A novel nonsense *DICER1* mutation identified in a family with the childhood onset multinodular goiter and various thyroid diseases

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Background

- Nontoxic multinodular goiter (MNG) is frequently encountered in the general population, but little is known about the underlying genetic susceptibility to this disease. A variety of genetic disorders can cause predisposition to benign and malignant thyroid tumors (Table 1).
- The *Dicer1* encodes for an RNase III-family endonuclease that cleaves precursor microRNAs into active miRNA. Germline mutations in *DICER1* cause predisposition to rare childhood tumours in lungs, kidneys, ovaries, and thyroid, etc [1)] (Table 2).
- We report a family exhibiting various thyroid diseases in which a *DICER1* germline mutation was revealed first in the proband with the childhood onset MNG and subsequently in the family members.

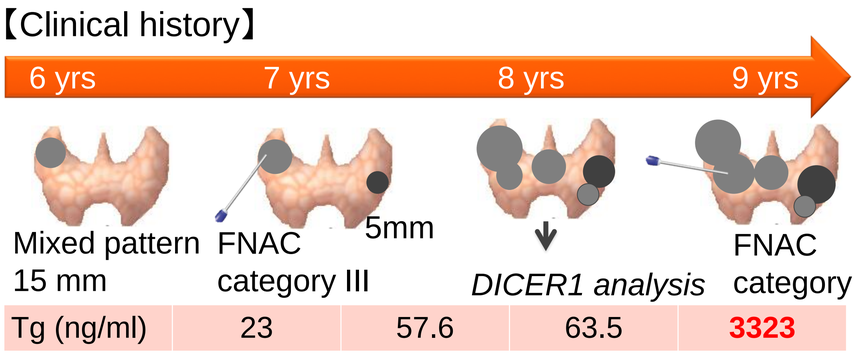
Table 2. *DICER1* germline mutations and associated diseases

	Age range of onset (highly susceptible age)	Benign or malignant
Pleuropulmonary blastoma (PPB)	0−72 months (depends on type)	Malignant
Cystic nephroma	0–48 months (unknown)	Benign
Sertoli–Leydig cell tumors	2–45 years (10–25)	Malignant
MNG	5–40 years (10–20)	Benign
Embryonal Rhabdomyosarcoma	4–45 years (10–20)	Malignant

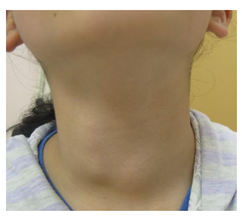
Patient：6-year-old Japanese girl

【Chief complaint】Cervical mass
【Past history】 No abnormality in the growth and development. No history of any cancers.
【Family history】 Table 3, Fig.1
- II-2(Mother): at age 15 years: partial thyroidectomy for MNG
  at age 39 years: total thyroidectomy for poor DTC and MNG
- II-3(Mother's sister): at age 14 years: partial thyroidectomy for MNG
  at age 30 years: ovarian surgery (Details unknown)
- I-2 (maternal grandmother)：at age 20 years: thyroid lobectomy for MNG

【Clinical history】

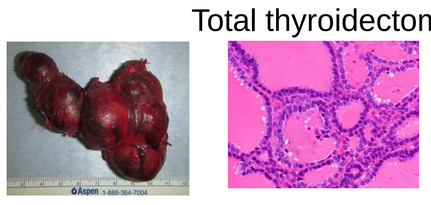


Tg (ng/ml)	23	57.6	63.5	**3323**



Thyroid function tests		
TSH	0.92	μU/ml
FT3	4.2	pg/ml
FT4	1.2	ng/dl
Tg	23	ng/ml
Calcitonin	22	pg/ml

Total thyroidectomy



Pathological diagnosis：Adenomatous goiter, no malignancy

Total thyroidectomy was performed because of a significant increase in thyroglobulin level, an increase in tumor mass, and discomfort during swallowing.

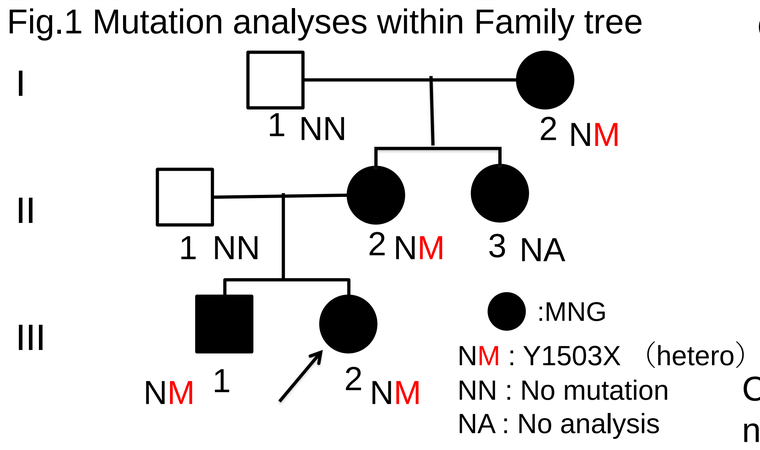
Table 1.
Hereditary Tumor Syndrome Associated with Thyroid Nodules/DTC

	Gene (Chromosomal Location)	Types of Thyroid Neoplasia
APC-Associated Polyposis	APC (5q21-q22)	PTC (cribriform-morular variant)
Carney complex	PRKAR1A (17q24.2) "CNC2" (2p16)	MNG, Follicular adenomas DTC (PTC & FTC)
PTEN Hamartoma Tumor Syndrome	PTEN (10q23)	MNG, Follicular adenomas DTC (FTC)
Werner syndrome	WRN (8p12)	DTC (PTC and FTC)
DICER1 Syndrome	**DICER1 (14q32.13)**	**MNG, DTC**

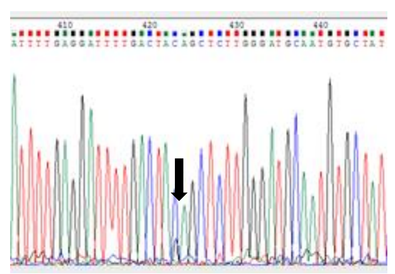
PTC; papillary thyroid cancer, FTC; follicular thyroid cancer, DTC differentiated thyroid cancer
Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2015; 25:716

DICER1 mutation analysis

Fig.1 Mutation analyses within Family tree

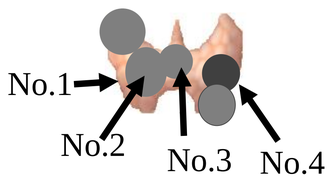


Chromatogram of proband



c.4509C＞G（p.Y1503X）
Chromatogram showing the novel nonsence mutation (c.4509 C>G, p.Y1503X) of *DICER1.*

DICER1 mutation analysis with several thyroid nodule and normal thyroid tissue



		Allele 1	Allele 2
No.1	Macroscopic normal thyroid tissue	Y1503X	No mutation
No.2	Nodule	Y1503X	Asp1810Val
No.3	Nodule	Y1503X	Asp1709Gly
No.4	Nodule	Y1503X	Glu1813Lys

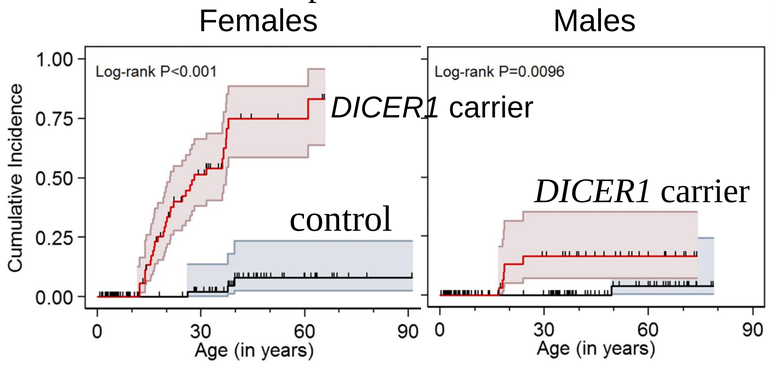
Table 3

	Present age	Clinical phenotypes of thyroid diseases	TSH (μIU/mL)	FT4 (ng/dL)	FT3 (pg/mL)	Tg (ng/mL)	DICER1 c.4509C>G
I-1		Normal	0.85	1.3	3.25	19.5	Wild
I-2		20 yrs: thyroid lobectomy Graves' disease	2.90	0.93	2.82	15.7	Mut
II-1	47	Normal	2.16	1.15	2.95	1.26	Wild
II-2	47	15 yrs：partial thyroidectomy 39 yrs：total thyroidectomy（MNG, poorly differentiated carcinoma）	9.14	1.16	2.21	>500	Mut
II-3	44	14 yrs：partial thyroidectomy (MNG) 30 yrs: ovarian tumor					NA
III-1	17	MNG	0.94	1.22	3.27	53.7	Mut
III-2	10	MNG（total thyroidectomy）	0.92	1.2	4.2	23	Mut

Discussion：*DICER1* mutation and developing MNG or DTC[2)]

DICER1 mutation and developing MNG

Time course in 154 patients with *DICER1* mutation

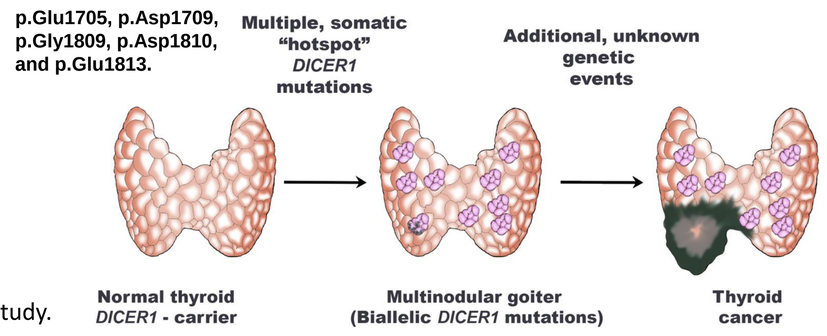


Time of onset of MNG：5-40 years of age (Mainly 10 to 20 years old)[3)]

	Developing DTC	
Dicer1 carrier	4/154 (/3937 person･year)	Average 34 years of age (18.6 to 43 yrs)
	*16-fold (95% [CI], 4.3 to 41) compared to SEER	

SEER: The Surveillance, Epidemiology, and End Results

Models for thyroid tumor development [2)]



Conclusions

- Although patients with *DICER1* mutation have been reported to have familial DTC, there are no reports of poorly DTC, suggesting that an additional somatic mutation might be responsible for the observed neoplastic transformation.
- *DICER1* mutation analysis is considered to be very important in the treatment protocol and for the management of complications in childhood onset MNG.

Selected References

1) Slade I, Bacchelli C, Davies H, et al. DICER1 syndrome: clarifying the diagnosis, clinical features and management implications of a pleiotropic tumour predisposition syndrome. J Med Genet. 2011 Apr;48(4):273-8.
2) Khan NE, Bauer AJ, Schultz KAP, et al. Quantification of Thyroid Cancer and Multinodular Goiter Risk in the DICER1 Syndrome: A Family-Based Cohort Study. J Clin Endocrinol Metab. 2017;102(5):1614-1622
3) Schultz KAP, Rednam SP, Kamihara J, et al. *PTEN, DICER1, FH*, and Their Associated Tumor Susceptibility Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood. Clin Cancer Res. 2017 Jun 15;23(12):e76-e82.

【Disclosure Statement of COI】
The authors have no financial conflicts of interest disclose concerning the study.

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