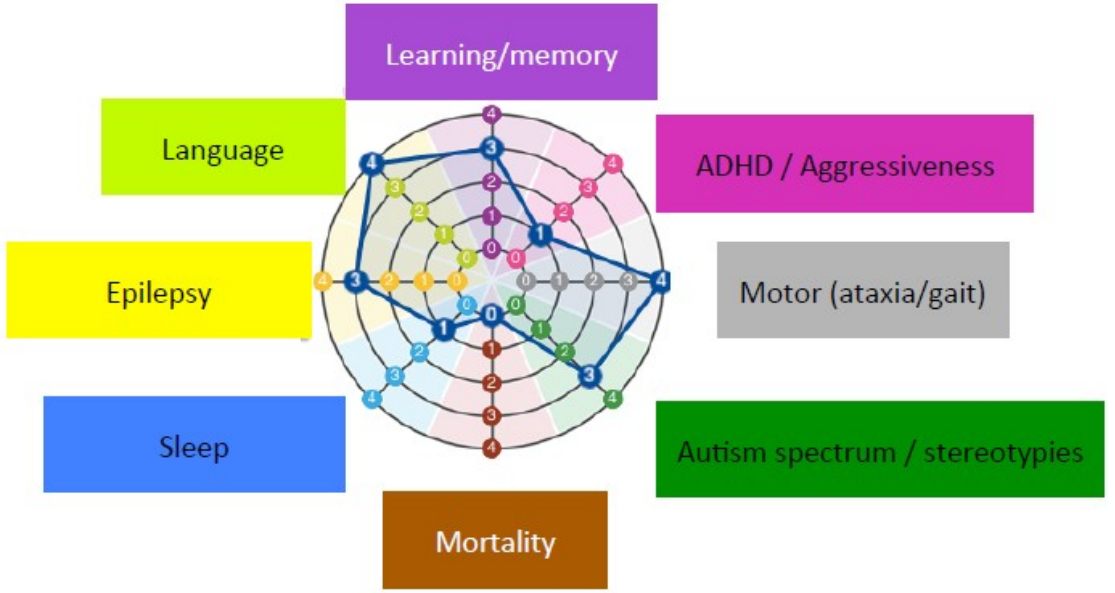
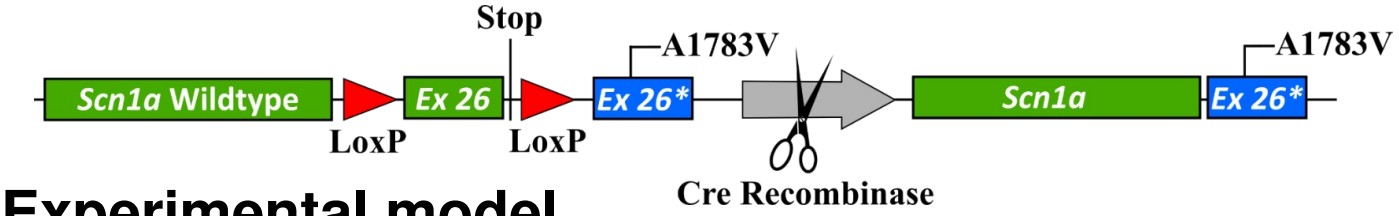
Dravet syndrome – disease characteristics

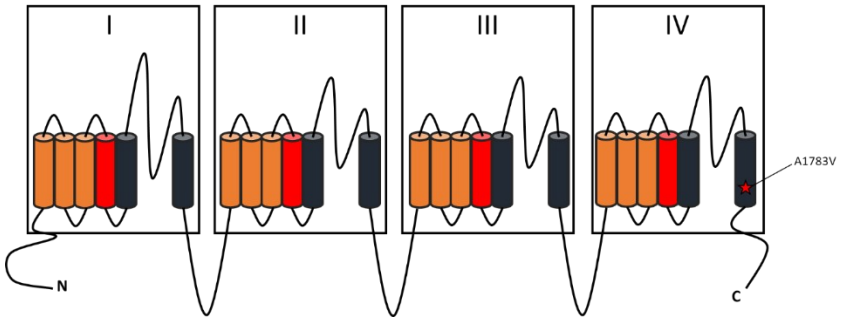
- Early onset between 3 and 9 month
- High seizure frequency with different seizure types
- Caused mostly by de-novo loss of function mutations in *SCN1A* encoding voltage-gated Na-channel $Na_V1.1$
- $Na_V1.1$ is predominantly expressed in inhibitory and excitatory in the CNS and is important for action potential initiation and propagation



Dravet Syndrome Foundation, Spain

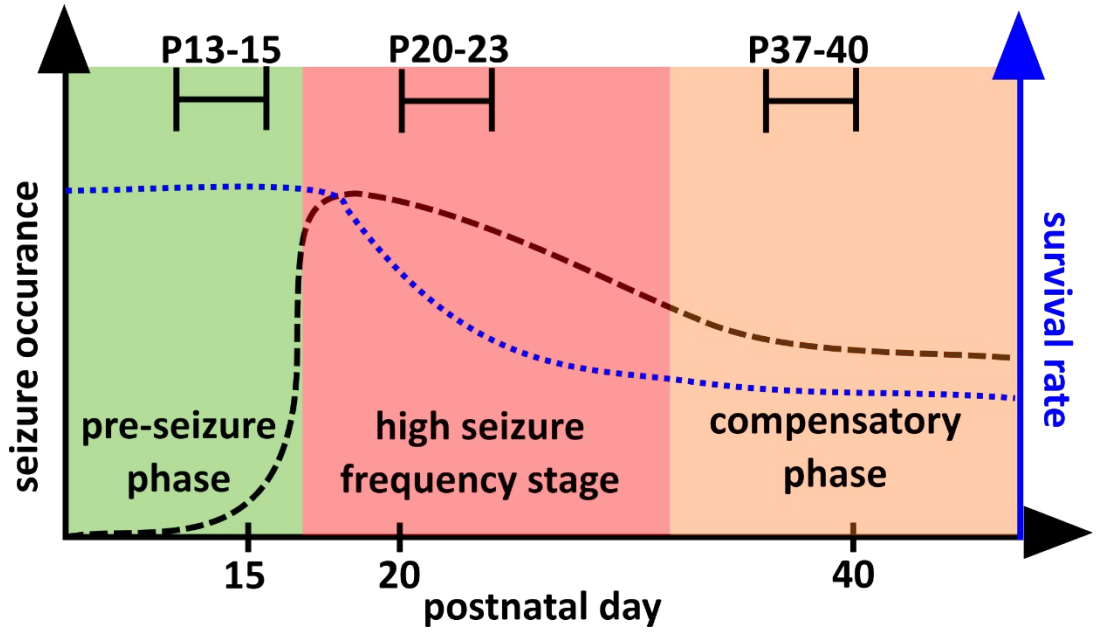


Experimental model




```
48) A1783T
SCN1A       V N M Y I A V I L E N
SCN2A       - - - - - - - - - - -
SCN3A       - - - - - - - - - - -
SCN8A       - - - - - - I - - - -
CHIMPANZEE  - - - - - - - - - - -
RAT         - - - - - - - - - - -
MOUSE       - - - - - - I - - - -
FUGU        - - - - - - I - - - -
DROS        I - - - - - - - - - -
```

- Missense-mutation A1783V is located in sixth tm-domain of channel subunit IV
- High conservation of the affected amino acid
- Conditional B6(Cg)-*Scn1a*$^{tm1.1Dsf}$/J male mice were crossed with females of the ubiquitous Cre-Driver line S129-Hprt-Cre
- Recombination in oocyte ✉ global monoallelic activation of Dravet mutation
- Observed behaviour alterations:
  - spontaneous seizures from P18
  - repetitive jumping behaviour and hyperactivity
  - reduced weight and size



The experimental setup

- Recordings in brain slices of wildtype and heterocygote animals as PN 20 - 23
- Horizontal brain slice, simultaneous measurement of Ca-activity and multi unit activity (MUA)
- 25 µM 4-AP and 0.5 mM Mg^{2+} in the bath solution to increase susceptibility for neuronal excitation and synchronisation
- Stimulation in temporal cortex layer IV/V with 10 mM NMDA, 2 puffs for 400 ms, 3 seconds pause between application
- Local spread of epileptiform activity in temporal cortex
- Adapted from Losi et al

Basic neuroscience

A brain slice experimental model to study the generation and the propagation of focally-induced epileptiform activity

Gabriele Losi, Iacopo Marcon, Letizia Mariotti, Michele Sessolo, Angela Chiavegato, Giorgio Carmignoto

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Simultanous Ca-Imaging