Focal Dermal Hypoplasia - a *de novo* variant in the *PORCN* gene

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Background

- Focal dermal hypoplasia (FDH), or Goltz Syndrome, is a rare X-linked dominant disorder.
- Caused by mutations in the *PORCN* (porcupine homolog-drosophila) gene at Xp11.23, resulting in failure in the differentiation of the endoderm and mesoderm.
- Systemic malformations of FDH include dental, skeletal, neurological, ocular, cardiac, renal and genitourinary abnormalities.

Case Report

Perinatal history

- Newborn girl born full-term, via vaginal delivery, from healthy nonconsanguineous parents.
- Pregnancy complicated with intrauterine growth restriction since the 2nd trimester.
- Apgar score 10/10. Birth weight 2980g.

Physical Exam

- Findings included:
  - Craniotabes, sparse hair, cleft lip (fig. 1A).
  - Syndactyly (fig. 1B) and hypoplasia/anonychia of toenails.
  - Dermal hypoplasia (fig, 1C), hyper and hypopigmentation areas following Blaschko lines distribution (fig. 1D).

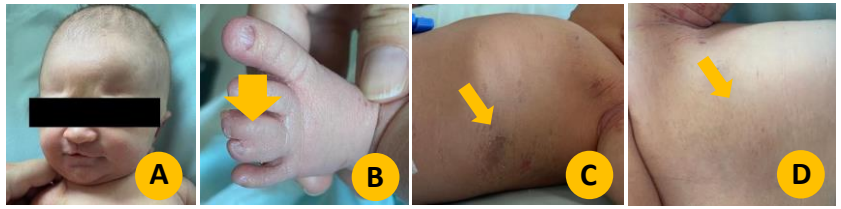

Figure 1 – Physical examination's findings

Specialty	Evaluation
Dermatology	• Atrophic depressed areas, discretely hypopigmented, distributed in the entire skin integument, in some areas outlining a linear distribution.
Ophthalmology	• Peridisc hemorrhages in the left eye (probably related to childbirth)
Genetics	• Polymalformed newborn with facial dysmorphisms, medial cleft lip, with no cleft palate or other pits or tags; areas of dermal hypoplasia, hypoplasia/aplasia of the toenails, and syndactyly of the 2/3 and 3/4 toes

Table 1 – Multidisciplinary approach to the patient

Next generation sequencing panel for Dermal Hypoplasia based on whole exome sequencing was performed

Identification of a **frameshift variant c.95del p.(Leu32Profs*20)** in the *PORCN* gene

This variant was not yet described in the literature nor is reported in genomic databases. Parents testing allowed to conclude a very likely de novo inherited variant and allowed to its reclassification as pathogenic.

Discussion

- ✓ FDH usually occurs as *de novo* variants.
- ✓ FDH phenotype varies widely from mild defects to severe forms.
- ✓ Our patient's phenotype is consistent with the expected findings in FDH.
- ✓ We report a most likely de *novo* frameshift variant in the *PORCN* gene, classified as **pathogenic**.
- ✓ Given the possibility of various organs involvement, a multidisciplinary approach is advised.
- ✓ Molecular diagnosis allows specific genetic counselling for the newborn but also for the parents, namely a risk of recurrence in future pregnancies <1% and the possibility of invasive prenatal molecular diagnosis in future pregnancies, considering the possibility of gonadal mosaicism.

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