Focal dermal hypoplasia: report of a Taiwanese case

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CASE REPORT

Focal dermal hypoplasia (FDH), or Goltz syndrome (OMIM 305600), first described by Goltz in 1962 and Gorlin in 1963, is a rare X-linked dominant ectodermal and mesodermal disease involving the skin, distal limbs, and eyes. About 95% of the cases appear de novo, and 90% are females. Recent studies reveal that FDH is caused by mutations in the PORCN gene. Female patients are either heterozygous or mosaic for PORCN mutations, whereas all male patients are mosaic. About 5% of the female patients analyzed have no detectable mutations or microdeletions of PORCN gene. We report a sporadic case of FDH in a 16-year-old girl presenting with atrophic or erythematous macules and patches distributed along the lines of Blaschko over the trunk and extremities with prominent soft yellowish fat herniation over the left axilla and left groin, and papillomas in the oral and genital areas.

Multiple developmental anomalies of the digits and ear were also noted. Histopathology of the skin lesion revealed severe dermal hypoplasia. Mutation analysis of all coding regions and flanking intron boundaries of the genomic DNA revealed no detectable mutation of the PORCN gene. Our case manifested mucocutaneous and multiple developmental anomalies typical of FDH, but no mutation in the PORCN gene was detected by mutation analysis.

Keywords:
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Goltz syndrome
Pathology
PORCN mutation

Introduction

Focal dermal hypoplasia (FDH), or Goltz syndrome (OMIM 305600), first described by Goltz in 1962 and Gorlin in 1963, is a rare ectodermal and mesodermal disease characterized by patchy dermal hypoplasia along the lines of Blaschko with herniation or deposition of subcutaneous fat into the dermis. Other mucocutaneous lesions include papillomas, dystrophic nails, and sparse brittle hair. Patients with FDH often have various developmental anomalies of the limbs, eyes, and head, including ectrodactyly, syndactyly, brachydactyly, oligodactyly, anophthalmia/microphthalmia and coloboma, facial asymmetry, ear abnormalities, notched alae nasi, cleft lip and palate, and pointed chin. Herein, we report a case of FDH with typical clinical and pathologic findings.

Case report

A 16-year-old Taiwanese girl presented to our clinic with generalized skin lesions since birth. Examination revealed numerous hypopigmented atrophic or erythematous macules and patches with telangiectasia, distributed in a whorled pattern along the lines of Blaschko over the trunk and extremities (Figure 1). Multiple yellowish, soft, fat lobule-like protrusions were found over the left axilla and left groin (Figure 2). Additional findings were an erythematous plaque on the vertex of the scalp; nail dystrophy of the left axilla and left groin (Figure 2); syndactyly of the right index and middle fingers as well as left second and third toes; hypoplasia of the left little finger; and multiple papillomatous lesions over the throat, upper lip, hard palate, and vulva area (Figure 2). Multiple developmental anomalies were found, including helical deformity of right ear and a notch over the incisor. A supernumerary digit of the left hand had been removed at 4 years of age. Her menarche was at the age of 12 years with regular menstrual cycle. She was born to nonconsanguineous parents, and no other family members had similar condition.

Roentgenographic examination showed absent phalangeal bone of the left little finger but normal bony structures of the right second and third toes. The results of chromosome karyotyping, ophthalmic examination, and renal ultrasonography were unremarkable. Two skin specimens were taken from the left thigh. One revealed severe dermal hypoplasia, consistent with FDH (Figure 3), whereas the other showed slight papillomatous epidermal hyperplasia with focal basal hyperpigmentation. Polymerase chain reaction (PCR) amplification of the coding regions of PORCN gene and flanking intron-exon boundaries (http://www.
ncbi.nlm.nih.gov/nuccore/45439334) of the genomic DNA from her peripheral blood cells using primers (Table 1) followed by direct sequence analysis revealed no detectable PORCN gene mutation.

**Discussion**

We report a sporadic case of FDH occurring in a Taiwanese girl manifesting typical cutaneous lesions accompanied with multiple

Figure 1 Typical skin lesions of focal dermal hypoplasia manifesting linear hypoplastic macules and patches with telangiectasia distributed along the lines of Blaschko over the (A) trunk and (B) extremities.

Figure 2 Additional findings of focal dermal hypoplasia. (A) A papilloma on the hard palate. (B) Syndactyly of right index and middle fingers and hypoplasia of left little finger. (C) Prominent yellowish fat herniation in the axillary area. (D) Syndactyly of left second and third toes. Note the presence of nail dystrophy.
papillomas of mouth, throat, and vulva area; dystrophic nails, limb malformation; and right ear deformities. Her mucocutaneous lesions and developmental anomalies were bilateral but were more prominent on the left side. The histopathological findings were consistent with FDH. However, the mutation analysis of the PORCN gene of her genomic DNA yielded no detectable mutation. Some Asian patients, including 73 Japanese, 3 Thai, 4 Korean, 5 1 Indian, 6 and 1 Chinese, 7 have been reported in the literature. To our understanding, this is the first reported case from Taiwan.

The inheritance of FDH is thought to be X-link dominant, 8 however, more than 95% of all cases and 100% of all male patients appear de novo. 2 PORCN gene, located at Xp11.23, is the only gene known to cause FDH. 3-11 The affected females are either heterozygous or have somatic mosaicism for a PORCN mutation, whereas all affected males have somatic mosaicism for PORCN mutations. 9,10 When a PORCN mutation occurs postzygotically in early embryos, the presence of the cells with the mutated PORCN allele might not be represented in blood cells in all cases. 10 The negative finding in our patient might be attributed to postzygotic mosaicism, large deletion, or splice-site mutation occurring in the intronic sequences. 12 Because fresh tissue from the lesional skin was not available, direct mutation analysis of the skin lesion was not performed in our study.

Figure 3 (A and B) Skin biopsy from the left groin shows severe hypoplasia of the dermis with telangiectasia and upward extension of the subcutaneous tissue (hematoxylin and eosin stain, 20x and 100x).
**Table 1** Polymerase chain reaction primers for amplification of **PORCN** from genomic DNA.

<table>
<thead>
<tr>
<th>Exon</th>
<th>Forward primer (5’→3’)</th>
<th>Backward primer (5’→3’)</th>
<th>Product size (bp)</th>
<th>AT</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>CTGAAATCTGACGACCAAGAC</td>
<td>CTGGAATCCAGAACATCAGG</td>
<td>533</td>
<td>55°C</td>
</tr>
<tr>
<td>E3</td>
<td>CTTCCTACACTGCAACACAC</td>
<td>CAGACCTCTCTTCTTCGGGG</td>
<td>453</td>
<td>55°C</td>
</tr>
<tr>
<td>E4</td>
<td>CACCACTGAGACGTGTTAGG</td>
<td>CAGACCTGAGAAATATGCC</td>
<td>356</td>
<td>55°C</td>
</tr>
<tr>
<td>E5–E7</td>
<td>CTACCACATCTACCTGGT</td>
<td>CAGGAGTACGCTGTCAGAC</td>
<td>723</td>
<td>55°C</td>
</tr>
<tr>
<td>E8–E10</td>
<td>CTTCCTCACTGGCTTTTCCT</td>
<td>CAGACAAAGATGGCTTCCT</td>
<td>631</td>
<td>60°C</td>
</tr>
<tr>
<td>E11–E13</td>
<td>GTTGGGCGCTTAAAGGAC</td>
<td>CGCTGAGGAAACGATGCGG</td>
<td>723</td>
<td>55°C</td>
</tr>
<tr>
<td>E14</td>
<td>CAGCTTGGCAACCCCTCTGG</td>
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</tr>
<tr>
<td>E15</td>
<td>CTCGCCAGAGCAGGTACAGC</td>
<td>CAAAGTGGACGGGGTCTAC</td>
<td>312</td>
<td>55°C</td>
</tr>
</tbody>
</table>

**AT** = annealing temperature; **bp** = base pair.

**PORCN** gene consists of 15 exons, which are alternatively spliced into five variants that encode five protein isoforms with tissue-specific variability in expression.\(^{1,11,13}\) **PORCN** protein, a membrane-bound endoplasmic reticulum protein O-acyltransferase with eight transmembrane domains, is responsible for attachment of palmitoleic acid to Wnt and prepares Wnt maturation and secretion, which is important in the development of affected organs in FDH.\(^{3,11,13}\)

The types of **PORCN** mutations are quite diversified and could be categorized into four classes: (1) microdeletions extending beyond this gene; (2) deletions, insertions, or duplications within the gene; (3) point mutations; and (4) splice-site mutations.\(^{13}\) More than 70 mutations, including 19 nonsense mutations, 18 premature termination codons-generating frameshift mutations, 6 splice-site mutations, 18 missense mutations, and 9 microdeletions, have been reported to date.\(^{4,9,10,12–15}\) The mutations span nearly all exons of the **PORCN** gene except for Exons 7 and 8. There is no significant correlation between the locations and types of the mutations and phenotype.\(^{17}\)

A great majority (75 of 79) of female patients with FDH analyzed have detectable mutations or microdeletions by direct sequence analysis, quantitative PCR, fluorescence in situ hybridization, or array-based comparative genomic hybridization.\(^{4,9,10,12–15}\) However, no mutations were detected in a number of patients. In a study by Maas et al,\(^{17}\) no mutations were detected in 3 of 16 female patients using direct sequence analysis and multiplex ligation-dependent probe amplification methods. Another study by Froyen et al\(^{10}\) also showed that eight patients of unspecified gender, no mutations were detected in five patients whose **PORCN** expression levels in lymphocytes were normal.

It is interesting to note that five of nine female FDH patients with detectable microdeletions occurred in a familial setting, and all five showed extreme skewing of X-chromosome inactivation (>95%).\(^{9,10,13,16}\) To explain this phenomenon, it has been hypothesized that female offspring with microdeletions involving other genes adjacent to **PORCN** must undergo extreme skewing of X-inactivation to result in a less severe phenotype that can be viable and is capable of transmitting through generations.\(^{9,10,13,16}\) By contrast, extreme skewing of X-chromosome inactivation is only seen in one of the six familial female offspring patients with intragenic mutations.\(^{9,10,13,16}\) Moreover, with the same intragenic mutation, more severe phenotypes occur in offspring compared with their parents.\(^{9,10,13,17}\)

In conclusion, we report a sporadic case of FDH in a Taiwanese girl with typical clinical and pathological findings. No mutation in the **PORCN** gene was detected by PCR amplification of genomic DNA and direct sequence analysis. Further laboratory study is needed to elucidate the nature of the mutation in this patient.

**References**