A Case of Syndromic Hypopituitarism

P3-202

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Objectives:

Majority of syndromic hypopituitarism is linked to mutation in transcription factor genes. Forkhead box A2 (Foxa2) is a transcription factor that plays a role in foregut differentiation, central nervous system and pancreatic development, and regulation of insulin secretion. Here, we describe a 7 years old boy with syndromic hypopituaritism due to FOXA2 haploinsufficiency.

Case:

A 3 months old boy was referred for recurrent hypoglycemia. He was born to unrelated parents at term with a birth weight of 3690 gr. At 6 hours of life he had severe hypoglycemia (venous glucose= 5mg/dl). Other biochemical measurements were consistent with hypopituitarism and hyperinsulinism (cortisol: 3mcg/dL, growth hormone: 0.6 mcg/L, b-hydroxybutyrate 0.3 mmol/L, insulin 1.2 mU/L). Hydrocortisone and growth hormone replacement was initiated. He also had central hypothyroidism (TSH: 7mU/L (1.12-8.21); fT4:0.61 ng/dL (0.71-1.96)) and low prolactin levels (4.64 ng/mL) (5-26). On his initial examination height SDS was -1.19 (57cm), weight SDS was -1.56 (4.8kg). He was noted to have wide nasal bridge, bulbous nasal tip and smooth philtrum **(Figure 1)**, bilateral cryptorchidism, micropenis and mild developmental delay. MRI of the pituitary gland revealed pituitary agenesis **(Figure 2)**. Abdominal MRI showed midline liver, polysplenia, situs inversus abdominalis, dorsal pancreatic agenesis, retroaortic left renal vein and inferior vena cava with azygos continuation. At two years old he was diagnosed with epilepsy and at 5 years with diabetes insipidus. At 5 years 8 months he developed postprandial hyperglycemia and upper normal HbA1c (5.7%) with negative diabetes autoantibodies; GADA, IAA, ICA. The oral glucose tolerance test showed impaired glucose tolerance (glucose [mg/dl]/insulin [mIU/mL] at 120 min: 151 / 69.28). *FOXA2* mutation was considered in the etiology and Sanger sequencing of *FOXA2* gene revealed a novel heterozygous c.616C>T (p.Gln206Ter) *de novo* nonsense mutation **(Figure 3)**.

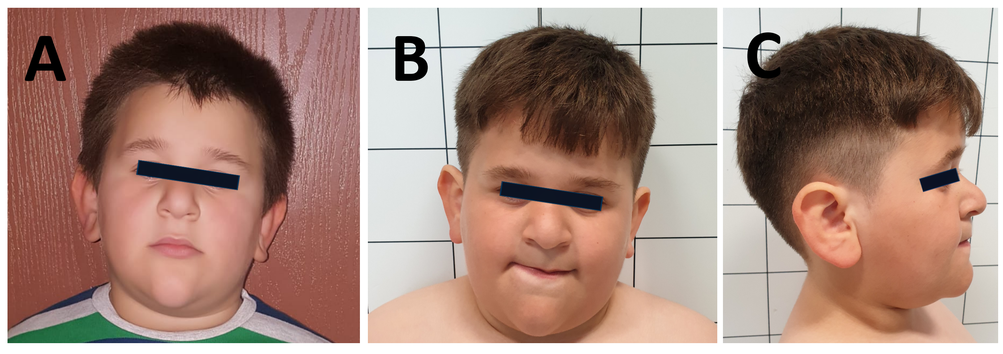

Figure 1: *Patient at $6^{11/12}$ years (A) and $7^{4/12}$ years (B, C). Note the wide nasal bridge, bulbous nasal tip and smooth philtrum.*

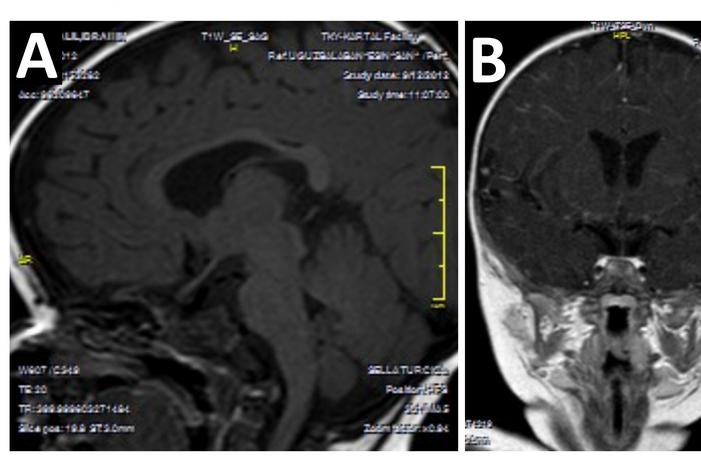

Figure 2: *Sagittal (A) and coronal (B) T1 view of the MRI scan of the pituitary: the normal pituitary gland cannot be identified; anterior pituitary is hypoplastic, the sella turcica is shallow and poorly defined with no evidence of the normal high signal of the posterior pituitary.*

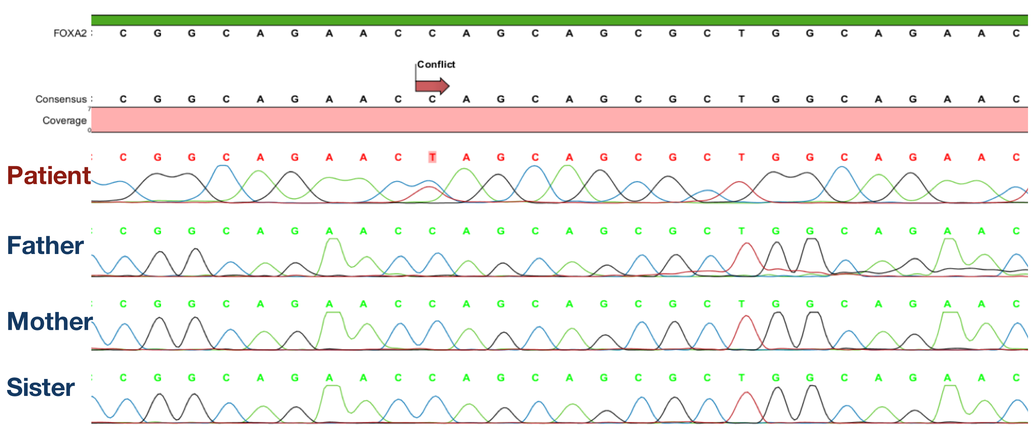

Figure 3: *Sanger sequencing data of the FOXA2 gene*

Table 1:*Summary of phenotypes of cases with FOXA2 mutations.*

	Giri et al.	Vajravelu et al .	Boda et al.	Stekelenburg et al.	Dines et al.	Present Case
Age/Sex	5 yrs/F	2 yrs 2 mo/F	1 yrs 4 mo/F	9 yrs/M	14 mo/M	7 yrs 3 mo/M
Origin	Caucasian British	Ashkenazi Jewish	Japanese	Turkish	NS	Turkish
FOXA2 variant	c.505T>C (p.S169P)	c.770G>T (p.R257L)	c.664T >G (p.Cys222Gly)	c.633C>A (p.Asn211Lys)	c.766C>A (p.R256S)	c.616C>T (p.Gln206Ter)
Panhypopituitarism	+	+	+	*	+	+
MRI findings	Hypoplastic anterior pituitary, absent posterior pituitary, interrupted pituitary stalk	Hypoplastic anterior pituitary, ectopic posterior pituitary bright spot along the tuber cinereum, absence of the infundibulum,small and shallow sella turcica	Absence of anterior pituitary, absence of posterior pituitary bright spot, no sella turcica	Hypoplastic anterior pituitary	Empty sella , ectopic posterior pituitary in the region of the floor of the hypothalamus	Hypoplastic anterior pituitary, absence of posterior pituitary bright spot, shallow and poorly defined sella turcica,thin pituitary stalk
Pancreatic Function	Persistent hyperinsulinism	Persistent hyperinsulinism	Severe hypoglycemia at neonatal period, without hyperinsulinism.	Diabetes Mellitus	Severe hypoglycemia at neonatal period (insulin was 21.52 pmoL/L).	Impaired glucose tolerance
Dysmorphism	Single median maxillary central incisor, pyriform aperture stenosis, choroidal coloboma	Coarse facial features, hypertelorism, thin upper lip, low-set ears, widely spaced nipples	The patient did not have a dysmorphic face	NS	NS	Wide nasal bridge, bulbous nasal tip, smooth philtrum
Gastrointestinal Malformation	Feed intolerance, GERD, elevated transaminases, dense chronic inflammation with portal-portal bridging fibrosis of liver.	NS	Low anal atresia with anocutaneous fistula , intestinal malrotation	Anal atresia	Anal stenosis, feed intolerance, GERD, dysmotility, and malabsorption.	Midline liver, polysplenia, situs inversus abdominalis, dorsal pancreatic agenesis
Cardiovasculary	Supravalvular pulmonary stenosis	NS	NS	Double outlet right ventricle, patent ductus arteriosus	Patent foramen ovale that spontaneously resolved, prolonged QT, bradycardia	Retroaortic left renal vein and inferior vena cava with azygos continuation
Neuro-developmental	Speech and motor developmental delay	NS	Normal psychomotor development	NS	Hypotonia at birth	Speech and motor developmental delay, epilepsy

*Critical sample at the time of hypoglycemia showed low growth hormone and high cortisol, otherwise pituitary function not specified. NS: Not specified. GERD: Gastroesophageal reflux disease

Refererences:

- Boda et al.(2018). "FOXA2 gene mutation in a patient with congenital complex pituitary hormone deficiency." European journal of medical genetics.
- Dines, et al.(2019). "Expanding phenotype with severe midline brain anomalies and missense variant supports a causal role for FOXA2 in 20p11.2 deletion syndrome." Am J Med Genet A.
- Giri et al.(2017). "Novel FOXA2 mutation causes Hyperinsulinism, Hypopituitarism with Craniofacial and Endoderm-derived organ abnormalities." Hum Mol Genet 26(22): 4315-4326.
- Stekelenburg et al. (2019). "Exome sequencing identifies a de novo FOXA2 variant in a patient with syndromic diabetes." Pediatric diabetes 20(3): 366-369.
- Vajravelu, et al.(2018). "Congenital Hyperinsulinism and Hypopituitarism Attributable to a Mutation in FOXA2." The Journal of Clinical Endocrinology & Metabolism 103(3): 1042-1047.