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**Case Report**

# A novel homozygous *CYP19A1* gene mutation: Aromatase deficiency mimicking congenital adrenal hyperplasia in an infant without obvious maternal virilisation

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**What is already known on this topic?**
In aromatase deficiency, the accumulated androgens may cause signs of maternal virilisation during pregnancy. Large multiple cysts have been described in aromatase deficient girls during infancy and childhood. In previous reports of aromatase deficiency, cases were term neonates with average weight for gestational age.
**What this study adds?**
We report a novel large deletion in the *CYP19A1* gene. Maternal virilisation was not a marked finding in our case, except a mild deep voice. The absence of virilisation in our patient's mother could likely be due to premature delivery of the patient. In this report, we describe a case of aromatase deficiency in a 23-week born preterm with disorder of external genital development.

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**Abstract**
Aromatase deficiency is a rare autosomal recessive disorder in which affected patients cannot have a normal estrogen synthesis. Herein, we report a 46, XX patient born with virilised external genitalia. A novel homozygous mutation in the *CYP19A1* gene, causing aromatase deficiency, was detected.
A 30-day infant was referred to pediatric endocrinology because of a uterus, detected in an ultrasonography examination. He was born at 23$^{th}$ gestational week with C-section because of preeclampsia and premature membrane rupture. There was not an evidence of virilisation, such as acne, hirsutism, deep voice, clitoris enlargement, in maternal history. Physical examination revealed complete scrotal fusion and a single urogenital meatus, consistent with Prader stage-3. Standard dose ACTH test revealed an inadequate cortisol response and high 17-OH-progesterone levels, suggesting simple virilising congenital adrenal hyperplasia due to 21-hydroxylase deficiency. However no mutation in *CYP21A2* gene was detected. At the age of 2.5 years of age we repeated ACTH test after suspension of hydrocortisone treatment for 48 hours. This time, cortisol and androgen levels were normal. The patient was re-evaluated in terms of 46, XX disorder of sex development (DSD), especially with the suspicion of aromatase deficiency. A novel homozygous exon 6 deletion was identified in the *CYP19A1* gene.
Aromatase deficiency could easily be confused with congenital adrenal hyperplasia in newborn period. In a case of 46, XX DSD aromatase deficiency can present without the history of maternal virilisation or without large and multycystic ovaries.
**Keywords:** 46 XX DSD, CYP19A1, aromatase deficiency

## Introduction
Aromatase (cP450arom) catalyses the conversion of androgens to estrogens. The biological importance of the aromatase is related not only to its role in the estrogen biosynthesis, but also to its potential influence on the balance of the androgen-estrogen ratio in different tissues. In humans, cP450arom is encoded by a single gene (*CYP19A1)* that is localized in chromosome 15q21.1. The protein-coding sequence is contained within nine exons (E2–E10), spanning approximately 35 kb (1-3). CP450arom enzyme is mainly located in the endoplasmic reticulum of estrogen-producing cells in the ovary, placenta, testis, brain, adipose tissue, liver, muscle, and hair follicles (4, 5).

Aromatase deficiency is a rare autosomal recessive disorder in which affected patients cannot have a normal estrogen synthesis (1). During pregnancy, dehydroepiandrosterone sulphate (DHEAS) and 16OH-DHEAS, arising from the fetal adrenal gland and liver, respectively, become important sources for the synthesis of placental estrogens (4-6). Fetuses lacking aromatase activity are not able to convert DHEAS to estrogens in the placenta; DHEAS is therefore converted to testosterone, resulting in the virilization of both fetus and mother. Since the first description of aromatase deficiency by Shozu et al (7) in 1991, around 40 cases have been reported (1, 3, 4, 5, 7- 20).

In aromatase deficiency, the accumulated androgens may cause signs of maternal virilisation (acne, deep voice, clitoris enlargement) during pregnancy. After delivery these symptoms usually disappear gradually. In the postpartum period, some clinical and laboratory findings of androgen excess regress and androgen levels return to normal levels. In most female cases exposed in utero to excessive androgen levels, ambiguous genitalia have been reported. Delayed skeletal maturation has been described and most affected girls have multiple ovarian cysts and failure of breast development at puberty (3, 5).

Herein, we report a 46, XX patient born with virilised external genitalia. A novel homozygous mutation in the *CYP19A1* gene, causing aromatase deficiency, was detected.

**Case Report**

A 30-day infant with a male-dominant genital appearance was referred to pediatric endocrinology because of a uterus, detected in an ultrasonography examination. He was born at 23th gestational week with C-section because of preeclampsia and premature membrane rupture. Birth weight was 680gr. He was intubated, given surfactant treatment and needed mechanical ventilation support. Bilateral cryptorchidism and hypospadias were thought to be associated with severe prematurity. Since gender assessment at birth was made as male, baby received a male name and identity card. He was the first baby of a 25-year old healthy mother and a 27-year old healthy father, who were first cousins. The mother had two abortions before, so she was treated with progesterone for one month between 16$^{th}$ and 20$^{th}$ gestational weeks and also with salicylic acid during whole pregnancy. There was not an evidence of virilisation, such as acne, hirsutism, deep voice, clitoris enlargement, in maternal history. Physical examination revealed complete labioscrotal fusion and a single urogenital meatus, consistent with Prader stage-3. Gonads were not palpable, a chordae was present and phallus was measured as 2x1 cm in dorsal and 1.6x1 cm in ventral side. Patient was still followed in neonatal intensive care unit having mechanical respiratory support. **At postnatal 30$^{th}$ day,** hormone levels were as follows: 17-OH-progesterone (17OHP): 41 ng/ml ( < 35.5 ng/ml), DHEA-SO4: 1500 µg/dl (123- 882 µg/dl ), testosterone: 2.94 ng/ml ( 0.05-0.16 ng/ml), FSH: 1.3 IU/L (0.3- 2.6 IU/L), LH: 0.48 IU/L ( 0.1- 8.5 IU/L), estradiol <10 pg/ml (<15 pg/ml), progesteron: 4.7 ng/ml ( 0.18- 6.4 ng/ml). Karyotype was 46, XX. Standard dose ACTH test (30 µg/kg/dose) revealed an inadequate stimulated cortisol and high 17OHP levels, suggesting simple virilising congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (Table-1). The patient was being treated on mechanical ventilation due to severe prematurity in this period. Additionally there were several problems, such as septicemia, surfactant deficiency, respiratory distress. Although classical findings of adrenal insufficiency were not present, we had to give hydrocortisone® replacement since we could not exclude cortisol deficiency. Hydrocortisone® was commenced as 10 mg/m$^2$/day, three times a day. The name and identity card of baby were changed as female with the agreement of parents and the decision of multidisciplinary gender assessment committee.

In the follow-up period androgen levels were quite low despite hydrocortisone doses as low as 6-7 mg/m$^2$/day and no mutation in *CYP21A2* gene was detected. This unusual clinical condition and lack of a mutation in *CYP21A2* gene leaded to doubt about the diagnosis of 21-hydroxylase deficiency. At the age of 2 years and 6 months we repeated standard dose ACTH test after suspension of hydrocortisone treatment for 48 hours. This time, cortisol and androgen levels were normal (Table-1). When the maternal history was re-visited, she remembered that she had a mild deep voice. The patient was re-evaluated in terms of 46, XX DSD, especially with the suspicion of aromatase deficiency (Table 2). Finally, aromatase deficiency was confirmed by genetic analysis (Figure-1).

In the last clinical visit, the patient was 4-year and 4-month. The height was 95.5 cm (-2.3 SD), the weight was 14.5 kg (-1.27 SD), and breasts were in Tanner stage-1. Further examinations were performed for disorders, which could be associated with aromatase deficiency (Table-2). An informed consent was obtained from parents of the patient.

**Genetic analysis**

EDTA blood sample was taken for *CYP19A1* gene Sequence analysis. At the PCR step, as we could not amplify very large region including exon 6, we planned a long PCR and sequence analysis to detect exact breakpoints. Sequence analysis with Next Generation Sequencing Method (Illumina-MISEQ- San Diego) was done and 3212 bp deletion within chr15:51.511.985 – 51.508.774 was detected (NM_000103.3:c.629-1453_744-486del). This large deletion evaluated as a “pathogenic” variant due to ACMG criteria’s.

*CYP19A1* gene contains 10 exons and exon 6 was deleted with some parts of introns of both site and 2 canonical splice site. This is a null variant. Allele was not found in GnomAD exomes. This is a conserved region in different species. This is a novel variant.

**Discussion**

In this report, we describe a case of aromatase deficiency in a 23-week born preterm with disorder of external genital development. We report a novel large deletion in the *CYP19A1* gene (Figure-1). To date, more than 33 different mutations in the *CYP19A1* gene have been reported in patients with aromatase deficiency. These mutations include missense, splice site, nonsense, insertions and small deletions, and one large intragenic deletion (1, 3, 4, 5, 8- 22). The majority of the mutations reported are located in exons 9 and 10, which encode the substrate-binding site and haem-binding domains, respectively (12). Our patients had large deletion in exon 6. Although we did not make a functional study, this variant is a null variant and classified as a likely pathogenic variant due to ACMG criteria's. The fact that we did not have any functional study related to the mutation we identified was stated as the limiting factor of our study.

Aromatase deficiency causes virilisation (acne, deep voice, clitoris enlargement) of mother because placental androgens could not be converted to estrogens, as the result excessive androgen levels lead to virilisation of mother during pregnancy (16). Besides being an important clue, maternal virilisation is not a rule. In the study of Marino et al (3), three of six cases had a history of gestational virilisation. Maternal virilisation was not a marked finding in our case, except a mild deep voice. Why some mothers do not have virilisation signs can be explained by either decreased fetal adrenal androgen secretion or adequate estrogen production of placenta (16). Grumbach et al (23) reported that as low as 1% of normal aromatase activity is enough to prevent mother from virilisation. Furthermore, massive placental estrogens are produced especially in the 3$^{rd}$ trimester of gestation (16). The absence of virilisation in our patient's mother could likely be due to premature delivery of the patient or presence of partial aromatase activity.

In most female cases of aromatase deficiency, disorders of external genitalia with various degrees of masculinization have been reported. Gonads were non-palpable and internal genitalia differentiation was normal female (1, 3- 5). For this reason, patients can receive the diagnosis of CAH, which is the most common cause of virilisation of external genitalia in a female fetus (1). Similarly, our patient was considered as CAH because of physical findings and also quite high androgen levels. Also the severe prematurity and the lack of data about normal androgen levels of these severely preterm neonates leaded to initial diagnostic confusion in our patient. Low androgen levels despite low hydrocortisone doses on the follow-up were very unusual in patients with classical CAH patients. This important observation together with the lack of mutation in *CYP21A2* discouraged us from the diagnosis of 21-hydroxylase deficiency.

A clinical phenotype, including changes in the hypothalamic-pituitary-gonadal axis, ovarian cyst development, skeletal maturation and growth, as well as changes in insulin sensitivity and lipid profile, has been reported in aromatase deficiency (5). Marino et al (3) investigated the hypothalamic-pituitary-gonadal axis and described high levels of LH and FSH in neonatal period. A two-month old girl, reported by Mullis et al (17), had elevated FSH levels (baseline and GnRH-stimulated) but normal LH levels (baseline and GnRH-stimulated). Contrary to this, our patient had normal gonadotropin levels at postnatal 60$^{th}$ day (Table-2). LH and FSH were elevated at the ages of two and four (Table-2). In previous reports of aromatase deficiency, cases were term neonates with average weight for gestational age (5, 7, 17, 18). Our patient was born at 23th gestational week, so gonadotropin levels might be meaningless in early infancy. In premature without aromatase deficiency, gonadotrophin levels are very high after birth, but a sharp decrease in FSH levels is seen around term age. Also, in term neonate without aromatase deficiency, gonadotrophin levels are low at birth and increase progressively afterwards (24, 25). Since we measured gonadotropin levels near term-equivalent age, it might have been come to the time of rapid decrease.

Large multiple cysts have been described in aromatase deficient girls during infancy and childhood due to the chronic stimulation by gonadotropins that cannot be suppressed because of estrogen deficiency (3, 5, 17, 18). Marino et al (3) reported a case series of five patients. Four of them, aged 18, 7, 12, 10 respectively, had increased ovarian size with large cysts. They were at pubertal stage except one 7-year old one. Only a one 3-year old girl had normal ovaries. There are some patients who do not have large cysts, even hypoplastic ovaries. Up to date, seven patients with hypoplastic ovaries have been reported (4, 12, 16, 19-20). Actually, there is no consistent ovarian phenotype in patients with aromatase deficiency as some had large and polycystic ovaries, while others had normal ovarian morphology (16). Despite quite elevated levels of FSH, we did not observe any ovarian cyst in periodic ultrasonographic screening of our patient; she still has normal ovarian morphology.

Little is known about the bone phenotype of girls with aromatase deficiency (26). It is accepted that estrogens are important in preserving adequate bone mineral density (BMD) (5). However, data on the role of estrogens on bone mineralization during childhood are scarce. Janner et al (26) found decreased BMD in a 3.5-year old patient, but Belgorosky et al (18) found normal BMD in a 6-year old patient. Therefore, some expression of cP450arom protein might be enough to maintain a normal mineral bone density. On the other hand, men with

aromatase deficiency show a distinct bone phenotype characterized by osteopenia (27). We performed a BMD measurement at the age of four, revealing osteopenia (- 1.4 SDS) when re-calculated for height age of patient. The usefulness of estrogen treatment during infancy and childhood in affected female patients is not clear. Mullis et al (17) reported that low doses of estradiol in a 3-year-old affected girl resulted in normalization of serum gonadotropins, regression of enlarged ovaries and improvement in BMD. Janner et al (26) showed the impact of oral 17-β estradiol treatment, on longitudinal growth, bone age maturation, pituitary gonadotropin feedback, multicystic ovaries and bone density in the long-term follow-up of a girl with a compound heterozygote mutation in *CYP19A1* gene. So far, we did not need a treatment for our patient, since ovaries are still normal and data on the estrogen treatment are inadequate for these patients.

In conclusion; a novel mutation in *CYP19A1* gene explains virilisation of our patient. Aromatase deficiency could easily be confused with CAH especially preterm infant. In a case of 46, XX DSD aromatase deficiency can present without the history of maternal virilisation or without large and multycystic ovaries. **The absence of virilisation in our patient's mother could likely be due to premature delivery of the patient or presence of partial aromatase activity.** It is not clear if premature delivery and aromatase deficiency are releated or it is co-incidental in our patient. Inadequate androgen-estrogen conversion in plasenta and its effects on the continuation of the gestational process is not very well known in aromatase deficiency. However it is worthy to investigate this relationship and possible mechanisms with further studies. This case report emphasizes the importance of considering aromatase deficiency as a very rare cause of 46, XX disorders of sex development and perform genetic analyses to patients especially whose definitive diagnosis is absent. More cases should be reported to enhance our knowledge on the phenotypic spectrum of aromatase deficiency.

**Conflict of interest**

The author declares that there is no conflict of interest.

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**Authorship Contributions**

Concept: FD, Design: FD, Data collection or processing: FD, SC, Analysis or interpretation: FD, SC, Literature Search: FD, Writing: FD, SC

**Table Legends**

**Table 1:** Results of classical ACTH stimulation test at 60$^{th}$ day and 2 years old

**Table-2:** Laboratory findings of the patient at diagnosis and follow-up

**Figure Legend**

**Figure 1:** Identification of deletion in NGS, as visualized in integrative genomics viewer (IGV) soft ware. A 3212 bp deletion represented by blue arrows, was detected within chr15: 51.511.985 – 51.508.774 (NM_000103.3:c.629-1453_744-486del).

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**Table 1:** Results of classical ACTH stimulation test at 60th day and 2 years old

| | **Postnatal 60th day** | | **2 years old** | | |
|---|---|---|---|---|---|
| **Time of blood sampling (minute')** | **0'** | **30'** | **0'** | **30'** | **60'** |
| **Cortisol (µg/dL)** (NL: 0': 6.5/ 30': 20) | 1.7 | 12.8 | 6.5 | 20.3 | 21 |
| 17**OHP (ng/mL)** (NL: 0':1.2- 8.4/ 60': 40 ) | 65 | 80 | 0.28 | 1.35 | 1.4 |
| **Progesterone (ng/mL)** (NL: 0': 0.34/ 60': 1 ) | 7.9 | 9.5 | 0.1 | 0.8 | 1 |
| **Testosterone (ng/mL)** (NL: 0.05-1.6) | 0.9 | 2.1 | < 0.13 | < 0.13 | < 0.13 |
| $\Delta^4$ **androstenodion (ng/mL)** (NL: 0.1- 0.3) | 1.5 | 2.3 | <0.3 | | < 0.3 |
| **ACTH (IU/L)** (NL: 0-63) | 12 | | 12 | | |
| **DHEAS (µg/dL)** (NL: 123- 882) | 1500 | | 5.5 | | |
| **Renin (ng/mL/hour)** (NL: 0.48-4.8) | 5.4 | | 0.8 | | |
| **Aldosterone (pg/ mL)** (NL:35- 300) | 375 | | 144 | | |

*17OHP: 17-hydroxy progesterone, ACTH: adrenocorticotropic hormone, DHEAS: dehydroepiandrosteron sulphate, NL: normal level*

**Table-2:** Laboratory findings of the patient at diagnosis and follow-up

| | **2 months** | **26 months** | **52 months** |
|---|---|---|---|
| **LH (IU/L)** | 0.48 | 2.43 | 0.61 |

| | | | |
|---|---|---|---|
| **FSH (IU/L)** | 1.3 | 46.67 | 32.8 |
| **Estradiol (pg/ml)** | <10 | 10 | <10 |
| **IGF-1(ng/ml)** | - | 117 | 144 |
| **Bone age(year)** | - | 2 | 3 |
| **Pelvic ultrasonography** | Uterus: 20 mm | Uterus:16 mm, right ovary: 0.6 ml, left ovary: 0.5 ml | Uterus: 30 mm, right ovary: 0.4 ml, left ovary: could not be detected |
| **BMD** | - | - | -1.4 SD |

*LH: luteinizing hormone, FSH: follicle- stimulating hormone, IGF-1: insulin growth factor-1, BMD: bone mineral density*