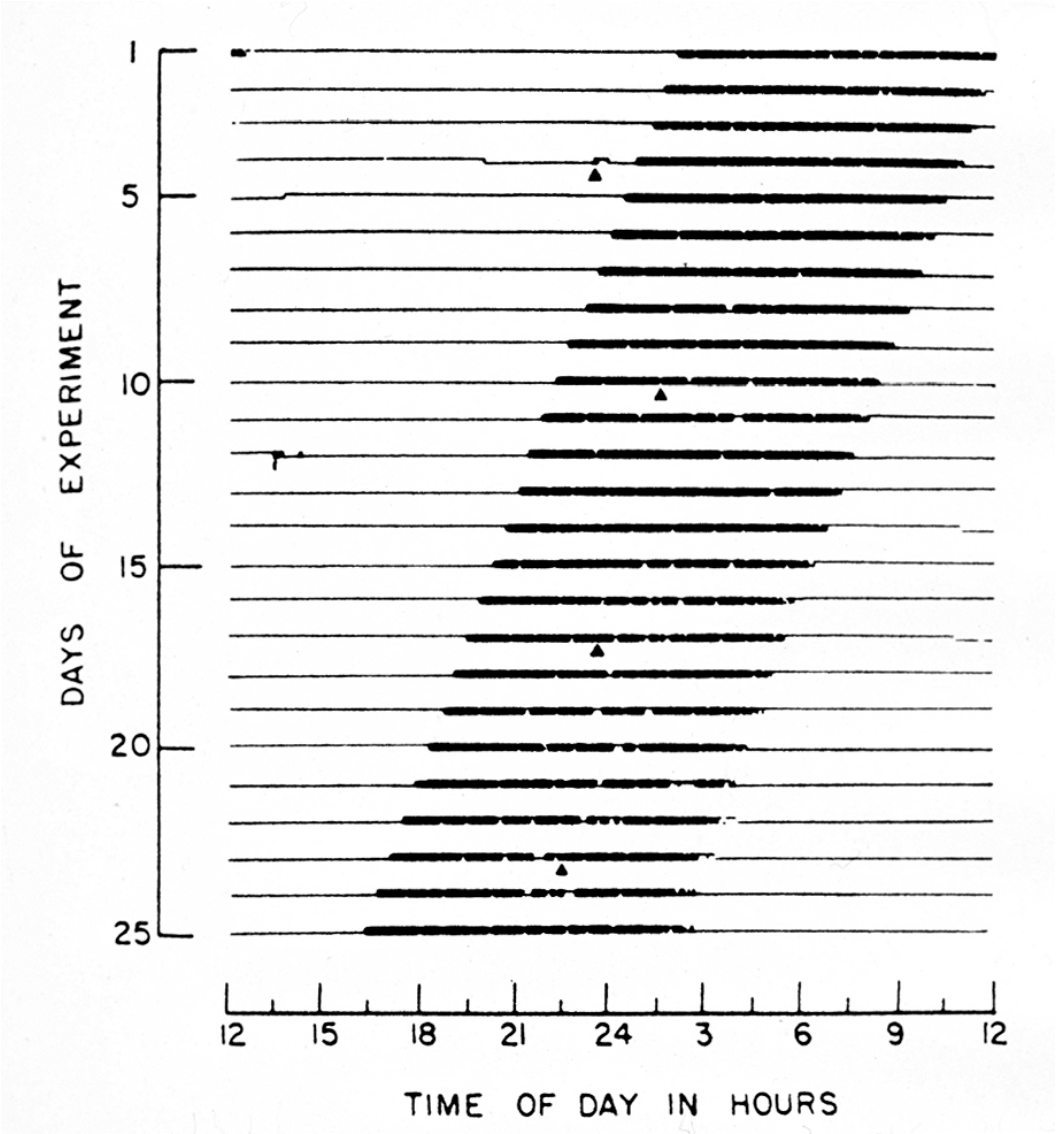
A 40 Year Journey from *Drosophila*'s Clock Mutants to Human Circadian Disorders

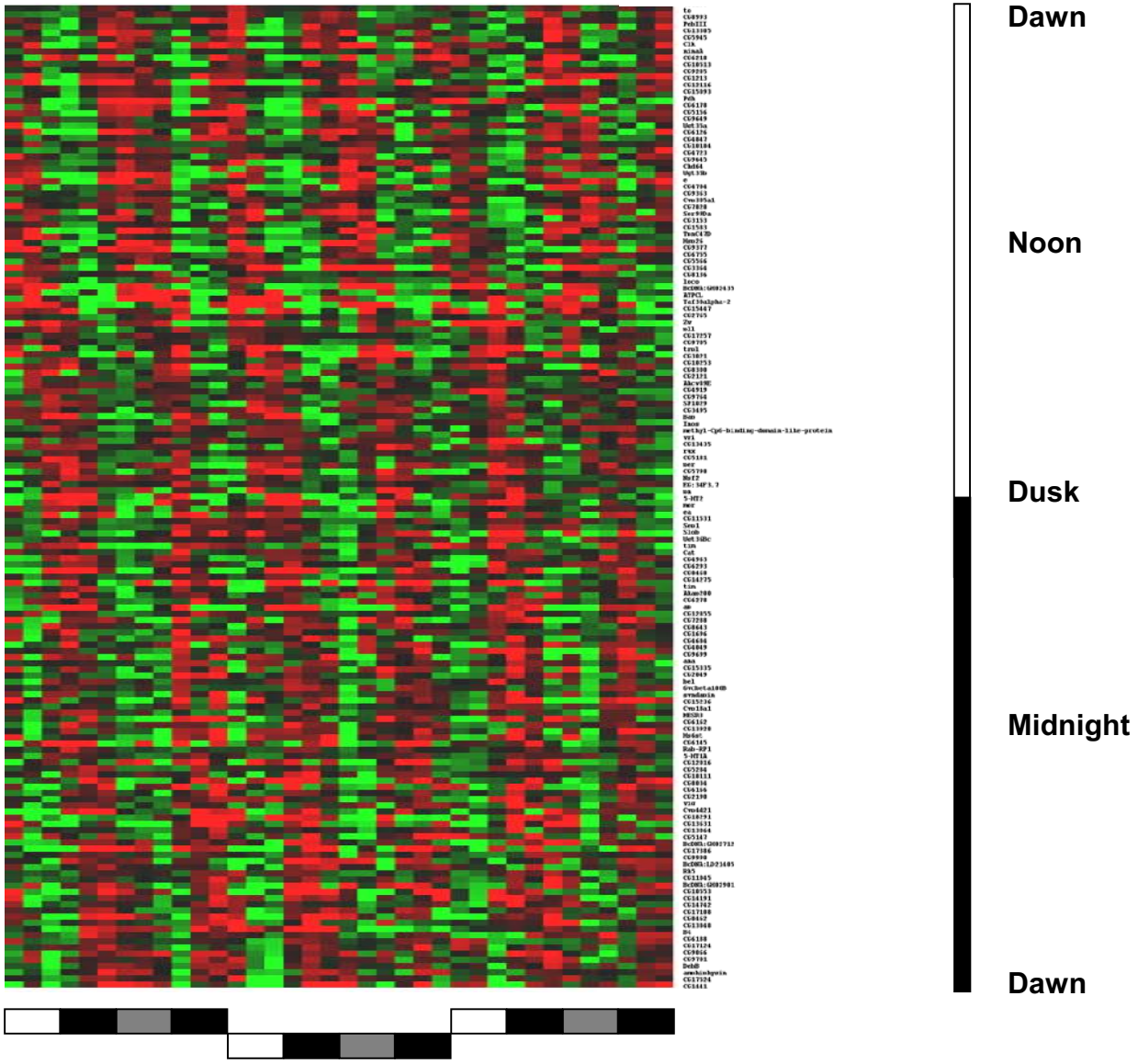
Mirabilis (Four O’Clocks) at 2pm

Mirabilis (Four O'Clocks) at 6pm

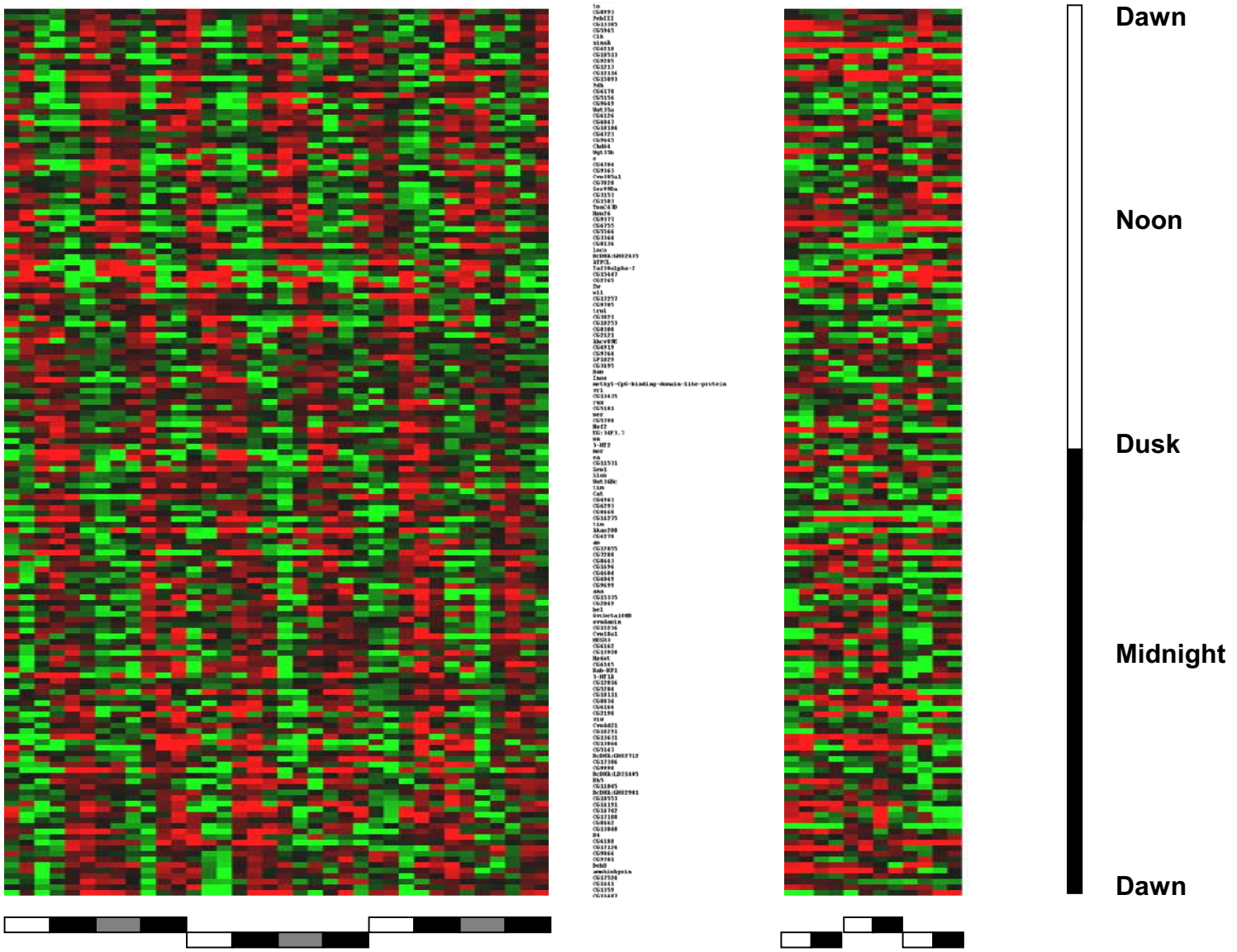
Hamster Activity Record – Constant Darkness

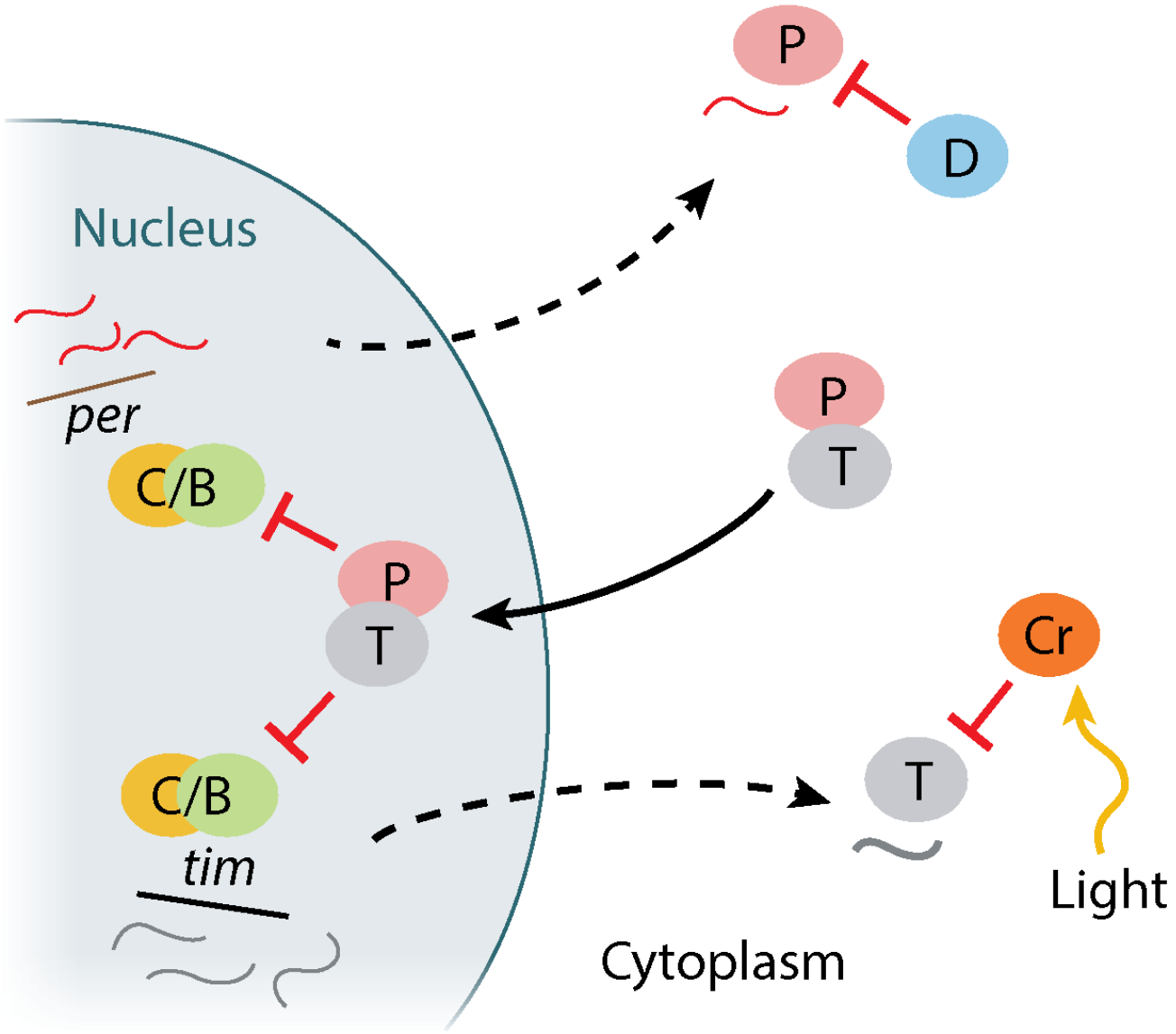


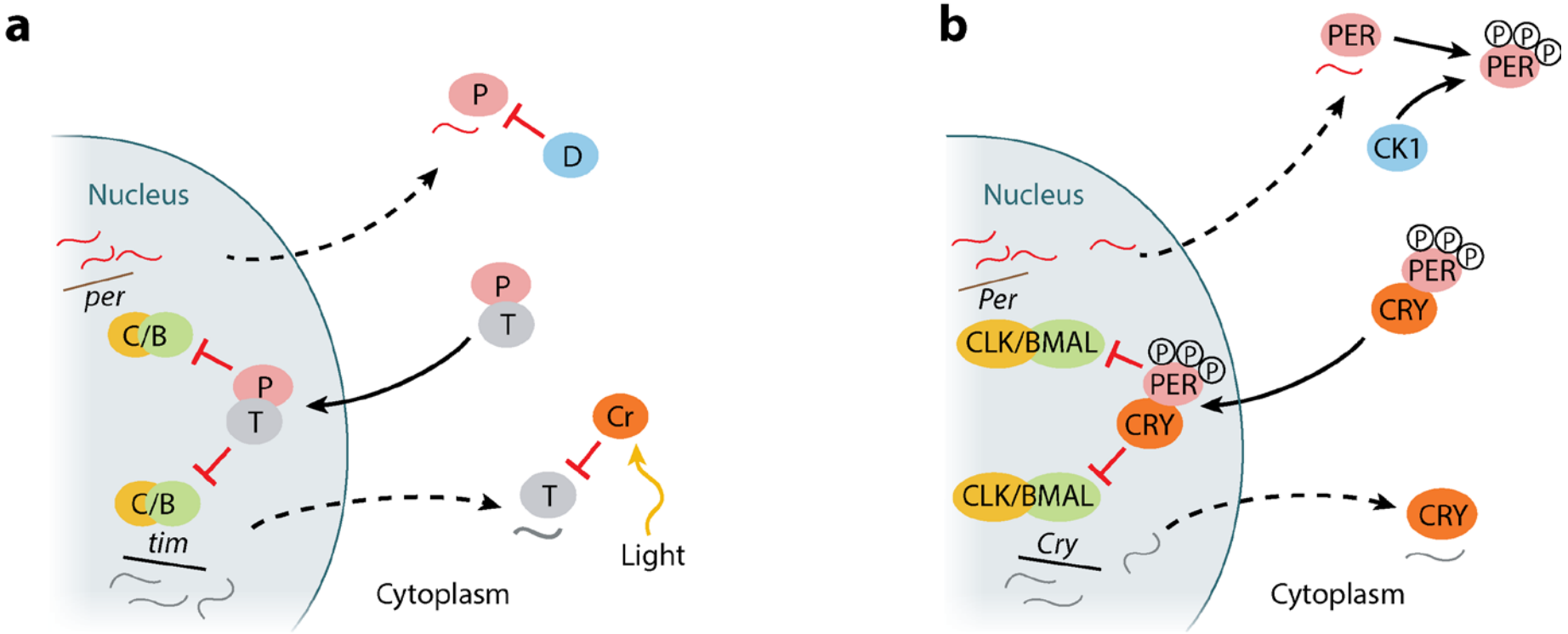
Hundreds of Genes Cycle with a Circadian Rhythm



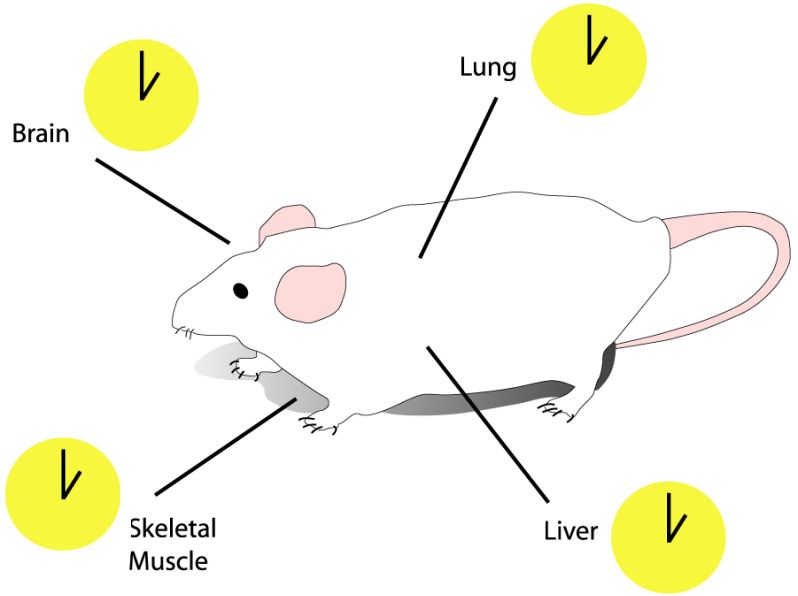
Mutations that Stop the Clock Stop All Rhythmic Gene Activity



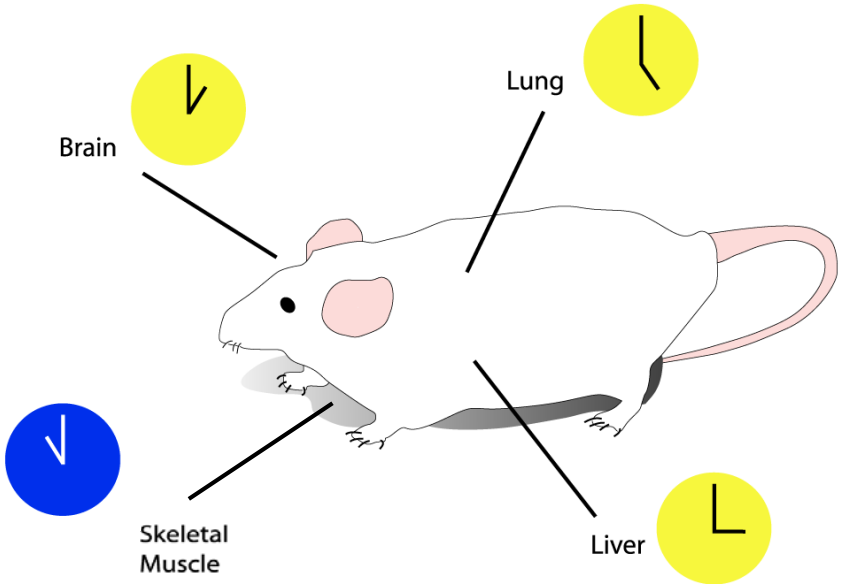

P
D
Nucleus
per
C/B
P
T
P
T
C/B
tim
Cr
T
Light
Cytoplasm


a
Nucleus
per
C/B
P
T
C/B
tim
P
D
P
T
Cr
T
Light
Cytoplasm
b
PER
PER
CK1
Nucleus
Per
CLK/BMAL
PER
CRY
CLK/BMAL
Cry
PER
CRY
CRY
Cytoplasm

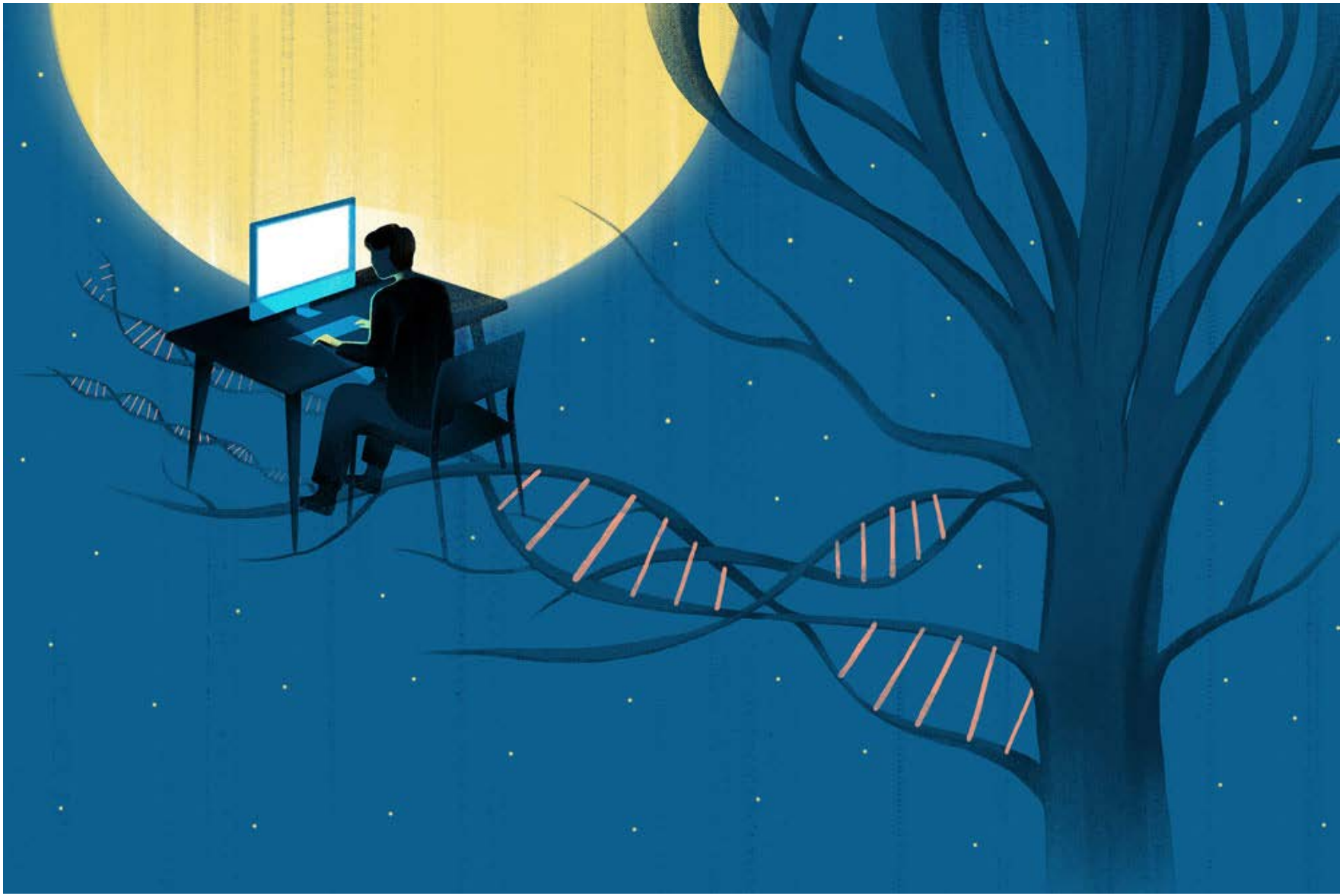
NYC Time



A Brain / Body Conflict



Delayed Sleep Phase Disorder (DSPD)



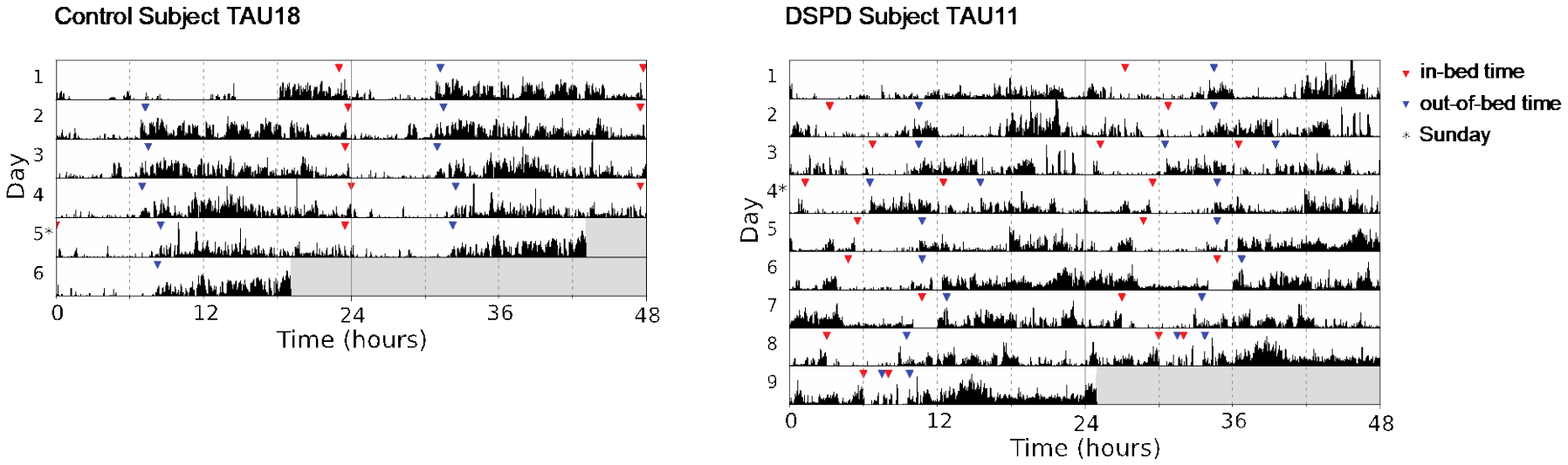
Delayed Sleep Phase Disorder (DSPD)

-Among the most commonly diagnosed sleep disorders in the USA (~5%).

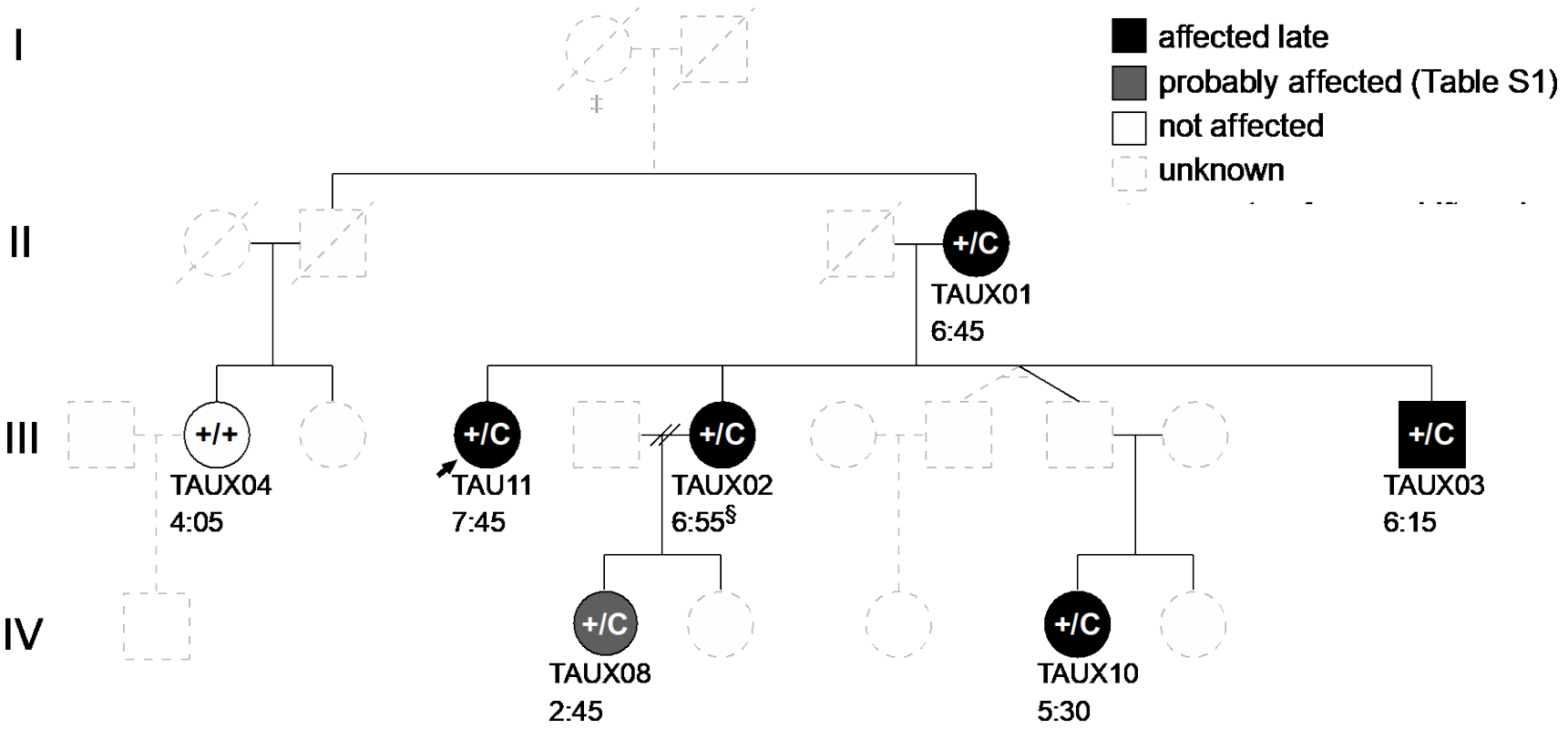
-Persistent delay in the timing of the major sleep episode.

-Resistance to efforts to advance sleep phase.

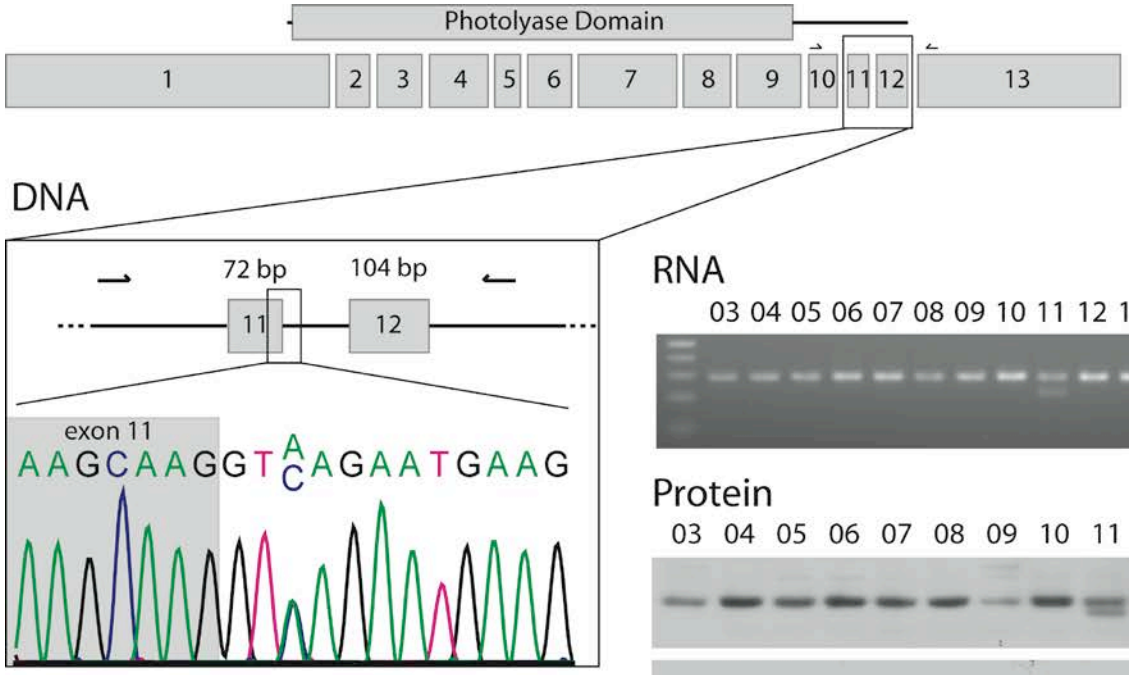
Home Actigraphy and Sleep Log

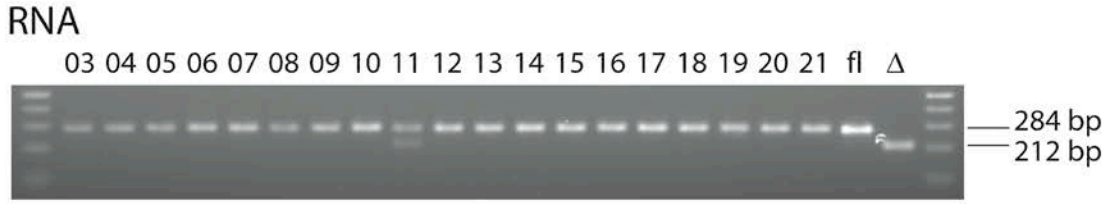


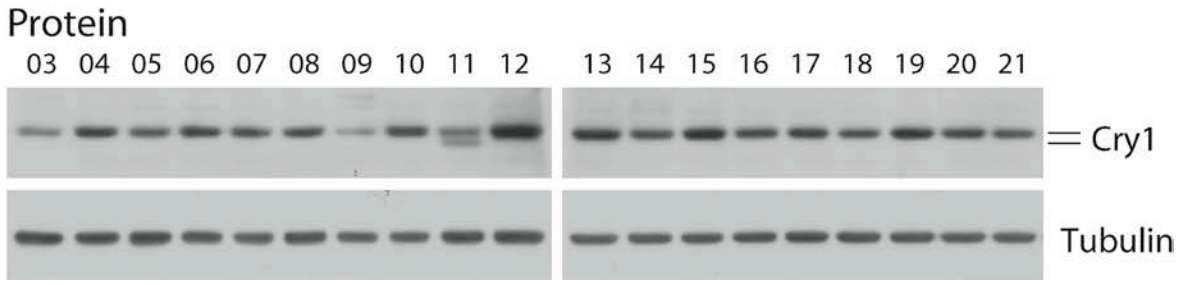
DSPD subject Tau11 kindred

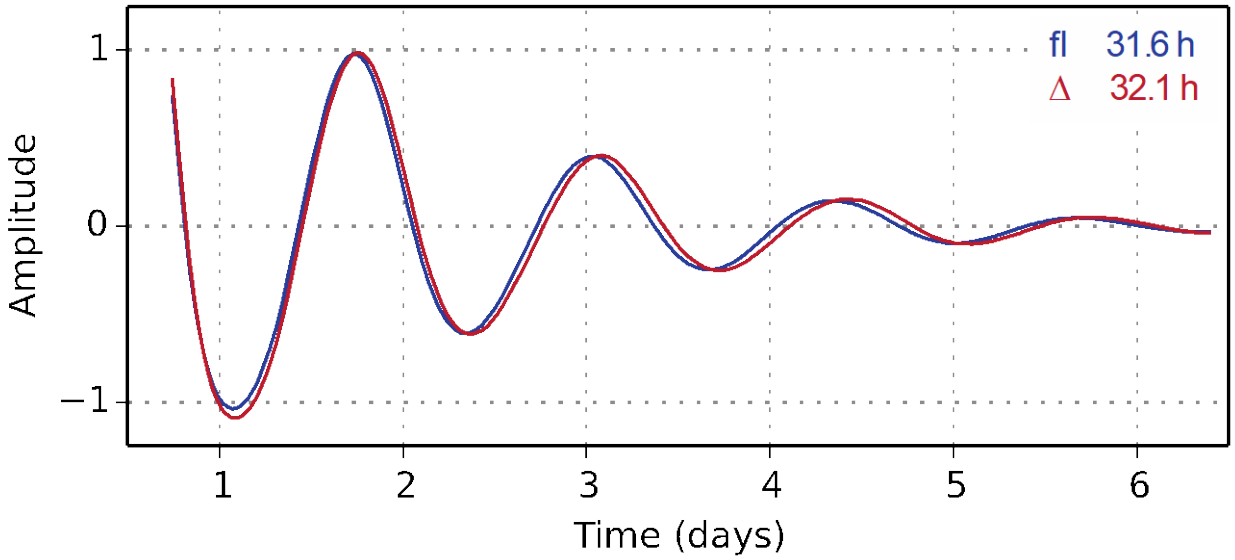


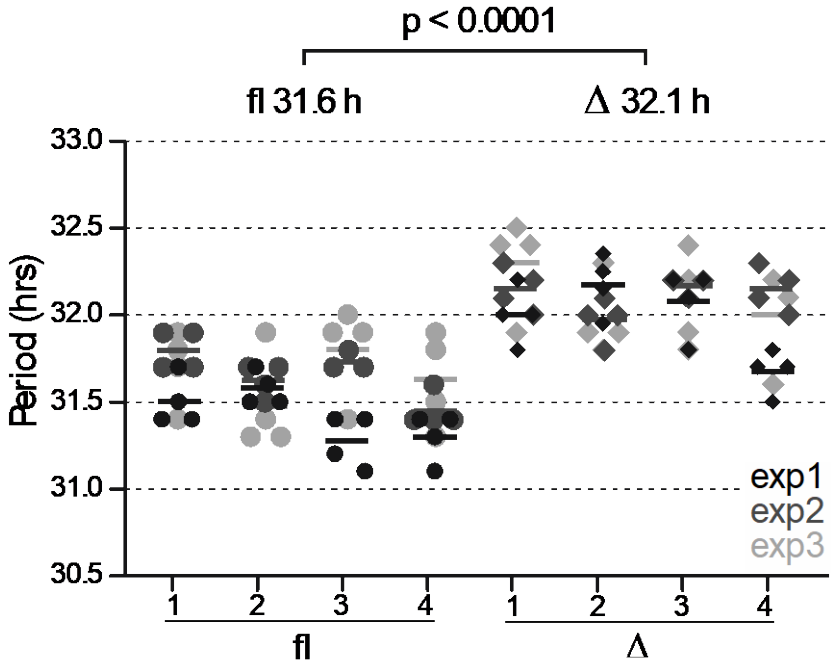
A Cry1 Mutation in Tau11

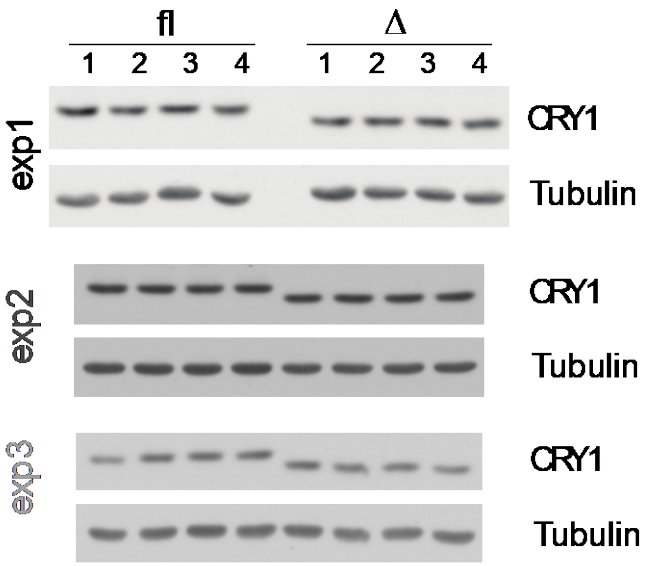


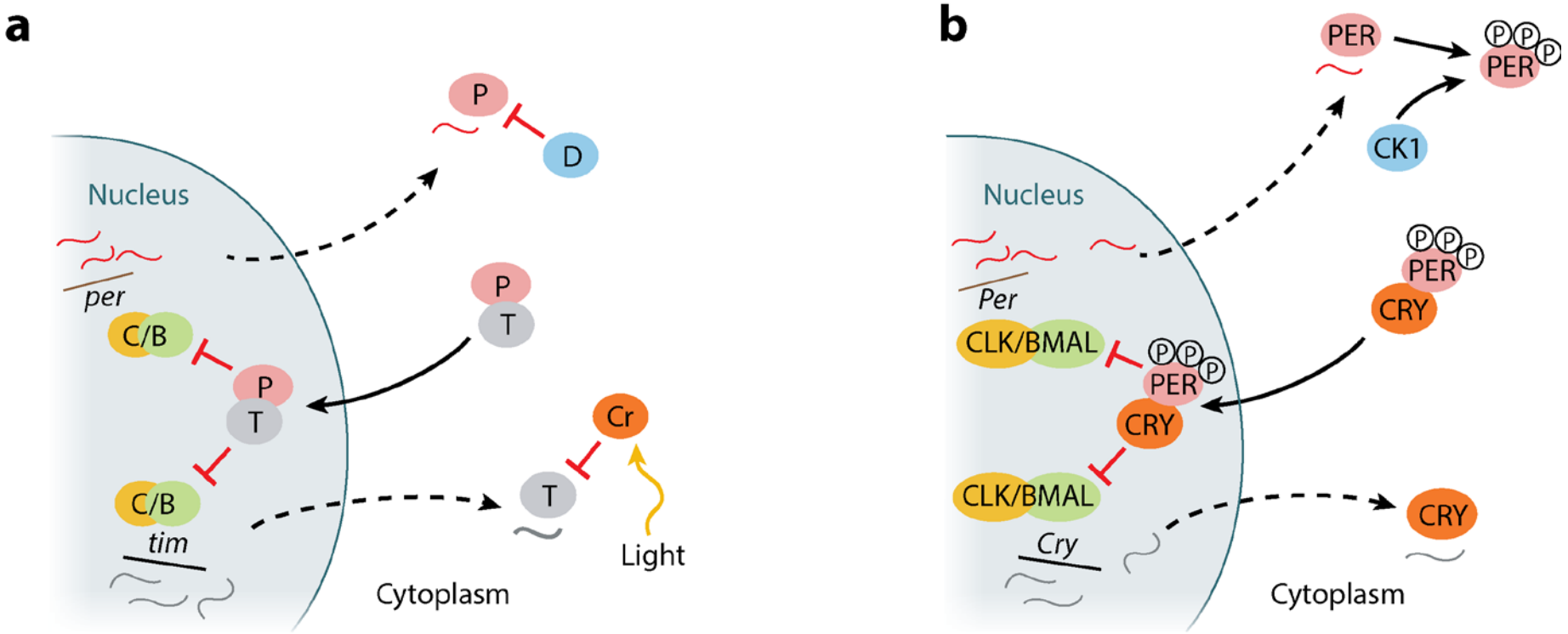




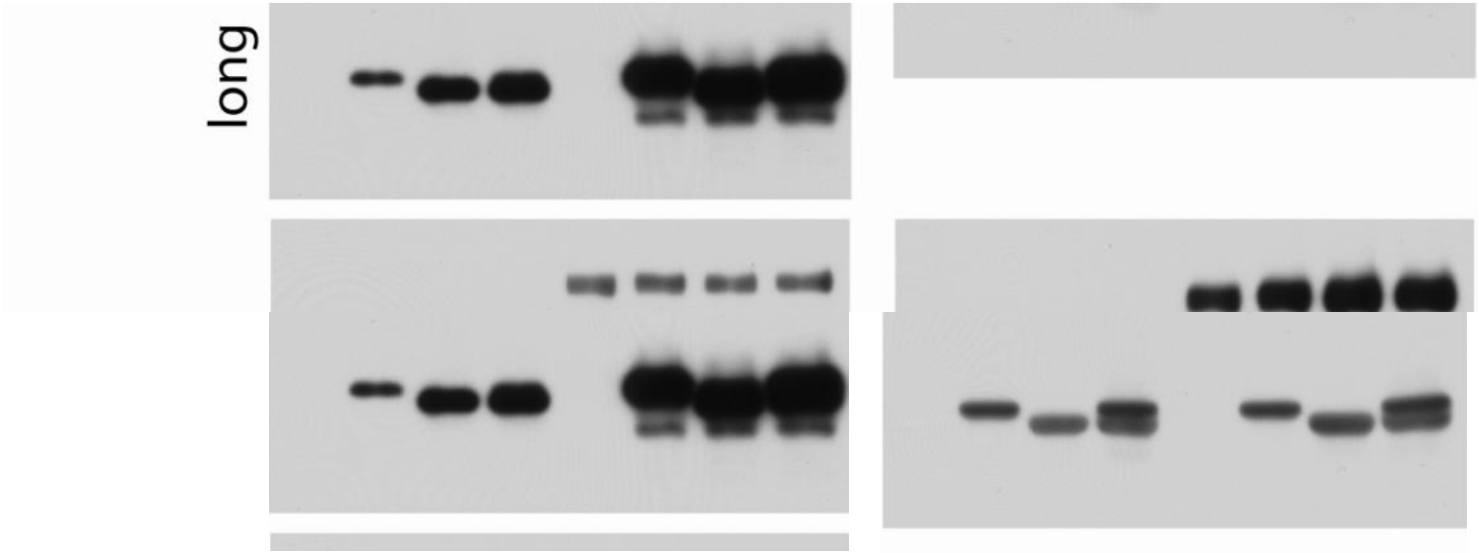

fl 31.6 h
Δ 32.1 h
Amplitude
1
0
−1
1
2
3
4
5
6
Time (days)

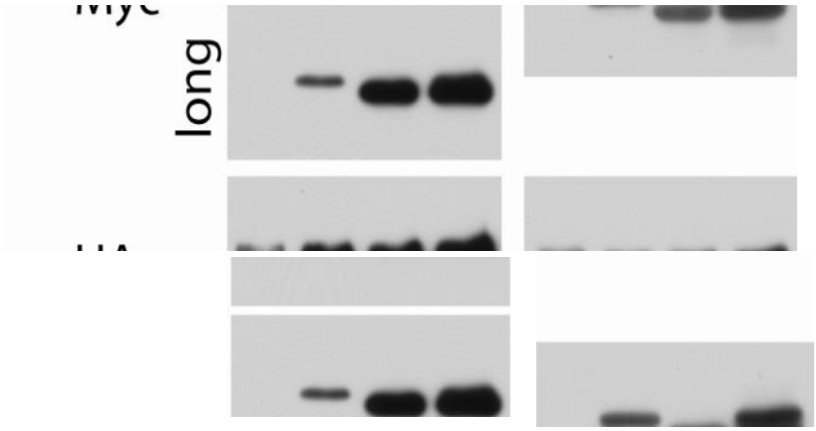

p < 0.0001
fl 31.6 h
Δ 32.1 h
Period (hrs)
33.0
32.5
32.0
31.5
31.0
30.5
exp1
exp2
exp3
1
2
3
4
1
2
3
4
fl
Δ


fl
Δ
1
2
3
4
1
2
3
4
exp1
CRY1
Tubulin
exp2
CRY1
Tubulin
exp3
CRY1
Tubulin


a
Nucleus
per
C/B
P
T
C/B
tim
P
D
P
T
Cr
T
Light
Cytoplasm
b
PER
PER
CK1
Nucleus
Per
CLK/BMAL
PER
CRY
CLK/BMAL
Cry
PER
CRY
CRY
Cytoplasm

Cry1/Bmal1/Clock Interaction in Transfected HEK 293 Cells

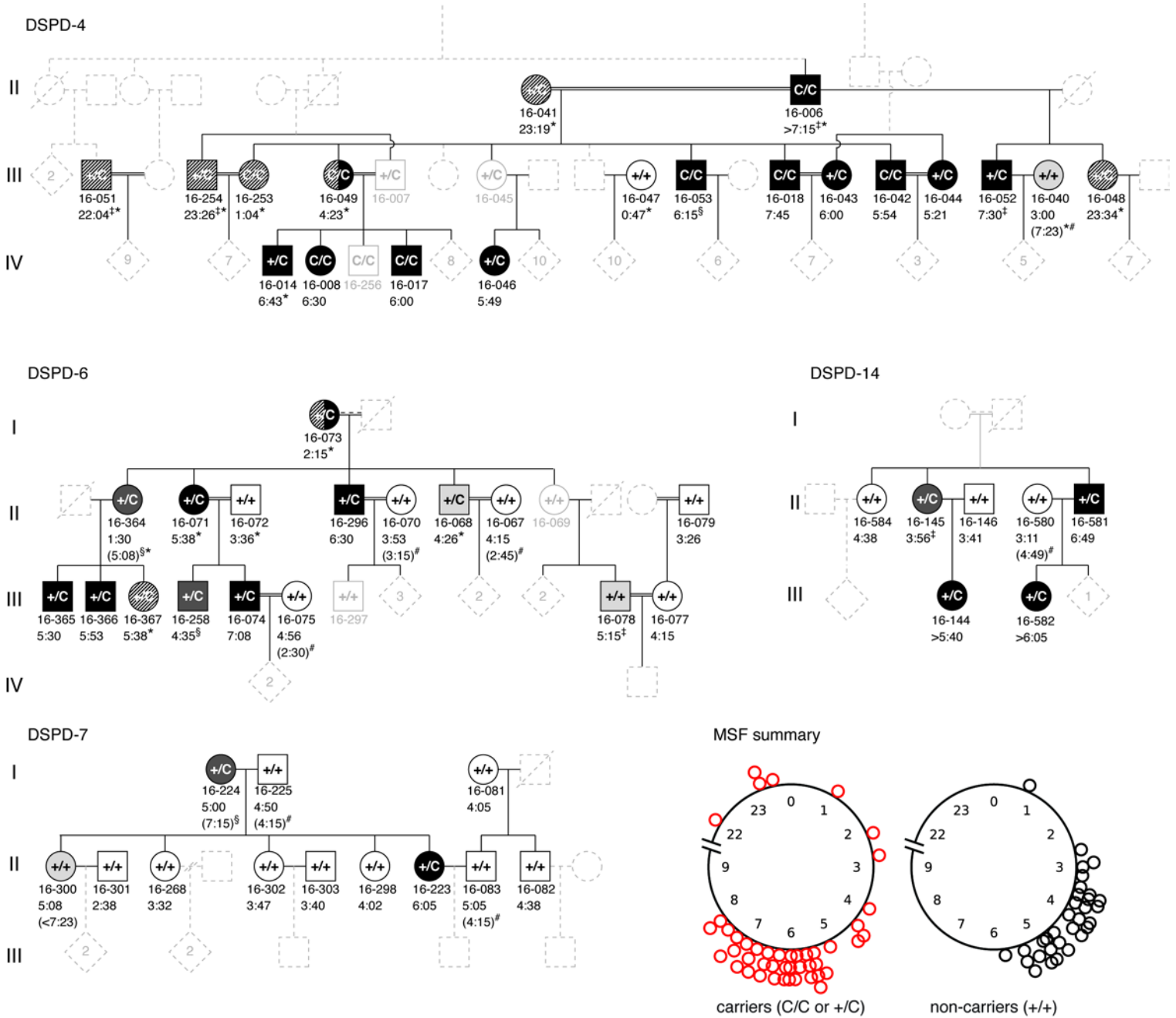




Exome Aggregation Consortium (ExAC), Cambridge, MA

Population Frequencies

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Other	9	906	0	0.009934
European (Non-Finnish)	436	66696	6	0.006537
Latino	41	11564	0	0.003545
South Asian	31	16504	0	0.001878
African	6	10394	0	0.0005773
European (Finnish)	3	6608	0	0.000454
East Asian	0	8652	0	0
Total	**526**	**121324**	**6**	**0.004335**


DSPD-4
II
III
IV
16-041
23:19*
C/C
16-006
>7:15‡*
16-051
22:04‡*
16-254
23:26‡*
16-253
1:04*
16-049
4:23*
16-007
16-045
16-047
0:47*
16-053
6:15§
16-018
7:45
16-043
6:00
16-042
5:54
16-044
5:21
16-052
7:30‡
16-040
3:00
(7:23)*#
16-048
23:34*
16-014
6:43*
16-008
6:30
16-256
16-017
6:00
16-046
5:49
DSPD-6
I
II
III
IV
16-073
2:15*
16-364
1:30
(5:08)§*
16-071
5:38*
16-072
3:36*
16-296
6:30
16-070
3:53
(3:15)#
16-068
4:26*
16-067
4:15
(2:45)#
16-069
16-079
3:26
16-365
5:30
16-366
5:53
16-367
5:38*
16-258
4:35§
16-074
7:08
16-075
4:56
(2:30)#
16-297
16-078
5:15‡
16-077
4:15
DSPD-14
I
II
III
16-584
4:38
16-145
3:56‡
16-146
3:41
16-580
3:11
(4:49)#
16-581
6:49
16-144
>5:40
16-582
>6:05
DSPD-7
I
II
III
16-224
5:00
(7:15)§
16-225
4:50
(4:15)#
16-081
4:05
16-300
5:08
(<7:23)
16-301
2:38
16-268
3:32
16-302
3:47
16-303
3:40
16-298
4:02
16-223
6:05
16-083
5:05
(4:15)#
16-082
4:38
MSF summary
0
1
2
3
4
5
6
7
8
9
22
23
carriers (C/C or +/C)
non-carriers (+/+)

Summary

- In studies of several unrelated families, presence of Cry1Δ11 predicted DSPD. The penetrance and frequency of this allele suggests a broad contribution to DSPD world-wide.

- Since the mutation is found in multiple members of each family, all tissues should be affected.

- Cry1Δ11 shows enhanced binding to Clock and Bmal1 in mouse and human cultured cells, and Cry1Δ11 appears to be a strengthened transcriptional inhibitor.

- Competitive binding to Clock/Bmal1 suggests a basis for inheritance as a dominant trait.

- Cry1Δ11 expression is sufficient to lengthen the period of mouse and human fibroblast rhythms.

What's Ahead?

Metabolic and psychiatric disorders are often accompanied by problems with sleep, but it has not been possible to determine if these reflect *causal* relationships.

If large numbers of subjects are available to study, we can rigorously test whether the impact of a particular sleep mutation extends to other medical problems.

When the mutation can be studied in multiple, unrelated families, we can rule out non-genetic (environmental sources) for the disorder.

1980s

Ted Bargiello

Rob Jackson

1990s

Leslie Vosshall

Amita Sehgal

Jeff Price

Lino Saez

Adrian Rothenfluh

Justin Blau

Brian Kloss

2000s

Adam Claridge-Chang

Hermann Wijnan

Sebastian Martinek

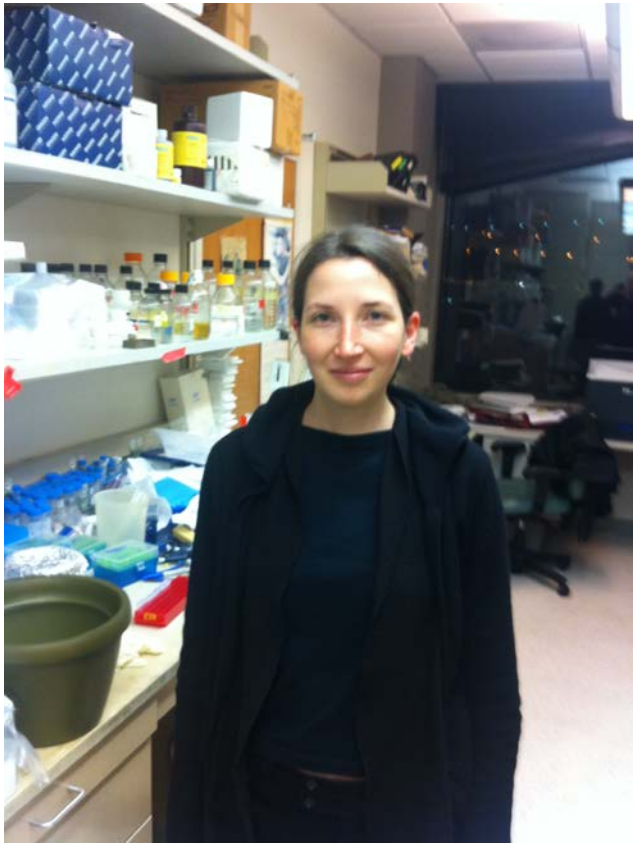
2010s

Dragana Rogulja

Nick Stavropoulos

Alina Patke

Lino Saez



Alina Patke