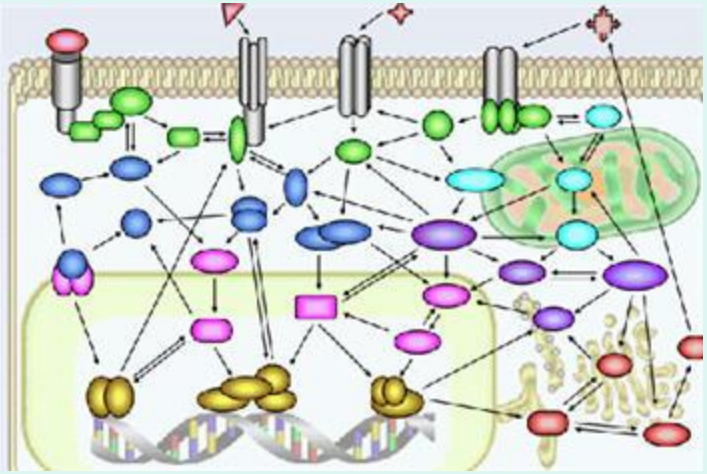
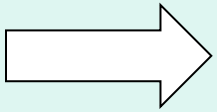
Psych 3102
Introduction to Behavior genetics

Lecture 13

Identifying genes for behavioral traits





SCIENCE

Scientists Discover Gene Responsible For Eating Whole Goddamn Bag Of Chips

ITHACA, NY—In an announcement with major implications for future generations of big fat hogs, Cornell University geneticists announced Monday that they have isolated the specific DNA series that makes an individual susceptible to eating a whole goddamn bag of chips.

"We have long known that the tendency to sit down and eat the whole goddamn bag runs in certain families," said team leader Dr. Edward Alvaro. "However, until we completed our work, we weren't sure whether the disposition to cram chips down your greasy gullet was genetic or whether it was a behavioral trait learned from one or both fat-fuck parents. With the discovery of gene series CHP-48/OZ-379, we have proof positive that single-case serial chip-eating is indeed hereditary."

Above: According to Cornell researchers, the tendency to eat a whole goddamn bag of chips (above) may be genetic.

For years, scientists have been aware of the numerous health complications linked to a person's predisposition to plop down and mow through a whole bag of chips, but it wasn't until now that they were able to isolate the gene that carries the trait.

According to the Cornell team, series CHP-48/OZ-379 is a set of "alleles," or collections of genetic material, that cause chip-eaters to develop a markedly larger number of chip-responsive nerve endings in their cerebral material.

"People with this gene have up to four times the amount of fritoceptors normally found in a human," Alvaro said. "This increases their pleasure response to snaxamine-2, the human body's principal chip-eating hormone, which is released in response to giant handfuls of chips being shoveled into the mouth. This tends to promote entire-goddamn-bag-eating behavior in those individuals who possess the series."

One of the most interesting characteristics of the newly discovered series, researcher Dr. Paul Bergleiter said, is its tendency to appear more than once in the gene strands of a human subject.

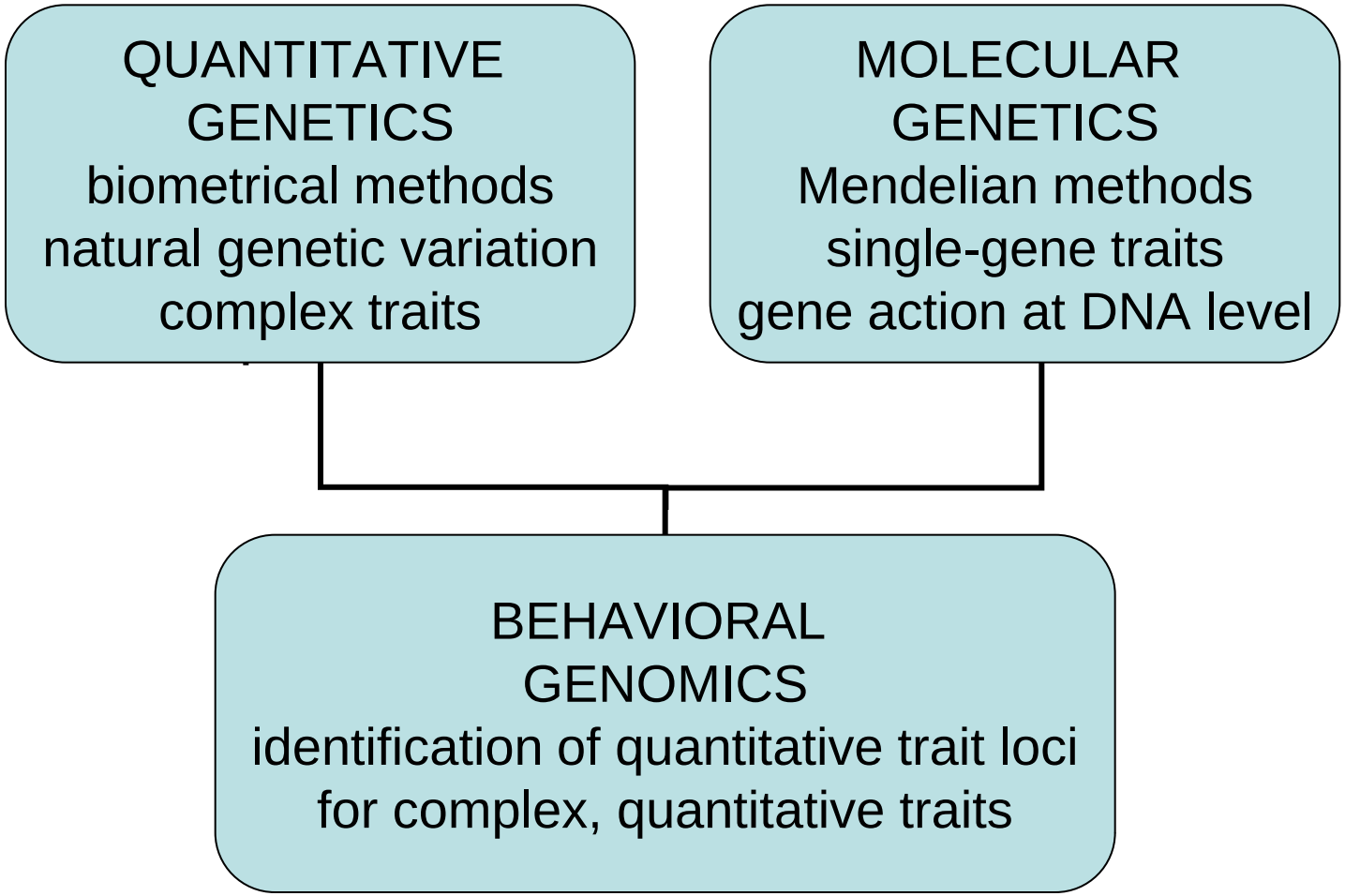
"Series CHP-48/OZ-379, because it is a fairly large, or 'fat-assed,' allele, tends to just lie around at convenient sites on the DNA sequence," Bergleiter said. "Though many subjects exhibit only one instance of this gene, on others we have found as many as four. This, of course, led these rather rare subjects to eat four times as many whole goddamn bags of chips as those in our control group."

Though many more fatsos must be studied to determine CHP-48/OZ-379's transmission pattern, conventional wisdom seems to indicate that the gene is recessive.

"Who would want to pass on their own intact genetic material to someone who just sat around eating chips all goddamn day?" Bergleiter asked. "Unless, of course, that was the only person you could find because you were such a big lard-ass yourself. That would probably be the only source of friendly RNA-transcriptive culture you could find."

Carriers of the CHP-48/OZ-379 gene are hailing the Cornell find.

- towards behavioral genomics



positional cloning

quantitative trait locus (QTL

Behavior across the living kingdoms

Bacteria prokaryote

flagella

positive & negative taxes

chemotaxis phototaxis

- most genes found control rotation of flagella

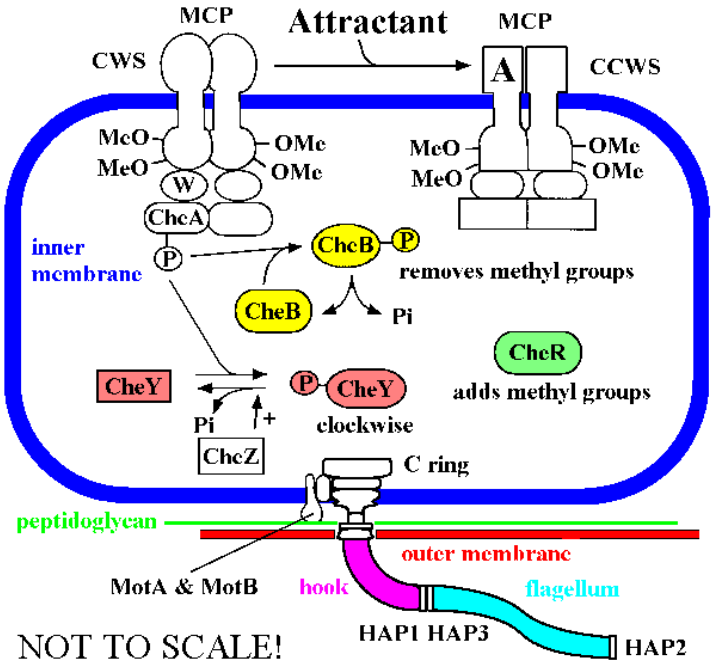
Paramecium eukaryote

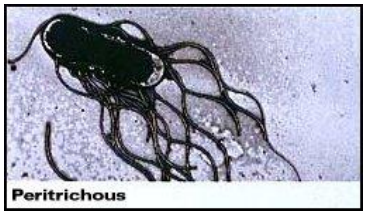
Protist cilia, flagella

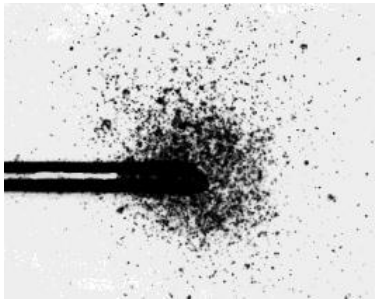
positive, negative chemotaxis

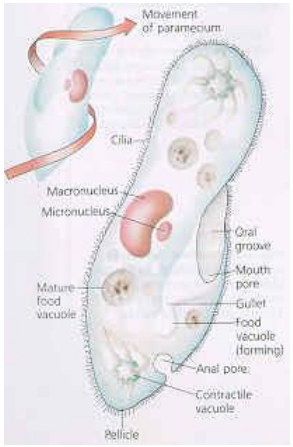
- 20 genes involved in avoidance of noxious chemicals, heat

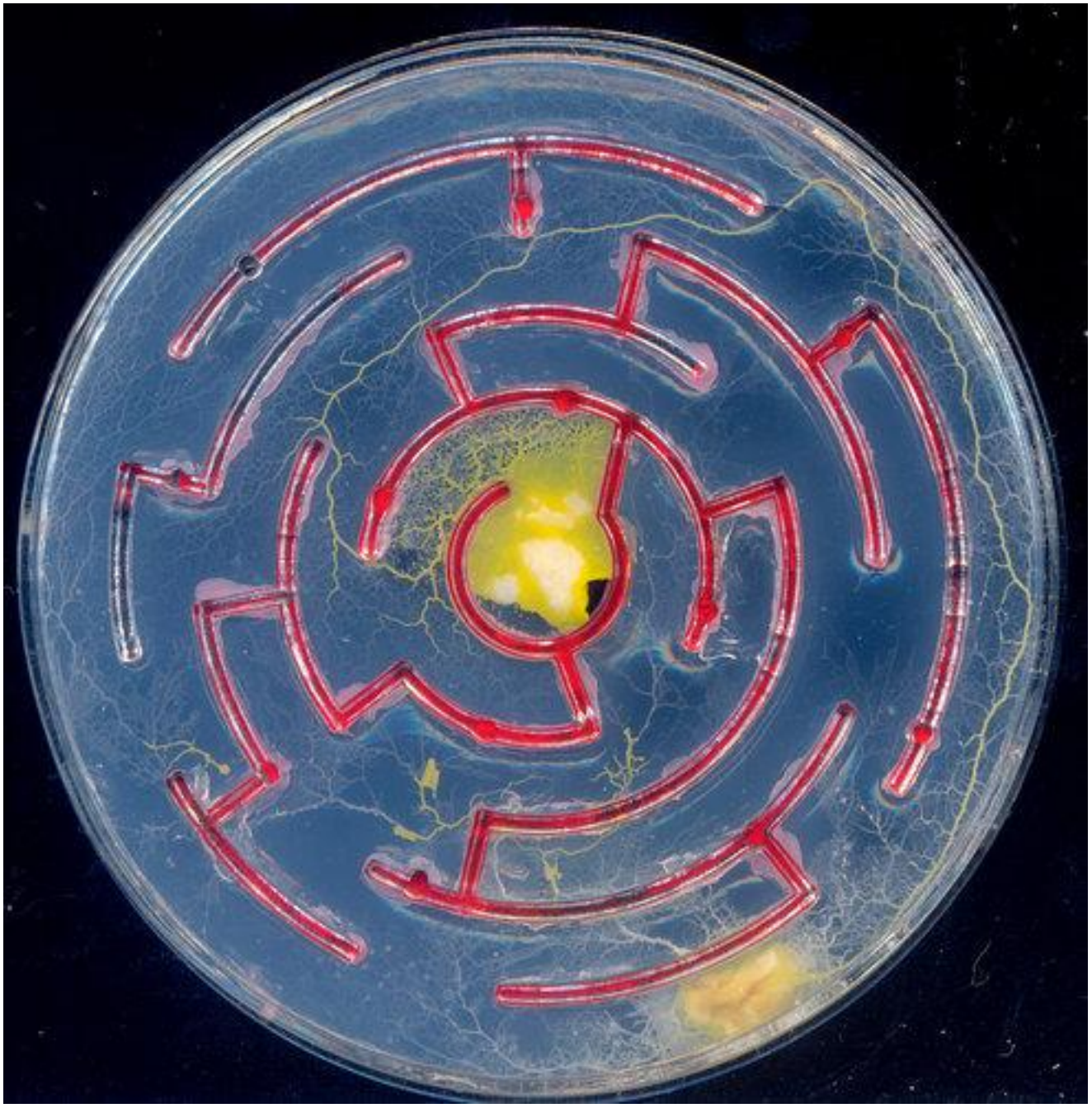
mutagenesis











Slime mold finding oat flake in center of maze

What is a slime mold?

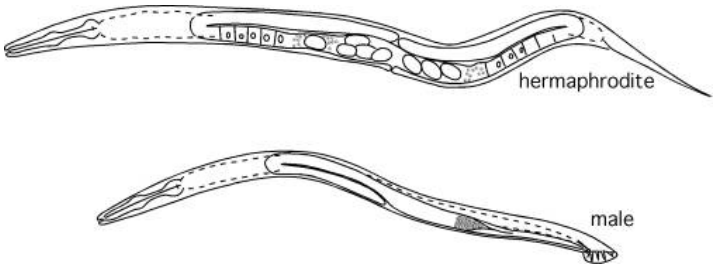
What type of behavior is this?

Positive chemotaxis

C. elegans Nematode (roundworm) induced mutations transgenics

6 chromosomes XO= male, produces sperm XX=hermaphrodite(eggs and sperm)

1mm long, 3 week lifespan



Caenorhabditis elegans (Nematode)

Worm Project 1990 - 1998

97 Mb - 19.000 Genes

1024 cells - 302 nerve cells

402 gene clusters

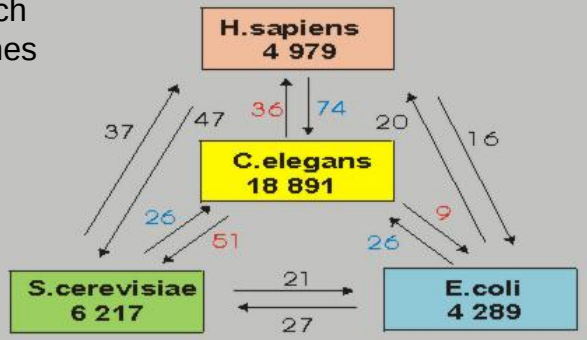
25% of genes in operons

Matches:

42% to predicted functions

34% only to nematode proteins

50% C.elegans genes match human genes



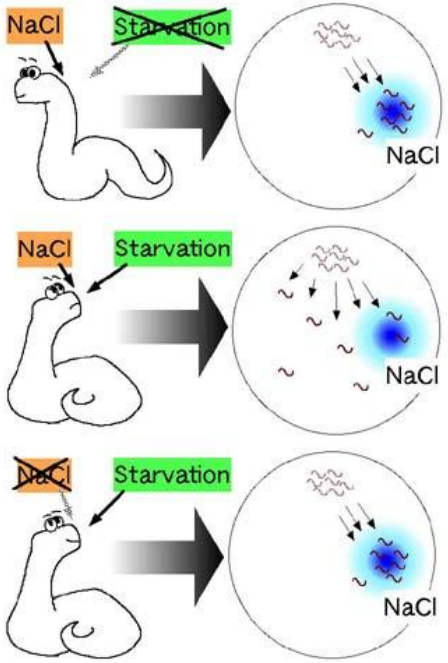
Pathogenic Relatives:

Ascaris lumbricoides (gut roundworm) 1 Bio people infected

Ancylostoma duodenale (hook-worm) 600 Mio people infected

Trichinella spiralis (pork trichina worm)

Xiphinena & Trichodorus sp.(transferring viruses to plant roots)



foraging, locomotion, associative learning behaviors only

ARTICLE

doi:10.1038/nature09821

Catecholamine receptor polymorphisms affect decision-making in *C. elegans*

Andres Bendesky[1], Makoto Tsunozaki[1], Matthew V. Rockman[2], Leonid Kruglyak[3] & Cornelia I. Bargmann[1]

Innate behaviours are flexible: they change rapidly in response to transient environmental conditions, and are modified slowly by changes in the genome. A classical flexible behaviour is the exploration–exploitation decision, which describes the time at which foraging animals choose to abandon a depleting food supply. We have used quantitative genetic analysis to examine the decision to leave a food patch in *Caenorhabditis elegans*. Here we show that patch-leaving is a multigenic trait regulated in part by naturally occurring non-coding polymorphisms in *tyra-3* (*tyramine receptor 3*), which encodes a G-protein-coupled catecholamine receptor related to vertebrate adrenergic receptors. *tyra-3* acts in sensory neurons that detect environmental cues, suggesting that the internal catecholamines detected by *tyra-3* regulate responses to external conditions. These results indicate that genetic variation and environmental cues converge on common circuits to regulate behaviour, and suggest that catecholamines have an ancient role in regulating behavioural decisions.

Despite abundant evidence for heritability of behavioural traits within and between species, only a few naturally varying traits have been associated with polymorphisms in specific genes[1]. Foraging for food is an ecologically relevant, environmentally regulated behaviour that is suitable for genetic analysis, as it can differ between populations of a species that live in different habitats[2]. An essential foraging decision is the choice between exploiting existing resources and exploring other options that may provide new resources. This decision can be described by Charnov's marginal value theorem, which proposes that the optimal time for an animal to leave a foraging ground occurs when local resource levels fall below the average level in the entire habitat[3]. The marginal value theorem was developed for animals foraging for food in patchy environments, but has analogies with diverse decision-making processes in field biology, cognitive neuroscience and economics[2,4–6].

Studies of patch-leaving behaviour in the nematode *C. elegans* have revealed innate, environmental and experience-dependent factors that affect its foraging decisions. *C. elegans* rarely leaves a dense lawn of high-quality bacterial food[7,8], but more frequently leaves lawns of pathogenic bacteria or lawns that are spiked with chemical repellents[9,10]. Males will leave lawns that do not contain potential mates[11], while hermaphrodites leave lawns when animal density is high[12]. In addition, wild-type strains vary in their propensity to leave bacterial lawns based on a genetic polymorphism that affects the G-protein-coupled neuropeptide receptor NPR-1 (refs 12–14). This *npr-1* polymorphism affects many foraging behaviours; low-activity *npr-1* strains aggregate into social feeding groups, move quickly on food, and have altered responses to oxygen, carbon dioxide and pheromones compared to the N2 laboratory strain[15–20]. The high-activity allele of *npr-1* in N2 arose in the laboratory, probably as an adaptation to laboratory conditions[19], so it is not known whether genetic variation affects *C. elegans* foraging in natural environments.

Natural genetic variation within a species can generate diversity in foraging behaviour, as exemplified by the polymorphic *Drosophila melanogaster foraging* (*for*) gene, which encodes a cyclic guanosine monophosphate (cGMP)-dependent protein kinase[21]. A low-activity allele of *for* is present in *Drosophila* sitter larvae, which move slowly on a food patch; a high-activity allele of *for* is present in rover larvae, which move quickly and disperse rapidly[22]. A *for*-related cGMP-dependent kinase affects foraging in honeybees, ants and nematodes, suggesting that diverse animals share molecular mechanisms for behavioural regulation[23,24].

To gain further insight into the genetics and neurobiology of exploratory behaviour in *C. elegans*, we here use quantitative genetic analysis to examine this behaviour's genetic architecture in wild-type strains, and show that genetic variation in multiple loci, including a catecholamine receptor, interacts with environmental conditions to regulate the exploitation–exploration decision.

Multiple loci affect leaving behaviour

Different wild-type strains of *C. elegans* vary in their tendency to leave or remain on a standardized small lawn of bacterial food (Fig. 1a). For example, adult hermaphrodites from the laboratory strain N2 leave the lawn only once every 100 min, whereas animals from the CB4856 (HW) strain isolated from pineapple fields in Hawaii leave the lawn once every 5–6 min (Fig. 1b, Supplementary Movies 1 and 2). To determine the genetic architecture of this behavioural difference between N2 and HW, we quantified leaving rates in 91 N2-HW recombinant inbred advanced intercross lines (RIAILs)[24]. 58 of the RIAILs had low leaving rates comparable to N2, only 6–10 had high leaving rates comparable to HW, and 23 had intermediate rates (Fig. 1c). The excess of low leaving rates and the continuous behavioural distribution in RIAILs suggest that leaving is a multigenic quantitative trait.

Quantitative trait locus (QTL) analysis of the RIAILs uncovered two regions with significant effects on leaving rates, one on the X chromosome and one on chromosome II (Fig. 1d). The X chromosome QTL overlapped with the location of the polymorphic G-protein-coupled neuropeptide receptor NPR-1, which affects many food-related behaviours[12,15]. The *npr-1* polymorphism has previously

[1]Howard Hughes Medical Institute, Laboratory of Neural Circuits and Behavior, The Rockefeller University, New York, New York 10065, USA. [2]Department of Biology and Center for Genomics and Systems Biology, New York University, New York, New York 10003, USA. [3]Howard Hughes Medical Institute, Lewis-Sigler Institute for Integrative Genomics and Department of Ecology and Evolutionary Biology, Carl Icahn Laboratory, Princeton University, Princeton, New Jersey 08544, USA.

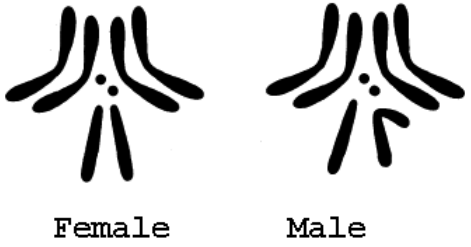
Drosophila Arthropod, Insect

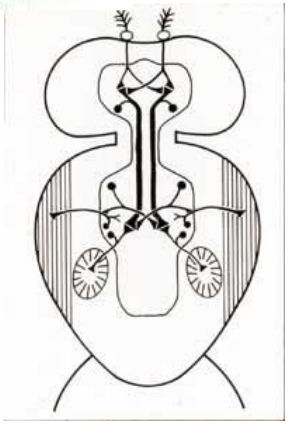
phototaxis, geotaxis

genetic mosaics

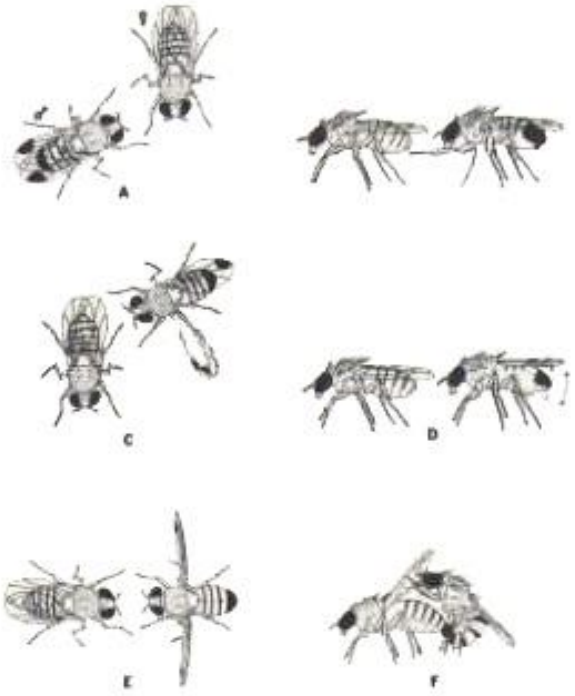
induced mutations

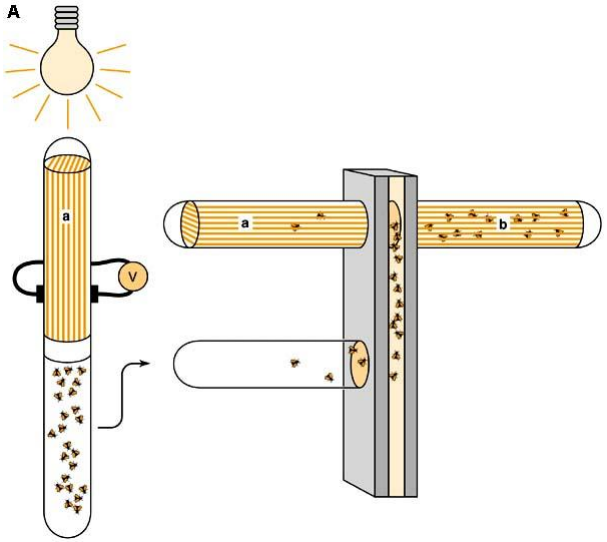
transgenics





courtship





Example of single gene influencing behavior

Gypsy moth caterpillars (Science, September, 2011)

Moth lays eggs on tree, eggs hatch, eat tree leaves, move down tree during daytime to avoid predators

Caterpillars infected with Lymantria virus typically move up tree, die in canopy and virus rains down infecting caterpillars below

How does virus cause this change in behavior?

genome sequencing knock-out

egt gene – virus gene, product inhibits molting, keeps caterpillar moving up tree (normally stops when molting)

Sequencing identified egt gene as suspect

Virus engineered with knock-out egt did not induce climbing like virus with gene intact

Virus with egt gene re-inserted induced climbing again

Mice Mammals

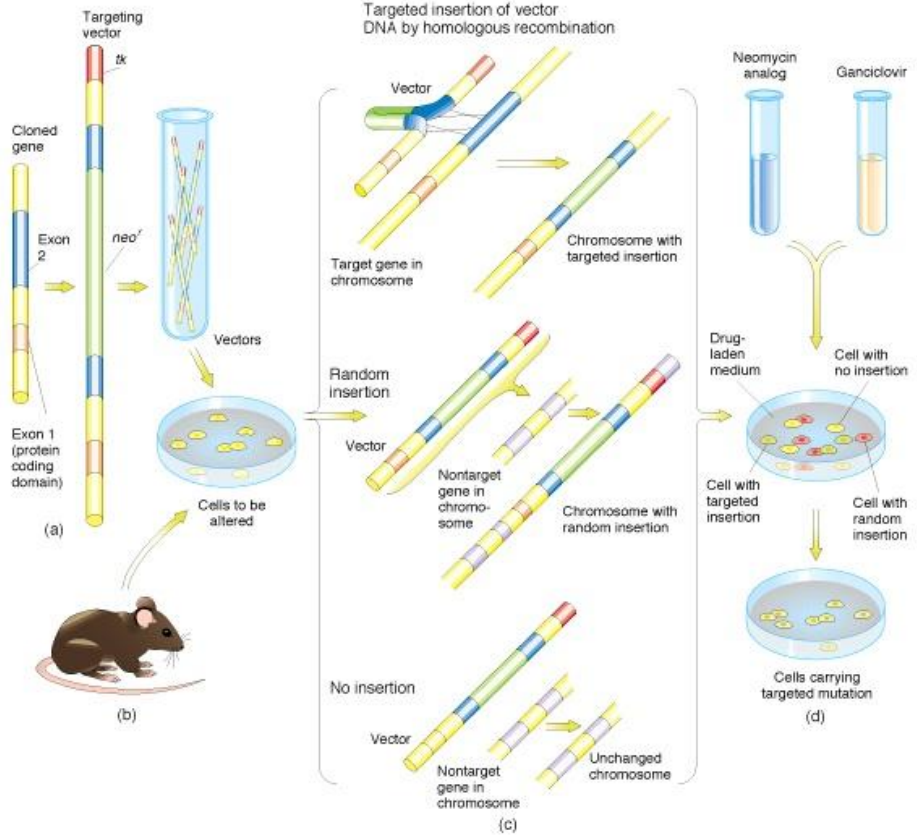
optogenetics - controlled firing of targeted neurons

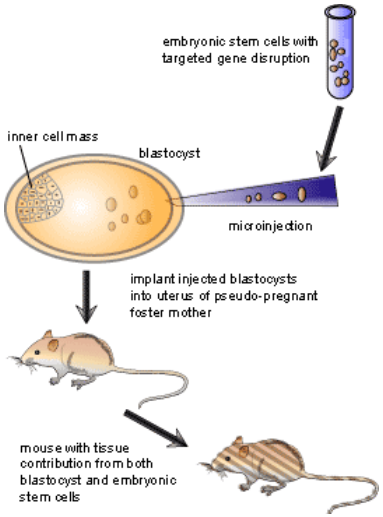
gene targeting methods:

knock-out mutants knock-down (RNAi) conditional knock-outs

transgenics knock-in

long-term memory, aggression





Example of use of transgenic mice
Investigating BDNF locus and risk for anxiety and depression

- Chen et al, Science (2006, 314,140)
- SNP allele in BDNF gene (brain-derived neurotrophic factor)

- previously found to be associated with alterations in brain anatomy (decrease in hippocampus volume) & memory, regulation of synaptic plasticity

- implicated by some studies in anxiety and depression (20-30% of Caucasians have risk allele)

BDNF val66met risk allele introduced into genome of mouse, making transgenic

mice tested for levels of anxiety in open field and other measures

- transgenic mice showed increased levels of stress-related behaviors
- confirms role of gene in anxiety

- not relieved by fluoxetine (Prozac)

- may explain why some humans suffering from anxiety disorder do not respond to fluoxetine

-

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Genetic Variant BDNF (Val66Met) Polymorphism Alters Anxiety-Related Behavior

Zhe-Yu Chen[1,4,†], Deqiang Jing[1,*], Kevin G. Bath[1,*], Alessandro Ieraci[1], Tanvir Khan[1], Chia-Jen Siao[2], Daniel G. Herrera[1], Miklos Toth[3], Chingwen Yang[5], Bruce S. McEwen[6], Barbara L. Hempstead[2], and Francis S. Lee[1,3,†]

1 Department of Psychiatry, Weill Medical College of Cornell University, New York, NY 10021, USA

2 Division of Hematology, Department of Medicine, Weill Medical College of Cornell University, New York, NY 10021, USA

3 Department of Pharmacology, Weill Medical College of Cornell University, New York, NY 10021, USA

4 School of Medicine, Shandong University, Jinan, Shandong 250012, People's Republic of China

5 Gene Targeting Facility, The Rockefeller University, New York, NY 10021, USA

6 Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10021, USA

Abstract

A common single-nucleotide polymorphism in the brain-derived neurotrophic factor (BDNF) gene, a methionine (Met) substitution for valine (Val) at codon 66 (Val66Met), is associated with alterations in brain anatomy and memory, but its relevance to clinical disorders is unclear. We generated a variant BDNF mouse ($BDNF^{Met/Met}$) that reproduces the phenotypic hallmarks in humans with the variant allele. $BDNF_{Met}$ was expressed in brain at normal levels, but its secretion from neurons was defective. When placed in stressful settings, $BDNF^{Met/Met}$ mice exhibited increased anxiety-related behaviors that were not normalized by the antidepressant, fluoxetine. A variant BDNF may thus play a key role in genetic predispositions to anxiety and depressive disorders.

Depression and anxiety disorders have genetic predispositions, yet the particular genes that contribute to this pathology are not known. One candidate gene is BDNF, because of its established roles in neuronal survival, differentiation, and synaptic plasticity. The recent discovery of a single-nucleotide polymorphism (SNP) in the *bdnf* gene (Val66Met), found only in humans, leading to a Met substitution for Val at codon 66 in the prodomain, has provided a valuable tool to assess potential contributions of BDNF to affective disorders. This polymorphism is common in human populations with an allele frequency of 20 to 30% in Caucasian populations (1). This alteration in a neurotrophin gene correlates with reproducible alterations in human carriers. Humans heterozygous for the Met allele have smaller hippocampal volumes (2–4) and perform poorly on hippocampal-dependent memory tasks (5,6). However, in genetic association studies for depression and anxiety disorders, there is little consensus as to whether this allele confers susceptibility.

The mechanisms that contribute to altered $BDNF_{Met}$ function have been studied in neuronal culture systems. The distribution of $BDNF_{Met}$ to neuronal dendrites and its activity-dependent secretion are decreased (6–8). These trafficking abnormalities are likely to reflect impaired binding of $BDNF_{Met}$ to a sorting protein, sortilin, which interacts with BDNF in the prodomain

†To whom correspondence should be addressed. E-mail: zheyuchen@sdu.edu.cn (Z.-Y.C.); fslee@med.cornell.edu (F.S.L.)
*These authors contributed equally to this work

Example: Use of linkage method Flint et al (Science,1995)

A simple genetic basis for a complex psychological trait in lab. mice

Aim: to map QTLs underlying measures of emotionality in mice

Methods

1. made F2 intercross mice from high and low selected lines for open-field activity - this provided optimum spread of genotypes

2. tested 879 of these F2 mice in open field for activity levels

3. genotyped the highest and lowest 10% of these mice (96 mice in each case) using 84 markers spread across mouse genome

4. obtained significant linkage to 6 loci on mouse genome
   - these may be loci that influence activity level in open field ,

   but are they specific just for activity only in open field?

5. bred another 384 F_2 intercross mice
6. obtained various other measures of emotionality by testing these mice
   defecation in open field (r = -.86 with activity)

   entry into open arms of elevated plus maze

   activity in Y maze (dark, enclosed)

7. to control for activity not associated to fear, tested mice for entry into closed arms of elevated plus maze.

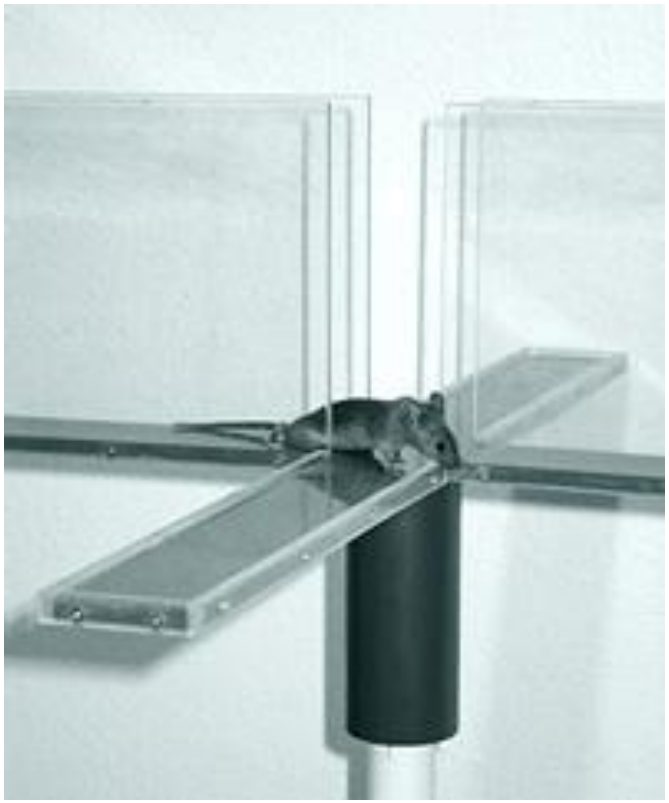
8. genotyped highest and lowest 10% of mice from these tests

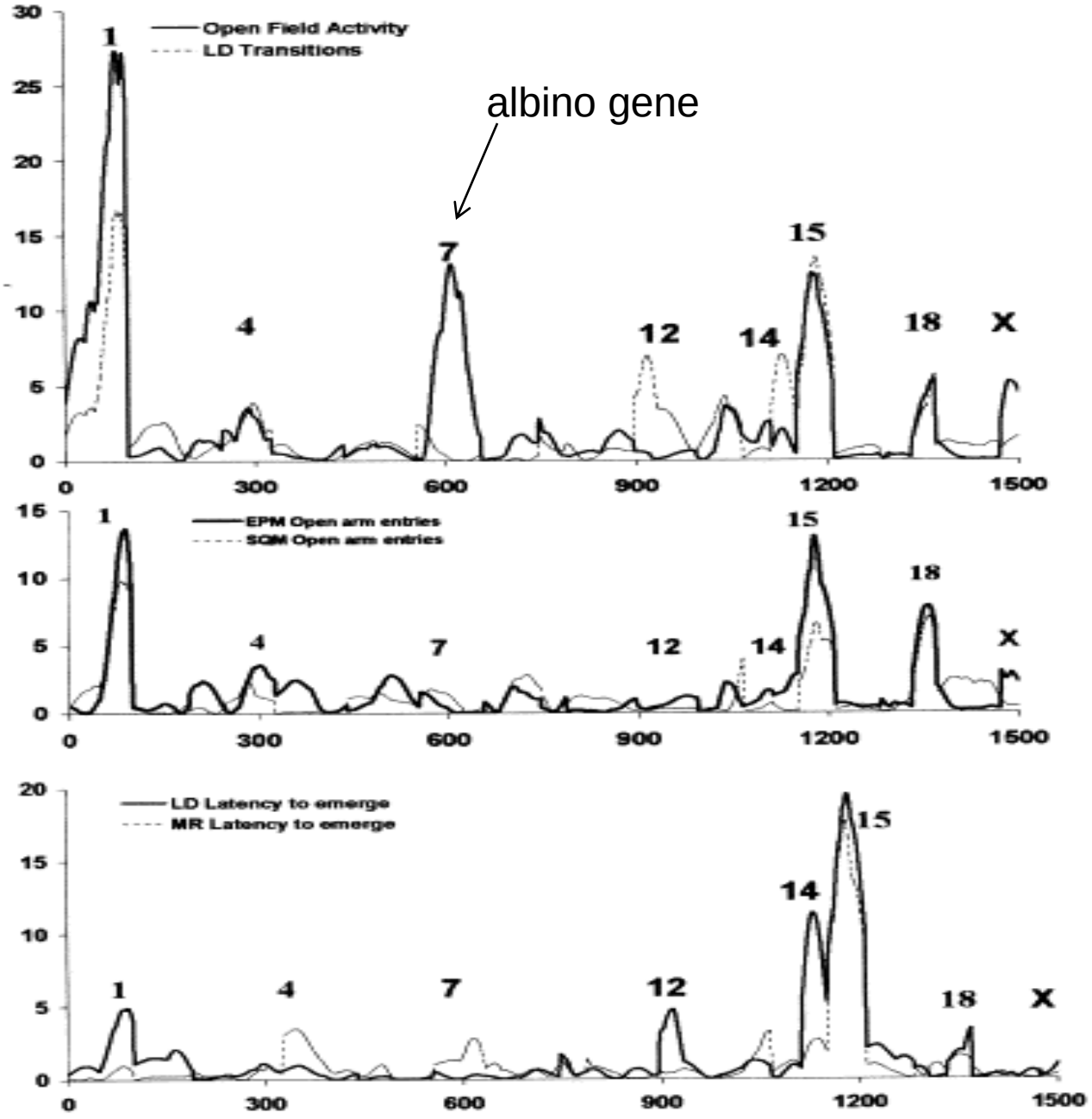
Obtained significant linkage to 3 loci for the correlated measures of emotionality but not the control

- analysis showed these 3 loci accounted for almost ALL of the genetic variation for these measures
- analysis also showed the gene effects were ADDITIVE and independent (no epistasis)

Y maze

Elevated plus maze




albino gene
Open Field Activity
LD Transitions
EPM Open arm entries
SQM Open arm entries
LD Latency to emerge
MR Latency to emerge
1
4
7
12
14
15
18
X
0
300
600
900
1200
1500

Results have been replicated and refined in further studies

Why is this result important? Can we relate it to emotionality (anxiety) in humans? 3 reasons:

1. synteny homology - mouse and human chromosomes are similar in the layout of genes – if we know where a mouse gene is we can locate that same gene in humans much of the time

OK, so mice might have similar genes to humans, but is the trait the same?

2. anxiolytic drug action – drugs that relieve anxiety in humans also work on mice - indicates common neurophysiology

3. electrophysiological and lesion experiments - indicate a common neural substrate between mouse and humans for anxiety