Case Report

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Differential Diagnosis of RASopathies. Description of a Novel Variant Causing Cardiofaciocutaneous Syndrome

Short Title: RASopathies. Novel Variant Causing Cariofaciocutaneous Syndrome

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Abstract

Cardiofaciocutaneous (CFC) syndrome is a rare RASopathy caused by RAS/MAPK pathway mutations, often overlapping clinically with Noonan and Costello syndromes, making molecular testing crucial for accurate diagnosis. We describe an infant with macrocephaly, hydrocephalus requiring shunt, axial hypotonia, hypertrophic cardiomyopathy, and mitral valve dysplasia. MRI showed ventriculomegaly and cerebellar tonsillar descent; echocardiography revealed concentric left ventricular hypertrophy. Genetic testing identified a de novo KRAS missense variant (p.Pro34Arg), a rare CFC cause (<2% cases), not previously reported in our population. This case broadens the mutational spectrum of CFC and underscores molecular analysis for diagnosis, prognosis, and genetic counseling.

Keywords: cardiofaciocutaneous syndrome; RASopathies; KRAS variant; congenital heart disease; molecular diagnosis

1. Introduction

RASopathies constitute a group of clinically and genetically heterogeneous developmental syndromes caused by germline mutations that dysregulate the RAS/MAPK signaling pathway. This pathway is crucial for normal cell proliferation, differentiation, and programmed cell death during both embryonic and postnatal development. Pathogenic activation of this cascade leads to overlapping phenotypes that include developmental delay, craniofacial dysmorphism, cardiac defects, cutaneous anomalies, and impaired growth [1].

The principal disorders in this spectrum are Noonan syndrome (NS), cardiofaciocutaneous syndrome (CFC), Costello syndrome (CS), LEOPARD syndrome, neurofibromatosis type 1, and Legius syndrome. Although they share many clinical stereotypes, the severity and distribution of specific features differ, making clinical distinction challenging, especially in infancy.

Cardiofaciocutaneous syndrome (OMIM #115150), first described in 1986, is an uncommon phenotype characterized by distinct facial appearance, dermatologic changes, congenital heart disease, and significant neurodevelopmental involvement. Mutations most frequently occur in *BRAF* (approximately three-quarters of cases), followed by *MAP2K1* and *MAP2K2*, and rarely *KRAS*. These genes encode proteins that tightly regulate the MAPK cascade; pathogenic changes lead to

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hyperactivation of ERK1/2, resulting in abnormal cell signaling, disturbed tissue development, and exaggerated phenotypes [2,3].

Clinically, diagnosis without molecular testing is difficult because of the considerable overlap with NS and CS. However, certain clues such as partial alopecia, keratosis pilaris, cutaneous hemangiomas, and hypertrophic cardiomyopathy appear more commonly in CFC and can guide diagnostic suspicion. Despite genetic heterogeneity, all RASopathies share the same disrupted molecular pathway, explaining their similarities in presentation.

Facial features evolve over time but typically in CFC include a broad or high forehead, hypertelorism, downslanting palpebral fissures, wide nasal tip, thick lips, recessed chin, and thin, arched eyebrows. Cardiac abnormalities are common; up to 80% of CFC patients present with congenital heart disease [4]. Hypertrophic cardiomyopathy is particularly frequent and can be identified at birth. Growth restriction after birth is more marked in CFC and CS than in NS, and neurodevelopmental delay tends to be moderate to severe in CFC, often associated with structural brain anomalies such as ventriculomegaly or hypoplasia of the corpus callosum [5,6]. Dermatologic findings in CFC are striking: rough, dry, ichthyotic skin; keratosis pilaris; partial alopecia; sparse curly hair; hemangiomas; and nail irregularities. Musculoskeletal features can include joint laxity or contractures, chest deformities, scoliosis, and ulnar deviations. Gastrointestinal manifestations such as reflux and feeding issues, delayed puberty, and genitourinary malformations are also possible. Although cancer risk is not absent, it is considerably lower than in CS [7].

2. Case Presentation

The proband, a one-year-old Arab boy, was the youngest of three siblings. He was born abroad at 38 weeks via vacuum-assisted vaginal delivery for failure of labor progression. His birth weight was 3.4 kg and Apgar scores were 9/10. Neonatal physical examination was unremarkable. Following relocation to Spain, he was hospitalized twice: once for a urinary tract infection, treated successfully with antibiotics, and once for gastroesophageal reflux, which resolved after a change in milk formula.

2.1. Presentation and Imaging

At seven months, the child was referred to pediatric neurosurgery due to macrocephaly with frontal prominence. He remained clinically well—alert, responsive, no irritability or vomiting—but exhibited mild axial hypotonia. Cranial CT scan revealed ventricular enlargement compatible with hydrocephalus. MRI confirmed supratentorial ventricular dilatation (Evans index of 0.54, previously 0.46), periventricular gliosis in the frontal lobes, and aqueductal dilation.

2.2. Cardiac Assessment

Echocardiography documented mild tricuspid regurgitation with normal pulmonary artery pressure, concentric hypertrophy of the left ventricle with preserved systolic function, and unobstructed left ventricular outflow. The aortic valve morphology and function were normal, with normal coronary origins. Pulmonary arteries, aortic arch, and venous return were structurally normal. No patent ductus arteriosus was detected. Electrocardiography showed sinus rhythm at 124 bpm, right-axis deviation, subtle prolongation of PR interval, signs of right ventricular enlargement, and positive T waves in precordial leads up to V1. QTc was normal.

2.3. Neurological and Developmental Examination

Neurological follow-up occurred every six months. Examination revealed frontal bossing, scaphocephaly, a mildly bulging anterior fontanelle, and low-set ears, within a facial gestalt typical of CFC. The occipitofrontal circumference measured 47.5 cm (+0.6 SD). Social engagement was appropriate, with normal eye tracking and response to auditory stimuli. Babbling was present. Motor assessment showed normal limb mobility, symmetric reflexes, and flexor plantar responses. He could not sit independently but could roll over and stand with support. Hypotonia was more pronounced

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centrally. There were no asymmetries, clonus, or abnormal movements. Metabolic screens were negative.

2.4. Genetic Testing

Standard chromosome analysis revealed a normal male karyotype (46,XY). Given suspicion of a RASopathy, targeted next-generation sequencing was performed via a custom panel including genes linked to congenital hydrocephalus, central hypotonia, and motor delay. Genomic DNA from peripheral blood underwent library preparation and hybrid capture; sequencing was performed on an Illumina MiSeq system. Mean coverage was 300×, with >99% call rate at 20× depth. Bioinformatic analysis excluded common polymorphisms (frequency <1% in gnomAD) and classified variants per ACMG-AMP guidelines.

Four rare variants were detected: three of uncertain significance in *ABCC9*, *CACNA1G*, and *DES*, and a pathogenic heterozygous *KRAS* variant c.101C>G (p.Pro34Arg). This change has been reported previously in only one de novo CFC case and is absent from population databases. ClinVar submissions largely classify it as pathogenic. Alternate substitutions at the same residue (*p.Pro34Gln*, *p.Pro34Leu*) are also pathogenic. Predictive algorithms indicated high pathogenic probability (REVEL score = 0.905). Sanger sequencing confirmed the mutation.

3. Discussion

CFC syndrome remains exceptionally rare, with roughly 300 documented cases worldwide. Clinical presentation varies but typically includes craniofacial dysmorphism, cardiac anomalies, developmental delay, dermatologic features, and feeding difficulties.

At birth, infants often exhibit a large forehead, low-set ears, ptosis, and high-arched palate. Cardiac lesions such as pulmonary valve stenosis, atrial septal defects, and hypertrophic cardiomyopathy are common. Gastroesophageal reflux and early feeding problems can cause growth failure. Hallmark skin changes include sparse, curly hair; dry, hyperkeratotic skin; and areas of hyperpigmentation or café-au-lait macules. Eye involvement such as nystagmus or optic nerve hypoplasia may impair vision. Neurologically, hypotonia, learning difficulty, delayed speech, and seizure occurrence in up to half of cases characterize the syndrome.

The principle diagnostic contenders are NS and CS. NS is comparatively common and features facial changes without the coarse appearance of CFC (Table 1). Cardiac disease often centers on pulmonary valve stenosis; hypertrophic cardiomyopathy can occur but is less prevalent. Neurological deficits are milder, and some gene subtypes carry leukemia risk. CS is rare but marked at birth by hydrops, severe feeding problems, coarse facies, fine curly hair, loose skin with papillomas, and skeletal deformities. Cardiac manifestations can include valve disease, rhythm disturbances, and HCM. Hydrocephalus and seizures are prevalent, with tumor risk notably higher.

Molecular distinctions are clear: CFC stems from *BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* variants; NS from *PTPN11*, *SOS1*, *RAF1*, *RIT1*, *LZTR1*; and CS from *HRAS*. Our patient's *KRAS* p.Pro34Arg mutation aligns with known phenotypes: macrocephaly, ventriculomegaly, hypotonia, hypertrophic cardiomyopathy, and skin changes consistent with CFC.

This case illustrates the diagnostic complexity within RASopathies. Despite superficial similarities with NS and CS, detailed evaluation across craniofacial, cardiac, neurological, and dermatologic systems supports a CFC diagnosis. The identification of a rare *KRAS* mutation reinforces genotype–phenotype correlations: KRAS-related CFC cases often present with severe nervous system involvement and pronounced cardiac hypertrophy. The rarity of such mutations underscores the need for continued reporting to refine prognostic knowledge and management strategies.

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Table 1. Comparative table. RASopathies clinical features.

Feature/ Symptom	Noonan Syndrome	Cardiofaciocutaneous (CFC) Syndrome	Costello Syndrome	LEOPARD Syndrome	This study
Common Genes Involved	PTPN11, SOS1, RAF1	BRAF, MEK1 (MAP2K1), MEK2 (MAP2K2), KRAS	HRAS	PTPN11, RAF1	KRAS
Developmental Delay	Mild to moderate	Moderate to severe	Moderate to severe	Mild or absent	Moderate
Facial Features	Triangular face, ptosis, hypertelorism	Similar to Noonan but coarser, thick lips	Coarse face, full lips	Similar to Noonan, coarse features	Thick lips
Cardiac Abnormalities	Pulmonary valve stenosis, hypertrophic cardiomyopathy	Hypertrophic cardiomyopathy, pulmonary stenosis	Hypertrophic cardiomyopathy, arrhythmias	Hypertrophic cardiomyopathy	Hypertrophic cardiomyopathy, pulmonary stenosis
Hair and Skin	Fine hair, normal skin	Dry skin, eczema, sparse or curly hair	Soft, loose skin, palmar/plantar papillomas	Multiple lentigines, café-au-lait spots	Dry skin
Short Stature	Common	Common	Common	Common	Common
Hypotonia	Mild to moderate	Prominent in infancy	Prominent	Mild or absent	Central hipotony
Pigmentary Lesions	Not typical	Absent	Absent	Present (multiple lentigines)	Absent
Gastrointestinal Issues	Common in infancy (feeding)	GERD, feeding difficulties	GERD, constipation, vomiting	Less frequent	GERD, feeding difficulties
Skin Anomalies	Mild or none	Marked (eczema, keratosis)	Redundant skin, papillomas	Lentigines	Eczema
Cognitive Function	Normal to mildly impaired	More significant delays	Variable cognitive delay	Normal to mildly affected	Mildly delay
Other Findings	Cryptorchidism, lymphedema	Seizures, ocular issues	Benign tumors, increased cancer risk	Occasional sensorineural deafness	Absent

Early recognition and genetic confirmation are vital. Management requires multidisciplinary follow-up: cardiology for surveillance of cardiac hypertrophy; neurology for developmental support; dermatology for skin concerns; ophthalmology for vision monitoring; and nutrition guidance for feeding difficulties and growth optimization. Families benefit from genetic counseling regarding recurrence risk, which is very low given the de novo nature in most cases.

Cardiofaciocutaneous (CFC) syndrome is a rare RASopathy characterized by a combination of distinctive craniofacial features, dermatologic abnormalities, congenital heart disease, and significant neurodevelopmental delay. Early clinical suspicion is challenging due to phenotypic overlap with other RASopathies such as Noonan and Costello syndromes, but molecular diagnosis through targeted genetic testing is indispensable for confirmation. The novel *KRAS* c.101C>G (p.Pro34Arg) mutation in this case expands the known pathogenic spectrum associated with *KRAS*-related CFC and highlights the importance of integrating detailed phenotypic assessment with advanced genomic testing. Early detection allows for anticipatory guidance, tailored clinical surveillance, and family counseling, improving patient care and outcomes despite the absence of curative therapy.

4. Conclusions

1. Genetic Basis—CFC syndrome arises from pathogenic variants in *BRAF*, *MAP2K1*, *MAP2K2*, or rarely *KRAS*, all affecting the RAS/MAPK signaling pathway.

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2. Distinctive Clinical Features—Common manifestations include macrocephaly, facial dysmorphism, hypertrophic cardiomyopathy, hypotonia, dermatologic changes, and developmental delay.
3. Diagnostic Challenge—Phenotypic overlap with Noonan and Costello syndromes necessitates molecular genetic confirmation for accurate diagnosis.
4. Clinical Surveillance Needs—Multisystem involvement requires a coordinated care plan, including cardiology, neurology, dermatology, ophthalmology, and developmental monitoring.
5. Novel Variant Significance—The identification of the de novo *KRAS* p.Pro34Arg mutation broadens the mutational landscape of CFC and reinforces the role of next-generation sequencing in rare disease diagnostics.

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Informed Consent Statement: Written informed consent for genetic testing and publication of anonymized data was obtained from the patient's legal guardians.

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