The authors have no relevant conflicts of interest

CONGENITAL HYPERINSULINISM CAUSED BY A COMBINATION OF NOVEL HETEROZYGOUS *ABCC8* AND *KCNJ11* MUTATIONS

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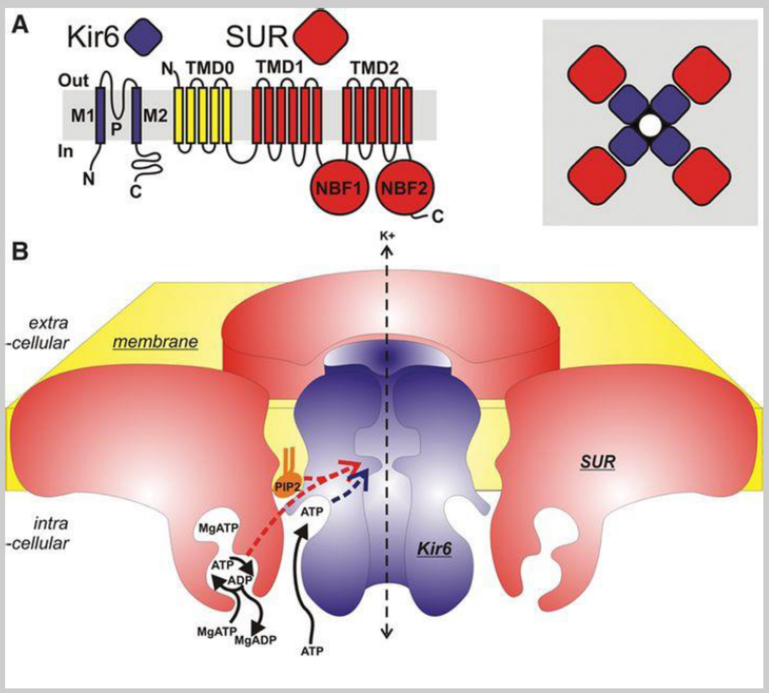


KATP channel of the pancreatic B-cell

Nichols CG et al., Circ Research, 2013

Background

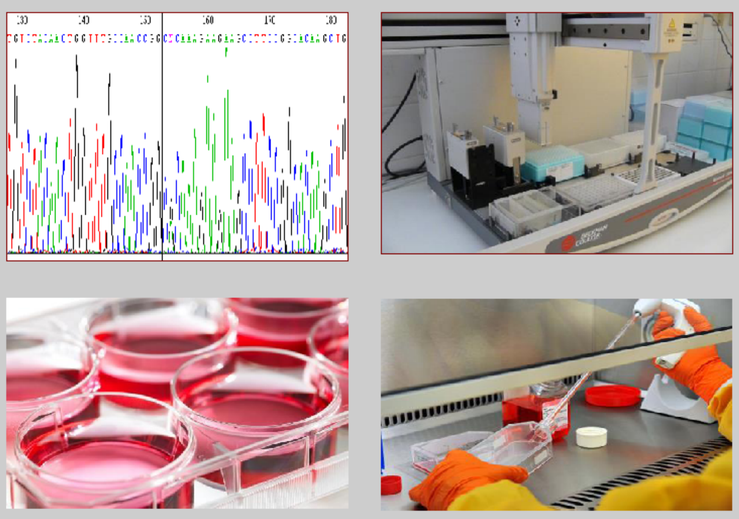
- Congenital Hyperinsulinism (CHI) is a common cause of persistent hypoglycaemia in the neonatal and infant period. It is most commonly caused by mutations in one of the K_{ATP} channel subunits, either SUR1 encoded by the gene *ABCC8* or Kir6.2 encoded by the gene *KCNJ11*. Patients carrying mutations in the *ABCC8* and *KCNJ11* genes simultaneously have not been reported yet.

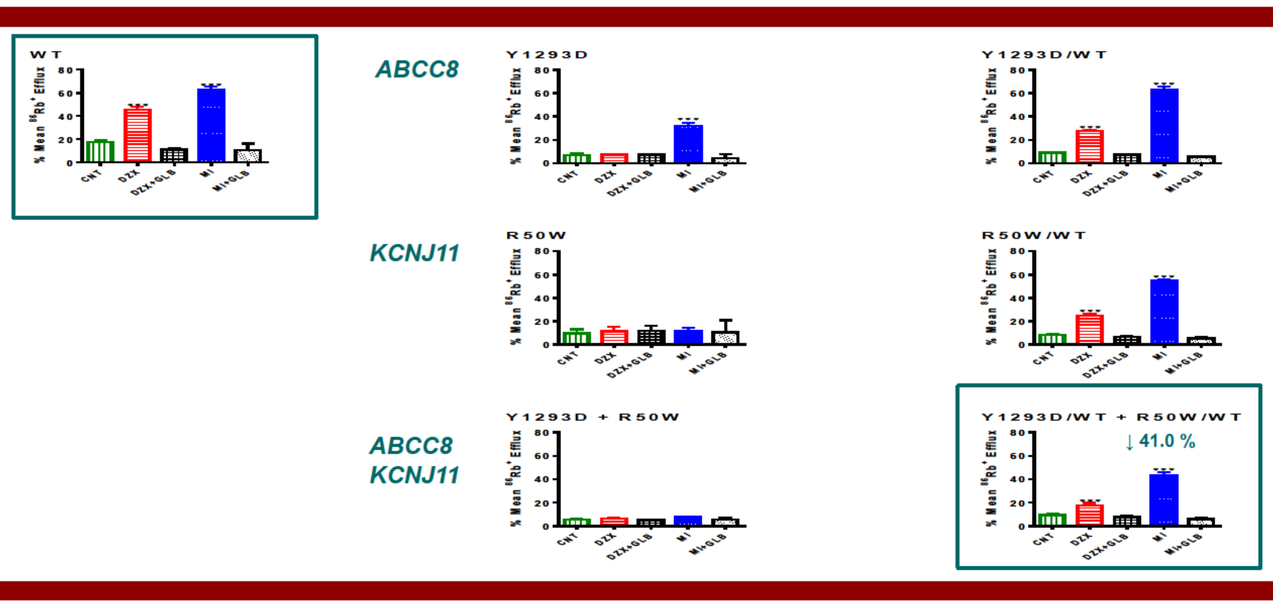
Objective and Hypothesis

- Our aim was to perform in-vitro functional analysis of a combination of novel heterozygous *ABCC8* (Y1293D) and *KCNJ11* (R50W) mutations found in one Czech patient with CHI in order to clarify the pathogenic effect on the pancreatic β-cell function.

Methods

- Novel heterozygous *ABCC8* (Y1293D) and *KCNJ11* (R50W) mutations were created in-vitro using site-directed mutagenesis. The functional analysis using radioactive Rubidium ($^{86+}$Rb) was performed in HEK293 cell cultures transfected with a combination of these novel heterozygous *ABCC8* and *KCNJ11* genes mutations. Mutant and wild type (WT) channels were exposed to different drug conditions: control (DMSO), 100μM diazoxide, 100μM diazoxide and 10μM glibenclamide, 2.5mM NaCN and 20mM 2-deoxy-D-glucose and 2.5mM NaCN, 20mM 2-deoxy-D-glucose and 10μM glibenclamide. $^{86+}$Rb efflux was measured in a liquid scintillation counter using Cherenkov radiation.





Results

- **The functional study of this unique heterozygous combination of *ABCC8* (Y1293D) and *KCNJ11* (R50W) mutations revealed that the activation by diazoxide in mutated K_{ATP} channels was decreased by 60.1 % when compared to WT channels.**

Conclusion

- We report for the first time a patient with CHI caused by a combination of novel heterozygous mutations in both of the genes (*ABCC8* and *KCNJ11*) encoding the K_{ATP} channel subunits. We have proved a pathogenic effect on the pancreatic β-cell function of this combination of mutations by an in-vitro functional study.

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