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Cardio-Facio-Cutaneous Syndrome Caused by a De Novo BRAF P. Gln257Arg Variant Without Cardiac Defect: A Case Report

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Abstract **Case Report**

Cardio-facio-cutaneous (CFC) syndrome is an exceptionally rare RASopathy, with fewer than 300 cases reported worldwide, caused predominantly by de novo pathogenic variants in BRAF. We report the first molecularly confirmed Moroccan case, a 4-year-9-month-old girl born to non-consanguineous parents, presenting with severe global developmental delay (absent autonomous walking, marked speech delay, intellectual disability), severe growth retardation (height 86 cm), cutaneous xerosis, and subclinical hypothyroidism (TSH 7.58 µIU/mL with normal free T4). Brain and pituitary MRI, echocardiography, EEG, and karyotype were normal. Clinical exome sequencing identified a heterozygous pathogenic missense variant in BRAF (NM_004333.6: c.770A>G; p. Gln257Arg), classified as pathogenic in ClinVar (rs180177035), confirming the diagnosis of CFC syndrome. The variant was presumed de novo given the absence of parental consanguinity and the sporadic presentation; parental Sanger sequencing was recommended for formal confirmation. This case illustrates the phenotypic variability of CFC syndrome, showing that absence of structural cardiac malformation does not exclude the diagnosis when the molecular signature is present. The concurrent subclinical hypothyroidism represents an underrecognized endocrine complication warranting systematic thyroid screening in all affected patients. This report is the first molecularly confirmed case of CFC syndrome from Morocco, contributing to the geographic expansion of the known phenotypic spectrum of BRAF-related RASopathies.

Keywords: BRAF; Cardio-facio-cutaneous syndrome; De novo variant; Developmental delay; Morocco; Phenotypic variability; RASopathy; Subclinical hypothyroidism; Whole exome sequencing.

INTRODUCTION

Cardio-facio-cutaneous (CFC) syndrome (OMIM #115150) is a rare multiple congenital anomaly syndrome belonging to the RASopathy family, a group of disorders caused by germline dysregulation of the RAS/MAPK signaling pathway [1]. First described by Reynolds *et al.,* in 1986, CFC syndrome has an estimated prevalence below 1 in 810,000 live births, with approximately 300 cases documented worldwide [2]. Around 75% of cases are caused by de novo heterozygous pathogenic variants in BRAF, with the remainder attributable to variants in MAP2K1, MAP2K2, and KRAS [3]. BRAF (OMIM #164757) encodes a serine/threonine protein kinase acting as a key effector of RAS signaling, mediating downstream activation of the MEK/ERK cascade; pathogenic missense variants produce gain-of-function dysregulation of this pathway, driving the multisystem phenotype [3,4]. Clinical hallmarks encompass craniofacial dysmorphism, ectodermal abnormalities, congenital heart defects most commonly pulmonary valve stenosis and hypertrophic cardiomyopathy and neurodevelopmental involvement including intellectual disability, hypotonia, and seizures [2,5]. Substantial phenotypic overlap with Noonan and Costello syndromes frequently complicates clinical diagnosis and mandates molecular confirmation [1]. We report the first molecularly confirmed case of CFC syndrome from Morocco, caused by a heterozygous pathogenic BRAF p.Gln257Arg variant, in a girl with global developmental delay, growth retardation, cutaneous xerosis, and subclinical hypothyroidism, but without structural cardiac malformation, a combination expanding the recognized clinical spectrum of the condition.

CASE REPORT

The proband, a 4-year-9-month-old Moroccan girl, was the only child of non-consanguineous parents

with no family history of genetic disorders or congenital malformations. Pregnancy was medically supervised and uneventful; delivery occurred at term by spontaneous vaginal delivery with a birth weight of 2,600 g. The neonatal period was complicated by a 5-day hospitalization for unspecified adaptation difficulties. She was referred for a syndromic presentation combining craniofacial dysmorphism, severe global psychomotor delay, and growth retardation. Developmental history showed markedly delayed motor milestones with absent autonomous walking at evaluation, expressive and receptive language delay, and intellectual disability; she was enrolled in a multidisciplinary rehabilitation program (physiotherapy, speech therapy, psychomotor therapy, ENT follow-up).

Serial anthropometry documented severe, progressive growth retardation: at 2 years 4 months, weight was 7.4 kg, height 73 cm, head circumference 45 cm; at 3 years 5 months, weight was 9.5 kg and height 76 cm; at the latest evaluation (4 years 9 months), height measured 86 cm all well below the 3rd percentile (Table 1). Physical examination showed craniofacial dysmorphism consistent with a RASopathy phenotype, a globally small child with reduced subcutaneous adipose tissue, diffuse cutaneous xerosis, and marked axial and peripheral hypotonia with limited purposeful upper-limb movement; osteoarticular examination and cardiac auscultation were normal.

Table 1: Serial anthropometric measurements

Age	Weight (kg)	Height (cm)	HC (cm)
2 years 4 months	7.4	73	45
3 years 5 months	9.5	76	N/A
4 years 9 months (latest)	N/A	86	N/A

Endocrine work-up revealed subclinical hypothyroidism (ultrasensitive TSH 7.58 µIU/mL, reference 0.25–5.0; free T4 19.85 pmol/L, reference 11.9–21.6); IGF-1 was normal for age, and ferritin was at the lower limit of normal (30.60 ng/mL). Complete blood count was unremarkable. Bone age, assessed by the Greulich and Pyle method, was 3 years against a chronological age of approximately 4 years (~1-year delay). Brain and pituitary MRI, abdominal ultrasonography, transthoracic echocardiography with Doppler, EEG, and constitutional karyotype (46,XX) were all normal (Table 2).

Table 2: Laboratory and ancillary investigation results with reference ranges

Parameter	Result	Reference Range
TSH (ultrasensitive)	7.58 µIU/mL (↑)	0.25–5.0 µIU/mL
Free T4	19.85 pmol/L	11.9–21.6 pmol/L
IGF-1	Normal	Age-appropriate
Ferritin	30.60 ng/mL	12–150 ng/mL
Hemoglobin	Normal	11.5–14.5 g/dL
White blood cell count	Normal	4.5–13.0 × 10^3/µL
Platelet count	Normal	150–400 × 10^3/µL
Bone age	3 years	= Chronological age
Brain MRI	Normal	—
Echocardiography	Normal no structural defect	—
Abdominal ultrasound	Normal	—
EEG	Normal	—
Karyotype	46,XX normal	—

Clinical exome sequencing, with a phenotype-directed in silico filter covering 24 genes associated with CFC syndrome and related RASopathies, identified a heterozygous pathogenic missense variant in BRAF (NM_004333.6: c.770A>G; p.Gln257Arg; chr7:140501302, hg19; ClinVar ID rs180177035), detected at high sequencing depth (95 reference/109 alternate reads) and classified as pathogenic per ACMG guidelines [6,9] (Table 3). The variant, located in the cysteine-rich domain of BRAF, has been previously reported in association with CFC syndrome, Noonan syndrome, and Costello syndrome [6]. It was presumed de novo given the absence of parental consanguinity and the sporadic presentation; parental Sanger sequencing was recommended for formal confirmation.

Table 3: BRAF variant identified by clinical exome sequencing

Parameter	Details
Gene	BRAF
Transcript	NM_004333.6
cDNA change	c.770A>G

Parameter	Details
Protein change	p.Gln257Arg
Genomic position (hg19)	chr7:140501302
Variant type	Missense (SNV)
Zygosity	Heterozygous
Sequencing depth	95 ref / 109 alt reads
ClinVar ID	rs180177035
ClinVar classification	Pathogenic
ACMG classification	Pathogenic
Disease association	CFC syndrome (OMIM #115150); Noonan syndrome; Costello syndrome
Presumed origin	De novo (parental Sanger confirmation recommended)

Following molecular confirmation, the patient was enrolled in comprehensive multidisciplinary follow-up: endocrinological monitoring of thyroid function with consideration of levothyroxine according to clinical evolution, continued neurodevelopmental rehabilitation, and scheduled ophthalmological and audiological evaluations. Genetic counseling addressed the de novo nature of the condition, a recurrence risk estimated below 1% (accounting for theoretical parental germline mosaicism), and the availability of prenatal molecular diagnosis.

Discussion

This case illustrates two clinically relevant aspects of CFC syndrome. First, the absence of structural cardiac malformation does not exclude the diagnosis when the molecular signature is present: congenital heart defects, chiefly pulmonary valve stenosis and hypertrophic cardiomyopathy, occur in about 75% of CFC cases [2,5], leaving roughly one-quarter of patients, including ours, with a structurally normal heart. This phenotypic variability is well recognized in BRAF-related CFC syndrome, though normal echocardiography still warrants serial cardiac follow-up, as hypertrophic cardiomyopathy may develop later in childhood [5]. Second, the concurrent subclinical hypothyroidism elevated TSH with normal free T4 represents an underrecognized endocrine complication attributed to the role of RAS/MAPK signaling in thyroid gland development and function [7]; it may contribute to growth retardation, cognitive impairment, and fatigue, manifestations difficult to disentangle from the primary neurological phenotype, supporting systematic thyroid screening in all newly diagnosed CFC patients [7].

The BRAF p.Gln257Arg variant lies within the cysteine-rich domain, a regulatory region involved in autoinhibition of kinase activity; substitution of glutamine by arginine at this position is predicted to disrupt autoinhibition, resulting in constitutive activation of BRAF kinase and downstream MEK/ERK signaling the molecular basis of the CFC phenotype [3,4]. The severe growth retardation observed, with a bone age delay of about one year, is consistent with the growth failure characteristic of CFC syndrome; normal IGF-1 argues against classical growth hormone deficiency, though a formal GH stimulation test may be warranted given the severity of short stature [8]. Given the significant clinical overlap between CFC, Noonan, and Costello syndromes, molecular confirmation by exome sequencing remains indispensable for definitive diagnosis [1,6], and multidisciplinary management should follow established clinical care guidelines to optimize neurodevelopmental, cardiac, and endocrine outcomes [10].

Conclusion

We report the first molecularly confirmed case of cardio-facio-cutaneous syndrome from Morocco, caused by a heterozygous pathogenic BRAF p.Gln257Arg variant. This case expands the phenotypic spectrum of CFC syndrome by documenting a presentation without structural cardiac malformation and highlights subclinical hypothyroidism as a clinically actionable endocrine complication warranting systematic thyroid screening in all newly diagnosed patients. It further underscores the indispensable role of clinical exome sequencing in diagnosing RASopathies, where clinical overlap alone is insufficient for a definitive diagnosis. Increased recognition of CFC syndrome in North African populations, as molecular genetic testing becomes more accessible, is essential for timely diagnosis, appropriate multidisciplinary management, and accurate genetic counseling.

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Conflicts of Interest

The authors declare no conflicts of interest.

Informed Consent

Written informed consent was obtained from the patient's parents/legal guardians for publication of this case report, including clinical and genetic data.

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