La pubertà precoce: genetica

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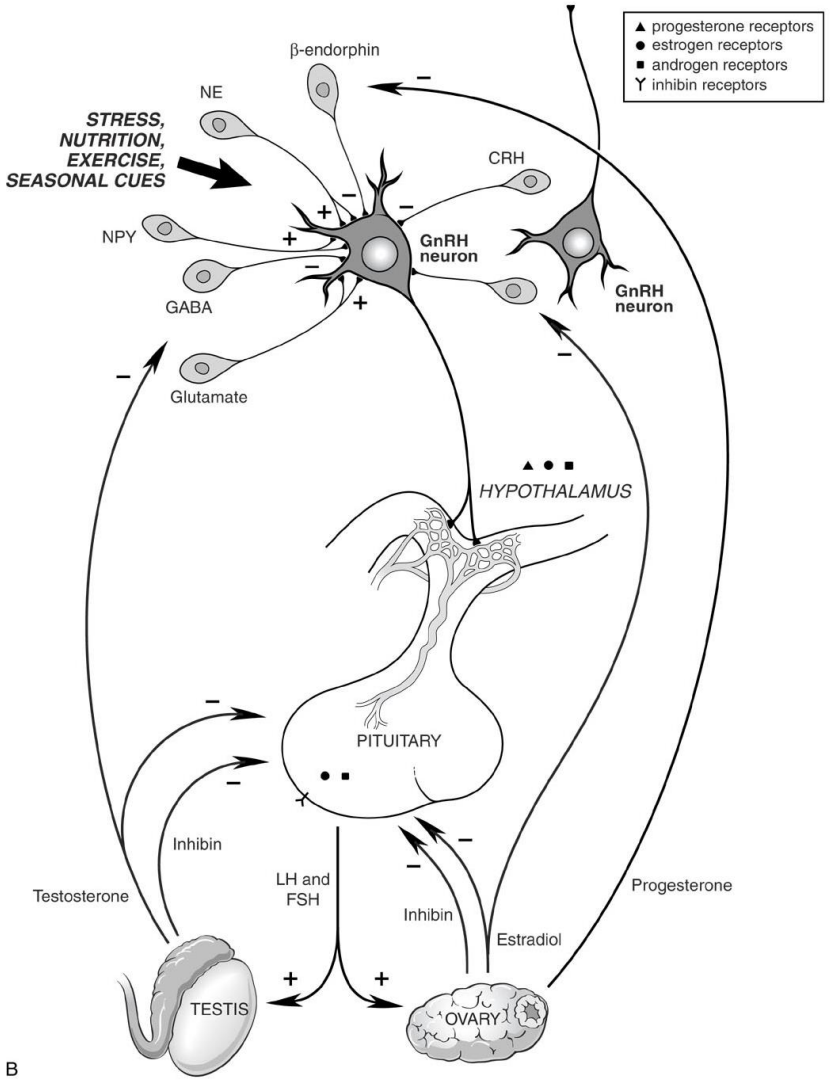
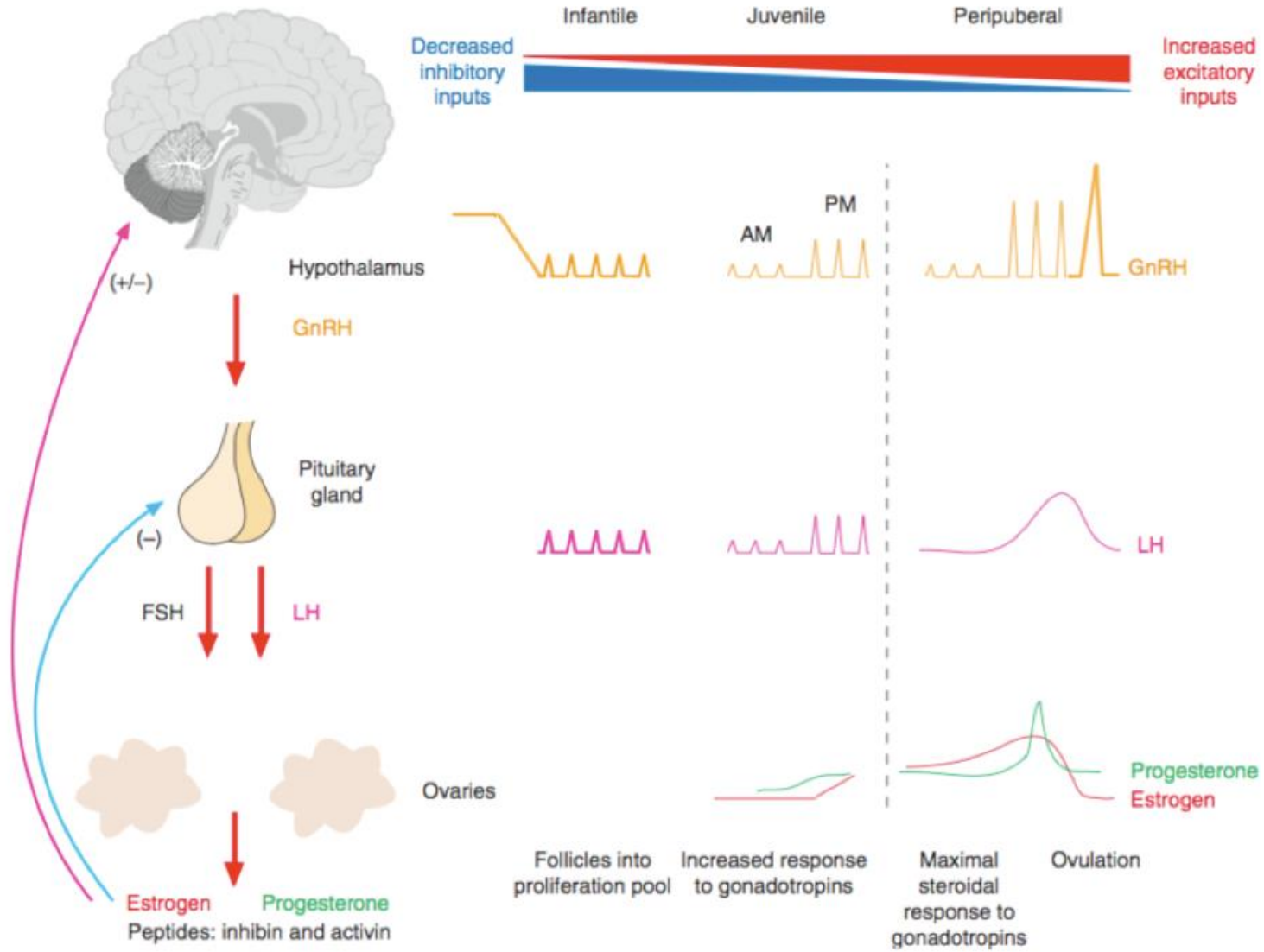
AO Brotzu, Cagliari

AOBrotzu

Cagliari, 14 maggio 2016

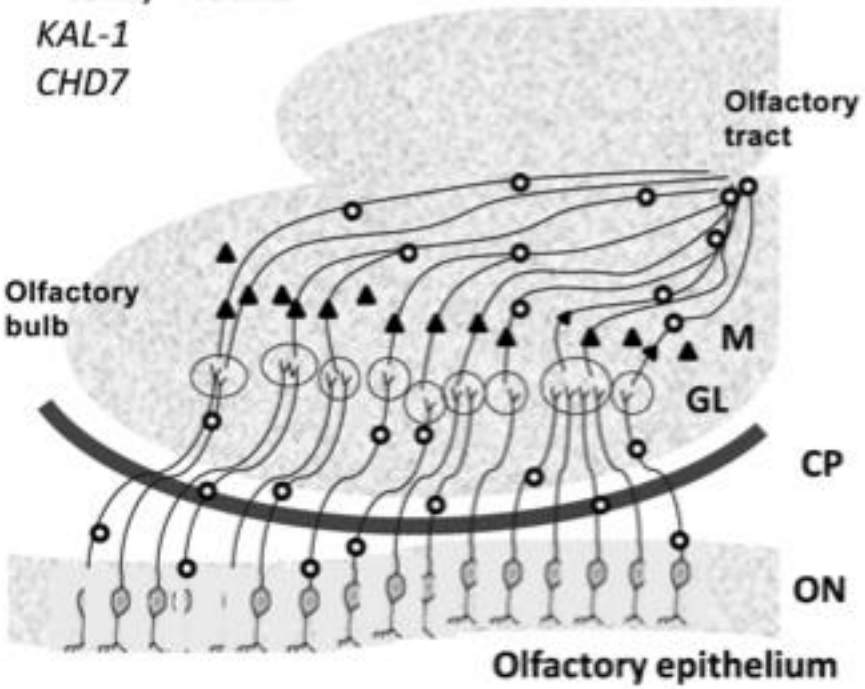
L’asse ipotalamo-ipofisi-gonadi




Infantile
Juvenile
Peripuberal
Decreased inhibitory inputs
Increased excitatory inputs
PM
AM
Hypothalamus
(+/–)
GnRH
GnRH
Pituitary gland
(–)
FSH
LH
LH
Ovaries
Progesterone
Estrogen
Estrogen
Progesterone
Peptides: inhibin and activin
Follicles into proliferation pool
Increased response to gonadotropins
Maximal steroidal response to gonadotropins
Ovulation

Migration

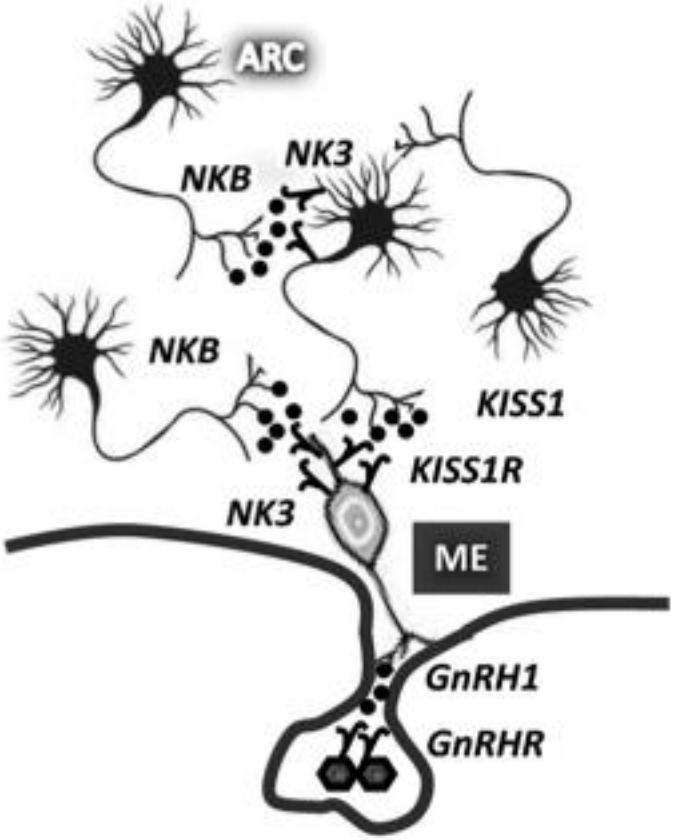
PROK2/PROKR2
KAL-1
CHD7



GnRH neuron genesis

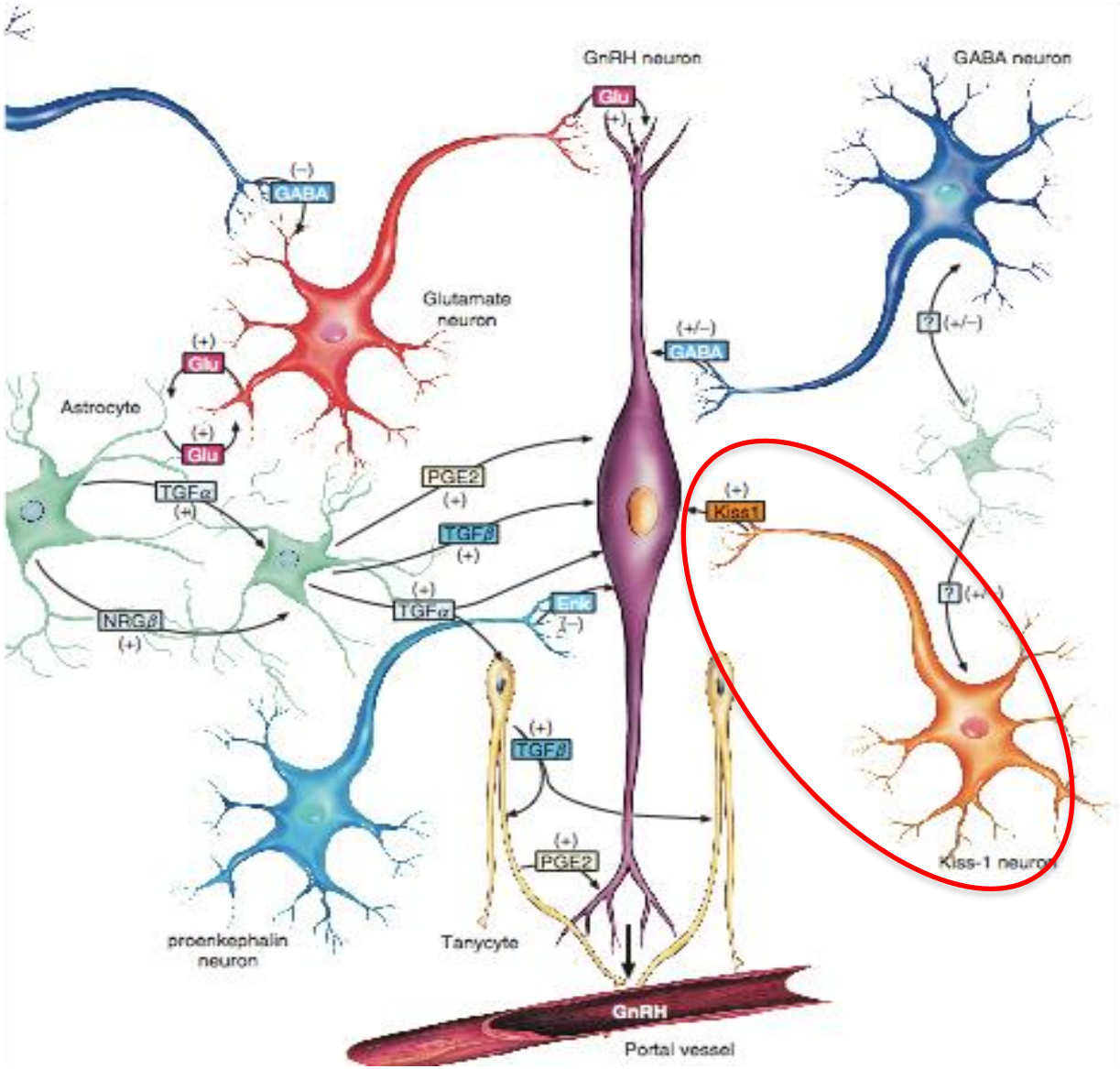
FGF8/FGFR1
HS6ST1

Upstream signals



GnRH synthesis/action

Un complesso network cellulare regola la secrezione di GnRH



Recenti sviluppi nella ricerca dei meccanismi molecolari alla base della pubertà: La Kisspeptina

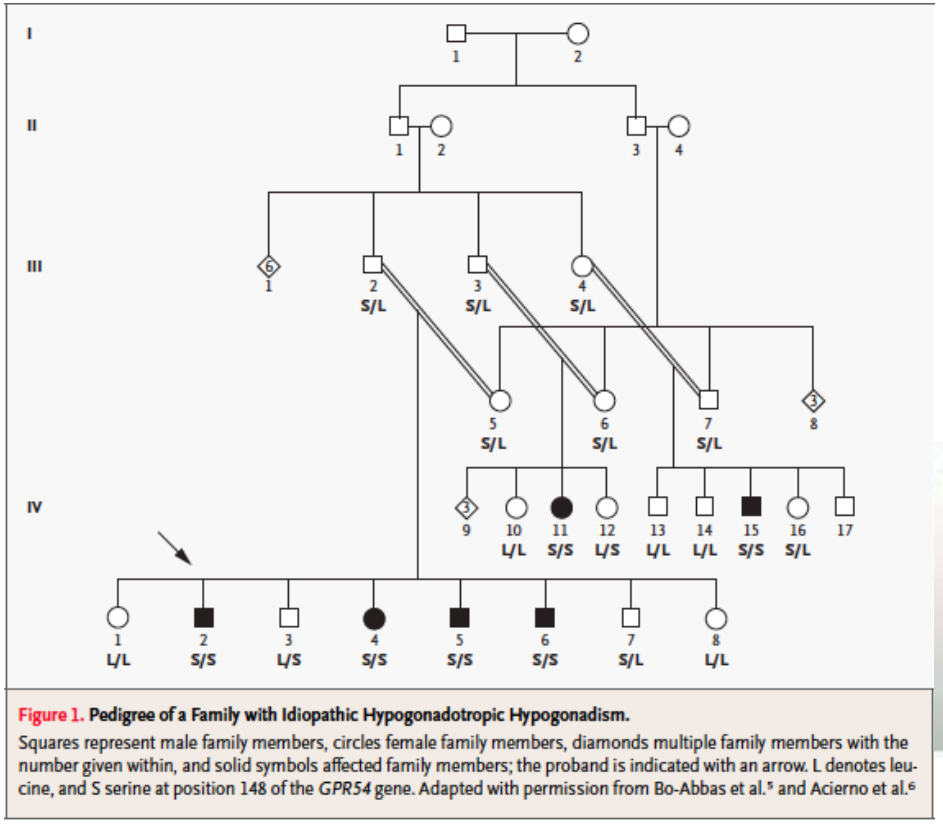
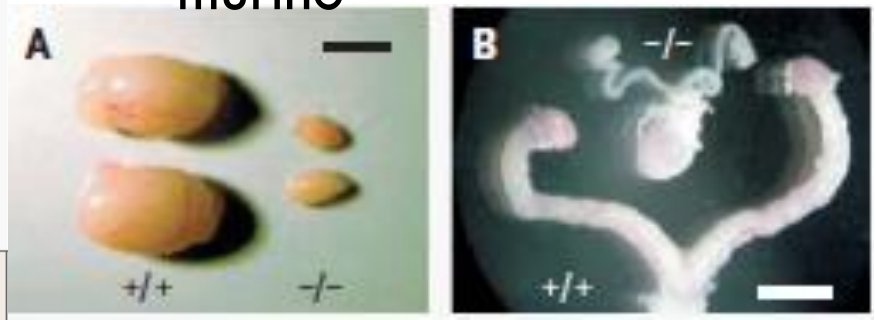


Figure 1. Pedigree of a Family with Idiopathic Hypogonadotropic Hypogonadism.

Squares represent male family members, circles female family members, diamonds multiple family members with the number given within, and solid symbols affected family members; the proband is indicated with an arrow. L denotes leucine, and S serine at position 148 of the *GPR54* gene. Adapted with permission from Bo-Abbas et al.[5] and Acierno et al.[6]

Effetto del knock-out di Kiss1 nel modello murino



Seminara et al, NEJM 2003

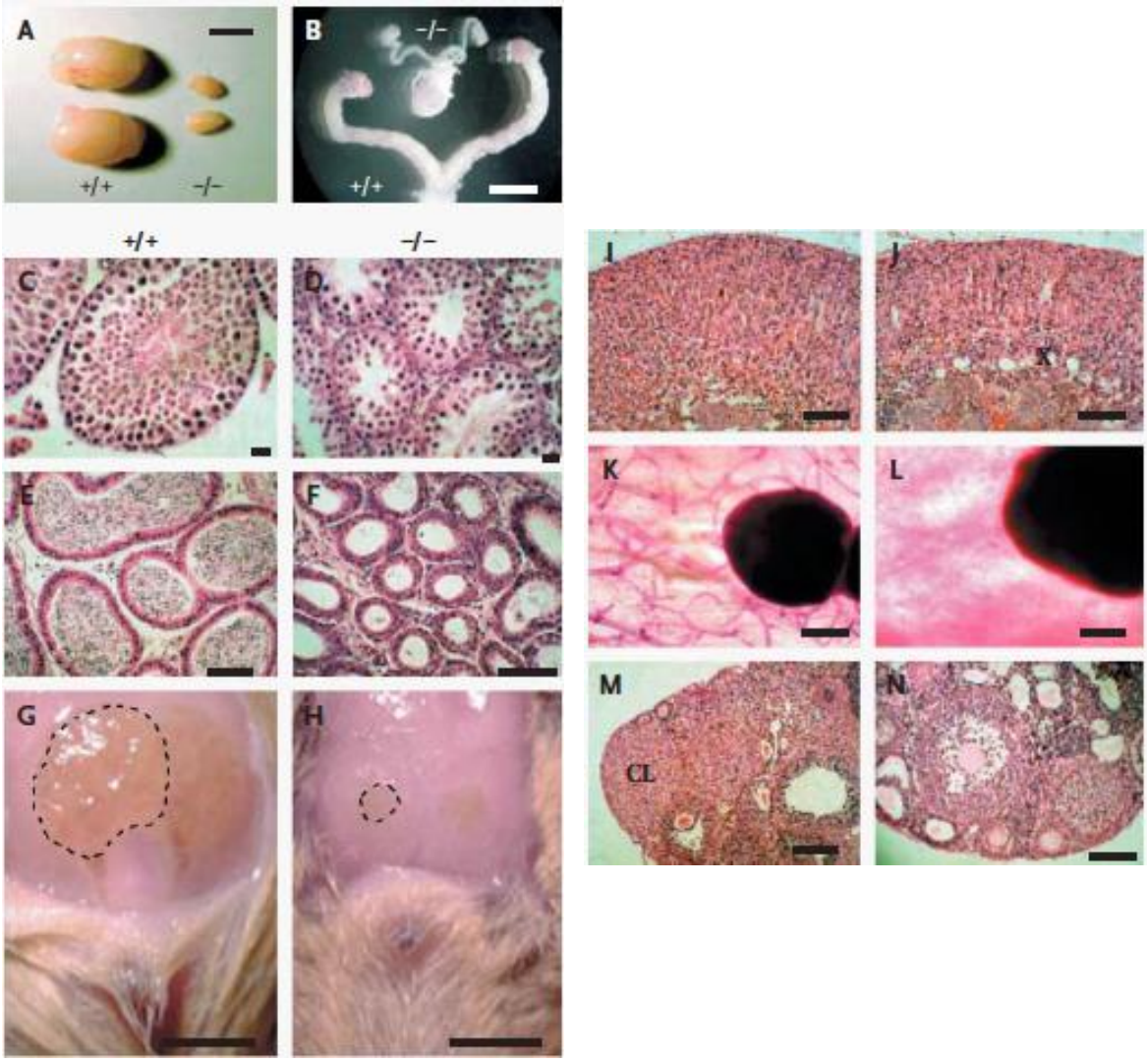


Figure 5. Gonadal Anatomy and Secondary Sexual Characteristics of *Gpr54* −/− Mice.

Panel A shows the reduction in the size of the testes (wild-type as compared with mutant male mice), and Panel B shows the small ovaries and uteri found in female *Gpr54* −/− mice; the scale bars represent 0.5 cm. In Panels C through N, the wild-type mouse is represented by the left-hand column and the mutant mouse is represented by the right-hand column. Panel D shows the reduction in the number of spermatozoa in the seminiferous tubules, as compared with Panel C; the scale bars represent 50 μm. Panels E and F show the presence and absence, respectively, of sperm in the epididymis; the scale bars represent 100 μm. Panel H shows reduced development of the preputial gland, as compared with Panel G; the scale bars represent 1 cm. Panels I and J show the absence and presence, respectively, of the prepubescent zone X in the adrenal gland; the scale bars represent 20 μm. Panel L shows reduced mammary-duct formation, as compared with Panel K (the dark mass is lymph node); the scale bars represent 0.5 cm. Panels M and N show the presence and absence, respectively, of graafian follicles and corpora lutea; CL denotes corpus luteum; the scale bars represent 300 μm.

Seminara et al, NEJM 2003

Genetics of precocious puberty

AOBrotzu

- GDPP can be familial in up to 27,5% of cases
- Single gene mutations can cause GDPP

0021-972X/04/$15.00/0
Printed in U.S.A.

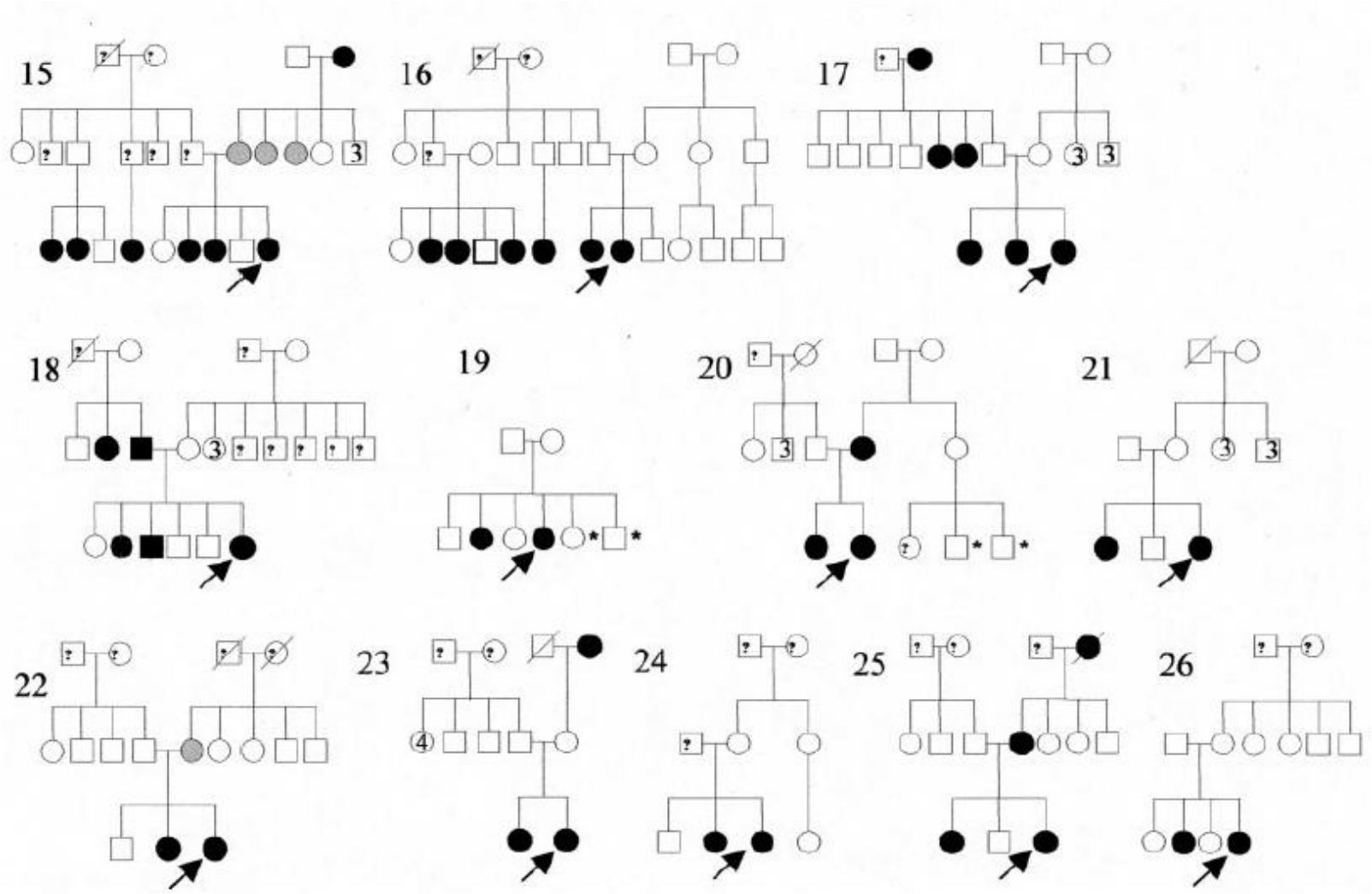
The Journal of Clinical Endocrinology & Metabolism 89(4):1794–1800

doi: 10.1210/jc.2003-030361

Familial Central Precocious Puberty Suggests Autosomal Dominant Inheritance

LIAT DE VRIES, ARIEH KAUSCHANSKY, MORDECHAI SHOHAT, AND MOSHE PHILLIP

Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes (L.d.V., A.K., M.P.), and Institute of Genetics (M.S.), Schneider Children's Medical Center of Israel, Petah Tiqva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel 49202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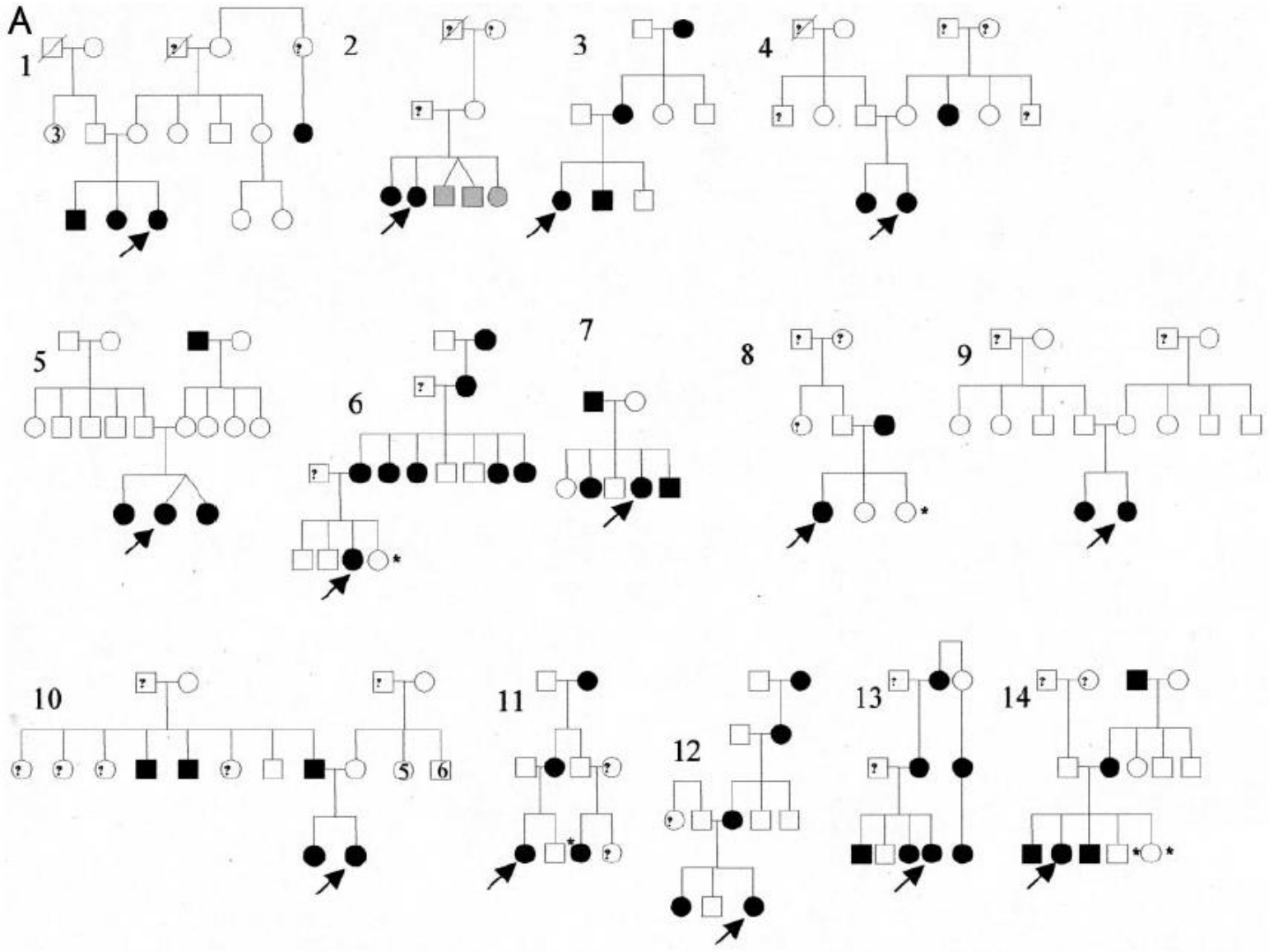
A
1
2
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14

Genetic contribution to the timing of puberty

AOBrotzu

- Timing of puberty varies among racial groups
- Correlation between age of menarche of mothers and daughters
- Greater concordance of pubertal development between monozygotic than dizygotic twins
- GWAS showing association with genetic loci to the age of menarche

50-80% of the variation in the timing of puberty is due to genetic differences between individuals

Nat Genet. 2009 June ; 41(6): 729–733. doi:10.1038/ng.382.

Genetic variation in *LIN28B* is associated with the timing of puberty

Ken K Ong[1,2,3], **Cathy E Elks**[1,2], **Shengxu Li**[1,2], **Jing Hua Zhao**[1,2], **Jian'an Luan**[1,2], **Lars B Andersen**[4], **Sheila A Bingham**[5,6], **Soren Brage**[1,2], **George Davey Smith**[7], **Ulf Ekelund**[1,2,8], **Christopher J Gillson**[1,2], **Beate Glaser**[7], **Jean Golding**[9], **Rebecca Hardy**[10], **Kay-Tee Khaw**[11], **Diana Kuh**[10], **Robert Luben**[11], **Michele Marcus**[12,13,14], **Michael A McGeehin**[12], **Andrew R Ness**[15], **Kate Northstone**[16], **Susan M Ring**[16], **Carol Rubin**[12], **Matthew A Sims**[1,2], **Kijoung Song**[17], **David P Strachan**[18], **Peter Vollenweider**[19], **Gerard Waeber**[19], **Dawn M Waterworth**[17], **Andrew Wong**[10], **Panagiotis Deloukas**[20], **Inês Barroso**[20], **Vincent Mooser**[17], **Ruth J Loos**[1,2], and **Nicholas J Wareham**[1,2]

Nat Genet. 2010 December ; 42(12): 1077–1085. doi:10.1038/ng.714.

Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies

Cathy E. Elks[1,*], John R.B. Perry[2,*], Patrick Sulem[3,*], Daniel I. Chasman[4,5], Nora Franceschini[6], Chunyan He[7,8], Kathryn L. Lunetta[9,10], Jenny A. Visser[11], Enda M. Byrne[12,13], Diana L. Cousminer[14], Daniel F. Gudbjartsson[3], Tõnu Esko[15,16,17], Bjarke Feenstra[18], Jouke-Jan Hottenga[19], Daniel L. Koller[20], Zoltán Kutalik[21,22], Peng Lin[23], Massimo Mangino[24], Mara Marongiu[25], Patrick F. McArdle[26], Albert V. Smith[27,28], Lisette Stolk[11,29], Sophie W. van Wingerden[30], Jing Hua Zhao[1], Eva Albrecht[31], Tanguy Corre[32], Erik Ingelsson[33], Caroline Hayward[34], Patrik K.E. Magnusson[33], Erin N. Smith[35], Shelia Ulivi[36], Nicole M. Warrington[37], Lina Zgaga[38], Helen Alavere[15], Najaf Amin[30], Thor Aspelund[27,28], Stefania Bandinelli[39], Ines Barroso[40], Gerald S. Berenson[41], Sven Bergmann[21,22], Hannah Blackburn[40], Eric Boerwinkle[42], Julie E. Buring[4,43], Fabio Busonero[25], Harry Campbell[38], Stephen J. Chanock[44], Wei Chen[41], Marilyn C. Cornelis[45], David Couper[46], Andrea D. Coviello[47], Pio d'Adamo[36], Ulf de Faire[48], Eco J.C. de Geus[19], Panos Deloukas[40], Angela Döring[31], George Davey Smith[49], Douglas F. Easton[50], Gudny Eiriksdottir[27], Valur Emilsson[51], Johan Eriksson[52,53,54,55], Luigi Ferrucci[56], Aaron R. Folsom[57], Tatiana Foroud[20], Melissa Garcia[58], Paolo Gasparini[36], Frank Geller[18], Christian Gieger[31], The GIANT Consortium[59], Vilmundur Gudnason[27,28], Per Hall[33], Susan E. Hankinson[43,60], Liana Ferreli[25], Andrew C. Heath[61], Dena G. Hernandez[62], Albert Hofman[63], Frank B. Hu[43,45,60], Thomas Illig[31], Marjo-Riitta Järvelin[64], Andrew D. Johnson[9,65], David

Original Paper

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr
DOI: 10.1159/000342212

Received: March 21, 2012
Accepted: July 24, 2012
Published online: September 6, 2012

Absence of Functional *LIN28B* Mutations in a Large Cohort of Patients with Idiopathic Central Precocious Puberty

Acácio P. Silveira-Neto[a] Leticia Ferro Leal[b] Amy B. Emerman[e]
Katherine D. Henderson[c] Elena Piskounova[e] Brian E. Henderson[d] Richard I. Gregory[e]
Letícia F. Gontijo Silveira[a] Joel N. Hirschhorn[f–i] Thutrang T. Nguyen[g, i]
Daiane Beneduzzi[a] Cintia Tusset[a] Ana Claudia S. Reis[b] Vinicius N. Brito[a]
Berenice B. Mendonca[a] Mark R. Palmert[j] Sonir R. Antonini[b] Ana Claudia Latronico[a]

178 children with CPP, 16.8% familial cases
Rare variations in this gene do not seem to be commonly involved in the molecular pathogenesis of CPP

0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(6):2432–2436

doi: 10.1210/jc.2005-2657

BRIEF REPORT

Allelic Variants of the γ-Aminobutyric Acid-A Receptor α1-Subunit Gene (*GABRA1*) Are Not Associated with Idiopathic Gonadotropin-Dependent Precocious Puberty in Girls with and without Electroencephalographic Abnormalities

Vinicius Nahime Brito, Berenice Bilharinho Mendonca, Laura M. F. F. Guilhoto, Karina Cocco Monteiro Freitas, Ivo J. Prado Arnhold, and Ana Claudia Latronico

23 girls with GDPP
No mutations or polymorphism associated with GDPP

The NEW ENGLAND JOURNAL of MEDICINE
2008

BRIEF REPORT

A *GPR54*-Activating Mutation in a Patient with Central Precocious Puberty

Milena Gurgel Teles, M.D., Suzy D.C. Bianco, Ph.D., Vinicius Nahime Brito, M.D., Ericka B. Trarbach, Ph.D., Wendy Kuohung, M.D., Shuyun Xu, M.D., Stephanie B. Seminara, M.D., Berenice B. Mendonca, M.D., Ursula B. Kaiser, M.D., and Ana Claudia Latronico, M.D.

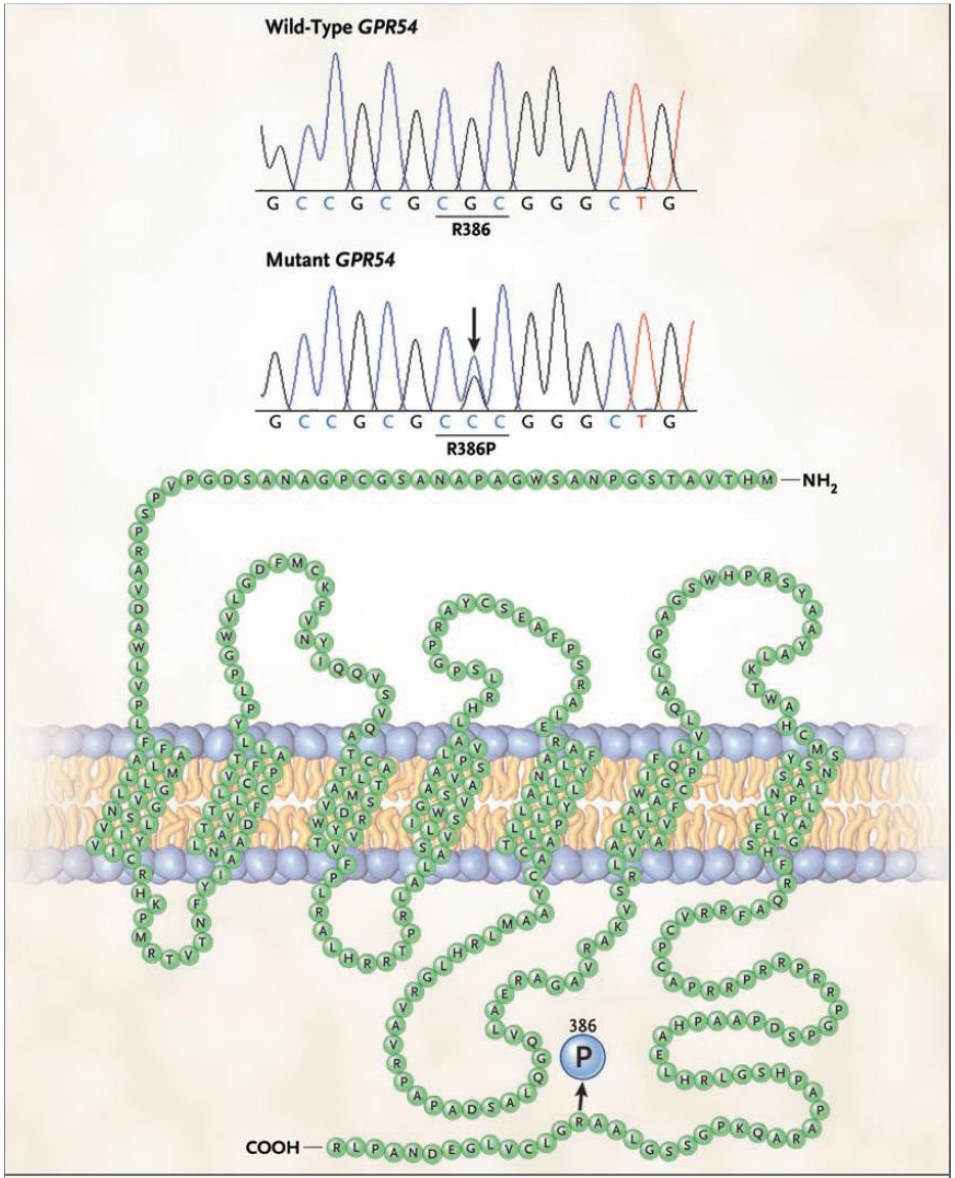
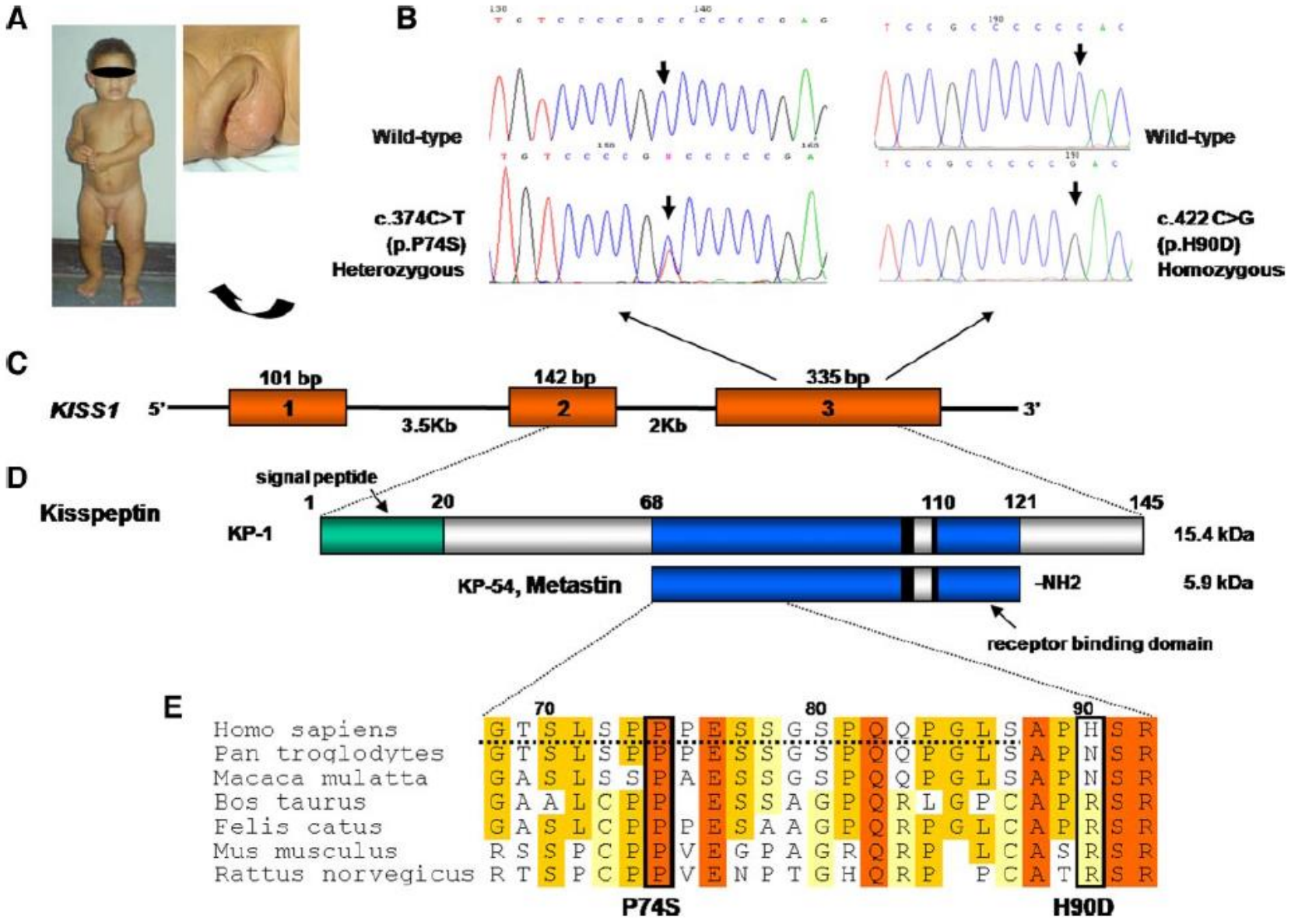


Figure 1. Sequences of Wild-Type and Mutant *GPR54*.

The wild-type cytosine–guanine–cytosine (CGC) sequence in *GPR54* exon 5 encodes arginine (R) at codon 386 (R386). The heterozygous substitution of C for G (shown for our patient with an arrow) results in the substitution of proline (P) for R (R386P) in the carboxy-terminal tail of the protein (shown embedded in a cellular membrane). In the nucleotide sequences (shown immediately under the two plots), T denotes the nucleotide thymidine.

Teles et al., NEJM 2008


A
B
Wild-type
c.374C>T
(p.P74S)
Heterozygous
Wild-type
c.422 C>G
(p.H90D)
Homozygous
C
KISS1
5'
101 bp
1
3.5Kb
142 bp
2
2Kb
335 bp
3
3'
D
Kisspeptin
signal peptide
1
20
68
110
121
145
KP-1
15.4 kDa
KP-54, Metastin
-NH2
5.9 kDa
receptor binding domain
E
70
80
90
Homo sapiens G T S L S P P P E S S G S P Q Q P G L S A P H S R
Pan troglodytes G T S L S P P P E S S G S P Q Q P G L S A P N S R
Macaca mulatta G A S L S S P A E S S G S P Q Q P G L S A P N S R
Bos taurus G A A L C P P E S S A G P Q R L G P C A P R S R
Felis catus G A S L C P P P E S A A G P Q R P G L C A P R S R
Mus musculus R S S P C P P V E G P A G R Q R P L C A S R S R
Rattus norvegicus R T S P C P P V E N P T G H Q R P P C A T R S R
P74S
H90D

Tommiska et al. BMC Research Notes 2011, 4:363
http://www.biomedcentral.com/1756-0500/4/363

BMC Research Notes

RESEARCH ARTICLE Open Access

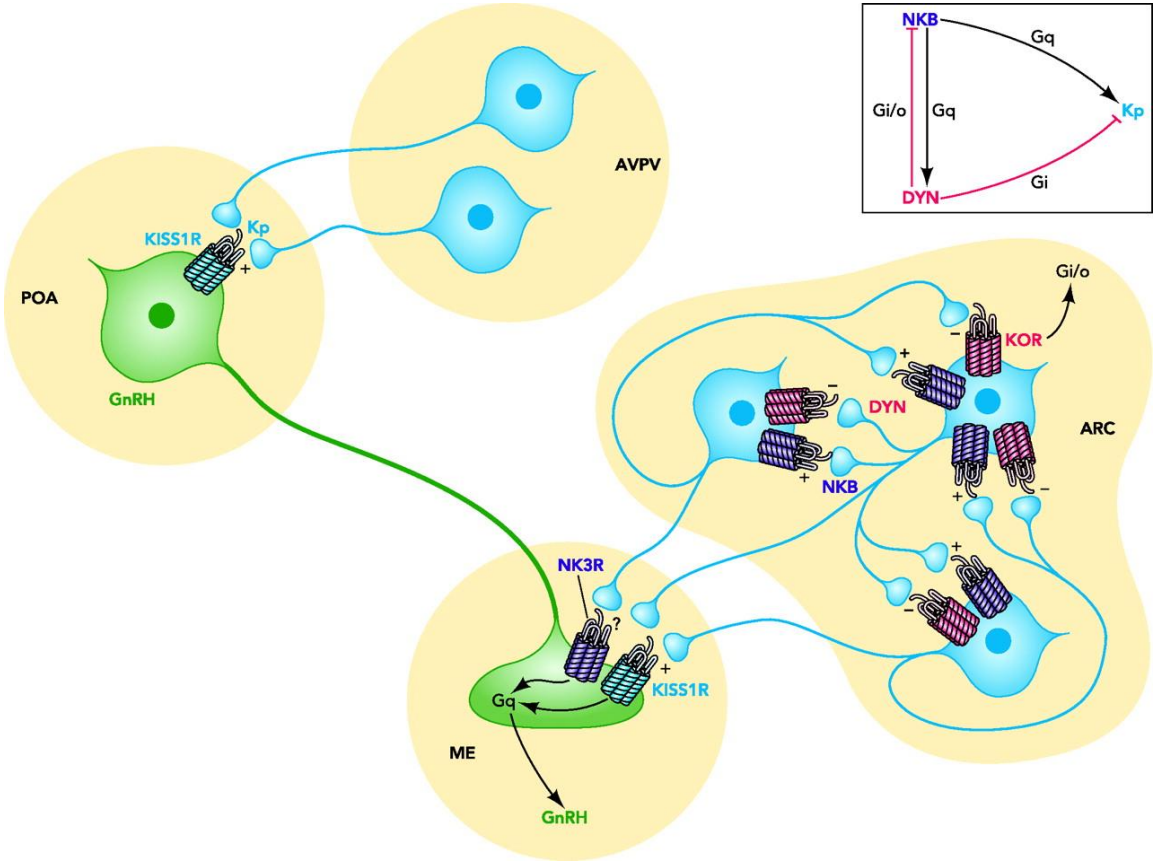
LIN28B, *LIN28A*, *KISS1*, and *KISS1R* in idiopathic central precocious puberty

Johanna Tommiska[1,2*], Kaspar Sørensen[3], Lise Aksglaede[3], Rosanna Koivu[1,2], Lea Puhakka[1,2], Anders Juul[3] and Taneli Raivio[1,2]

Conclusions

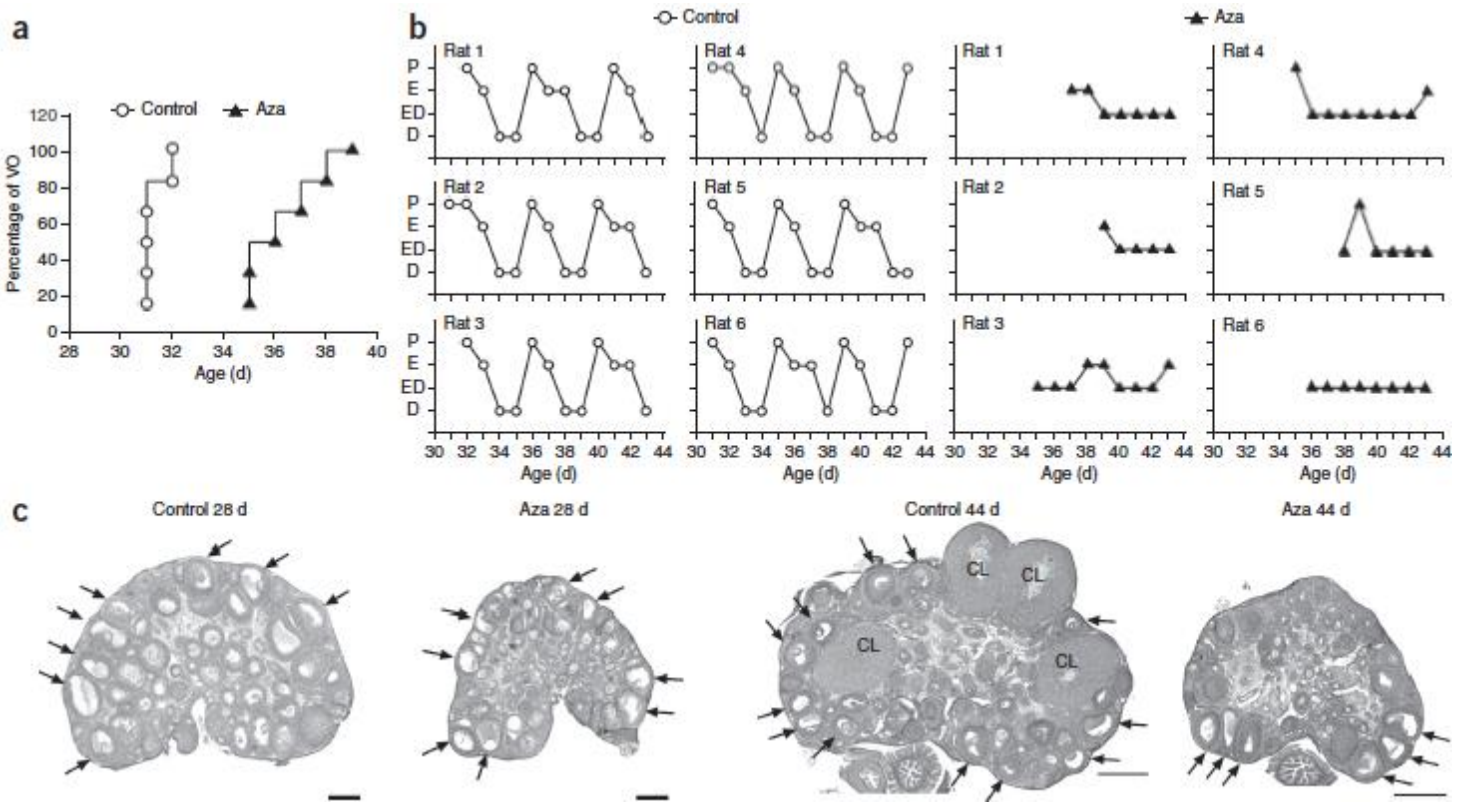
Our results suggest that mutations in the coding region of *LIN28B* or *LIN28A* do not play a major role, if any, in the genetic etiology of ICPP. In addition, we confirmed that mutations in *KISS1* and *KISS1R* are not common causes of ICPP in girls.

Il gene Kiss1 controlla lo sviluppo puberale agendo a livello del sistema nervoso centrale



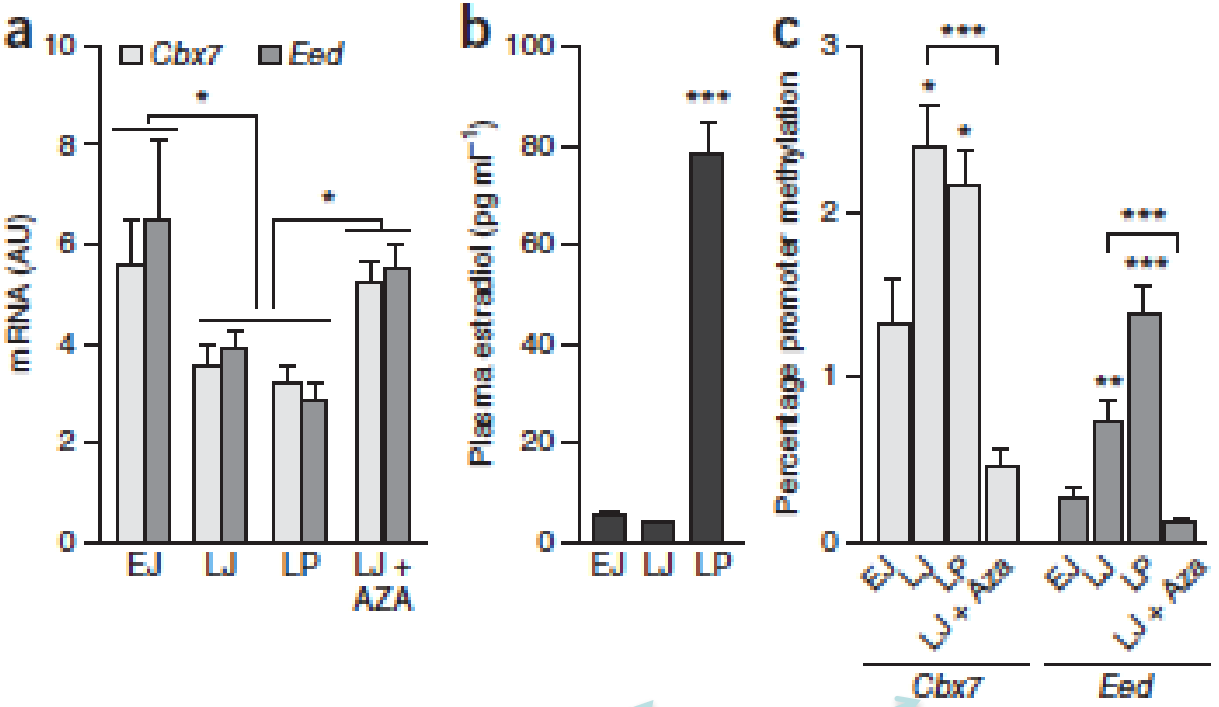
Cosa controlla il gene Kiss1 durante lo sviluppo puberale: la regolazione epigenetica

Effetto degli inibitori della metilazione del DNA sull'ovulazione e la maturazione delle ovaie



Lomniczi et al., Nature Neuroscience 2013

Nell'Ipotalamo i geni Polycomb sono repressi dalla metilazione del loro promotore col progredire dello sviluppo puberale

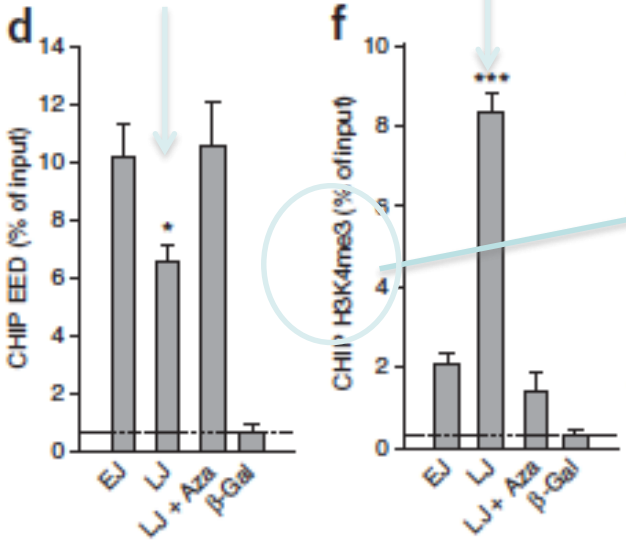


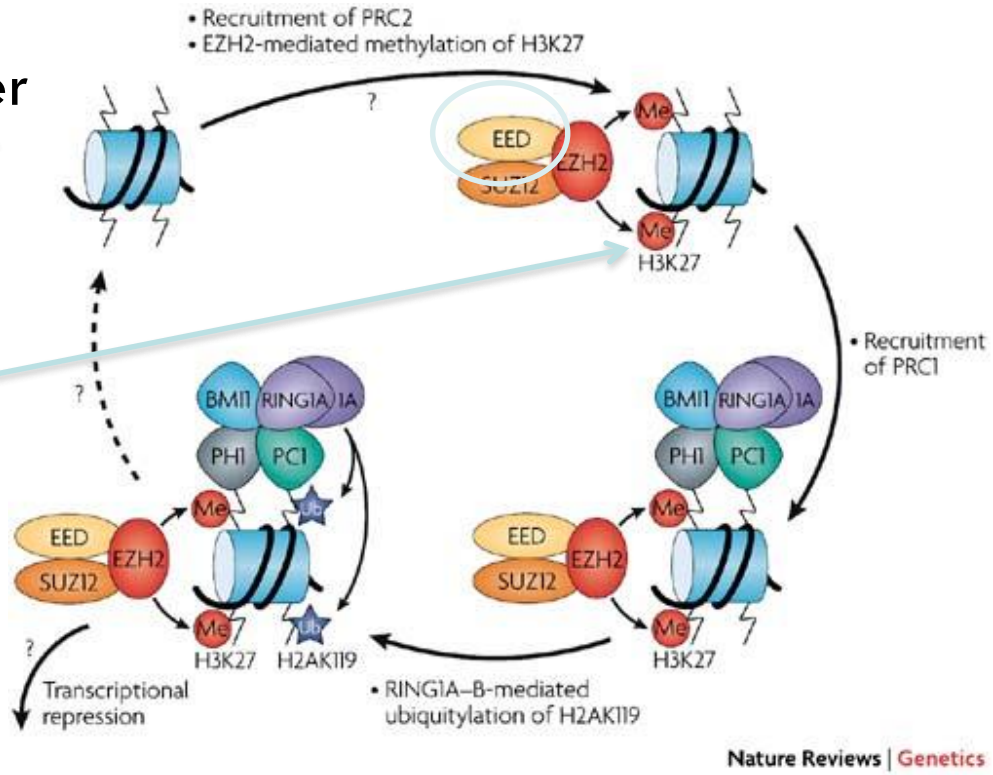
La repressione di questi geni avviene prima dell'innalzamento dei livelli di estradiolo nel plasma

Lomniczi et al., Nature Neuroscience 2013

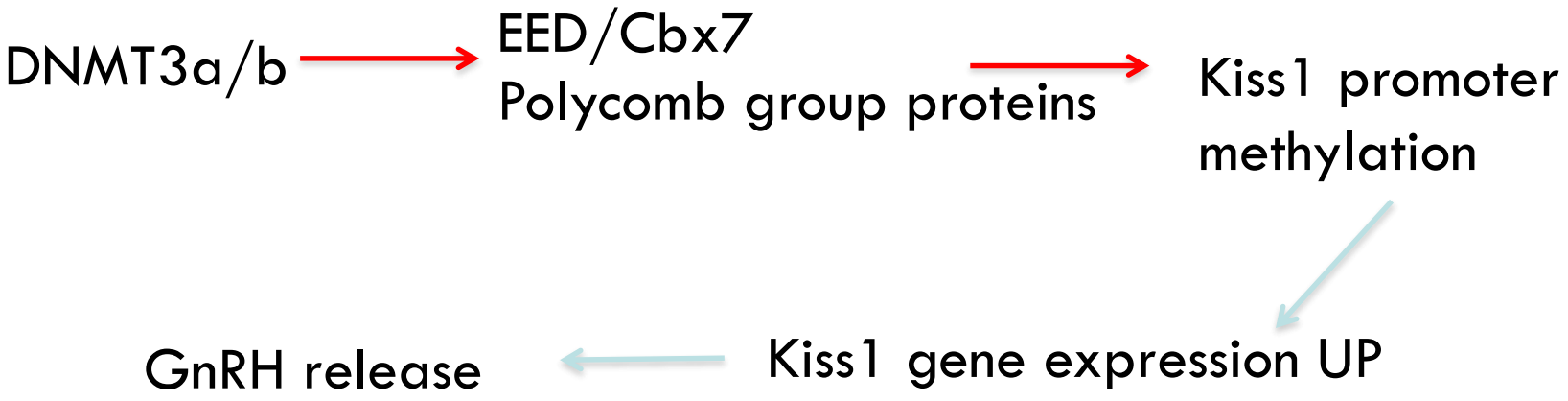
Il meccanismo di repressione di KiSS1 e il suo rilascio all'inizio della pubertà sono regolati epigeneticamente

Histones at KiSS1 promoter

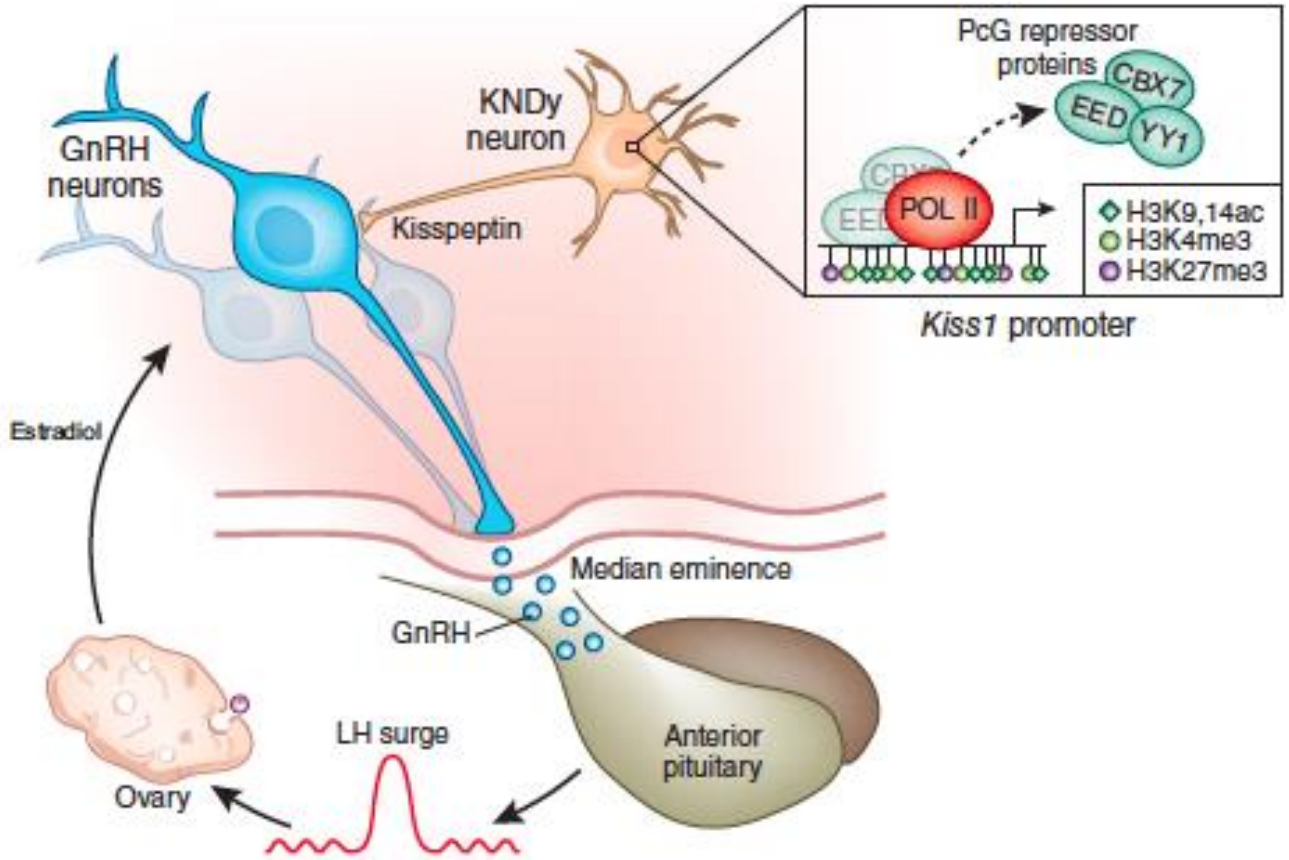




Lomniczi et al., Nature Neuroscience 2013


DNMT3a/b
EED/Cbx7
Polycomb group proteins
Kiss1 promoter
methylation
Kiss1 gene expression UP
GnRH release

Summary



McCarthy, Nature Neuroscience 2013

The NEW ENGLAND JOURNAL of MEDICINE

2013

ORIGINAL ARTICLE

Central Precocious Puberty Caused by Mutations in the Imprinted Gene *MKRN3*

Ana Paula Abreu, M.D., Ph.D., Andrew Dauber, M.D., Delanie B. Macedo, M.D., Sekoni D. Noel, Ph.D., Vinicius N. Brito, M.D., Ph.D., John C. Gill, Ph.D., Priscilla Cukier, M.D., Iain R. Thompson, Ph.D., Victor M. Navarro, Ph.D., Priscila C. Gagliardi, M.D., Tânia Rodrigues, M.D., Cristiane Kochi, M.D., Carlos Alberto Longui, M.D., Dominique Beckers, M.D., Francis de Zegher, M.D., Ph.D., Luciana R. Montenegro, Ph.D., Berenice B. Mendonca, M.D., Ph.D., Rona S. Carroll, Ph.D., Joel N. Hirschhorn, M.D., Ph.D., Ana Claudia Latronico, M.D., Ph.D., and Ursula B. Kaiser, M.D.

JCEM ONLINE

Brief Report—Endocrine Care

Central Precocious Puberty in a Girl and Early Puberty in Her Brother Caused by a Novel Mutation in the *MKRN3* Gene

Nikolaos Settas, Catherine Dacou-Voutetakis, Maria Karantza, Christina Kanaka-Gantenbein, George P. Chrousos, and Antonis Voutetakis

JCEM 2014

Central Precocious Puberty that appears to be sporadic caused by Paternally inherited mutations in the imprinted GENE makorin ring finger 3

Delanie B. Macedo*, Ana Paula Abreu*, Ana Claudia S. Reis, Luciana R. Montenegro, Andrew Dauber, Daiane Beneduzzi, Priscilla Cukier, Leticia F.G. Silveira, Milena G. Teles, Rona S. Carroll, Gil Guerra Junior, Guilherme Guaragna Filho, Zoran Gucev, Ivo J.P. Arnhold, Margaret de Castro, Ayrton C. Moreira, Carlos Eduardo Martinelli Jr, Joel N. Hirschhorn, Berenice B. Mendonca, Vinicius N. Brito, Sonir R. Antonini, Ursula B. Kaiser*, & Ana Claudia Latronico*

JCEM 2014

Grandone et al. BMC Endocrine Disorders (2015) 15:60
DOI 10.1186/s12902-015-0056-8

BMC
Endocrine Disorders

CASE REPORT Open Access

A case of familial central precocious puberty caused by a novel mutation in the *makorin RING finger protein 3* gene

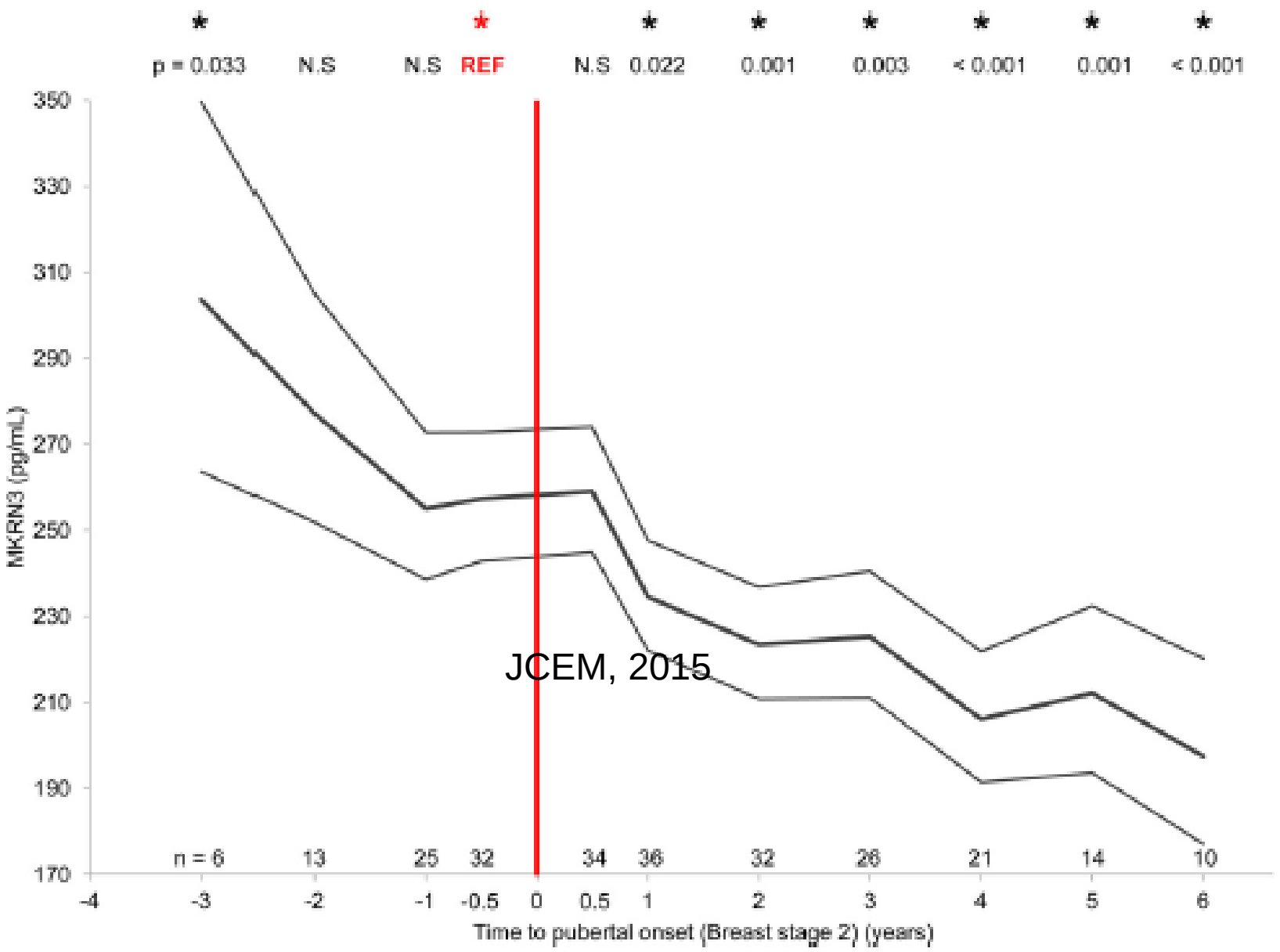
Anna Grandone, Grazia Cantelmi, Grazia Cirillo, Pierluigi Marzuillo*, Caterina Luongo, Emanuele Miraglia del Giudice and Laura Perrone

ORIGINAL ARTICLE

In silico analysis of a novel *MKRN3* missense mutation in familial central precocious puberty

Vassos Neocleous*, Christos Shammas*, Marie M. Phelan†, Stella Nicolaou‡, Leonidas A. Phylactou* and Nicos Skordis*·§¶

*Department of Molecular Genetics, Function & Therapy, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus, †NMR Centre for Structural Biology, Institute of Integrative Biology, University of Liverpool, Liverpool, UK, ‡Division of Pediatric Endocrinology, Makarios III Hospital, §Division of Pediatric Endocrinology, Paedi Center for specialized Pediatrics, and ¶St George's University of London Medical School at the University of Nicosia, Nicosia, Cyprus


p = 0.033
N.S
N.S
REF
N.S
0.022
0.001
0.003
< 0.001
0.001
< 0.001
MKRN3 (pg/mL)
350
330
310
290
270
250
230
210
190
170
n = 6
13
25
32
34
36
32
26
21
14
10
-4
-3
-2
-1
-0.5
0
0.5
1
2
3
4
5
6
Time to pubertal onset (Breast stage 2) (years)
JCEM, 2015

A new pathway in the control of the initiation of puberty: the *MKRN3* gene

Ana Paula Abreu, Delanie B Macedo[1], Vinicius N Brito[1], Ursula B Kaiser and Ana Claudia Latronico[1]

Division of Endocrinology, Diabetes and Hypertension, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA
[1]Unidade de Endocrinologia do Desenvolvimento, Disciplina de Endocrinologia e Metabologia, Laboratório de Hormônios e Genética Molecular, LIM 42, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Avenida Dr Enéas de Carvalho Aguiar, 255, 7° andar, sala 7037, CEP: 05403-900, São Paulo, Brazil

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Email
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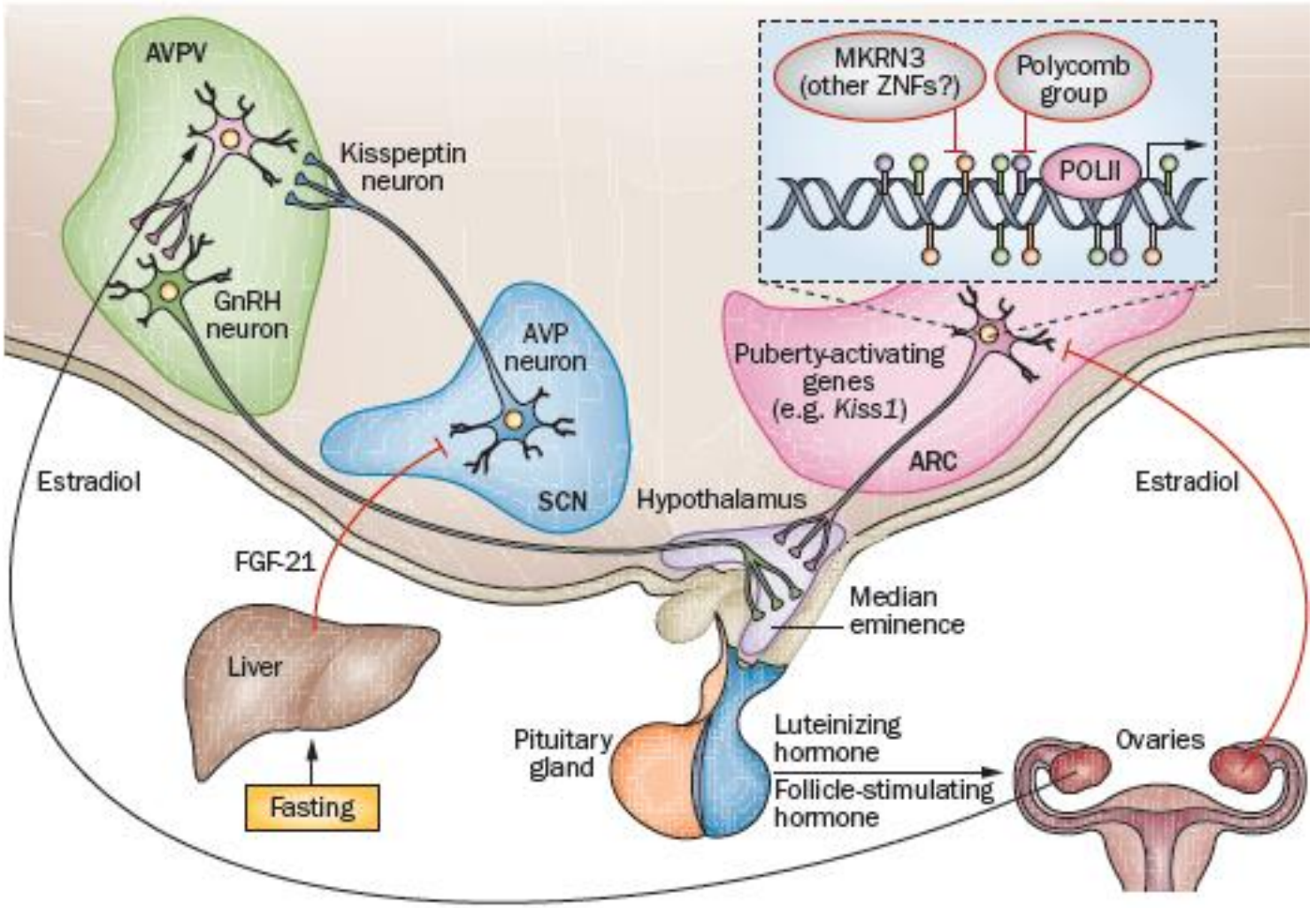

Ojeda, Nature Rev Endocrinol 2014

GRAZIE PER L'ATTENZIONE