Rothmund-Thomson Syndrome: **RECQL4 Gene Sequencing**

Test Code: QZ  
Turnaround time: 4 weeks  
CPT Codes: 81479 x1

### Condition Description

**RECQL4**-related disorders result from mutations in the **RECQL4** gene (8q24.3) and include Rothmund-Thomson syndrome (RTS), Baller-Gerold syndrome (BGS), and Rapadilino syndrome.

Features of RTS include:
- sparse hair, eyelashes, and/or eyebrows  
- poikiloderma  
- skeletal and dental abnormalities  
- small stature  
- cataracts  
- predisposition to cancer, especially osteosarcoma [1]

BGS is characterized by:
- premature fusion of certain skull bones (craniosynostosis)  
- bulging eyes with shallow eye sockets (ocular proptosis)  
- widely spaced eyes (hypertelorism)  
- oligodactaly (reduction in number of digits)  
- aplasia/hypoplasia of the thumb and/or radius  
- poikiloderma (abnormal skin pigmentation)  
- growth retardation [2]

Rapadilino syndrome is an acronym for:
- RA [radial ray defect]  
- PA [tellae hypoplasia/aplasia and cleft/highly arched PA]late  
- DI [larrow and DI [slocated joints]  
- LI [ittle size and Limb malformation]  
- slender NO [ose]  
- NO [ormal intelligence]

Clinical examinations are the primary method for diagnosis of **RECQL4**-related disorders.

Sequencing of the **RECQL4** gene is recommended to help confirm the presence of mutations in a proband, identify at-risk individuals among the proband's relatives, and provide prenatal diagnosis in families with known mutations. Approximately 66% of individuals with a clinical diagnosis of RTS will have **RECQL4** mutations. Close to 100% of **RECQL4** mutations associated with BGS have been found in fewer than ten families. All **RECQL4**-related disorders are inherited in an autosomal recessive manner. The **RECQL4** gene (8q24.3) has 21 exons and appears to play a role in DNA repair.

For patients with suspected RTS or a **RECQL4**-related disorder, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

### References:

- GeneTests Summary for RTS  
- GeneTests Summary for BGS  

### Genes

**RECQL4**

### Indications

This test is indicated for:
- Mutation identification in an individual with a clinical diagnosis of a **RECQL4**-related disorder.  
- Individuals at risk for a **RECQL4**-related disorder due to family history.
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.

Detection

Clinical Sensitivity: Sequence analysis of the **RECQL4** gene is expected to identify mutations in approximately 66% of individuals with RTS. Close to 100% of **RECQL4** mutations associated with BGS have been found in fewer than ten families. Mutations in the promoter region, some mutations in the introns, other regulatory element mutations, and large deletions cannot be detected by this analysis.

Analytical Sensitivity: ~99%.

Results of molecular analysis must be interpreted in the context of the patient's clinical presentation and family history.

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 24 hours of collection. Do not refrigerate or freeze.

**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.

**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.

Special Instructions

Please submit copies of family history information along with the sample. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- **Rothmund-Thomson Syndrome:** _RECQL4_ Gene Deletion/Duplication (RH) is available for those individuals in whom sequence analysis is negative.
- **Known Mutation Analysis (KM)** is available to family members if mutations are identified by sequencing.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.