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Familial non-medullary thyroid carcinoma: 10-years clinical follow-up and genetic study of a multiple-hit portuguese family

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Familial non-medullary thyroid carcinoma: 10-years clinical follow-up and genetic study of a multiple-hit portuguese family

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Para a minha adorada família .
Para os meus inestimáveis amigos.

Familial non-medullary thyroid carcinoma: 10-years clinical follow-up and genetic study of a multiple-hit Portuguese family

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Abstract

Non-medullary thyroid carcinoma is an entity mostly recognized as sporadic and non-aggressive. Although the definition of its familial form (FNMTC) is still controversial, it has increasingly been identified by epidemiologic studies that suggest a more aggressive behavior and worse prognosis than the sporadic counterpart. Recent studies have identified six susceptibility *loci* that may be responsible for FNMTC inheritance. We intend to contribute to the increasing evidence that justify the investment on a more close surveillance and follow-up of members of affected families. Reachable members of a previously identified family with FNMTC were clinically evaluated by thyroid palpation, thyroid ultrasound and thyroid blood tests. Blood samples were drawn for genotyping. From eight NMTC cases in this family, 2 were diagnosed before the commencement of the family screening, 5 during the screening and 1 during this evaluation. However, these cases did not present with characteristics of aggressiveness. In addition, various benign thyroid disorders were also identified. Linkage analysis excluded MNG1 and TCO as susceptibility *loci* in this family. The high incidence of cases in these kindreds and the aggressiveness that these tumors may present justify the recommendation for a closer follow-up and more intensive treatment approach.

Keywords: Non-medullary thyroid carcinoma, Familial non-medullary thyroid carcinoma, FNMTC, susceptibility *loci,* follow-up, treatment approach

Introduction

Thyroid carcinomas are an extremely important clinical entity. Over the last three decades its incidence has increased more than twofold in the United States, with similar patterns of increase reported all over the world, which may be due to a real incidence augmentation or to increased medical surveillance and more sensitive diagnostic tests.[1, 2] Although it presents a modest prevalence (~1% of human malignancies) and a generally good prognosis and non-aggressive behavior, its revision is embedded with a special significance: it is a magnificent oncogenesis model which may help to bring light to the study of a wide variety of carcinomas. Almost 95% of patients have well-differentiated cancer of follicular cell origin, including papillary carcinoma and its variants (80-90%) and follicular carcinoma(10-15%).[3] Undifferentiated neoplasms, like anaplastic carcinoma, account for minimal percentage of cases. Usually, these kind of neoplasm are taken as sporadic, unlike medullary thyroid cancer (neoplasm arising from the calcitonin-producing C cells), which account for 5% of thyroid cancers. Twenty percent of these patients have a well established familial occurrence as part of the multiple endocrine neoplasia type 2 (MEN-2) or in a familial form without neoplasia of other tissues (MTC-only syndrome).[4]

The occurrence of non-medullary thyroid cancers (NMTC) is traditionally considered to be sporadic and associated with radiation exposure but recently, data from epidemiologic studies has brought to light the evidence of a familial form of NMTC (FNMTC). In fact, several multiple-hit familial clusters, non-exposed to environmental risk factors, brought the need for testing these families genetic background. FNMTC accounts for approximately 5% of all thyroid cancers of follicular cell origin, ranging from 2,5% to 10,5%. [5, 6]

Carcinoma of thyroid follicular cells in a familial setting was first described in 1955, in identical 24-years-old twins. [7] Recently, Fallah et al. estimated the lifetime cumulative risk of thyroid cancer (CRTC) in first-degree relatives of patients with papillary thyroid carcinoma (PTC) to be 2% in females (1% in males), representing a threefold increase over the general population risk. When there were more than 2 PTC patients diagnosed at age <60 years in a family, the CRTC increased to 10% in females (24% in males). [8] This underlines the issue regarding the definition of FNMTC. In 2000, Musholt et al. created a series of clinical criteria for the diagnosis of FNMTC based on its associations with benign thyroid disease, and its clinical and aggressiveness characteristic.[9] Still, these criteria did not reach a general acceptance. Most recent reports establish the presence of FNMTC in kindreds with 2 affected members. However, Charkes' work state that in 2-hit families, 62%–69% of affected members are sporadic cases. In families having 3 or more affected members, more than 96% would have the familial trait.[10] Therefore, although still controversial, recent studies assume the real definition for FNMTC as being the presence of NMTC in 3 or more family members, in the absence of other known associated syndromes or exposure to environmental factors known to cause thyroid cancer.

FNMTC encompass a heterogeneous set of diseases and is divided into two groups. The first includes familial syndromes characterized by predominance of non-thyroidal tumors and associated with higher risk of NMTC (Table 1), such as familial adenomatous polyposis (FAP), PTEN hamartoma tumor syndrome (PHTS), Carney complex type 1 and Werner syndrome.

Table 1| Hereditary tumor syndromes associated with thyroid cancer.

Disorder	Chromosomal location	Gene	Inheritance	Thyroid pathology
PHTS	10q22-23	PTEN	AD	FTC (5-10%); MNG, MAN, FA, PTC (50-67%)
FAP	5q21	APC	AD	PTC (cribiform pattern)
Carney complex	2p15-15, 17q22-24	PRKAR1a	AD	PTC, FTC (15%)
Werner syndrome	8p11-21	WRN	AR	PTC, FTC, ATC
MEN1	11q13	MEN1	AD	Rare
MEN2A	10q11.2	RET	AD	Micro PTC
McCune Albright syndrome	20q13.1-13.2	GNAS1	Mosaic	FA, FTC

Abbreviations: PHTS – PTEN hamartoma tumor syndrome; FAP – Familial adenomatous polyposis; MEN – multiple endocrine neoplasia; AD – autosomal dominant; AR – autosomal recessive; FTC – Follicular thyroid carcinoma; MNG – multinodular goiter; MAN – multiple adenomatous nodules; FA – follicular adenoma; PTC – papillary thyroid carcinoma; ATC – anaplastic thyroid carcinoma.[11]

The second includes familial syndromes characterized by predominance of NMTC (Table 2). The focus of this report is on this second group. FNMTC is 2 to 3 times more common in women than men, as is sporadic PTC, and presents with an increased incidence of benign thyroid neoplasia. [12] The pathological subtype is more frequently PTC, although cases of familial follicular thyroid carcinoma have been described.

The genetic inheritance of FNMTC remains unknown and no susceptibility genes have yet been identified. Therefore, it remains to be definitively proven that FNMTC is a classical familial tumor syndrome. Several reports postulated an autosomal dominant way of inheritance, with incomplete penetrance and variable expressivity. Six potential regions for harboring an FNMTC gene have been pointed out as targets: MNG1 (14q23), thyroid carcinoma with oxyphilia (TCO; 19p13.2), fPTC/PRN (PRN; 1q21), NMTC (2q21), FTEN (8p23.1-p22), and telomere-telomerase complex.

Table 2| Familial tumor syndromes characterized by predominance of NMTC

Disorder	Chromosomal location	Candidate Genes	Inheritance	Tissue Pathology
PTC associated with PRN (fPTC/PRN)	1q21	Unknown	Unknown	PTC, BTN, PRN
Familial MNG with PTC	14q31	Unknown	AD	MNG, PTC
FPTC	2q21	Unknown	Unknown	PTC
Familial TCO and without oxyphilia	19p13.2	Unknown/ TCO/ TIMM44	AD	PTC with/without oxyphilia

Abbreviations: PTC – papillary thyroid carcinoma; PRN – papillary renal neoplasia; BTN – benign thyroid nodules; MNG – multinodular goiter; FPTC – familial papillary thyroid cancer; TCO – thyroid carcinoma with oxyphilia; AD – autosomal dominant.[11]

There are still important difficulties regarding the diagnosis of FNMTC. Because of the inability to genetically test for this condition, the diagnosis is based solely on family history. The identification of the susceptibility genes responsible for FNMTC would make screening and early diagnosis much easier, contributing for improved survival and disease-free rates. Although still controversial, the strength of the current epidemiologic data underlines the importance of considering this a special entity that justify the investment on a more close surveillance and follow-up of members of affected families. Our study presents one identified 8-hits, four generations Portuguese family with FNMTC and its clinical follow-up during a 10-years period. We also formulate an attempt on the genetic analysis of the affected members of the family by studying MNG1 (14q32) and TCO (19p13.2) as possible susceptibility loci.

Methods

Family

Based on the previous identification of this multiple-hit portuguese family by Costa, E. ("Carcinoma não-medular familiar da glândula tireóide – Identificação e caracterização de agregados familiares"), we collected the clinical data from all the reachable family members. The trial was approved by the Ethics Committee of Centro Hospitalar de São João, E.P.E.. Informed consent was obtained from all the enrolled subjects. We have not examined members of the family who were under the age of 5 years old. Where available, the results of isotope imaging, ultrasound and histopathology of tissue from surgery have been reviewed. The subjects were reviewed regarding previous medical history and screened with thyroid palpation, thyroid ultrasound and thyroid blood tests. When indicated by the results of the previous tests, fine-needle biopsy aspiration and/or thyroid scintigraphy were performed. Blood samples were drawn for genotyping.

DNA extraction and Microsatellite markers genotyping

Blood samples were collected from seven affected persons [five with PTC (A, B, J, M and N) and two with benign lesions (L and O) and from one unaffected person (III-3)], after

their informed consent was obtained. Genomic DNAs were extracted according to a standard phenol-chloroform protocol. The eight samples were genotyped with fluorescently labelled microsatellite markers of chromosomes 14 (D14S74, D14S1030 and D14S611) and 19 (D19S413, D19S586 and D19S407), from Invitrogen™.

Each PCR reaction included 1 X PCR buffer, 1.5 mM MgCl2, 200 mM of each dNTP, 100 ng DNA, 0.2 U Red Hot DNA polymerase (Advanced Biotechnologies), and 5 pmol of each primer (one of them fluorescently labeled) in a 10-µl final reaction volume. Thermocycling conditions, using a GeneAmp PCR system 9700 thermocycler (Applied Biosystems, Foster City, CA, USA) were: 94ºC for 10 min; 30 cycles of 94ºC for 30 s, 55ºC [markers (D14S74, D14S1030, D19S586)] or 58ºC [markers (D14S611, D19S413, D19S407)] for 30 s, and 72ºC for 30 s; and final extension at 72ºC for 5 min. Separation and detection were performed using the ABI PRISM 3100 Genetic Analyser 16-capillary electrophoresis system. To each PCR product, 9.5 µl of HiDi formamide (Applied Biosystems) and 1.5 µl of internal size standard GS500 LIZ (Applied Biosystems) were added. Fragment sizes were automatically determined using GeneScan Analysis 2.1.

Results

A pedigree chart of the family, referring to the commencement of the screening, is displayed in Figure 1. The pedigree chart referring to the present situation is displayed in Figure 2. In this kindred there were 61 members that would fall onto the inclusion criteria, but we were able to contact and study only 37 (59%). The prevalence of PTC was 21,6%. Eight members of the family presented with papillary thyroid carcinoma (PTC), 2 with thyroid nodule, 5 with multinodular goiter (MNG) and 2 with thyroiditis. The mode of inheritance suggests autosomal dominancy with incomplete penetrance, and women seem to be affected more frequently than men. The pathological characteristics and treatment of the 8 PTC cases are summarized on Table 3.

From the initial evaluation of this family, in 2003, by Costa, E., 4 new cases of PTC were identified (A, P, Q and R), all of them in previously affected patients: three patients with thyroid nodules and one with MNG (A). The patient A was initially diagnosed with follicular adenoma and treated with chirurgical enucleation of benign nodule in 1985; MNG was diagnosed at 43 years of age and PTC developed at the age of 67, on family screening. Patient P was diagnosed with a multifocal and bilateral PTC at the age of 28, but we were unable to screen him by the time of the present report. Patients Q and R had initially been diagnosed with benign cystic nodules of 10 and 6 mm of diameter, respectively; patient Q developed PTC at the age of 30 and patient Q at the age of 34, both of them detected in the context of family screening (patient R at this evaluation). Also, the 2 siblings previously diagnosed with PTC (M and N) had been identified independently without knowledge of positive family history, both at the age 32; patient N was diagnosed with relapse by thyroid scintigraphy, during this follow-up, one year after the initial diagnosis. He was treated with central and lateral neck dissection. Patient B was diagnosed at the commencement of the prospective family screening with MNG without cytologic evidences of malignancy; subsequent total thyroidectomy due to compressive symptoms at the age of 61 revealed an Hurthle cell variant of PTC embedded on MNG. Patient J was diagnosed with MNG and multifocal bilateral PTC at the age of 41, on family screening.

Table 3| Pathological characteristics and treatment of the PTC cases.

Patient	Age at diagnosis	Ultrasonographic characteristics	Thyroid histopathology	Treatment
A	67	MNG 2 right lobe nodules (23 and 17mm Ø)	MNG PTC, classic variant	Total thyroidectomy

B	61	MNG 1 right lobe nodule (30 mm Ø) 1 left lobe nodule (26mm Ø)	MNG Hurthle cell variant of PTC	Total thyroidectomy
J	41	MNG 2 right lobe nodules (18 and 16mm Ø)	MNG Multifocal, non-capsulated, classic variant PTC	Total thyroidectomy + I^{131} therapy
M	32	Thyroid nodule (18mm Ø)	PTC, classic variant	Total thyroidectomy
N	32	Thyroid nodule (13mm Ø)	PTC, classic variant	Total thyroidectomy + Central and lateral neck dissection
P	28	Thyroid nodule (15mm Ø)	Encapsulated PTC	Total thyroidectomy
Q	30	Right lobe solitary nodule (14mm Ø)	Non-capsulated, classic variant PTC	Total thyroidectomy
R	34	MNG Predominant right lobe nodule (30mm Ø)	NA	NA

Abbreviations: NA – not available.

Patients C and D were diagnosed with thyroid nodule and MNG at the age of 49 and 46, respectively; both feature with benign cytologic and ultrasonographic characteristics. The five siblings E to I all presented with thyroid pathology at the commencement of family screening; the results of FNBA were all consistent with benign findings (cystic and colloid nodules). Patient L was diagnosed at the age of 31 with MNG and at 35 with Hashimoto's thyroiditis/hypothyroidism with high titers of autoantibodies (anti-thyroid peroxidase of 28,51 UI/ml), subsequently treated with thyroxine. Patient O was diagnosed with hypothyroidism after her last pregnancy and presents with ultrasonographic characteristics of thyroiditis.

Linkage analysis

We verified that affected and non-affected members shared the same haplotype (data not shown), therefore excluding linkage to the aforementioned susceptibility *loci* (TCO and MNG1). The limit of detection (LOD) score for this family was not calculated because there were few members and markers.

Discussion

In this report we describe a Portuguese family with 8 cases of PTC associated with thyroid nodules (2 cases), MNG (5 cases) and thyroiditis (2 cases).

There are well-knonw risk factors to develop PTC, namely exposure to radiation, deficient or excessive iodine intake, TSH levels, autoimmune thyroiditis, obesity and environmental polluents. [13] Low iodine intake causing high prevalence of endemic goiter have remained for many years the most important risk factor for follicular carcinoma. Iodine

Figure 1| Pedigree chart of the family studied - 2003

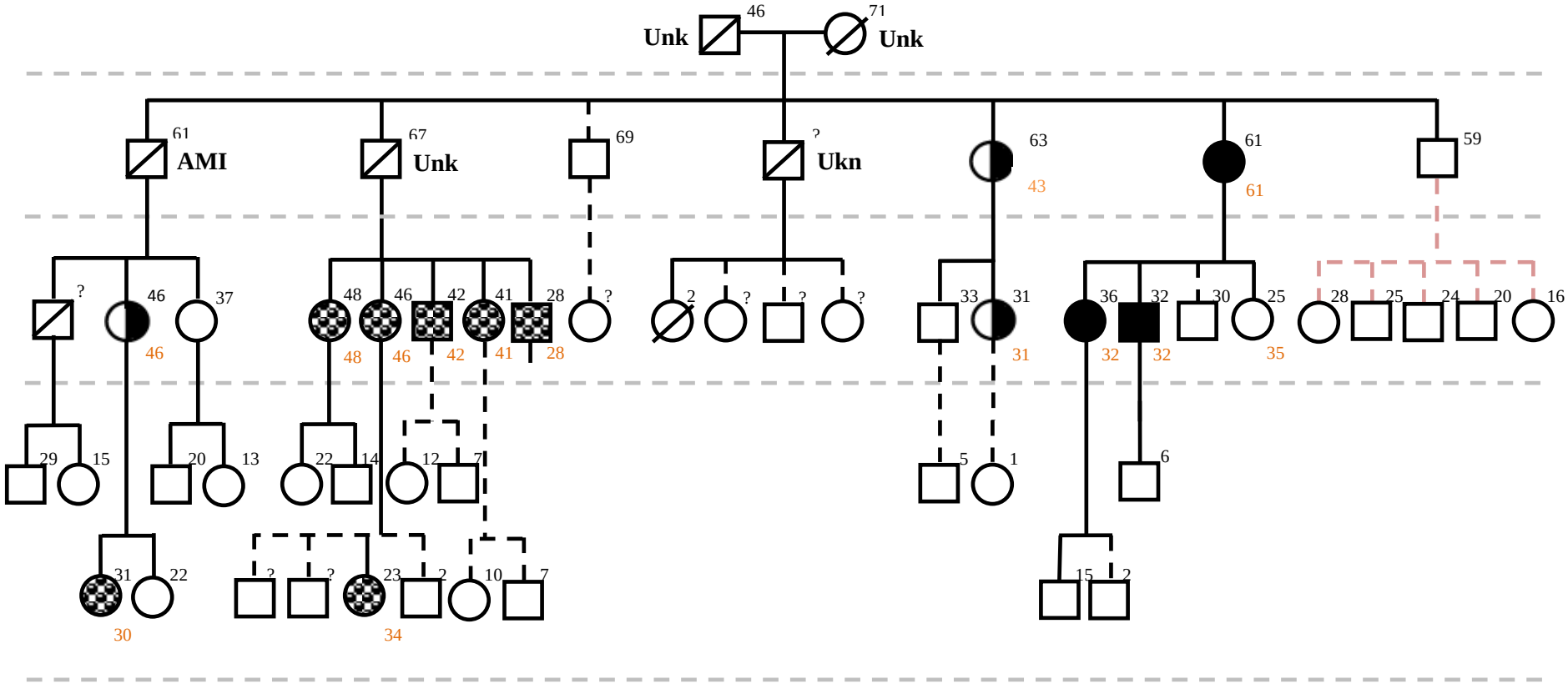
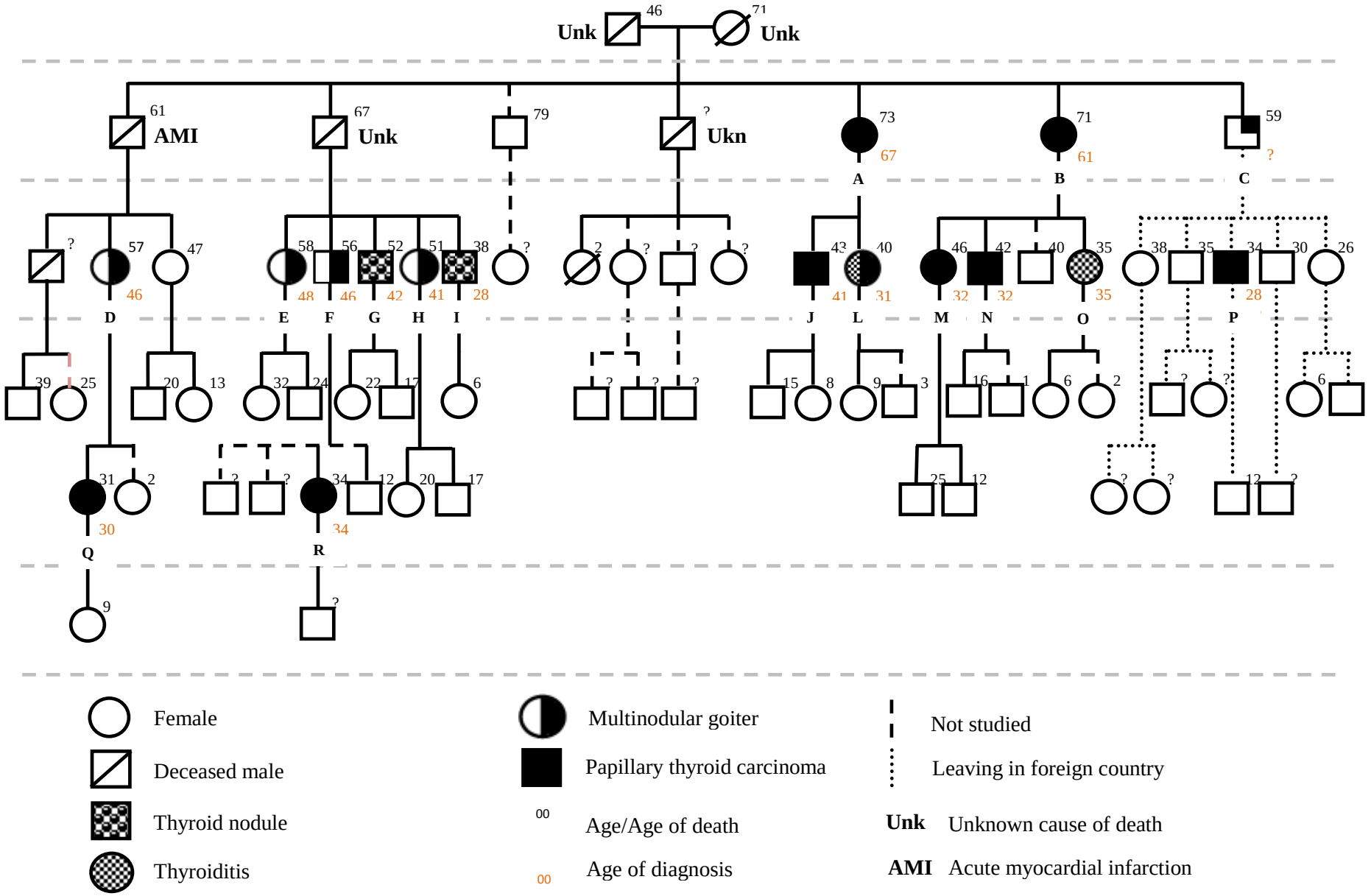


Figure 1| Pedigree chart of the family studied – 2013



intake is known to influence the thyroid cancer histotype distribution, rather than the overall incidence, with more follicular and fewer papillary carcinomas in iodine-deficient areas. When iodine prophylaxis was introduced the papillary/follicular ratio increased. The gender-ratio distribution has also been modified by introduction of iodine enriched salt in 1971 in Portugal, with female patients being more affected. This could partly explain the preponderance of PTC and female cases in this family, but not the high incidence within the family. The majority of the family members described here live in the North coastal zone of the country, an area with no endemic goiter and low incidence of environmental iodine deficiency or excess. Therefore, the proportion of family members with MNG or PTC in this kindred is considered to be too high to be explained by iodine influence. Also, there is no indication that any member of the family had been exposed to ionizing radiation. There are several members that present with MNG or PTC at very early age, thus suggesting a genetic predisposition rather than exposure to environmental risk factors.

One of the most controversial issues regarding FNMTC is whether it presents with a more aggressive behavior and a worse prognosis than sporadic neoplasias. Most studies advocate that FNMTC has a predisposition to characteristics that attest tumor aggressiveness such as younger age at presentation, multifocality, bilaterality, local invasion, extrathyroidal invasion, lymph node metastases, and high recurrence rates. [12, 14-18] FNMTC patients have shorter disease-free survival than do sporadic disease patients,[9, 10, 12, 14, 19, 20] and Uchino et al. and Alsanea et al. even consider it an independent predictor of shorter disease-free survival.[12, 14] Recently, Mazeh et al. even postulated that patients with NMTC having a family history of thyroid cancer have more aggressive disease, regardless of whether they meet the current definition of FNMTC regarding number of affected family members.[21] However, some studies fail to recognize any significant difference between familial and sporadic tumor's characteristics or survival rates.[22-25] In this study, from 8 FPTC cases, 1 was histopathologically described as multifocal and 2 as non-capsulated, locally infiltrative carcinomas. One case (patient N) relapsed during the follow-up. The majority of the cases, however, did not present the aggressive characteristics commonly associated with FPTC. Recent studies have also underline the issue of clinical anticipation: compared with their parents, patients in the second generation had younger age at diagnosis, after ruling out the bias of screening effect, greater multicentricity and bilaterality, higher metastasis rate and worst prognosis.[16, 17] This effect is concordant with our findings, namely, the median age of diagnosis in the second generation was 29 years younger than the first generation.

As the genetic causes of most cases of FNMTC remain unknown, widespread genetic testing is not available. We performed linkage analysis of two of the susceptibility *loci* previously identified: MNG1 (14q32) and TCO (19p13.2). We did not find any association with the 2 aforementioned *loci*. Our data suggest that these two candidate regions are not frequently involved in Portuguese FNMTC. Since the linkage analysis in this informative family showed no evidence for the involvement of any of the two candidate regions, we decided to perform a subsequent Whole-Genome Association Study in an attempt to find new *loci* predisposing to FNMTC. This study is utilizing the Affymetrix® Genome-Wide Human SNP Array 6.0, that features 1.8 million genetic markers, including more than 906,600 single nucleotide polymorphisms (SNPs) and more than 946,000 probes for the detection of copy number variations (data not available).

Considering the relative higher aggressiveness of FNMTC compared with its sporadic counterpart, the screening, management and treatment of the members of these families constitute a challenge. Most authors advocate that all members of affected families should undergo a careful history and thorough physical examination, followed by ultrasonography of the thyroid gland and cervical lymph nodes. This would warrant early detection of smaller, earlier stage tumors which probably improves clinical outcome. In our study, 6 of the 8 FPTC cases were diagnosed on family screening, both in previously affected and non-affected patients, re-enforcing the importance for systematically screen these patients. Most case

reports/series find the mean age of diagnosis for patients with FNMTC to be similar to those with sporadic NMTC,[1, 12, 25] but there are some that have noted a slightly earlier presentation, as occurs in most familial syndromes.[9, 14, 19] A meta-analysis found that patients with FNMTC presented up to a decade earlier than their sporadic counterparts, with a peak age of onset in FNMTC patients of the fourth decade. [5] Therefore, we would advice that the commencement of screening was done 5 to 10 before the youngest age of onset, for most families around age 20, with a regular yearly follow-up if screening history, physical examination, and ultrasound are negative. [26] Fine-needle aspiration (FNA) is an important part of the diagnostic evaluation of a thyroid nodule. However, FNA has been shown to be less reliable in patients with FNMTC, due to the higher incidence of multifocality, bilaterality and multiple benign nodules. [1] Taking into account the aforementioned aggressiveness of these tumors, we recommend a prophylactic total thyroidectomy in any patient with a thyroid nodule and a strong family history, regardless of the FNA result, as do many other authors. This recommendation is supported by the fact that many of the FPTC develop in previously affected patients with benign thyroid nodules by FNA, as seen in this family. This somehow aggressive approach has important advantages: 1) it allows the use of radioactive iodine ablation to treat and scan patients; 2) it provides serum thyroglobulin as a sensitive tumor marker post-operativly; 3) it may improve prognosis of these patients as it provides an earlier treatment, before the tumor is clinical, radiological or cytologically apparent.

All patients with biopsy-proven FNMTC should undergo total thyroidectomy. As all thyroid tissue has similar genetic predisposition to develop malignancy, residual tissue should be avoided whenever possible. Due to the high lymph node involvement, prophylactic central neck dissection and postoperative radioactive iodine ablation followed by thyroid hormone suppression should be considered because of the elevated recurrence rate and mortality associated with recurrence rate. The optimal follow-up for patients with a diagnosis of FNMTC is unknown, but it would be, at very least, the standard of care for their stage of disease, if not closer.

Conclusion

The kindred studied represent a good example of FNMTC cases. Our report supports the idea that a close follow-up and surveillance of these families constitutes a way of improving the precocity of diagnoses, and thereby, the prognosis of these patients. An aggressive treatment approach seems to be beneficial, since papillary carcinoma was found even on a patient operated with an initial diagnosis of benign MNG. The demographic characteristics of this kindred and the new genetic approach now used may provide clues for the final understanding of this entity.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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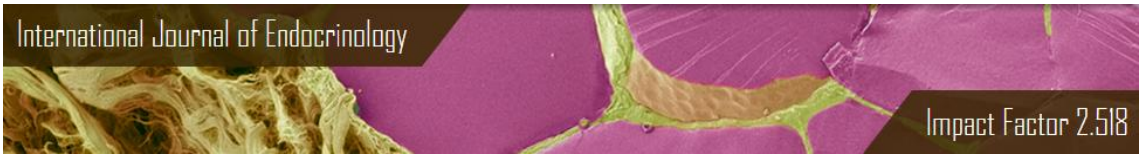
À Drª. Ana Beatriz Caldeira e aos enfermeiros de Cirurgia, pela colaboração espontânea.

À minha família, em especial aos meus pais e avó, pelo apoio incondicional.

Aos meus amigos, eternos companheiros dos bons e maus momentos, por me ensinarem a relativizar.

ANEXOS



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CES 281-13

Exmo. Senhor

Presidente do Conselho de Administração do

Centro Hospitalar de S. João – EPE

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO DE REUNIÃO DE 06 MAR 2014

Presidente do Conselho de Administração

(Prof. Doutor António Ferreira)

Directora Clínica | Enfermeira Directora | Vogal Executivo | Vogal Executivo

(Dra. Margarida Tavares) (Enfermeira Eurídice Portela) (Dr. João Oliveira) (Dr. Arnaldo Ferreira)

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Eduardo Jorge Lima da Costa

Título do projecto de investigação: *Carcinoma Papilar Familiar da Glândula Tiróide: Follow-up clínico a 10 ano e estudo genético da primeira família portuguesa identificada*

Pretendendo realizar no(s) Serviço(s) de Cirurgia Geral do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 7 / Outubro / 2013

O INVESTIGADOR/PROMOTOR

Comissão de Ética para a Saúde – Centro Hospitalar São João

Parecer

Título do Projecto: Carcinoma Papilar Familiar da Glândula Tiróide: Follow-up clínico a 10 anos e estudo genético da primeira família portuguesa identificada.

Nome do Investigador Principal: Dr. Eduardo Lima da Costa

Local onde sera realizado o estudo: Serviço de Cirurgia Geral – CHSJ, havendo autorização do respectivo Diretor de Serviço para a realização do mesmo.

Objectivo do estudo: Orientação de tese de MIM da FMUP (aluna Ana Luísa Veiga de Sá).
-Avaliar o estado e progressão de doença tireóideia no maior número possível de membros da primeira família portuguesa identificada com carcinoma papilar familiar da tiróide, através da realização de colheita de sangue, ecografia da tiróide e biopsia aspirativa por agulha fina (BAAF), se necessário.
-Realizar estudo genético dos membros da referida família.

Período previsto de conclusão: Março 2014

Benefício: Está referido como benefício, o seguimento da sua situação clínica, uma vez que pertencem a uma família com risco acrescido de desenvolvimento de carcinoma da tiróide.

Risco: Está referido o incómodo de serem submetidos a colheita de sangue, ecografia da tiróide e, caso seja necessário, BAAF da tiróide.

Respeito pela liberdade e autonomia do sujeito do ensaio: Está previsto a obtenção de um consentimento informado, livre e esclarecido, bem como uma informação escrita para o participante, clarificadora dos objectivos, riscos benefícios, bem como a inteira liberdade para decidir da sua aceitação em participar. Uma vez que o estudo prevê a possibilidade de serem incluídos crianças > 5 anos, está incluído um consentimento apropriado para ser assinado pelo Representante Legal.

Tratando-se de um estudo prospectivo preditivo de conhecimento genético, o investigador assegura, na equipa de investigação, um profissional genético e que o resultado terá um impacto positivo com acesso a terapêutica adequada nos casos com doença.

Confidencialidade dos dados: está garantida a confidencialidade dos dados e esta informação será restrita ao investigador principal. Todas as informações clínicas serão individualizadas e respeitada a vontade dos participantes em conhecer ou não o resultado genético. Está assegurado pelo investigador que o material de DNA será destruído no fim da investigação.

O Investigador Principal dispõe de competência técnica e científica para a realização do estudo.

Não prevê a realização de questionário.

Custos: O estudo não prevê custos acrescidos para a instituição. O estudo será financiado pelo IPATIMUP.

Parecer: Em face da análise do protocolo de estudo, proponho a sua aprovação pela CES do CHSJ.

Porto, CHSJ, 15 de janeiro de 2014

O Relator

Dr. John Preto

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO ☒

NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu,_____,

abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 7 / Outubro / 2013

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 24 / Janeiro / 2014

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética