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Limb defect

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Case description - *no limb defect?*

- A/
  - 38+4: sectio due to maternal trombopenia
  - APGAR 8 (1 min) and 10 (5 min)
  - 1 day after birth:
    - Cyanosis
    - Tonic-clonic insult (Luminal®)
  - Persisting hypoglycemia
  - No distinct dysmorphic features/ **micropenis, cryptorchidism**
- MRI/
  - Ectopic neurohypophysis posterior pituitary
  - Absent pituitary stalk
  - Hypoplastic adenohypophysis anterior pituitary

  => *pituitary stalk interruption syndrome (**PSIS**)*
- FAM/
  - 1st son of non-consanguineous parents
  - Not contributive (1st visit, however…)

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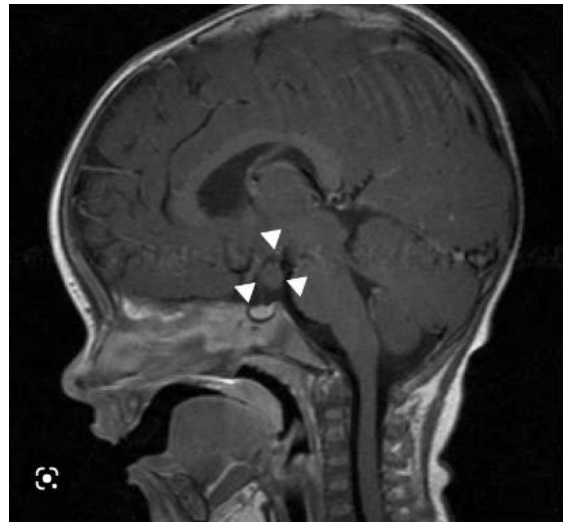
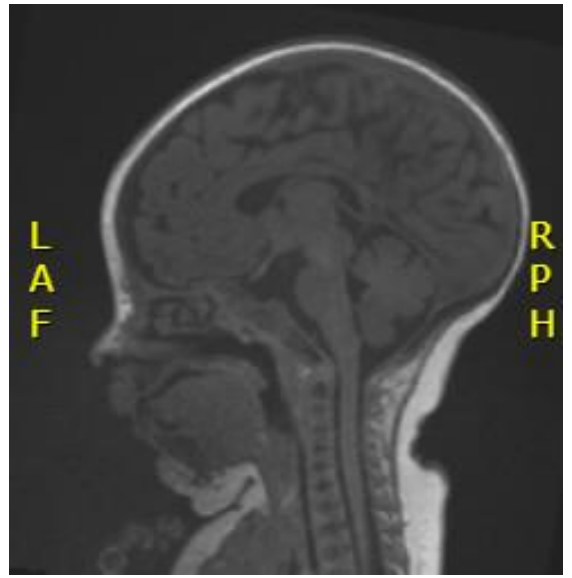
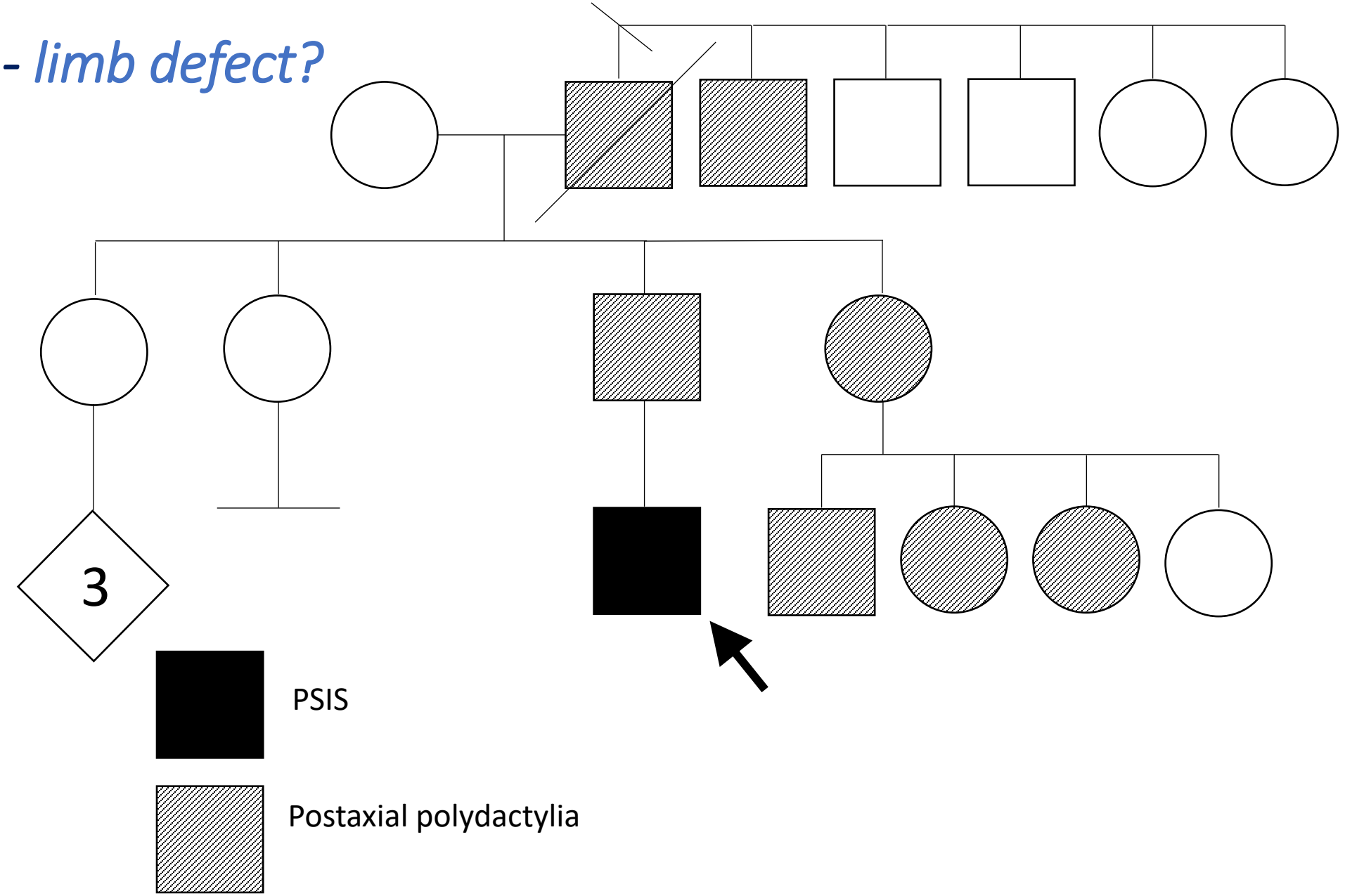




Pedigree - *limb defect?*



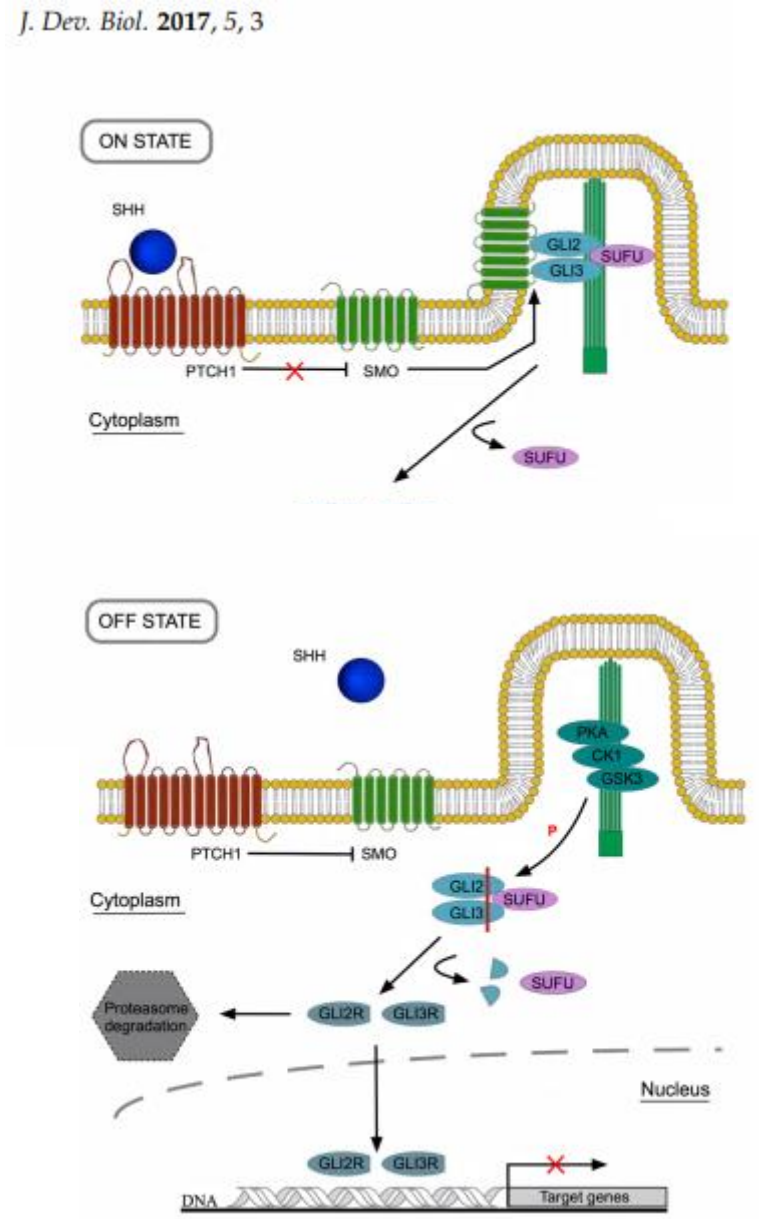
Any thoughts?

Diagnosis?

CNV: normal

WES ID/EPI: heterozygous splice site variant (class 5) in ***GLI2*** *c.1684-1G>C*

- *Zinc finger protein GLI2*
- ***TF**, binding to DNA via Zinc finger motifs*
- *Mediators of Sonic hedgehog (**Shh**) signaling*
  *During **embryogenesis** proper cell differentation*
- *Zebrafish study*
  "GLI2 acquired a high level of complexity in the genetic mechanisms regulating its expression during spatio-temporal patterning of the central nervous system (CNS) and limbs"(Developmental Dynamics 244:681–692, 2015)



Conclusion

Culler Jones syndrome

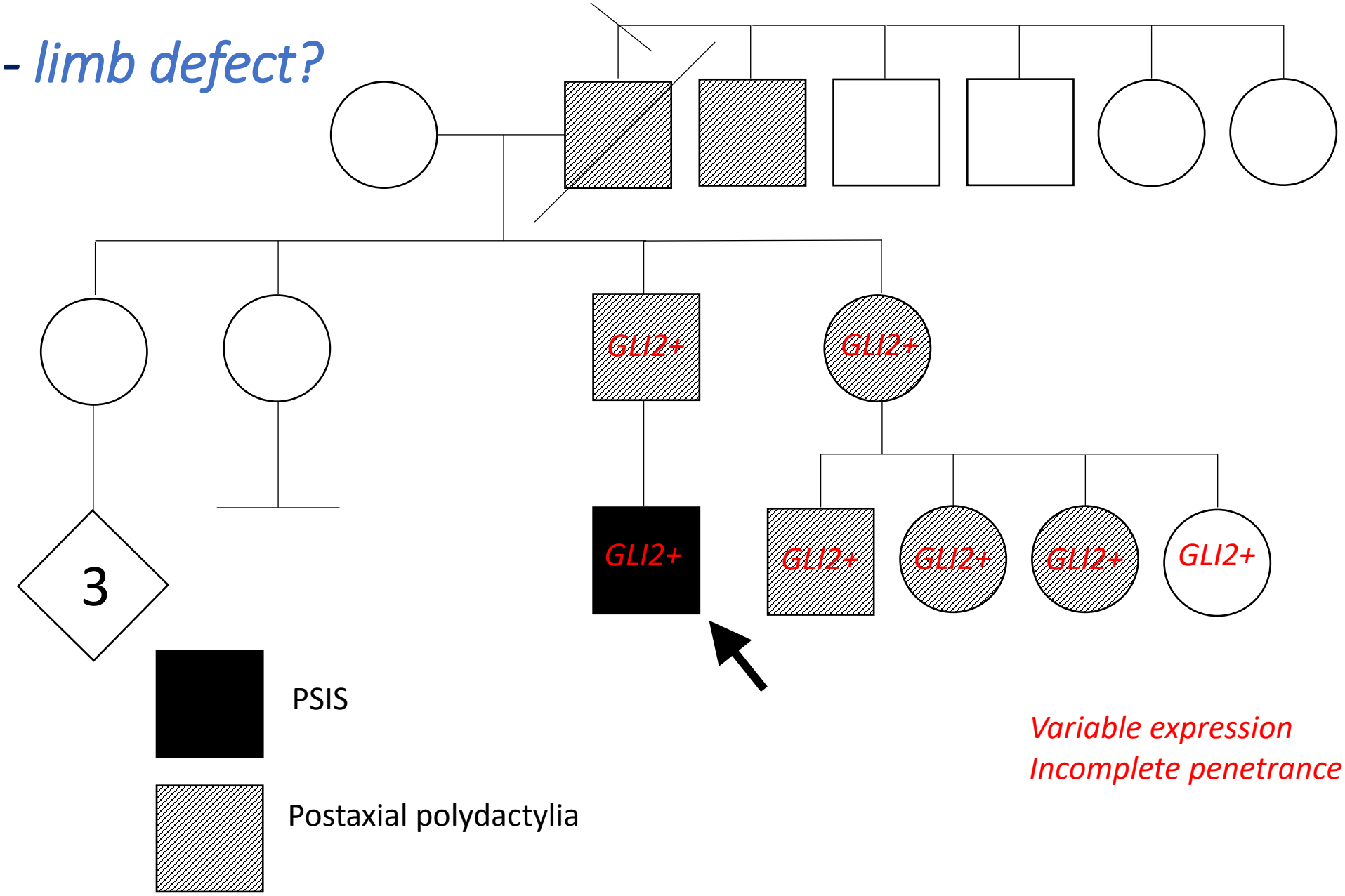
- Postaxial polydactyly, cleft palate
- CNS anomalies / ID: 15% (PMID: 34921505)
- Previously thought to be associated to holoprosencephaly (HPE) = not true (!)
- Congenital hypopituitarism (w/wo anomalies pituitary stalk; PSIS):
  - Isolated growth hormone deficiency (mild) – panhypopituitarism (severe) = **spectrum** (!)
  - **Treatment**? L-thyroxine + Hydrocortisone; from 6m: Growth hormone; from 9y: testosteron

- *GLI2* mutation
  - Incomplete penetrance
  - Variable expression
- Follow-up
- PND/PGT

PSIS (general)

- rare, 5% familial, heterogenous clinical presentation
- 2020 Brauner et al.: 45 genes in total linked to PSIS: e.g.
  - *LHX4, OTX2, HEX1, SOX3, PROKR2, GPR161*
  - *CDON and ROBO1* genes (PSIS and ophthalmic anomalies)
  - *BMP4, CDON, **GLI2**, GLI3, HESX1, KIAA0556, LHX9, NKX2-1, PROP1, PTCH1, SHH, TBX19, TGIF1* (midline development and/or pituitary development or function)

Pedigree - *limb defect?*



Variable expression
Incomplete penetrance