



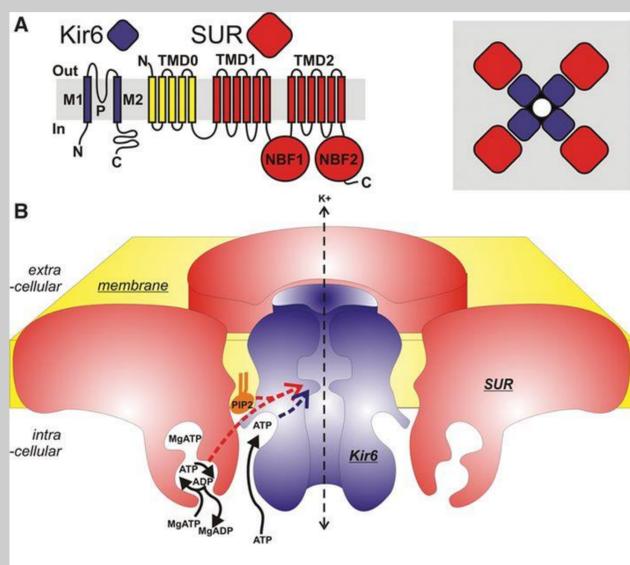
# PHENOTYPIC VARIABILITY OF IDENTICAL MUTATIONS IN THE ABCC8 GENE IN TWO FAMILIES



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K<sub>ATP</sub> channel of the pancreatic B-cell  
Nichols CG et al., Circ Research, 2013

## Background

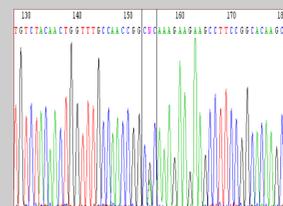
Mutations in the SUR1 subunit of the K<sub>ATP</sub> channel encoded by the ABCC8 gene can result in diverse phenotypes ranging from Transient Neonatal Diabetes (TNDM) to type 2 diabetes in adulthood. These patients may benefit from sulphonylurea treatment.

## Objective and Hypothesis

To describe the course of diabetes in two families with ABCC8 gene mutations and to assess the effect of sulphonylurea treatment.

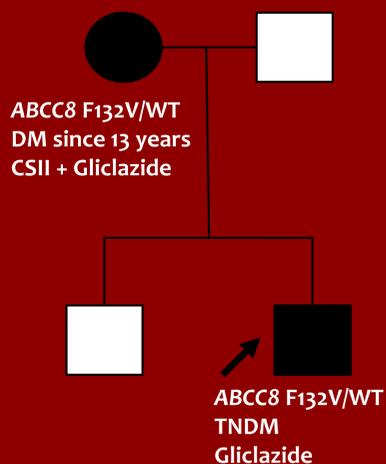
## Methods

Direct sequencing of the ABCC8 gene.  
Trial of sulphonylurea treatment.



## RESULTS

### Family 1:

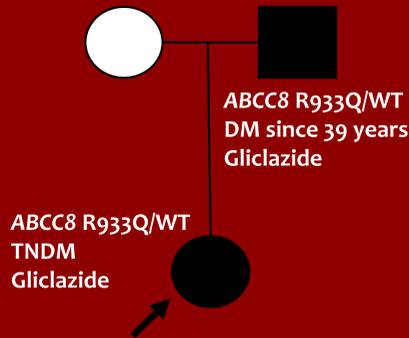


A boy presented with TNDM at the age of 12 days with glycaemia of 25 mmol/l (BW 2240 g at 35 weeks gestation). Genetic analysis revealed mutation F132V in ABCC8 in this patient. Although this mutation had been previously described in a case of Permanent NDM unresponsive to sulphonylurea (Klupa et al., Clinical Endocrinology, 2009), we performed test with glibenclamide with C-peptide increase (63.6 pmol/l to 502.5 pmol/l). The boy was then successfully treated with gliclazide which could be stopped at the age of 5 weeks. The same mutation was identified in his mother having diabetes since the age of 13 years. She was treated with insulin pump and after her son's diagnosis she was started on gliclazide which led to significant insulin dose reduction.

Time	Glycaemia	C-peptide	Insulin
0 min	5.9 mmol/l	63.6 pmol/l	<0.200 mIU/l
120 min	3.9 mmol/l	502.5 pmol/l	8.5 mIU/l

Trial of sulphonylurea treatment  
Glibenclamide dose 0,5 mg/kg

### Family 2:



A girl presented with TNDM immediately after birth with glycaemia of 30 mmol/l (BW 1530 g at 37 weeks gestation). Novel mutation R933Q in ABCC8 was identified and the response to glibenclamide was positive (C-peptide increase from 199 pmol/l to 776 pmol/l). She was successfully treated with gliclazide until the age of 7 weeks when the treatment could be stopped. The same mutation was found in her father who had been on sulphonylurea treatment for diabetes since the age of 39 years.

Time	Glycaemia	C-peptide	Insulin
0 min	8.3 mmol/l	199.0 pmol/l	<0.200 mIU/l
120 min	5.2 mmol/l	776.0 pmol/l	11.3 mIU/l

Trial of sulphonylurea treatment  
Glibenclamide dose 0,5 mg/kg

## Conclusion

• Identical mutations in the ABCC8 gene show different phenotypic expressivity and responsiveness to sulphonylurea therapy. The predictors that influence the diabetic phenotype remain unclear. We have shown that the F132V mutation previously described as unresponsive could be responsive to sulphonylurea.

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