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CASE REPORT

Novel mutation in *ABBC9* gene associated with congenital hypertrichosis and acromegaloid facial features, without cardiac or skeletal anomalies: a new phenotype

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Introduction: Mutations in *ABCC9* are associated with Cantú syndrome (CS), a very rare genetic disorder characterized by congenital hypertrichosis, acromegaloid facial appearance (AFA), cardiomegaly, and skeletal anomalies.

Case report: We report an 8-year-old female patient with congenital generalized hypertrichosis and coarse facial appearance but without cardiovascular or skeletal compromise. Whole exome sequencing revealed a novel de novo heterozygous mutation in *ABCC9*. In addition, the genotype and phenotype of the patient were compared with those of the patients reported in the literature and with other related conditions that include AFA, hypertrichosis and AFA, and CS.

Conclusion: This is the first report of a South-American patient with mutation in *ABCC9*. We propose that her phenotype is a part of a spectrum of features associated with congenital hypertrichosis and mutations in *ABCC9,* which differs from CS and related disorders. Whole exome sequencing enabled the identification of the causality of this disease characterized by high clinical and genetic heterogeneity.

Keywords: hypertrichosis, acromegaloid features, AFA syndrome, Cantú syndrome

Introduction

Hypertrichosis is defined as increase in body hair (lanugo, vellus hair, or terminal hair) that is abnormal for a patient reference group. Hypertrichosis may be classified as congenital or acquired, with generalized or regional hair growth. Congenital hypertrichosis may be isolated or part of a syndrome that is associated with dysmorphic features or metabolic disorders. The genetic basis of hypertrichosis is not well understood. Non-androgen-related excessive growth of terminal hair is associated with several rare genetic conditions.[1] Three entities with clinical features of hypertrichosis and acromegaloid facial features have been published: 1) Acromegaloid facial appearance syndrome (AFA, MIM: 102150), 2) Hypertrichosis with acromegaloid facial appearance (HAFA, MIM: #135400), and 3) Cantú syndrome (CS), also known as hypertrichotic osteochondrodysplasia (MIM #239850). CS is the best known of these three genetic disorders. This condition was first described by Cantú et al,[2] in 1982, and is characterized by autosomal dominant inheritance, congenital hypertrichosis, distinctive coarse facial features, skeletal abnormalities, and cardiac defects.[2,3]

About 35 patients with CS have been reported in literature. CS appears to be prevalent among all populations, affecting males and females equally, and the

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disease seems to typically originate by de novo mutations.[4–7] Reported patients with AFA and HAFA syndrome have been documented occasionally with cardiac involvement, like pericardial effusion[8] and skeletal malformation, like scoliosis,[9] suggesting that cardiovascular and skeletal anomalies are not exclusive to CS. Clinical features of AFA, HAFA and CS are summarized in Table 1. Clinical overlap between CS and other genetic syndromes with hypertrichosis, including lysosomal storage disease, and poor knowledge about this disease may lead to its underdiagnosis.

In 2012, Harakalova et al[5] performed exome sequencing in 16 individuals with clinical features of CS and described a novel dominant missense mutation in the *ABCC9* gene in 14 of them. They concluded that heterozygous missense mutations in *ABCC9* cause CS.[5] Deletion/duplication type mutations have not yet been reported, and only two cases have been associated with mutations in another gene (*KCNJ8*).[10,11] *ABCC9* gene (previously known as *SUR2*) encodes a transmembrane protein that is part of an ATP-dependent potassium (K_{ATP}) channel that couples the metabolic state of a cell with its electrical activity. Two spliced forms with tissue-specific expression have been reported, namely, SUR2A, expressed in cardiac and skeletal muscles, and SUR2B, expressed in vascular smooth muscle and hair follicles. Mutations in *ABCC9* gene reduce ATP-mediated K channel inhibition, resulting in dominant channel opening. This effect of this mutation is similar to the side effects produced by treatment with K_{ATP} channel agonist (Minoxidil).[10] Only two patients with HAFA syndrome have been reported with mutations in *ABCC9*.[9]

However, CS is a part of a wide phenotypic spectrum with variable severity including, AFA, HAFA syndromes, and skeletal dysplasia or CS, which is the most severe form. We report a case of an 8-year-old girl from Colombia, with clinical features of congenital HAFA without skeletal abnormalities or cardiac involvement. Whole exome sequencing (WES) was performed in the patient, and a novel heterozygous missense, likely pathogenic variant in *ABCC9* was identified.

Case report

We report a case of an 8-year-old girl, from southwest Colombia, who was the first child of a 29-year-old mother and nonconsanguineous 34-year-old father. Pregnancy was uncomplicated, and prenatal ultrasounds were normal, without history of polyhydramnios. Vaginal delivery at the 37th week of gestation was without complications, and the birth weight was 3,650 g (94th centile) and length was 50 cm (83th centile). At birth, the proband presented neonatal respiratory distress, which required monitoring in the neonatal intensive care unit for 8 days. Clinical findings at birth included excessively thick facial hair, mainly in the forehead region, broad nose, wide mouth, full lips, umbilical hernia, and general hypertrichosis moderately distributed on the trunk and limbs. No history of patent ductus arteriosus or another congenital cardiomyopathy was detected.

The patient experienced multiple episodes of respiratory infection during childhood, which improved after turbinoplasty and adenoidectomy at 4 years of age. At 2 years of age, pubic hair appeared, and follow-up was started with a pediatric endocrinologist who ruled out androgenic hormonal disorder (with normal levels of testosterone, α-OH-progesterone, and somatomedin C). Psychomotor development was unaffected. Although she presented language development delay, she exhibited a dysarthria-like speech and mild learning disabilities; however, IQ test results were within the normal range, and she had no motor developmental concerns. Similar clinical pictures were negative in her family history.

At 8 years of age, she was assessed medically. Her weight was 27.6 kg (48th centile) and height was 128 cm (27th centile). Physical examination revealed generalized hypertrichosis mainly on the face, limbs, back region, and genitals (Figure 1). Other findings included low anterior hairline, synophrys, long eyelashes, dolichocephaly, hypoplastic nasal bones, broad nose and lips, dental malocclusion with inferior wide-spaced teeth, bilateral epicanthic folds, and AFA without corneal opacity. Osteomuscular examination revealed right fifth finger clinodactyly, bilateral sandal gap, and dorsal scoliosis.

At 7 years of age, radiological findings did not reveal any alterations of the extremities, hips, and spine. Radiography of the hand bone age correlated with her biological age. In addition, endocrinological laboratory test results were normal (thyroid-stimulating hormone, free T4, growth hormone, insulin-like growth factor-1, follicle-stimulating hormone, and leutinizing hormone). Echocardiography showed normal biventricular function, normal left ventricular size, no pericardial effusion, no pulmonary hypertension or signs of cardiomyopathy, and electrocardiogram (ECG) was within normal range. Audiometry reported mild hearing loss in the left ear. Metabolic impairment screening studies for mucopolysaccharides (mucopolysaccharide electrophoresis, enzyme activity of α-L-iduronidase, and arylsulfatase B) and quantitative chromatography of amino acids using plasma and urine revealed normal results.

Further investigation was performed using WES by trio approach with massive sequencing platform with Ion Proton™ technology. The library preparation was designed

Table 1 Summary of clinical features of reported patients with AFA, HAFA, and CS

	Clinically diagnosed			Molecularly diagnosed							
	AFA Syndrome (Hughes et al,[23] 1985; Dallapiccola et al,[24] 1992; Kini and Clayton-Smit,[25] 2004)	**HAFA Syndrome (Sun et al,[20] 2009; Canún et al,[26] 2003; Irvine et al,[27] 1996)**	**CS (Scurr et al,[28] 2011)**	**CS (Van Bon et al,[4] 2012)**	**CS (Harakalova et al,[5] 2012)**	**HAFA Syndrome (Czeschik et al,[9] 2013)**	**CS (Brownstein et al,[10] 2013)**	**CS (Cooper et al,[11] 2014)**	**CS (Afifi et al,[30] 2016)**	**CS (Fryssira et al,[29] 2017)**	**This Study**
N=	19	27	9	14	16	2	1	1	1	1	1
ABBC9 mutation	NA	NA	NA	11/14	14/16	2/2	–	–	+	+	+
KCNJ8 mutation	NA	NA	NA	–	–	–	+	+	–	–	–
Pregnancy/Birth											
Polyhidramnios	0	0	NA	NA	8/16	2/2	NA	–	NA	+	–
Birth weight >90th centile	6/19	NA	4/10	8/14	11/16	1/2	+	+	+	+	+
Clinical features											
Hypertrichosis	1/19	27/27	6/10	14/14	16/16	2/2	+	+	+	+	+
Coarse facial features	19/19	27/27	10/10	14/14	16/16	2/2	+	+	+	+	+
Macrocephaly	1/1	12/23	8/10	13/14	11/16	1/2	NA	+	–	+	+
Gingival hyperplasia	NA	2/27	4/10	7/14	NA	1/2	+	+	+	NA	+
Recurrent upper respiratory tract infections	NA	NA	7/10	4/14	8/16	2/2	NA	–	NA	NA	+
Hyperextensible joints	19/19	2/2	5/10	6/14	7/14	2/2	+	+	NA	+	+
Developmental delay	7/19	0/22	8/10	6/14	4/16	1/2	+	+	–	NA	–
Umbilical hernia	NA	NA	NA	6/14	NA	NA	+	+	NA	NA	–
Cardiac features											
Hypertrophic and or dilated cardiomyopathy	0	0	5/10	7/14	8/16	1/2	+	+	–	–	–
Cardiomegaly	0	0	8/10	10/14	5/16	1/2	+	+	–	–	–
PDA	0	0	6/10	1/14	9/16	1/2	–	+	–	+	–
Radiological findings											
Broad ribs	NA	0	10/10	8/14	9/16	0	+	+	–	NA	–
Thick calvarium	3/19	0	3/10	9/14	2/16	NA	+	+	–	NA	–
Metaphyseal flare and/or enlarged medullary canal	NA	0	7/10	10/14	1/16	NA	NA	–	–	NA	–

Abbreviations: AFA, acromegaloid-like appearance; CS, Cantú syndrome; HAFA, hypertrichosis with acromegaloid facial appearance; NA, not applicable; PDA, patent ductus arteriosus.

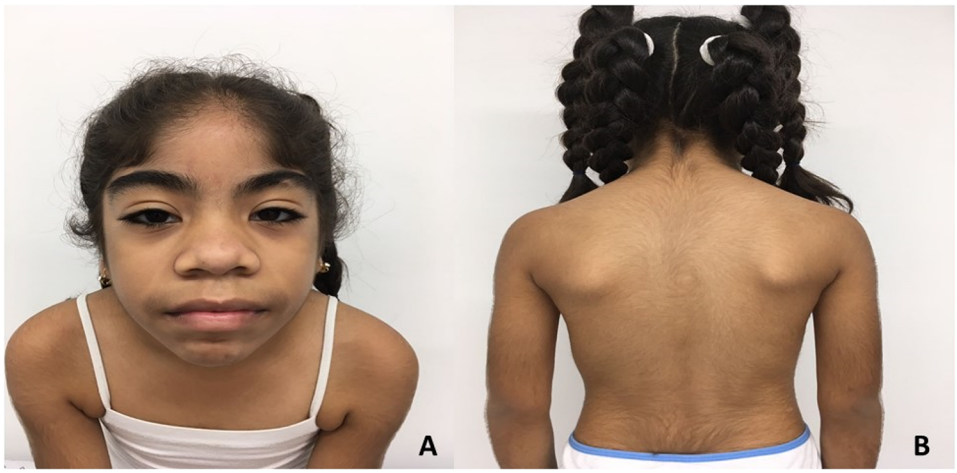

Figure 1 Patient phenotype.
Notes: (A) Coarse facial features, AFA, low anterior hairline, synophrys, long eyelashes, epicanthic folds, broad lips, bulbous nose, and broad mouth. Phenotypic similarities with CS. **(B)** Generalized hypertrichosis predominantly on back and extremities.
Abbreviations: AFA, acromegaloid-like appearance; CS, Cantú syndrome.

with Ion AmpliSeq Exome technology (Life Technologies, Carlsbad, CA, USA) which captures >97% of Consensus coding DNA sequencing (CCDS) (>19,000 genes and >198,000 exons) and flanking intronic regions (±5 bp). Only variants in the coding region and flanking intronic regions with a minor allele frequency <1.5% were evaluated. Minor allele frequencies were based on the following databases: 1,000 Genomes, dbSNP, Exome Variant Server (ESVor in-house), and Exome Aggregation Consortium (ExAc). A novel missense, likely pathogenic variant in heterozygous state in *ABCC9* (NM_005691.3) was identified: c.3625T>C (p.Tyr1209Hys) (Figure 2). This variant has not been previously reported in the literature, and the finding was confirmed by Sanger sequencing (Figure 2) and was compatible with the diagnosis of CS. Variant functional prediction software tools Mutation taster, Condel, SIFT, and FATHMM classified it as a Damaging variant (disease causing) (Table 2). Protein localization of the change is in the transmembrane domain 2 of ABCC9 (Figure 2). No additional variants were identified, including in genes associated with lysosomal storage disease, like mucopolysaccharidoses.

Ethics and consent to participate

Written informed consent was obtained from patient's parents for publication of her images and clinical data for scientific purposes. Data were collected in the context of studies performed in accordance with the Declaration of Helsinki Good Clinical Guidelines and protocol #509 "registry of surveillance and survival of congenital defects of the Colombian South-West" approved by the Ethics Committee of Universidad Icesi (Act 192/2011).

Discussion

An important feature of CS is high phenotypic variability. Neonatal characteristics including macrosomia, observed in our patient, soft tissue swelling, and edema have been reported in approximately 50% of the affected individuals.[2,3,13,14] During childhood, patients usually have low subcutaneous fat and muscular appearance,[4] but our patient did not manifest these features. The phenotypic characteristics in our proband, including coarse facial features, low nasal bridge, epicanthic folds, synophris, and broad mouth and lips, are similar to those described in previously reported cases. In addition, coarse facial features and hypertrichosis are also associated with certain lysosomal storage diseases, such as Hurler and Hunter syndromes. Therefore, a clinical diagnostic workup to rule out these pathologies is necessary.

Cardiac manifestations, including patent ductus arteriosus, ventricular hypertrophy, pulmonary hypertension, pericardial effusion, and increased vascular tortuosity, have been reported in 80% of the patients.[4,12–14] Transthoracic echocardiography and electrocardiography results were within the normal range. These findings may suggest HAFA (MIM #135400) as a diagnosis. However, only one individual with HAFA has been identified with a mutation in *ABCC9*.[9] Mutations in this gene are associated with isolated atrial fibrillation, dilated cardiomyopathy,[15] myocardial infarction,[16]

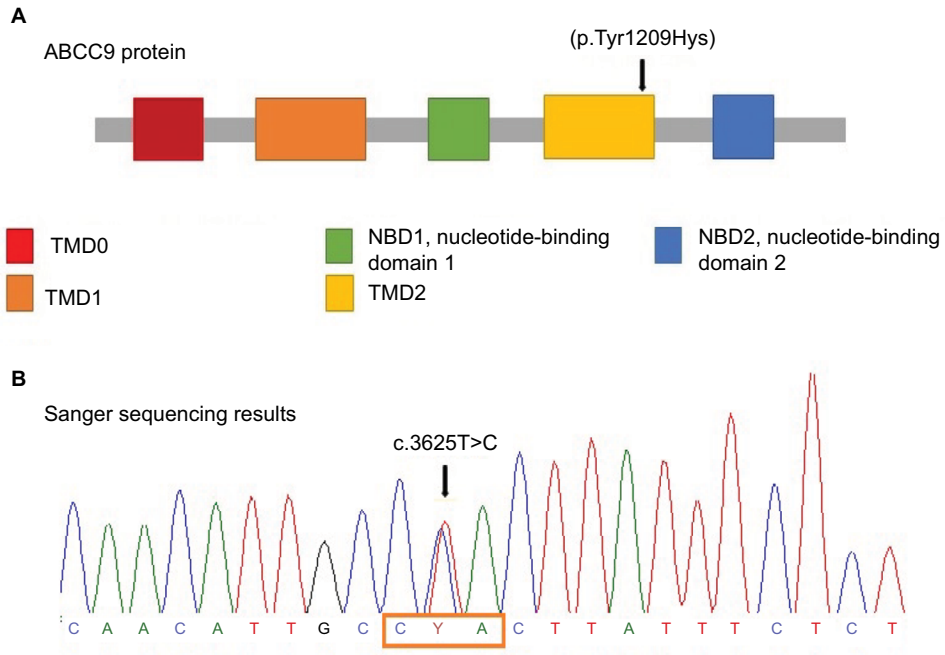

Figure 2 ABCC9 protein structure and Sanger sequencing results.
Notes: (A) ABCC9 protein structure: mutation is located on TMD2 domain. Mutations at this point result in gain of function in the KATP channel resulting in the opening of the potassium channel. The arrow indicates the novel variant that was present in the patient. **(B)** Sanger sequencing results: The box frames the affected codon and the arrow indicates the heterozygous state of the identified variant.
Abbreviation: TMD, transmembrane domain.

Table 2 Prediction of novel variant in ABCC9

Variant in this report	
Location on DNA	
Genomic position	g.21981936 T>C (on Assembly GRCh38)
Codon change	cTa/cCa
Position in DNA	c.3625T>C
Position in protein	p.Tyr1209His
Effect predictions (Variant predictor tools)[a]	
Ensembl variant effect predictor	Missense (Exon 29)
SIFT	Tolerated (Score 0.186)
Condel[b]	Deleterious (Combined score 0.541)
Mutation taster	Disease causing (Accuracy 0.999)
FATHMM	Damaging (Score –2.55)
Occurrence in public databases	
dbSNP v.150	Not present
1,000 Genomes Project	Not present
ExAC	Not present
EVSor in-house database	Not reported
Classification of variant:	
ACMG guidelines for the interpretation of sequence variants.	Likely Pathogenic (3 moderate criteria: PM2-PM5-PM6; and 2 supporting criteria: PP2-PP4)

Notes: [a]Available from: https://varsome.com/variant/hg19/ENST00000261200.4:3Ac.3625T>C. [b]Available from: http://bbglab.irbbarcelona.org/fannsdb/query/condel.
Abbreviations: ACMG, American College of Medical Genetics and Genomics; dbSNP, Single-nucleotide polymorphism database (NCBI); EVS, Exome variant service; ExAC, Exome aggregation consortium; PM, pathogenic moderate criteria; PP, pathogenic supporting criteria.

and repolarization syndrome.[17] This indicates that *ABCC9* plays a key role in K_{ATP} channels, which function primarily in the heart and smooth muscles. This phenomenon may explain that mutations could greatly affect the cardiovascular system. Previous reports have described that cardiac manifestations appear early in life, including congenital presentation of hypertrophic and/or dilated cardiomiopathy.[4,5] The absence of this feature in our proband was definitive; however, clinical follow-up is necessary regarding possible progressive behavior not previously reported.

Affected individuals with CS have skeletal abnormalities and craniofacial features including thickening of cranial vault, narrow thorax, broad ribs, long bones with metaphyseal widening of long bones, flat-ovoid vertebral bodies, enlarged medullary canals, and coxa valga.[4,13,14] Skeletal abnormalities were not found by X-ray imaging. However, clinically, the patient exhibited scoliosis. Similar to cardiac manifestations, absence of skeletal abnormalities in X-ray studies suggest that they are unlikely to appear later in life.[4,5] Other neurologic manifestations may include hypotonia, language and motor delays, and light to severe intellectual impairment.[4] In our proband, we observed mild dysarthria, without other neurological compromise. Recurrent infections in lower and upper respiratory tract appear in reported patients and in our patient.

ABCC9 gene (also known as *SUR2*) is located on locus 12p12.1 of human chromosomes and encodes a transmembrane protein of 1,549 amino acids. *SUR2* forms the regulatory part of an ATP-sensitive potassium complex that consists of four subunits of a transmembrane pore (KCNJ8). The protein has two splice variants SUR2A (expressed in cardiac and skeletal muscle) and SUR2B (expressed in smooth muscle), which contains three transmembrane cytoplasmic domains (TMD0, TMD1, TMD2), and two nucleotide binding folds (NFB1 and NFB2) (Figure 2). Mutations in CS located in ABCC9 transmembrane domain result from a gain of function in the K_{ATP} channel regulated by these subunits.[4–6,9] Therefore, missense mutations are believed to cause the opening of the potassium channel, causing metabolic and electric disequilibrium essentially in cardiomyocytes.[5,18] We identified a de novo pathogenic missense mutation c.3625T>C (p.Tyr1209Hys), which was not found in the 1,000 Genomes Project, ExAC, EVSor in-house database, and so it was considered as previously not reported. Based on the American College of Medical Genetics and Genomics (AMCG) variant interpretation guideline,[19] this variant is classified as likely pathogenic (Table 2), and was validated by Mutation taster, Condel, SIFT, and FATHMM; it is predicted to have deleterious effect. This change occurs in a genomic position highly evolutionarily conserved in vertebrates.

Two similar mutations have been reported in the TMD2 domain, which were associated with AFA and HAFA syndrome. The phenotype of these patients included AFA, gingival hyperplasia, enlarged hands and foot, and arched eyebrows, in combination with congenital severe generalized hypertrichosis.[9] In addition, the HAFA phenotype is described as having AFA, congenital hypertrichosis terminalis, and gingival hyperplasia; although the gene is unknown, it has been demonstrated that this condition is a contiguous gene syndrome, comprised on chromosomic region 17q (q24.2-q24.3).[20] The data suggest that HAFA might be related with less severe manifestations of CS, with a different genetic cause than ABCC9 and KCNJ8.[20] Despite some authors distinguishing AFA, HAFA, and CS, we suggest they should be considered as the same disorder with a variable severity in phenotype rather than as separate conditions.

Furthermore, it is important to mention that WES is an effective diagnostic tool that is useful for a geneticist to identify monogenic conditions. Exome sequencing has greatly influenced the timeframe within which new disease genes are identified. In the last decade, exome sequencing has improved diagnostic performance by more than 25%, leading to identification of disease-causing genes in cases where the diagnosis was previously unknown, and allows a complete characterization of genetic variations.[21] Confirmatory identification of the underlying genetic cause of CS mutations in ABCC9 by WES technology has been done in about 28 of 35 patients. This technology helps to clarify the spectrum of this condition and its overlap with other similar syndromes mentioned previously.[22]

Conclusion

In summary, we report on a Colombian patient with congenital hypertrichosis, acromegaloid facial features, and no skeletal abnormalities or cardiac manifestations, with a novel missense mutation in ABCC9 gene, which may suggest a wide spectrum of phenotypes associated with mutations in this gene. We propose that her mild phenotype could be similar to the patient reported by Czeschik et al[9] in 2013, and hence is suggestive of a new genetic condition. However, additional reports are needed to confirm this observation and experimental studies are necessary to demonstrate those findings.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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