Hereditary Thyroid Cancer Panel, Sequencing and Deletion/Duplication

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Pathogenic germline variants in multiple genes have been implicated in hereditary thyroid cancer. Hereditary thyroid cancer syndromes are often characterized by early age of onset (typically before 50 years of age), the presence of any number of related thyroid cancers (eg, pheochromocytoma, medullary thyroid carcinoma, C-cell hyperplasia), and/or similar cancers in one or more closely related family members.

Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, refer to the ARUP Hereditary Cancer Panel Comparison table.

Hereditary Thyroid Cancer Panel, Sequencing and Deletion/Duplication 3005944

Method: Massively Parallel Sequencing/Sequencing

- Recommended test to confirm a diagnosis of a hereditary cause of thyroid cancer in individuals with a personal or family history
- For additional information, please contact an ARUP genetic counselor at 800-242-2787 ext. 2141.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Genetics

Genes

See the Genes Tested table for genes included in the panel.

Etiology

Approximately 5% of thyroid cancers are associated with a hereditary cause.

Inheritance

Autosomal dominant

Test Interpretation

Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low with methodology used for germline assays.
- Individuals with hematological malignancy and/or a previous allogeneic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen.
  - Testing of cultured fibroblasts is required for accurate interpretation of test results.

Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.
- Bidirectional Sanger sequencing is performed on the following gene and exon:
  - *PTEN* (NM_000314) 9

Sensitivity/Specificity

Clinical Sensitivity

Variable, dependent on phenotype

Analytic Sensitivity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region	Analytic Specificity (NPA) Estimate (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] deletions	97.8 (90.3-99.8) [2 exons or larger] 62.5 (38.3-82.6) [single exon]	>99.9
Exon-level[c] duplications	83.3 (56.4-96.4) [3 exons or larger]	>99.9

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a heritable form of thyroid cancer or other cancer.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
  - The following exons are not sequenced due to technical limitations of the assay:
    - *APC* (NM_001354896) exon 12
    - *APC* (NM_001354898, NM_001354904) exon 2
    - *APC* (NM_001354900) exon 11
    - *MEN1* (NM_001370251) exon 8
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes and/or repetitive/homologous regions
  - Deletions/duplications in the following exons:
    - *APC* (NM_001354896) 12
    - *APC* (NM_001354898, NM_001354904) 2
    - *APC* (NM_001354900) 11
    - *MEN1* (NM_001370251) 8
    - *PTEN* (NM_000314, NM_001304718) 9
    - *PTEN* (NM_001304717) 1,10

Genes Tested

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, see the ARUP Hereditary Cancer Panel Comparison table.

Gene	MIM Number	Disorder/Associated Cancer(s)/Tumor(s)	Inheritance
APC	611731	FAP AFAP GAPPS Colorectal adenomas and cancer, duodenal adenomas and cancer, gastric fundic gland polyps, medulloblastoma, osteomas, pancreatic, thyroid, and others	AD
DICER1	606241	DICER1-related disorders Pleuropulmonary blastoma, ovarian sex cord-stromal tumors, cystic nephroma, thyroid	AD
MEN1	613733	MEN type 1 Adrenocortical, carcinoid, gastro-entero-pancreatic (GEP) neuroendocrine tumors, meningioma, parathyroid, pituitary, thyroid	AD
PRKAR1A	188830	Carney complex Endocrine tumor or overactivity, myxoma, schwannoma	AD
PTEN	601728	Cowden syndrome/PTEN hamartoma tumor syndrome Breast, colorectal, endometrial, Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma), melanoma,[a] renal cell carcinoma, thyroid, and others	AD
RET	164761	MEN2 Medullary thyroid carcinoma, parathyroid adenoma or hyperplasia, pheochromocytoma	AD
TP53	191170	LFS Adrenocortical carcinoma, breast, choroid plexus carcinoma, CNS, colorectal, melanoma, osteosarcoma, pancreas, prostate, renal, rhabdomyosarcoma, soft tissue sarcoma, stomach, thyroid, and others	AD

[a]Association is suggested but not well-established at this time.

AD, autosomal dominant; AFAP, attenuated FAP; CNS, central nervous system; FAP, familial adenomatous polyposis; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; LFS, Li-Fraumeni syndrome; MEN, multiple endocrine neoplasia

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