Test Definition: CAH21

CAH 21-Hydroxylase Profile

Overview

Useful For

Preferred screening test for congenital adrenal hyperplasia (CAH) that is caused by 21-hydroxylase deficiency

Part of a battery of tests to evaluate females with hirsutism or infertility, which can result from adult-onset CAH

Genetics Test Information

Preferred screening test for congenital adrenal hyperplasia (CAH) that is caused by 21-hydroxylase deficiency. Also useful as part of a battery of tests to evaluate females with hirsutism or infertility, which can result from adult-onset CAH.

Profile Information

Test ID	Reporting Name	Available Separately	Always Performed
CORTI	Cortisol, S	Yes, (order CINP)	Yes
ANDRO	Androstenedione, S	Yes, (order ANST)	Yes
H17	17-Hydroxyprogesterone, S	Yes, (order OHPG)	Yes

Method Name

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

Portions of this test are covered by patent(s) held by Quest Diagnostics

NY State Available

Yes

Specimen

Specimen Type

Serum Red

Specimen Required

Container/Tube: Red top

SpecimenVolume: 0.6 mL

Collection Instructions:

1. Morning (8 a.m.) and afternoon (4 p.m.) specimens are preferred.

2. Include time of draw.

Additional Information: If multiple specimens are drawn, send separateorder for each specimen.

Forms

If not ordering electronically, complete, print, and send an Inborn Errors of Metabolism Test Request (T798) with the specimen.

Specimen Minimum Volume

0.25 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	OK
Other	Serum gel tube

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum Red	Refrigerated (preferred)	14 days	
	Frozen	28 days	
	Ambient	7 days	

Clinical and Interpretive

Clinical Information

The cause of congenital adrenal hyperplasia (CAH) is an inherited genetic defect that results in decreased formation of 1 of the many enzymes that are involved in the production of cortisol. The enzyme defect results in reduced glucocorticoids and mineralocorticoids, and elevated 17-hydroxyprogesterone (OHPG) and androgens. The resulting hormone imbalances can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. Adult-onset CAH may result in hirsutism or infertility in females.

The adrenal glands, ovaries, testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 positions to produce cortisol. Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and the feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequently, increased pituitary release of ACTH increases production of OHPG. In contrast, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-ol-dehydrogenase (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone, respectively.

Most (90%) cases of CAH are due to mutations in the 21-hydroxylase gene (*CYP21A2*). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione with decreased cortisol. By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (DCRN / 11-Deoxycorticosterone, Serum), respectively, are necessary for diagnosis.

OHPG is bound to both transcortin and albumin, and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests than pregnanetriol measurement are available to diagnose disorders of steroid metabolism.

The CAH profile allows the simultaneous determination of OHPG, androstenedione, and cortisol. These steroids can also be ordered individually (OHPG / 17-Hydroxyprogesterone, Serum; ANST / Androstenedione, Serum; CINP / Cortisol, Serum, LC-MS/MS).

Reference Values

CORTISOL

5-25 mcg/dL (a.m.)

2-14 mcg/dL (p.m.)

Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.

Petersen KE: ACTH in normal children and children with pituitary and adrenal diseases. I. Measurement in plasma by radioimmunoassay-basal values. Acta Paediatr Scand 1981;70:341-345

ANDROSTENEDIONE

PEDIATRICS*
Premature infants
26-28 weeks, day 4: 92-282 ng/dL
31-35 weeks, day 4: 80-446 ng/dL
Full-term infants
1-7 days: 20-290 ng/dL
1 month-1 year: <69 ng/dL

Males*

Tanner Stages	Age (Years)	Reference Range (ng/dL)
Stage I (prepubertal)	<9.8	<51
Stage II	9.8-14.5	31-65
Stage III	10.7-15.4	50-100
Stage IV	11.8-16.2	48-140
Stage V	12.8-17.3	65-210

Females*

Tanner Stages	Age (Years)	Reference Range (ng/dL)
Stage I (prepubertal)	<9.2	<51
Stage II	9.2-13.7	42-100
Stage III	10.0-14.4	80-190
Stage IV	10.7-15.6	77-225
Stage V	11.8-18.6	80-240

*Source: Androstenedione. In Pediatric Reference Ranges. Fourth Edition. Edited by SJ Soldin, C Brugnara, EC Wong. Washington, DC, AACC Press, 2003, pp 32-34

ADULTS
Males: 40-150 ng/dL
Females: 30-200 ng/dL

17-HYDROXYPROGESTERONE

Children

Preterm infants: Preterm infants may exceed 630 ng/dL, however, it is uncommon to see levels reach 1,000 ng/dL.

Term infants

0-28 days: <630 ng/dL

Levels fall from newborn (<630 ng/dL) to prepubertal gradually within 6 months.

Prepubertal males: <110 ng/dL

Prepubertal females: <100 ng/dL

Adults

Males: <220 ng/dL

Females

Follicular: <80 ng/dL

Luteal: <285 ng/dL

Postmenopausal: <51 ng/dL

Note: For pregnancy reference ranges, see:Soldin OP, Guo T, Weiderpass E, et al:Steroid hormone levels in pregnancy and 1 year postpartum using isotope dilution tandem mass spectrometry. Fertil Steril 2005 Sept;84(3):701-710

Interpretation

Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (*CYP21A2*) mutations usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-Hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested.

In the much less common *CYP11A* mutation, androstenedione levels are elevated to a similar extent as in *CYP21A2* mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated.

Also less common is 3 beta-hydroxysteroid dehydrogenase type 2 (3 beta HSD-2) deficiency, characterized by low cortisol and substantial elevations in dehydroepiandrosterone sulfate (DHEA-S) and 17-alpha-hydroxypregnenolone, while androstenedione is either low, normal, or rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3 beta HSD-1).

In the very rare steroidogenic acute regulatory protein deficiency, all steroid hormone levels are low and cholesterol is elevated.

In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are increased.

The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. OHPG is measured to guide treatment, but this test correlates only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable.

Cautions

Androstenedione and, to a lesser degree, dehydroepiandrosterone sulfate supplements can result in elevations of serum androstenedione level. With large androstenedione doses of 300 to 400 mg/day, serum androstenedione levels can almost double in some patients. Testosterone levels and, particularly in men, estrone and estradiol levels may also increase, but to a much lesser degree.

This test provides merely supplementary information and should, therefore, never be employed as the sole diagnostic tool.

Clinical Reference

1. Von Schnakenburg K, Bidlingmaier F, Knorr D: 17-hydroxyprogesterone, androstenedione, and testosterone in normal children and in prepubertal patients with congenital adrenal hyperplasia. Eur J Pediatr 1980;133(3):259-267

2. Sciarra F, Tosti-Croce C, Toscano V: Androgen-secreting adrenal tumors. Minerva Endocrinol 1995;20(1):63-68

3. Collett-Solberg PF: Congenital adrenal hyperplasia: from genetics and biochemistry to clinical practice, part I. Clin Pediatr 2001;40(1):1-16

4. Speiser PW, Azziz R, Baskin LS, et al: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2010;95(9):4133-4160; Available at: jcem.endojournals.org

Performance

Method Description

Deuterated stable isotopes (d4-cortisol, d7-androstenedione, d8-17-hydroxyprogesterone) are added to a 0.1-mL serum sample as internal standards. Cortisol, androstenedione, 17-hydroxyprogesterone, and the internal standards are extracted from specimens using a Strata X 30-mg cartridge and eluted from the cartridge with methanol. The extracts are then dried down under nitrogen, reconstituted with 75 mcL of 70/30 methanol/H2O containing 1 g/mL of estriol and analyzed by liquid chromatography-tandem mass spectrometry using multiple-reaction monitoring. A calibration curve is generated by spiking standards into a bovine serum albumin buffer and extracted with each batch of new working internal standard. Controls are extracted with each batch.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Monday through Friday; 4 p.m.

Analytic Time

2 days

Maximum Laboratory Time

5 days

Specimen Retention Time

See Individual Unit Codes

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

82157-Androstenedione

82533-Cortisol; total

83498-Hydroxyprogesterone, 17-d

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
CAH21	CAH 21-Hydroxylase Profile	In Process

Result ID	Test Result Name	Result LOINC Value
30041	Androstenedione, S	1854-9
30042	17-Hydroxyprogesterone, S	1668-3
30040	Cortisol, S	2143-6
30070	AM Cortisol	9813-7
30071	PM Cortisol	9812-9