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BIO333 Comparative Physiology and Pharmacology of Sleep

Genetics of Sleep

December 3, 2011

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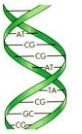
Genetics of Sleep



Quantitative traits are determined by:

- small, additive effects of many genes
- the environment
- interaction between genes and environment

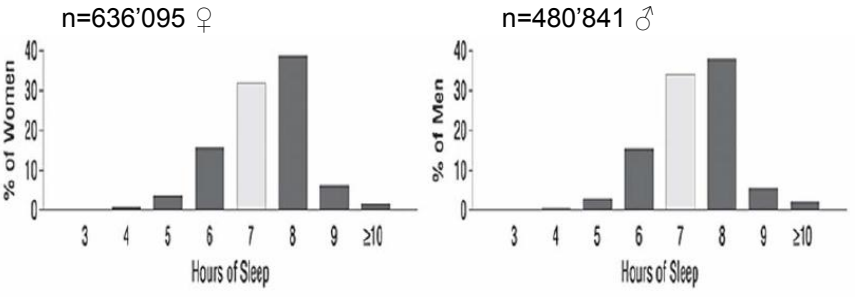
Sleep is a complex phenotype

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

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

Geyer, 1937; *Gedda & Brenci, 1979*; *Chouvet et al, 1980*; *Heath et al, 1990; Partinen et al, 1983*; *Linkowski et al, 1989; 1991*

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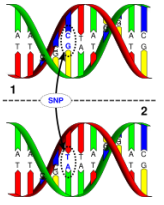
Are you a "night owl" or a "lark"? Prediction of diurnal preference

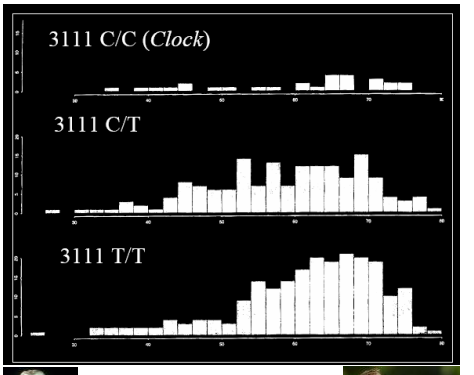
Several genes are involved in the generation of circadian rhythmicity

CLOCK polymorphisms?

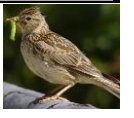
⇓

Extreme morningness-eveningness preference?





Horne-Östberg Score



Katzenberg et al, Sleep 1998

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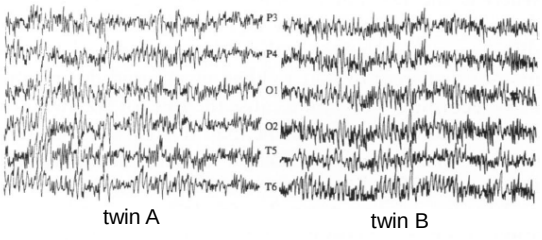
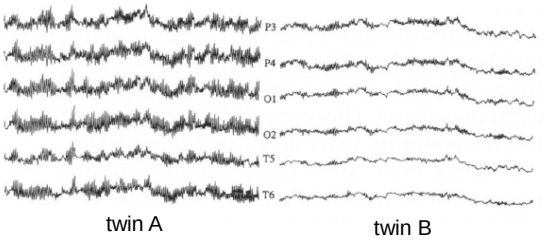
Genetics of human sleep: twin studies

Remarkable similarity of EEG signals in MZ twins

Monozygotic twins (MZ)

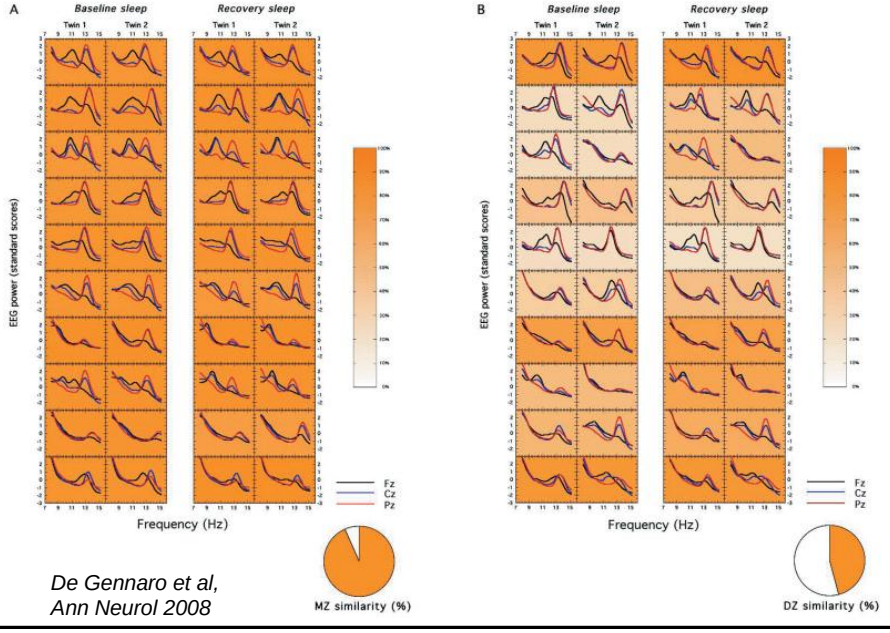


Dizygotic twins (DZ)



van Beijsterveldt et al,
Am J Hum Genet 1996

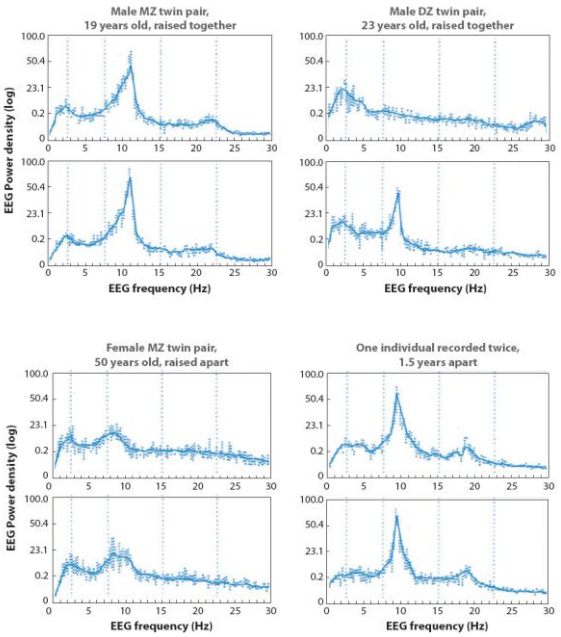
The "EEG fingerprint" of sleep in Twins



De Gennaro et al,
Ann Neurol 2008

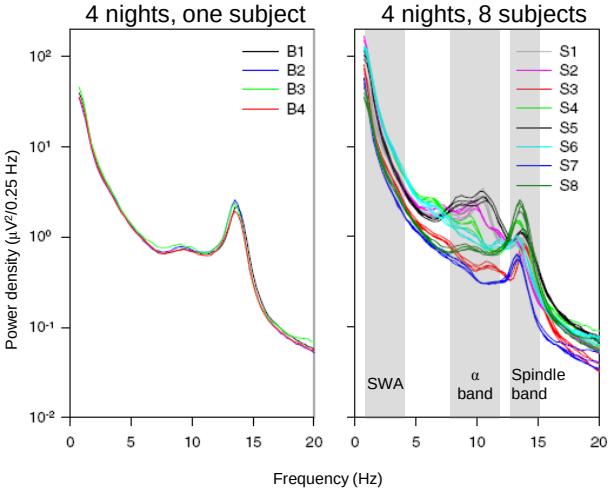
EEG activity during resting wakefulness is largely determined by genetic factors

- Within-individual stability
- Inter-individual variability



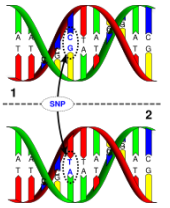
Andretic et al, Annu Rev Genet 2008;
modified from Stassen et al, Eur Arch Psychiatry Neurol Sci 1998

Trait-like individual differences in the NREM sleep EEG



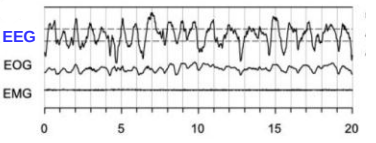
Buckelmüller et al, Neuroscience 2006

Gene polymorphisms and Sleep in humans

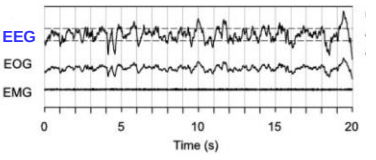


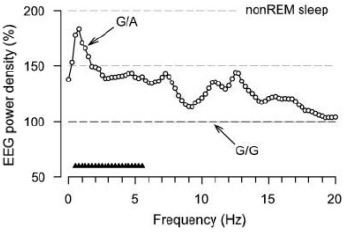
A genetic variant of adenosine deaminase affects the duration and intensity (SWA) of NREM sleep

Subject #1
G/A polymorphism



Subject #2
G/G polymorphism



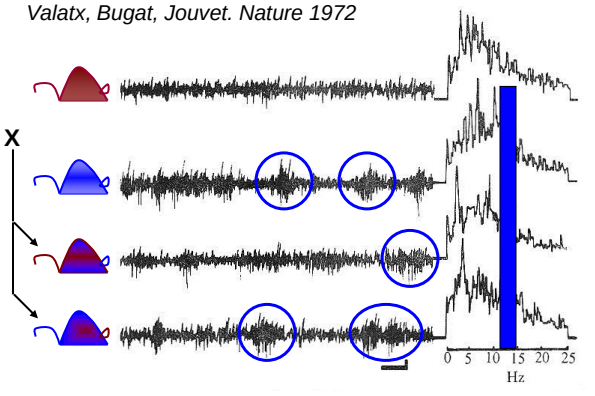


Retey et al, PNAS 2005

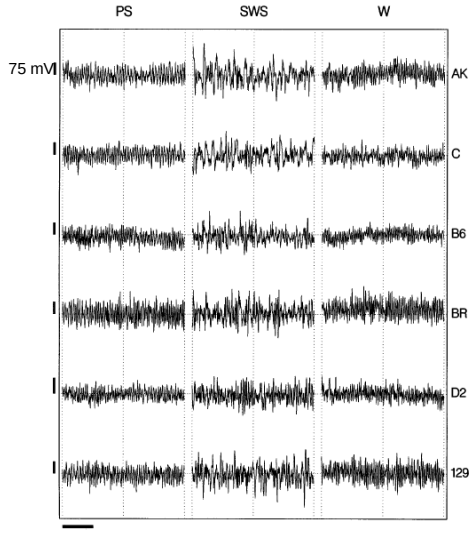
Are spindles determined by genetics factors?

Genetic Studies of Sleep in Mice

Valatx, Bugat, Jouvet. Nature 1972

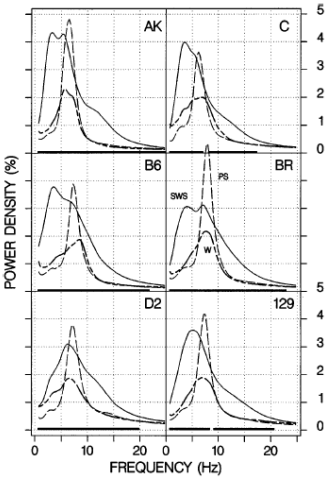


Genotype-specific variations of the EEG in inbred mice



Franken et al, Am J Physiol 1998

EEG spectra



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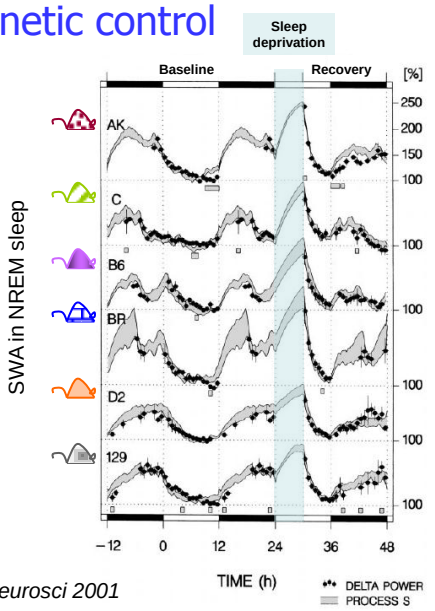
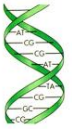
Genetics of sleep are relatively unknown

The homeostatic regulation of sleep is under genetic control





Genes?

Franken et al, J Neurosci 2001

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")
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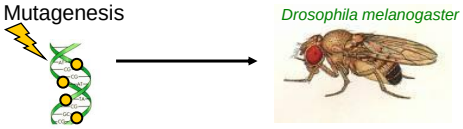
- Molecular genetics ("from phenotype-to-mRNA")
  - Transcriptome analyses
  - Proteomics

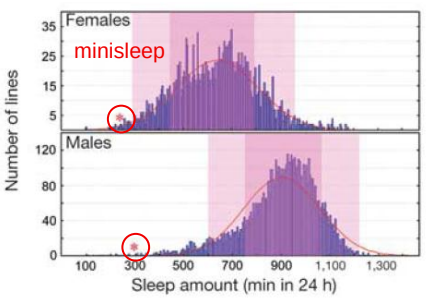
Mus musculus *Drosophila melanogaster* *Danio rerio* *Caenorhabditis elegans*

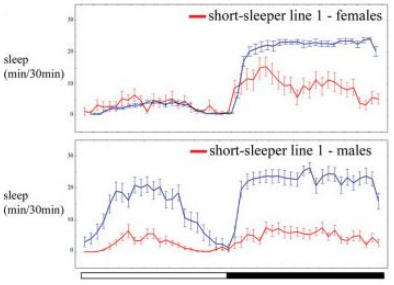
From phenotype to genes: looking for sleep mutants- the Drosophila model



Screening the sleep phenotype of 9000 different mutations

⇒ Identification of novel genes involved in sleep regulation





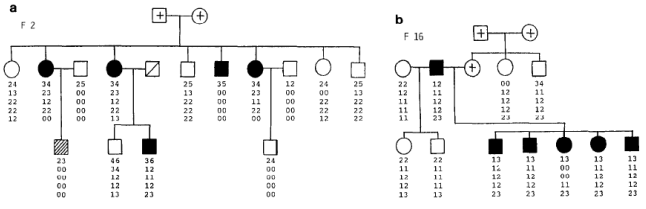
Cirelli et al, Nature 2005

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 YPING, EDDA SCHALT, AND FRIEDRICH VOGEL

GENOMICS **12**, 69–73 (1992)



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

Tafti et al, Ann Med 2005; Hamet & Tremblay, Met Clin & Exp 2006

Genetics of human sleep disorders

Sleep Disorder	Mode of Inheritance	Genetic Evidence
Fatal familial insomnia	Autosomal Dominant	Mutation at codon 178 of the prion protein gene
Primary nocturnal enuresis	Autosomal Dominant	Linkage to chromosome 13 Linkage to chromosome 8 Linkage to chromosome 12 Linkage to chromosome 22
Familial advanced sleep-phase syndrome	Autosomal Dominant	Mutation at codon 662 of the period2 gene
Familial restless legs syndrome	Autosomal Recessive	Linkage to chromosome 12 Association with MAO-A
	Autosomal Dominant	Segregation analysis
Familial sleep paralysis	Autosomal Dominant	Family analyses
Sleep apnea syndrome	Autosomal Dominant Or Unknown	Family and segregation analyses
Sleepwalking	Autosomal Dominant Or Unknown	Family and twin analyses Association with HLA-DQB1*05/04
Sleep talking	Autosomal Dominant Or Unknown	Family and twin analyses
Bruxism	Autosomal Dominant Or Unknown	Family and twin analyses
Night terrors and nightmares	Autosomal Dominant Or Unknown	Family, twin, and segregation analyses
Kleine-Levin syndrome	Unknown	Association with HLA-DQB1*0201
REM-sleep disorder behavior	Unknown	Association with HLA-DQB1*05/06
Narcolepsy	Autosomal Dominant Or Unknown	Family, twin, and segregation analyses, Association with HLA-DQB1*0602

Franken & Tafti, Front Biosci 2003

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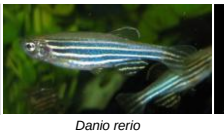
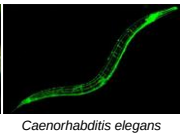
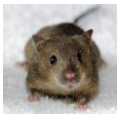
Mus musculus


Drosophila melanogaster

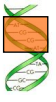

Danio rerio


Caenorhabditis elegans

Reverse genetics: "from gene to phenotype" target candidate genes



Knockout & Transgenic



Point-mutation

Mutagenesis

Gene	Main Effect
Knockout	
Albumin D-binding protein	Decreased sleep continuity Decreased SWA amplitude
c-*fos*	Increased W, decreased SWS
Dopamine transporter	No response to amphetamines and modafinil
*fos*B	Decreased PS
Histamine H_1 receptor	No response to orexin A
Interleukin-1 type I receptor	Decreased TST during the dark period No response to IL-1β
Interleukin-10	Increased SWS during the dark period Altered response to lipopolysaccharide challenge
Preproorexin	Narcolepsy
Prion protein	Decreased sleep continuity
Prostaglandin D synthase	Increased SWS after tail clipping
Serotonin receptor 1B	Increased PS, decreased SWS
TNF 55-kDa receptor	Decreased TST No response to TNF-α
Point-mutation	
GABA-A α_1	No effect on diazepam-induced sleep changes
Mutagenesis	
Clock	Decreased TST
Transgenic	
Growth hormone	Decreased SWS
Insulin	Nonspecific background effect
Orexin/ataxin-3	Narcolepsy

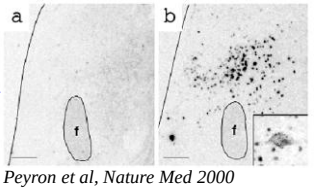
Tafti & Franken, J Appl Physiol 2002

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

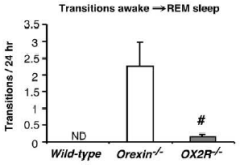
Dog

Human

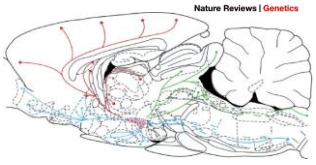


Peyron et al, Nature Med 2000

Mouse and rat (genetic models)



Willie et al, Neuron 2003



Lin et al, Cell 1999

Zebrafish (genetic models)

Yokogawa et al, PLoS 2007

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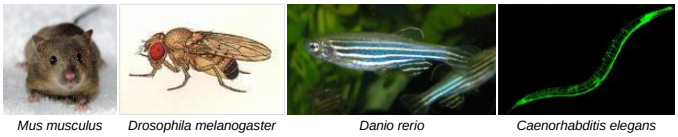
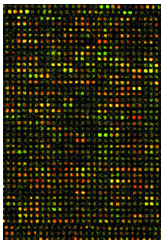


Mus musculus *Drosophila melanogaster* *Danio rerio* *Caenorhabditis elegans*

Molecular genetics: transcriptomics

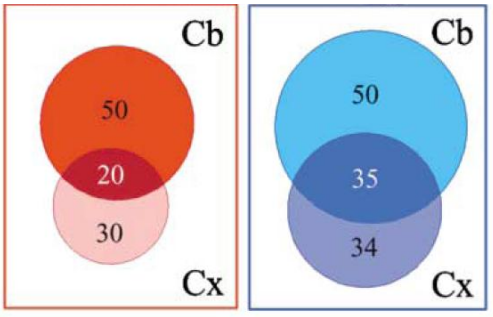


cDNA microarray technology
mRNA differential display

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