City of Hope

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Assay Summary

ATM Gene Mutation Analysis

Ataxia-Telangiectasia, breast cancer predisposition, certain leukemias and lymphomas (T-PLL, B-CLL, Mantle Cell Lymphomas)

Synopsis

Germline mutations in the ATM gene cause the autosomal recessive neurological disease ataxia telangiectasia (A-T). The prevalence of A-T is ~1/40,000 – 1/100,000 affected individuals, with a carrier frequency of ~1/100. A-T is characterized by progressive cerebellar degeneration, immunodeficiency, radiation sensitivity, and a predisposition to cancer development. Heterozygous ATM mutations have also been found in some patients with T-cell prolymphocytic leukemia (T-PLL)[1], B-cell chronic lymphocytic leukemia (B-CLL)[2, 3] and mantle cell lymphoma[4]. Identification of both ATM gene mutations in A-T patients may permit identification of carriers in these families. Greater than 500 uniuqe mutations have been identified in ATM. Identification of heterozygous ATM mutations may also identify individuals with an increased risk for certain cancers, such as leukemias, lymphomas, and breast.

Indications for testing

Patients with ataxia telangiectasia may consider, with genetic counseling, ATM gene mutation analysis. If a mutation is identified in the patient, other at-risk family members may be tested for carrier status. In patients with certain leukemias and lymphomas, identification of an ATM mutation may suggest an increased risk for these cancers in other family members who carry the mutation.

Methodology

Sequence analysis: Coding exons and associated intron junctions are captured and enriched using custom Agilent SureSelect technology. Next-generation sequencing is performed on Illumina MiSeq. Additional Sanger sequencing is performed for any regions with insufficient depth of coverage or for verification of suspect variant calls. Targeted testing for known familial mutation is performed by Sanger sequencing.

MLPA analysis for large deletions or duplications: Multiplex Ligation-Dependent Probe Amplification (MLPA, MRC-Holland) technology is used for detection of large deletions and duplications of one or more exons of the ATM gene.

Limitations

ATM sequence: The mutation analysis will not detect mutations located in regions of the ATM gene that are not analyzed (non-coding exon regions, intron regions other than the splice junctions, and upstream and downstream regions). The method also will not detect gross genetic alterations including duplications, inversions, or deletions (other than those regions set-up for MLPA analysis). Some sequence alterations that may be detected (such as those causing missense or synonymous changes) will be of unknown clinical significance. **MLPA analysis**: The MLPA method is designed to detect deletions/duplications of one or more exons of the ATM gene. However, mutations and/or polymorphisms very close to the probe ligation

site may also result in a reduced relative peak area. Therefore, apparent deletions detected by a single probe need to be confirmed by a second method, whenever it's possible.
Interpretation of test results should be in the context of the patient's ethnicity, clinical and family histories, and other laboratory test results.

Specimen Requirements

Blood samples: 2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes.

Keep at ambient temperature and ship by overnight courier. Samples must be received in our laboratory within 72 hours of draw.

Note:

i) for infants, a minimum of 3 ccs is sufficient.

ii) we accept DNA; at least 10 micrograms is required.

Test Request Form (TRF)

A completed CMDL TRF is required for each specimen. Please submit the completed TRF with the specimen. Complete testing and billing information must be provided before the specimen is processed.

Order Codes	***CPT Codes***	***TAT***
ATM-SEQ (ATM gene, full gene sequencing by NGS)	81408, G0452	3 wks
ATM-CAS (ATM gene, targeted mutation analysis, known mutation)	81403, G0452	2 wks
ATM-DEL (ATM gene, MLPA analysis, all exons)	81479, G0452	3 wks
ATM-DEL-CAS (ATM gene, MLPA analysis, known deletions/duplications)	81479, G0452	3 wks

References

1. Vorechovsky, I. et al. (1997). Nature Genet. 17: 96-99.
2. Bullrich, F. et al. (1999). Cancer Res. 59: 24-27.
3. Stankovic, T. et al. (1999). The Lancet 353: 26-29.
4. Stilgenbauer, S. et al. (1999). Blood 94: 3262-3264.
5. Cavalieri S. et al. (2006) *Hum Mutat.* 27: 1061
6. Cavalieri S. et al. (2008). *Ann Hum Genet.* 72: 10–18.
7. Bernstein J.L. et al (2003) Hum Mutat 21:542-50.

NOTE: This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.