BIO333 Comparative Physiology
and Pharmacology of Sleep

Genetics of Sleep
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Genetics of Sleep

Quantitative traits are determined by:

• small, additive effects of many genes
• the environment
• interaction between genes and environment
Sleep is a complex phenotype

Each component of sleep is a complex phenotype

- Sleep duration
- Preferred timing for activity or sleep: diurnal preference
- Characteristic EEG oscillations
- Homeostasis of sleep

Genetics of sleep are relatively unknown

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Sleep duration: large variability in the population

Kripke et al, Arch Gen Psychiatry, 2002
Sleep studies in Twins

Concordance of sleep habits: MZ > DZ

Genetic factors contribute to:

- Duration of NREM sleep (Stages 2 and 4, SWA)
- Density of REM sleep
- 35-45 % of the variance in sleep quality, quantity, and sleep disorders


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Genetics of sleep are relatively unknown
Are you a “night owl” or a “lark”? Prediction of diurnal preference

Several genes are involved in the generation of circadian rhythmicity

\[ CLOCK \text{ polymorphisms?} \]

\[ \downarrow \]

Extreme morningness-eveningness preference?

![DNA double helix](image)

**Horne-Östberg Score**
Katzenberg et al, Sleep 1998

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**Sleep is a complex phenotype**

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Genetics of sleep are relatively unknown
Genetics of human sleep: twin studies
Remarkable similarity of EEG signals in MZ twins

Monozygotic twins (MZ)

Dizygotic twins (DZ)

van Beijsterveldt et al,
Am J Hum Genet 1996

The “EEG fingerprint” of sleep in Twins

De Gennaro et al,
Ann Neurol 2008
EEG activity during resting wakefulness is largely determined by genetic factors

- Within-individual stability
- Inter-individual variability


Trait-like individual differences in the NREM sleep EEG

Buckelmüller et al, Neuroscience 2006
Gene polymorphisms and Sleep in humans

A genetic variant of adenosine deaminase affects the duration and intensity (SWA) of NREM sleep

Subject #1
G/A polymorphism

Subject #2
G/G polymorphism

Are spindles determined by genetics factors?

Genetic Studies of Sleep in Mice
Genotype-specific variations of the EEG in inbred mice


Sleep is a complex phenotype

Each component of sleep is a complex phenotype

• Sleep duration
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• Characteristic EEG oscillations
• Homeostasis of sleep

Genetics of sleep are relatively unknown
The homeostatic regulation of sleep is under genetic control

Genetic analysis of sleep

- **Forward genetics** (“from phenotype-to-gene”)
  - Mutagenesis screens
  - Quantitative-Trait-Loci (QTL) approach
  - Family-based linkage studies
  - Genome-wide association studies

- **Reverse genetics** (“from-gene-to-phenotype”)
  - Candidate genes in knock-out and transgenic animal models
  - Knock-down (iRNA)
  - Association and candidate gene studies

- **Molecular genetics** (“from phenotype-to-mRNA”)
  - Transcriptome analyses
  - Proteomics
**From phenotype to genes: looking for sleep mutants - the Drosophila model**

- **Mutagenesis** → **Drosophila melanogaster**
- Screening the sleep phenotype of 9000 different mutations
  ⇒ Identification of novel genes involved in sleep regulation

*Fig. 1.* Mutagenesis of *Drosophila melanogaster* leads to screening of sleep phenotype in 9000 different mutations, identifying novel genes involved in sleep regulation. 

*Fig. 2.* Graphs showing the sleep amount distribution in males and females for a short-sleeper line. 

*Cirelli et al., Nature 2005*

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**Forward genetics in humans: two examples**

**Localization of a Gene for the Human Low-Voltage EEG on 20q and Genetic Heterogeneity**

*Ortrud Steinlein, Andrej Anokhin, Mao Yiping, Edda Schalt, and Friedrich Vogel*

*Genome 12, 60–73 (1992)*

*Fig. 3.* Pedigree analysis showing genetic heterogeneity in the localization of a gene for the human low-voltage EEG on 20q.

*Fig. 4.* Graph showing the association of a gene variant with restless legs syndrome.

Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions.

*Winkelmann et al., Volume 39 | Number 8 | August 2007 Nature Genetics*
Forward genetics to study human sleep disorders

The contribution of genes, environment and gene-environment to sleep disorders is increasingly recognized.

Only few sleep disorders have an established genetic basis, incl. 4 rare diseases that may result from a single gene mutation (fatal familial insomnia, familial advanced sleep-phase syndrome, chronic primary insomnia, and narcolepsy with cataplexy).

Most sleep disorders are complex in terms of their genetic susceptibility together with the variable expression of the phenotype even within a same family.

Recent linkage, genome-wide and candidate gene association studies resulted in the identification of gene mutations, gene localizations, or evidence for susceptibility genes and/or loci in several sleep disorders.


Genetics of human sleep disorders

<table>
<thead>
<tr>
<th>Sleep Disorder</th>
<th>Mode of Inheritance</th>
<th>Genetic Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal familial insomnia</td>
<td>Autosomal Dominant</td>
<td>Mutation at codon 178 of the prion protein gene</td>
</tr>
<tr>
<td>Primary nocturnal enuresis</td>
<td>Autosomal Dominant</td>
<td>Linkage to chromosome 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linkage to chromosome 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linkage to chromosome 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linkage to chromosome 22</td>
</tr>
<tr>
<td>Familial advanced sleep-phase</td>
<td>Autosomal Dominant</td>
<td>Mutation at codon 652 of the perox2 gene</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td>Linkage to chromosome 12</td>
</tr>
<tr>
<td>Familial restless legs syndrome</td>
<td>Autosomal Recessive</td>
<td>Linkage to chromosome 12</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>Autosomal Dominant</td>
<td>Association with M&amp;O-A</td>
</tr>
<tr>
<td></td>
<td>Or Unknown</td>
<td>Separation analysis</td>
</tr>
<tr>
<td>Sleepwalking</td>
<td>Autosomal Dominant</td>
<td>Family and twin analyses</td>
</tr>
<tr>
<td></td>
<td>Or Unknown</td>
<td>Association with HLA-DQB1*0504</td>
</tr>
<tr>
<td>Sleep talking</td>
<td>Autosomal Dominant</td>
<td>Family and twin analyses</td>
</tr>
<tr>
<td></td>
<td>Or Unknown</td>
<td>Association with HLA-DQB1*0506</td>
</tr>
<tr>
<td>Bruxism</td>
<td>Autosomal Dominant</td>
<td>Family and twin analyses</td>
</tr>
<tr>
<td></td>
<td>Or Unknown</td>
<td>Association with HLA-DQB1*0602</td>
</tr>
<tr>
<td>Night terrors and nightmares</td>
<td>Autosomal Dominant</td>
<td>Family, twin, and segregation analyses</td>
</tr>
<tr>
<td></td>
<td>Or Unknown</td>
<td>Association with HLA-DQB1*0201</td>
</tr>
<tr>
<td>Kleine-Levin syndrome</td>
<td>Unknown</td>
<td>Association with HLA-DQB1*0506</td>
</tr>
<tr>
<td>REM-sleep disorder behavior</td>
<td>Unknown</td>
<td>Association with HLA-DQB1*0602</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>Autosomal Dominant</td>
<td>Family, twin, and segregation analyses, Association</td>
</tr>
<tr>
<td></td>
<td>Or Unknown</td>
<td>with HLA-DQB1*0602</td>
</tr>
</tbody>
</table>

Franken & Tafiti, Front Biosci 2003
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Reverse genetics: “from gene to phenotype”

target candidate genes

Knockout & Transgenic

<table>
<thead>
<tr>
<th>Gene</th>
<th>Main Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased sleep continuity</td>
<td></td>
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<tr>
<td>Decreased SWA amplitude</td>
<td></td>
</tr>
<tr>
<td>Increased W, decreased SWS</td>
<td></td>
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<tr>
<td>No response to amphetamine and modafinil</td>
<td></td>
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<tr>
<td>Decreased PS</td>
<td></td>
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<tr>
<td>No response to orexin A</td>
<td></td>
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<tr>
<td>Decreased TST during the dark period</td>
<td></td>
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<tr>
<td>No response to IL-1β</td>
<td></td>
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<tr>
<td>Increased SWS during the dark period</td>
<td></td>
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<tr>
<td>Altered response to lipopolysacharide challenge</td>
<td></td>
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<tr>
<td>Narcolepsy</td>
<td></td>
</tr>
<tr>
<td>Decreased sleep continuity</td>
<td></td>
</tr>
<tr>
<td>Increased SWS after tail clipping</td>
<td></td>
</tr>
<tr>
<td>Increased PS, decreased SWS</td>
<td></td>
</tr>
<tr>
<td>Decreased TST</td>
<td></td>
</tr>
<tr>
<td>No response to TNF-α</td>
<td></td>
</tr>
</tbody>
</table>

Point-mutation

- No effect on diazepam-induced sleep changes

Mutagenesis

- Decreased TST
- Decreased SWS
- Non-specific background effect
- Narcolepsy

Tafti & Franken, J Appl Physiol 2002
Study of a sleep disorder: narcolepsy

Narcolepsy is a neurological disorder characterized by:
- excessive daytime sleepiness
- cataplexy (sudden onset of muscle atonia)
- direct transition from wakefulness to REM sleep

Dog

Human

Mouse and rat (genetic models)

Mouse and rat (genetic models)

Zebrafish (genetic models)

Lin et al, Cell 1999


Willie et al, Neuron 2003


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Molecular genetics: transcriptomics

- cDNA microarray technology
- mRNA differential display

Cb: cerebellum
Cx: cortex

Rat

Wakefulness
- Energy metabolism
- Response to cellular stress
- Synaptic potentiation

Sleep
- Lipid metabolism
- Maintenance of membranes
- Synaptic depression

Cirelli et al. Neuron 2004