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

Test Code: XM010
Turnaround time: 6 weeks
CPT Codes: 81209 x1, 81404 x1, 81405 x1, 81406 x1, 81407 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 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.

The short stature panel is comprised of four separate tests designed to diagnose the most common causes of short stature: the CytoScan SNP Array detecting chromosome abnormalities, deletions, duplications and uniparental disomy; 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. Clients will be able to order the panel with or without the CytoScan SNP Array and with or without the Russell-Silver panel depending on if the patient had these tests done previously.

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, CREBBP, CUL7, DICR7, EP300, ERCC6, ERCC8, FGQ1, GH1, GHR, GHRHR, GLU1, HESX1, IGF1, IGF1R, INSR, KDM6A, KMT2D, KRAS, LHX3, NBN, NIPBL, PITX2, POU1F1, PROP1, PTPN11, RAF1, ROR2, RPS6KA3, SHOX, SMARCAL1, SMCA1A, SMC3, SOS1, SOX2, SOX3, SRCAP, STAT5B, TBCE, THRB, TRIM37, WRN

Indications

This test is indicated for:
- Individuals with a clinical diagnosis of proportionate short stature.

Methodology
DNA isolated from peripheral blood is hybridized to an array containing oligonucleotide and SNP probes across the genome to detect copy number imbalances and regions of homozygosity. FISH analysis or another method, such as G-banding, is used to confirm any abnormal findings either at the time of initial testing or upon receipt of parental samples, depending on the abnormality. If possible UPD is identified, methylation testing may be used, if available, for confirmation.

**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.

**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

**CytoScan SNP Array:** The detection of deletions and duplications of 400 kb or greater is expected to be very high. Deletions and duplications of 400 kb or greater are reported. Smaller deletions or duplications in regions of known microdeletion/microduplication syndromes or in clinically relevant genes will also be reported. The clinical sensitivity for known microdeletion or microduplication syndromes is available in our detection rate chart. The clinical sensitivity for other disorders is dependent on the proportion of cases caused by deletions/duplications compared with other mutations not detectable by array analysis. Microarray will not detect balanced translocations, balanced inversions, imbalances smaller than the resolution of this array, point mutations or low level mosaicism (usually less than 25%) that may underlie the clinical presentation of the patient.

This test is designed to detect whole and partial chromosome UPD, multiple long stretches of absence of heterozygosity (AOH) greater than 3 Mb and AOH in clinically relevant regions. Possible UPD will be reported when a chromosome has at least one homozygous region >10 kb. Homozygosity due to apparent common descent will be reported when >5% of the genome is homozygous. These regions of AOH will be specified, allowing for the identification of recessive risk alleles.

**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. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical Sensitivity: ~99%.

**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

**Additional Specimen Collection/Handling Instructions Required for this Test**

Both tube types are required for this test.

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) AND sodium heparin (green top) tubes:

- Infants (2 years): 3-5 ml in both tubes
- Older Children & Adults: 7-10 ml in both tubes.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Parental samples may be requested to interpret the clinical significance of some findings.

**Sample Storage and Data Usage:** As a participant in the ISCA (International Standard Cytogenomic Array) Consortium, EGL Genetics retains patient samples indefinitely for validation, educational purposes and/or research. The submitted clinical information and test results are also included in a HIPAA-compliant, de-identified public database as part of the National Institute of Health's effort to improve diagnostic testing and our understanding of the relationships between genetic changes and clinical symptoms (for information about the molecular cytogenetic database visit the consortium website at [https://www.iscaconsortium.org/](https://www.iscaconsortium.org/)). Confidentiality of each sample is maintained.

Patients may request to have their samples discarded upon test completion and to opt-out of participation in the database by:

1. Checking the box provided on the test requisition or consent form
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. These 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.