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## A novel *DICER1* mutation causes multi-nodular goiter in children

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### Abstract

**Background**—To present a rare case of an adolescent with multinodular goiter (MNG) found to have a *DICER1* mutation.

**Methods**—Chart review including endocrine hormone tests, thyroid ultrasound, and genetic testing for *DICER1*.

**Results**—A 12-year-old female presented with a diffusely enlarged thyroid gland. Family history revealed an older sister with a history of bilateral ovarian Sertoli-Leydig cell tumors and MNG. Thyroid function tests were normal. Serial thyroid ultrasounds showed enlarging multiple bilateral nodules. Fine needle aspiration suggested MNG. Genetic testing revealed a novel heterozygous premature termination mutation (c.1525C>T p.R509X) in the *DICER1* gene.

**Conclusion**—Thyroid nodules are rare in children but carry a higher risk for malignancy. It is essential to inquire about family history and refer for genetic evaluation with a family history of MNG. In patients with *DICER1* mutations, tumor surveillance is critical due to the increased risk of multiple tumors, including ovarian tumors and pleuropulmonary blastoma.

### Keywords

DICER1; multi-nodular goiter; ovarian Sertoli-Leydig cell tumors; tumor surveillance; family history

### Introduction

Multinodular goiter (MNG) is a common disorder characterized by non-neoplastic enlargement of the thyroid gland due to the development of multiple nodules. MNG is noted to have a greater incidence in females (5:1 ratio of females: males) and in low iodine intake

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regions (1). However, the incidence of MNG is still quite common in regions of sufficient iodine intake, supporting the notion of a possible genetic basis for this disorder (2). Two loci for familial MNG have been identified, MNG1 on chromosome 14q and MNG2 on chromosome X (3, 4). Germline mutations in *DICER1*, on chromosome 14q32, have been linked to familial MNG with and without ovarian Sertoli-Leydig cell tumors (SLCTs) (5).

*DICER1* is a member of the ribonuclease III (RNase III) family of genes involved in the generation of microRNAs (miRNAs). miRNAs are a class of short, double-stranded, non-coding regulatory RNAs that modulate gene expression post-transcriptionally (6). A global downregulation of miRNAs has been shown to promote tumorigenesis (7). *DICER1* and other miRNAs have been implicated as having a critical role(s) in the molecular regulation of multiple organ systems. The importance of *DICER1* was emphasized in a study of *Dicer1* knockout mice which showed that a null-mutation of *Dicer1* is embryologically lethal (8). Tissue-specific conditional knockout experiments have demonstrated the essential organogenetic role of *Dicer1* in multiple organ systems, including the lung (9), adrenal cortex and testis (10), female reproductive system (11), retina (12), glomerulus (13, 14), limb (15), and skeletal muscle (16). Jacks and colleagues (17) found that heterozygous loss of *Dicer1* accelerated tumor formation in Kras-induced mouse models of cancer and provided evidence for an active selection against complete loss of *Dicer1* during tumor progression in these tumors, implicating *Dicer1* as a haploinsufficient tumor suppressor gene (17). Germline mutations of *DICER1* have not only been reported in MNG with and without Sertoli-Leydig cell tumors, but also in pleuropulmonary blastoma (PPB), cystic nephroma (CN), cervix embryonal rhabdomyosarcoma (cERMS), primitive neuroectodermal tumor (cPNET), and Wilms tumor (18, 19, 20, 21, 22). *DICER1* mutations exhibit low penetrance in PPB and CN, but high penetrance in MNG (5). We report two siblings with MNG and a germline *DICER1* mutation, in which the older sibling also manifested bilateral SLCTs.

## Materials and Methods

This study was approved by the University of Michigan IRB committee. A chart review was performed for both siblings.

The otolaryngology, genetic, and endocrinology evaluations as well as the CT scan, thyroid ultrasound, and endocrine hormone tests were performed at the University of Michigan (Ann Arbor, MI). The gynecologic evaluation, pelvic ultrasound, chest CT and CA-125 laboratory tests were performed at the National Institutes of Health (Bethesda, MD). *DICER1* sequence analysis was performed at Ambry Genetics Laboratory (Aliso Viejo, CA).

## Results

### Sibling 1

A twelve year old female was noticed to have an enlarged thyroid earlier in January 2011. History was negative for symptoms of hypo- or hyperthyroidism, including palpitation, sweating, nervousness, tremor, diarrhea, insomnia, cold- or heat-intolerance, fatigue, constipation, or hair loss. She reported a recent 4 pound weight loss attributed to increased physical activity. She had no signs of hyperandrogenism such as hirsutism, excessive acne, or excessive hair loss. She had regular menses. The patient was evaluated by a pediatric otolaryngologist, a pediatric endocrinologist, and a pediatric geneticist.

Her birth history was unremarkable without teratogenic exposures. Her past medical history was significant for eustachian tube dysfunction and right tympanic membrane perforation status post right paper patch myringoplasty. She also underwent surgical excision of a midline neck mass at age 6; pathological examination was consistent with dermoid cyst.

Family history was significant for colon cancer in a paternal grandfather, esophageal cancer in a paternal great uncle, and possible thyroid disorders in a grandmother and a grandaunt. Furthermore, the patient's sister had a significant oncological history (See Sibling 2, below).

Physical examination was notable for a small right tympanic membrane perforation and a thyroid gland with diffuse slight enlargement without discrete palpable nodules. The rest of the head and neck examination was normal.

Thyroid ultrasound showed a right thyroid lobe measuring  $4.2 \times 1.5 \times 1$  cm and a left thyroid lobe measuring  $4.5 \times 1.9 \times 1.7$  cm. Three complex cystic lesions were noted, one within the isthmus (approximately  $1.6 \times 1 \times 1.9$  cm) and two in the left lobe measuring approximately  $1.2 \times 1.1$  and  $1.6 \times 1.2$  cm. In addition, there was a nonspecific 5 mm echogenic right lobe lesion. In summary, the ultrasound was consistent with a multinodular goiter, without suspicious calcifications or appreciable internal vascularity. Subsequent thyroid ultrasound 9 months later showed a right thyroid lobe measuring  $4.5 \times 1.6 \times 1.8$  cm, with the largest nodule in the right thyroid measures  $1.7 \times 1.2 \times 1.1$  cm. The left thyroid lobe measured  $4.1 \times 2.2 \times 1.9$  cm with the two largest nodules in the left measuring  $1.6 \times 1.4 \times 1.2$  (superior pole) and  $1.5 \times 1.5 \times 1.2$  cm (inferior pole). The solid portions of multiple nodules demonstrated internal vascularity, and many of the nodules had enlarged. Fine needle aspiration showed benign follicular cells, colloid and histiocytes, consistent with multinodular goiter.

Transabdominal pelvic ultrasound showed a uterus measuring  $3.6 \times 2.8 \times 6.7$  cm with an endometrial thickness of 5 mm. The right ovary was  $2.75 \times 1.3 \times 3.03$  cm with a 1.8 cm cyst and left ovary was  $2.13 \times 1.33 \times 2.29$  cm with no fluid seen in the endometrial canal or cul-de-sac and no evidence of uterine fibroids. Chest CT showed bilateral pleuropulmonary blebs and a nonspecific 3 mm right pleural based nodule. The pleuropulmonary blebs need further work up to rule out type I pleuropulmonary blastomas.

Laboratory test results including thyroid stimulating hormone (TSH), free T4, thyroid stimulating immunoglobulin, thyroid peroxidase antibodies, alpha fetoprotein (AFP) tumor marker, serum total testosterone levels, dehydroepiandrosterone sulfate (DHEA-S), and -HCG tumor markers were all normal. Genetic testing showed a novel heterozygous premature termination mutation (c.1525C>T p.R509X) in the *DICER1* gene.

## Sibling 2

The 23-year-old sister of Sibling 1 has also been followed at our institution for post-surgical hypothyroidism and SLCT. She initially presented with abdominal distention and abdominal pain at age 8 years. A CT scan revealed a left ovarian mass for which she underwent left oophorectomy and omentectomy. Pathology revealed Sertoli-Leydig cell tumor of intermediate differentiation. Testosterone level was not obtained at that time, and she did not have hirsutism. She had her menarche at age of 11 years.

At age 14 years, sibling 2 was found to have an enlarged thyroid gland. Thyroid ultrasound and scan revealed a cold nodule of the left thyroid gland and absence of a right thyroid lobe, consistent with unilateral agenesis. Hemithyroidectomy (functional total thyroidectomy) was eventually performed. The pathology showed multiple benign nodules indicating a multinodular goiter. Furthermore, at 14 years of age, she had hirsutism and irregular menses without excessive weight gain. The testosterone level was increased to 68 ng/dL (normal range 20–38). CT scan revealed a new right-sided ovarian mass. She underwent right oophorectomy and bilateral salpingectomy. The mass was identified also to be a SLCT of intermediate differentiation that was thought to be asynchronous and an independent primary tumor. She therefore did not receive chemotherapy, though 10% of intermediate

differentiated tumors are clinically malignant. She was started on Levoxyl and Ortho Evra patch for hormone replacement. The family moved to Michigan and transferred her endocrine care to our institution when she was 15 year old.

## Discussion

Current recommendations for the management of non-toxic MNG are based on the fact that it carries a risk for thyroid cancer similar to a solitary thyroid nodule, about 1–5% (23, 24). To date, thyroid cancer has not been reported in *DICER1* syndrome. However, new guidelines for MNG management are warranted given recent advancements in the genetic cause for this disorder. Most cases of “MNG” referred to endocrine clinics are more often due to conditions of autoimmunity such as Hashimoto thyroiditis and not true MNG. Careful interpretation of the sonographic findings is paramount. Hyperthyroidism associated with toxic MNG warrants treatment. Occasionally, toxic MNG may be associated with McCune-Albright syndrome. If the patient indeed has true MNG without abnormality in thyroid function and without thyroid autoimmunity, a thorough inquiry into the family oncologic history and monitoring of tumor markers are warranted. We believe measurement of testosterone, DHEA/DHEA-S, AFP, -HCG, and CA-125 levels along with TSH, free T4 and T3 should be performed annually or sooner if signs or symptoms warrant.

Our patient has a heterozygous mutation in *DICER1* which is most likely the reason for her MNG. The father and older sister were tested at an outside institution and found to carry the familial *DICER1* mutation first identified in the younger sister at our institution. Consequently, the clinical phenotype of the older sister is consistent with her molecular result. To date, no comprehensive guidelines are available for tumor surveillance in this new syndrome. Due to our patient’s mutation and her family history of tumors, close monitoring is warranted.

Most *DICER1* mutations noted in patients with PPB were predicted to result in truncated proteins (20, 26). Rio Frio et al. (5) noted three mutations that were non-truncating with high penetrance for MNG. The nonsense *DICER1* mutation in codon 509 in our patient most likely results in a truncated protein. Thus, though penetrance is low, our patient underwent a chest CT showing two small cystic lesions. Analysis of germline *DICER1* mutations from a large series of probands with differentiated thyroid cancer with and without MNG showed no correlation between the *DICER1* mutation and thyroid carcinoma (5). As *DICER1* mutations have not been associated with thyroid carcinoma to date, and our patient is asymptomatic, surgical intervention is currently not recommended. In addition, we recommend tumor surveillance for our patient for SLCT via laboratory and annual ultrasound.

Our report stresses the importance of a thorough inquiry into the family oncologic history in patients who have multi-nodular goiter without abnormality in thyroid function and without thyroid autoimmunity. Genetic testing is warranted for patients with a family history of cold multinodular goiter and/or ovarian Sertoli-Leydig cell tumors.

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