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CLINICAL SERIES

Syndromic craniosynostoses related to *FGFR* genes: clinical and molecular study

Craneosinostosis sindrómicas relacionadas con genes *FGFR*: estudio clínico y molecular

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What do we know about the subject matter of this study?

Most cases of syndromic craniosynostosis, associated with other malformations and/or deformities, are related to pathogenic variants in the *FGFR1*, *FGFR2*, or *FGFR3* genes.

What does this study contribute to what is already known?

We present a series of molecularly confirmed cases of syndromic craniosynostosis, contributing to knowledge about the distribution and clinical characteristics of these syndromes. Although no unique genetic variants or clinical manifestations were identified, the findings reinforce the usefulness of molecular diagnosis in guiding clinical management and genetic counseling.

Abstract

Syndromic craniosynostosis (SC) is characterized by the premature fusion of cranial sutures with extracranial anomalies and is associated with pathogenic variants in the genes encoding Fibroblast Growth Factor Receptors (FGFRs). In low-income countries, there are few studies on the genotype-phenotype correlation in patients with SC, which limits diagnosis and genetic counseling. **Objective:** To describe a series of cases of syndromic craniosynostosis related to *FGFR* genes, with molecular confirmation. **Patients and Method:** Descriptive case series conducted at the Genet-

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ics Institute of the *Universidad Mayor de San Andrés*, with patients diagnosed between 2017 and 2020. Demographic data, clinical findings, and syndromic diagnosis were recorded. Specific exons of *FGFR1, FGFR2*, and *FGFR3* were sequenced in DNA extracted from peripheral blood using the Sanger technique. **Results:** Nine patients were included: five with Apert syndrome, two with Crouzon syndrome, one with Pfeiffer syndrome, and one with Muenke syndrome. The median age was 3 years, with a male-to-female ratio of 7:2. Pathogenic variants were identified in *FGFR2* in seven cases and in *FGFR3* in one case, all consistent with the clinical diagnosis. One patient with a Pfeiffer phenotype was unable to complete the genetic study but met the clinical criteria for this condition. **Conclusions:** We present a case series of Crouzon syndrome (CS), with clinically delineated and molecularly confirmed diagnosis. The clinical characteristics were consistent with the genetic findings, highlighting the importance of applying evaluation protocols in patients with CS. This strengthened the diagnostic capabilities of the research center and provided a confirmatory diagnosis to guide management and genetic counseling.

Introduction

Craniosynostosis is a congenital anomaly in which there is premature fusion of one or more cranial sutures, leading to craniofacial abnormalities[1]. It can occur alongside other malformations or deformities, and when observed along with a defined and repetitive pattern of congenital anomalies attributed to a known etiology, it is considered part of a genetic syndrome, which accounts for 15% of cases[2]. When it occurs as an isolated event, it is considered a single or isolated congenital anomaly, which accounts for the remaining percentage of craniosynostosis cases[3].

Epidemiologically, craniosynostosis has an incidence at birth of 4 to 5 cases per 10,000 live births (LB)[4,5], while the incidence at birth of syndromic craniosynostosis (SCS) is 0.4/10,000 LB[6]. Of the syndromic cases, 66-70% correspond to Apert syndrome, Crouzon syndrome, Muenke syndrome, or Pfeiffer syndrome[7].

In general, SCS requires multidisciplinary teams for evaluation, follow-up, treatment, and rehabilitation. Among the activities related to basic studies for patients with SCS, genetics plays a fundamental role, considering that most cases are due to pathogenic variants in genes *FGFR1*, *FGFR2*, or *FGFR3*[2].

These genes encode fibroblast growth factor receptors (FGFR), which are normally responsible for bone cell maturation[8] by inducing cell differentiation and migration in bone growth plates[9].

In general, pathogenic variants in these genes increase ligand-binding affinity, leading to constitutive receptor activation and a gain-of-function effect compared with wild-type receptors[10,11]. This excessive activation leads to premature maturation of bone structures and closure of the growth plates in the skull and skeleton[12].

More than 50% of SCS cases are due to *de novo* variants, especially in children of older parents, while in hereditary cases, where the father or mother is affected, the autosomal dominant pattern carries a 50% risk of recurrence for each pregnancy, with varying degrees of expressivity, especially in Crouzon syndrome and Muenke syndrome[9]. Therefore, adequate evidence-based genetic counseling, including molecular studies of the patient and first-degree relatives, is essential for health promotion and prevention policies.

The objective of the study was to describe a series of cases of SCS related to the *FGFR* gene, with molecular confirmation based on Sanger sequencing of the *FGFR1*, *FGFR2*, and *FGFR3* genes for diagnostic conclusions.

Patients and Method

Descriptive cross-sectional study with intentional sample selection that included all cases with a clinical diagnosis of SCS seen at the Medical Genetics clinic of the Genetics Institute of the *Universidad Mayor de San Andrés* (UMSA) in La Paz, Bolivia, between 2017 and 2020.

The age and sex of each patient, maternal and paternal ages at birth, family history, mortality, characteristics, and clinical diagnosis were recorded, as well as the characteristics of the molecular findings of the genes studied.

Regarding the clinical diagnosis of SCS, patients were classified into four conditions: Apert syndrome, Crouzon syndrome, Muenke syndrome, and Pfeiffer syndrome. This criterion allowed us to define the gene and exon to be studied for each patient (Table 1). Patients with incomplete medical histories or without signed informed consent were excluded. After explaining the study and inviting them to participate, patients, parents, and/or guardians signed informed consent forms, medical histories were collected, and clinical examinations focused on syndromic pathology were performed.

This study was reviewed and approved by resolutions 666/17 and 562/21 of the Honorable Faculty Council of Medicine, Nursing, Nutrition, and Medical Technology of the UMSA. In addition, this study was approved by the bioethics committee of the Institute of Technical and Scientific Research of the *Universidad Policial Mcal. Antonio Jose de Sucre* under code IIT-CUP-DIC-001/17.

Molecular study

Peripheral blood (3 mL) was collected in EDTA tubes from each patient at the Center for Genetic Research (CINGEN) of the *Universidad Policial Mcal. José Antonio de Sucre*. DNA was extracted using the Wizard® Genomic DNA Purification Kit (Promega, USA) following the manufacturer's instructions. Extracted DNA was visualized on 1% agarose gel and quantified by fluorometry. According to first-line genetic testing recommendations[9] for SC, conventional PCR amplification was performed targeting specific exons of the gene associated with the clinically diagnosed SC subtype (Table 1).

After 35 amplification cycles and subsequent visualization on 1.5% agarose gel, amplicons were purified with alcohol precipitation. Unbalanced PCR was performed using the BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems USA), followed by an additional purification. Unidirectional sequencing was performed using the ABI 3500 Genetic Analyzer (Applied Biosystems) according to the manufacturer›s specifications. Genetic analysis was conducted using MEGA7[13] and Sequencing Analysis v.6.0 software, comparing sequences against ClinVar databases (http://www.ncbi.nlm.nih.gov/clinvar/), and the resulting sequences were compared with those in the GenBank (NM_000141.4 for *FGFR2* exons 8 and 10; NM_000142.4 for *FGFR3* exon 8; NM_23110.3 for *FGFR1* exon 8). The variants detected were classified according to the American College of Medical Genetics and Genomics (ACMG 2015) guidelines[14].

Finally, the results were delivered to patients and their families with genetic counseling and referral for multidisciplinary management[3,4,9].

Statistical analysis

Categorical variables were described in absolute (n) and relative (%) frequencies. Due to the small sample size, medians (m) and interquartile ranges (IQR) were obtained for quantitative variables. The percentage of cases diagnosed with each type of SCS was calculated considering all patients who were part of the study, as well as the total number of patients who attended the UMSA Medical Genetics clinic with a probable diagnosis of a genetic condition during the study period.

Results

Clinical findings

Of the 1,390 patients who attended the medical genetics clinic at the UMSA Institute of Genetics during the study period with suspected genetic conditions, 9 patients (0.65%) had a clinical diagnosis of SCS. The median age at the time of molecular diagnosis was 3.0 years (IQR: 0.4-8.0), with a male/female ratio of 7:2; 2 patients died in the neonatal stage (Apert syndrome and Pfeiffer syndrome) (Table 2). Only one case had a family history of a similar condition (Muenke syndrome), with marked variable expressivity. The median maternal age was 30 years (IQR: 27-32), and the median paternal age was 35 years (IQR: 28-46) at the time of birth. Table 3 describes in detail the clinical characteristics of each case, as well as the follow-up performed.

The common feature in all patients was craniosynostosis with varying degrees of involvement, including craniofacial dysmorphia. Extracranial manifestations varied for each SCS. While in cases of Apert syndrome, all four limbs were affected (complete syndactyly), the case with Pfeiffer syndrome only presented with broad thumbs, and the cases of Crouzon syndrome and Muenke syndrome did not present with limb manifestations. Moderate psychomotor developmental delay was evident in one case with Crouzon syndrome and in the case with Muenke syndrome. None of the reported cases presented with obvious brain malformations on neuroimaging studies.

All patients received multidisciplinary treatment and follow-up. Depending on the severity of the craniofacial condition, patients required corrective surgery, a ventriculoperitoneal shunt, or corrective limb surgery.

Molecular findings

Cases 1 and 2 were diagnosed with Crouzon syndrome. In case 1, the c.1040C>G variant was detected in exon 10 of *FGFR2*, leading to a serine-to-cysteine substitution at position 347, while in case 2, the c.1025A>G variant was detected, leading to a cysteine-to-tyrosine substitution at position 324. Cases 3, 4, 5, and 6 were diagnosed with Apert syndrome, and variant c.755C>G was detected, leading to a serine-to-tryptophan substitution at position 252 of *FGFR2*, while in case 7, also diagnosed with Apert syndrome, the variant was c.758C>G, leading to a proline-to-arginine substitution at position 253.

Case 8 had a clinical diagnosis of Pfeiffer syndrome, but the molecular study could not be performed because the patient died before a sample could be collected. In case 9 with Muenke syndrome, the c.749C>G variant was detected, leading to a proline-to-arginine

Table 1. General characteristics of syndromic craniosynostosis.

Condition	Molecular Bases	Locus	Characteristics (OMIM)
Muenke Syndrome	Gene: *FGFR3*	4p16.3 Exon:8 VP: p.Pro250Arg	*Affected suture:* Coronal *Manifestations:* Brachycephaly, macrocephaly, plagiocephaly, midface hypoplasia, sensorineural deafness, hypertelorism, downward slanting palpebral fissures, eyelid ptosis, strabismus, arched palate, dental malocclusion, clinodactyly, brachydactyly, broad hallux, psychomotor retardation, intellectual disability.
Crouzon Syndrome	Gene: *FGFR2*	10q26.13 Exons: 8, 10, with less frequency 3, 5, 14, 15, 16 y 17. VP: Cys278Phe, Trp289Gly, Tyr290Gly, Ser267Pro, Tyr328Cys, Gly338Arg, Tyr340His, Cys342Tyr, Cys342Arg, Cys342Phe, Cys342Ser, Cys342Trp, Ala344Gly, Asn549Thr, Ser347Cys, Ser354Cys	*Affected suture:* Multiple (coronal, sagittal y lambdoid). *Manifestations:* Brachycephaly, frontal protrusion, maxillary hypoplasia, prognathism, conductive hearing loss, auditory canal atresia, optic atrophy, narrow orbits, proptosis, strabismus, hypertelorism, prominent nose, sleep apnea.
Apert Syndrome	Gene: *FGFR2*	10q26.13 Exon: 8 VP: like Ser252Trp (75%) Pro253Arg (25%)	*Affected suture:* Multiple (coronal, sagittal y lambdoid). *Manifestations:* Hypertelorism, exophthalmos, strabismus, downward slanting palpebral fissures, midfacial hypoplasia, high palate, mitten-like syndactyly, cardiac and genitourinary abnormalities, gastrointestinal abnormalities, intellectual disability.
Pfeiffer Syndrome	Gene: *FGFR2* 96%	10q26.13 Exons: 8, 10 VP: Ala314Ser, Asp321Ala, Thr342Pro, Cys278Phe, Cys342Tyr, Trp290Cys, Tyr340Cys, Cys342Tyr, Cys342Arg, Cys342Ser, Cys342Trp, Ser351Arg, Val359Phe Gene: FGFR1 4% Locus 8p11.23 Exon 7 VP: p.Pro252Arg	*Affected suture:* Multiple (coronal, sagittal y lambdoid). *Manifestations:* Cloverleaf skull, hypertelorism, exophthalmos, strabismus, prominent nose, airway abnormalities, broad thumbs deviated medially, syndactyly, varying degrees of intellectual disability.

Table 2. Distribution of cases by sex, age, family history, and mortality.

Syndrome	Female (N)	Male (N)	Age at molecular diagnosis (median)	Affected family members (N)	Neonatal mortality (N)
Crouzon	1	1	9,8 years	0	0
Apert	1	4	7,0 years (3 - 9)	0	1
Pfeiffer	0	1	0 years***	0	1
Muenke	0	1	5,0 years	1	0
Total	2/9 (22,2%)*	7/9 (77,7%)*	3,0 (0,4-8,0)**	1/9 (11,1%)*	2/9 (22,2%)

*Percentage calculated based on the total number of cases (N = 9). **Median (Interquartile range). ***Newborn case.

substitution at position 250 of *FGFR3*. All these variants were interpreted as pathogenic according to the 2015 ACMG recommendations[14], causing the syndromes in these patients (Table 3 and Figure 1).

Genetic counseling

Based on these results, the corresponding genetic counseling was provided. In simple terms, it was explained that SCS is a condition that will follow an autosomal dominant pattern from the first individual diagnosed in a family, that each patient corresponds to a *de novo* mutation, and that the risk of recurrence in the children of each patient is 50% for each pregnancy, with variable expressivity, complete penetrance, and pleiotropic effects depending on each type of SCS.

Discussion

A clinical and molecular study involving nine patients was conducted. Both the clinical and molecular aspects of the series analyzed were consistent with those published in international literature, although with some differences that did not differ significantly from those reported[1,9]. The median age of patients at the time of molecular diagnosis was between 0.4 and 8 years, unlike the report by Tønne et al.[7], whose patients were younger than 6 months. However, this difference could be explained by a different methodology. Therefore, it is important to consider the phenotypic manifestations and neurological and/or functional complications of SCS, which require referral to a specialist at an early age for timely management.

Besides, the distribution by sex is consistent with what is reported in the literature, with males being more affected than females (ratio 1.8-4.7:1)[7]. It is known that in the embryonic stage, there is a different pattern of cell differentiation in female versus male osteoblasts[15]. While the sagittal and metopic sutures tend to fuse prematurely more frequently in males, coronal craniosynostosis is more prevalent in females, suggesting that estrogens are a factor that stimulates the development of cranial sutures due to the distribution of their receptors in growth plates and endochondral ossification, inducing vasculogenesis, which would explain the lower frequency of this condition in women[16].

Although in this series of cases, the average paternal age was not high, it is important to consider advanced paternal age as a risk factor[17], due to high rates of *de novo* variants in male gametes, related to a higher frequency of asymmetric mitotic divisions that generate more sperm with pathogenic variants in genes such as *FGFR3*, *FGFR2*, and RET[18]. At the functional level, pathogenic germline variants in *FGFR2* give a

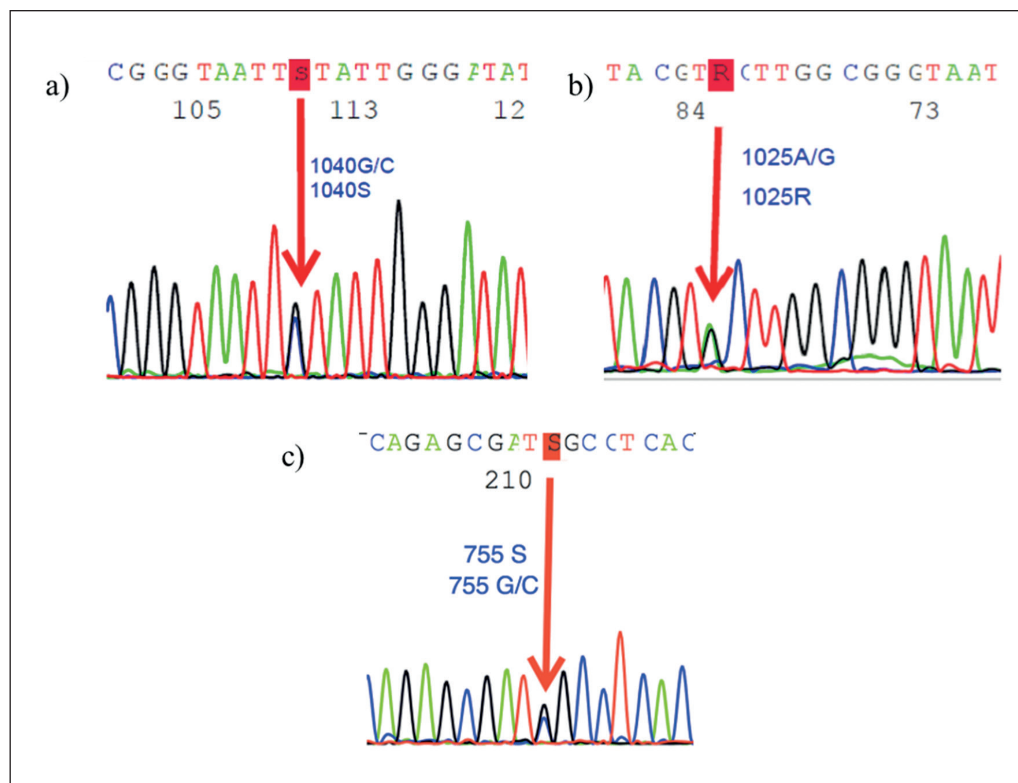

Figure 1. Electropherograms representative of the patients studied. Representative electropherograms showing double fluorescence peaks: **a)** case 1 (Crouzon syndrome) presents c.1040C>G in exon 10 of *FGFR2*, **b)** case 2 (Crouzon syndrome) corresponds to c.1025A>G in exon 10 of *FGFR2*, and **c)** cases 3, 4, and 6 (Apert syndrome) correspond to c.755C>G in exon 8 of *FGFR2*.

Table 3. Summary of clinical and molecular results obtained

Case	Sex	Facial and body dysmorphias	Affected suture	Intervention and medical follow-up	**Mutation**	**Clinical and molecular diagnosis**
1	M	Plagiocephaly, marked midface retrusion, bilateral ocular proptosis, prominent nose, low-set ears.	Coronal and parietal	Hydrocephalus (+) Corrective skull surgery performed, with shunt valve. Delayed psychomotor development. Follow-up by ophthalmology and dentistry.	c.1040 C>G p.Ser347Cys *FGFR2*, Exon 10	Crouzon Syndrome
2	F	Turribrachycephaly, bilateral ocular proptosis, telecanthus, midfacial hypoplasia, ogival palate.	Bicoronal, lambdoid and saggital.	Hydrocephalus (-) Corrective skull surgery not required. Normal psychomotor development. Follow-up by ophthalmology.	c.1025 A>G p.Cys342Tyr *FGFR2*, Exon 10	Crouzon Syndrome
3	M	Cloverleaf skull, bilateral ocular proptosis, prominent nose, low-set ears, mitten-like syndactyly in all four limbs.	Coronal, saggital and lambdoid	Hydrocephalus (+) Corrective skull surgery performed, with shunt valve. Corrective limb surgery performed. Normal psychomotor development. Follow-up by ophthalmology and dentistry.	c.755C>G p.Ser252Trp *FGFR2*, Exon 8	Apert Syndrome
4	F	Cloverleaf skull, marked bilateral exophthalmos, low-set ears, short neck and chest, with mitten-like syndactyly in all four limbs.	Coronal, saggital and lambdoid	Hydrocephalus (+) Corrective skull surgery not performed. Corrective limb surgery not performed. Dies in the neonatal stage	c.755C>G p.Ser252Trp *FGFR2*, Exon 8	Apert Syndrome
5	M	Turribrachycephaly, high forehead, bifrontal pinching, bilateral ocular proptosis, telecanthus, midfacial hypoplasia, low-set ears, ogival palate, mitten syndactyly in upper and lower limbs.	Coronal, saggital and lambdoid	Hydrocephalus (+) Corrective skull surgery performed, no shunt valve placed. Corrective limb surgery performed. Normal psychomotor development. Follow-up by ophthalmology and dentistry.	c.758C>G p.Pro253Arg *FGFR2*, Exon 8	Apert Syndrome
6	M	Turribrachycephaly, high forehead, bilateral ocular proptosis, telecanthus, midfacial hypoplasia, low-set ears, ogival palate, mitten syndactyly in all four extremities.	Coronal, saggital and lambdoid	Hydrocephalus (+) Corrective skull surgery performed, no shunt valve placed. Corrective limb surgery performed. Normal psychomotor development. Follow-up by ophthalmology and dentistry.	c.755C>G p.Ser252Trp *FGFR2*, Exon 8	Apert Syndrome
7	M	Turribrachycephaly, high forehead, bifrontal pinching, ocular proptosis, telecanthus, midfacial hypoplasia, low-set ears, ogival palate, mitten syndactyly in all four extremities.	Bicoronal, saggital	Hydrocephalus (+) Corrective skull surgery performed, with shunt valve. Corrective limb surgery performed. Normal psychomotor development	c.755C>G p.Ser252Trp *FGFR2*, Exon 8	Apert Syndrome
8	M	Cloverleaf skull, bilateral exophthalmos, clubfoot (spatula) with medial deviation in all four limbs.	Coronal, saggital and lambdoid	Hydrocephalus (+) Corrective skull surgery not performed. Dies in the neonatal stage	-----	Pfeiffer Syndrome
9	M	Generalized hypotonia, brachycephaly, mild bilateral ocular proptosis, low-set ears.	Bicoronal	Hydrocephalus (-) Corrective skull surgery not required. Delayed psychomotor development.	c.749 C>G p.Pro250Arg *FGFR3*, Exon	Muenke Syndrome

*Molecular study not performed due to lack of access to the patient sample, who died in the neonatal stage. However, it was planned to study the FGFR2 exon 10 gene, and if no pathogenic variants were found, the *FGFR1* exon 8 gene. M: Male. F: Female.

selective advantage to the mutant male gamete, with clonal expansion[19]. Therefore, the gain of function in the resulting mutant proteins would favor the survival and proliferation of the gametes expressing them[2]. However, when these pathogenic germline variants are inherited from the paternal gamete to the embryo, they would increase the mutant receptor's affinity for its ligand, leading to constitutive activation of its signaling pathway and causing premature closure of ossification sites[19].

The distribution of SCS types was consistent with that reported in various studies. Wilkie et al.[20] identified that most cases of SCS corresponded to Apert syndrome, followed in frequency by Crouzon syndrome and Muenke syndrome, and finally Pfeiffer syndrome. Similarly, Tønne E et al.[7] described a higher frequency of cases of Apert syndrome (0.1/10,000 LB) compared to the other three syndromes (0.08/10,000 LB). In any case, it is important to consider other sources of variation in the distribution of syndromic causes, such as clinical heterogeneity that determines severity, age, referral protocols for patients to genetic centers, mortality, and the sample size of this study.

It is important to note that case 9 of Muenke syndrome underwent genetic evaluation for hypotonic syndrome and psychomotor developmental delay, with subsequent evidence of dysmorphic facial features that led to the diagnostic suspicion. A minor structural condition has been proposed in cases of Muenke syndrome compared to other SCS, attributed to the spatial receptor expression, which is limited to the chondrocytes at the base of the skull[21].

The clinical characteristics of the patient series are consistent with the molecular findings, highlighting the importance of applying assessment protocols for patients with SCS, such as the one used in this study[3]. Most cases of SCS do not present significant cognitive impairments; however, they are at high risk of neurodevelopmental delay, especially in individuals with hydrocephalus and increased intracranial pressure, with improved prognosis with timely decompressive craniectomy[22]. The degree of neurodevelopmental impairment also depends on early stimulation or brain malformations associated with these syndromes, the most common being those affecting the septum pellucidum or corpus callosum[20].

On the other hand, the distribution of pathogenic variants found in this study is similar to that reported in the literature[1,9,11]. For example, in cases with Apert syndrome, we detected the two most common pathogenic variants in *FGFR2* with the expected frequencies[23]. Both variants, p.Ser252Trp and p.Pro253Arg, are associated with a wide range of phenotypes, including acrocephalosyndactyly, various forms of SCS such as Pfeiffer syndrome, McGillivray syndrome, Jackson-Weiss syndrome, and Saethre-Chotzen syndrome, as well as various neoplasms of the digestive tract[24].

In patients with Crouzon syndrome, allelic heterogeneity was observed in relation to the location of pathogenic variants detected in exon 10 of *FGFR2*. In this regard, it has been reported that 94% of pathogenic variants are in exon 8 or exon 10[25–27], so it is recommended to consider the study of the remaining *FGFR2* exons as a second line of investigation[1,26]. In the case of Muenke syndrome, the specific pathogenic variant was found that, by definition, corresponds exclusively to this genetic condition[9,27]. Together, all pathogenic variants described in *FGFR2* alter the IgIII domain of its extracellular component, causing a hyperfunctional protein with selective enhancement of ligand affinity for the receptor and the consequent constitutive activation of Ras/MAPK cell signaling pathways[11,27,28]. In addition, in Apert syndrome, an additional effect of reduced *FGFR2* ligand dissociation capacity has been described, which, according to various hypotheses, would lead to an imbalance between cellular proliferation and differentiation, with insufficient apoptosis at the ossification fronts and accelerated closure of cranial sutures and other bony structures, ultimately resulting in craniosynostosis and involvement of other skeletal structures.

Furthermore, the pathogenic *FGFR3* variant in case 9 is located at the interface between the IgII and IgIII domains of the extracellular segment of *FGFR3*, enhancing its ligand-binding capacity and, consequently, its specificity is altered, promoting regulation and proliferation of mature chondrocytes in the cartilage growth plates with accelerated bone differentiation[29], and its expression is higher in chondrocytes at the base of the skull in weeks 10 to 13 of gestation[23].

Pathogenic variants in Pfeiffer syndrome are located in exons 8 or 10 of the *FGFR2* gene in 94% of cases, with "hotspots" at cysteine residues. For example, the p.Cys278Phe variant would promote, as in previous cases, receptor dimerization and its constitutive activation, with effects at the skeletal level[29,30].

All the information obtained allowed for targeted genetic counseling for each patient's family, as well as a multidisciplinary approach, emphasizing that one of the most relevant complications of SCS is intracranial hypertension secondary to the restrictive factor of cranial growth and highlighting the importance of timely diagnosis and treatment with cranial decompression when indicated[31].

Conclusions

A molecular clinical study was conducted considering the craniofacial and bodily features that pointed to

a specific pathology, which at the same time guided the study of the *FGFR2* (exons 8 and 10) and *FGFR3* (exon 8) genes in patients with SCS. Among our findings, the clinical characteristics are consistent with the molecular results, allowing us to link clinical and molecular evaluation for adequate genetic counseling. This study allowed us to implement molecular diagnosis with Sanger sequencing to confirm clinical diagnosis, which is essential for adequate management in pediatrics and medical genetics units.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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