

A Case of Almost Unilateral Focal Dermal Hypoplasia Resulting From a Novel Mutation in the *PORCN* Gene

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Accepted April 11, 2012.

Focal dermal hypoplasia (FDH), also known as Goltz syndrome, is an X-linked dominant disorder of ectomesenchymal development. In general, FDH presents with characteristic linear streaks of hypoplastic dermis and various abnormalities in some organs (1). Although this disorder is normally lethal in male patients, approximately 10% of cases of FDH are male, and most represent post-zygotic mosaicism (2–4).

The molecular basis of FDH involves mutations in the *PORCN* (human porcupine locus MG61/PORC) gene (5). *PORCN* is a member of the porcupine (*porc*) gene family and is located on chromosome Xp11.23 (1, 6). The gene is thought to encode an O-acyltransferase that catalyses cysteine N-palmitoylation and serine O-acylation in the endoplasmic reticulum that allows membrane targeting and secretion of several Wnt proteins that have key roles in embryonic tissue development, notably for fibroblast proliferation and osteogenesis (1, 7).

We describe here a case of FDH with a novel deletion mutation at exon 14 (c.1179_1193 del) detected by PCR-sequencing analysis of the entire coding sequences of the *PORCN* gene. Interestingly, in this case, the characteristic symptom was prominent in the patient's left hemibody. To the best of our knowledge, this is the second case report that reveals a mutation of the *PORCN* gene in a patient with almost unilateral FDH.

CASE REPORT

A 2-year-old Japanese girl visited our outpatient clinic for hypopigmented and atrophic linear skin lesions on the trunk and extremities. She had been surgically treated one year

before for syndactyly of the left middle and ring finger. On her first visit to our hospital, physical examination disclosed hypo-pigmented patches of dermal hypoplasia distributed along Blaschko's lines on the arms, legs and trunk (Fig. 1). Interestingly, these symptoms in lesions were prominent on her left hemibody. Her hair was sparse and brittle and she had non-scarring alopecia. In addition, extensive dental caries was noted. From the above information, we diagnosed this patient as having almost unilateral FDH.

To confirm the diagnosis, we examined the *PORCN* gene for mutations. After receiving informed consent, DNA was extracted from the peripheral blood sample taken from affected individual using standard methods. Primers were designed to amplify individual exons and the flanking intron of the *PORCN* gene, as described previously (1). PCR-sequencing analysis of the entire coding sequences of *PORCN* revealed c.1179_1193 del mutation at exon 14 (Fig. 2). This variant was predicted to result in altered residues 394–412 and to produce a truncated protein (p.G394 fs X20). The sequence chromatograms showed low signal intensities at the site of mutation, indicating post-zygotic mutation. To verify the mosaic state, the PCR products were cloned into the pCR4 TOPO TA Cloning Vector (Invitrogen, Karlsruhe, Germany), transfected. *E. coli* clones were chosen and subjected to colony PCR, and PCR products from individual clones were sequenced. By DNA sequence analysis of selected clones we could assign the wild-type and the mutant sequence to either of the 2 banding patterns and identified a ratio of 5/26 (~19%; mutant vs. wild-type sequence).

DISCUSSION

FDH is characterized by linear and whorled lesions of hypoplastic dermis and variable abnormalities of organs including the bone, nails, hair, limbs and teeth (1–3). Cutaneous features that predominate at birth are red atrophic, linear lesions following Blaschko's lines



Fig. 1. Skin manifestation in the patient. (A) Hair loss on the left temporal scalp. (B, C) Small whitish depigmented spots, slightly depressed from the skin surface, distributed linearly on the left side of the arm (B) buttocks and lower limbs (C).

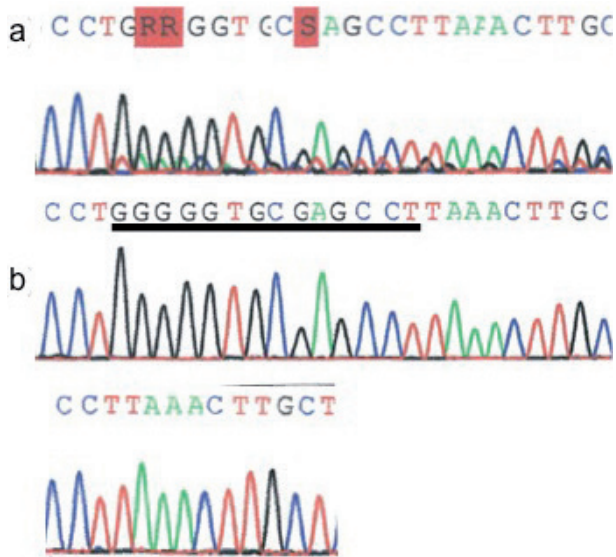


Fig. 2. Molecular basis of focal dermal hypoplasia (FDH). (a) Sequencing of exon 14 of the *PORCN* gene in the patient's DNA reveals c.1179_1193 del mutation. (b) Sequencing of control DNA shows the wild-type and mutant sequences.

and telangiectasias. It is presumed to be lethal in men who are fully hemizygous for a mutation in *PORCN* (4). FDH generally involves both sides of the body. Only 6 cases of unilateral FDH have been published (8–10). Recently, Maalouf et al. (8) reviewed all cases of unilateral FDH and found no side predilection. One case was male (17%) and the other 5 were females (83%). Moreover, they described that gene sequence analysis on the *PORCN* gene detected a novel heterogeneous mutation in exon 10, c.854-855insACCTGAC [p.T285fsX316]. In addition, a substantial majority of cases of FDH have previously been reported to result from post-zygotic mutations (11). In the present case, sequencing analysis of the entire coding sequences of *PORCN* gene revealed a novel deletion mutation at exon 14 (c.1179_1193 del). As a ratio of 5/26 mutant vs. wild-type alleles was found, a post-zygotic mutation is the likely cause of the syndrome in our case. A germline mutation would have resulted in a 1:1 distribution of both alleles in functional X-chromosome-mosaicism as described previously by Bornholdt et al. (11). Although

we did not perform the X-chromosome inactivation analysis using DNA extracted from the affected and non-affected skin, the present case suggests that the deletion mutation at exon 14 might be connected with the unilateral involvement of FDH. To confirm our hypothesis, further case reports and molecular studies of patients with unilateral FDH are necessary.

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