

## Clinical and genetic findings of two cases with Apert syndrome

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### Abstract

**Background:** Craniosynostosis is described as the premature fusion of cranial sutures that belongs to a group of alterations which produce an abnormal phenotype. **Case report:** Two unrelated female patients with clinical findings of Apert syndrome—characterized by acrocephaly, prominent frontal region, flat occiput, ocular proptosis, hypertelorism, down-slanted palpebral fissures, midfacial hypoplasia, high-arched or cleft palate, short neck, cardiac anomalies and symmetrical syndactyly of the hands and feet—are present. In both patients, a heterozygous missense mutation (c.755C>G, p.Ser252Trp) in the FGFR2 gene was identified. **Conclusions:** Two cases of Apert syndrome are described. It is important to recognize this uncommon entity through clinical findings, highlight interdisciplinary medical evaluation, and provide timely genetic counseling for the family.

**Key words:** Apert syndrome. Clinical. FGFR2 gene. c.755C>G, p.Ser252Trp. Genetic counseling.

### Hallazgos clínicos y genéticos de dos casos con síndrome de Apert

#### Resumen

**Introducción:** Las craneosinostosis se describen como la fusión prematura de las suturas craneales y resultan un grupo de alteraciones que producen un fenotipo anormal. **Caso clínico:** En este informe de casos se presentan dos pacientes de sexo femenino no emparentadas con hallazgos clínicos del síndrome de Apert, caracterizado por acrocefalia, región frontal prominente, occipucio plano, proptosis ocular, hipertelorismo, fisuras palpebrales hacia abajo, hipoplasia medifacial, paladar alto o hendido, cuello corto, cardiopatía congénita y sindactilia simétrica en manos y pies. En ambas pacientes se identificó una mutación cambio de sentido en heterocigosis (c.755C>G, p.Ser252Trp) en el gen FGFR2. **Conclusiones:** Se presentan dos casos de síndrome de Apert. Es importante reconocer a través de los hallazgos clínicos esta entidad infrecuente, resaltar la evaluación médica interdisciplinaria y proporcionar un oportuno asesoramiento genético a la familia.

**Palabras clave:** Síndrome de Apert. Clínica. Gen FGFR2. c.755C>G, p.Ser252Trp. Asesoramiento genético.

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## Introduction

Craniosynostosis is characterized by a premature sutural fusion that can occur as a sole entity or associated with other anomalies. As a syndrome, craniosynostosis is a heterogeneous condition related to more than 180 syndromes<sup>1</sup>. Apert syndrome (AS) (OMIM 101200) was first described in 1906 by Dr. Eugene Apert, a French pediatrician, who designed it as acrocephalosyndactyly type I<sup>2,3</sup>. Craniosynostosis occurs in approximately 1/65,000 to 200,000 live births with Apert syndrome<sup>2,3-5</sup>, which represents 3% of all craniosynostosis. This syndrome affects equally male and female patients<sup>3,5</sup>. Two different types of mutations have been found on the fibroblast growth factor receptor-2 gene (*FGFR2*, OMIM 176943, NM\_001144916.1) in several syndromic craniosynostoses, including AS. Inheritance pattern of AS is autosomal dominant, and over 98% of cases have *de novo* mutations<sup>2-7</sup>.

Clinical features of AS, including craniosynostosis<sup>3</sup>, are characterized by bilateral coronal suture fusion (acrocephaly)<sup>2</sup> with a diminished anteroposterior diameter, flat occiput<sup>3</sup>, and abnormal cranial base development<sup>2</sup>, prominent forehead, hypertelorism<sup>3,6</sup>, downward sloping palpebral fissures<sup>6</sup>, proptosis<sup>3,6</sup>, strabismus<sup>4</sup>, depressed nasal bridge<sup>3</sup>, midface hypoplasia<sup>3,4,6</sup>, low-set ears<sup>8</sup>, a trapezoidal-shaped mouth<sup>6</sup>, prominent mandible<sup>3</sup>, high-arched or cleft palate<sup>3</sup>, bifid uvula<sup>2</sup>, delay in dentition, abnormal and crowded dentition<sup>3,6</sup> and pharynx defects frequently result in airway compromise<sup>8</sup>, symmetrical syndactyly of the hands and feet<sup>3,5,6</sup>, symphalangism and radio-humeral fusion. The multiple abnormalities of the central nervous alterations include hydrocephalus<sup>2</sup>, ventriculomegaly<sup>2,4</sup>, alterations of the *septum pellucidum*<sup>2</sup>, *corpus callosum*<sup>2,4</sup>, and limbic structures<sup>2</sup>. Additionally, cardiac, gastrointestinal, urogenital, vertebral anomalies<sup>4</sup> and short stature have been reported<sup>4,5</sup>. Furthermore, psychomotor development may be delayed<sup>3,6</sup>, with variable degrees of neurocognitive impairment<sup>2,8</sup>; blindness and hearing loss<sup>6</sup> can be observed. A multidisciplinary approach is required for the management of this entity due to this multisystem involvement<sup>3</sup>.

In this work, we report two Venezuelan female patients with clinical features of AS with heterozygous mutations (c.755C>G; p.Ser252Trp) in the *FGFR2* gene, with the objective of recognizing this uncommon entity through clinical findings, highlighting interdisciplinary medical evaluation, and providing timely genetic counseling for the family.

## Methods

Both patients diagnosed with AS were clinically evaluated in the Unit of Medical Genetics, Department of Pediatrics, University of The Andes, Mérida, Venezuela. Diagnostic molecular genetic tests were performed in the Department of Medical Biology and Genetics, Akdeniz University Medical School, Antalya, Turkey, in concordance with the institutional review board protocols approved by the ethics committees under the most recent version of Helsinki Declaration. Signed informed consent was obtained from the parents of the patients.

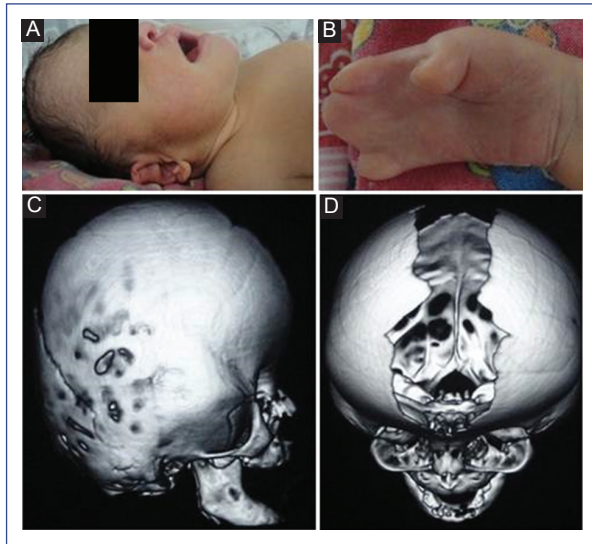
Genomic DNA of the patients and the parents were isolated from peripheral blood samples for diagnostic molecular genetic analysis by a modified non-enzymatic method from Lahiri and Nurnberger<sup>9</sup>. Amplification of genomic DNA was performed using previously described primers and conditions in a standard polymerase chain reaction<sup>10</sup>. DNA sequencing analysis was performed using the Big Dye Terminator Kit v3.1 (Applied Biosystems) and an ABI 3130XL Genetic Analyzer (ABI Prism, USA). The sequencing data were compared with GenBank (NM\_022976) sequences by using NCBI blast suite (<https://blast.ncbi.nlm.nih.gov>). Mutation nomenclature was done based on Human Genome Variations Guidelines.

## Case reports

### Case 1

A three-day-old newborn female patient with craniosynostosis and symmetric syndactyly of hands and feet. Healthy and non-consanguineous parents, a 27-year-old mother and a 24-year-old father. She was born at term at 38 weeks of gestation by vaginal delivery after a complicated pregnancy with urinary tract infection, which was treated. Weight at birth, 2,840 g (-1 standard deviation (SD)); length, 50 cm (-0.1 SD); head circumference, 38 cm (> 97<sup>th</sup> percentile). Apgar scores of 7 at 1 minute, and 9 at 5 minutes. No family history of similar alterations or any other congenital anomalies were reported.

Physical examination of the patient revealed abnormal acrocephaly, prominent frontal region, and flat occiput. She also had ocular proptosis, hypertelorism, and down-slanting palpebral fissures. In addition to these symptoms, she had midfacial hypoplasia, broad nasal root, depressed nasal bridge, thick nose with a bulbous tip, open mouth with crossbow-shaped lips and



**Figure 1.** **A.** Acrocephaly, prominent frontal region, depressed nasal bridge, bulbous tip, open mouth, low ear implantation, overfolded helix, dysplasia of the auricle and short neck. **B.** Cutaneous syndactyly of the hand. **C.** Computed tomography of the skull in 3D shows diminished anteroposterior diameter. **D.** Complete closure of both coronal sutures and diastasis of the parietal and metopic sutures.

intraorally cleft soft palate; also, low ear implantation, overfolded helix, dysplasia of the auricle and short neck (Fig. 1A). She had symmetrical syndactyly of hands (Fig. 1B), feet and bilateral pes cavus.

The newborn screening tests results were normal. 3D-Computed tomography of the skull showed asymmetry with increased cross-sectional and diminished anteroposterior diameters. Complete closure of both coronal sutures and diastasis of the parietal and metopic sutures (Figs. 1C and 1D) were observed. Besides, facial hypoplasia and hypertelorism were evident, without other alterations. Transthoracic echocardiogram showed patent foramen oval and patent ductus arteriosus with subsequent successful closure. Abdominal ultrasound was normal. The molecular genetic analysis for exons IIIa and IIIc of *FGFR2* gene (Fig. 2) revealed a heterozygous missense mutation (c.755C>G; p.Ser252Trp).

## Case 2

A two-month-old female patient with craniosynostosis and symmetric syndactyly of hands and feet. She was born at term at 40 weeks of gestation by cesarean delivery without complications. Healthy and

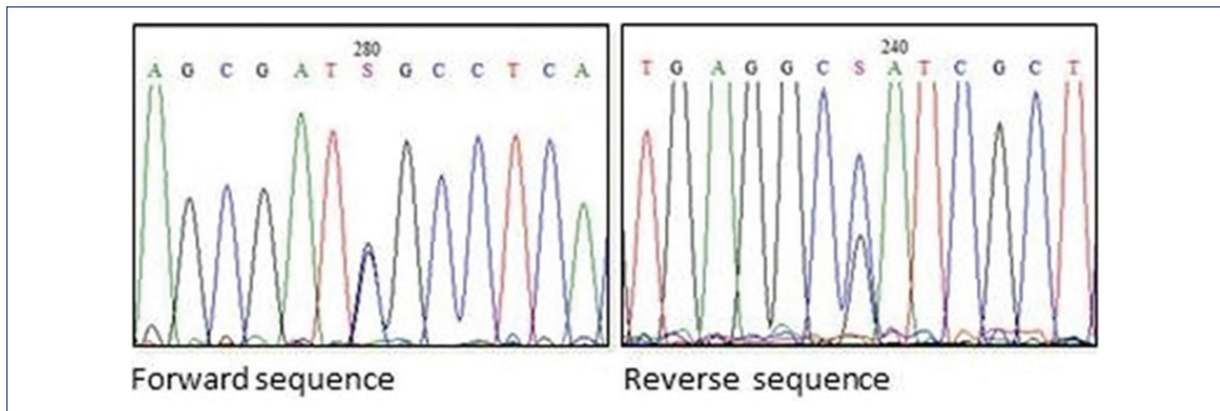
non-consanguineous parents, a 23-year-old mother and a 24-year-old father. Weight at birth, 3,390 g (0.6 SD); length, 52 cm (2.1 SD); and head circumference, 37.8 cm (> 97<sup>th</sup> percentile). Apgar scores of 8 at 1 minute, and 9 at 5 minutes. No family history of similar alterations or any other congenital anomalies were reported.

As a result of physical examination, abnormal acrocephaly, prominent frontal region and flat occiput, ocular proptosis, hypertelorism, and down-slanting palpebral fissures were observed. Additionally, the patient showed midfacial hypoplasia broad nasal root, depressed nasal bridge, thick nose with a bulbous tip, open mouth with crossbow-shaped lips and intraorally high arched palate. Short neck and symmetrical syndactyly of hands and feet were also determined (Fig. 3).

The newborn screening tests results were normal. Transthoracic echocardiogram showed large ostium secundum atrial septal defect with moderate hemodynamic repercussion and small muscular ventricular septal defect. Abdominal ultrasound was normal. Genetic analysis of the patient revealed a heterozygous mutation (c.755C>G; p.Ser252Trp) in the *FGFR2* gene.

## Discussion

Mutations in the *FGFR2* gene can be found in several syndromic craniosynostoses, including Apert (OMIM 101200), Crouzon (OMIM 123500), Pfeiffer (OMIM 101600), Beare-Stevenson (OMIM 123790) and Jackson-Weiss (OMIM 123150) syndromes<sup>1,11</sup>. Genetic mutations in AS were discovered for the first time in 1995 by Wilkie, et al.<sup>2</sup>; they occur as a result of heterozygous mutations in *FGFR2* gene located at 10q25.3-26<sup>4,7</sup>, which encodes a tyrosine kinase receptor gene that regulates multiple cellular activities, such as cell growth, differentiation, and embryonic development<sup>13</sup>. Two adjacent missense mutations—c.755C>G and c.758C>G, resulting in p.Ser252Trp (66%) and p.Pro253Arg (32%) respectively<sup>2,5,8,11,12,14</sup>—are related to AS. These mutations occur in a highly conserved region in the immunoglobulin-like extracellular subdomains of exon IIIa of *FGFR2* gene in >98% of the cases of AS<sup>8,11,14</sup>. The first mutation is tightly associated with a more severe craniofacial phenotype<sup>11,13</sup> and cleft palate<sup>13</sup>, while the second is associated with more severe syndactyly<sup>11,13</sup>. Of the two cases reported here, only case 1 presented cleft palate. Other uncommon mutations in *FGFR2* gene have been described in AS, such as c.756\_758delGCCinsCTT<sup>15</sup>, c.755\_757delCGCinsTCT<sup>16</sup>, c.755\_756CG>TC, c.755\_756CG>TT<sup>17</sup>, partial gene deletion, and Alu element insertion<sup>18</sup>.



**Figure 2.** *FGFR2* gene, forward and reverse sequences of exon 3a.



**Figure 3.** Syndactyly in both feet.

AS is an entity with an autosomal dominant inheritance pattern, with 98% of cases due to *de novo* mutations<sup>2</sup>. These causative mutations are transmitted in the paternal chromosome, which is why advanced paternal age could be a risk factor for this entity<sup>2,8,13</sup>. However, the parents of the two cases described in this article are not of advanced age.

Craniosynostosis is a group of various symptoms that exhibit distinctive clinical findings with a wide range of clinical manifestations; the severe ones could result in neonatal death. Syndromic craniosynostosis is the hereditary form of alterations of the skull associated with extracranial phenotypes such as the central nervous system, cardiac and limbs malformations<sup>8</sup>. Both of the present cases showed congenital heart disease. Therefore, it is suggested that the cardiovascular evaluation should be part of the medical studies. The significant phenotypic variability observed in AS is not only due to genetic alterations, but also the environmental

or supplemental genetic factors<sup>2</sup>. Thus, a team of clinicians and medical geneticists is required for diverse evaluations<sup>1</sup>.

Prenatal diagnosis of AS is based on the ultrasonographic findings of abnormal skull shape, which include prematurely ossified coronal sutures, widely separated metopic suture, midfacial hypoplasia, and bony or cutaneous syndactyly of extremities<sup>19</sup>. The recurrence risk of having a child with this entity for an affected parent is of 50%<sup>20</sup>. Since the presence of unaffected/healthy parents, the condition described here is accepted as sporadic. The diagnosis is usually based on the physical features of the patients, and the molecular genetic analysis may be very helpful to confirm the diagnosis<sup>4</sup>.

In the case of a patient diagnosed with AS, an interdisciplinary medical evaluation consisting of assessments by Neurosurgery, Neuropediatrics, Stimulation Therapies, Psychology, Ophthalmology, Otorhinolaryngology, Maxillofacial Surgery, Cardiology, Orthopedics, and Medical Genetics is necessary. In the cases presented here, the molecular studies performed on the parents did not show the mutation. In cases with *de novo* mutations, the risk is 50% for the descendants of those affected and not for their siblings; however, germinal mosaicism cannot be rule out.

In conclusion, two cases of AS are presented in order to highlight the differences in clinical findings. These cases were recognized by the different treating physicians who intervened in their interdisciplinary evaluation. The interpretation of the *FGFR2* mutations in patients with clinical features of syndromic craniosynostosis offers a significant benefit regarding prognosis, genetic counseling, and prenatal diagnosis.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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## Conflicts of interest

The authors declare no conflict of interest.

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