UNEXPLAINED NEONATAL DEATHS AMONG KURDISH CONSANGUINEOUS FAMILIES

IMPORTANCE OF RECOGNIZING CONGENITAL HYPERINSULINISM AND TESTING FOR K_{ATP} CHANNEL GENE VARIANTS

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BACKGROUND

Neonatal hypoglycemia due to congenital hyperinsulinism (CHI) is a potentially life-threatening condition. Severe forms of CHI, caused by autosomal recessive variants in K_{ATP} channel subunit genes (*ABCC8*, *KCNJ11*), are more prevalent in regions with a high level of consanguinity. These regions also have a high neonatal mortality rate with many deaths remaining unexplained.

AIM

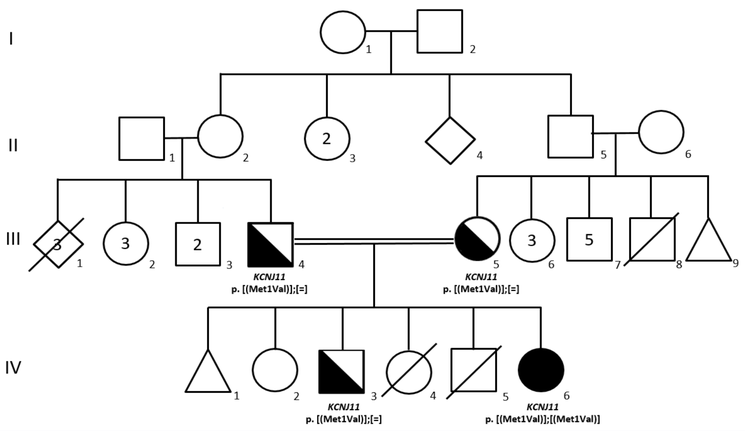
To elucidate the genetic etiology of CHI in three children coming from three different families from Sulaymani, Iraq. To provide an probable explanation for the unexplained neonatal deaths in two of these families.

METHODS

DNA was extracted from blood of the patients, their parents and unaffected siblings. *ABCC8* and *KCNJ11* genes were tested in the patients by Sanger sequencing. Pathogenicity of variants were evaluated by the American College of Medical Genetics (ACMG) standards. Thereafter, selected variants were tested in family members.

PATIENTS

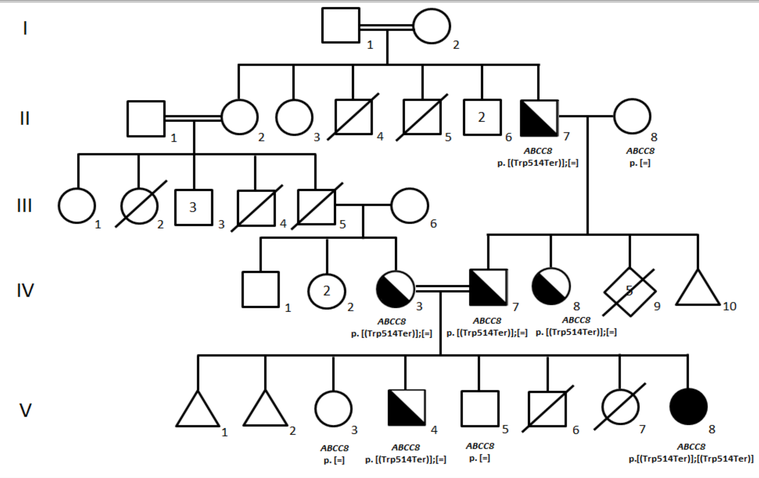
GALA



	FINDING
Current age / Age at presentation	5.5 months / 10 days
Height, Weight	65.5 cm (0.4 SD), 9.4 kg (2.2 SD)
Physical findings	Normal appearance, normal psychomotor development, no organomegaly
Clinical history	Full term, birth weight estimated above 4 kg (large for gestational age - LGA), unknown length During the neonatal period - recurrent convulsions due to hypoglycemia. Hyperinsulinism was suspected and she was put on short acting Octreotide. At 4 months of age, when a partial pancreatectomy was being considered, she was referred to a pediatric endocrinologist
Critical sample	Blood glucose 2.05 mmol/l (37 mg/dl) Insulin 58 mIU/l C-peptide 2242 pmol/l Cortisol of 8.15 nmol/l (normal range 171 – 536) ACTH 4.65 ng/l (normal range 7.2 - 63.6) ACTH stimulation test (Synacthen test with i.m. depot Synacthen) - stimulated cortisol 943 nmol/l.

A novel homozygous pathogenic variant p.Met1Val (c.1A>G) was found in the *KCNJ11* gene causing CHI. ACMG guidelines classification: Pathogenic (Ia)

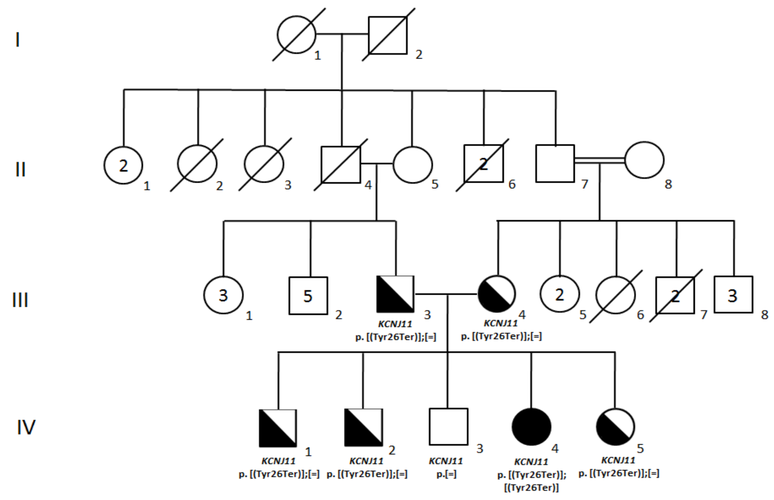
ROZA



	FINDING
Current age / Age at presentation	4 years / 4 days
Physical findings	Microcephaly, mental retardation, severe developmental delay, no organomegaly
Clinical history	Born preterm at the 35th week of gestation with a birth weight of 3.3 kg (LGA). From four days of age, she had recurrent symptomatic hypoglycemia but was only treated with frequent feeding and sugar. At the age of three years and eight months, she was referred to the pediatric endocrinologist
Critical sample	Blood glucose 2.78 mmol (50 mg/dl) Insulin 8.1 mIU/l C-peptide 2300 pmol/l Cortisol 893 nmol/l (normal range 171 - 536)

A novel homozygous pathogenic variant p. Trp514Ter (c. 1541G>A) was found in the *ABCC8* gene causing CHI. ACMG guidelines classification : Pathogenic (Ia)

DALIA



	FINDING
Current age / Age at presentation	2.5 years / 3 weeks
Physical findings	No dysmorphic features, no organomegaly, developmental assessment is appropriate for age, normal anthropometry
Clinical history	born full term, birth weight 3.0 kg – appropriate for gestational age (AGA) Presented with hypoglycemia at three weeks of life causing convulsions and loss of consciousness At three months of age she was referred to the pediatric endocrinologist
Critical sample	Blood glucose 2.5 mmol/l (45 mg/dl) Insulin 14.6 mIU/l (normal range 2.6 - 24.9 C peptide was 1580 pmol/l Cortisol 220 nmol/l (normal range 171 - 536)

A novel homozygous pathogenic variant p. Tyr26Ter (c. 78C>A) was found in the *KCNJ11* gene causing CHI. ACMG guidelines classification : Pathogenic (Ia)

CONCLUSIONS

- CHI caused by K_{ATP} channel variants was elucidated in these three children, providing a highly probable explanation for their siblings who died as neonates.
- In each of the three patients, novel pathogenic homozygous variants were found. All have heterozygous healthy parents and unaffected siblings who tested negative or heterozygous.
- One variant changes the start codon of the *KCNJ11* gene, causing the loss of the initiating Methionine and changing the Kozak sequence. It could be presumed that this protein is shortened or not coded at all.
- Two of the novel variants cause a stop signal leading to premature protein termination.
- All three patients are now successfully controlled on long acting octreotide.
- In regions with high consanguinity, a small but significant percentage of all unexplained neonatal deaths could be due to CHI.
- Future lives could be saved by the timely diagnosis of CHI when encountering a neonate with unexplained seizures or other signs of recurrent and/or persistent hypoglycemia.

All pictures were published with parents' permission.
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