

## Exploring the Association Between *DICER1* Mutations and Differentiated Thyroid Carcinoma

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**Context:** Carriers of germline *DICER1* mutations are predisposed to a rare cancer syndrome, the *DICER1* syndrome. Thyroid abnormalities are a common finding in *DICER1* syndrome with multinodular goiter frequently present in many families in which a germline *DICER1* mutation is segregating. Differentiated thyroid carcinoma (DTC) is infrequently seen in such pedigrees. In addition to germline *DICER1* mutations, specific somatic mutations have been identified in the *DICER1* ribonuclease IIIb catalytic domain in several tumor types.

**Objective:** We aimed to determine whether such characteristic somatic *DICER1* mutations are present in DTCs that arise within germline *DICER1* mutation carriers.

**Design and Setting:** The study involved an opportunistic collection of 3 cases of DTC arising in individuals suspected to have *DICER1* syndrome and hospital-based ascertainment and testing was implemented.

**Results:** We identified somatic *DICER1* mutations in 3 DTCs arising in unrelated germline *DICER1* mutation carriers, all of whom had been diagnosed in infancy with pleuropulmonary blastoma (PPB), were treated with chemotherapy, exposed frequently to diagnostic radiation, and subsequently developed DTC. The somatic mutations occurred within the *DICER1* ribonuclease IIIb domain, affecting highly conserved amino acid residues central to the catalytic activity of the domain.

**Conclusion:** This report of somatic *DICER1* mutations in DTC strengthens the association between DTC and the *DICER1* syndrome. The possible association between germline *DICER1* mutations, PPB treatment, and the risk of subsequent DTC must be considered by clinicians when treating PPB. (*J Clin Endocrinol Metab* 99: E1072–E1077, 2014)

The *DICER1* protein, a member of the ribonuclease (RNase) III family of proteins, cleaves noncoding small RNA precursors (pre-microRNAs [miRNAs]) to generate mature miRNAs, which in turn posttranscriptionally regulate gene expression (1). Germline mutations

in *DICER1* predispose the carrier to a rare cancer syndrome, the pleuropulmonary blastoma (PPB) familial tumor and dysplasia syndrome (OMIM 601200), also known as the *DICER1* syndrome (2–4), characterized by PPB, cystic nephroma (CN), Sertoli-Leydig cell tumors

ISSN Print 0021-972X ISSN Online 1945-7197  
Printed in U.S.A.

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Received November 25, 2013. Accepted March 4, 2014.

First Published Online March 11, 2014

Abbreviations: BMT, bone marrow transplantation; CN, cystic nephroma; CT, computed tomography; DTC, differentiated thyroid carcinoma; ERMS, embryonal rhabdomyosarcoma; FFPE, formalin-fixed paraffin-embedded; gDNA, genomic DNA; miRNA, microRNA; MNG, multinodular goiter; PPB, pleuropulmonary blastoma; RNase, ribonuclease; SLCT, Sertoli-Leydig cell tumor; WT, Wilms tumor.

(SLCTs), embryonal rhabdomyosarcomas (ERMSs), multinodular goiter (MNG), Wilms tumors (WT), and other very rare entities (4–7). In addition to germline mutations, highly characteristic second somatic mutations occurring within the RNase IIIb domain of *DICER1* have been identified in patients harboring SLCTs, ERMS, WTs, and PPB (8–10). These RNase IIIb mutations, termed hotspot mutations (9), affect the metal ion-binding capacity of the domain, interfering with the catalytic site of the enzyme, and thereby reducing the production of 5p miRNAs derived from the 5' arm of pre-miRNAs (11).

Cystic and hyperplastic thyroid abnormalities are a common finding in the *DICER1* syndrome with MNG, characterized by multinodular thyroid hyperplasia (OMIM 138800) being particularly prevalent. The penetrance of *DICER1* mutations for MNG is unknown but is likely to be higher than that observed for neoplasms in the *DICER1* syndrome and may be in the range of 10% to 20% in mutation carriers. As a result, MNG is frequently present in many families in which a germline *DICER1* mutation is segregating. Differentiated thyroid carcinoma (DTC) is, however, very infrequently seen in *DICER1* pedigrees (3, 6). In a series of 401 next-generation sequenced DTCs, the Cancer Genome Atlas Research Network reported only 3 somatic *DICER1* mutations (p.Glu1813Gly, p.Asp1810His, and p.Arg1906Ser), the first 2 of which are hotspot mutations within the RNase IIIb domain. The 2 cases with hotspot mutations also carried germline *DICER1* mutations: p.Leu81fs coupled with p.Glu1813Gly and p.Lys376fs with p.Asp1810His (12) ([http://press.endocrine.org/doi/suppl/10.1210/jc.2013-4206/suppl\\_file/jc-13-4206.pdf](http://press.endocrine.org/doi/suppl/10.1210/jc.2013-4206/suppl_file/jc-13-4206.pdf) Supplemental Table 1). These data from the Cancer Genome Atlas, which revealed a somatic mutation frequency of 0.7%, suggest somatic *DICER1* hotspot mutations are rare in DTC and, moreover, are likely to be extremely rare outside the context of a coexisting germline mutation in *DICER1* (Supplemental Tables 2 and 3). The coexistence of the germline and somatic RNase IIIb mutations in these 2 cases, taken together with the data that we present below, confirms that DTC is a minor manifestation of the *DICER1* syndrome.

Here we provide a first detailed report of somatic *DICER1* mutations occurring in 3 DTCs that arose in unrelated germline *DICER1* mutation carriers.

## Case 1

Shin et al (13) first described a girl who was diagnosed at age 23 months with type II PPB. At 4.3 years of age, a PPB recurrence occurred in her left back musculature. Treatment included high-dose chemotherapy and hematopoi-

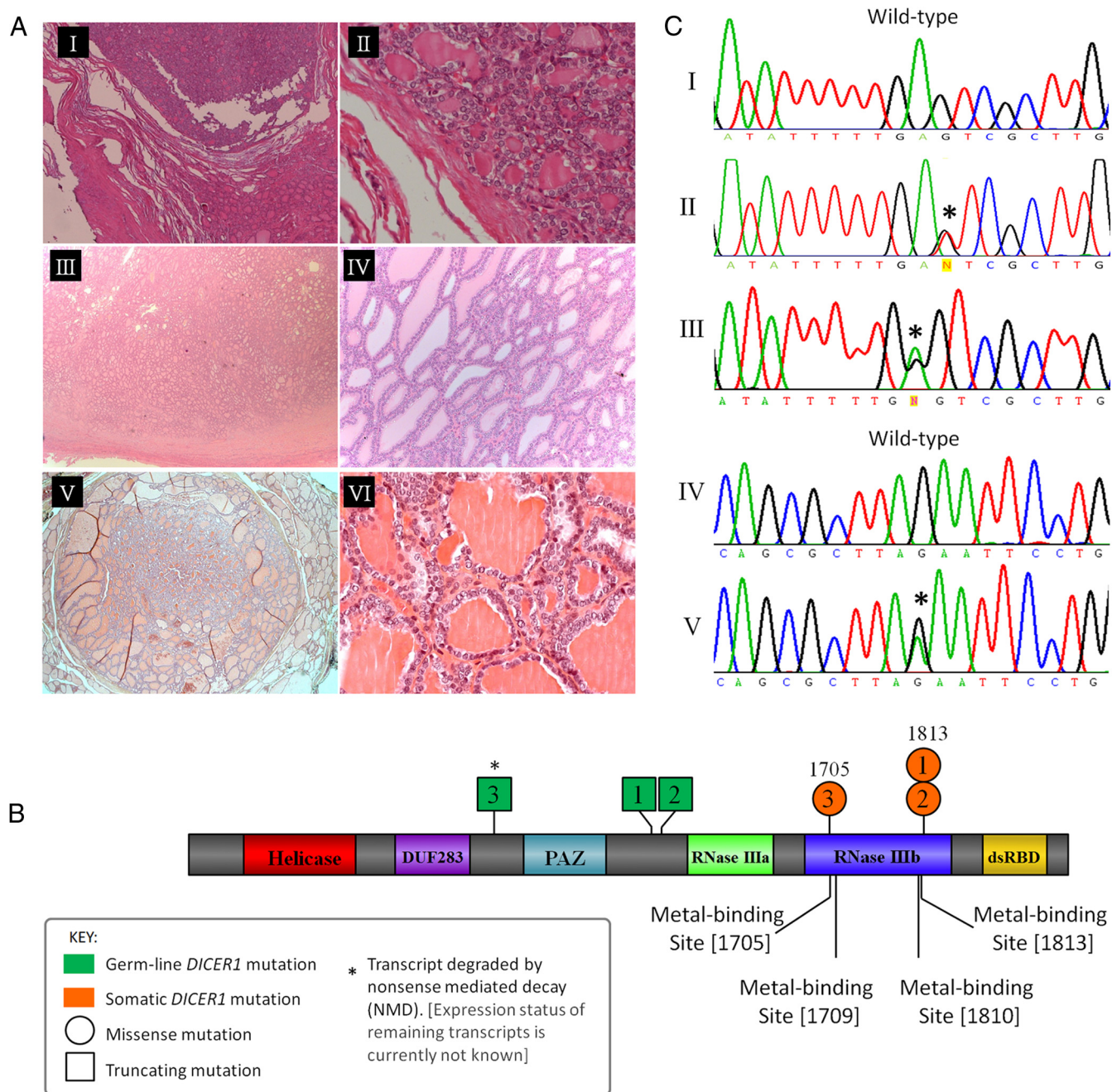
etic stem cell transplantation as previously described. At 7 years of age, she developed a goiter. Ultrasonography revealed multiple nodules within both lobes. At 9 years, she underwent a total thyroidectomy due to the continued growth of the thyroid mass, and pathological review revealed invasive follicular variant papillary thyroid carcinoma (Figure 1A, panels I and II).

Suspecting *DICER1* syndrome based on personal medical history (Supplemental Figure 1A, case 1), we conducted genetic testing on the patient and identified a deleterious germline *DICER1* mutation c.3505dupT (p.[Ser1169Phefs\*8]) in exon 21, occurring just before the nucleotides coding for the catalytically active RNase IIIa domain (Figure 1B). This transcript likely encodes a truncated protein in which the PAZ domain is preserved, but the RNase IIIa, RNase IIIb, and double-stranded RNA-binding domains are lost. Genetic screening of tumor genomic DNA (gDNA) extracted from formalin-fixed paraffin-embedded (FFPE) samples from the follicular variant papillary thyroid carcinoma was undertaken and we identified an acquired somatic mutation, c.5439G→T (p.[Glu1813Asp]) (Figure 1C, panel II). This mutation affects a highly conserved amino acid residue within the RNase IIIb domain of *DICER1* and is predicted to be damaging by both SIFT and PolyPhen2 (c.5439G→T: SIFT = 0; PolyPhen2 = 0.98). Genetic screening of the proband's parents, who to our knowledge are unaffected, revealed that her mother is a carrier of the c.3505dupT germline mutation (Supplemental Figure 1A, case 1).

## Case 2

At 1.3 years of age, the female infant presented with shortness of breath. Multiple bullous cysts were detected within the right middle lobe of the lung, and a pathological diagnosis of type I PPB was made. Type I PPB cystic lesions later developed within the left lung lobe. Additional surgery was performed to resect the lesions, and chemotherapy was administered. At age 6 years, progressive cataracts within her right eye developed. Two months later, a mass was noted in the right globe, enucleation was performed, and a ciliary body medulloepithelioma was diagnosed (14). At age 7 years, a clinically unsuspected thyroid nodule within the left lobe of the thyroid gland was detected on a treatment follow-up surveillance scan and removed, and a diagnosis of follicular variant papillary thyroid carcinoma was made (Figure 1A, panels III and IV).

Molecular genetic testing performed on the proband and her unaffected father (Supplemental Figure 1B, case 2) revealed the presence of an inherited, deleterious germline *DICER1* mutation (c.3579\_3580delCA; initially reported



**Figure 1.** A, Case 1: panel I, hematoxylin and eosin stain (HE) ( $\times 25$ ) showing tumoral thyroid nodule surrounded by normal thyroid; panel II, HE ( $\times 200$ ) showing characteristic follicular variant papillary thyroid carcinoma cells with clear tumoral nuclei. Case 2: panel III, HE ( $\times 25$ ) showing follicular variant papillary thyroid carcinoma within a nodule at low magnification; panel IV, HE ( $\times 200$ ) showing tumoral cells at high magnification showing overlapping clear nuclei. Case 3: panel V, HE ( $\times 50$ ) showing papillary thyroid carcinoma at low magnification; panel VI, HE ( $\times 200$ ) showing tumoral cells at high magnification showing overlapping clear nuclei. B, Graphic representation of the *DICER1* protein structure (NP\_001258211.1) indicating the approximate positions of the germline and somatic *DICER1* mutations observed in the 3 cases being reported: case 1, germline *DICER1* amino acid change, p.(Ser1169Phefs\*8) and somatic *DICER1* amino acid change, p.(Glu1813Asp); case 2, germline *DICER1* amino acid change, p.(Asn1193Lysfs\*41) and somatic *DICER1* amino acid change, p.(Glu1813Gly); case 3, germline *DICER1* amino acid change, p.(Tyr793X) and somatic *DICER1* amino acid change, p.(Glu1705Lys). The case number is indicated at the position of each mutation. C, Case 1, chromatogram showing the somatic (c.5439G $\rightarrow$ T) mutation in the FFPE tumor gDNA extracted from the follicular variant papillary thyroid carcinoma of case 1 (panel II) compared with the wild-type sequence (panel I); case 2, the follicular variant papillary thyroid carcinoma FFPE gDNA of case 2 was found to have a c.5438A $\rightarrow$ G somatic mutation (panel III); case 3, chromatogram showing the somatic (c.5113G $\rightarrow$ A) mutation identified within tumor gDNA extracted from the fresh-frozen papillary thyroid carcinoma of case 3 (panel V) compared with the wild-type sequence (panel IV). Mutations are indicated by asterisks. The expression of each mutation within the respective thyroid tumor was confirmed by the sequencing of cDNA synthesized from tumor RNA (data not shown).

**Table 1.** Summary of Cases of Thyroid Carcinoma Arising in Patients With PPB and/or a Germline *DICER1* Mutation

Case	Diagnosis	Germline <i>DICER1</i> Status	Somatic <i>DICER1</i> Status in Thyroid Carcinoma	Other <i>DICER1</i> -Associated Lesions	Family History of Thyroid Disease	HDC	Bone Marrow Transplantation	Reference
1	Follicular variant papillary thyroid carcinoma	Positive: c.3505dupT	Positive: c.5439G→T	PPB, PPB metastasis	Mother: thyroid hypothyroidism	Yes	Autologous peripheral blood stem cell transplantation	Case 1 (this report); Shin et al (13)
2	Follicular variant papillary thyroid carcinoma	Positive: c.3579_3580delCA <sup>a</sup>	Positive: c.5438A→G	PPB, CBME	Unknown	Yes	No	Case 2 (this report); Slade et al (4) <sup>b</sup>
3	Bilateral papillary thyroid carcinoma	Positive: c.2379T→G	Positive: c.5113G→A	PPB, CN	Unconfirmed	Yes	No	Case 3 (this report)
4	Follicular thyroid carcinoma	Unknown	Unknown	PPB	Mother: thyroid adenoma	Yes	Double Auto-BMT	Oue et al (17)
5	Follicular thyroid carcinoma	Unknown	Unknown	PPB, cERMS, bladder RMS, MNG	Unknown	Yes	Autologous peripheral blood stem cell transplantation	Rome et al (21)

Abbreviations: CBME, ciliary body medulloepithelioma; cERMS, cervical ERMS; HDC, high-dose chemotherapy.

<sup>a</sup> Initially reported as c.3583\_3584delGA (4).

<sup>b</sup> Thyroid cancer was not reported by Slade et al (4).

as c.3583\_3584delGA) (4) (Figure 1B). This mutation, predicted to result in p.Asn1193Lysfs\*41 at the protein level, induces a premature stop codon just before the sequence encoding the RNase IIIa domain of *DICER1*. The translation of the mutant mRNA transcript, if not degraded by nonsense-mediated decay, would result in the expression of a truncated protein. An acquired somatic mutation, c.5438A→G (p.[Glu1813Gly]), was observed within the RNase IIIb domain of *DICER1* in gDNA extracted from the FFPE of the follicular variant papillary thyroid carcinoma (Figure 1C, panel III). This mutation, reported previously in both WTs and SLCTs (9, 10), is predicted in silico to induce exclusion of the exon 25 amino acid sequence from the resulting *DICER1* protein, eliminating most of the RNase IIIb domain and, in so doing, hampering the protein's ability to cleave precursor miRNAs. Interestingly, further experiments performed by Wu et al (10) show that this transcript lacking exon 25 can be translated *in vitro*. The effect of the mutant *DICER1* protein on miRNA processing remains to be determined.

### Case 3

At 32 months of age, a male infant was diagnosed with type II PPB and CN. After surgical removal of the CN, chemotherapy was administered, and once the pulmonary mass had regressed, surgery for PPB was performed (15). At 11.5 years, a bilateral papillary thyroid carcinoma arising within a follicular adenoma was diagnosed after the removal of 2 thyroid nodules detected on ultrasound that was performed on account of his personal medical history (Figure 1A, panels V and VI). In the interval between the PPB and thyroid diagnoses, surveillance involving fre-

quent computed tomography (CT) and conventional x-rays had been employed. The dose of radiation to thyroid from the 9 thoraco-abdominal CT scans, using CT imaging techniques employed at that time, was estimated as 180 mGy.

Sequencing of *DICER1* in blood gDNA identified an inherited (Supplemental Figure 1C, case 3) deleterious germline mutation, c.2379T→G (Figure 1B). At the level of the mRNA transcript, this mutation, p.(Tyr793X), is predicted to induce a premature stop codon just before the sequence encoding the PAZ domain of *DICER1*, which, if translated, would result in the production of a truncated protein. However, the analysis of cDNA synthesized from blood RNA revealed only the wild-type sequence. This observation suggests the transcript containing the c.2379T→G mutation is degraded by nonsense-mediated decay (data not shown). Sequencing of tumor gDNA extracted from frozen papillary thyroid carcinoma revealed an acquired somatic mutation (c.5113G→A; p.[Glu1705Lys]) within the RNase IIIb domain of *DICER1* (Figure 1C, panel V). Consistent with the 2 somatic mutations reported above, this mutation affects a highly conserved amino acid residue, central to the catalytic activity of the RNase IIIb domain. In vitro experiments performed by Anglesio et al (11) show that mouse *Dicer1*-deficient embryonic stem cells expressing the p.Glu1705Lys variant exhibit a dramatic loss in the processing of mature 5p miRNA strands, but retain the 3p strand miRNA processing. This shift in mature miRNA expression has been hypothesized to be a significant oncogenic factor induced by such hotspot somatic *DICER1* mutations (11). The mutation is predicted to be damaging by both SIFT and PolyPhen2 with respective scores of 0 and 1.

## Discussion

The three described cases suggest children carrying germline *DICER1* mutations are at increased risk of thyroid carcinoma, but only 5 cases of DTC arising in association with PPB and/or germline *DICER1* mutations have been reported (Table 1). These 5 cases exhibit some salient parallels, and as discussed by Shin et al (13), the risk of developing DTC may be elevated when high-dose chemotherapy and/or bone marrow transplantation (BMT) is applied in the treatment of patients with PPB. Chemotherapy, irradiation treatments, and BMTs are known to predispose to second malignant neoplasms (16), and the thyroid is particularly susceptible (17, 18). In addition, for children with PPB, multiple diagnostic radiation exposures, as well as the occasional use of therapeutic thoracic radiation, may contribute to development of DTC. The age-standardized risk for thyroid carcinoma by age 10 years in Canadian males is ~1 per million. Based on data cited by Schonfeld et al (18), one can estimate an excess absolute risk of DTC of 80 per million person-years from the cumulative thyroid dose of 180 mGy from chest CT received by the child of case 3. This may be considered a possible contributing factor in thyroid tumorigenesis in this case. It should be noted that this dose estimate is severalfold higher than the dose received from a chest CT performed with current techniques in which the excess relative risk from the cumulative thyroid dose is <1, and therefore the probability of causation from the thyroid irradiation becomes <50%. The 50% probability of causation threshold is ~130 mGy in total, or ~14 mGy to the thyroid per chest CT.

The risk for DTC arising in association with a germline *DICER1* mutation appears to be only modestly elevated, but implementation of intensive treatment protocols, for example, for PPB, may increase the risk for thyroid carcinoma in those predisposed on the basis of a preexisting germline *DICER1* mutation.

Furthermore, the discovery of somatic RNase IIIb *DICER1* mutations in the DTCs of the 3 children investigated here, who also have germline *DICER1* mutations, adds to the growing evidence from other tumors that these RNase IIIb mutations affecting the metal-binding residues of the domain are consistent and critical second hits in *DICER1* tumorigenesis. It is therefore hypothesized that this second somatic hit is required in addition to a loss-of-function germline *DICER1* mutation to initiate thyroid carcinoma development. The specific downstream miRNA perturbations and mechanisms of tumorigenesis remain to be explored. It is also known that the occurrence of radiation-related gene rearrangements, most commonly involving the *RET* gene, are overrepresented in children ex-

posed to large doses of ionizing radiation (19, 20). A cooperation between such *RET* rearrangements and the *DICER1* somatic mutations in these DTCs is also a possibility that may be explored.

An implication of this report is that attention be paid to the protection of the thyroid bed when screening children with *DICER1* germline mutations for PPB and/or other *DICER1*-related tumors. Adhering to the guidelines delineated by the Pleuropulmonary Blastoma Registry (<http://www.ppbregistry.org/doctors/surveillance.htm>) is recommended. Yearly thyroid ultrasound during childhood and adolescence, together with appropriate endocrine referral, may be warranted for these young *DICER1* mutation carriers.

## Conclusion

This report of somatic *DICER1* mutations in DTC occurring in association with PPB, CN, and MNG expands the spectrum of entities considered to occur within the *DICER1* syndrome. The results are highly suggestive of an association between germline *DICER1* mutations, PPB treatment, and DTC, but further confirmation is required. Especially vigilant surveillance for thyroid neoplasms in these children may be justified because children carrying germline *DICER1* mutations exposed to diagnostic and therapeutic radiation may be at increased risk compared with other *DICER1* mutation-positive children.

## Acknowledgments

We thank the families involved in this research for their consent to participation; Marie-Anne Brundler, MD, for her help with case 2; and Jiamin Chen, PhD, for his assistance with obtaining the Cancer Genome Atlas Research Network data.

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This research was made possible thanks to the support of the Lady Davis Institute/TD Bank Studentship Award and Alex's Lemonade Stand Foundation.

Disclosure Summary: The authors have nothing to disclose.

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