NGO THI THU HUONG

My Birth
1980

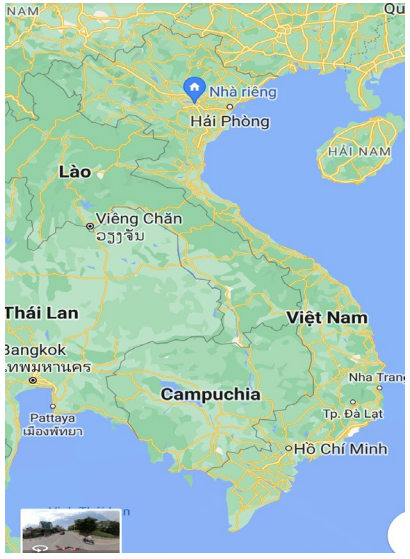
1998 -2005
General Medicine
HN Medical University

2006
Work as a doctor
at Saint Paul
hospital

2009
Master Pediatrics

2012- 2017.
PhD. Endocrinology
Pediatrics
HN Medical University

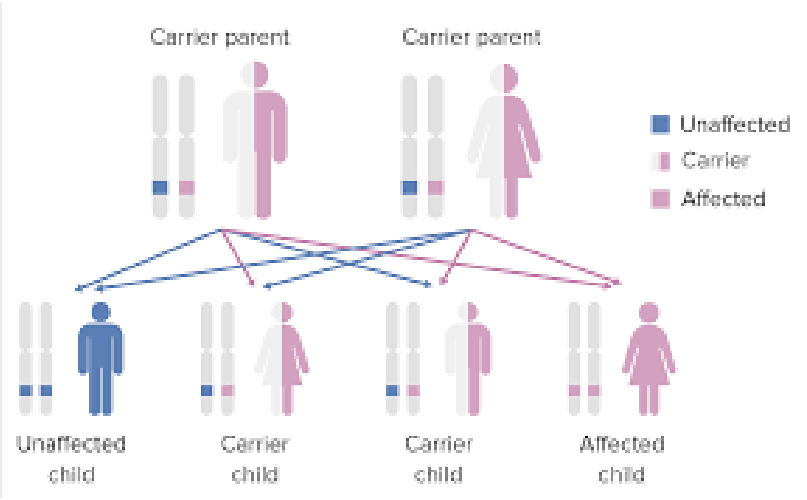
2006- now
Doctor. Saint Paul hospital
Teacher Ha Noi medical
University



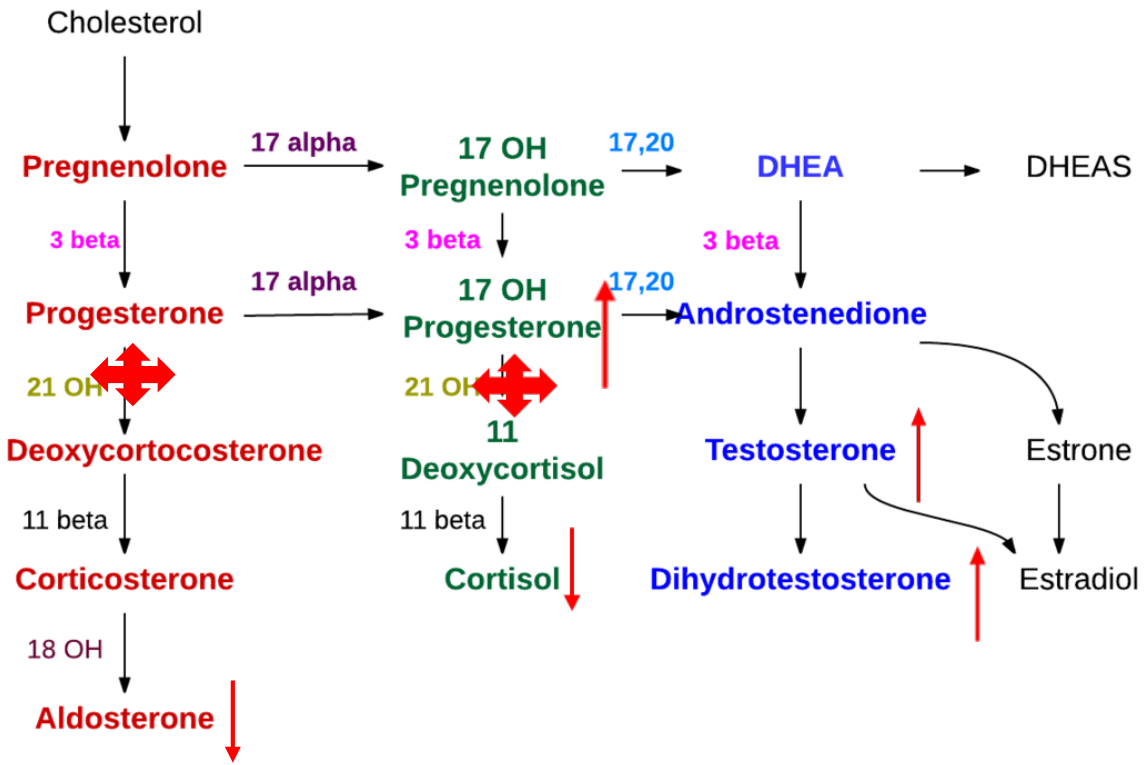
CAH: CONGENITAL ADRENAL HYPERPLASIA

- CAH: an autosomal recessive disorder caused by deficiencies in adrenal steroid synthesis enzymes
- Most common: 21 – hydroxylase deficiency (90%) encoded by the *CYP21A2* gene
- Others:

- 11 b –hydroxylase deficiency
- 3b hydroxysteroid dehydrogenase deficiency

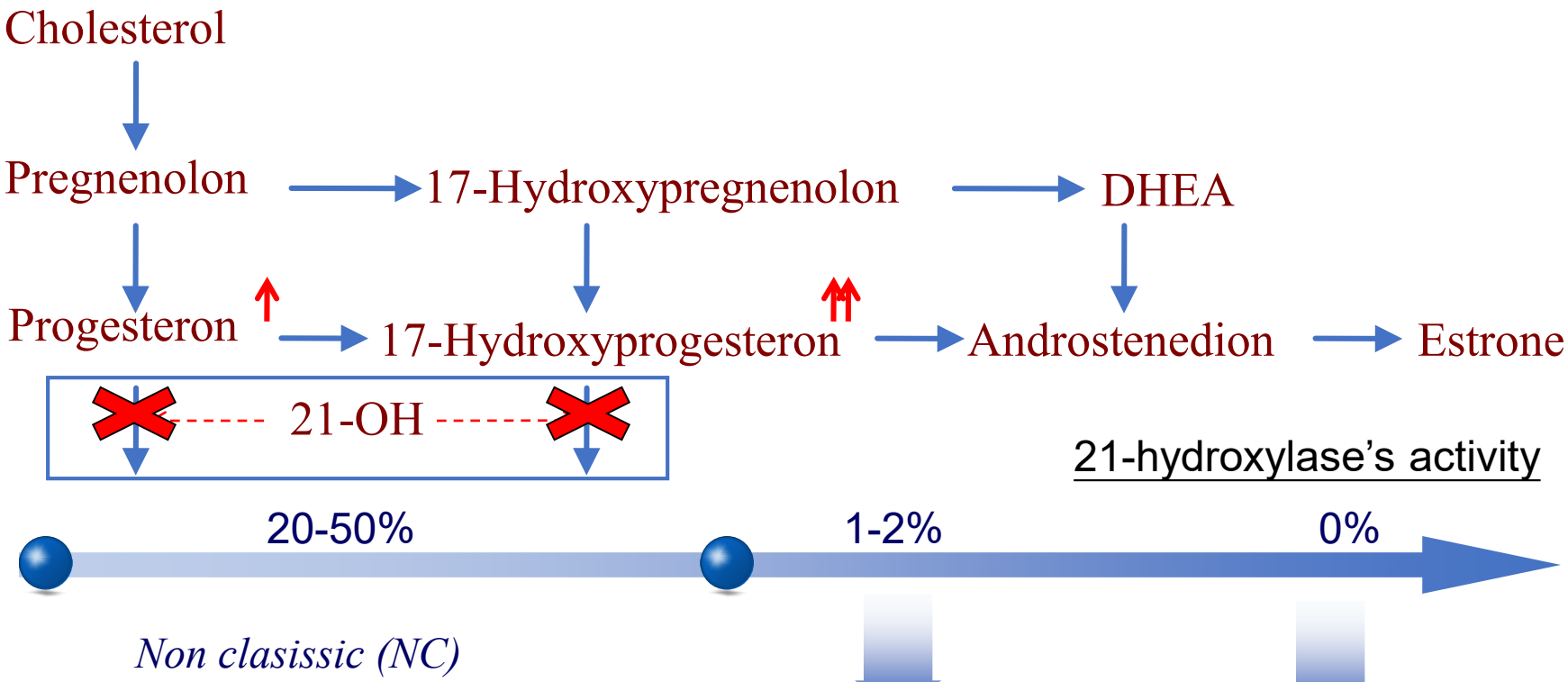


PATHWAY OF ADRENAL STEROID SYNTHESIS



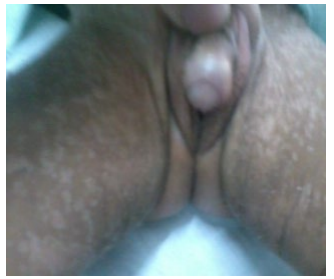
- https://commons.wikimedia.org/wiki/File:Adrenal_steroid_hormone_synthesis.png

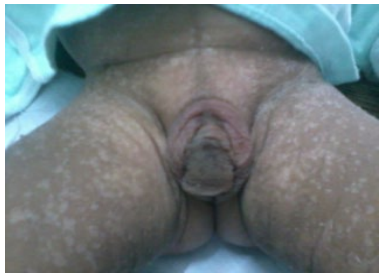
CAH- 21- HYDROXYLASE DEFICIENCY



Female:
- External genitalia can be ambiguous
- Rapid growth
- Appearance of pubic and armpit hair

Male:
- Well-developed muscles
- Enlarged penis
- Severe acne, early bear
- Early signs of puberty

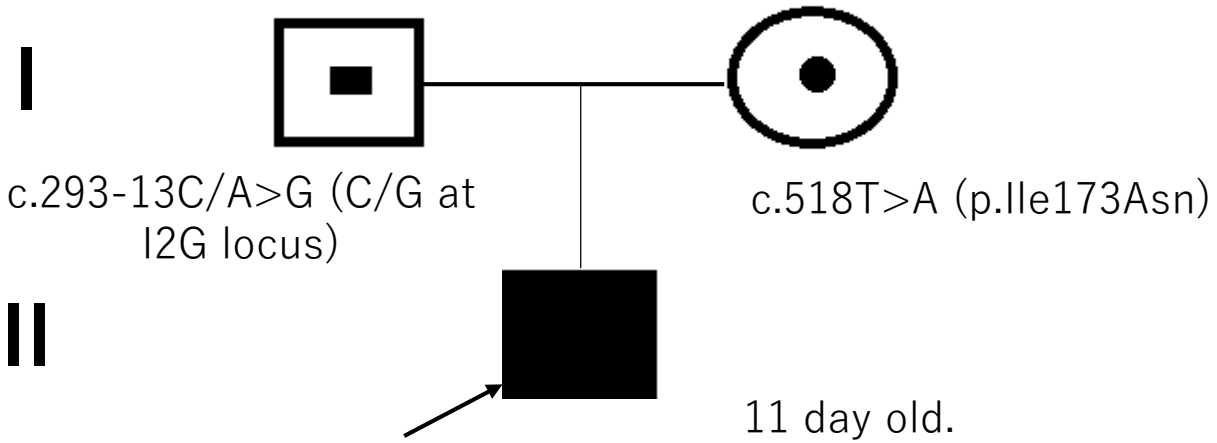




- https://commons.wikimedia.org/wiki/File:Adrenal_steroid_hormone_synthesis.png

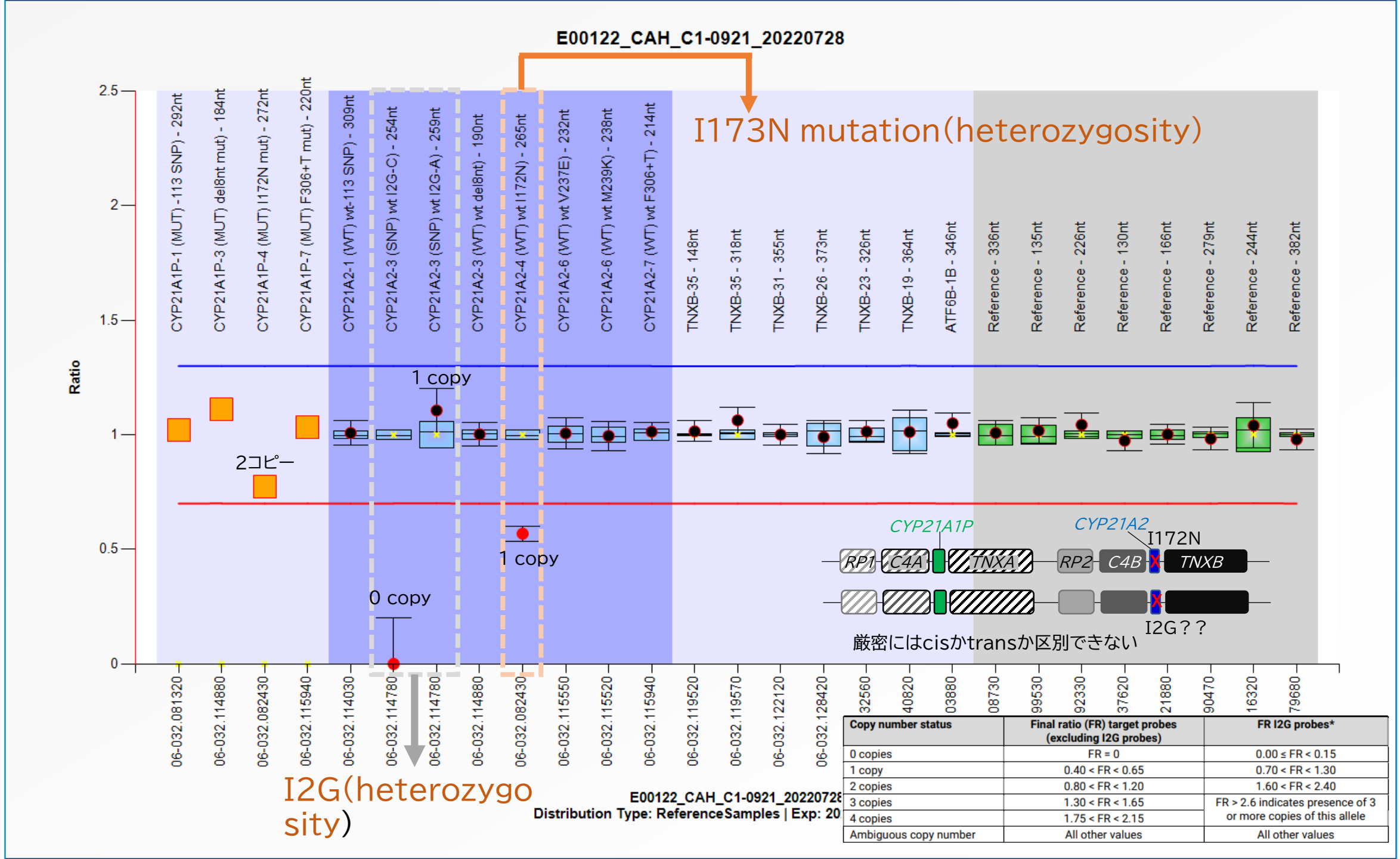
Those figures are the results of our research

Pedigree of a family in Japan- E00122 CAH 1 (MLPA + Sanger Sequencing)



11 day old.
17-OHP elevated in a newborn mass screening
His urinary steroid profile (+)
His phenotype: normal
The parents are healthy, and no age information is available.

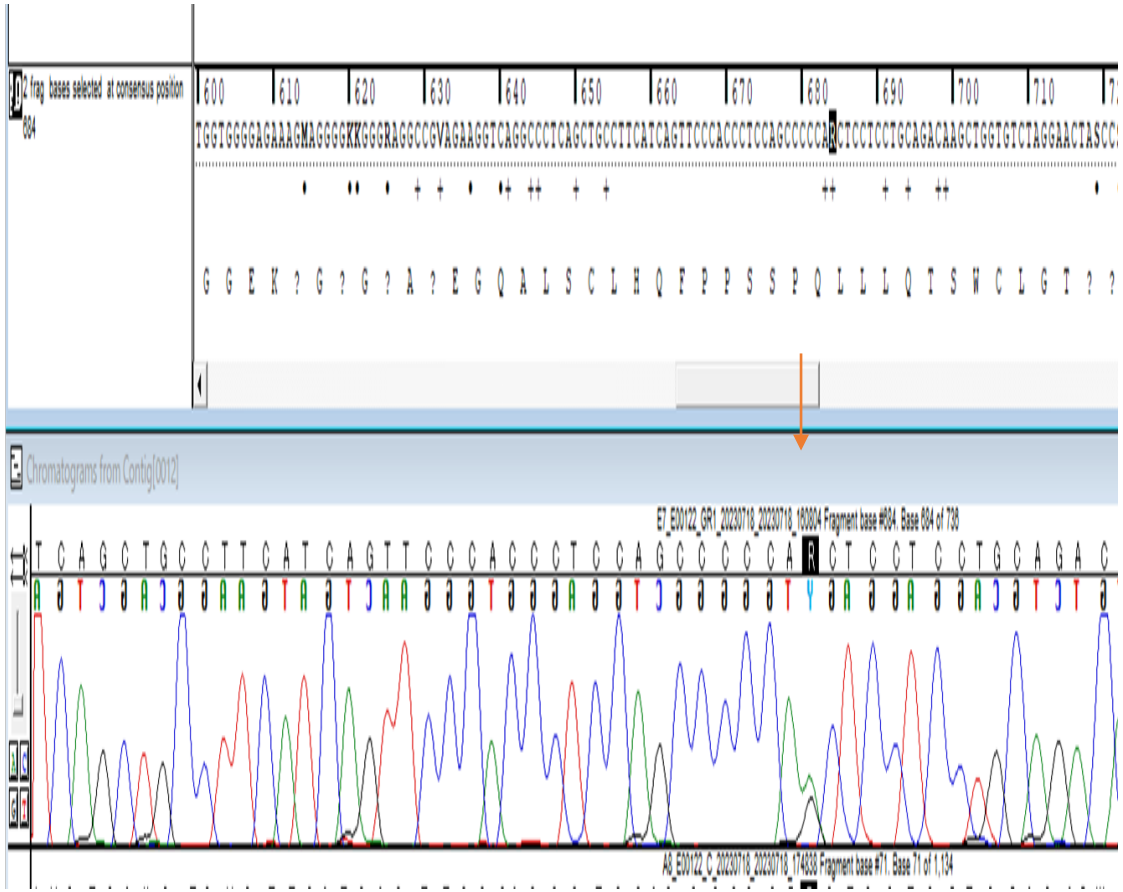
Simple Virilizing?
Salt – wasting ?

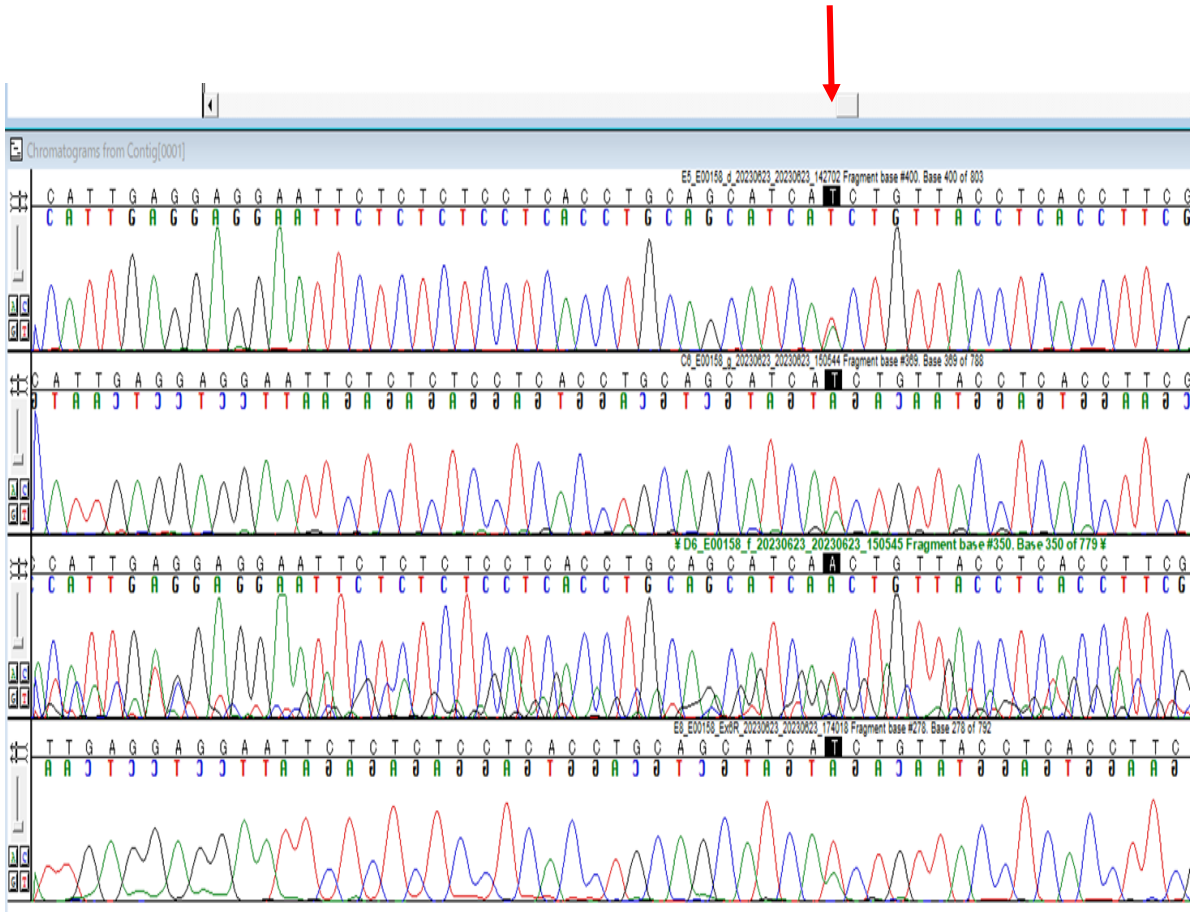


Copy number status	Final ratio (FR) target probes (excluding I2G probes)	FR I2G probes*
0 copies	FR = 0	0.00 ≤ FR < 0.15
1 copy	0.40 < FR < 0.65	0.70 < FR < 1.30
2 copies	0.80 < FR < 1.20	1.60 < FR < 2.40
3 copies	1.30 < FR < 1.65	FR > 2.6 indicates presence of 3 or more copies of this allele
4 copies	1.75 < FR < 2.15	
Ambiguous copy number	All other values	All other values

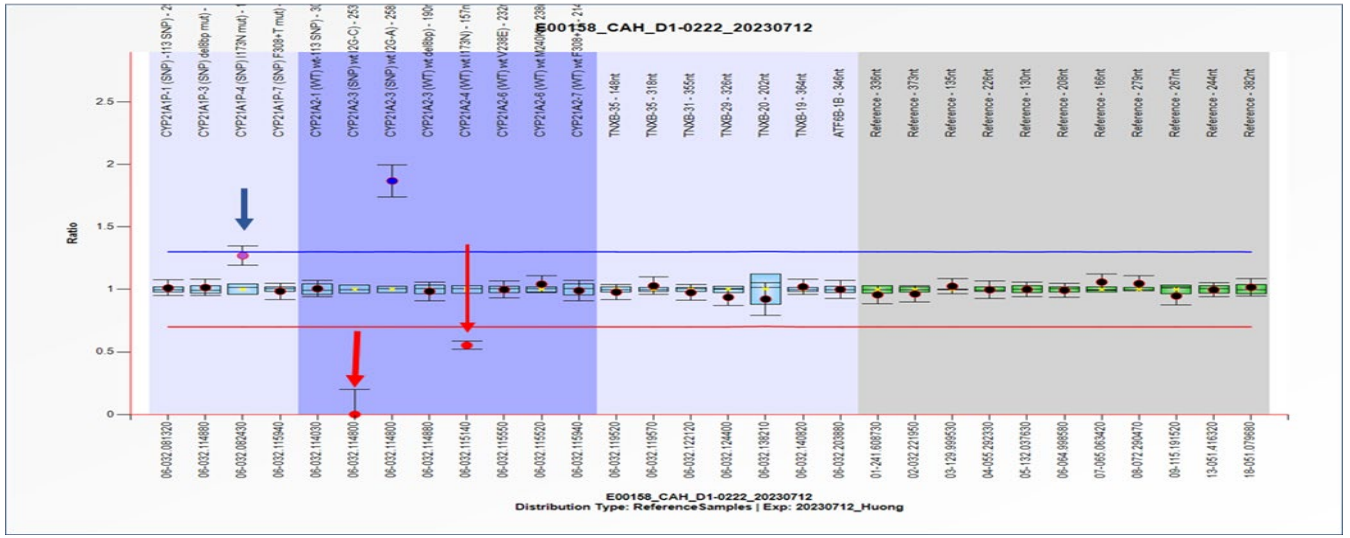
Proband I2G (A/G)/ I173N

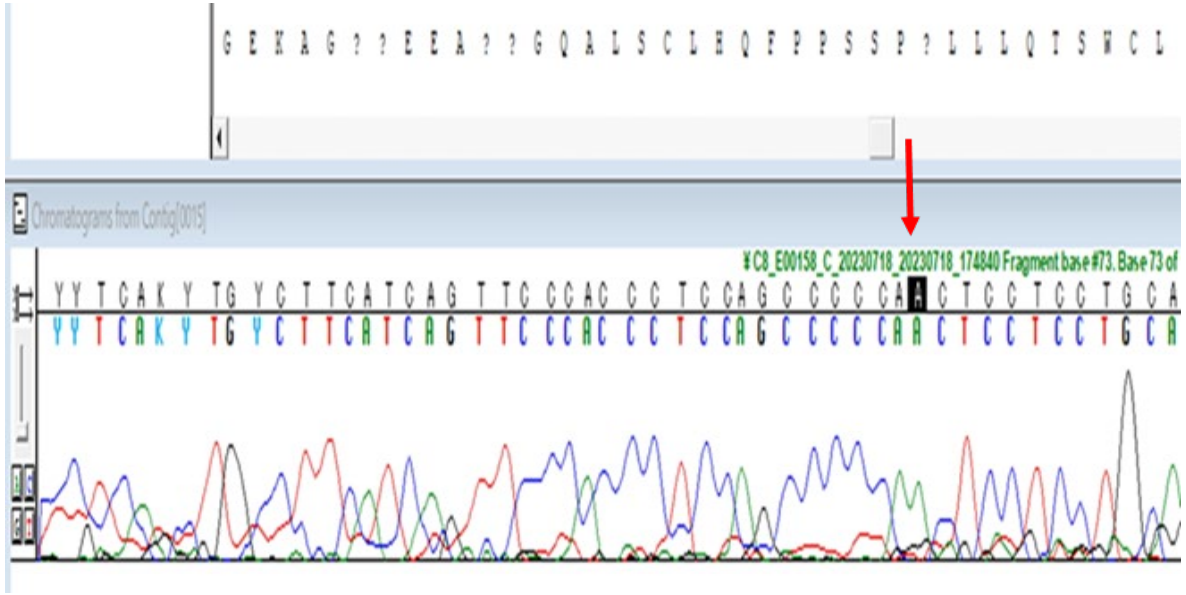
Seq -method

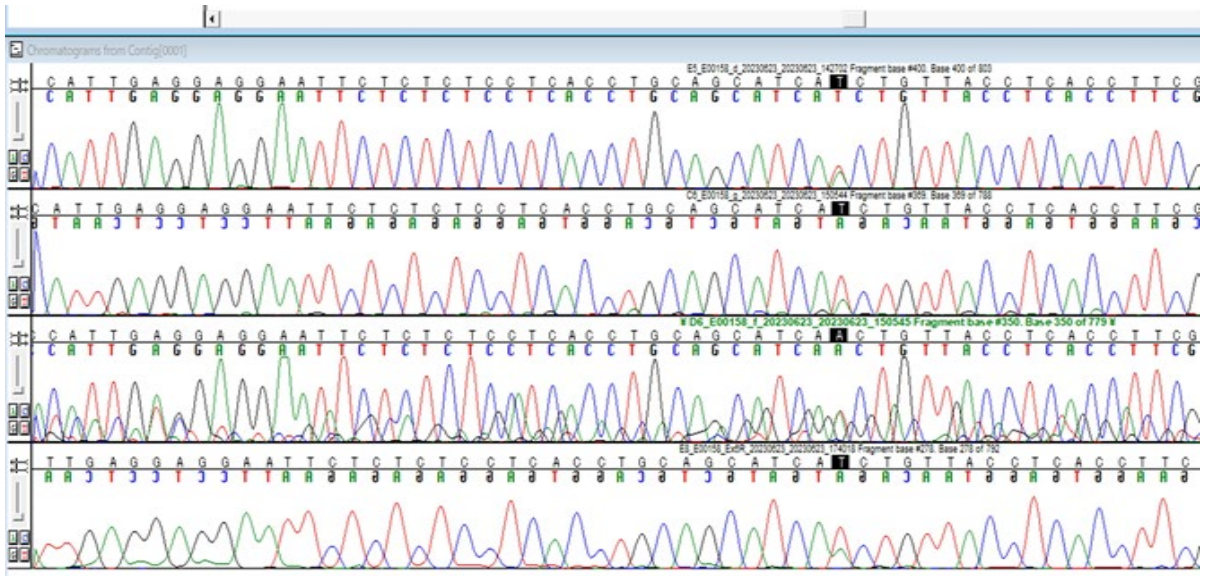




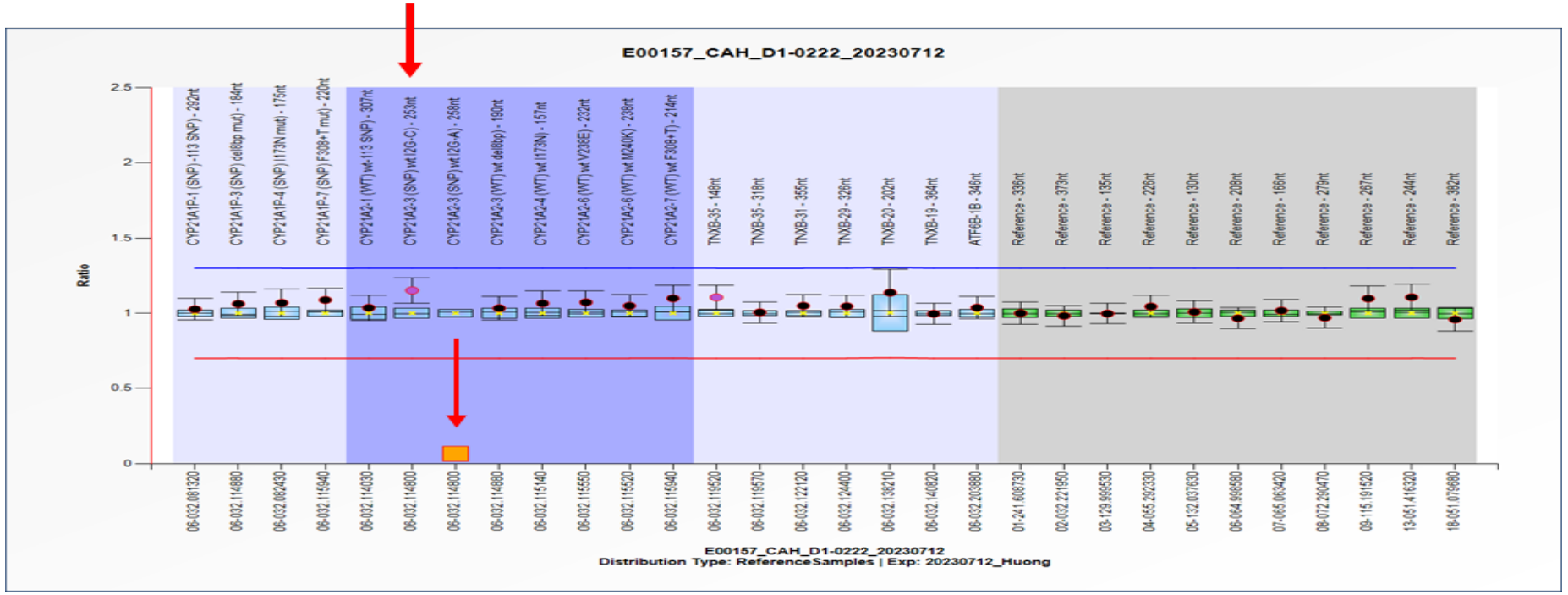
Mother I2G ⇒ A/A and I173N



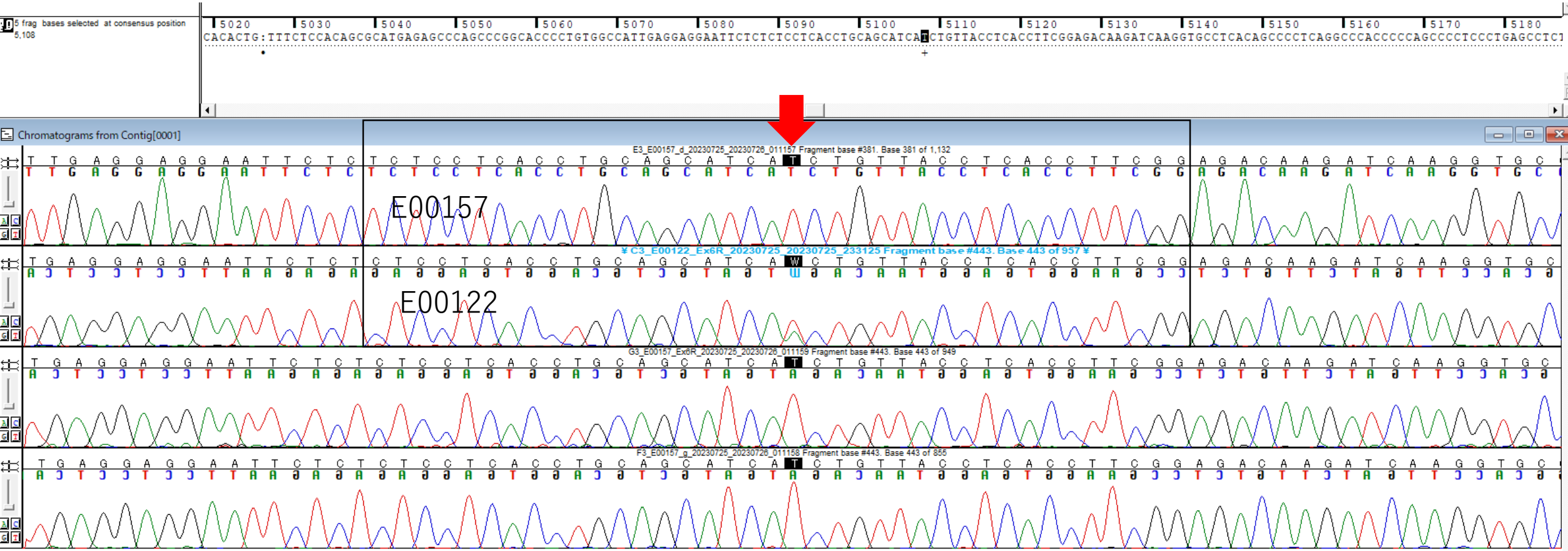




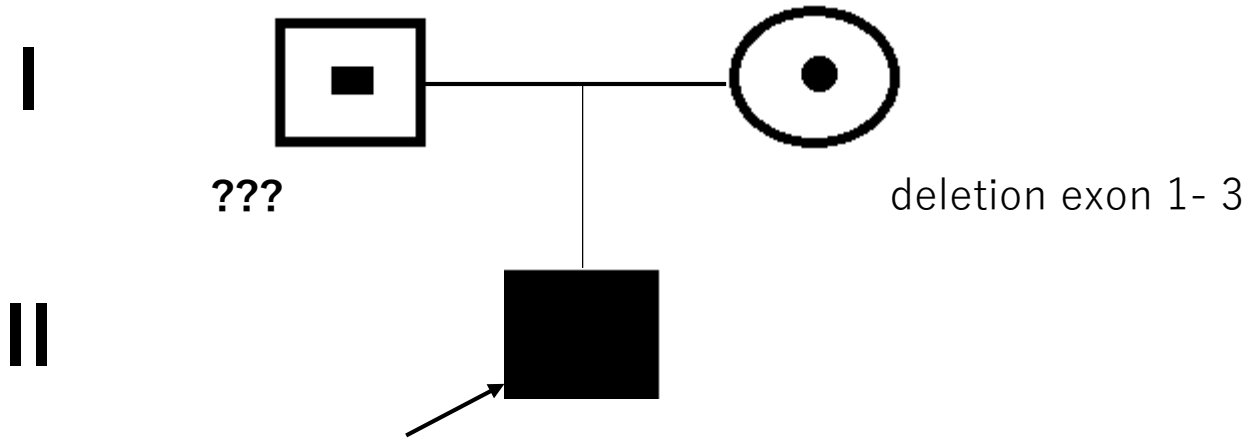
Father I2G (G/C)



The results of sanger seq for E00122 (Pt) and E00157 (Father)

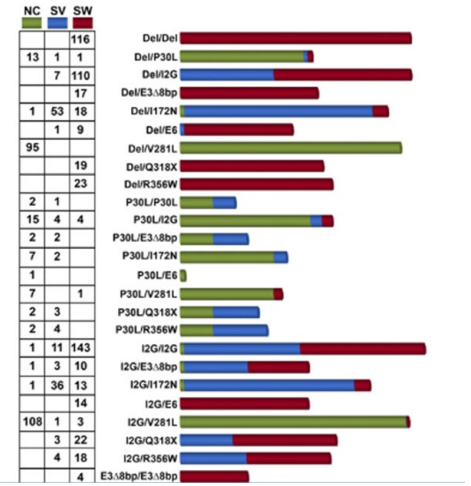


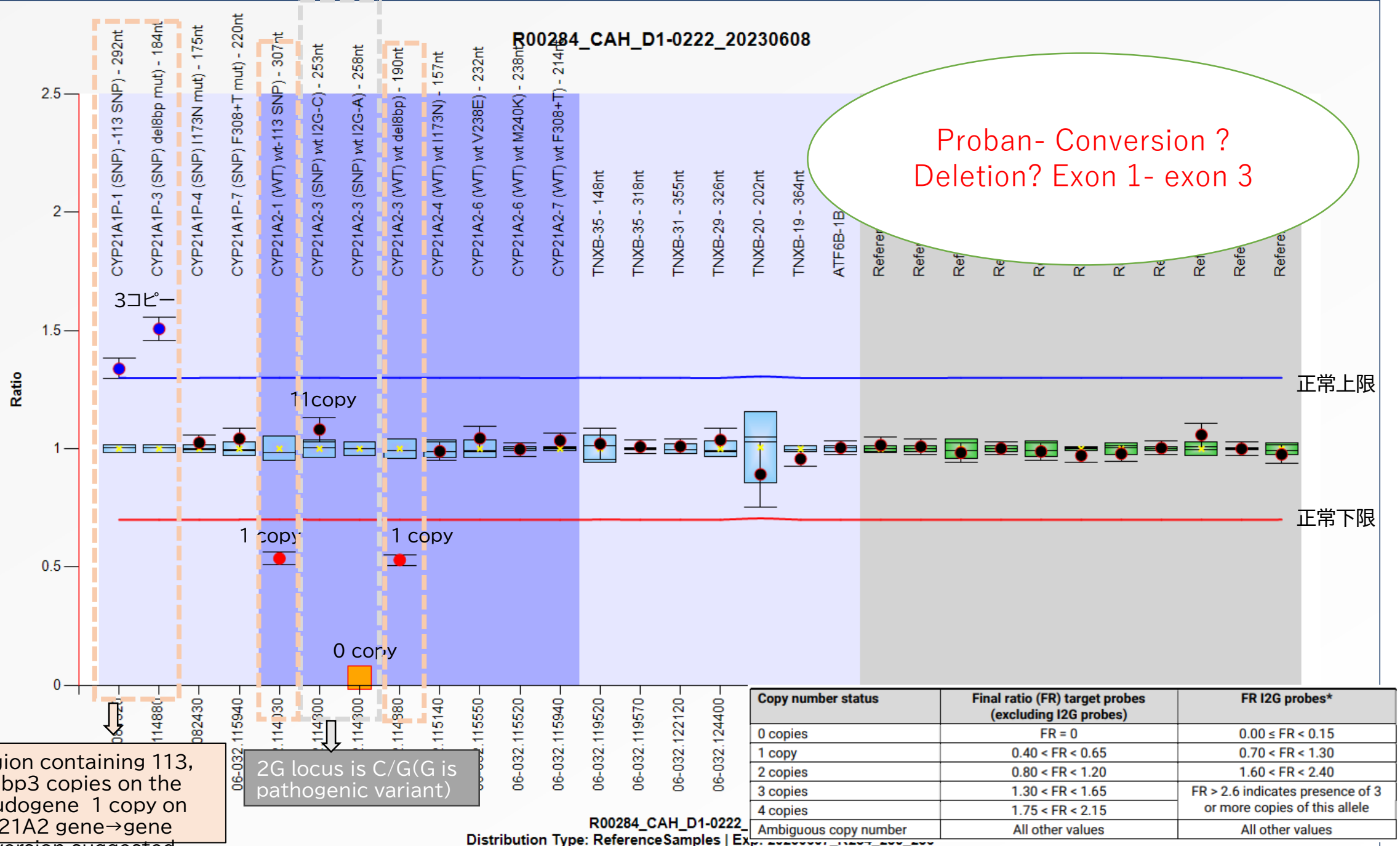
Pedigree of a family in Japan - CAH 2 (MLPA + Sanger Sequencing)



Del8bp3 .

Phenotype?





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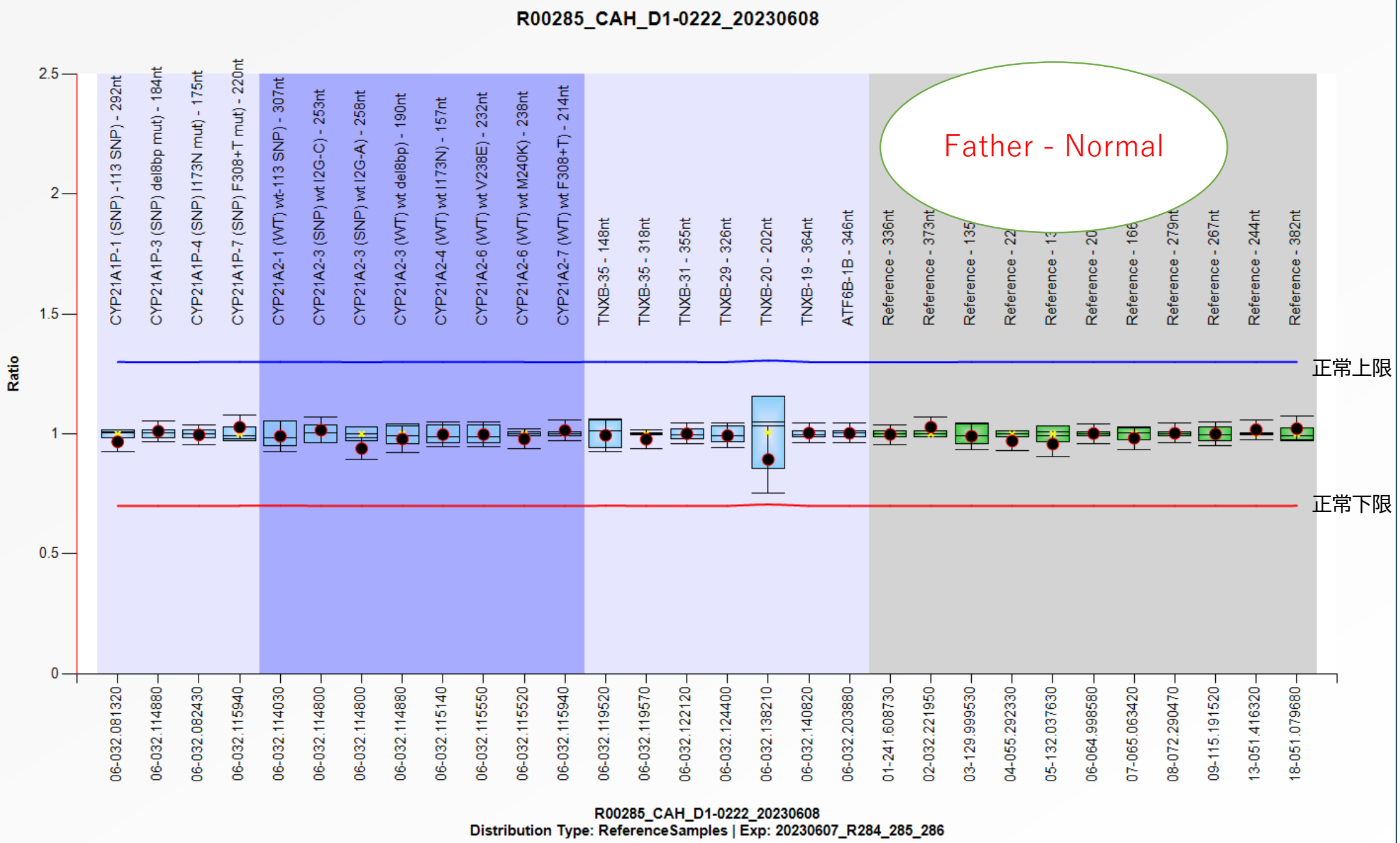
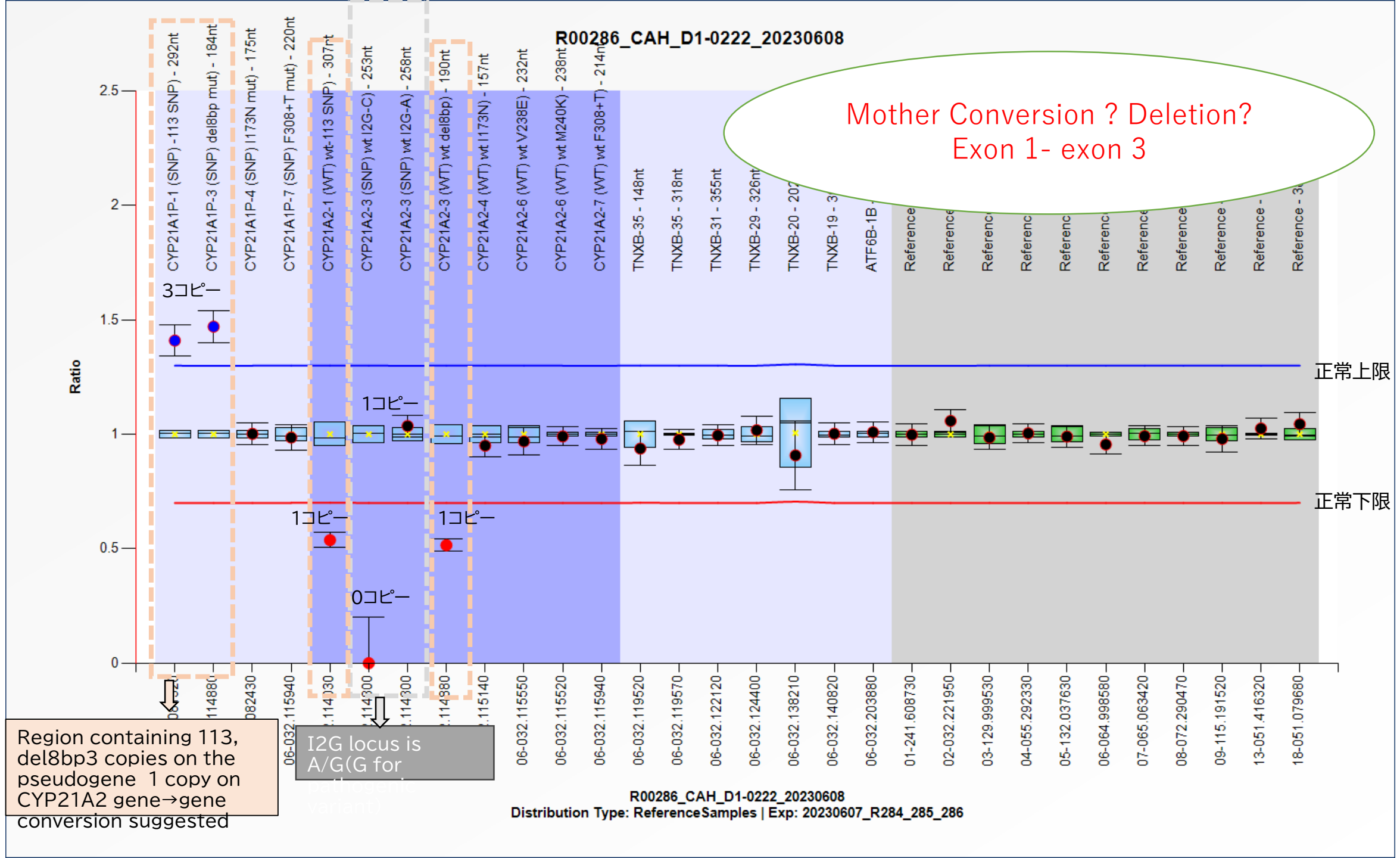
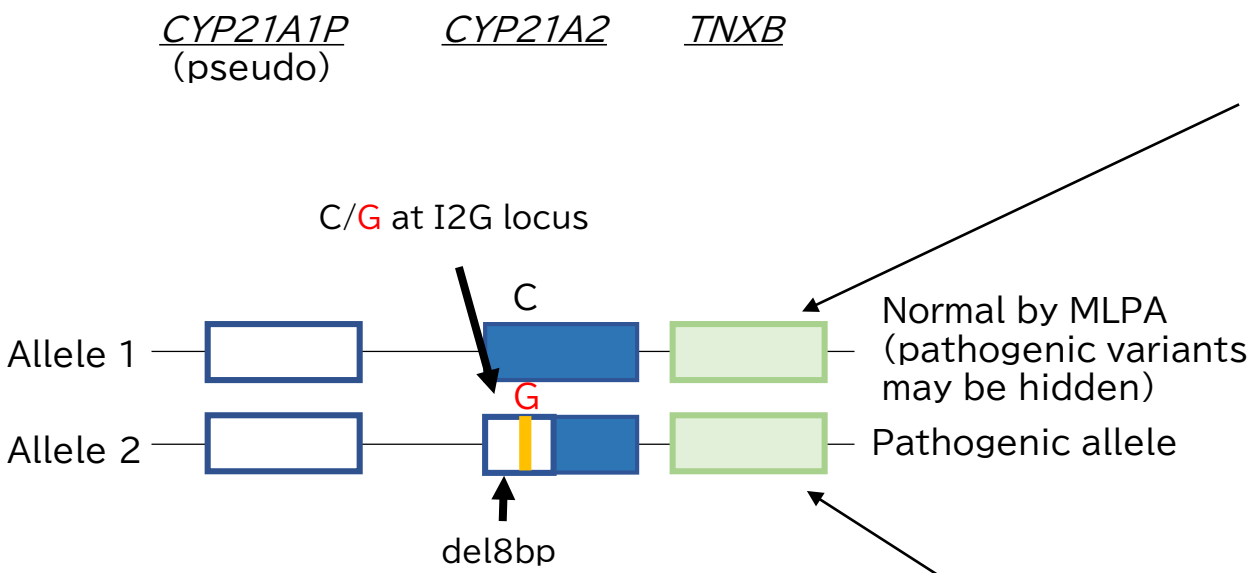
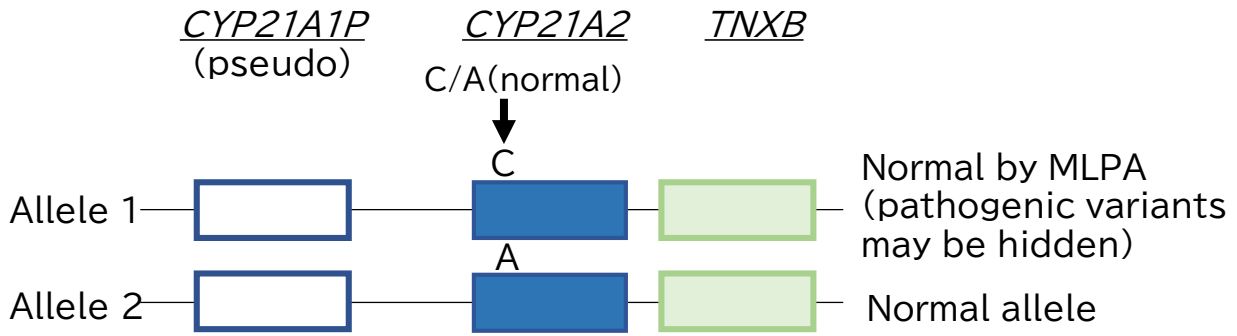

R00285_CAH_D1-0222_20230608
Father - Normal
Ratio
2.5
2
1.5
1
0.5
0
CYP21A1P-1 (SNP) -113 SNP) - 292nt
CYP21A1P-3 (SNP) del8bp mut) - 184nt
CYP21A1P-4 (SNP) I173N mut) - 175nt
CYP21A1P-7 (SNP) F308+T mut) - 220nt
CYP21A2-1 (WT) wt-113 SNP) - 307nt
CYP21A2-3 (SNP) wt I2G-C) - 253nt
CYP21A2-3 (SNP) wt I2G-A) - 258nt
CYP21A2-3 (WT) wt del8bp) - 190nt
CYP21A2-4 (WT) wt I173N) - 157nt
CYP21A2-6 (WT) wt V238E) - 232nt
CYP21A2-6 (WT) wt M240K) - 238nt
CYP21A2-7 (WT) wt F308+T) - 214nt
TNXB-35 - 148nt
TNXB-35 - 318nt
TNXB-31 - 355nt
TNXB-29 - 326nt
TNXB-20 - 202nt
TNXB-19 - 364nt
ATF6B-1B - 346nt
Reference - 336nt
Reference - 373nt
Reference - 135
Reference - 22
Reference - 13
Reference - 20
Reference - 166
Reference - 279nt
Reference - 267nt
Reference - 244nt
Reference - 382nt
正常上限
正常下限
06-032.081320
06-032.114880
06-032.082430
06-032.115940
06-032.114030
06-032.114800
06-032.114800
06-032.114880
06-032.115140
06-032.115550
06-032.115520
06-032.115940
06-032.119520
06-032.119570
06-032.122120
06-032.124400
06-032.138210
06-032.140820
06-032.203880
01-241.608730
02-032.221950
03-129.999530
04-055.292330
05-132.037630
06-064.998580
07-065.063420
08-072.290470
09-115.191520
13-051.416320
18-051.079680
R00285_CAH_D1-0222_20230608
Distribution Type: ReferenceSamples | Exp: 20230607_R284_285_286


R00286_CAH_D1-0222_20230608
Mother Conversion ? Deletion?
Exon 1- exon 3
CYP21A1P-1 (SNP) -113 SNP) - 292nt
CYP21A1P-3 (SNP) del8bp mut) - 184nt
CYP21A1P-4 (SNP) I173N mut) - 175nt
CYP21A1P-7 (SNP) F308+T mut) - 220nt
CYP21A2-1 (WT) wt-113 SNP) - 307nt
CYP21A2-3 (SNP) wt I2G-C) - 253nt
CYP21A2-3 (SNP) wt I2G-A) - 258nt
CYP21A2-3 (WT) wt del8bp) - 190nt
CYP21A2-4 (WT) wt I173N) - 157nt
CYP21A2-6 (WT) wt V238E) - 232nt
CYP21A2-6 (WT) wt M240K) - 238nt
CYP21A2-7 (WT) wt F308+T) - 214nt
TNXB-35 - 148nt
TNXB-35 - 318nt
TNXB-31 - 355nt
TNXB-29 - 326nt
TNXB-20 - 20
TNXB-19 - 3
ATF6B-1B
Reference
Ratio
3コピー
1コピー
1コピー
1コピー
0コピー
正常上限
正常下限
Region containing 113, del8bp3 copies on the pseudogene 1 copy on CYP21A2 gene→gene conversion suggested
I2G locus is A/G(G for
R00286_CAH_D1-0222_20230608
Distribution Type: ReferenceSamples | Exp: 20230607_R284_285_286

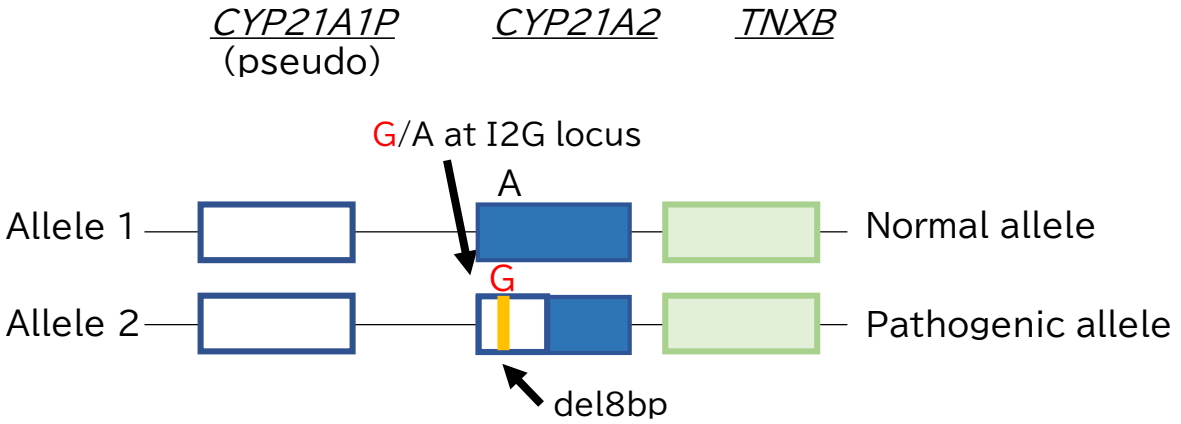
Predicted structure (R00284 Pt)



Predicted structure (R00285 Father)

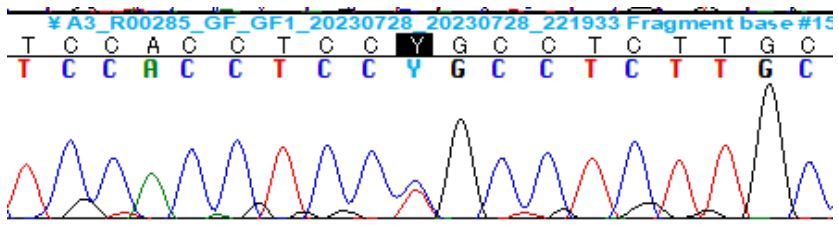


Predicted structure (R00286 Mother)

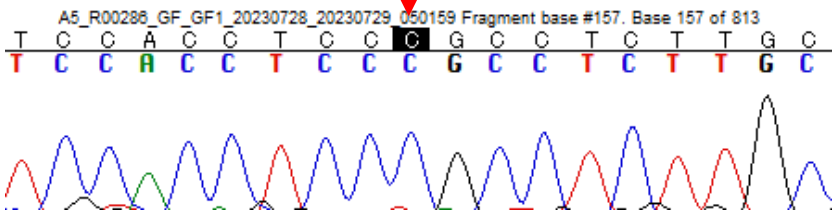


CYP21A2(NM_000500.9):c.94C>T (p.Pro32Ser)

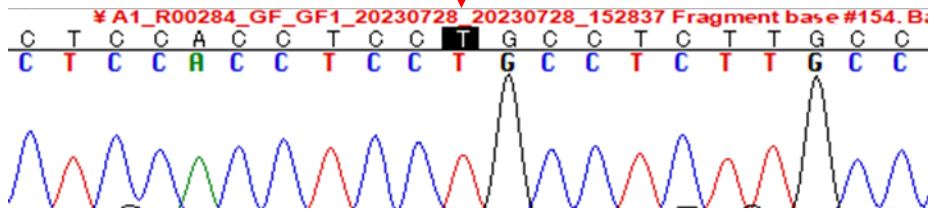
Father C/T



Mother C/C



Pat T/T T/T



One very rare variant was identified. According to gnomAD, the allele frequency is 0.00000418, and ToMMo has no information.
It is registered as 'Uncertain significance' in Clinvar.
Predictions of protein function show conflicting results.
The possibility that this variant is responsible for the development of the disease in the patient cannot be ruled out.

The Situation Related to Childbirth and Newborn Screening (NBS)

In Vietnam

Day 0

Day 1

Day 3-5

NBS

2 weeks

The hospital will send their result via e-mail after 2 weeks . They will note the result as normal or abnormal. If it is abnormal, they will write location to check again for this newborn

Vaginal delivery

Home care

Some children born by vaginal delivery are not examined because they must visit a hospital for testing.

Who will inform the patient of the results and when?
If the values are abnormal, would you call the patient to the hospital?

Caesarean section

Home care

NSB Test need doing 3-5 days so they will be come back home after 1 day of giving birth. NSB test is only performed at hospital not at home. By the way, NSB tests isn't required for all newborns. Their parent have to pay an amount of 15.000¥.

Day 5-7

Results

1 week

The hospital will send the results via email and ask them to visit another hospital for checkup. CAH is common in Vietnam so we always pay attention to it.

Vaginal delivery

Caesarean section

Hospitalized

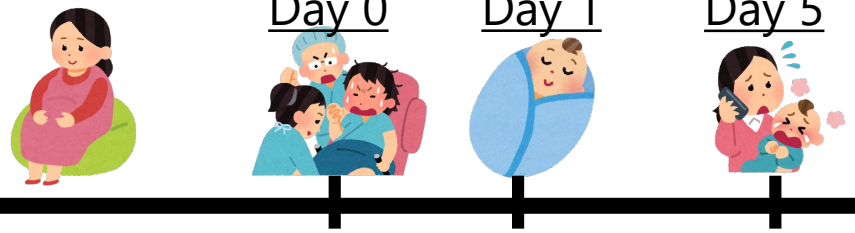
Home care

If a detailed examination is needed, the patient is asked to visit hospital for re-examined.

If the test results are normal, the patient will receive the result.

How to treat typical case with salt-wasting type CAH

In Vietnam



What if:
39w3d, normal vaginal delivery,
Probably a girl with clitoromegaly
No family history of CAH
On Day 5, the baby became 'not being well'.

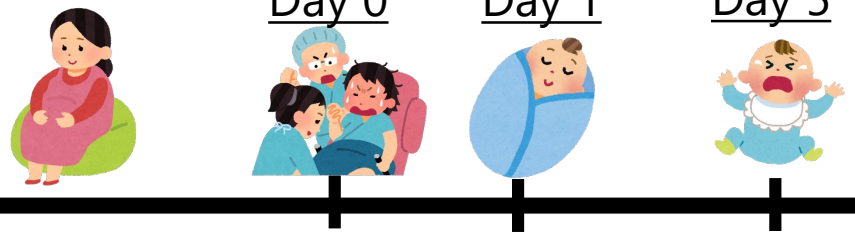
Dr. Huong will:
- Follow some symptoms (vomiting or nausea, irritability, dehydration)
- Check electrolytes (every 4- 6 hours)
- Perform endocrinological test including17- OHP, progesterone, and testosterone (available one day after) and ACTH, steroid urine (available one week after)

When the baby is diagnosed with CAH. Firstly, I use hydrocortisone with low dose. According to the symptoms, Florinef might be utilized.

The patients often get their results of NBS after 2 weeks. So it is late for treating with CAH. Therefore, we always carefully diagnose these girls with clitoromegaly or the boy with decrease serum Na in blood and increses serum Kali in blood.

Some of our patients with SV type are diagnosed late.

In Japan



Often referred to an endocrinologist

I will:
- Check electrolytes
- Observe carefully
- (optional) Perform endocrinological test

I will:
- Perform endocrinological test including cortisol, ACTH, 17-Hydroxyprogesterone (available three days after) and steroid profiling using urine (laboratory test)

Depending on the severity of clitoromegaly, I might test for cortisol at the time of the consultation.

Since adrenal insufficiency is suspected, I will start steroid replacement without waiting for the results.

Dr. Akiba and Dr. Uehara, is this correct?

1. I know that there are over 150 mutations in gene CYP21A2 leading to CAH disease. Firstly , the patients need diagnosing and treating early. Can we manage gene carrier (heterozygous) ?
2. Give genetic advice to them before they get married or have a baby.
3. Need to decrease the rate of this type of disease in the community.
4. The carrier frequency of CAH seems high
5. NSB test is important to diagnose early.
6. NSB test is not required for all newborns.
The doctors explain the importance of this test for the parents. If they agree, they have to pay an amount of 15.000¥ for 6 different diseases (CAH,G6PD, hypothyroidism, Thalasemia, metabolic disease (MS/MS). Phenylketon urina (PKU))

> J Clin Endocrinol Metab. 2005 Feb;90(2):775-8. doi: 10.1210/jc.2004-1728. Epub 2004 Nov 30.

Carrier frequency of congenital adrenal hyperplasia (21-hydroxylase deficiency) in a middle European population

S M Baumgartner-Parzer [1], P Nowotny, G Heinze, W Waldhäusl, H Vierhapper

Affiliations + expand

PMID: 15572419 DOI: 10.1210/jc.2004-1728

Abstract

Based on newborn screening data, the carrier frequency of congenital adrenal hyperplasia (CAH) in the general population has been estimated to be 1:55. The higher CAH frequency (particularly of milder forms of the disease) reported for certain populations including Yugoslavs (1.6%) relates to population genetic and hormonal data. However, so far, true carrier frequency for CAH due to 21-OH deficiency has not been determined by comprehensive mutation analysis of the 21-OH gene (CYP21A2) in an unselected European population. This study used CYP21A2 genotyping (sequence/Southern blot analysis) to determine CAH carrier frequency in a middle European (Austrian) population. The study included 100 migrants from the former Yugoslavia and 100 individuals of non-

> J Clin Endocrinol Metab. 2000 Feb;85(2):597-600. doi: 10.1210/jcem.85.2.6367.

Carrier analysis and prenatal diagnosis of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency in Chinese

H H Lee [1], J M Kuo, H T Chao, Y J Lee, J G Chang, C H Tsai, B C Chung

Affiliations + expand

PMID: 10690861 DOI: 10.1210/jcem.85.2.6367

Abstract

Congenital adrenal hyperplasia (CAH) is a common autosomal recessive disorder mainly caused by defects in the steroid 21-hydroxylase (CYP21) gene. We screened 1,000 healthy people, using a previously developed differential PCR method combined with single-strand conformation polymorphism and amplification-created restriction site methods for the carrier detection of the CYP21 gene deficiency. Our results indicated that the rate of occurrence of the heterozygous CAH carrier was about 12 in 1,000, with a gene frequency of 0.0060 and an incidence frequency of 1 in 28,000 in the Chinese population. In addition, 9 cases of CAH families were performed with prenatal diagnosis. Among them, 3 cases were diagnosed as the severe form, 4 cases carried the heterozygous

Thank you for your support

6/8 TSTTBS là trẻ gái cần phẫu thuật chỉnh hình SD

6/8 CAH patients are hospitalized for 1-2 days by surgery. (2008)