GENOTYPE –PHENOTYPE DISCORDANT PATIENTS WITH HOMOZYGOUS INTRON 2 MUTATION (IVS2) OF *CYP21 GENE*

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There is no disclosure

Background

21 hydroylase deficiency is the most common cause of congenital adrenal hyperplasia (CAH) and resulted from *CYP21 gene* mutations. Genotype and phenotype are usually concordant. Homozygous intron 2 splice mutation (IVS2/IVS2), is frequently associated with severe enzyme deficit, and causes classical CAH.
Here we present genotype-phenotype discordant members of two different families with IVS2/IVS2 mutation.

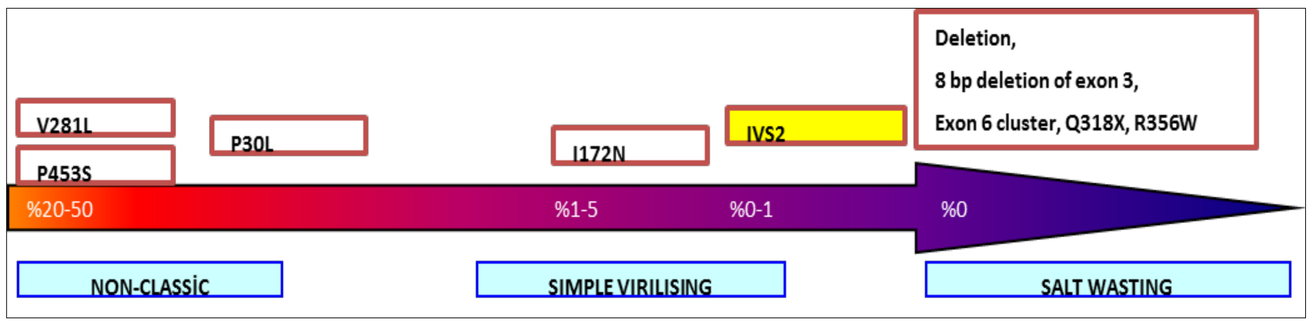

Figure1: Genotype- fenotype association of *CYP21A gene* mutations

Family 1

First child of family 1 was a girl (F1.1) diagnosed as salt wasting (SW) CAH, died at six days old and IVS2/IVS2 mutation of *CYP 21 gene* was detected. Analysis of chorion villus sample showed 46,XX karyotype and IVS2/IVS2 mutation in the second pregnancy and Dexamethasone treatment was started to mother. Postnatally, child (F1.2) was treated with Hydrocortisone (HC) up to 21 months old. Due to suppressed hormone profile with low dose HC, treatment was discontinued. Finally ,she was admitted to our hospital at 25 months. She was followed–up for three years without medicine and she is still hormonally and clinically normal. The third child (F1.3) was diagnosed as SWCAH with IVS2/IVS2 mutation.

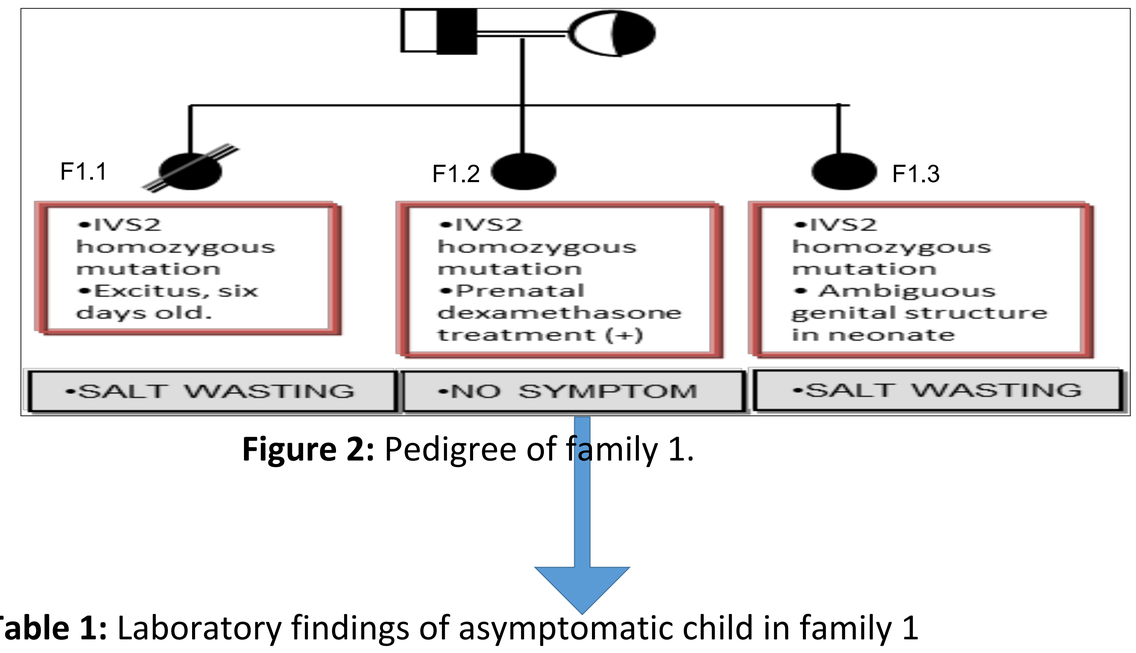

Figure 2: Pedigree of family 1.

Family 2

The daughter of family 2 (F2.1) was diagnosed with Type 1 DM at 4.7 years old. On her follow-up, premature thelarche and axillary hair was detected. Her basal and stimulated 17 hydroxyprogesterone levels were high (7.5 and 18.4 ng/ml respectively), compatible with Nonclassical CAH. Her genetic analysis revealed IVS2/IVS2 mutation. Asymptomatic brother (F2.2) also had the same mutation.

Considering pseudogene state, molecular analysis of asymptomatic homozygous cases were reevaluated and the same result was observed. Sequence analysis still is going on.

Table 1: Laboratory findings of asymptomatic child in family 1

On admission without therapy

Na/ K	138/4,2 mEq/l
17-OH progesterone	0,29 ng/ml
Cortisole	6,8 µg/dl
ACTH	15,55 pg/ml
DHEA-SO4	0,91 µg/dl
Testosterone	2 ng/dl
Plasma renin activation	2,5 ng/ml/h
Aldosterone	6,5 ng/dl

ACTH stimulation test.

	Basal	Peak
17-OH Progesterone	0,83 ng/ml	4,9 ng/ml
DHEA/SO4	4,3 mcg/dl	4,2 mcg/dl
Cortisole	9,35 mcg/dl	27,38 mcg/dl

Table 2: Laboratory findings of daughter of family 2

On admission

LH	<0,2 mIU/ml
FSH	3,27 mIU/ml
E2	<20 pg/ml
fT4	11,91 pmol/l
TSH	1,98 mcIU/ml
DHEA/SO4	60,1 mcg/dl
17-OH Progesterone	7.5 ng/ml
Total testosterone	<20 ng/dl

ACTH stimulation test.

	Basal	Peak
17- OH Progesterone	6,6 ng/ml	18,4 ng/ml
Cortisole	18,4 mcg/dl	30,7 mcg/dl
DHEA/SO4	67 mcg/dl	70,2 mcg/dl

Result

Although patients who has IVS2/IVS2 mutation can present with Nonclassical CAH infrequently, asymptomatic patient as seen in our two cases have not been reported yet. In the *CYP21 gene* mutations, genotype-phenotype discordance is an issue still open for debate.