A case of 46,Y,dup(X)(p21.2p22.2) DSD caused by overexpressed DAX1

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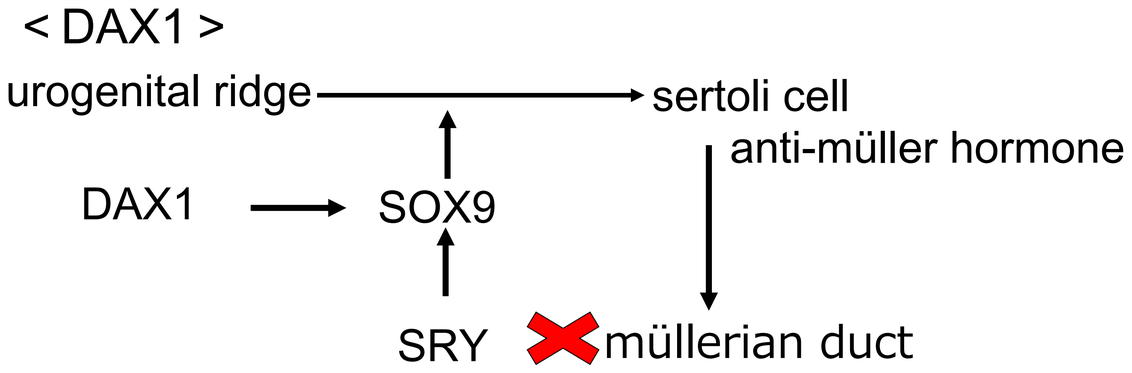
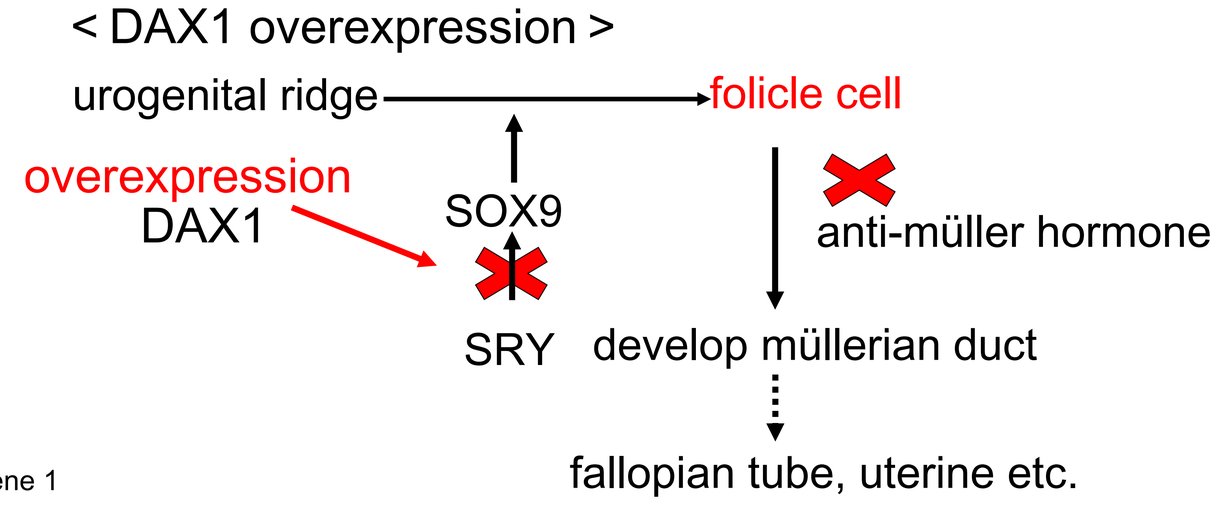
1. Introduction

< DAX1 >



< DAX1 overexpression >



DSD: disorders of sex development
DAX1: dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1
SOX9: SRY (sex determining region Y)-box 9

2. Case Report

【case】 5Y8M, female socially

【physical examination】

H: 100 cm (-2.4 SD), BW: 12.7 kg (-2.1 SD)
BP: 90/53 mmHg

head: low-set ears, telecanthus and cleft palate
external genitalia: complete female (Quigley scale 6)

【laboratory data and imaging studies】

<blood examination>

fT_4	1.20	ng/dL	17α-OHP	0.33	ng/mL
TSH	8.85	μIU/dL	T	< 0.03	ng/ml
LH	0.26	mIU/mL	ACTH	31.0	pg/mL
FSH	13.26	mIU/mL	cortisol	7.8	μg/dL
E_2	19	pg/mL	IGF-1	67	ng/mL

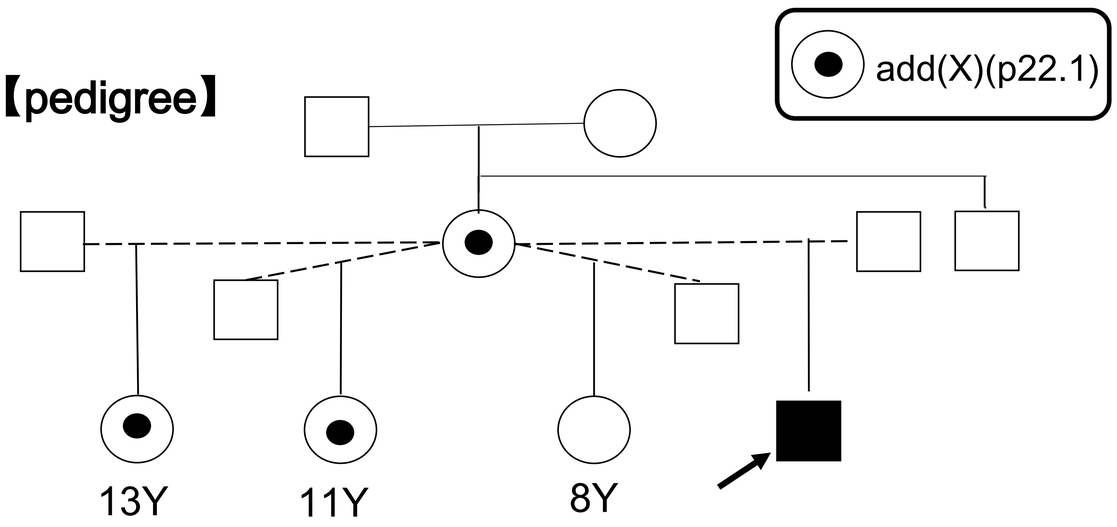
< bone age > 5 years old
< steroid profile in urine > no abnormal findings
< MRI > head: no abnormal findings
pelvis: not detected ovaries, testes, and uterus.
< US > no abnormal findings

【stimulation test 】

LHRH (2.5μg/kg) TRH(7μg/kg)	0min	30min	60min	90min	120min
LH (mIU/mL)	1.16	18.00	17.50	15.58	11.12
FSH(mIU/mL)	15.14	23.75	28.41	29.48	30.88
TSH (μU/dl)	11.8	135	93.5	74.8	58.8

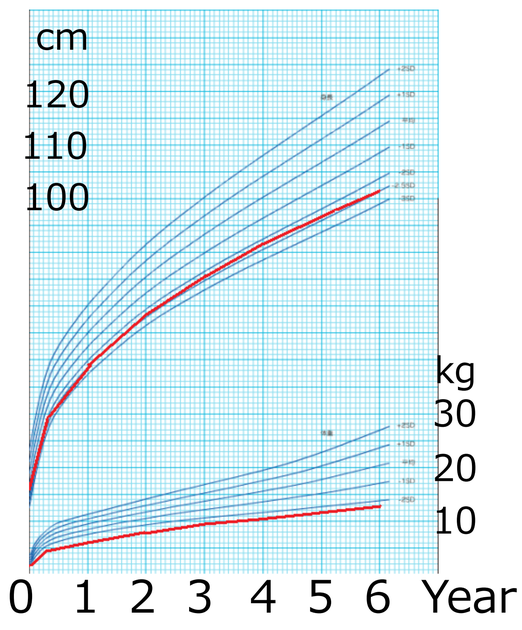
hCG (3000 units) for 3days	0hr	24hr	48hr	72hr
T (ng/mL)	< 0.03	< 0.03	< 0.03	< 0.03

【pedigree】



【past history】

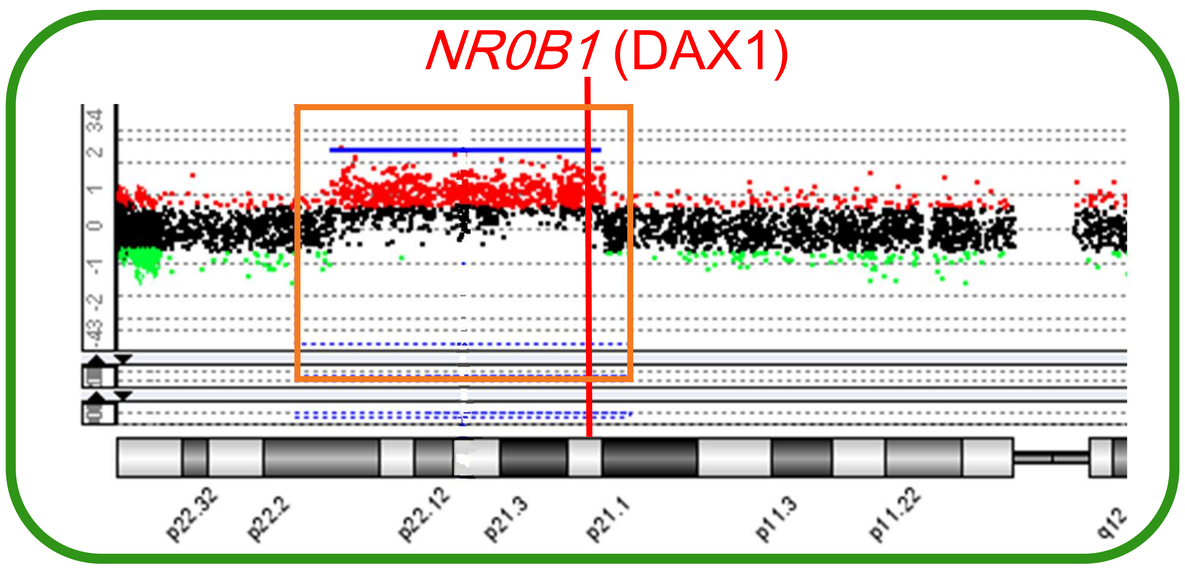
birth at about 40 week of gestation
birth height 45cm
birth weight 2112 g
respiratory distress syndrome
ventricular septum defect
(closed naturally)
cleft palate (operated)
otitis media, seizer, hard hearing



【chromosome examination】

46, Y, add(X)(p22.1) (G-BAND)
SRY positive, SHOX positive (FISH)

【array CGH: Xp chromosome 】



46,Y,dup(X)(p21.2p22.2)

3. Discussion

In mice, Dax1 exposure to both low- and high-dose Dax1 can induce DSD (1). However, while the mechanisms behind Dax1 overexpression have been clarified in mice (1), details regarding the process in humans remain unclear.

No major differences have been noted between overexpressed Xp patients with or without DSD (2). While nearly all female patients with DAX1 overexpression and DSD have complete female external genitalia. Similarly, our patient also had complete female external genitalia while further exhibiting short stature. Short stature has been reported in a proportion of cases (2-4), although in our present case, the height might be due to her being small-for-gestational age (SGA) or having subclinical hypothyroidism.

The present case occurred with subclinical hypothyroidism, indicating that thyroid gland function was not normal. However, DAX1 overexpression and the region surrounding the DAX1 gene is not related to thyroid function. Therefore, we believe that the patient's subclinical hypothyroidism was unrelated to overexpression of DAX1, occurring naturally. We need further research. Excluding her short stature, we were unable to explain the source of the patient's symptoms.

4.Conclusion

- To our knowledge, this is the first case of DAX1 overexpression with subclinical hypothyroidism.
- Thyroid function should be ascertained to examine DAX1 overexpression in patients.

references (1) Ludbrook L, et al. 2004, (2)Baumstrk A , et al. 1995
(3) Bernstein R, et al. 1980, (4) Wyandt H. , et al. 1991