

TAR Syndrome: Sequencing and 1q21.1 Deletion/Duplication Panel

Test Code: XM060

Turnaround time: 4 weeks

CPT Codes: 81228 x1

Condition Description

As of March 1, 2021, NTD Genetics no longer accepts samples for this test. For questions, please call: 470-378-2200.

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 genitourinary 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.

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 *RBM8A* full gene sequence analysis. Comprehensive TAR testing can provide confirmation of a clinical diagnosis and carrier testing for family members. The two components of the TAR panel may also be ordered as stand-alone tests (1q21.1 deletion/duplication, test code CC061, and *RBM8A* gene sequencing, test code MS061).

References:

- GeneReviews
- [OMIM #274000](#): Thrombocytopenia-absent radius syndrome
- [OMIM #605313](#): *RBM8A* gene
- Albers *et al.* (2012), *Nat Genet* 44:435-439.

Genes

[RBM8A](#)

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

1q21.1 Deletion/Duplication: DNA isolated from peripheral blood is hybridized to a custom array containing oligonucleotide probes across the entire 1q21.1 region (approximately 5.6 Megabases 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.

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. The c.-21G>A and c.67+32G>C nucleotide changes associated with TAR syndrome will be detected by this assay.

Detection

1q21.1 Deletion/Duplication: 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.

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 phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

Type: DNA, Isolated

Specimen Requirements:

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ 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: Whole Blood (EDTA and Sodium Heparin)

Specimen Requirements:

Sodium Heparin and EDTA

Infants (Children (>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.

Related Tests

- Custom diagnostic mutation analysis (KM) is available to family members for mutations identified by sequencing.
- Deletion testing is available to test for whole *RBM8A* gene deletions, as part of recurring TAR deletions on chromosome 1q21.1 that range from ~200 kb to 2 Mb (1q21.1 deletion/duplication, test code CC061).
- 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).