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Penetrance of a rare familial mutation predisposing to papillary thyroid cancer

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Abstract

Familial non-medullary thyroid cancer (FNMTc) is clinically defined as two or more first-degree relatives with NMTC and appears to follow an autosomal dominant inheritance pattern. Approximately 5–7% of NMTC is hereditary and affects multiple generations with a young age of onset. The primary aim of this study was to determine the age-specific penetrance of NMTC in individuals from a large family with FNMTc with a previously identified private mutation at 4q32, with a secondary aim to determine the penetrance for benign thyroid disease in this family. We present a large family with NMTC in which we had previously described a culpable mutation. Participants provided their personal medical history and family history. The germline 4q32 A > C mutation was detected in 34 of 68 tested individuals. Age-specific penetrance of thyroid cancer and benign thyroid disease was determined using the inverted Kaplan–Meier method of segregation analysis. Individuals who tested positive for the 4q32 mutation have a 68.9% (95% CI 46.5–88.7) risk of developing thyroid cancer by age 70 and a 65.3% (95% CI 46.0–83.8) risk of developing benign thyroid disease by age 70. The 4q32 A > C mutation significantly increases the

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Compliance with ethical standards

Conflict of interest No competing financial interests exist.

risk to develop thyroid cancer but not benign thyroid disease in members of this family. The female:male sex ratio of 1.33 that we observed in affected mutation carriers differs greatly from the ratio of approximately 3:1 observed in PTC, supporting a central role of the mutation. Early thyroid surveillance with annual ultrasound is recommended to individuals testing positive for this private familial mutation.

Keywords

Familial non-medullary thyroid cancer; Papillary thyroid cancer; Anaplastic thyroid cancer; Penetrance; Benign thyroid disease; Risk

Introduction

Thyroid cancer is the most common malignancy of the endocrine system and accounts for 3.8% of newly diagnosed cancers annually [1]. The incidence of thyroid cancer is rapidly increasing in America, from 7.6 to 14.9 per 100,000 between 2000 and 2012. Approximately 62,450 new cases of thyroid cancer were diagnosed in the United State in 2015, compared to roughly 22,000 in 2004 [1, 2]. While the majority of cases are sporadic, approximately 5–7% of thyroid cancers are familial [3]. Familial non-medullary thyroid cancer (FNMTc) is clinically defined as two or more first-degree relatives with NMTC and appears to follow an autosomal dominant inheritance pattern [4]. FNMTc is often described as a polygenic disorder associated with multiple low to moderate penetrance susceptibility genes and incomplete penetrance [5]. As one of the most heritable cancers, first degree relatives of an affected individual have an 8- to 10-fold increased risk of developing disease which suggests that there must be underlying germline mutations that have not yet been discovered [5–7].

A large multi-generational family with FNMTc participated in an IRB-approved study that performed genome-wide linkage analysis of 39 families with FNMTc [8]. The family included 13 known cases of thyroid cancer at that time, with two anaplastic thyroid cancer (ATC) cases, early onset of papillary thyroid cancer (PTC), and a high rate of benign thyroid disease (e.g. Hashimoto's thyroiditis, Graves' disease, thyroid nodules, hyperthyroidism, and hypothyroidism). A strong linkage peak at 4q32 was detected in this single family but not in any others. Further investigation of this region identified a specific intergenic 4q32 A > C single nucleotide mutation that segregated at that time with all but one, and now all but two family members with PTC [8]. Gene expression and functional studies suggest this mutation occurs in an enhancer element and is likely the causative factor predisposing to thyroid cancer [8]. This novel mutation was not identified in any of the other 38 NMTC families in the study or any other thyroid cancer patients in a large endocrine neoplasia biorepository at The Ohio State University [8]. Herein, we attempt to characterize the phenotypic implications and penetrance of the 4q32 A > C mutation.

Materials and methods

Participation in the study was offered to individuals who participated in the original study, as well as all other family members who were interested [8]. An invitation letter was sent describing our study and requesting consent to participate. The letter, questionnaires

(medical and family history), consent forms, and medical records request forms were approved by The Ohio State University (OSU) Institutional Review Board and were mailed and/or emailed to the prospective study participants. The survey was open for 6 months to obtain as many participants as possible. At-risk individuals in this family were also offered the opportunity to undergo free genetic testing to determine whether or not they inherited the 4q32 mutation.

Personal medical and family history information was collected from all participants including demographics (e.g. age, sex, and ethnicity), major medical concerns, family medical history, screening practices, history of thyroid cancer and benign thyroid disease, and surgery history. We inquired about the specific timing and cause of any thyroid evaluation, screening and/or surgery. Additional risk factors pertaining to thyroid cancer, such as therapeutic radiation at a young age and other work-related exposures, were also ascertained. Cancer diagnoses and information regarding reported thyroid disease were confirmed with medical records in the majority of cases. Of the 14 thyroid cancers diagnosed in this family, 8 were confirmed by pathology reports, 2 were confirmed by medical records, and 4 were based on reported history. The pathology reports were reviewed independently by two expert pathologists. Mutation status and additional data were extracted from the OSU Division of Human Genetics database to confirm who was affected and unaffected in the family.

Statistical analysis

All 34 mutation positive individuals were used in the penetrance analysis. In order to determine the age-specific penetrance of thyroid cancer, cumulative risk was estimated using the inverted Kaplan–Meier function with age at diagnosis as the survival variable. All individuals with or without the 4q32 mutation who had not been diagnosed with thyroid cancer were censored at their age at thyroidectomy, current age or age at death. Moreover, stratified penetrance analysis was performed within male and female groups. Inverted Kaplan–Meier survival curves representing cumulative risk, and their 95% confidence intervals (CI) were computed. Cumulative risk curves in thyroid carcinoma between mutation positive and mutation negative groups were compared by log-rank test.

Although thyroid cancer and benign thyroid disease may not be independent factors in this large family, the penetrance of benign thyroid cancer was analyzed. The diagnoses of Hashimoto's thyroiditis, Graves' disease, thyroid nodules, hyperthyroidism, and hypothyroidism were grouped under "benign thyroid disease". Similarly, the age-specific penetrance of benign thyroid disease and the 95% CI was calculated using the inverted Kaplan–Meier method with all the 34 mutation positive individuals. Cumulative risk of thyroid cancer and benign thyroid disease in mutation negative individuals and their 95% CI were also estimated with inverted Kaplan–Meier method.

Results

Individuals with the 4q32 mutation were found to have a significantly increased risk compared to individuals without the mutation (P value = 3.58×10^{-3}). Meanwhile,

individuals with the 4q32 mutation show no difference in benign thyroid disease risk compared to individuals without the mutation (P value = 8.03×10^{-1}).

Our data predict that those with the 4q32 mutation have a 68.9% risk to develop thyroid cancer by age 70 (Fig. 1; Table 1). Of those who tested positive for the mutation and were diagnosed with thyroid cancer, 8 are female and 6 are male. This nearly 1:1 ratio is in contrast to the 3:1 female to male ratio observed in the general papillary thyroid cancer population and supports a strong genetic cause of thyroid cancer in this family with autosomal dominant inheritance.

Individuals in this family with the 4q32 mutation have a 65.3% risk to develop benign thyroid disease (e.g. Hashimoto, Graves' disease, nodules, hyperthyroidism, or hypothyroidism) by age 70 (Fig. 2; Table 2). This risk was very similar to that of the individuals who tested negative for the mutation, who had a 70.7% risk for benign thyroid disease by age 70.

Discussion

This study demonstrates that individuals with the 4q32 mutation in this family are at significantly increased risk to develop thyroid cancer. The high risk of thyroid cancer in this family may be in part due to over-surveillance that led to more incidental findings of benign thyroid disease and thyroid cancer. The family history caused heightened awareness of thyroid cancer and an increase in the thyroid palpation and ultrasounds compared to the general population. This may have resulted in earlier ages of diagnosis and it is possible that some cases of PTC may have never been diagnosed if increased surveillance had not been implemented. Screening in mutation positive individuals should begin prior to the youngest age of diagnosis, in this family, 12 years of age. Medical management recommendations should be discussed with their endocrinologist.

Two individuals diagnosed with PTC tested negative for the 4q32 mutation, representing phenocopies. This may suggest the influence of additional factors, such as modifier genes and environmental factors. Thyroid cancer in these individuals may have also been detected due to the intensive screening occurring in this exceptionally large family, which may have led to detection of thyroid cancers that may have never become clinically relevant.

Since mutation positive and mutation negative individuals in this family had similar risks for benign thyroid disease, this suggests that the mutation is not contributing to the high predisposition to benign thyroid disease risk. The issue of benign thyroid disease as a factor contributing to thyroid cancer risk remains unclear [9]. Based on our findings, no clear association has been established.

Limitations of this study include the small sample size. While information for 115 individuals was collected, a smaller proportion ($n = 68$) underwent genetic testing (or were known obligate carriers). This is a private mutation found only in a single family to date, thus, the estimated penetrance of this mutation determined from this study cannot be generalized to the population. Additionally, prophylactic thyroidectomies censor whether or not individuals would have developed thyroid cancer and/or benign thyroid disease.

Assessing an accurate thyroid cancer risk for this family is a challenge because of the heightened awareness of the phenotype and increased surveillance paired with prophylactic surgery decisions. Other limitations include the lack of some clinical data and non-uniform treatment (i.e. independent decisions made regarding the appropriate timing of thyroid removal, decision to undergo prophylactic surgery versus screening, limited reports confirming dates/treatments/diagnoses). Combined, these factors may bias the penetrance estimate and should be taken into consideration when discussing treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Cumulative risk of thyroid cancer in individuals with the 4q32 mutation compared to individuals without the 4q32 mutation (P-value = 3.58×10^{-3})

Fig. 2. Cumulative risk of benign thyroid disease in individuals with the 4q32 mutation compared to individuals without the 4q32 mutation (P-value = 8.03×10^{-1})

Table 1

Cumulative risk of thyroid cancer in individuals with and without the 4q32 mutation with 95% confidence interval

Age	Cumulative risk					
	4q32 negative (n=34), %	95% CI	4q32 positive (n=34), %	95% CI	4q32 positive female only (n=17), %	95% CI
10	0.0	(0.0, 0.0)	0.0	(0.0, 0.0)	0.0	(0.0, 0.0)
20	3.2	(0.5, 20.8)	6.1	(1.6, 22.2)	0.0	(0.0, 0.0)
30	3.2	(0.5, 20.8)	13.0	(5.0, 31.0)	13.9	(3.6, 45.0)
40	7.6	(1.9, 27.7)	25.7	(13.0, 47.1)	31.5	(12.8, 64.7)
50	7.6	(1.9, 27.7)	36.3	(20.3, 59.3)	54.3	(27.9, 84.6)
60	7.6	(1.9, 27.7)	41.6	(24.3, 64.7)	65.7	(37.4, 91.4)
70	7.6	(1.9, 27.7)	68.9	(46.5, 88.7)	82.9	(50.1, 98.9)
					57.2	(28.8, 88.1)

Table 2

Cumulative risk of benign thyroid disease in individuals with and without the 4q32 mutation with 95% confidence interval

Age	Cumulative risk			
	4q32 negative (n=34)	95% CI	4q32 positive (n=34)	95% CI
10	2.3	(0.4, 19.1)	0.0	(0.0, 0.0)
20	6.2	(1.6, 22.6)	9.8	(3.3, 27.4)
30	22.3	(11.6, 42.2)	20.3	(9.6, 39.8)
40	38.1	(23.0, 58.4)	40.5	(24.6, 61.5)
50	56.0	(37.9, 75.7)	50.4	(32.6, 71.3)
60	70.7	(51.6, 87.4)	65.3	(46.0, 83.8)
70	70.7	(51.6, 87.4)	65.3	(46.0, 83.8)