City of Hope

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Assay Summary

CDH1 (E-cadherin) Gene Mutation Analysis

Hereditary Diffuse Gastric Cancer, Lobular breast cancer, Early Onset Sporadic Diffuse Gastric Cancer, Signet ring colon cancer

Synopsis

E-cadherin (epithelial cadherin, CDH1, OMIM# 192090) is a member of the cadherin family of adhesion molecules, which are transmembrane glycoproteins mediating calcium-dependent cell-cell adhesion[1]. Germline mutations in the CDH1 gene have been demonstrated to underlie in diffuse gastric cancer (DGC) in various ethnic Backgrounds [2, 3, 4]. CDH1 germ line mutations have also been identified in a small portion of early onset DGC patients without a family history[5, 6, 12]. Associations between CDH1 germ line mutations and both lobular breast cancer and signet ring carcinoma of the colon have been reported in DGC families[7, 8, 9]. DGC is a highly penetrant autosomal dominant disorder that has been reported to occur in many ethnicities. The offspring of an affected individual has a 50% risk of also being affected. The estimated cumulative risk of gastric cancer by age 80 years is 67% (95% CI: 39-99) for men and 83% (95% CI: 58-99) for women[10]. Women also have a 39% risk for lobular breast cancer[10]. Germline truncating CDH1 mutations are found in 48% of families with multiple cases of diffuse gastric cancer[7].

Indications for testing

1. Two or more cases of gastric cancer in a family, with at least one diffuse gastric cancer diagnosed before age 50 years.
2. Three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer.
3. An individual diagnosed with diffuse gastric cancer before 45 years of age.
4. An individual diagnosed with both diffuse gastric cancer and lobular breast cancer (no other criteria met).
5. One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer (no other criteria met).
6. One family member diagnosed with diffuse gastric cancer and another with signet ring colon cancer (no other criteria met).

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 deletion/duplication analysis of *CDH1*: CDH1 large deletions are found in 6.5% of hereditary diffuse gastric cancer patient who test negative in gene sequencing[13]. We have incorporated the SALSA MLPA kit which is a rapid, high-throughput technique for copy number quantification, specifically testing for large deletions/duplications for the CDH1 gene. This assay should be considered for patients with DGC where full gene sequencing did not detect a mutation.

Limitations

This method will not detect mutations located in regions of the genes that are not analyzed (non-coding exon sequences, intron sequences other than the splice junctions, and upstream and downstream sequences). The method also will not detect inversions. Some sequence alterations that may be detected (such as those causing missense or

synonymous changes) will be of unknown clinical significance. Interpretation of test results should be in the context of the patient's diagnosis, 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) 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.

b) CDH1 Patient Information Form: Include a completed CDH1 Patient Information Form for the proband and a complete pedigree.

Order Codes	***CPT Codes***	***TAT***
CDH1-SEQ (CDH1 gene, full gene sequencing by NGS)	81406, G0452	3 wks
CDH1-CAS (CDH1 gene, targeted mutation analysis, known mutation)	81403, G0452	2 wks
CDH1-DEL (CDH1 gene, MLPA analysis)	81479, G0452	3 wks
CDH1-DEL-CAS (CDH1 gene, MLPA analysis, known deletions/duplications)	81479, G0452	3 wks

References

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