Mesial Temporal Lobe Epilepsy Mouse Model (épi/épi mice)

Core Benefit:

- The adult épi/épi mouse is a mutant mouse that constantly exhibit generalized tonic-clonic seizures (GTCSs; alternatively, grand-mal seizures) for life (up to two years) without any epileptogenic induction.
- The mutated gene in the épi/épi mouse is Girdin/ccdc88a gene, which is a mouse homolog for a causative gene of human epilepsy.
- The adult épi/épi mice unexceptionally (n=38) exhibited GTCSs, of which cumulative video-archived seizures reached 5,839 counts.
- The basic aspects and the duration of GTCSs of an épi/épi mouse closely resembles human patients' GTCSs.
- Pathological findings in the hippocampus and its surrounding cortex indicate that the épi/épi mouse is the excellent model for human refractory mesial temporal lobe epilepsy (MTLE), of which seizure is derived from the hippocampus.
- The adult épi/épi mouse allows pharmacological tests for anti-epilepsy drugs (AEDs) or anti-epilepsy device with low-cost and high-objectivity compared with human clinical trials.

Superiority of this mouse model:

- There is no precedent example of epilepsy model mice except épi/épi mice, which exhibit GTCSs at 100% certainty without any epileptogenic induction (such as chemical induction or electrical stimulation).
- There is no precedent example of epilepsy model mice except épi/épi mice, which exhibit typical pathological changes for human refractory MTLE, including bilateral granule cell dispersion (GCD) and bilateral hippocampal sclerosis (HS).

Background:

Mesial temporal lobe epilepsy (MTLE) is the most frequent cause of adult epilepsy. At a same time, MTLE is the most frequent cause of adult 'refractory' epilepsy, which is resistant to anti-epilepsy drugs (AEDs). The main causes of delayed development of fundamental treatment for MTLE are due to the insufficient knowledge in pathogenic principle, and due to the absence of proper animal models, which enable the evaluation of therapeutic effect of AEDs. Of course, animals subjected to chemoconvulsant-induced status epilepticus (SE) have long been considered as the most popular models of human MTLE, which can be easily produced simply by injecting a chemoconvulsant into a normal rodent1.
However, Kudrimoti *et al.* pointed out serious flaws in such models that extra-hippocampal brain regions are more severely damaged than the hippocampus, and that there is no convincing origin of spontaneous seizures1. Therefore, Kudrimoti *et al.* concluded that an animal model of hippocampal epileptogenesis should ideally and reproducibly involve: 1) endfolium or classic hippocampal sclerosis, 2) limited extrahippocampal brain damage, and 3) verified spontaneous hippocampal-onset seizures. However, such an ideal model has not emerged for .
In 2014, Asai *et al.* incidentally discovered the first animal model, which fulfills all these criteria by surmounting the complete pre-weaning lethality of homozygous Girdin/ccdc88a knockout mice with a

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special feeding technique2,3. Nahorski *et al.* reported a multiplex consanguineous family where three severely disabled patients with epilepsy were carrying a homozygous frame-shift deletion in human Girdin/ccdc88a gene in 20164. Asai *et al.* patented this mouse model in 20155, and named this model as 'épi/épi mouse' with a meaning of homozygous recessive gene mutation (épi) causing 'épilepsie'(a French word for epilepsy) in 2018.

Data:

- Although obtaining the adult épi/épi mice required our special feeding technique, once performed properly, more than 60% of the newly born épi/épi mice were safely weaned, which acquired more stable viability thereafter .
- Our special feeding technique is simple and inexpensive, which does not require skill.
- Since 2014, all épi/épi mice (n=38) exhibited spontaneous GTCSs (Morrison's Score 6)6 without any epileptogenic induction, of which 5,839 times were video-archived, while wild-type (Épi/Épi) or heterozygous (Épi/épi) never did once. Concomitant circumstances of épi/épi mice's seizures (**e.g.** most of grand-mal seizures occurs during sleep, not during meal) also resembled those of human MTLE patients.
- All épi/épi mice exhibited overt GTCSs (Morrison's Score 6) almost every day since around one-month-old through lifetime (Figure 1). Frequency of grand- mal seizures was typically 5-20 times per day per mouse. All épi/épi mice more frequently exhibited lower levels of seizures (Morrison's Score 1-5. e.g. myoclonic jerks of the head and neck).
- Once GTCSs were established in an épi/épi mouse, any kind of subtle sensory stimulus (sound, vibration, light, or touch) acted as a trigger for a GTCS.
- Besides GTCSs, all épi/épi mice were jumpy and hyper-sensitive to any kind of sensory stimulus. These traits of mice coincided with impulsive behavioral tendency of human MTLE patients, called 'a syndrome of sensory-limbic hyperconnection'.
- Pathological analyses of brain tissues of épi/épi mice revealed: 1) bilateral hippocampal sclerosis (HS) characterized by activated astrocytes, and 2) bilateral granule cell layer dispersion (GCD) at around postnatal Day14, and both of which progressed with advancing age. Neither sclerosis nor cell dispersion was observed in extra-hippocampal regions in the brain of épi/épi mice.
- Electroencephalogram (EEG) of tested épi/épi mice (n=7) exhibited continuous abnormalities (waves with higher amplitudes and higher frequency) compared with wild-type littermates. A gigantic EEG burst wave was synchronized with a GTCS. Highest amplitudes of EEG waves were observed on the electrode above the hippocampus.
- Thus, épi/épi mice turned out to be the first MTLE animal model, which completely fulfills Kudrimoti's three requirements.

Patent info: WO2016060109A1; Knock-out mouse, method of screening material suppressing mesial temporal lobe epilepsy, and method of selecting technique for suppressing mesial temporal lobe epilepsy

Further Details:

(* The name of the primary inventor is underlined.)

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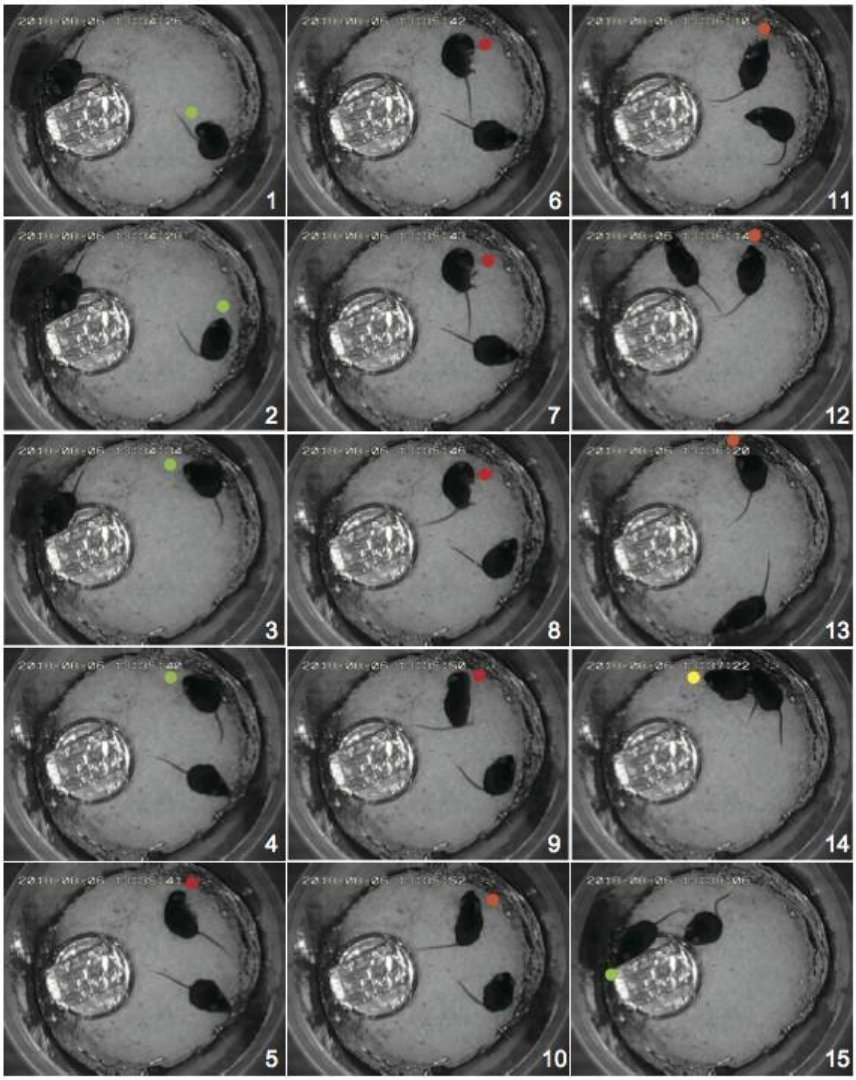
Figuare:

A typical example of a generalized tonic-clonic seizure (GTCS) in the épi/épi mice.
Fifteen panels (top left; 1-15) represent the chronological images extrated from a videoclip containing a GTCS in an épi/épi mouse. Colored dots mark the positions of the épi/épi mouse, which exhibited a GTCS in this videoclip. Each color of the dot displays each phase in a GTCS: green, for the normal phase; red, for the tonic phase; orange, for the clonic phase; and yellow, for the postictal phase. Absolute time is displayed on the top-left position in each panel. Phases, panel numbers, absolute time, timing (h:m:s) from the GTCS onset, and description of the behaviors of the épi/épi mouse are summarized in a table on the bottom. Typical GTCSs of the épi/épi mouse started while sleeping, and lasted for 30-60 sec.



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Phase	Panel#	Absolute Time	Timing from GTCS onset	Action
Normal	1	13:34:26	-00:01:15	Walking
	2	13:34:28	-00:01:13	Halt
	3	13:34:34	-00:01:07	Fell asleep
	4	13:35:40	-00:00:01	Sleeping
Tonic	5	13:35:41	00:00:00	Fell on the ground
	6	13:35:42	00:00:01	Tail contracted
	7	13:35:43	00:00:02	Tetanic spasm
	8	13:35:46	00:00:05	Flexed position
	9	13:35:50	00:00:09	Turned to prone position
Clonic	10	13:35:52	00:00:11	Rhythmical jerking
	11	13:36:10	00:00:29	Rhythmical jerking
	12	13:36:14	00:00:33	Rhythmical jerking
	13	13:36:20	00:00:39	Termination of jerking
Postictal	14	13:37:22	00:01:41	Being pushed by another
Normal	15	13:38:06	00:02:19	Normal walking

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