Heterozygous glucokinase splicing mutation
Identical genotype with variable phenotype in a single family

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Introduction

Heterozygous loss of function glucokinase mutations causes maturity onset diabetes of the young (MODY) with fasting hyperglycaemia.

MODY accounts for 1-4% of paediatric diabetes cases. GCK-MODY is the most common subtype of monogenic diabetes.

The affected parent of the index case often remains undiagnosed or are misdiagnosed with early-onset type 2 diabetes.

The molecular diagnosis of MODY is important to classify the diabetes, predict prognosis and screen asymptomatic family members.

We report a 2 year girl with a glucokinase mutation who presented unusually with stress induced hyperglycaemia and normal fasting blood glucose levels.

Genetic analysis revealed that other family members, including one who had been diagnosed to have Type 2 diabetes carried the same mutation.

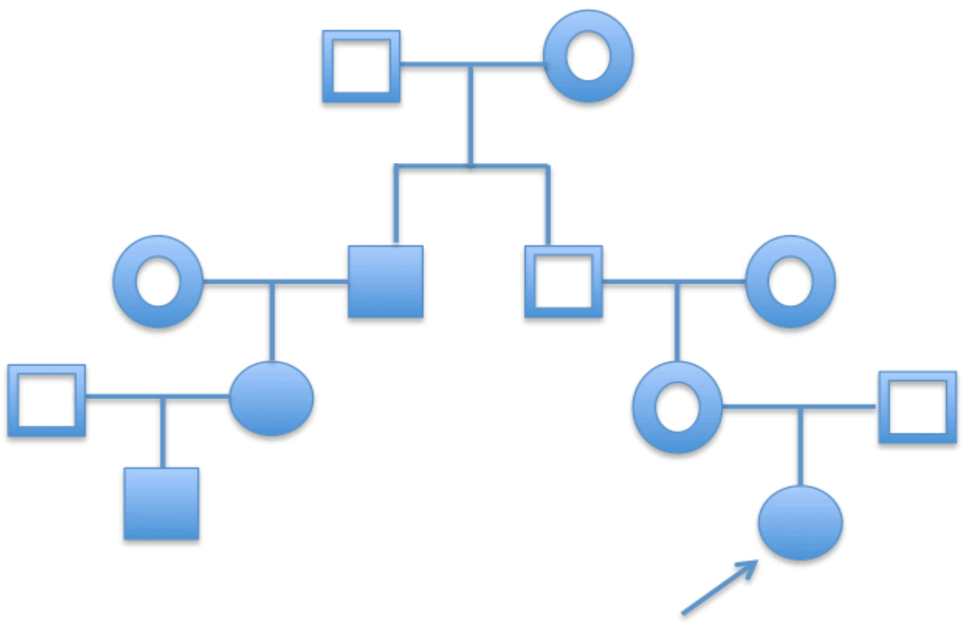

Figure 1 – Family tree

Case report

A 2 year old girl presented with wheeze and was started on Salbutamol. Her blood glucose rose to 16 mmol/L with ketonuria.

The hyperglycaemia settled after medication was stopped. Her fasting blood glucose levels were less than 4 mmol/L.

The blood glucose levels were disproportionate to the illness. Hence an OGTT was done which showed a fasting glucose level of 3.3 mmol/L and a 2 hour glucose level of 8 mmol/L.

When the results of the OGTT were discussed with mother she disclosed a family history of diabetes.

Genetic analysis revealed that the child had a heterozygous GCK mutation(c.483+2_483+16del15) predicted to cause abnormal splicing.

Mother's uncle had been previously diagnosed with type 2 diabetes. Genetic analysis revealed that he had the same GCK mutation. His daughter and grandson had fasting hyperglycaemia and also tested positive for the same mutation.

The child's mother had gestational diabetes and is awaiting genetic testing.

Conclusions

The molecular diagnosis of MODY is important to classify the diabetes, predict prognosis and screen asymptomatic family members.

In this family 4 members carried the identical mutation but presented with varying phenotypes.

Interestingly, the index case did not have fasting hyperglycaemia which is unusual for MODY with a glucokinase mutation.