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***Pituitary stalk interruption syndrome, polydactyly,
polymicrogyria and a ZRSR2 variant***

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Background: Pituitary stalk interruption syndrome (PSIS) may associate with brain midline defects and also with polydactyly (GLI2 mutations) but rarely with brain cortex anomalies.

Clinical Case: We report a boy referred at age 19 months because of growth failure. Bilateral postaxial polydactyly, syndactyly of the toes, and a nodule on the tongue were noted at term birth. The neonatal course was complicated by marked but transient hypoglycemia. During infancy, the acquisition of gross motor skills was slightly delayed. Upon referral, body length was 4.1 SD below the level of mid-parental height. Extremely low concentrations of circulating IGF-I (8 mcg/L) and IGFBP-3 (861 mcg/L) were suggestive of growth hormone (GH) deficiency which was corroborated by glucagon test (peak GH 3.3 mcg/L, peak cortisol 14.6 mcg/dL) in an euthyroid and normoprolactinemic state, and in the absence of polydipsia or polyuria. Brain MRI disclosed not only a PSIS triad (with a virtual absence of the pituitary stalk and the anterior pituitary, and with an ectopic position of the posterior pituitary) but also abnormal sulcation and polymicrogyria (pointing to abnormal lamination in the cortex) on both sides in the posterior cingulum. Familial history is positive for holoprosencephaly and polydactyly in two male relatives, who died neonatally.

Whole exome sequencing showed a rare maternally inherited variant in ZRSR2 on the X chromosome (c.1207_1208delAG (p.Arg403Glyfs*24)) (OMIM 300028). ZRSR2 is depleted from loss-of-function variants in the reference population, and has not been associated with congenital anomalies or with pituitary dysfunction. This ZRSR2 variant escapes nonsense mediated decay and segregates in this family according to an X-linked recessive pattern. X-inactivation studies and gene expression studies are ongoing to correlate the ZRSR2 variant to the patient's phenotype.

Conclusion: This case describes a toddler with polydactyly and short stature, based on GH deficiency due to PSIS, in combination with polymicrogyria. Studies are ongoing to link the patient's phenotype to a rare variant in ZRSR2.

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