54th Annual Meeting 1-3 October
ESPE 2015 BARCELONA
European Society for Paediatric Endocrinology

A NOVEL MUTATION IN THE *ABCC8* GENE CAUSING A VARIABLE PHENOTYPE OF IMPAIRED GLUCOSE METABOLISM IN THE SAME FAMILY

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Background:
Dominantly acting loss-of-function mutations in the *ABCC8* gene, encoding the sulfonylurea receptor 1 (SUR1) subunit of the β-cell potassium channel (KATP), are usually responsible for mild diazoxide-responsive congenital hyperinsulinism (CHI). In rare cases dominant *ABCC8* mutations can cause diffuse diazoxide-unresponsive CHI.
Recent reports suggest that medically responsive CHI due to a dominant *ABCC8* mutation may confer an increased risk of diabetes mellitus (DM) in adulthood. The mechanism is not clear at present; possible explanations include a progressive failure in β-cell function due to "exhaustion", increased β-cell apoptosis as a result of raised intracellular calcium concentration and the influence of other genetic or environment factors.

Case Presentation:
The index patient (**patient n.1**) was born at 35 weeks to non consanguineous parents with a birth weight of 3900 g (> 97th percentile). Pregnancy was complicated by gestational diabetes. Biochemical diagnosis of CHI was performed during the first week of life. The patient started diazoxide (5 mg/Kg/day) when he was 3 months old because the drug was not available in his country (Albania). He was diazoxide-responder.
F-DOPA PET/CT scanning was not conclusive.
Molecular genetic analysis revealed a novel heterozygous *ABCC8* missense mutation (p.A478T). His mother (**patient n. 2**) had gestational diabetes and after delivery she fulfilled the criteria for DM. She did not present hypoglycemia during childhood. The patient's grandfather (**patient n. 3**) was diagnosed with DM at the age of 45 years. He also had no past history of hypoglycaemia.
Patient's mother and grandfather were heterozygous for the p.A478T *ABCC8* mutation.

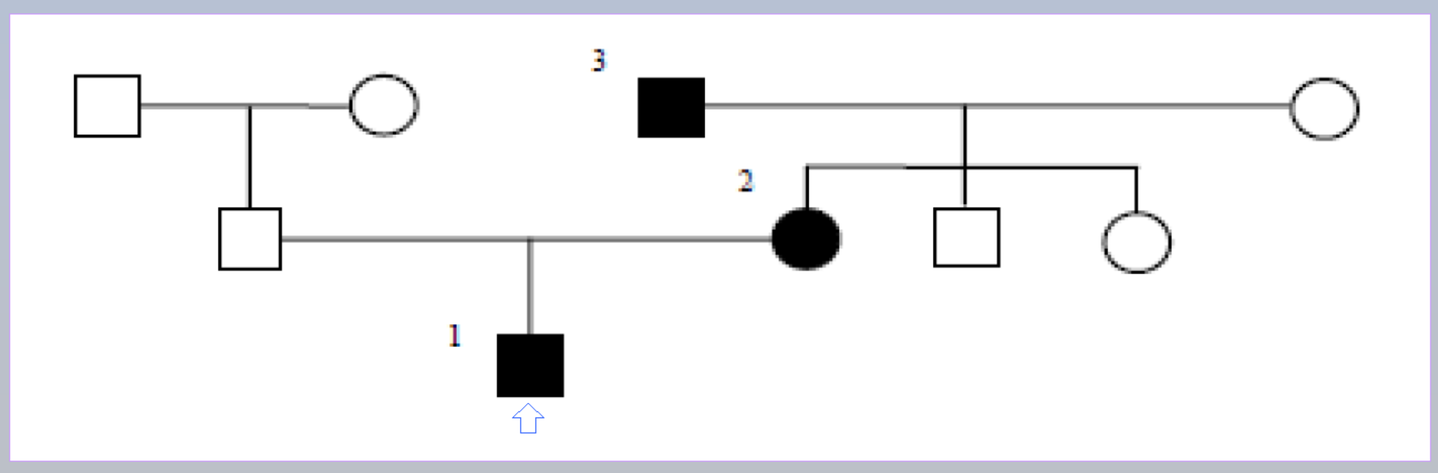

Figure: family tree (the arrow indicates the proband).

Conclusions:
Our experience confirms that dominantly acting *ABCC8* mutations can cause CHI during childhood and/or gestational diabetes and DM later in life (1,2).
The novel mutation identified in our patient was not previously reported in diazoxide-responsive forms of CHI; nevertheless a different mutation at the same residue has been reported in a family with CHI (3).
The p.A478T *ABCC8* mutation confers an increased risk of diabetes in adulthood but, as observed in our family, seems to be associated to an incomplete penetrance of hypoglycaemia in infancy.

References:
1. Huopio et al, Dominantly inherited hyperinsulinism caused by a mutation in the sulfonylurea receptor type 1. JCI 2000; 106(7):897-906.
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DOI: 10.3252/pso.eu.54espe.2015