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)
- oligodactyly (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:
- **R**adial ray defect
- **P**allestae hypoplasia/aplasia and cleft/highly arched **P**a**l**ate
- **D**iarrhoea and **D**islocated joints
- **L**ittle size and **L**imb malformation
- **N**oar**S**e
- **N**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

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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

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

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

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 Emory Genetics Laboratory, 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.

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