Transgenic rabbit models of long QT syndromes: implications for arrhythmia prediction and testing novel therapeutic modalities

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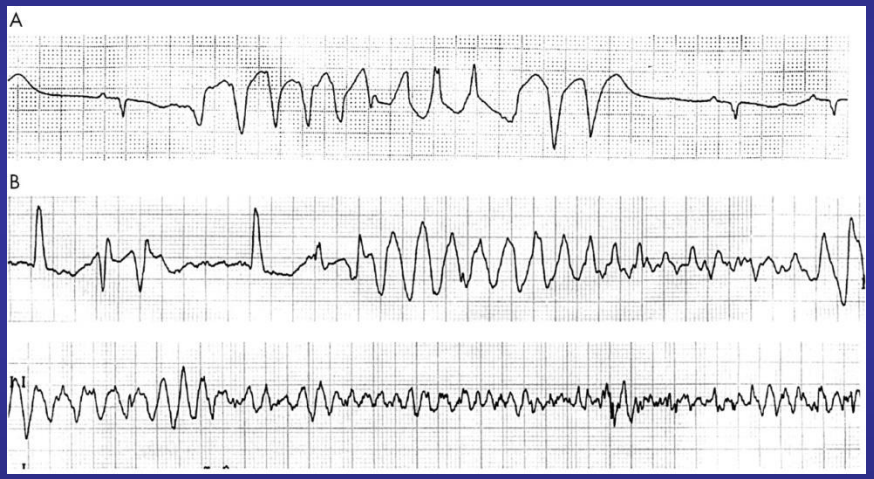
Drug-induced arrhythmias: Torsades de Pointes ventricular tachycardia

- Drug-induced Torsades de Pointes (TdP) challenges pharmaceutical and regulatory communities, poses threat to patients, leads to drug attrition



- Notoriously hard to predict in clinical settings
- Clinical incidence: 1:10 000 – 1:100 000 with non-cardiac drugs

International guidelines on non-clinical cardiac safety testing ICH-S7B

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

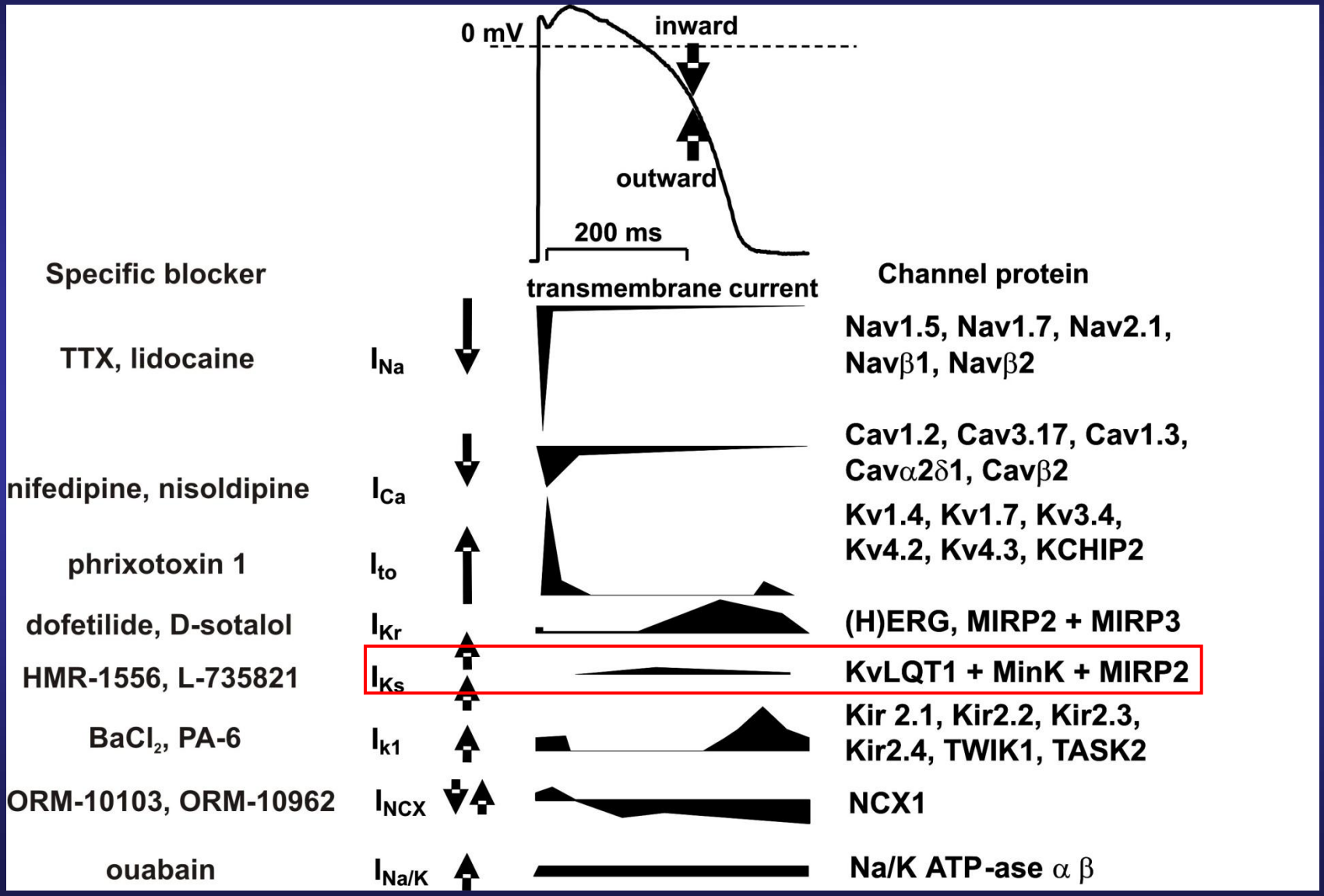
THE NON-CLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED VENTRICULAR REPOLARIZATION (QT INTERVAL PROLONGATION) BY HUMAN PHARMACEUTICALS

S7B

Current *Step 4* version
dated 12 May 2005

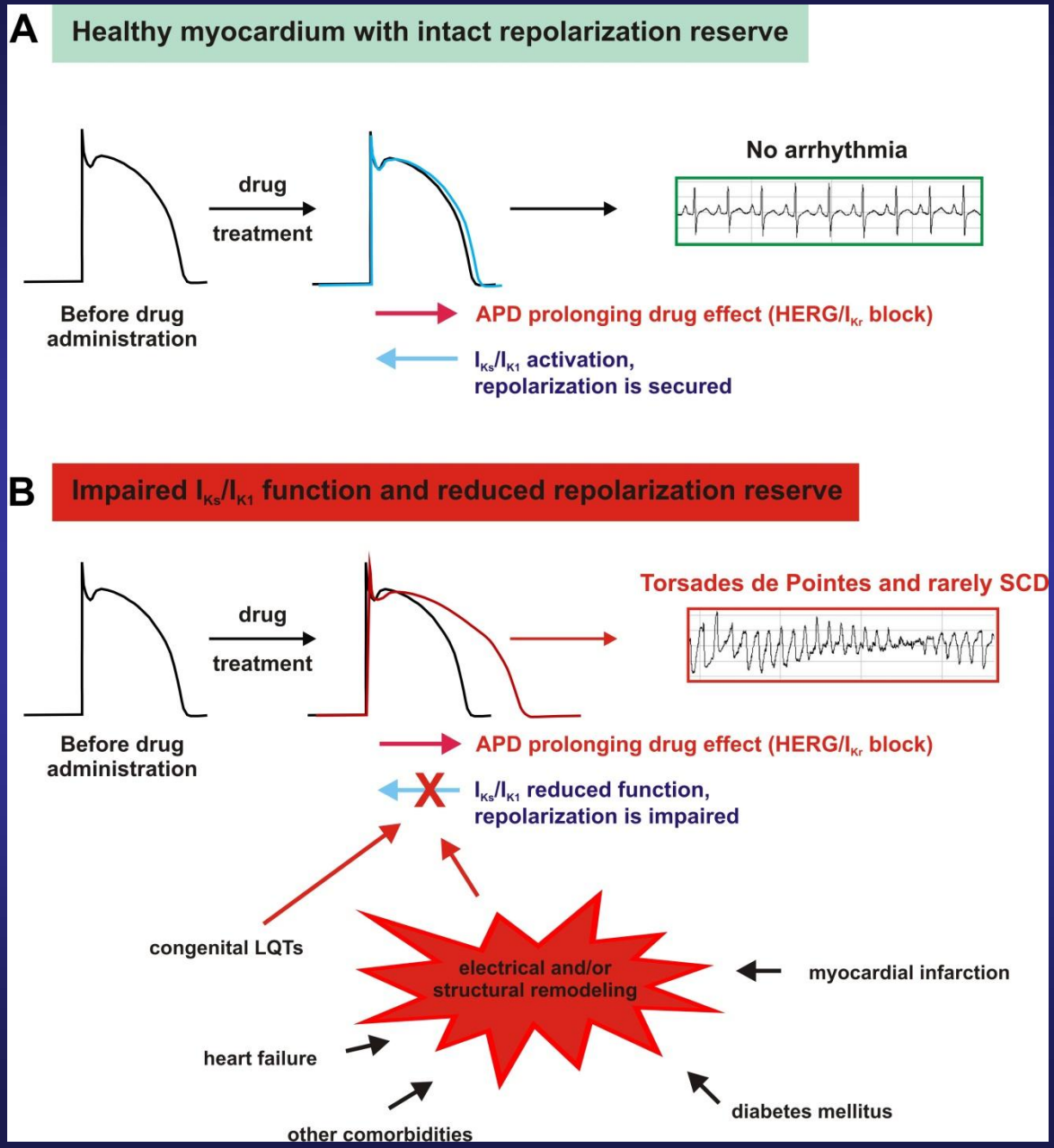
2005 guidelines recently updated: 2020

The role of I_{Ks} in cardiac repolarization



Baczkó *et al*, *Prog Biophys Mol Biol* 2016

Cardiac repolarization reserve and the role of I_{Ks} function



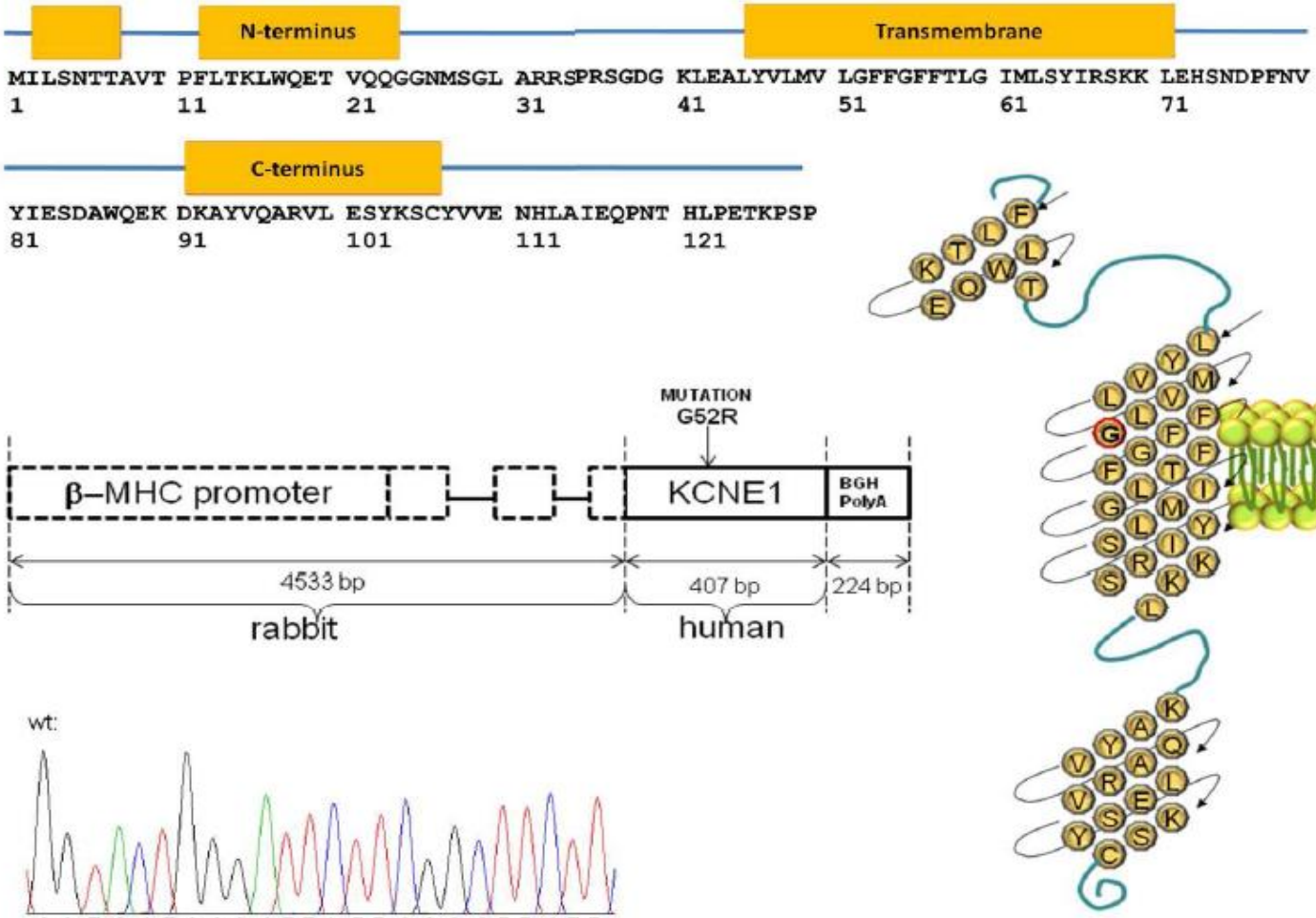
Preclinical models:

Current safety testing

Unmet need:

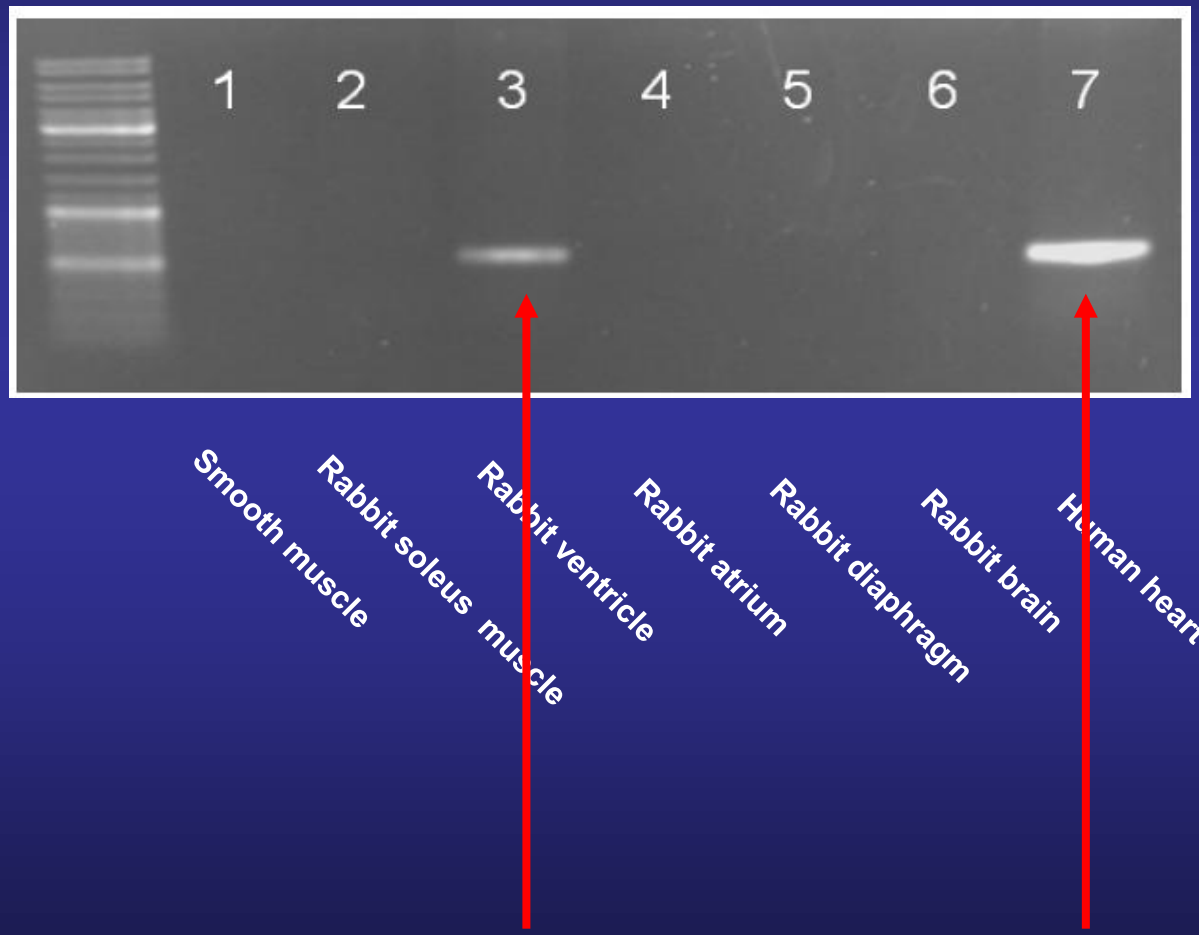
Models with remodeling & impaired repolarization reserve

Ferdinandy, Baczkó *et al*, *Eur Heart J* 2019

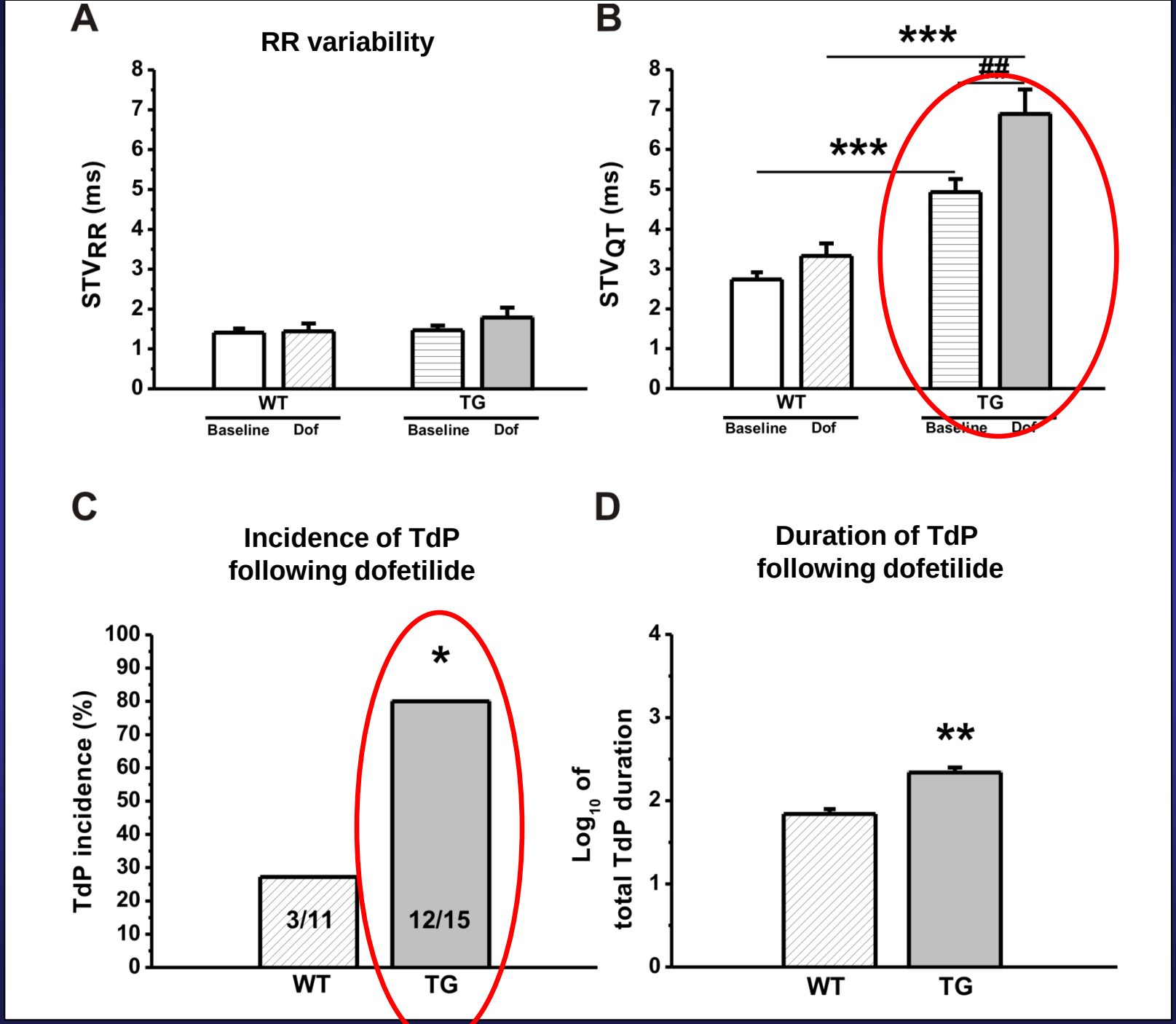


Schematic drawing of the mutation in KCNE1 polypeptide (top) and the transgene construct (middle). Mutation G to A at position 154 of human KCNE1 cDNA and wild type sequence. Sense-strand sequences are shown (bottom).

Expression profile of hKCNE1 specific mRNAs detected by RT-PCR in transgenic rabbits

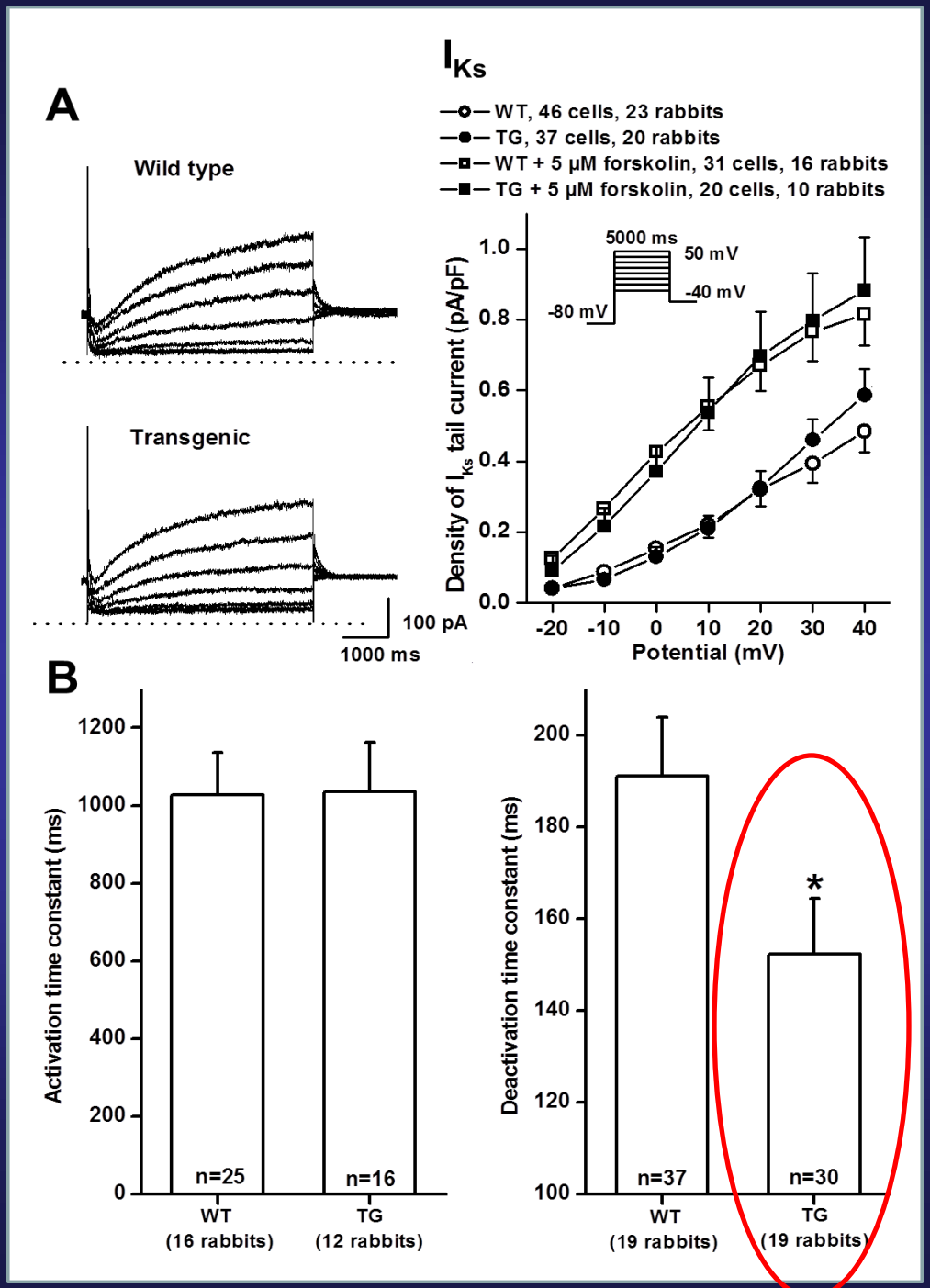


Major, Baczkó *et al*., *Brit J Pharmacol* 2016

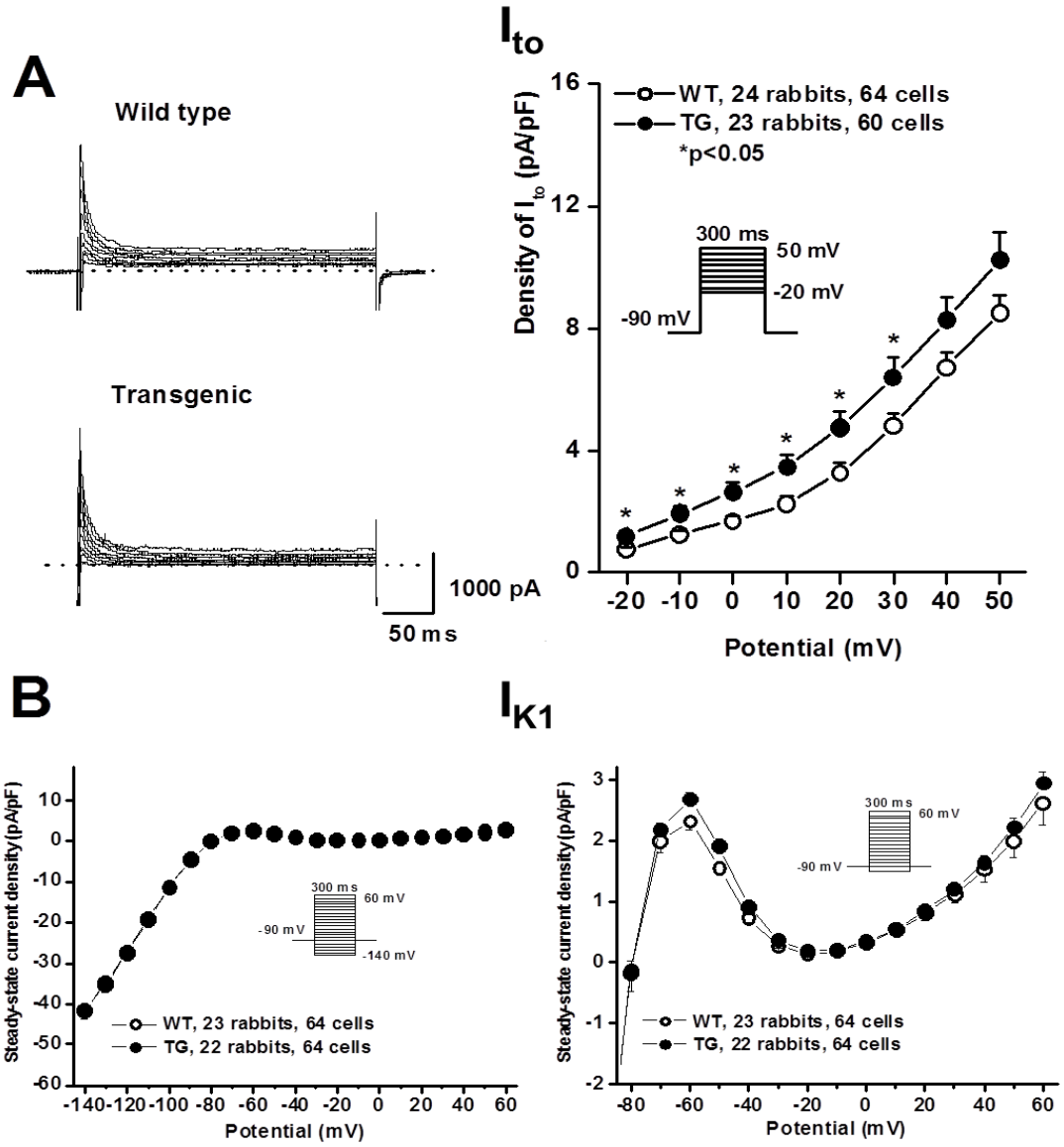


n=11-15 animals/group

Major, Baczkó *et al.*, *Brit J Pharmacol* 2016



Major, Baczkó *et al.*,
Brit J Pharmacol 2016

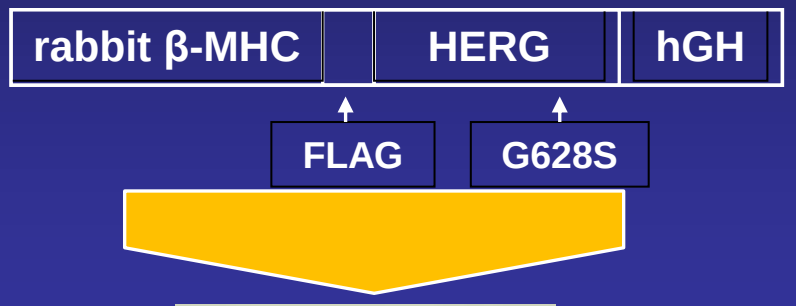


Major, Baczkó *et al.*, *Brit J Pharmacol* 2016

Double transgenic LQT2-5 rabbits

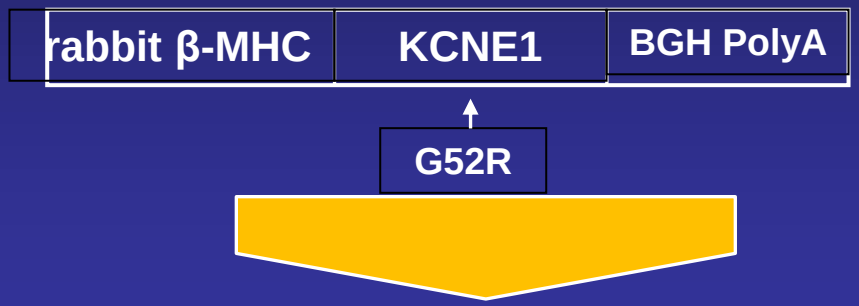
LQT2

(Brunner et al, JCI 2008)



LQT5

(Major, Baczkó et al, BJP 2016)



pathological HERG

$\underline{\text{Loss of } I_{Kr}}$

pathological minK

$\underline{I_{Ks} \text{ reduction}}$

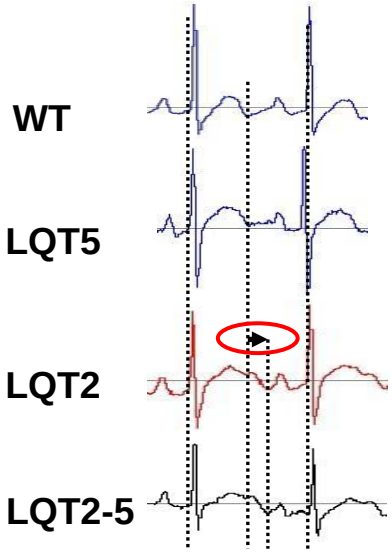
LQT2-5

(Hornyik,… Bősze, Baczkó, Odening, Brit J Pharmacol 2020)

β-MHC: beta - myosin heavy chain promoter

Telemetric ECG from conscious rabbits

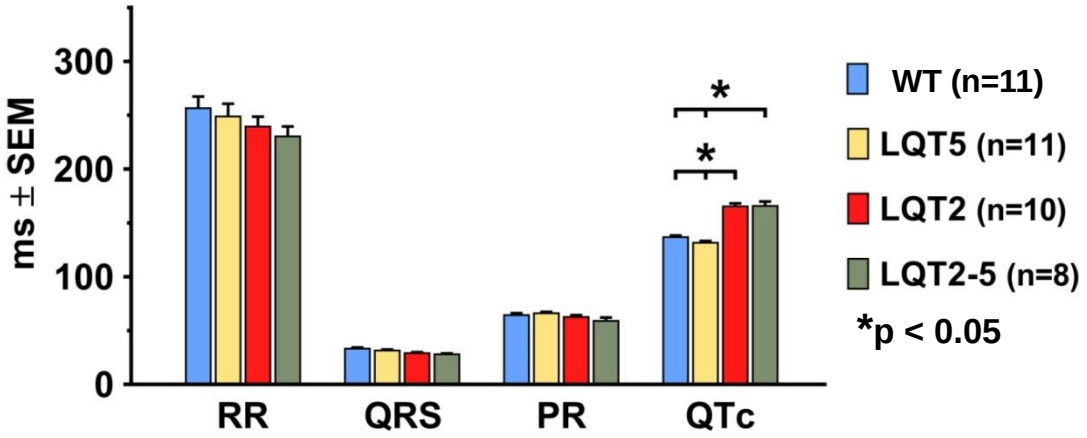
Control ECG



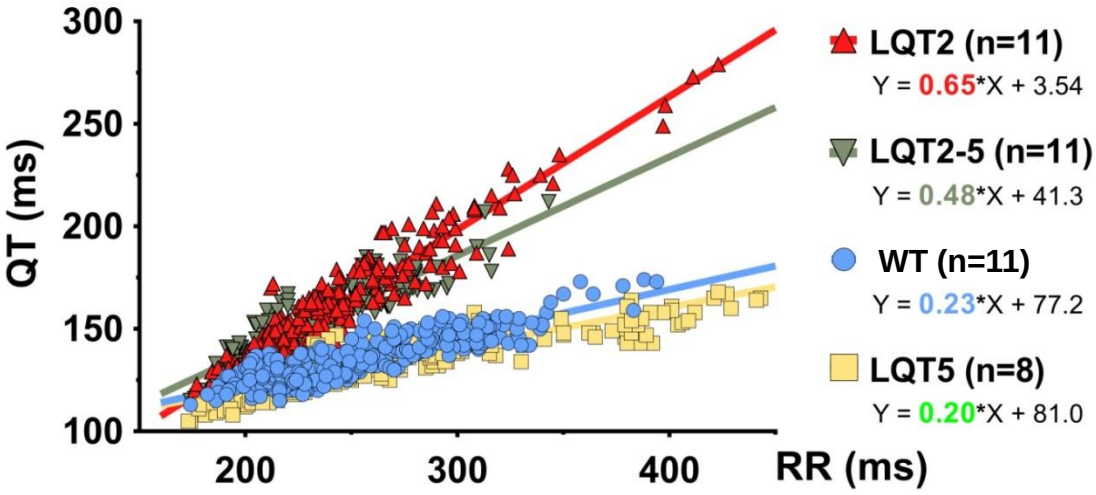
	STV_{QT}	$T_{peak-end}$ (ms)
WT	2.2±0.3	32.2±1.2
LQT5	2.1±0.2	32.2±1.5
LQT2	3.0±0.1	42.6±1.7
LQT2-5	3.1±0.3	41.5±0.7

*p < 0.05

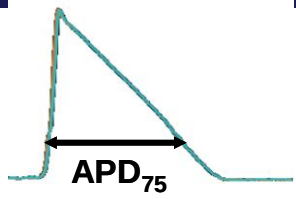
ECG parameters (24 h average values)

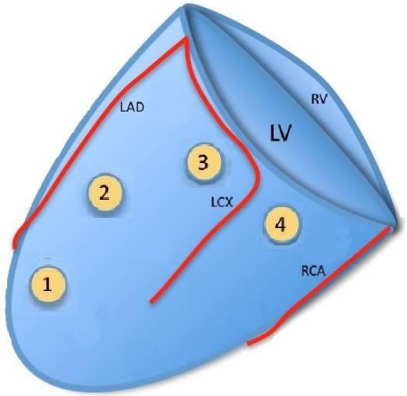


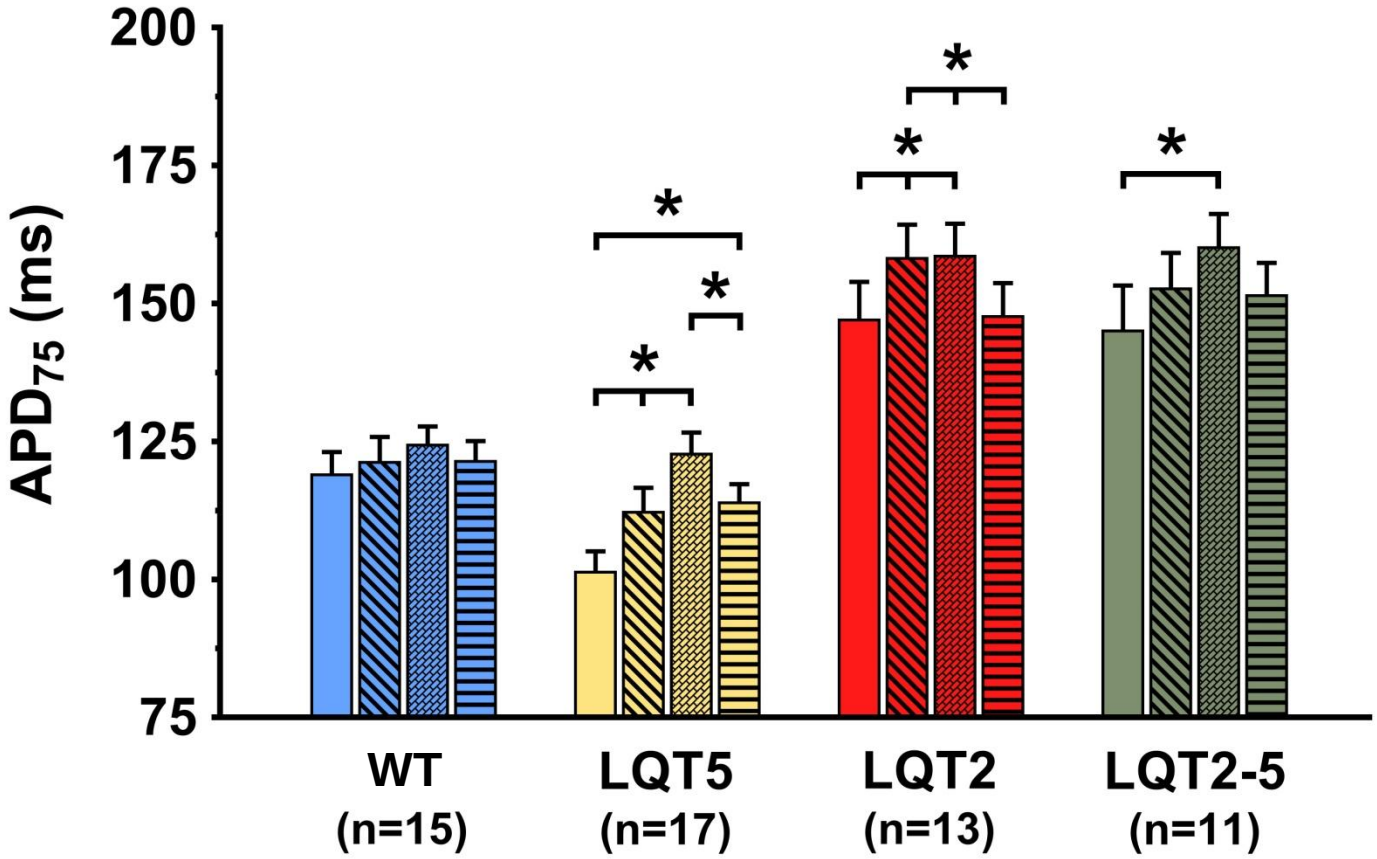
QT - RR relationship



Regional differences in APD_{75} (*ex vivo*)



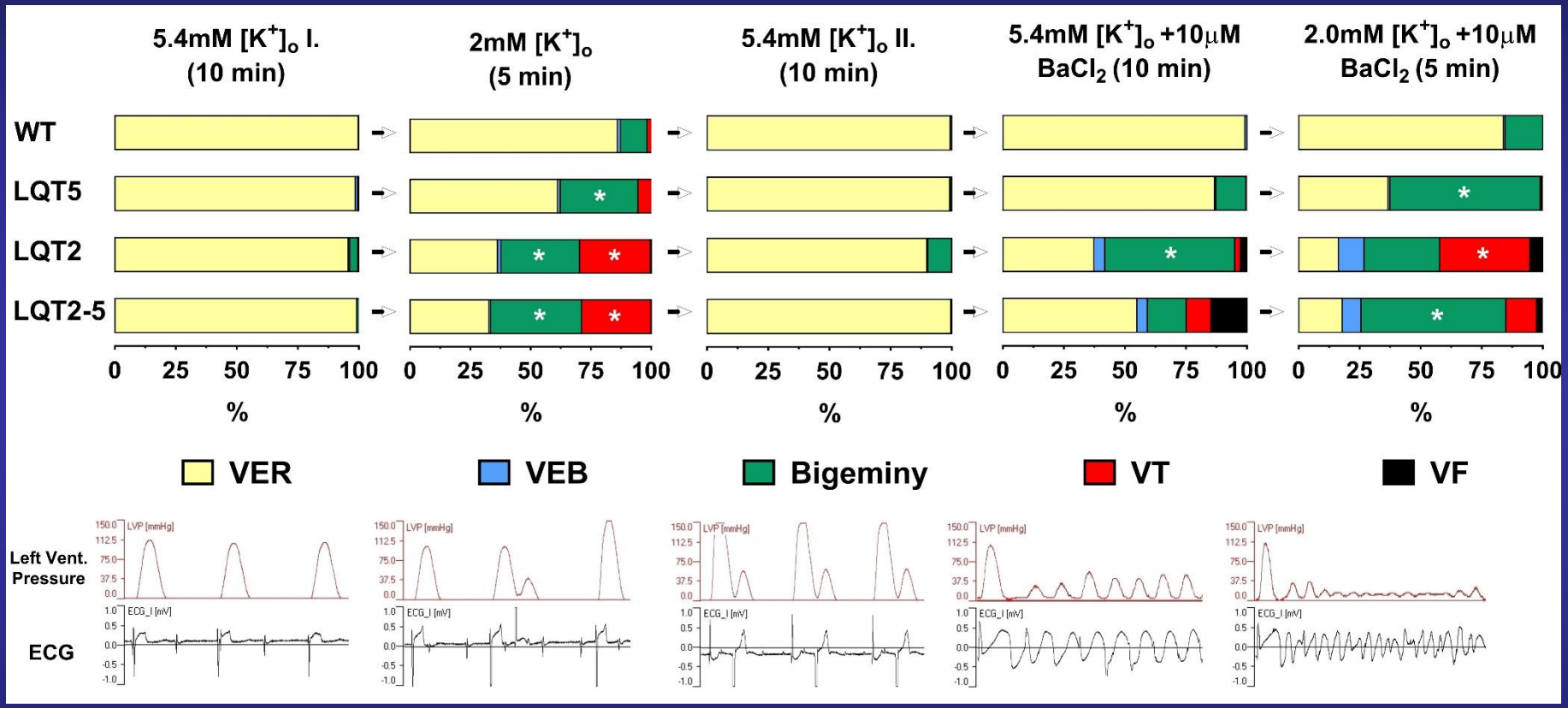




MAP1 1
MAP2 2
MAP3 3
MAP4 4

*p < 0.05

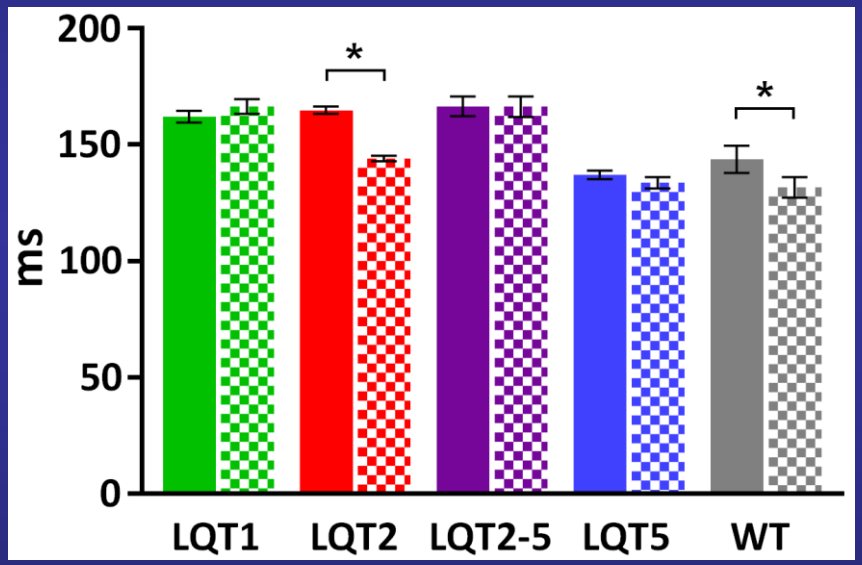
Arrhythmia provocation (*ex vivo*, AV-ablated hearts)



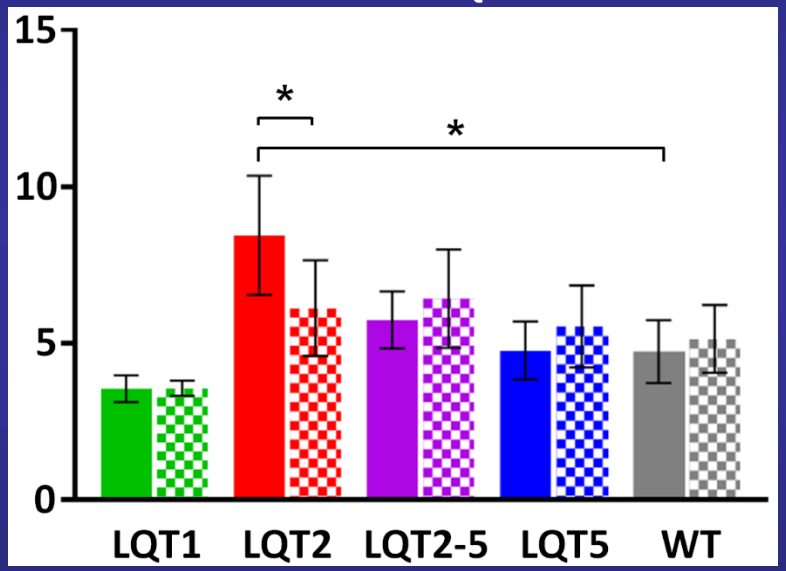
Hornyik, … Baczkó, Odening *Brit J Pharmacol* 2020

Repolarization-normalizing effect of DHA in the transgenic LQT2 rabbit model

DHA-induced QTc shortening



DHA-induced STV_{QT} changes

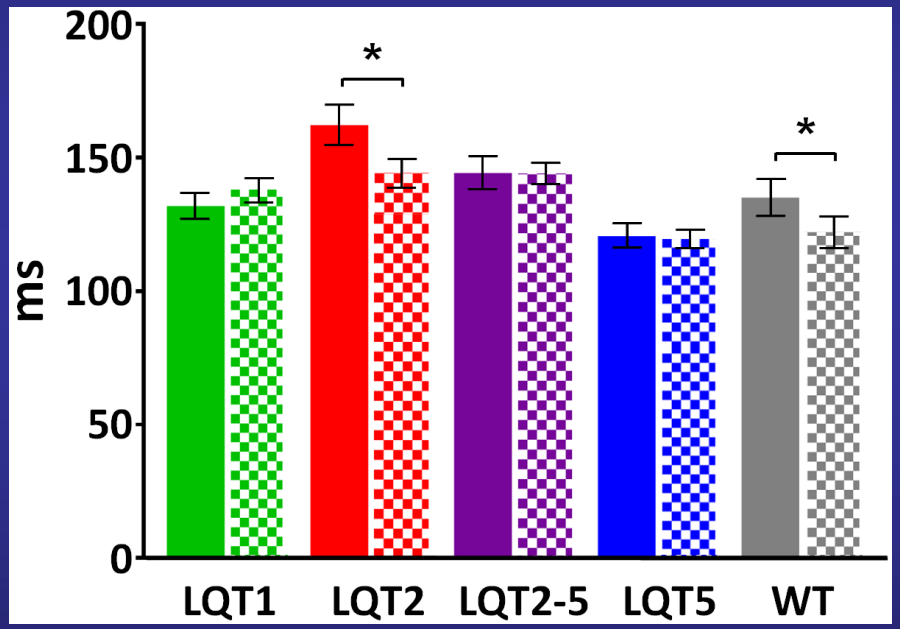


DHA: docosahexaenoic acid (I_{Ks} activator, 10 μM); STV_{QT}: short-term variability of the QT interval

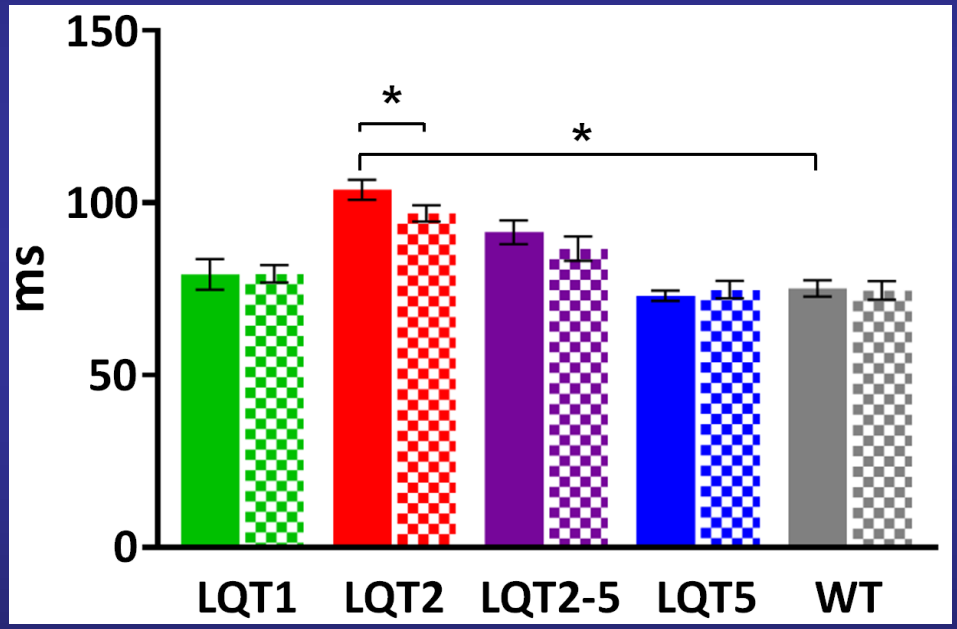
Castiglione, Hornyik, … Baczkó, Odening *Europace* 2022

Repolarization-normalizing effect of DHA in the transgenic LQT2 rabbit model

DHA-induced APD_{75} shortening



DHA-induced APD_{90-30} changes



DHA: docosahexaenoic acid (I_{Ks} activator, 10 μM); APD: action potential duration

Castiglione, Hornyik, … Baczkó, Odening *Europace* 2022

Conclusions

- LQT2, LQT5 and LQT2-5 transgenic rabbits demonstrate pronounced increase in various pro-arrhythmic biomarkers
- cLQT rabbits are susceptible to arrhythmia development and may represent useful models for testing the proarrhythmic potential of new drugs under development
- cLQT rabbits are suitable for testing novel therapeutic modalities in LQT syndromes

Acknowledgements

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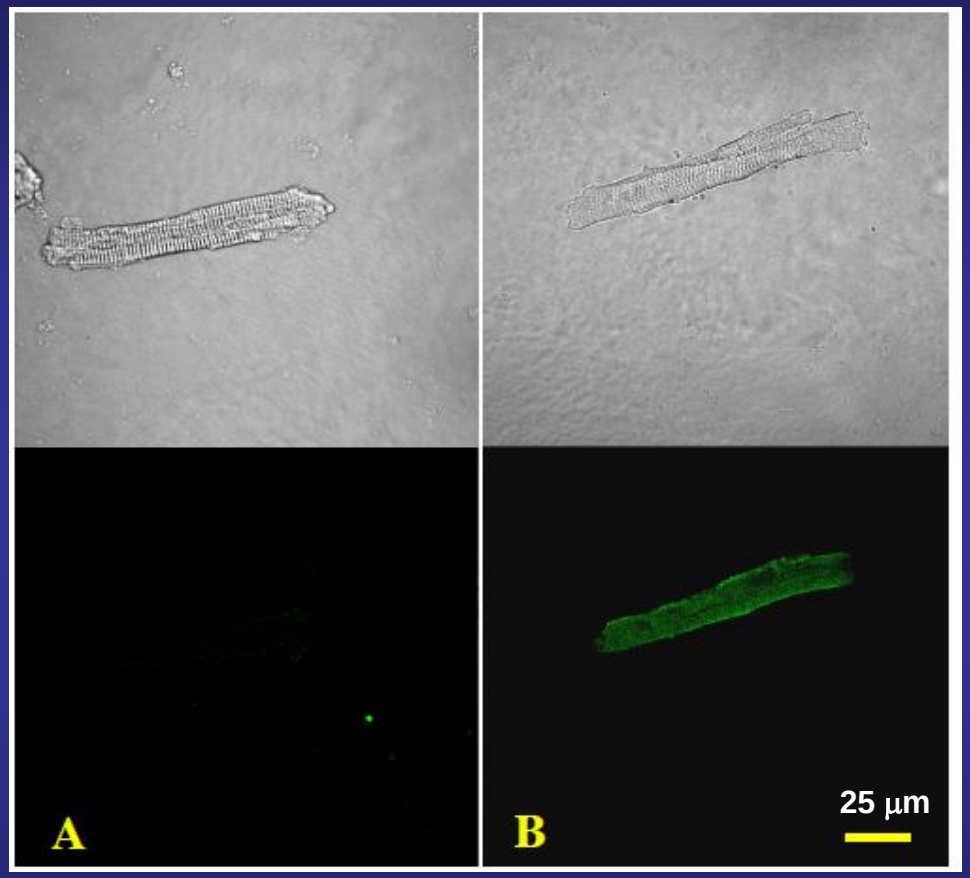
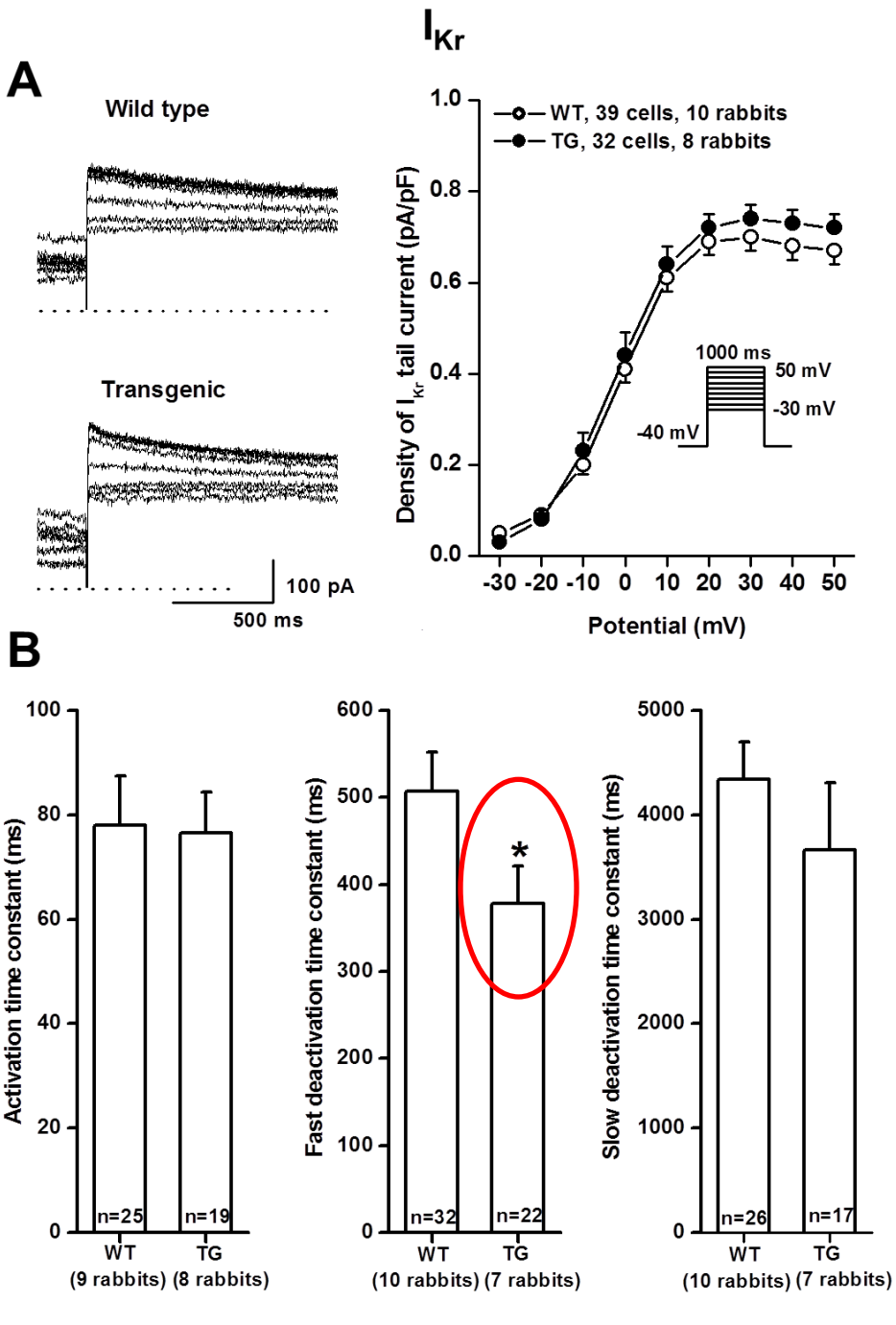
Rabbit ventricular myocytes labelled with anti-human KCNE1 antibody



non-transgenic G52R transgenic

Major, Baczkó *et al*., *Brit J Pharmacol* 2016



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Brit J Pharmacol 2016