

CDC73 (HRPT2) Gene Analysis in Hyperparathyroidism-Jaw Tumor Syndrome

Disorder Also Known As: Familial primary hyperparathyroidism with multiple ossifying jaw fibromas; Familial isolated primary hyperparathyroidism (FIHP); Familial cystic parathyroid adenomatosis; *CDC73*-related disorders

Clinical Features:

Hyperparathyroidism-jaw tumor syndrome (HPT-JT) is characterized by primary hyperparathyroidism caused by tumors of the parathyroid gland. Parathyroid tumors are most often benign, but are malignant in 15% of cases.¹ Approximately 25-50% of individuals with HPT-JT develop ossifying fibromas of the maxilla or mandible, and 15-20% of affected individuals have renal involvement, including cysts, hamartomas, or, less frequently, Wilms' tumor or renal cell carcinoma.² Females with HPT-JT have up to a 75% risk for developing benign and/or malignant uterine tumors.³ Individuals with *CDC73* pathogenic variants may also present with isolated parathyroid carcinoma or with familial isolated hyperparathyroidism (FIHP), a nonsyndromic disorder characterized by the presence of multiple family members with hyperparathyroidism.

Inheritance Pattern:

HPT-JT is inherited in an autosomal dominant manner. While *de novo* (new) cases have been reported, the percentage of cases due to *de novo* pathogenic variants is unknown.^{4,9}

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *CDC73* are PCR amplified and capillary sequencing is performed. Bi directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. Data analysis is performed using gene-specific filtering. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of *CDC73* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of hyperparathyroidism-jaw tumor syndrome (HPT-JT) as outlined above. Sequencing and deletion/duplication analysis are expected to identify pathogenic variants in 50-75% of patients with HPT-JT, in approximately 14% of families with FIHP, and in up to 30% of individuals with apparently sporadic parathyroid carcinoma.^{5,6,11}

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH 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 array CGH.

References:

1. Newey, P. J., Bowl, M. R., Cranston, T. & Thakker, R. V. Cell division cycle protein 73 homolog (*CDC73*) mutations in the hyperparathyroidism-jaw tumor syndrome (HPT-JT) and parathyroid tumors. *Hum. Mutat.* **31**, 295–307 (2010).
2. Chen, J. D. *et al.* Hyperparathyroidism-jaw tumour syndrome. *J. Intern. Med.* **253**, 634–642 (2003).
3. Bradley, K. J. *et al.* Uterine tumours are a phenotypic manifestation of the hyperparathyroidism-jaw tumour syndrome. *J. Intern. Med.* **257**, 18–26 (2005).
4. Cavaco, B. M. *et al.* Identification of de novo germline mutations in the *HRPT2* gene in two apparently sporadic cases with challenging parathyroid tumor diagnoses. *Endocr. Pathol.* **22**, 44–52 (2011).
5. Shattuck, T. M. *et al.* Somatic and germ-line mutations of the *HRPT2* gene in sporadic parathyroid carcinoma. *N. Engl. J. Med.* **349**, 1722–1729 (2003).
6. Cetani, F. *et al.* *CDC73* mutational status and loss of parafibromin in the outcome of parathyroid cancer. *Endocr. Connect.* **2**, 186–195 (2013).
7. Carpten, J. D. *et al.* *HRPT2*, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. *Nat. Genet.* **32**, 676–680 (2002).
8. Tan, M. H. & Teh, B. T. Renal neoplasia in the hyperparathyroidism-jaw tumor syndrome. *Curr. Mol. Med.* **4**, 895–897 (2004).
9. 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).
10. Frank-Raue, K. *et al.* *CDC73*-related hereditary hyperparathyroidism: five new mutations and the clinical spectrum. *Eur. J. Endocrinol.* **165**, 477–483 (2011).
11. Bricaire, L. *et al.* Frequent large germline *HRPT2* deletions in a French National cohort of patients with primary hyperparathyroidism. *J. Clin. Endocrinol. Metab.* **98**, E403-408 (2013).
12. Davidson, J. T., Lam, C. G., McGee, R. B., Bahrami, A. & Diaz-Thomas, A. Parathyroid Cancer in the Pediatric Patient. *J. Pediatr. Hematol. Oncol.* **38**, 32–37 (2016).