Louis Ptáček, Dept. of Neurology
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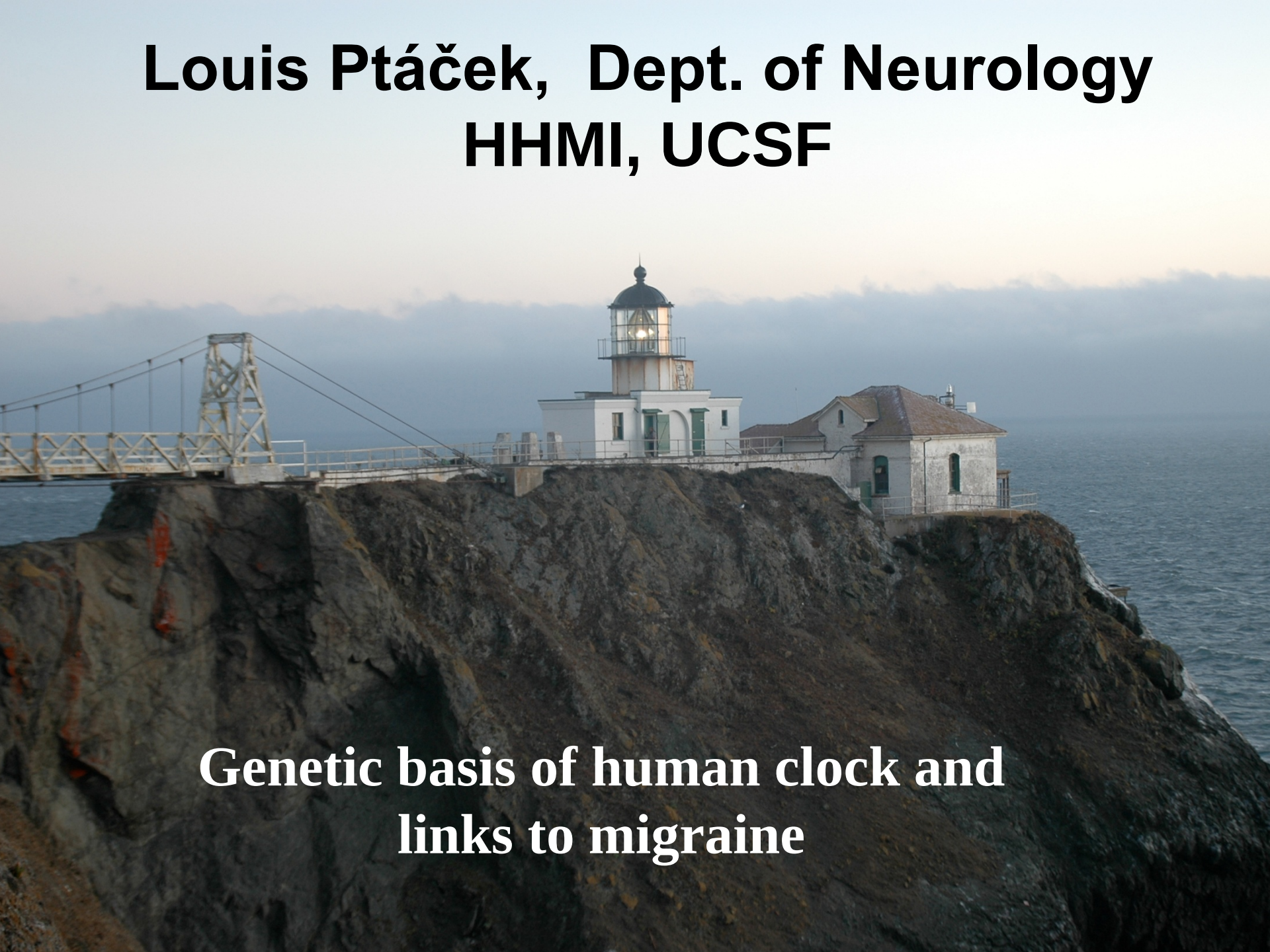


Genetic basis of human clock and links to migraine

- **Episodic Disorders**
  - *Periodic Paralysis*
  - *Episodic Movement Disorders*
  - *Epilepsy*
  - *Migraine*
- **Circadian/Sleep Traits**
  - *Advanced Sleep Phase Syndrome*
  - *Delayed Sleep Phase Syndrome*
  - *Natural Short Sleepers*

Episodic Nervous System Diseases

Migraine

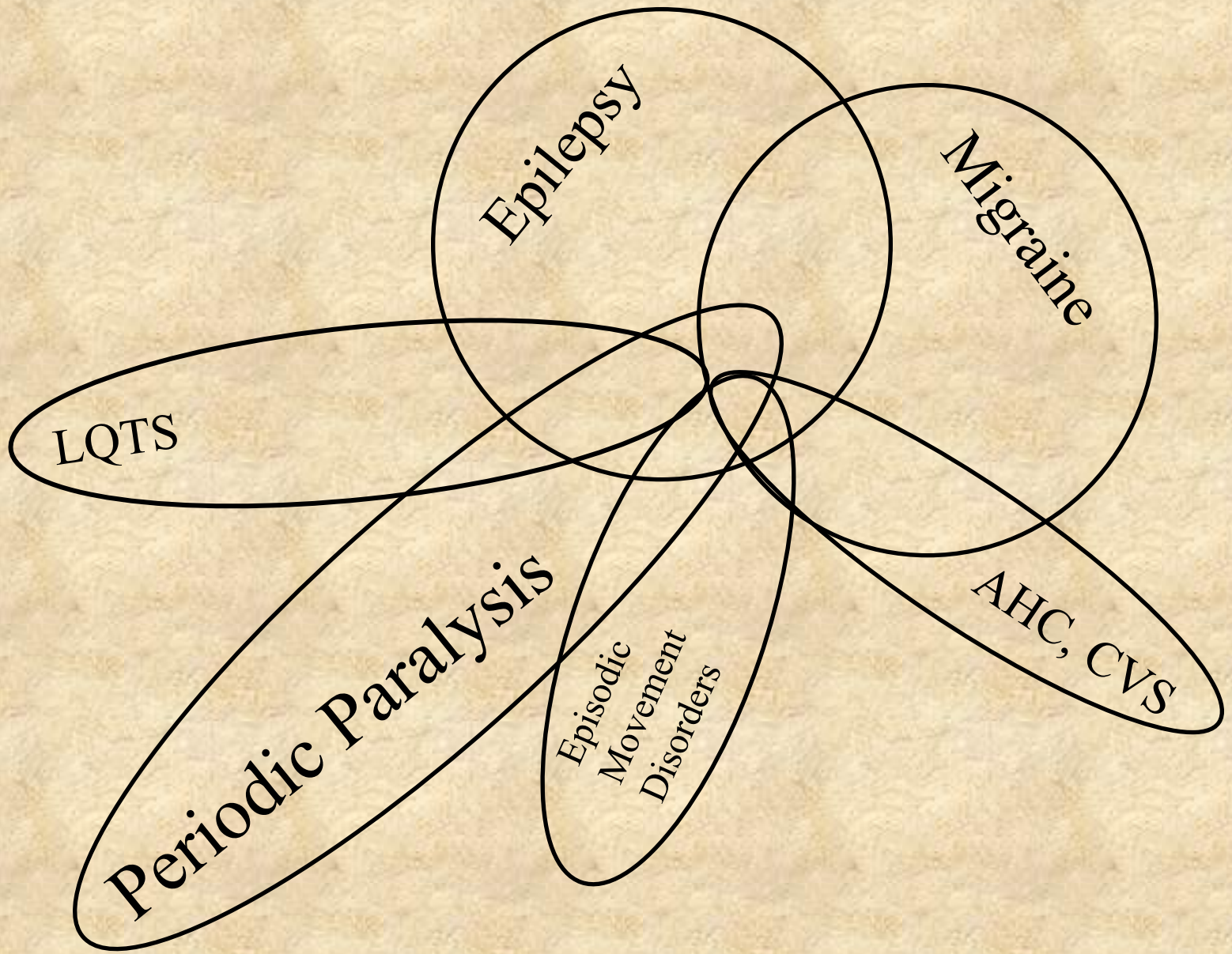
Epilepsy

Periodic Paralysis

LQTS

Episodic Ataxia

Paroxysmal Dyskinesias


Epilepsy
Migraine
LQTS
Periodic Paralysis
Episodic Movement Disorders
AHC, CVS

Similarities Among These Disorders

Episodic

Precipitating Factors

Stress, Fatigue, Dietary Factors, Alcohol, Caffeine

Therapeutic Responses

eg. CAI, Tegretol

Hormonal Factors

Stigmatization

Natural History

Non-dystrophic Myotonia/Periodic Paralysis

Hyperkalemic Periodic Paralysis

Hypokalemic Periodic Paralysis

Paramyotonia Congenita

Potassium Aggravated Myotonia

AR Myotonia Congenita

AD Myotonia Congenita

Andersen-Tawil Syndrome

Thyrotoxic Hypokalemic PP

SCN4A

CACNA1S

CLCN1

KCNJ2

KCNJ18

Cell, Vol. 67, 1021–1027, November 29, 1991, Copyright © 1991 by Cell Press

Identification of a Mutation in the Gene Causing Hyperkalemic Periodic Paralysis

Louis J. Ptáček,*† Alfred L. George, Jr.,‡
Robert C. Griggs,§ Rabi Tawil,§
Roland G. Kallen,‡‖ Robert L. Barchi,‡#
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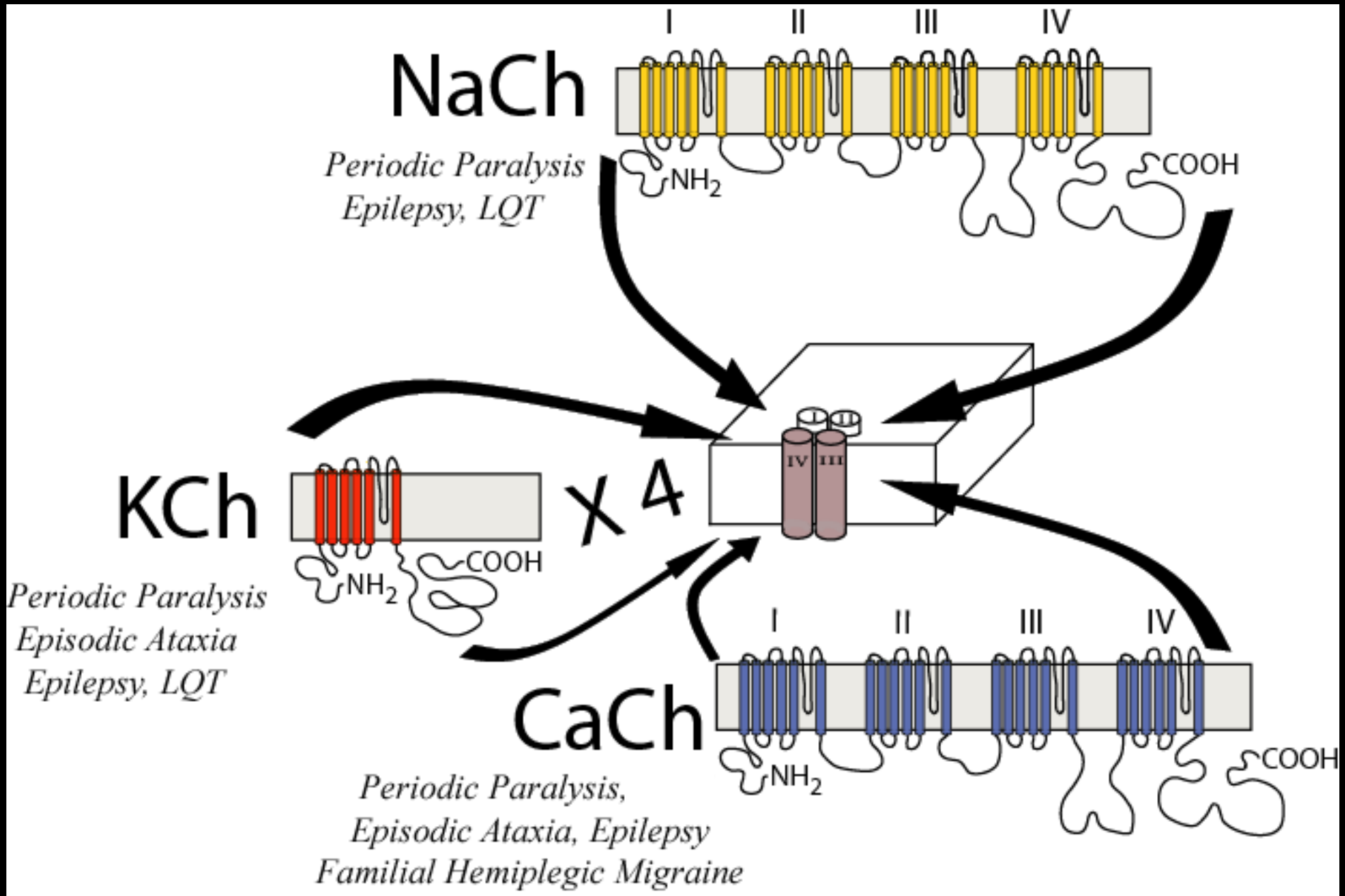
Rochester, New York 14642

sion system would then allow analysis of ion channel response to pharmacologic interventions. Understanding HYPP and related disease states will lead to better understanding of normal muscle and other excitable tissues. Furthermore, the periodic paralyses and nondystrophic myotonic disorders may serve as a useful paradigm for studying other disorders in which abnormalities in electrical properties of cell membranes are known to be important. Such diseases include epilepsy, peripheral nerve disorders, and cardiac dysrhythmias.

•*Ptáček et al., Cell 1991*


NaCh
I
II
III
IV
NH2
COOH
Periodic Paralysis
Epilepsy, LQT
KCh
X 4
NH2
COOH
Periodic Paralysis
Episodic Ataxia
Epilepsy, LQT
I
II
III
IV
CaCh
NH2
COOH
Periodic Paralysis,
Episodic Ataxia, Epilepsy
Familial Hemiplegic Migraine

Migraine headache

--affects 10-15% of the population

--highly heritable

--mode of heritability not clear

Migraine Genetics

Familial hemiplegic migraine (FHM)

CACNA1A-Calcium channel

SCN1A-Sodium channel

ATP1A2-Na+/K+ ATPase

Alternating hemiplegia of Childhood with epilepsy and migraine

ATP1A2-Na+/K+ ATPase

ATP1A3-Na+/K+ ATPase

Familial migraine with aura

KCNK18-TRESK postassium channel

CSNK1d-Casein Kinase Iδ

Not all episodic disorders are channelopathies!

GPR98

Neuron, Vol. 31, 537–544, August 30, 2001, Copyright ©2001 by Cell Press

A Novel Gene Causing a Mendelian Audiogenic Mouse Epilepsy

Shana L. Skradski,[1] Anna M. Clark,[2] Hiamio Jiang,[3]
H. Steve White,[1,4] Ying-Hui Fu,[5] and
Louis J. Ptáček[2,3,6,7,8]
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[4] Anticonvulsant Screening Project
[5] Department of Neurobiology and Anatomy
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Salt Lake City, Utah 84112

Human Molecular Genetics, 2004, Vol. 13, No. 24 **3161–3170**
doi:10.1093/hmg/ddh330
Advance Access published on October 20, 2004

The gene for paroxysmal non-kinesigenic dyskinesia encodes an enzyme in a stress response pathway

Hsien-Yang Lee[1,2], Ying Xu[1], Yong Huang[1], Andrew H. Ahn[1], Georg W.J. Auburger[3], Massimo Pandolfo[4], Hubert Kwieciński[5], David A. Grimes[6], Anthony E. Lang[7], Jorgen E. Nielsen[8], Yuri Averyanov[9], Serenella Servidei[10], Andrzej Friedman[5], Patrick Van Bogaert[4], Marc J. Abramowicz[4], Michiko K. Bruno[1,11], Beatrice F. Sorensen[1], Ling Tang[2], Ying-Hui Fu[1] and Louis J. Ptáček[1,12,*]

Cell PRESS
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Cell Reports
Report

Mutations in the Gene *PRRT2* Cause Paroxysmal Kinesigenic Dyskinesia with Infantile Convulsions

Hsien-Yang Lee,[1] Yong Huang,[1,2] Nadine Bruneau,[3] Patrice Roll,[4] Elisha D.O. Roberson,[5] Mark Hermann,[1] Emily Quinn,[1,2] James Maas,[1] Robert Edwards,[1] Tetsuo Ashizawa,[6] Betul Baykan,[7] Kailash Bhatia,[8] Susan Bressman,[9] Michiko K. Bruno,[1,10] Ewout R. Brunt,[11] Roberto Caraballo,[12] Bernard Echenne,[13] Natalio Fejerman,[12] Steve Frucht,[14] Christina A. Gurnett,[15] Edouard Hirsch,[16] Henry Houlden,[8] Joseph Jankovic,[17] Wei-Ling Lee,[18] David R. Lynch,[19] Shehla Mohammed,[20] Ulrich Müller,[21] Mark P. Nespeca,[22] David Renner,[23] Jacques Rochette,[24] Gabrielle Rudolf,[16] Shinji Saiki,[25,29] Bing-Wen Soong,[26,27] Kathryn J. Swoboda,[23] Sam Tucker,[19] Nicholas Wood,[8] Michael Hanna,[8,28] Anne M. Bowcock,[5,28] Pierre Szepetowski,[3,28] Ying-Hui Fu,[1,28,*] and Louis J. Ptáček[1,2,28,*]
[1]Department of Neurology, UCSF, San Francisco, CA 94158, USA

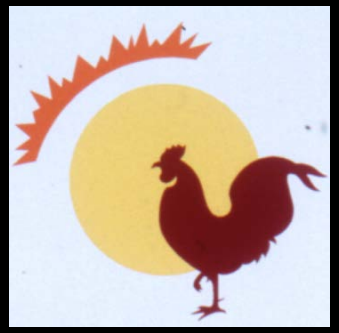
ORIGNAL ARTICLE

Familial Cortical Myoclonus with a Mutation in *NOL3*

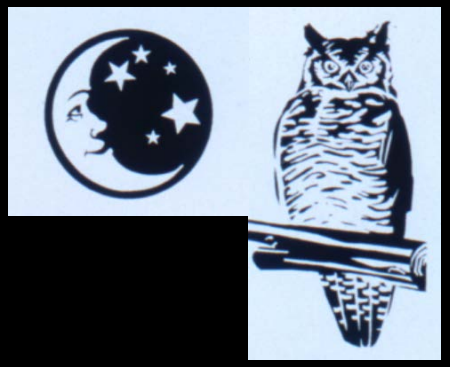
Jonathan F. Russell, BS,[1,2,3] Jamie L. Steckley, MD,[4*] Giovanni Coppola, MD,[5]
Angelika F. G. Hahn, MD,[4] MacKenzie A. Howard, PhD,[6] Zachary Kornberg,[1,2]
Alden Huang, BS,[5] Seyed M. Mirsattari, MD,[4,7] Barry Merriman, PhD,[5] Eric Klein, MS,[5]
Murim Choi, PhD,[8] Hsien-Yang Lee, PhD,[1,2] Andrew Kirk, MD,[9] Carol Nelson-Williams, MS,[8]
Gillian Gibson, MD,[10] Scott C. Baraban, PhD,[6] Richard P. Lifton, MD, PhD,[8]
Daniel H. Geschwind, MD, PhD,[5] Ying-Hui Fu, PhD,[1] and Louis J. Ptáček, MD[1,2]

Annals of Neurology, 2012

Selected Familial Sleep-Wake Phenotypes



Advanced sleep phase



Delayed sleep phase

Natural short sleep

Familial Advance Sleep Phase

Autosomal dominant behavioral phenotype where affected individuals fall asleep early and wake early

Genes\mutations identified: Per2, CKId, et al.

PTMs critical to regulation of clock speed (CKIδ, CKIε, GSK3β)

Nature Med, 1999;5:1062-65

Circadian rhythm/Sleep in Human health and disease

Metabolism/Obesity

Cancer

Mood disorder

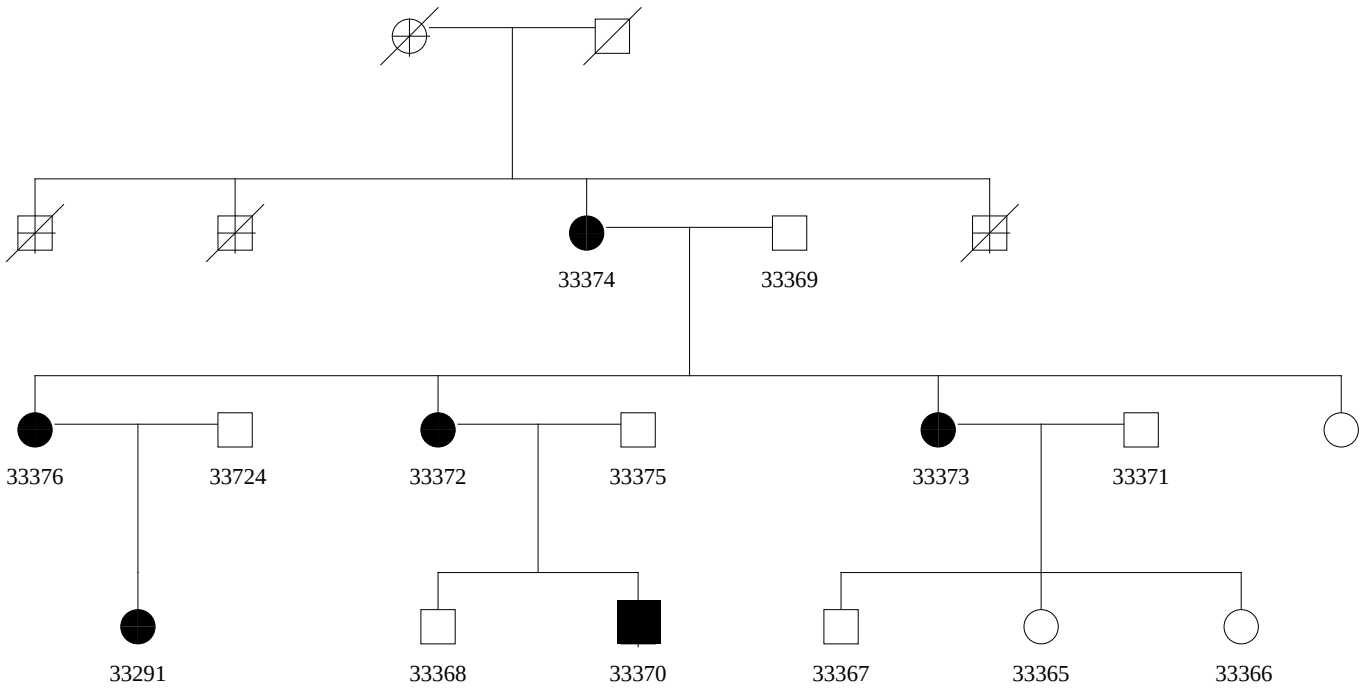
Clock/Sleep

Learning & Memory

Migraine

Immunity

K5231



Sleep onset time 18:12 +/- 1.4 hr vs. 23:24 +/- 1.1 hr

Sleep offset time 04:06 +/- 0.7 hr vs. 08:00 +/- 1.6 hr

UCSF University of California San Francisco

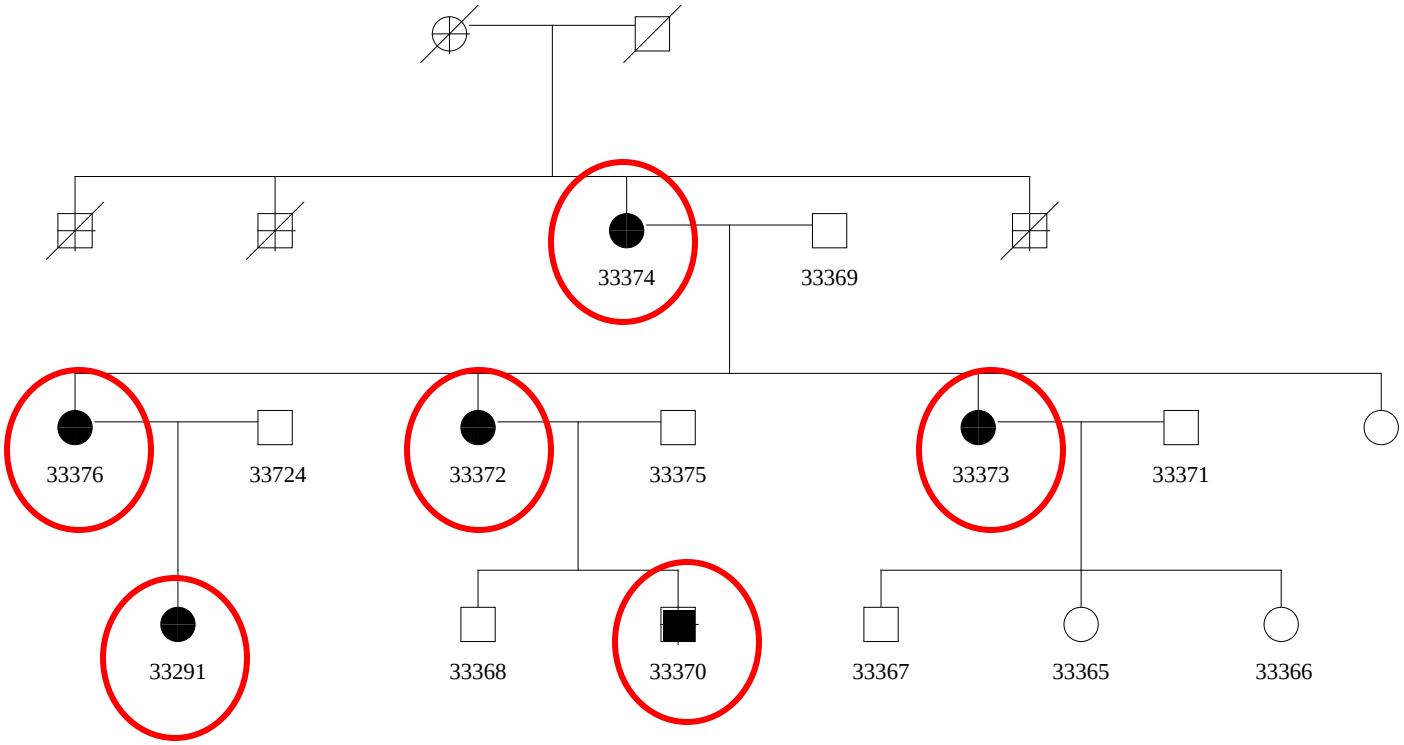
Functional consequences of a *CKIδ* mutation causing familial advanced sleep phase syndrome

Ying Xu[1*], Quasar S. Padiath[1*], Robert E. Shapiro[2], Christopher R. Jones[3], Susan C. Wu[1], Noriko Saigoh[1], Kazumasa Saigoh[1†], Louis J. Ptáček[1,4] & Ying-Hui Fu[1]

[1]*Department of Neurology, University of California, San Francisco, San Francisco, California 94143-2922, USA*
[2]*Department of Neurology, College of Medicine, University of Vermont, Burlington, Vermont 05405, USA*
[3]*Department of Neurology, University of Utah, Salt Lake City, Utah 84132-2305, USA*
[4]*Howard Hughes Medical Institute, UCSF, San Francisco, California 94143-2922, USA*

Nature, 2005;434:640-4

K5231



Sleep onset time 18:12 +/- 1.4 hr vs. 23:24 +/- 1.1 hr

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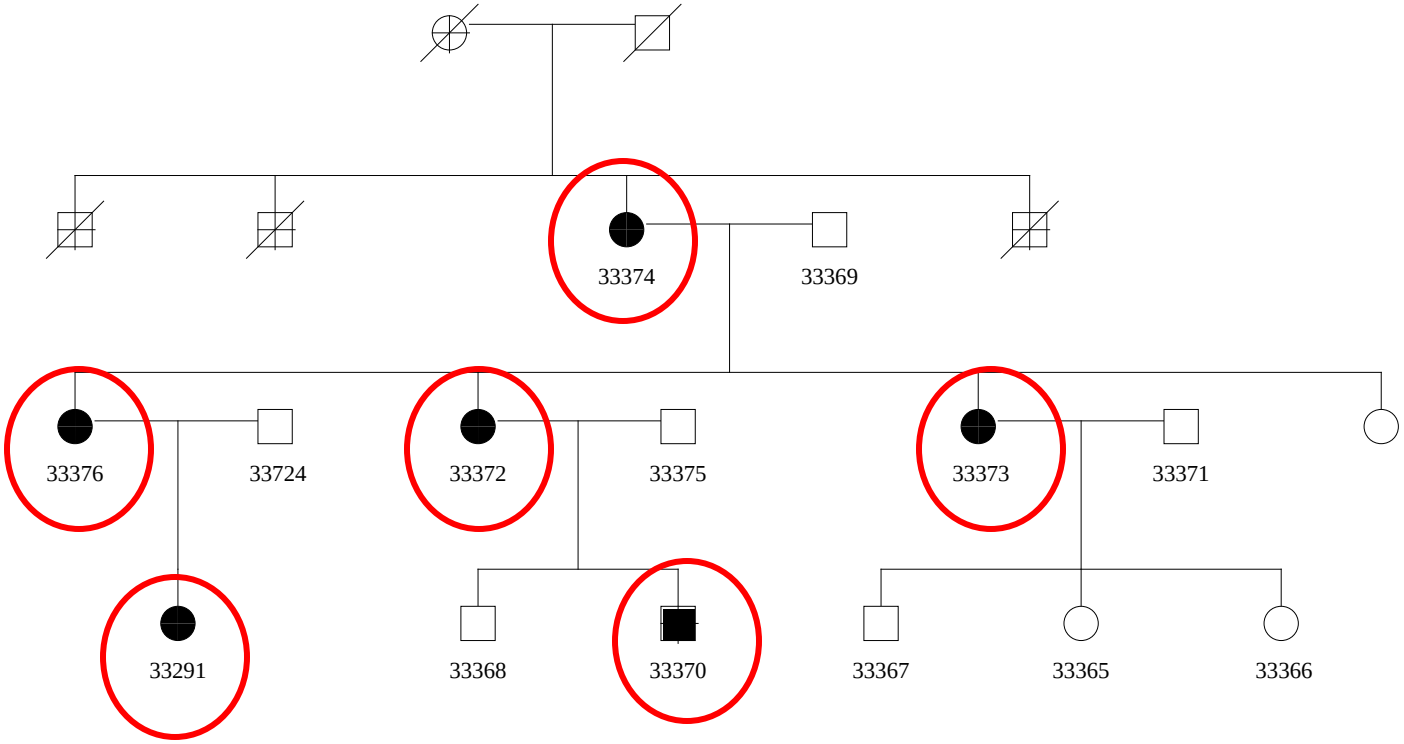
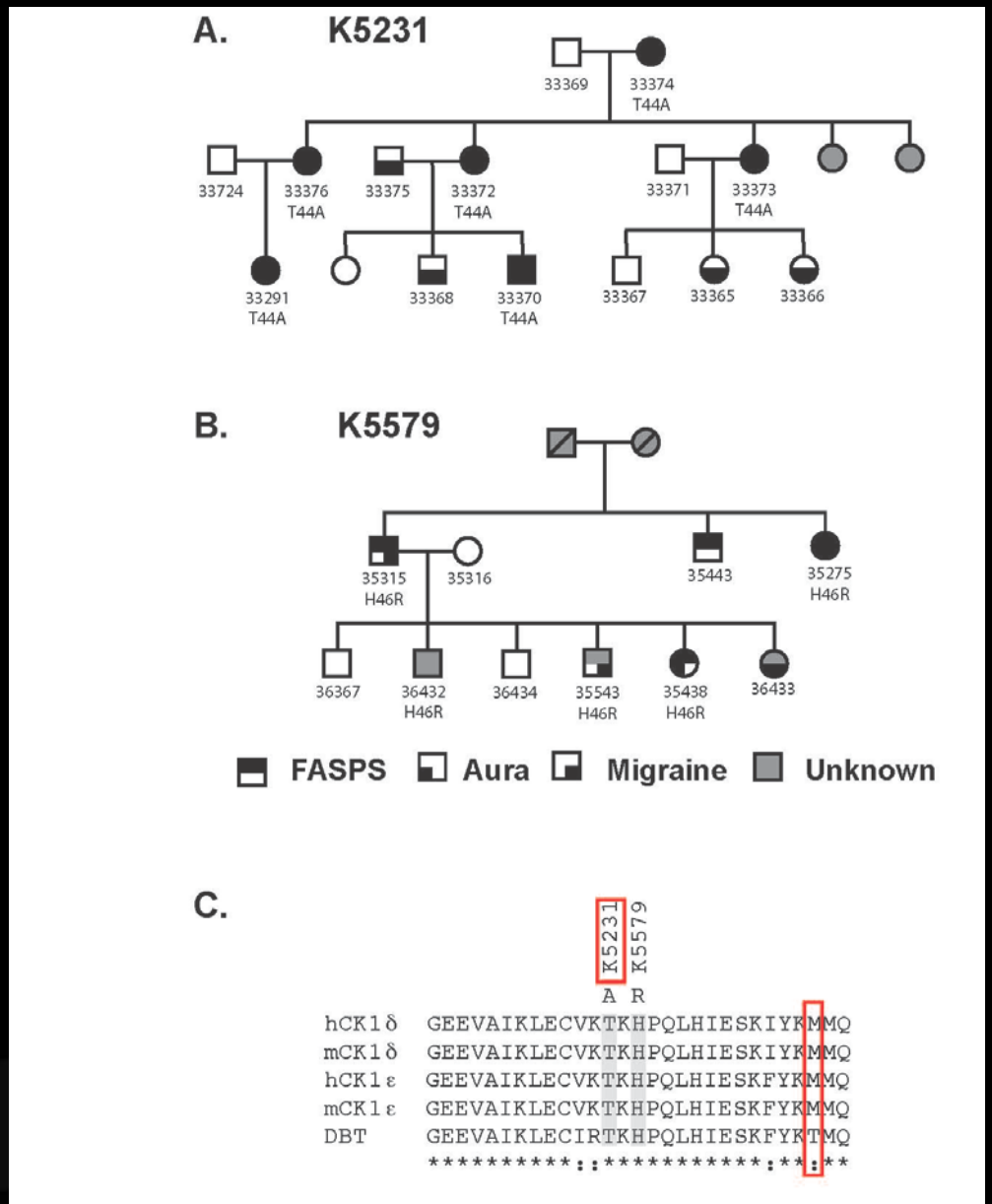
K5231



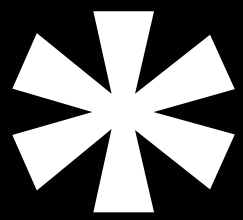
All mutation carriers have asthma and migraine with aura

A second family with migraine and a CKIδ mutation



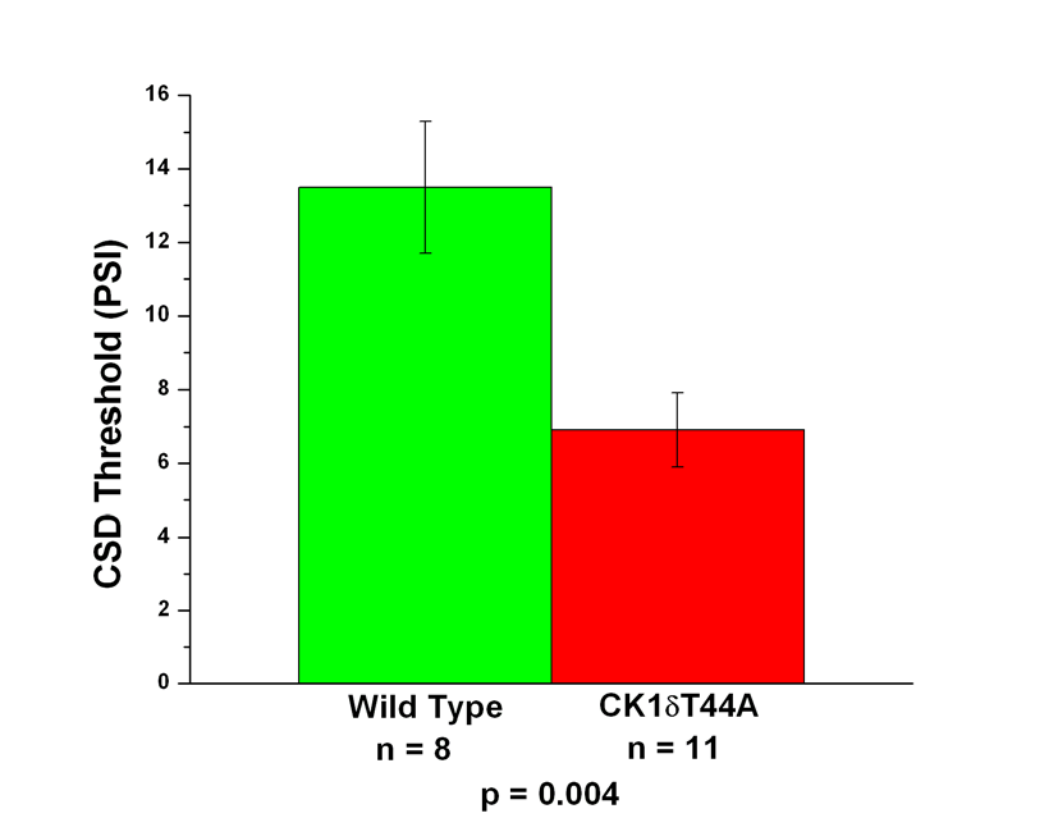
UCSF
University of California
San Francisco

Migrainous Brain State



- Headache
- Aura (CSD)
- Photo/Phonophobia
- Decreased Periph. Pain Thresholds
- Cognitive dysfunction

Lower threshold for CSD induction in CK1δ T44A mutants



CKIδ is a migraine gene

T44A & MA cosegregate in K5231

H46R & MA cosegregate in K5579

↓ CSD thresholds in CKIδ T44A mice

↑ Arterial dilation in CKIδ T44A mice

↑ Sensitivity of CKIδ T44A mice to NTG induced peripheral allodynia

Astrocytes from CKId-T44A mice showed increased spontaneous and evoked calcium signaling

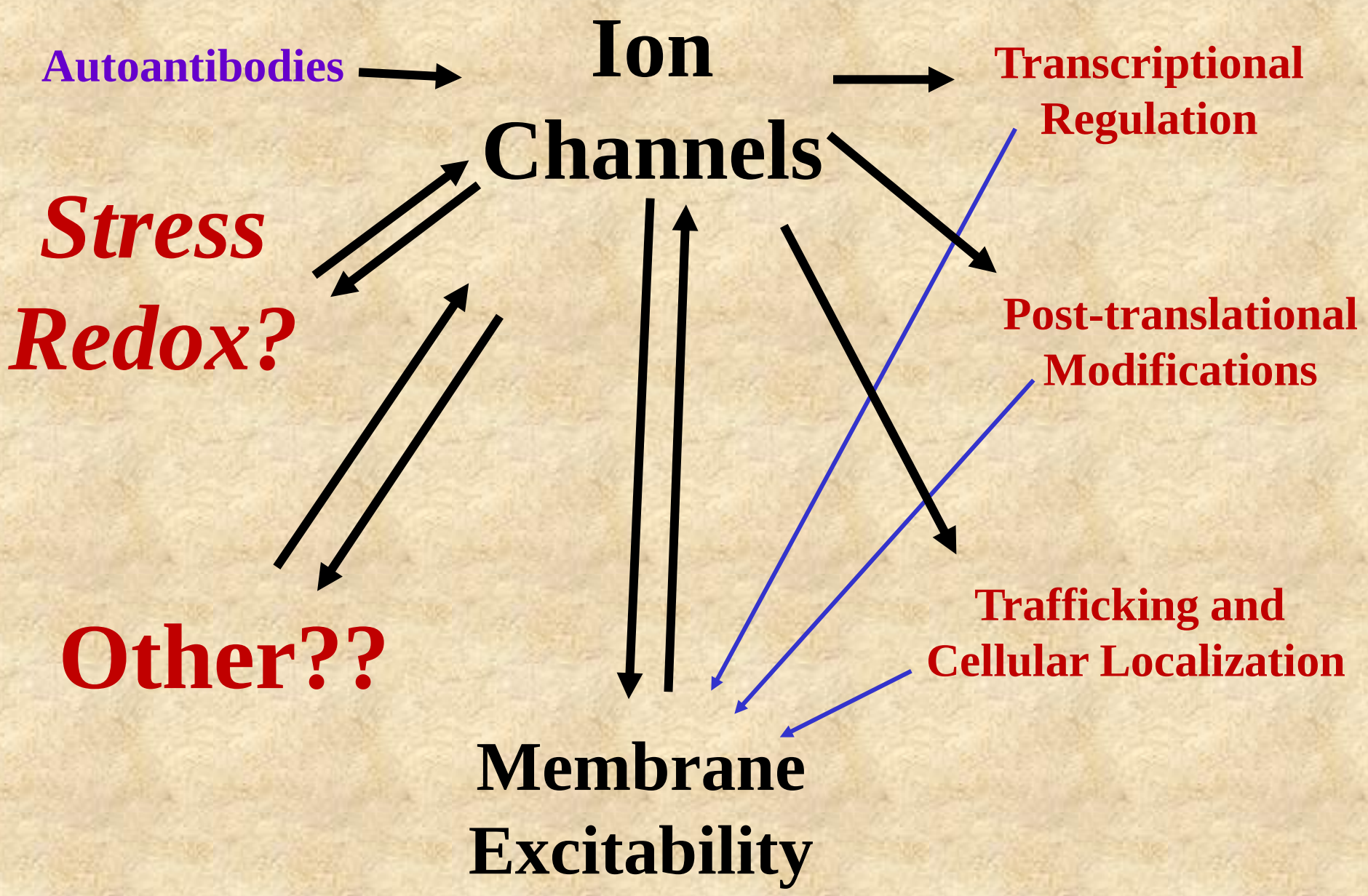
RESEARCH ARTICLE

MIGRAINE

Casein Kinase Iδ Mutations in Familial Migraine and Advanced Sleep Phase

K. C. Brennan,[1,2]* Emily A. Bates,[3,4]* Robert E. Shapiro,[5]* Jekaterina Zyuzin,[1] William C. Hallows,[3] Yong Huang,[3] Hsien-Yang Lee,[3] Christopher R. Jones,[2] Ying-Hui Fu,[3] Andrew C. Charles,[1†] Louis J. Ptáček[3,6†]

Migraine is a common disabling disorder with a significant genetic component, characterized by severe headache and often accompanied by nausea, vomiting, and light sensitivity. We identified two families, each with a distinct missense mutation in the gene encoding casein kinase Iδ (CKIδ), in which the mutation cosegregated with both the presence of migraine and advanced sleep phase. The resulting alterations (T44A and H46R) occurred in the conserved catalytic domain of CKIδ, where they caused reduced enzyme activity. Mice engineered to carry the CKIδ-T44A allele were more sensitive to pain after treatment with the migraine trigger nitroglycerin. CKIδ-T44A mice also exhibited a reduced threshold for cortical spreading depression (believed to be the physiological analog of migraine aura) and greater arterial dilation during cortical spreading depression. Astrocytes from CKIδ-T44A mice showed increased spontaneous and evoked calcium signaling. These genetic, cellular, physiological, and behavioral analyses suggest that decreases in CKIδ activity can contribute to the pathogenesis of migraine.


Autoantibodies
Ion Channels
Transcriptional Regulation
Stress
Redox?
Post-translational Modifications
Other??
Trafficking and Cellular Localization
Membrane Excitability

Circadian rhythm/Sleep in Human health and disease

Metabolism/Obesity

Cancer

Mood disorder

Clock/Sleep

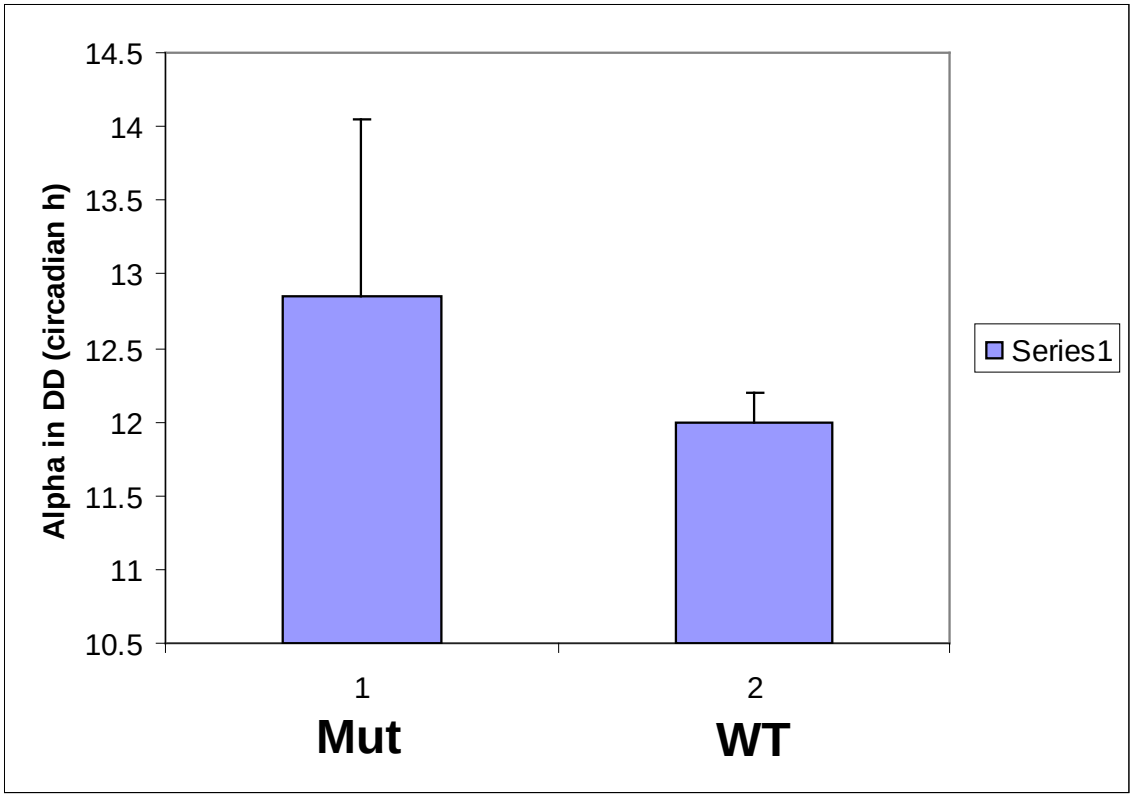
Learning & Memory

Migraine

Immunity

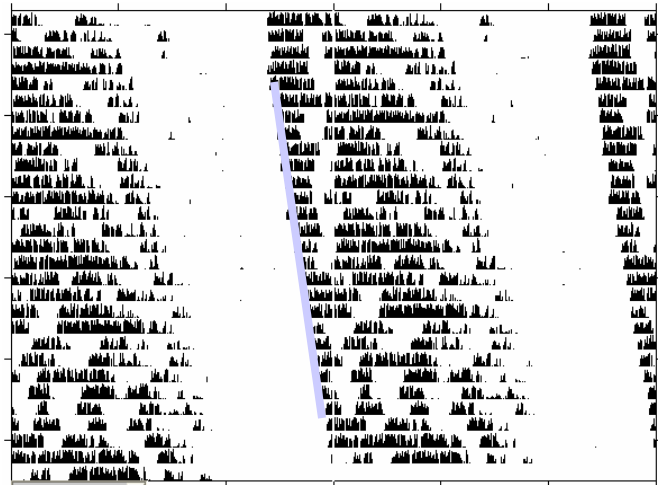
K7107 clinical phenotype

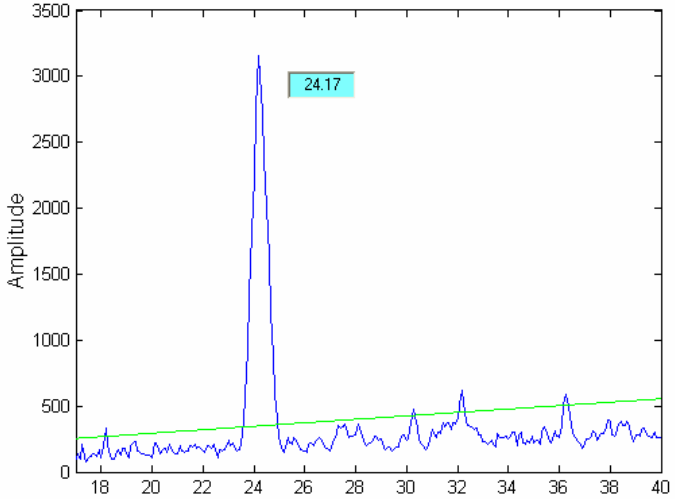
- FASPS, early rise time -21.00 pm sleep onset, offset 3-4 am, on vacation 7.30pm-2.30am
- Short sleepers 6 - 6.5 hrs
- Severe depression and anxiety
- Lexapro


14.5
14
13.5
13
12.5
12
11.5
11
10.5
Alpha in DD (circadian h)
1
2
Mut
WT
Series1

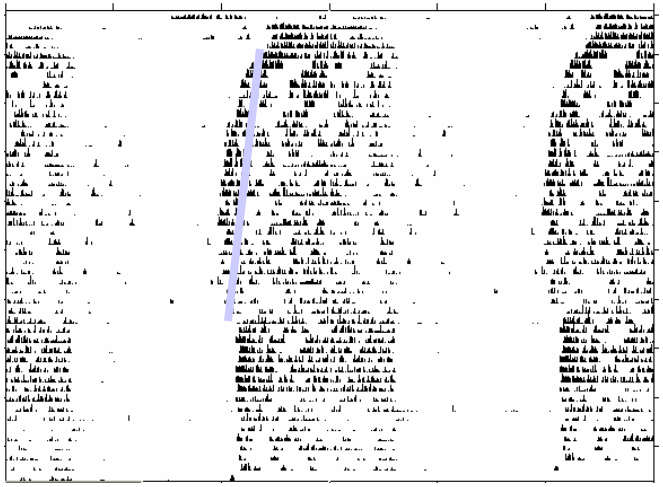
Lexapro treatment normalizes period lengthening

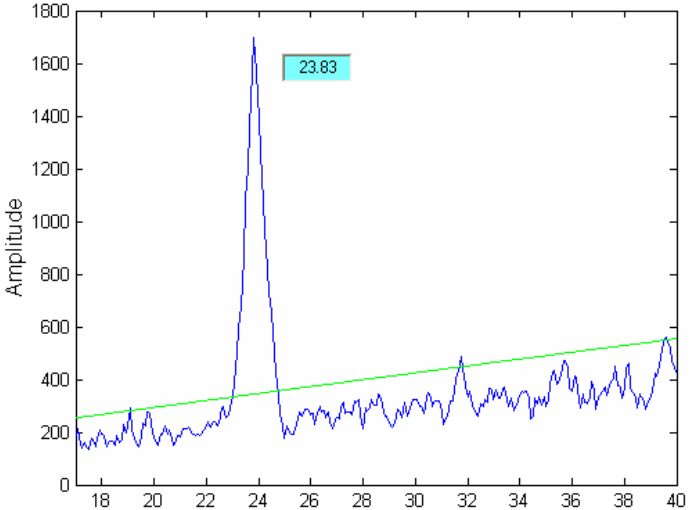
92 mouse run before

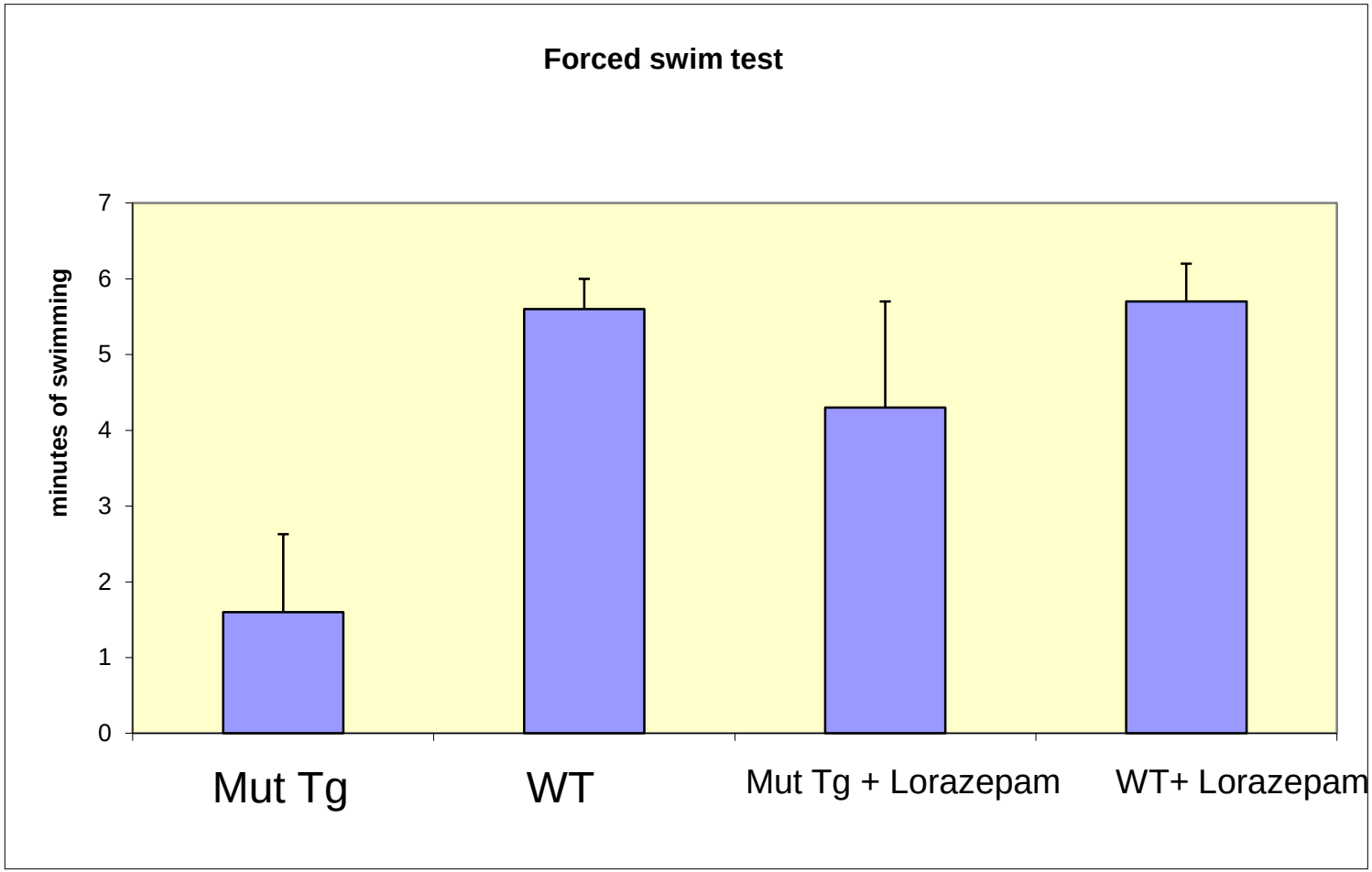




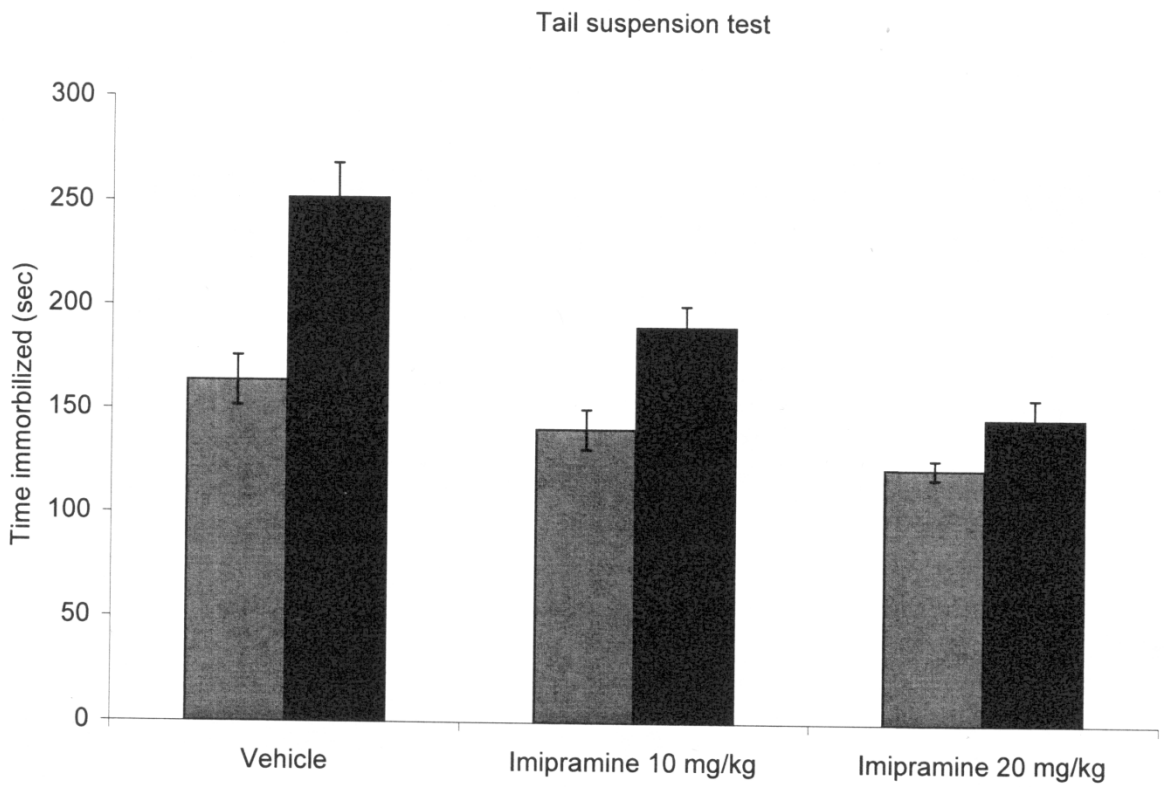
92 lorazepam treatment



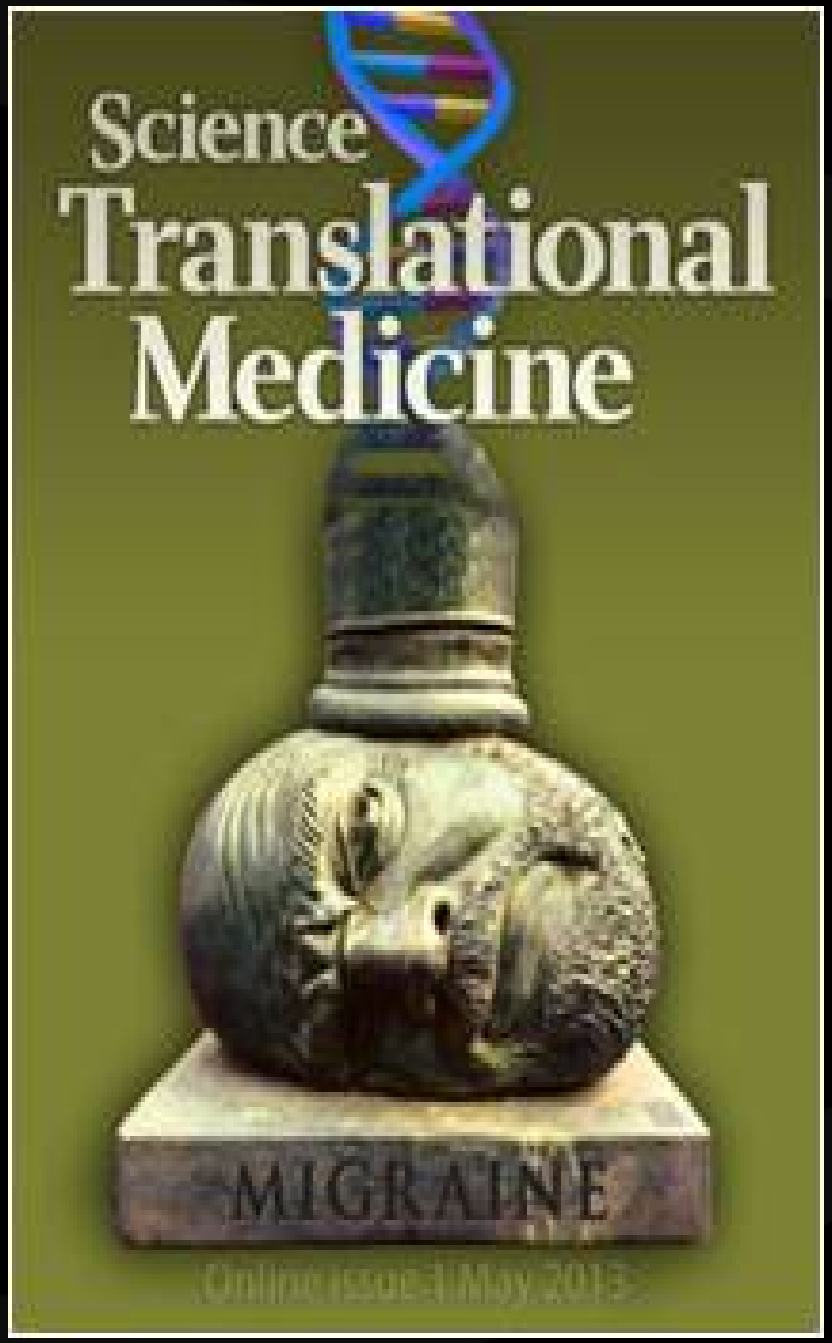



Forced swim test
minutes of swimming
7
6
5
4
3
2
1
0
Mut Tg
WT
Mut Tg + Lorazepam
WT+ Lorazepam

•Tail suspension test: dose dependent rescue of increased immobility by Imipramine



Seiji Nishino



- ***Louis Ptacek***

Terry Toh

Emily Bates

- ***Ying-Hui Fu***

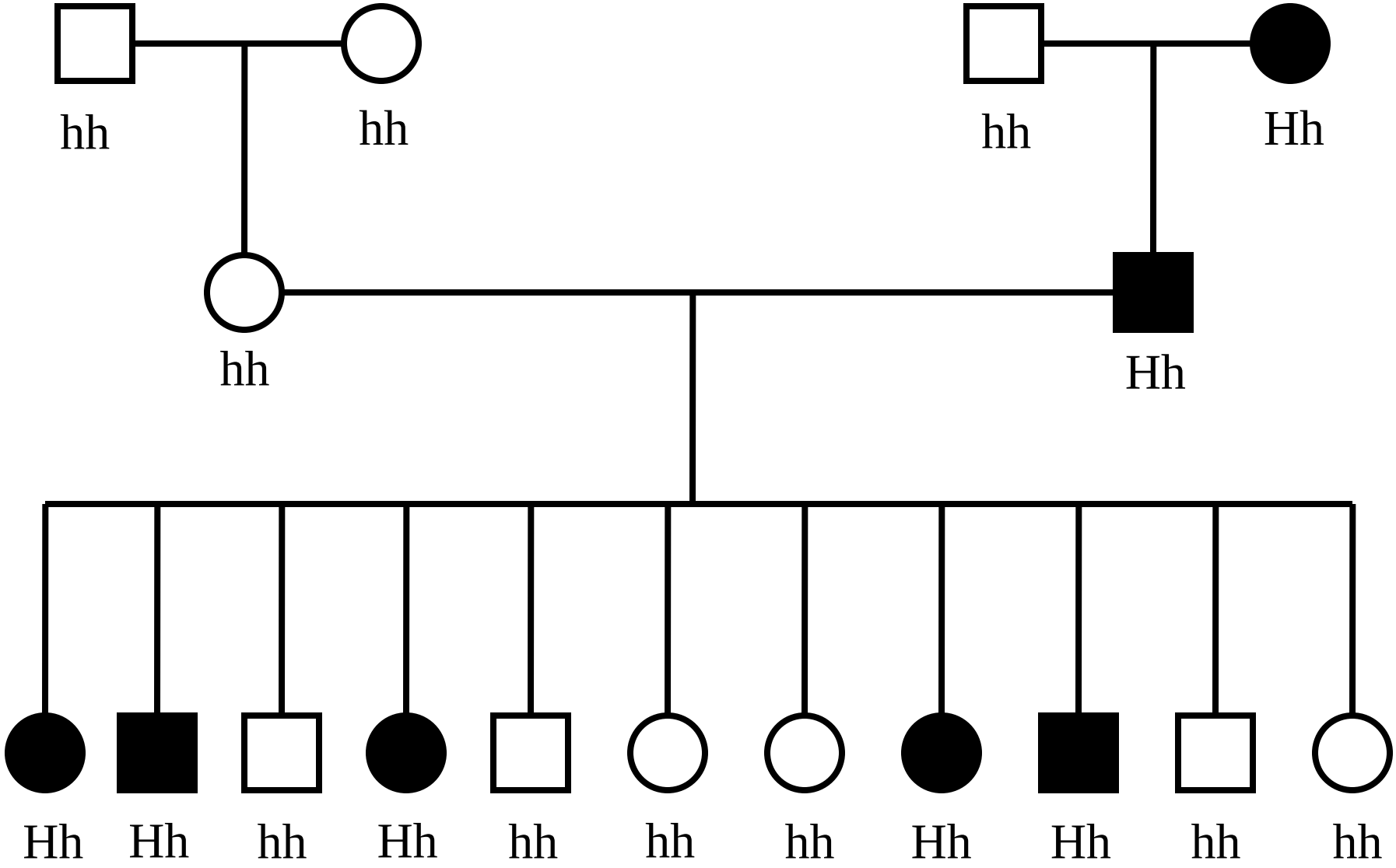
Ying Xu

Krista Kaasik

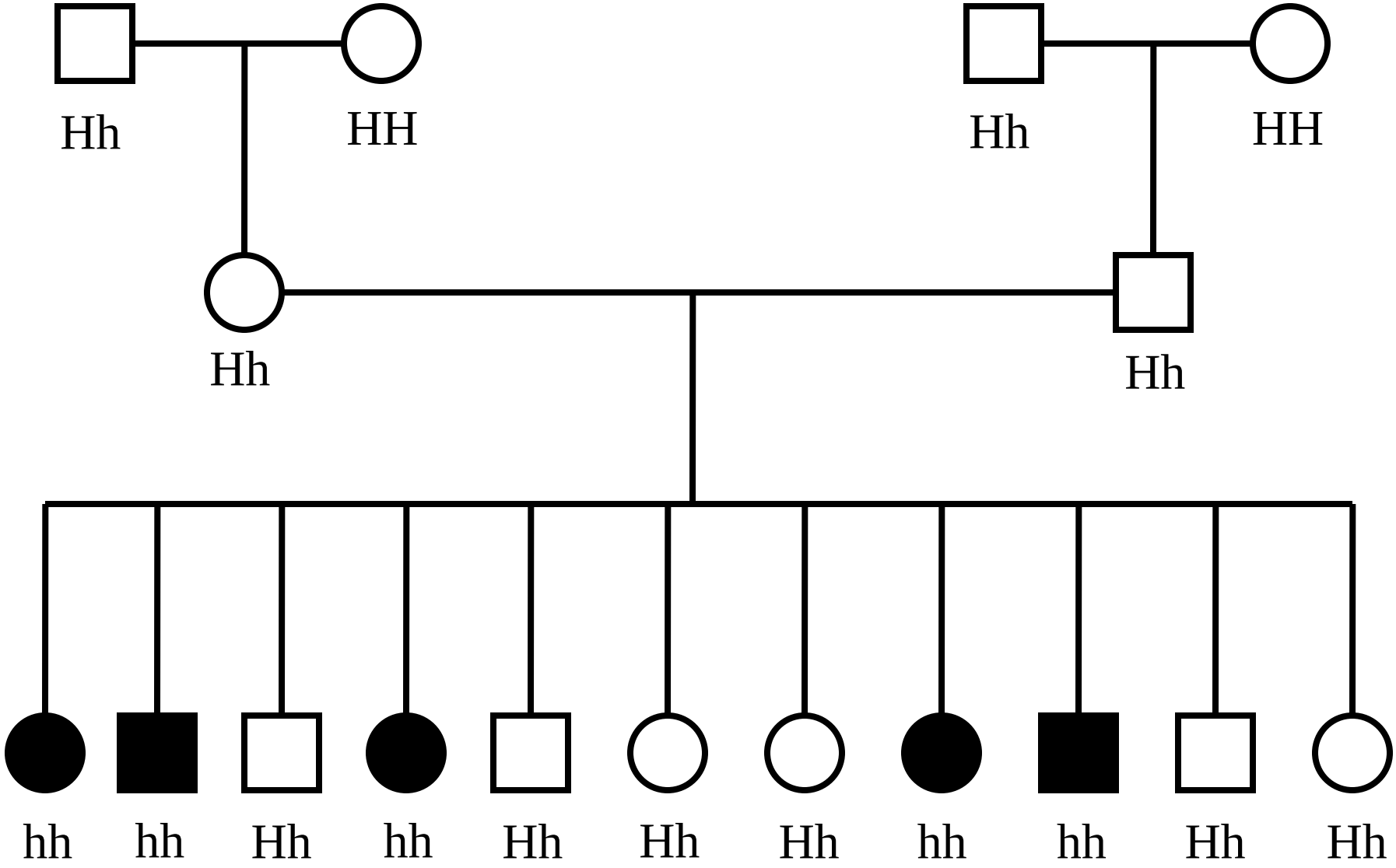
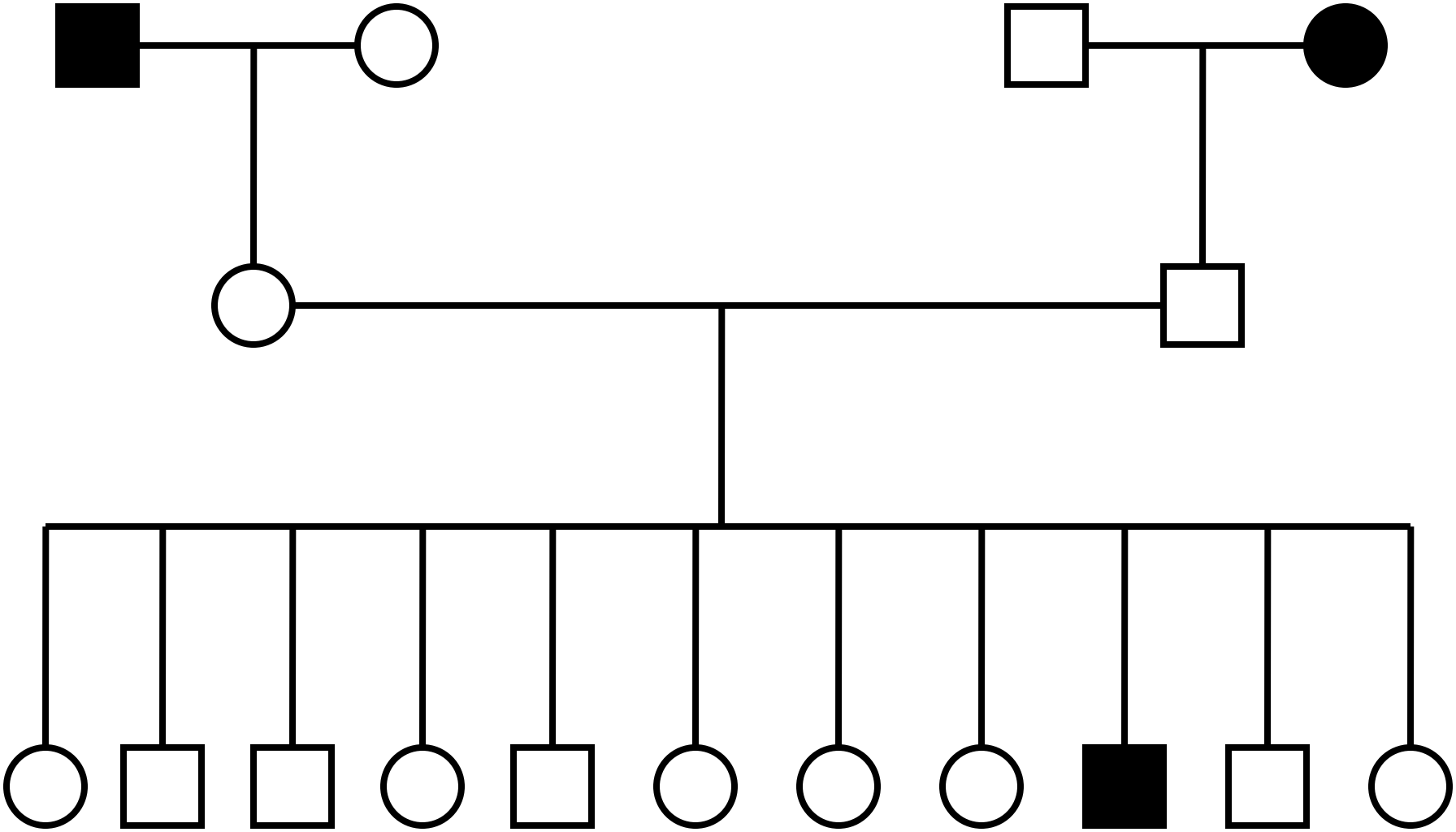
- ***Andrew Charles***
- ***Allan Basbaum***
- ***Robert Shapiro***
- ***Chris Jones***

Funding—HHMI

Dominant Allele (H = disease allele)



Recessive Allele (h = disease allele)



Polygenic Inheritance