For difference determined by one gene…

Five year survival rates, in %.

<table>
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<tr>
<td>Brain &amp; Other Nervous</td>
<td>18.3</td>
<td>24.9</td>
<td>26.8</td>
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<td>Breast (Female)</td>
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<td>Colon &amp; Rectum</td>
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<td>51.0</td>
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<td>Lymph &amp; Myeloma</td>
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A Russian proverb that aptly describes most current cancer treatment modalities

«Лучшее средство от кровотечения из носа — жгут на шею».

“The best cure for a nosebleed is a torniquet on the neck.”

“Chemo” drugs

**Intrastrand DNA crosslinking**

**Depolymerization of microtubules**

**Apoptosis (programmed cell death)**

“Malignancy of somatic cell hybrids”

The studies of Ephrussi et al. and Harris provided compelling evidence that the ability of cells to form a tumor is a recessive trait. They observed that the growth of murine tumor cells in syngeneic animals could be suppressed when the malignant cells were fused to nonmalignant cells, although reversion to tumorigenicity often occurred when the hybrids were propagated for extended periods in culture. The reappearance of malignancy was found to be associated with chromosome losses. Stanbridge and his colleagues studied hybrids made by fusing human tumor cell lines to normal, diploid human fibroblasts. Their analysis confirmed that hybrids retaining both sets of parental chromosomes were suppressed, with tumorigenic variants arising only rarely after chromosome losses in the hybrids. Moreover, it was demonstrated that the loss of specific chromosomes, and not simply chromosome loss in general, correlated with the reversion to tumorigenicity.

The observation that the loss of specific chromosomes was associated with the reversion to malignancy suggested that a single chromosome (and perhaps even a single gene) might be sufficient to suppress tumorigenicity. To directly test this hypothesis, single chromosomes were transferred from normal cells to tumor cells, using the technique of microcell-mediated chromosome transfer. It was found that the transfer of a single chromosome 11 into the HeLa cervical carcinoma cell line suppressed the tumorigenic phenotype of the cells. Many studies have now demonstrated that transfer of even very small chromosome fragments will specifically suppress the tumorigenic properties of certain cancer cell lines.
Why does restoration of p53 function lead to tumor regression?

Epistasis
(or: an epistatic interaction between two loci)
1. Pick a trait.
2. Find a mutant → phenotype #1
3. Find a different mutant → different phenotype (#2)
4. Cross the two mutants: get not a mix of phenotypes, but instead, either phenotype #1 or #2.

The term "epistasis" refers to a phenomenon in which an allele of one gene masks ("stops") the effects on the phenotype of an allele of a different gene.

How can one tell, if two organisms under study that exhibit mutant phenotypes for a particular trait have a mutation in different genes or in the same gene?
Complementation test

“Complementation is the production of a wild-type phenotype when two haploid genomes bearing different recessive mutations are united in the same cell.”

The cis-trans test
(aka complementation test)

Are two different recessive mutations that appear to affect the same trait in the SAME gene or in DIFFERENT genes?

Edward Lewis (NP 1995)

Orgo

cis-2-butene

trans-2-butene

The cis-trans test, 1949: lozenge (M. Greene)

Two different recessive mutants, both with the same phenotype (small eyes and fused facets).

Are they mutations in the same gene?

Make two different fly lines and compare their phenotypes.

Cis:

wt

lz(BS)

wt

lz(g)

Trans:

wt

lz(BS)

lz(g)

wt

Gene A

Gene B

This is a control experiment.
The flies will be wild-type regardless of whether BS and g are in the same gene or not.

If flies are normal, then mutations are in different genes.
If the phenotype is still mutant, then BS and g must be in the same gene!!!
The data

- Colonies screened: 675,000
- Colonies that mated to a: 295
- Major complementation groups: 4

silent information regulators:

$$SIR1, SIR2, SIR3, SIR4$$

**Xeroderma pigmentosum**

**What was actually done**

1. By linkage analysis, it was discovered that the same disease (XP) can be caused by mutations in 7 distinct loci.
2. The cDNA from each gene was cloned.
3. An assay was developed to measure how sensitive to UV light cells are.
4. Experiment: take cells from patient type A, and introduce each of the 7 cDNAs, one after another.
5. Whichever cDNA restores the wild-type phenotype corresponds to the gene that is mutated in that cell.

→ Bin XP mutations into “complementation groups”!
Wait a minute

Ahem.
Fine. You take a cell that’s mutant, stick in a gene, the cell is now wild-type, and you tell us this means the gene you stuck in is the gene that is mutated in the cell.
What if the cell has a mutation in a completely different gene, and the gene you stuck in is just epistatic to the first one?! Good question.

Auf Wiedersehen (with respect to phenotype), Herr Mendel

Gene interactions in the establishment of phenotype

For complete clarity

1. All genotypes – except in cases of nondisjunction – follow Mendel’s first law, and – except in cases of linked genes < 50 cM away from each other – Mendel’s second law.
2. With the exception of human genetic disease, which is, let’s face it, very rare, and things like blood group inheritance, which belongs mostly on the MCAT (note – its inheritance, not blood groups themselves), the inheritance of phenotype seldom follows Mendel’s laws.

“… the stadium capacity is now officially listed as 75,662”
An SCN9A channelopathy causes congenital inability to experience pain”  

“...the index case for the present study was a ten-year-old child, well known to the medical service after regularly performing ‘street theatre’. He placed knives through his arms and walked on burning coals, but experienced no pain. He died before being seen on his fourteenth birthday, after jumping off a house roof.”

So – let’s think about this

The small fraction of African Americans who are relatively pain free ... could they be heterozygous for a loss of function mutation in SCN9A?

... In other words, could this be recessive epistasis?

If yes, could this suggest that a small molecule inhibitor of that specific pain receptor could be a more effective analgesic for SCA patients than God awful parenteral morphine!

Strict definition

Epistasis is revealed in modified Mendelian ratios in dihybrid crosses.
Future e-mail

Professor,
Thanks for nothing, BUSTER.
First you tell us that modified Mendelian ratios can occur in monohybrid crosses (e.g., in a dominance series), then you tell us they occur in dihybrid crosses and are, in fact, a hallmark of epistasis.
How can one tell the difference?
Genetics of continuous variation

In a population, phenotypes of individuals for a quantitative trait tend to be normally distributed.

The Great Schism (1901-1935)

“Naturalists”
- the origin and meaning of diversity
- populations, groups, higher taxa
- gradualism
- ultimate causation

“The Mendelians”
- transformation of genes
- individual genes/loci
- saltationism
- no “why” questions

“The only experimental method would permit an objective discussion of the theory of evolution, in striking contrast to the older speculative method of treating evolution as a problem of history.” (T.H. Morgan)

Synthesis: Population Genetics

- H. Nilsson-Ehle, R.A. Fisher, J.B.S. Haldane, S. Wright: continuous phenotypic variation is not at odds with particulate inheritance:
  - multiple loci + epistasis
- S.S. Chetverikov: naturally occurring recessives as food for natural selection.
Central limit theorem
Carl Friedrich Gauss →

If a variable is the sum of many independent variables, then its distribution will be normal:

\[ e^{-x^2} \]

“Additive effects of genes”

Next time:
why are all calico cats female? –
and a related question:
why is metastatic prostate cancer almost always incurably lethal?