"Hey! Look what Zog do!"

IS IT GENETIC? How do genes, environment and chance interact to specify a complex trait such as intelligence?

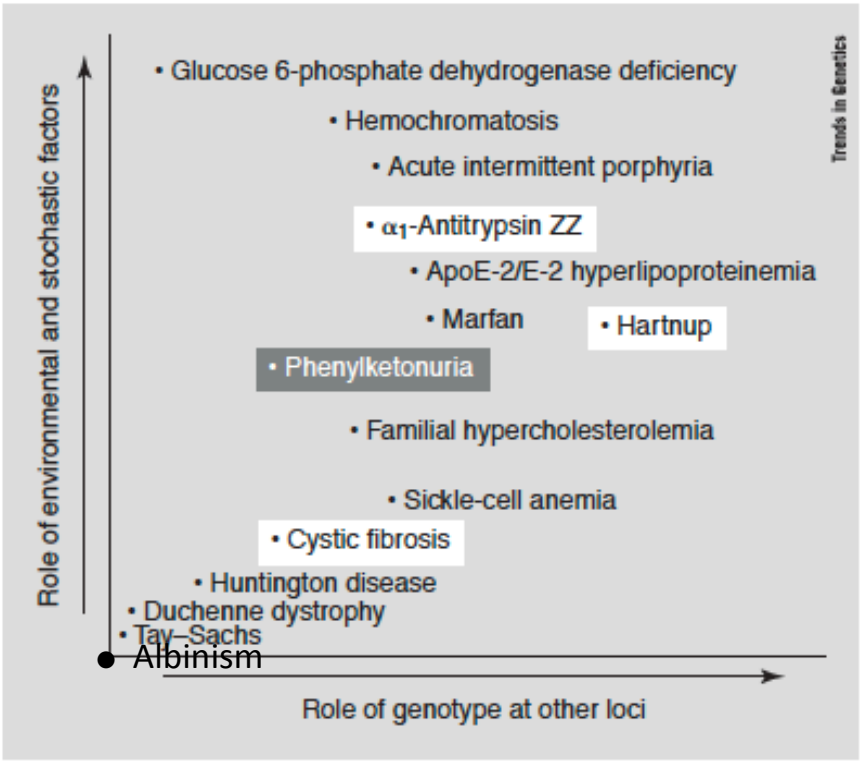
Complex inheritance patterns: sorting out the terminology

- ***Polygenic inheritance:*** the phenotypic variation in a single trait is due to allelic differences in *more than one gene* -- usually implies several genes with additive effects that control the phenotype

- ***Multifactorial inheritance:*** the phenotypic variation in a trait is due to allelic differences in *more than one gene AND* the environment also influences the trait

Complexities arise when the association between genotype and phenotype breaks down

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.

HEY -- NOT SO FAST: *even the expression of monogenic traits can be complicated*

TIG July 1999, volume 15, No. 7
Monogenic Traits are Not Simple: lessons from phenylketonuria

Single-gene (monogenic) traits

- Phenotypic variation is typically discrete (often comparing sharply contrasting phenotypes)
- Single-gene differences can explain the difference between these discrete phenotypes
- *If there is phenotypic variability that doesn't fit easily into discrete categories, the phenotypic extremes (such as normal and profoundly deaf individuals below) can be explained by differences in a single gene*

Inherited deafness is a genetically heterogeneous, monogenic trait:

- mutations in *any one* of 30 different genes can cause profound deafness

phenotype W ↔ phenotype D

only one* gene is different

W= wild-type (normal hearing) D= deaf

****of many possible genes***

Complex inheritance patterns: sorting out the terminology

From your textbook:

- ***Complex inheritance:*** *involves multiple genes plus environmental factors – essentially the same as multifactorial*

Types of traits

Quantitative traits: *show a* ***continuous*** *range of variation and do not behave in a simple mendelian fashion*

Threshold traits: *the expression of the different phenotypic states depends on a combination of multiple genetic and/or environmental factors that place an individual above or below a critical value for trait expression*

Human Molecular Genetics 4th edition: Sorting out terms

complex phenotype – one that can have a variety of different causes and modes of inheritance in different people

multifactorial: a character that is determined by some unspecified combination of genetic and environmental factors

polygenic: a character determined by the combined action of a number of different genetic loci; *mathematical polygenic theory assumes there are very many loci, each with a small, additive effect*

quantitative character: a character that shows *continuous distribution*

- like height, which everyone has, but to differing degree
- as contrasted with dichotomous (discrete) character, like polydactyly, which some people have and others do not

Complex Traits

- Allelic variations in a single gene cannot explain the phenotypic variation (especially phenotypic extremes)
- Two or more genetic differences (and the environment in some cases) determine the phenotypic difference between two individuals with respect to a specific trait
- Continuous rather than discrete variation OR threshold trait

In multifactorial traits [such as NIDDM (late onset) diabetes]

- the difference between a normal and diabetic individual reflects ***allelic differences in more than one gene***
- in other words a *single gene difference* isn't sufficient to generate a "NIDDM diabetic" phenotype

phenotype W ↔ phenotype D
multiple genetic differences
W= wild-type (not diabetic) D = severe NIDDM diabetic

Notice the how the genetic component is described here:

Variant Gene Linked to Diabetes Is Carried by 38% of People

By Michael Smith , MedPage Today Staff Writer

Type 2 diabetes is a ***complicated multifactorial*** disease, which is linked to obesity and inactivity, although there are ***clear genetic predispositions*** to the disease in some groups.

REYKYAVIK, Iceland, Jan. 16, 2006 - A variant gene (a variant allele or polymorphism) carried by about 40% of the population sharply increases the risk of type 2 diabetes, researchers here have reported.

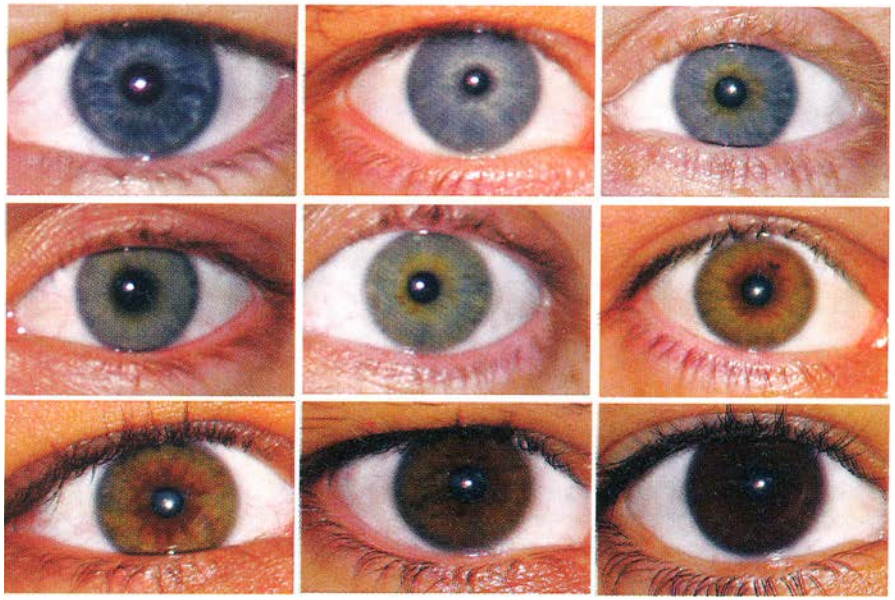
The link between the gene **TCF7L2 (transcription factor 7-like 2 gene) and diabetes** was found by analyzing genetic records of Icelanders, and was confirmed in a Danish and a European-American cohort, according to scientists from Iceland's deCODE Genetics Inc.

Carrying ***one copy of the variant increases the risk of type 2 diabetes by 45% and carrying two copies increases the risk by 141%,*** said Kari Stefansson, M.D., chief executive officer of deCODE and senior author of a study reported online in the journal *Nature Genetics*.

Dr. Stefansson and colleagues estimated that 38% of the population carries one copy of the variant allele and 7% carries two copies. The researchers estimated the population attributable risk of the gene variant to be 21%. In other words, if all of the variant alleles were somehow eliminated, 21% of diabetes cases would also vanish.

IRIS color is a polygenic trait

- Human iris color is considered a polygenic trait and exists on a continuum from the lightest shades of blue to the darkest of brown or black
- At least eight genes are known to be associated with eye colour.
- These genes code for proteins involved in the production or distribution of eumelanin and pheomelanin pigments in the iris, skin, and the hair
- ***The strongest effect on eye color is determined by two adjacent genes, OCA2 and HERC2, on chromosome 15***
- but even these two genes don't paint the full picture.



Am J Hum Genet. 2007 February; 80(2): 241–252.

ARTICLE

A Three–Single-Nucleotide Polymorphism Haplotype in Intron 1 of *OCA2* Explains Most Human Eye-Color Variation

David L. Duffy,* Grant W. Montgomery,* Wei Chen, Zhen Zhen Zhao, Lien Le, Michael R. James, Nicholas K. Hayward, Nicholas G. Martin, and Richard A. Sturm

We have previously shown that a quantitative-trait locus linked to the *OCA2* region of 15q accounts for 74% of variation in human eye color. We conducted additional genotyping to clarify the role of the *OCA2* locus in the inheritance of eye color and other pigmentary traits associated with skin-cancer risk in white populations. Fifty-eight synonymous and nonsynonymous exonic single-nucleotide polymorphisms (SNPs) and tagging SNPs were typed in a collection of 3,839 adolescent twins, their siblings, and their parents. The highest association for blue/nonblue eye color was found with three *OCA2* SNPs: *rs7495174* T/C, *rs6497268* G/T, and *rs11855019* T/C (*P* values of 1.02×10^{-61}, 1.57×10^{-96}, and 4.45×10^{-54}, respectively) in intron 1. These three SNPs are in one major haplotype block, with TGT representing 78.4% of alleles. The TGT/TGT diplotype found in 62.2% of samples was the major genotype seen to modify eye color, with a frequency of 0.905 in blue or green compared with only 0.095 in brown eye color. This genotype was also at highest frequency in subjects with light brown hair and was more frequent in fair and medium skin types, consistent with the TGT haplotype acting as a recessive modifier of lighter pigmentary phenotypes. Homozygotes for *rs11855019* C/C were predominantly without freckles and had lower mole counts. The minor population impact of the nonsynonymous coding-region polymorphisms Arg305Trp and Arg419Gln associated with nonblue eyes and the tight linkage of the major TGT haplotype within the intron 1 of *OCA2* with blue eye color and lighter hair and skin tones suggest that differences within the 5′ proximal regulatory control region of the *OCA2* gene alter expression or messenger RNA–transcript levels and may be responsible for these associations.

Table 5. Frequencies (%) of *OCA2* Intron 1 Diplotypes,

Genotype	Diplotype Number	*N* (%)[a]	Eye Color		
			Blue/ Gray	Green/ Hazel	Brown
1:					
TGT/TGT	1/1	1,772 (62.22)	62.5	28.0	9.5
TGT/TTC	1/4	138 (4.85)	47.1	20.3	32.6
TGT/CGT	1/5	7 (.25)	**28.6**	**14.3**	**57.1**
TGT/TGC	1/3	154 (5.41)	**27.9**	**22.1**	**50.0**
TGC/TTC	**3/4**	12 (.42)	**25.0**	**08.3**	**66.7**
TTT/TGC	**2/3**	29 (1.02)	**20.7**	**31.0**	**48.3**
TTT/CGC	**2/7**	5 (.18)	**20.0**	**20.0**	**60.0**
TGT/TTT	1/2	364 (12.78)	**17.6**	**38.5**	**44.0**
TGT/CTC	1/8	253 (8.88)	**7.9**	**23.3**	**68.8**
TTT/TTC	**2/4**	18 (.63)	**5.6**	**11.1**	**83.3**
CTC/CTC	**8/8**	22 (.77)	**4.5**	**00.0**	**95.5**
TTT/TTT	**2/2**	17 (.60)	**.0**	**35.3**	**64.7**
TTC/CGT	**4/5**	3 (.11)	**.0**	**33.3**	**66.7**
TTC/CTC	**4/8**	13 (.46)	**.0**	**23.1**	**76.9**
TTT/CTC	**2/8**	14 (.49)	**.0**	**21.4**	**78.6**
TGC/CTC	**3/8**	18 (.63)	**.0**	**5.6**	**94.4**
TTC/TTC	**4/4**	6 (.21)	**.0**	**.0**	**100.0**
TGT/CTT	1/6	1 (.03)	**.0**	**.0**	**100.0**
TTT/CGT	**2/5**	1 (.03)	**.0**	**.0**	**100.0**
TGC/TGC	**3/3**	1 (.03)	**.0**	**.0**	**100.0**
2:					
WR/RQ[b]	10/11	24 (.86)	50.0	29.2	20.8
RR/RR	9/9	2,114 (75.55)	49.0	26.5	24.5
RR/WR	9/10	251 (8.97)	46.6	19.1	34.3
WR/WR	10/10	7 (.25)	42.9	14.3	42.9
RR/RQ	***9/11***	387 (13.83)	***31.8***	***39.3***	***28.9***
RQ/RQ	***11/11***	15 (.54)	***.0***	***66.7***	***33.3***

NOTE.—Genotypes and diplotype numbers are as listed in table 4 for *rs749* underlined, with haplotype 1 (TGT) always underlined. Genotypes and diplot with green/hazel eyes are shown in bold italics.

[a] For eye color, there were 2,848 subjects assessed in sample 1 and 2,798 1 and 2,797 assessed in sample 2; for skin color, there were 2,717 subjects

[b] Amino acids corresponding to SNP changes *rs1800401* = Arg305Trp and *r*

Continuous variation is characteristic of complex traits

DISCRETE VS. CONTINUOUS TRAITS

- Most of the traits that we've examined thus far are discrete in the sense that they vary discontinuously
- the phenotypic variations show clear-cut, clearly defined differences.
- In contrast many traits vary continuously, and exhibit many intermediate forms

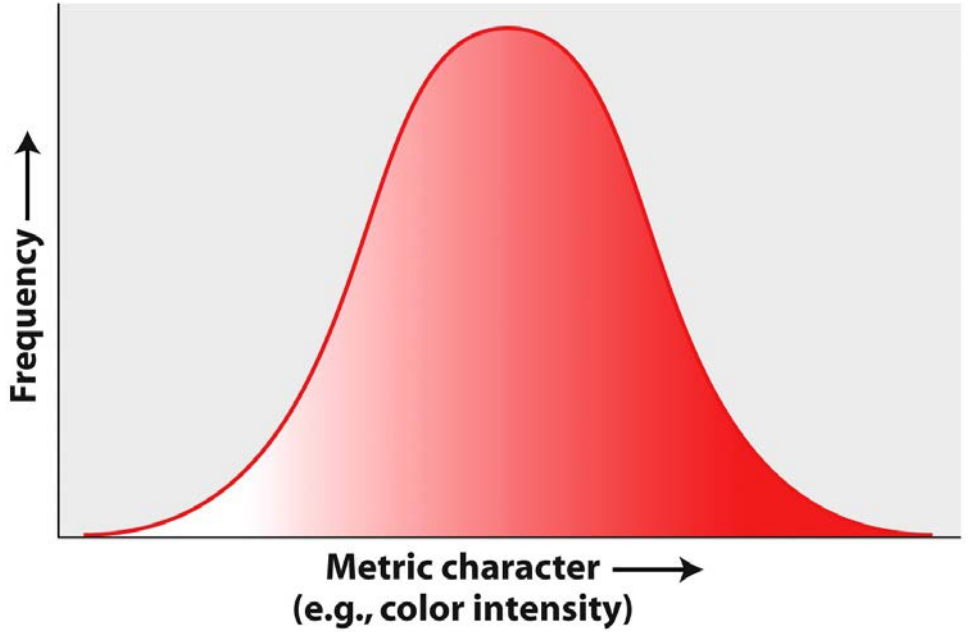
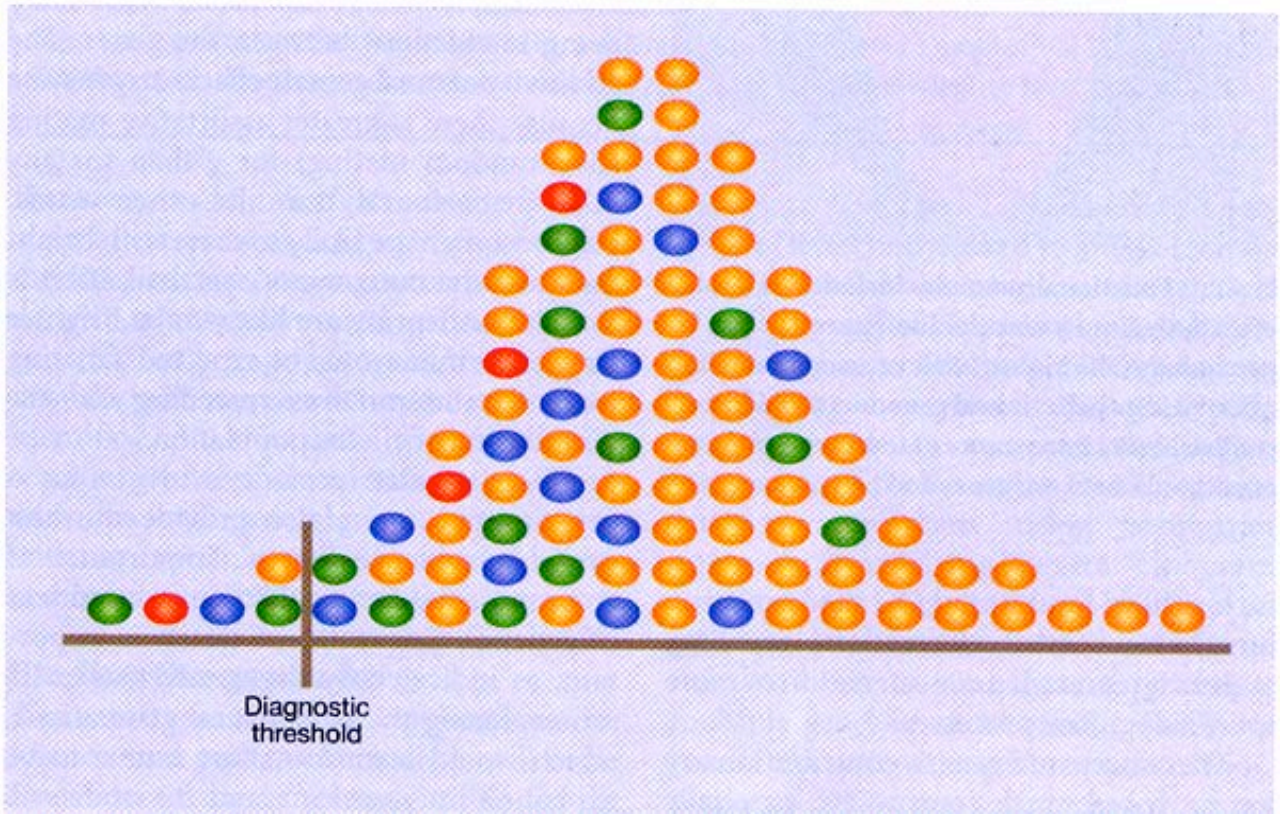


Figure 3-14
Introduction to Genetic Analysis, Ninth Edition

Reading ability is an example of a continuous trait specified by a complex interaction between genotype and environment



- green oval - individual has the disabling variant of one gene
- blue oval - individual has the disabling variant of one gene
- red oval - individual has disabling variants of both genes

Y axis: number of individuals X axis= reading ability

See also next page

Graph show a phenotypic distribution typical of a continuous trait:

- the smallest proportion of the population is on the phenotypic extremes
- the largest proportion of the population exhibits the intermediate phenotype

- Graph shows 100 individuals each represented by an oval
- Oval color indicates the genotype of each individual with respect to *two hypothetical genes involved in reading ability*
- green oval - individual has the disabling variant of one gene
- blue oval - individual has the disabling variant of one gene
- red oval - individual has disabling variants of both genes

What does this graph suggest about the genetic control of reading ability?

These genes influence reading ability as *probabilistic propensities* *rather than as predetermined programs*

<u>in this example genes relating to</u>

attention deficit disorder?

dyslexia?

nervous system development?

intelligence?

Non-genetic influences on the expression of genetic propensities

Teacher Quality Moderates the Genetic Effects on Early Reading

J. Taylor,[1]* A. D. Roehrig,[2] B. Soden Hensler,[1] C. M. Connor,[1,3] C. Schatschneider[1,3]

Children's reading achievement is influenced by genetics as well as by family and school environments. The importance of teacher quality as a specific school environmental influence on reading achievement is unknown. We studied first- and second-grade students in Florida from schools representing diverse environments. Comparison of monozygotic and dizygotic twins, differentiating genetic similarities of 100% and 50%, provided an estimate of genetic variance in reading achievement. Teacher quality was measured by how much reading gain the non-twin classmates achieved. The magnitude of genetic variance associated with twins' oral reading fluency increased as the quality of their teacher increased. In circumstances where the teachers are all excellent, the variability in student reading achievement may appear to be largely due to genetics. However, poor teaching impedes the ability of children to reach their potential.

The ability to read proficiently is a critical skill, and children who fail in that skill are more likely to be retained a grade, drop out of school, and enter the juvenile criminal justice system (*1*)—all at substantial cost to society. Hence, we look to educators to ensure that children achieve proficient literacy skills; yet, a large proportion of the variability in children's reading skills is associated with nonmalleable factors like genes (*2*). Small differences in heritability (estimate of genetic influence) from twins that do versus do not share a teacher raise doubts about the effect of teachers on students' reading development (*3*). At the same time, accumulating evidence from samples of unrelated children shows that teachers do affect children's reading skill gains (*4*, *5*).

The dilemma is that research examining unrelated children cannot address whether effects are associated with genes or with the shared

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Non-genetic influences on the expression of genetic propensities

PSYCHOLOGICAL SCIENCE

Research Article

Parental Education Moderates Genetic Influences on Reading Disability

Angela Friend,[1] John C. DeFries,[1,2] and Richard K. Olson[1,2]

[1]Department of Psychology, University of Colorado at Boulder, and [2]Institute for Behavioral Genetics, University of Colorado at Boulder

ABSTRACT—*Environmental moderation of the level of genetic influence on children's reading disabilities was explored in a sample of 545 identical and fraternal twins (mean age = 11.5 years). Parents' number of years of education, which is correlated with a broad range of environmental factors related to reading development, was significantly related to the level of genetic influence on reading disability. Genetic influence was higher and environmental influence was lower among children whose parents had a high level of education, compared with children whose parents had a lower level of education. We discuss the implications of these results for behavior genetic and molecular genetic research, for the diagnosis and remediation of reading disabilities, and for policy in public education.*

gene-environment interactions (G × E interactions) in group deficits (i.e., the low tail of the normal distribution) in reading, referred to as reading disability, the most commonly identified learning disability.

We investigated whether there are G × E interactions between parental education (our proxy measure for SES and related environmental influences) and the heritability of group deficits in a composite measure of word recognition, spelling, and reading comprehension. Like other measures of SES, parental education has been shown to be a strong predictor for a variety of health and cognitive outcomes in childhood and adulthood (Bradley & Corwyn, 2002). Moreover, parental education may be indicative of level of investment in children's performance in school and educational attainment (Craig, 2006).

In behavior genetic studies, a G × E interaction is indicated by a significant difference in heritability that is moderated by a

Parental Education Moderates Genetic Influences on Reading Disability
Angela Friend, John C. DeFries and Richard K. Olson
Psychological Science 2008 19: 1124
DOI: 10.1111/j.1467-9280.2008.02213.x

How do we identify genes conferring probabilistic propensities?

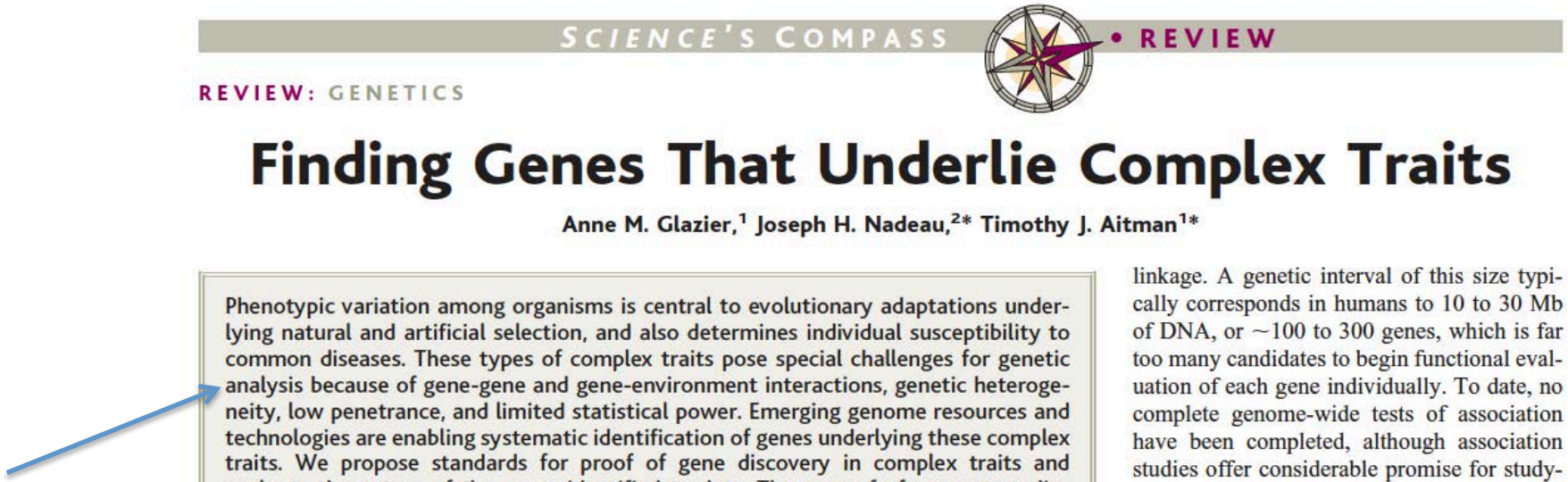
genome-wide linkage studies

- establish statistically significant genome-wide evidence for **linkage** between a trait or disease state and a specific chromosomal location
- *apply the positional cloning strategy to a complex trait*

genome-wide association studies

- *establish significant genome-wide evidence for a statistical* ***association*** *between a particular SNP and a disease state or trait*

Identifying such genes has been very difficult because of the absence of an absolute correlation between genotype and phenotype



SCIENCE'S COMPASS • REVIEW

REVIEW: GENETICS

Finding Genes That Underlie Complex Traits

Anne M. Glazier,[1] Joseph H. Nadeau,[2]* Timothy J. Aitman[1]*

Phenotypic variation among organisms is central to evolutionary adaptations underlying natural and artificial selection, and also determines individual susceptibility to common diseases. These types of complex traits pose special challenges for genetic analysis because of gene-gene and gene-environment interactions, genetic heterogeneity, low penetrance, and limited statistical power. Emerging genome resources and technologies are enabling systematic identification of genes underlying these complex traits. We propose standards for proof of gene discovery in complex traits and evaluate the nature of the genes identified to date. These proof-of-concept studies demonstrate the insights that can be expected from the accelerating pace of gene discovery in this field.

linkage. A genetic interval of this size typically corresponds in humans to 10 to 30 Mb of DNA, or ~100 to 300 genes, which is far too many candidates to begin functional evaluation of each gene individually. To date, no complete genome-wide tests of association have been completed, although association studies offer considerable promise for studying complex traits in populations. In the absence of such proof-of-concept studies for genome-wide association, we focus in this review on those complex trait genes identified in whole-genome linkage studies.

Science 298, 2345 (2002)

Science 18 July 2003: Vol. 301. no. 5631, pp. 386 - 389

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

In a prospective-longitudinal study of a representative birth cohort, we tested why stressful experiences lead to depression in some people but not in others. *A functional polymorphism in the promoter region of the serotonin transporter (5-HT T) gene was found to moderate the influence of stressful life events on depression.* Individuals with one or two copies of the short allele of the 5-HT T promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. *This epidemiological study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.*

LINK to summary of this article:
http://fire.biol.wwu.edu/trent/trent/depressionpolymorph.htm

LINK to original journal article:
http://fire.biol.wwu.edu/trent/trent/lifestress.pdf

Gene–environment interaction (aka **genotype–environment interaction** or **GxE**): *the phenotypic effect of interactions between genes and the environment.*

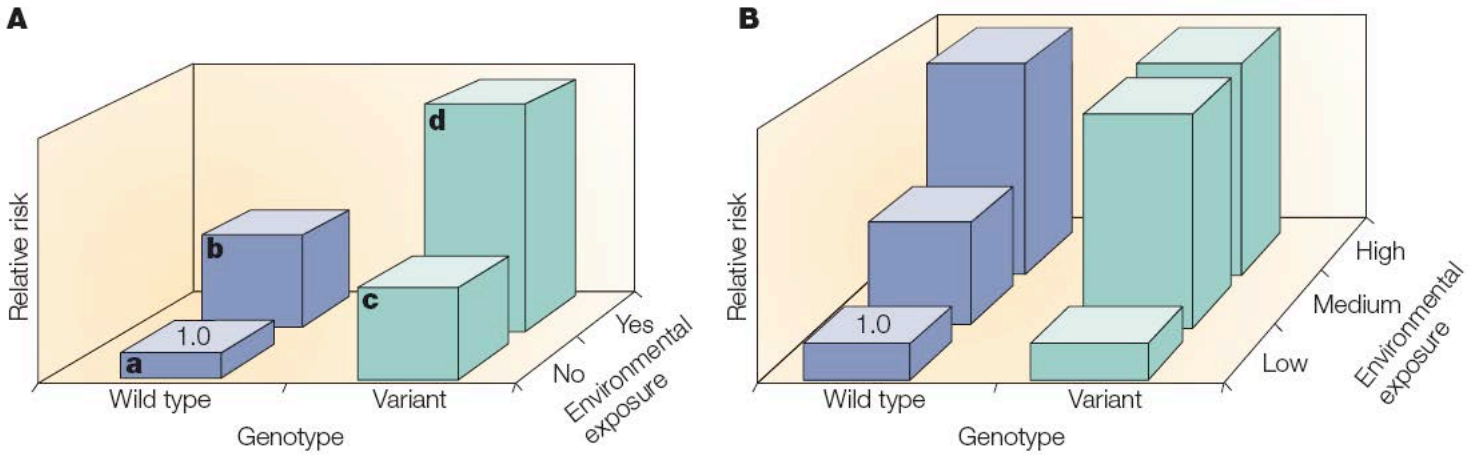
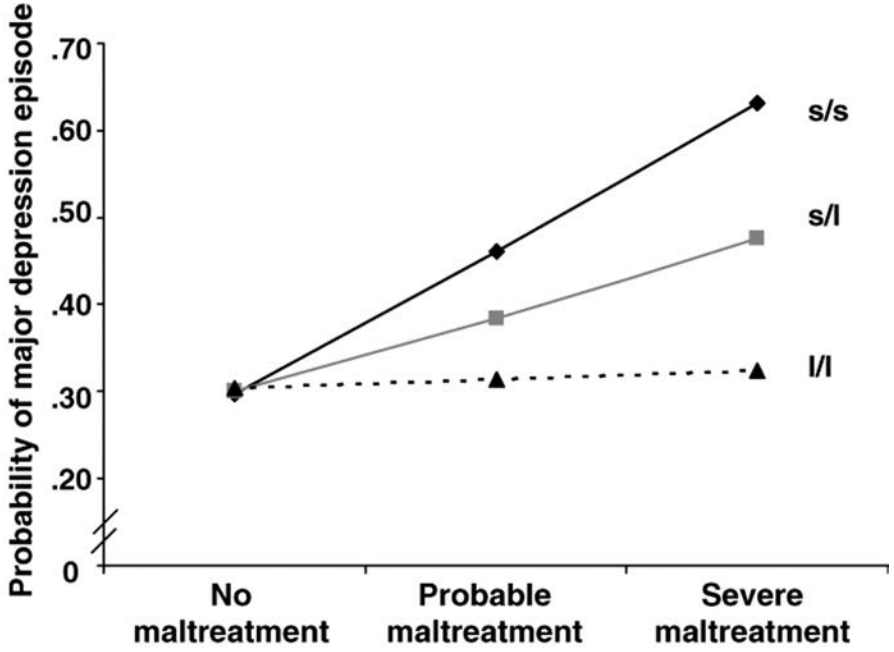


Figure 1 | **Models of gene–environment interactions. A** | In the most simplified example of a dichotomous genotype (for example, carriers versus non-carriers of an allele corresponding to a dominant trait), and dichotomous exposure (for example, 'exposed' versus 'non-exposed'), three categories of joint exposure can be compared with a reference category (for which the relative risk is, by definition, 1.0). Using this simple scheme, BOX 2 shows the different patterns of risk that are observed in some diseases in which inherited susceptibility clearly interacts with environmental exposures to jointly determine disease risk. In the example shown here, the relative risk of developing a disease is much greater in individuals who are both genetically susceptible to the condition and have been exposed to the environmental variable (cell **d**), than in individuals who carry the wild-type genotype and are not exposed to the environmental variable (cell **a**), or who are either only exposed to the environment or genetically susceptible (cells **b** and **c**, respectively). **B** | In the slightly more complex situation in which there are three categories of exposure, it has been proposed that genetically susceptible individuals could be at risk of disease at lower levels of exposure; in this model, the difference in risk between genotypes among individuals at the medium level of exposure is the only indication of an interaction.

Fig. 2. *Results of regression analysis estimating the association between childhood maltreatment (between the ages of 3 and 11 years) and adult depression (ages 18 to 26), as a function of 5-HT T genotype.*

- Among the 147s/s homozygotes, 92 (63%), 39 (27%), and 16 (11%) study members were in the no maltreatment, probable maltreatment, and severe maltreatment groups, respectively.
- Among the 435 s/l heterozygotes, 286 (66%), 116 (27%), and 33 (8%) were in the no, probable, and severe maltreatment groups.
- Among the 265 l/l homozygotes, 172 (65%), 69 (26%), and 24 (9%) were in the no, probable, and severe maltreatment groups.



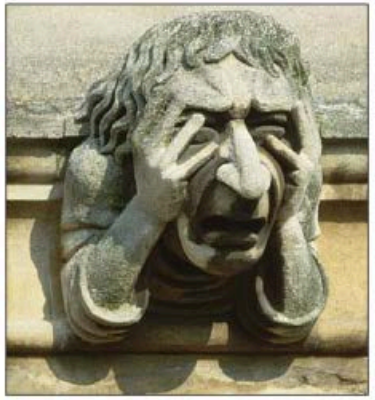
Science – Depression Polymorph Runner up for discovery of the year in 2003

THE RUNNERS–UP

This year's discoveries illuminated realms as small as a single molecule and as large as a gamma ray burst.

#2 Decoding mental illness. Schizophrenia, depression, and bipolar disorder often run in families, but only recently have researchers identified particular genes that reliably increase one's risk of disease. Now they're unraveling how these genes can distort the brain's information processing and nudge someone into mental illness.

The chemical messenger serotonin relays its signal through a receptor that's a target of antidepressant drugs. The gene for this receptor comes in two common flavors, or alleles, one of which had been tenuously linked to an increased risk of depression. This year, researchers revealed why the link had been so elusive: The allele increases the risk of depression only when combined with stress. Among people who had suffered bereavement, romantic rejection, or job loss in their early 20s, those who carried the vulnerability gene were more likely to be depressed than those with the other gene variant.

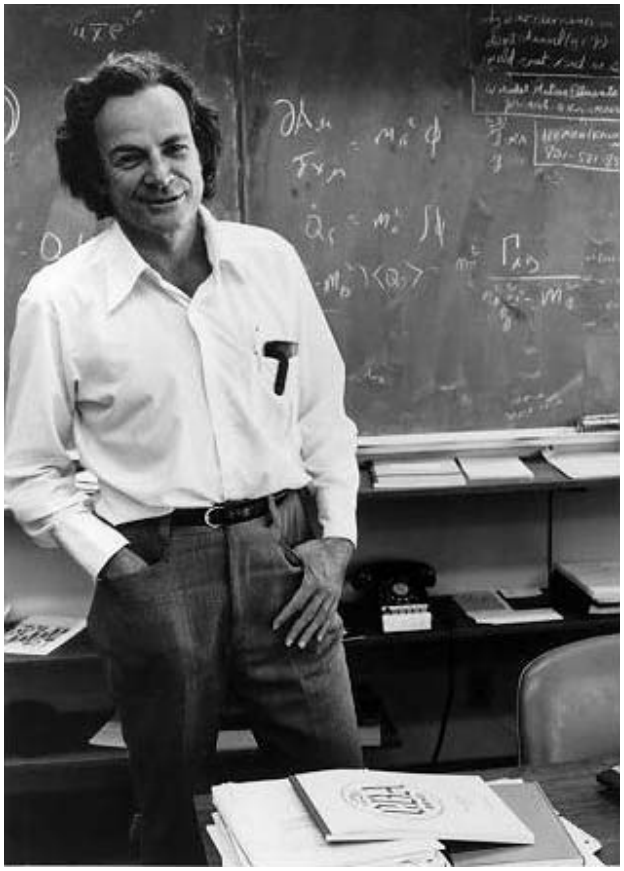


Agony antecedents. New work links genes, brain activity biases, and mental illness.

People with the high-risk allele have unusually heightened activity in a fear-focused brain region called the amygdala when viewing scary pictures. Together, these studies suggest that the gene variant biases people to perceive the world as highly menacing, which amplifies life stresses to the point of inducing depression.

A different brain area, the prefrontal cortex, is regulated in part by a gene called *COMT*, one of the handful associated with risk of schizophrenia. It encodes an enzyme that breaks down neurotransmitters such as dopamine. Two years ago, one version of this gene was shown to muddle the prefrontal cortex, which is necessary for planning and problem-solving skills that are impaired by schizophrenia. Even healthy people who carry the schizophrenia risk allele have extra activity in the prefrontal cortex even when doing relatively simple tasks. The nonschizophrenia allele, which allows more efficient activity in the prefrontal cortex, appears to increase the risk of anxiety, suggesting that the two diseases lie at opposite ends of a spectrum.

Late in 2002, an allele of a gene for brain-derived neurotrophic factor (BDNF) was implicated in bipolar disorder, once known as manic depression. This year the allele was found to curb activity in the hippocampus, a structure necessary for memory that is shrunken in people with mood disorders. BDNF encourages the birth of new neurons in the hippocampus; other work this year showed that antidepressants require this neurogenesis to be effective. Through these and similar insights, researchers hope to understand brain biases underlying mental illnesses well enough to correct them.



Who is this anyway?

"If you thought that science was certain - well, that is just an error on your part."

"It doesn't matter how beautiful your theory is, if it doesn't agree with experiment, it's wrong."

GENETICS

Depression link revoked

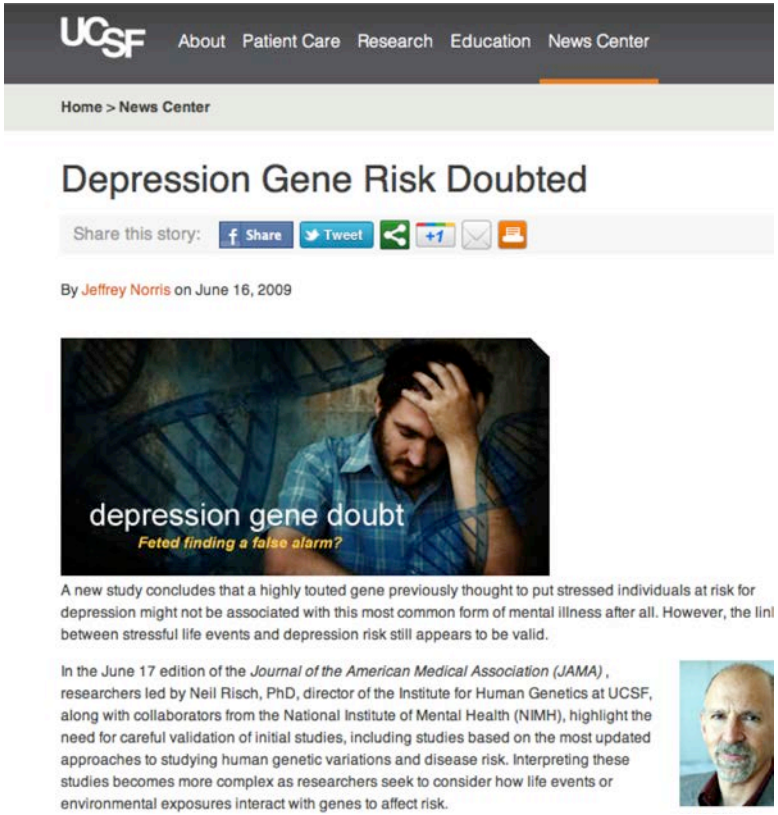
J. Am. Med. Assoc. **301,** 2462–2471 (2009)

An analysis of the literature affirms doubts about a much-hailed gene–environment link for depression.

In 2003, researchers found that individuals with specific versions of the serotonin receptor gene *5-HTTLPR* are more susceptible to depression when challenged by stressful life events (*Science* 301, 386–389; 2003). The finding made intuitive sense, and many studies attempted to replicate and build on the results.

Now, Kathleen Ries Merikangas at the National Institute of Mental Health in Bethesda, Maryland, and her colleagues have evaluated the original study together with 13 others that closely replicated its conditions, re-coding data where necessary to match the original. Looking at a total of more than 14,000 study participants, they find no association between *5-HTTLPR* type and risk of depression, regardless of life events.

http://www.ucsf.edu/news/2009/06/8186/depression-gene-risk-doubted



2011 The Debate Continues
A challenge to the challengers of the depression polymorph

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http://fire.biol.wwu.edu/trent/trent/resurrecting%20depression%20gene.pdf

ScienceDaily
Your source for the latest research news

Web address:
http://www.sciencedaily.com/releases/2011/01/110103161105.htm

Resurrecting the So-Called 'Depression Gene': New Evidence That Our Genes Play a Role in Our Response to Adversity

ScienceDaily (Jan. 4, 2011) — University of Michigan Health System researchers have found new evidence that our genes help determine our susceptibility to depression.

Their findings, published online in the *Archives of General Psychiatry*, challenge a 2009 study that called the genetic link into question and add new support to earlier research hailed as a medical breakthrough.

In the summer of 2003, scientists announced they had discovered a connection between a gene that regulates the neurotransmitter serotonin and an individual's ability to rebound from serious emotional trauma, such as childhood physical or sexual abuse.

Our genes help determine our susceptibility to depression, new research suggests. (Credit: iStockphoto/Nicholas Belton)

The journal *Science* ranked the findings among the top discoveries of the year and the director of the National Institute of Mental Health proclaimed, "It is a very important discovery and a real advance for the field."