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Phenotypic Variation in Patients with Homozygous c.1678G>T Mutation in EVC Gene: Report of Two Mexican Families with Ellis-van Creveld Syndrome

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Case series
Patient: —
Final Diagnosis: Ellis van Creveld syndrome
Symptoms: Conical teeth • polydactyly • short stature
Medication: —
Clinical Procedure: —
Specialty: Pediatrics and Neonatology

Objective: Rare disease

Background: Ellis-van Creveld syndrome is an autosomal recessive chondro-ectodermal dysplasia characterized by disproportionate short stature, limb shortening, narrow chest, postaxial polydactyly and dysplastic nails and teeth. In addition, 60% of cases present congenital heart defects. Ellis-van Creveld syndrome is predominantly caused by mutations in the *EVC* or *EVC2* (4p16) genes, with only a few cases caused by mutations in *WDR35*.

Case Report: Here, we report on two Mexican families with patients diagnosed with Ellis-van Creveld syndrome. Family 1 includes four patients: three females of 15, 18, and 23 years of age and a 7-year old male. Family 2 has only one affected newborn male. All patients exhibited multiple features including hypodontia, dysplastic teeth, extra frenula, mild short stature, distal limb shortening, postaxial polydactyly of hands and feet, nail dystrophy, and knee joint abnormalities. Only two patients had an atrial septal defect. In all cases, molecular analysis by Sanger sequencing identified the same homozygous mutation in exon 12 of *EVC*, c.1678G>T, which leads to a premature stop codon.

Conclusions: The mutation c.1678G>T has been previously reported in another Mexican patient and it appears to be a recurrent mutation in Mexico which could represent a founder mutation. The large number of patients in this case allows the clinical variability and spectrum of manifestations present in individuals with Ellis-van Creveld syndrome even if they carry the same homozygous mutation in a same family.

MeSH Keywords: Ellis-Van Creveld Syndrome • Genes, Recessive • Rare Diseases

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/905976

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Background

Ellis-van Creveld syndrome (EvC; OMIM: 225500) is an autosomal recessive chondro-ectodermal dysplasia, first described by Ellis and van Creveld in 1940 [1]. This syndrome is characterized by disproportionate short stature, with shortening of limbs, narrow chest, post-axial polydactyly, dysplastic nails, conical shaped teeth, and multiple frenula. In addition, congenital heart defects occur in 60% of cases [1–3]. The incidence of this condition is about 0.7 cases per 100,000 live births [4], although in some populations, like the Amish community of Pennsylvania, it is as high as 5/1,000 [5].

The large majority of Ellis-van Creveld syndrome cases are associated with mutations in either *EVC* or *EVC2* which are adjacent genes located on chromosome 4p16 [6–8]. The EVC and EVC2 proteins form a protein complex that localizes at the base of primary cilia and which acts as a positive regulator of Hedgehog (Hh) signaling, especially in chondrocytes [9–13]. Using model organisms, it has been shown that *EVC* and *EVC2* are essential for perichondrium formation and for the proliferation and differentiation of chondrocytes [8,9]. The clinical presentation of patients with mutations in either *EVC* or *EVC2* is indistinguishable, and is characterized by variable expressivity even in individuals of the same family. About 16% of Ellis-van Creveld syndrome patients have been reported with no mutations in *EVC* or *EVC2* [14]. Recently, three of these cases were found to have mutations in *WDR35* gene, which encodes a protein that is part of the IFT complex A, which is involved in the formation and maintenance of cilia and which also regulates Hh signaling [10]. Here, we report the clinical characterization of Ellis-van Creveld syndrome patients from two Mexican families and the molecular identification of the causing mutation.

Case Report

In the case of Family 1, the clinical history includes affected individuals of three generations (Figure 1). The parents of these patients (III-6 and III-7) were non-consanguineous and healthy, although two members from the paternal lineage had Ellis-van Creveld syndrome (II-2 and III-3). The paternal grandparents (II-3 and II-4) were consanguineous. Patients IV-2, IV-4 and IV-6 were females of 18, 15, and 23 years of age, respectively and patient IV-7 was a seven-year-old male. IV-5 was a miscarriage. IV-2 male and IV-7 female both died at one-year-old from unknown causes. It is important to mention that this family belonged to a very low income population from rural areas, where there was not access to hospitals or medical specialist, thus making it difficult to acquire medical records and which also explains the delay in diagnosis.

All affected individuals showed multiple clinical features (Table 1, Figure 2) including hypodontia, dysplastic teeth, multiple frenula, mild short stature, distal limb shortening, post-axial polydactyly of hands, and nail dysplasia. Chest x-rays showed abnormal morphology of the clavicle without narrow chest or short ribs. Patient IV-2 had an atrial septal defect (ASD) shown by echocardiogram, while the other patients had a structurally normal heart. Abdominal ultrasound was performed and reported normal in all patients.

In the case of Family 2, the patient was a newborn male, born at 38 weeks of gestation by cesarean section delivery with a birth weight of 2,770 g (fifth percentile) and a length of 45 cm (–4 SD WHO growth charts). The mother and father were 26 and 27 years old respectively, were both healthy and unrelated, with no relevant family history. The patient had short stature, distal limb shortening, multiple frenula, post-axial polydactyly of hands and feet, nail dysplasia, and micropenis.

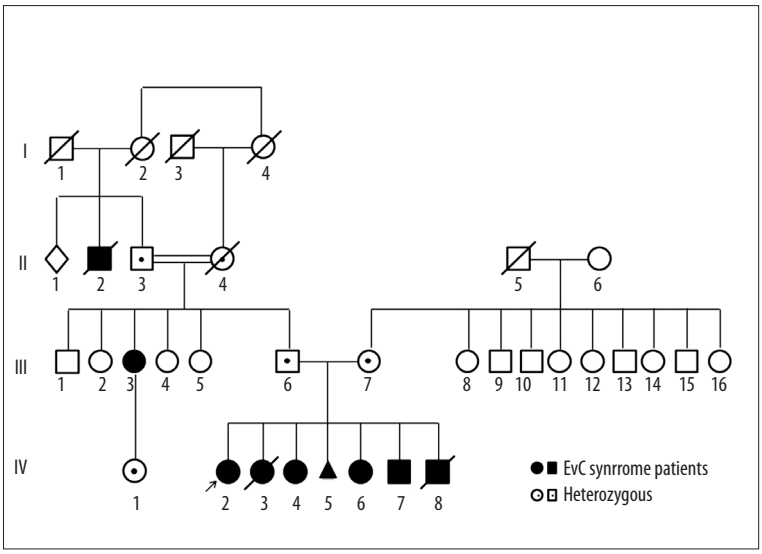

Figure 1. Pedigree of Family 1. The pedigree shows presence of Ellis-van Creveld syndrome patients in three generations.

Table 1. Clinical features of Ellis-van Creveld syndrome patients.

	IV-2	IV-4	IV-6	IV-7	Newborn (Family 2)
Age	18 years old	15 years old	13 years old	7 years old	Newborn
Sex	Female	Female	Female	Male	Male
Weight	32.7 kg (–3.4DS)	34.9 kg (–2.9DS)	26.3 kg (–3.2DS)	18.1 kg (–2DS)	2.770 kg (p3)
Length	132.8 cm (–3.8DS)	134.9 cm (–3.5DS)	133.9 cm (–3.6DS)	103.9 cm (–3.2DS)	45 cm (–4SD)
OFC	51.8 cm (p3)	51.8 cm (p3)	50.8 cm (–2.5DS)	49.7 cm (p10–25)	36.5 cm (p50)
Spam	128 cm	132 cm	128 cm	101 cm	36.5 cm
Congenital heart defects	ASD	–	–	–	ASD/ductus arteriosus
Postaxial polydactyly in hands	+	+s	+	+	+
Postaxial polydactyly in feet	–	–	+s	–	+s
Fusion of capitate and hamate	+	+	+	+	–
Genu valgum	+	–	+	+	–
Nail dystrophy	+	+	+	+	+
Conical shaped teeth	+	+	+	+	–
Multiple frenulae	+	+	+	+	+
Long narrow chest	+	+	+	+	+

ASD – atrial septum defect; OFC – occipital-frontal circumference; s – polysyndactyly.

Echocardiogram showed ASD of 6 mm and ductus arteriosus. Abdominal and pelvic ultrasound were both normal (Table 1). The patient died at five months of age of unknown causes.

The molecular analysis using Sanger sequencing of EVC and EVC2 in the proband of Family 1 (IV-2) revealed a homozygous mutation in exon 12 of EVC, NM_153717.2: c.1678G>T, which causes a premature stop codon p.(Glu560Ter).

The same mutation was confirmed in homozygosis in the other affected siblings (IV-3, IV-5, IV-6) and was found in the heterozygous state in the parents (III-6 and III-7). As no DNA of the newborn patient of Family 2 was available, mutation analysis was performed for his parents. Both parents were found to carry the same NM_153717.2: c.1678G>T mutation in the heterozygous state. Thus, we inferred that this mutation present as homozygosis in their affected son.

Discussion

EVC and EVC2 are two ciliary proteins that are not required for ciliogenesis, but are essential mediators of Hh signaling. Accordingly, Ellis-van Creveld syndrome is included in the pathological group of ciliopathies [15]. So far, more than 100 mutations have been reported in *EVC* and *EVC2,* most of which introduce premature stop codons and therefore are predicted to lead to non-functional truncated proteins [13,16].

Ellis-van Creveld syndrome is a rare condition with only around 300 cases reported [4]. However, there are very few Mexican cases reported. We have performed clinical and molecular analysis of a group of patients from two independent Mexican families and have found that all the patients have a homozygous mutation in exon 12 of *EVC*, NM_153717.2: c.1678G>T, which introduces a premature stop codon p.(Glu560Ter). Interestingly, the same mutation was previously reported by Valencia et al. [16] in another Mexican patient who was described as a compound heterozygote having in addition to the c.1678G>T change another nonsense mutation in *EVC* exon 3, also in the ExAC browser the only carrier of this variant is a Latino [17].

Family 1 showed a non-classic pedigree of autosomal recessive inheritance. However, after the molecular analysis, this pattern of inheritance could be explained by ethnic inbreeding and the consanguinity of the grandparents. A high frequency of Ellis-van

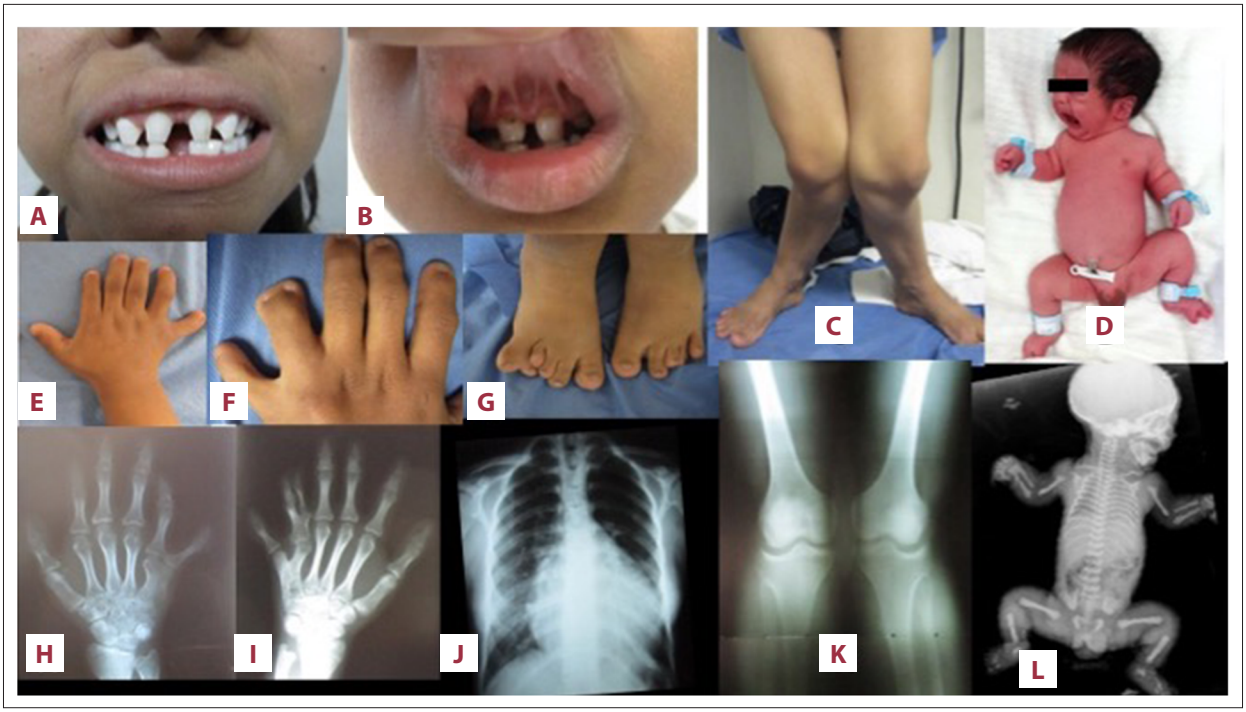

Figure 2. Clinical Features of patients with Ellis-van Creveld syndrome. (**A, B**) Patient IV-4 and IV-7 showing conical shaped teeth and multiple frenulae. (**E–G**) Showed postaxial polydactyly of hands or feet, syndactyly and nail dysplasia. (**H, I**). X-rays of the hands showed postaxial polydactyly and syndactyly, short middle, and distal phalanges with cone shaped epiphyses and carpal fusion. (**J**) Radiological abnormalities of the patient IV-2: short ribs and cardiomegaly, due to ASD. (**C, K**) The x-rays of the patient IV-6 showed lateral tibial metaphysis slanted giving rise to genu valgum deformity. (**D, L**) Male newborn from Family 2 present shortening of limbs, narrow chest, and the radiological abnormalities of the short ribs and short longs bones.

Creveld syndrome has been reported in inbreeding communities like the Amish population [5]. Our patients from Family 1 belonged to a very small rural population of less than 2,000 people, and it is likely that inbreeding and founder mutation may account for the increased frequency of cases in this family.

The analysis of carrier frequency of the c.1678G>T mutation in this population would provide valuable information about the prevalence of this recurrent mutation and would facilitate offering appropriate genetic counseling.

Parents of Family 2 were not consanguineous or related to Family 1. They live in a metropolitan area and were, nevertheless, carriers of the same mutation. The geographic region of origin of the family reported by Valencia et al. [16] is unknown; therefore, we cannot determine whether that patient was from a community near to the place where Family 1 lived. From these data, we can conclude that c.1678G>T is a recurrent mutation in Mexico.

The clinical features of the patients from our report were consistent with the previous literature. The affected individuals from Family 1 all had disproportionate short stature, which ranged from 133 cm to 135 cm (patients IV-2, IV-4, and IV-6) and similarly the newborn male of Family 2 was below normal length at birth (45 cm, –4 SD) [2,9]. The phalanges of these patients also showed disproportionate shortening, with the distal phalanges more affected than the proximal phalanges [2]. Nail dysplasia, which is one of the cardinal features of Ellis-van Creveld syndrome, was detected in all the patients. Patients IV-2, IV-6, and IV-7 had severe genu valgum, which is also frequent in patients with Ellis-van Creveld syndrome.

Bilateral postaxial polydactyly type A in hands (Figure 2), conical teeth, and multiple frenula were observed in all patients, however, only patient IV-6 and the child of Family 2 had feet polysyndactyly.

Previous studies have reported polydactyly of the feet in only 10% of the cases [2]. Patient IV-2 (Family 1) and the patient of Family 2 had an ASD, which is the most common heart defect in Ellis-van Creveld syndrome. Heart abnormalities are observed in approximately 60% of Ellis-van Creveld syndrome patients and are a major cause of morbidity in this syndrome [18]. Hh signaling, that is affected when *EVC* and *EVC2* are mutated, has been shown to play an important role in intracardiac septation [19]. Thus, it is very likely that altered Hh signaling underlies the cardiac malformations reported in Ellis-van Creveld syndrome patients [20].

Conclusions

The large number of cases in Family 1 illustrated the clinical variability and spectrum of manifestations present in individuals with Ellis-van Creveld syndrome even if they carry the same homozygous mutation. To our knowledge, this is the first report of two Ellis-van Creveld syndrome Mexican families described with both clinical and molecular findings.

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