1q21.1 Deletion/Duplication Analysis

Test Code: CC061
Turnaround time: 2 weeks - 1 week
CPT Codes: 81228 x1

Condition Description

Thrombocytopenia with absent radius (TAR) syndrome is characterized by low blood platelet counts (thrombocytopenia) and absence of the radius bone in each forearm. Thrombocytopenia can lead to easy bruising and potentially severe bleeding episodes (hemorrhage) in infancy that may become less severe or nonexistent over time. The absence of radius bones results in shortened forearms. The ulna and humeral bones may also be short or missing, with the most severe phenotype being near absence of upper limbs (phocomelia). The preservation of both thumbs distinguishes TAR syndrome from other conditions involving absent radius bones. Other anomalies of the skeleton (lower limbs, ribs, and vertebrae), heart, and genitalourinary system may be present in TAR syndrome. Allergy to cow's milk is common. The estimated prevalence of TAR syndrome is 1 in 100,000 to 1 in 200,000.

TAR syndrome is inherited in an autosomal recessive manner and is due to changes in the gene RBM8A (1q21.1). Compound inheritance of one RBM8A null allele and one RBM8A partial loss-of-function allele cause TAR syndrome. For the majority of individuals with TAR syndrome, the null allele is a total RBM8A gene deletion, as part of a recurring deletion of chromosome 1q21.1 that removes RBM8A as well as several other genes. Two partial loss-of-function RBM8A alleles have been described: a c.-21G>A nucleotide change in the 5'UTR and a c.67+32G>C nucleotide change in the first intron. These two nucleotide changes lower RBM8A transcription in vitro (Albers et al., 2012).

TAR clinical testing requires a comprehensive strategy to detect large deletions and RBM8A sequence variants. The 1q21.1 TAR deletion is mediated by segmental duplications and varies in size from ~200 kilobases (kb) to more than 2 Megabases (Mb); thus, high-resolution array Comparative Genome Hybridization (aCGH) is the most appropriate method to detect 1q21.1 deletions. RBM8A sequence variants are best detected with Sanger sequencing. The comprehensive TAR Syndrome Panel (Test Code: XM060) includes 1q21.1 deletion/duplication analysis by high-resolution aCGH and full RBM8A gene sequence analysis. Comprehensive TAR testing can provide confirmation of a clinical diagnosis and carrier testing for family members. This test is one of the two components of the TAR panel that may be ordered as a stand-alone test (1q21.1 deletion/duplication, test code CC061). Sequencing analysis only for the RBM8A gene is available also (Test Code: MS061).

References:
- GeneReviews
- OMIM #274000: Thrombocytopenia-absent radius syndrome
- OMIM #605313: RBM8A gene

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of TAR syndrome
- Carrier testing in adults with a family history of TAR syndrome.

Methodology

DNA isolated from peripheral blood is hybridized to a custom array containing oligonucleotide probes across the entire 1q21.1 region (approximately 5.6 Mb in size) to detect copy number imbalances. The 1q21.1 region includes both the proximal TAR region as well as the distal 1q21.1 region associated with variable neurodevelopmental phenotypes (Rosenfeld et al., 2012). Genomic regions outside of 1q21.1 are not analyzed.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

Detection

Detection is limited to loss of copy number (deletion), gain of copy number (duplication), or normal copy number. The detection of deletions and duplications of 400 kb or greater is expected to be very high. Smaller deletions or duplications in the TAR critical region will also be detected, with a resolution of approximately 75 kb. 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.
Specimen Requirements

Additional Specimen Collection/Handling Instructions Required for this Test
If sending whole blood, both tube types are required for this test.

Submit only 1 of the following specimen types

**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: Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

**Type: Dried Blood Spot**

Specimen Requirements:

Minimum of three standard blood spot circles

Specimen Collection and Shipping: Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

**Related Tests**

- Custom diagnostic mutation analysis (Test Code: KM or DKMDD) is available to family members for mutations identified by sequencing.
- TAR Panel - includes *RBM8A* sequencing and 1q21.1 deletion/duplication testing (Test Code: XM060)
- Full gene sequence analysis of the *RBM8A* gene is available to test for point mutations and low-frequency SNPs in the 5'UTR and first intron (Test Code: MS061).