

CIRCADIAN GENE EXPRESSION PATTERNS ON THE PERIPHERY DEPEND ON GENOTYPE

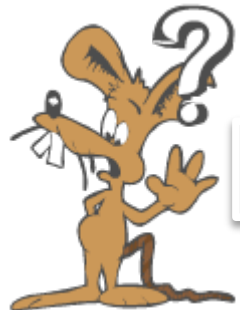
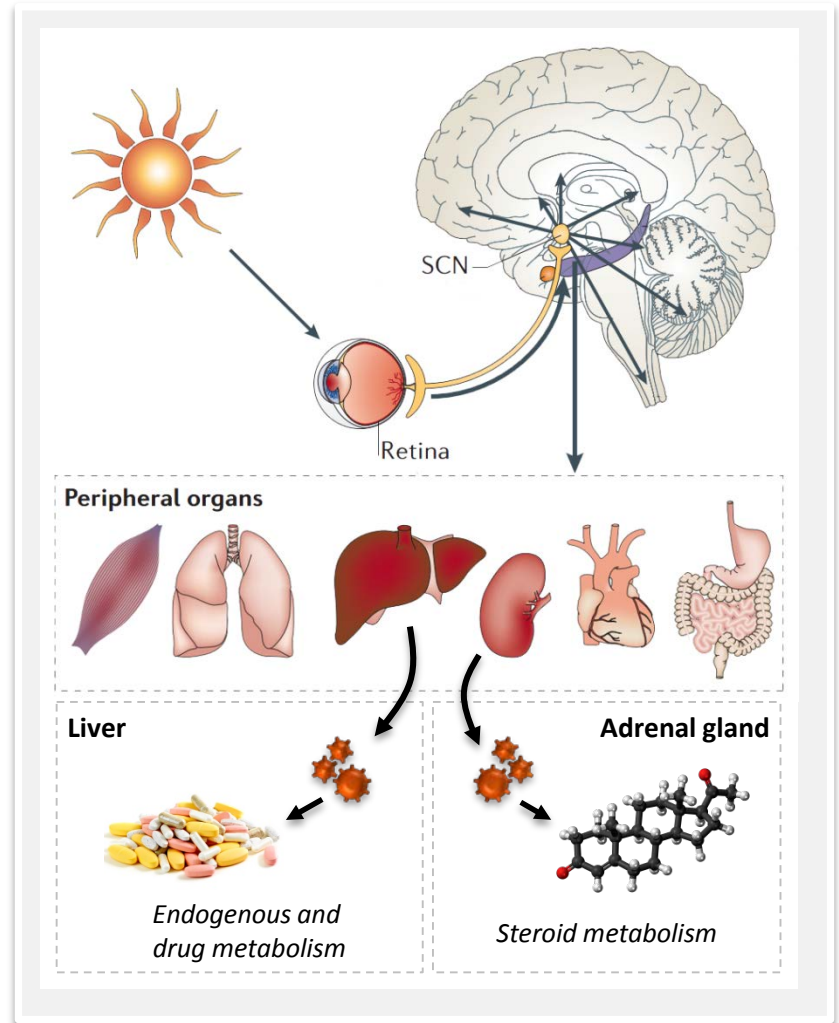


Rok Kosir

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University of Ljubljana
Slovenia

THE CIRCADIAN CLOCK AND MOUSE STRAINS

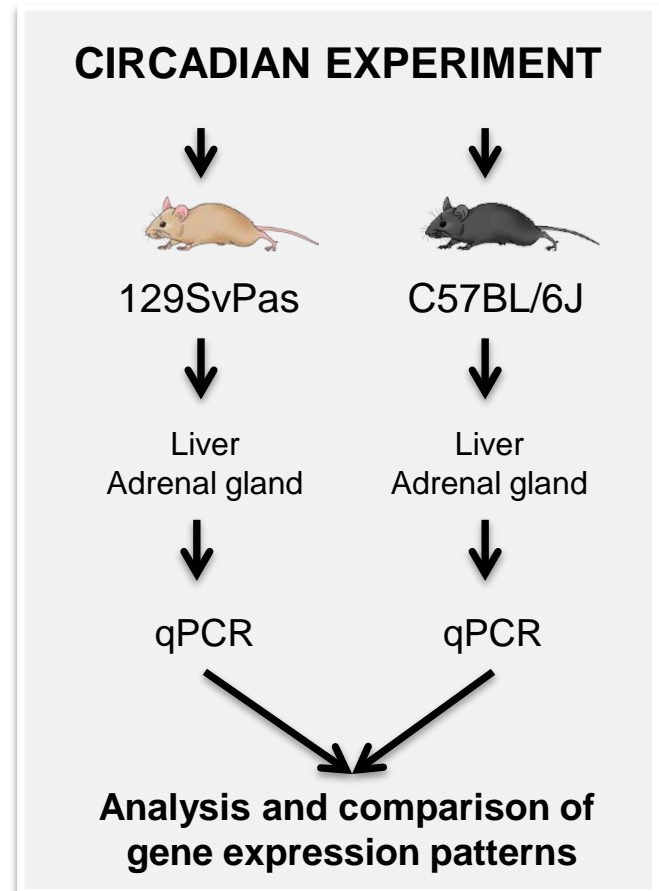
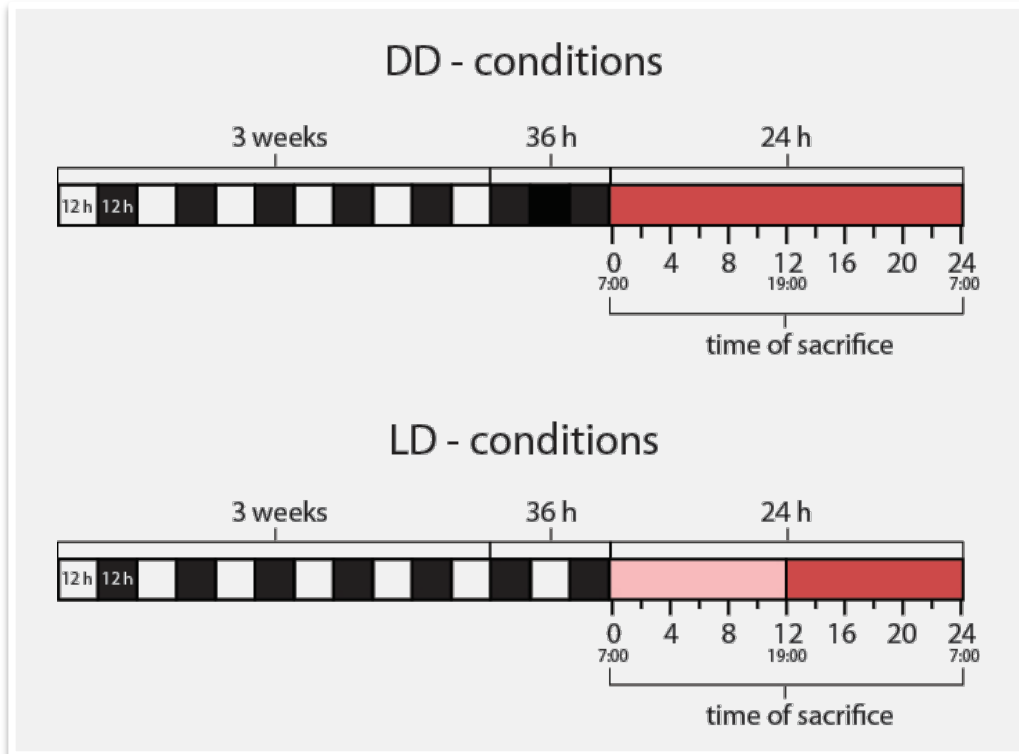
- CIRCADIAN CLOCKS
 - Evolutionary adaptation
 - Affect physiological processes
 - Hierarchical structure
- MOUSE STRAINS
 - Biomedical models
 - Many different strains
 - Genetic variability



Are there differences in circadian gene expression between strains.

CIRCADIAN GENE EXPRESSION IN MOUSE STRAINS 129SvPAS AND C57BL/6

- Sampling of mice every 4h.
- Liver and adrenal glands.
- Measure expression of genes using qPCR .



MAJOR CORE CLOCK AND METABOLIC OUTPUT GENE EXPRESSION DIFFERENCES IN ADRENALS OF 129SvPAS AND C57BL/6

- Liver differs in *Bmal1* and *Cry1*.

Genes of interest

Core clock

Bmal1, *Per1*, *Per2*, *Per3*, *Cry1*,
Cry2

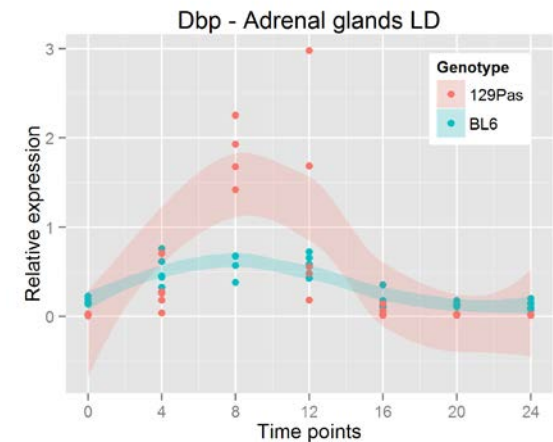
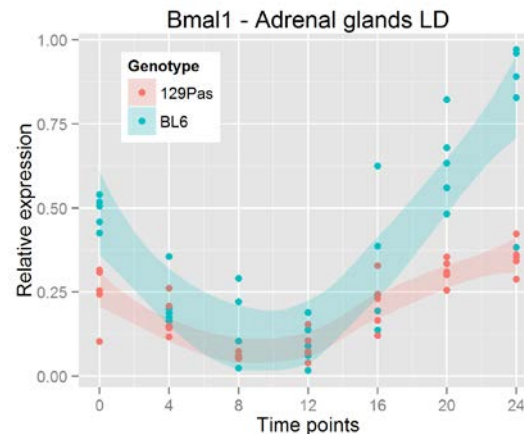
Transcription factors

Dbp, *Dec1*, *Dec2*, *Car*, *Pgc-1a*,
Ppar's, *RevERBa*

Metabolic genes

Cyp7, *Cyp11*, *Cyp17*, *Cyp21*,
Cyp39, *Cyp51*, *Por*, *Hmgcr*

Circadian expression profiles



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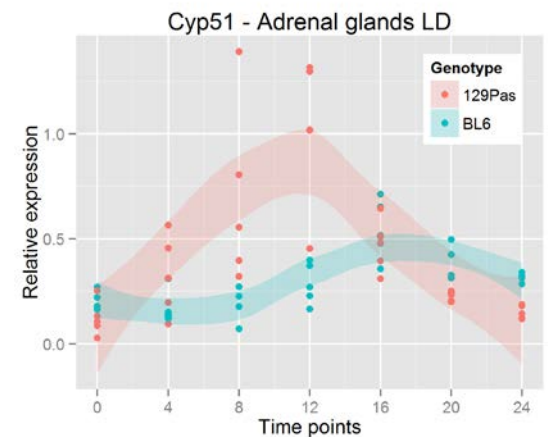
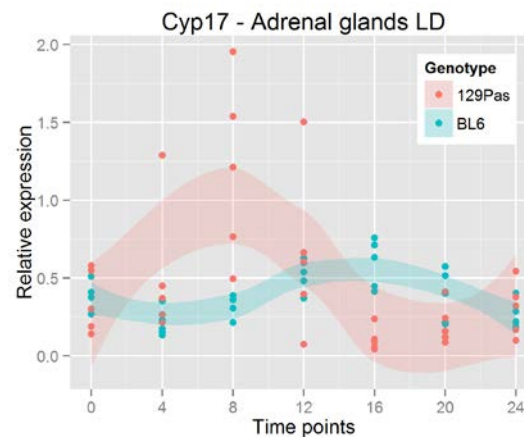
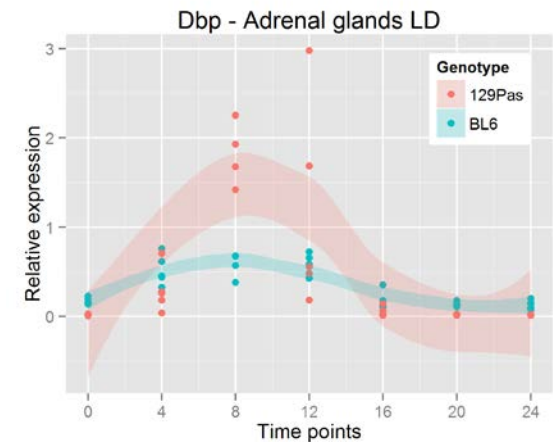
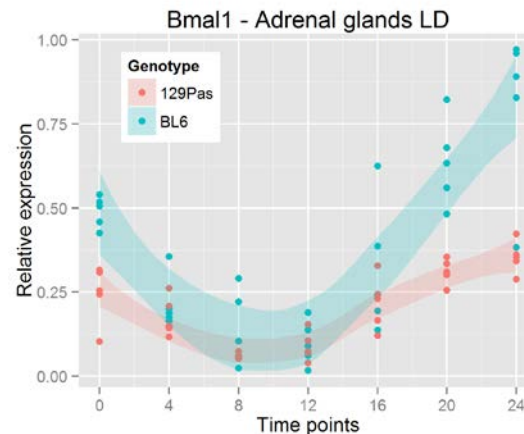
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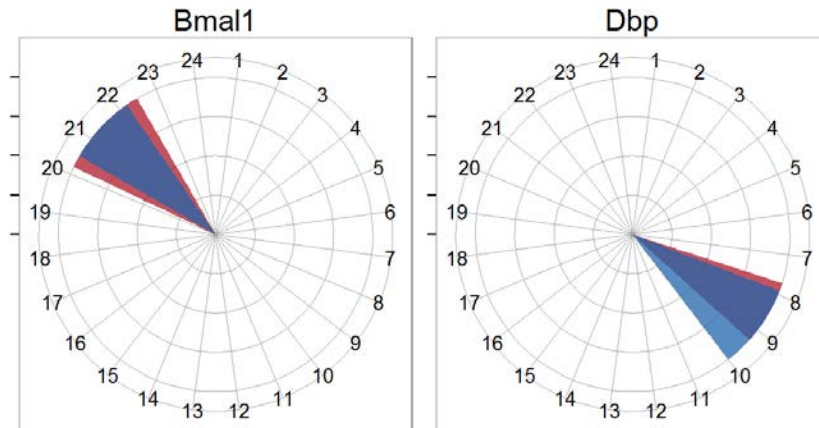
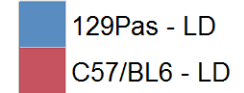
Circadian expression profiles



DIFFERENCES IN PEAK EXPRESSION (PHASE) ARE MOST PROMINENT FOR METABOLIC GENES

- Adrenal glands, LD

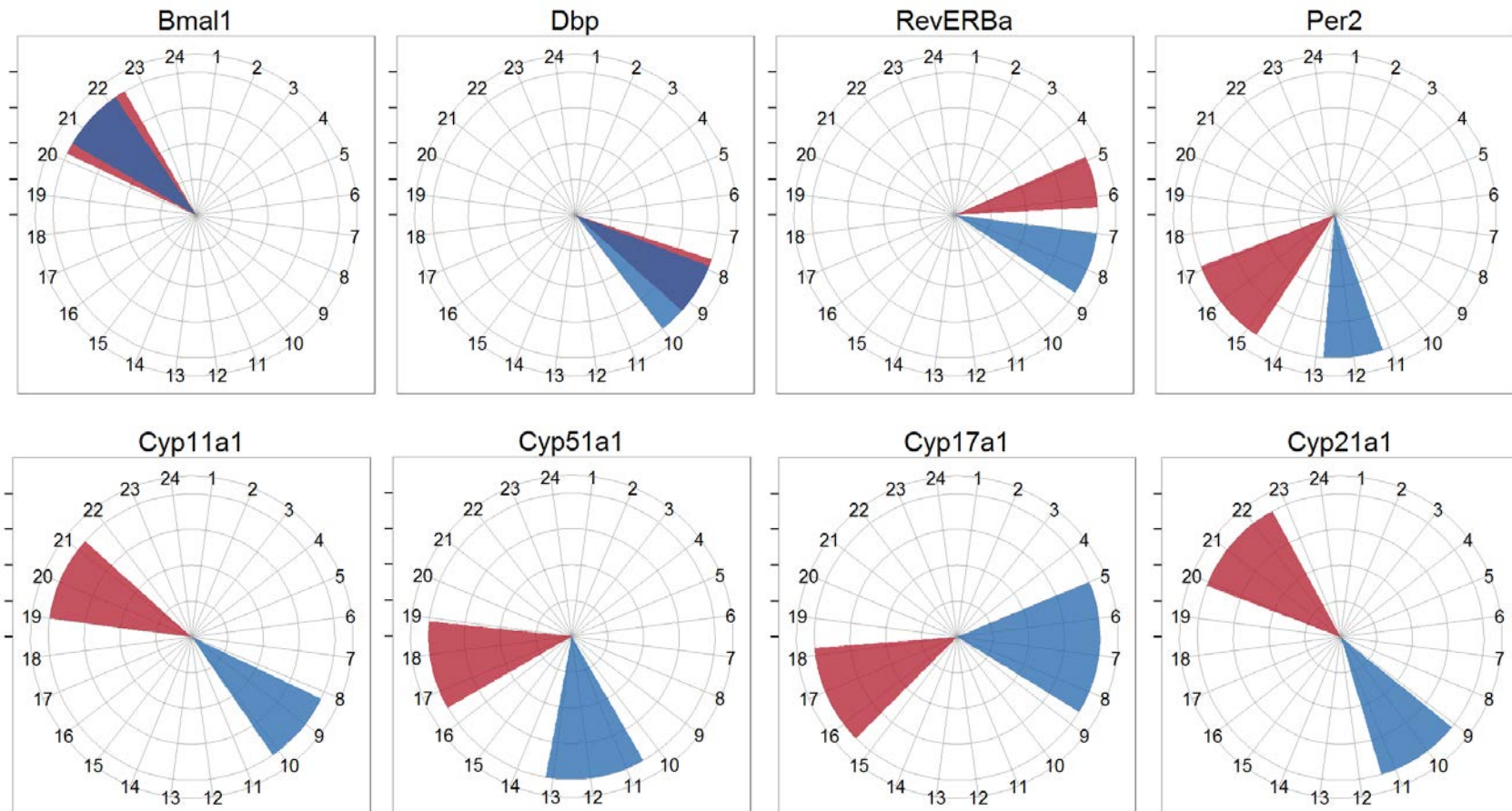
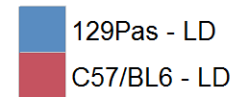
Condition



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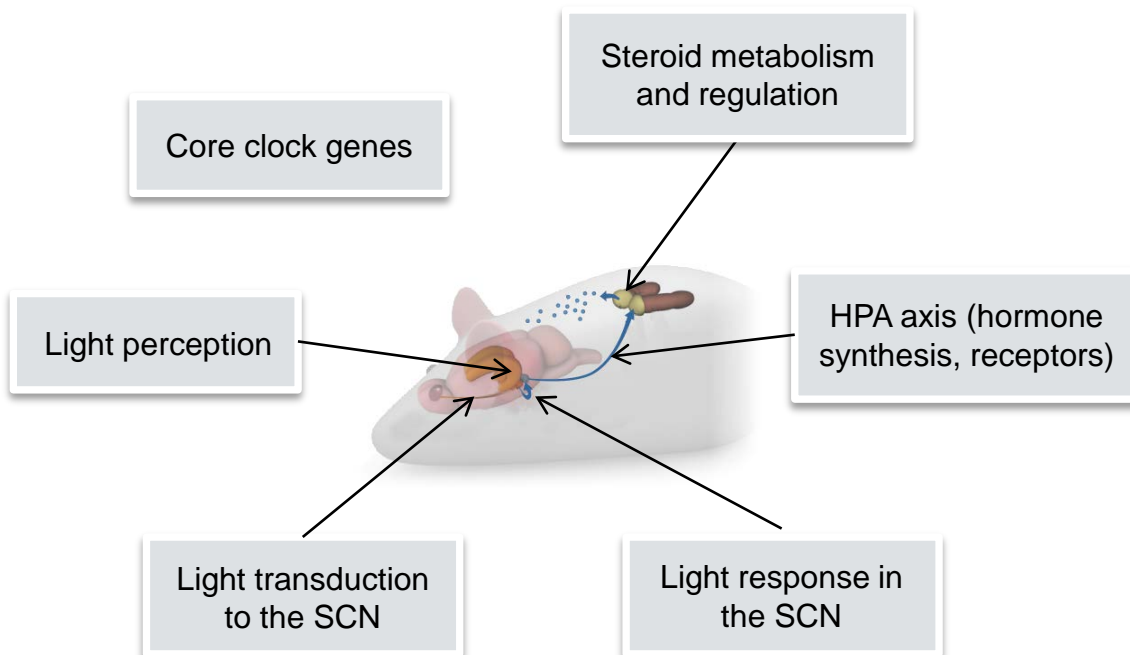
COULD DIFFERENCES IN PEAK EXPRESSION BE EXPLAINED BY GENOMIC VARIATION OF 129 AND C57BL/6 ?

- To answer this:
 - Data on structural variation of the three available 129 strains and comparison to the reference strain C57BL/6
 - Database resources: **Mouse Genomes Db** (SANGER) and **dbVar** (NCBI)
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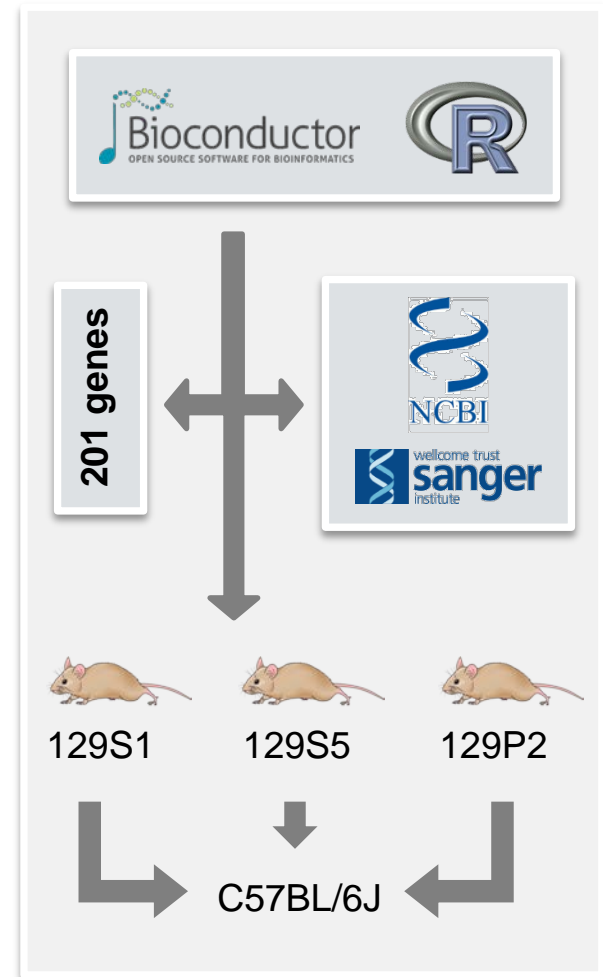
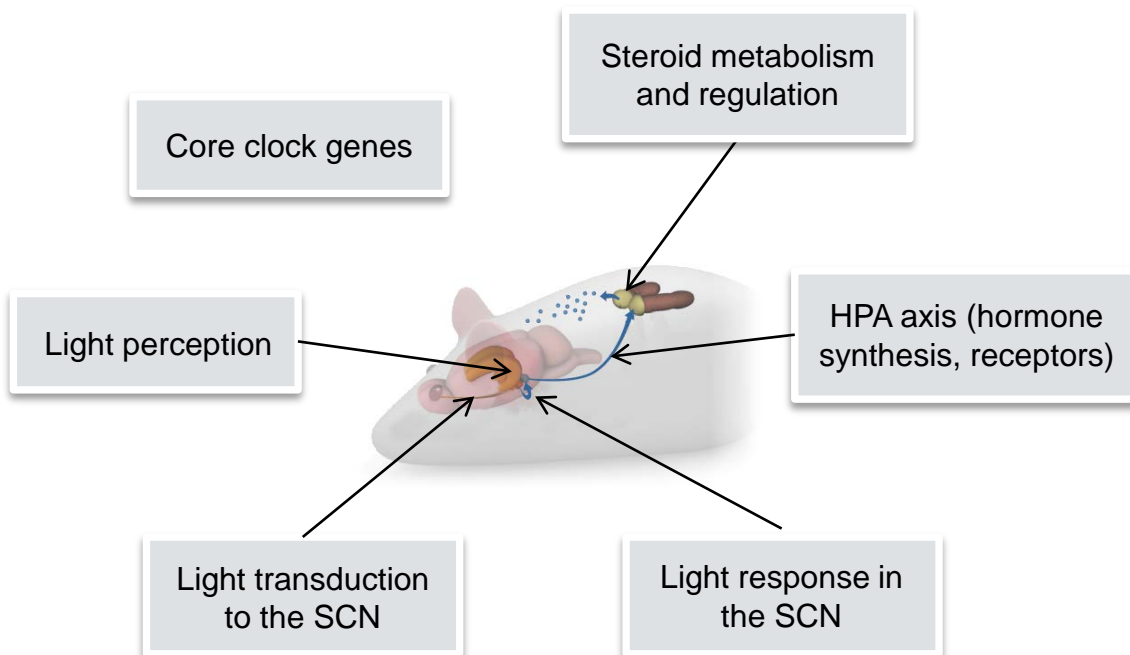
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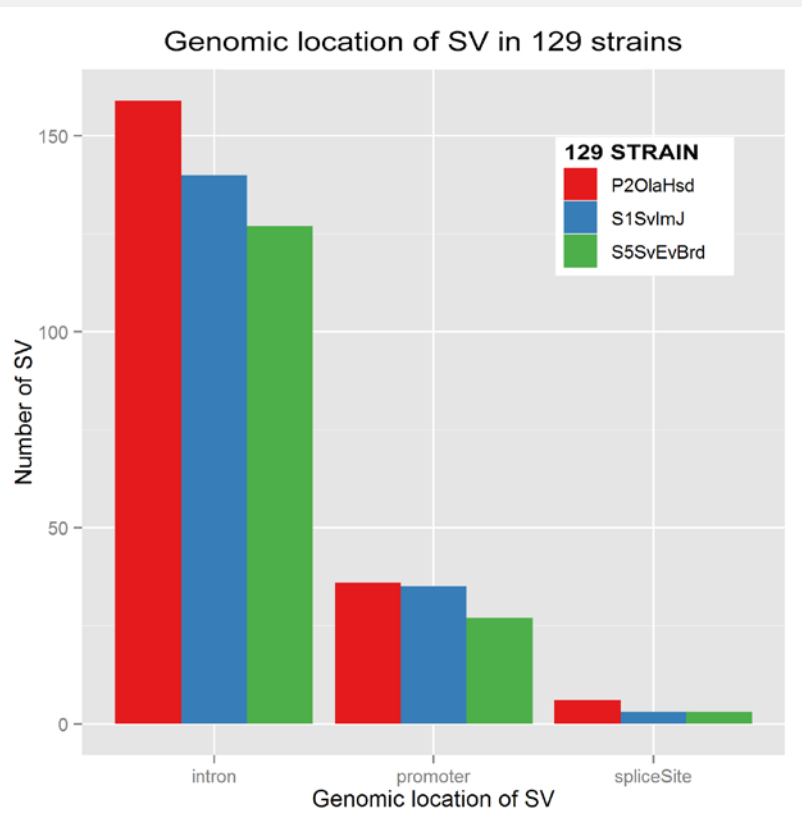
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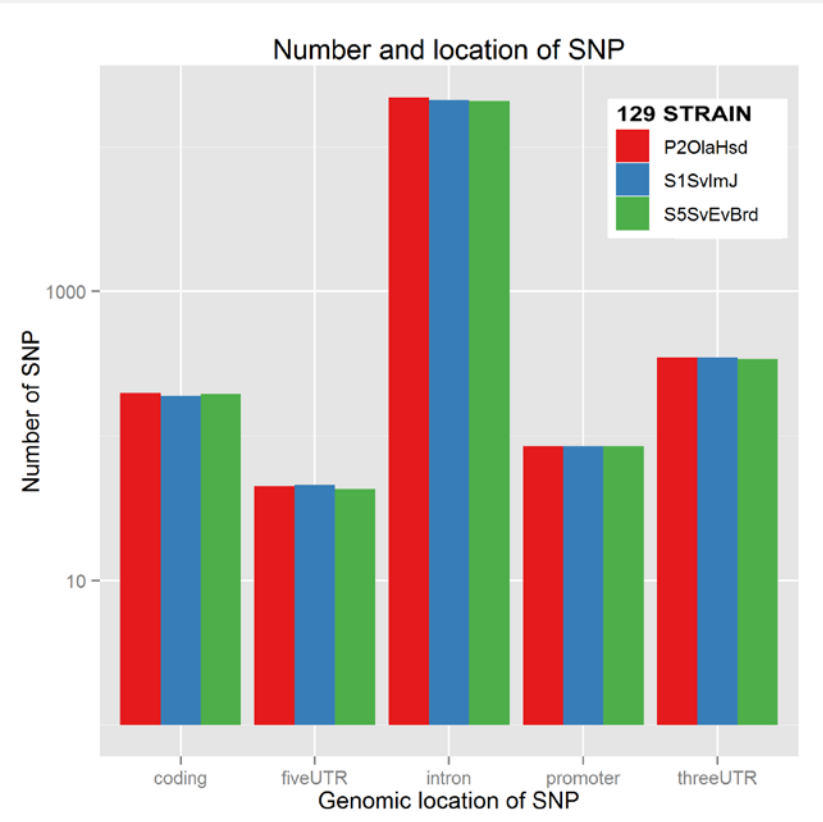
C57BL6 AND 129 STRAINS DIFFER IN OVER 20.000 SNVS AND OVER 150 STRUCTURAL VARIANTS

Structural variation



% of GOI with SV = 24.71%

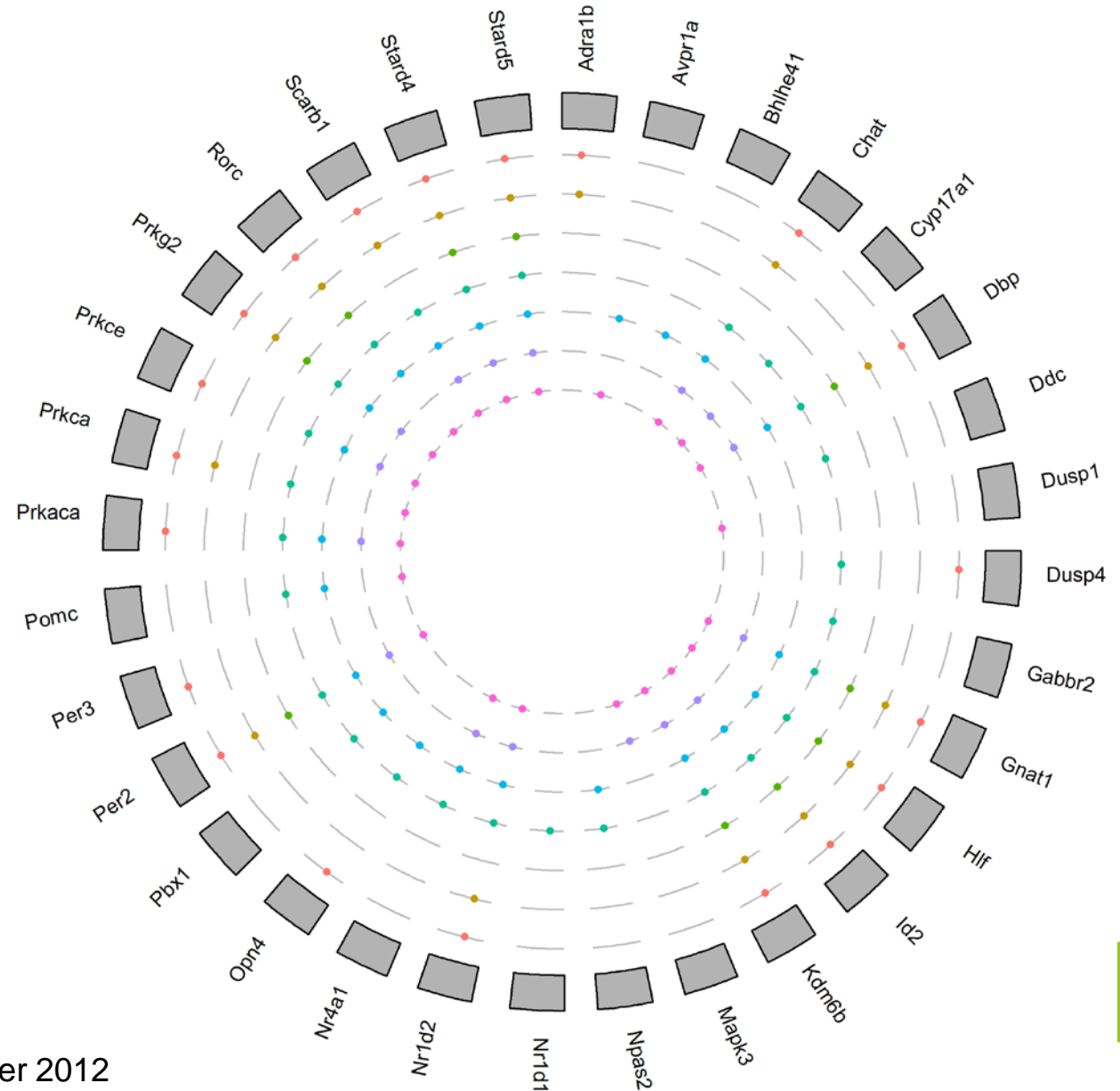
SNV



% of GOI with SNP = 76.12 %

SEVERAL SNV VARIANTS RESIDE IN CLOCK –DEPENDENT PROMOTERS OF METABOLIC OUTPUT AND CIRCADIAN GENES

ChIPSeq binding region

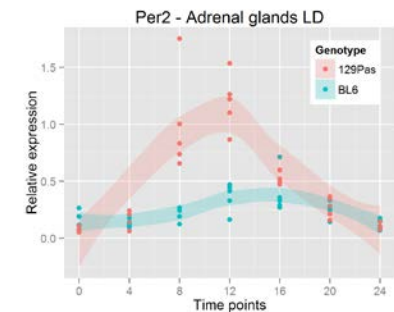
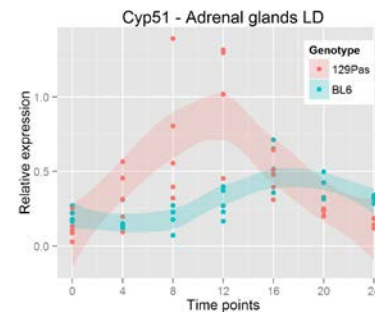
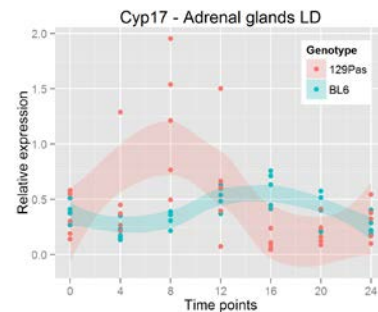
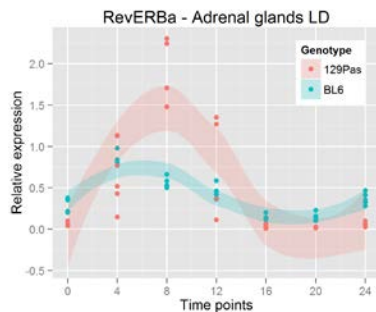


ChIPSeq data:

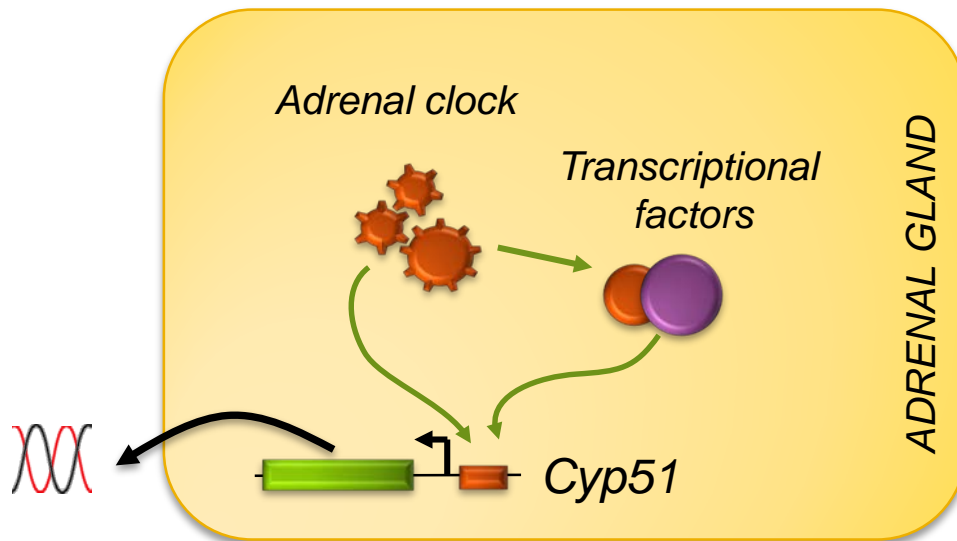
Koike et al., Science 19 October 2012

DNA VARIATIONS IN GENES THAT SHOWED DIFFERENTIAL CIRCADIAN EXPRESSION IN C57BL/6 AND 129 MICE

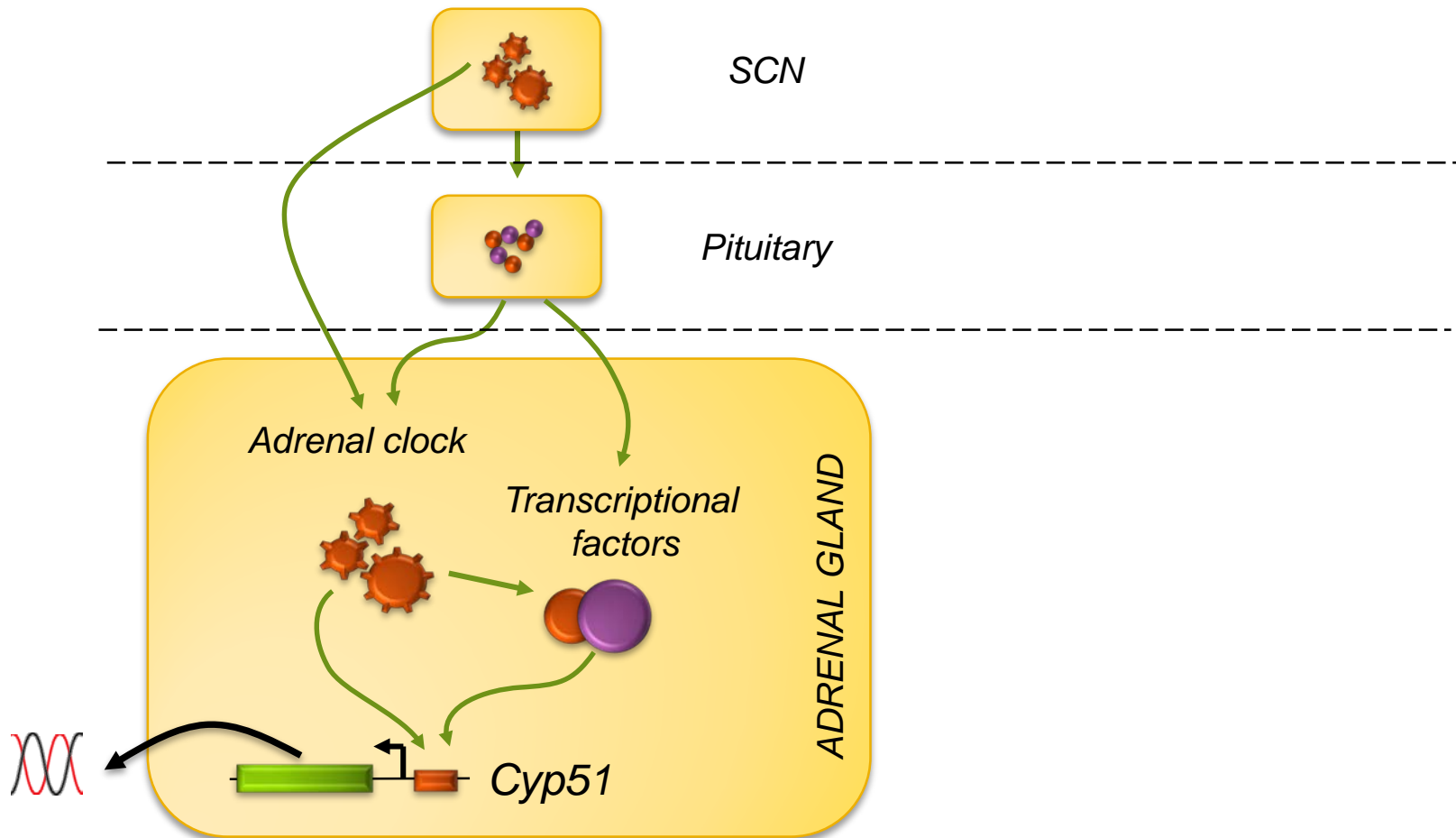
| Gene | Promoter mutations | | | Structural variants | | | SNVs | | |
|----------------|--------------------|-----------|-----------|---------------------|-----------|-----------|-----------|-----------|-----------|
| | <i>P2</i> | <i>S1</i> | <i>S5</i> | <i>P2</i> | <i>S1</i> | <i>S5</i> | <i>P2</i> | <i>S1</i> | <i>S5</i> |
| <i>Per2</i> | 7 | 7 | 7 | | | | 63 | 66 | 61 |
| <i>RevERBa</i> | 1 | 1 | 1 | | | | 8 | 8 | 8 |
| <i>Bmal1</i> | | | | 4 | 5 | 4 | 183 | 181 | 179 |
| <i>Cyp11</i> | | | | | | | | | 1 |
| <i>Cyp17</i> | 3 | 3 | 3 | | | | 3 | 3 | 3 |
| <i>Cyp51</i> | | | | | | | 25 | 25 | 25 |



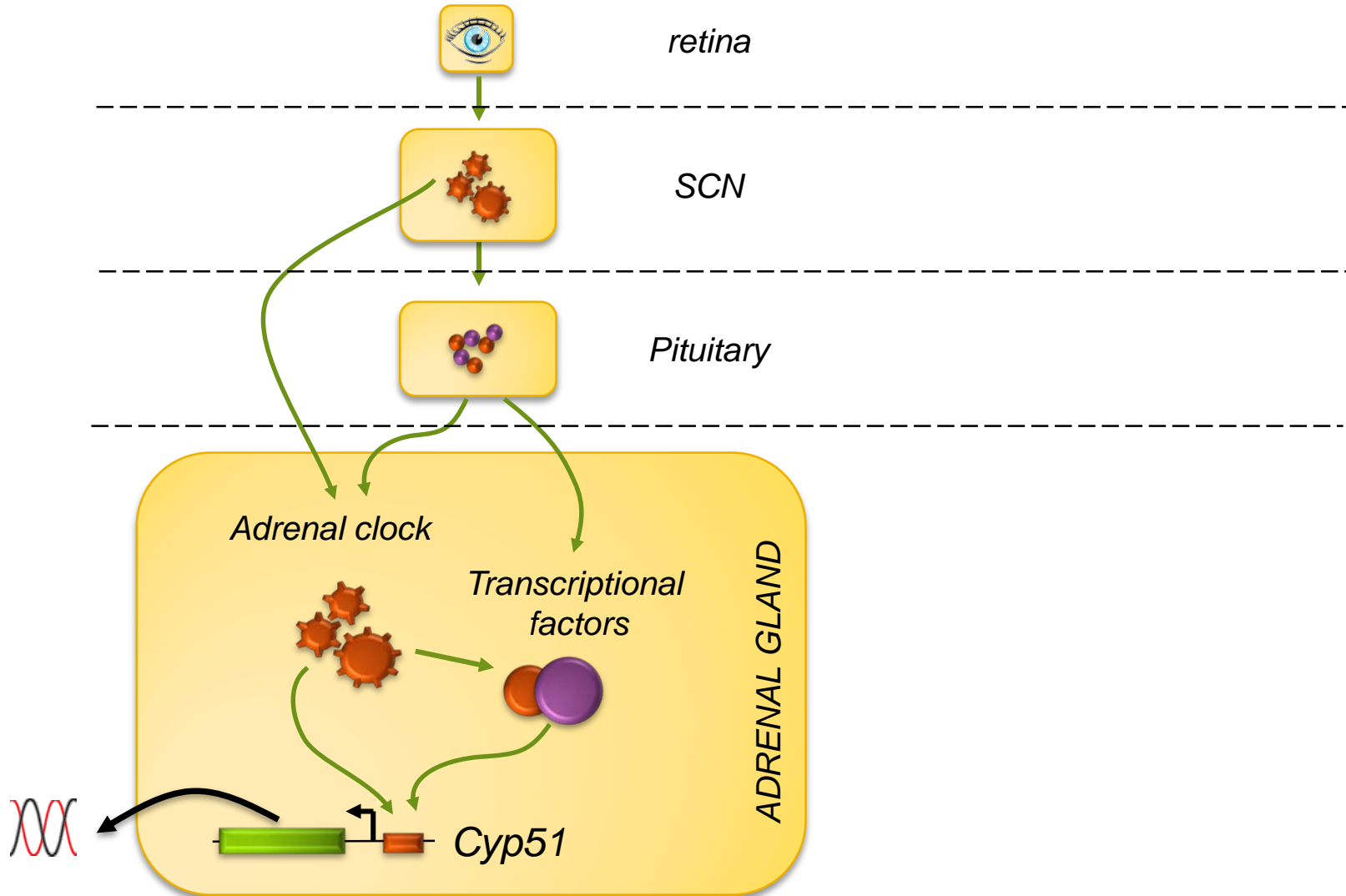
WHAT COULD EXPLAIN THE DIFFERENT CIRCADIAN PATTERNS OBSERVED IN MOUSE STRAINS?



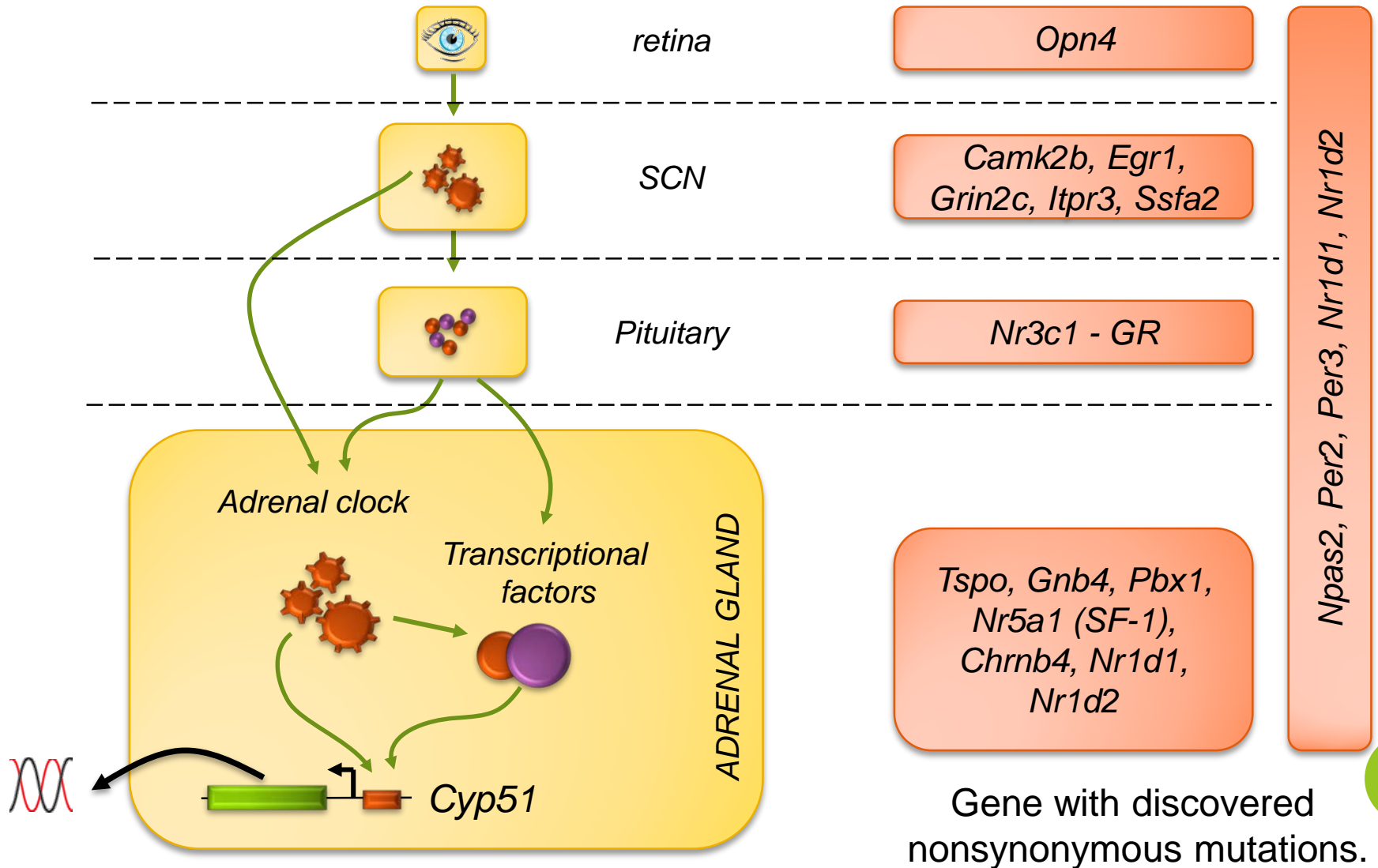
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CONCLUSION

- Circadian expression of many core clock and metabolic output genes differs between 129 and C57Bl/6 mouse strains. Most variations were observed in adrenal glands under LD, where several CYPs exhibit crucial differences in peak expression (phase).
- Core clock and metabolic genes that vary in gene expression 129 to C57Bl/6 gene expression harbor numerous DNA variants in promoter, intron and coding regions.
- The genomes of the three 129 strains investigated are genetically very similar. Many SNVs and structural variants lie at the same location in the genome.
- These findings are relevant for future chronopharmacology studies since the genotype could crucially affect the circadian expression of drug metabolizing genes.

Acknowledgments

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J7-4053: *Functional genomics of cholesterol homeostasis: the role of lanosterol
14alpha-demethylase in development of metabolic disorders*

Thank you for your attention!



