Complications to the 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 effects 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 diseases that are caused by a single gene mutation
Genes that sense gravity in plants may play a role in Waardenburg syndrome in humans: [http://fire.biol.wwu.edu/trent/trent/BizarreModels.pdf](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?

His left eye shows the typical red-eye effect seen when the retina reflects light from a camera flash.

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
- \( \text{Rb}^- = \text{mutant} \quad \text{Rb}^+ = \text{normal} \)
- \( \text{Rb}^+ \text{ Rb}^+ \) eye cancers rare (normal)
- \( \text{Rb}^+ \text{ Rb}^- \) 90% of hets get eye cancers (# tumors varies)
- \( \text{Rb}^+ \text{ Rb}^- \) 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*
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) variations in the environment to which the individuals are exposed

(ii) inherent element of randomness (noise) in molecular, biochemical and developmental processes such as:
   - random variation in the growth and division 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 -- somatic mutations that produce cancer

(iii) variations in the genotype at other loci -- that is, variation in genetic background (such as at modifier or suppressor loci)
Genetic and environmental effects on eye size in Drosophila

a. Scanning electron micrograph of a fly eye showing compound eye made of many individual light receptors (eye facets)
b. Infrabar and ultrabar flies carry mutations that affect the number of eye facets
Required Reading:

*The Interpretation of Genes*
Natural History 10/02 pg. 52-58
http://fire.biol.wwu.edu/trent/trent/interpretationofgenes.pdf

The theme of this article:
*The “expression of a genome is best understood as a dialogue with an organism’s environment.*

SEE examples on the following pages: we will not discuss all of them in class. *If you find a interesting example of a gene X environment interaction in the specification of a well-defined phenotype, please bring it to CT’s attention.*
Other dramatic examples of the effects of environment on phenotype

The water flea *Daphnia lumholtzi* usually reproduces parthenogenetically:
- diploid females produce diploid daughters without interference by the rare and much smaller males.
- the progeny of this form of parthenogenesis are genetic clones of the female (in contrast to what we saw with the Komodo Dragon)

The individuals shown 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
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

from Natural History article referenced above
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.

The finding was a lucky break. Immunologist Thaddeus Stappenbeck
NEUROSCIENCE

Early stress marks genes


Changes in gene expression caused by factors other than variation in the DNA code — ‘epigenetic’ changes — are partly responsible for the mental and physical health problems often associated with stress in early life.

Dietmar Spengler and his colleagues at the Max Planck Institute of Psychiatry in Munich, Germany, stressed newborn mice by separating them from their mothers. As adults, the mice secreted abnormally high levels of the stress hormone corticosterone, were less able to cope with stressful situations and had memory impairments. They also had fewer methyl groups attached to the regulatory region for the gene that encodes the hormone vasopressin, a key player in the biochemical pathway that leads to corticosterone release. The reduced methylation resulted in a rise in vasopressin expression.

See also optional reading

*Identical twins grow apart as they age*


*About DNA methylation: pg 341 in 10th edition*
PKU = recessive, loss-of-function mutation in enzyme 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/

![Diagram showing the conversion of L-Phenylalanine to L-Tyrosine](image-url)
PKU = recessive, loss-of-function mutation in enzyme that catalyzes step A

See also Figure 2-21 in text
aspartame: nutrasweet Asp-Phe dipeptide
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
Mechanisms underlying incomplete penetrance and variable expressivity

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

(ii) 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

(iii) variations in the genotype at other loci -- that is, variation in genetic background (such as at modifier or suppressor loci)
Inherited retinoblastoma: autosomal dominant predisposition to the development of retinoblastomas but the mutant allele is recessive at the cellular level HUH?

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

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.
the stochastic nature of mutational events explains the incomplete penetrance and variable expressivity

what are the elements of randomness?
if an Rb $\rightarrow$ rb mutation occurs in a retinoblast (accounts for incomplete penetrance)

when and where (which eye and which retinoblast) 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
Let’s look at yet another example of a genotype/phenotype relationship under conditions where we know the genotype for a particular trait:

- Direct detection of genotype of the CEL (carboxyl ester lipase) gene:
- CEL is a major component of pancreatic juice and is responsible for the hydrolysis of cholesterol esters
- \( N \) = normal allele \( M \) = mutant allele

Is this mutant allele:
- Completely or Incompletely dominant?
- Pleiotropic?
- Variably expressed?
- Incompletely penetrant?