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.[1] 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).[2] 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%[3,4] (the most recent of these studies estimated an 18% detection rate).[5]

References:

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3. Villablanca, A. et al., Germline and de novo mutations in the HRPT2 tumour suppressor gene in familial isolated hyperparathyroidism (FIHP). J Med Genet. 41: e32, 2004
4. Warner, J. et al., Genetic testing in familial isolated hyperparathyroidism: unexpected results and their implications. J Med Genet. 41: 155-60, 2004
5. Mizusawa, N. et al., Genetic analyses in patients with familial isolated hyperparathyroidism and hyperparathyroidism-jaw tumour syndrome. Clin Endocrinol. 65: 9-16, 2006.