THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Hereditary Thyroid Cancer

Clinical Features: Thyroid cancer is the most common endocrine malignancy and can occur sporadically or as part of an inherited syndrome or familial predisposition. Based on the cell line from which the cancer originates, thyroid cancer is divided into two subtypes: medullary thyroid cancer (MTC) and nonmedullary thyroid cancer (NMTC). NMTC can be further subdivided into papillary and follicular thyroid cancers (PTC and FTC). MTC accounts for 5% or less of thyroid malignancies, and a significant subset is hereditary, mainly due to germline mutations in the *RET* proto-oncogene. A germline mutation in the *RET* oncogene is identified in 98% of individuals with multiple endocrine neoplasia type 2 type A (MEN2A), almost 95% with familial MTC (FMTC), and more than 98% with multiple endocrine neoplasia type 2 type B (MEN2B). Susceptibility to NMTC is observed in a number of genetic syndromes including Cowden syndrome, familial adenomatous polyposis, Gardner syndrome, Carney complex type 1, Werner syndrome and DICER1 syndrome. For patients with thyroid cancer, it is important for the clinician to recognize the underlying genetic etiology if present, to enable surveillance for associated malignancies and genetic testing of family members [1-3].

Our Hereditary Thyroid Cancer Panel includes mutation analysis of all 13 genes listed below.

Thyroid Cancer Panel					
APC	AKT1	CHEK2	DICER1	PIK3CA	PRKAR1A
PTEN	RET	SDHB	SDHD	SRGAP1	TP53
WRN (RECQL2)					

Hereditary Thyroid Cancer Panel genes and associated cancers

Gene	Thyroid Cancer Risk	Associated Cancer Syndrome	Other tumors	References
APC	Up to 12%	Familial adenomatous polyposis (FAP)	colon, duodenal, pancreatic, hepatic, central nervous system	[4]
AKT1	Elevated	Cowden and Cowden-like Syndromes	breast, colon, uterine, kidney, skin findings	[5]
CHEK2	Elevated	CHEK2-related conditions	breast, colon, prostate, kidney	[6-8]
DICER1	Elevated for benign thyroid lesions and thyroid cancer	DICER1 syndrome	pleuropulmonary blastoma, cystic nephroma, Sertoli-Leydig cell tumors, juvenile granulosa cell tumors, gynandroblastoma	[9, 10]
PIK3CA	Elevated	Cowden syndrome	breast, uterine, kidney, colon, skin	[5, 11]
PRKAR1A	Elevated for thyroid adenoma/carcinoma and multiple thyroid nodules	Carney complex	myxomas, schwannomas, Sertoli cell tumors, skin pigmentary findings	[12]
PTEN	35%	Cowden syndrome	breast, uterine, kidney, colon, skin	[13]

RET	>98% for medullary thyroid cancer	Multiple endocrine neoplasia type 2	pheochromocytoma, paragangliomas	[14, 15]
SDHB	Elevated risk for differentiated thyroid cancer	hereditary pheochromocytoma–paraganglioma syndrome; Cowden and Cowden-like Syndromes	Kidney, stomach, pheochromocytoma, paraganglioma	[16]
SDHD	Elevated risk for differentiated thyroid cancer	hereditary pheochromocytoma–paraganglioma syndrome; Cowden and Cowden-like Syndromes	Kidney, stomach, pheochromocytoma, paraganglioma	[16]
SRGAP1	Elevated risk for Papillary thyroid cancer	NA	NA	[17]
TP53	Elevated	Li-Fraumeni syndrome	Sarcomas of bone and soft tissues, carcinomas of the breast and adrenal cortex, brain tumors, and acute leukemias, etc.	[18]
WRN (RECQL2)	Elevated	Werner syndrome	Melanoma, meningioma, soft tissue sarcomas, leukemia, pre-leukemic conditions and osteosarcoma/bone neoplasms.	[19]

NA: Not available

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Hereditary Thyroid Cancer Panel (13 genes)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $3500
CPT codes: 81406, 81407
Turn-around time: 4 weeks

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. All abnormal results are reported by telephone

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

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