Missense Mutation of GLIS3 Gene Resulting in Neonatal Diabetes and Congenital Hypothyroidism

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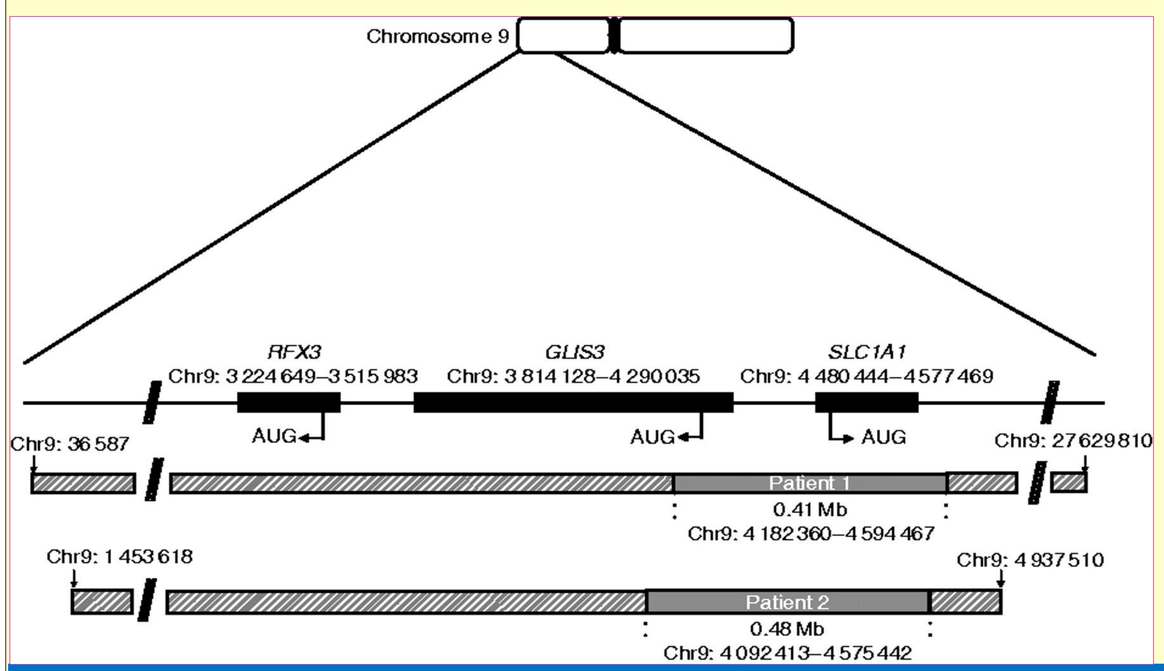
In relation to this presentation ,I have no conflict of interest that need to be disclosed

Introduction

Neonatal diabetes is a diabetes diagnosed before six months of age, it is rare, with incidence of approximately 1:90,000-160,000 live births. Mutations in the GLI-similar 3 (GLIS3) gene encoding the transcription factor *GLIS3* are rare causes of permanent neonatal diabetes and congenital hypothyroidism with 8 affected patients reported to date.(1). We are reporting first *missense mutation* in *GLIS3* resulting in neonatal diabetes and congenital hypothyroidism. This mutation has neither been annotated in databases nor been described in the literature so far.

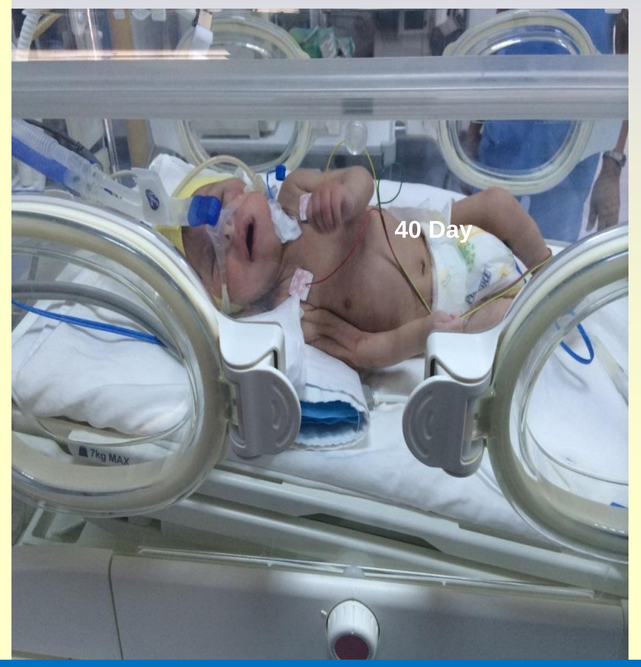
Genetic analysis

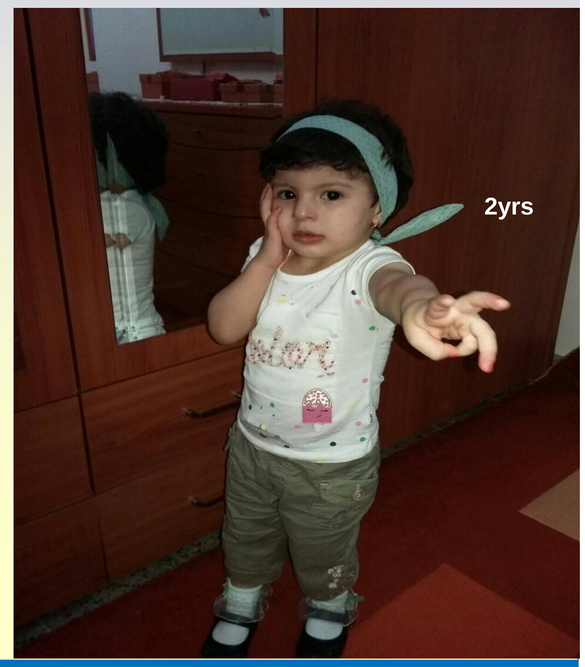
Consent was obtained from the family to perform familial genetic analysis. *GLIS3* gene mutations were sought by PCR amplification and sequence analysis of exons 2–11 by comparison with the reference sequence NM_001042413. sequence analysis reveal the homozygous exchange from A toT at position c 1924 in exon 6 of the GLIS3 gene leading to substitution of the evolutionary highly conserved amino acid serine to cystine at position 642 of the protein sequence (pser642cys.)in the patient ,and a heterozygous in parents



The Case

AISHA was born to first cousins of Libyan origin, she was proportionately growth retarded weighing 2kg with a head circumference of 33 cm.
Neonatal diabetes was diagnosed with a blood sugar of 1200 mg/dl on day 40 ,with severe dehydration and mild metabolic acidosis, where she was managed with IV insulin and rehydration in intensive care unit.
Subcutaneous insulin was commenced with insulin requirement ranging from 0.5 to 0.8 unit/kg in the form of detemir without meal bolus, the blood sugar was easy to control on that, the HbA1c at 6 months of age was 7.1%, then shifted to insulin glargine at 2 doses/day up to date .
At 2 months of her age; hypothyroidism was identified, initial TSH concentration 14.1((normal range 0.3-5.88 miu/l)) and free T4 8.4((10.3-21.9)) pmol/l, well controlled on L-thyroxine 25 µg daily. Thyroid gland anatomy and echotexture appeared normal on US scan, also she had a normal liver and renal structure by US examination with normal biochemical function .
No radiological evidence of any bone abnormality with normal serum calcium and PTH. Ophthalmic examination revealed severe myopia and nystagmus with convergent sequent corrected with optical lenses with normal hearing on testing. Patient now is at 2 yrs. of age with normal developmental milestones, as well as physical development and requires 0.5-0.8 units/kg/day of basal insulin with HbA1c 6.3%.





RESULTS

Family	Country of origin	Exon	GLIS3 genotype	IUGR	ND	Thyroid phenotype	CG	LF	RCD	SA	EPI	Deaf-ness	ST I	Age at death
1	Saudi Arabia	5-9	Frameshift mutation 2067insC	+	+	Thyroid anatomy not documented but THR	+	+	+	–	–	–	+	16 months
1	Saudi Arabia	5-9	Frameshift mutation 2067insC	+	+	Thyroid anatomy normal but THR	+	+	+	–	–	–	+	6 months
1	Saudi Arabia	5-9	Frameshift mutation 2067insC	+	+	Not described	+	+	–	–	–	–	+	10 days
2	Saudi Arabia	4	426kb deletion Chr9: 4176077–4601776	+	+	Athyreosis	+	–	–	–	–	–	–	Alive
3	France	1-4	149kb deletion Chr9: 4249915–4398572	+	+	Athyreosis	–	–	–	–	–	–	–	Alive
3	France	1-4	149kb deletion Chr9: 4249915–4398572	+	+	Thyroid hypoplasia/non-functional tissue	–	–	–	–	–	–	–	Alive
4	Bangladesh	1-2	412kb deletion Chr9: 4182360–4594467	+	+	Thyroid anatomy normal but THR	–	+	+	+	+	–	+	Alive
5	UK (Welsh)	9-11	482kb deletion Chr9: 4092413–4575442	+	+	Thyroid anatomy normal but THR	–	+	+	–	+	+	–	Alive
6	Libya	6	Chr:9 (c.1924A>T(p.ser642cys)	+	+	Thyroid anatomy normal, TSH raised	-	-	-	-	-	-	-	Alive

THR, thyroid hormone resistance; **ND**, neonatal diabetes; **CG**, congenital glaucoma; **LF**, liver fibrosis; **RCD**, renal cystic dysplasia; SA, skeletal abnormalities; EPI, exocrine pancreatic insufficiency; STI, susceptibility to infection.

Thus mutations of GLIS3 have been previously described resulting in neonatal diabetes and hypothyroidism syndrome in 12 patients(4). Phenotypic differences have resulted from different gene mutations with variations in tissue-specific GLIS3 transcript expression between probands. The most severe clinical phenotype in a Saudi Arabian family kindred with consanguineous parents. Apart from the consistent presentation of neonatal diabetes and hypothyroidism, additional features included renal cystic dysplasia and progressive hepatic fibrosis culminating in cirrhosis. All three children from this Saudi Arabian family died between 10 days and 16 months from infection. as with our patient all previously described patients with mutation in GLIS3 were born to consanguineous parents.(3).*dimitri et al 2015 sequenced the GLIS3 gene in un related patients with NDH where he suggested that R 589 w might represent a hypomorphic change with residual function* . We are describing the first case of *GLIS3* gene missense mutation c.1924A>T (p.Ser642Cys) resulted in neonatal diabetes and congenital hypothyroidism, whose hypothyrodisim and diabetes have proved to be easily responded to conventional therapy . Mutations in *GLIS3* should be considered in all children with neonatal diabetes without an established cause, irrespective of insulin requirements.

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