

OncoGeneDx: Hyperparathyroidism/Endocrine Tumor Panel

Panel Gene List: *AIP, APC, CASR, CDC73, CDKN1B, CHEK2, DICER1, MEN1, PRKAR1A, PTEN, RET**

*Testing includes sequencing and deletion/duplication analysis for all genes except *RET* (seq only).

Clinical Features:

In the general population, approximately 0.1-1% of individuals are affected by hyperparathyroidism in their lifetime.¹ Most cases of hyperparathyroidism develop sporadically; however, approximately 5% are thought to be due to a hereditary predisposition.¹ Endocrine tumors and cancers comprise a diverse group of conditions, and the exact lifetime risk and percentage of cancers/tumors attributable to a hereditary predisposition are difficult to define. Some types of endocrine tumors, such as medullary thyroid cancer, are quite rare and a significant portion can be attributed to a hereditary cause, while others, such as differentiated thyroid cancer, are common in the general population and most often develop sporadically.²

Features suggestive of hereditary hyperparathyroidism or endocrine tumor predisposition may include a personal history of parathyroid cancer, hyperparathyroidism due to multi-glandular parathyroid disease, or family history of multiple endocrine tumors/disorders in the same or different family members, including primary hyperparathyroidism, pituitary adenoma, thyroid cancer, benign thyroid disease, neuroendocrine tumors of the pancreas or GI tract, or carcinoid tumors.

The OncoGeneDx Hyperparathyroidism/Endocrine Tumor Panel includes analysis of 11 genes that have been implicated in hyperparathyroidism and/or endocrine tumors. This panel includes several genes that predispose to well-defined syndromes for which consensus management guidelines are available. These include Familial adenomatous polyposis (*APC*), Multiple endocrine neoplasia type 1 (*MEN1*), *PTEN* hamartoma tumor syndrome (*PTEN*), and Multiple endocrine neoplasia type 2 (*RET*). Additional genes for which consensus management guidelines are available include *CDKN1B*, *CHEK2*, and *PRKAR1A*. The four other genes on this panel, *AIP*, *CASR*, *CDC73*, and *DICER1*, have also been reported in association with hereditary hyperparathyroidism and endocrine tumors. Since the risks for these of these genes are not yet well defined, no consensus guidelines have been published, but management guidelines have been asserted by disease-specific experts.

Inheritance Pattern:

All of the genes on this panel are associated with an autosomal dominant risk. Some of the genes on this panel are also associated with rare conditions when inherited in an autosomal recessive fashion. The specifics of this inheritance are outlined in the table below.

Test Methods:

Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. This DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next generation sequencing with CNV calling (NGS-CNV). For *PTEN* nucleotides c.-700 through c.-1300 in the promoter region, and for *APC*, promoters 1A and 1B are also captured. The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. For *RET*, only sequencing is performed. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the 11 genes included in the OncoGeneDx Hyperparathyroidism/Endocrine Tumor Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of a hereditary predisposition as outlined above. DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while NGS-CNV analysis, array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable by this test. The methods used cannot reliably detect deletions of 20bp to 250bp in size, or insertions of 10bp to 250 bp in size. Sequencing cannot detect low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect mosaicism and cannot identify balanced chromosome aberrations. Rarely, incidental findings of large chromosomal rearrangements outside the gene of interest may be identified. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results. False negatives may also occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In individuals with active or chronic hematologic neoplasms or conditions, there is a possibility that testing may detect an acquired somatic variant, resulting in a false positive result. As the

ability to detect genetic variants and naming conventions can differ among laboratories, rare false negative results may occur when no positive control is provided for testing of a specific variant identified at another laboratory. The chance of a false positive or false negative result due to laboratory errors incurred during any phase of testing cannot be completely excluded. Interpretations are made with the assumption that any clinical information provided, including family relationships, are accurate. Consultation with a genetics professional is recommended for interpretation of results.

Gene	Protein	Inheritance	Disease Associations
<i>AIP</i> ³	ARYL HYDROCARBON RECEPTOR-INTERACTING PROTEIN	AD	Pituitary adenomas
<i>APC</i> ⁴	ADENOMATOUS POLYPOSIS COLI PROTEIN	AD	Familial adenomatous polyposis (FAP)-associated condition: colorectal, duodenal or periampullary, gastric, thyroid, pancreatic, brain (medulloblastoma) & liver (hepatoblastoma) cancers, desmoid tumors, gastrointestinal polyps
<i>CASR</i> ⁵	CALCIUM SENSING RECEPTOR	Multifactorial	Pancreatitis: Risk Allele(s)
		AD	Familial Hypocalciuric Hypercalcemia type 1 (FHH), Familial Isolated Hyperparathyroidism (FIHP), Autosomal Dominant Hypocalcemia (ADH), and Familial Isolated Hypoparathyroidism (FIH)
		AR, AD (Rare)	Neonatal Severe Primary Hyperparathyroidism (NSHPT)
<i>CDC73</i> ⁶	PARAFIBROMIN	AD	Parathyroid cancer, jaw fibromas, renal tumors, uterine tumors, hyperparathyroidism
<i>CDKN1B</i> ⁷	CYCLIN-DEPENDENT KINASE INHIBITOR 1B	AD	Multiple endocrine neoplasia type 4 (MEN4): primary hyperparathyroidism, pituitary adenomas, gastroenteropancreatic neuroendocrine tumors, parathyroid adenomas
<i>CHEK2</i> ⁸	SERINE/THREONINE-PROTEIN KINASE CHK2	AD	Breast, colon, prostate, gastric, thyroid cancer
<i>DICER1</i> ⁹	ENDORIBONUCLEASE DICER	AD	Pleuropulmonary blastoma,

			multinodular thyroid goiter and thyroid cancer, pineal and pituitary gland tumors/cancers, cystic nephroma, ovarian cancer (SLCT), cervical embryonal rhabdomyosarcoma, among others
<i>MEN1</i> ^{10,11}	MENIN	AD	Multiple endocrine neoplasia type 1 (MEN1): parathyroid tumors, pancreatic neuroendocrine tumors, anterior pituitary tumors, pheochromocytoma, meningioma, ependymoma, hyperparathyroidism
<i>PRKAR1A</i> ¹²	CAMP-DEPENDENT PROTEIN KINASE TYPE 1-ALPHA REGULATORY SUBUNIT	AD	Thyroid cancer, testicular tumors (LCCSCT), myxomas, psammomatous melanotic schwannomas (PMSs), primary pigmented nodular adrenocortical disease, pituitary adenomas, among others
<i>PTEN</i> ¹³	PHOSPHATIDYLINOSITOL 3,4,5-TRISPHOSPHATE 3-PHOSPHATASE AND DUAL-SPECIFICITY PROTEIN PHOSPHATASE PTEN	AD	<i>PTEN</i> hamartoma tumor syndrome (PHTS): breast, thyroid, endometrial, colon, melanoma & renal cancer, gastrointestinal polyps, Lhermitte-Duclos Disease
<i>RET</i> ¹⁴	PROTO-ONCOGENE TYROSINE-PROTEIN KINASE RECEPTOR RET	AD	Multiple endocrine neoplasia type 2 (MEN2): medullary thyroid cancer, pheochromocytoma, hyperparathyroidism

Because of evolving and expanding phenotypes, this list of cancer/tumor types is not exhaustive. Gene-specific risk for some of the cancers/tumors and other features listed are not well-defined.

Abbreviations:

AD – Autosomal dominant

AR – Autosomal recessive

CGH – Comparative genomic hybridization

LCCSCT - Large cell-calcifying Sertoli cell tumors

MLPA – Multiplex ligation-dependent probe amplification

SLCT - Sertoli-Leydig cell tumor

References:

1. Madkhali, T., Alhefthi, A., Chen, H. & Eifenbein, D. Primary hyperparathyroidism. *Ulus. Cerrahi Derg.* **32**, 58–66 (2016).
2. Petr, E. J. & Else, T. Genetic predisposition to endocrine tumors: Diagnosis, surveillance and challenges in care. *Semin. Oncol.* **43**, 582–590 (2016).

3. Beckers, A., Aaltonen, L. A., Daly, A. F. & Karhu, A. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. *Endocr. Rev.* **34**, 239–277 (2013).
4. Steinhagen, E. *et al.* The prevalence of thyroid cancer and benign thyroid disease in patients with familial adenomatous polyposis may be higher than previously recognized. *Clin. Colorectal Cancer* **11**, 304–308 (2012).
5. Christensen, S. E., Nissen, P. H., Vestergaard, P. & Mosekilde, L. Familial hypocalciuric hypercalcaemia: a review. *Curr. Opin. Endocrinol. Diabetes Obes.* **18**, 359–370 (2011).
6. Jackson, M. A., Rich, T. A., Hu, M. I., Perrier, N. D. & Waguespack, S. G. CDC73-Related Disorders. in *GeneReviews*(®) (eds. Pagon, R. A. *et al.*) (University of Washington, Seattle, 1993).
7. Alrezk, R., Hannah-Shmouni, F. & Stratakis, C. A. MEN4 and CDKN1B mutations: the latest of the MEN syndromes. *Endocr. Relat. Cancer* **24**, T195–T208 (2017).
8. Cybulski, C. *et al.* CHEK2 is a multiorgan cancer susceptibility gene. *Am. J. Hum. Genet.* **75**, 1131–1135 (2004).
9. Doros, L. *et al.* DICER1-Related Disorders. in *GeneReviews*(®) (eds. Adam, M. P. *et al.*) (University of Washington, Seattle, 1993).
10. Marini, F., Falchetti, A., Luzzi, E., Tonelli, F. & Maria Luisa, B. Multiple Endocrine Neoplasia Type 1 (MEN1) Syndrome. in *Cancer Syndromes* (eds. Riegert-Johnson, D. L., Boardman, L. A., Hefferon, T. & Roberts, M.) (National Center for Biotechnology Information (US), 2009).
11. Giusti, F. *et al.* Multiple endocrine neoplasia syndrome type 1: institution, management, and data analysis of a nationwide multicenter patient database. *Endocrine* **58**, 349–359 (2017).
12. Stratakis, C. A. Carney complex: A familial lentiginosis predisposing to a variety of tumors. *Rev. Endocr. Metab. Disord.* **17**, 367–371 (2016).
13. Tan, M.-H. *et al.* Lifetime cancer risks in individuals with germline PTEN mutations. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **18**, 400–407 (2012).
14. Marquard, J. & Eng, C. Multiple Endocrine Neoplasia Type 2. in *GeneReviews*(®) (eds. Pagon, R. A. *et al.*) (University of Washington, Seattle, 1993).