Proportionate Short Stature/Small for Gestational Age Panel: Sequencing and CNV Analysis

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 gestational 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 a next generation sequencing (NGS) panel testing for syndromic and non-syndromic causes of short stature. For the complete version of the short stature panel, please see the Proportionate Short Stature/Small for Gestational Age Panel – Comprehensive 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:

Genes

ATRX, BLM, BTK, CREEBBP, CUL7, DHCR7, EP300, ERCC6, ERCC8, EGD1, GH1, GHR, GHRHR, GLI2, HESX1, IGF1, IGF1R, INSR, KDM6A, KMT2D, Kras, LHX3, NBN, NIPBL, PITX2, POU1F1, PROP1, PTEN, RAF1, ROR2, RPS6KA3, SHOX, SMARCA1, SMCA1A, SMCA3, 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, 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 10x 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.

**Detection**

**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 10x 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.
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.

### Specimen Requirements

**Submit only 1 of the following specimen types**

**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.

**Type: Saliva**

Specimen Requirements:
Oragene™ Saliva Collection Kit
Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Type: DNA, Isolated**

Specimen Requirements:
Microtainer 8µg
Isolation using the Perkin Elmer™ 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.

### 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, including:
  - 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.

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