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.
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. Hypnogogic hallucinations
4. Abnormal sleep-wake cycle

Figure 3-6 A single gene, periods, 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

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 showing 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 Hcrt Activation:

2. Cholinergic Brainstem and Basal Forebrain: cause sleepiness associated with narcolepsy.
3. Dense Hcrt Projections to the Suprachiasmatic Nucleus: reduced amplitude of circadian sleep rhythms, and thereby increased sleepiness during the day and interrupted sleep at night.

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.

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).
   - \textit{Tsien \textit{et al.}} use cre/loxP recombination system to delete NMDA receptor function only in CA1 subregion.
   - \textit{Thus:} By effecting CA1-specific NMDA receptor inactivation, the studies relate synaptic plasticity to neuronal activity (place fields) and its spatial learning.
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.

Hypothetical Transmission of Autism Predisposing Alleles

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.
Heritability of Psychiatric Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Heritability</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>

Alzheimer’s Disease is currently the best example of a complex disease with known genetic etiology.

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

Richard P. Ebstein\(^1,3\), Olga Novick\(^2\), Roberto Umansky\(^3\), Beatrice Priel\(^2\), Yaminia Osher\(^2\), Darren Blaine\(^1\), Estelle R. Bennett\(^1\), Lubov Nemanov\(^1\), Miri Katz\(^1\) & Robert H. Belmaker\(^2\)

Alzheimer’s Disease

1. Degenerating disorder of the CNS leading to a progressive decline in memory, reasoning, judgment and orientation
2. Affects 2-6 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 36 will suffer some form of dementia.  

Etiology of Alzheimer’s Disease

1. Classically: considered non-genetic
2. Affects: 1 in 10 over age of 65, 1 in 3 over age of 65
3. Epidemiology Studies: Increased risk among relatives of patients with A.D.
4. Pedigrees: Autosomal dominant form of inheritance usually characterized by early age of onset (Familial Alzheimer’s Disease)
**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.

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**Table 1. Genetic susceptibility loci in Alzheimer 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 Volga 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 - 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.