Constitutional Delay of Growth and Puberty and Isolated Hypogonadotropic Hypogonadism: Two Sides of the Same Coin? Can We tell Heads from Tails?

Mark R. Palmert, M.D., Ph.D

The Hospital for Sick Children

The University of Toronto

SickKids®

UNIVERSITY OF TORONTO

Conflicts of Interest

None to declare

Objectives

1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotropic Hypogonadism (IHH/CHH), with focus on areas of overlap

2. Recognize clinical features that may allow for discrimination of one condition from the other

3. Discuss utility of diagnostic laboratory tests

Let’s discuss a couple cases

A 14 yr old young man with no significant past medical history presents to your clinic due to lack of pubertal development

Let’s discuss a couple cases

A 14 yr old young man with no significant past medical history presents to your clinic due to lack of pubertal development

Which does he have: CDGP/SLDP or IHH/CHH?

Let’s discuss a couple cases

OK. Here’s another case:

A 14 yr old young man with no significant past medical history presents to your clinic due to lack of pubertal development

Let’s discuss a couple cases

OK. Here’s another case:

A 14 yr old young man with no significant past medical history presents to your clinic due to lack of pubertal development.

Which does he have: CDGP/SLDP or IHH/CHH?

Let's discuss a couple cases

OK. Here's another case:

A 14 yr old young man with no significant past medical history presents to your clinic due to lack of pubertal development.

Which does he have: CDGP/SLDP or IHH/CHH?

Statistics makes it most likely that both have CDGP/SLDP.
But, is it possible to distinguish reliably these two conditions otherwise? Especially in absence of "classic" clinical features?

Let's discuss a couple cases

OK. Here's another case:

A 14 yr old young man with no significant past medical history presents to your clinic due to lack of pubertal development.

Which does he have: CDGP or IHH?

Statistics makes it most likely that both have CDGP.
But, is it possible to distinguish reliably these two conditions otherwise? Especially in absence of "classic" clinical features?

Often not!

But Distinguishing (when possible) is important

Allows for appropriate counselling of youth and family

Alleviates distress--lack of diagnosis generates anxiety and worry about a potential lifelong condition with attendant fertility implications

Avoids unnecessary testing, such as MRIs, that may be done

Simplifies treatment decisions as regimens for CDGP/SLDP are complicated by need to interrupt therapy and reassess for endogenous puberty

Objectives

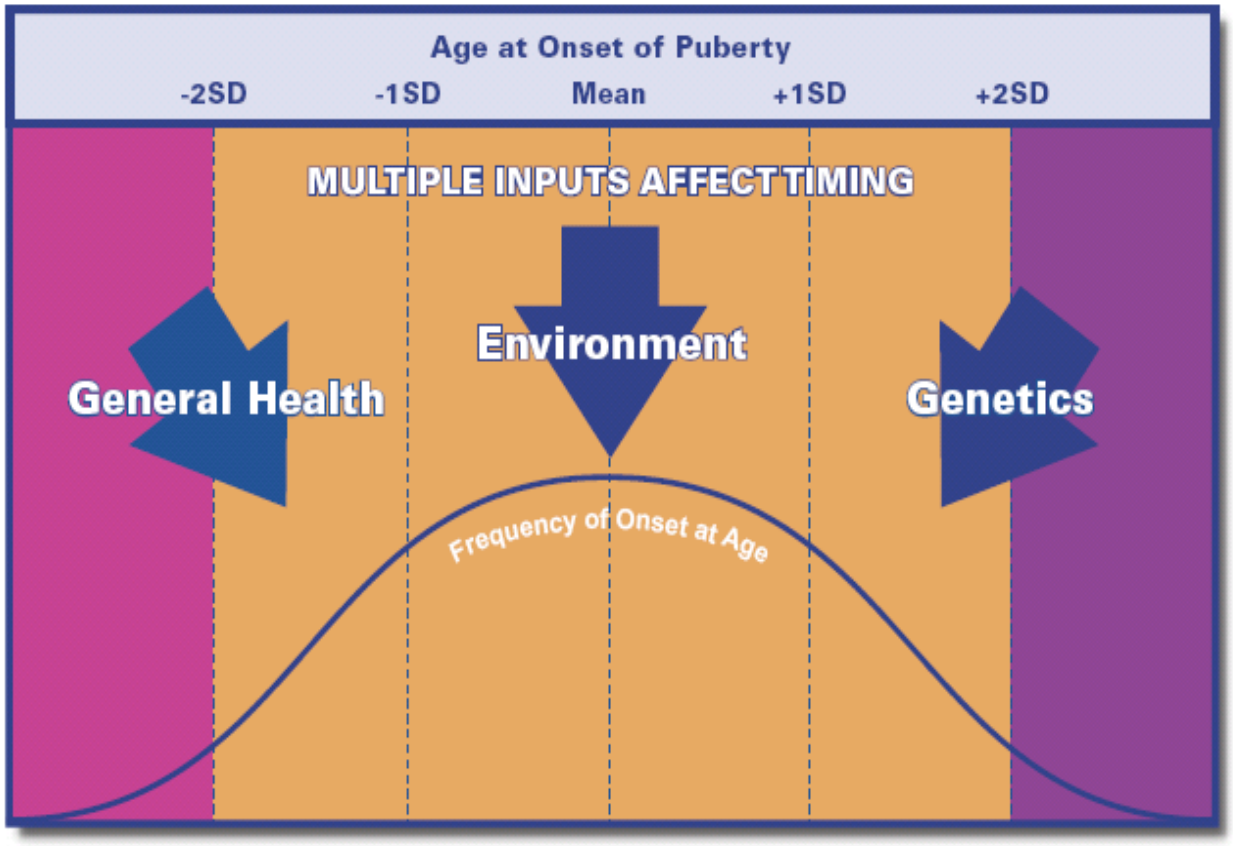
1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotropic Hypogonadism (IHH/CHH), with focus on areas of overlap.

2. Recognize clinical features that may allow for discrimination of one condition from the other.

3. Discuss utility of diagnostic laboratory tests.

CDGP & IHH: On a Spectrum but also Distinct

Both CDGP/SLDP and IHH/CHH are Genetic Conditions

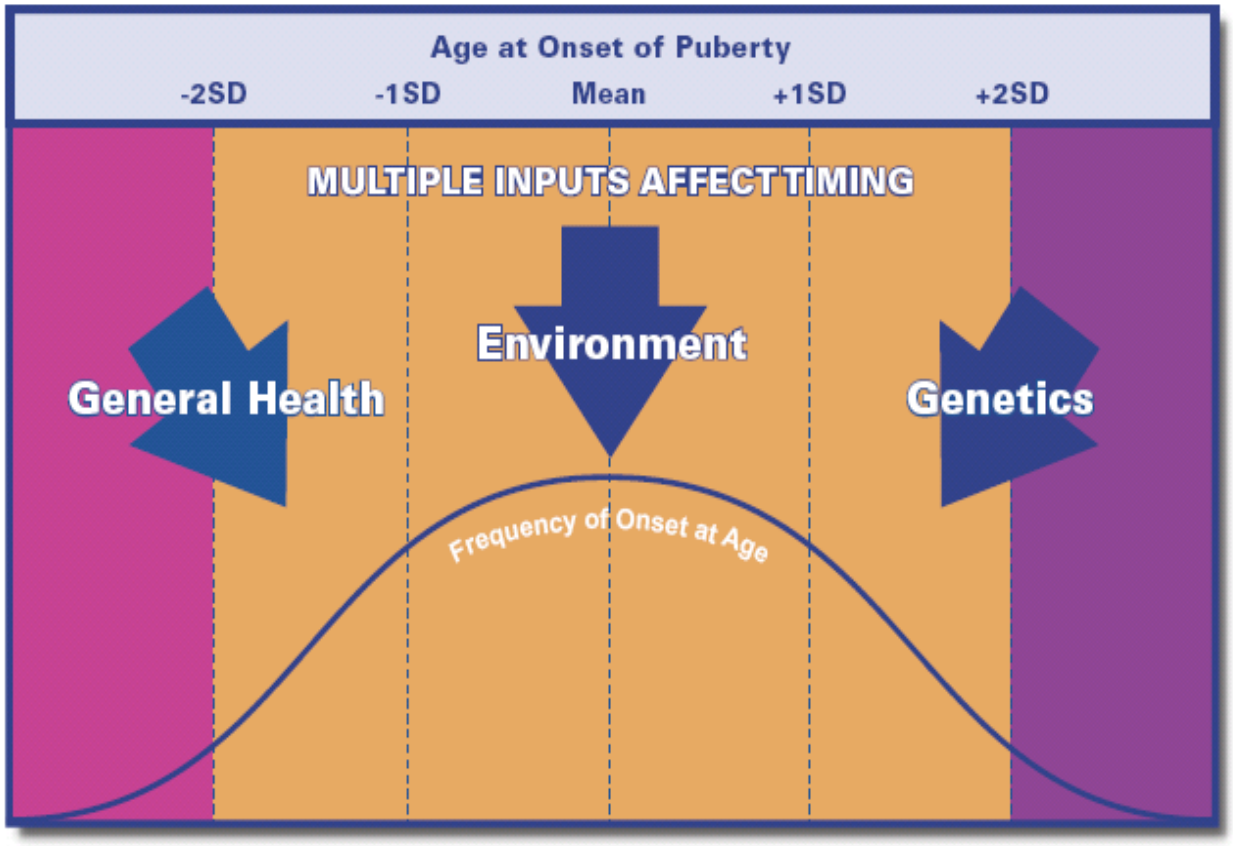


Common Variants: GWAS Studies

Common/Rare Variants

Mutations: IHH/CHH

Both CDGP/SLDP and IHH/CHH are Genetic Conditions



Common Variants: GWAS Studies

Common/Rare Variants

Mutations: IHH/CHH

More and more genes are being identified as causes of IHH/CHH

ELSEVIER

Molecular and Cellular Endocrinology

Volumes 254–255, 25 July 2006, Pages 60-69

Mutations in fibroblast growth factor receptor 1 cause Kallmann syndrome with a wide spectrum of reproductive phenotypes

Nelly Pitteloud [a], Astrid Meysing [a], Richard Quinton [b], James S. Acierno Jr. [a], Andrew A. Dwyer [a], Lacey Plummer [a], Eric Fliers [c], Paul Boepple [a], Frances Hayes [a], Stephanie Seminara [a], Viriginia A. Hughes [a], Jinghong Ma [d], Pierre Bouloux [b], Moosa Mohammadi [d], William F. Crowley Jr. [a]

More and more genes are being identified as causes of IHH/CHH

ELSEVIER

Molecular and Cellular Endocrinology

Volumes 254–255, 25 July 2006, Pages 60-69

PNAS

Heparan sulfate 6-O-sulfotransferase 1, a gene involved in extracellular sugar modifications, is mutated in patients with idiopathic hypogonadotrophic hypogonadism

Janne Tornberg[a], Gerasimos P. Sykiotis[b], Kimberly Keefe[b], Lacey Plummer[b], Xuan Hoang[b], Janet E. Hall[b], Richard Quinton[c], Stephanie B. Seminara[b], Virginia Hughes[b], Guy Van Vliet[d], Stan Van Uum[e], William F. Crowley[b], Hiroko Habuchi[f], Koji Kimata[f], Nelly Pitteloud[b,1,2,3], and Hannes E. Bülow[a,g,2,3]

11524–11529 | PNAS | July 12, 2011 | vol. 108 | no. 28

More and more genes are being identified as causes of IHH/CHH

ELSEVIER

Molecular and Cellular Endocrinology

Volumes 254–255, 25 July 2006, Pages 60-69

PNAS

Heparan sulfate in extracellular s with idiopathic

Janne Tornberg[a], Gerasimos P. Sy
Richard Quinton[c], Stephanie B. Se
Hiroko Habuchi[f], Koji Kimata[f], Ne

11524–11529 | PNAS | July

2017

Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

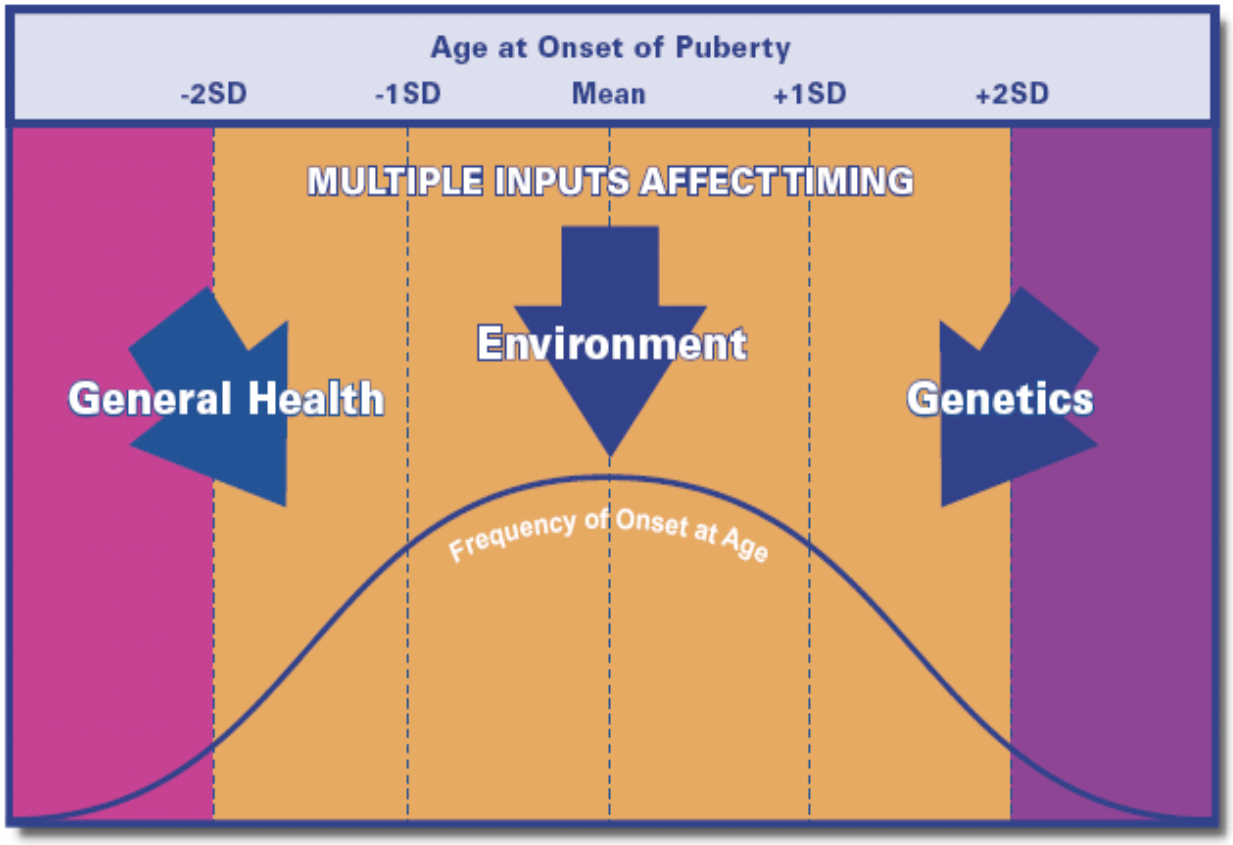
KLB, encoding β-Klotho, is mutated in patients with congenital hypogonadotropic hypogonadism

Cheng Xu[1], Andrea Messina[1], Emmanuel Somm[1], Hichem Miraoui[1,†], Tarja Kinnunen[2], James Acierno Jr[1], Nicolas J Niederländer[1], Justine Bouilly[1], Andrew A Dwyer[1,3], Yisrael Sidis[1], Daniele Cassatella[1], Gerasimos P Sykiotis[1], Richard Quinton[4], Christian De Geyter[5], Mirjam Dirlewanger[6], Valérie Schwitzgebel[6], Trevor R Cole[7], Andrew A Toogood[8], Jeremy MW Kirk[9], Lacey Plummer[10], Urs Albrecht[11], William F Crowley Jr[10], Moosa Mohammadi[12], Manuel Tena-Sempere[13,14,15], Vincent Prevot[16,17] & Nelly Pitteloud[1,*]

40 genes have been identified to cause IHH/CHH

Over 50% of cases genetic cause is unknown

Both CDGP/SLDP and IHH/CHH are Genetic Conditions



Common Variants: GWAS Studies

Common/Rare Variants

Mutations: IHH/CHH 40 genes

GWAS provide insight into common variants associated with age at menarche and voice breaking

nature genetics

Elks et al. Nature Genetics, 2010

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

nature COMMUNICATIONS

ARTICLE

Received 22 Jun 2015 | Accepted 7 Oct 2015 | Published 9 Nov 2015 DOI: 10.1038/ncomms9842 OPEN

Shared genetic aetiology of puberty timing between sexes and with health-related outcomes

Felix R. Day[1], Brendan Bulik-Sullivan[2,3,4], David A. Hinds[5], Hilary K. Finucane[6,7], Joanne M. Murabito[8,9], Joyce Y. Tung[5], Ken K. Ong[1,10,*] & John R.B. Perry[1,*]

LETTER Perry et al. Nature, 2014

doi:10.1038/nature13545

Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche

nature genetics

Article | Published: 24 April 2017

Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk

Felix R Day, Deborah J Thompson [...] John R B Perry

Nature Genetics **49**, 834–841 (2017) | Download Citation

GWAS provide insight into common variants associated with age at menarche and voice breaking

nature COMMUNICATIONS

ARTICLE

Received 22 Jun 2015 | Accepted 7 Oct 2015 | Published 9 Nov 2015

DOI: 10.1038/ncomms9842 OPEN

Shared genetic aetiology of puberty timing between sexes and with health-related outcomes

Felix R. Day[1], Brendan Bulik-Sullivan[2,3,4], David A. Hinds[5], Hilary K. Finucane[6,7], Joanne M. Murabito[8,9], Joyce Y. Tung[5], Ken K. Ong[1,10,*] & John R.B. Perry[1,*]

GWAS provide insight into common variants associated with age at menarche and voice breaking

JCEM: 2020

CLINICAL RESEARCH ARTICLE

A Polygenic Risk Score Suggests Shared Genetic Architecture of Voice Break With Early Markers of Pubertal Onset in Boys

María C. Lardone,[1] Alexander S. Busch,[2] José L. Santos,[3] Patricio Miranda,[3] Susana Eyheramendy,[4] Ana Pereira,[5] Anders Juul,[2] Kristian Almstrup,[2] and Verónica Mericq[1]

GWAS provide insight into common variants associated with age at menarche and voice breaking

nature COMMUNICATIONS

ARTICLE

Received 22 Jun 2015 | Accepted 7 Oct 2015 | Published 9 Nov 2015

DOI: 10.1038/ncomms9842 OPEN

Shared genetic aetiology c
sexes and with health-rel

Felix R. Day[1], Brendan Bulik-Sullivan[2,3,4], David A. Hinds
Joyce Y. Tung[5], Ken K. Ong[1,10,*] & John R.B. Perry[1,*]

Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2016 February ; 23(1): 57–65. doi:10.1097/MED.0000000000000213.

The genetics of pubertal timing in the general population: recent advances and evidence for sex-specificity

Diana L. Cousminer[1], **Elisabeth Widén**[2], and **Mark R. Palmert**[3,4]

GWAS provide insight into common variants associated with age at menarche and voice breaking

nature COMMUNICATIONS

ARTICLE

Received 22 Jun 2015 | Accepted 7 Oct 2015 | Published 9 Nov 2015 DOI: 10.1038/ncomms9642 OPEN

Shared genetic aetiology of puberty timing between sexes and with health-related outcomes

Felix R. Day[1], Brendan Bulik-Sullivan[2,3,4], David A. Hinds[5], Hilary K. Finucane[6,7], Joanne M. Murabito[8,9], Joyce Y. Tung[5], Ken K. Ong[1,10,*] & John R.B. Perry[1,*]

GWAS provide insight into common variants associated with age at menarche and voice breaking

OXFORD

Human Molecular Genetics, 2017, Vol. 26, No. 18 3585–3599

doi: 10.1093/hmg/ddx246
Advance Access Publication Date: 27 June 2017
Original Article

ORIGINAL ARTICLE

Gene expression profiling of puberty-associated genes reveals abundant tissue and sex-specific changes across postnatal development

Huayun Hou[1,2,†], Liis Uusküla-Reimand[1,3,†], Maisam Makarem[1], Christina Corre[1], Shems Saleh[1,4], Ariane Metcalf[1], Anna Goldenberg[1,4,*,‡], Mark R. Palmert[1,5,6,*,‡] and Michael D. Wilson[1,2,*,‡]

GWAS provide insight into common variants associated with age at menarche and voice breaking

Human Molecular Genetics, 2017, Vol. 26, No. 18 3585–3599

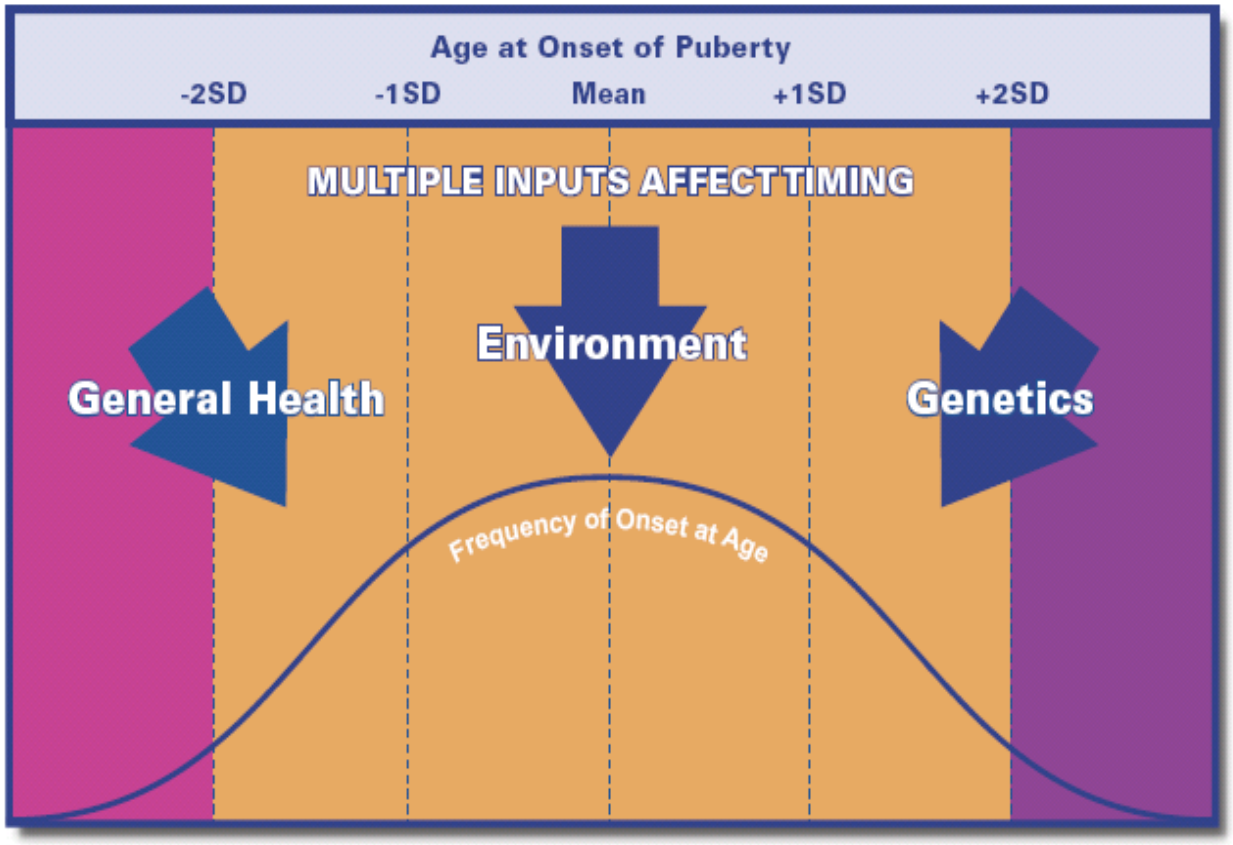
doi: 10.1093/hmg/ddx246
Advance Access Publication Date: 27 June 2017
Original Article

ORIGINAL ARTICLE

Gene expression profiling of puberty-associated genes reveals abundant tissue and sex-specific changes across postnatal development

Huayun Hou[1,2,†], Liis Uusküla-Reimand[1,3,†], Maisam Makarem[1], Christina Corre[1], Shems Saleh[1,4], Ariane Metcalf[1], Anna Goldenberg[1,4,*,‡], Mark R. Palmert[1,5,6,*,‡] and Michael D. Wilson[1,2,*,‡]

Both CDGP/SLDP and IHH/CHH are Genetic Conditions

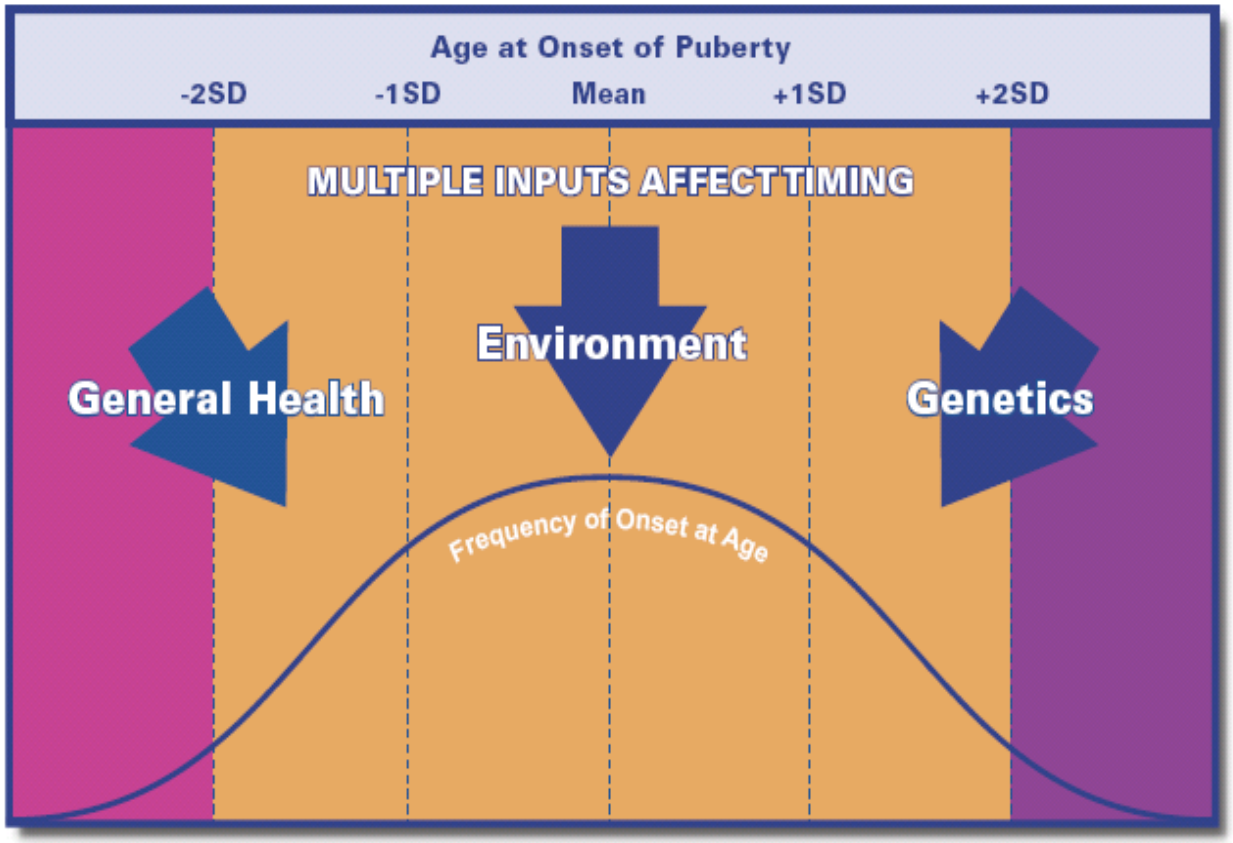


Common Variants:
GWAS Studies
400 loci
largely shared ♀♂

Common/Rare Variants

Mutations: IHH/CHH
40 Genes

Both CDGP/SLDP and IHH/CHH are Genetic Conditions



Common Variants:
GWAS Studies
400 loci
mostly shared ♀♂

Common/Rare Variants

Mutations: IHH/CHH
40 genes

Sequencing studies uncovering genes that cause CDGP/SLDP

2016

Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

IGSF10 mutations dysregulate gonadotropin-releasing hormone neuronal migration resulting in delayed puberty

Sasha R Howard[†,1], Leonardo Guasti[†,1], Gerard Ruiz-Babot[1], Alessandra Mancini[1], Alessia David[2], Helen L Storr[1], Lousie A Metherell[1], Michael JE Sternberg[2], Claudia P Cabrera[3,4], Helen R Warren[4,5], Michael R Barnes[3,4], Richard Quinton[6], Nicolas de Roux[7,8,9], Jacques Young[10,11,12,13], Anne Guiochon-Mantel[10,11,12], Karoliina Wehkalampi[14], Valentina André[15], Yoav Gothilf[16], Anna Cariboni[15,17] & Leo Dunkel[1,*]

Sequencing studies uncovering genes that cause CDGP/SLDP

2016

Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

IGSF10 mutations dysregulate gonadotropin-releasing hormone neuronal migration resulting in delayed puberty

Sasha R Howard[†,1], Leonardo Guasti[†,1], Gerard Ruiz-Babot[1], Alessandra Manci
Helen L Storr[1], Lousie A Metherell[1], Michael JE Sternberg[2], Claudia P Cabrera[3]
Michael R Barnes[3,4], Richard Quinton[6], Nicolas de Roux[7,8,9], Jacques Young[10,1
Anne Guiochon-Mantel[10,11,12], Karoliina Wehkalampi[14], Valentina André[15], Yoa
Anna Cariboni[15,17] & Leo Dunkel[1,*]

Human Molecular Genetics, 2019, Vol. 28, No. 8 1357–1368

doi: 10.1093/hmg/ddy451
Advance Access Publication Date: 4 January 2019
General Article

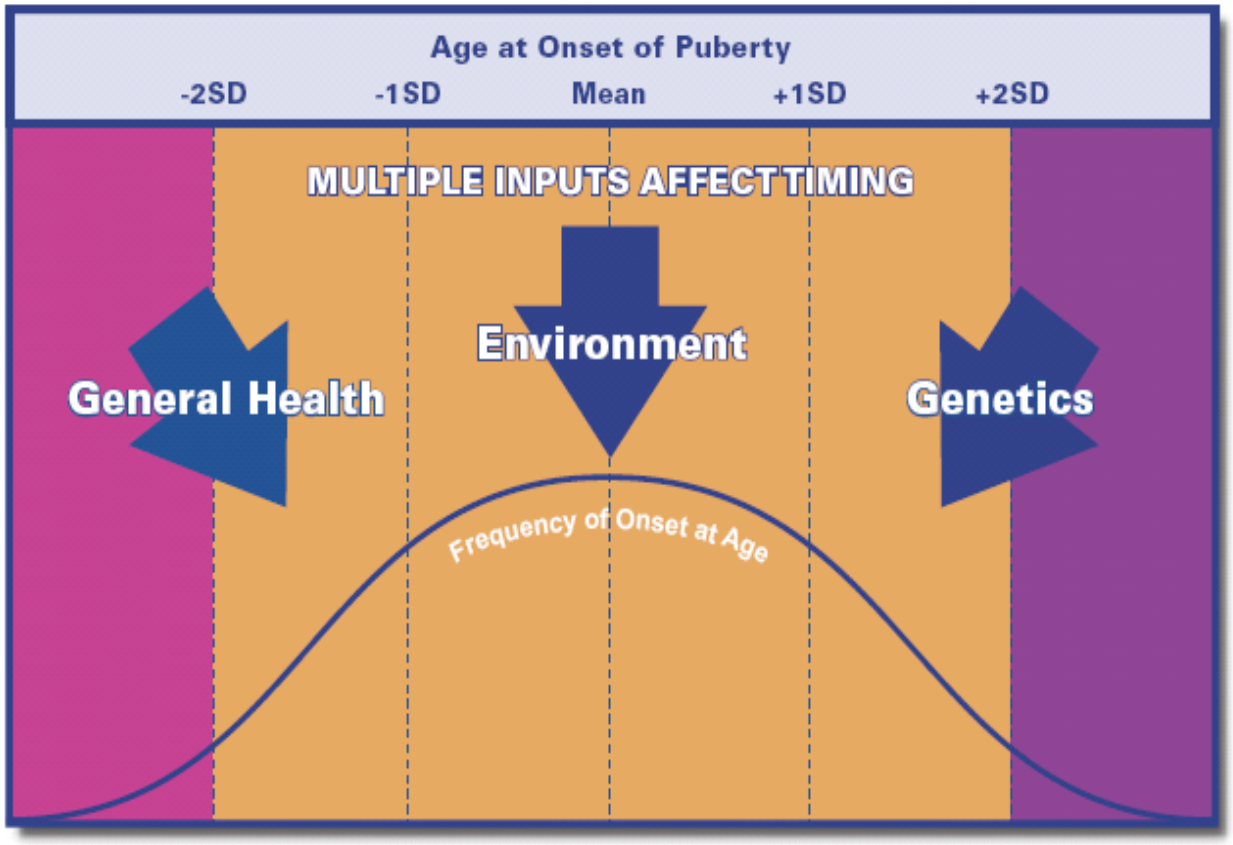
OXFORD

GENERAL ARTICLE

EAP1 regulation of GnRH promoter activity is important for human pubertal timing

Alessandra Mancini[1], Sasha R. Howard[1], Claudia P. Cabrera[2], Michael R. Barnes[2], Alessia David[3], Karoliina Wehkalampi[4], Sabine Heger[5], Alejandro Lomniczi[6], Leonardo Guasti[1,†], Sergio R. Ojeda[6,†] and Leo Dunkel[1,†,*]

Both CDGP/SLDP and IHH/CHH are Genetic Conditions

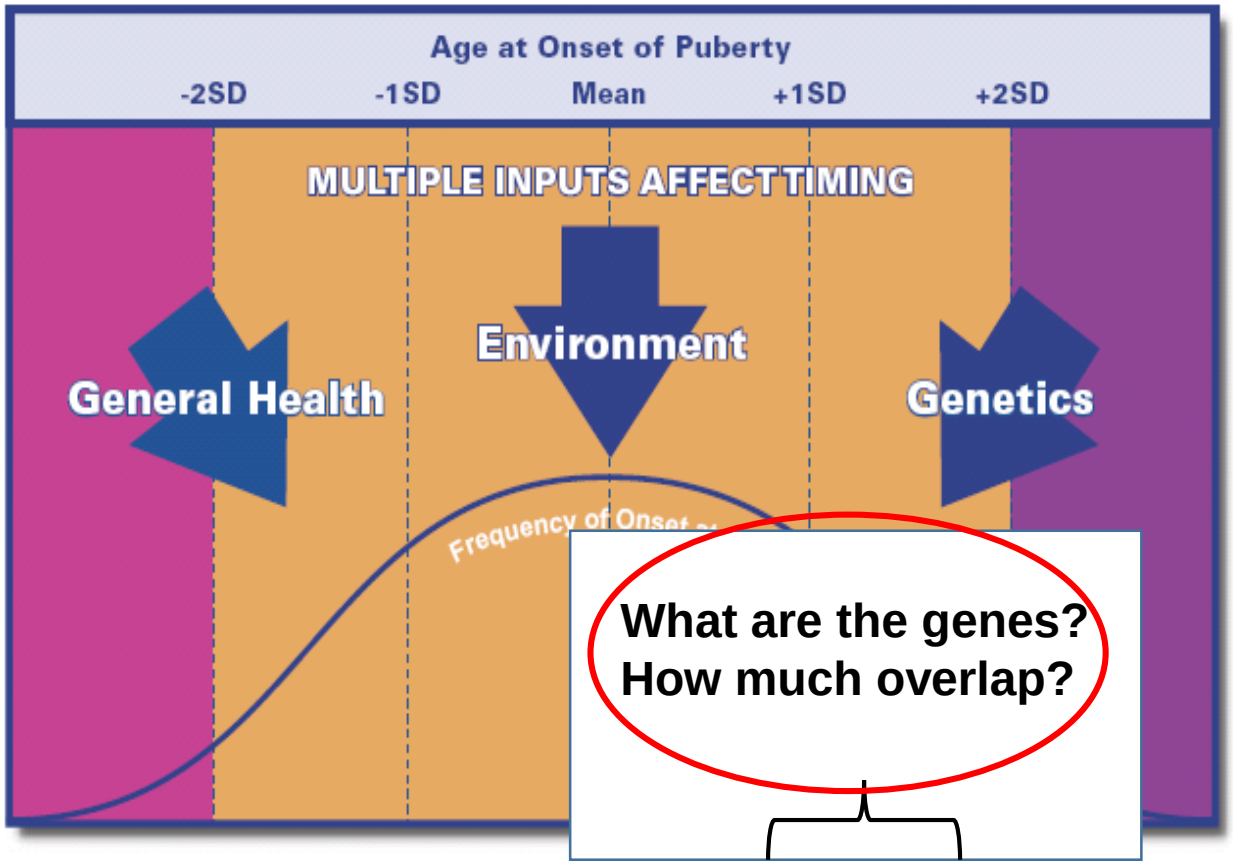


Common Variants: GWAS Studies 400 loci mostly shared ♀♂

~~Common~~/Rare Variants—few genes

Mutations: IHH/CHH 40 genes

Both CDGP/SLDP and IHH/CHH are Genetic Conditions

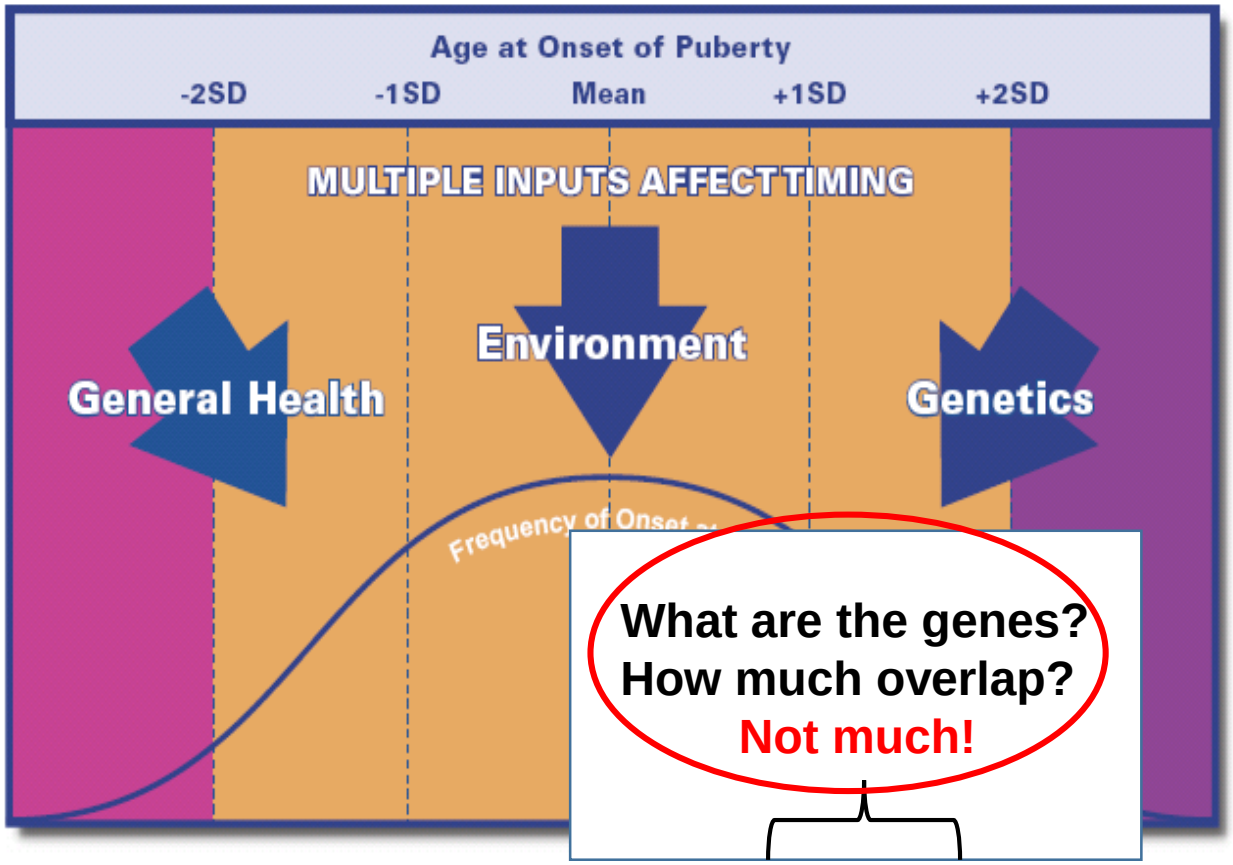


Common Variants:
GWAS Studies
400 loci
mostly shared ♀♂

~~Common~~/Rare Variants—few genes

Mutations: IHH/CHH
40 genes

Both CDGP/SLDP and IHH/CHH are Genetic Conditions

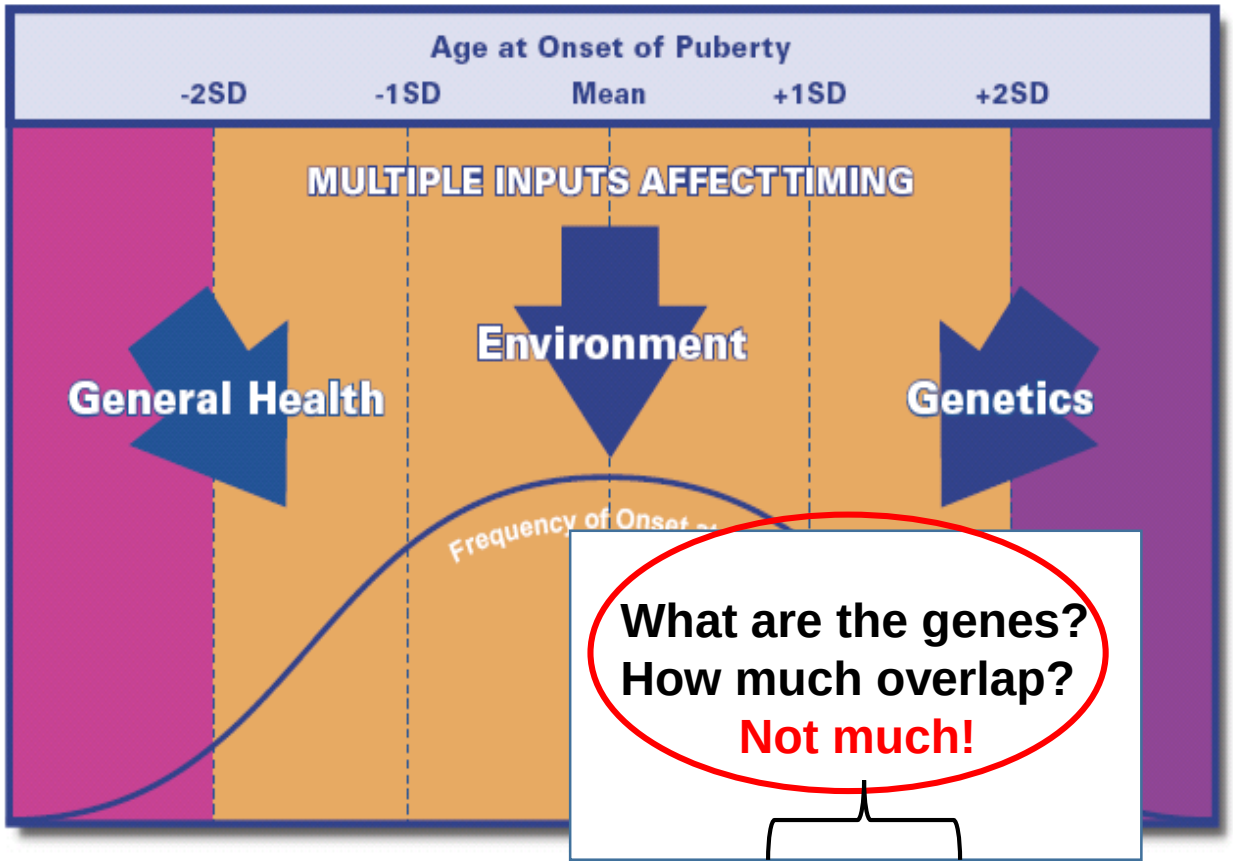


Common Variants:
GWAS Studies
400 loci
mostly shared ♀♂

~~Common~~/Rare Variants—few genes

Mutations: IHH/CHH
40 genes

Both CDGP/SLDP and IHH/CHH are Genetic Conditions



Common Variants: GWAS Studies
400 loci
mostly shared ♀♂

~~Common~~/Rare Variants—few genes

Mutations: IHH/CHH
40 genes

What are the genes?
How much overlap?

Sequencing studies uncovering genes that cause CDGP/SLDP

2016

Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

IGSF10 mutation releasing hormo delayed puberty

Sasha R Howard[†,1], Leonardo G
Helen L Storr[1], Lousie A Mether
Michael R Barnes[3,4], Richard Qu
Anne Guiochon-Mantel[10,11,12], K
Anna Cariboni[15,17] & Leo Dunke

HS6ST1 Insufficiency Causes Self-Limited Delayed Puberty in Contrast With Other GnRH Deficiency Genes

(*J Clin Endocrinol Metab* 103: 3420–3429, 2018)

Sasha R. Howard,[1]* Roberto Oleari,[2]* Ariel Poliandri,[1] Vasiliki Chantzara,[3] Alessandro Fantin,[3] Gerard Ruiz-Babot,[1] Louise A. Metherell,[1] Claudia P. Cabrera,[4,5] Michael R. Barnes,[4,5] Karoliina Wehkalampi,[6] Leonardo Guasti,[1]* Christiana Ruhrberg,[3]* Anna Cariboni,[2,3]* and Leo Dunkel[1]*

GENERAL ARTICLE

EAP1 regulation of GnRH promoter activity is important for human pubertal timing

Alessandra Mancini[1], Sasha R. Howard[1], Claudia P. Cabrera[2], Michael R. Barnes[2], Alessia David[3], Karoliina Wehkalampi[4], Sabine Heger[5], Alejandro Lomniczi[6], Leonardo Guasti[1,†], Sergio R. Ojeda[6,†] and Leo Dunkel[1,†,*]

Sequencing studies uncovering genes that cause CDGP/SLDP

JCEM ONLINE

Advances in Genetics

A Shared Genetic Basis for Self-Limited Delayed Puberty and Idiopathic Hypogonadotropic Hypogonadism

Jia Zhu, Ruth E.-Y. Choa, Michael H. Guo, Lacey Plummer, Cassandra Buck, Mark R. Palmert, Joel N. Hirschhorn, Stephanie B. Seminara,* and Yee-Ming Chan*

With whole exome sequencing,

-- Demonstrated shared genetic basis of self-limited delayed puberty & IHH.

--IHH causing variants enriched in family members with DP compared with family members without DP (variants in *FGFR1, KAL1, TAC3*) (53% vs 12%)

Sequencing studies uncovering genes that cause CDGP/SLDP

JCEM ONLINE

Advances in Genetics

A Shared Genetic Basis for Self-Limited Delayed Puberty and Idiopathic Hypogonadotropic Hypogonadism

Jia Zhu, Ruth E.-Y. Choa, Michael H. Guo, Lacey Plummer, Cassandra Buck, Mark R. Palmert, Joel N. Hirschhorn, Stephanie B. Seminara,* and Yee-Ming Chan*

With whole exome sequencing,

-- Demonstrated shared genetic basis of self-limited delayed puberty & IHH.

--IHH causing variants enriched in family members with DP compared with family members without DP (variants in *FGFR1, KAL1, TAC3*) (53% vs 12%)

--Sequencing of 57 additional individuals with DP found enrichment for IHH variants in DP subjects compared to ethnicity matched controls (*IS17RD* and *TAC3*) (14% vs 5.6%)

The genetic architecture of CDGP/SLDP and IHH/CHH are largely distinct

Clinical Study | D Cassatella and others | Diverse genetic patterns in CHH and CDGP | 178:4 | 377–388

EJE 2018

Congenital hypogonadotropic hypogonadism and constitutional delay of growth and puberty have distinct genetic architectures

Daniele Cassatella[1,2,*], Sasha R Howard[3,*], James S Acierno[1,2,*], Cheng Xu[1,2], Georgios E Papadakis[1], Federico A Santoni[1], Andrew A Dwyer[1,2], Sara Santini[1], Gerasimos P Sykiotis[1], Caroline Chambion[1], Jenny Meylan[1], Laura Marino[1], Lucie Favre[1], Jiankang Li[45], Xuanzhu Liu[4], Jianguo Zhang[4,5], Pierre-Marc Bouloux[6], Christian De Geyter[7], Anne De Paepe[8], Waljit S Dhillo[9], Jean-Marc Ferrara[10], Michael Hauschild[1], Mariarosaria Lang-Muritano[11], Johannes R Lemke[12], Christa Flück[13], Attila Nemeth[14], Franziska Phan-Hug[1], Duarte Pignatelli[15], Vera Popovic[16], Sandra Pekic[16,17], Richard Quinton[18], Gabor Szinnai[19], Dagmar l'Allemand[20], Daniel Konrad[11], Saba Sharif[21], Özlem Turhan Iyidir[22], Brian J Stevenson[23], Huanming Yang[4,24], Leo Dunkel[3,*] and Nelly Pitteloud[1,2,†]

The genetic architecture of CDGP/SLDP and IHH/CHH are largely distinct

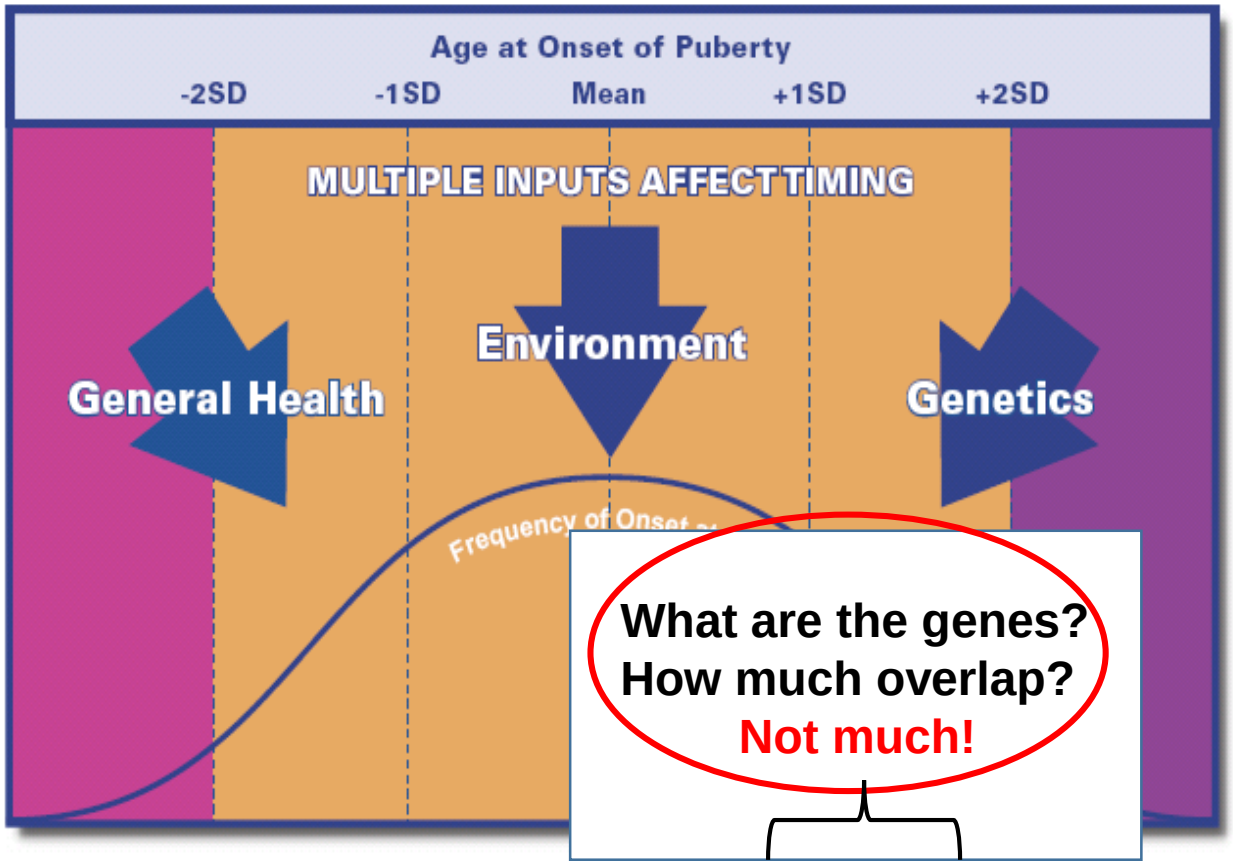
Clinical Study | D Cassatella and others | Diverse genetic patterns in CHH and CDGP | 178:4 | 377–388

Congenital hypogonadotropic hypogonadism and constitutional delay of growth and puberty have distinct genetic architectures

Daniele Cassatella[1,2,*], Sasha R Howard[3,*], James S Acierno[1,2,*], Cheng Xu[1,2], Georgios E Papadakis[1], Federico A Santoni[1], Andrew A Dwyer[1,2], Sara Santini[1], Gerasimos P Sykiotis[1], Caroline Chambion[1], Jenny Meylan[1], Laura Marino[1], Lucie Favre[1], Jiankang Li[4,5], Xuanzhu Liu[4], Jianguo Zhang[4,5], Pierre-Marc Bouloux[6], Christian De Geyter[7], Anne De Paepe[8], Waljit S Dhillo[9], Jean-Marc Ferrara[10], Michael Hauschild[1], Mariarosaria Lang-Muritano[11], Johannes R Lemke[12], Christa Flück[13], Attila Nemeth[14], Franziska Phan-Hug[1], Duarte Pignatelli[15], Vera Popovic[16], Sandra Pekic[16,17], Richard Quinton[18], Gabor Szinnai[19], Dagmar l'Allemand[20], Daniel Konrad[11], Saba Sharif[21], Özlem Turhan Iyidir[22], Brian J Stevenson[23], Huanming Yang[4,24], Leo Dunkel[3,*] and Nelly Pitteloud[1,2,†]

EJE 2018

Both CDGP/SLDP and IHH/CHH are Genetic Conditions



Common Variants: GWAS Studies
400 loci
mostly shared ♀♂

~~Common~~/Rare Variants—few genes

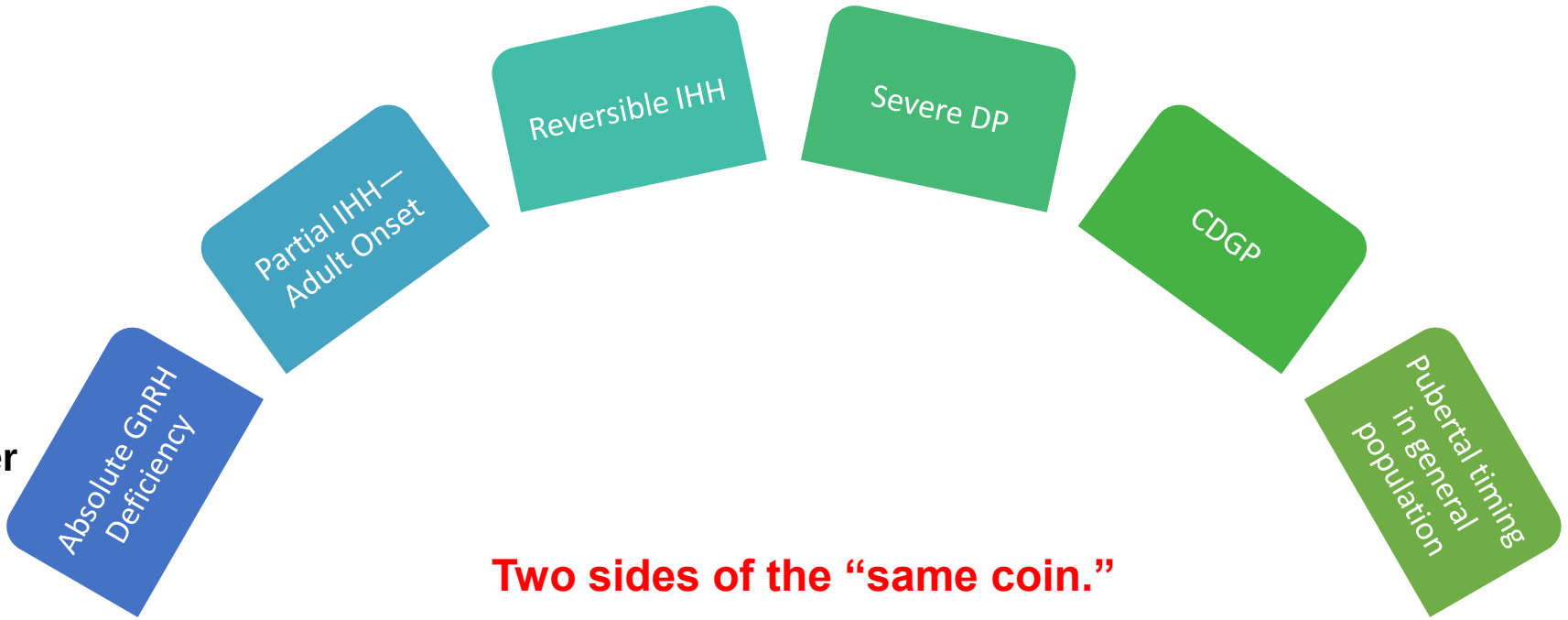
Mutations: IHH/CHH
40 genes

What are the genes?
How much overlap?
Not Much!

Some genetic causes of disorders of puberty overlap; most don't

Howard S and Dunkel L
2019 Oct; 40(5): 1285–1317

CDGP & IHH: On a Spectrum but also Distinct



Genetic Disorder
Monogenic
Polygenic
40+ genes

Few overlap with GWAS
Or CDGP/SLDP

Two sides of the "same coin."

Polygenic Trait
GWAS
400+ loci

Few overlap with IHH/ CHH

Greater Genetic Burden

Objectives

1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotropic Hypogonadism (IHH/CHH), with focus on areas of overlap. Both disorders have strong genetic basis but causative genes are largely distinct

2. Recognize clinical features that may allow for discrimination of one condition from the other

3. Discuss utility of diagnostic laboratory tests

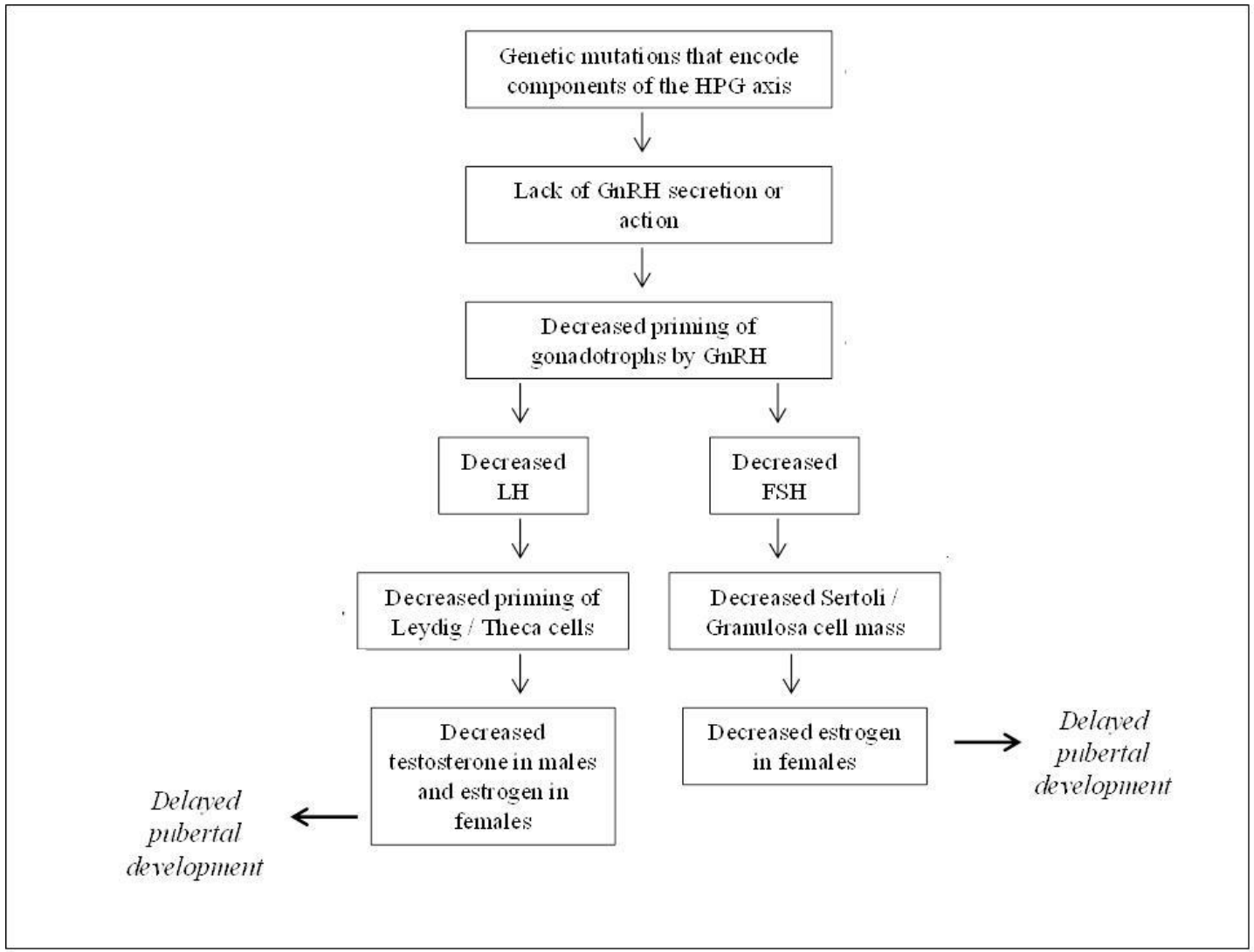
Objectives

1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotropic Hypogonadism (IHH/CHH), with focus on areas of overlap. Both disorders have strong genetic basis but causative genes are largely distinct

2. Recognize clinical features that may allow for discrimination of one condition from the other.

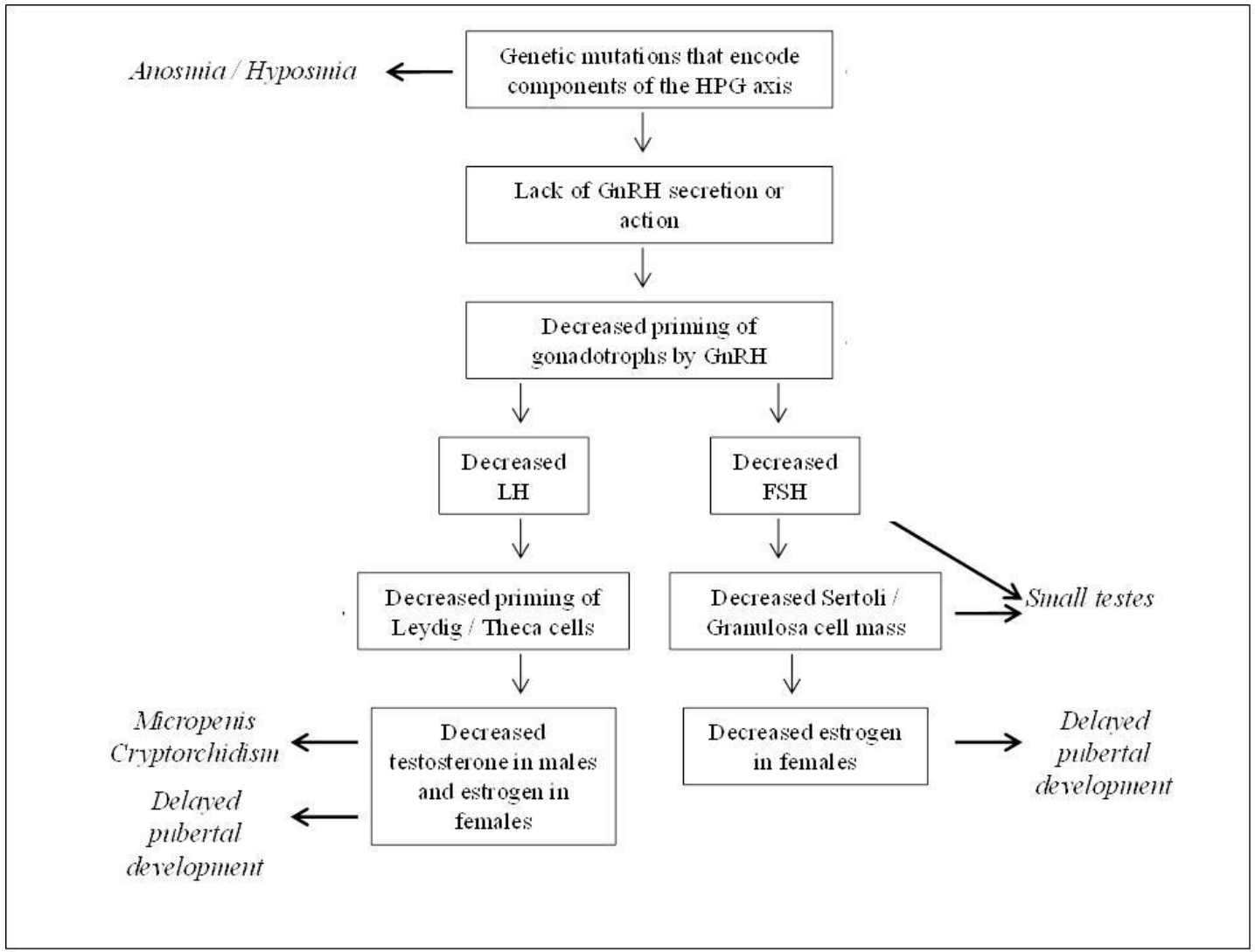
3. Discuss utility of diagnostic laboratory tests.

Differentiating CDGP/SLDP from IHH/CHH



***JCEM*, Harrington J and Palmert MR ; 2012**

Differentiating CDGP/SLDP from IHH/CHH



JCEM, Harrington J and Palmert MR ; 2012

Differentiating CDGP/SLDP from IHH/CHH: History

Classic Features/Questions*—IHH/CHH*:

Abnormal sense of smell

Small tests/cryptorchidism

Micropenis

And, of course:

Family History of Delayed Puberty—CDGP/SLDP

Family History of IHH or infertility—IHH/CHH

And one other:

Timing of adrenarche—Often delayed in CDGP/SLDP; "on time" with IHH/CHH

***Arch Dis Child*, Abitbol L, Zborovski S, Palmert MR; 2016**

Histories pointing to syndromic CHH can also be useful

ENDOCRINE SOCIETY endocrine reviews
Howard S and Dunkel L
2019 Oct; 40(5): 1285–1317

Physical exams complement histories

***Arch Dis Child*, Abitbol L, Zborovski S, Palmert MR; 2016**

Differentiating CDGP/SLDP from IHH/CHH: History

Human Reproduction, Vol.32, No.1 pp. 147–153, 2017
Advanced Access publication on December 6, 2016 doi:10.1093/humrep/dew294

human reproduction ORIGINAL ARTICLE *Puberty, ageing and HRT*

Congenital hypogonadotropic hypogonadism, functional hypogonadotropism or constitutional delay of growth and puberty? An analysis of a large patient series from a single tertiary center

Tero Varimo[1], Päivi J. Miettinen[1,2], Johanna Känsäkoski[3], Taneli Raivio[1,3,*], and Matti Hero[1]

Clinical and biochemical criteria met by
174 boys and 70 girls

Findings:

No feature of history among girls identified IHH/CHH

Among boys, cryptorchidism was associated with IHH/CHH
(odds ratio of 17.2 (95% CI 3.4-85.4)

Testicular volume of ≤ 1 ml had sensitivity of 100% and specificity of 91% for IHH/CHH

Objectives

1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotropic Hypogonadism (IHH/CHH), with focus on areas of overlap. Both disorders have strong genetic basis but causative genes are largely distinct

2. Recognize clinical features that may allow for discrimination of one condition from the other. History and physical exam can be informative, and some features are discriminatory

3. Discuss utility of diagnostic laboratory tests

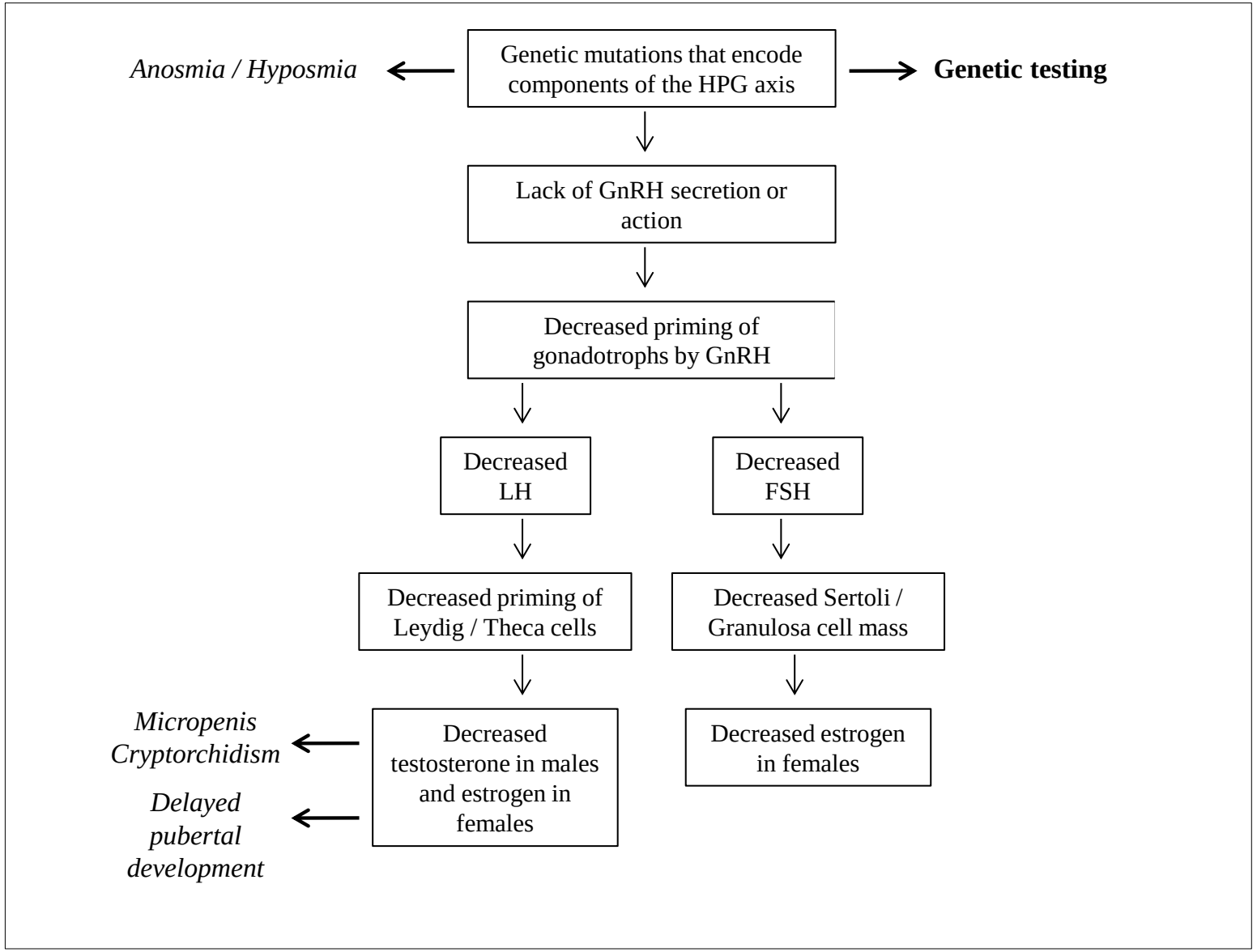
Objectives

1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotropic Hypogonadism (IHH/CHH), with focus on areas of overlap. Both disorders have strong genetic basis but causative genes are largely distinct

2. Recognize clinical features that may allow for discrimination of one condition from the other. History and physical exam can be informative, and some features are discriminatory

3. Discuss utility of diagnostic laboratory tests.

Differentiating: Rationale for diagnostic tests



***JCEM*, Harrington J and Palmert MR ; 2012**

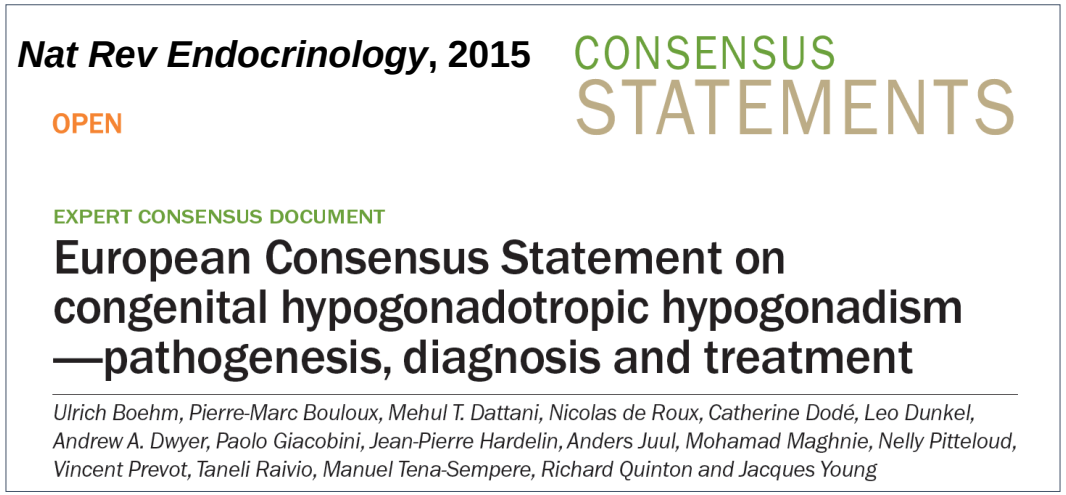
Differentiating: Rationale for diagnostic tests

Specific clinical features may help prioritize genetic screening

Differentiating: Rationale for diagnostic tests

European Consensus*: Nat Rev Endocrinology*, 2015

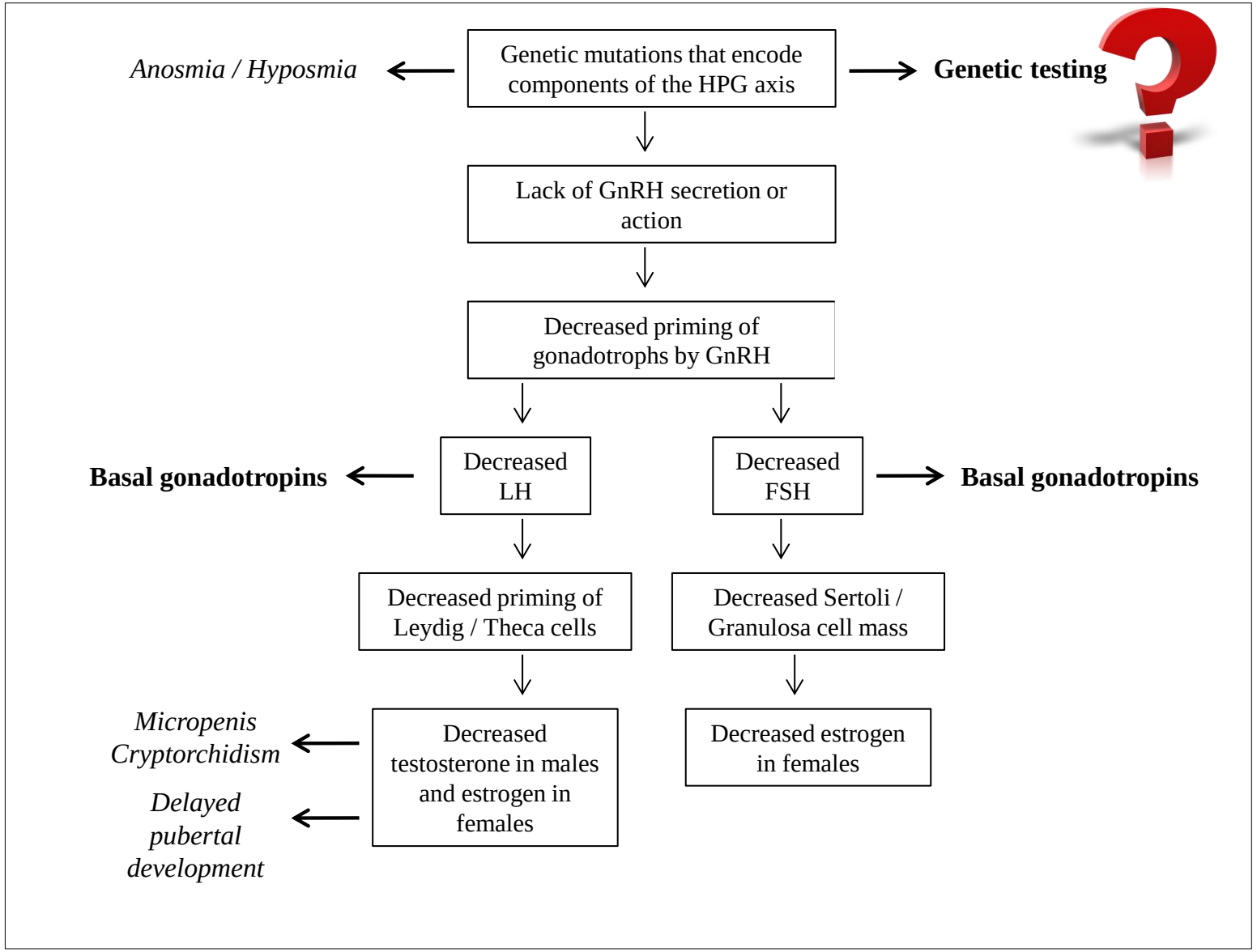
Differentiating: Rationale for diagnostic tests



But routine testing to distinguish CDGP/SLDP from IHH/CHH—no recommendation made

Utility and use will likely increase as panels become more available, costs decrease and % of unknown causes decreases.

Differentiating: Rationale for diagnostic tests



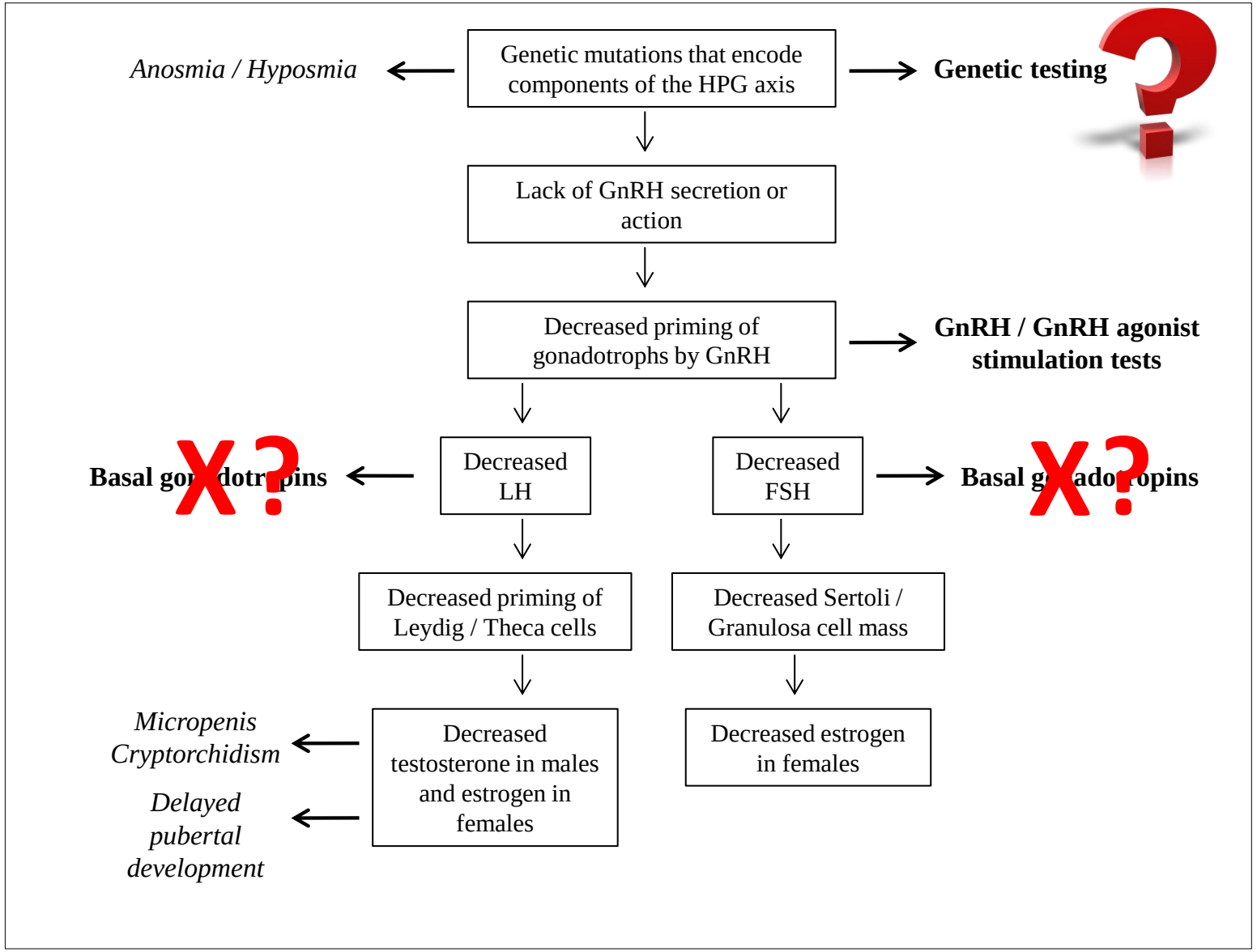
***JCEM*, Harrington J and Palmert MR ; 2012**

Differentiating: Rationale for diagnostic tests

Primary gonadal failure

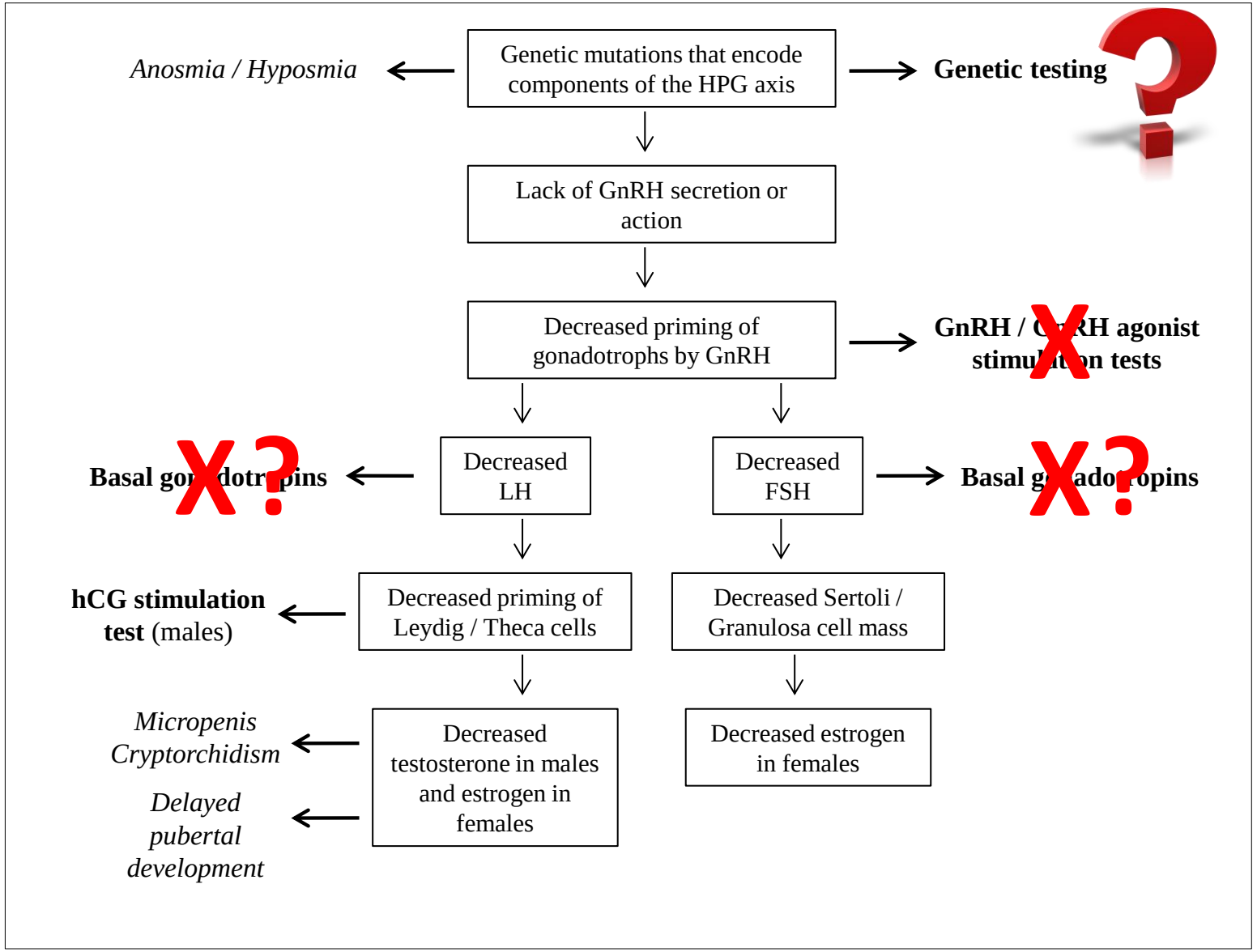
Arch Dis Child, Abitbol L, Zborovski S, Palmert MR; 2016

Differentiating: Rationale for diagnostic tests



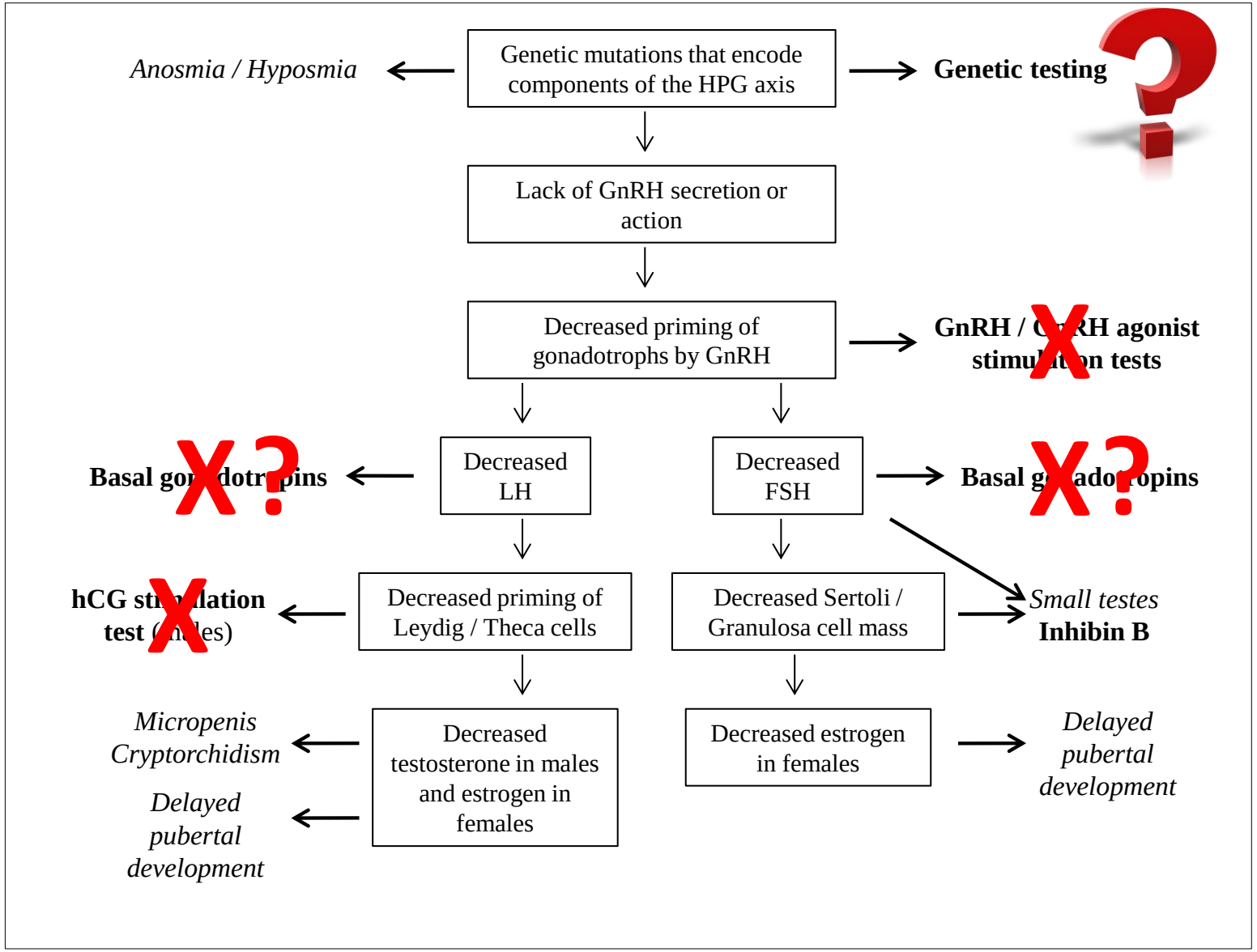
***JCEM*, Harrington J and Palmert MR ; 2012**

Differentiating: Rationale for diagnostic tests



***JCEM*, Harrington J and Palmert MR ; 2012**

Differentiating: Rationale for diagnostic tests



***JCEM*, Harrington J and Palmert MR ; 2012**

Rationale for Inhibin B as distinguishing test

Paediatric and adult-onset male hypogonadism

Andrea Salonia[1,2], Giulia Rastrelli[3], Geoffrey Hackett[4], Stephanie B. Seminara[5], Ilpo T. Huhtaniemi[6,7], Rodolfo A. Rey[8], Wayne J. G. Hellstrom[9], Mark R. Palmert[10,11], Giovanni Corona[3,12], Gert R. Dohle[13], Mohit Khera[14], Yee-Ming Chan[15,16] and Mario Maggi[3,17]*

NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2019) 5:38

Rationale for Inhibin B as distinguishing test

First report, Coutant R et al (JCEM 2010) reported value of < 35 pg/ml to be discriminatory—CHH

A subsequent report, Binder et al Clin Endo 2015, was also promising but reported a different cut off

- While inhibin B concentrations are lower in IHH, there is some overlap with boys with CDGP/SLDP

Rationale for Inhibin B as distinguishing test

First report, Coutant R et al (JCEM 2010) reported value of < 35 pg/ml to be discriminatory—CHH

A subsequent report, Binder et al Clin Endo 2015, was also promising but reported a different cut off

- While inhibin B concentrations are lower in IHH/CHH, there is some overlap with boys with CDGP/SLDP
- Combination of basal inhibin B (< 111pg/ml) and basal LH (<0.3IU/L) has been demonstrated to have 100% sensitivity and a 98% specificity to differentiate IHH from CDGP/SLDP

Differentiating CDGP/SLDP from IHH/CHH: Some Numbers

Human Reproduction, Vol.32, No.1 pp. 147–153, 2017
Advanced Access publication on December 6, 2016 doi:10.1093/humrep/dew294

human reproduction ORIGINAL ARTICLE *Puberty, ageing and HRT*

Congenital hypogonadotropic hypogonadism, functional hypogonadotropism or constitutional delay of growth and puberty? An analysis of a large patient series from a single tertiary center

Tero Varimo[1], Päivi J. Miettinen[1,2], Johanna Känsäkoski[3], Taneli Raivio[1,3,*], and Matti Hero[1]

Clinical and biochemical data met by
174 boys and 70 girls

Findings:

No feature of history among girls identified CHH

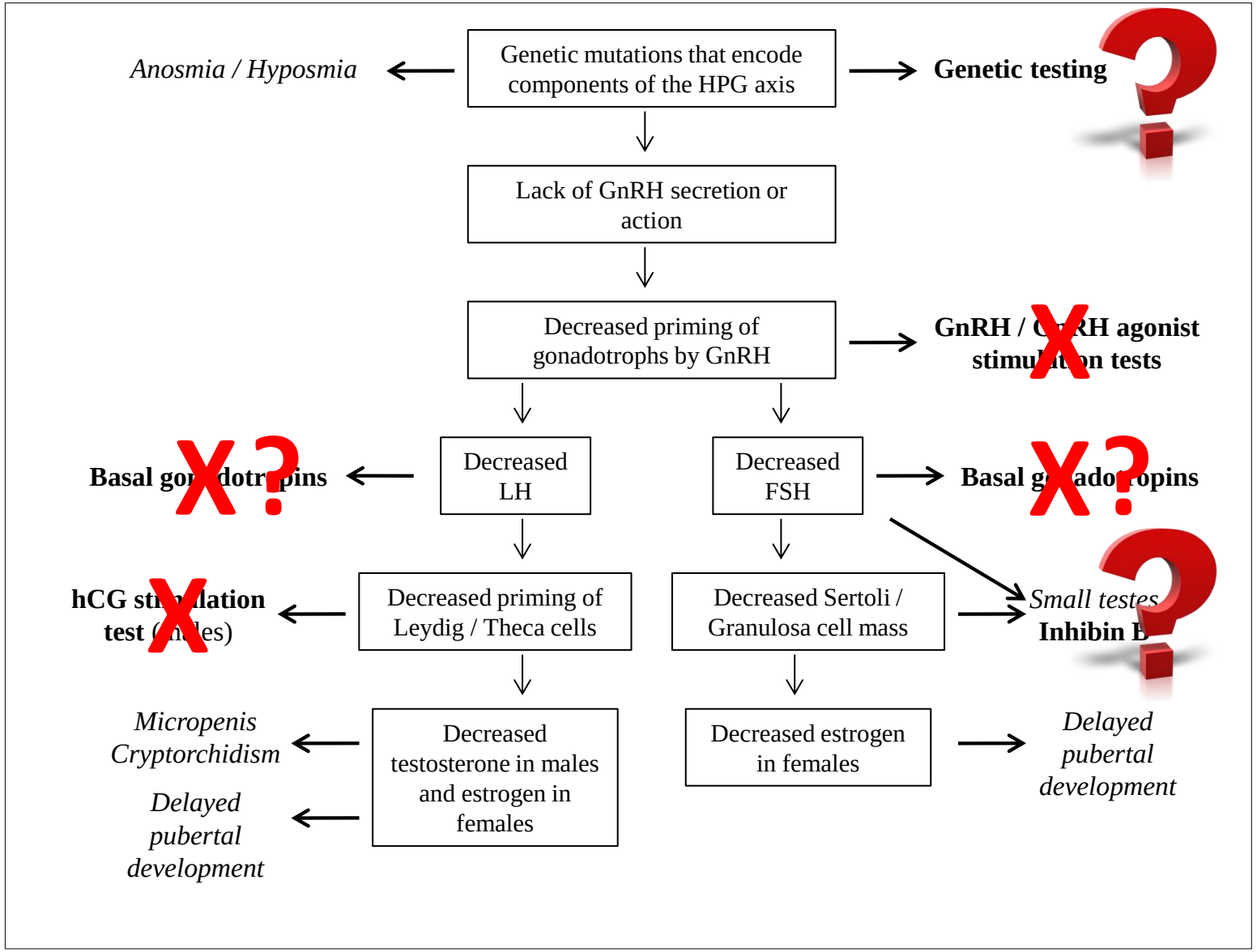
Among boys, cryptorchidism was associated with CHH (odds ratio of 17.2 (95% CI 3.4-85.4)

Testicular volume of ≤ 1 ml had sensitivity of 100% and specificity of 91% for CHH

What about tests? Not great……

Inhibin B cut-off of 61 ng/L had 83% specificity

Differentiating: Rationale for diagnostic tests



***JCEM*, Harrington J and Palmert MR ; 2012**

Newest Test on the Block

JCI insight

2018

CLINICAL MEDICINE

Divergent responses to kisspeptin in children with delayed puberty

Yee-Ming Chan,[1,2] Margaret F. Lippincott,[1] Temitope O. Kusa,[1] and Stephanie B. Seminara[1]

HPG Axis……Just a reminder……

Paediatric and adult-onset male hypogonadism

Andrea Salonia[1,2*], Giulia Rastrelli[3], Geoffrey Hackett[4], Stephanie B. Seminara[5], Ilpo T. Huhtaniemi[6,7], Rodolfo A. Rey[8], Wayne J. G. Hellstrom[9], Mark R. Palmert[10,11], Giovanni Corona[3,12], Gert R. Dohle[13], Mohit Khera[14], Yee-Ming Chan[15,16] and Mario Maggi[3,17]

NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2019) 5:38

Newest Test on the Block

JCI insight

2018

CLINICAL MEDICINE

Divergent responses to kisspeptin in children with delayed puberty

Yee-Ming Chan,[1,2] Margaret F. Lippincott,[1] Temitope O. Kusa,[1] and Stephanie B. Seminara[1]

Rationale/Design:

-Hypothesis: kisspeptin would elicit LH response in youth with intact/emerging reproductive endocrine function

--Verify intact axis by measurement of overnight pulses

-Compare kisspeptin response to GnRH response

Kisspeptin as a diagnostic test

Kisspeptin as a diagnostic test

Kisspeptin as a diagnostic test

In their study:

First morning LH
First morning FSH
Response to exogenous GnRH

All overlapped—CDGP/SLDP and IHH/CHH, at least partially

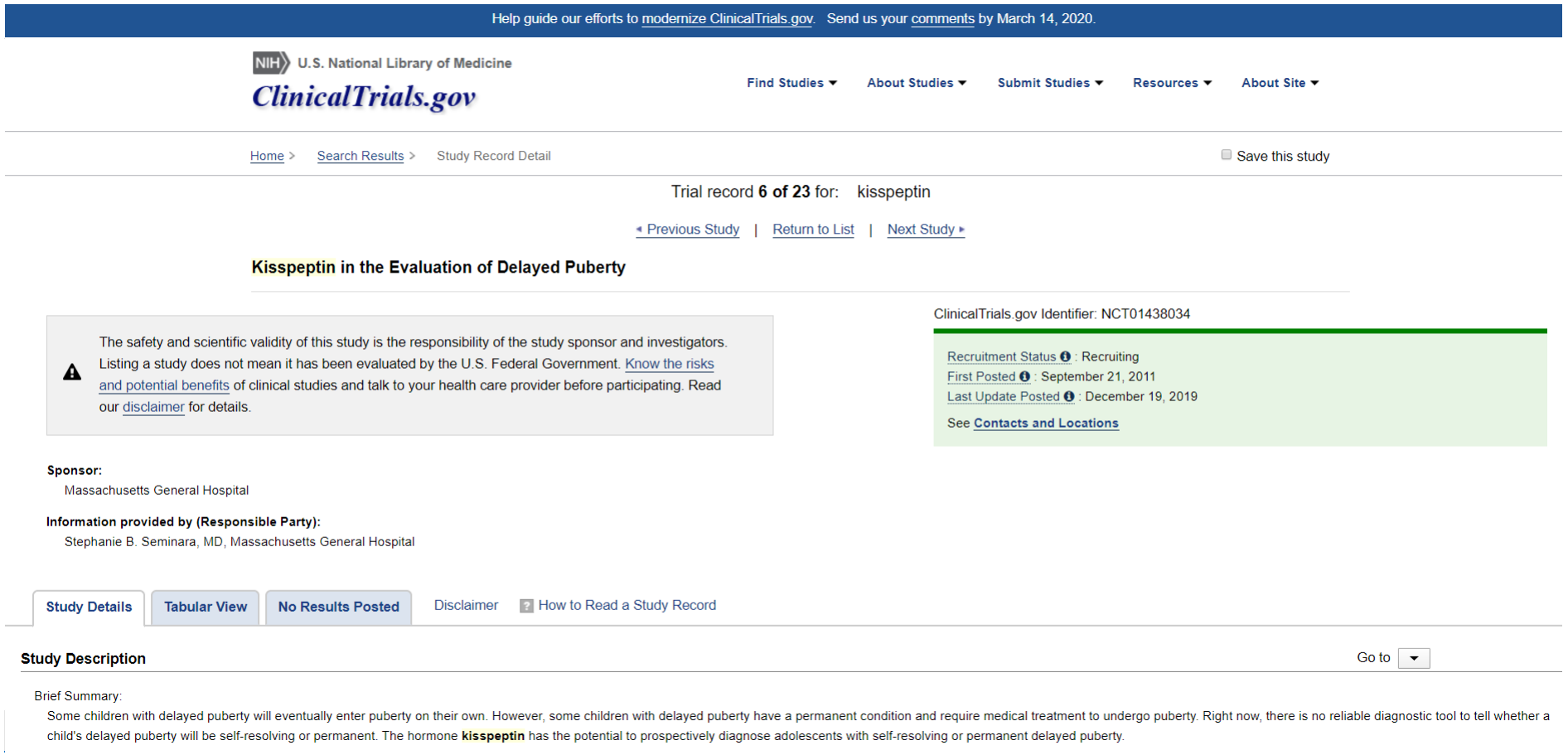
However,

Overnight LH pulses
Response to kisspeptin

CDGP/SLDP differed from IHH/CHH

Will this really work? Who knows? This study included only 15 subjects (4 girls and 11 boys)

Kisspeptin as a diagnostic test



Help guide our efforts to modernize ClinicalTrials.gov. Send us your comments by March 14, 2020.

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site

Home > Search Results > Study Record Detail

Save this study

Trial record **6 of 23** for: kisspeptin

◂ Previous Study | Return to List | Next Study ▸

Kisspeptin in the Evaluation of Delayed Puberty

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT01438034

Recruitment Status : Recruiting
First Posted : September 21, 2011
Last Update Posted : December 19, 2019

See Contacts and Locations

Sponsor:
Massachusetts General Hospital

Information provided by (Responsible Party):
Stephanie B. Seminara, MD, Massachusetts General Hospital

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description Go to

Brief Summary:
Some children with delayed puberty will eventually enter puberty on their own. However, some children with delayed puberty have a permanent condition and require medical treatment to undergo puberty. Right now, there is no reliable diagnostic tool to tell whether a child's delayed puberty will be self-resolving or permanent. The hormone **kisspeptin** has the potential to prospectively diagnose adolescents with self-resolving or permanent delayed puberty.

Objectives

1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotropic Hypogonadism (IHH/CHH), with focus on areas of overlap. Both disorders have strong genetic basis but causative genes are largely distinct

2. Recognize clinical features that may allow for discrimination of one condition from the other. History and physical exam can be informative, and some features are discriminatory

3. Discuss utility of diagnostic laboratory tests There is an increasing role for genetic testing, though not yet routine; other tests are being evaluated, including (??) inhibin B measurements and dynamic testing with Kisspeptin.

Objectives

1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotropic Hypogonadism (IHH/CHH), with focus on areas of overlap. Both disorders have strong genetic basis but causative genes are largely distinct

2. Recognize clinical features that may allow for discrimination of one condition from the other. History and physical exam can be informative, and some features are discriminatory

3. Discuss utility of diagnostic laboratory tests There is an increasing role for genetic testing, though not yet routine; other tests are being evaluated, including (??) inhibin B measurements and dynamic testing with Kisspeptin. MRI to be considered to rule out CNS abnormality if endogenous puberty has not started by age 15 in boys and 14 in girls. (Sometimes provides clue to IHH/CHH, e.g. absent olfactory bulbs.)

Let’s discuss a couple cases

A 14 yr old young man with history of delayed puberty……

Can we separate CDGP/SLDP from IHH/CHH?

Let's discuss a couple cases

A 14 yr old young man with history of delayed puberty and….

--bilateral cryptorchidism and micropenis at birth
--absent sense of smell
--development of pubic hair at age 11.5 yrs

And family history of father who started puberty late, experienced stalled development, and required treatment for masculinization and to induce fertility

And physical exam that reveals 1 cc testes

Which does he have: CDGP/SLDP or IHH/CHH?

Let's discuss a couple cases

A 14 yr old young man with history of delayed puberty and……

--no previous medical problems
--intact sense of small
--development of pubic hair at age 13 yrs

And family history of mom with menarche at age 15 yrs and father who grew in height after high school

And physical exam that reveals testes that are 3 cc in volume

Which does he have: CDGP/SLDP or IHH/CHH?

Summary

1. Genetically CDGP/SLDP and IHH/CHH represent two sides of the same (similar) coin

2. In some ways we can even differentiate heads from tails. But not always…

3. In unclear cases, time and evidence of spontaneous, endogenous puberty may be our best discriminatory “tests.”