The complicated relationship between genotype to phenotype

Commentary written in response to the release of the first draft of the human genome sequence

From Science Compass August 3, 2001

- Human genome sequencing will reveal thousands of genetic variations among individuals that many will assume are associated with disease or phenotypic variation
- ***But translating such genotypic differences into phenotypic states is prone to pitfalls***
- **for example, genetic abnormalities *differ in their penetrance*; *environmental effect*s have not been taken into consideration; and *many diseases have complex etiologies that depend on variations in a number of different genes***
- There are very few common diseases that are caused by a single gene mutation

http://www.genomesunzipped.org/

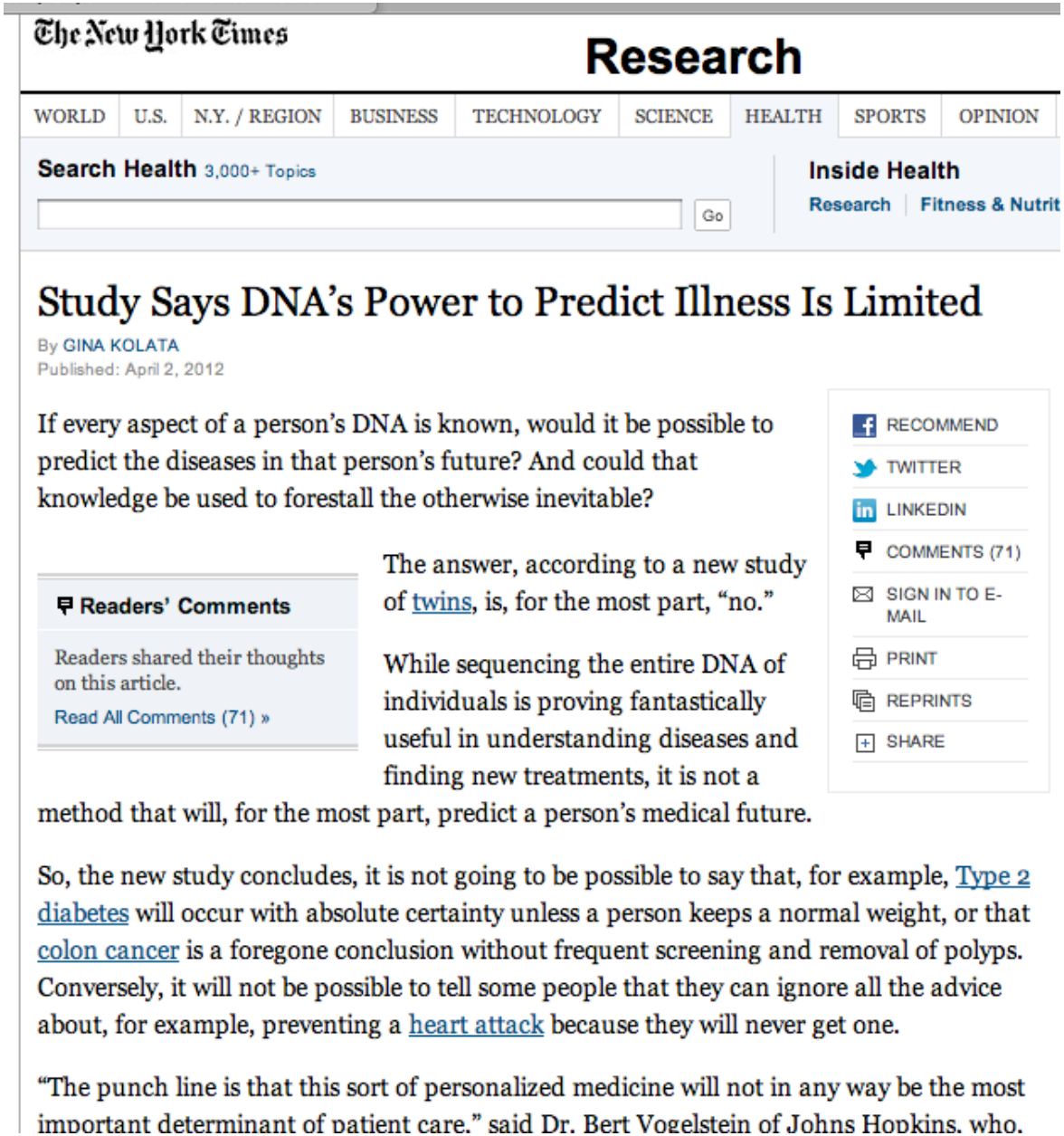
Identical twins usually do not die from the same thing

http://www.genomesunzipped.org/2012/04/identical-twins-usually-do-not-die-from-the-same-thing.php

04/04/2012 Written by Luke Jostins

……People with exactly the same weight, height, sex, race, diet, childhood infection exposures, vaccination history, family history and environmental toxin levels will usually not get the same disease. ***Identical twins, despite sharing the same DNA, the same socioeconomic background, the same childhood environment and (usually) the same bloody placenta, will usually not get the same disease***. There is no health destiny, there is always ***a strong random component*** in anything that happens to your body. This does not mean that none of these things are important; being aware of your disease risks is one of the most important things you can do for your own future health. **But risk is not destiny**.

If there is one take-home message, one bite-sized bit of knowledge that everyone should know about genetic health, it is that ***identical twins usually do not die from the same thing, BUT that they are far more likely to than two random individuals***. This is a perfect analogy for how well (and badly) risk prediction can work: you will never have a better prediction than knowing the health outcomes of essentially another copy of you*. The health outcomes of another version of you will be invaluable, and will help guide you, your doctor and the health-care establishment, if they use this information properly. But it won't let them know exactly what will happen to you, because identical twins usually do not die from the same thing.



The New York Times

Research

WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS | OPINION

Search Health 3,000+ Topics

Go

Inside Health

Research | Fitness & Nutrit

Study Says DNA's Power to Predict Illness Is Limited

By GINA KOLATA
Published: April 2, 2012

If every aspect of a person's DNA is known, would it be possible to predict the diseases in that person's future? And could that knowledge be used to forestall the otherwise inevitable?

Readers' Comments

Readers shared their thoughts on this article.

Read All Comments (71) »

RECOMMEND
TWITTER
LINKEDIN
COMMENTS (71)
SIGN IN TO E-MAIL
PRINT
REPRINTS
SHARE

The answer, according to a new study of twins, is, for the most part, "no."

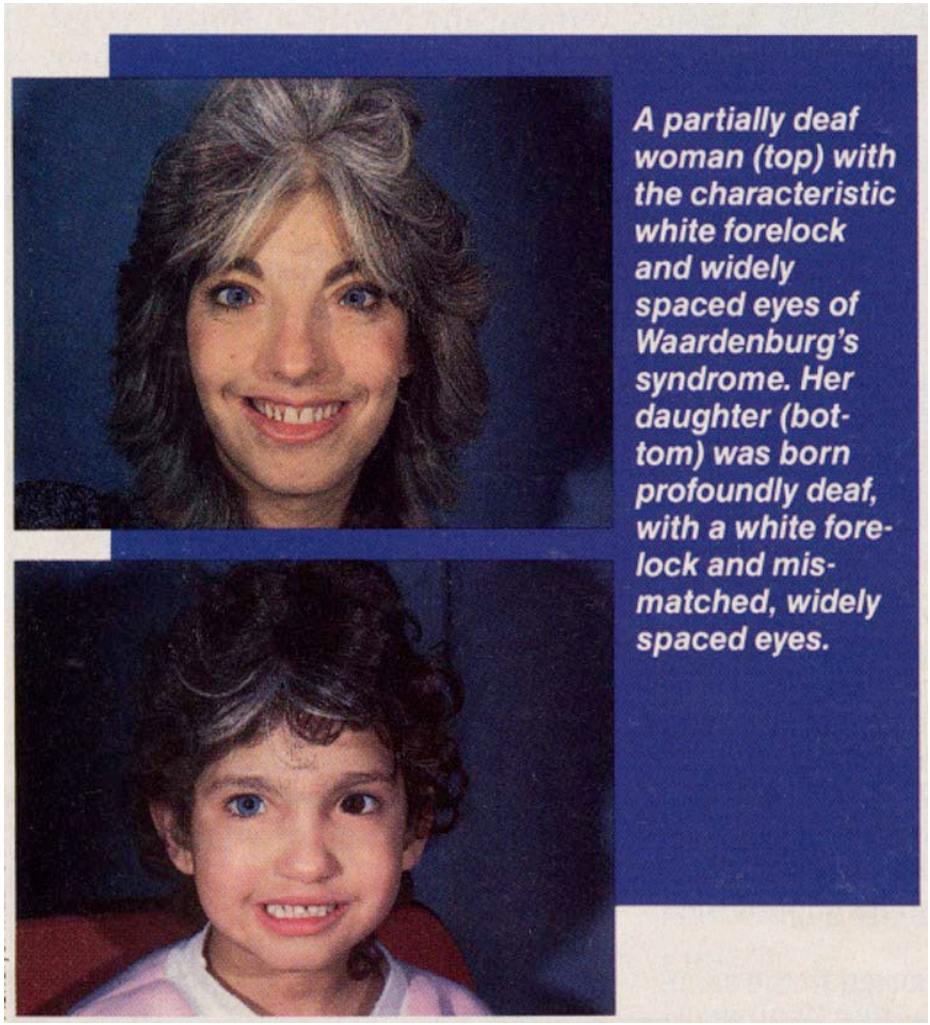
While sequencing the entire DNA of individuals is proving fantastically useful in understanding diseases and finding new treatments, it is not a method that will, for the most part, predict a person's medical future.

So, the new study concludes, it is not going to be possible to say that, for example, Type 2 diabetes will occur with absolute certainty unless a person keeps a normal weight, or that colon cancer is a foregone conclusion without frequent screening and removal of polyps. Conversely, it will not be possible to tell some people that they can ignore all the advice about, for example, preventing a heart attack because they will never get one.

"The punch line is that this sort of personalized medicine will not in any way be the most important determinant of patient care," said Dr. Bert Vogelstein of Johns Hopkins, who,

Start with Phenomenology

Then, where possible, work our way to explanatory mechanisms



Genes that sense gravity in plants may play a role in Waardenburg syndome in humans:
http://fire.biol.wwu.edu/trent/trent/BizarreModels.pdf

The mother and daughter are heterozygous for ***the same dominant mutant allele*** *of the pax-3 gene*

This mutant allele shows ***variable expressivity***

Expressivity: the degree to which a particular genotype is expressed in the phenotype

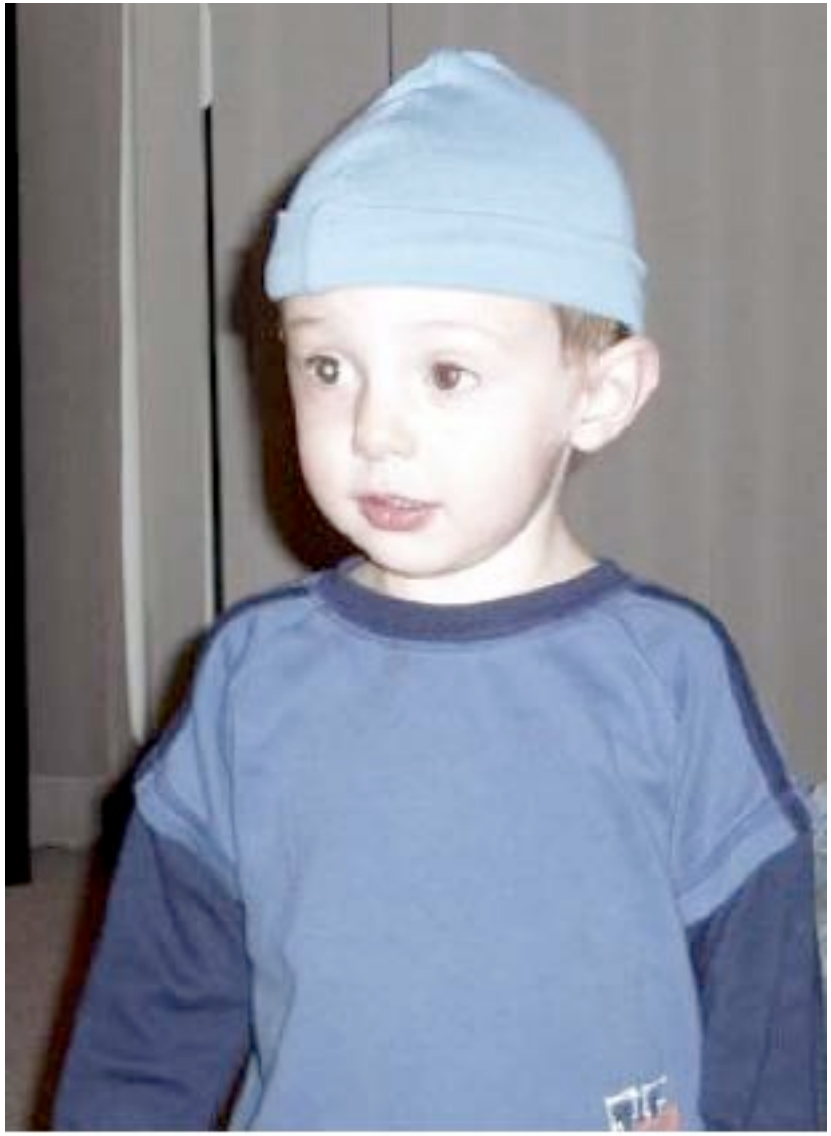
Variable expressivity: a variable phenotype is seen among individuals of the same genotype (with respect to the trait in question)

*→To assess expressivity, you must examine a **two or more** individuals who are the same genotype with respect to the specific gene under examination*

An "extreme" form of variable expressivity:

Penetrance: *the proportion of individuals with a specific genotype who manifest that genotype at the phenotype level*

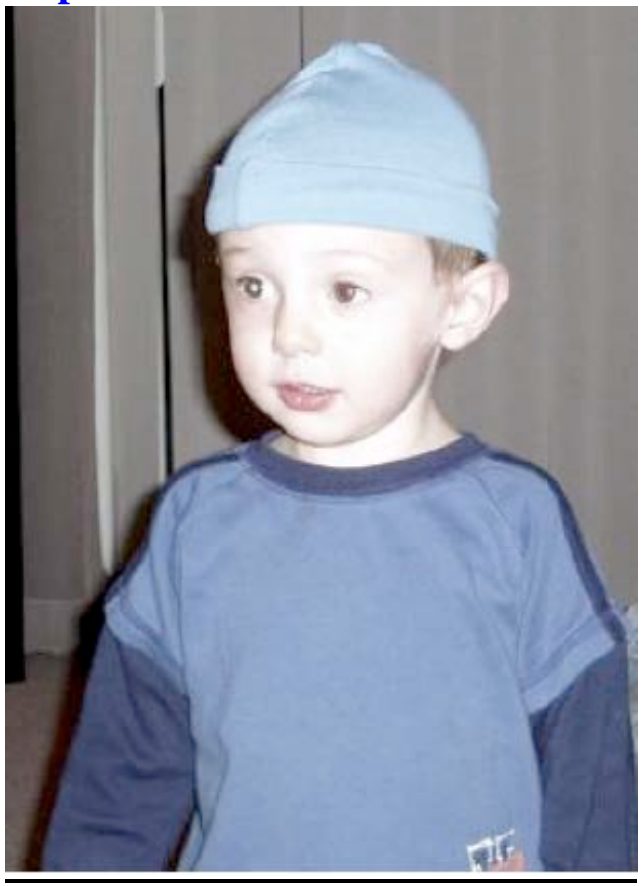
Incomplete penetrance: not every individual of a given genotype shows the expected phenotype; that is, the phenotypic effects of the allele are not always seen in the individual



Attention to detail.

Is there anything unusual in this photo?

http://fire.biol.wwu.edu/trent/trent/JakeMooreRetinoblastoma.pdf



Meet Jake Moore. In Nov (2005) a family friend noticed an odd white reflection in his right eye.

His left eye shows the typical red-eye effect seen when the retina

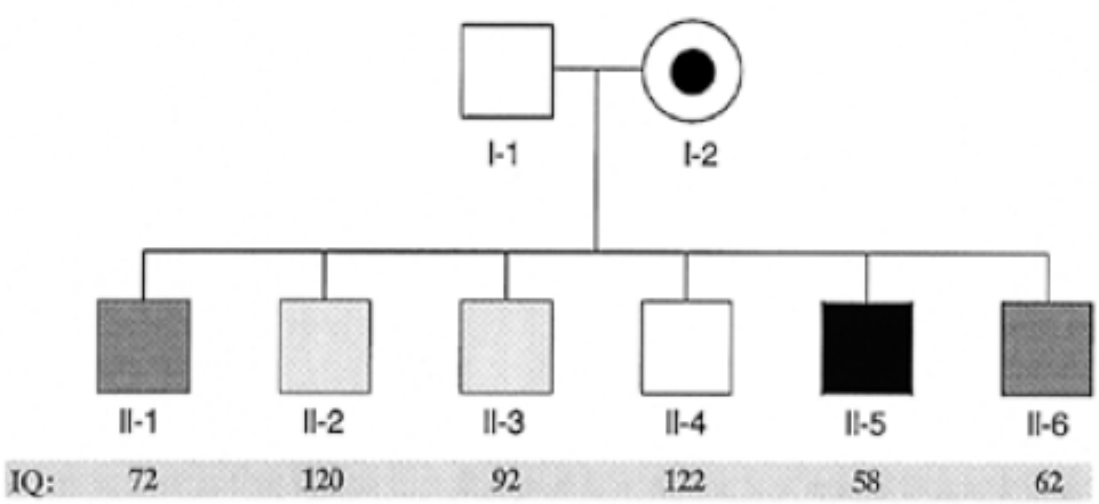
Jake was subsequently diagnosed with retinoblastoma, a pediatric eye cancer that affects 1 in 20,000 children. Jake's right eye already had two advanced tumors

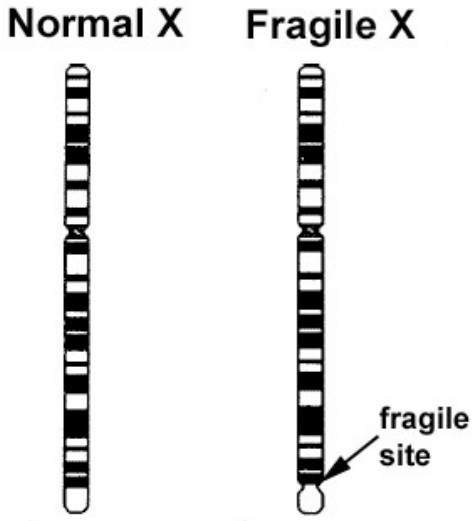
Retinoblastoma in humans

- Tumor of the retina that forms in retinoblasts (retinal stem cells)
- Can be inherited via an autosomal dominant predisposition
- Rb^-= mutant Rb^+= normal
- Rb^+ Rb^+ eye cancers rare (normal)
- **Rb^+ Rb^- 90% of hets get eye cancers (# tumors varies)**
- **Rb^+ Rb^- *10% of hets never get eye cancers***
- mechanism of *incomplete penetrance* known (see below)
- Variable # tumors in affected individuals an example of *variation in expressivity*

Fragile X Syndrome Phenomenology

Fragile X syndrome is one of the most common forms of inherited mental retardation. The syndrome occurs in approximately 1 in 3600 males and 1 in 4000 to 6000 females" (fragilex.org). Fragile X results in apparently normal neurological development, with the effects becoming apparent during early learning (age 3-5). This disease is one of several CAG expansion diseases



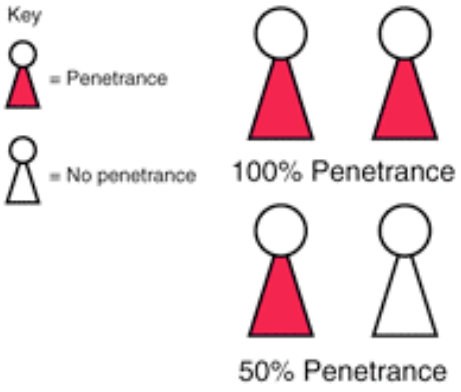


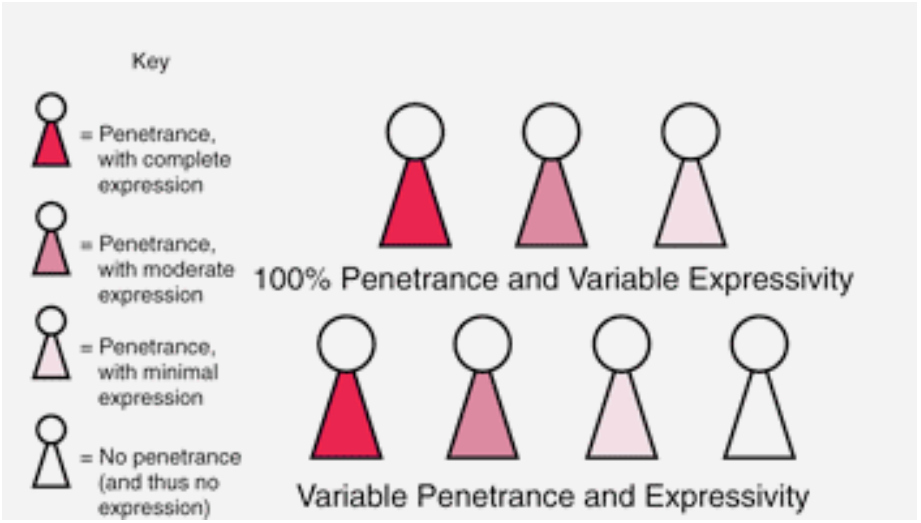
Human Molecular Genetics, 1997, Vol. 6, No. 11 1791–1801

One son (II-4) inherited a normal chromosome and the other five inherited the fragile-X chromosome

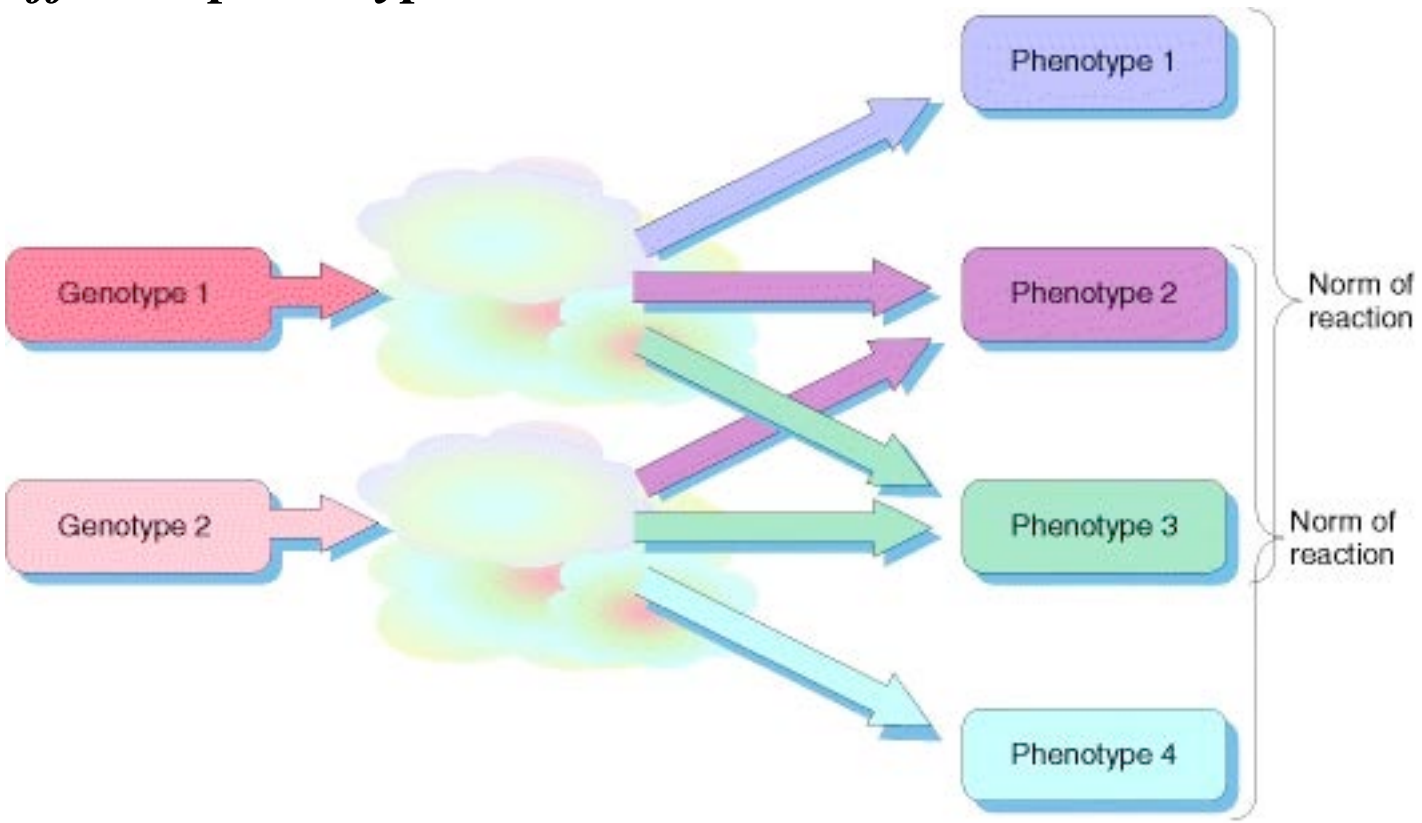
Explore Genetics Home Reference http://ghr.nlm.nih.gov/gene/FMR1

What mechanisms could explain incomplete penetrance and variable expressivity?





How can two individuals with the same genotype (for a particular trait) show different phenotypes?



A **norm of reaction** describes the pattern of phenotypic expression of a single genotype across a range of environments

Mechanisms underlying incomplete penetrance and variable expressivity

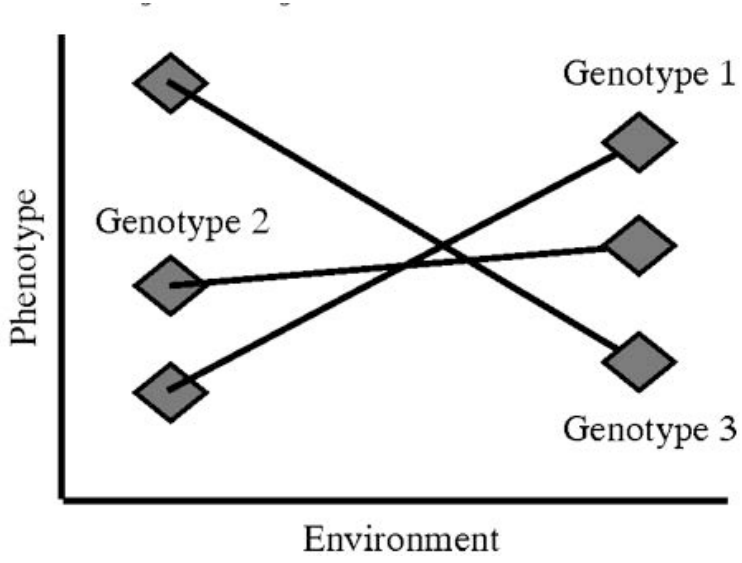
(i) variation in the genetic background in which the genotype in question is expressed: variations in the genotype at other loci (such as at modifier or suppressor loci) can influence the phenotypic expression of a particular trait

(ii) variations in the environment to which the individuals are exposed

(iii) inherent element of randomness (noise) in molecular, biochemical and developmental processes

Phenotypic plasticity:

- *is usually defined as a property of individual genotypes to produce different phenotypes when exposed to different environmental conditions*
- *provides the potential for organisms to respond rapidly and effectively to environmental change*
- *see examples in the Natural History article and also on the following pages: we will not discuss all of them in class.*



An example of genotypic reaction norms illustrating the concept of phenotypic plasticity. In the simple case of two environments, the lines represent the norms of reaction of each genotype, while the slope is a measure of the degree and pattern (positive or negative) of phenotypic plasticity. So, for example, genotypes 1 and 3 are both plastic, but display opposite patterns in response to the same environments; genotype 2, on the other hand, shows little plasticity for this trait in this environmental set.

J Exp Biol 209, 2362-2367 2006

Required Reading: ***The Interpretation of Genes***

The "expression of a genome is best understood as a dialogue with an organism's environment.

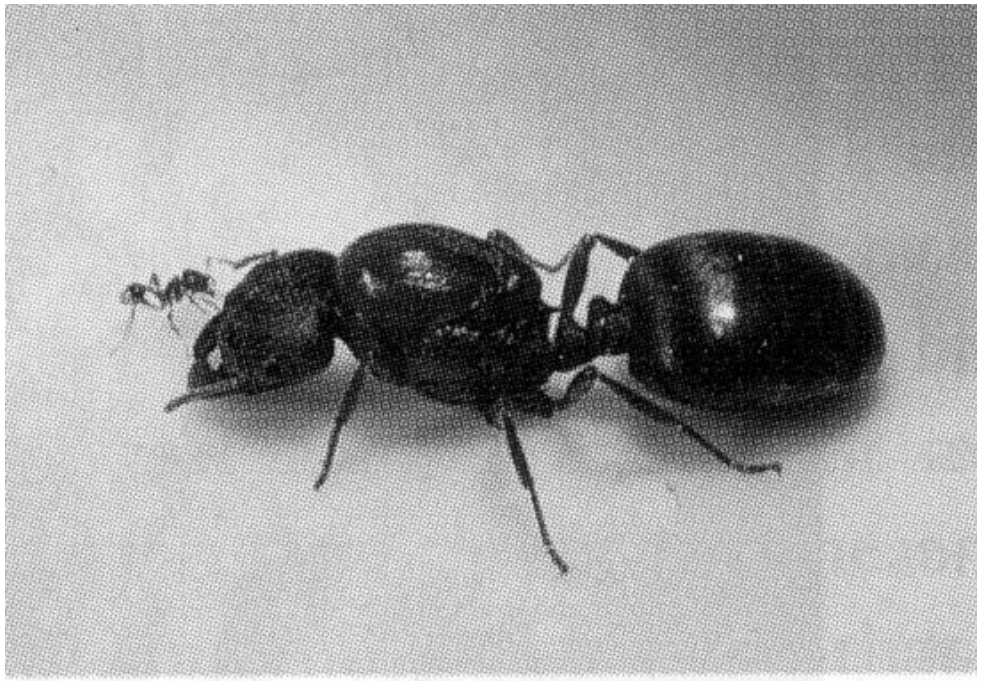
Natural History Oct 2002 pg. 52-58

http://fire.biol.wwu.edu/trent/trent/interpretationofgenes.pdf

Science 294: 321 Oct 12, 2001

These water fleas are genetic clones:

- **the animal on the left was exposed to chemical cues from predaceous fish**
- **the animal on the right was a control**
- **The sharp helmet and extended tail spine of the flea on the left protects it from predators**



from Natural History article referenced above

These sisters are 75% identical in genotype

Whether they become soldiers, workers or queens depends on a set of environmental cues -- food, temperature and light

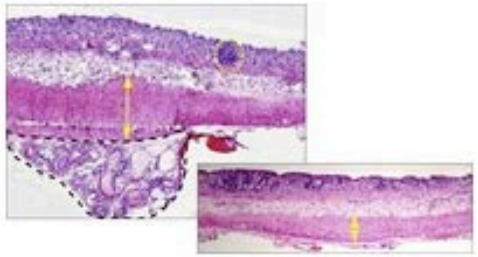
Science NOW UP TO THE MINUTE NEWS FROM SCIENCE

Recipe for Disease: A Gene and a Virus

by Jennifer Couzin-Frankel on June 24, 2010 4:34 PM | Permanent Link | 4 Comments

Many of us carry genes for diseases that we'll never get. Take Crohn's disease, an autoimmune disorder that attacks the digestive system: Well over half the population harbors at least one genetic variant linked to Crohn's, but just a fraction of them currently have it. Scientists have known for a long time that environmental triggers help explain this discrepancy, but they don't know exactly how. Now, a chance discovery in mice shows that when animals with a particular Crohn's gene are exposed to a specific virus, they develop features similar to those in people with the disease—the first time scientists have noted that genes and environment have intersected in this way in Crohn's. Scientists hope that the finding is just the beginning of many that will show how genes and environment combine in specific ways to produce all sorts of chronic diseases.

ENLARGE IMAGE



Double punch. Mice needed both a gene and a virus to develop symptoms of Crohn's disease in their intestines (*left*, arrow shows thickening of smooth muscle); animals with just the bad gene stayed healthy (*right*).

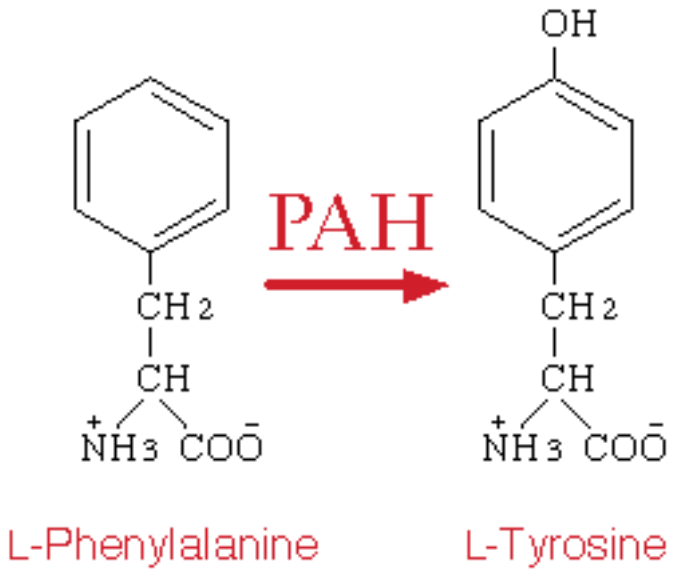
The finding was a lucky break. Immunologist Thaddeus Stappenbeck

PKU= *recessive, loss-of-function mutation in enyzme that catalyzes step A in the diagram on the next page*

1/12,000 (Caucasian births) affected with PKU (autosomal recessive)

Info about PKU
http://www.ygyh.org/

PAH = phenyl alanine hydroxylase



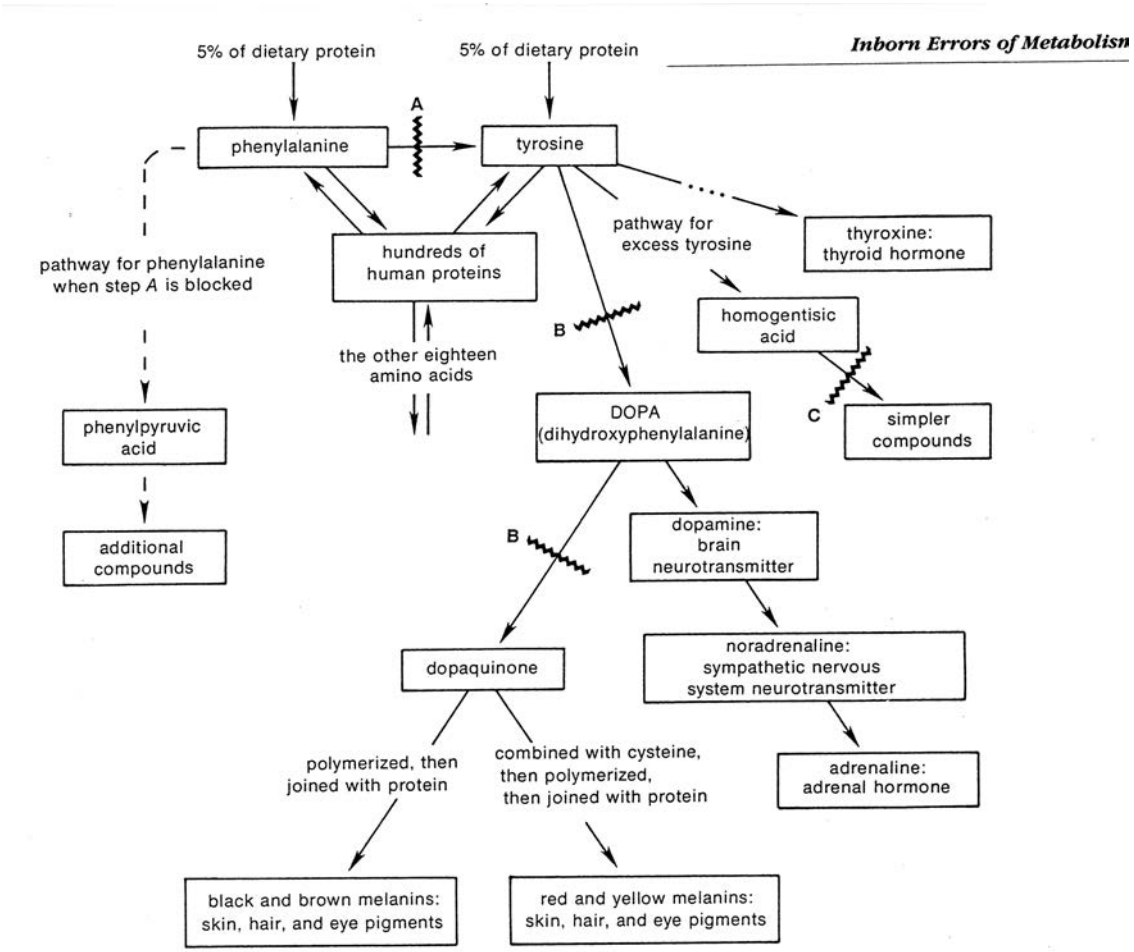
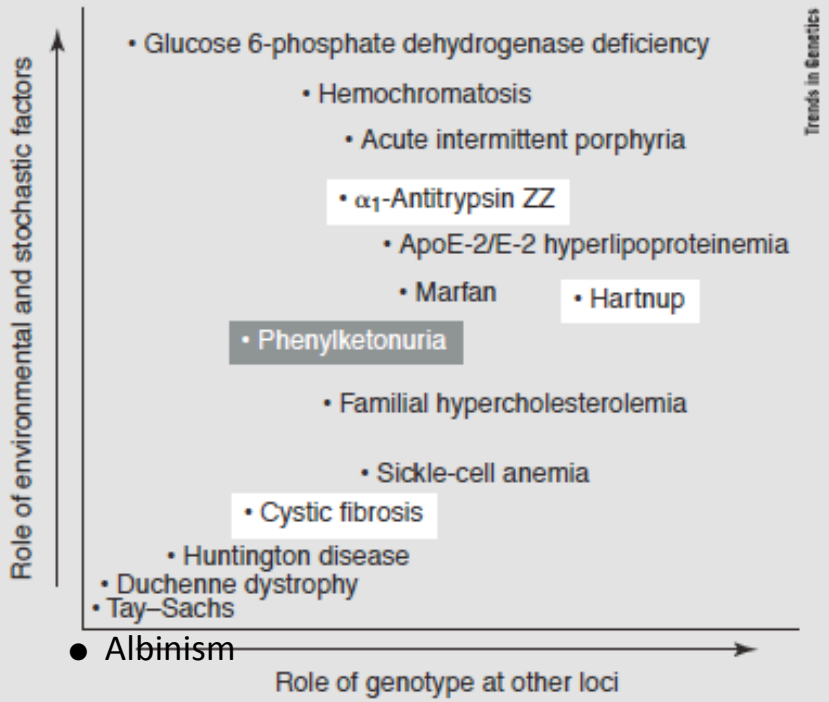


Figure 3 The metabolic blocks in three genetic disorders involving the metabolism of phenylalanine and tyrosine. (A) In phenylketonuria, phenylalanine cannot be converted to tyrosine; as a consequence, phenylalanine and its breakdown products accumulate and are excreted in the urine. The nonfunctional enzyme is phenylalanine hydroxylase. (B) In classical albinism, tyrosine cannot be converted to DOPA and dopaquinone, thereby preventing the formation of melanin pigments. The nonfunctional enzyme is tyrosinase. (C) In alkaptonuria, homogentisic acid cannot be broken down further and appears in the urine (see Figure 1). The nonfunctional enzyme is homogentisic acid oxidase.

PKU= recessive, loss-of-function mutation in enzyme (PAH) that catalyzes step A

See also text reading assignments

FIGURE 1. Genotype–phenotype relationship

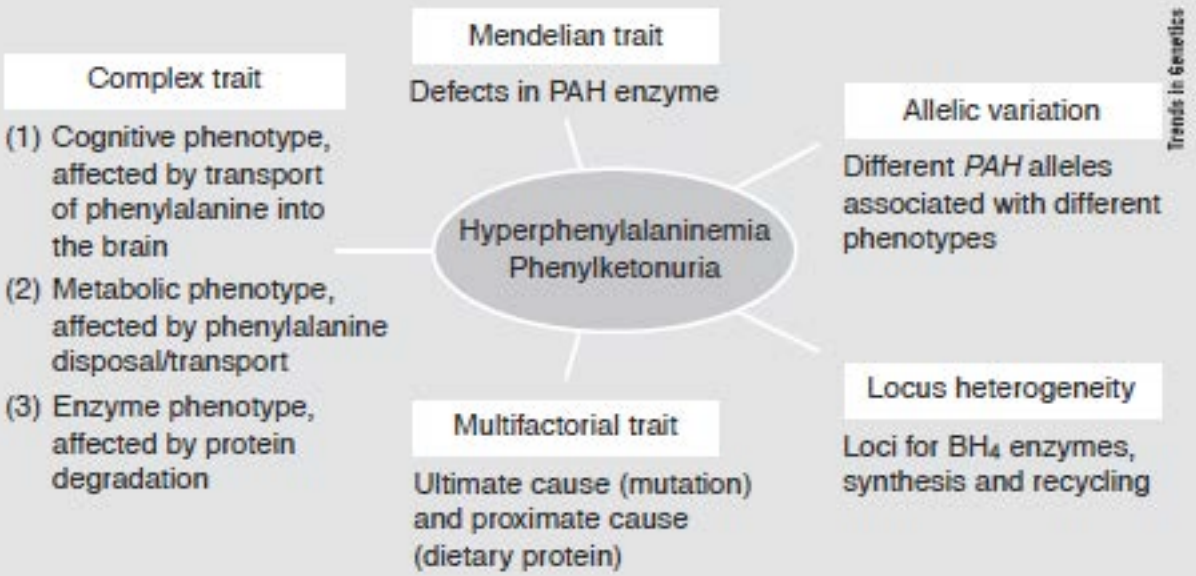


The potential influence of genotype and non-genetic factors on the phenotype of various monogenic disorders. The equation $V_P = V_G + V_E$ (Ref. 61) implies that variation in genotype and environment contribute to variation in phenotype. The diagram indicates the estimated relative importance of background genotype and environment as contributors to the phenotype of several monogenic diseases. The figure does not include the effect of allelic variation at the major locus. Boxed entries are mentioned in the text. Adapted from Ref. 62.

TIG July 1999

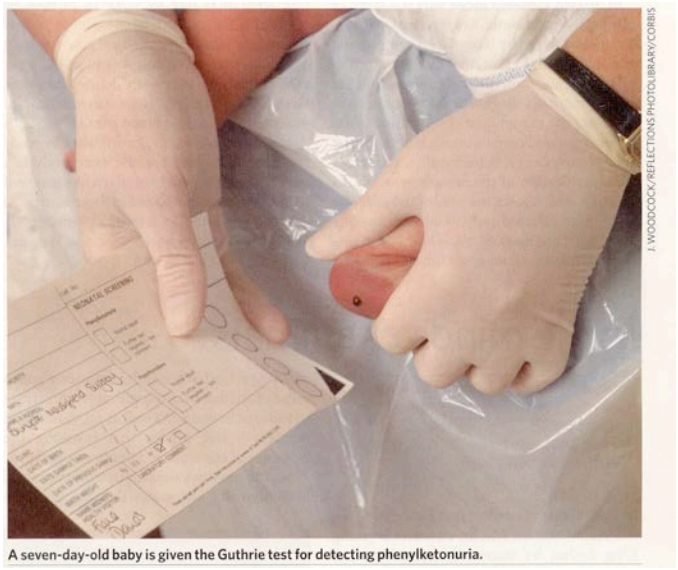
Monogenic Traits are Not Simple: lessons from phenylketonuria

FIGURE 2. Factors influencing phenotype in phenylketonuria



The autosomal recessive trait (hyperphenylalaninemia; HPA in text) and associated disease (phenylketonuria; PKU) have explanations for phenotype beyond a monogenic (mendelian) cause. PKU is MIM 261600 in the McKusick catalog[2]. Other monogenic causes of HPA are the disorders of tetrahydrobiopterin (BH_4) homeostasis, (locus heterogeneity for HPA): they are entered in MIM under 233910, 261630, 261640 and 264070). Symbols: *PAH* for the gene on chromosome 12q24.1; PAH for the homotetrameric enzyme product.

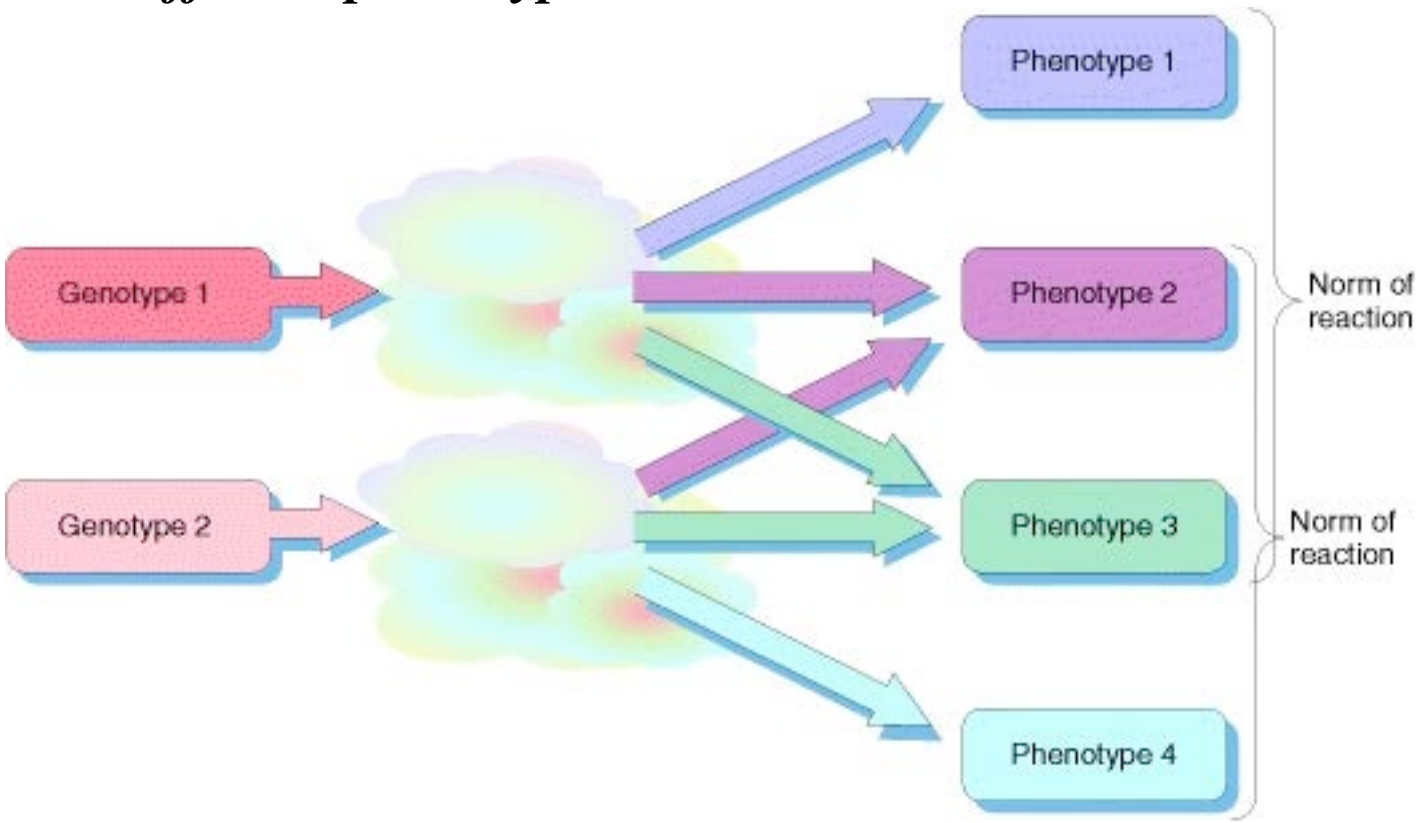
TIG July 1999 *Monogenic Traits are Not Simple: lessons from phenylketonuria*


J. WOODCOCK/REFLECTIONS PHOTOLIBRARY/CORBIS

A seven-day-old baby is given the Guthrie test for detecting phenylketonuria.

aspartame: nutrasweet Asp-Phe dipeptide

How can two individuals with the same genotype (for a particular trait) show different phenotypes?



A **norm of reaction** describes the pattern of phenotypic expression of a single genotype across a range of environments

Mechanisms underlying incomplete penetrance and variable expressivity

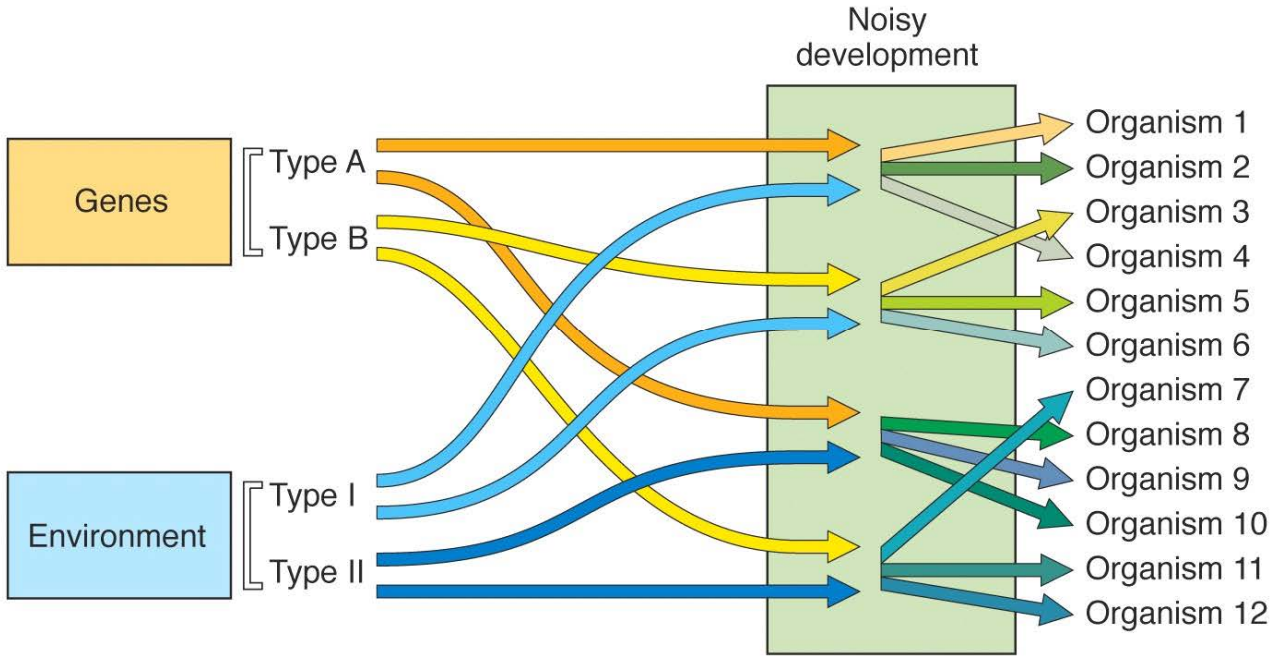
(i) variation in the genetic background in which the genotype in question is expressed: variations in the genotype at other loci (such as at modifier or suppressor loci) can influence the phenotypic expression of a particular trait

(ii) variations in the environment to which the individuals are exposed

(iii) inherent element of randomness (noise) in molecular, biochemical and developmental processes

What does the term *stochastic* mean?

→involving a random variable
→having an inherent element of randomness or chance



A model of phenotypic determination that shows how genes, environment and developmental noise interact to produce a phenotype

There is an inherent element of randomness (noise) in molecular, biochemical and developmental processes such as:

- random variation in the growth, division, migration* or differentiation of cells during development
- random variation in gene expression – perhaps related to epigenetic events such as DNA methylation and/or histone modification
- effects of random events such as somatic mutations that produce cancer

* recall the neural crest cells

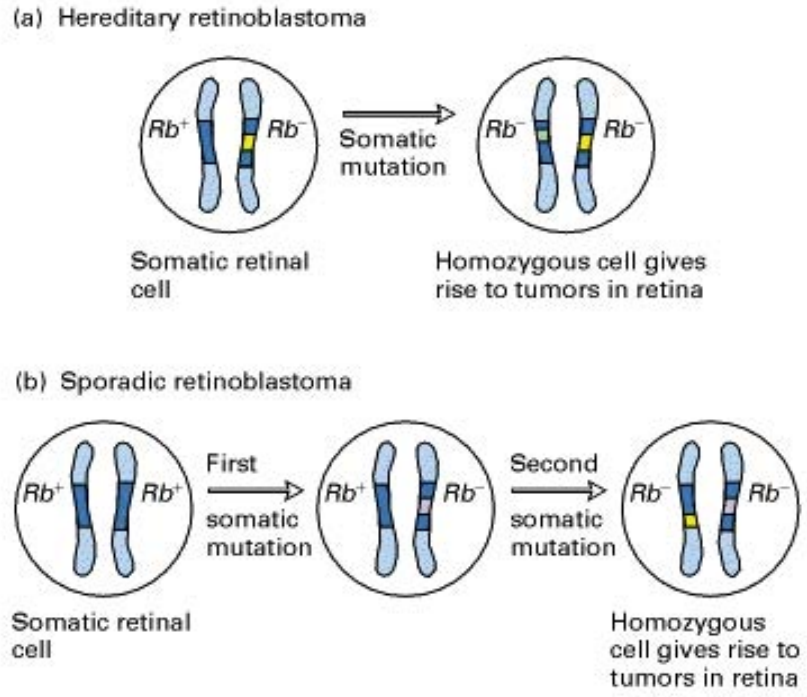
Role of spontaneous somatic mutation in retinoblastoma, a childhood disease marked by retinal tumors

Inherited retinoblastoma: autosomal dominant predisposition to the development of retinoblastomas *but the mutant allele is recessive at the cellular level*

HUH?

Tumors only arise from retinal cells that carry two mutant Rb^- alleles.

(a) In hereditary retinoblastoma, a child receives a normal Rb^+ allele from one parent and a mutant Rb^- allele from the other parent. A single mutagenic event in a heterozygous somatic retinal cell that inactivates the normal allele will result in a cell homozygous for two mutant Rb^- alleles.
(b) In sporadic retinoblastoma, a child receives two normal Rb^+ alleles. Two separate somatic mutations, inactivating both alleles in a particular cell, are required to produce a homozygous Rb^-/Rb^- retinal cell. (about 1 in 30,000 Rb^+/Rb^+ individuals will develop retinoblastoma)



The stochastic nature of mutational events explains the incomplete penetrance and variable expressivity seen in inherited retinoblastoma

What is certain?

Mutations in retinoblasts will happen

What role does chance play?

what is not certain:

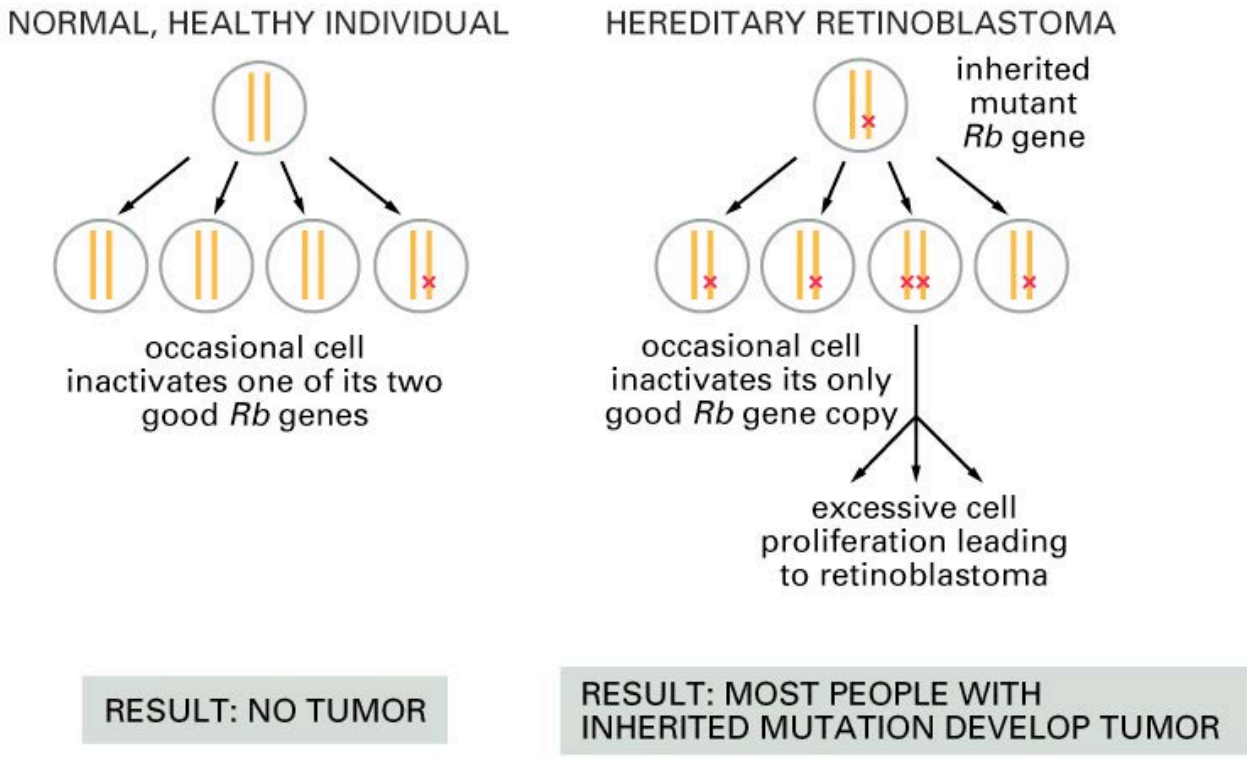
where the mutation(s) will occur in the cell – what gene or genes are hit and what is the nature of the hit?

if **an Rb → rb mutation occurs in a retinoblast --accounts for incomplete penetrance**

when and where **(which eye and which retinoblast) a mutation occurs -- accounts for at least some aspects of variable expressivity**

Frequency of retinoblastoma worldwide:

1/30,000 - 1/20,000 children
5-10% of cases are inherited (pre-existing germline mutation)
20-30% of cases result from a *new* germline mutation in one parent
60-70% are sporadic somatic mutations



CLICK HERE FOR MORE INTERESTING INFO ON RETINOBLASTOMA:
http://fire.biol.wwu.edu/trent/trent/RBinfo.pdf

NOTE: most examples of incomplete penetrance or variable expressivity are **NOT** explained by the requirement of a second mutation to reveal the mutant phenotype

The neural crest cells joyride through the embryo

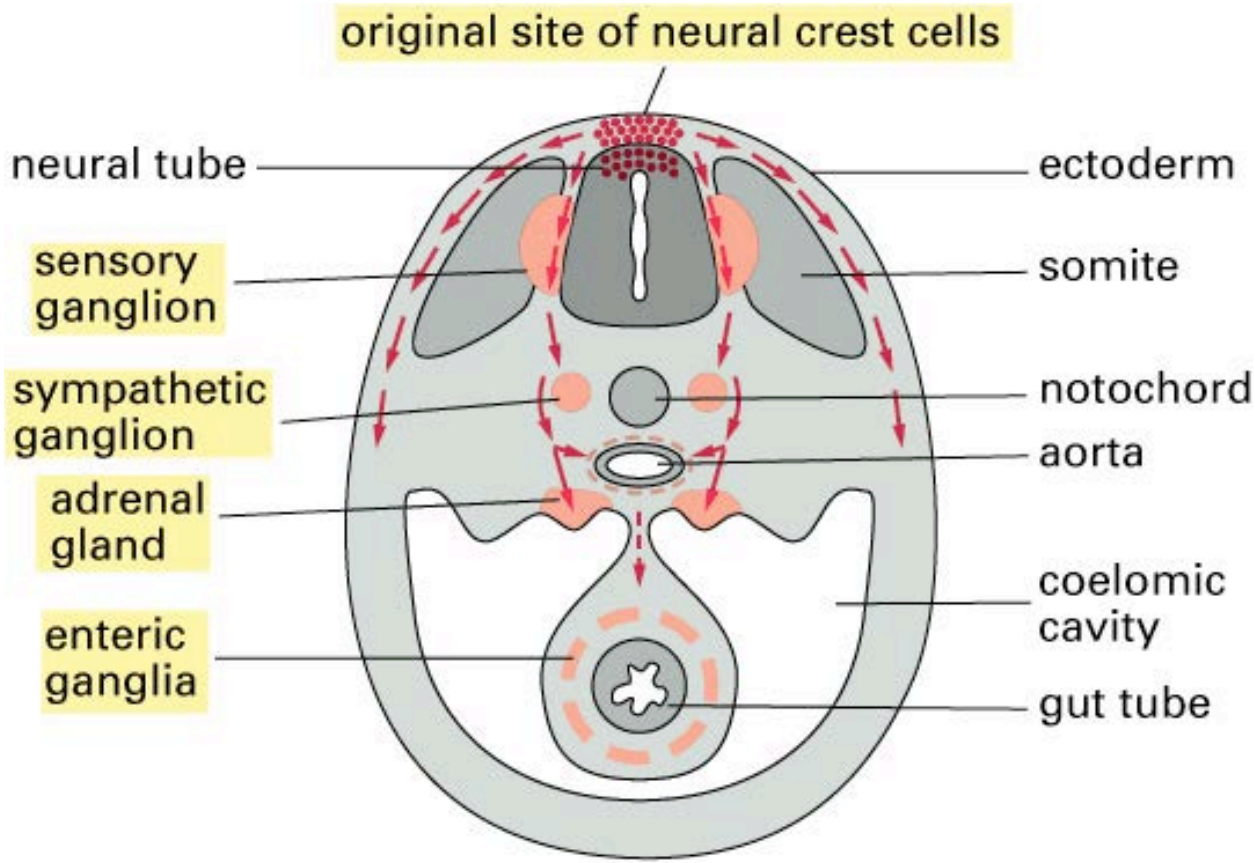
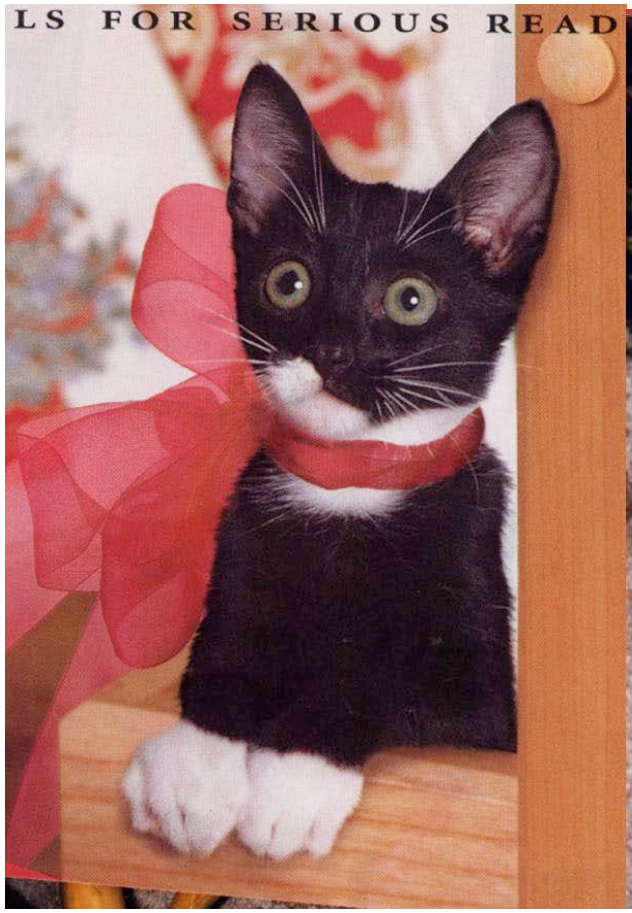


Figure 21–80. Molecular Biology of the Cell, 4th Edition.

Cross-section of a vertebrate embryo showing the main pathways of neural crest cell migration. The cells that take the pathway just beneath the ectoderm will form pigment cells of the skin

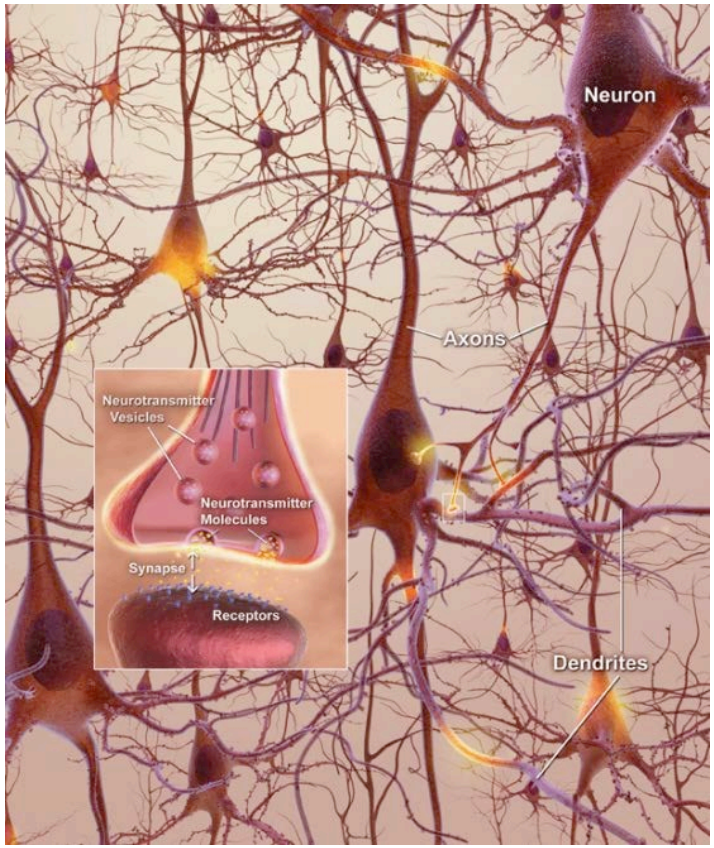
An small inherent element of randomness in any cell migration

- Consider a black cat either homozygous or hemizygous for the X-linked black pigment allele
- What might happen is not all regions of the embryonic periphery are populated by neural crest cells destined to become pigment cells (melanocytes)?



The cats above could be heterozygous for a dominant white-spotting allele (S), **but it is possible (and likely for the cat at the right) that the cats are genetically non-spotted (ss) paws are white because of *developmental noise***

Development and wiring of the nervous system



All human brains share fundamental similarities defined by "rules" of neuron shape and connectivity that are encoded in our genes.

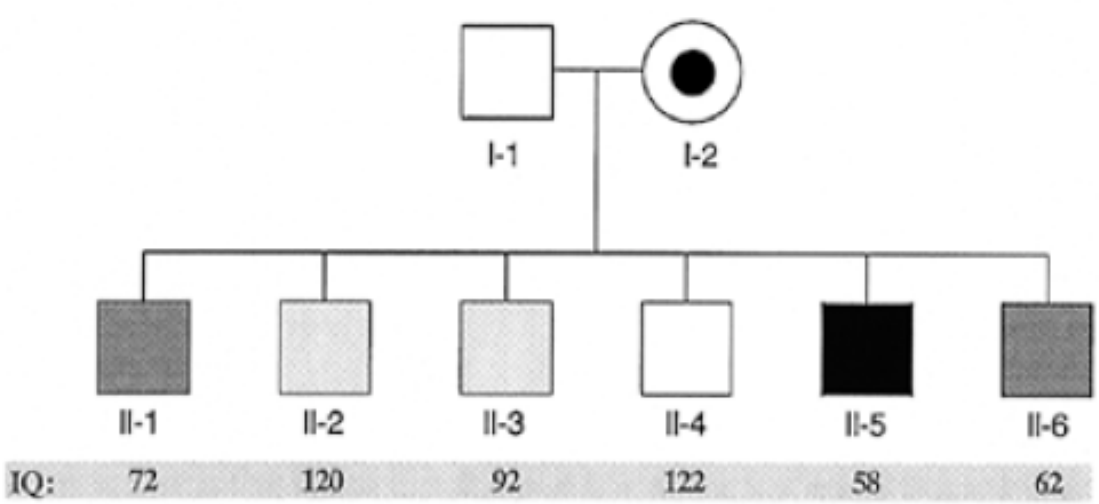
But, my brain does not look like your brain

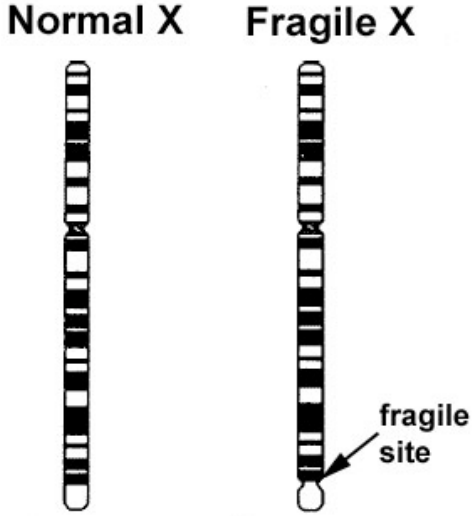
The arrangement and connectivity of our nerve cells differ due to stochastic developmental noise and experience-dependent plasticity

paraphrased from http://www.hms.harvard.edu/dms/neuroscience/fac/HeimanMax.php

Fragile X Syndrome Phenomenology

Fragile X syndrome is one of the most common forms of inherited mental retardation. The syndrome occurs in approximately 1 in 3600 males and 1 in 4000 to 6000 females" (fragilex.org). Fragile X results in apparently normal neurological development, with the effects becoming apparent during early learning (age 3-5). This disease is one of several CAG expansion diseases





Human Molecular Genetics, 1997, Vol. 6, No. 11 1791–1801

One son (II-4) inherited a normal chromosome and the other five inherited the fragile-X chromosome

Explore Genetics Home Reference http://ghr.nlm.nih.gov/gene/FMR1