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CASE REPORT

Novel *PORCN* mutation in a severe case of Focal Dermal Hypoplasia

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ABSTRACT **Focal dermal hypoplasia is a rare genetic disease characterized 8-year-old female who sought genetic counseling for multiple malformations, aggressive behavior and intellectual disability. Gene analysis confirmed focal dermal hypoplasia.**

Key Words: focal dermal hypoplasia, intellectual disability, *PORCN* gene

INTRODUCTION

Focal dermal hypoplasia (MIM #305600, FDH), is an unusual genetic disease that affects ectodermal and mesodermal derivatives (Suskan et al. 1990; Sacoor and Motswaledi 2005; Mallipeddi et al. 2006; Reddy and Laufer 2009; Jones et al. 2013). It is inherited as an X-linked dominant disease with females accounting for 90% of affected individuals (Jones et al. 2013). It has been determined that 5% of the affected females inherit this disease from their parents (usually the mother), since 95% of them have *de novo* mutations (Larrègue and Duterque 1975; Jones et al. 2013). The incidence of the disease is unknown (Sutton and Veyver 2013).

CASE REPORT

This is the case of an 8-year-old female from Colombia with multiple congenital malformations. She is the daughter of healthy unrelated parents, without any familial history of genetic diseases. At the time of pregnancy the mother was 23 and the father was 30 years old. She was born at 32 weeks via cesarean delivery with perinatal hypoxia that required a long-term hospitalization.

At the age of 8 years, the patient was referred to genetic counseling and physical examination revealed severe intellectual disability and evidence of auto and heteroaggressive conduct. Additionally, a weight of 12 kg, a height of 104 cm and a cephalic perimeter of 43 cm (all below < P_3) were noted. The patient exhibited facial asymmetry, left microphtalmia, low set dysplastic ears, a narrow auditory canal, bifid lower lip, oligodontia, an arborescent papilloma in the mental region, prognathism and pointed chin, anteverted nares, a narrow nasal bridge and sparse hair with patchy alopecia (Fig. 1). Moreover, the examination revealed generalized atrophy of the skin, syndactyly of the third and fourth finger of the right hand, a split left hand (Fig. 2), a cleft right foot and adactylia of the left hallux. The patient had a brain tomography at age 6 with normal results. Due to severe cognitive impairment, it was not possible to determine her intellectual quotient by any battery; however, the Barthel Index determined total dependence.

GENETIC ANALYSIS AND RESULTS

Genetic analysis was performed on high quality purified DNA. Bidirectional Sanger sequencing of the entire coding region and the highly conserved exon-intron splice junctions was performed with gene and amplicon specific primers. Polymerase chain reaction (PCR) was followed by Shrimp Alkaline phosphatase/exonuclease I treatment, and the following cycle PCR was carried out using

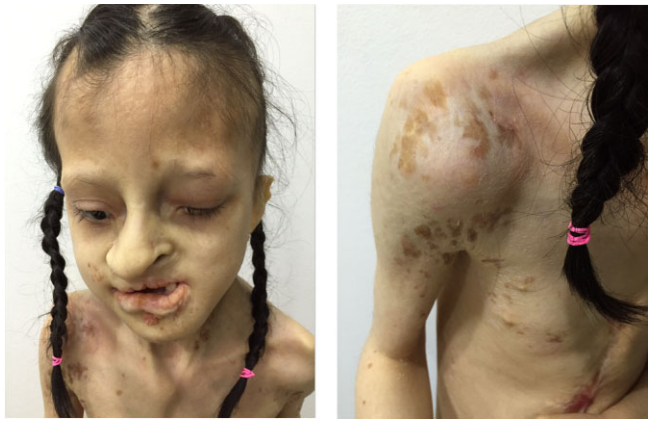

Fig. 1 Left image: a frontal view of the patient. Right image: right deltoid region. Permission was obtained from the parents for presentation.

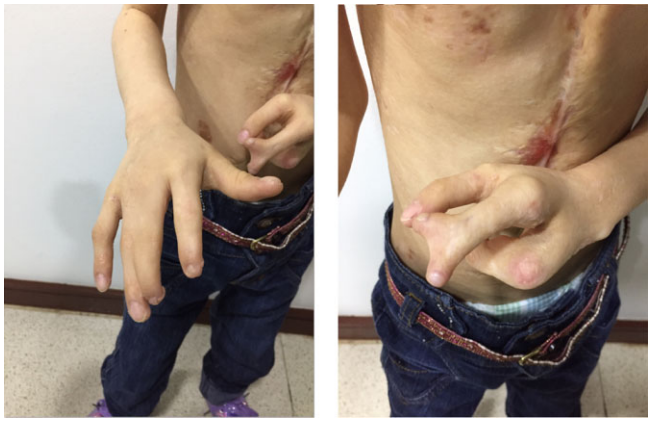

Fig. 2 Left image: the patient's right hand. Right image: the patient's left hand. Permission was obtained from the parents for presentation.

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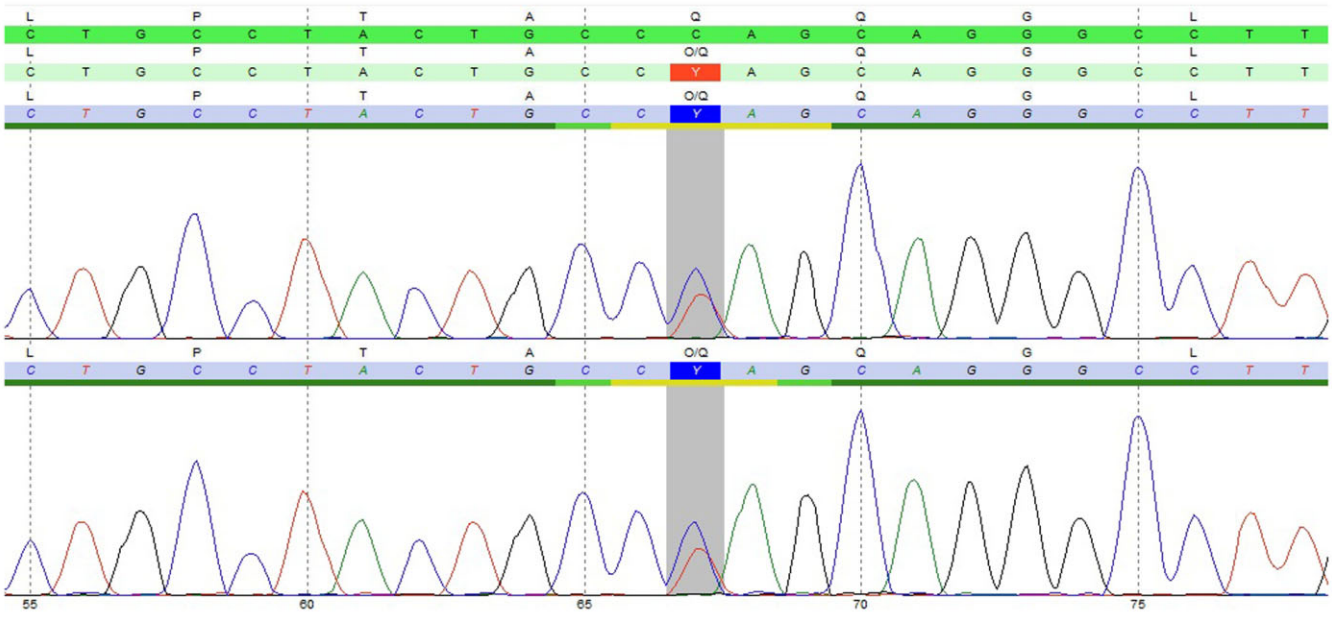

Fig. 3 *PORCN* gene analysis demonstrating the heterozygous mutation NM_203475.2(PORCN):c.67C>T(p.Gln23*). Image courtesy of Centogene.

BigDye Terminator kit v3.1 (ThermoFisher Scientific, Waltham, MA, USA) and subsequent purification. Sequencing was performed using ABI 3730xl sequencer (ThermoFisher Scientific). The test has been developed and validated by *Centogene AG* for clinical purposes only. Reference sequence is of *PORCN* gene is NM_203475.2.

The heterozygous nonsense mutation NM_203475.2(PORCN): c.67C>T(p.Gln23*) was detected in exon 2 on the patient genetically diagnosing FDH (Fig. 3); the gene analysis for the mother was normal.

DISCUSSION

Focal dermal hypoplasia is a rare disease, with clinical features that include atrophy and linear pigmentation of the skin, localized cutaneous deposits of superficial fat, papillomas in the mucous membranes or in the skin, digital anomalies, oral abnormalities, ocular anomalies and in 15% of cases intellectual disability (Mass et al. 2009; Sutton and Veyver 2013).

The patient carries the novel heterozygous mutation NM_203475.2(PORCN):c.67C>T(p.Gln23*) (Clements et al. 2008, 2009; Froyen et al. 2009; Leoyklang et al. 2008; Bornholdt et al. 2009; Lombardi et al. 2011; Arias-Llorente et al. 2015). Table 1 evidences the phenotypic similarities between the patients described by Maas and collaborators (Mass et al. 2009) and the patient in the present report; nevertheless, the patient exhibits severe intellectual impairment, which is not a common finding. FDH does not exhibit an evident genotype-phenotype correlation (Mass et al. 2009). After considering she has a normal brain CT scan, the severe intellectual disability can be due to prematurity, perinatal hypoxia, complications derived from a prolonged hospitalization after birth and the lack of schooling.

Patients with FDH and their families must receive genetic counseling and a parental carrier testing; in this case, confirming a *de novo* mutation in the patient. It is imperative to consider that in familial cases, affected females inherit this mutation from the mother (Shimaoka et al. 2009). During conception, there is a 50% risk that the mutant allele for *PORCN* will be transmitted, and if one takes into account that most male fetuses will be spontaneously aborted, the expected outcomes of the pregnancy are the following: 33% unaffected females, 33% affected females and 33% unaffected males; on the contrary, if the affected female has a somatic

Table 1 Phenotypical comparison between focal dermal hypoplasia (FDH) patients (Mass et al. 2009)

Patients with focal dermal hypoplasia (FDH)	17	1
Reference	Maas et al.	Present report
Gender	m, f	f
Mutation in *PORCN* gene	14/17	Present
Height <P3-P10	11/17	Yes
Sparse scalp hair	13/17	Yes
Unitaleral microphtalmia	7/17 Unilateral	Unilateral (left eye)
Unilateral Coloboma	6/17 Unilateral	Unilateral (right eye)
Cleft lip/palate anomalies	4/17	Both present
Oligodontia	4/17	Present
Acral abnormalities	15/17	Four limbs affected
Oligodactyly	13/17	Present
Syndactyly	11/17	Present
Nail hypoplasia	14/17	Present
Skin hipoplasia	17/17	Present
Papillomas	9/17	Present
Severe intellectual disability	1/17	Present

mosaicism mutation, the risk of her descendants may be as high as 50% (Sutton and Veyver 2013). On the other hand, affected males have a somatic mosaicism for mutations in *PORCN*; hence, the risk of affected daughters is as high as 100% and for sons is 0% (Sutton and Veyver 2013).

When comparing literature of previously reported FDH cases to the present case, many phenotypical similarities are observed; however, severe intellectual disability and auto/heteroaggressive behaviors are not common. This leads to the question if this new undocumented mutation is related with such traits.

DISCLOSURES

None.

REFERENCES

Arias-Llorente RP, Rodriguez-Dehli C, López-Martínez A et al. 2015. Focal Dermal Hypoplasia Due to De Novo Mutation c.1061T>C(p.Leu354Pro) in the PORCN Gene: Importance of Early Diagnosis and Multidisciplinary Follow-Up. Fetal Pediatr Pathol 34(6):375–382.

Bornholdt D, Oeffner F, König A et al. 2009. *PORCN* mutations in focal dermal hypoplasia: coping with lethality. Hum Mutat 30:E618–E628.

Clements SE, Mellerio JE, Holden ST et al. 2009. *PORCN* gene mutations and the protean nature of focal dermal hypoplasia. Br J Dermatol 160:1103–1109.

Clements SE, Wessagowit V, Lai-Cheong JE et al. 2008. Focal dermal hypoplasia resulting from a new nonsense mutation, p.E300X, in the *PORCN* gene. J Dermatol Sci 49:39–42.

Froyen G, Govaerts K, Van Esch H et al. 2009. Novel *PORCN* mutations in focal dermal hypoplasia. Clin Genet 76:535–543.

Jones KL, Jones MC, Del Campo M. 2013. Smith's recognizable patterns of human malformation, 7th edn. Philadelphia: Elsevier Saunders.

Larrègue M, Duterque M. 1975. Letter: striated osteopathy in focal dermal hypoplasia. Arch Dermatol 111:1365.

Leoyklang P, Suphapeetiporn K, Wananukul S et al. 2008. Three novel mutations in the PORCN gene underlying focal dermal hypoplasia. Clin Genet 73:373–379.

Lombardi MP, Bulk S, Celli J et al. 2011. Mutation update for the *PORCN* gene. Hum Mutat 32:723–728.

Mallipeddi R, Chaudhry SI, Darley CR et al. 2006. A case of focal dermal hipoplasia (Goltz) syndrome with exophytic granulation tissue treated by curettage and photodynamic therapy. Clin Exp Dermatol 31:228–231.

Mass SM, Lombardi MP, Van Essen AJ et al. 2009. Phenotype and genotype in 17 patients with Goltz-Gorlin Syndrome. J Med Genet 46:716–720.

Reddy J, Laufer MR. 2009. Congenital Anormalities of the female reproductive tract in a patient with Goltz syndrome. J Pediatr Adolesc Gynecol 22:71–72.

Sacoor MF, Motswaledi MH. 2005. Three cases of focal dermal hypoplasia (Goltz syndrome). Clin Exp Dermatol 30:35–37.

Shimaoka Y, Hatamochi A, Hamasaki Y et al. 2009. Severe focal dermal hypoplasia in a female patient transmitted from a mildly affected mother. J Dermatol 36:181–183.

Suskan E, Kurkcuoglu N, Uluoglu O. 1990. Focal dermal hipoplasia (Goltz syndrome) with horseshoe kidney abnormality. Pediatr Dermatol 7:283–286.

Sutton V, Veyver I. 2013. Focal Dermal Hypoplasia. University of Washington, Seattle. [online] Available at: http://www.ncbi.nlm.nih.gov/books/NBK1543/ [Accessed 19 Aug 2015].