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Department Of Pediatric Genetic -division

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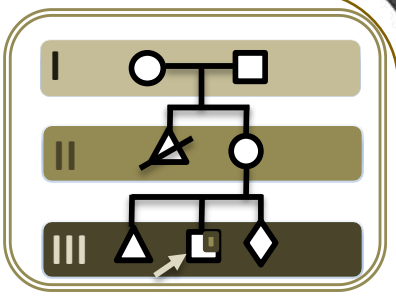

From the desk of Editor

The genetic division of the Pediatric Department is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

Neurogenetics -XIV- Neurometabolic/Intellectual Disability/ X-Linked/ PORCN-Related Developmental Disorders/ Focal dermal hypoplasia; FDH / GOLTZ-GORLIN SYNDROME- (Part -II)

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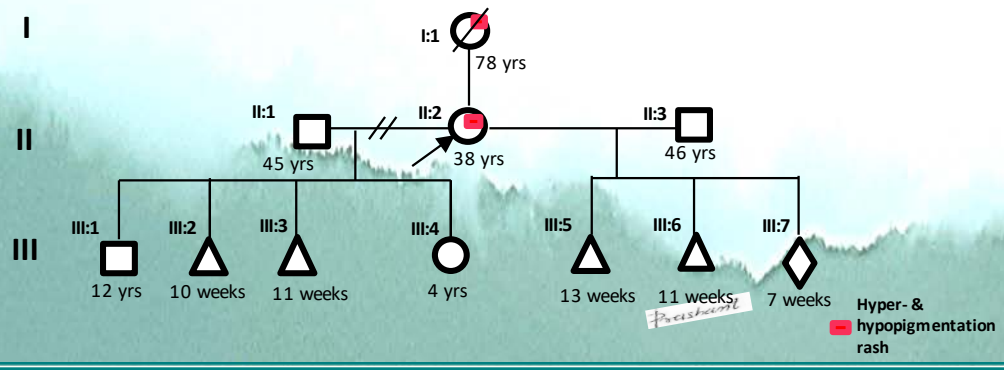
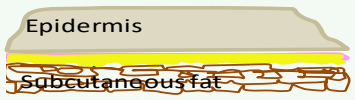


Distinguish: Normal skin versus focal dermal hypoplasia (FDH) skin

- FDH: significant paucity of dermis leads to visible fat (yellowish-pink areas), variable pigmentation, and vascular lesion on the skin

- Not pathognomonic for PORCN mutation, and reported in more than thirty genetic entries



Insight:

1. What is the PORCN gene and its functions?
2. What are the histopathological differences among aplasia cutis congenita, focal facial dermal dysplasia & focal dermal hypoplasia?
3. What is the recurrence risk of the mother's phenotype in case III:7?
4. What is the molecular testing strategy for the genetic disorders reported with mosaicism?

Protein sequence

MATFSRQEFF
QQLLQGCLLP
TAQQGLDQIW
LLLAICLACR
LLWRLGLPSY
LKHASTVAGG
FFSLYHFFQL
HMVWVVLLSL
LCYLVLFLCR
HSSHRGVFLS
VTILIYLLMG
EMHMVDTVTW
HKMRGAQMIV
AMKAVSLGFD
LDRGEVGTVP
SPVEFMGYLY
FVGTIVFGPW
ISFHSYLQAV
QGRPLSCRWL
QKVARSLALA
LLCLVLSTCV
GPYLFPYFIP
LNGDRLLRNK
KRKARGTMVR
WLRAYESAVS
FHFSNYFVGF
LSEATATLAG
AGFTEEKDHL
EWDLTVSKPL
NVELPRSMVE
VVTSWNLPMS
YWLNNYVFKN
ALRLGTFSAV
LVTYAASALL
HGFSFHLAAV
LLSLAFITYV
EHVLRKRLAR
ILSACVLSKR
CPPDCSHQHR
LGLGVRALNL
LFGALAIFHL
AYLGSLFDVD
VDDTTEEQGY
GMAYTVHKWS
ELSWASHWVT
FGCWIFYRLI
G

- Each Exon in different colours **(Residue overlaps splice site)**

Plausible tenets:

Gene: PORCN(Xp11.23) Genomic coordinates (GRCh38) **X:48,508,992-48,520,814**

- **PORCN (Porcupine O-Acyltransferase), a membrane-bound O-acyltransferase (MBOAT), belongs to a porcupine (Porc) gene family**
- **ncRNAs (non-coding RNAs) of related gene family reported with hepatocellular cancer**
- Gene: eighteen splice variants, two hundred sixty-six orthologues, & five paralogues
- Transcript: **Coding exons: 14 (total exons -15, first work as promoter)**; **1,867 bps**, 17 domains, and features,
- Protein has 461 amino acids, with a molecular weight of 52,317.58 g/mol
- Transcripts for endoplasmic reticulum transmembrane protein, which modified the "Wnt proteins" by attaching palmitoleate, a 16-carbon monounsaturated fatty acid, which unable proper binding of Wnt protein with its receptor, so works as a **principal controller** of the Wnt signaling pathway.

Molecular testing strategy for the genetic disorders reported with mosaicism

- Mechanism for mosaicism:
  - Congenital Form: a similar de novo mutation in somatic +/- germline in the developing embryo
  - Acquired: Different somatic or germline mutations after birth
- Technique: High through output - sequence analysis- NGS based [also detect >100bp (≈ 90%)- 10Kbp (≈ 95%) CNV additionally] & CNV studies (Microarray-based).

Sample collection sites

1st Standard: blood sample (yielding is less for mitochondrial)

2nd source –Fibroblast (skin) or Saliva (Preferable)

3rd affected part- tissue sample (post -surgically)

Distinguish features of Aplasia cutis congenita (ACC), focal facial dermal dysplasias (FFDDs), and focal dermal hypoplasia (FDH)

FDH: Rudimentary dermis with a normal epidermis & subcutaneous fat. Usual Site: any part of the body
ACC: Besides the dermis, the epidermis is obliterated or absent with reduced subcutaneous fat. Usual Site: scalp
FFDDs: mesodermal dysplasia, skeletal muscle attached with epidermis with no subcutaneous fat. Usual Site: bitemporal or preauricular skin

Counsel the family for case III:5- Only 5 % of cases show familial inheritance. X-linked dominant disorders are **considered lethal in males without mosaicism** (**10% reported cases**). Only ¾ of fetuses are presumed to survive in utero, so the recurrence risk in each pregnancy in an affected female: **33%** unaffected males, **33%** unaffected females, and **33%** affected females.

Thought Riveting:

- ***Why is the oligodactyly more frequently reported in Central digits in FDH?***
- ***Can isolated limbs (specifically acral parts) or urogenital anomalies in a male child be the extended spectrum of de novo embryonic PORCN mutations in particular cell lines?***
- ***What are the most likely environmental modifiers for highly variable mosaic phenotype of PORCN?***
- ***Will pharmacologically targeting the Porcupine O-Acyltransferase be useful for Wnt pathway regulations in colorectal cancer (CRC)?***
- ***Can intracellular plastic microfibers interrupt DNA replication, transcription, and repair mechanisms?***

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