



# Mouse models of *SCN8A* encephalopathy

SCN8A research: progress and prospects

Houston

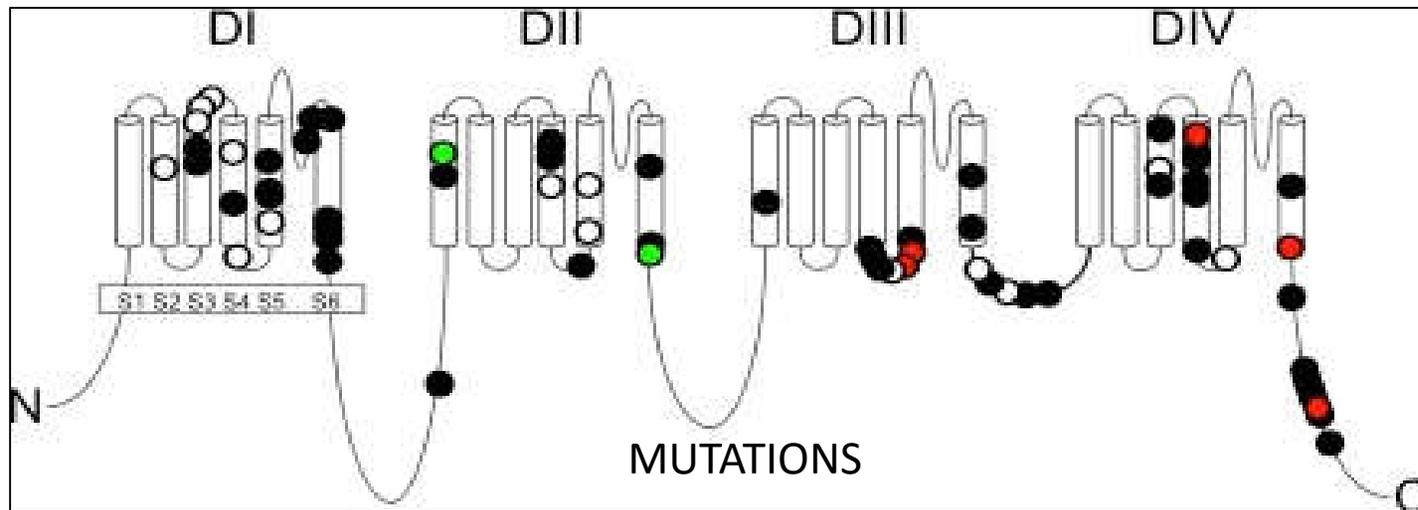
December 1, 2016

Miriam H. Meisler, Ph. D.

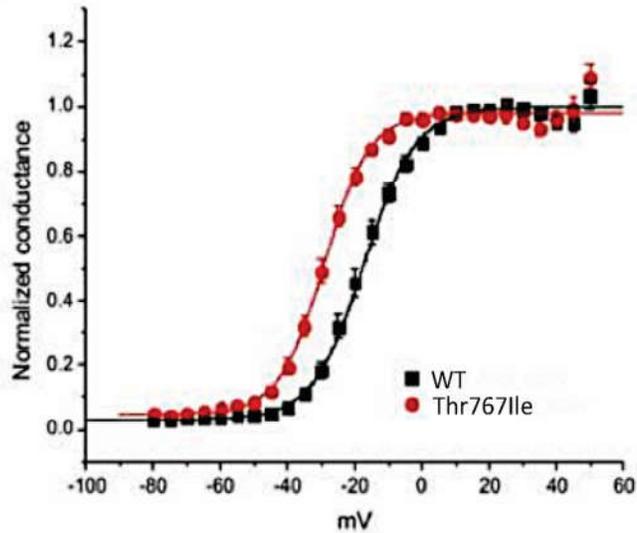
Departments of Human Genetics and Neurology

University of Michigan, Ann Arbor

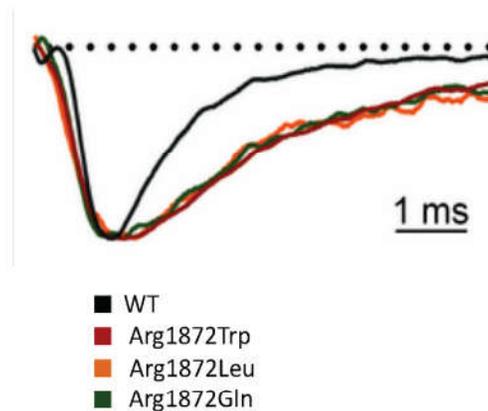
# SCN8A and epileptic encephalopathy: MUTATIONS & MECHANISMS



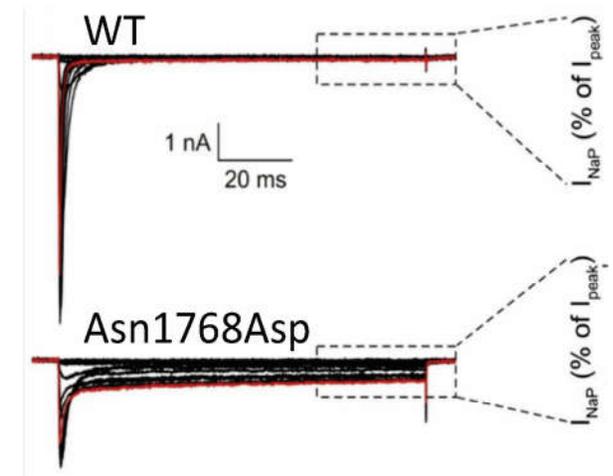
A. Premature opening



B. Impaired inactivation



C. Elevated persistent current



updated from report on March, 2015 SCN8A meeting, in Epilepsia 2016

What can we learn from mouse models of *SCN8A* patient mutations?

Does this mutation alone **cause** epilepsy and sudden death?

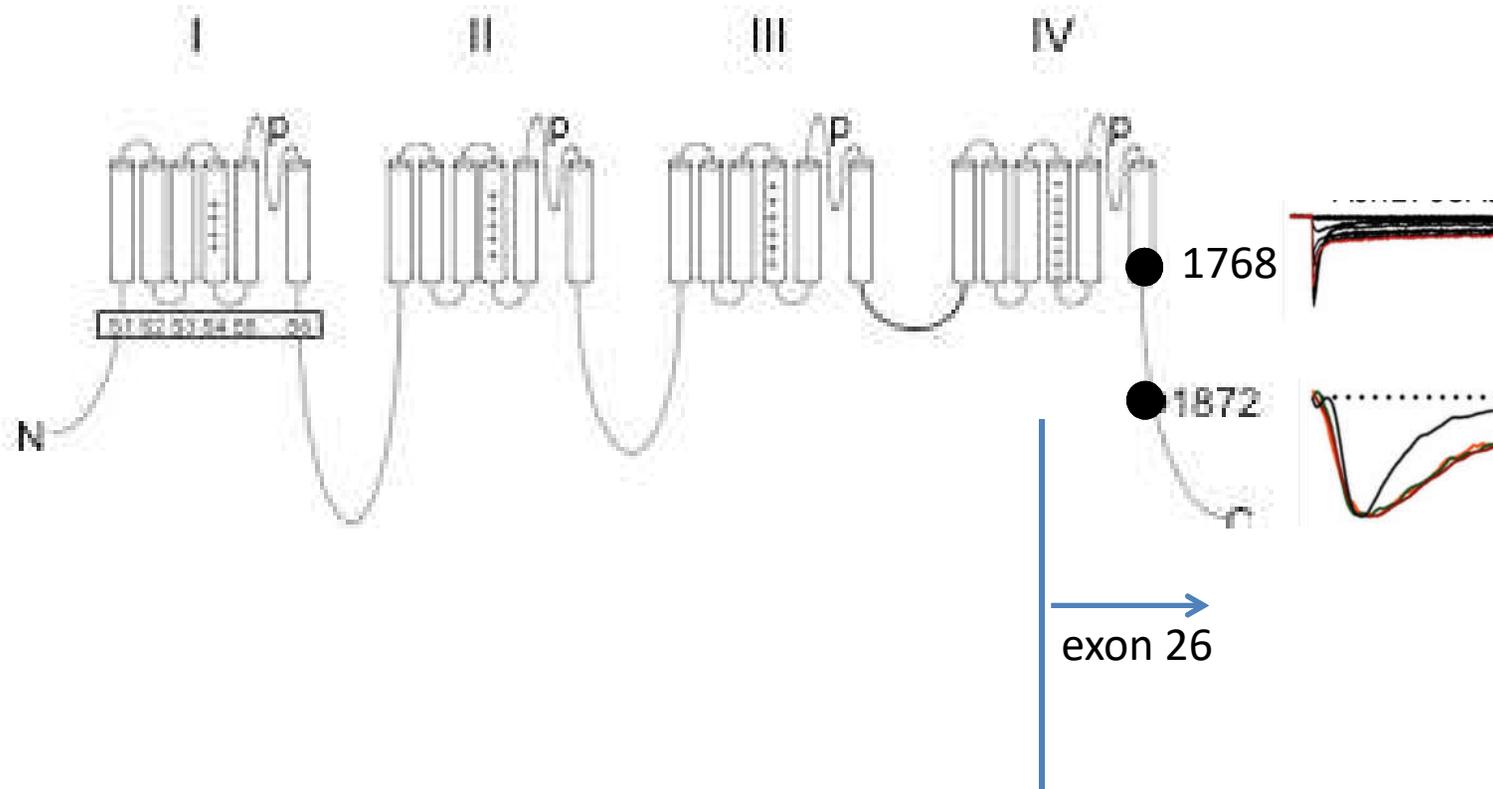
What are the effects on different types of **neurons**?

What is the cause of **sudden death**?

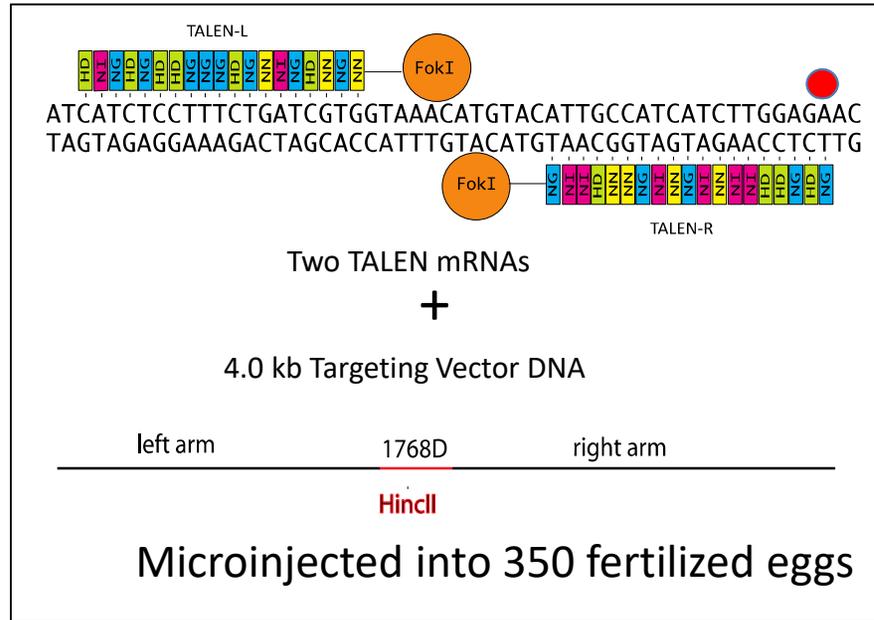
Which **drugs** are effective against this type of mutation?

Which other **genes** can modify the effects of *SCN8A* mutations?

# Two mouse models of *SCN8A* epileptic encephalopathy



# Mouse knock-in of *Scn8a*-p.Asn1768Asp using TALEN endonuclease



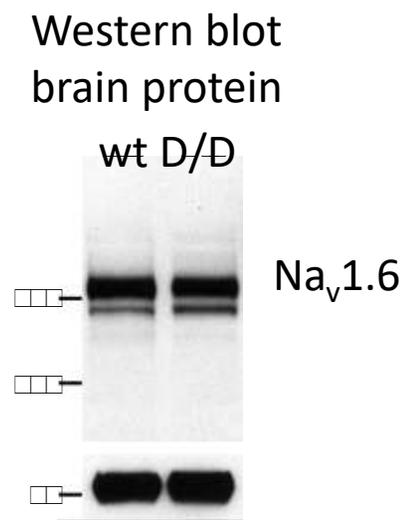
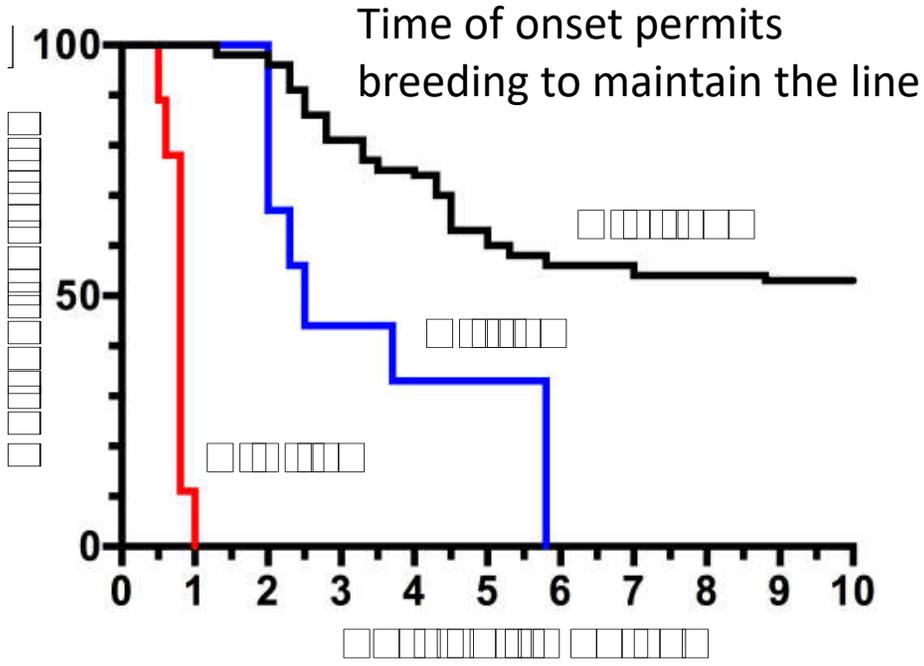
1768

knock-in vector with point mutation N1768D



67 potential founders  
5 with the targeted mutation (7%)  
26 with indels (null alleles)

# Seizures and sudden death in the *Scn8a* –N1768D mouse



D/D



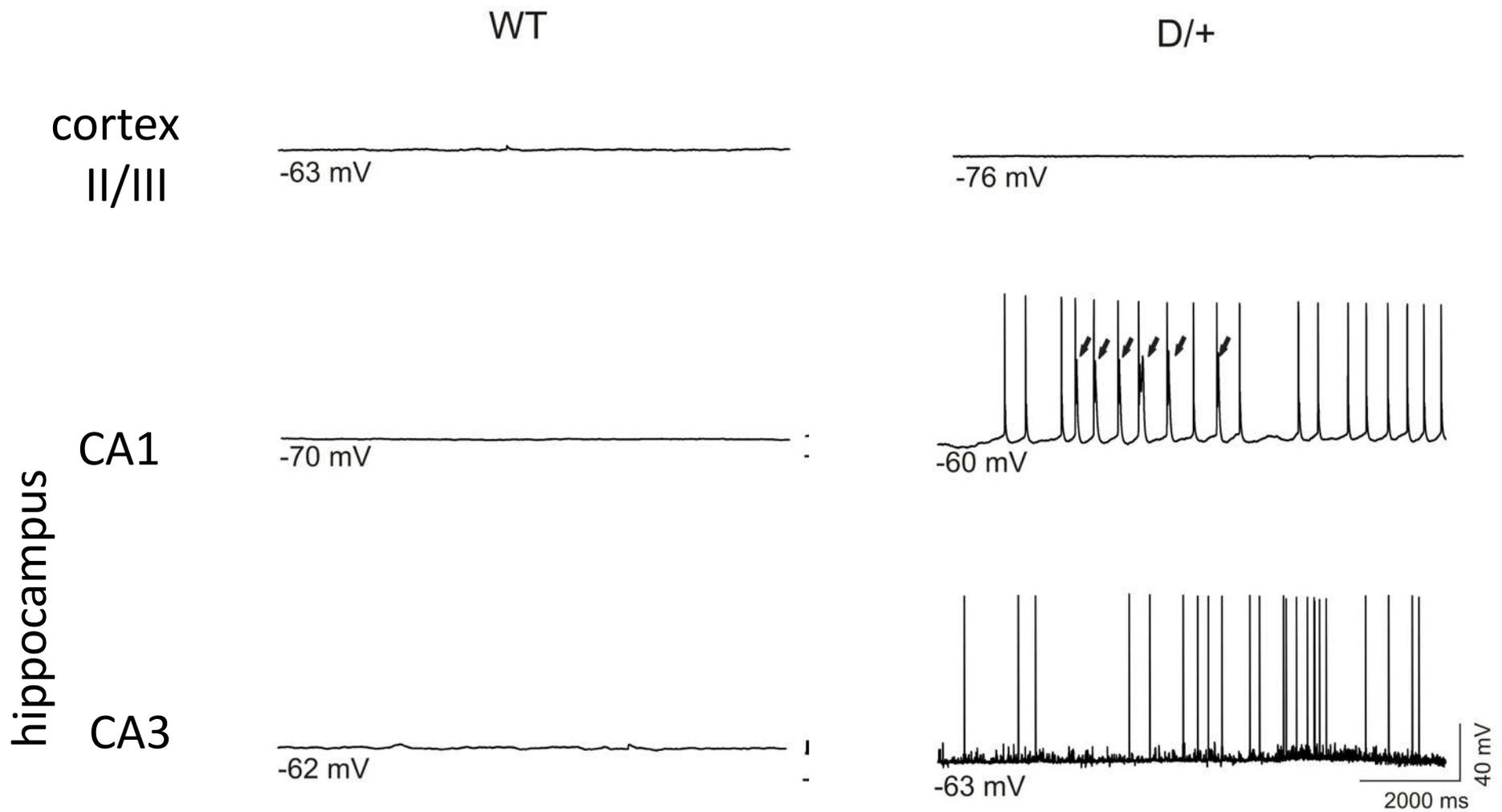
D/-



D/+



# Abnormal spontaneous firing of hippocampal neurons



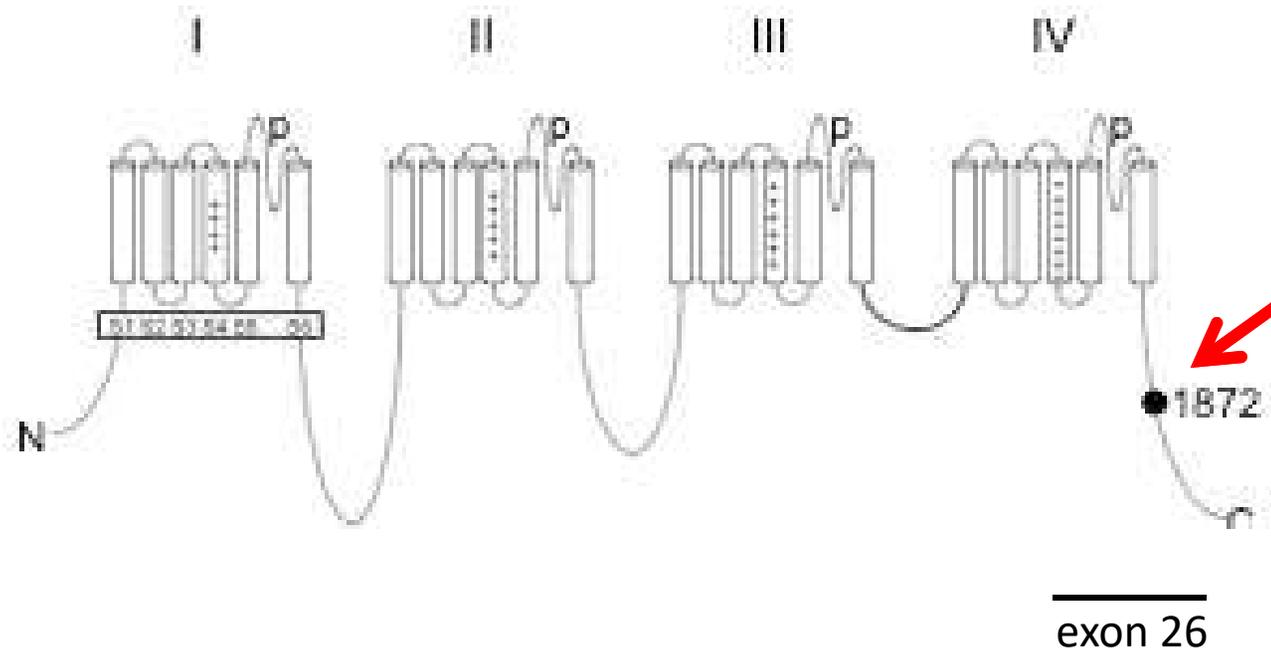
(slice recordings for 10 sec)

Yukun Yuan and Lori Isom, MSS IN REVIEW

Four talks in this session describe studies  
of the N1768D mouse model  
addressing questions including  
drug responsiveness.

A new mouse mutant with conditional activation of Arg1872Trp.

This mutation results in EE with severe hypotonia as well as seizures. There have been 18 independent mutations of this residue, Arg1872. The conditional mutant permits activation in specific neurons and ages.



## Goals for conditional mutant, R1872W

Effects of activating the mutation in excitatory neurons only

Effects of activating the mutation in inhibitory neurons only

Which neurons are responsible for hypotonia?

Effects of activation the mutation after development of the brain

Using specific CRE lines to obtain localized expression of R1872W

Ubiquitous activation with E2A-CRE: drug sensitivity, modifiers, etc.



April, 2015, Washington D. C.