

DUOX2の複合ヘテロ接合体変異遺伝子を有するTSH抵抗症の一家系



高松 順太, Panudda Srichomkwun, Deborah Nickerson,
Michael Bamshad, Jessica Chong, Samuel Refetoff

TSH抵抗症とは

生物学的活性の正常なTSHに対する感受性が低下している病態

血中TSHは高値を示す。

甲状腺腫大はない。(甲状腺体積は正常～縮小)

血中甲状腺ホルモンレベルは正常～低値である。

シカゴ大学サミュエル・レフェトフ教授の研究：77家系の解析結果

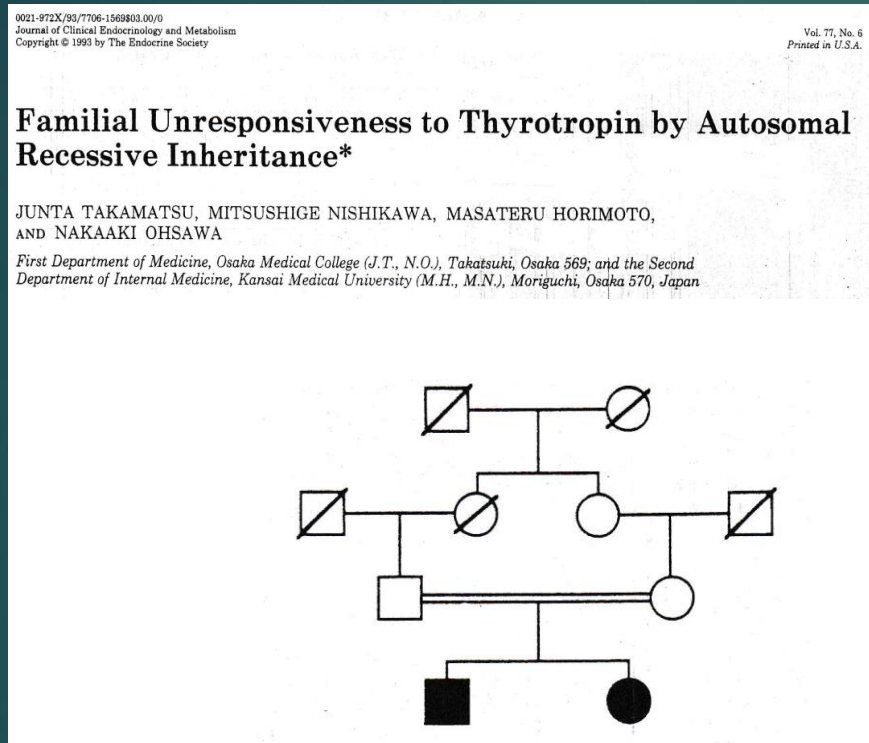
TSHレセプターの遺伝子変異 11家系

PAX8の遺伝子変異 4家系

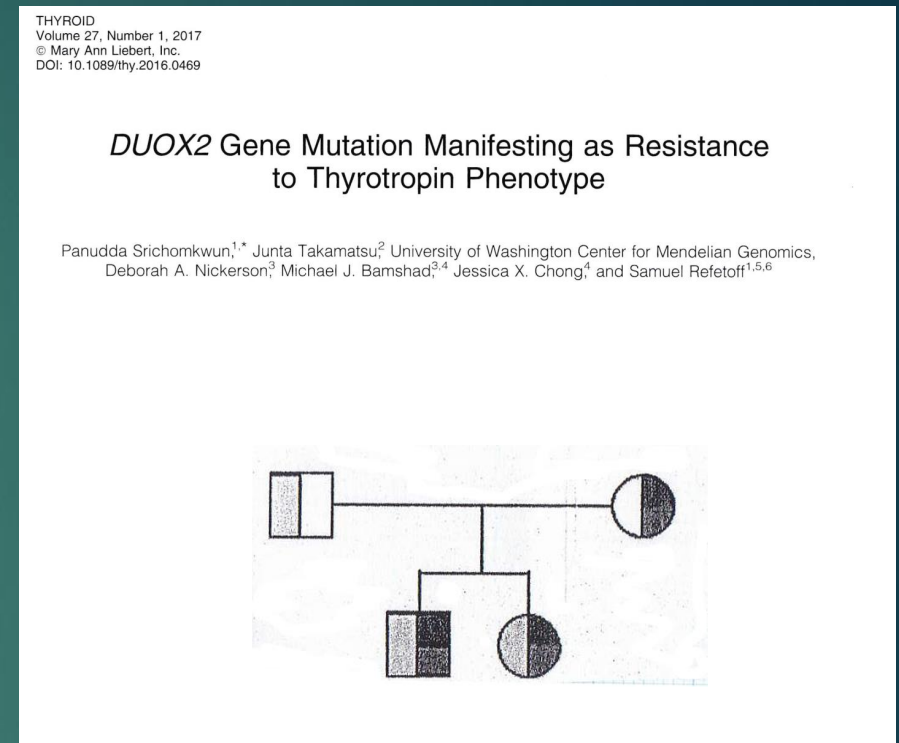
第15染色体長腕に関連 11家系

DUOX2遺伝子変異 2家系(ロンドン、高槻)

Family A (JCEM, 1993)



Family B (THYROID, 2017)



TSHレセプター

NL

NL

PAX8

NL

NL

DUOX2

NL

Mutations

Family A (JCEM, 1993)

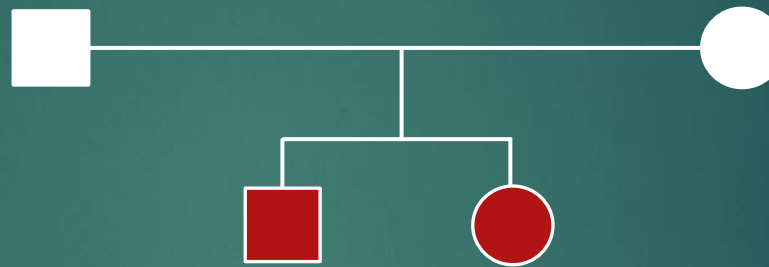
0021-972X/93/7706-1569\$03.00/0
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Familial Unresponsiveness to Thyrotropin by Autosomal Recessive Inheritance*

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AND NAKAAKI OHSAWA

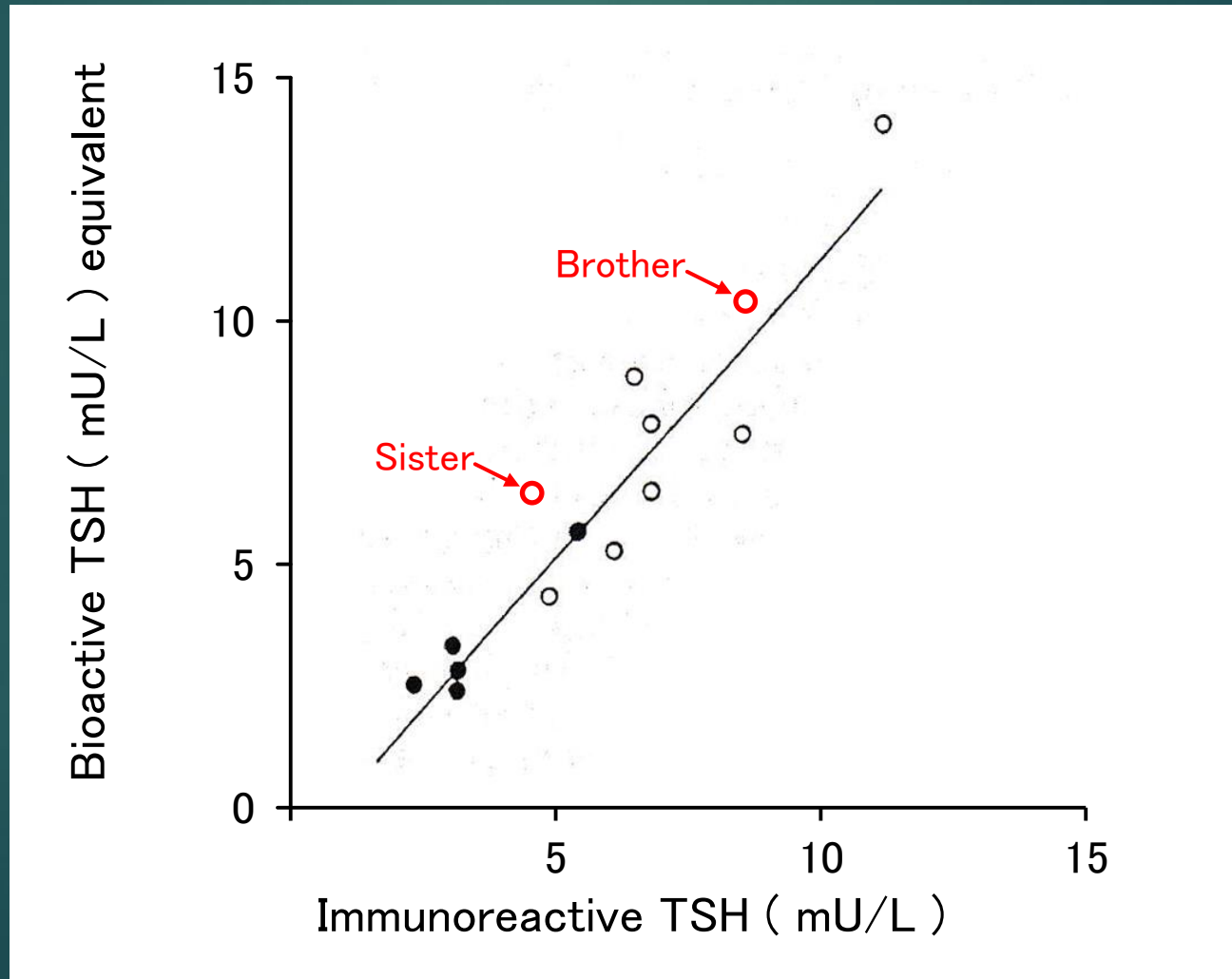
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Department of Internal Medicine, Kansai Medical University (M.H., M.N.), Moriguchi, Osaka 570, Japan



	55	29	26	52	Normal Values
Age	55	29	26	52	Normal Values
FT4 (ng/dL)	1.20	<0.2	<0.2	1.38	1.0—2.0
TSH (mU/L)	0.5	220.1	125.4	4.8	0.5—3.5
TG (ng/mL)	<5.0	2.3	0.3	69.0	5—30
TGAb/TPOAb	—/—	—/—	—/—	—/—	—/—
Thyroid Volume (mL)	15.0	<0.3	0.8	23.4	7—20

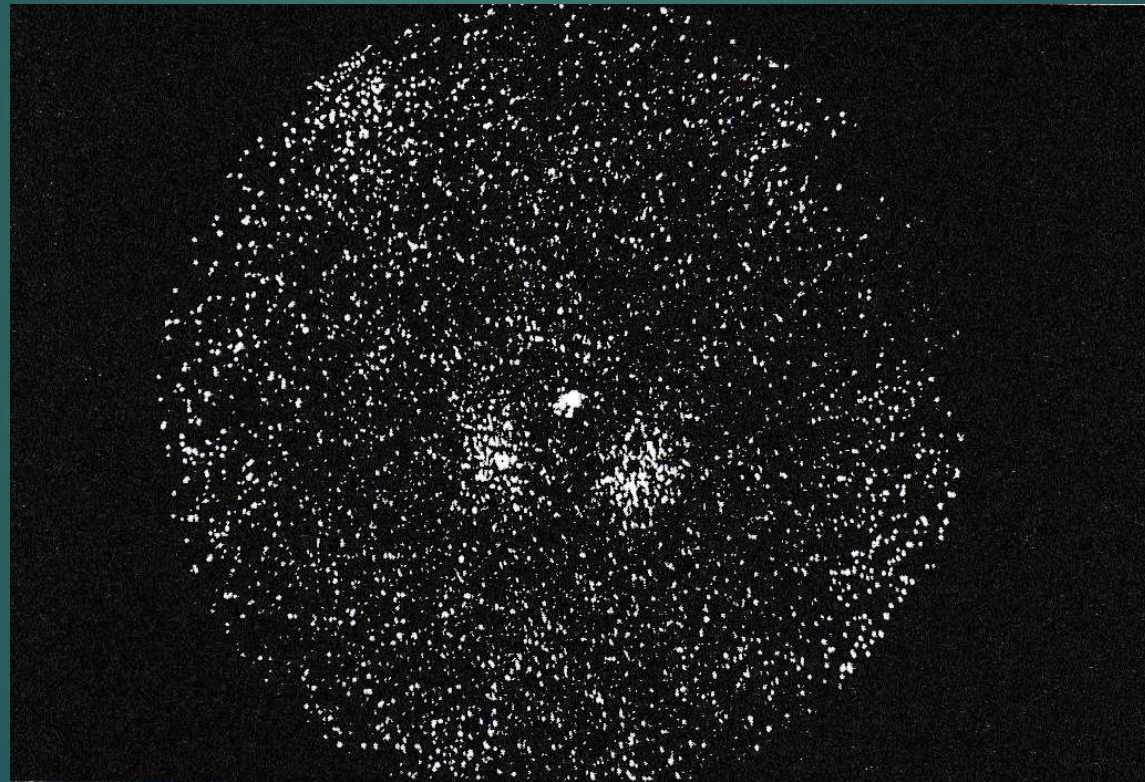
Family A (1993)

TSHの生物学的活性

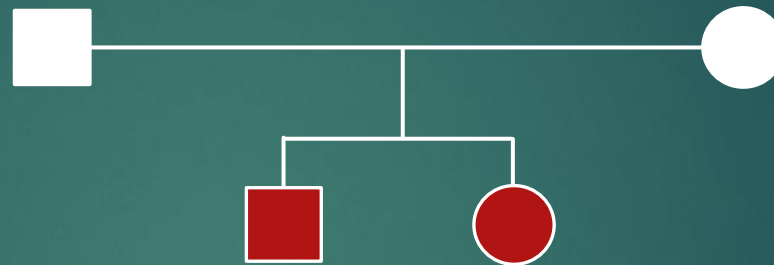


Family A (1993)

甲状腺¹²³I シンチグラフィ



Family B (THYROID, 2017)



Age	69	40	37	68	Normal Values
FT4 (ng/dL)	1.06	1.09	1.29	1.1	0.8—1.9
FT3 (pg/mL)	2.28	2.48	2.61	1.64	1.6—4.2
TSH (mU/L)	5.97	12.4	5.4	1.6	0.4—3.6
TG (ng/mL)	NE	56	17	27	2—38
TGab/TPOab	—/—	—/—	—/—	—/—	—/—
Thyroid Volume (mL)	NE	9	10	13	7—20

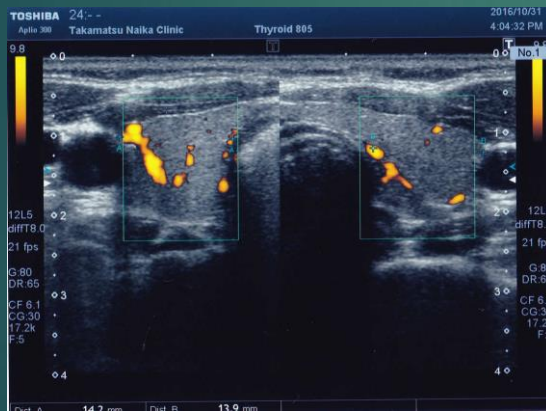
Family B (THYROID, 2017)

THYROID
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DUOX2 Gene Mutation Manifesting as Resistance to Thyrotropin Phenotype

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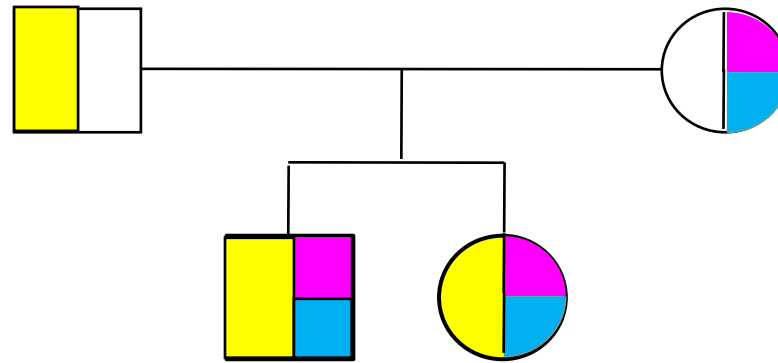
Brother



Sister

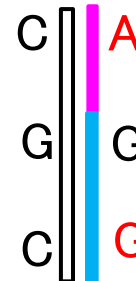


Family B (2017)

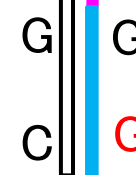
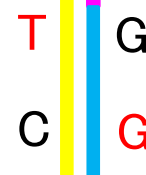
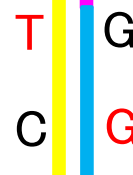
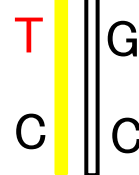


MUTATION

rs748793969 A 649 E



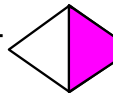
rs181461079 R 885 Q



rs771198569 P 1391 A



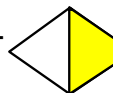
DUOX2

WT  Mut

GCG → GAG

Ala → Glu

A 649 E

WT  Mut

CGA → CTA

Arg → Leu

R 885 Q

WT  Mut

CCC → GCC

Pro → Ala

P 1391 A

Wild-type nucleotide in **BLACK**, mutated nucleotide in **RED**

FamilyBでのDUOX2遺伝子の変異

Exon17

rs748793969

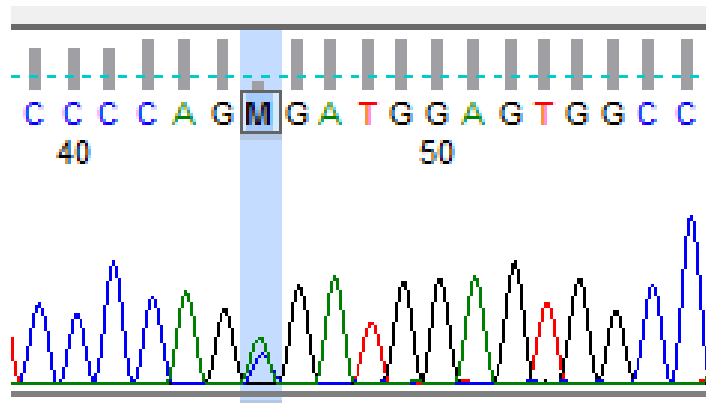
15:45106327

c.1946C>A (GCG◇GAG)

p.Ala649Glu

MAF <0.01

Polyphen: 0.736 SIFT: 0



Exon20

rs181461079

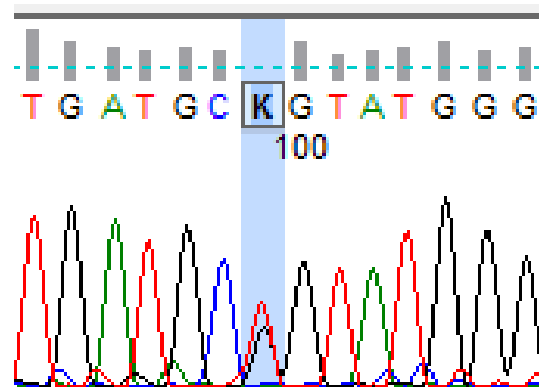
15:45103960

c.2654G>T (CGA◇CTA)

p.Arg885Leu

MAF <0.01

Polyphen: 0.631 SIFT: 0



Exon31

rs771198569

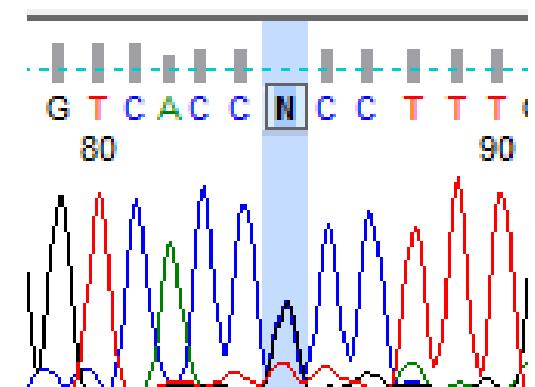
15:45095505

c.4171C>G (CCC◇GCC)

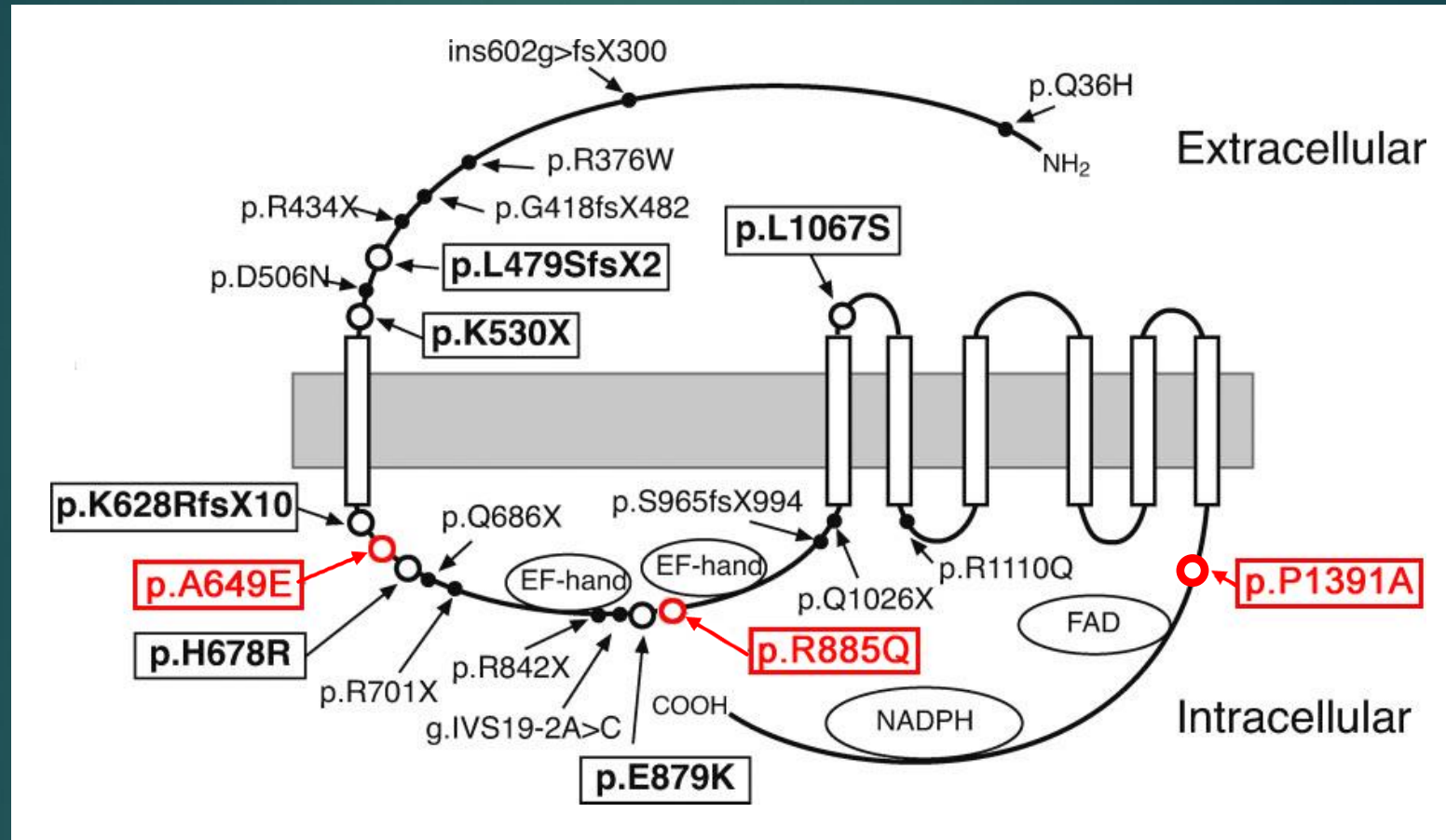
Pro1391Ala

MAF <0.01

Polyphen: 0.542 SIFT: 0



DUOX2遺伝子の構造とFamilyBでの変異



(Maruo et al. JCEM, 2008より引用)

考 察

DUOX2遺伝子変異は先天性甲状腺機能低下症の原因のひとつである。

Family B の兄妹例で幼少期に機能低下が強い理由は、遺伝子変異が複合ヘテロ接合体のためと考えられる。

現在の状態は高TSH血症と正常甲状腺ホルモン値が併存しており甲状腺の大きさも小さいことから、TSH抵抗症の病態に合致する。

DUOX2遺伝子変異は dyshormonogenesisを呈するものとTSH抵抗症を呈する臨床型がある。

TSH抵抗症の原因として、TSHレセプター、PAX8、PENDRINに加え、DUOX2の遺伝子変異が挙げられる。