Controversy on the Management of *Patients Carrying RET p.V804M Mutation*

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Abstract

Context: *RET* p.V804M is classified as a moderate-risk mutation for familial medullary thyroid cancer (FMTC). There is a significant controversy on the management of patients carrying this mutation. We describe a family incidentally discovered to have this mutation during evaluation of a newborn with dysmorphic features. We provide a comprehensive literature review of *RET* p.V804M mutation.

Results: The proband was born to a first-degree relative parents with hypertrophy of some parts of the body and vascular skin changes. Whole exome sequencing of DNA extracted from a skin biopsy showed a mutation in the *PIK3CA* (c.3132T>G, p.ASN1044LYS). This variant was not found in DNA extracted from blood. This confirmed the diagnosis CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Scoliosis, skeletal or spinal anomalies). Another incidentally found mutation in the skin biopsy and blood sample was *RET* p.V804M. Although there was no family history of MTC or MEN 2 syndromes, family screening revealed *RET* p.V804M mutation and FMTC in the proband's father, paternal grandmother, one sister and one aunt. There was significant interfamilial heterogeneity in age of presentation and pathology. Review of data showed that *RET* p.V804M mutation is an indolent mutation that may be discovered incidentally and associated with low risk of FMTC, usually at middle to old age.

Conclusion: This and other recent studies raise questions about whether the American Thyroid Association (ATA) guidelines for management of patients with moderate risk *RET* mutations should also be applied to this seemingly "low" risk *RET* p.V804M mutation.

Introduction

Medullary thyroid cancer (MTC) accounts for about 5% of all cases of thyroid cancer [1, 2]. It is sporadic in around 75–80% and familial in the other 20–25% of cases [2, 3]. The underlying genetic alteration in the familial types are germline mutations in the rearranged during transfection (*RET*) gene[4]. Familial MTC presents as part of multiple endocrine neoplasia (MEN) 2a or 2b [5]. MEN 2a presents in 4 variants; an isolated familial MTC (FMTC), part of the classical form of MEN type 2a (MTC, primary hyperparathyroidism and pheochromocytoma), MEN 2a with cutaneous lichen amyloidosis, or MEN2a with Hirschsprung disease[5]. MEN type 2b presents with MTC, pheochromocytoma, mucocutaneous ganglioneuromas and marfanoid habitus [5]. There is good genotype-phenotype correlation with certain mutations associated with specific subtypes and with more aggressive features [3, 5–8]. For example, C634Y is characteristic of MEN 2a and M918T is pathognomonic of MEN type 2b and both mutations are associated with more aggressive forms of MTC [3, 5].

The *RET* mutation c.2410G > A, p.V804M is one of the most commonly reported mutations [6, 9, 10]. However, there is some controversy about its pathogenicity, age of penetrance and phenotypes [11–13]. It is classified as a moderate risk mutation by the American Thyroid Association (ATA) guidelines and as such, it is recommended that children with moderate risk *RET* mutations should have an annual physical examination, neck ultrasonography and serum calcitonin measurement starting at age 5 years. Thyroidectomy should be performed when serum calcitonin rises unless parents are concerned about long-term evaluation program and opt for prophylactic thyroidectomy at around age 5 years [5].

A recent analysis of population data based on non-cancer Exome Aggregation Consortium (ExAC) Databases found a high frequency of p.V804M mutation with a low lifetime penetrance of MTC of only 4% (95% CI, 0.9–8%) [6]. The authors suggested that the current ATA guidelines that call for prophylactic thyroidectomy in essentially all *RET* positive individuals should be revised for those carrying p.V804M [6]. *RET* p.V804M mutation is mostly associated with FMTC without other components of MEN 2 syndromes but there are some reports of pheochromocytoma and primary hyperparathyroidism in some families carrying this mutation [11, 13–15]. It is possible that other genetic or environmental modifiers operate in those cases with more phenotypic manifestations.

CLOVES syndrome (OMIM 612918) was described for the first time in 2007 and is characterized by tissue overgrowth and complex vascular anomalies [16]. CLOVES is an acronym for Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Scoliosis, skeletal or spinal anomalies [17]. It is caused by a somatic postzygotic mosaic activating *PIK3CA* mutations [18]. It is part of a complex group of diseases called *PIK3CA*-related overgrowth spectrum (PROS) [19]. This includes overlapping clinical syndromes such as Fibroadipose Overgrowth/Hemihyperplasia-Multiple Lipomatosis, Isolated Large Lymphatic Malformation, Epidermal Nevi, Seborrheic Keratoses, Benign Lichenoid Keratoses, Megalencephaly-Capillary Malformation, Hemimegalencephaly and Dysplastic Megalencephaly [19].

In this report, we describe a family with FMTC due to the *RET* p.V804M mutation, which was discovered incidentally when a newborn (index case) was found to have significant dysmorphic features of unclear cause. Whole exome sequencing (WES) was performed to understand the reason for these dysmorphia. An underlying *PIK3CA* mutation was found in DNA extracted from skin biopsy with an allele

frequency of 33% in 89 reads but not from blood sample indicating a post zygotic mosaic mutation of CLOVES syndrome. In addition, *RET* p.V840M was discovered incidentally in his WES of the skin and blood samples. Family screening revealed that the child's father has the same *RET* mutation and a 5-cm thyroid mass what turned out to be MTC. Further family screening revealed the presence of the p.V804M mutation in a number of family members and MTC and C cell hyperplasia (CCH) in some of them. The findings in this family suggest that this mutation is of moderate risk and tends to affect patients at an older age than usual for other *RET* mutations. There was also significant intrafamilial heterogeneity of p.V804M-related FMTC/CCH. In this report, we describe all of these aspects and provide a comprehensive review of the literature on this common *RET* mutation.

Patients

YK is now a 2-year old boy who was born to consanguineous parents at full term after an uneventful pregnancy and without any history of maternal exposure to toxic substances, alcohol or drugs. His birth weight was below the 3rd percentile and he was immediately observed to have gross hypertrophy of the right side of his body involving the skull, face, arms, trunk and right leg (Fig. 1a). He also had some hypertrophy of the left index finger and thumb and cutaneous changes consistent with vascular abnormalities. He had a large vascular malformation (hemangioma) over the right buttock. This was surgically removed and confirmed to be a hemangioma. The diagnosis was unclear and for that reason, WES was carried out to look for any genetic cause for his congenital anomaly. This was performed in DNA extracted from skin biopsy and a blood sample. It revealed a *PIK3CA* mutation (NM_006218.2: c.3132T > G, p.ASN1044LYS) in the skin biopsy but not in the blood sample confirming that this mutation is a postzygotic mosaic mutation and that the patient has CLOVES syndrome. This mutation was classified as a variant of unknown significance but was predicted to be probably damaging by PolyPhen, deleterious by SIFT, disease-causing by MutationTaster, Alig-GVGD: C65 (most likely to interfere with function) and the amino acid Aspraginase is highly conserved. This variant was not reported in Genome Aggregation Database (GenomAD), 1000Genome project, and Exome Sequencing Project (ESP). In addition to the *PIK3CA* mutation, a *RET* p.V804M mutation was reported as an incidental finding from the skin and blood samples. Further evaluation of the newborn revealed normal thyroid gland on ultrasonography without nodules and normal calcitonin level (4.1 pg/dl, normal range 0–5.0 pg/dl). Magnetic Resonance Imaging (MRI) of the brain showed hemimegalencephaly and thickened facial subcutaneous tissue, bulky right choroid plexus and prominent periventricular veins. The brain parenchyma was normal. MRI Lumbar spine was normal. Skeletal survey showed short big toes bilaterally and hypoplastic phalanges. He suffered from seizures that are currently controlled by three antiepileptic drugs. He also has significant developmental delay in his milestones. After obtaining informed consents and an Institutional Review Board Approval from the Office of Research Affairs, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, the family was screened for the p.V804M mutation. The child's father, 2 sisters, a brother, paternal grandmother, paternal aunt and her daughter were found to carry p.V804M mutation (Fig. 2). Clinical evaluation showed that the father has an asymptomatic 5-cm thyroid mass and some pathological cervical lymph nodes. A fine needle aspiration biopsy confirmed the diagnosis of MTC. Before referred to us, the father and several members of the family underwent total thyroidectomy either as a treatment of pre-existing FMTC or as prophylactic thyroidectomy. The family pedigree is shown in Fig. 2 and the clinical, biochemical and pathological features, management and outcome of the family are shown in Table 1.

Table 1

The clinical, biochemical, and pathological features and management and outcome of the family with *RET* p.V804M mutation

Patient	Age (yrs)	Sex	Calcitonin Pg/ml	US neck*	PTH Pg/dl	Calcium mmol/l	Urine Metanephrines	Thyroidectomy	Pathology*	Outcome*
III.1	1	M	< 0.2	N			N	No		NED
III.2	8	M		N			N	Yes	CCH	NED
III.4	9	F	< 0.2	A 2-mm cyst	33	2.32	N	Yes	CCH	NED
III.5	13	F	0.6	N	55	2.39	N	Yes	MTC 0.2 cm, CCH	NED
II.2	43	M	3150	A 5-cm nodule	35		N	Yes	MTC 5 cm, 6 LNM, PTC 2mm, Nodular hyperplasia	Persistent disease
II.8	46	F	38.9	A 5-mm nodule	58	2.35	N	Yes	MTC 0.5 cm, Multifocal, 0/5 LN PTC 0.6 cm, Multifocal	NED
III.6	21	F	< 0.2	N	43.7	2.38	N	Not yet		NED
II.10	26	F	< 0.2	N	51.3	2.45	N	Not yet		NED
I.1	65	F	5.5	Bilateral nodules, largest 1 cm (FNA benign)			N	Yes	MTC 0.2 cm, Multifocal, CCH PTC 0.5, MF	
*N, normal; PTH, parathyroid hormone; CCH, C cell hyperplasia, LNM, lymph node metastases; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; NED, No evidence of disease										
Normal ranges: Calcitonin up to 5 pg/ml; PTH 10–65 pg/dl; Calcium 2.1–2.6 mmol/l.										

***RET* M804V mutation in the literature**

We searched the literature for studies reporting the p.V804M mutation, its clinical presentations, age of presentation and penetrance. We used the terms *RET*, Rearranged during transfection, familial medullary thyroid cancer, multiple endocrine neoplasia, *RET* p.V804M. We found a number of case reports (Table 2), descriptions of extended families (Table 3) and large case series (Table 4).

Table 2
Summary of previously described reports of single patients or small families with *RET* p.V804M mutation

Reference	Number of families	Number of patients	Ages	Sex	Phenotype*	Remarks
Kasprzak L et al, 2001 [21]	1	3	53, 26, 35	M, F, M	FMTC, CNT One pt had bone mets	Had V778I and V804M on same allele
Gibelin et al, 2004[11]	1	2	55, 30 (daughter)	F, F	MEN 2a (PHP, MTC)	A 46-year half-sister had the mutation but no CCH
Shaha A et al, 2006[12]	1	4	69, 45, 42, 47	F, M, F, F	MTC with LNM, CCH, normal in 2 individuals	Mother, son and 2 daughters
Recasens, M. et al. 2007[15]	1	5	54, 50, 42, 29	M, F, F, M	Bilateral PCC + MTC, MTC, CCH (2)	4/5 had thyroidectomy
Rothberg A.E et al, 2009[26]	1	1	51	M	MTC + CLA	2 other sibs had the mutation but no info
Griffith, C. et al. 2010[27]	1	1	48	M	MTC + PTC	PTC BRAF+, MTC BRAF-
Choi Y.S. et al, 2013[35]	1	1	33	M	FMTC	
Nakao K.T. et al, 2013[22]	1	1	32	F	MEN2B-like (MTC and mucosal neuromas)	Tandem mutations ((Q781R/V804M)
Ercolino, T., et al. (2014)[36]	1	1	57	M	CCH	A patient with both germline NF1 and RET V804M mutations
Pendrick, D. M., et al. (2019)[20]	1	1	43	M	MTC with LNM	A 3-year old boy with leukemia led to discovery of V804M in the family, father and 3 sibs had MEN2A
*FMTC, familial medullary thyroid cancer; CNT, corneal nerve thickening; pt, patient; PHP, primary hyperparathyroidism; LNM, lymph node metastasis; PCC, pheochromocytoma; CLA, cutaneous lichen amyloidosis; CCH, C cell hyperplasia; Sibs, siblings						

Table 3
Summary of extended families or case series with *RET* p.V804M mutation

Reference	Number of families	Number of patients	Number of patients with p.V804M	Number of patients who underwent Surgery	Phenotype*
Lombardo F et al, 2002	5	61	61	31	12 CCH 18 CCH + MTC
Learoyd, D. L. et al, 2005[25]	1	5	5	3	MTC in 1 (LNM), CCH in 2
Shifrin, A. L et al, 2010[13]	1	40	40	15	15 Thyroidectomy; all had MTC, 6 PTC (40%), PHP in 1 and no PCC
Basaran, M. N., et al. (2015)[14]	1	30	17	14	7/14 MTC, 2/14 PTC, no PCC or PHP
*CCH, C-cell hyperplasia; MTC, medullary thyroid cancer; LNM, lymph node metastasis, PTC, papillary thyroid cancer; PHP, primary hyperparathyroidism; PCC, pheochromocytoma.					

Table 4

prevalence and findings of patients with *RET* p.V804M mutation reported in large series of patients with FMTC or MEN 2a or MEN 2b

Reference	Country	Number of families	Number of families with p. V804M	Number of patients	Number of patients with p. V804M	Number of patients underwent Surgery	Phenotype*
Fink et al, 1996[29]	Austria	16	1 (6.25%)	85	7	7	FMTC in 2, CCH in 5
Romi et al. 2010[24]	Italy	250	49 (19.6%)	NM		NM	3 MEN2a, 46 FMTC 3 FMTC (V804L)
Elisei, R., et al. (2019)[9]	Italy	195 (117 Familial + 78 apparently sporadic)	50 (25.6%)	NM	NM	NM	FMTC 47 families PCC 2 families PHP 1 family PTC 12 families
Maciel, R. M. B., et al. (2019) [7]	Brazil	176	15 (8.5%)	554	32	NM	32 FMTC, 1 PHP, no PCC
Machens, A., et al. (2013)[23]	Germany	191	19 (9.9%)	NM	NM		
(2017) French study [10]	France	444	95 (21.4%)				
*NM, not mentioned; FMTC, familial medullary thyroid cancer; CCH, C-cell hyperplasia; PCC, pheochromocytoma; PHP, primary hyperparathyroidism; PTC, papillary thyroid cancer							

Clinical phenotype

The case reports, large families and case series show the different phenotypes and frequencies of the p.V804M mutation in different populations (Tables 2, 3, 4). Most cases carrying the *RET* p.V804M mutation present with FMTC or CCH (Table 2). MEN 2a, primary hyperparathyroidism and pheochromocytomas occur rarely (Tables 2, 3, 4). Corneal nerve thickening was described in one report and cutaneous lichen amyloidosis in another report (Table 2). Although lymph node metastases appear to be relatively uncommon, distant metastases are rare. We found only one report of bone metastasis. Interestingly, more than one report described the presence of papillary thyroid cancer (PTC) with MTC suggesting that they cosegregate more frequently than incidentally in carriers of p.V804M mutations (Tables 2, 3, 4).

Frequency of *RET* p.V804M mutation

Although the frequency of the p.V804M mutation varies between different series, it is common and is the most common *RET* mutation in some populations (Table 4). There are a number of large series of patients with familial and/or sporadic MTC who were screened for various *RET* mutations (Table 4). In these series, the frequency of the p.V804M mutation varied between 6.25–25.6% (Table 4). This mutation was the most frequent *RET* mutation in two series conducted in Italy a decade apart, with rates of 19.6% and 25.6% (Table 4). It was also common in a large series from France (21.4%) but less common in Germany and Austria and Brazil with rates of 9.9%, 6.25% and 8.5%, respectively (Table 4).

Discussion

In this report, we describe a family with p.V804M mutation with many interesting aspects. Initially, this was found incidentally while evaluating a newborn with congenital anomalies that eventually turned out to be part of CLOVES syndrome. The finding of two rare genetic alterations, one is germline (*RET* p.V804M) and the other is a mosaic somatic mutation (PIK3CA c. 3132 T > GP), has never been

reported to our knowledge. It is unlikely that the two mutations are related but it is tempting to speculate that the germline *RET* mutation has induced some chromosomal instability leading to the development of postzygotic mosaic *PIK3CA* mutation. Although distinct from the hypertrophy of CLOVES syndrome, *RET* mutations are sometimes associated with some forms of growth such as cutaneous lichen amyloidosis and thickened corneal nerves, the pathogenesis of which is not fully understood. It is also tempting to speculate that these are similar to hypertrophy in this newborn and are related to postzygotic mutations limited to the areas of growth but this has not been studied.

It is also interesting how the congenital anomaly and its evaluation led to the discovery of FMTC in this family, which was not known to have any cancer syndromes. A similar situation was described in a 3-year old boy with leukemia who had WES as part of work up for the leukemia and this revealed a p.V804M *RET* mutation [20]. Evaluation of his family led to detection of this mutation and MEN 2a in his father and 3 siblings [20]. These two cases reflect the relatively indolent nature of this mutation and the previously shown observation of late development of MTC and MEN 2a in carriers of this mutation. The other interesting aspect of the *RET* p.V804M mutation is the intrafamilial heterogeneity (Table 1). While the father of the index case had a large MTC of 5 cm size with lymph node metastases at his age of 43 years, his 65-year old mother (paternal grandmother of the index case) had only a multifocal microMTC of 2 mm size and CCH. The 13-year old sister also had a 2-mm micro-MTC and CCH while a 46-year old aunt had a 5-mm micro-MTC and CCH. Two younger siblings of 8 and 9 years had CCH only (Table 1). A previously reported family with p.V804M mutation showed a skipping of a 93-year old mother (no disease) of a 53-year old son who had FMTC and corneal nerve thickening and his cousin (daughter of his mother's brother) and her daughter both had FMTC [21]. In our family and this reported family, males seem to be more affected but it is not clear whether these different phenotypic expressions are due to sex differences. Another possible explanation is the presence of other genetic modifiers that may lead to more manifestations in some family members. For example, it has been shown that the presence of tandem or double mutations in *RET* are associated with more aggressive tumors and higher likelihood of MEN 2a syndromes rather than FMTC alone [21, 22]. No other genetic alteration in *RET* or other genes was found in our family to explain this intrafamilial heterogeneity.

A review of the literature since the initial description of this mutation in 1996 [8] shows that the p.V804M mutation is relatively indolent and associated with old age of development of MTC [6, 7, 9, 12, 14, 23]. FMTC and CCH are the most dominant presentations [6, 9, 14]. However, complete or partial MEN 2a syndromes also occur [9, 11, 22, 24]. Lymph node and especially distant metastases are rare in patients with p.V804M [12, 21, 25]. Pheochromocytoma appears to be rare as well [9, 15] as are other less classic manifestations of MEN 2a such as thickened corneal nerves [21] and cutaneous lichen amyloidosis [26]. These seemingly indolent features and the low lifetime risk of FMTC in patients with p.V804M mutations raised questions about the general ATA recommendations of prophylactic thyroidectomy for patients carrying the p.V804M mutation [6]. Some suggested that a "wait-and-see" approach guided by plasma calcitonin level monitoring is a better and safer strategy than routine prophylactic thyroidectomy for patients with this mutation [6, 12].

A number of reports have described the concomitant occurrence of PTC and FMTC in patients with p.V804M mutation [13, 14, 27, 28]. While this could be coincidental as PTC is very common, the several reports describing this combination in patients with p.V804M mutation suggest a possible association related to the transforming capacity of this mutation [13, 23, 27]. In our family, 3 out of 6 members (50%) who underwent thyroidectomy had micro-PTC (2–6 mm in size) in addition to MTC.

The prevalence of the *RET* p.V804M mutation varies between populations (Table 4) but overall, it is a common mutation [3, 6, 9, 24]. Two reports from Italy in 2010 and 2019 which included 250 and 195 families, respectively showed that the p.V804M mutation was the most common mutation occurring in 19.6% and 25.6% of families with *RET* mutations, respectively, suggesting that this variant might be a founder mutation in the Italian population [9, 24]. Similar prevalence has also been reported from a large study from France (*RET* Variants) which included 444 families with FMTC/MEN 2 syndromes and showed p.V804M mutations in 95 of them (21.2%)[10]. However, less prevalence rates were found in Germany (9.9%) and Austria (6.25%) and Brazil (8.5%) [7, 23, 29].

With the widespread use of next generation sequencing, large databases have now become available. These databases include some for patients with cancer and some non-cancer databases. Studies that have looked at the chance occurrence of p.V804M in these databases showed occasional occurrence of this mutation in patients with other diagnoses. In a study that included 1566 patients with different cancers who underwent tumor and normal tissue genomic sequencing for possible target therapies, 246 patients (15.7%) were found to have presumed pathogenic germline mutations including 198 subjects having mutations in cancer susceptibility genes [30]. Interestingly only around 41% of these germline mutations were concordant with the patient's underlying cancer diagnosis. Six *RET* germline mutations were found in this series including p.V804M in a patient with colorectal cancer [30]. In another study that included 165 patients with metastatic lung and colorectal cancer who underwent WES on tumor tissue and matching blood samples, of 806 curated germline mutations, 5% were clinically relevant and 56% of unknown significance [31]. *RET* p.V804M mutation was found in 1 patient with metastatic lung adenocarcinoma [31]. In a large study of this type of analysis, Kuan-Lin Huang et al. analysed the pathogenic variants

from 10,389 individuals across 33 cancer types in The Cancer Genome Atlas (TCGA) cohort [32]. They found 8% of cases carrying pathogenic or likely pathogenic germline variants, ranging in prevalence from 22.9% in pheochromocytoma and paraganglioma (PPGL) to a scarce 2.2% in cholangiocarcinoma [32]. *RET* p.V804M mutation was found in 3 cases [32]. However, this analysis included patients with MTC, MEN 2a and 2b and PPGL [32]. Therefore, it was not surprising to find this mutation in the 3 cases. In fact, the three cases had MEN 2a syndrome [32]. Loveday et al, evaluated 61 *RET* mutations in non-cancer ExAC database of around 51000 individuals [6]. They found only 10 of the 61 *RET* mutations present in this non-cancer database including p.V804M mutation [6]. However, they estimated the lifetime penetrance for MTC for this mutation to be quite low at about 4% (95% CI, 0.9-8%) and questioned the current ATA recommendations of prophylactic thyroidectomy for carriers of this mutation [6].

The age at which the risk of FMTC in p.V804M mutation starts to appear has been a subject of controversy. Although most studies show that the majority of patients carrying this mutation develop MTC in their 5th or 6th decade of life, some reported FMTC and MEN 2a syndrome in as early as second decade of life [33]. A comprehensive analysis of a large sample of patients with low risk mutations (class A and B according to the ATA old classification [34] and moderate risk according to the more updated classification in 2015 [5] included 160 patients with p.V804M mutations [33]. Their age ranged between 2–74 years and 52% were females. No cases developed MTC at 5, 10 and 15 years but the probability was 0.02, 0.03, 0.17, 0.31, 0.67 and 0.87 at 20, 30, 40, 50, 60 and 70 years, respectively and the median age to develop MTC was 54 years (range 52–60) [33]. However, other studies of large families showed variable expression of the disease even within the same family with some carriers not developing MTC in their 70s and 80s and some developing metastatic disease in their 20s and 30s (Table 2). This was also the case in our family where the youngest member with MTC was the 13-year old girl. An 8 and 9-year old boy and girl had only CCH. The literature is conflicting on this subject with some recommending prophylactic thyroidectomy in childhood [25] and most recommending surveillance and thyroidectomy when serum calcitonin starts to rise [12, 25, 33]. Based on our family and the literature review, it seems reasonable to adopt a surveillance strategy for carriers of p.V804M mutation and proceeding with thyroidectomy only when serum calcitonin starts to rise.

In summary, we have described an interesting patient born with congenital anomaly that turned out to be the rare and recently described CLOVES syndrome. WES to investigate for the congenital anomaly revealed a post zygotic *PIK3CA* mutation consistent with his diagnosis of CLOVES syndrome but incidentally reported *RET* p.V804M mutation. Evaluation of this family found several members with this mutation and therapeutic or prophylactic thyroidectomy showed CCH or MTC at different ages with clear intrafamilial heterogeneity with respect to the features of MTC and the age of the patients. Comprehensive literature review showed that p.V804M *RET* mutation is common especially in Europe and is associated mostly with FMTC/CCH and rarely with other components of MEN 2a syndromes. The age of MTC development is variable but generally is late (4th to 5th decade of life) suggesting that prophylactic thyroidectomy might be deferred until serum calcitonin starts to rise. This is probably a reasonable approach since the disease associated with this mutation is generally indolent and small even when they develop early in life.

Declarations

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Figures

Figure 1

Photographs of the index case at age 2 years showing hypertrophic changes involving the right side of the skull and face, right arm, right hand fingers, right side of the trunk, right thigh, the left thumb and index finger. It also shows extensive cutaneous vascular changes over the trunk, back and left hand

Figure 2

The sequence chromatogram (A) of the father (patient II.2) showing normal sequence in the upper panel and the patient's sequence in the lower panel with the c.2410G>A, p.V804M mutation. The family pedigree (B) is shown on the left side