EGL Genetics | Eurofins Clinical Diagnostics

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Proportionate Short Stature/Small for Gestational Age Panel: Russell-Silver Panel, UPD14 Analysis, Sequencing, and CNV Analysis

Test Code: MM011
Turnaround time: 6 weeks
CPT Codes: 81406 x1, 81401 x1, 81402 x1

Condition Description

Short stature is defined as a height less than two standard deviations from the mean for a given age and gender (i.e height is less than the third percentile on standard growth curves). Based on the clinical presentation, short stature can be broken down into three subcategories; small for gestational age (SGA), non-SGA proportionate short stature, and disproportionate short stature (e.g. skeletal dysplasias). SGA, which is sometimes called intrauterine growth restriction (IUGR), is used to describe a fetal weight below the 10th percentile when controlled for gender and gestation age. It can also be used to describe a newborn whose birth weight is below the 10th percentile.

Short stature can have either a non-genetic or a genetic etiology. Examples of non-genetic causes of short stature are malnutrition, infections, growth hormone deficiency and chronic diseases such as kidney disease and congenital heart disease. Examples of genetic causes of short stature are chromosome abnormalities such as Turner syndrome (45,X), epigenetic abnormalities such as aberrant methylation at 11p15.5 and uniparental disomy, as well as autosomal dominant, autosomal recessive and X-linked genetic defects. Short stature due to genetic causes can be an isolated finding or part of the clinical spectrum of a genetic syndrome.

This version of the short stature panel is comprised of three separate tests: a next generation sequencing (NGS) panel testing for syndromic and non-syndromic causes of short stature, the Russell-Silver panel (*H19* methylation and UPD7), and UPD14 analysis. For the complete version of the short stature panel, please see the Proportionate Short Stature/Small for Gestation Age Panel: Comprehensive Panel webpage.

Please note that this panel only includes testing for SGA and non-SGA proportionate short stature subcategories and does not include testing for disproportionate short stature (e.g. skeletal dysplasias).

In addition, this panel does not include testing for growth hormone deficiency, which may be an integral part of the workup for an individual with short stature.

References:

- Johnston Rohrbasser (2011). *Horm Res Paediatr*, 76: 13-16.
- Wit *et al.* (2011). *Best Pract Res Cl En*, 25:1-17.

Genes

ATRX, BLM, BTK, CREBBP, CUL7, DHCR7, EP300, ERCC6, ERCC8, FGD1, GH1, GHR, GHRHR, GLI2, HESX1, IGF1, IGF1R, INSR, KDM6A, KMT2D, KRAS, LHX3, NBN, NIPBL, PITX2, POU1F1, PROP1, PTPN11, RAF1, ROR2, RPS6KA3, SHOX, SMARCAL1, SMC1A, SMC3, SOS1, SOX2, SOX3, SRCAP, STAT5B, TBCE, THRB, TRIM37, WRN

Indications

This test is indicated for:

- Individuals with a clinical diagnosis of short stature.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Copy Number Analysis: Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

Russell-Silver Panel: Methylation-specific MLPA (MS-MLPA) is used to test for hypomethylation of DMR1 at 11p15 for RSS. One advantage of MS-MLPA is that it not only detects DNA methylation abnormalities (epimutations), similar to Southern blot and quantitative methylation sensitive PCR, but it will also detect deletions and duplications (CNVs) of the 11p15 region. The presence of a CNV can increase the recurrence risk from that of the general population up to a 50% risk. Both methylation and CNVs will be reported from this analysis.

UPD14 Analysis: DNA methylation specific PCR assay targeting the differentially methylated region (DMR) upstream of the MEG3 gene on chromosome 14q32.2 is used to test for maternal or paternal uniparental disomy of chromosome 14 (matUPD14, patUPD14). Parental samples are NOT required for patUPD14 analysis, but may be requested to confirm a diagnosis.

Detection

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Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

Copy Number Analysis: The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

Russell-Silver Panel: Hypomethylation of *H19* is expected to detect up to 35% of individuals with a clinical diagnosis of SRS. Maternal uniparental disomy (UPD) for chromosome 7 will be detected in an additional 10% of patients with a clinical diagnosis, for a total detection of up to 45%.

Specimen Requirements

Submit only 1 of the following specimen types

Type: DNA, Isolated

Specimen Requirements:
Microtainer
12μg
Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/μL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old: 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Related Tests

- Individual sequencing analysis is available for the *SHOX, NIPBL, SMC1A, CREBBP, EP300, DHCR7, KMT2D, PTPN11, RAF1, KRAS, SOS1,* and *FGD1* genes.
- Variations of this panel are available if previous genetic testing has been performed. Variations include:
  -PSS/SGA Panel: Comprehensive
  -PSS/SGA Panel: EmArray Cyto + SNP & NGS
  -PSS/SGA Panel: Russell-Silver Panel & NGS
  -PSS/SGA Panel: NGS
- A next generation sequencing panel is also available for Noonan syndrome and related disorders.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Proportionate Short Stature/Small for Gestational Age: Deletion/Duplication Panel.