

Prader-Willi Syndrome Genetic Testing

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Introduction

Prader-Willi syndrome genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Chromosomal Microarray [BAC], Constitutional	81228
Chromosomal Microarray [CGH], Constitutional	S3870
Chromosomal Microarray [SNP], Constitutional	81229
Chromosome 15 Uniparental Disomy	81402
Cytogenomic (Genome-wide) Analysis for Constitutional Chromosomal Abnormalities; Interrogation of Genomic Regions for Copy Number and Loss-of-heterozygosity Variants, Low-pass Sequencing Analysis	81349
FISH Probe for 15q11-q13 Deletion	88271
Imprinting Center Defect Analysis	81479
Imprinting Center Known Familial Mutation Analysis	81403
SNRPN/UBE3A Methylation Analysis	81331

Criteria

Introduction

Requests for Prader-Willi syndrome genetic testing are reviewed using these criteria.

Imprinting Center (IC) Known Familial Mutation Analysis

- Genetic Counseling:
 - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
 - No previous IC defect analysis testing that would detect the familial mutation, AND
- Family History:
 - Familial IC defect mutation known in blood relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SNRPN Methylation Analysis

- Genetic Counseling:
 - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
 - No previous SNRPN methylation analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Neonatal hypotonia and feeding problems (i.e., poor suck), OR
 - Developmental delay/intellectual disability, with some combination of the following:
 - Neonatal hypotonia, or
 - Feeding problems (i.e., poor suck) or poor growth in infancy, or
 - Obesity and/or food-related behavior problems (i.e., hyperphagia; obsession with food), or
 - Characteristic facial features, or
 - Hypogonadism AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Deletion Analysis (FISH Analysis for 15q11-q13 Deletion or Chromosomal Microarray)

- Genetic Counseling:

- Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
 - No previous 15q11-q13 deletion analysis, and
 - No previous chromosomal microarray, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Neonatal hypotonia and feeding problems (i.e., poor suck), OR
 - Developmental delay/intellectual disability, with some combination of the following:
 - Neonatal hypotonia, or
 - Feeding problems (i.e., poor suck) or poor growth in infancy, or
 - Obesity and/or food-related behavior problems (i.e., hyperphagia; obsession with food) or
 - Characteristic facial features, or
 - Hypogonadism, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Chromosome 15 Uniparental Disomy (UPD)

- Genetic Counseling:
 - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
 - SNRPN methylation analysis results are abnormal, and
 - 15q11-q13 deletion analysis is negative, and
 - No previous chromosome 15 UPD studies, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Meets clinical criteria for SNRPN methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Imprinting Center (IC) Defect Analysis

- Genetic Counseling:

- Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
 - SNRPN methylation analysis results are abnormal, and
 - 15q11-q13 deletion analysis is negative, and
 - Previous chromosome 15 UPD studies negative, and
 - No previous IC analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
 - Meets clinical criteria for SNRPN methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

What is Prader-Willi syndrome?

Definition

Prader-Willi syndrome (PWS) is a multi-system genetic disorder that is due to a loss of specific genes on chromosome 15. Infants present with low muscle tone (hypotonia) and feeding difficulties which can result in failure to thrive. In the childhood years, children with Prader-Willi syndrome develop an increased appetite with decreased satiety which, without proper management, results in obesity and an increased risk of type 2 diabetes. Cognitive impairment and behavioral problems are usually present in addition to an increased risk for specific medical diagnoses.¹

Prevalence

The prevalence is estimated to be 1/10,000 to 1/30,000.¹

Symptoms

Prader-Willi syndrome is characterized by:^{1,2}

- Decreased muscle tone (hypotonia) and feeding difficulties in early infancy
- Strabismus
- Insatiable appetite in childhood that often results in obesity
- Developmental delay
- Short stature
- Behavior problems
- Small hands and feet
- Underdeveloped genitalia and infertility

Cause

The features of Prader-Willi syndrome are caused when the Prader-Willi critical region (PWCR) on chromosome 15 is only inherited from the mother and there is no copy from the father.

Prader-Willi syndrome can be caused by a chromosome deletion, uniparental disomy (two copies of the maternal chromosome), or imprinting center (IC) defect. There are several genetic tests available that can help diagnose Prader-Willi syndrome.¹⁻⁴

Diagnosis

If an individual has all of the clinical findings denoted below at the indicated age, diagnostic testing is recommended.^{1,5} Prader-Willi syndrome is established in individuals who have abnormal DNA methylation analysis consistent with absence of the paternal contribution of the PWCR.¹

Neonatal period

- Hypotonia with poor suck

One month to two years

- Hypotonia with poor appetite and poor suck
- Developmental delay

Two to six years

- Hypotonia with history of poor suck
- Developmental delay

Six year to 12 years

- History of hypotonia with poor suck
- Developmental delay
- Excessive eating and, if uncontrolled, central obesity

13 years to adulthood

- Cognitive impairment which is most often mild intellectual disability
- Excessive eating and, if uncontrolled, central obesity
- Hypothalamic hypogonadism and/or typical behavior problems

Determination of recurrence risk following a diagnosis of PWS may require additional genetic testing of the individual and testing of one or both parents depending on the identified molecular cause.⁴

Management

Individuals with Prader-Willi syndrome have age-specific medical needs. Some of the more common treatments and management include: ¹

Infancy

- Ensuring adequate nutrition through feeding support
- Physical therapy for improved muscle strength
- Screening for strabismus
- Managing cryptorchidism through hormonal and surgical treatments
- Growth hormone treatment may be initiated in infancy

Childhood through adulthood

- Monitoring of daily food intake
- Determining if calcium and vitamin D supplementation is indicated
- Encouraging physical activity
- Growth hormone replacement therapy
- Evaluating for sleep disturbance
- Educational planning
- Addressing behavioral concerns with applied behavioral analysis therapy, behavior management strategies, and/or medication
- Assessing for hypothyroidism
- Assessing for scoliosis

Teenage years

- Sex hormone replacement at puberty as indicated

Adulthood

- Housing in a group home familiar with the needs of individuals with PWS to regulate behavior and weight management
- Growth hormone may help with maintaining muscle bulk
- Evaluate for possible osteoporosis every two years

Survival

Obesity and the associated complications contribute to the higher mortality rate in individuals with Prader-Willi syndrome. The current death rate is 1.25% per year and is lower than previous reports. The decrease is attributed to improved management. ¹

Test information

Introduction

Testing for Prader-Willi syndrome may include known familial mutation analysis, SNRPN methylation analysis, chromosomal microarray, FISH analysis for 15q11-q13 deletion, chromosome 15 uniparental disomy (UPD), or imprinting center defect analysis.

Known Familial Mutation Analysis: Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing. Analysis for known familial mutations typically includes only the specific mutation identified in the family, but if available, a targeted mutation panel that includes the familial mutation(s) may be performed.

SNRPN/UBE3A Methylation Analysis: This test is typically the first test in the evaluation of both Angelman syndrome (AS) and Prader-Willi syndrome (PWS). It will detect about 80% of individuals with AS and greater than 99% of individuals with PWS. However, DNA methylation analysis does not identify the underlying cause, which is important for determining the risk to future siblings. This risk ranges from less than 1% to up to 50%, depending on the genetic mechanism. Follow-up testing for these causes may be appropriate.

Chromosomal Microarray or FISH Analysis for 15q11-q13 Deletion: If DNA methylation analysis for AS or PWS is abnormal, deletion analysis is typically the next step. Approximately 70% of cases of both AS and PWS have a deletion in one copy of chromosome 15 involving the 15q11.2-q13 region. FISH (fluorescence in situ hybridization) analysis and chromosomal microarray (CMA, array CGH) can detect such deletions. If CMA has already been done, FISH is not likely to be necessary.

Chromosome 15 Uniparental Disomy (UPD): If DNA methylation analysis is abnormal but deletion analysis is normal, UPD analysis may be an appropriate next step for evaluation of both AS and PWS. About 28% of PWS cases are due to maternal UPD (both chromosome 15s are inherited from the mother). About 7% of cases of AS are due to paternal UPD (both chromosome 15s are inherited from the father). Both parents must be tested to diagnose UPD.

Imprinting Center Defect Analysis: This test may be considered in the evaluation of AS and PWS when methylation is abnormal, but FISH (or array CGH) and UPD studies are normal. Individuals with such results are presumed to have an imprinting defect. An abnormality in the imprinting process has been described in a minority of cases. However, imprinting center deletions may be familial, and if familial, the recurrence risk can be up to 50%.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Prader-Willi syndrome testing.

Prader-Willi Syndrome Association

The Prader-Willi Syndrome Association (PWSA, 2023) stated the following in regards to PWS genetic testing and diagnosis.³

- "The physical examination and history are very important parts of making the diagnosis and should be done before genetic testing. All hypotonic children in the Neonatal Intensive Care Unit (NICU) who do not have a diagnosis should be tested for PWS."
- "All persons suspected of having PWS should be tested with a DNA methylation analysis. This test detects nearly all (>99%) cases of PWS."

Selected Relevant Publications

An expert-authored review (2023) stated the following regarding testing for Prader-Willi syndrome:¹

- Methylation-specific analysis ... can establish the diagnosis of PWS by identification of maternal-only imprinting at 15q11.2-q13 but cannot identify the cause of the abnormal DNA methylation."
- Additional testing is necessary to establish the mechanism of disease and recurrence risk.
- This review recommended the following test strategy:
 - Methylation analysis and deletion analysis (Oligo-SNP Array) as first-tier testing.
 - If methylation is normal and deletion analysis is abnormal but does not include the SNORD116 gene cluster, workup for a chromosomal abnormality may be considered.
 - Absence of heterozygosity (AOH) analysis of chromosome 15: If only the maternal methylated imprint is present but deletion testing is normal, AOH analysis is recommended.
 - DNA polymorphism analysis: If only the maternal methylated imprint is present but deletion and AOH analysis are normal, DNA polymorphism analysis is recommended.

References

Introduction

These references are cited in this guideline.

1. Driscoll DJ, Miller JL, Schwartz S, Cassidy SB. Prader-Willi Syndrome. 1988 Oct 6 [Updated 2023 Nov 2]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1330/>
2. Butler MG, Miller JL, Forster JL. Prader-Willi Syndrome - Clinical genetics, diagnosis and treatment approaches: An update. *Curr Pediatr Rev*. 2019;15(4):207-244.
3. Prader-Willi Syndrome Association (USA). Testing and diagnosis. Updated April 10, 2023. <https://www.pwsausa.org/wp-content/uploads/2023/04/TESTING-AND-DIAGNOSIS-PWSA-USA-3-3-2023-DJD-revisions.pdf>.
4. Beygo J, Buiting K, Ransden SC, et al. Update of the EMQN/ACGS best practice guidelines for molecular analysis of Prader-Willi and Angelman syndromes. *Eur J Hum Genet*. 2019;27(9): 1326-1340.
5. Gunay-Aygun M, Schwartz S, Heeger S, et al. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. *Pediatrics*. 2001;108(5):E92.