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 (fPTC) was recently attributed to monogenic defects in a reduced number of genes including *DICER1*. *DICER1* codes for a ribonuclease of the RNaseIII 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 (fvPTC1). Her mother presented MNG at age 9 and fvPTC at age 11 (fvPTC2), 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**).

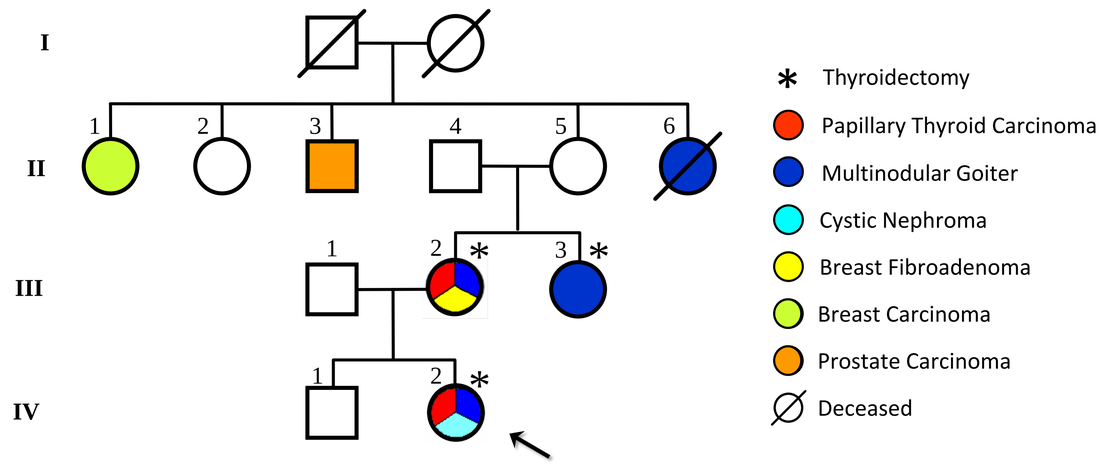

Figure 1. *Pedigree with familial Papillary Thyroid Cancer (follicular variant), Multinodular Goiter and defects in DICER1.*

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 fvPTC1/2 and *H/K/N-RAS* mutations in fvPTC1 were also analyzed.

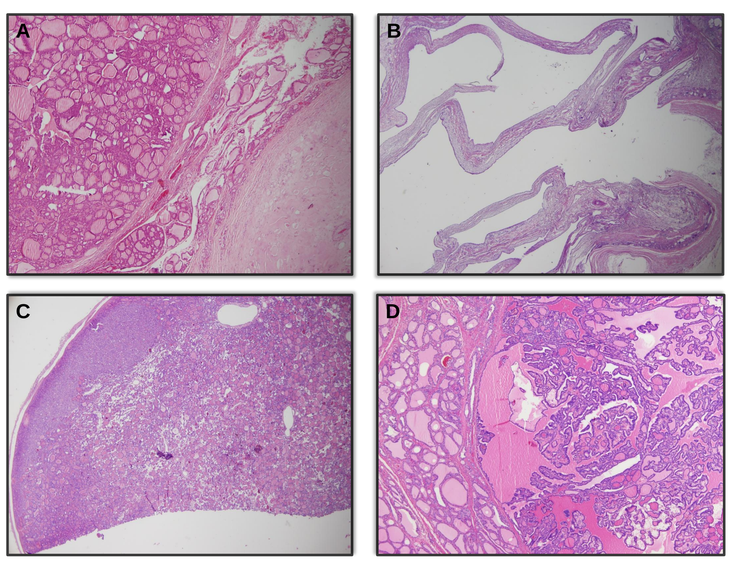

Figure 2. *Hematoxylin and eosin-stained histological sections from paraffin-embedded surgical specimens. **A**: Patient IV.2 follicular variant PTC (10 years). **B**: Patient IV.2 Cystic Nephroblastoma (18 months). **C**: Patient III.2 follicular variant PTC (11 years). **D**: Patient III.3 MNG with papillary hyperplastic nodules (9 years).*

Disclosure statement

The authors report no conflicts of interest in this study.

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 IIIb 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 IIIb domain (**Figure 4**): c.5438A>G (p.Glu1813Gly) in fvPTC1, c.5113G>A (p.Glu1705Lys) in fvPTC2 and CN, and c.5429A>T (p.Asp1810Val) in MNG1. *BRAF* and *RAS* mutations were absent in the studied tissues.

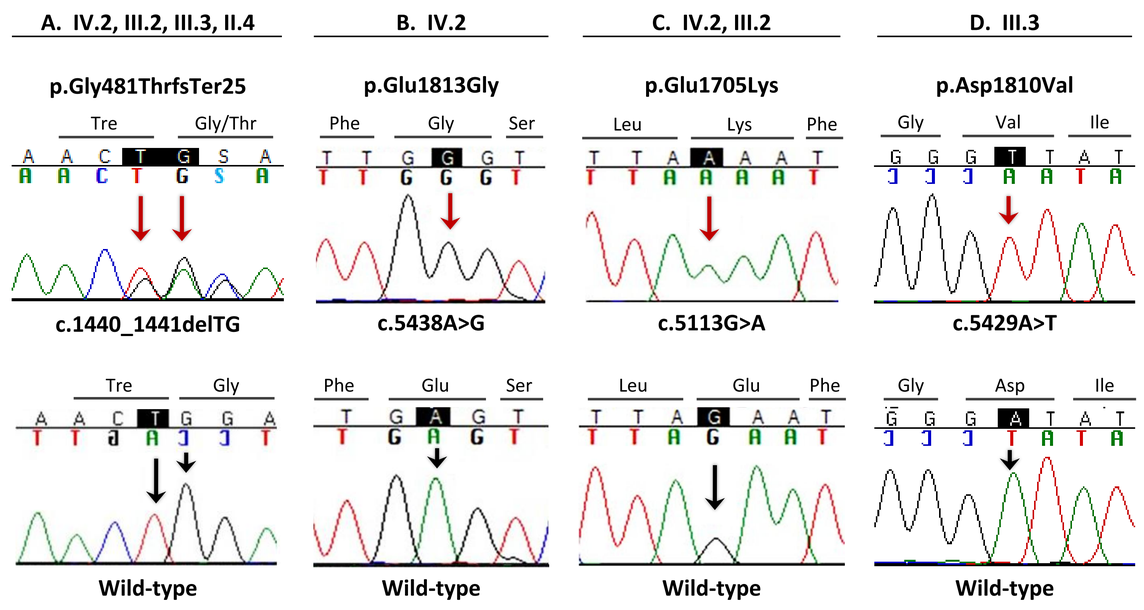

Figure 3. *Genomic DNA sequencing results (**A**: lymphocytes), and tissue-specific somatic DNA results after T-A cloning of the PCR products (**B**: IV.2 follicular variant PTC. **C**: IV.2 Cystic Nephroblastoma and III.2 follicular variant PTC. **D**: III.3 MNG).*

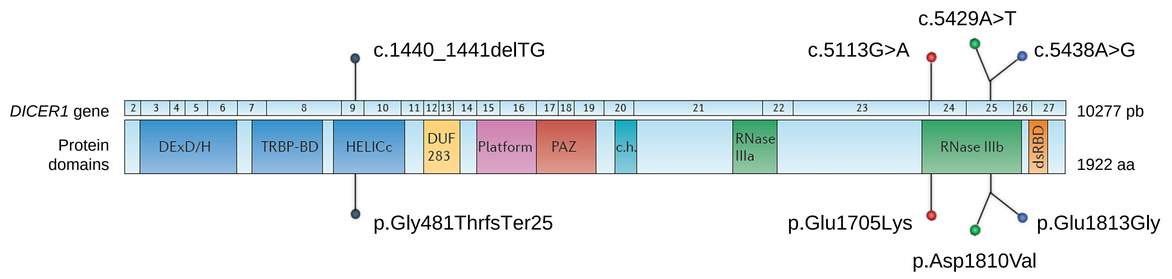

Figure 4. *Nonsense germline mutation (stop codon) in exon 9, and somatic mutations in “hotspots” of the exons 24 and 25 affecting the DICER1 RNase IIIb domain. Modified from Foulkes W.D. et al. (2014).*

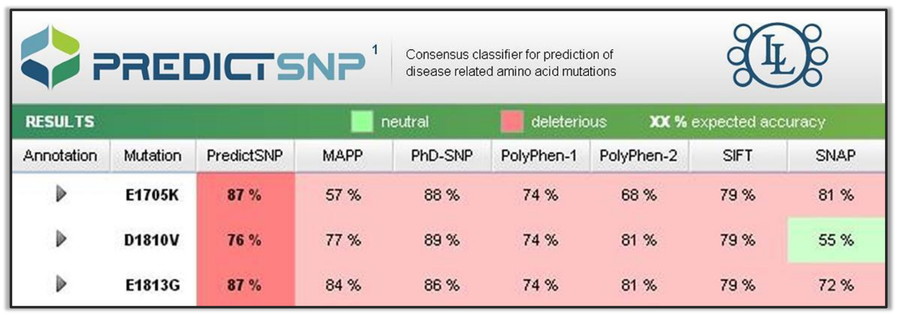

Figure 5. *In silico pathogenicity assessment of the discovered amino-acid changes E1705K, D1810V y E1813G according to the established prediction tools MAPP, PhD-SNP, PolyPhen-1, PolyPhen-2, SIFT and SNAP.*

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 IIIb domain, unreported to date in PTC, are necessary for the efficient neoplastic or hyperplastic transformation of the thyroid tissue in the *DICER1* Syndrome [3].

References

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