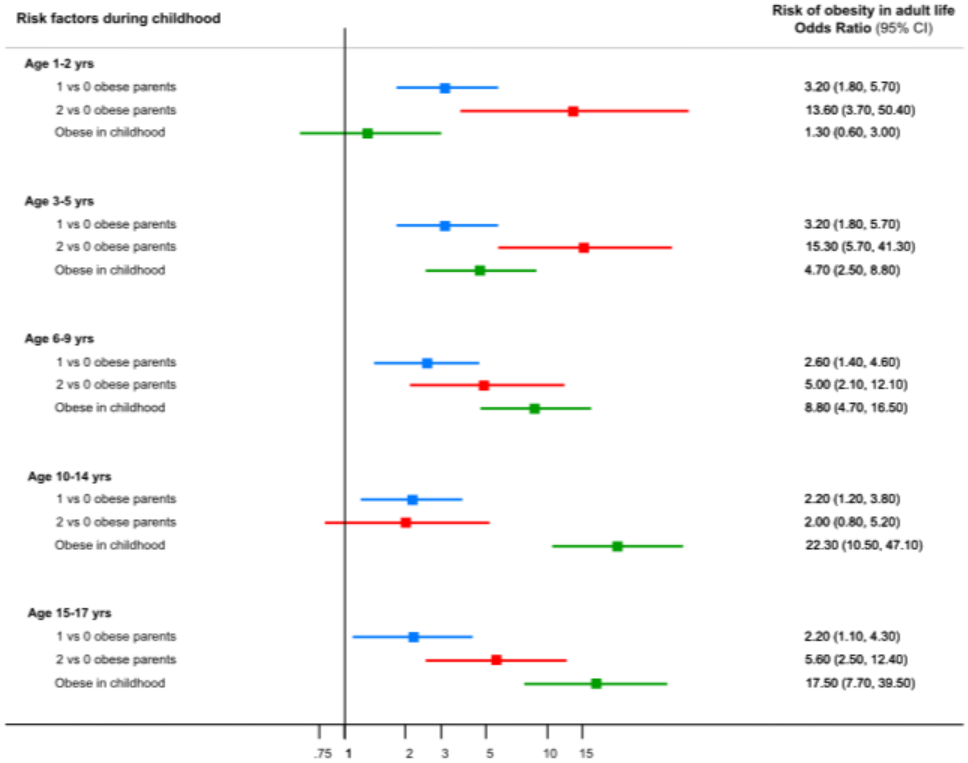
Monozygotic twins



Dizygotic twins



CONTRIBUTION OF PARENTAL AND CHILDHOOD OBESITY TO FUTURE RISK OF OBESITY



CI, confidence interval

Loos RJF, et al. Cell Metab. 2017;25:535-43

Positional cloning of the mouse *obese* gene and its human homologue

Yiying Zhang[*†], Ricardo Proenca[*†], Margherita Maffei[†], Marisa Barone[*†], Lori Leopold[*†] & Jeffrey M. Friedman[*†‡]

* Howard Hughes Medical Institute, † The Rockefeller University, 1230 York Avenue, New York, New York 10021, USA

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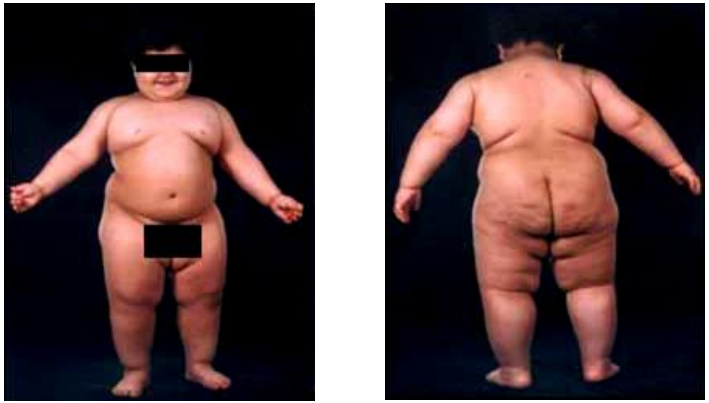
Leptin
from Greek λεπτός
= lean, skinny

Xhang Y, et al. Nature. 1994;372:425-32

Congenital leptin deficiency is associated with severe early-onset obesity in humans

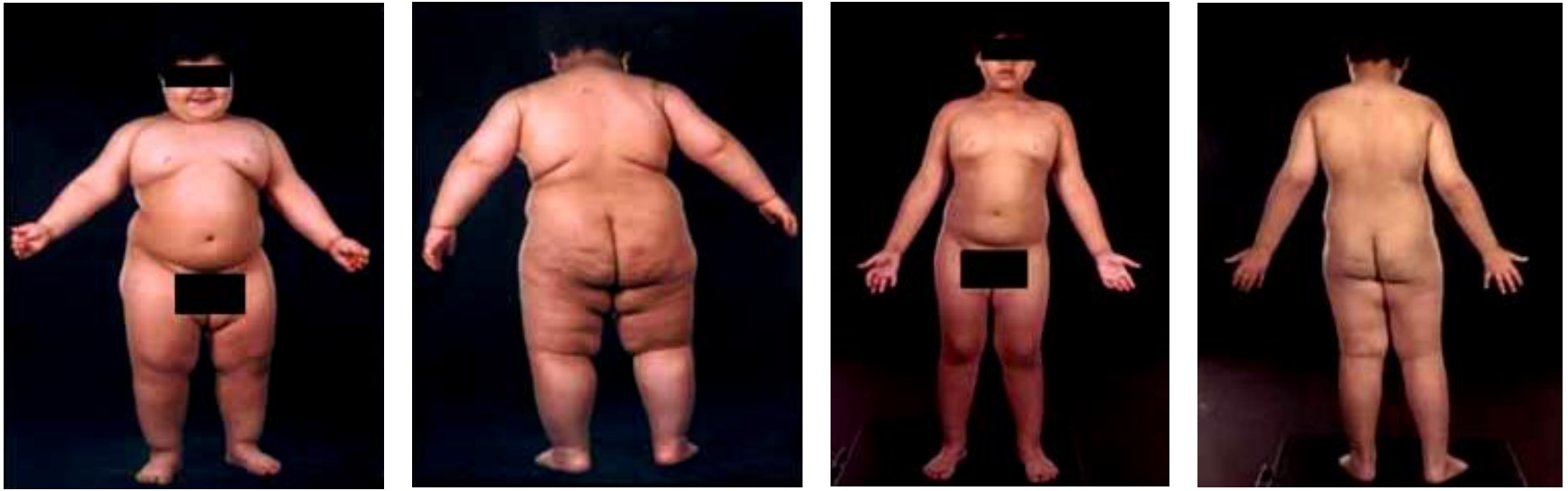
Carl T. Montague*†, I. Sadaf Farooqi*†‡, Jonathan P. Whitehead*‡, Maria A. Soos*‡, Harald Rau*‡, Nicholas J. Wareham§, Ciaran P. Sewter*‡, Janet E. Digby*‡, Shehla N. Mohammed‖, Jane A. Hurst¶, Christopher H. Cheetham#, Alison R. Earley#, Anthony H. Barnett☆, Johannes B. Prins*‡ & Stephen O'Rahilly*‡

*University of Cambridge, Departments of * Medicine, ‡ Clinical Biochemistry and § Community Medicine, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QR, UK*



Montague CT, et al. Nature. 1997;387:903-8

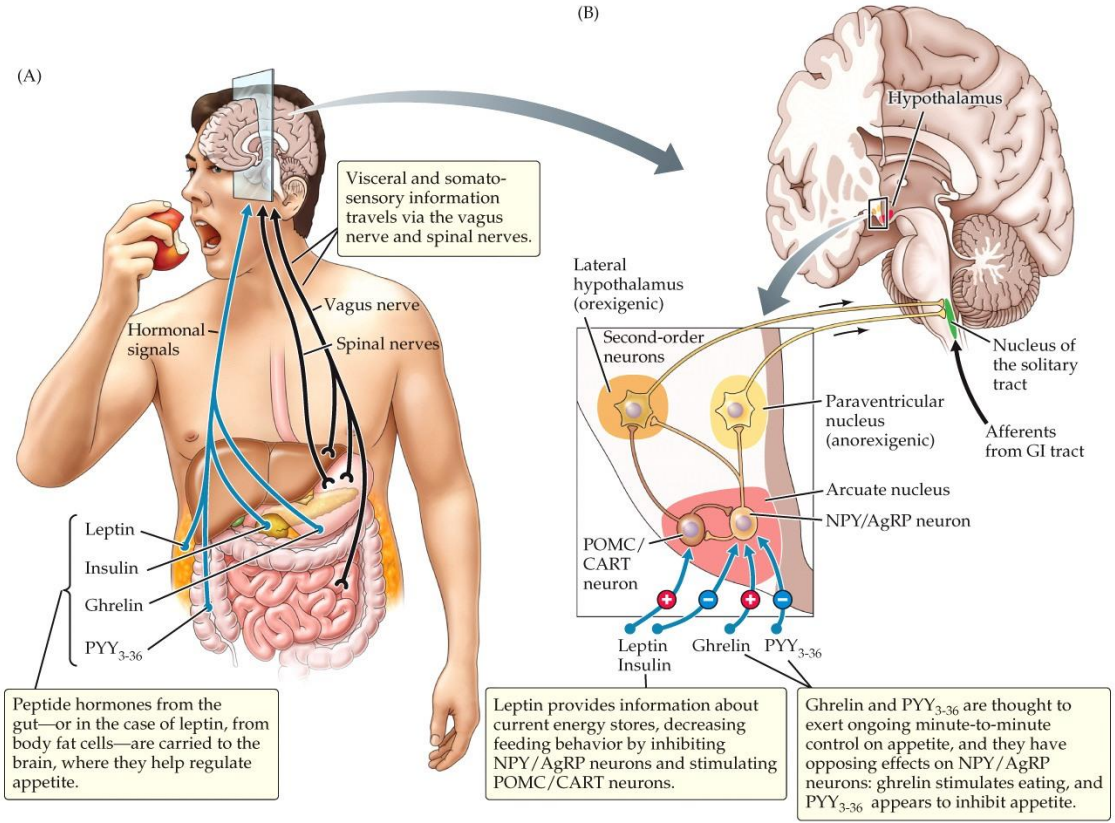
CONGENITAL LEPTIN DEFICIENCY: RESPONSE TO THERAPY



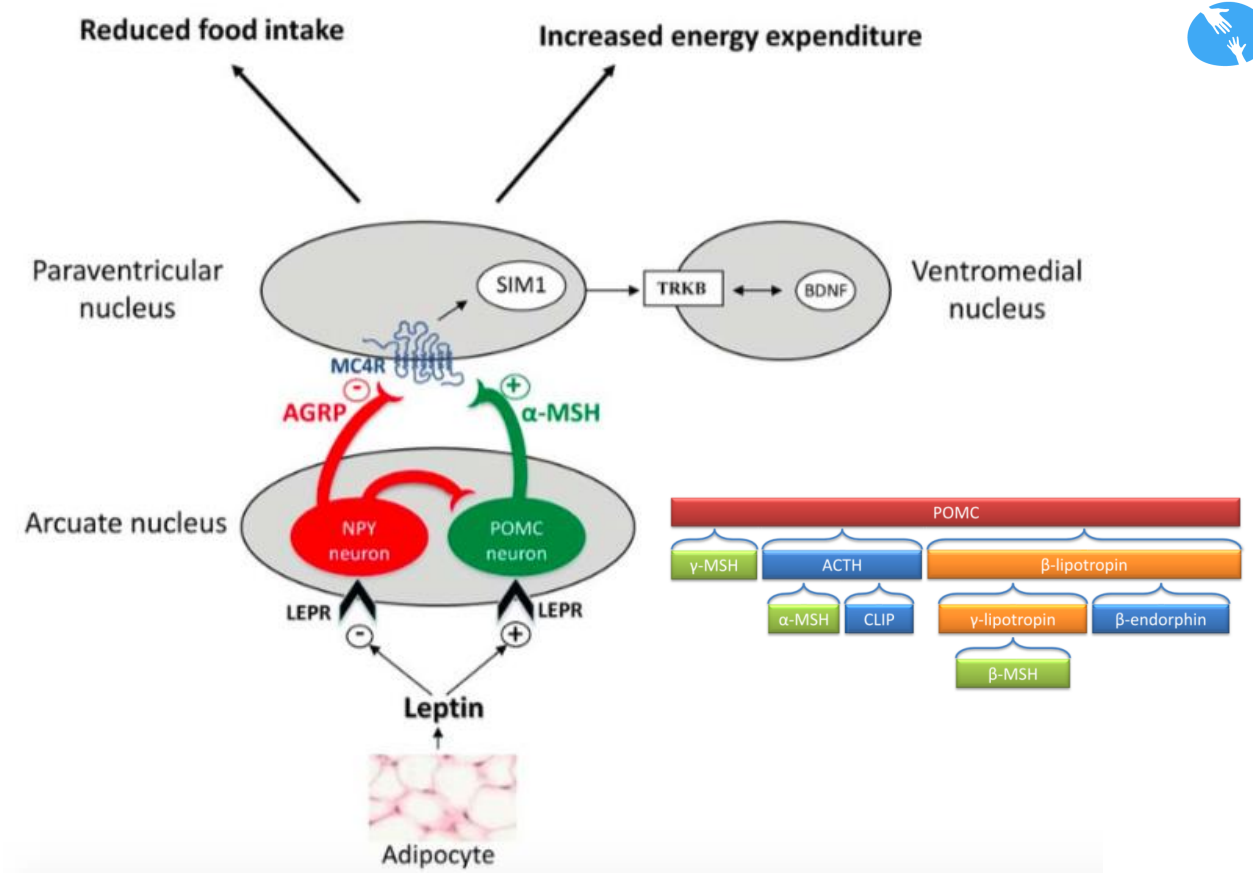
Farooqi IS, et al. N Engl J Med. 1999;341:879-84

CONGENITAL LEPTIN DEFICIENCY: RESPONSE TO THERAPY

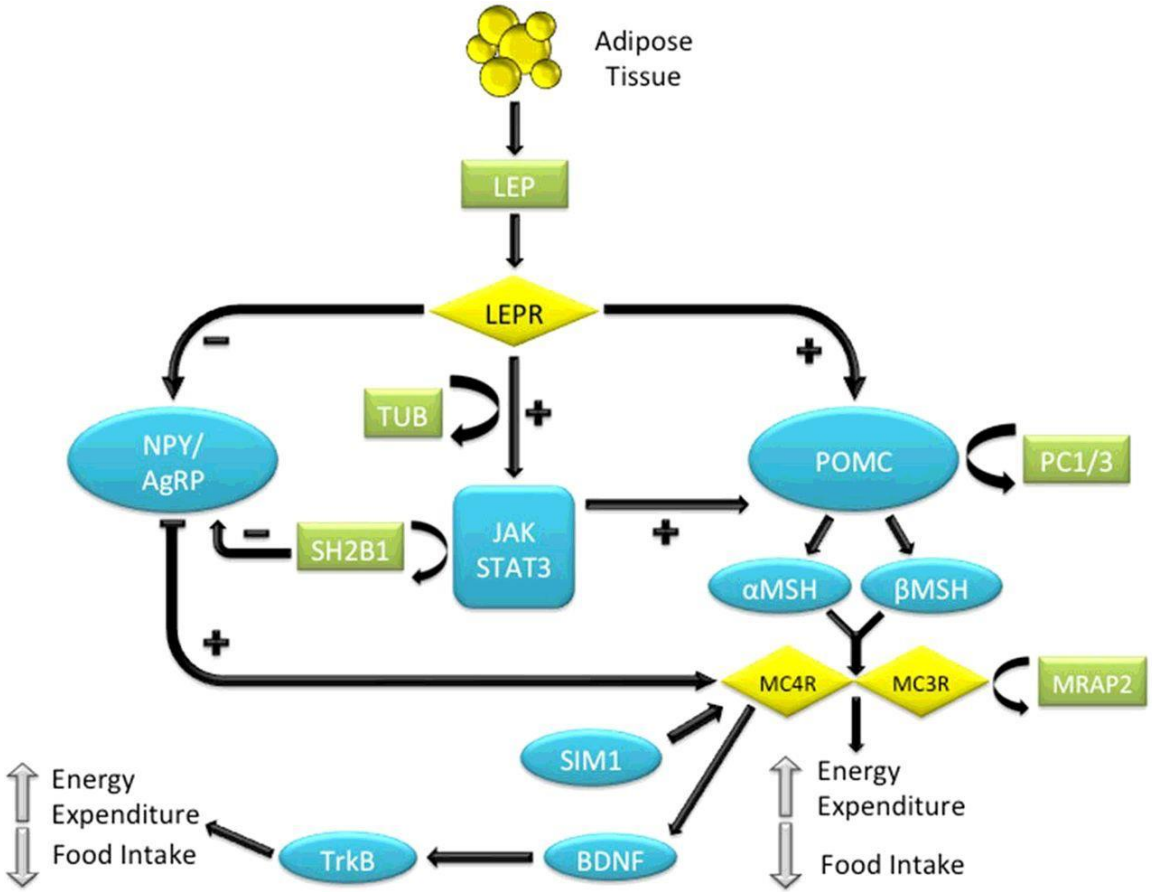
Farooqi IS, et al. N Engl J Med. 1999;341:879-84



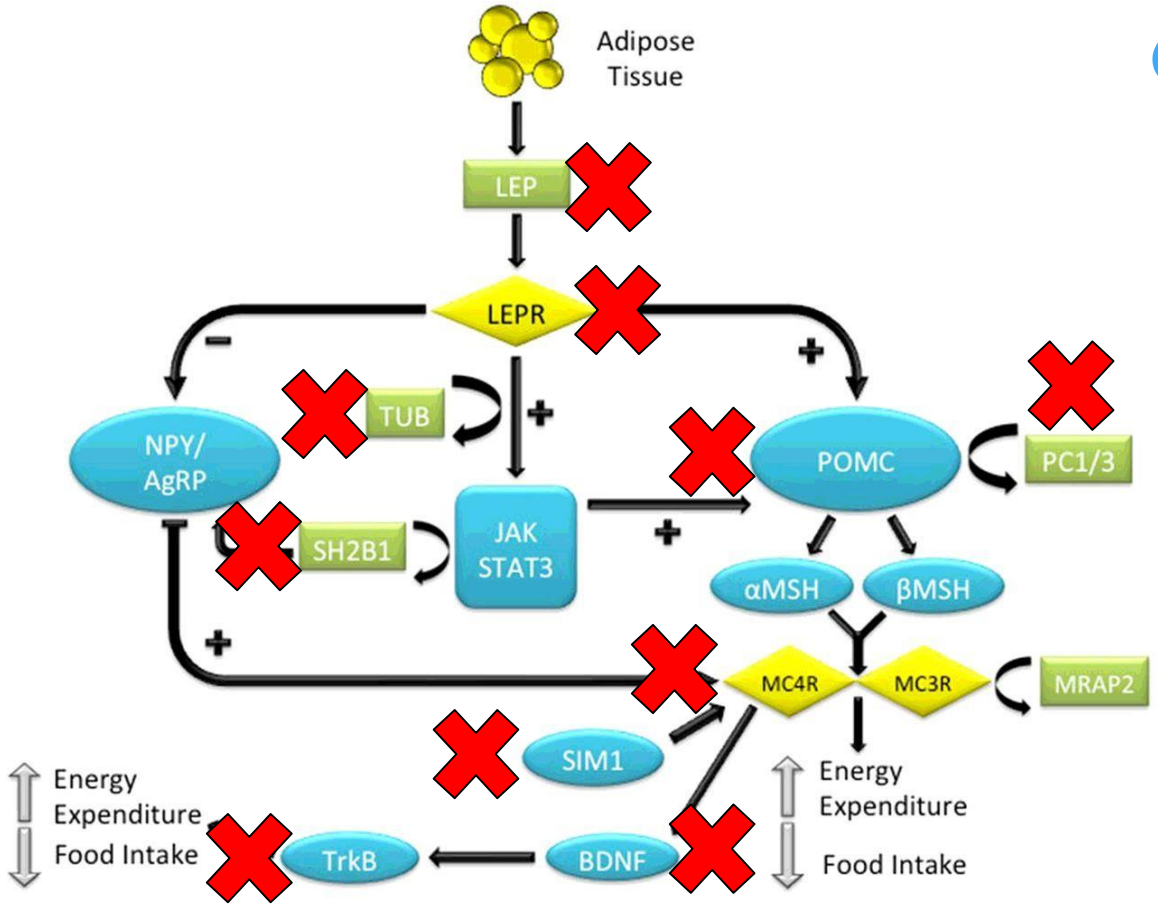
AgRP, agouti-related peptide; CART, cocaine- and amphetamine-related transcript; GI, gastrointestinal; NPY, neuropeptide Y; PYY, peptide YY; POMC, pro-opiomelanocortin



ACTH, adrenocorticotropic hormone; AGRP, agouti-related peptide; BDNF, brain-derived neurotrophic factor; CLIP, corticotropin-like intermediate peptide; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; MSH; melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; TrkB, tyrosine kinase receptor B



AgRP, agouti-related peptide; BDNF, brain-derived neurotrophic factor; JAK, janus kinase; LEP, leptin; LEPR, leptin receptor; MC3R, melanocortin 3 receptor; MC4R, melanocortin 4 receptor; MRAP2, melanocortin 2 receptor accessory protein 2; MSH; melanocyte-stimulating hormone; NPY, neuropeptide Y; PC1/3, prohormone convertase 1/3; POMC, pro-opiomelanocortin; SH2B1, Src homology 2 B adaptor protein 1; TrkB, tyrosine kinase receptor B; STAT3, signal transducer and activator of transcription 3



AgRP, agouti-related peptide; BDNF, brain-derived neurotrophic factor; JAK, janus kinase; LEP, leptin; LEPR, leptin receptor; MC3R, melanocortin 3 receptor; MC4R, melanocortin 4 receptor; MRAP2, melanocortin 2 receptor accessory protein 2; MSH; melanocyte-stimulating hormone; NPY, neuropeptide Y; PC1/3, prohormone convertase 1/3; POMC, pro-opiomelanocortin; SH2B1, Src homology 2 B adaptor protein 1; TrkB, tyrosine kinase receptor B; STAT3, signal transducer and activator of transcription 3

Leptin	Rapid weight gain, behavioural problems when food is denied, hyperphagia, hypogonadotrophic hypogonadism, defective T-cell mediated immunity, low blood pressure	Autosomal recessive	*LEP*
Leptin receptor	Rapid weight gain, behavioural problems when food is denied, hyperphagia, hypogonadotrophic hypogonadism, defective T-cell mediated immunity, low blood pressure	Autosomal recessive	*LEPR*
SH2B adaptor protein 1	Hyperphagia, childhood onset obesity, insulin resistance, reduced height, behavioural abnormalities	NA	*SH2B1*
Proopiomelanocortin	Obesity, hypocortisolism, red hair and skin hypopigmentation, neonatal hypoglycaemia, seizures, cholestasis, voracious appetite	Autosomal recessive	*POMC*
Pro-protein convertase subtilisin / kexin type 1	Early-onset obesity, hyperphagia, postprandial hypoglycaemia, endocrine dysfunction, diarrhoea, diabetes insipidus	Autosomal dominant or recessive	*PCSK1*
Melanocortin 4 receptor	Hyperphagia, rapid weight gain, hyperinsulinaemia, increased linear growth, increase in bone mass, increase in both fat and lean mass	Autosomal dominant or recessive	*MC4R*

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Pygeyre M, et al. Clin Sci (Lond). 2016;130:943-86

Neurotrophic tyrosine kinase receptor type 2 (tyrosine receptor kinase B)	Early-onset obesity, hyperphagia, developmental delay, impairment in short-term memory, impaired nociception	NA	*NTRK2 (TrkB)*
Brain-derived neurotrophic factor	Hyperphagia, severe obesity, cognitive impairment, hyperactivity	NA	*BDNF*
Single-minded homologue 1	Hyperphagia, obesity, reduction in paraventricular nucleus, excessive growth, Prader–Willi like neurobehavioural features	NA	*SIM1*
Kinase suppressor of Ras 2	Hyperphagia, early-onset obesity, low heart rate, reduced basal metabolic rate, severe insulin resistance	NA	*KSR2*
Tubby bipartite transcription factor	Deteriorating vision, obesity, normal glucose, cholesterol, triacylglycerols levels	Autosomal recessive	*TUB*

Pygeyre M, et al. Clin Sci (Lond). 2016;130:943-86

nature genetics
LETTERS
https://doi.org/10.1038/s41588-017-0023-6

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Loss-of-function mutations in *ADCY3* cause monogenic severe obesity

Sadia Saeed[1,2], Amélie Bonnefond[1], Filippo Tamanini[2], Muhammad Usman Mirza[3], Jaida Manzoor[4], Qasim M. Janjua[5], Sadia M. Din[6], Julien Gaitan[7,8], Alexandra Milochau[7,8], Emmanuelle Durand[1], Emmanuel Vaillant[1], Attiya Haseeb[6], Franck De Graeve[1], Iandry Rabearivelo[1], Olivier Sand[1], Gurvan Queniat[1], Raphaël Boutry[1], Dina A. Schott[9], Hina Ayesha[10], Muhammad Ali[11], Waqas I. Khan[12], Taeed A. Butt[13], Tuula Rinne[14], Connie Stumpel[15], Amar Abderrahmani[1,2], Jochen Lang[7,8], Muhammad Arslan[5,6] and Philippe Froguel[1,2*]

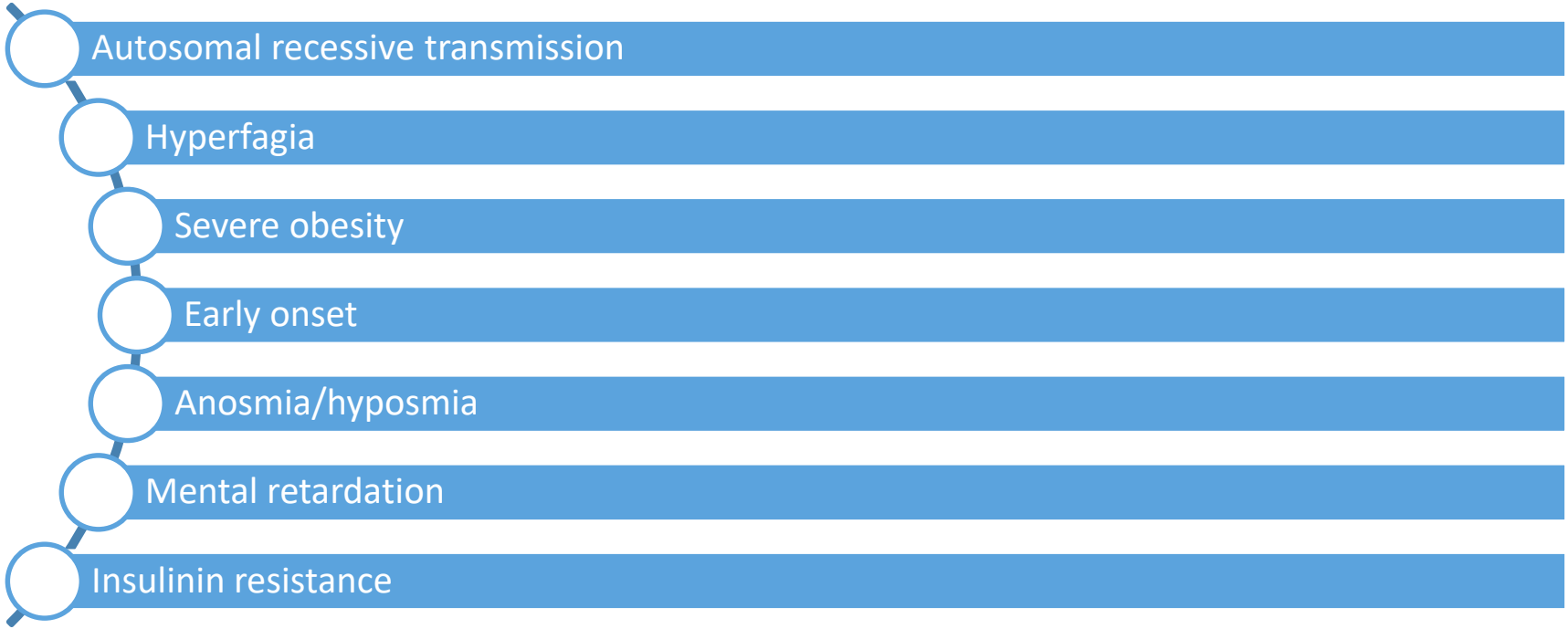
Loss-of-function variants in *ADCY3* increase risk of obesity and type 2 diabetes

Niels Grarup[#1], Ida Moltke[#2], Mette K. Andersen[1], Maria Dalby[2], Kristoffer Vitting-Seerup[2,3], Timo Kern[1], Yuvaraj Mahendran[1], Emil Jørsboe[2], Christina V. L. Larsen[4,5], Inger K. Dahl-Petersen[4], Arthur Gilly[6], Daniel Suveges[6], George Dedoussis[7], Eleftheria Zeggini[6], Oluf Pedersen[1], Robin Andersson[2], Peter Bjerregaard[4,5], Marit E. Jørgensen[4,5,8], Anders Albrechtsen[2], and Torben Hansen[1,9]

ADCY3, adenylate cyclase 3

Saeed S, et al. Nat Genet. 2018;50:175-79

ADCY3 MUTATIONS: PHENOTYPE

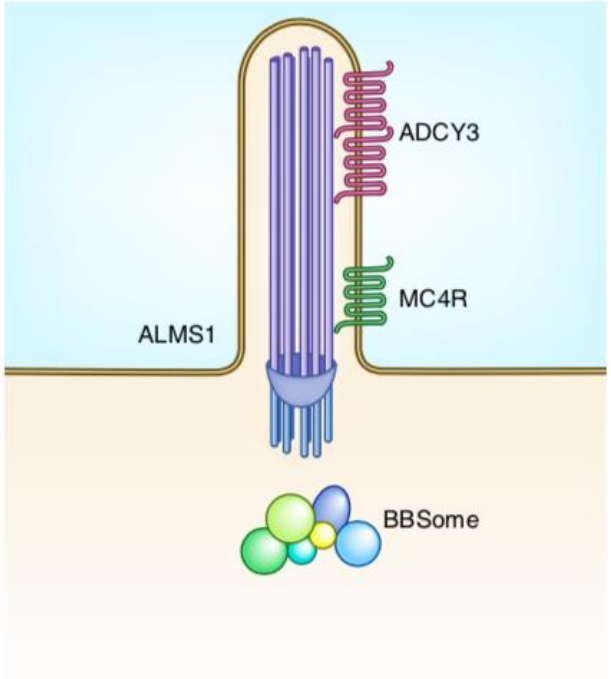


ADCY3, adenylate cyclase 3

nature genetics
LETTERS
https://doi.org/10.1038/s41588-017-0020-9

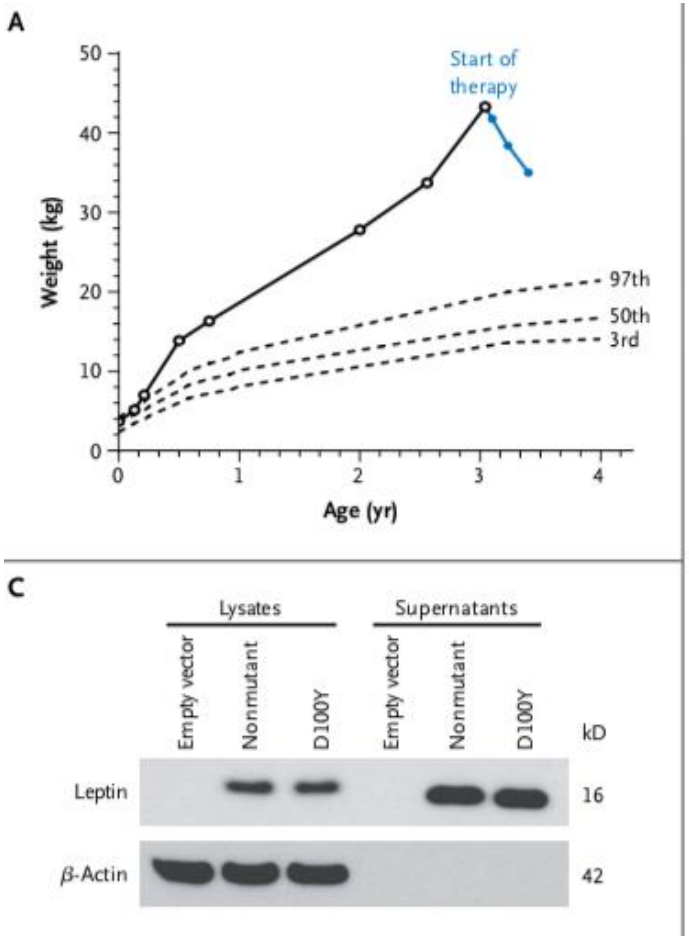
Subcellular localization of MC4R with ADCY3 at neuronal primary cilia underlies a common pathway for genetic predisposition to obesity

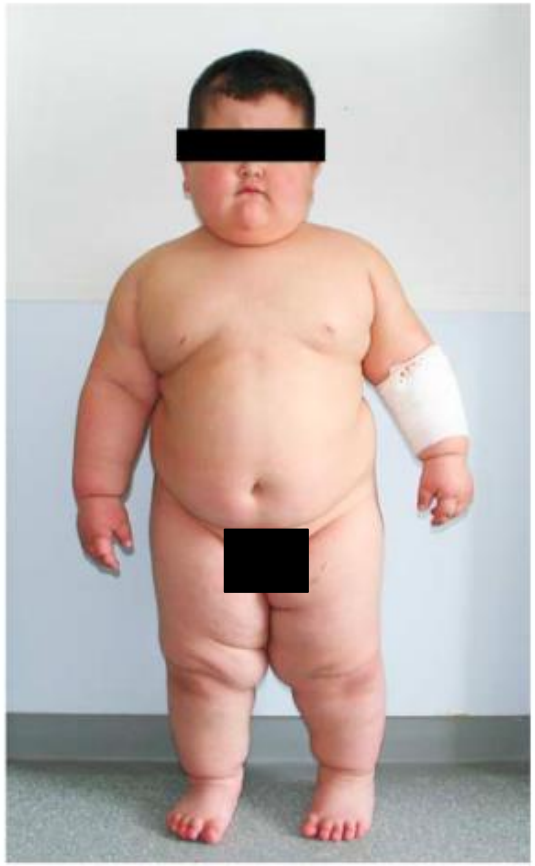
Jacqueline E. Siljee[1], Yi Wang[1], Adelaide A. Bernard[1], Baran A. Ersoy[1,4], Sumei Zhang[1], Aaron Marley[2], Mark Von Zastrow[2], Jeremy F. Reiter[3] and Christian Vaisse[1*]



ALMS1, centrosome and basal body associated protein; ADCY3, adenylate cyclase 3; BBSome, complex of Bardet-Biedl syndrome proteins; MC4R, melanocortin 4 receptor

Siljee JE, et al. Nat Genet. 2018;50:180-5





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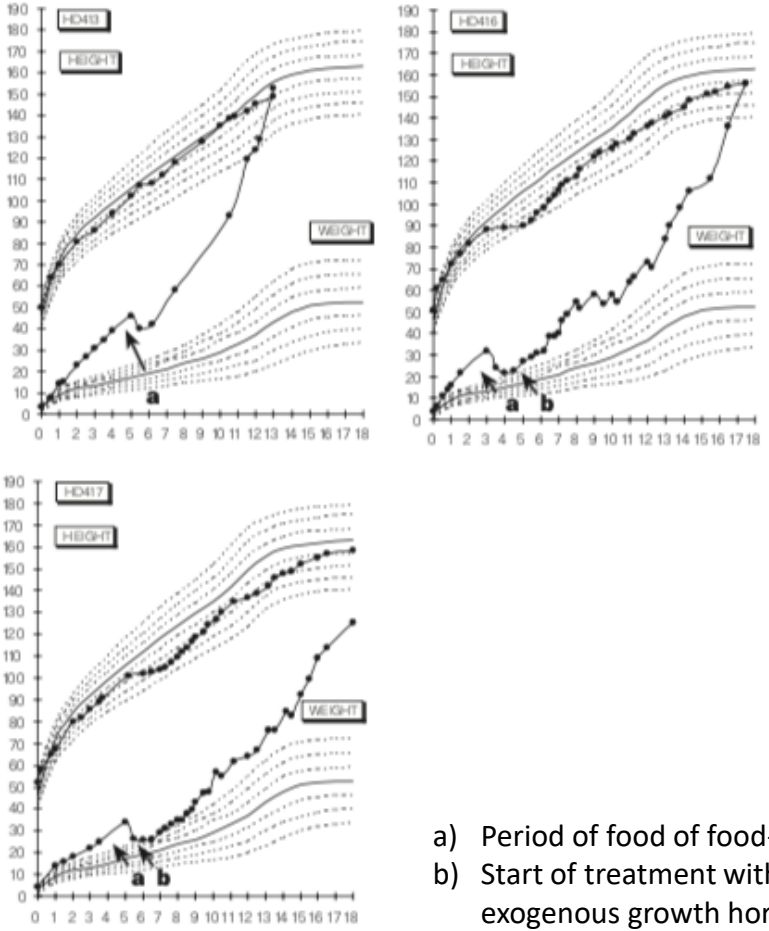
Wabitsch M, et al. N Engl J Med 2015;372:48-54

letters to nature

A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction

Karine Clément*†‡, Christian Vaisse*†‡, Najiba Lahlou§, Sylvie Cabrol‖, Veronique Pelloux*, Dominique Cassuto*, Micheline Gourmelen‖, Christian Dina†, Jean Chambaz¶, Jean-Marc Lacorte¶, Arnaud Basdevant*†, Pierre Bougnères¶, Yves Lebouc‖, Philippe Froguel*† & Bernard Guy-Grand*†



a) Period of food of food-intake restriction
b) Start of treatment with levothyroxine and exogenous growth hormone

Clément K, et al. Nature. 1998;392:398-401

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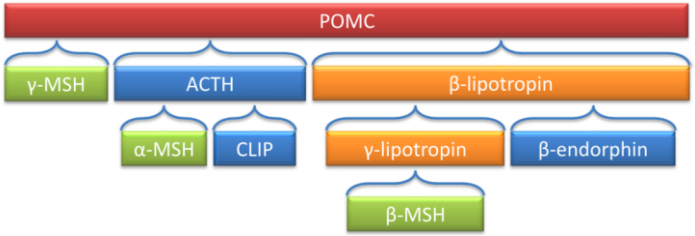
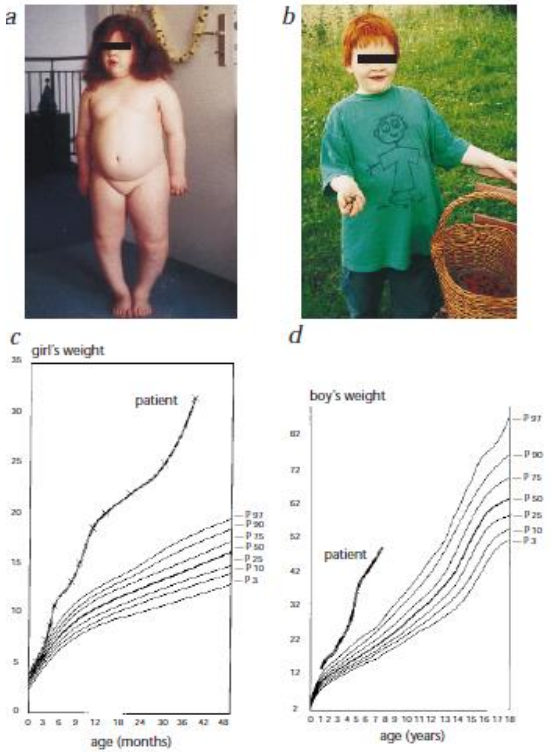
Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by *POMC* mutations in humans

Heiko Krude[1], Heike Biebermann[1], Werner Luck[1], Rüdiger Horn[2], Georg Brabant[2] & Annette Grüters[1]



Phenotype:

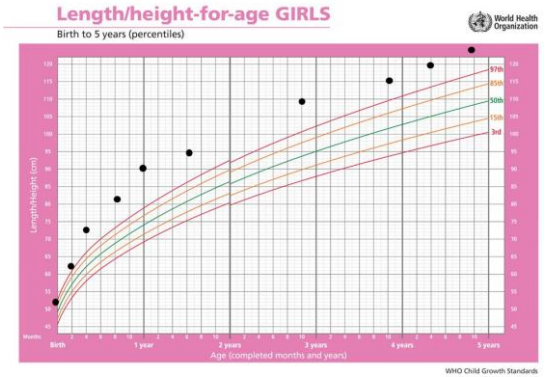
- **Red hair (MC1R)**
- **Adrenal insufficiency (MC2R)**
- **Obesity (MC4R)**

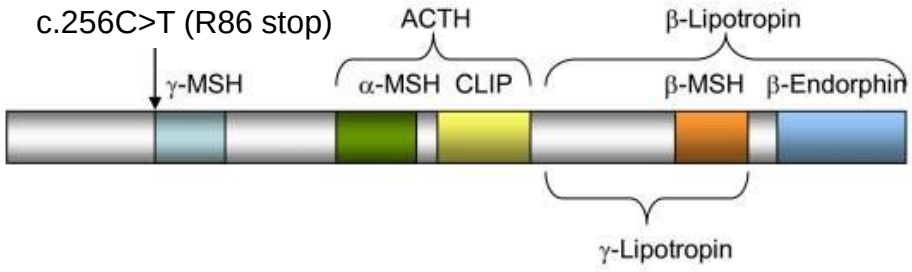


ACTH, adrenocorticotropic hormone; CLIP, corticotropin-like intermediate peptide; MC1R, melanocortin 1 receptor; MC2R, melanocortin 2 receptor; MC4R, melanocortin 4 receptor; MSH; melanocyte-stimulating hormone; POMC, pro-opiomelanocortin

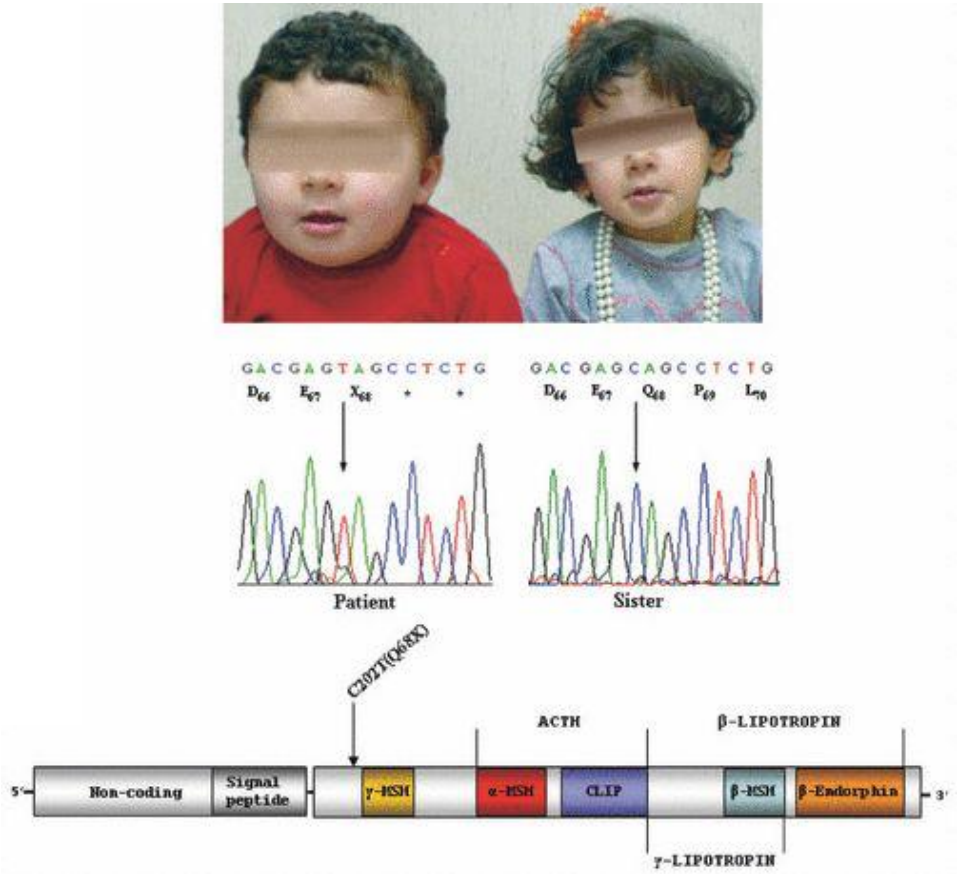
Krude H, et al. Nat Genet. 1998;19:155-7

- **Early onset obesity**
- **Adrenal insufficiency**
- **Mental retardation**





ACTH, adrenocorticotropic hormone; CLIP, corticotropin-like intermediate peptide; MSH; melanocyte-stimulating hormone



ACTH, adrenocorticotropic hormone; CLIP, corticotropin-like intermediate peptide; MSH; melanocyte-stimulating hormone

Cirillo G, et al. Br J Dermatol. 2012;167:1393-5

The NEW ENGLAND JOURNAL of MEDICINE

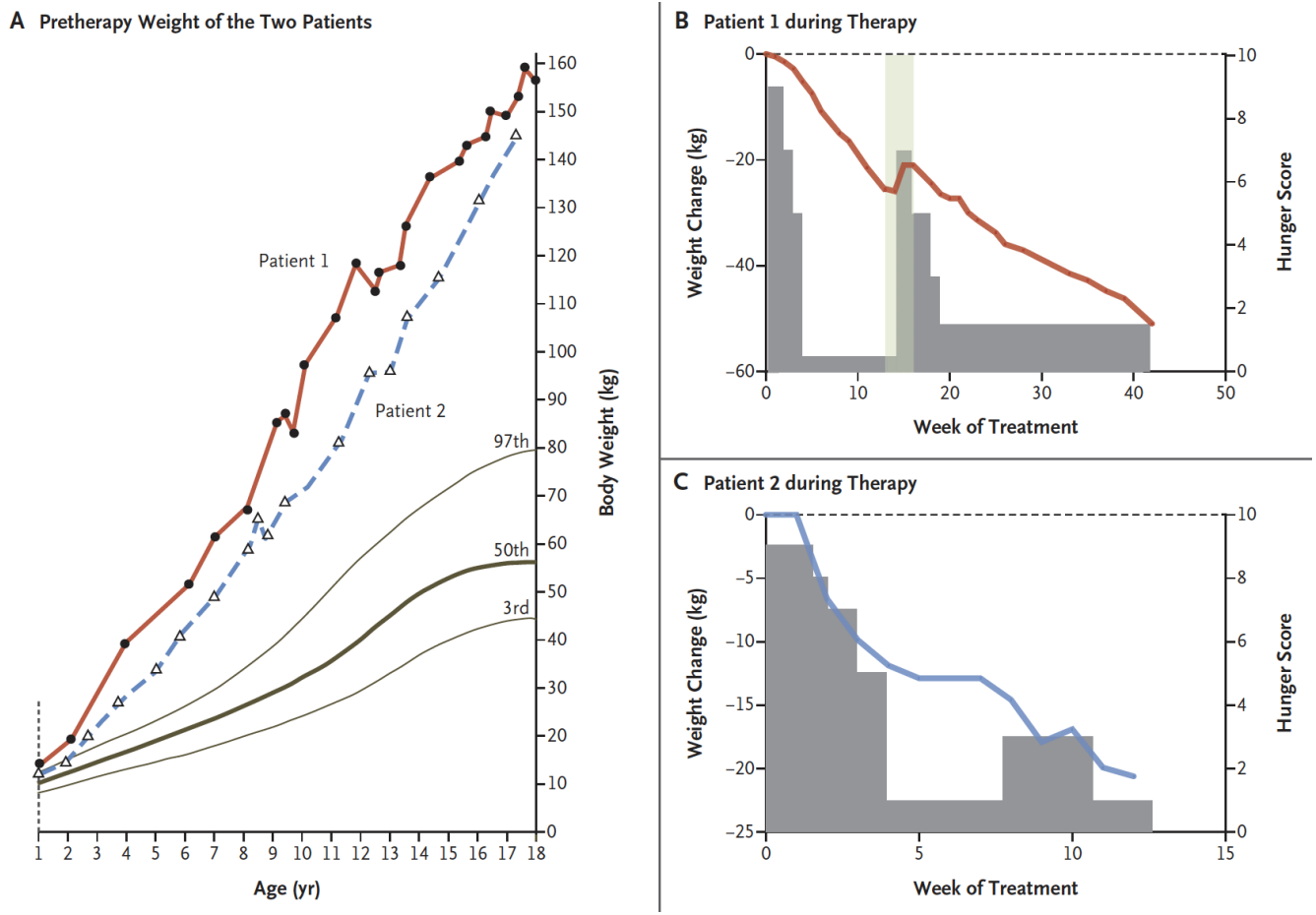
BRIEF REPORT

Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist

Peter Kühnen, M.D., Karine Clément, M.D., Ph.D., Susanna Wiegand, M.D., Oliver Blankenstein, M.D., Keith Gottesdiener, M.D., Lea L. Martini, M.D., Knut Mai, M.D., Ulrike Blume-Peytavi, M.D., Annette Grüters, M.D., and Heiko Krude, M.D.

July 2016

Kühnen P, et al. N Engl J Med. 2016;375:240-6



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nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-018-0015-9

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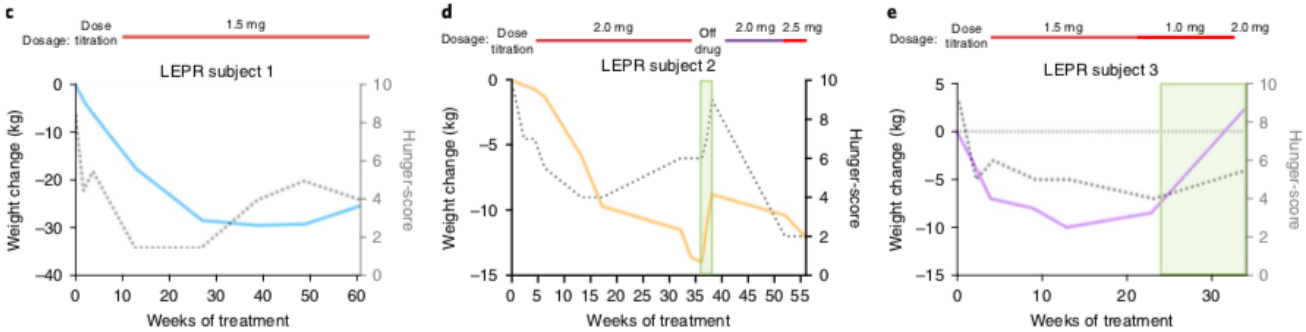
MC4R agonism promotes durable weight loss in patients with leptin receptor deficiency

Karine Clément[1,12], Heike Biebermann[2,12], I. Sadaf Farooqi[3,12], Lex Van der Ploeg[4,12], Barbara Wolters[2], Christine Poitou[1], Lia Puder[2], Fred Fiedorek[4], Keith Gottesdiener[4], Gunnar Kleinau[5], Nicolas Heyder[5], Patrick Scheerer[5,6], Ulrike Blume-Peytavi[7], Irina Jahnke[7], Shubh Sharma[4], Jacek Mokrosinski[3], Susanna Wiegand[8], Anne Müller[2], Katja Weiß[9], Knut Mai[6,10], Joachim Spranger[6,10], Annette Grüters[11], Oliver Blankenstein[2], Heiko Krude[2] and Peter Kühnen[2]*



LEPR, leptin receptor; MC4R, melanocortin 4 receptor

Clément K, et al. Nat Med. 2018;24:551-55

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 20, 2003 VOL. 348 NO. 12

Clinical Spectrum of Obesity and Mutations in the Melanocortin 4 Receptor Gene

I. Sadaf Farooqi, M.D., Ph.D., Julia M. Keogh, B.Sc., Giles S.H. Yeo, Ph.D., Emma J. Lank, B.Sc., Tim Cheetham, M.D., and Stephen O'Rahilly, M.D.

Most frequent cause of monogenic obesity
Up to 6% in some studies

Farooqi IS, et al. N Engl J Med. 2003;348:1085-95

CHILDREN AND ADOLESCENTS WITH MC4R MUTATIONS DISPLAY A PARTICULAR PHENOTYPE

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- Autosomal dominant transmission
- Hyperphagia
- Severe obesity (BMI SDS >3)
- Early onset of obesity (<10 years)
- Tall stature
- Hyperinsulinemia
- Increased bone mineral density

BMI, body mass index; MC4R, melanocortin 4 receptor; SDS, standard deviation score

Farooqi IS, et al. N Engl J Med. 2003;348:1085-95

PREVALENCE OF MC4R GENE MUTATIONS IN ITALIAN OBESE ADULTS AND CHILDREN

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	JCEM '04[1]	Clin. Chem. '05[2]	BMC Medical Genetics, 2009[3]
Number of patients	120	196	240
Age, years +/- SD (range)	12-71	17-70	1-11
Prevalence of mutations, %	1.7	2.5	1.6

Sardinia ≈ 300 children <1%[4]

SD, standard deviation; MC4R, melanocortin 4 receptor

1. Santini F, et al. J Clin Endocrinol Metab. 2004;89:904-8. 2. Buono P, et al. Clin Chem. 2005;51:1358-64. 3. Santoro N, et al. BMC Med Genet. 2009;10:25. 4. Ibba et al., unpublished

Monogenic obesity

- A single gene mutation causes the disease
- Rare
- Some can be treated

Syndromic obesity

- At least 20 syndromes
- All rare conditions
- Often associated with mental retardation

PRADER-WILLI SYNDROME

Hyperphagia

Growth retardation

Hypothermia

Hypotonia

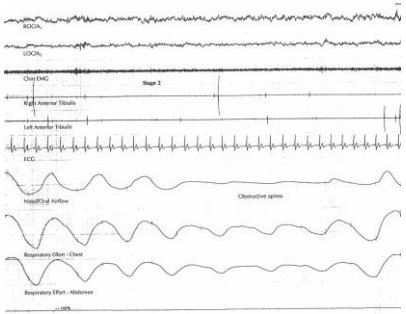
Hypogonadism

Dysmorphism

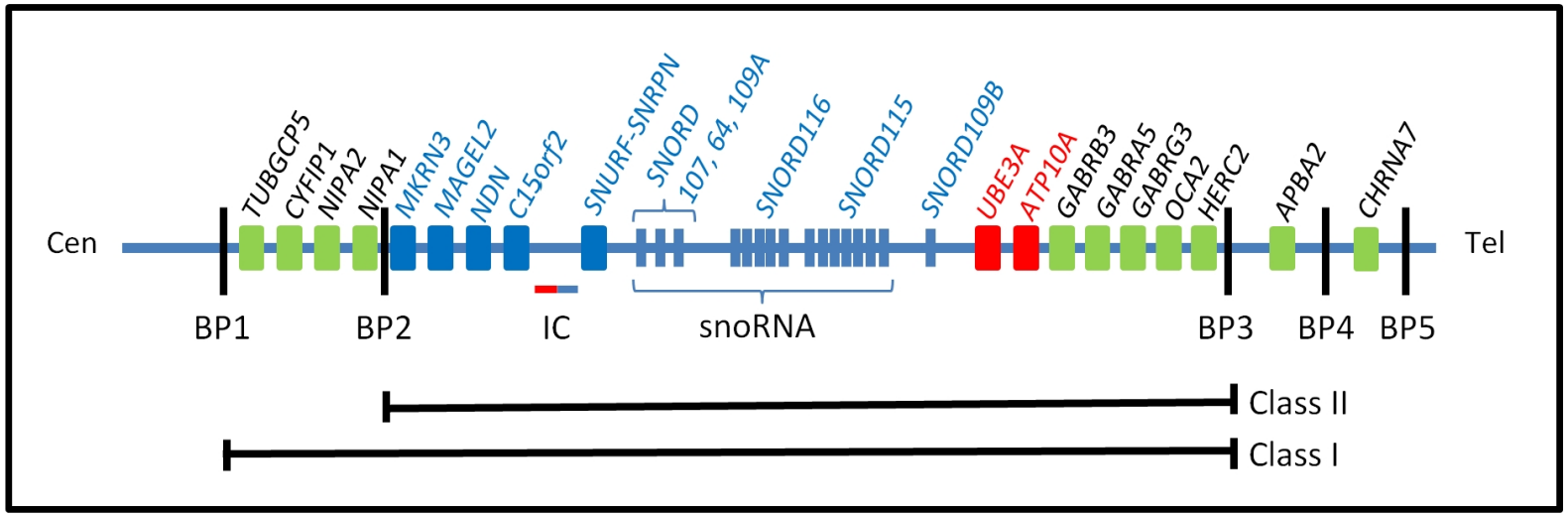
Mental retardation

Behavioural problems

Nocturnal apnoea → **Polysomnography**

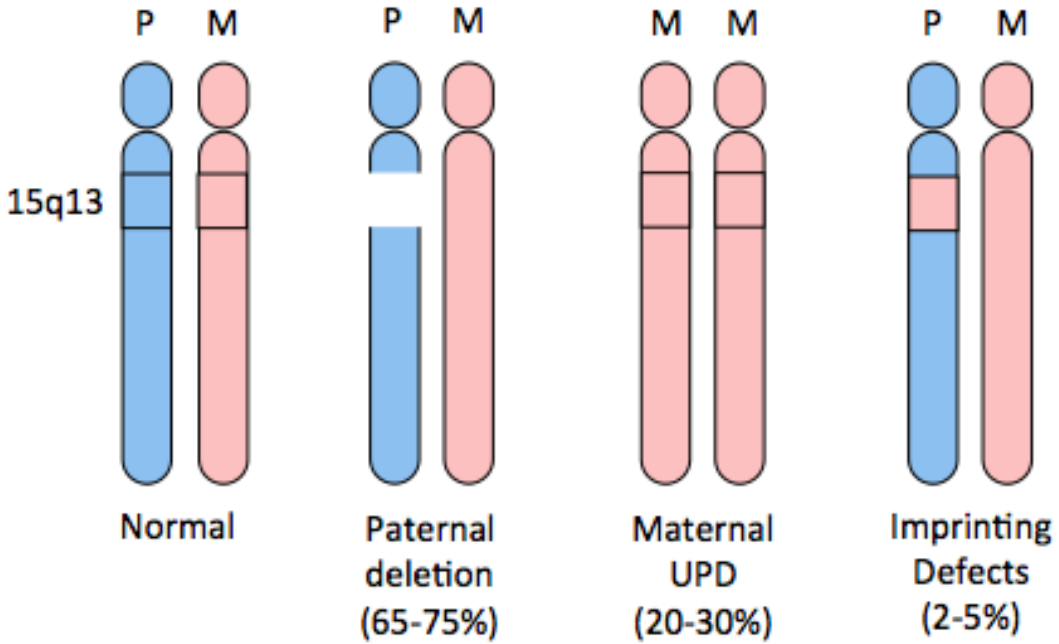


LOCUS 15q11q13



BP, breakpoint; Cen, centromere; IC, imprinting control; Tel, telomeric

PRADER-WILLI SYNDROME: GENETIC MECHANISMS



M, maternal; P, paternal; UPD, uniparental disomy

http://genetics4medics.com/prader-willi-syndrome.html. Accessed on January 7, 2020.

BARDET BIEDL SYNDROME

Table 1

Clinical phenotypes associated with ciliopathies

	MKS	BBS	JBTS	JATD	OFD1	MKKS	SLS	NPH	LCA
Retinopathy	+	+	+	–	–	–	+	+	+
Polydactyly	+	+	+	–	+	+	–	–	–
Kidney disease	+	+	+	+	+	–	+	+	–
Situs inversus	+	+	+	–	–	–	+	–	–
Mental retardation/developmental delay	+	+	+	–	+	–	–	+	+
Hypoplasia of cerebellum	+	+	+	–	+	–	–	+	–
Hydrometrocolpos	–	+	–	–	–	+	–	–	–
Obesity	–	+	+	–	–	–	–	–	–
Hepatic dysfunction	+	+	+	–	–	–	+	+	–

JATD, Jeune syndrome; OFD1, orofaciodigital syndrome 1; MKKS, McKusick-Kaufman syndrome; SLS, Senior-Loken syndrome.

Bardet-Biedl	Mental retardation, retinal dystrophy or pigmentary retinopathy, dysmorphic extremities, hypogonadism, kidney anomalies	1/125,000 to 1/175,000 births	BBS1 (11q13); BBS2 (16q12.2); BBS3 (*ARL6*, 3q11); BBS4 (15q24.1); BBS5 (2q31.1); BBS6 (*MKKS*, 20p12); BBS7 (4q27); BBS8 (*TTC8*, 14q31); BBS9 (*PTHB1*, 7p14); BBS10 (*C12ORF58*, 12q21.2); BBS 11 (*TRIM32*, 9q33.1); BBS12 (*FLJ35630*, 4q27); BBS13 (*MKS1*, 17q23); BBS14 (*CEP290*, 12q21.3); BBS15 (*WDPCP*, 2p15); BBS16 (*SDCCAG8*, 1q43); BBS17 (*LZTFL1*, 3p21); BBS18 (*BBIP1*, 10q25); BBS19 (*IFT27*, 22q12)

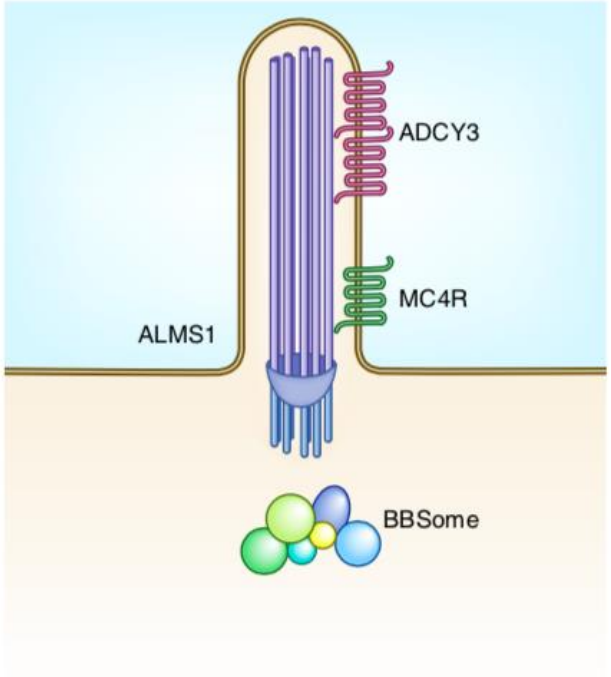
BBS, Bardet Biedl syndrome; JATD, Jeune syndrome; JBTS, Joubert syndrome; LCA, Leber congenital amaurosis; OFD1, orofaciodigital syndrome 1; MKKS, McKusick-Kaufman syndrome; MKS, Meckel-Gruber syndrome; NPH, nephronophthisis; SLS, Senior-Loken syndrome.

Zaghloul NA, et al. J Clin Invest. 2009;119:428-37; Huvenne H, et al. Obesity Facts 2016; 9:158-173

nature genetics
LETTERS
https://doi.org/10.1038/s41588-017-0020-9

Subcellular localization of MC4R with ADCY3 at neuronal primary cilia underlies a common pathway for genetic predisposition to obesity

Jacqueline E. Siljee[1], Yi Wang[1], Adelaide A. Bernard[1], Baran A. Ersoy[1,4], Sumei Zhang[1], Aaron Marley[2], Mark Von Zastrow[2], Jeremy F. Reiter[3] and Christian Vaisse[1*]



ALMS1, centrosome and basal body associated protein; ADCY3, adenylate cyclase 3; BBSome, complex of Bardet-Biedl syndrome proteins; MC4R, melanocortin 4 receptor

Siljee JE, et al. Nat Genet. 2018;50:180-5

Monogenic obesity

- A single gene mutation causes the disease
- Rare
- Some can be treated

Syndromic obesity

- At least 20 syndromes
- All rare conditions
- Often associated with mental retardation

Polygenic obesity

- ~30% of obese children have ≥ 1 obese parent
- Common condition!
- Overall 40-60% of the obesity susceptibility is due to genetic influences

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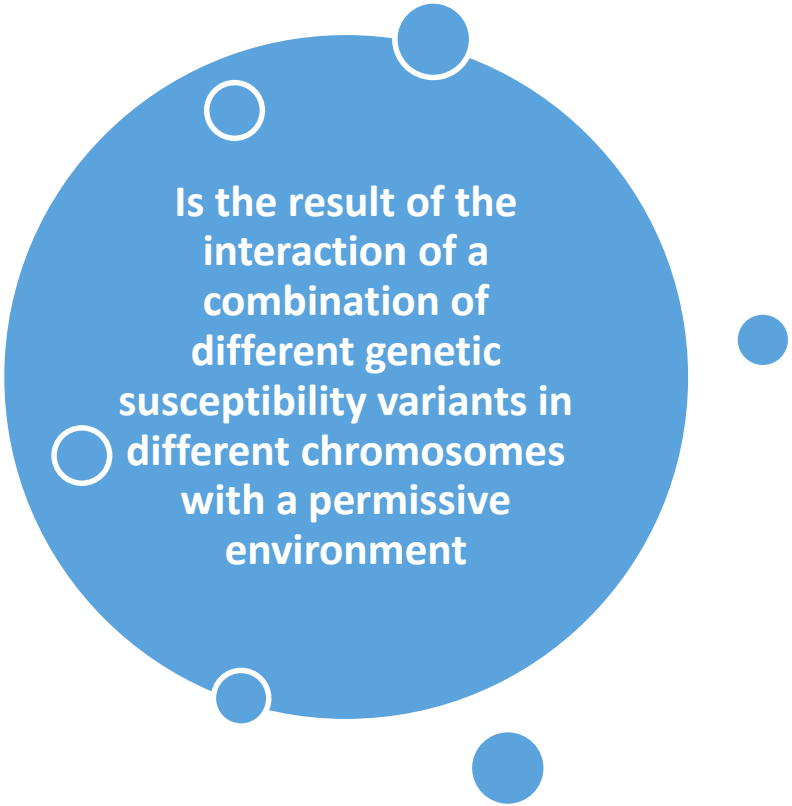
SOCIAL SECURITY
BY ALLAN SLOAN
WATER ON MARS
New Hints of Life
'ME, MYSELF & IRENE'
The Wild Men of Comedy
Fat for Life?
Six Million Kids
Are Seriously Overweight

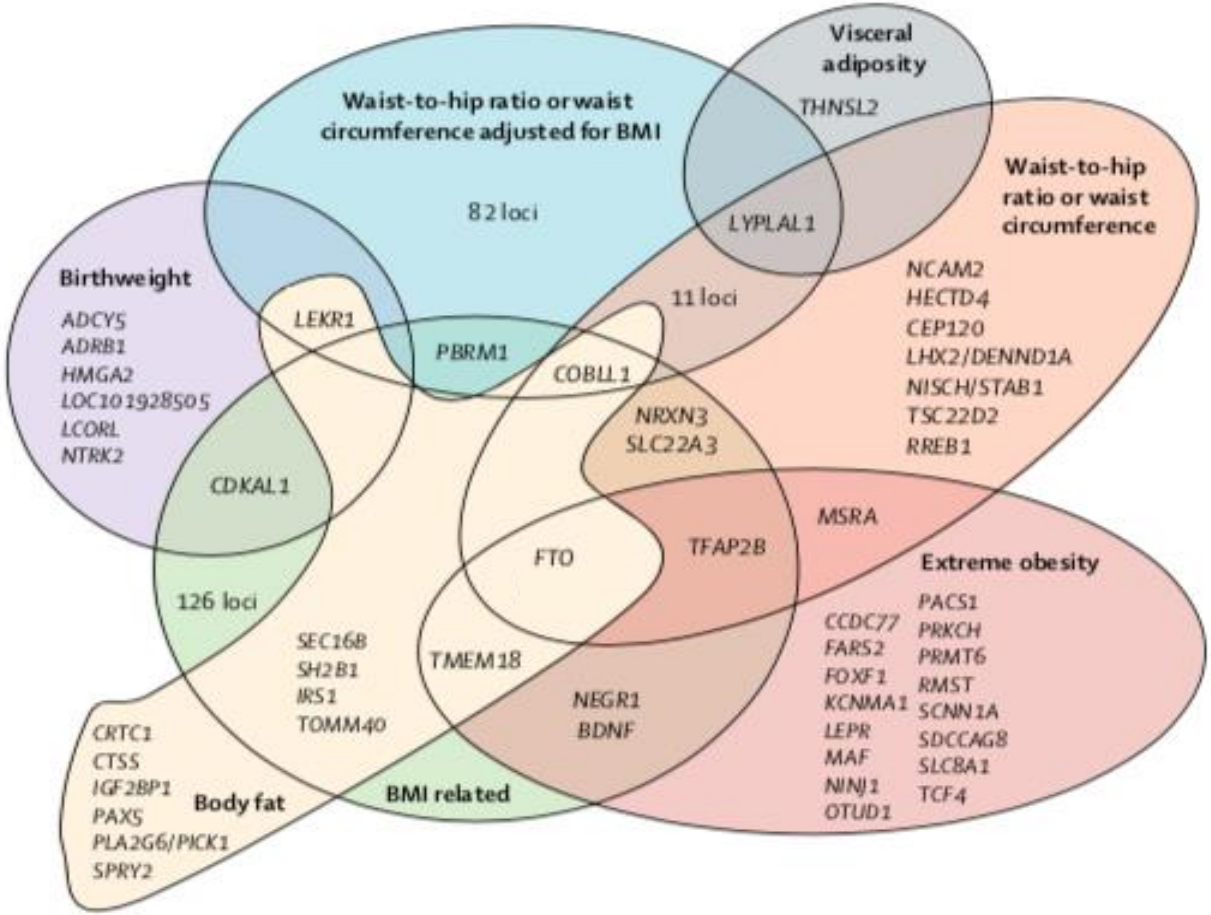

settimanale del CORRIERE DELLA SERA
Sette
TRECENTO MILIONI DI
GUERRA PREVENTIVA
MA SIAMO SICURI DI VOLERLA?


PRIMA TV
ADOLESCENTI XXL


oventù bruciata
lle calorie

POLYGENIC OBESITY



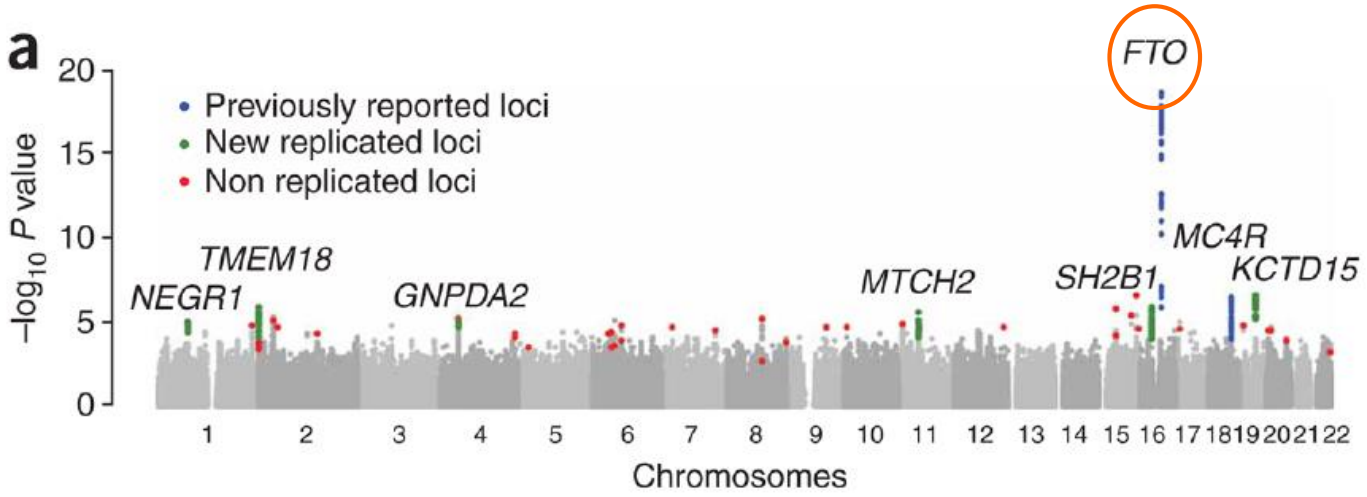


BMI, body mass index; FTO, fat mass and obesity-associated gene

Goodarzi MO. Lancet Diabetes Endocrinol. 2018;6:223-36

FTO IS A DNA DEMETHYLASE

Genetic effect: Homozygous for the most significantly associated SNP carry 1.67 higher risk of developing obesity



FTO, fat mass and obesity-associated gene; SNP, single nucleotide polymorphism

Willer CJ, et al. Nat Genet. 2009;41:25-34

FTO IN 912 OBESE CHILDREN AND ADOLESCENTS FROM SARDINIA

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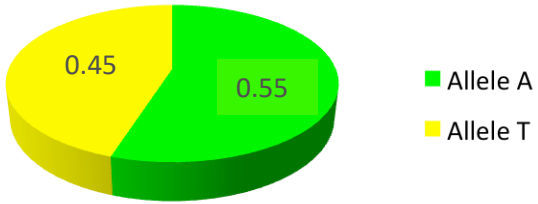
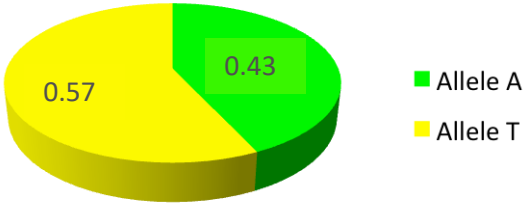
Patients



Controls



FTO (rs9939609)		Patients		Controls		Odds ratio	95% CI	X^2	P value
		Observed	Frequency	Observed	Frequency				
N. samples		912		543					
Allele A		1000	0.55	466	0.43	1.6	1.3–1.8	35.5	$<1 \times 10^{-5}$
Allele T		824	0.45	620	0.57				
Individuals AA		285	0.31	106	0.20				
Individuals AT		430	0.47	254	0.47				
Individuals TT		197	0.22	183	0.34				

Homozygous for the A variant have 1.6 increased risk to develop obesity

CI, confidence interval; FTO, fat mass and obesity-associated gene

Zavattari P, et al. Ann Hum Genet. 2011;75:648-54

nature genetics

Overexpression of *Fto* leads to increased food intake and results in obesity

Chris Church[1], Lee Moir[1], Fiona McMurray[1], Christophe Girard[2], Gareth T Banks[1], Lydia Teboul[1], Sara Wells[1], Jens C Brüning[3], Patrick M Nolan[1], Frances M Ashcroft[2] & Roger D Cox[1]

FTO, fat mass and obesity-associated gene

Church C, et al. Nat Genet. 2010;42:1086-92

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Loss-of-Function Mutation in the Dioxygenase-Encoding *FTO* Gene Causes Severe Growth Retardation and Multiple Malformations

Sarah Boissel,[1,7] Orit Reish,[2,7] Karine Proulx,[3,7] Hiroko Kawagoe-Takaki,[4] Barbara Sedgwick,[4] Giles S.H. Yeo,[3] David Meyre,[5] Christelle Golzio,[1] Florence Molinari,[1] Noman Kadhom,[1] Heather C. Etchevers,[1] Vladimir Saudek,[3] I. Sadaf Farooqi,[3] Philippe Froguel,[5,6] Tomas Lindahl,[4] Stephen O'Rahilly,[3] Arnold Munnich,[1] and Laurence Colleaux[1,*]

8 cases described

All died in the first three years of life

FTO, fat mass and obesity-associated gene

Boissel S, et al. Am J Hum Genet. 2009;85:106-11

Prevalence of Loss-of-Function *FTO* Mutations in Lean and Obese Individuals

David Meyre,[1] Karine Proulx,[2] Hiroko Kawagoe-Takaki,[3] Vincent Vatin,[1] Ruth Gutiérrez-Aguilar,[1] Debbie Lyon,[3] Marcella Ma,[2] Helene Choquet,[1] Fritz Horber,[4] Wim Van Hul,[5] Luc Van Gaal,[6] Beverley Balkau,[7] Sophie Visvikis-Siest,[8] François Pattou,[9] I. Sadaf Farooqi,[2] Vladimir Saudek,[2] Stephen O'Rahilly,[2] Philippe Froguel,[1,10] Barbara Sedgwick,[3] and Giles S.H. Yeo[2]

TABLE 3
Summary of nonsynonymous mutations unique to the lean or the obese group

Nonsynonymous mutations	*n*
Obese subjects	
A134T	1
G187A	2
M223V	1
A241T	2
H419R	1
E471G	1
I492V	1
V493F	1
Prevalence of mutations (%)	0.91
Lean subjects	
P5L	1
E24K	1
R80P	1
P93R	1
V94I	1
N143S	1
I148R	1
D189N	1
E234D	1
R316Q	1
P399H	1
Prevalence of mutations (%)	0.77

FTO, fat mass and obesity-associated gene

Meyre D, et al. Diabetes. 2010;59:311-8

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

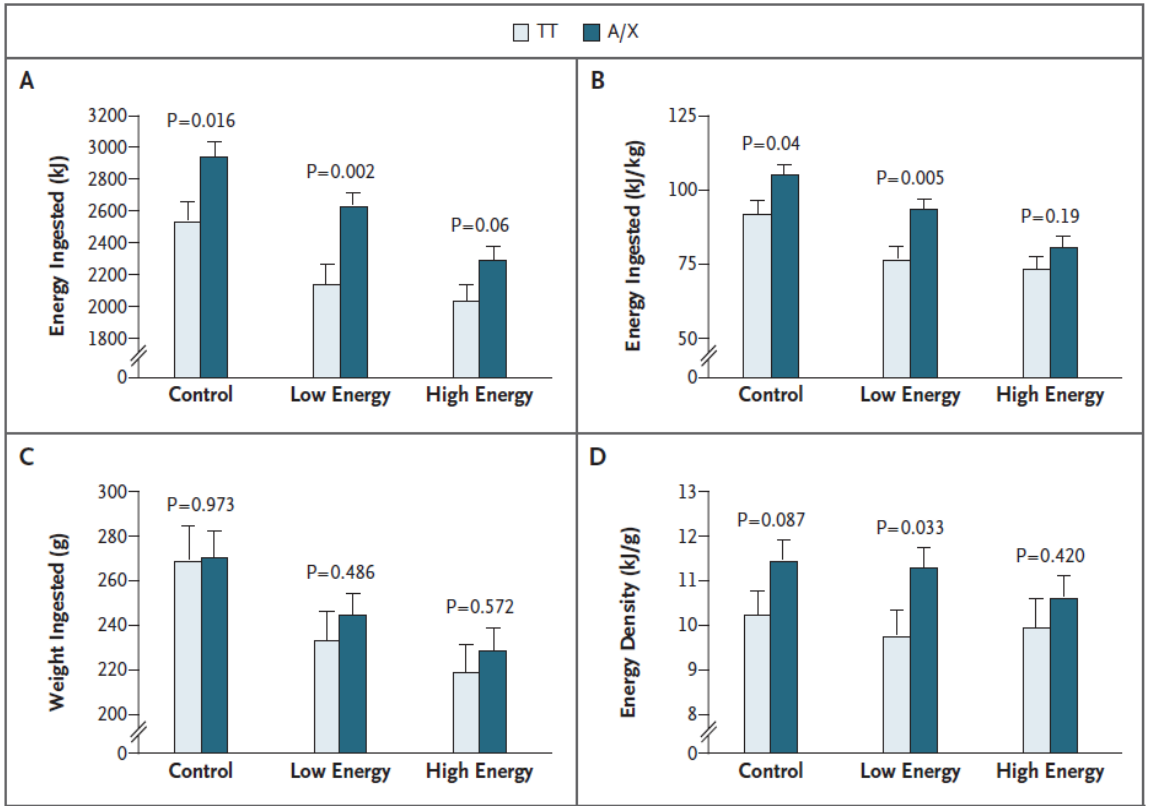
An Obesity-Associated *FTO* Gene Variant and Increased Energy Intake in Children

Joanne E. Cecil, Ph.D., Roger Tavendale, Ph.D., Peter Watt, Ph.D., Marion M. Hetherington, Ph.D., and Colin N.A. Palmer, Ph.D.

Jane Wardle, Susan Carnell, Claire M. A. Haworth, I. Sadaf Farooqi, Stephen O'Rahilly, and Robert Plomin

FTO, fat mass and obesity-associated gene

Cecil JE, et al. N Engl J Med. 2008;359:2558-66



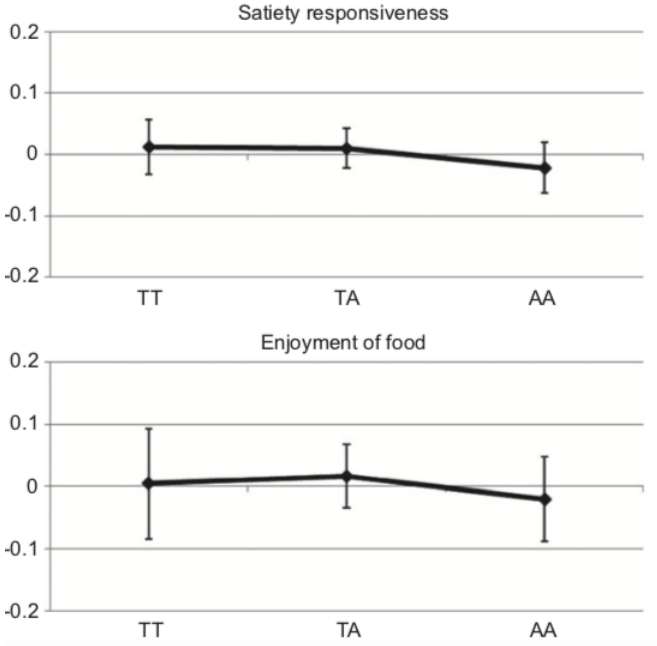
A/X, heterozygous carriers; TT, noncarriers

Cecil JE, et al. N Engl J Med. 2008;359:2558-66

DE GRUYTER DOI 10.1515/jpem-2012-0417 — J Pediatr Endocr Met 2013; 26(5-6): 539–544

Anastasia Ibba, Sabrina Pilia, Patrizia Zavattari, Alberto Loche, Chiara Guzzetti, Maria Rosaria Casini, Luigi Minerba and Sandro Loche*

The role of *FTO* genotype on eating behavior in obese Sardinian children and adolescents

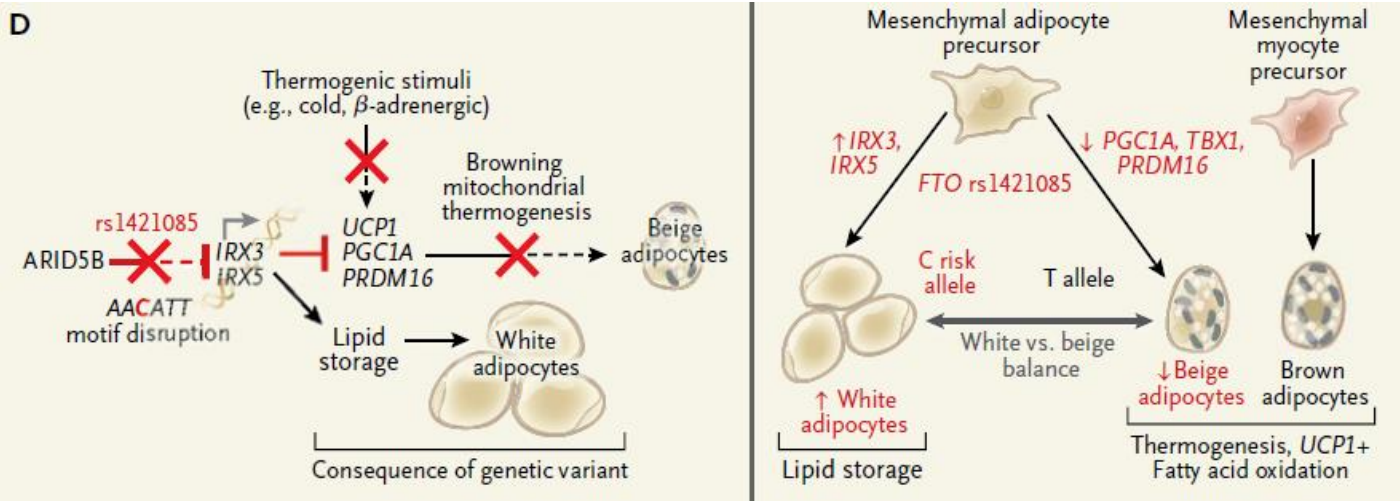


AA, homozygous carriers; TA, heterozygous carriers; TT, noncarriers

Ibba A, et al. J Pediatr Endocrinol Metab. 2013;26(5-6):539-44

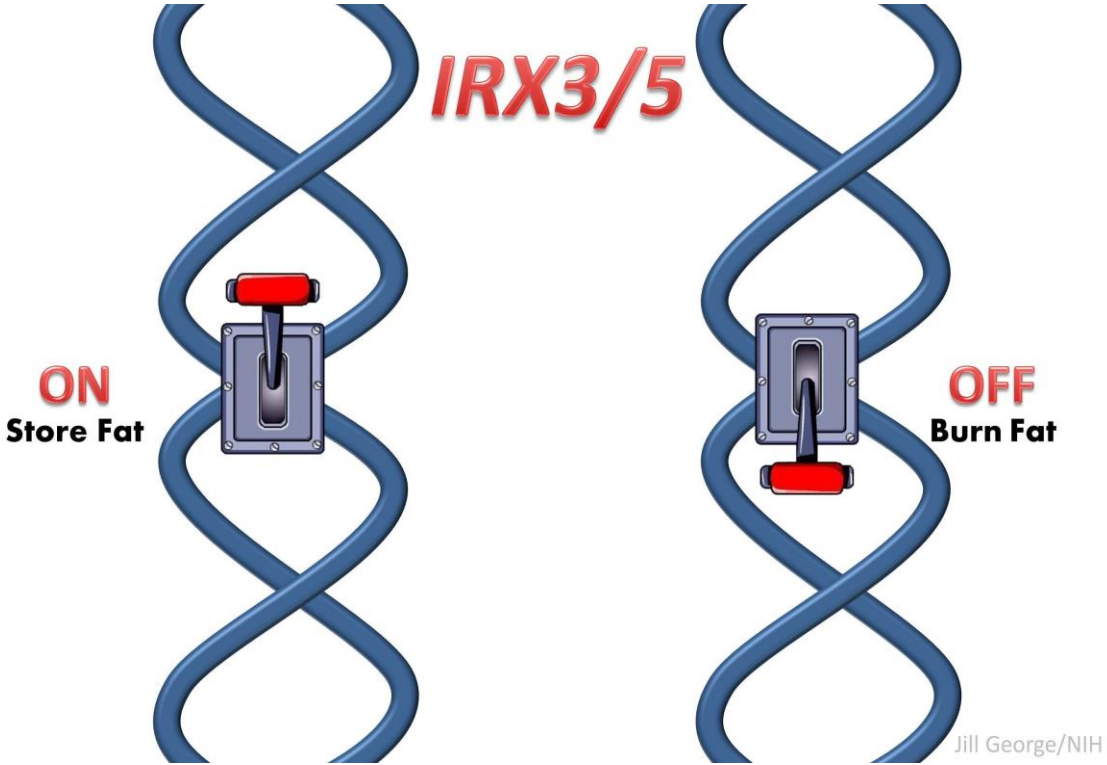
FTO Obesity Variant Circuitry and Adipocyte Browning in Humans

Melina Claussnitzer, Ph.D., Simon N. Dankel, Ph.D., Kyoung-Han Kim, Ph.D., Gerald Quon, Ph.D., Wouter Meuleman, Ph.D., Christine Haugen, M.Sc., Viktoria Glunk, M.Sc., Isabel S. Sousa, M.Sc., Jacqueline L. Beaudry, Ph.D., Vijitha Puviindran, B.Sc., Nezar A. Abdennur, M.Sc., Jannel Liu, B.Sc., Per-Arne Svensson, Ph.D., Yi-Hsiang Hsu, Ph.D., Daniel J. Drucker, M.D., Gunnar Mellgren, M.D., Ph.D., Chi-Chung Hui, Ph.D., Hans Hauner, M.D., and Manolis Kellis, Ph.D.



FTO, fat mass and obesity-associated gene

Claussnitzer M, et al. N Engl J Med. 2015;373:895-907


IRX3/5
ON
Store Fat
OFF
Burn Fat
Jill George/NIH

COMPLICATIONS OF OBESITY

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Insulin resistance/ Type II diabetes	Dyslipidaemia	Liver steatosis (NAFLD)
Tumours	Hypertension	Cardiovascular complications

NAFLD, nonalcoholic fatty liver disease

Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

2013

A 360-degree overview of paediatric NAFLD: Recent insights

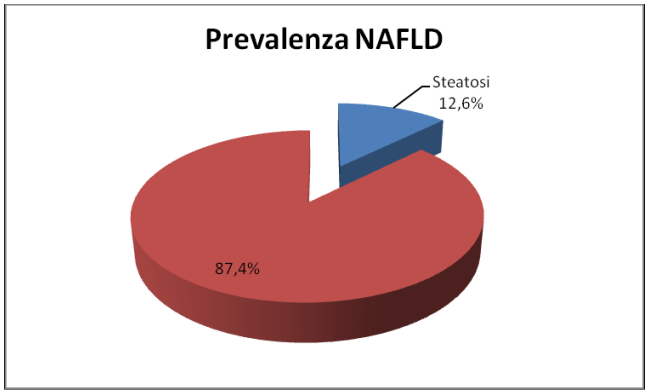
Valerio Nobili[1,*], Gianluca Svegliati-Baroni[2], Anna Alisi[1], Luca Miele[3], Luca Valenti[4], Pietro Vajro[5]

Overweight and obesity are consistently indicated as the most significant risk factors for the development of NAFLD. About 25% of obese children have increased ALT.

ALT, alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease

Nobili V, et al. J Hepatol. 2013;58(6):1218-29

PREVALENCE OF NAFLD IN OUR COHORT OF 410 OBESE CHILDREN AND ADOLESCENTS



	Gruppo 1	Gruppo 2	p-value
Età (anni±DS)	11.77±2.94	10.24±3.27	0,0008
Sesso (maschi/femmine)	29/23	172/358	
Prepuberi/puberi	20/32	211/147	
BMI-SDS	2.72±0.44	2.64±0.52	0.11
Glicemia (mg/dl)	90.23±6.24	89.05±8.11	0.17
Colesterolo totale	165.10±20.73	171.5±30.35	0.15
Colesterolo HDL	50.54±13.12	53.10±13.51	0.09
Colesterolo LDL	99.94±27.32	104.2±27.37	0.29
Trigliceridi	74.50±45.16	69.51±42.06	0.74
AST	28.77±8.68	23.99±5.99	<0.0001
ALT	37.29±22.42	22.12±9.72	<0.0001
HOMA-IR	4.09±2.65	2.8±2.2	<0.0001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; SDS, standard deviation score

Ibba et al. unpublished data

SNPs REPRODUCIBLY ASSOCIATED WITH PEDIATRIC FATTY LIVER DISEASE

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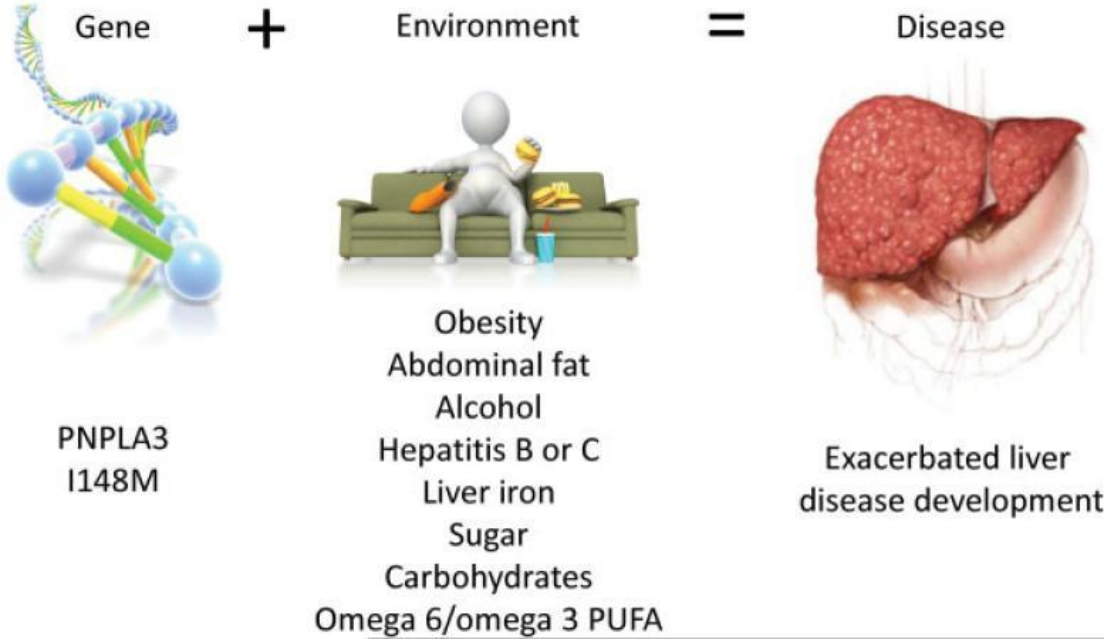
Gene	SNP	Function	Hepatic Fat	Circulating Lipids
PNPLA3	rs738409	Remodeling of lipid droplets	↑	=
GCKR	rs1260360	Modulation of hepatic lipogenesis	↑	↑
TM6SF2	rs58542926	Modulation lipoprotein secretion	↑	↓

GCKR: Glucokinase Regulatory Protein; *PNPLA3*: Patatin-like phospholipase domain-containing 3; *TM6SF2*: Transmembrane 6 Superfamily Member 2; SNP: Single Nucleotide Polymorphism.

SNP, single nucleotide polymorphism

Umano GR, et al. Children (Basel). 2017;4(6). pii: E49

ADIPONUTRIN-LIKE PHOSPHOLIPASE-3 GENE (PNPLA3) IS EXPRESSED IN THE LIVER AND ADIPOSE TISSUE IT CAN BOTH SYNTHESIZE AND HYDROLYSE TRIGLYCERIDES



PNPLA3, adiponutrin-like phospholipase-3 gene; PUFA, polyunsaturated fatty acid

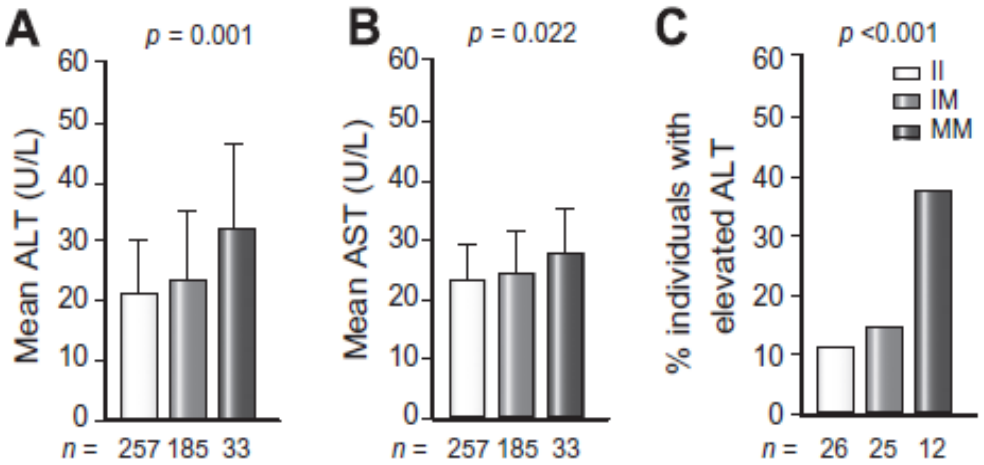
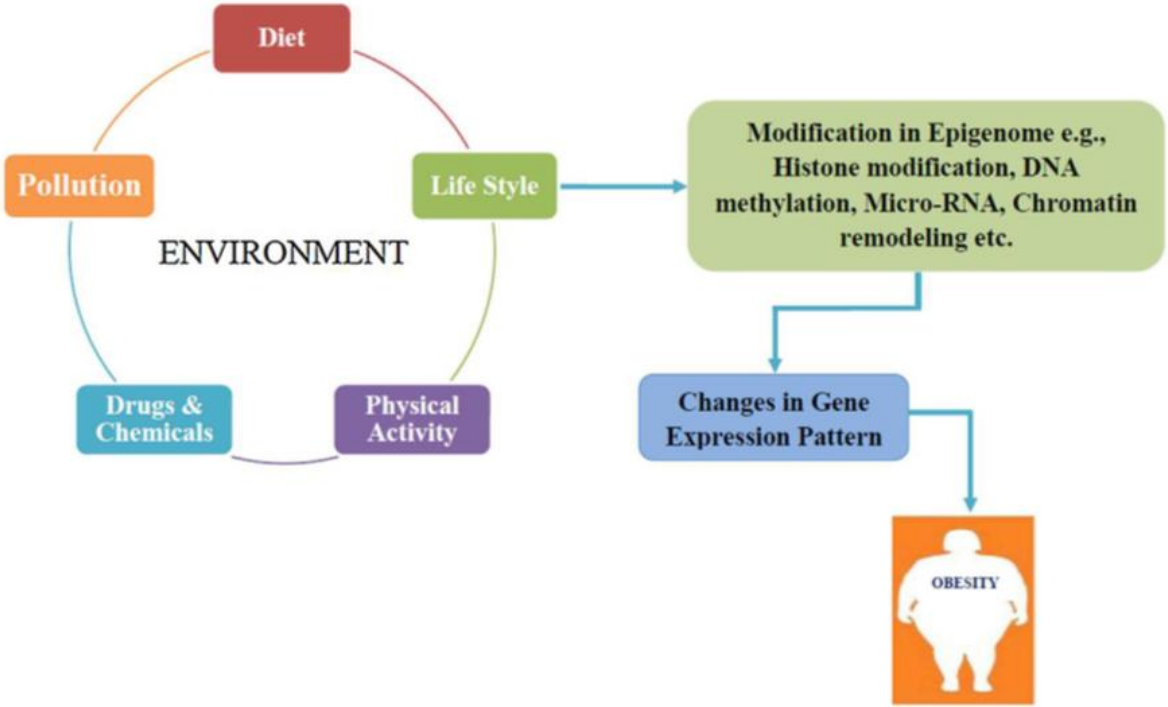


Fig. 1. Association between *PNPLA3* I148 M (rs738409) and transaminase levels in a cohort of obese children and adolescents (*n* = 475). Mean plasma levels ± standard deviations of (A) alanine transaminase (ALT) and (B) aspartate transaminase (AST) stratified by *PNPLA3* genotype. *p*-values are calculated using linear regression including age, gender, BMI, and Tanner stage as covariates. (C) Distribution of obese children and adolescents with pathological levels of circulating alanine transferase (ALT) in the different PNPLA3 genotypes. ALT >30 U/L was classified as elevated. The *p* value is calculated from χ^2. II = individuals with two I 148 alleles, MM = individuals with two M alleles, IM heterozygotes.

II, individuals with two I 148 alleles, ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IM, heterozygotes; MM, individuals with two M alleles; PNPLA3, adiponutrin-like phospholipase-3 gene

Romeo S, et al. J Hepatol. 2010;53:335-8

EPIGENETICS AND OBESITY



OBESITY: A POLYGENIC, EPIGENETIC AND MULTIFACTORIAL DISEASE

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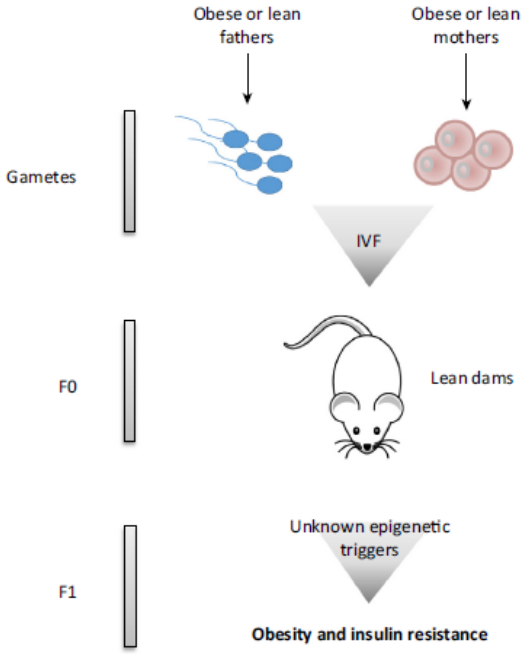
Spotlight

Non-Genetic Transmission of Obesity – It's in Your Epigenes

Elena Loche[1] and
Susan E. Ozanne[1,*]

Obesity and its related metabolic comorbidities can be inherited across generations through non-genetic mechanisms. In a recent report, Huypens *et al.*, using an *in vitro* fertilization approach, provide evidence that exposure to a high-fat diet modifies egg and sperm epigenetic information, rendering the progeny more prone to obesity.

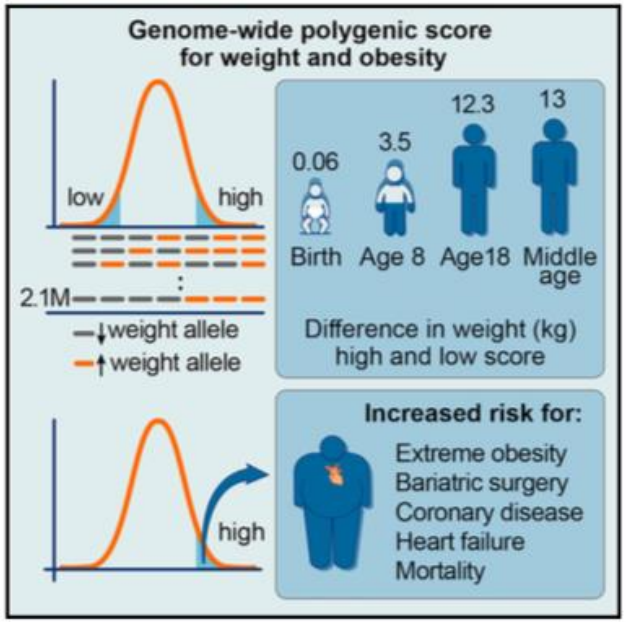


Loche E, et al. Trends Endocrinol Metab. 2016;27:349-50

Cell

Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood

Graphical Abstract



Authors

Amit V. Khera, Mark Chaffin, Kaitlin H. Wade, ..., Nicholas J. Timpson, Lee M. Kaplan, Sekar Kathiresan

Correspondence

avkhera@mgh.harvard.edu (A.V.K.), skathiresan1@mgh.harvard.edu (S.K.)

In Brief

A genome-wide polygenic score quantifies inherited susceptibility to obesity, integrating information from 2.1 million common genetic variants to identify adults at risk of severe obesity.

POLYGENIC PREDICTION OF WEIGHT AND OBESITY TRAJECTORIES

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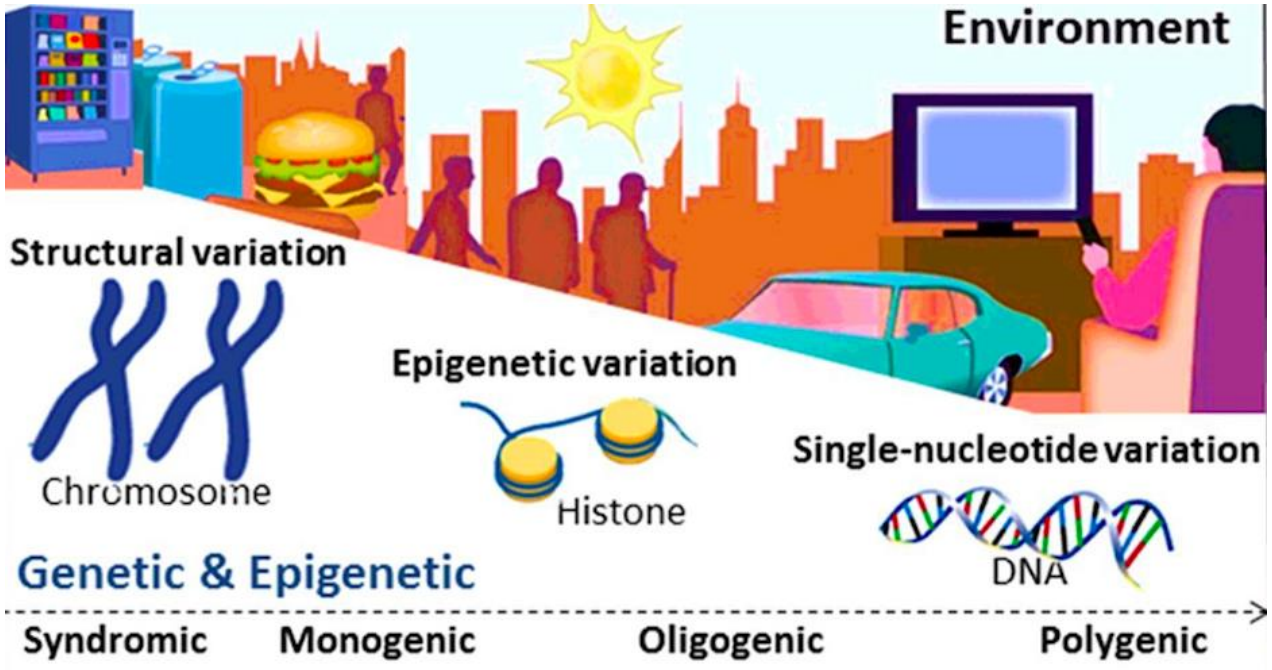
A genome-wide polygenic score can quantify inherited susceptibility to obesity

Polygenic score effect on weight emerges early in life and increases into adulthood

Effect of polygenic score can be similar to a rare, monogenic obesity mutation

High polygenic score is a strong risk factor for severe obesity and associated diseases

Khera AV, et al. Cell. 2019;177(3):587-596.e9


Environment
Structural variation
Chromosome
Epigenetic variation
Histone
Single-nucleotide variation
DNA
Genetic & Epigenetic
Syndromic
Monogenic
Oligogenic
Polygenic

OBESITY

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