Single Genes can modify behavior: Worms; Flies; Mice: Humans
Social Behavior in *C. elegans*.

- Mutation in a neuropeptide-Y-like protein; the NPR-1 receptor. In mammals, important for “feeding”.
- Clumping is controlled by an unknown neuropeptide acting through the receptor.
- Secretion of the neuropeptide is probably regulated by food.

**Proposed Model:**

Dispersing strains have a repellant response (mediated by NPR-1 receptor) that masks the attractant response.
<table>
<thead>
<tr>
<th>Normal</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-day mutant</td>
<td>19 hours</td>
</tr>
<tr>
<td>Long-day mutant</td>
<td>28 hours</td>
</tr>
<tr>
<td>Arrhythmic mutant</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3-6** A single gene, *period* (*per*), governs the circadian rhythms of specific behaviors in *Drosophila*. (From Konopka and Benzer 1971.)
The Sleep Disorder Canine Narcolepsy is Caused by a Mutation in the Hypocretin (Orexin) Receptor 2 Gene.
L. Lin et al., Cell 98 365 1999

Narcolepsy in orexin Knockout Mice: Molecular Genetics of Sleep Regulation.
RM Chemelli et al., Cell 98, 437 1999

Narcolepsy: debilitating, neurological disorder characterized by:
1. Sleep attacks
2. Episodic loss of muscle tone (cataplexy)
3. Hypnagogic hallucinations
4. Abnormal sleep-wake cycle

Reduced Number of Hypocretin Neurons in Human Narcolepsy
TC Thannickal et al., Neuron 27; 469 2000

Distribution of Cells in Perifornical and Dorsomedial Hypothalamic Regions of Normal and Narcoleptic Humans
- On average, narcoleptics have 7% of the Hcrt cells seen in normals
- C and D - low power covering regions shown in grey at top
- E and G - normal subjects
- F and H - narcoleptic subjects

Most human narcolepsy is NOT familial; is discordant in identical twins; and NOT linked to mutations in hypocretin.
**Narcolepsy: summary**

**Hypothetical Effect of Blunted nCt Activation:**


2. Cholinergic Brainstem and Basal Forebrain: cause sleepiness associated with narcolepsy.

3. Dense nCt Projections to the Suprachiasmatic Nucleus: reduced amplitude of circadian sleep rhythms, and thereby increased sleepiness during the day and interrupted sleep at night.

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**The Essential Role of Hippocampal CA1 NMDA Receptor-Dependent Synaptic Plasticity in Spatial Memory**


**Summary of Hippocampal Studies since 1957:**

1. Required for certain kinds of memory; spatial in rodents; facts and faces in humans.
2. Rodent hippocampal neurons are “place cells”; ‘fire’ when animal moves into marked area.
3. Hippocampal synapses exhibit LTP (paradigm for synaptic plasticity).
   - Tsien et al: use cre/loxP recombination system to delete NMDA receptor function only in CA1 subregion.
   - THUS: By effecting CA1-specific NMDA receptor inactivation, the studies relate synaptic plasticity to neuronal activity (place fields) and to spatial learning.
The Essential Role of Hippocampal CA1 NMDA Receptor-Dependent Synaptic Plasticity in Spatial Memory
JZ Tsien, PT Huerta, and S. Tonegawa, Cell 87 1327 1996.

Table 3.1: Neuronal diseases involving trinucleotide repeats

<table>
<thead>
<tr>
<th>Disease</th>
<th>Repeat</th>
<th>Repeat length</th>
<th>Gene product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysinocarboxamiduria and inulin-resistant dystrophy</td>
<td>CAG</td>
<td>Normal 15-24</td>
<td>Adenosine receptor</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>CGG</td>
<td>Normal 6-158</td>
<td>Tuberous sclerosis 1</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>CTG</td>
<td>Normal 5-80</td>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>CAG</td>
<td>Normal 15-101</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 1</td>
<td>CAG</td>
<td>Normal 19-56</td>
<td>Absent</td>
</tr>
<tr>
<td>TSC2 mental retardation</td>
<td>GCC</td>
<td>Normal 6-27</td>
<td>?</td>
</tr>
<tr>
<td>Huntington’s polyglutamine amyotrophy</td>
<td>CAG</td>
<td>Normal 15-75</td>
<td>?</td>
</tr>
</tbody>
</table>
Most Human Behaviors are Likely to be Genetically Complex: i.e., result from the complex interaction of multiple genes together with non-genetic (environment; stochastic) factors.

Genetics of Autism

Twin Studies
- Monozygotic twins are about 78% concordant for autism and spectrum disorders.
- Dizygotic twins are about 17% concordant.

Recurrence Risk
- Approximately 3% of affected probands have an affected sibling with autism (15% for autism + spectrum).

Relative risk
- Recurrence risk/prevalence
- 50-100 fold increase risk to first-degree relatives compared to general population.
Genetics of Autism

- Very high: MZ:DZ twin ratio
- Relatively low: ‘sibling-risk’ (recurrence risk)
- Very high: ‘relative risk’

Interpretation: Autism is strongly influenced by genetic factors; multiple genes contribute; each single gene effect is probably small; epistatic interactions are likely.

Hypothetical Transmission of Autism Predisposing Alleles

Model of Complex Trait Alleles

- Phenotype might occur due to any of several combinations of mutations, for example mutations in genes 3, 8, & 9; or genes 2 & 5. Some or all combinations may be dependent upon environmental factors.
Heritability of Psychiatric Disorders

Degree to which heritable (genetic) factors influence expression of disease or trait

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Heritability (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>50-60%</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>60-70%</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>30-40%</td>
</tr>
<tr>
<td>Obsessive-Compulsive Disorder</td>
<td>60-80% (small studies)</td>
</tr>
<tr>
<td>ADHD</td>
<td>60%</td>
</tr>
<tr>
<td>Reading Disability</td>
<td>50%</td>
</tr>
<tr>
<td>Autism (+ spectrum)</td>
<td>90%</td>
</tr>
<tr>
<td>Personality</td>
<td>40-60%</td>
</tr>
<tr>
<td>Nicotine Addiction</td>
<td>50% for initiation, 70% for 10 yr. persistence</td>
</tr>
</tbody>
</table>

Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking

Richard P. Ebstein\textsuperscript{1,3}, Olga Novick\textsuperscript{2}, Roberto Umansky\textsuperscript{2}, Beatrice Priet\textsuperscript{2}, Yamina Osher\textsuperscript{2}, Darren Blaine\textsuperscript{1}, Estelle R. Bennett\textsuperscript{1}, Lubov Nemanov\textsuperscript{1}, Miri Katz\textsuperscript{1} & Robert H. Belmaker\textsuperscript{2}
Alzheimer’s Disease is currently the best example of a complex disease with known genetic etiology.

**Alzheimer’s Disease**

1. Degenerating disorder of the CNS leading to a progressive decline in memory, reasoning, judgement and orientation.
2. Affects 2-5 million people in the U.S.A.
3. Fourth leading cause of death in the U.S.A.
4. Patients generally live 5-10 years after onset and often require institutionalized care; 25 billion dollars / year in U.S.A.
5. By the early 21st century, due to the increasing rate of life-expectancy, approximately 1 in every 5 people in the U.S.A. will suffer some form of dementia.

**Etiology of Alzheimer’s Disease**

1. Classically considered non-genetic
2. Affects 1/10 over age of 65, 1/3 over age of 85
3. Epidemiology Studies: Increased risk among relatives of patients with A.D.
4. Pedigrees: Autosomal dominant form of inheritance usually characterized by an early age of onset (Familial Alzheimer’s Disease).
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Onset</th>
<th>Proportion of cases (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Presenilin II</td>
<td>Early</td>
<td>&lt;1</td>
<td>Mainly Velga German</td>
</tr>
<tr>
<td>14</td>
<td>Presenilin I</td>
<td>Early</td>
<td>&lt;5</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>19</td>
<td>APOE</td>
<td>Both</td>
<td>40-50</td>
<td>Dose effect on risk</td>
</tr>
<tr>
<td>21</td>
<td>APP</td>
<td>Early</td>
<td>&lt;&lt;1</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>?</td>
<td>?</td>
<td>Late</td>
<td>&gt;50</td>
<td>Unknown number of genes</td>
</tr>
</tbody>
</table>

**Apolipoprotein E (APOE) and AD**

- APOE is a major serum lipoprotein involved in cholesterol metabolism.
- Synthesized in the brain by astrocytes
- In the brain, APOE is thought to be involved in mobilization and redistribution of cholesterol and phospholipid during membrane remodeling associated with plasticity of synapses.
Apolipoprotein E - e4

- e4/e4 AD patients show markedly more APP deposition in plaques relative to non-e4 AD patients
- ApoE e4 binds BA4 peptide with greater avidity than e3 isoform.
- ApoE e4 shows significant allelic association in familial and sporadic late onset AD, and in familial early onset AD.
  - e4 heterozygote is 3X more likely to be affected than e2/e3 or e3/e3
  - e4 homozygote is 8X more likely to be affected

Conclusion: ApoE e4 gene dose is a major risk factor for late (and possibly early) onset AD. Inheritance of two e4 alleles is not necessary and probably not sufficient to cause AD.