**Single Genes can modify behavior: Worms; Flies; Mice: Humans**

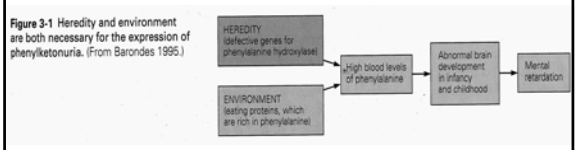



**Figure 3-1** Heredity and environment are both necessary for the expression of phenylketonuria. (From Barondes 1995.)

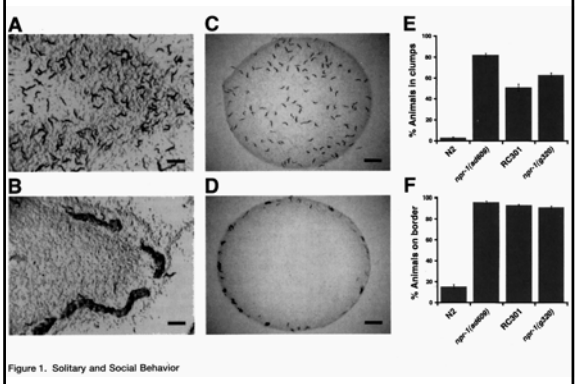
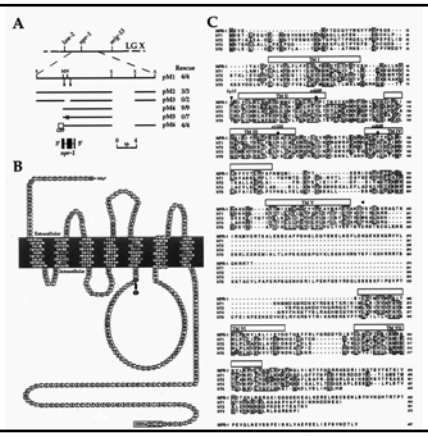



Figure 1. Solitary and Social Behavior




**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.

- **<u>Proposed Model:</u>**

**Dispersing strains have a repellant response (mediated by NPR-1 receptor) that masks the attractant response.**

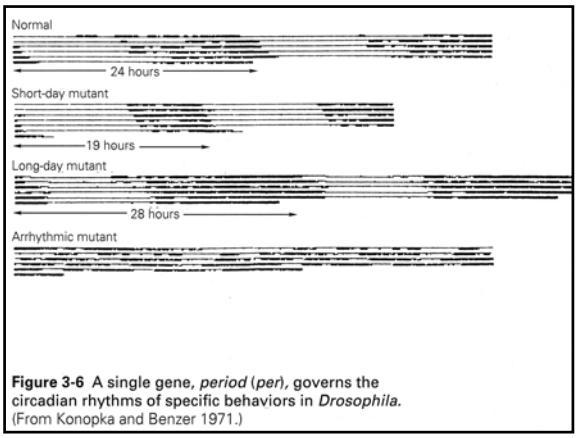
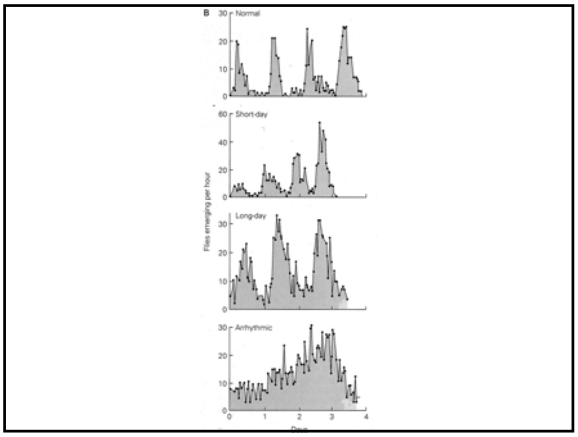
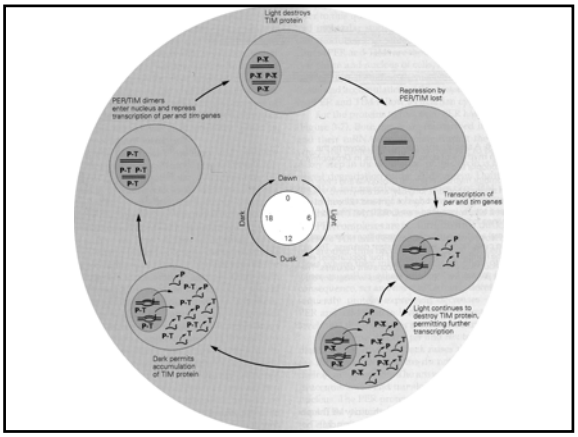


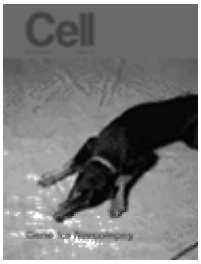

**Figure 3-6** A single gene, *period* (*per*), governs the circadian rhythms of specific behaviors in *Drosophila*. (From Konopka and Benzer 1971.)




**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.**

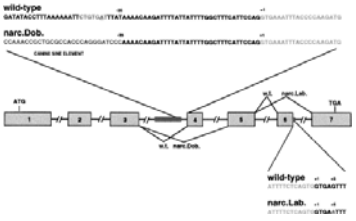
*RM Chemelli et al., Cell 98, 437 1999*

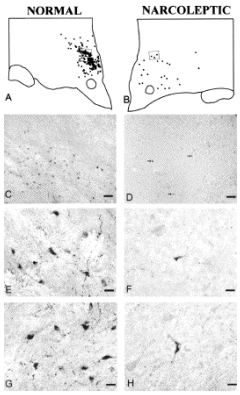
**Narcolepsy: debilitating, neurological disorder characterized by:**

1. **Sleep attacks**
2. **Episodic loss of muscle tone (cataplexy)**
3. **Hypnogogic hallucinations**
4. **Abnormal sleep-wake cycle**

**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 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 *Hcrt* Activation:

1. Monoaminergic Nuclei of the Brainstem: induce cataplexy.
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:

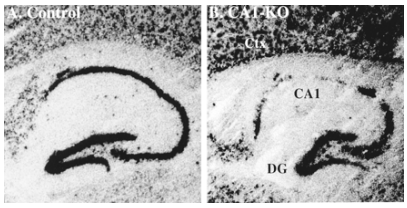
1. **Required for certain kinds of memory; spatial in rodents; facts and faces in humans.**
2. **Rodent hippocampal neurons are "place cells"; 'fire' when animal moves into marked area.**
3. **Hippocampal synapses exhibit LTP (paradigm for synaptic plasticity).**

– ***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 MNDA Receptor-Dependent Synaptic Plasticity in Spatial Memory**

***JZ Tsien, PT Huerta, and S. Tonegawa, Cell 87 1327 1996.***




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

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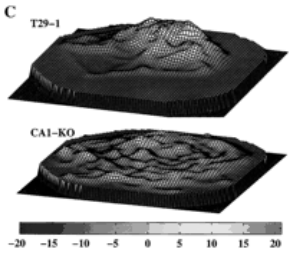


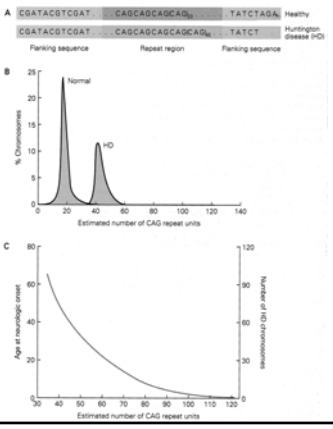
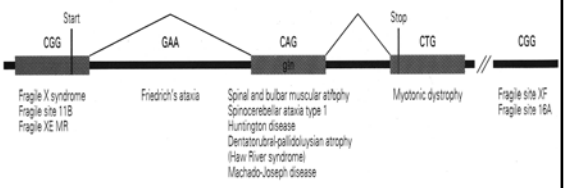




**Table 3-1** Neurological Diseases Involving Trinucleotide Repeats[1]

| Disease | Repeat | Repeat length[2] | Gene product |
|---|---|---|---|
| X-linked spinal and bulbar muscular atrophy | CAG | Normal: 11–34<br>Disease: 40–62 | Androgen receptor |
| Fragile X mental retardation[3] | CGG | Normal: 6 to ~50<br>Premutation: 52–200<br>Disease: 200 to >1000 | FMR-1 protein |
| Myotonic dystrophy[3] | CTG | Normal: 5–30<br>Premutation: 42–180<br>Disease: 200 to >1000 | Myotonin protein kinase |
| Huntington disease | CAG | Normal: 11–34<br>Disease: 37–121 | Huntingtin |
| Spinocerebellar ataxia type 1 | CAG | Normal: 19–36<br>Disease: 43–81 | Ataxin-1 |
| FRAXE mental retardation[3] | GCC | Normal: 6–25<br>Disease: >200 | ? |
| Dentatorubral-pallidoluysian atrophy | CAG | Normal: 7–23<br>Disease: 49–75 | ? |




**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**

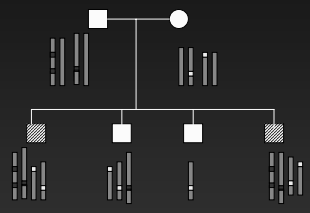
- **Approximately 3% of affected probands have an affected sibling with autism (15% for autism + spectrum).**
- **Relative risk**
- **Recurrence risk/prevalence**
- **50-100 fold increase risk to first-degree relatives compared to general population.**

## Genetics of Autism

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

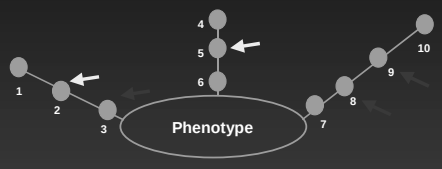
**Interpretation:** **Autism is strongly influenced by genetic factors; multiple genes contribute; each single gene effect is probably small; epistatic interactions are likely.**

## Hypothetical Transmission of Autism Predisposing Alleles

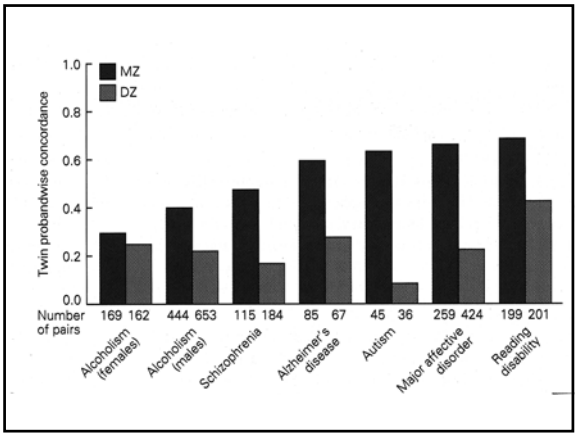


Paternal predisposition allele
Maternal predisposition allele
Autism
Unaffected

## 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*

| | |
|---|---|
| **Schizophrenia** | **50-60%** |
| **Bipolar Disorder** | **60-70%** |
| **Panic Disorder** | **30-40%** |
| **Obsessive-Compulsive Disorder** | **60-80% (small studies)** |
| **ADHD** | **60%** |
| **Reading Disability** | **50%** |
| **Autism (+ spectrum)** | **90%** |
| **Personality** | **40-60%** |
| **Nicotine Addiction** | **50% for initiation, 70% for 10 yr. persistence** |

## 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[2], Beatrice Priel[2], Yamima Osher[2], Darren Blaine[1], Estelle R. Bennett[1], Lubov Nemanov[1], Miri Katz[1] & Robert H. Belmaker[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

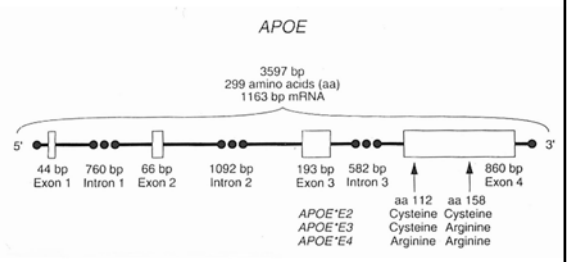
1. Classically: considered non-genetic
2. Affects: 1/10 over age of 65, 1/3 over age of 85
3. Epidemiology Studies: increased risk among relatives of patients with A.D.
4. Pedigrees: Autosomal dominant form of inheritance usually characterized by and early age of onset (Familial Alzheimer's Disease).

**TABLE 1. Genetic susceptibility loci in Alzheimer disease**

| Chromosome | Gene | Onset | Proportion of cases (%) | Comments |
|---|---|---|---|---|
| 1 | Presenilin II | Early | <1 | Mainly Volga German |
| 14 | Presenilin I | Early | <5 | Autosomal dominant |
| 19 | APOE | Both | 40-50 | Dose effect on risk |
| 21 | APP | Early | <<1 | Autosomal dominant |
| ? | ? | Late | =50 | Unknown number of genes |

## 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 mobolization and redistribution of cholesterol and phospholipid during membrane remodeling associated with plasticity of synapses.



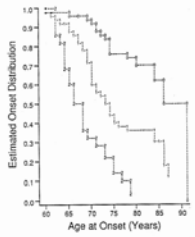




FIG. 1. Age of onset for subjects in late-onset Alzheimer disease families with zero, one, and two APOE4 alleles. Each curve is labeled with the number of inherited APOE4 alleles. An asterisk indicates multiple diagnoses within a short interval. Onset curves were estimated by Kaplan–Meier product limit distributions (SAS Institute Inc.). For example, at age 75, an estimated 24% of subjects without APOE4 were diagnosed with AD compared to 61% of subjects with one APOE4 allele and 86% of subjects with two APOE4 alleles. Note that there is a dose-dependent effect of each APOE4 allele. [Reprinted from Corder *et al.* (5). © 1988 by the AAAS.]

## 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 <u>and</u> 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**

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