# Familial medullary thyroid cancer

## Key facts

- Familial medullary thyroid cancer (FMTC) is an inherited condition and a subtype of MEN2 (multiple endocrine neoplasia type 2), a hereditary endocrine cancer syndrome.
- Individuals with FMTC have a high probability of developing medullary thyroid cancer (MTC) with a lower probability (<5%) of developing the other specific endocrine tumours (phaeochromocytoma or parathyroid hyperplasia) usually associated with MEN2.
- FMTC accounts for 10-20% of all MEN2 cases.
- Genetic testing is essential for all MTC patients, even if there is no known family history.
- The age of onset of FMTC is usually later than in other types of MEN2 (typically middle age).
- FMTC is an autosomal dominant condition, and occurs due to genetic variants in the *RET* proto-oncogene.
- Approximately 80% of individuals with a *RET* genetic variant will develop medullary thyroid cancer at some point in their lives.
- Early diagnosis, treatment and management of the condition improves outcome and quality of life.
- The prevalence of MEN2 (including FMTC) is estimated to be between 1 and 9 in 100,000 individuals.
- Prenatal counselling and genetic testing are available.

## Clinical features

- The clinical features of FMTC are due to the onset of medullary thyroid cancer. Features may include:
  - a neck lump or neck pain; and
  - diarrhoea due to raised calcitonin levels.

## Diagnosis of medullary thyroid cancer (MTC)

- ultrasound or CT imaging confirming a suspicious node/mass;
- fine needle aspiration, or other histology confirming MTC; and
- raised calcitonin levels.

## Genetic basis and genetic testing

- FMTC is caused by genetic variants in the *RET* gene, which are inherited in an autosomal dominant manner. Children of an affected individual have a 50% (one-in-two) chance of inheriting the gene alteration.
- Due to the particular genetic variants that cause FMTC, the patient has a high probability of developing MTC and a low probability of developing other endocrine tumours.
- Genetic testing can detect over 95% of variants in the *RET* gene.
- Indications for genetic counselling and testing include:
  - a confirmed diagnosis of medullary thyroid cancer;
  - a confirmed *RET* genetic variant in a blood relative;
  - predictive testing for parents, siblings and offspring of someone with a confirmed *RET* genetic

variant. (For children, this would involve a cord blood sample at birth, or testing before four or five years of age. For children older than five years of age, genetic testing is recommended as matter of urgency); and
    - prenatal diagnosis.

- Genetic testing is available in the UK and is usually provided through specialist clinics or regional genetic centres.

## Clinical management

Patients with FMTC should always be managed by a specialist multidisciplinary team consisting of an endocrinologist, an experienced thyroid surgeon (skilled at operating on medullary thyroid cancers) and a clinical geneticist and genetic counsellor.

Annual screening is recommended, and may include the following tests:

- Individuals with medullary thyroid cancer
    - annual plasma calcitonin level;
    - annual neck and thorax MRI; and
    - somatostatin receptor nuclear medicine imaging, where available.
- Individuals with phaeochromocytoma
    - annual 24-hour urine or plasma metanephrines measurement;
    - annual blood pressure; and
    - abdominal scan if metanephrines become elevated.
- Individuals with primary hyperparathyroidism
    - annual serum calcium test.
- Pregnant individuals
    - up to date phaeochromocytoma screening; and
    - referral to a specialist endocrine antenatal clinic.

### Treatment of medullary thyroid cancer

- total thyroidectomy and neck dissection, with removal of lymph nodes as required, followed by lifelong thyroid hormone replacement;
- prophylactic thyroidectomy in children who are identified as carrying *RET* gene variants, to be considered at an early age, depending on the exact variant identified.
- tyrosine kinase inhibitors as promising potential treatments for patients with unresectable (unable to be removed with surgery), locally advanced or metastatic MTC.

## Direction to further reading, society guidelines and patient groups

- AMEND
- GeneReviews for MEN-2
- Revised American Thyroid Association Guidelines for management of MTC

*This information is intended for educational use and was current in January 2020. For clinical management, it is recommended that local guidelines and protocols are used.*

*Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Imperial College Healthcare NHS Trust.*