ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Shokery-Awadalla/452

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Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 4 & **Iss:** 1

Case Report

Genotype Description in Patients with Congenital Adrenal Hyperplasia in Bogotá, Colombia

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Citation: Awadalla S, Beltran GM, Navarro-Pinilla AM. Genotype Description in Patients with Congenital Adrenal Hyperplasia in Bogotá, Colombia. *Medi Clin Case Rep J* 2026;4(1):1644-1647. DOI: doi.org/10.51219/MCCRJ/Shokery-Awadalla/452

Received: 06 March, 2026; **Accepted:** 09 March, 2026; **Published:** 11 March, 2026

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A B S T R A C T

Introduction: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by enzymatic deficiencies in the steroidogenic pathway. Approximately 90% of cases are due to pathogenic variants in the CYP21A2 gene, leading to 21-hydroxylase deficiency (21-OHD). This enzyme is essential for the synthesis of cortisol and aldosterone.

Objective: To evaluate an Advanced Regenerative and Immunomodulatory Drainage Protocol (ARDIP) as a treatment strategy in patients presenting with facial tissue necrosis unresponsive to conventional management.

Case presentation: We report a case series of seven patients aged between 4 and 9 years who presented with growth acceleration and/or premature pubarche and had a confirmed molecular genetic diagnosis.

Results are expressed as mean ± standard deviation. The mean age was 7.11 ± 2.61 years. Basal 17-alpha-hydroxyprogesterone (17-OHP) levels were 22.9 ± 26.72, increasing to 37.43 ± 22.53 following ACTH stimulation testing. The mean bone age was 9.86 ± 2.86 years, with an average advancement of 2.74 ± 0.86 years compared with chronological age.

Molecular genetic studies were performed using sequencing, copy number variant (CNV) and insertion–deletion (InDel) analysis, multiplex ligation-dependent probe amplification (MLPA) of the CYP21A2 gene or clinical exome sequencing. Pathogenic variants were identified in homozygosity, compound heterozygosity (CH) or carrier status (Table 1).

Discussion: Approximately 75% of pathogenic variants result from rearrangements between the CYP21A1P pseudogene and the functional CYP21A2 gene, typically manifesting as copy number variants. Around 20-25% are caused by single nucleotide variants, including missense, nonsense, splice-site variants and small insertions and deletions. The remaining 1-2% correspond to de novo variants arising from unequal crossover events during meiosis[1].

Clinical presentation may be classified as classical or non-classical CAH depending on residual enzymatic activity, consistent with the established genotype–phenotype correlation2. In non-classical CAH, reported variants retain approximately 20-80% of enzymatic activity, resulting in milder clinical manifestations[2].

Conclusions: n our study, the most frequent pathogenic variant was CYP21A2 (p. Val282Leu), identified in five cases presenting with clinical manifestations during prepubertal ages and no history of adrenal crises. Two cases harbored variants associated with classical CAH. Finally, two patients were identified as carriers; however, their phenotype was consistent with CAH.

Keywords: Non-classical congenital adrenal hyperplasia; CYP21A2; premature pubarche; 17-OHP; accelerated growth

Introduction

Congenital adrenal hyperplasia (CAH) is a heterogeneous group of autosomal recessive disorders caused by enzymatic defects in adrenal steroidogenesis, resulting in impaired cortisol biosynthesis[3]. The clinical spectrum ranges from severe, life-threatening forms presenting in the neonatal period to milder, non-classic forms that may manifest later in childhood or adulthood[2]. The incidence varies according to the specific enzymatic defect and the population studied; however, overall, CAH represents one of the most common inborn errors of metabolism[1].

Approximately 90% of cases are attributable to pathogenic variants in the CYP21A2 gene, which encodes the enzyme 21-hydroxylase, leading to 21-hydroxylase deficiency (21-OHD)[4]. This enzyme plays a critical role in the biosynthesis of both cortisol and aldosterone by catalysing the conversion of 17-hydroxyprogesterone to 11-deoxycortisol in the glucocorticoid pathway and progesterone to 11-deoxycorticosterone in the mineralocorticoid pathway[5]. Impaired 21-hydroxylase activity results in decreased cortisol production, leading to chronic adrenocorticotropic hormone (ACTH) stimulation due to loss of negative feedback. Persistent ACTH stimulation causes adrenal hyperplasia and accumulation of steroid precursors, which are shunted toward androgen synthesis, resulting in hyperandrogenism[1].

Clinically, 21-hydroxylase deficiency is classified into classic (salt-wasting and simple virilizing) and non-classic forms, depending on residual enzymatic activity[4]. The salt-wasting form is characterized by cortisol and aldosterone deficiency, potentially leading to hyponatremia, hyperkalaemia, dehydration and shock if untreated. In contrast, the simple virilizing form primarily presents with androgen excess, whereas the non-classic form typically manifests with milder symptoms such as premature pubarche, hirsutism, menstrual irregularities or infertility[6]. Early diagnosis and appropriate glucocorticoid therapy, with mineralocorticoid replacement when indicated, are essential to prevent morbidity and mortality and to optimize long-term outcomes[1].

Case Presentation

We report a case series of seven pediatric patients aged between 4 and 9 years who were referred for evaluation of growth acceleration and/or premature pubarche, with subsequent confirmation of the diagnosis by molecular genetic testing. All patients underwent comprehensive clinical, biochemical and radiological assessment as part of the diagnostic workup for suspected non-classic congenital adrenal hyperplasia.

Descriptive statistical analysis was performed and results are presented as mean ± standard deviation. The mean chronological age at evaluation was 7.11 ± 2.61 years. Basal serum 17-alpha-hydroxyprogesterone (17-OHP) levels had a mean value of 22.9 ± 26.72 ng/mL, reflecting wide interindividual variability. Following ACTH stimulation testing, the mean stimulated 17-OHP level increased to 37.43 ± 22.53 ng/mL, supporting the biochemical diagnosis.

Assessment of skeletal maturation revealed a mean bone age of 9.86 ± 2.86 years. Compared with chronological age, the average advancement in bone maturation was 2.74 ± 0.86 years, consistent with the effect of chronic androgen exposure on epiphyseal maturation and linear growth velocity.

Molecular genetic studies were performed in all cases to confirm the underlying etiology. Depending on availability and clinical indication, testing included sequencing analysis, detection of copy number variations (CNVs) and small insertions/deletions (InDels), multiplex ligation-dependent probe amplification (MLPA) of the CYP21A2 gene or a clinical exome approach. Pathogenic variants were identified in different zygosity states, including homozygous variants, compound heterozygous variants and heterozygous carrier states **(Table 1)**.

Discussion

Approximately 75% of pathogenic variants associated with 21-hydroxylase deficiency arise from gene rearrangements between the active CYP21A2 gene and its highly homologous pseudogene, CYP21A1P[3]. These two genes are located on chromosome 6p21.3 and share approximately 98% sequence homology in exonic regions, which predisposes them to misalignment during meiosis. As a result, pathogenic variants frequently occur through gene conversion events, in which deleterious sequences from the pseudogene are transferred to the functional gene[1].

The complex genomic architecture of this locus explains both the high mutation rate and the technical challenges in molecular diagnosis, often requiring specialized methods such as MLPA or long-range PCR to accurately characterize gene rearrangements[6]. The clinical presentation of congenital adrenal hyperplasia due to 21-hydroxylase deficiency can be classified as classical or non-classical, largely depending on the residual enzymatic activity determined by the specific genotype[5]. This well-established genotype–phenotype correlation reflects the degree to which cortisol and, in some cases, aldosterone synthesis is impaired[5]. Severe pathogenic variants, such as large deletions, nonsense mutations or severe splice-site defects, are typically associated with minimal or absent enzyme activity and result in the classical forms (salt-wasting or simple virilizing). In contrast, milder missense variants that partially preserve enzyme function are generally associated with the non-classical form[5].

Table 1: Genotype-phenotype correlation.

Patient	Age (years)	Sex	Initial finding	17 OHP (ng/dl)	17 OHP after ACTH stimulation (ng/dl)	Bone age (years)	Gene	Variant	Type	Classification	Zygosity	Inheritance mechanism	Diagnosis	Treatment
1	9,2	F	Growth acceleration	8,3	Basal 4,2 post ACTH 18,3	11,5	CYP21A2	c.844G>T (p.Val282Leu)	Missense	Pathogenic	Homozygous	AR Homozygous	Non classical CAH	Hydrocortisone 15 mg/m^2
2	9	M	Premature pubarche and growth acceleration	-	Basal 5,3 post ACTH 48,5	12	CYP21A2	c.844G>T (p.Val282Leu)	Missense	Pathogenic	Heterozygous	Carrier		
3	8,9	M	Growth acceleration	3,2	Basal 3,6 post ACTH 44,8	13	CYP21A2	c.844G>T (p.Val282Leu)	Missense	Pathogenic	Heterozygous	AR Compound heterozygosity		
								Exon 6 cluster c.710T>A (p.Ile237Asn) + c. 713T>A (p.Val238Glu) + c. 719T>A (p.Met240Lys)	Missense	Pathogenic	Heterozygous			
4	4,4	F	Premature pubarche	17,4	-	6	CYP21A2	c. 518T>A (p.Ile173Asn)	Missense	Pathogenic	Heterozygous	AR Compound heterozygosity		
								c. 923dup (p.Leu308Phefs*6)	Frameshift	Pathogenic	Heterozygous			
5	2	F	Premature pubarche	81	-	5	CYP21A2	Intron 2 (I2G) c.293-13C>G (p.?)	Intronic	Pathogenic	Heterozygous	AR Compound heterozygosity		
								c.515T>A (p.Ile172Asn)	Missense	Pathogenic	Heterozygous			
6	8,8	F	Premature pubarche	-	Basal 4,1 post ACTH 11.01	10,5	CYP21A2	c.844G>T (p.Val282Leu)	Missense	Pathogenic	Heterozygous	Carrier		
7	7,5	F	Growth acceleration	41	-	11	CYP21A2	c.92C>T (p.Pro31Leu)	Missense	Pathogenic	Heterozygous	AR- Compound heterozygosity		
								c.844G>T (p.Val282Leu)	Missense	Pathogenic	Heterozygous			

In non-classical CAH, reported variants usually retain approximately 20-80% of normal 21-hydroxylase enzymatic activity. This partial deficiency leads to subtler biochemical abnormalities and milder clinical manifestations compared with the classical forms[4]. Patients may present with premature pubarche, accelerated growth velocity, advanced bone age, acne, hirsutism, menstrual irregularities or infertility, while severe neonatal salt-wasting is absent[4]. The variability in residual enzymatic capacity explains the broad phenotypic spectrum observed even among individuals carrying similar genotypes[6]. In our study, the most frequently identified pathogenic variant was CYP21A2 (p.Val282Leu), detected in five cases. This variant is classically associated with non-classical congenital adrenal hyperplasia and is known to preserve partial 21-hydroxylase enzymatic activity (1). Consistent with the expected genotype-phenotype correlation, these patients presented at prepubertal ages with signs of androgen excess and their clinical course supports the milder biochemical impact typically described for this variant. Two patients carried variants commonly associated with classical CAH. Although these genotypes are generally linked to markedly reduced or absent enzymatic activity, the clinical presentation in our series was consistent with a non-classical phenotype. This finding highlights the phenotypic variability that may occur even among individuals harboring severe variants in compound heterozygosity with milder alleles. Finally, two patients were identified as heterozygous carriers. Interestingly, despite carrying only a single pathogenic variant, their clinical and biochemical phenotype was compatible with CAH. Therefore, complementary studies such as MLPA and long-range PCR should be performed to improve gene amplification and to identify potential additional pathogenic variants. Overall, our case series reinforces the relevance of comprehensive molecular characterization of the CYP21A2 gene in patients with suspected CAH, particularly in those presenting with early signs of androgen excess. Accurate genotyping not only supports the diagnosis but also contributes to prognostic assessment, therapeutic decision-making and appropriate genetic counseling.

Competing interests: The authors declare that they have no competing interests.

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