A Novel Mutation in the PORCN Gene Underlying a Case of Almost Unilateral Focal Dermal Hypoplasia

Diane Maalouf, MD; Hala Mégarbaneé, MD; Eliane Chouery, PhD; Joanna Nasr, MD; Catherine Badens, MD; Caroline Lacoste, MS; Karl-Heinz Grzeschik, MD, PhD

Background: Focal dermal hypoplasia (also known as Goltz syndrome) is an X-linked dominant syndrome characterized by patchy hypoplastic skin with soft-tissue, skeletal, dental, and ocular defects that are secondary to mutations in the PORCN gene. To our knowledge, only 5 cases of focal dermal hypoplasia with unilateral presentation have been reported, and molecular studies were not performed in any of the cases.

Observations: A 17-year-old girl was seen with features of almost unilateral focal dermal hypoplasia. These included left cleft hand, dental dysplasia, left mammary hypoplasia, deviation of the sacral line, raspberrylike papillomas in the perianal region, syndactyly of the second and third digits of the left foot, and linear streaks of dermal hypoplasia and pigmented lesions on her left hemibody.

Conclusions: Mutation analysis of PORCN revealed a novel heterozygous mutation in exon 10, c.854-855insACCTGAC; [p.T285fsX316], resulting in a premature stop signal. Analysis of the X-chromosome inactivation status was performed on blood and skin DNA samples, showing random inactivation in blood and unaffected skin and skewed inactivation in affected skin, highlighting the role of X-chromosome inactivation in X-linked disease expression.


Focal dermal hypoplasia (also known as Goltz syndrome) is an X-linked dominant genodermatosis characterized by developmental defects in ectodermal and mesodermal structures, leading primarily to patchy hypoplastic skin and pigmentary changes, often following Blaschko lines, with skeletal, ocular, and dental malformations. It is secondary to mutations in the PORCN gene (OMIM 300651) located on chromosome Xp11.23. PORCN encodes an O-acyltransferase involved in the palmitoylation and secretion of Wnt signaling proteins that are required for embryonic tissue development, notably for fibroblast proliferation and osteogenesis. Among more than 100 patients with focal dermal hypoplasia described in the literature, only 5 had unilateral presentation, and molecular studies were not performed in any of the cases.

In this case report, a Lebanese girl with almost unilateral focal dermal hypoplasia and a novel heterozygous mutation is described. X-chromosome inactivation status in blood and skin samples was examined to further delineate the lateralization pattern.

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Figure. Present case. A, Atrophic lesions and pigmentary changes on the left side of the back. B, Abnormally shaped and irregularly spaced teeth. C, Left cleft hand. D, Syndactyly of the second and third digits of the left foot.

Table. Summary of Findings in Cases of Unilateral Focal Dermal Hypoplasia Reported in the Literature and in the Present Case

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<td>Sex</td>
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<td>Side of the body involved</td>
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<td>Linear skin lesions</td>
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<td>Dermal hypoplasia</td>
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Abbreviations: −, negative or absent; +, positive or present.
Gene sequence analysis was performed on the PORCN gene. After informed consent was obtained, genomic DNA was extracted from peripheral leukocytes, and the 14 coding exons of PORCN were amplified. A novel heterozygous mutation was detected in exon 10, c.854-855insACCTGAC; [p.T285fsX316], resulting in a premature stop signal. This mutation was confirmed by single-strand confirmation polymorphism analysis and was not found in 100 unrelated control subjects.

X-CHROMOSOME INACTIVATION ANALYSIS

Analysis of the X-chromosome inactivation status pattern using the human androgen receptor methylation assay was performed on blood and skin DNA samples.12 The X-chromosome inactivation pattern in DNA isolated from blood identified random inactivation, with a ratio of 30:70. Using a kit (QIAGEN, Studio City, California), DNA was then extracted from small skin samples of affected and unaffected sites. The DNA from apparently healthy skin of the right arm showed random inactivation (45:55 ratio). On the affected (left) side, there was skewed inactivation in DNA extracted from an atrophic hyperpigmented lesion of the left arm (87:13 ratio) and borderline random inactivation in DNA extracted from apparently healthy skin of the left arm (75:25 ratio).

A female patient having focal dermal hypoplasia with classic features of the disease also had mammary hypoplasia and cleft hand, which are rare.3,13 Her skin lesions were predominantly on the left side of the body. Only 5 cases of focal dermal hypoplasia with unilateral presentation have been previously reported, 1 boy and 4 girls (Table). There was no preferential left-sided or right-sided unilateral involvement. Four patients had asymmetric skeletal defects, and 3 girls had ocular anomalies. Molecular studies were not performed in any of these cases. In the present case, a novel heterozygous frameshift mutation in exon 10 of PORCN, resulting in a premature stop signal, was encountered. Six cases with exon 10 mutations have been reported.3,14-17 Clinical comparison showed no genotype-phenotype correlation, which can be secondary to lyonization or postzygotic mosaicism or various environmental and epigenetic factors.3,4

To better understand the lateralization pattern seen in our patient, we performed X-chromosome inactivation studies on blood and skin DNA samples from both sides of her body. X-chromosome inactivation has been previously studied using DNA derived from peripheral leukocytes of patients with focal dermal hypoplasia.3,14-20 Patients with de novo point mutations usually demonstrated random inactivation, whereas patients with familial focal dermal hypoplasia and all patients with microdeletions encompassing PORCN and neighboring genes showed extreme skewing, possibly to allow the viability of individuals with such deleterious mutations. As expected in the present case, a random pattern of X-chromosome inactivation was identified in blood and in skin on the right side of the body. However, on the left side, there was consistent preferential bias to inactivate 1 of the 2 alleles, and skewed X-chromosome inactivation was found in DNA extracted from an atrophic skin lesion. It is probable that the bias observed on the affected side is due to an expansion of cells carrying the active mutated X, leading to the left-sided distribution of the disease features. Another explanation for this lateralization pattern is somatic mosaicism, resulting from an early somatic mutation in the precursor cells on the left side of the body. In this case, X-chromosome inactivation would be superimposed on the mosaicism and cause Blaschko lines.

In conclusion, more case reports and further molecular studies of patients with unilateral focal dermal hypoplasia are warranted. Examination of differential X-chromosome expression in involved tissues will better correlate the X-chromosome inactivation pattern and the observed phenotype.

Accepted for Publication: August 24, 2011.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Maalouf, H. Mégarbané, and Nasr.

Analysis and interpretation of data: Maalouf, H. Mégarbané, Badens, and Grzeschik.

Drafting of the manuscript: Maalouf and A. Mégarbané.

Critical revision of the manuscript for important intellectual content: Badens, Grzeschik, and A. Mégarbané.

Administrative, technical, or material support: Chouery, Badens, and Lacoste.

Study supervision: A. Mégarbané.

Financial Disclosure: None reported.

Funding/Support: This study was supported by Université Saint Joseph.

REFERENCES


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**Notable Notes**

Tonsuring and the Western Wig and Hair Extension Market

Tonsuring is a ritual hair offering that is performed worldwide by pious populations, particularly some Hindu groups in South India. As recently publicized by comedian Chris Rock’s HBO documentary, *Good Hair*, devotees customarily donate an entire head of shaved hair in return for purification, honor, and good fortune. Each day in South India, more than 50,000 men, women, and children flock to the temple in Tirupati to partake in Chudakarana (tonsuring ceremony). The temple's authorities auction the collected hair, which is then cleansed, processed, and sold in the West for wigs and hair extensions, an industry that generates more than a billion dollars annually. Many tonsured participants know of the entrepreneurial market for their tresses, yet the tonsuring tradition prevails among certain Hindu communities, which expect followers to complete the saintly task.

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