KCNQ2 discovery and research: what do we know and where to go

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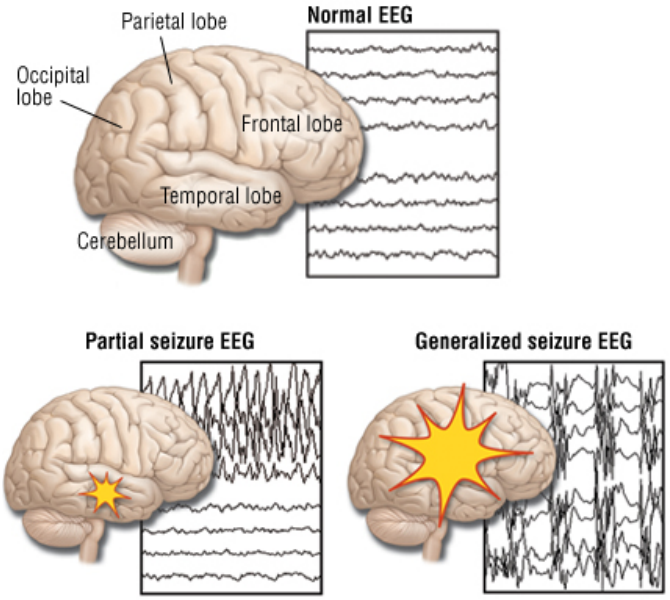
INTRODUCTION: WHAT IS EPILEPSY?

Epilepsy

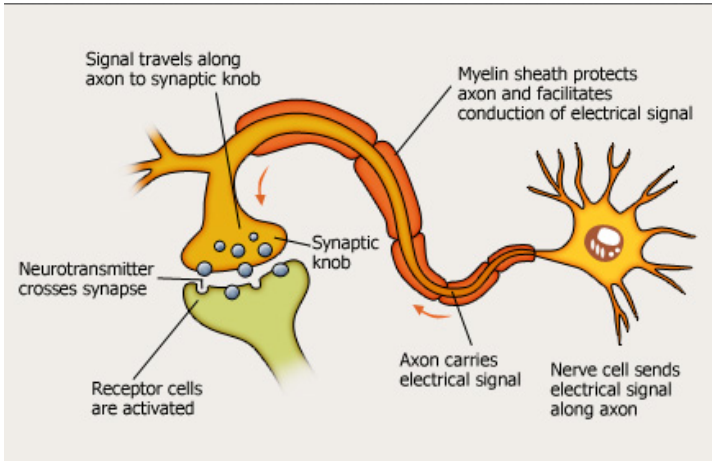
Common

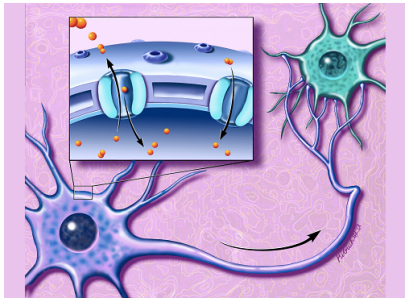
- Prevalence 4-8/1000
- Life time incidence 3%

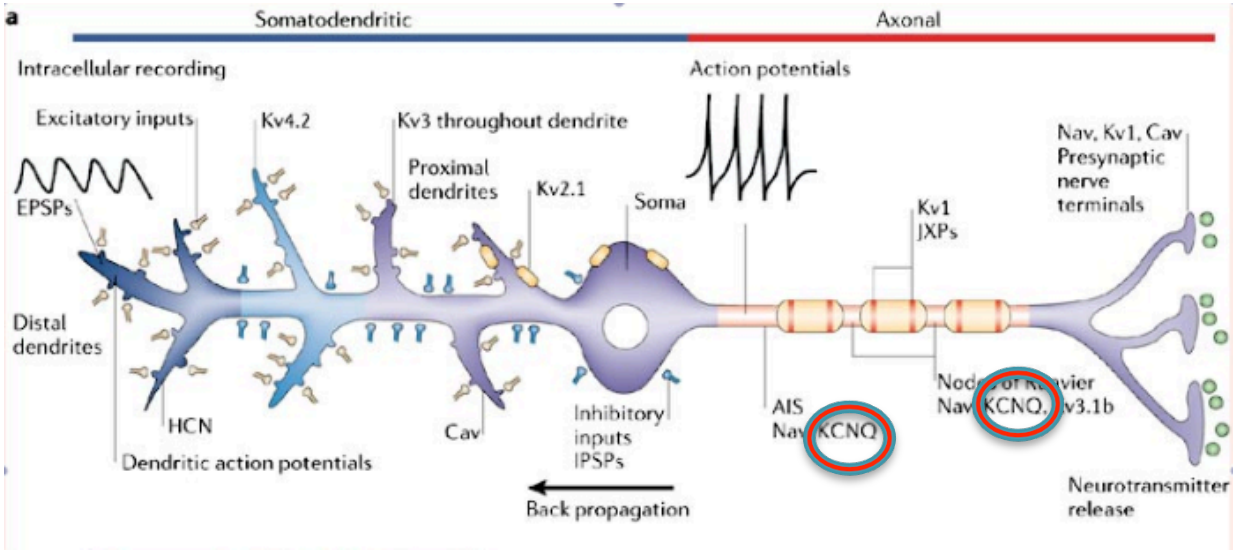
Key symptom = seizures



Normal neuronal function

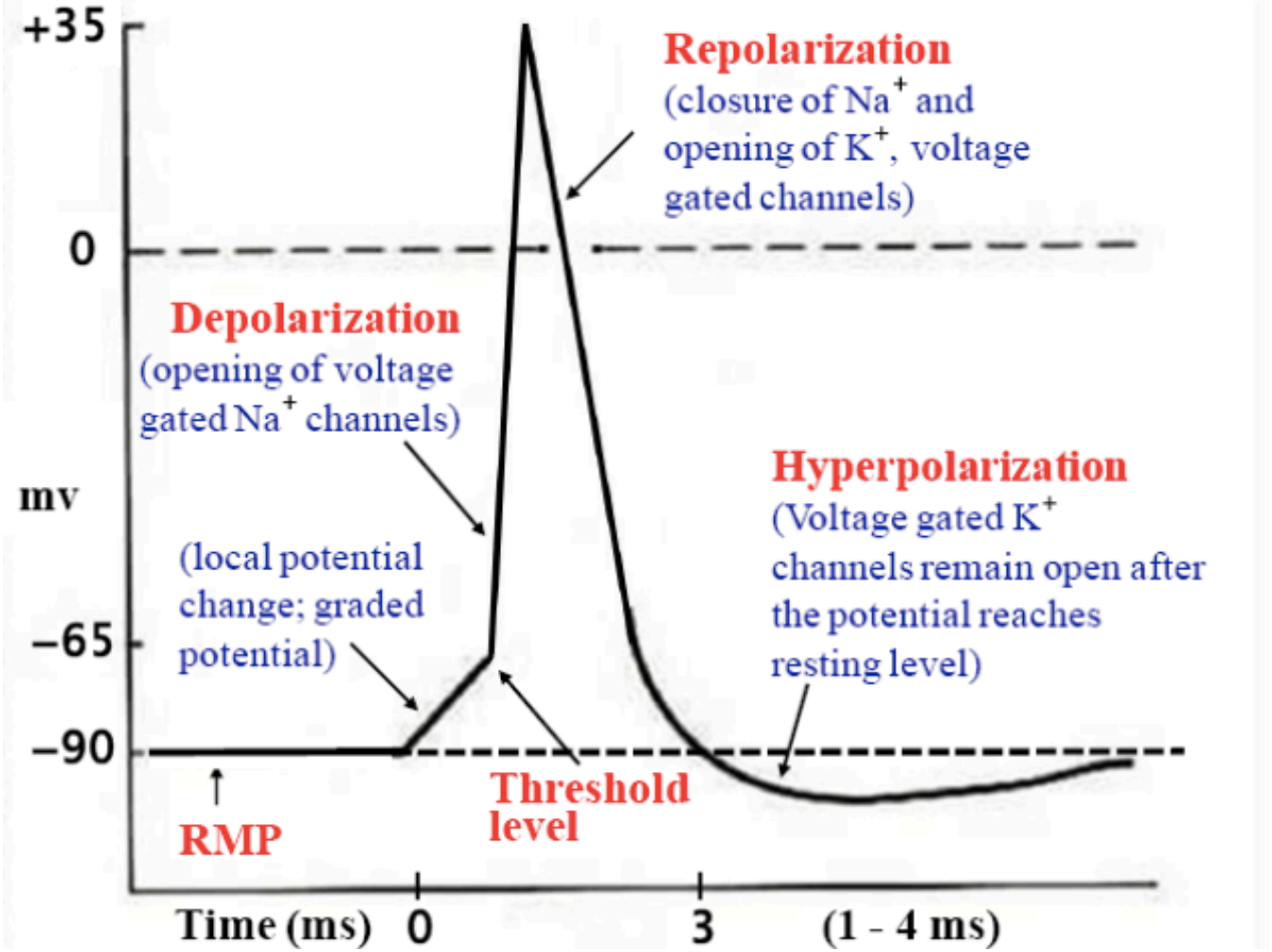






Nature Reviews 2006

Action potential



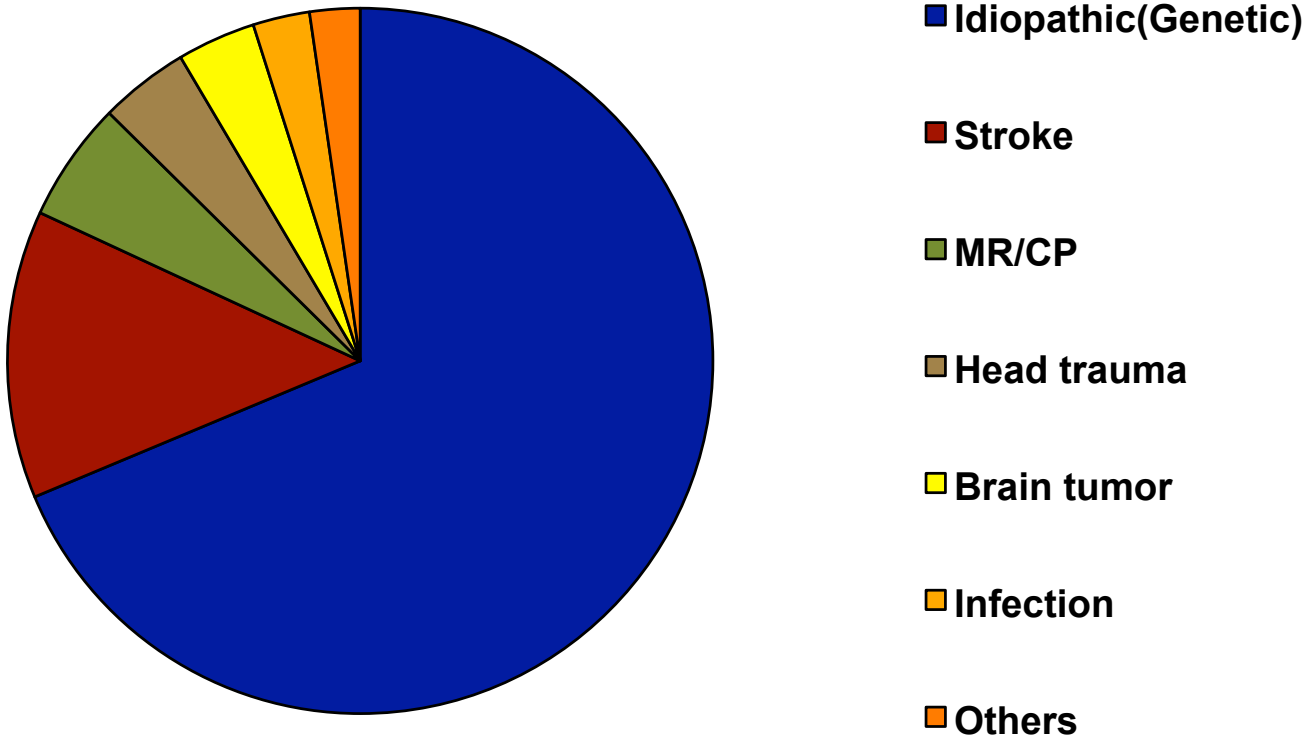
Epilepsy

- Disturbance in balance excitatory / inhibitory forces

↓ Inhibition

↑ Excitation

Causes of epilepsy



From: Annegers JF. The Epidemiology of epilepsy. In: Elaine Wyllie. The Treatment of Epilepsy.

Genes linked to epilepsy

ALG13	GABRG2	PLCB1
ARHGEF9	GRIN2A	PRRT2
ARX	GRIN2B	PNKP
ATP1A2	HCN1	SCN1A
CDKL5	KCNJ11	SCN1B
CHD2	KCNQ2	SCN2A
CHRNA4	KCNQ3	SCN8A
CHRNB2	KCNMA1	SLC25A22
CHRNA2	KCNT1	SLC2A1
DEPDC5	LGI1	SPTAN1
FOXG1	MEF2C	STXBP1
GABRA1	NRX1	SYNGAP1
GABRB3	PCDH19	TBC1D24

Ion channel genes

DISCOVERY OF KCNQ2 IN EPILEPSY

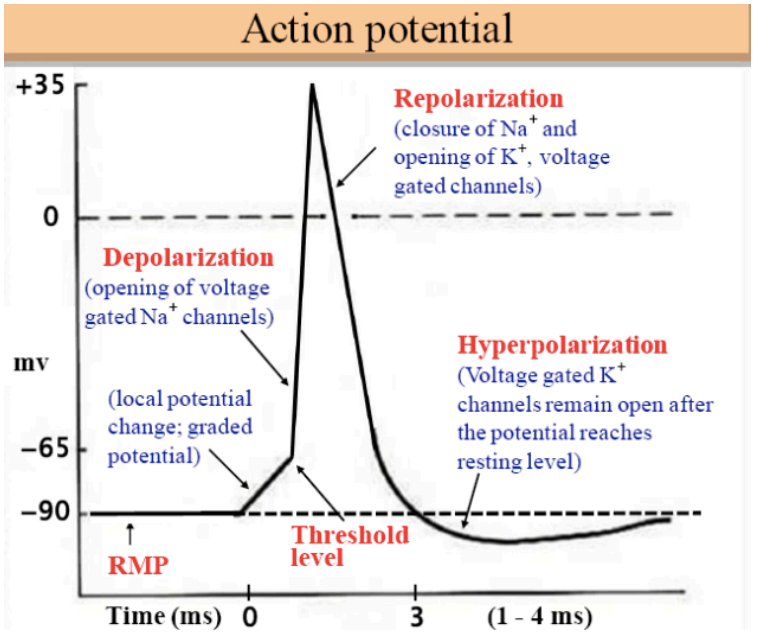
Voltage gated potassium channels

- Humans: > 70 potassium channel genes

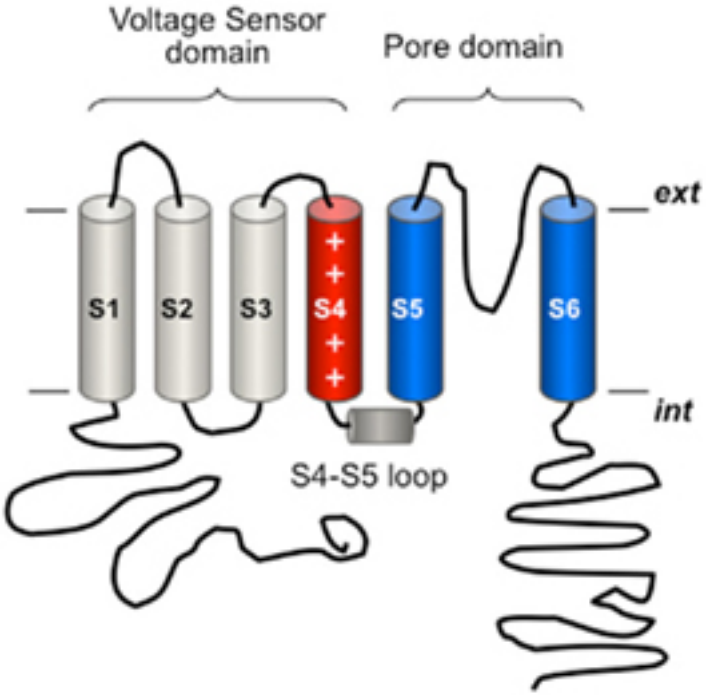
- Small family of voltage gated KCNQ genes: KCNQ1-5
  - KCNQ1: cardiac arrythmia
  - KCNQ2/3: epilepsy
  - KCNQ4: deafness

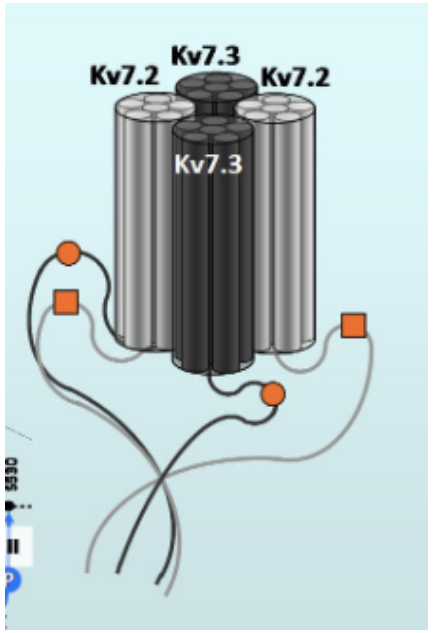
KCNQ2

- Encoding voltage gated potassium channel subunit $K_v7.2$
  - Hyperpolarisation
  - Stabilizes neuronal excitability



Heteromeric *KCNQ2/KCNQ3* channels



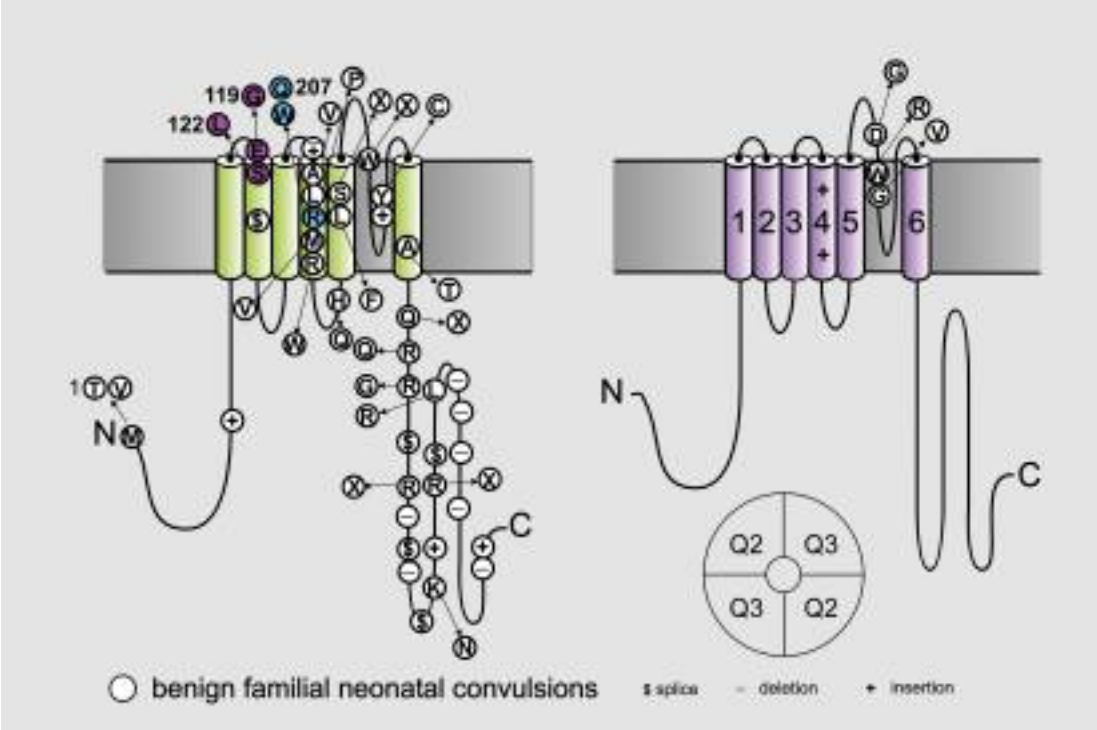


Front. Pharmacol., 23 March 2012

1998: *KCNQ2* mutations in Benign Familial Neonatal Seizures (BFNS)

- Mostly familial
- Seizures onset between 2 - 8 days, remission within first months of life
- Investigations normal
- Psychomotor development normal

KCNQ2 and *KCNQ3* in BFNS



Where the story starts

- *KCNQ2* screening offered for neonatal seizures in diagnostic unit
  - 2010: 1 patient: refractory seizures and psychomotor regression

- Literature
  - 4 case reports of patients with neonatal seizures and intellectual disability

(Dedek et al 2003, Borgatti et al 2004, Schmitt et al 2005, Steinlein et al. 2007)

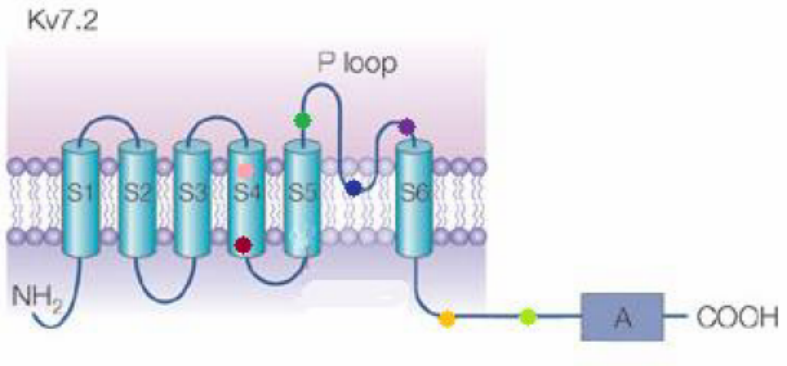
Methods

- *KCNQ2* and *KCNQ3* screening in 80 patients with unexplained neonatal or early onset epileptic encephalopathy
  - Onset of seizures < 3 months
  - Slowing of psychomotor development
  - Metabolic screening normal
  - Imaging: no explanation
  - Genetic screening for relevant genes normal

Weckhuysen et al, Ann. Neurol. 2012

Results

- No *KCNQ3* mutations
- 7 novel *KCNQ2* mutations in 8/80 patients (10%)
- Inheritance
  - Heterozygous
  - Almost all mutations *de novo*
  - 1 mosaic father with benign neonatal seizures



Weckhuysen et al, Ann. Neurol. 2012

Ann Neurol. 2012 Jan;71(1):15-25. doi: 10.1002/ana.22644.

KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy.

Weckhuysen S, Mandelstam S, Suls A, Audenaert D, Deconinck T, Claes LR, Deprez L, Smets K, Hristova D, Yordanova I, Jordanova A, Ceulemans B, Jansen A, Hasaerts D, Roelens F, Lagae L, Yendle S, Stanley T, Heron SE, Mulley JC, Berkovic SF, Scheffer IE, de Jonghe P.

Neurogenetics Group, VIB-Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium.

Whole Exome Sequencing Identifies *KCNQ2* Mutations in Ohtahara Syndrome

Hirotomo Saitsu, MD, PhD,[1] Mitsuhiro Kato, MD, PhD,[2] Ayaka Koide, MD, PhD,[3] Tomohide Goto, MD, PhD,[3] Takako Fujita, MD,[4] Kiyomi Nishiyama, PhD,[1]

Epilepsia. 2013 Jul;54(7):1282-7. doi: 10.1111/epi.12200. Epub 2013 Apr 26.

Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation.

Kato M, Yamagata T, Kubota M, Arai H, Yamashita S, Nakagawa T, Fujii T, Sugai K, Imai K, Uster T, Chitayat D, Weiss S, Kashii H, Kusano R, Matsumoto A, Nakamura K, Oyazato Y, Maeno M, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Saito K, Hayasaka K, Matsumoto N, Saitsu H.

Orphanet J Rare Dis. 2013 May 22;8:80. doi: 10.1186/1750-1172-8-80.

Similar early characteristics but variable neurological outcome of patients with a de novo mutation of KCNQ2.

Milh M, Boutry-Kryza N, Sutera-Sardo J, Mignot C, Auvin S, Lacoste C, Villeneuve N, Roubertie A, Heron B, Carneiro M, Kaminska A, Altuzarra C, Blanchard G, Ville D, Barthez MA, Heron D, Gras D, Afenjar A, Dorison N, Doummar D, Billette de Villemeur T, An I, Jacquette A, Charles P, Perrier J, Isidor B, Vercueil L, Chabrol B, Badens C, Lesca G, Villard L.

Neurology. 2013 Nov 5;81(19):1697-703. doi: 10.1212/01.wnl.0000435296.72400.a1. Epub 2013 Oct 9.

Extending the KCNQ2 encephalopathy spectrum: Clinical and neuroimaging findings in 17 patients.

Weckhuysen S, Ivanovic V, Hendrickx R, Van Coster R, Hjalgrim H, Møller RS, Grønborg S, Schoonjans AS, Ceulemans B, Heavin SB, Eltze C, Horvath R, Casara G, Pisano T, Giordano L, Rostasy K, Haberlandt E, Albrecht B, Bevot A, Benkel I, Syrbe S, Sheidley B, Guerrini R, Poduri A, Lemke JR, Mandelstam S, Scheffer I, Angriman M, Striano P, Marini C, Suls A, De Jonghe P; KCNQ2 Study Group.

Neurology. 2014 Jan 28;82(4):368-70. doi: 10.1212/WNL.0000000000000060. Epub 2013 Dec 26.

KCNQ2 encephalopathy: delineation of the electroclinical phenotype and treatment response.

Numis AL[1], Angriman M, Sullivan JE, Lewis AJ, Striano P, Nabbout R, Cilio MR.

- September 2014
  - 62 patients with KCNQ2 encephalopathy described in literature
    - 44 different mutations

WHAT DO WE KNOW ALREADY?

CLINICAL PRESENTATION

KCNQ2 encephalopathy

- 10% of patients with neonatal epileptic encephalopathy of unknown etiology
- *KCNQ2* encephalopathy mutations
  - Novel: not reported in BFNS
- Inheritance
  - *de novo*
  - 1 mosaic father with benign seizures

KCNQ2 encephalopathy

- Neonatal onset

  1 patient onset at 5 months

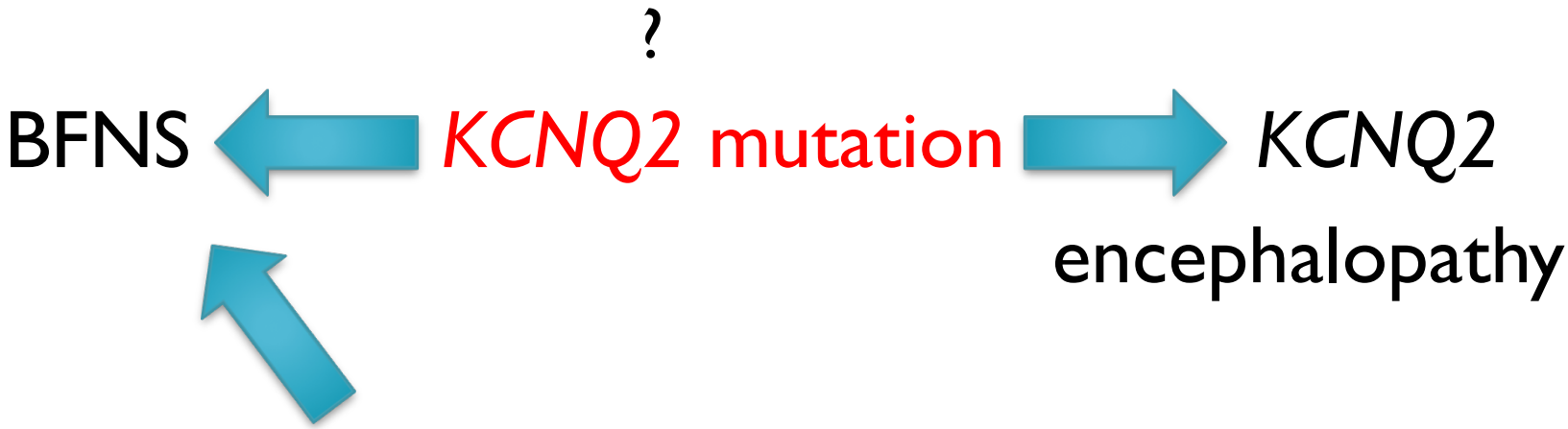
- Seizure type at onset

  Motor seizures, prominent tonic component

  Often autonomic features: apnea, desaturation, bradycardia

- Dramatic onset, multiple sz daily
- Abnormalities on EEG
- Range of severity of intellectual disability

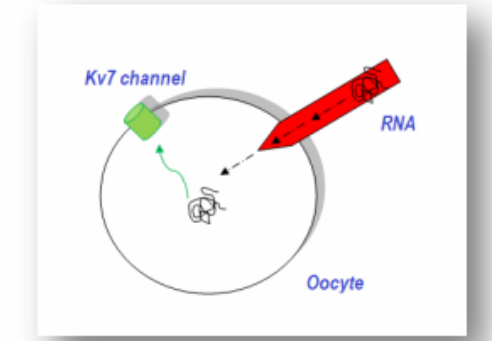
MECHANISM

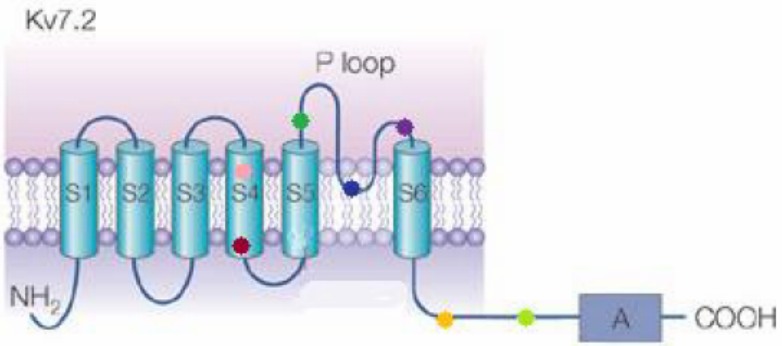


20-50% reduction of current.

Mechanism

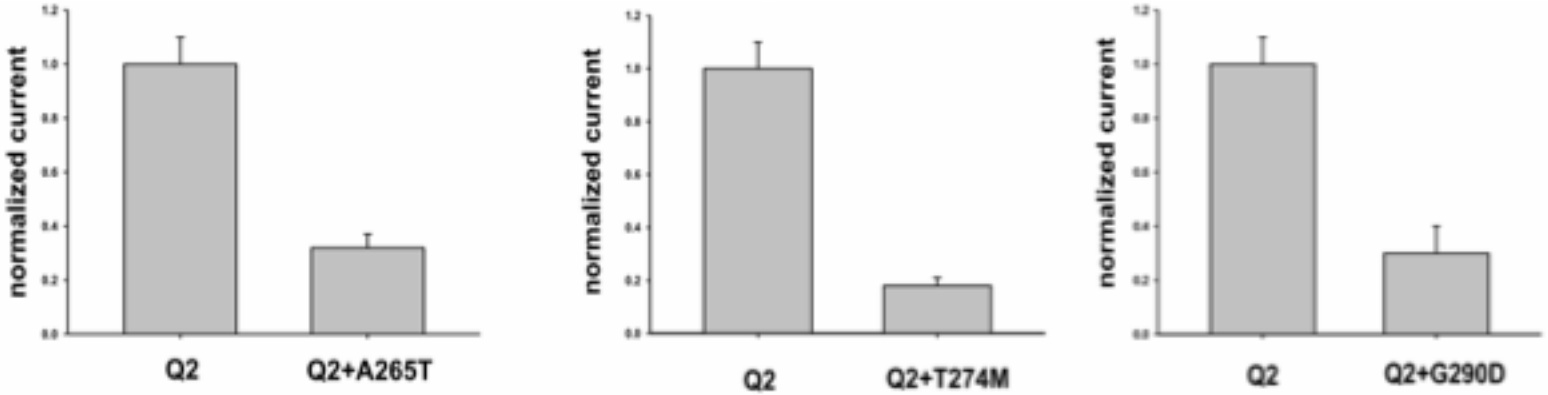
I205V (S4-segment)
R213Q (S4-segment)
A 256P (pore-loop)
T 273M (pore-loop)
G290D (S6-segment)
M518V (C-terminus)
R532W (C-terminus)





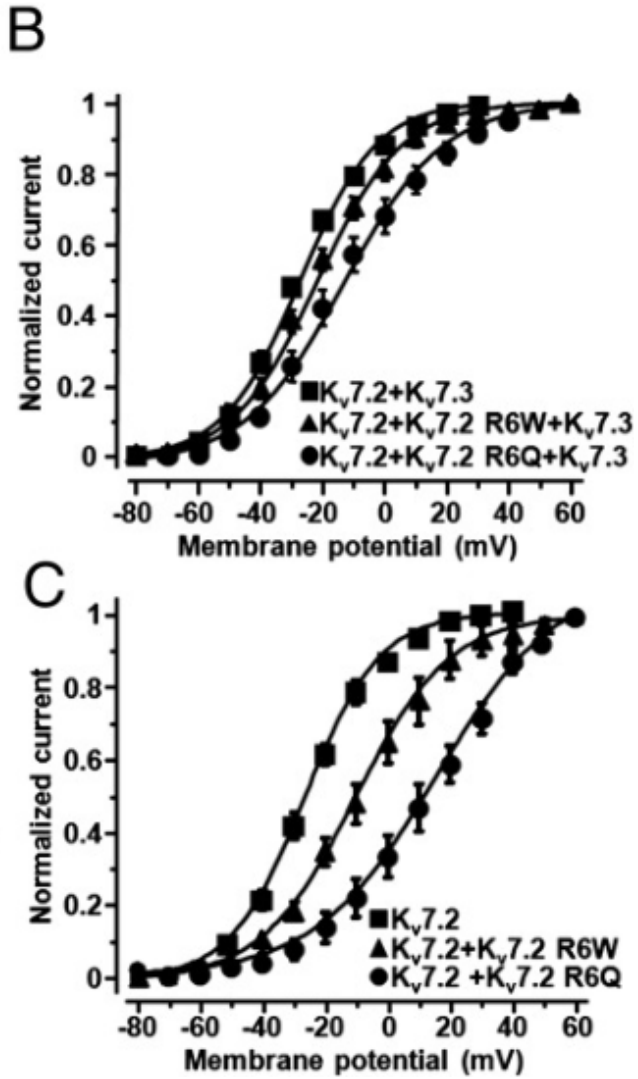
Orhan et al., Annals of Neurology, 2014

Mechanism



5/7 mutations: dominant negative effect on channel function

Orhan et al., Annals of Neurology, 2014



Miceli et al., PNAS 2013

Mouse model of dominant negative mutation

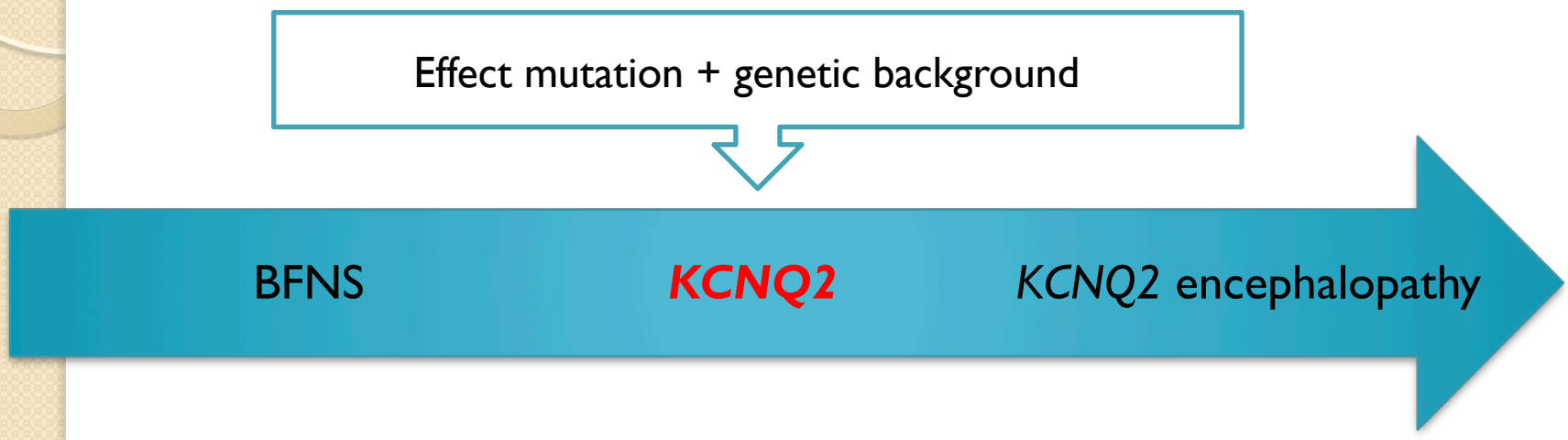
Nat Neurosci. 2005 Jan;8(1):51-60. Epub 2004 Dec 19.

Conditional transgenic suppression of M channels in mouse brain reveals functions in neuronal excitability, resonance and behavior.

Peters HC[1], Hu H, Pongs O, Storm JF, Isbrandt D.

- Transgenic adult mice carrying dominant negative *KCNQ2* mutation
  - recurrent spontaneous seizures
  - impaired spatial learning
  - marked hyperactivity

KCNQ2 spectrum



- Mostly Inherited

- Mostly *de novo*

TREATMENT?

Sodium channel blockers

Epilepsia. 2013 Jul;54(7):1282-7. doi: 10.1111/epi.12200. Epub 2013 Apr 26.

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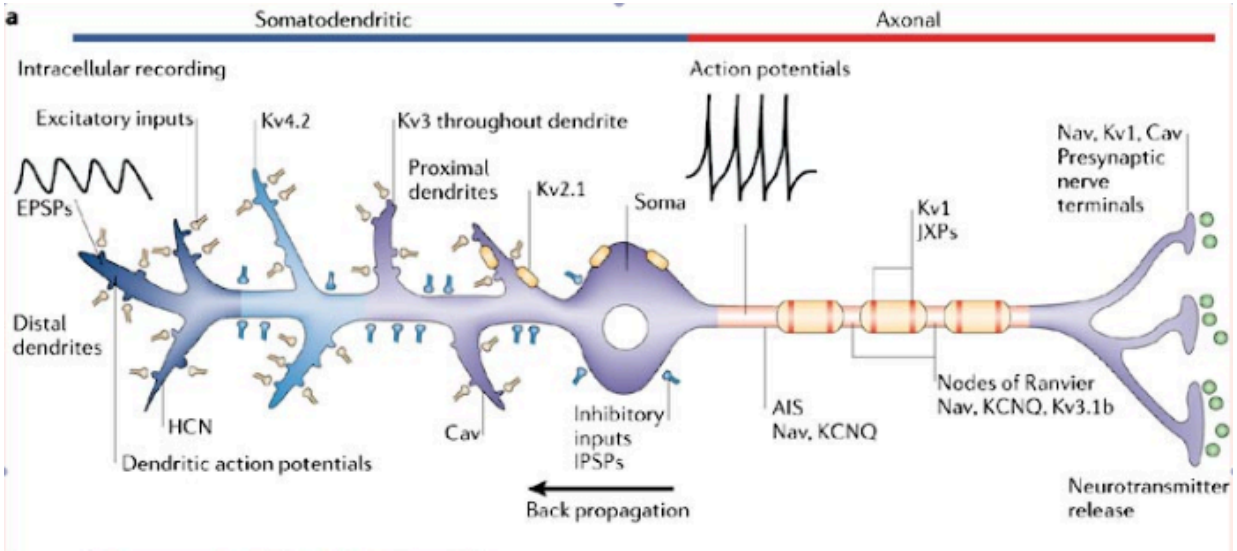
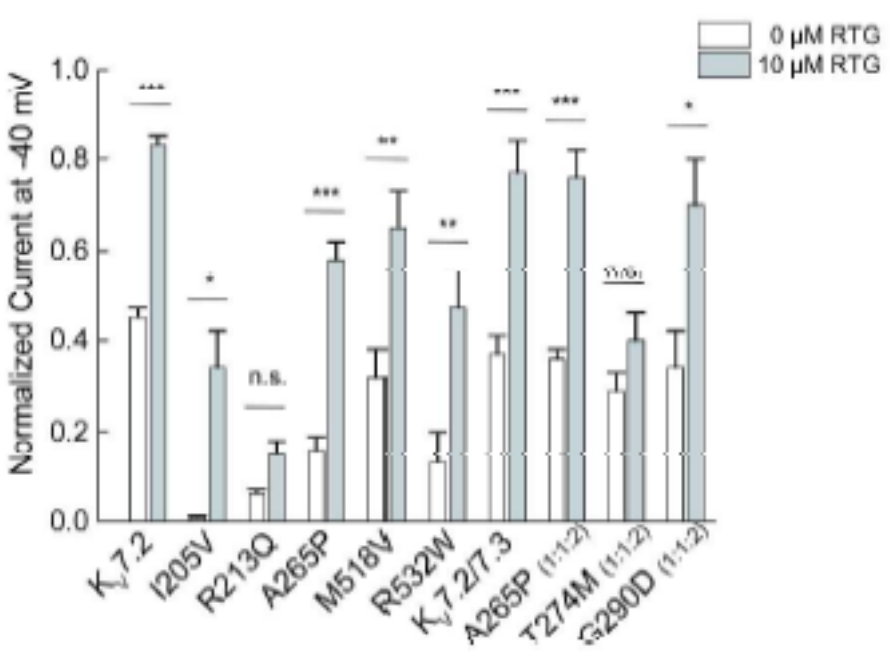
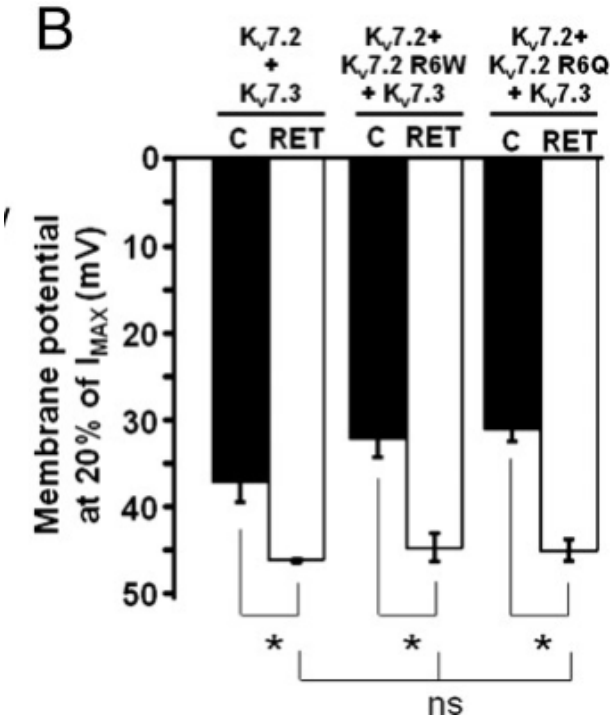

a
Somatodendritic
Axonal
Intracellular recording
Action potentials
Excitatory inputs
Kv4.2
Kv3 throughout dendrite
Proximal dendrites
Kv2.1
Soma
Nav, Kv1, Cav
Presynaptic nerve terminals
EPSPs
Kv1 JXPs
Distal dendrites
HCN
Cav
Inhibitory inputs IPSPs
AIS Nav, KCNQ
Nodes of Ranvier Nav, KCNQ, Kv3.1b
Dendritic action potentials
Back propagation
Neurotransmitter release

Retigabine

- Mutations => loss of function
  - Potassium channel opener retigabine



Orhan et al, 2014



Miceli et al, 2013

Retigabine

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ORIGIN OF INTELLECTUAL DISABILITY *KCNQ2* ENCEPHALOPATHY

KCNQ2 encephalopathy

- Clinical
  - No strict correlation seizure severity – outcome
- Functional

Nat Neurosci. 2005 Jan;8(1):51-60. Epub 2004 Dec 19.

Conditional transgenic suppression of M channels in mouse brain reveals functions in neuronal excitability, resonance and behavior.

Peters HC[1], Hu H, Pongs O, Storm JF, Isbrandt D.

  - Infrequent seizures
  - Impaired spatial learning

B. *KCNQ2* IN EPILEPSY: FURTHER RESEARCH QUESTIONS

CLINICAL QUESTIONS

Clinical

- Range of age of onset?
- Additional clinical features?
  - Severe metabolic acidosis during prolonged seizures
  - Severe behavioral problems, irritability
  - Autistic features, hypersensitivity to noise
  - ...
- Correlation seizure frequency/duration - outcome?
- Treatment response to existing AED?
  - Effect on seizures + cognition
- Effect of newer potassium channel openers?
- ……

Patient Registries

- USA: Rational Intervention for KCNQ2 Epileptic Encephalopathy (RIKEE) patient database

- Europe: ad hoc
  - 23 additional non-reported European patients
    - 7 Belgium
    - 8 new mutations
    - 5 treated with RTG
      - Prospective trial?

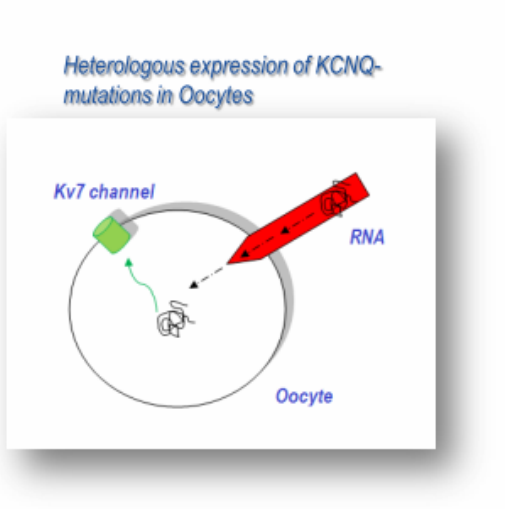
FUNCTIONAL QUESTIONS

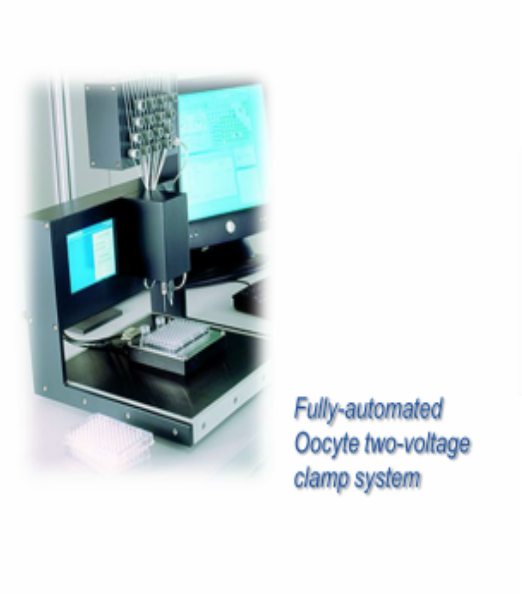
Functional

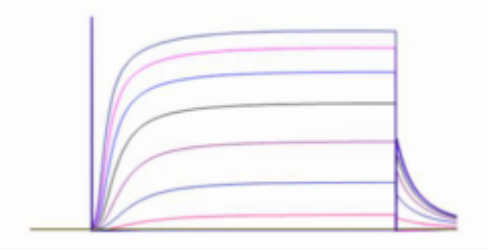
- What are the consequences of different *KCNQ2* mutations
  - Potassium channel function
  - Excitability of neurons
  - Brain functioning
  - Brain structure
- Reversal of mutational effect
  - Retigabine and other drugs
  - Gene therapy
  - Time frame

Models

- Oocytes

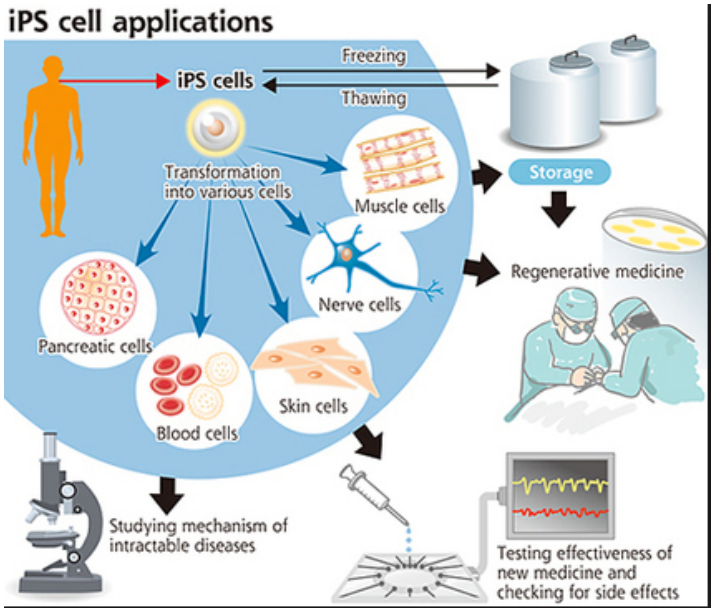






Models

- Neurons <= induced Pluripotent Stem Cells (iPSC)



- (Animal models)

Neurogenetics group - epilepsy

- Rik Hendrickx
- Tine Deconinck
- Jolien Roovers
- Tania Djémié
- Katia Hardies
- Arvid Suls
- Peter De Jonghe

SPECIAL THANKS TO:

Parents and patients with *KCNQ2* mutations

All collaborators and treating physicians of patients with *KCNQ2* mutations