UMC Utrecht

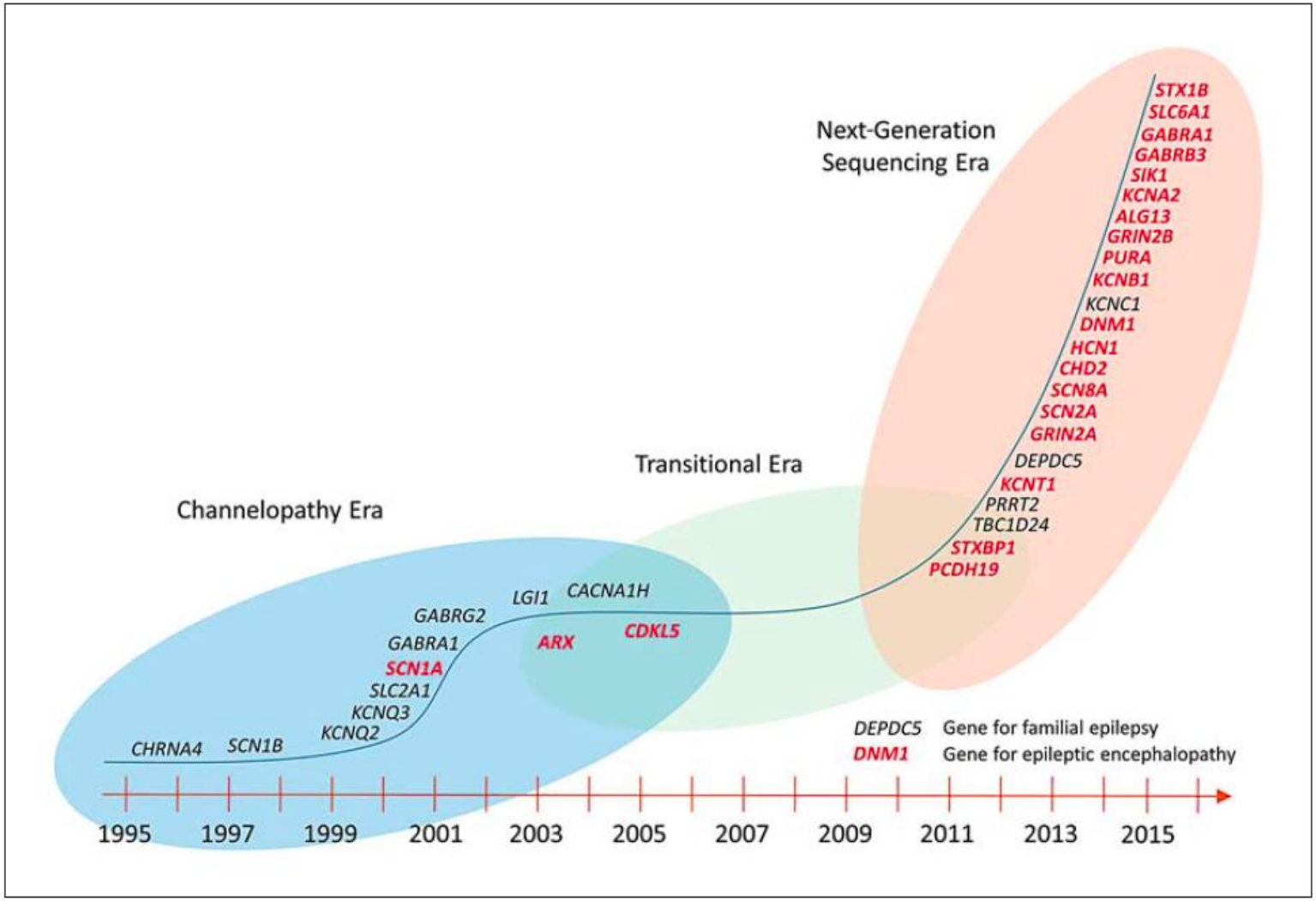
Precision Medicine in the epilepsies

Developments and Challenges

Disclosure belangen spreker

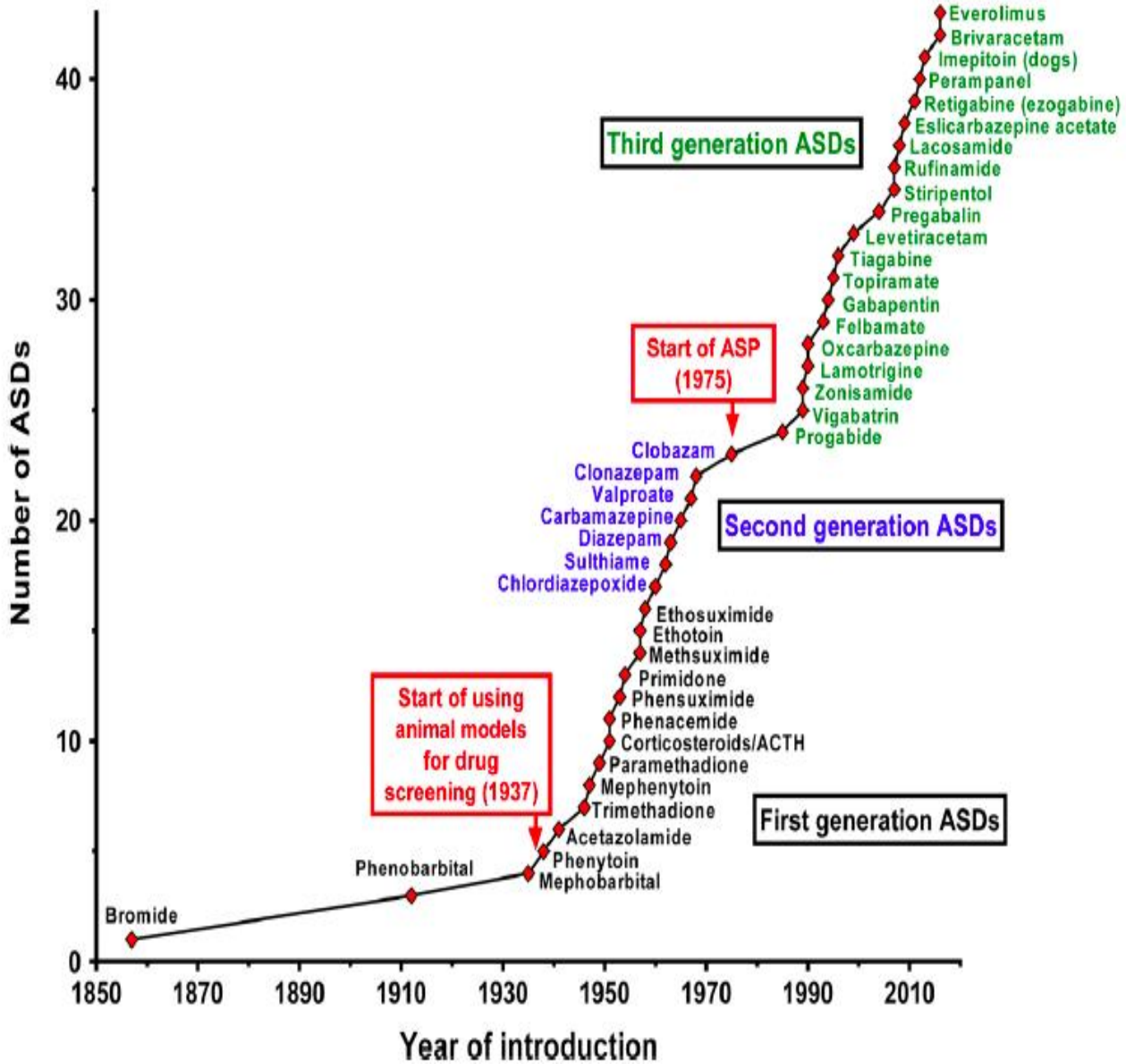
Potentiële Belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnaam
Sponsoring of onderzoeksgeld	nvt……..
Honorarium of andere (financiële vergoeding)	nvt……..
Aandeelhouder	nvt……..
Andere relatie, namelijk….	nvt……..

Accelerated discovery of new epilepsy genes
Increased rate DNA-diagnosis (40-70%)

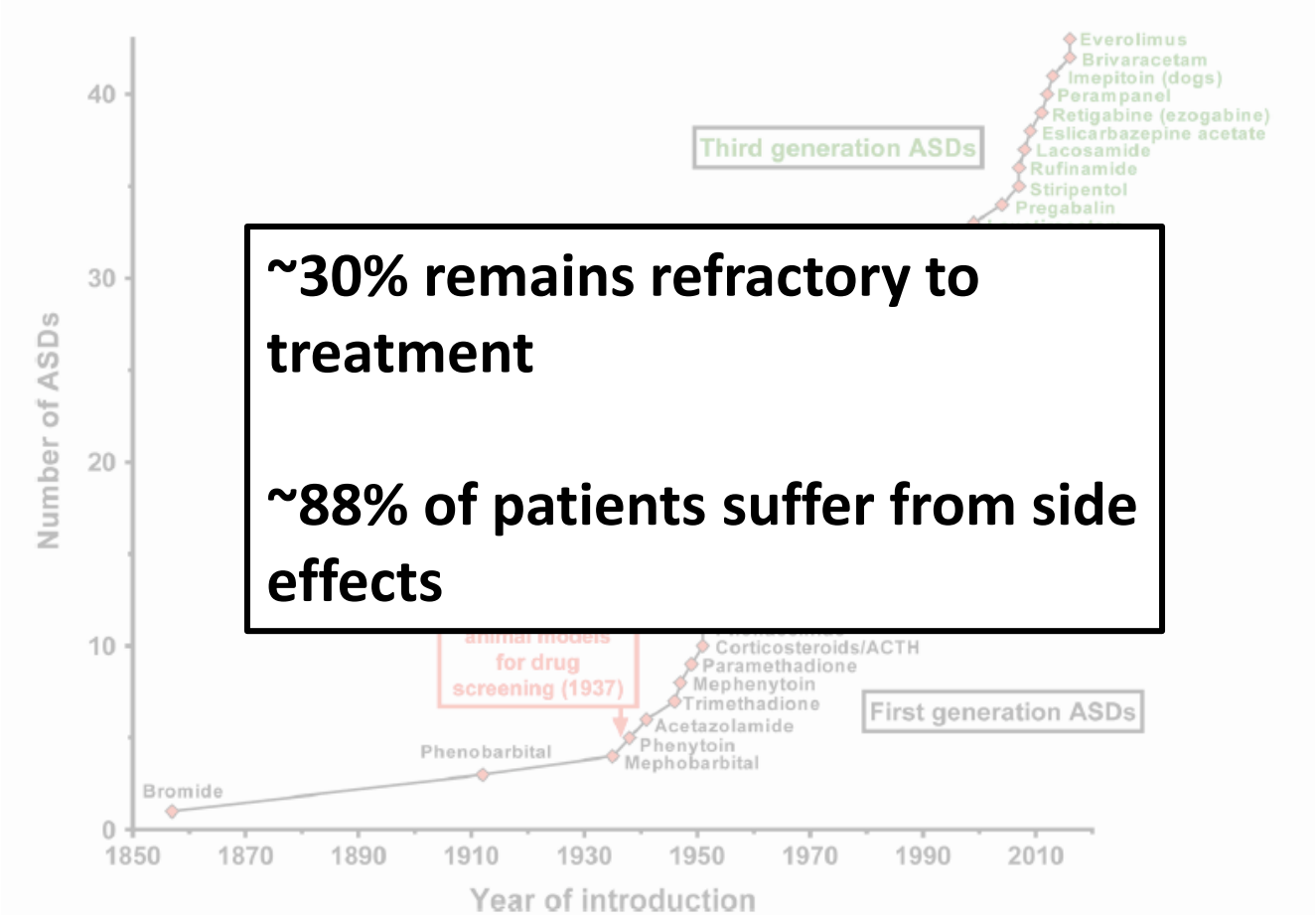


Helbig and Tayoun. Mol Syndromology 2016

Chronology of antiseizure drugs over the past 150 years



Chronologie van 150 jaar anti-epileptica



↑ GABA

Barbiturates
Benzodiazepines
Gabapentin
Levetiracetam
Tiagabine
Topiramate
Valproate
Vigabatrin

↓ Na^+

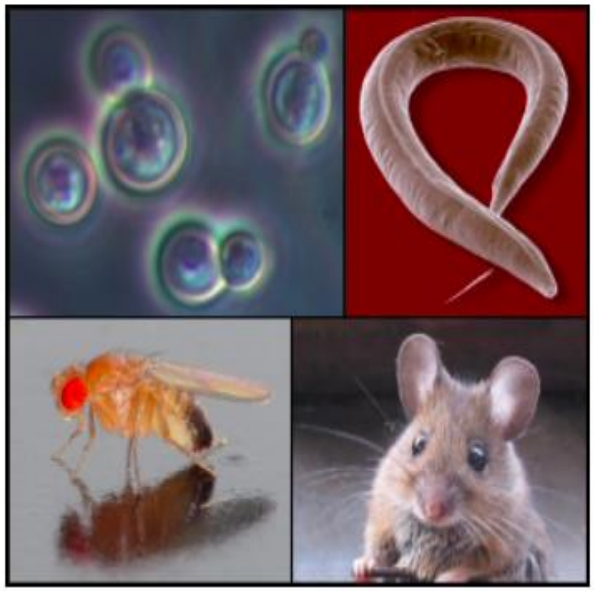
Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
Topiramate
Valproate

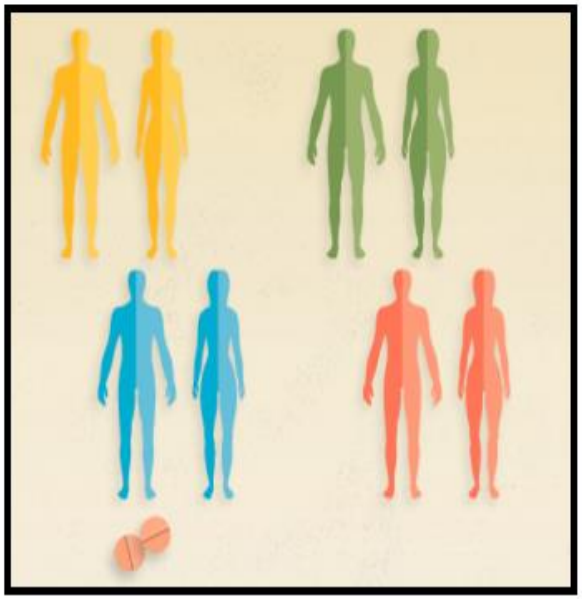
↓ Ca^{2+}

Ethosuximide
Levetiracetam
Pregabalin
Valproate

We relied on preclinical models to pick targets and estimate efficacy in heterogeneous human populations

It was…

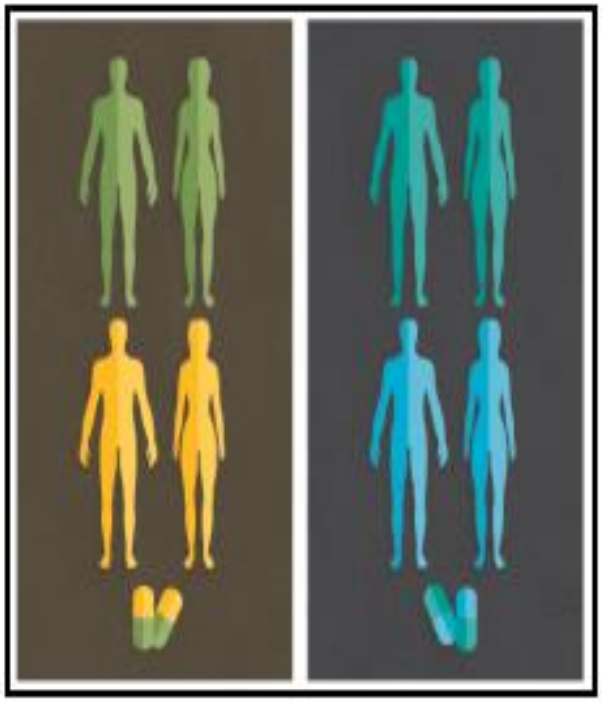




Discovery → Pre-clinical → Phase 1

Humans are the "model organism" of choice for new targets and precision medicine

But today…



Discovery → Pre-clinical → Phase 1

Plenge, Scolnick, Altshuler *Nature Reviews Drug Discovery* (2013)

De Novo Pathogenic *SCN8A* Mutation Identified by Whole-Genome Sequencing of a Family Quartet Affected by Infantile Epileptic Encephalopathy and SUDEP

Krishna R. Veeramah,[1] Janelle E. O'Brien,[4] Miriam H. Meisler,[4] Xiaoyang Cheng,[5] Sulayman D. Dib-Hajj,[5] Stephen G. Waxman,[5] Dinesh Talwar,[6,7,9] Santhosh Girirajan,[10] Evan E. Eichler,[10] Linda L. Restifo,[2,7,8] Robert P. Erickson,[3,6] and Michael F. Hammer[1,*]

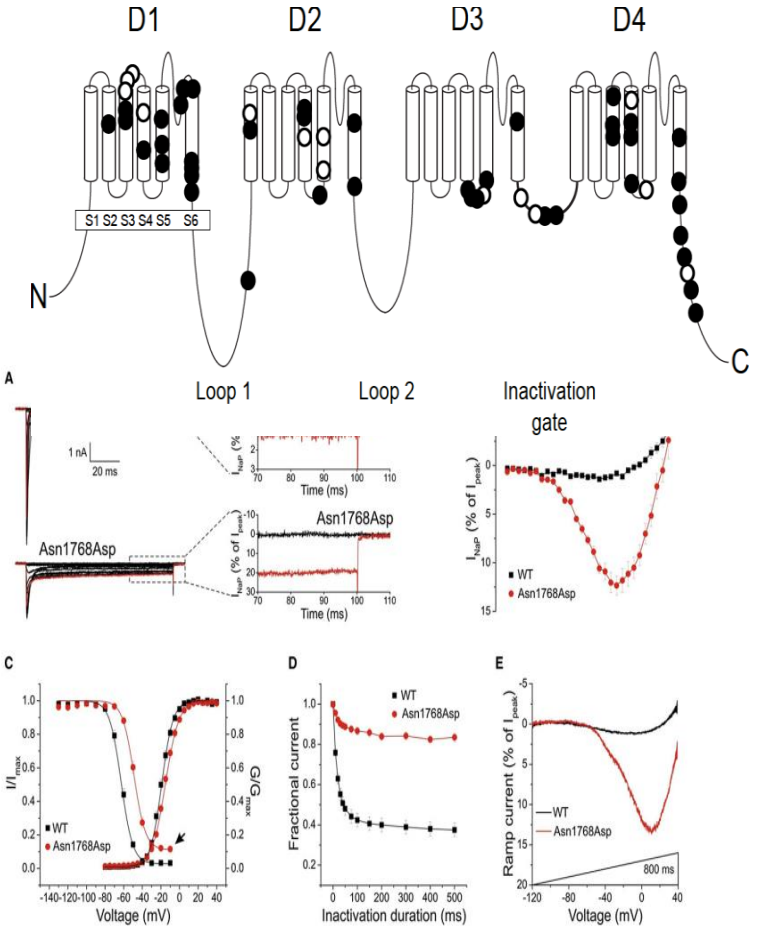
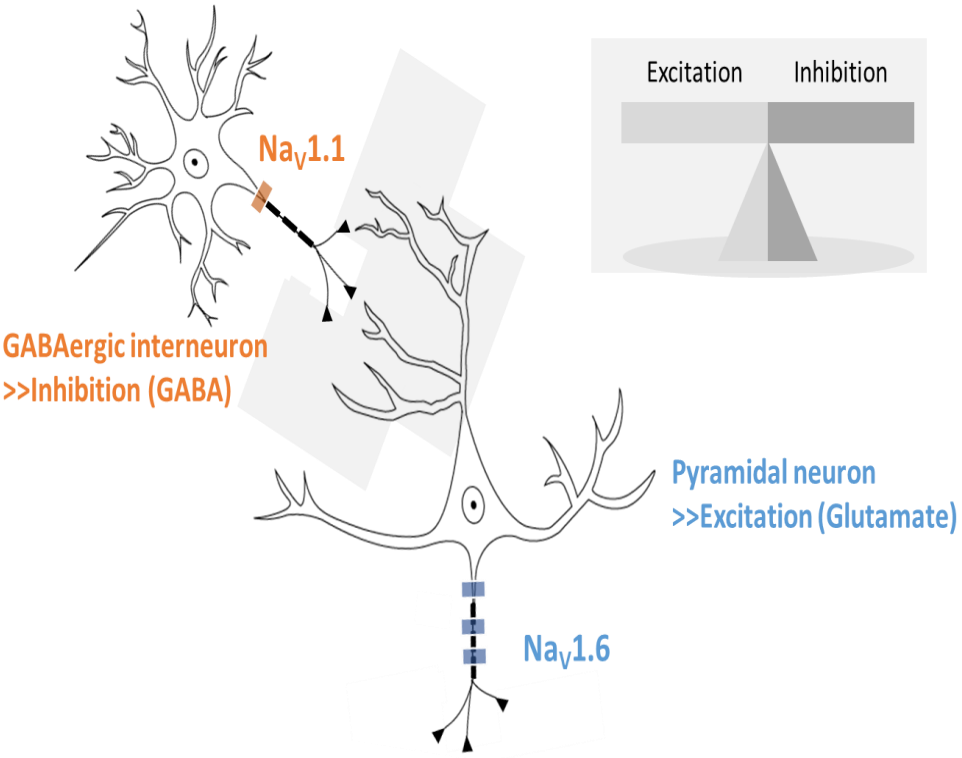


Figure 2. Effect of the De Novo SCN8A Substitution p.Asn1768Asp on Biophysical Properties of the Channel

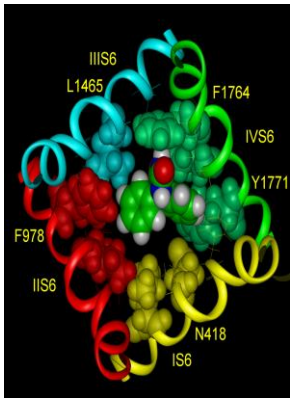


Important to predict functional effect *SCN8A* mutation for treatment options

TABLE 1 | Reported drug response in epileptic encephalopathy due to *SCN8A* mutations.

Amino acid substitution	Channel domain	Effect on function	Effective treatment	Seizure response	Reference
p.Val216Asp	DIS3-4		**VPA**	Seizure control	(23)
p.Leu407Phe	DIS6		**CBZ**	75% reduction	(53)
p.Phe846Ser	DIIS4		**PHT**, **LTG**, PB KD, VNS	Temporarily effective	(53)
p.Ala890Thr	DIIS5		**VPA** **VPA, OXC**	Seizure control	(25, 53)
p.Asn984Lys	Near DIIS6	GOF	**PHT**, **ZNS**, PB LEV, CLB	Seizure control	(24)
p.Ile1327Val	DIIIS4-5		High **PHT**	Temporarily effective	(27)
p.Gly1451Ser	DIIIS6	LOF	**CBZ**	Seizure control	(24)
p.Asn1466Lys	Inactivation gate		**PHT**, **TPM**, GBP, ACTH, MDL, LD	Temporarily effective	(23)
p.Asn1466Thr	Inactivation gate		**TPM**, LEV	Seizure control	(23)
p.Val1592Leu	DIVS3		**OXC**	Seizure control	(25)
p.Ser1596Cys	DIVS3		**OXC**, **LTG**, PB, LEV	75% reduction	(53)
p.Ile1605Arg	DIVS3		**CBZ**	Seizure control	(25)
p.Arg1617Gln	DIVS4		**CBZ** **OXC**	Temp. effective Seizure control	(23, 53)
p.Ala1650Thr	DIVS4-5		**CBZ**, **TPM**	Seizure control	(23)
p.Asn1768Asp	DIVS6	GOF	**VPA**, **LTG**, CLB	Temporarily effective	(15)
p.Arg1872Trp	C-term		**TPM**, **LCM**, LEV, VGB, KD	Febrile breakthrough	(23)

ACTH, adrenocorticotropic hormone; CBZ, carbamazepine; CLB, clobazam; GBP, gabapentin; KD, ketogenic diet; LCM, lacosamide; LD, lidocaine; LEV, levetiracetam; LTG, lamotrigine; MDL, midazolam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VGB, vigabatrin; VNS, vagal nerve stimulator; VPA, valproic acid; ZNS, zonisamide. Drugs classified as sodium channel blockers are indicated in bold.



Wagon and Meisler. Front. Neur. 2015
Boersma et al. Neurotherapeutics. 2016

KCNT1 and Epileptic Encephalopathies

- Mutations in KCNT1 have been implicated in two epilepsy disorders
  - Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)
  - Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)

- Expression of mutant and wild type protein in oocytes shows that all identified mutations are Gain of Function (Petrou Lab)

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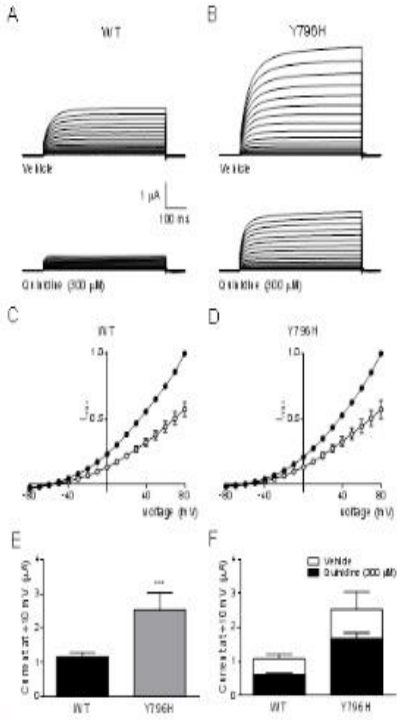
CHGV CENTER FOR HUMAN GENOME VARIATION

KCNT1 Y796H

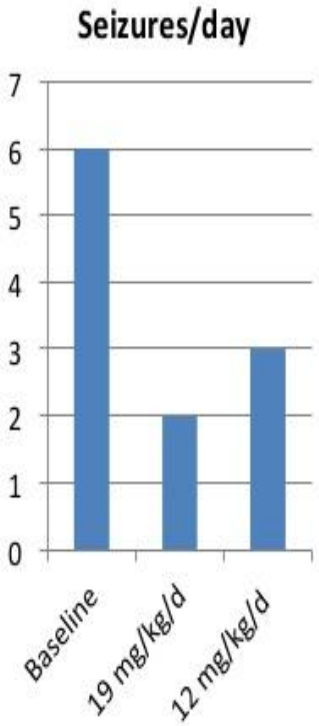


Courtesy of Steve Petrou, University of Melbourne

Duke University School of Medicine

Response to Quinidine Therapy

- Quinidine 12 mg/kg/d on first day
- Quinidine 19 mg/kg/d on second day
- Seizures dropped to 2/d, level 1.6 ug/ml (cardiac therapeutic 2-5).
- Dose maintained on 12 mg/kg/day
- Seizures over the next 2 weeks: 3/day, level 0.4 ug/ml
- Improved alertness head control sitting and interaction observed
- Plan to increase dose while monitoring ECG
- Duke a KCNT1 Related Epilepsy Clinic for other patients started



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The promise of Precision Medicine: Repurposing drugs

Table 1. Overview of the currently available or studied precision medicine therapies in genetic epilepsies.

Gene	Effect of mutation	Epilepsy syndrome	Therapy	Status as precision medicine treatment
DEPDC5, NPRL2, NPRL3	mTOR disinhibition	Familial focal epilepsy with variable foci	mTOR inhibitors (everolimus)	Hypothetical
GRIN2A/2B	Gain of f			cal
KCNA2	Gain of f			cal
KCNQ2	Loss of f			d
			Retigabine	potential
KCNT1	Gain of function	Epilepsy of infancy with migrating focal seizures, nocturnal frontal lobe epilepsy	Quinidine Beripril	Potential Hypothetical
SCN1A	Loss of function	Dravet syndrome	Avoid sodium channel blockers Stiripentol Fenfluramine	Established established potential
SCN2A	Gain of function	Various	Sodium channel blockers	Potential
SCN8A	Gain of function	Epileptic encephalopathy	Sodium channel blockers	Potential
SLC2A1 (GLUT1)	Loss of function	Various	Ketogenic diet	Established
TSC1, TSC2	mTOR disinhibition	Tuberous sclerosis	mTOR inhibitors (everolimus)	Established

~30% remains refractory to treatment

~88% of patients suffer from side effects

Current status of the precision medicine treatment is assessed as follows: 'established': in routine clinical use, 'potential': some case reports on its use in patients available, 'hypothetical': only based on theoretical considerations, data from animal models or single case reports in humans.

What's in it for common epilepsy?

People with epilepsy

People without epilepsy

Compare
Common
Variants

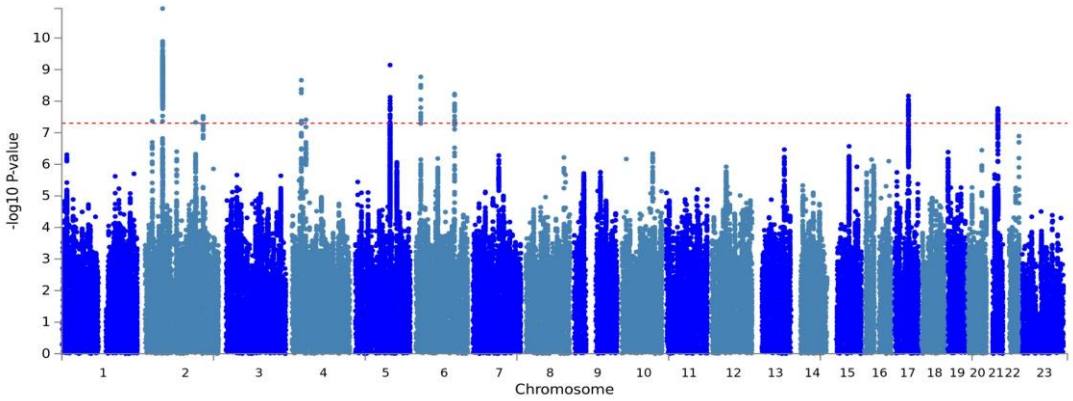
Genome-Wide
Association Study

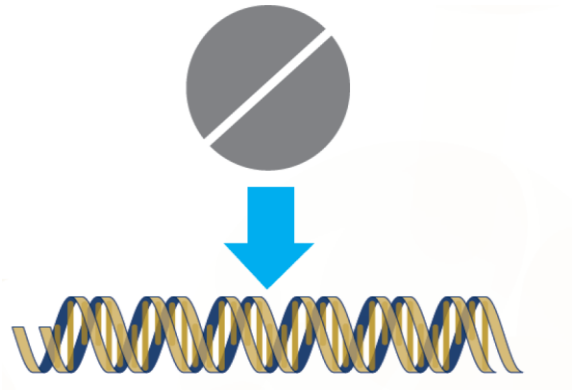
- Insight in biology
- Clinical Biomarkers
- Pleiotropy
- Drug Targets

DOI: 10.1038/s41467-018-07524-z OPEN

Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies

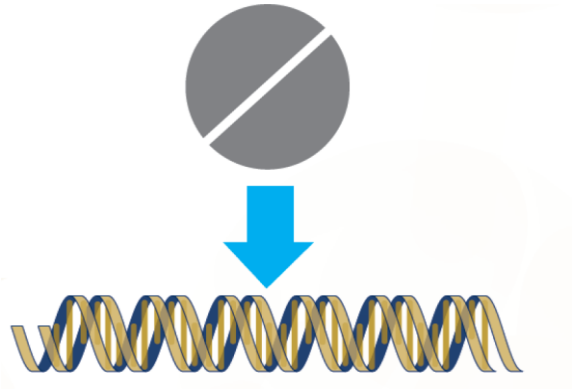
The International League Against Epilepsy Consortium on Complex Epilepsies





GWAS to identify drug targets

- Prioritized genes are enriched for known epilepsy genes (OR = 61.4, p= 1.3×10^{-5})
- 13 out 24 licensed anti-epileptic drugs target one of the prioritized genes (OR = 101.2, p=5.7×10^{-7})
- 166 FDA approved drugs target one of the prioritized genes



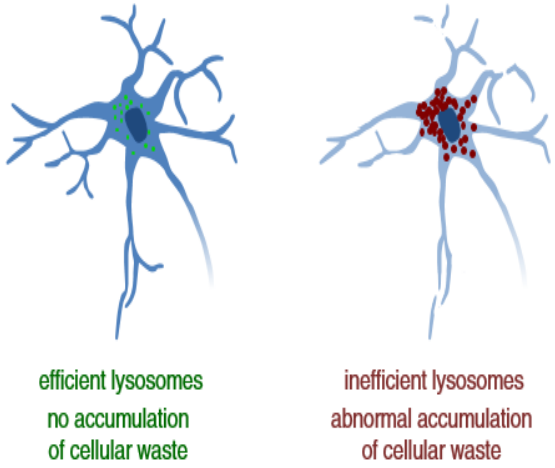
A custommade drug appears to be helping Mila, a 7-year-old born with Batten disease. JULIE AFFLERBAUGH

A tailormade drug developed in record time may save girl from fatal brain disease

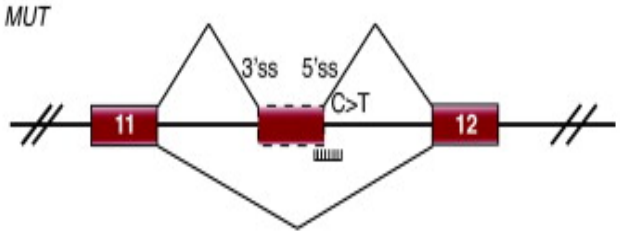
By Jocelyn Kaiser | Oct. 19, 2018 , 9:00 PM

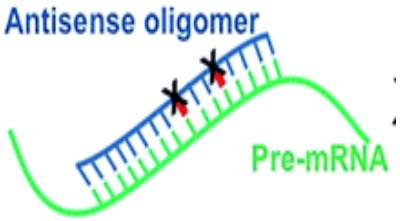
Batten disease

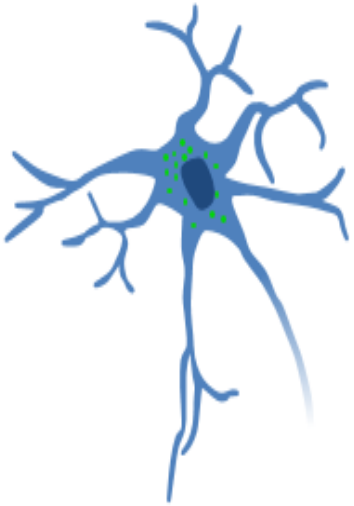
- Age at onset 2-10 years
- Neurodegenerative disorder, resulting in vision problems and seizures
- Recessive genetic disorder, associated with mutation in lysosomal genes
- Example is CLN7, a member of Ceroid-Lipofuscinosis Neuronal Protein genes, that have critical function in lysosomes



Batten disease

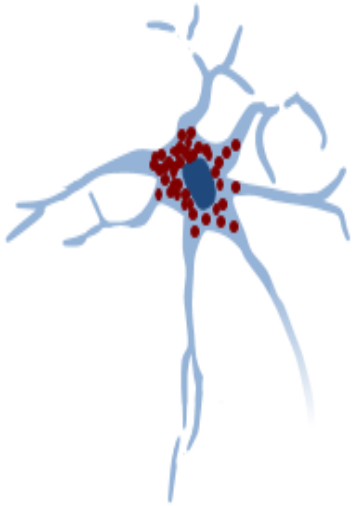






efficient lysosomes

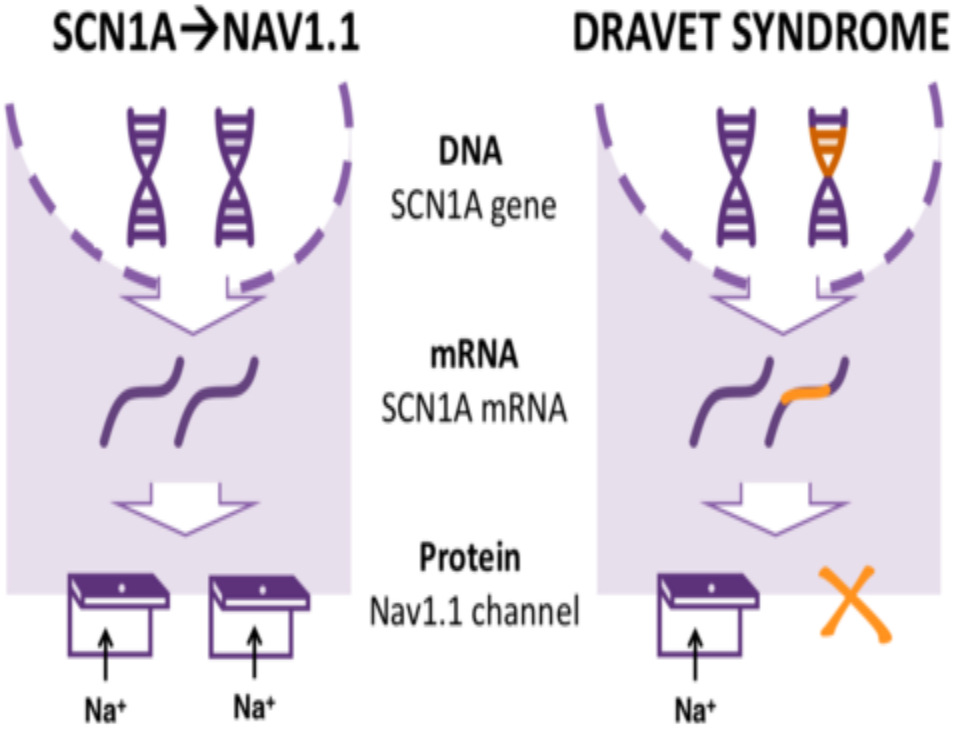
no accumulation of cellular waste



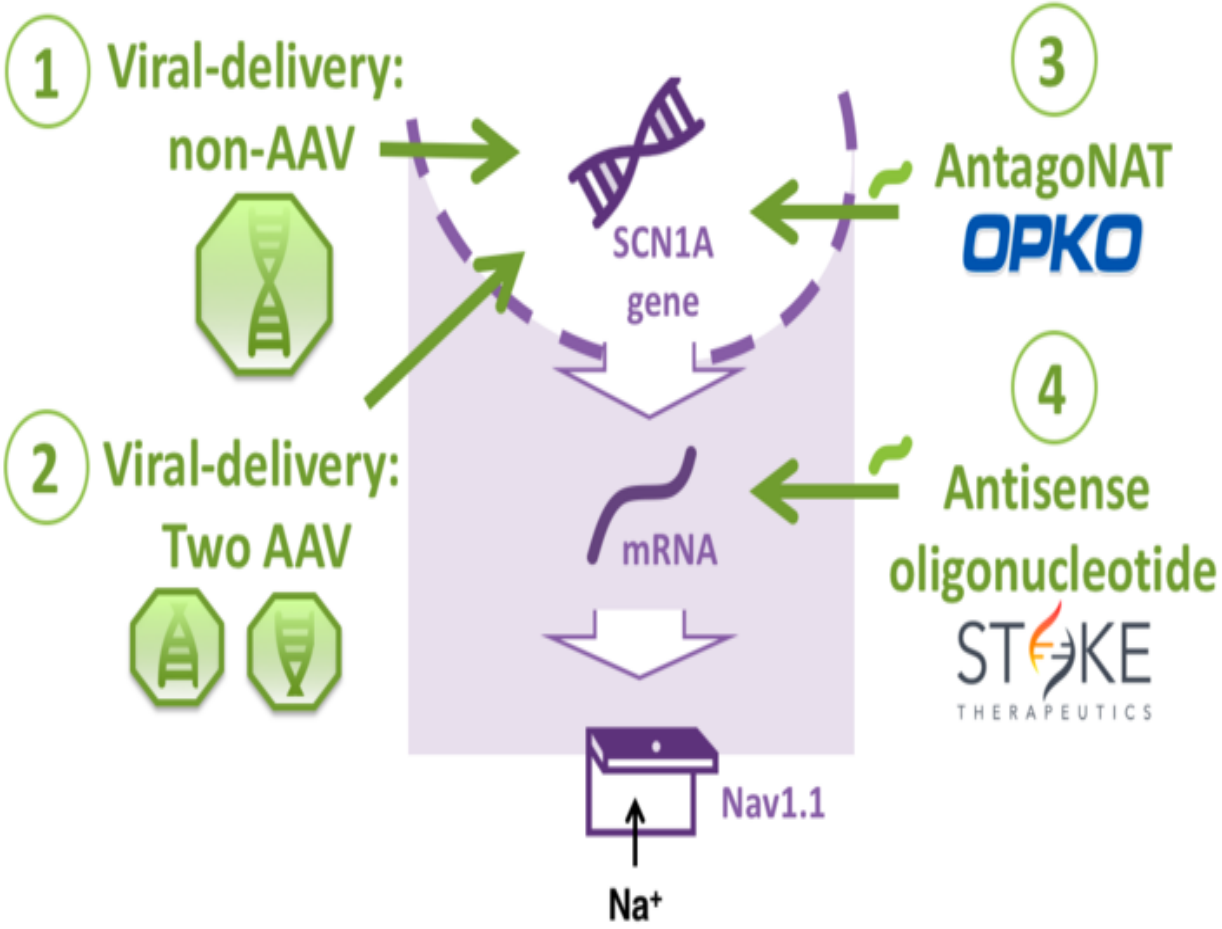
inefficient lysosomes

abnormal accumulation of cellular waste

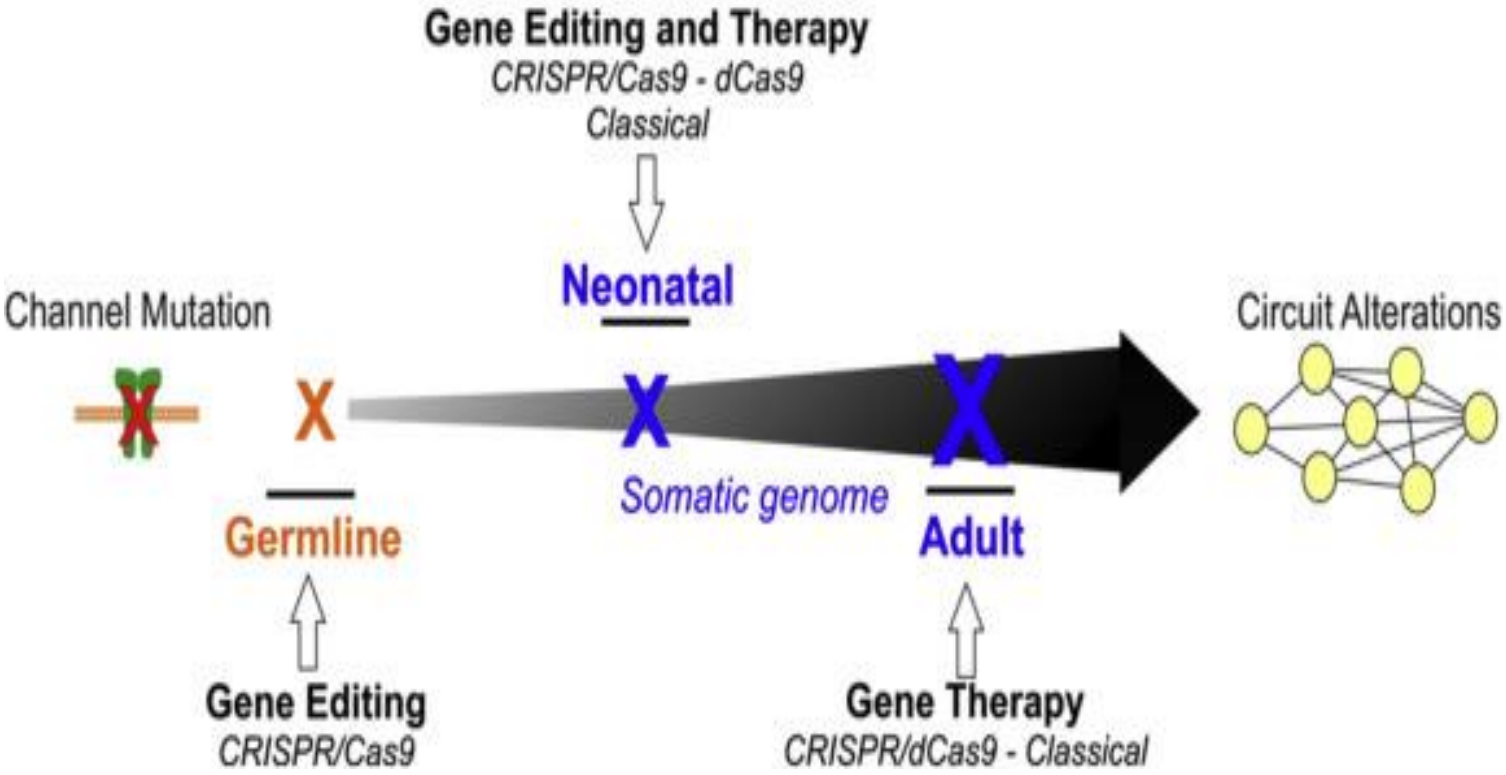
Gene therapies for Dravet syndrome



GENE THERAPY FOR DRAVET SYNDROME



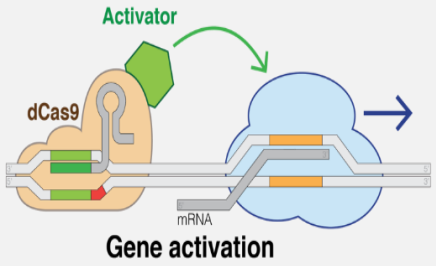
Gene Therapy and Gene Editing for Channelopathies

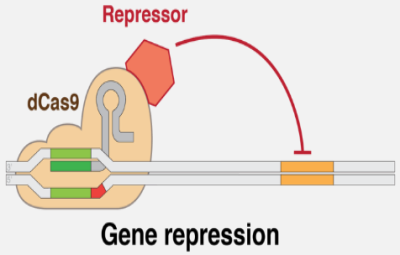


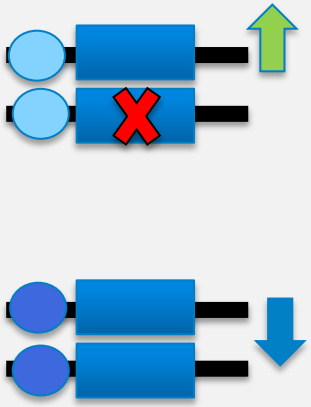
Wykes et al Neuropharmac 2018

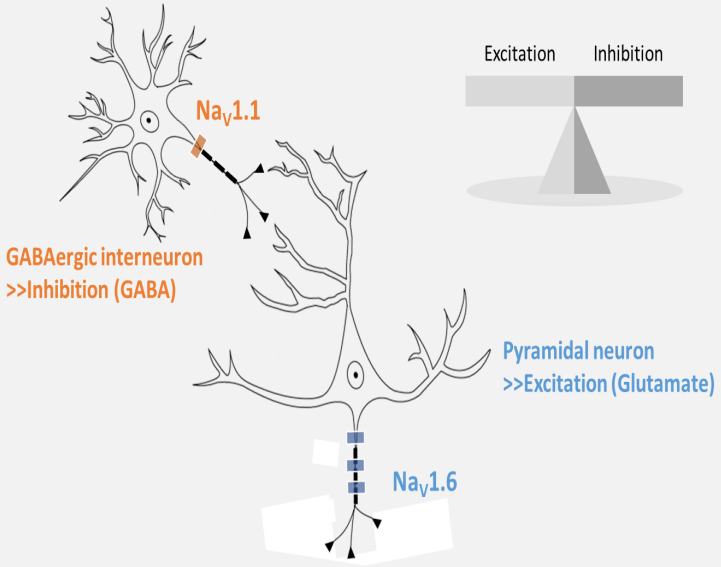
Gene modulation

increasing expression of $Na_V1.1$ <> inhibiting expression of $Na_V1.6$



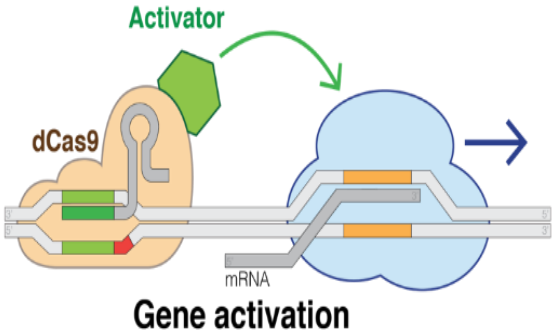


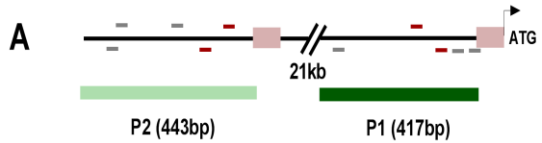


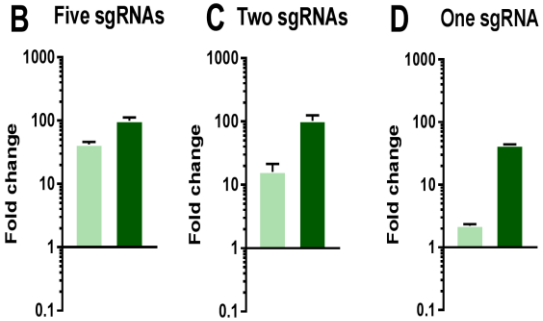


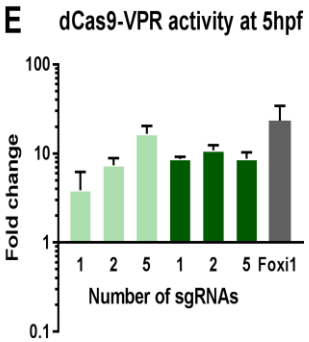
Gene modulation in zebrafish

increasing expression of $Na_V1.1$



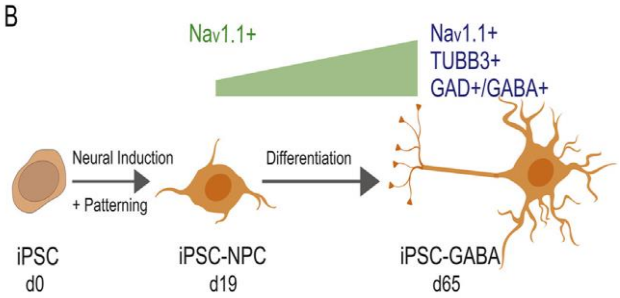




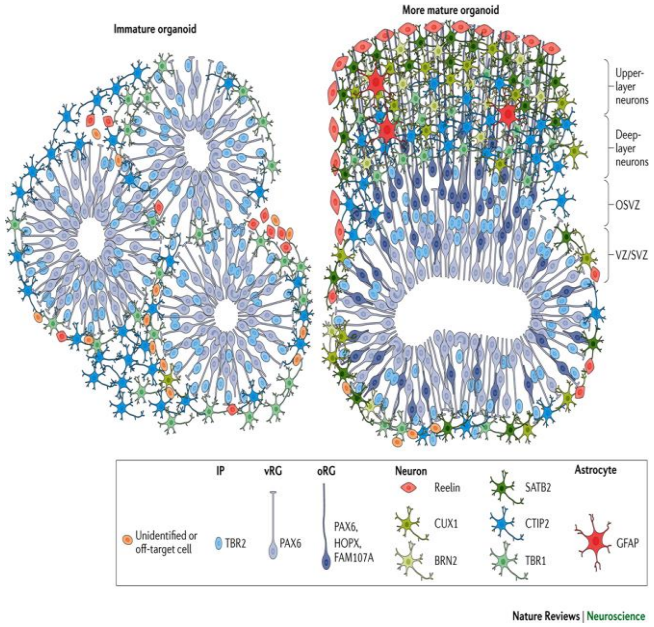


From zebrafish to human

MIND
IMAGING | IPSC | ORGANOID



Patient-derived iPSC



Patient-derived brain organoids

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