# Severe 21-hydroxylase deficiency Congenital Adrenal Hyperplasia and Congenital Hypothyroidism due to Thyroglobulin mutations : 2 distinct genetic disorders with phenotypic variability within a single family

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## Introduction

**21-Hydroxylase deficiency due to mutations in *CYP21A2* represents the commonest form of Congenital Adrenal Hyperplasia (CAH).**

**Dyshormoneogenetic congenital hypothyroidism (CH) may be due to *TPO, TG, DUOX2, DUOXA2, IYD, SLC5A5* and *SLC26A4* mutations.**

**We report a kindred of four affected siblings born to unrelated parents manifesting with three different forms of CAH.**

**Two of the siblings also show co-segregation of two distinct genetic disorders, namely salt-losing CAH and CH due to thyroglobulin mutations.**

## Genetics

**Siblings 1 and 2 were compound heterozygous for the maternal *CYP21A2* c.290-13C>G mutation and the paternal *CYP21A2* c.515T>A , p.Ile172Asn and *CYP21A2* c.841G>T, p.Val281Leu mutations and have a very severe form of salt losing CAH.**

**Sibling 3 was compound heterozygous for the *CYP21A2* c.290-13C>G and the *CYP21A2* c.841G>T, p.Val281Leu mutations and has a simple virilising form of CAH.**

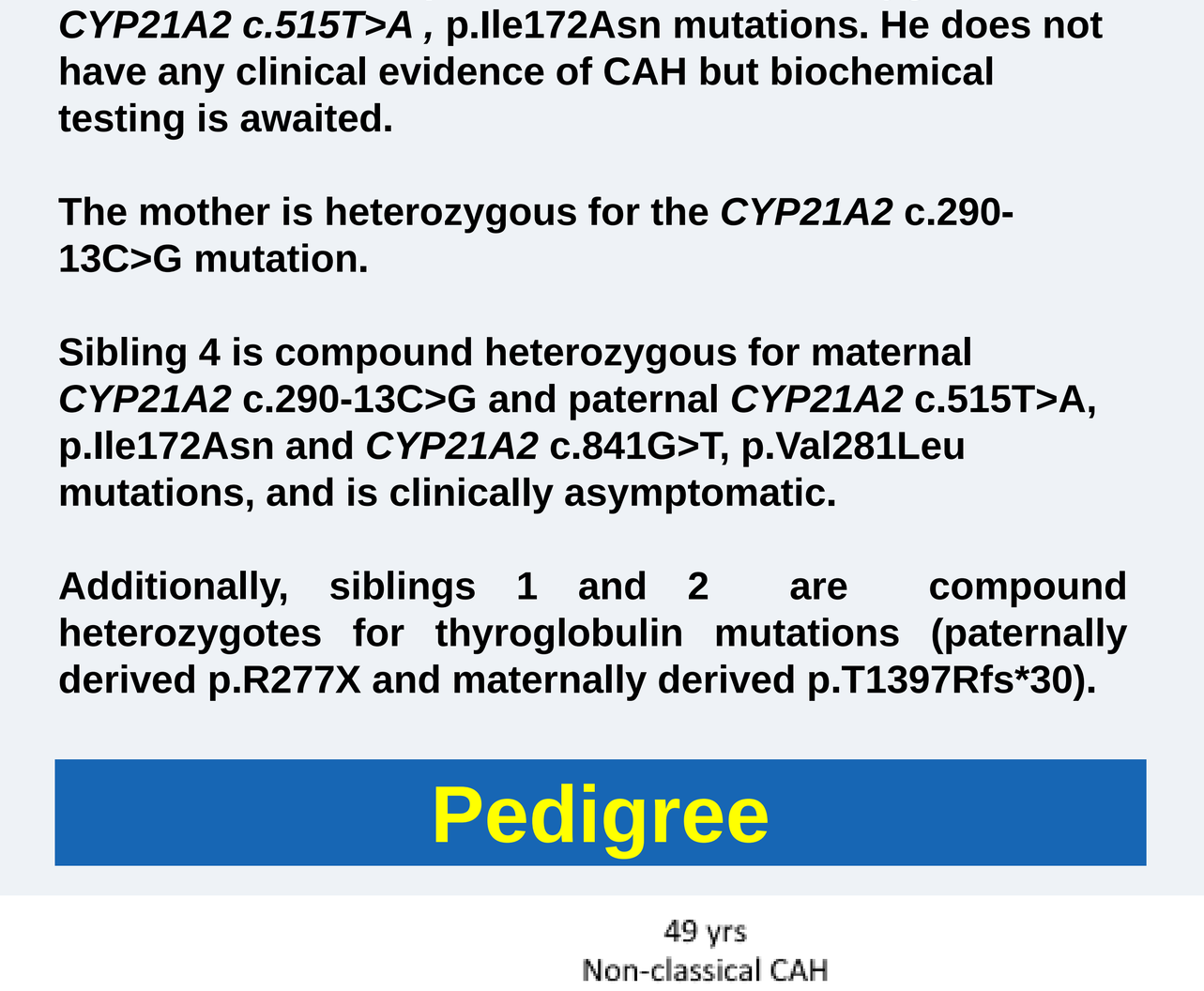
**The father is homozygous for the *CYP21A2 c.841G>T p.*Val281Leu and heterozygous for *CYP21A2 c.515T>A ,* p.Ile172Asn mutations. He does not have any clinical evidence of CAH but biochemical testing is awaited.**

**The mother is heterozygous for the *CYP21A2* c.290-13C>G mutation.**

**Sibling 4 is compound heterozygous for maternal *CYP21A2* c.290-13C>G and paternal *CYP21A2* c.515T>A, p.Ile172Asn and *CYP21A2* c.841G>T, p.Val281Leu mutations, and is clinically asymptomatic.**

**Additionally, siblings 1 and 2 are compound heterozygotes for thyroglobulin mutations (paternally derived p.R277X and maternally derived p.T1397Rfs*30).**

## Pedigree




## Sibling 1

**Presented at birth with virilised genitalia and was diagnosed to have a salt-losing form of CAH and commenced on hydrocortisone, fludrocortisone and sodium supplements. CH was diagnosed on neonatal screening; started on thyroxine at 20 days of age. Poor compliance with medication throughout childhood with raised ACTH, 17OHP and TSH concentrations. Precocious puberty diagnosed at 7.8 years, started on Gonapeptyl - stopped at 10.2 years.**

**She is now nineteen years old, short (height SDS –2.60) and has severe obesity (BMI 52.5), with insulin insensitivity, severe virilisation with marked hirsutism, primary amenorrhoea, voice changes, and polycystic ovarian disease. She is now on dexamethasone, fludrocortisone, flutamide and metformin. Abdominal MRI - bilaterally enlarged adrenals with a probable right adrenal adenoma, likely to be due to chronic ACTH stimulation. Normal plasma and urinary catecholamines and metanephrines.**

## Sibling 2

**Male screened electively for CAH at birth and found to have raised 17OHP in cord blood. Diagnosed to have salt-losing CAH and was started on hydrocortisone, fludrocortisone and sodium supplements. CH was diagnosed on neonatal screening and thyroxine was started at 7 days of age. Poor compliance with medication throughout childhood with raised ACTH, 17OHP and TSH concentrations.**

**Diagnosis of gonadotropin-dependent precocious puberty was made at 9.6 years and he was started on GnRH analogue therapy. He is now 13.1 years old, and GnRHa was stopped at 12.5 yrs of age; puberty has rapidly progressed (Tanner staging is G5P5A3).**

**His height is now 145.6cm (Ht SDS -0.90, weight SDS +1.39, BMI SDS +2.63). Bone age is 15.4 years, suggesting that he is close to his final height and will end up very short. He is currently on hydrocortisone and fludrocortisone.**

## Sibling 3

**Referred at 9.81 years with premature pubarche (Tanner staging: B1P3A1, bone age 11.4 years and growth velocity 6.7cm /year).**

**Synacthen test – suboptimal peak cortisol at 30 minutes (395nmol/L) and a raised basal 17-OHP which peaked further on stimulation (144 nmol/L). Normal plasma renin, aldosterone and thyroid function.**

**She was commenced on hydrocortisone and is now 11 years old with Tanner staging of B3P3A1, weight +0.64 SDS and height – 0.74 SDS.**

## Sibling 4

**The fourth sibling aged 17 years and the father of the siblings have genetic evidence of CAH but are phenotypically unaffected. The father is currently awaiting further investigation but has achieved a height of 165.4cm (-1.4SDS), whilst sibling 4 had a peak cortisol of 722 nmol/L at 30 minutes post-synacthen, with a 17OHP of 81.9 nmol/L, DHEAS of 13.1 µmol/L, testosterone of 2.4nmol/L, and an androstenedione of >20 nmol/L. Her height is 154cm and she is achieving regular periods.**

## Conclusions

**In this unusual pedigree, two siblings presented with two distinct genetic disorders (salt losing CAH and CH), while one sibling presented with simple virilising CAH. The cases also illustrates the importance of optimal disease control in CAH. Poor compliance with chronically elevated ACTH concentrations may result in short stature and adrenal adenoma formation, as demonstrated in sibling 1.**