CDC73 (HRPT2) Gene Analysis in Hyperparathyroidism-Jaw Tumor Syndrome, Parathyroid Carcinoma and Familial Isolated Hyperparathyroidism

Disorder also known as: HPT-JT; Hyperparathyroidism, familial primary, with multiple ossifying jaw fibromas; HPT-JT Parathyroid adenomatosis, familial cystic included; Hyperparathyroidism, familial isolated primary; FIHP; Parathyroid adenoma, familial, included; HRPT2-Related Disorders

Clinical Features:
Pathogenic variants in the CDC73 (HRPT2) gene are the cause of two related genetic disorders resulting in hyperparathyroidism. Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT) is a multiple endocrine neoplasia syndrome characterized by primary hyperparathyroidism due to tumors of the parathyroid gland, ossifying fibromas of the maxilla or mandible (in 30% of affected individuals), and renal involvement in some patients (bilateral cysts and less frequently solid tumors such as hamartomas and Wilms tumor). The risk of malignancy of the parathyroid glands in HPT-JT has been estimated to be 15%. Familial Isolated Hyperparathyroidism (FIHP) is a nonsyndromic disorder characterized by the presence of multiple family members with hyperparathyroidism.

Genetics:
Autosomal dominant

Test Methods:
Bi-directional sequence analysis of the CDC73 (HRPT2) gene is offered in two tiers, as evidence suggests a higher frequency of variants occurring in certain exons. Tier 1 includes analysis of exons 1-7, and is expected to identify the majority of CDC73 variants, while Tier 2 analysis is predicted to detect the remaining variants present in exons 8-17. Variants found in the first person of a family are confirmed by repeat analysis using sequencing, restriction digest, or other appropriate method. If no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene.

Test Sensitivity:
In one study, CDC73 (HRPT2) pathogenic variants were identified in 14 of 26 (54%) index cases with the diagnosis of HPT-JT. Another study which detected somatic CDC73 pathogenic variants in 10 of 15 parathyroid carcinomas, found that three of these patients also had germ-line CDC73 variants (thus, ~1/3 of those patients whose tumors had somatic
variants, or 1/5 of patients with apparently sporadic parathyroid carcinoma carried germline CDC73 variants). Finally, multiple groups have investigated the role of CDC73 variants in individuals/families with FIHP; published sensitivity data ranges broadly from 0% to 28.6% (the most recent of these studies estimated an 18% detection rate).

References: