

Diazoxide unresponsive Congenital Hyperinsulinism due to a Novel ABCC8 Missense Mutation.

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BACKGROUND

Persistent neonatal hypoglycemia is frequently due to congenital hyperinsulinism caused mostly by mutations in ABCC8 or KCNJ11 genes encoding the SUR1 and KIR6.2 subunits of the ATP-sensitive potassium (K_{ATP}) channel. Genetic testing has become a key tool, allowing diagnosis confirmation and predicting drug response. Mutations of the K_{ATP} channel subunit appear early in life with severe hypoglycemia and are usually diazoxide unresponsive. We are reporting a novel ABCC8 gene mutation causing a severe form of CHI in a newborn.

CASE REPORT

The Proband is a male newborn who was referred to us at 10 days of life for persistent hypoglycaemia. He is the third child of consanguineous parents, without any known family history of hypoglycemia. Pregnancy was uneventful, with no gestational diabetes notably. He was born via vaginal delivery at 38 weeks gestation, macrosomic with a birth weight of 4.46 kg (> 97th centile) and a birth length of 54.5 cm (>97th centile) causing severe perinatal asphyxia and maternal bleeding for which she underwent a hysterectomy. Hypoglycaemia started at birth needing a high dose glucose infusion (>15mg/kg/min) and investigations showed hyperinsulinimic hypoglycaemia with insulin levels of 22.9 µU/ml and C peptide: 8.55 ng/ml. Heart ultrasound revealed hypertrophic cardiomyopathy. Diazoxide was started and increased to 20 mg/kg/day but patient was unresponsive and he was then started on octreotide at 20 µ/kg/day. Genetic testing revealed a novel ABCC8 missense mutation located in exon 22 p.Asp861Tyr. This mutation has not been reported previously but is predicted to be pathogenic since the asparagine residue is highly conserved across species. A different pathogenic mutation at this codon, p.Asp861His, has previously been reported in a patient with autosomal recessive congenital hyperinsulinism who was unresponsive to Diazoxide (1). Our patient is homozygote for this mutation and both his parents are heterozygote, confirming the diagnosis of autosomal recessive congenital hyperinsulinism. Now aged 5 years, the patient shows good glycaemic control on octreotide in combination with frequent feeding. However, he has a developmental delay with epilepsy as a consequence of neonatal hypoglycemia and perinatal asphyxia requiring multiple anti-convulsant drugs.

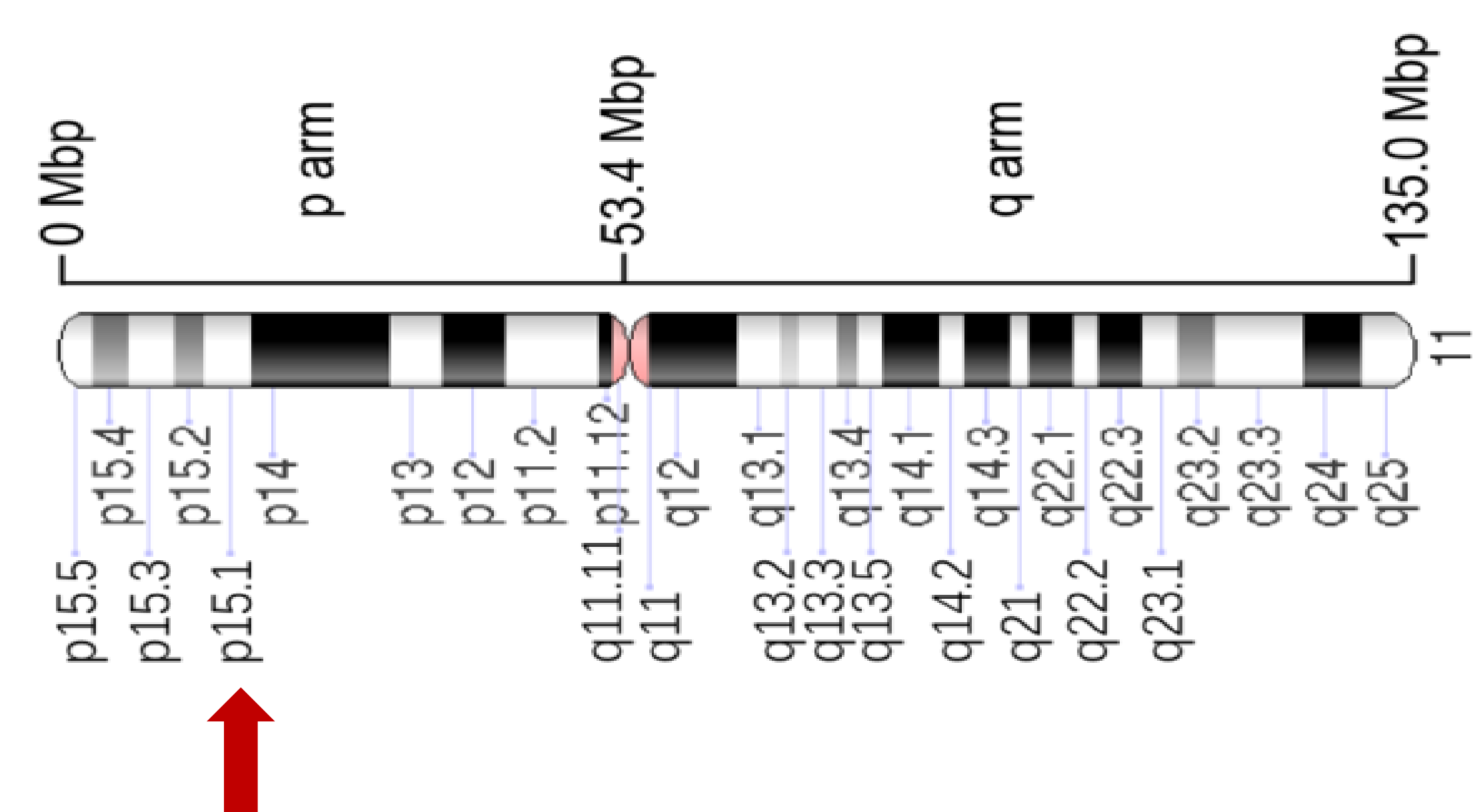


Fig 1: Chromosome 11

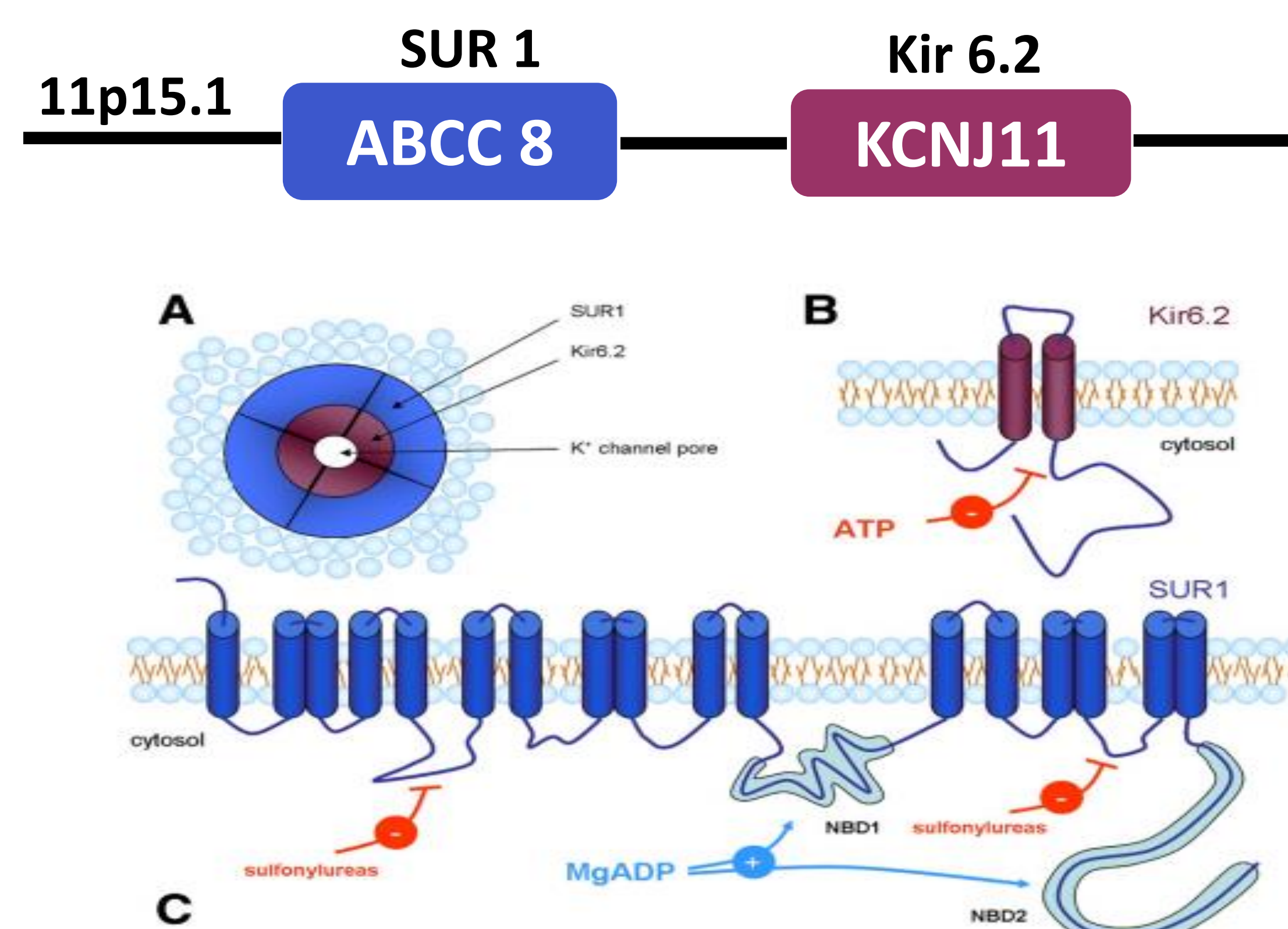


Fig 2: Schematic structure of the KATP β-cell channel. (A) Cross-section of the octameric KATP channel in the plasma membrane. (B) Transmembrane topology of a single Kir6.2 subunit. (C) Transmembrane topology of a single SUR1 subunit. Seminars in Ped Surg 2011; 20: 18-22

CONCLUSION

A novel ABCC8 gene mutation was responsible for congenital hyperinsulinism in our patient. International collaboration has opened new perspectives for patient care; in the absence of PET Scan in our country, genetic testing was the best option. Neurological outcome depends on early diagnosis and treatment and the molecular defect; in our patient birth asphyxia has worsened the prognosis.

REFERENCES

- (1) C Bellanné-Chantelot and all. ABCC8 and KCNJ11 molecular spectrum of 109 patients with diazoxide-unresponsive congenital hyperinsulinism. J Med Genet 2010; 47:752-759.
- (2) Francesca Menni and all. Neurologic Outcomes of 90 Neonates and Infants With Persistent Hyperinsulinemic Hypoglycemia. Pediatrics 2001;107;476
- (3) Zainaba Mohamed and all. Hyperinsulinaemic Hypoglycaemia: Genetic Mechanisms, Diagnosis and Management. J Clin Res Pediatr endocrinol 2012;4(4):169-181
- (4) Cécile Saint-Martin and all. KATP channel mutations in congenital hyperinsulinism. Seminars in Ped Surg 2011; 20:18-22



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