CDC73 – genetic testing

ID: 3574 v.6 **Under review**

eviQ cancer genetics consensus statement: scope of genetic testing protocols

Related pages:

- Guide for health professionals ordering genetic testing
- CDC73 (Hyperparathyroidism-jaw tumour syndrome) – risk management
- Considerations for germline testing for variants identified in solid tumours

Target population

- An individual with a parathyroid neoplasm with one or more of the following:
  - pathological diagnosis of parathyroid carcinoma or atypical parathyroid adenoma[1]
  - distinctive morphological features[2]
  - absent nuclear staining for parafibromin on immunohistochemistry
  - local or distant recurrence following resection
- An individual with familial isolated hyperparathyroidism (FIHPT) in the absence of a clinical or molecular diagnosis of MEN1
- An individual with primary hyperparathyroidism (PHPT) presenting ≤40 years of age*
- An individual with PHPT and a personal or family history of ossifying fibromas/cemento-ossifying fibromas of the maxilla or mandible
- Where a known germline pathogenic variant is identified in a relative.**
- Where a specific pathogenic variant has been identified on somatic tumour testing.**

*In these patients a gene panel which includes MEN1, CDKN1B, CDC73 and RET should be considered.

**In these settings a variant-specific test (rather than sequencing a single gene or gene panel) may be more appropriate and cost effective.

Genetic testing is important for good clinical care of individuals who are suspected of having a heritable pathogenic variant in this gene.

Investigations before genetic testing

The results of the following investigations may significantly influence the likelihood of detecting a heritable pathogenic variant in the CDC73 gene:

- verification of previous pathology and radiology
- consider expert pathology review and parafibromin immunohistochemistry on resected parathyroid neoplasms under age 40 years.
- orthopantogram (OPG) with neck shielding
- If hypercalcaemic, calcium creatinine clearance ratio (fractional calcium excretion) to exclude familial hypocalciuric hypercalcemia (FHH): to use the Hammersmith Urine Calcium: Creatinine Clearance Calculator, right click on the link, choose 'Copy link address' and paste it into a new browser, which will download the calculator spreadsheet

Probability of a heritable pathogenic variant

There is no data on the frequency of *de novo* CDC73 pathogenic variants .

Factors	Probability of detecting a heritable pathogenic variant
Individual with parafibromin deficient parathyroid neoplasm	at least 67%[2]
Patient has a first or second degree relative with documented pathogenic variant	Up to 50%

Circumstances in which testing is not indicated

Predictive testing should never be ordered for a variant of uncertain significance or a benign/likely benign variant.

Testing methods

A range of testing methodologies are needed to identify pathogenic changes in the CDC73 gene including:

- DNA sequencing with MLPA

Information about DNA tests and testing laboratories is available from:

- RCPA catalogue of genetic tests and laboratories
- GeneReviews®
- Genetic Testing Registry
- NHS National Genomic Test Directory

If a decision is made to test this gene as part of a cancer gene panel, care should be taken to select a panel where the individual genes tested have both clinical validity and clinical utility.

A variant-specific test (rather than sequencing a single gene or gene panel) may be more appropriate and cost effective where a relative is known to have a germline pathogenic variant or a pathogenic variant has been identified in the patient's tumour.

If this gene is/these genes are tested using genomic sequencing ("next generation sequencing" or NGS), and testing has not identified a pathogenic variant , the value of testing using another methodology should be considered.

If germline gene testing is uninformative and immunohistochemistry demonstrated loss of parafibromin, gene testing of tumour samples may be helpful in identifying somatic variants or possible germline mosaicism. If germline mosaicism is suspected, testing of two or more different tumour samples is ideal, if possible.

Result interpretation

Result	Reference databases	Considerations and advice
Pathogenic variant search		
Pathogenic variant	ClinVar LOVD	CDC73 (hyperparathyroidism-jaw tumour syndrome) – risk management
Variant of uncertain significance		Review pathogenicity of variants periodically Identify other genes for which a pathogenic variant search could be considered
No reportable variant		Identify other genes for which a pathogenic variant search could be considered
Predictive testing		
Family pathogenic variant identified		CDC73 (hyperparathyroidism-jaw tumour syndrome) – risk management
Family pathogenic variant not found		Screening based on revised risk estimate

If a pathogenic variant is identified, refer to a clinical genetics service or familial cancer centre for review, family risk notification and predictive testing.

If a variant of uncertain significance is identified, consider referral to a clinical genetics service or familial cancer centre for review and guidance.

If a mosaic pathogenic variant is identified, refer to a clinical genetics service or familial cancer centre for review and guidance about the penetrance of phenotypic features (including cancer risk).

For additional information about the management of genetic test results when ordered by a non-genetic healthcare professional refer to eviQ's Guide for health professionals ordering genetic testing.

Website resources

Centre for Genetics Education - NSW Health

References

1 Saponaro, F., E. Pardi, L. Mazoni, et al. 2021. "Do patients with atypical parathyroid adenoma need close follow-up?" J Clin Endocrinol Metab 106(11): e4565-e4579.

2 Gill, A. J., G. Lim, V.K.Y. Cheung, et al. 2019. "Parafibromin-deficient (HPT-JT type, CDC73 mutated) parathyroid tumors demonstrate distinctive morphologic features." Am J Surg Pathol 43(1): 35-46.

History

Version 6

Date	Summary of changes
20/02/2023	The following sections of the document were updated to align with the new eviQ cancer genetics genetic testing template: • Target population: ◦ Added "Where a specific pathogenic variant has been identified on somatic tumour testing *" ◦ Added "*In these settings a variant-specific test (rather than sequencing a single gene or gene panel) may be more appropriate and cost effective." • Circumstances in which testing is not indicated: ◦ Removed "A variant-specific test (rather than sequencing a single gene or gene panel) may be more cost effective and appropriate where: ▪ a known pathogenic variant has been identified in a relative ▪ a specific pathogenic variant has been identified on somatic tumour testing." • Testing methods: ◦ Added "A variant-specific test (rather than sequencing a single gene or gene panel) may be more appropriate and cost effective where a relative is known to have a germline pathogenic variant or a pathogenic variant has been identified in the patient's tumour." ◦ Removed "e.g. MLPA and Sanger sequencing" • Result interpretation: ◦ HGMD and DMuDB removed from table. ◦ Template sentence added. Version increased to V.6.

Version 5

Date	Summary of changes

Date	Summary of changes
14/11/2021	Protocol reviewed at September 2021 cancer genetics reference committee meeting. Discussions continued via MS Teams. Approved for publication with the following changes made: • Target population: ◦ Sub-bullet 1: 'or atypical parathyroid adenoma' added • Investigations before genetic testing: ◦ Bullet 4: 'urinary calcium excretion to exclude familial hypocalciuric hypercalcemia if FIHPT suspected' changed to 'If hypercalcaemic, calcium creatinine clearance ratio (fractional calcium excretion) to exclude familial hypocalciuric hypercalcemia (FHH)' and link to Hammersmith Urine Calcium:Creatinine Clearance Calculator added • Circumstances in which testing is not indicated: ◦ Removed 'Genetic testing for CDC73 is not indicated in an individual with a clinical or molecular diagnosis of MEN1.' • Testing methods: ◦ Removed link to European Directory of DNA Diagnostic Laboratories Version increased to V.5. Review in 2 years.

Version 4

Date	Summary of changes
09/12/2020	The following sections of the document were updated to align with the new eviQ cancer genetics genetic testing template: • Related pages: added link to "Guide for health professionals ordering genetic testing". Removed link to "Pre-test counselling" • Probability of a heritable pathogenic variant: last row of table - probability changed from "25-50%" to "Up to 50%" • Circumstances in which testing is not indicated: template wording updated • Testing methods: template wording updated • Result interpretation: table format updated. Reference databases added. Template sentence added (including link to "Guide for health professionals ordering genetic testing") • Counselling: section deleted • Website resources: section deleted • Version number increased to V.4.
14/11/2021	Protocol reviewed at September 2021 cancer genetics reference committee meeting. Discussions continued via MS Teams. Approved for publication with the following changes made: • Target population: ◦ Sub-bullet 1: 'or atypical parathyroid adenoma' added • Investigations before genetic testing: ◦ Bullet 4: 'urinary calcium excretion to exclude familial hypocalciuric hypercalcemia if FIHPT suspected' changed to 'If hypercalcaemic, calcium creatinine clearance ratio (fractional calcium excretion) to exclude familial hypocalciuric hypercalcemia (FHH)' and link to Hammersmith Urine Calcium:Creatinine Clearance Calculator added • Circumstances in which testing is not indicated: ◦ Removed 'Genetic testing for CDC73 is not indicated in an individual with a clinical or molecular diagnosis of MEN1.' • Testing methods: ◦ Removed link to European Directory of DNA Diagnostic Laboratories Review in 2 years.

Version 3

Date	Summary of changes
19/11/2019	• "Mutation" changed to "pathogenic variant" and "unknown significance" changed to "uncertain significance" throughout document for consistency among eviQ cancer genetics protocols per agreement among the cancer genetics reference committees' chairs • Definition of "pathogenic variant" added as a pop-up Version number increased to V.3.

Version 2

Date	Summary of changes
19/03/2019	New protocol developed and presented at Nov 2018 RCM. Discussion continued over email and approved for publication. Version V.1. Review second yearly
28/08/2019	Protocol title changed from 'Genetic testing for heritable mutations in the CDC73 gene' to 'CDC73 genetic testing' in accordance with Cancer Genetics Reference Committees' consensus. Version number increased to V.2.

Version 1

Date	Summary of changes
19/03/2019	New protocol developed and presented at Nov 2018 RCM. Discussion continued over email and approved for publication. Version V.1. Review second yearly

First approved: 19 March 2019
Last reviewed: 14 November 2021
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