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

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The Hospital for Sick Children
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None to declare
Objectives

1. Discuss the pathophysiology of Constitutional Delay of Growth and Puberty (CDGP/SLDP) and Isolated Hypogonadotrophic 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
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Which does he have: CDGP/SLDP or IHH/CHH?
Let’s discuss a couple cases

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

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

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

Janne Tornberg, Gerasimos P. Sykiotis, Kimberly Keefe, Lacey Plummer, Xuan Hoang, Janet E. Hall, Richard Quinton, Stephanie B. Seminara, Virginia Hughes, Guy Van Vliet, Stan Van Uum, William F. Crowley, Hiroko Habuchi, Koji Kimata, Nelly Pitteloud, and Hannes E. Bülow.
More and more genes are being identified as causes of IHH/CHH.

Heparan sulfate proteoglycans in extracellular matrix with idiopathic hypogonadotropic hypogonadism

Janne Tornberg¹, Gerasimos P. Sykiotis³, Richard Quinton⁵, Stephanie B. Seidel⁶, Hiroko Habuchi⁴, Koji Kimata⁵, Neal S. Sperling⁷, Robert A. Tuttle⁸, and Michael V. Schaison⁹

2017

Research Article

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

Cheng Xu¹, Andrea Messina³, Emmanuel Somm³, Hichem Miraoui³, Tarja Kinnunen³, James Acierno Jr³, Nicolas J Niederländer³, Justine Bouilly⁴, Andrew A Dwyer³,³, Yisrael Sidis³, Daniele Cassatella³, Gerasimos P Sykiotis³, Richard Quinton⁴, Christian De Geyter⁵, Mirjam Dirlewanger⁶, Valérie Schwitzgeb⁴, Trevor R Cole⁷, Andrew A Toogood⁸, Jeremy MW Kirk⁹, Lacey Plummer¹⁰, Urs Albrecht¹¹, William F Crowley Jr¹⁰, Moosa Mohammadi¹², Manuel Tena-Sempere¹³,¹⁴,¹⁵, Vincent Prevot¹⁶,¹⁷ & Nelly Pitteloud¹²,¹²
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

Elks et al. Nature Genetics, 2010

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

LETTER

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


doi:10.1038/nature13545

ARTICLE

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


Nature Communications 49, 834–841 (2017)
GWAS provide insight into common variants associated with age at menarche and voice breaking.

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

Felix R. Day1, Brendan Bulik-Sullivan2,3,4, Devid A. Hinds5, Hilary K. Finucane6,7, Joanne M. Murabito8,9, Joyce Y. Tung5, Ken K. Ong10,11, & John R.B. Perry1,11
GWAS provide insight into common variants associated with age at menarche and voice breaking

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

María C. Lardone, Alexander S. Busch, José L. Santos, Patricio Miranda, Susana Eyheramendy, Ana Pereira, Anders Juul, Kristian Almstrup, and Verónica Mericq
GWAS provide insight into common variants associated with age at menarche and voice breaking.
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GWAS provide insight into common variants associated with age at menarche and voice breaking

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

Huayun Hou¹,²,†, Liis Uusküla-Reimand¹,³,†, Maisam Makarem¹, Christina Corre¹, Shems Saleh¹,⁴, Ariane Metcalfe¹, Anna Goldenberg¹,⁴,‡, Mark R. Palmert¹,⁵,⁶,‡, and Michael D. Wilson¹,²,‡
Both CDGP/SLDP and IHH/CHH are Genetic Conditions

Common Variants:
GWAS Studies
400 loci
largely shared

Mutations: IHH/CHH
40 Genes
Both CDGP/SLDP and IHH/CHH are Genetic Conditions

400 loci mostly shared

♀♂

40 genes

Mutations: IHH/CHH

Common Variants: GWAS Studies

Common/Rare Variants

Frequency of Onset at Age

Multiple Inputs Affect Timing

General Health

Environment

Genetics

Age at Onset of Puberty

-2SD

-1SD

Mean

+1SD

+2SD
IGSF10 mutations dysregulate gonadotropin-releasing hormone neuronal migration resulting in delayed puberty

Sasha R Howard1,3, Leonardo Guasti1,3, Gerard Ruiz-Babot1, Alessandra Mancini1, Alessia David1, Helen L Strom1, Louise A Metherell1, Michael JE Sternberg1, Claudia P Cabrera2,4, Helen R Warren4,5, Michael R Barnes5,6, Richard Quinton6, Nicolas de Roux5,6, Jacques Young7,10,11,12, Anne Guirochet-Mantel1,10,11,12, Karolina Wehkalampi13, Valentina Andre13, Yoav Gozli13, Anna Carlone13,17 & Leo Dunkel1,7.
Sequencing studies uncovering genes that cause CDGP/SLDP

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

Sasha R Howard1,2, Leonardo Guasti1,3, Gerard Ruiz-Babot4, Alessandra Mancini1,5,6, Michael R Barnes2,5, Richard Quinton6, Nicolas de Roux7,8,9, Jacques Young10,11, Anne Guiochon-Mantel10,11,12, Karolina Wehkalmapi1, Valentina Andrei13, Yael Weisman14, Anna Carbone15,17 & Leo Dunkel1,3

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

Alessandra Mancini1, Sasha R. Howard1, Claudia P. Cabrera2, Michael R. Barnes2, Alessia David3, Karolina Wehkalmapi1, Sabine Heger5, Alejandro Lomniczi6, Leonardo Guasti1,†, Sergio R. Ojeda6,† and Leo Dunkel1,†,∗
Both CDGP/SLDP and IHH/CHH are Genetic Conditions

- **Common Variants:**
  - GWAS Studies: 400 loci mostly shared
  - Mutations: IHH/CHH 40 genes

- **Common/Rare Variants—few genes**
Both CDGP/SLDP and IHH/CHH are Genetic Conditions

Common Variants: GWAS Studies
- 400 loci mostly shared

Mutations: IHH/CHH
- 40 genes

Common/Rare Variants—few genes

What are the genes? How much overlap?
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!
Both CDGP/SLDP and IHH/CHH are Genetic Conditions

- Common Variants: GWAS Studies
  - 400 loci
  - mostly shared
- Mutations: IHH/CHH
  - 40 genes

What are the genes?
How much overlap?

Not much!
IGSF10 mutation releasing hormone delayed puberty

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

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 Dunkel1*
Sequencing studies uncovering genes that cause CDGP/SLDP

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 \textit{FGFR1}, \textit{KAL1}, \textit{TAC3}) (53% vs 12%)
Sequencing studies uncovering genes that cause CDGP/SLDP

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--IHH causing variants enriched in family members with DP compared with family members without DP (variants in \textit{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 (\textit{IS17RD} and \textit{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

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

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

What are the genes?
How much overlap?
Not Much!
Some genetic causes of disorders of puberty overlap; most don’t
CDGP & IHH: On a Spectrum but also Distinct

Genetic Disorder
Monogenic
40+ genes

Polygenic Trait
GWAS
400+ loci
Few overlap with IHH/CHH

Partial IHH—Adult Onset
Reversible IHH
Severe DP
CDGP
Pubertal timing in general population

Two sides of the “same coin.”

Greater Genetic Burden

Genetic Disorder
Polygenic
40+ genes
Few overlap with GWAS Or CDGP/SLDP
Objectives

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Differentiating CDGP/SLDP from IHH/CHH

- Genetic mutations that encode components of the HPG axis
- Lack of GnRH secretion or action
- Decreased priming of gonadotrophs by GnRH
- Decreased LH
- Decreased FSH
- Decreased priming of Leydig/Teca cells
- Decreased testicular development in males
- Decreased estrogen in females
- Decreased Sertoli/Granulosa cell mass
- Decreased estrogen in females
- Delayed pubertal development

JCEM, Harrington J & Palmert MR; 2012
Differentiating CDGP/SLDP from IHH/CHH

Anosmia/Hyposmia

- Genetic mutations that encode components of the HPG axis
- Lack of GnRH secretion or action
- Decreased priming of gonadotrophs by GnRH
  - Decreased LH
  - Decreased FSH
  - Decreased priming of Leydig/Theca cells
    - Decreased testosterone in males and estrogen in females
  - Decreased Sertoli/Granulosa cell mass
    - Decreased estrogen in females
- Small testes
- Delayed pubertal development

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
Histories pointing to syndromic CHH can also be useful
Physical exams complement histories
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 $\leq 1$ ml had sensitivity of 100% and specificity of 91% for IHH/CHH
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3. Discuss utility of diagnostic laboratory tests.
Differentiating: Rationale for diagnostic tests

Anosmia / Hyposmia

Genetic mutations that encode components of the HPG axis

Lack of GnRH secretion or action

Decreased priming of gonadotrophs by GnRH

Decreased LH

Decreased Sertoli / Granulosa cell mass

Decreased priming of Leydig / Theca cells

Decreased estrogen in females

Decreased testosterone in males and estrogen in females

Micropenis

Cryptorchidism

Delayed pubertal development

Genetic testing

Basal gonadotropins

hCG stimulation (males)

Small testes

Inhibin B

Delayed pubertal development

JCEM, Harrington J and Palmert MR ; 2012
Specific clinical features may help prioritize genetic screening
Differentiating: Rationale for diagnostic tests

European Consensus: Nat Rev Endocrinology, 2015
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

- Anosmia / Hyposmia
  - Lack of GnRH secretion or action
  - Decreased priming of gonadotrophs by GnRH
    - Decreased LH
    - Decreased FSH
    - Decreased priming of Leydig / Theca cells
    - Decreased Sertoli / Granulosa cell mass
    - Decreased estrogen in females

- Basal gonadotropins
  - Decreased LH
  - Decreased FSH

- Micropenis
- Cryptorchidism
- Delayed pubertal development
- Decreased testosterone in males and estrogen in females

Genetic mutations that encode components of the HPG axis

Genetic testing
Differentiating: Rationale for diagnostic tests

Primary gonadal failure
Genetic mutations that encode components of the HPG axis

Lack of GnRH secretion or action

Decreased priming of gonadotrophs by GnRH

Decreased priming of Leydig / Theca cells

Decreased testosterone in males and estrogen in females

Decreased Sertoli / Granulosa cell mass

Decreased estrogen in females

Basal gonadotropins

Micropenis
Cryptorchidism

Delayed pubertal development

Anosmia / Hyposmia

Genetic testing

GnRH / GnRH agonist stimulation tests

X?

Basal gonadotropins

X?
Genetic mutations that encode components of the HPG axis

Lack of GnRH secretion or action

Decreased priming of gonadotrophs by GnRH

Decreased LH

Decreased FSH

Decreased priming of Leydig / Theca cells

Decreased Sertoli / Granulosa cell mass

Decreased testosterone in males and estrogen in females

Decreased estrogen in females

Anosmia / Hyposmia

Basal gonadotropins

hCG stimulation test (males)

Micropenis
Cryptorchidism

Delayed pubertal development

GnRH / GnRH agonist stimulation tests

Basal gonadotropins

Genetic testing

JCEM, Harrington J and Palmert MR ; 2012
Genetic mutations that encode components of the HPG axis

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Genetic testing

GnRH / GnRH agonist stimulation tests

Small testes

Inhibin B

Delayed pubertal development

Anosmia / Hyposmia

Basal gonadotropins

hCG stimulation test (males)

Micropenis
Cryptorchidism

Delayed pubertal development

JCEM, Harrington J and Palmert MR ; 2012
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
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.
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
Genetic mutations that encode components of the HPG axis

Lack of GnRH secretion or action

Decreased priming of gonadotrophs by GnRH

 Decreased LH

 Decreased FSH

Basal gonadotropins

hCG stimulation test (males)

Micropenis
Cryptorchidism
Delayed pubertal development

Anosmia / Hyposmia

Genetic testing

GnRH / GnRH agonist stimulation tests

Small testes
Inhibin B

Delayed pubertal development

Decreased Sertoli / Granulosa cell mass

Decreased estrogen in females

JCEM, Harrington J and Palmert MR; 2012
Divergent responses to kisspeptin in children with delayed puberty

Yee-Ming Chan, Margaret F. Lippincott, Temitope O. Kusa, and Stephanie B. Seminara
HPG Axis......Just a reminder......
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

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. Learn more.

Study Details

Sponsor:
Massachusetts General Hospital

Information provided by (Responsible Party):
Stephanie G. Seminars, MD, Massachusetts General Hospital

Study Description

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.
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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?
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.”