Germline and Somatic DICER1 Mutations in Familial Papillary Thyroid Carcinoma and Multinodular Goiter

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Introduction
The inheritable component of familial Papillary Thyroid Cancer (IPTC) was recently attributed to monogenic defects in a reduced number of genes including DICER1. DICER1 codes for a ribonuclease of the RNasell family essential for the biogenesis of microRNAs 1,2.

Objectives
We aimed to identify germline and/or somatic mutations in DICER1 in a familial pedigree with PTC, multinodular goiter (MNG) and other tumours consistent with the DICER1 Syndrome.

Patients and Methods
The index patient, an 11-year-old girl, was diagnosed with cystic nephroma (CN) as an infant, MNG at age 8 and follicular variant PTC at age 10 (vPTC1). Her mother presented MNG at age 9 and vPTC at age 11 (vPTC2), and her maternal aunt was hemi-thyroidectomized for compressive MNG (MNG1) at ages 9 and 12, respectively. The patient’s father and maternal grandparents were healthy (Figure 1).

Germline DICER1 mutations were screened in peripheral blood lymphocyte DNA from 6 members (affected and non-affected) of the kindred. Somatic DICER1 mutations were studied in DNA from all paraffin-embedded tissues available (Figure 2) by PCR amplification of mutational “hotspots”, T-A cloning and Sanger sequencing. “Hotspots” for BRAF mutations in vPTC1/2 and H/K/R-RAS mutations in vPTC1 were also analyzed.

Results
The proband, her mother, and maternal aunt and grandfather carry a novel germline heterozygous pathogenic DICER1 2-bp deletion in exon 9 (c.1440_1441delTG) (Figure 3A), which prematurely truncates the functional RNase IIIa and IIb domains of the protein (p.Gly481ThrfsTer25) (Figure 4). Tissue samples showed three different heterozygous DICER1 missense mutations (Figures 3B, 3C and 3D) affecting the RNase IIb domain (Figure 4): c.5438A>G (p.Glu1813Gly) in vPTC1, c.5113G>A (p.Glu1705Lys) in vPTC2 and CN, and c.5429A>T (p.Asp1810Val) in MNG1. BRAF and RAS mutations were absent in the studied tissues.

Conclusions
• A novel monoallelic germline mutation in DICER1 increases the susceptibility to develop MNG and subsequently PTC.
• Phenotype segregation analyses suggests that additional tissue-specific DICER1 mutations located in the RNase IIb domain, unreported to date in PTC, are necessary for the efficient neoplastic or hyperplastic transformation of the thyroid tissue in the DICER1 Syndrome 3.

Disclosure statement
The authors report no conflicts of interest in this study.

References