7p15 deletion as the cause of hand-foot-genital syndrome: a case report, literature review and proposal of a minimum region for this phenotype

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Abstract

Background: Hand-foot-genital syndrome (HFGS) is a rare condition characterized by congenital malformations in the limbs and genitourinary tract. Generally, this syndrome occurs due to point mutations that cause loss of function of the HOXA13 gene, which is located on 7p15; however, there are some patients with HFGS caused by interstitial deletions in this region.

Case presentation: We describe a pediatric Mexican patient who came to the Medical Genetics Department at the National Institute of Pediatrics because he presented with genital, hand and feet anomalies, facial dysmorphisms, and learning difficulties. Array CGH reported a 12.7 Mb deletion that includes HOXA13.

Conclusions: We compared our patient with cases of HFGS reported in the literature caused by a microdeletion; we found a minimum shared region in 7p15.2. By analyzing the phenotype in these patients, we suggest that microdeletions in this region should be investigated in all patients with clinical characteristics of HFGS who also present with dysplastic ears, mainly low-set implantation with a prominent antihelix, as well as a low nasal bridge and long philtrum.

Keywords: Hand-foot-genital syndrome, HOXA13, 7p15 deletion

Background

Hand-foot-genital syndrome (HFGS; OMIM #140000) is an autosomal dominant condition that has been reported in 23 families [1–8] and 5 sporadic cases [9–12]. It is characterized by congenital limb malformations, mainly affecting the hands, such as short thumbs, and feet, as well as the genitourinary tract, such as hypospadias and cryptorchidism in males or urogenital septum and bicornate uterus in females [13]. HFGS is produced by mutations that cause loss of function of the HOXA13 gene, which is located on 7p15 and is important for the development of fetal limbs and the urinary tract. The mutations responsible for HFGS include missense mutations, nonsense mutations, polyalanine expansions, and in very few cases, interstitial deletions at 7p15. We describe a Mexican patient with HFGS caused by a 12.7 Mb deletion on chromosome 7, ranging from p15.3 to p14.3, including the HOXA13 gene. We compared previously reported patients with the purpose of determining a minimum shared region, as well as clinical characteristics that could guide the diagnosis of HFGS caused by a microdeletion.
Case presentation
The patient is a 14-year-old male, the third child of a 21-year-old mother and a 30-year-old father, both of whom are healthy and non-consanguineous. He has two healthy brothers aged 20 and 18 years old. He was born after an uneventful pregnancy; his birth weight was 2300 g (<3rd percentile), and his height was 49 cm (>15th percentile).

At 7 years old, the patient was referred to our hospital due to genital anomalies. Upon admission, a global developmental delay was detected, which was most profound in the area of language. He also presented with short stature, microcephaly, facial dysmorphisms, such as facial asymmetry, midface hypoplasia, a broad and prominent forehead, mild hypertelorism, strabismus, a broad nasal bridge, a long and smooth philtrum, a thin upper lip, a high palate (Fig. 1a), and low-set ears with a prominent antihelix (Fig. 1b). Additionally, we observed subglandular hypospadias and cryptorchidism, hands with fifth finger clinodactyly, abnormal palmar creases, and severe bilateral hallux valgus (Fig. 2a, b and 3a).

The patient's brain MRI was normal, while auditory evoked potentials revealed normal left hearing and right conductive superficial hearing loss (secondary to serous otitis media). An X-ray of the hands showed a three-year delayed bone age, feet with an absence of mid-foot bone structures, such as cuneiform bones, only cuboid and navicular bones were observed, as well as bilateral hallux valgus, which was surgically repaired at 13 years old (Figs. 2c and 3b). Karyotype and Array CGH Agilent 60 K reported a 12.7 Mb deletion at 7p14.2p15.3 (Fig. 4a and b; ISCN 2016), which was confirmed by FISH with a specific 54.95Kb probe targeted to 7p15.2 inside the deleted region (Fig. 4c). The specific nomenclature is as follows: 46,XY,del(7)(p15.2)(D7Z1+,HOXA6−,HOXA13−).arr[GRCh37/hg19] 7p15.3p14.3(22574164_35288260)x1dn (Fig. 5; ISCN 2016). Both parents were normal. Analysis of the
genomic alterations and the genotype-phenotype correlation enabled a diagnosis of hand-foot-genital syndrome.

**Discussion and conclusions**

**Clinical aspects of hand-foot-genital syndrome**

Some of the most frequent limb anomalies in HFGS are short thumbs, medial phalanges, small feet and clinodactyly of the fifth finger [13]. Hallux valgus is an important diagnostic sign, when present [11]. These anomalies have complete penetrance, but they can be so mild that imaging studies may be necessary to observe them. Short phalanges and pointed thumbs, hypoplasia of the first metacarpus and metatarsus, a small calcaneus, trapezium-scaphoid fusion, and cuneiform-navicular fusion can be observed radiologically [10]. Occasional findings include fusion of the medial and distal phalanges to the second to fifth toes [14], as well as delayed ossification [8].

It is estimated that half of the affected patients show urogenital malformations with variable expressivity. Male patients show hypospadias and cryptorchidism, while women present with a double uterus and partial or complete longitudinal urogenital septum. In the presence of any of these findings, HFGS must be investigated due to a 0.5–4% prevalence of the fusion of müllerian structures in the general population [8]. Fertility is conserved in HFGS, though there is an increased risk of spontaneous abortion, preterm birth, and stillbirth [2, 10, 11, 13].

In both genders, common findings include chronic urinary tract infections, ectopic ureteric orifices, vesioureteral reflux, and pelviureteric junction. Additionally, the disease is associated with complications, such as...
chronic pyelonephritis and renal failure, which may require transplant. Psychomotor development and cognitive abilities are within normal range [11].

Differential diagnosis to be considered are Fanconi anemia syndrome, Rothmund Thomson syndrome, Holt-Oram syndrome, SALL4-related disorders, Nager syndrome, Townes-Brocks syndrome, and Lacrimo-auriculo-dento-digital (LADD) syndrome, due to the thumb hypoplasia. Incomplete Müllerian fusion and/or longitudinal vaginal septum should be cause for consideration of acro-renal-mandibular, Bardet-Biedl, Beckwith-Wiedemann, Fraser, Fryns, Halal, and Meckel syndromes. Heterozygous mutations in the \( \text{HOXA13} \) gene cause HFGS, however the specific c.1112A > T (p.Gln371Leu) mutation causes Guttmacher syndrome which shares some, but not all, features of HFGS and includes postaxial polydactyly of the hands, preaxial hand and foot deficiencies, short second toes, and glandular hypospadias [14]. Moreover, when patients present with short or absent nails and absent or hypoplastic distal phalanges without genital anomalies, brachydactyly type B1 and Cooks syndrome, must be considered [14].

**Genetics of HFGS**

HOX genes are evolutionarily conserved; they participate in developmental processes and maintain their expression until adulthood [14]. They are organized into four clusters, \( \text{HOXA}, \text{HOXB}, \text{HOXC}, \text{and HOXD} \), localized in 7p15.2, 17q21.32, 12q13.2, and 2q31.1, respectively. They contain between 9 and 11 genes each and codify transcription factors essential for morphogenesis [2]. In particular, \( \text{HOXA13} \) has 2 exons: exon 1 contains five polyalanine regions, and exon 2 has a homeobox domain that is involved in the development of distal limbs and the fetal urogenital tract [12]. \( \text{HOXA13} \) was proposed as candidate gene for HFGS and its involvement in limb development was corroborated in murine models [15].

The first identified pathogenic variant that causes HFGS in humans was the nonsense mutation c.1107G > A (p.Trp369Ter) [15]. Since then, there have been reports of pathogenic variants in both familial and de novo cases, including missense mutations (p.Arg326Gly, p.Asn372His, p.Gln371 Leu), nonsense mutations (p.Ser1360Ter, p.Gln1960Ter, p.Gln3650Ter and p.Trp3690Ter), and triplet expansions that code for a polyalanine region (6, 8–12, and 14 additional polyalanines) [7, 12]. Approximately 35% of these variants are localized within the coding region and, of these, 50 to 60% are found in the polyalanine regions [13, 15]. The missense pathogenic variants produce a gain of function mechanism associated with a more severe phenotype, while the nonsense mutations and polyalanine expansion variants are responsible for loss of protein function, presenting a milder phenotype [15].
| Patients with microdeletion in 7p15 region | Patients with point mutations in HOXA13 |
|--------------------------------------------|------------------------------------------|
| **Patient 1** (Present case)               | **Patients with point mutations in HOXA13** |
| **Chromosomal region (size) or mutation in HOXA13 gene** |                                                                 |
| 7p14.3p15.3 (12.7 Mb)                      | p.Trp369Ter                               |
| **Neurodevelopmental delay**               | p.Asn372His                               |
| +                                          | p.Arg326Gly                               |
| **Height**                                 | p.Ile368Phe                               |
| Short stature                              |                                            |
| Normal                                     |                                            |
| **Frontal bossing**                        |                                            |
| +                                          |                                            |
| **Depressed nasal bridge**                 |                                            |
| +                                          |                                            |
| **Mild hypertelorism**                     |                                            |
| +                                          |                                            |
| **Long philtrum**                         |                                            |
| +                                          |                                            |
| **Ear anomalies**                          |                                            |
| Posteriorly rotated and dysplastic         |                                            |
| Low-set and malformed                      |                                            |
| **Hand anomalies**                         |                                            |
| Small, bilateral fifth finger clinodactyly |                                            |
| Small, bilateral fifth finger clinodactyly |                                            |
| Small, right fourth finger clinodactyly    |                                            |
| Small, bilateral fifth finger clinodactyly |                                            |
| **Feet anomalies**                         |                                            |
| Severe hallux valgus                      |                                            |
| Hypoplastic thumb, laterally deviated      |                                            |
| Small and broad thumb                      |                                            |
| Small thumb, pes planus                   |                                            |
| **Feet anomalies**                         |                                            |
| Small feet hypoplasia, hypoplastic thumb, |                                            |
| NA                                         |                                            |
| **Feet anomalies**                         |                                            |
| Small feet and short toes                  |                                            |
| Absent thumb                               |                                            |
| Small feet and short toes                  |                                            |
| Absent thumb                               |                                            |
| Small feet, right foot                    |                                            |
| Absent thumb                               |                                            |
| Small thumbs                               |                                            |
| Absent thumb                               |                                            |
| Small, right foot                          |                                            |
| Small thumbs                               |                                            |
| Normal                                     |                                            |
| **Hypospadias**                            |                                            |
| **Hypospadias**                            |                                            |
| Patients with microdeletion in 7p15 region | Patients with point mutations in HOXA13 |
|-------------------------------------------|------------------------------------------|
| Patient 1 (Present case)                   |                                          |
| Patient 2 [9] (Devriendt et al., 1999)^c  |                                          |
| Patient 3 [18] (Dunø et al., 2004)^b      |                                          |
| Patient 4 [18] (Kosaki et al., 2005)^c    |                                          |
| Patient 5 [18] (Jun et al., 2011)         |                                          |
| Patient 6 [20] (Fryssira et al., 2011)    |                                          |
| Patient 7 [17] (Hosoki et al., 2012)      |                                          |
| Patient 8 [16] (Pezzani et al., 2016)     |                                          |
| Patient 9 [16] (Pezzani et al., 2016)     |                                          |
| Patient A [2] (Mortlock & Innis, 1997)    |                                          |
| Patient B [3] (Goodman et al., 2000)      |                                          |
| Patient C [10] (Parker et al., 2011)      |                                          |
| Patient D [12] (Imagawa et al., 2014)     |                                          |

| Genital anomalies                     | Other dysmorphias                        | Patients with point mutations in HOXA13 |
|---------------------------------------|------------------------------------------|------------------------------------------|
| Cryptorchidism, hypospadias           | Facial asymmetry, strabism, thin upper lip| Double uterus and cervix                 |
| Cryptorchidism, ventral-bowed penis   | Anteverted nares, retrognathia, wide mouth, short uvula, short soft palate | Bicornis hypoplastic uterus              |
| Rectoperineal fistula                 | Anteverted nares, broad lips, upplanted palpebral fissures, broad nose |                                          |
|                                       | Broad neck, upplanted short palpebral fissures |                                          |
|                                       | Depressed supraorbital ridge on the left, maxillary hypoplasia, craniosynostosis, anal atresia |                                          |
|                                       | Accessory nipples | Bifrontal narrowing | Thin lips, micrognathia, short neck | – | – | – |
|                                       | Craniosynostosis, short palpebral fissures, epicanthus, ptosis, anteverted nostrils, micrognathia, high palate and soft-palate cleft, short neck, widely spaced nipples | Thin lips, micrognathia, short neck | – | – | – | – |

Superscript numbers indicate the references
NR Not reported
NA Not available
^ Observed in clinical picture but not referred in the corresponding article; ^CGH; ^Karyotype
Microdeletions in HFGS

Interstitial deletions including the 7p15 region are a rare cause of hand-foot-genital syndrome. To date, there are few reported patients with de novo deletions, which mostly occur between 7p15 and 7p21, with a variable size ranging from 2.5 to 12.7 Mb [9, 16–21]. We compared previously reported patients in the literature according to the genetic cause of the syndrome, polyalanine expansions, point mutations, and microdeletions; our patient was included in the latter group (Table 1). We found clinical features in patients with microdeletions that are not shared with patients carrying point mutations or those with polyalanine expansions (data not shown). Likewise, we found a minimum deleted region of 584,758 bp located at 7p15.2 that is shared by patients with HFGS. This region contains the HOXA cluster, the SKAP2 and EVX1 genes, and miRNA196b (Fig. 6).

From this analysis, we derived important phenotypic data that might suggest the presence of a microdeletion in the 7p15 region, which include the following: a) Neurodevelopmental delay or intellectual disability present in all patients with the microdeletion. HOXA1 gene is localized in the minimum shared region and is associated with central nervous system development [22]. Also, in this region is miRNA196b (Fig. 6; green circle) [22], in which the gene target NRC2 is implicated in neuronal development [23]. b) Short stature is shared by more than half of the patients (5 of 9) with the microdeletion. Both HOXA5 and HOXA11 are located within the HOXA cluster (Fig. 6; orange circle), dysregulation of which might affect growth and consequently generate short stature [22, 24]. c) Facial dysmorphias that are not present in patients with point mutations are found in 9 out of 9 patients with the microdeletion; the most common finding is dysplastic ears, particularly low-set ears with a prominent antihelix, observed in 8 out of 9 reported patients (in the ninth patient, the ears were not phenotypically described). Other facial features shared by most patients with microdeletion are a depressed nasal bridge and a long philtrum. The HOXA cluster is located within the minimum shared region and includes the HOXA1 and HOXA2 genes (Fig. 6; blue circle), both of which are related to external ear development. This has been verified in mouse models, where high Hoxa1 and Hoxa2 messenger expression levels and low mmu-miR-10a (a modulator of Hoxa1 expression during ear development) levels have been reported [25].

These genes, as members of the HOX gene family, play an important role in embryonic patterning and organogenesis, specifically in the developing region of the rhombencephalus and branchial arch [26–28]. Mouse Hoxa2 knockout models, as well as pig models with nonsense mutations in Hoxa1, have been associated with congenital microtia [29, 30].

Deleted region sizes are variable, so we looked for a minimum shared region in patients with HFGS caused by a 7p15 microdeletion to compare phenotypes and to determine if larger genomic losses cause more dysmorphisms or more severe phenotypes. We found that the patient that had the smallest deletion (2.5 Mb; including the 584,758 bp minimum shared region; Fig. 6)
[17], as well as our patient, who has the largest deletion reported so far (12.7 Mb), the classical clinical characteristics of HFGS were sufficient evidence to suggest haploinsufficiency of HOXA13, despite the absence of several other genes, responsible of a more severe phenotype, making diagnosis more difficult.

According to the information reviewed in every previously reported patient and the characteristics of our patient, we can suggest that a microdeletion in the 7p15 region must be investigated in every HFGS patient that presents with dysplastic ears, mainly low-set ears with a prominent antihelix, as well as a depressed nasal bridge and a long philtrum. Finally, the patient’s follow-up and management was based on the literature reports [16], and independent of the etiology, the recurrence risk for each pregnancy is 50% for carrier parents and less than 1% for healthy parents.

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Availability of data and materials
Authors declare that all relevant data are included in the article.

Authors’ contributions
EY and SF contributed to the design and development of the protocol, analyzed the results and wrote the manuscript. DLSP wrote the early manuscript. BM and RJ performed the G-banded karyotype. EL contributed to the protocol, clinical description and analysis of results. All authors read and approved the final version and are responsible for all aspects of the manuscript. SF and VC share the responsibility of corresponding authors for this paper.

Ethics approval and consent to participate
This study was approved by the ethics and research committees of the National Institute of Pediatrics (Mexico) (Project No. 06/2009).

Consent for publication
The parents read, accepted and signed the informed consent for the protocol and for the publication of photos and images of their son.

Competing interests
The authors declare that they have no competing interests.

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