

Introduction

DICER1 is an endoribonuclease that acts post-transcriptionally by processing mRNA into siRNA and microRNA, thus leading to mRNA downregulation. *DICER1* syndrome is usually caused by germline truncated variants and is characterized by a variety of benign or malignant tumors: pleuropulmonary blastoma, ovarian Sertoli-Leydig cell tumor, cystic nephroma, pituitary blastoma and multinodular goitre. Patients with germline aberrations in the *DICER1* gene usually carry characteristic somatic missense *DICER1* mutations within the associated tumors, located in highly specific metal ion-binding residues within the RNase IIIb domain.

Aim of the Study

The principal goal of this study was to investigate the genetic cause that led to the development of multinodular goitre and subsequently in an ovarian Sertoli-Leydig cell tumor in a 10 year old patient.

Case description

A 10 year old girl was evaluated for thyroid enlargement. Thyroid sonography revealed three nodules in the right lobe (diameter: 1.9, 2.3, and 3 cm, respectively; **Figure 1A**). Thyroid function tests were normal and thyroid autoantibodies negative. Thyroidectomy was carried out and the lesions proved hyperplastic nonmalignant. She entered puberty at age 11 years and at age 12 years, both breast and pubic hair were Tanner stage IV. Ten months later, during follow-up, breast had regressed to Tanner stage I, hirsutism was present and her voice had notably deepened. Her hormonal results revealed increased androgens: Testosterone 478ng/dL, DHEAS 2480ng/mL, 17OH-progesterone 11ng/mL, $\Delta 4$ androstenedione 7.9ng/mL. Ovarian sonography and MRI revealed the presence of an ovarian tumor (**Figure 1B and 1C**). Right salpingo-oophorectomy was carried out and biopsy revealed an ovarian Sertoli-Leydig cell tumor (**Figure 1D**). 10 days postoperatively androgens had returned to normal levels.

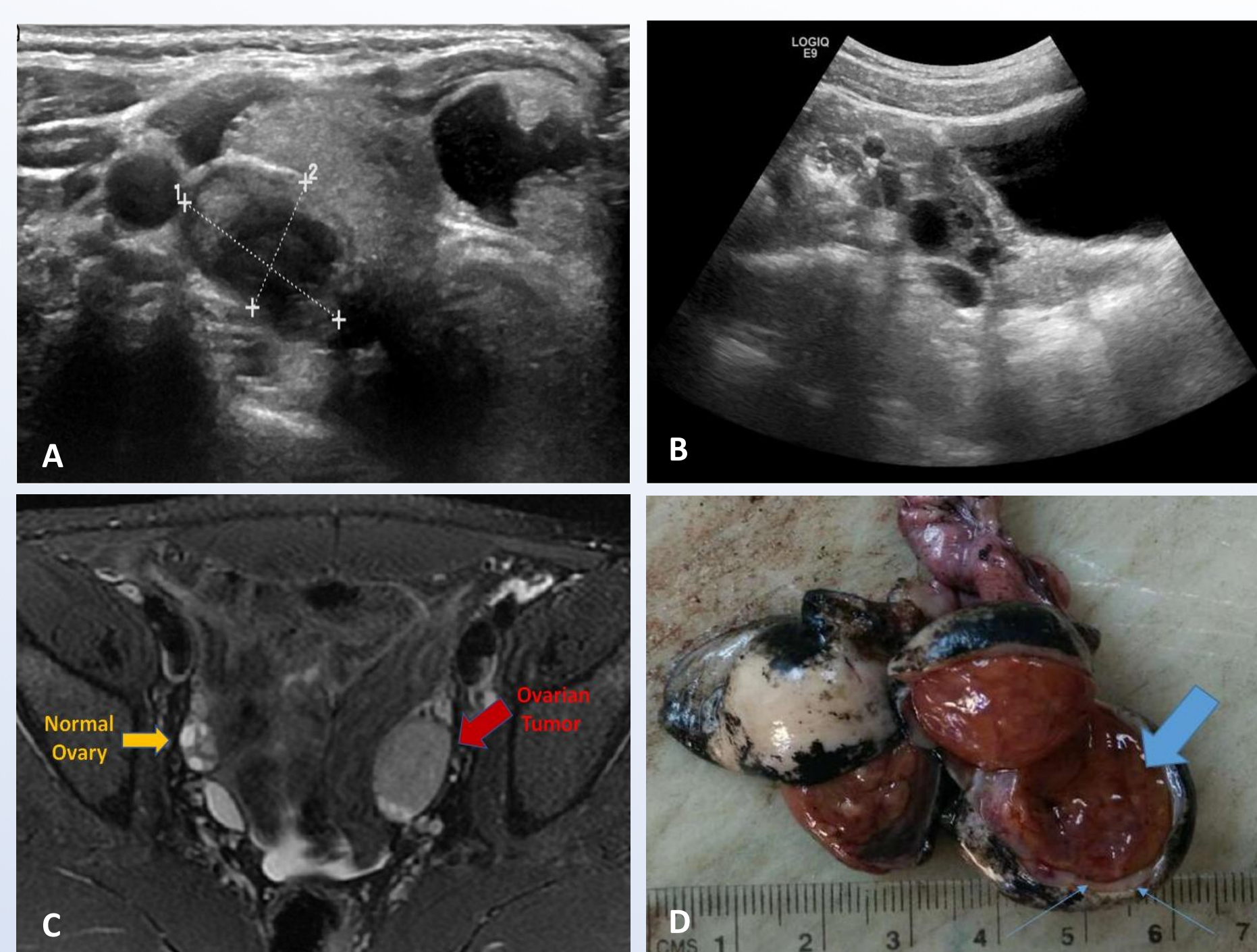


Figure 1: (A) Thyroid sonography revealing three nodules in the right lobe. (B) Ovarian sonography and (C) MRI revealing the presence of a tumor in the right ovary. (D) The excised ovarian tumor.

Reference:
White E, Schlackow M, Kamieniarz-Gdula K, Proudfoot NJ, Gullerova M. (2014) Human nuclear Dicer restricts the deleterious accumulation of endogenous double-stranded RNA. *Nat Struct Mol Biol.*;21(6):552-9.

Genetic studies

The *DICER1* gene was sequenced in both germline and somatic level. The patient carried a nonsense germline variant (c.4443G>A p.W1481*) leading to a truncated protein.

The genetic analysis performed in the thyroid and the ovarian tissue revealed two missense variants of the same codon leading to two different aminoacids (c. 5437G>C p.E1813Q; c.5439G>T p.E1813D, respectively; **Figure 2**).

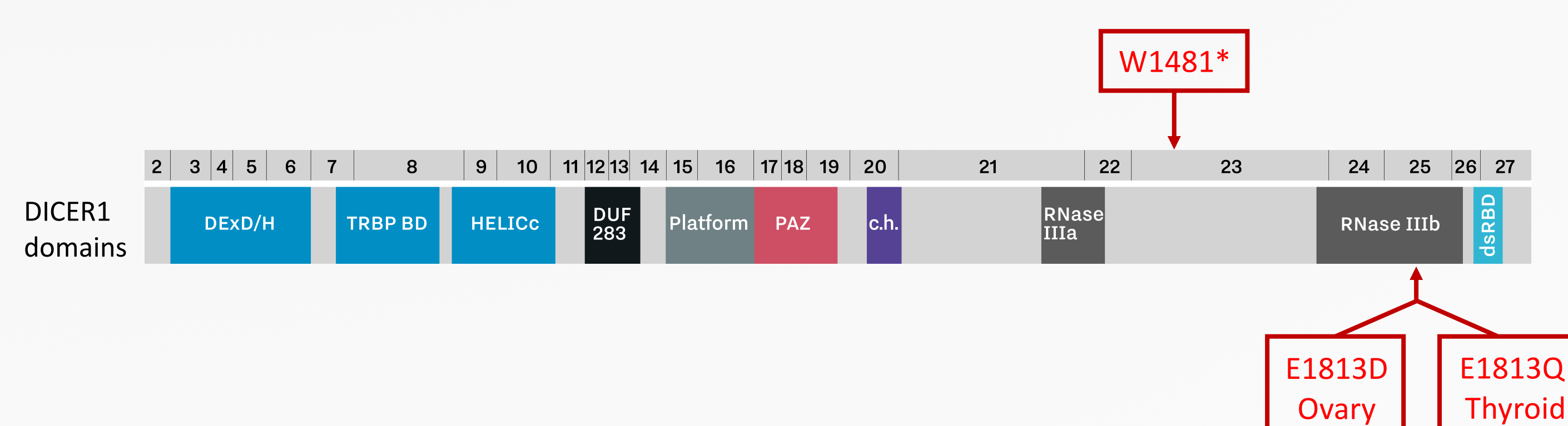


Figure 2: Depicts the *DICER1* gene structure and the location of the germline (top) and somatic (bottom) variants identified in our patient.

✓ Two different *DICER1* somatic variants were identified in ovarian and thyroid tissues.

Immunohistochemistry

DICER1 protein expression is drastically reduced within the thyroid nodules and ovarian tumor in our patient compared to control tissue (*DICER1* wild-type).

Interestingly, *DICER1* is mostly expressed in the nucleus of the tumor cells instead of the cytoplasm. Similar nuclear shift of the *DICER1* protein has previously been described in HEK293 Dicer1 knocked down cells and Dicer1-null mouse embryonic stem (ES) cells (White *et al.* 2014)

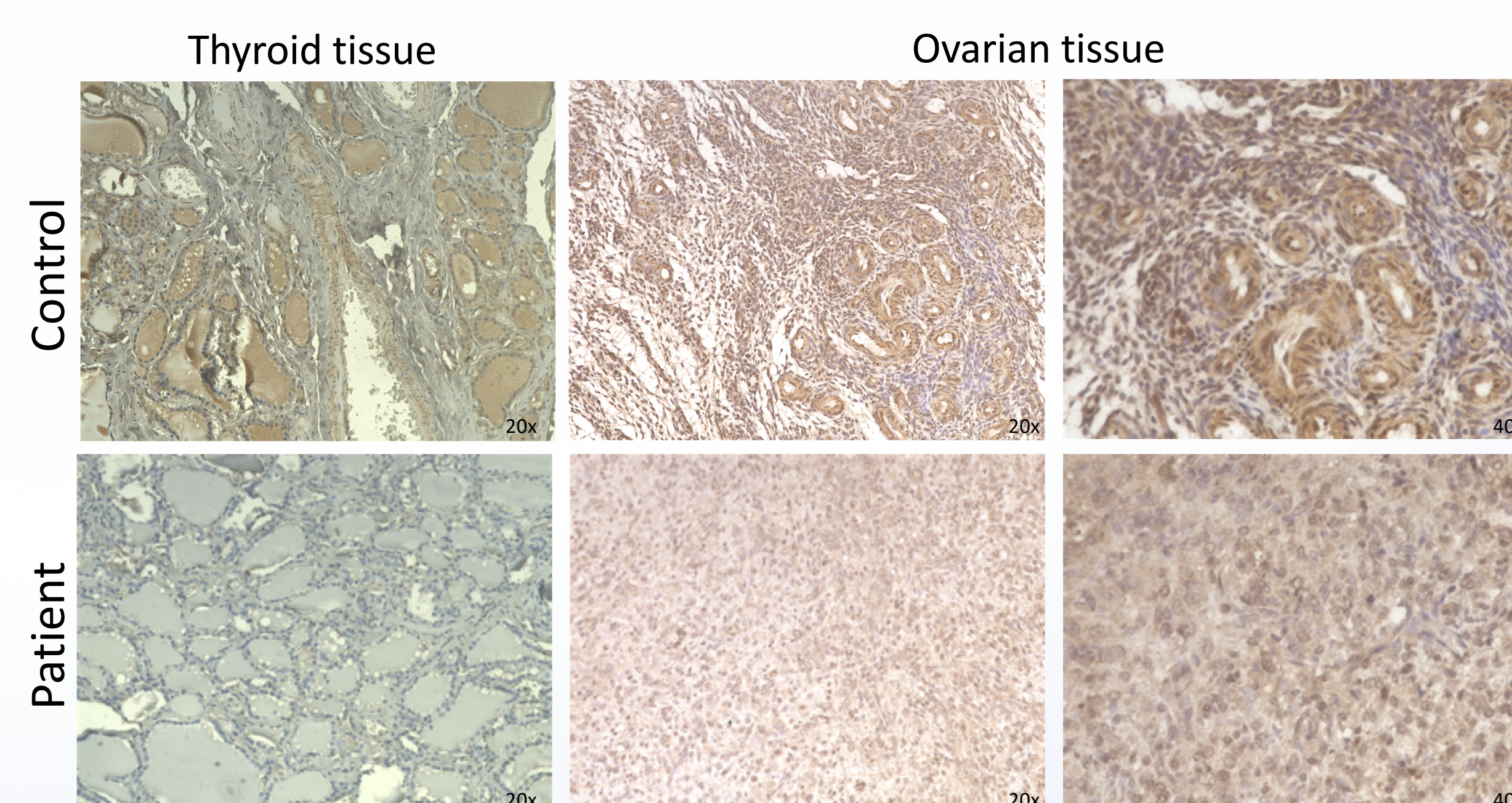


Figure 3: Analysis of *DICER1* expression by immunohistochemistry.

✓ *DICER1* expression is down-regulated in tumor tissues and is located within the nucleus rather than the cytoplasm of ovarian cells.

Conclusion

Our patient with multinodular goitre and an ovarian Sertoli-Leydig tumor harbored a novel truncating *DICER1* mutation (p.W1481*, c.4443G>A) at germline level associated with somatic mutations within the RNase IIIb domain within the tumor cells. Moreover, *DICER1* protein expression is drastically reduced within the tumor cells and located in the nucleus rather than the cytoplasm. *DICER1* is a tumorigenic driver during childhood.