

## Case Report

# Association Between Graves' Disease and Renal Coloboma Syndrome: A Case Report

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**Abstract.** Renal coloboma syndrome is an autosomal dominant condition characterized by renal lesions and optic nerve abnormalities. We report an 11-yr-old Japanese girl with familial renal coloboma syndrome, who also had Graves' disease. Four affected family members had a previously reported heterozygous mutation (c.76dupG, p.Val26Glyfs\*28) in the *PAX2* gene. We hypothesized that *PAX2* mutations may increase the risk of autoimmune diseases through alterations of human  $\beta$ -defensin 1 expression.

**Key words:** renal coloboma syndrome, *PAX2*, mutation, Graves' disease

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## Introduction

Renal coloboma syndrome (OMIM#120330) is an autosomal dominant condition characterized by renal lesions and optic nerve abnormalities (1). Renal manifestations include renal hypoplasia, enuresis due to urinary concentrating defect, multicystic dysplastic kidney, and renal insufficiency. Ocular manifestations include optic nerve dysplasia, scleral staphyloma, optic nerve cyst and retinal detachment. More than

170 affected individuals and 80 families have been reported to date (2).

*PAX2* is the only gene known to cause renal coloboma syndrome. Genotype-phenotype correlation is not evident among *PAX2* mutation carriers. Optic nerve abnormalities and renal lesions are variably manifested by patients with *PAX2* mutations, even within the same family (2, 3). While several nonrenal or non-ophthalmological features, such as hearing impairment, central nervous system anomalies, developmental delay, cardiac defects, abnormality of the hand, and ligamentous laxity, have been reported (4), there is no report documenting autoimmune diseases or thyroid diseases.

Here, we report a patient with Graves' disease and a familial *PAX2* mutation, and discuss the potential relationship between

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**Table 1** Renal and ocular manifestations of the patients

Patient, gender and age	Renal manifestations					Ocular manifestations	Associated findings	Other diseases
	Renal size	Enuresis	Onset of proteinuria	Initiation of hemodialysis	Current Scr (mg/dL)	Fundus		
I-2 F/53 yr <sup>a</sup>	Not available	Not available	29 yr	32 yr	9.64 <sup>b</sup>	Bilateral retinal detachment	None	Breast cancer
II-3 M/43 yr	Not available	(+)	10 yr	18 yr <sup>c</sup>	1.40	Bilateral optic nerve dysplasia, left retinal detachment	None	None
II-4 F/37 yr	Bilateral hypoplasia	(+)	12 yr	(-)	1.27	Normal	None	Obesity, hypertension, hyperlipidemia
III-3 Unknown/abortus <sup>d</sup>	Bilateral hypoplasia	ND	ND	(-)	ND	ND	Oligohydramnios	ND
III-4 F/11 yr	Normal	(+)	9 yr	(-)	0.60	Bilateral optic nerve dysplasia	Oligohydramnios, strabismus, nystagmus	Graves' disease, bronchial asthma
III-7 M/2 yr	Bilateral hypoplasia	ND	(-)	(-)	0.41	Normal	Oligohydramnios	None

F, female; M, male; Scr, serum creatinine concentration. <sup>a</sup> She died at 53 yr of age. <sup>b</sup> At the initiation of hemodialysis. <sup>c</sup> He had a kidney transplant at 19 yr of age. <sup>d</sup> The family elected to terminate the pregnancy at 20 wk of gestation.

Graves' disease and *PAX2* mutations.

### Case Report

Family pedigree is shown in Fig. 1A. Clinical information of the family members is summarized in Table 1. We describe clinical pictures of three affected family members.

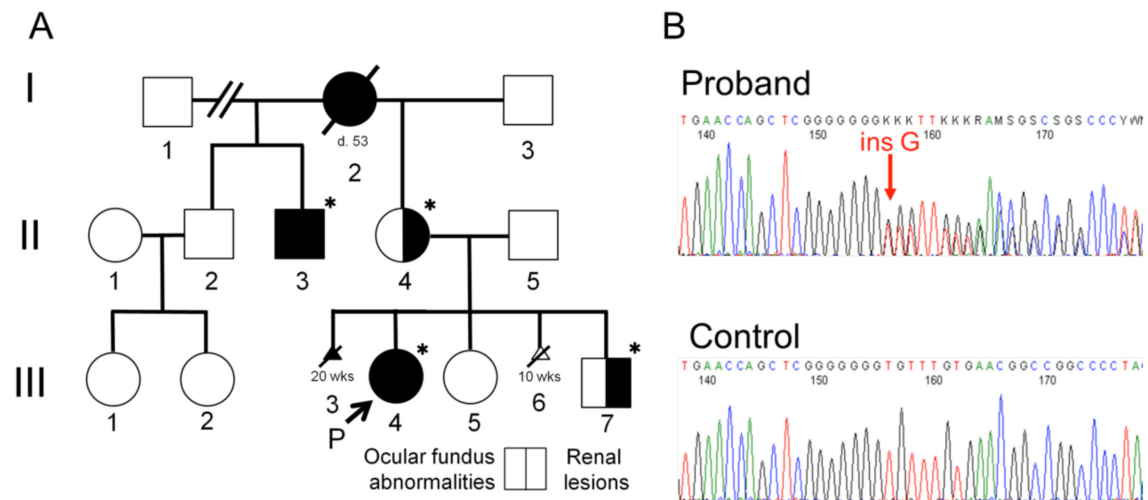
#### III-4

The proband is an 11-yr-old girl. She is the second child of non-consanguineous Japanese parents. Serial prenatal ultrasound examinations showed no renal anomalies, although oligohydramnios was noted. She was delivered vaginally at 39 wk of gestation. Her birth weight was 2,752 g (-0.6 SD), length was, 47.5 cm (-0.6 SD), and head circumference was, 31.0 cm (-1.6 SD).

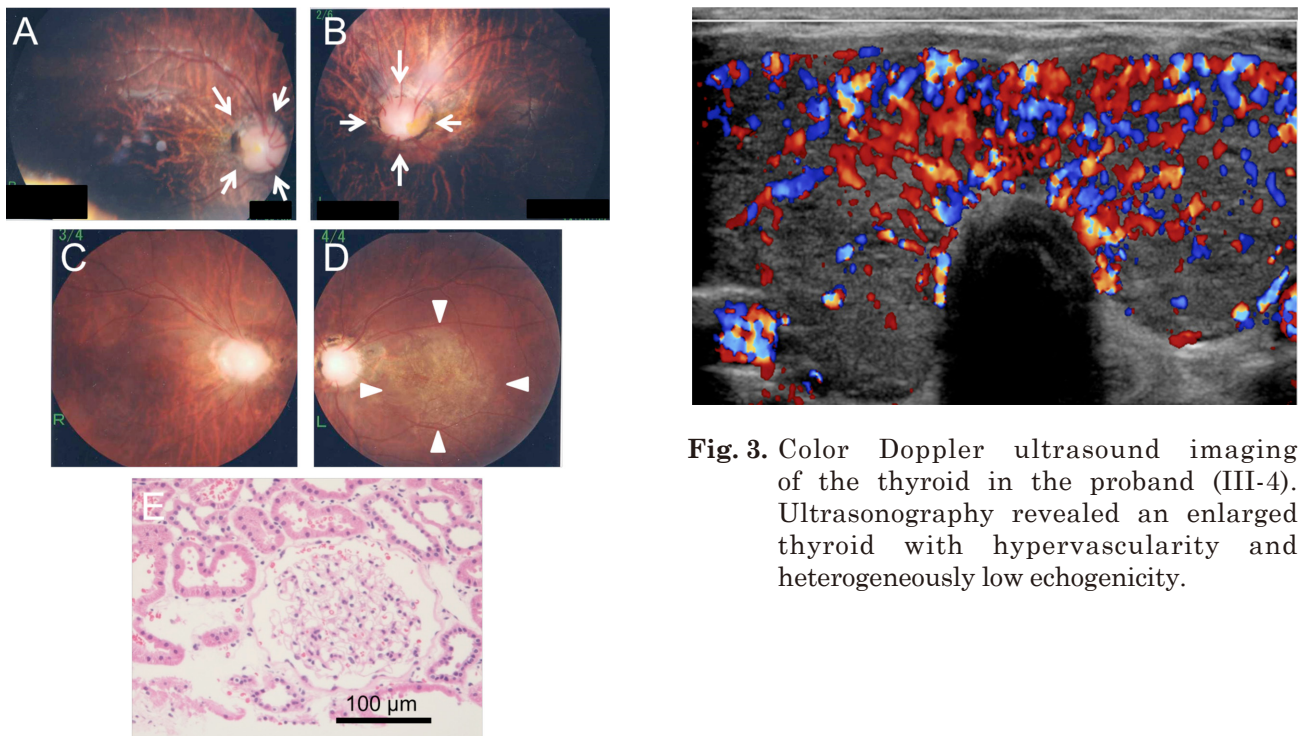
At 4 mo of age, internal strabismus and

horizontal nystagmus were noticed, and she was referred to our hospital. Ocular fundus examination showed bilateral optic nerve dysplasia (Fig. 2A, B). She has received patching treatment and worn glasses for myopia.

Nocturnal enuresis continued from birth. At 6 yr of age, diurnal enuresis developed. Lifestyle guidance, water restriction and alarm treatment did not result in a favorable response. At 9 yr of age, her kidneys were normal in size and structure according to an ultrasound examination. The Fishberg concentration test revealed that the maximal urine osmolality was 752 mOsm/kg with elevated antidiuretic hormone concentrations (antidiuretic hormone concentration, 8.7 pg/mL, at a serum sodium concentration of 136 mmol/L), suggestive of a mild urinary concentrating defect. A 24-h specimen of urine contained 0.33 g of protein, suggestive of mild proteinuria. Her blood pressure was within normal limits. Renal biopsy

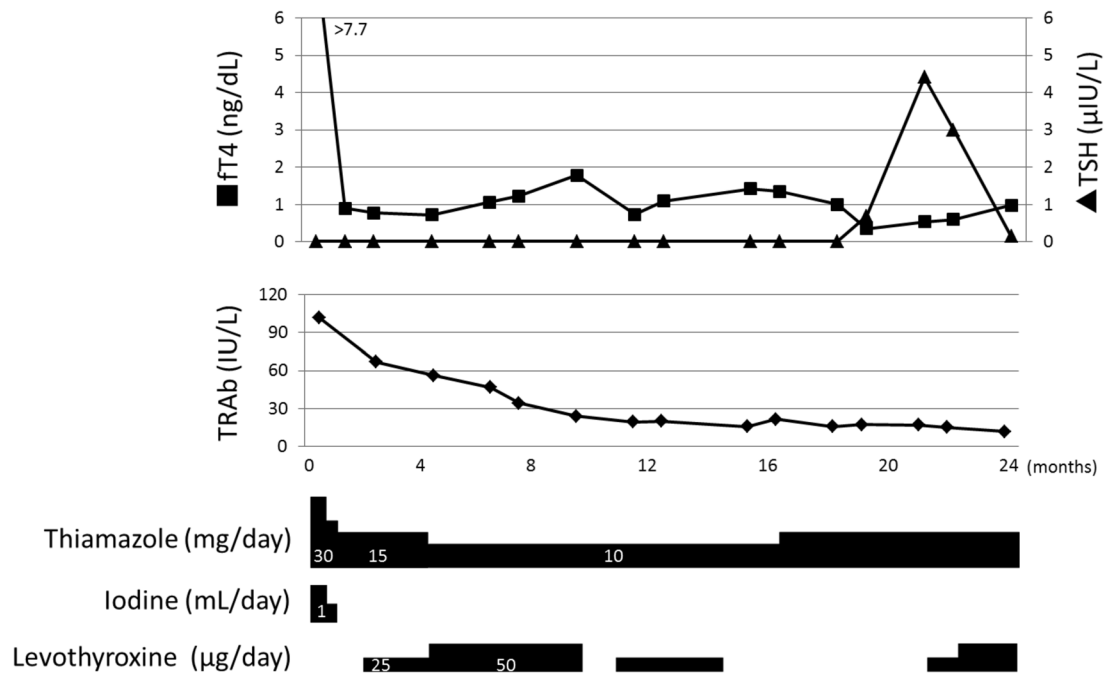


**Fig. 1.** A: Pedigree of the family. Family members who underwent the genetic testing are marked with an asterisk. B: Sequencing of exon 2 of the *PAX2* gene.



**Fig. 2.** A–D: Ophthalmological examination of the patients. Right (A) and left (B) eye of the proband (III-4). Bilateral optic discs were wide and deeply excavated (surrounded by arrows), suggestive of optic nerve dysplasia, so called “morning glory” variant. Right (C) and left (D) eye of patient II-3. Macular degeneration of his left eye (surrounded by arrowheads) and bilateral optic disc dysplasia were shown. E: Renal biopsy from patient II-4 at 26 yr of age. The glomerulus exhibits mesangial cell proliferation slightly. Hematoxylin and eosin stain.

**Fig. 3.** Color Doppler ultrasound imaging of the thyroid in the proband (III-4). Ultrasonography revealed an enlarged thyroid with hypervascularity and heterogeneously low echogenicity.



**Fig. 4.** Clinical course of the proband (III-4). Free thyroxine (fT4) was normalized within a month. Thyroid-stimulating hormone (TSH) levels had been suppressed. Anti-thyroid stimulating hormone receptor antibody (TRAb) titers were reduced.

was not performed.

She was referred to the pediatric endocrinology division at 10 yr of age because of weight loss. On examination, hand tremor and tachycardia (139 bpm) were apparent. Her thyroid was soft and large by palpation. She also had exophthalmos. Blood tests revealed marked hyperthyroidism with a suppressed thyroid-stimulating hormone level ( $<0.01 \mu\text{IU/L}$ , reference 0.5–5) and elevated free triiodothyronine ( $>32.55 \text{ pg/mL}$ , reference 2.3–4.0) and free thyroxine levels ( $>7.77 \text{ ng/dL}$ , reference 0.90–1.70). Ultrasonography revealed an enlarged thyroid (estimated size,  $>34.4 \text{ mL}$ , reference 2.9–6.3 (5, 6)), which had heterogeneously low echogenicity. Marked hypervascularity was shown by color Doppler imaging (Fig. 3). The diagnosis of Graves' disease was confirmed by elevated anti-thyroid stimulating hormone receptor antibody (102 IU/L, reference  $<1.0$ ). Treatment with 30 mg of thiamazole and 1 mL of 2.5% aqueous iodine solution improved clinical symptoms within

a month. Then, her anti-thyroid stimulating hormone receptor antibody titers were found to be reduced. Her serum thyroid-stimulating hormone levels had been suppressed. She needed 15 mg of thiamazole two years after diagnosis (Fig. 4).

She has suffered from bronchial asthma with a high immunoglobulin E (IgE) level (511 IU/mL, reference  $<173$ ) for five years. Her bronchial asthma has been well controlled with montelukast and inhaled beclomethasone. Other immunological tests, including serum levels of immunoglobulins (IgG, IgA, IgM) and blastoid transformation of lymphocytes in response to concanavalin-A and phytohemagglutinin, were within normal limits.

### II-3

The proband's uncle is 43 yr old. A periodic medical examination at school revealed proteinuria at 10 yr of age. He presented with enuresis until 11 yr of age. The results of renal

biopsy at 14 yr of age and information about medical treatment was not available. His renal function continued to deteriorate. At 18 yr of age, he was placed on chronic hemodialysis. At 19 yr of age, he had a kidney transplant from his elder brother (II-2). He had complained visual impairment since his late thirties. At 40 yr of age, an ocular fundus examination revealed macular degeneration of his left eye and bilateral optic nerve dysplasia (Fig. 2C, D). At 42 yr of age, retinal detachment of his left eye occurred.

#### II-4

The proband's mother is 37 yr old. She presented with enuresis until 12 yr old. At 12 yr of age, a periodic medical examination at school revealed proteinuria for the first time. Ultrasonography revealed bilateral renal hypoplasia. At 14 yr of age, left renal biopsy revealed no specific findings. At 26 yr of age, she became pregnant with the proband (III-4), and her renal function became worse. Repeated renal biopsy revealed no specific findings (Fig. 2E). When she became pregnant with a fetus (III-6) at 32 yr of age, her renal function further deteriorated and hypertension developed. The family elected to interrupt the pregnancy at 10 wk of gestation. She was obese, and her body mass index was 32.8 at her last visit.

#### Mutation analysis of the *PAX2* gene

After obtaining written informed consent, we extracted genomic DNA from peripheral blood samples or nails of four family members (II-3, II-4, III-4 and III-7) using standard protocols. Genomic DNA samples were PCR-amplified for the coding 11 exons and their splice sites of the *PAX2* gene (7), and the PCR products were subjected to direct sequencing from both directions on an autosequencer. All of them had a heterozygous mutation (c.76dupG, p.Val26Glyfs\*28) that inserts an extra guanine nucleotide in a stretch of seven guanine nucleotides (Fig. 1B).

#### Discussion

We described a Japanese family with renal coloboma syndrome and a heterozygous mutation (c.76dupG, p.Val26Glyfs\*28) in exon 2 of the *PAX2* gene. Clinical manifestations varied within the family. Ocular fundus manifestations included normal fundus, optic nerve dysplasia, and retinal detachment. Renal manifestations included renal hypoplasia, urinary concentrating defects, proteinuria and end-stage renal insufficiency. One of the two patients with renal failure had a kidney transplant.

The c.76dupG mutation is one of the most frequent *PAX2* mutations (8). It is predicted to have a premature termination codon located in 54–56 nucleotides upstream of the subsequent exon-intron junction. The c.76dupG mutation may trigger nonsense-mediated decay (NMD), although whether the mutation triggers NMD remains to be clarified. Even if the mutant RNA is not destroyed by NMD, the c.76dupG mutation would lead to a truncated protein lacking any functional domains. Clinical presentation of the c.76dupG carriers is known to be highly variable between individuals and even within a family (3, 7). Genotype-phenotype correlation is not evident among *PAX2* mutation carriers. It has been hypothesized that genetic, epigenetic or environmental factors may modulate the clinical manifestations in humans and mice with *PAX2* mutations (9, 10).

Interestingly, the proband had an atypical complication, Graves' disease. Graves' disease is an autoimmune disorder mediated by agonistic antibodies to the thyroid stimulating hormone receptor, which is the commonest cause of hyperthyroidism in childhood and adolescence. *PAX2* mutations or renal coloboma syndrome associated with Graves' disease has not been reported so far. One previous study showed that the increased risk of Henoch-Schönlein purpura nephritis, a putative immune-mediated glomerular disease, was associated with *PAX2* gene polymorphisms (11). Although coexistence



of renal coloboma syndrome and Graves' disease in the proband could be only coincidental, we think it probable that *PAX2* mutations may be associated with development of Graves' disease. *PAX2* has been known to be expressed in a subset of lymphocytes (12), and thus would have a physiological role in the immune system. *PAX2* represses human  $\beta$ -defensin 1 expression through binding to the promoter (13). Functional single nucleotide polymorphisms of  $\beta$ -defensin 1 were reported to be risk factors for development of systemic lupus erythematosus (14) and autoimmune thyroid diseases in type 1 diabetes patients (15). We speculate that *PAX2* mutations may increase the risk of autoimmune diseases, including Graves' disease, through alterations of human  $\beta$ -defensin 1 expression.

In summary, we reported a patient with a familial *PAX2* mutation, who also had Graves' disease. Further study will clarify whether *PAX2* mutations can be a risk factor for development of autoimmune diseases.

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