Published in final edited form as:

Int J Dermatol. 2014 December ; 53(12): 1481–1484. doi:10.1111/ijd.12605.

Goltz Syndrome and *PORCN* Mosaicism

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Abstract

Goltz syndrome, also known as focal dermal hypoplasia, is characterized primarily by ectodermal and mesodermal defects. Manifestations include cutis aplasia, dermal hypoplasia, papillomas, chorioretinal colobomas, absent/dysplastic teeth, and skeletal anomalies. Goltz syndrome is an X-linked disorder due to mutations in *PORCN*, with a predominance of females affected. Germline mutations in *PORCN* are thought to result in embryonically lethality in males. We present a boy with a phenotype consistent with Goltz syndrome with low level mosaicism for a novel mutation in *PORCN* from peripheral blood (c.956dupA; p.Asn320GlufsX99).

Keywords

Goltz syndrome; focal dermal hypoplasia; *PORCN*; mosaicism

Introduction

Goltz syndrome, also known as focal dermal hypoplasia, is a rare X-linked multisystem syndrome primarily affecting females.^{1,2} Common dermal findings include focal dermal hypoplasia often following the lines of Blaschko, suprapapillary deposits of subcutaneous fat, papillomas of the skin and mucous membranes, and abnormal nails.³ Ophthalmologic findings include iris and chorioretinal coloboma, lacrimal duct anomalies, and anophthalmia/microphthalmia. Facial anomalies include dysplastic or absent teeth, high arched palate, and enamel defects. Skeletal anomalies are found in approximately 80% of patients, including syndactyly, ectrodactyly, polydactyly, osteopathic striae, hypoplasia or absence of digits, scoliosis, and/or facial asymmetry.⁴

Goltz syndrome is caused by mutations in *PORCN* located on the X chromosome.^{5,6} *PORCN* is a regulator of Wnt signaling and is a member of the porcupine (Porc) gene family that encodes for endoplasmic reticulum proteins with multiple transmembrane domains.^{5,6} Although it is an X-linked condition, females are primarily affected with rarity in males, leading to suspicion that non-mosaic Goltz syndrome is embryonically lethal for males. We

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Conflicts of Interest: None for all authors

report a boy with the phenotype consistent with Goltz syndrome with mosaicism for a novel mutation in *PORCN*.

Case report

The infant was evaluated in the medical genetics clinic at 1 month of age. Growth parameters were at the 10th centile for weight, <5th centile for height, and 2nd centile for occipitofrontal circumference. He had dermal and skeletal anomalies consistent with the phenotype observed in Goltz syndrome.

He had multiple ectodermal findings. There were areas of cutis aplasia neighboring the anterior fontanelle. Focal dermal hypoplasia appeared to follow the lines of Blaschko on the lower extremities, and he had linear lesions bilaterally on his trunk. There was a region of focal dermal hypoplasia on his right inner thigh (Fig. 1). There were small papules of the fourth toe and a small mobile mass on the posterior scalp. He also had sparseness of hair and eyelashes. He had a slightly broad nasal tip with unusual linear erythema and dermal hypoplasia at the junction of the alae nasi, and asymmetry of the upper lip with hypoplastic tissue on the left. His ears showed underdevelopment of the superior helices and were slightly posteriorly rotated and large relative to his body.

Musculoskeletal anomalies included syndactyly on the right second and third finger (Fig. 2), ectrodactyly of the right foot (Fig. 3), and osteopathia striatum reported on a skeletal survey. Right foot ectrodactyly was present with absent right fifth toenail. Linear nail anomalies of the second and third left fingernails were noted, as well as ulnar deviation of the left fourth finger. Syndactyly release was subsequently performed at 14 months of age. The patient also had a diastasis recti.

Multiple ophthalmologic abnormalities were noted. He had bilateral colobomas, with concern for poor vision on the left. An ophthalmology exam under anesthesia at 19 months showed bilateral inferonasal iris colobomas and a retinal flap near the ora serrata of the right eye. The right optic nerve was reported to be within the coloboma but appeared to be within normal limits with the macular area split by the coloboma. In the left eye, the optic nerve was reported to be indistinguishable within a large inferonasal coloboma. The left eye was smaller than the right and visual evoked potentials were reported as subnormal in both eyes, left worse than right. Laser treatment was performed around the right retinal flap.

An initial echocardiogram showed a small secundum atrial septal defect, patent ductus arteriosus (PDA), and pulmonary hypertension, for which he required supplemental oxygen. The PDA was closed with a coil at 9 months of age. At one year of age he had normal pulmonary arterial pressures measured by cardiac catheterization with spontaneous closure of his secundum atrial septal defect.

At 2 months of age he was admitted to the inpatient unit for failure to thrive with weak swallow and required nasogastric feeds. He also had undescended testes, and at 1 year of age required a right orchiopexy and left orchiectomy. A renal ultrasound was performed which was normal.

Results

Overall, the phenotype was consistent with a clinical diagnosis of Goltz syndrome despite his sex. Therefore molecular testing with sequencing of *PORCN* was performed on a peripheral blood sample. This demonstrated mosaicism for a c.956dupA mutation (duplication of a single “A” nucleotide in exon 10). This mutation caused a frameshift starting with codon 320 changing the amino acid asparagine to a glutamic acid residue and created a premature stop codon at position 99 of the new reading frame (p.Asn320GlufsX99). This mutation is predicted to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay. The mutation was present in some, but not all, cells in the peripheral blood specimen. Concurrent targeted array comparative genomic hybridization analysis with exon-level resolution did not identify a deletion or duplication of *PORCN*. Mosaicism for the c956dupA mutation of *PORCN* was consistent with a diagnosis of Goltz syndrome for a male individual.

Comment

Goltz syndrome is an X-linked dominant condition primarily affecting ectodermal and mesodermal tissues. It is caused by mutations in *PORCN* located at Xp11.23. The condition exhibits variable expressivity and is typically more severe in females.³ The vast majority of reported cases occur in females, and to our knowledge only 1 male has been documented as being non-mosaic for *PORCN* mutations, and that individual had Klinefelter syndrome (47,XXY) which explains the survivability in a non-mosaic male individual.⁷ Affected individuals have been reported to have a history of spontaneous abortion and male stillbirth, leading to speculation that Goltz syndrome is an embryonically lethal condition. Mother-to-daughter and father-to-daughter transmission has been reported.⁸⁻¹⁰ In our proband, given the sex of the infant, a diagnosis of Goltz syndrome was disconcerting, given that it is hypothesized to be lethal in males, but the phenotype was consistent with Goltz syndrome and hence mosaicism was contemplated as the likely mechanism.

Although Goltz syndrome is an X-linked dominant disorder, it has been hypothesized that there is not significant increase in severity in live born males.^{11,12} It is possible that Goltz syndrome is underdiagnosed in males, as cases have been reported in which a father was minimally affected and only diagnosed retrospectively after the birth of a more severely affected daughter.^{8,10} One might suspect that surviving males with Goltz syndrome would be more severely affected, but it is more likely that males with Goltz syndrome are less impaired with broader variable expressivity secondary to varying degrees of mosaicism with true embryonic lethality in non-mosaic situations. The number of male cases reported is small and likely biased towards the more severely affected and hence conclusions are difficult. The degree of *PORCN* expression required particularly for survival and for the variability of expression is not known, and it is possible that lyonization in females contributes to the variable expression. However, although extreme skewed X-chromosome inactivation has been reported in females with microdeletions, it has not been uniformly observed in females with point mutations in *PORCN*.¹³ In males the variable expression is likely primarily due to the degree of mosaicism in specific tissues.⁵ However, even if the degree of mosaicism could be accurately identified on peripheral blood, it would still likely

not provide direct correlation with outcomes, based on mosaic differences of various tissues and other modifiers.

There are several reports of males with the clinical findings of Goltz syndrome,^{3,4,6-26} but most have not had confirmation of mosaicism for a *PORCN* mutation. Wang et al.⁶ reported 4 male individuals with mosaicism for the following respective loss of function *PORCN* mutations (c.1059_1071dup13, c.370C>T, c.1064_1081del18, c.1093C>G). The male individual reported by Maas et al.³ was confirmed to have mosaicism for a *PORCN* nonsense mutation in fibroblasts but they were unable to detect a mutation in lymphocytes. Bornholdt et al.¹³ reported 4 male individuals with mosaicism for the following *PORCN* mutations (c.502G>A; c.1110delG; c.1186C>T, c.1315T>C). Yoshihashi et al.¹⁵ reported a male with Goltz syndrome with mosaicism for a *PORCN* nonsense mutation in peripheral lymphocytes. Vreeburg et al.¹⁴ reported a male with mosaicism for a *PORCN* frameshift mutation in leukocytes and buccal mucosa, but did not detect the mutation in placental samples from the fetal side.

This case emphasizes that male sex in and of itself should not eliminate the consideration of a diagnosis of Goltz syndrome. Goltz syndrome can be seen in males; based on previous reports and this case, this condition in males is due to *PORCN* mosaicism. This case demonstrates that males with Goltz syndrome can be more severely affected than previously thought, while also aiding in further detailing the variable expressivity in males with Goltz syndrome. Accurate diagnosis is critical for reproductive planning, anticipatory guidance, and prognosis, as a minimally affected male could have a severely affected daughter.

In summary, we report a male child with Goltz syndrome with mosaicism for a previously unreported mutation in *PORCN*. To our knowledge the c.956dupA mutation in *PORCN* is a novel mutation, where, in a mosaic state, results in Goltz syndrome in a male child. This case further elucidates the phenotype of Goltz syndrome in males, but additional cases will be needed to better describe the variable expressivity of Goltz syndrome in male survivors.

Acknowledgments

We thank the family for their participation. This project was supported by the University of Utah Clinical Genetics Research Program: Phenotyping Core (CGRP), and the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1RR025764. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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Fig. 1.
Image of right posterior thigh showing focal dermal hypoplasia.

Fig. 2.
Image of hand showing syndactyly on the right second and third finger with abnormal nail.

Fig. 3.
Image of right foot showing ectrodactyly with small papules on the medial aspect of the 4th toe.