TAR Syndrome: \textit{RBM8A} Gene Sequencing

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

TAR clinical testing requires a comprehensive strategy to detect large deletions and \textit{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. \textit{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 \textit{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 \textit{RBM8A} gene sequencing, test code MS061).

Please note that this test is for the \textit{RBM8A} gene sequencing only.

\textbf{References:}

- GeneReviews
- OMIM \#274000: Thrombocytopenia-absent radius syndrome
- OMIM \#605313: \textit{RBM8A} gene

\textbf{Genes}

\textit{RBM8A}

\textbf{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.

\textbf{Methodology}

PCR amplification of the 6 exons contained in the \textit{RBM8A} gene is performed on the patient's genomic DNA. The \textit{c.-21G>A} and \textit{c.67+32G>C} nucleotide changes associated with TAR syndrome will be detected by this assay. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

\textbf{Detection}

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical phenotype.

Analytical Sensitivity: ~99%

\textbf{Specimen Requirements}

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

\textbf{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.

**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 (Test Code: CC061).
- TAR Panel - includes RBM8A sequencing and 1q21.1 deletion/duplication testing (Test Code: XM060).