

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

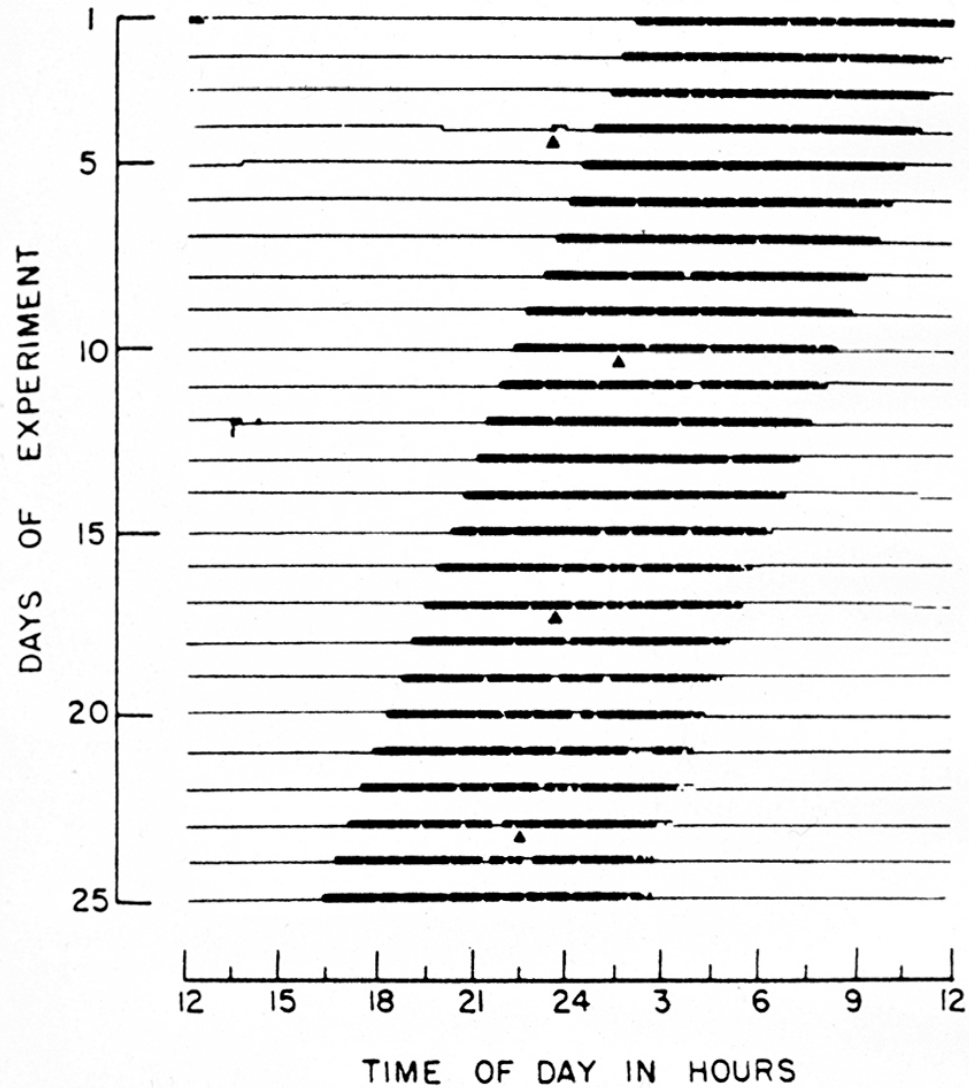
Mirabilis (Four O'Clocks) at 2pm



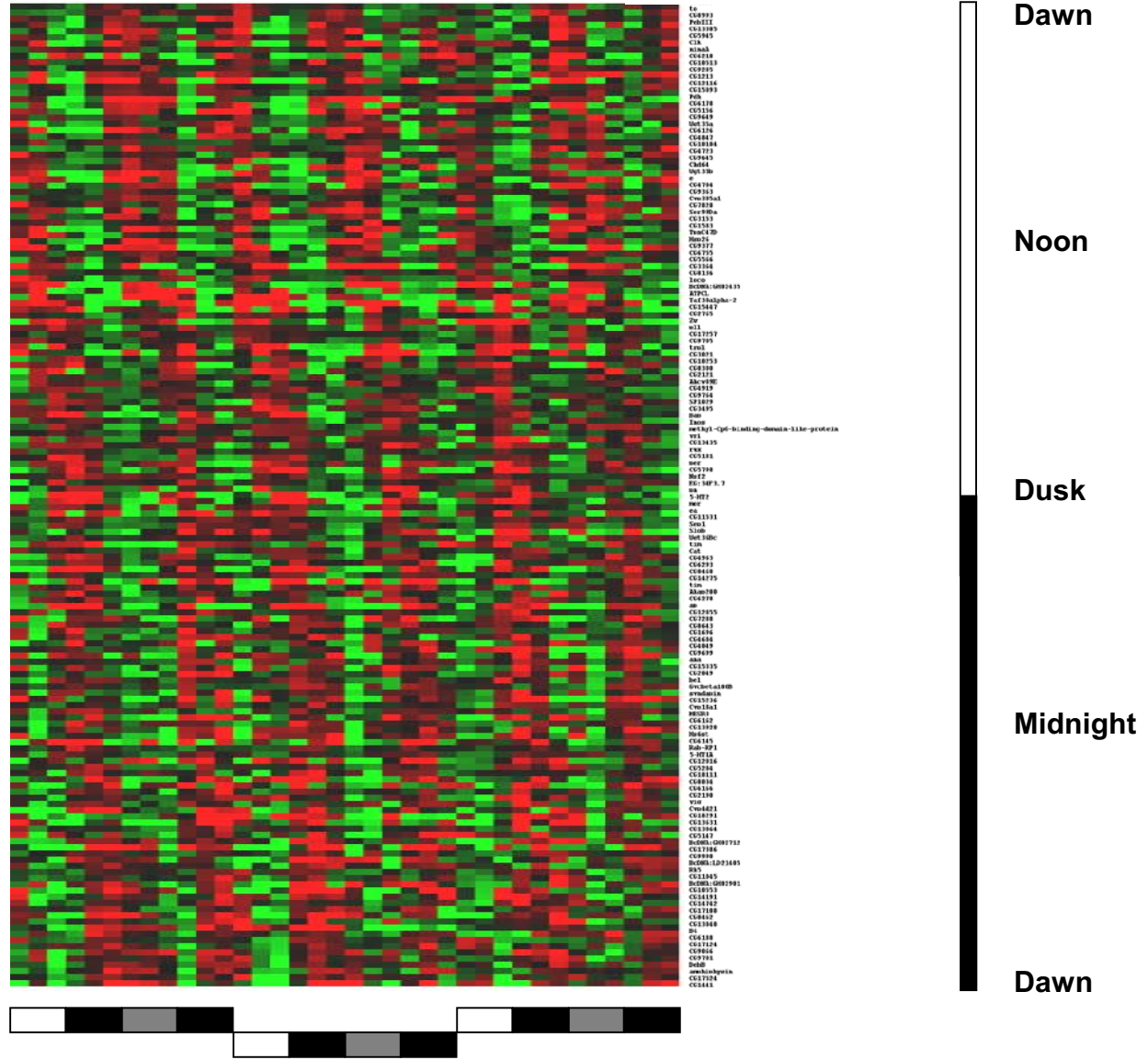
Mirabilis (Four O'Clocks) at 6pm

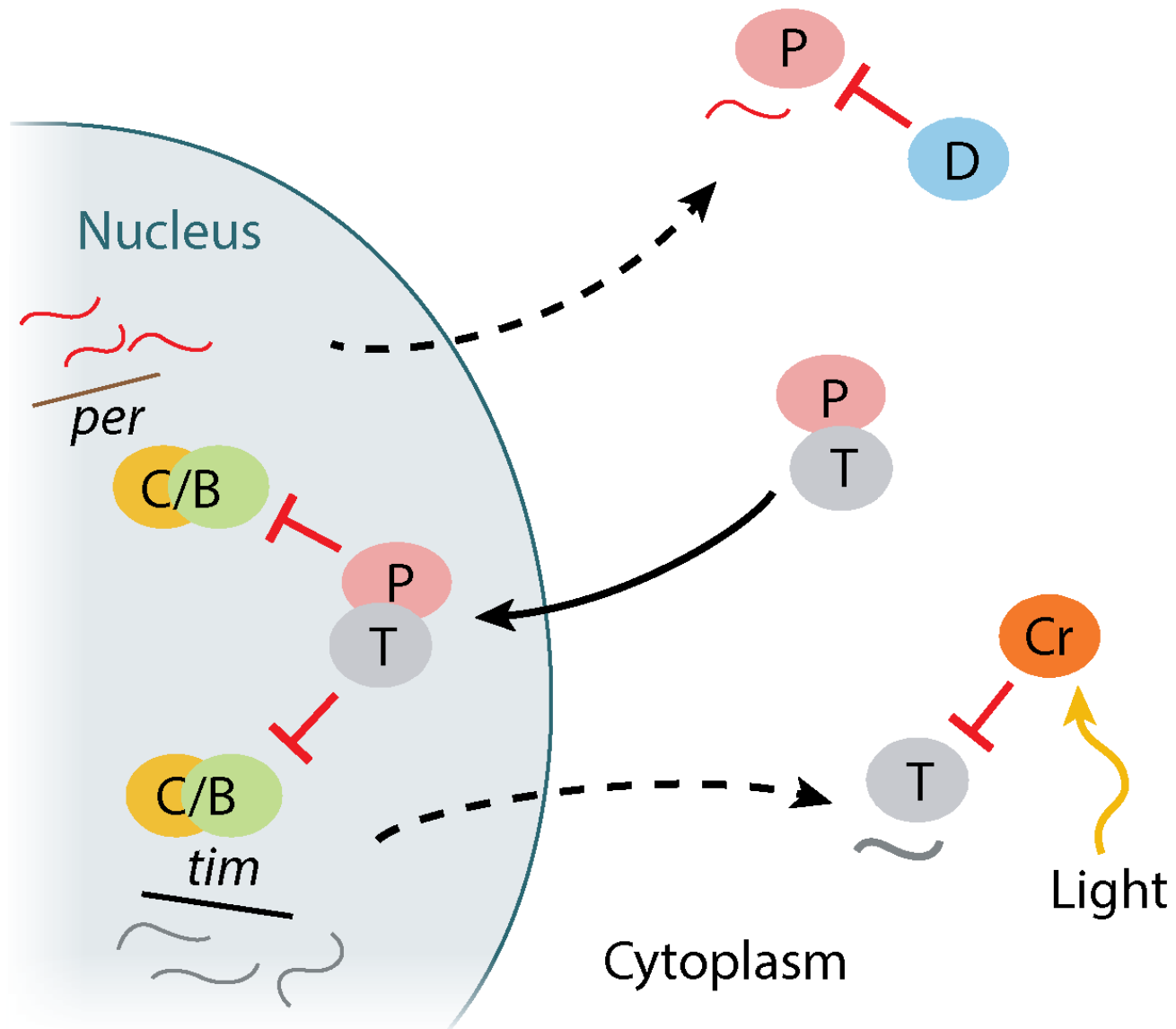


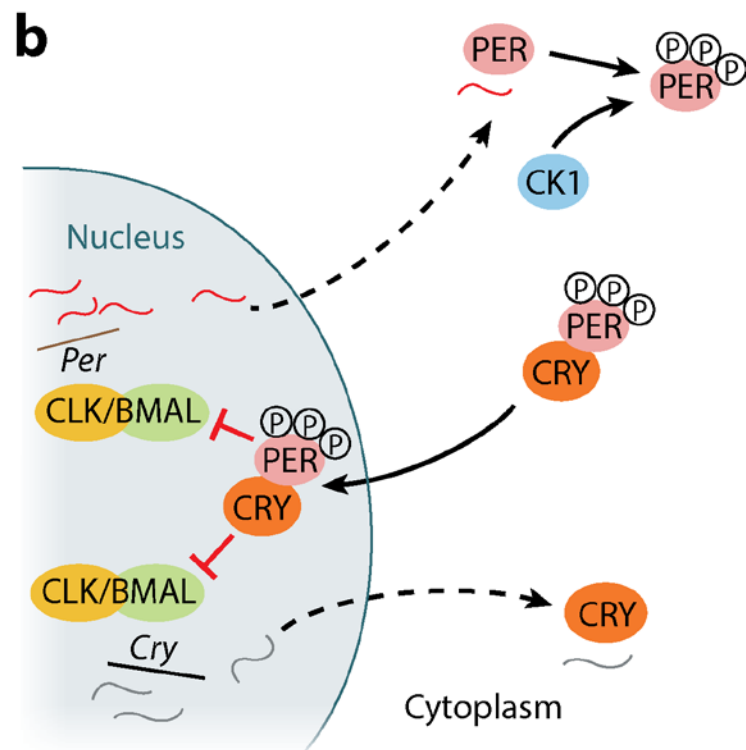
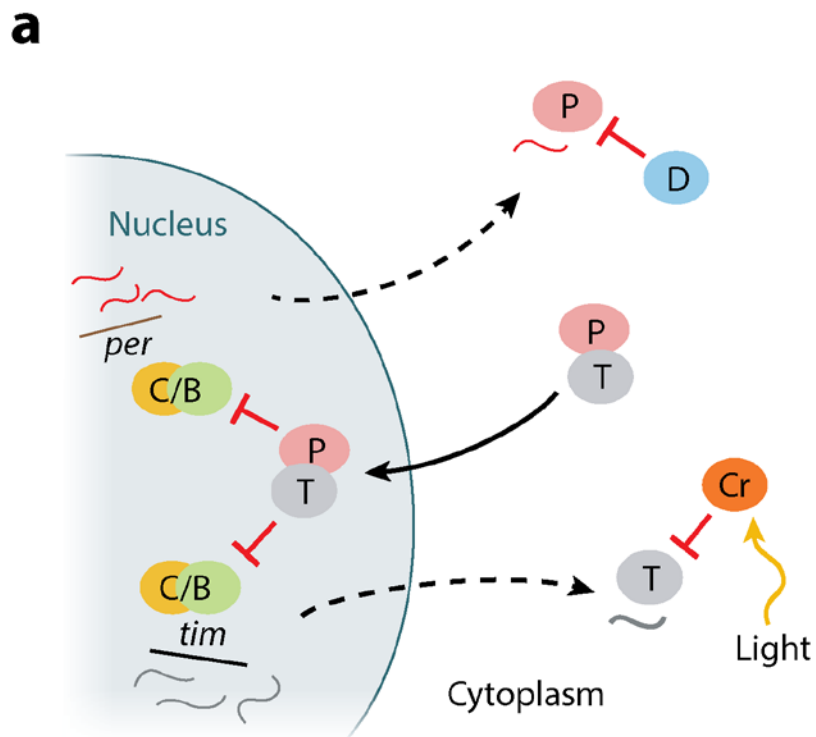
Hamster Activity Record – Constant Darkness



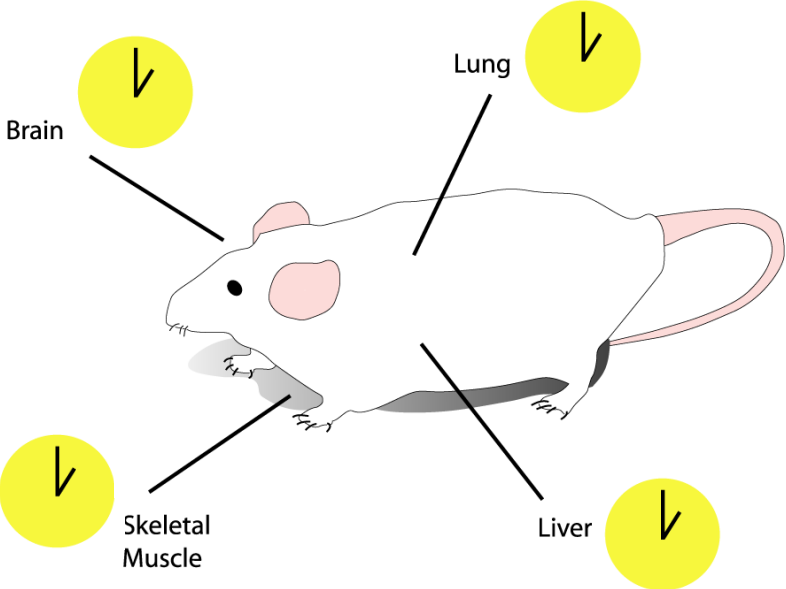
Hundreds of Genes Cycle with a Circadian Rhythm



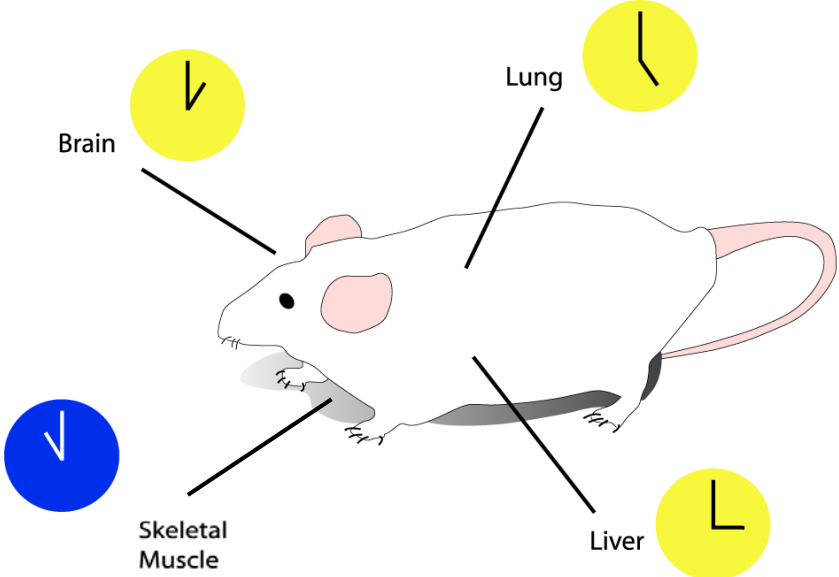




NYC Time



A Brain / Body Conflict



Delayed Sleep Phase Disorder (DSPD)

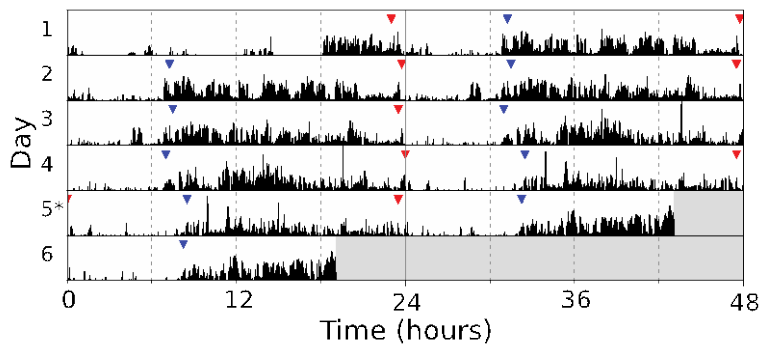


Delayed Sleep Phase Disorder (DSPD)

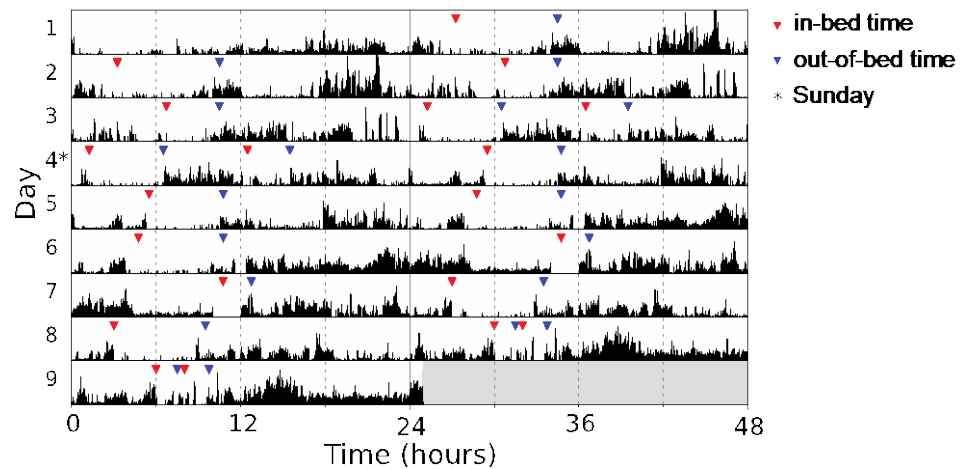
- Among the most commonly diagnosed sleep disorders in the USA (~5%).
- Persistent delay in the timing of the major sleep episode.
- Resistance to efforts to advance sleep phase.

Home Actigraphy and Sleep Log

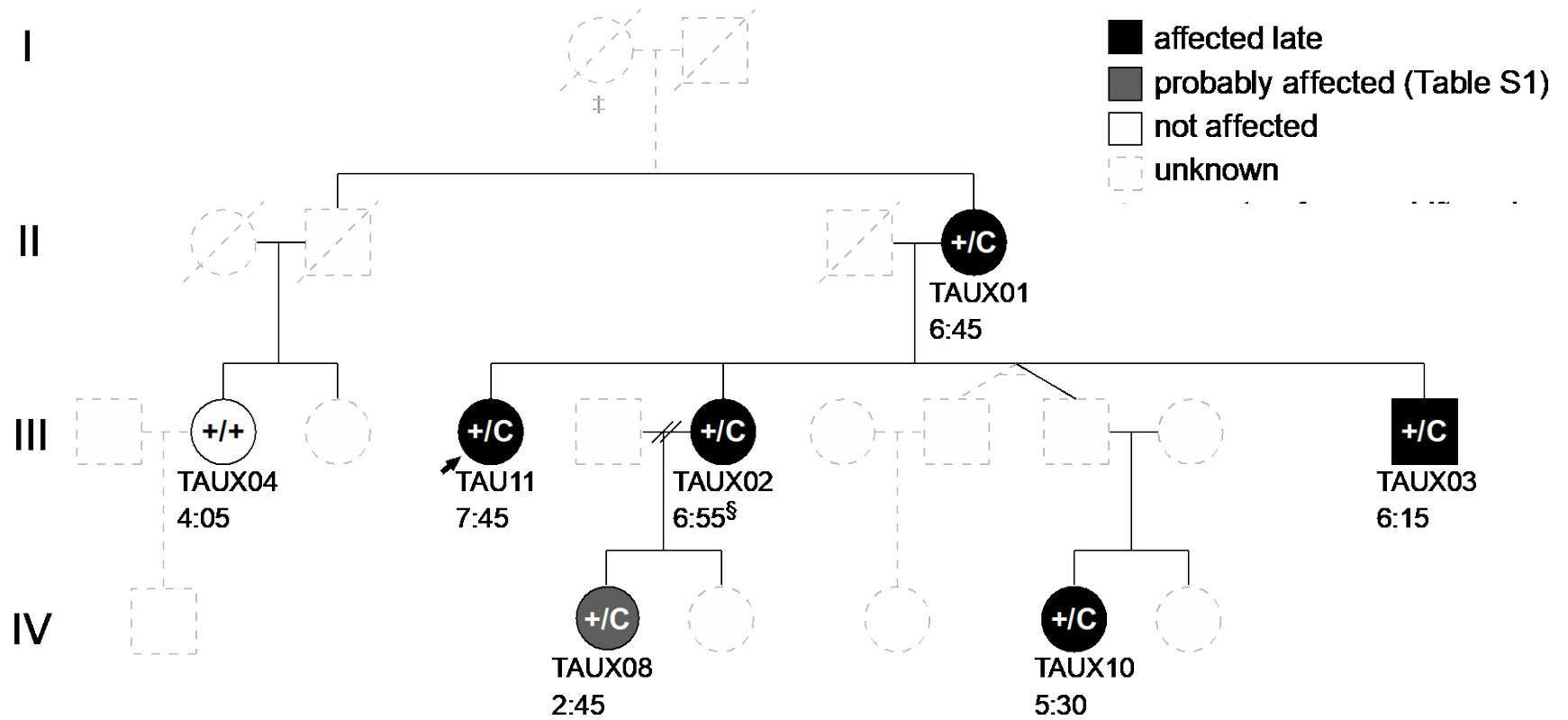
Control Subject TAU18



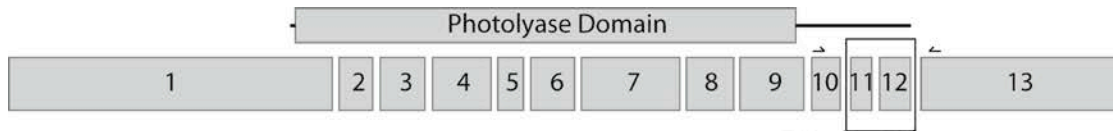
DSPD Subject TAU11



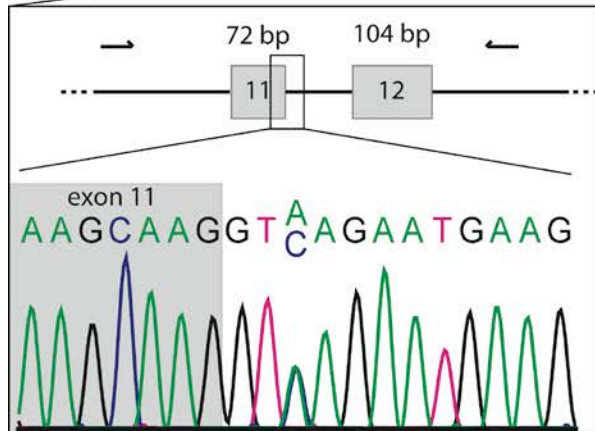
DSPD subject Tau11 kindred



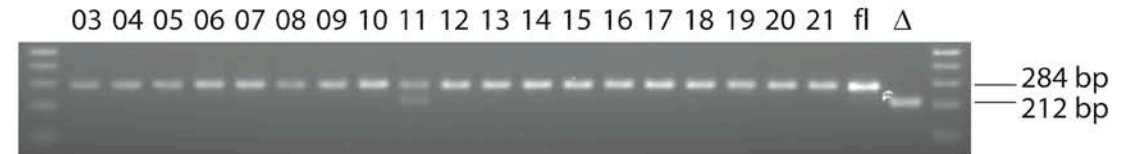
A Cry1 Mutation in Tau11



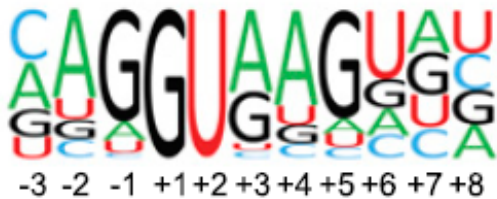
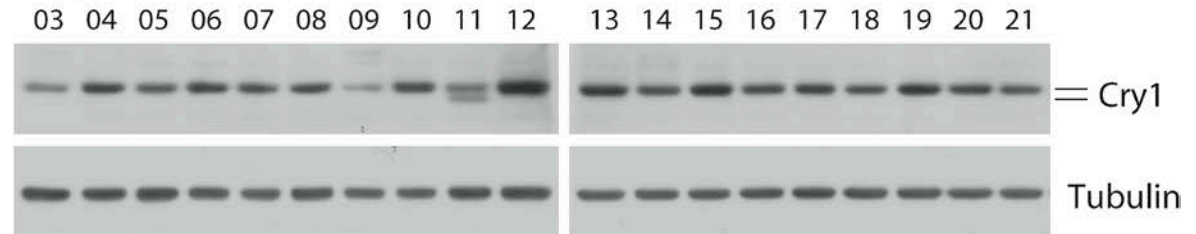
DNA

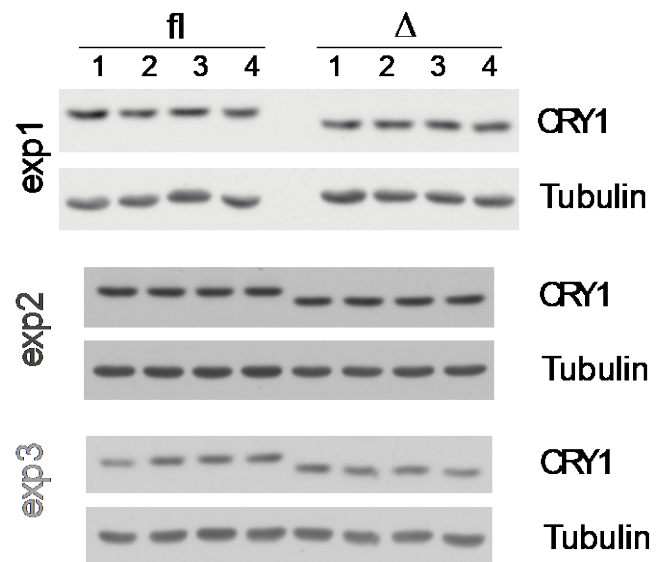
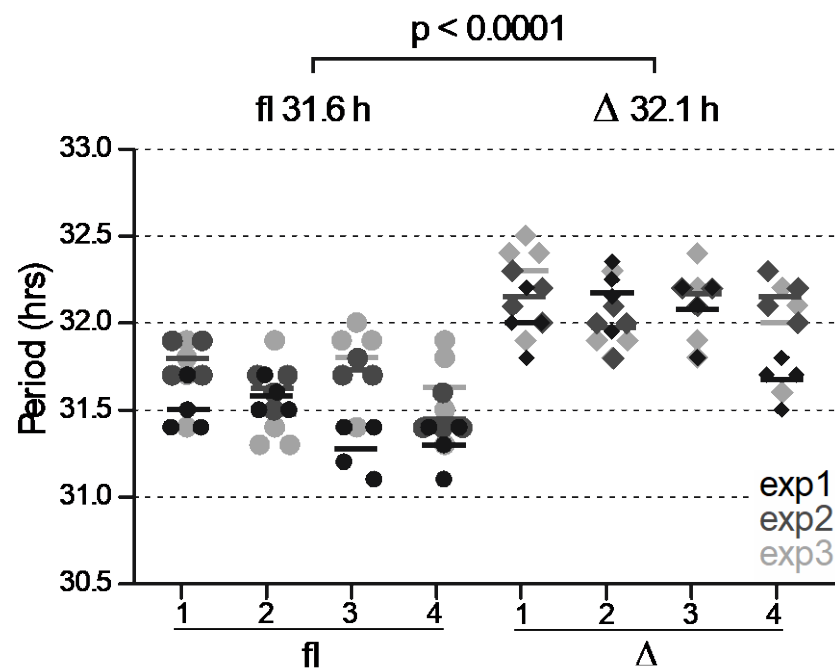
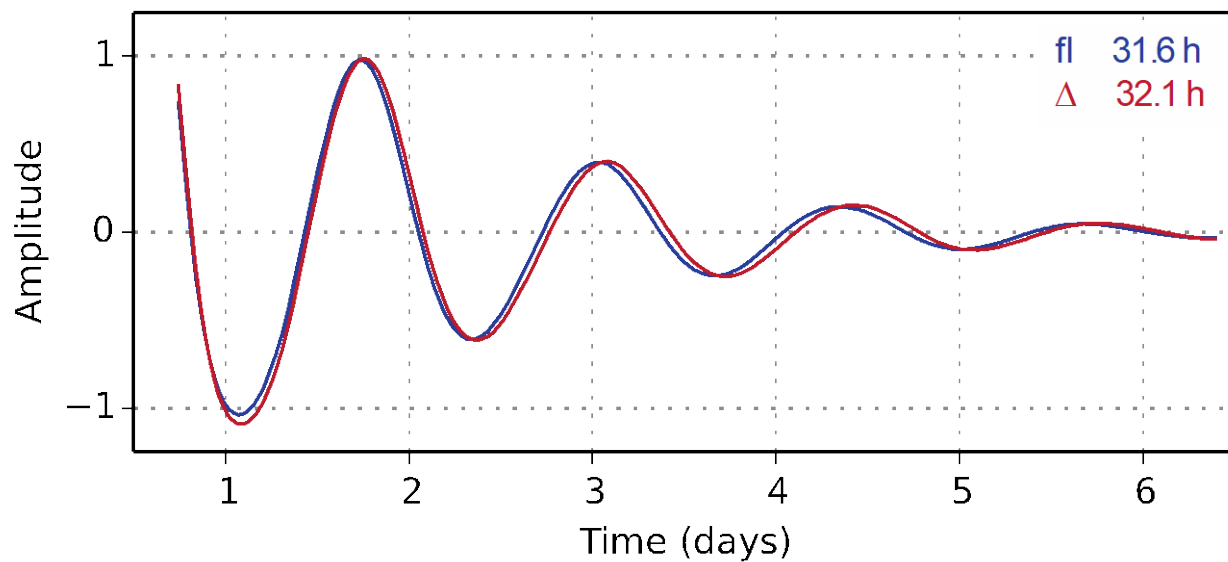


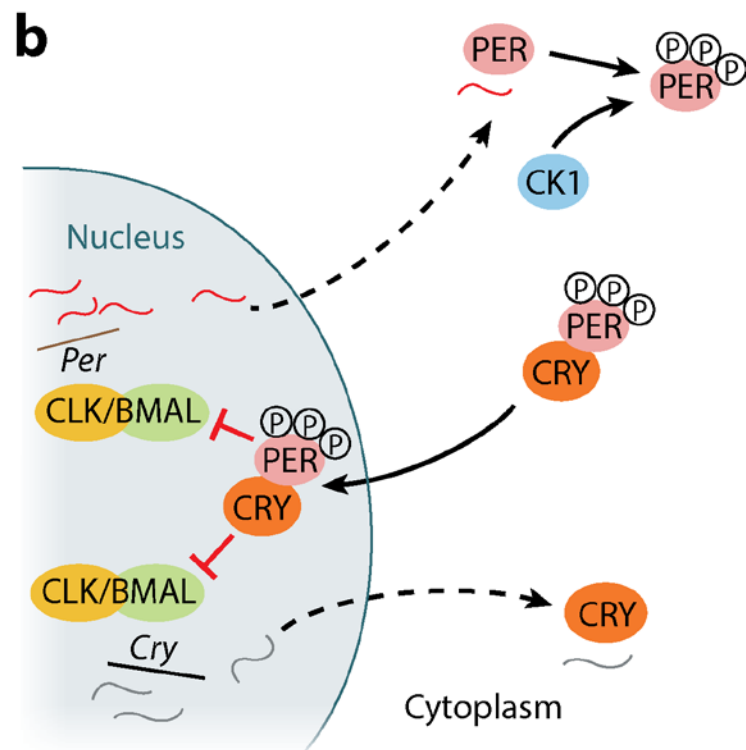
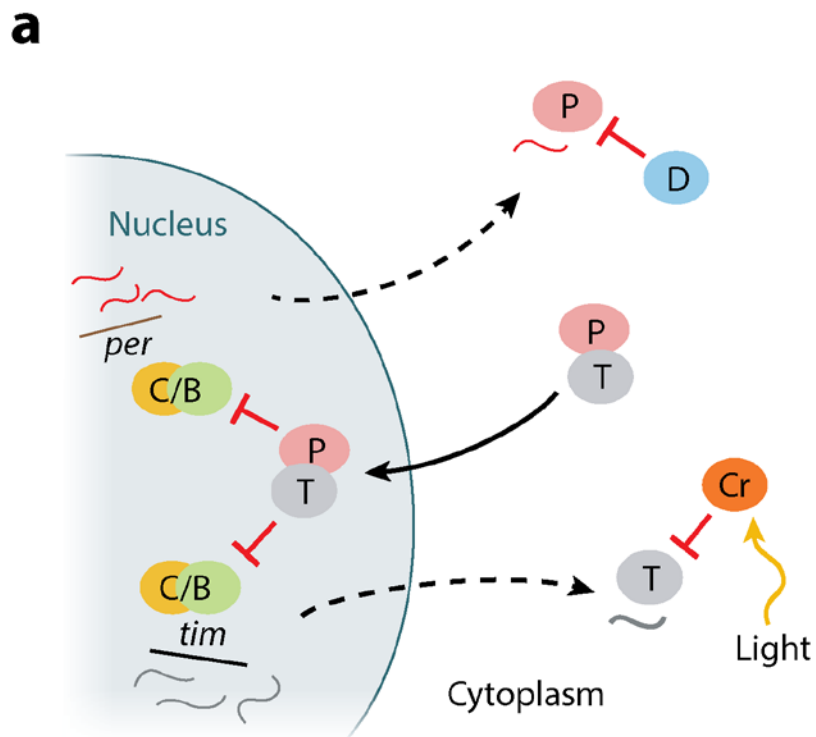
RNA



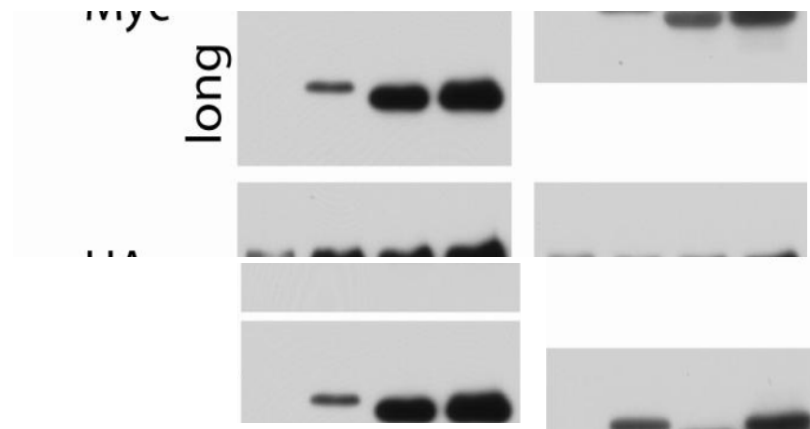
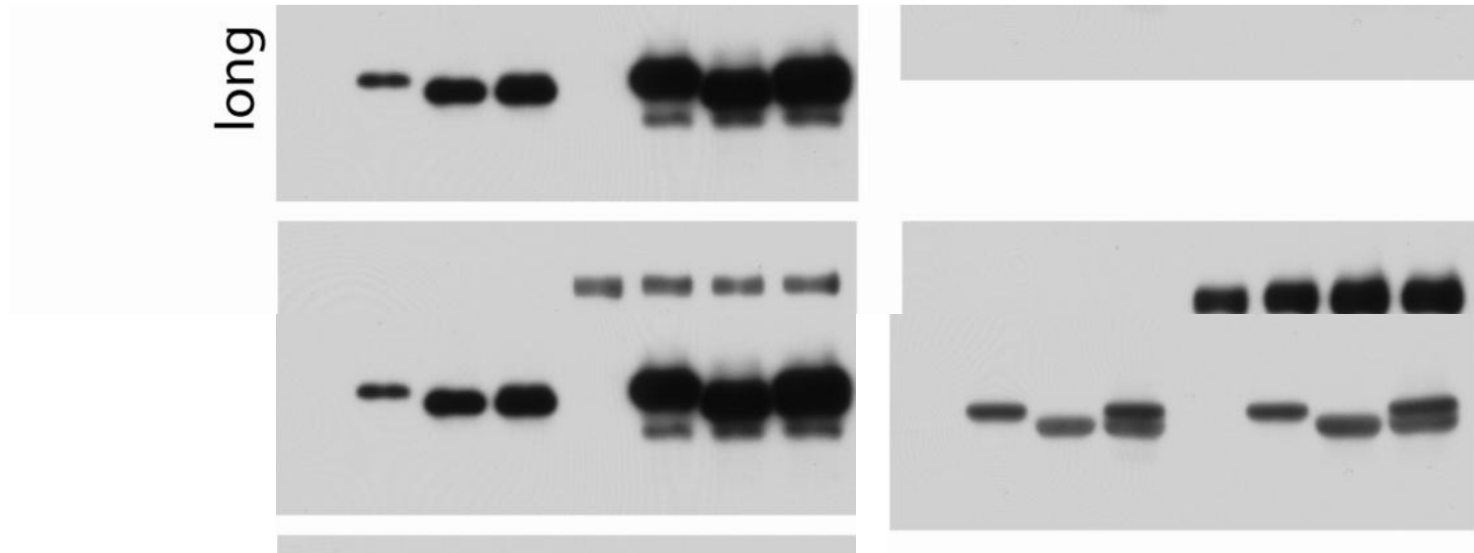
Protein







Cry1/Bmal1/Clock Interaction in Transfected HEK 293 Cells

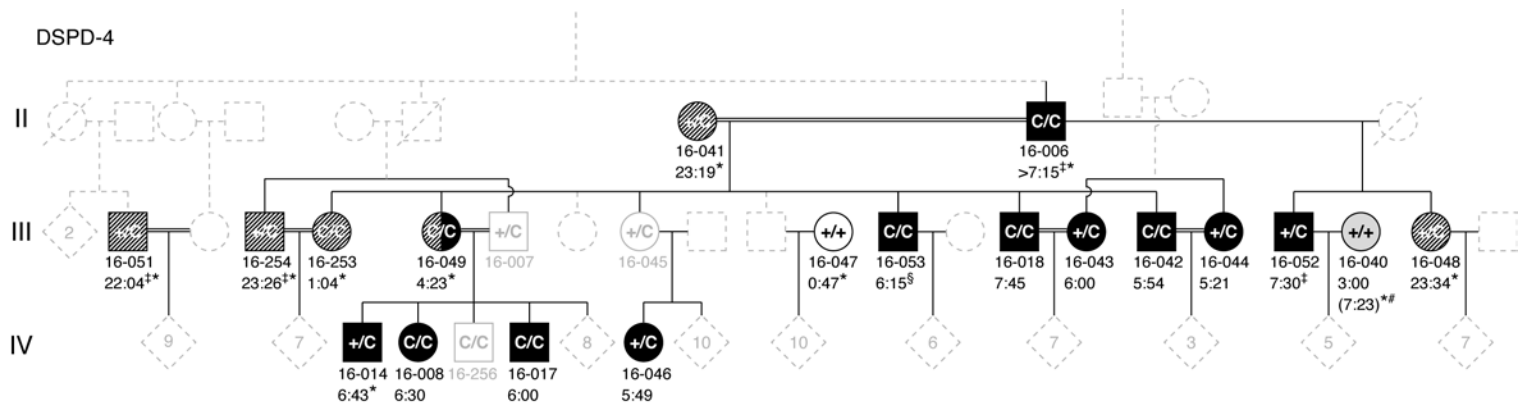


Exome Aggregation Consortium (ExAC), Cambridge, MA

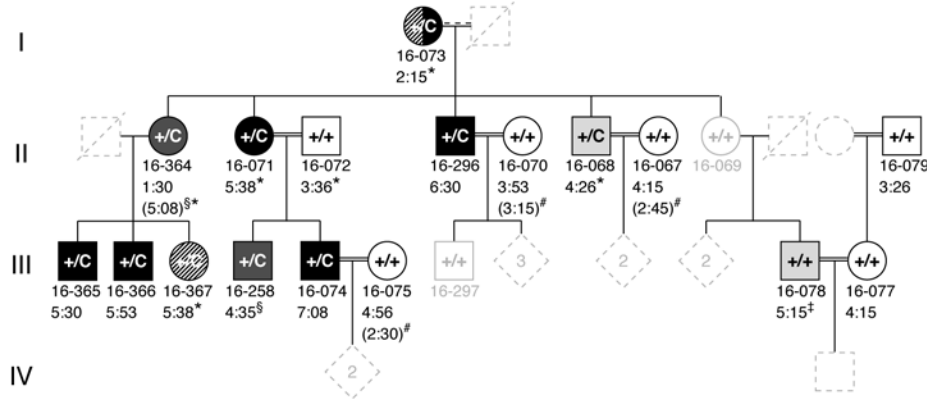
Population Frequencies

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

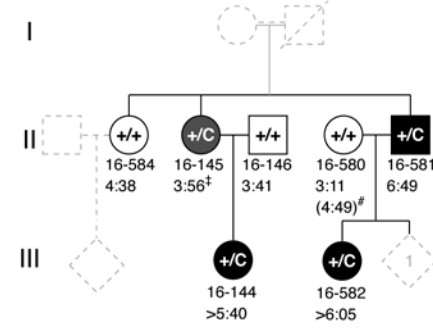
DSPD-4



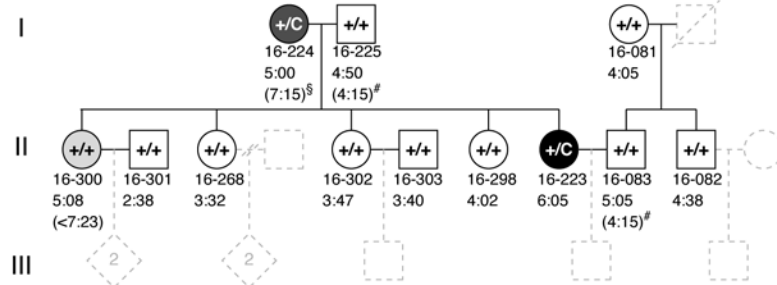
DSPD-6



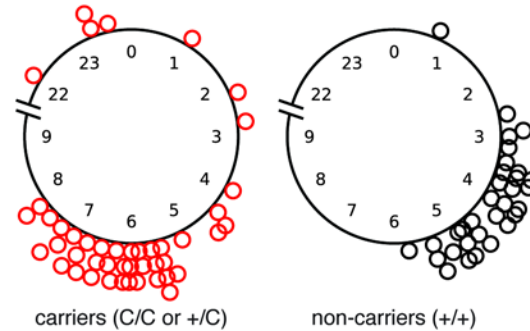
DSPD-14



DSPD-7



MSF summary



Summary

- In studies of several unrelated families, presence of Cry1 Δ 11 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.
- Cry1 Δ 11 shows enhanced binding to Clock and Bmal1 in mouse and human cultured cells, and Cry1 Δ 11 appears to be a strengthened transcriptional inhibitor.
- Competitive binding to Clock/Bmal1 suggests a basis for inheritance as a dominant trait.
- Cry1 Δ 11 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

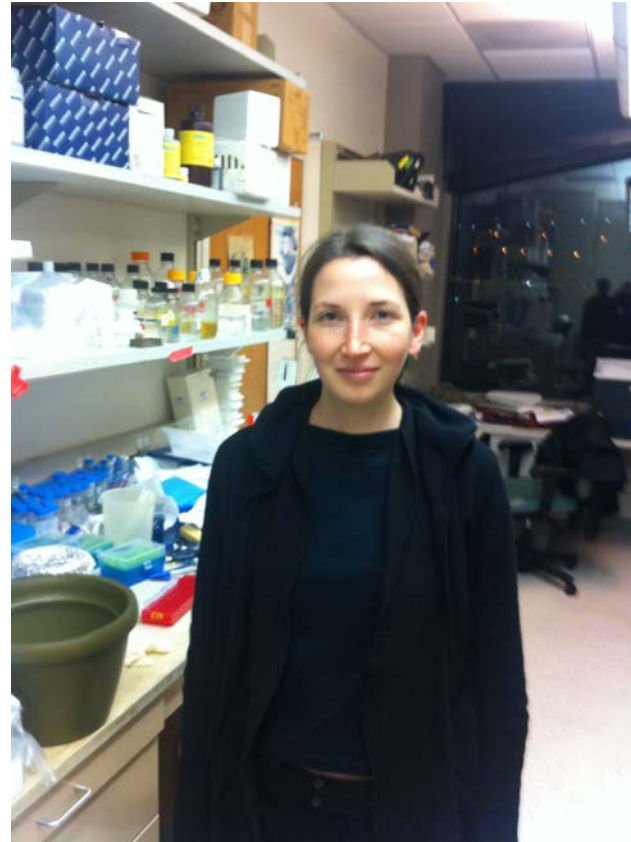
Dragana Rogulja

Nick Stavropoulos

Alina Patke



Lino Saez



Alina Patke

