COMPLEX TRAIT: This term has come to refer to any phenotype that does not exhibit classic Mendelian inheritance attributable to a single gene locus.

⇒ Often, complexities arise when a simple correspondence between genotype and phenotype breaks down
HEY -- NOT SO FAST: even the expression of monogenic traits can be complex.
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.

**PAH converts phenylalanine to tyrosine**
**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
- this means that at least 30 different genes contribute to normal hearing, but this doesn’t make deafness a multifactorial trait

\[
\text{phenotype W } \leftrightarrow \text{ phenotype D} \\
\text{only one* gene is different}
\]

\[
W= \text{wild-type (normal hearing) } \quad D= \text{deaf} \\
*\text{of many possible genes}
\]
Complex inheritance patterns:

- **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.

*Continuous variation* is characteristic of polygenic or multifactorial 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.
**Polygenic & Multifactorial 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

**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

\[
\text{phenotype W} \leftrightarrow \text{phenotype D}
\]

*multiple genetic differences*

\[
W= \text{wild-type (not diabetic)} \quad D = \text{severe NIDDM diabetic}
\]
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 color.
- 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 these two genes don't paint the full picture.
Proteins encoded by each gene:

- KITLG, KIT ligand;
- MC1R, melanocortin 1 receptor;
- OCA2, oculocutaneous albinism II;
- SLC24A4, solute carrier family 24, member 4;
- TYR, tyrosinase
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 pigmentation 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^{-9}, 1.57 × 10^{-9}, and 4.45 × 10^{-9}, 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 pigmentation phenotypes. Heterozygotes 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.
Many alleles of the OCA2 gene exist—some specifically affecting transcriptional level of the gene in the iris.
Multifactorial Traits

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

“Hey! Look what Zog did!”
Reading ability is an example of a continuous trait specified by a complex interaction of genotype and environment.

\[ X \text{ axis: number of individuals} \quad Y \text{ axis: reading ability} \]

Symbols in graph explained on 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.

*In this example genes relating to*

attention deficit disorder?
dyslexia?
nervous system development?
intelligence?
Identifying genes that confer probabilistic propensities rather than predetermined programs has been very difficult because of the absence of an absolute correlation between genotype and phenotype

A short review of false starts and broken promises
AIDS virus receptor.

When the researchers gave peptide T to rats and monkeys, they found that it seemed nontoxic and that it entered the animals' brains. In fact, says Peter Bridge, they "never found an LD_{50}," which is the dose that kills 50% of the animals receiving the drug. Standard toxicological studies of drugs always include an LD_{50} as an indicator of a drug's lethal dose.

In Sweden, says Wetterberg, the AIDS patients who received peptide T had no ill effects. The only adverse effect occurred when a nurse doubled the rate at which a patient was being infused with the drug. The patient's blood pressure dropped from 120 to 90. The patient, however, "did not feel anything. He had no subjective side effects," Wetterberg says.

Although the Swedish study was not meant to be a scientific test of the drug, Wetterberg says he was encouraged by the way the patients improved when they took it. Their lymphocytes increased in number and the virus' effects on their brains, as measured by nuclear magnetic resonance, declined. One patient had a severe case of psoriasis as a result of his AIDS infection and his lesions cleared up entirely after four weeks of treatment. The psoriasis has now returned, Wetterberg says. The patients have been off the drug since the end of October.

If indeed peptide T is relatively nontoxic,

Manic-Depression Gene Tied to Chromosome 11

A dominant gene causes this psychiatric disorder in 60 to 70% of those who inherit it

A group of researchers from the Massachusetts Institute of Technology, the University of Miami School of Medicine, and Yale University School of Medicine has found a genetic marker for manic-depression—a piece of DNA so near the manic-depression gene that it is inherited along with the disease-causing gene. This is the first genetic marker for a mental illness and the investigators stress that it is expected to lead to a new understanding of the biochemistry of manic-depression and also to new treatments. "We see this as a landmark study," says David Pauls, one of the study investigators.

At the same time, two other groups report that they have failed to find the marker in other populations of patients with manic-depression, indicating that there is more than one gene that predisposes to this mental illness. The three groups report their results in the 26 February issue of Nature.

The new study indicates that at least some cases of manic-depression are caused by a dominant gene on the tip of the short arm of chromosome 11. Although the researchers do not yet know what the manic-depression gene is, they are intrigued by the fact that at least one gene in this region of chromosome 11—the tyrosine hydroxylase gene—is involved in the synthesis of the neurotransmitter dopamine. Dopamine is thought to be involved in the genesis of manic-depression.

Yet, at least in the case of manic-depression, the gene is not necessarily destiny. Only 60 to 70% of those who inherit the gene get the disease, and investigators speculate that some as yet unknown environ-
Linkage Analyses of Chromosome 18 Markers Do Not Identify a Major Susceptibility Locus for Bipolar Affective Disorder in the Old Order Amish

David L. Pauls,1 Jurg Ott,2 Steven M. Paul,3,4 Cleona R. Allen,5 Cathy S. J. Fann,2 John P. Carulli,6 Kathleen M. Falls,6 Christine A. Bouthillier,6 Thomas C. Gravius,6 Tim P. Keith,6 Janice A. Egeland,5 and Edward I. Ginn3

1Child Study Center, Yale University School of Medicine, New Haven; 2Columbia University and New York State Psychiatric Institute, New York; 3Clinical Neuroscience Branch, NRP, National Institute of Mental Health, Bethesda; 4Lilly Research Laboratories, Indianapolis; 5Department of Psychiatry, University of Miami, Miami; and 6Genome Therapeutics Corporation, Waltham

Summary

Previously reported linkage of bipolar affective disorder to DNA markers in the pericentromeric region of chromosome 18 was reexamined in a larger homogeneous sample of Old Order Amish families. Four markers (D18S21, D18S53, D18S44, and D18S40) were examined in three kindreds containing 31 bipolar I (BP I) individuals. Although linkage findings were replicated in the one previously studied Amish pedigree containing four BP I individuals, linkage to this region was excluded in the larger sample. If a susceptibility locus for bipolar disorder is located in this region of chromosome 18, it is of minor significance in this population.

sion for bipolar I affective disorder (BP I) alone is consistent with an autosomal dominant mode of inheritance. Again, however, the findings are not consistent across all families studied (Sham et al. 1991).

Despite difficulty in understanding the complex inheritance patterns of bipolar disorder, a number of genetic linkage studies have attempted to identify a single gene of major effect (Nurnberger 1993). Initially, there were reports of linkage to markers near the color-blindness locus on the X chromosome (Risch et al. 1986). In 1987, Egeland and colleagues reported strong evidence for linkage of a susceptibility locus for bipolar disorder to markers on 11p15 (Egeland et al. 1987). Unfortunately, there have been no replications of this finding in other
LOCATION OF A MAJOR SUSCEPTIBILITY LOCUS FOR FAMILIAL SCHIZOPHRENIA ON CHROMOSOME 1q21–q22

Linda M. Brzustowicz, 12* Kathleen A. Hodgkinson, 3 Eva W. C. Chow, 3,4 William G. Honer, 5 Anne S. Bassett 3,4

Schizophrenia is a complex disorder, and there is substantial evidence supporting a genetic etiology. Despite this, prior attempts to localize susceptibility loci have produced predominantly suggestive findings. A genome-wide scan for schizophrenia susceptibility loci in 22 extended families with high rates of schizophrenia provided highly significant evidence of linkage to chromosome 1 (1q21–q22), with a maximum heterogeneity logarithm of the likelihood of linkage (lod) score of 6.50. This linkage result should provide sufficient power to allow the positional cloning of the underlying susceptibility gene.

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* Corresponding author.
No Major Schizophrenia Locus Detected on Chromosome 1q in a Large Multicenter Sample

Douglas F. Levinson,1* Peter A. Holmans,2 Claudine Laurent,3 Brien Riley,4 Ann E. Pulver,5 Pablo V. Gejman,6 Sibylle G. Schwab,7 Nigel M. Williams,8 Michael J. Owen,8 Dieter B. Wildenauer,7 Alan R. Sanders,6 Gerald Nestadt,5 Bryan J. Mowry,9,10 Brandon Wormley,4 Stéphanie Bauché,3 Stéphane Soubigou,11 Robert Ribble,4 Deborah A. Nertney,9 Kung Yee Liang,12 Laura Martinolich,6 Wolfgang Maier,7 Nadine Norton,8 Hywel Williams,8 Margot Albus,13 Eric B. Carpenter,6 Nicola deMarchi,14 Kelly R. Ewen–White,15 Dermot Walsh,16 Maurice Jay,3 Jean–François Deleuze,11 F. Anthony O'Neill,17 George Papadimitriou,18 Ann Weilbaecher,6 Bernard Lerer,19 Michael C. O'Donovan,8 Dimitris Dikeos,18 Jeremy M. Silverman,20 Kenneth S. Kendler,4 Jacques Mallet,3 Raymond R. Crowe,21 Marilyn Walters22

Reports of substantial evidence for genetic linkage of schizophrenia to chromosome 1q were evaluated by genotyping 16 DNA markers across 107 centimorgans of this chromosome in a multicenter sample of 779 informative schizophrenia pedigrees. No significant evidence was observed for such linkage, nor for heterogeneity in allele sharing among the eight individual samples. Separate analyses of European–origin families, recessive models of inheritance, and families with larger numbers of affected cases also failed to produce significant evidence for linkage. If schizophrenia susceptibility genes are present on chromosome 1q, their population–wide genetic effects are likely to be small.
Physical mapping, linkage analysis of a putative schizophrenia locus on chromosome 5q.

**Kaufmann CA, DeLisi LE, Lehner T, Gilliam TC.**

Department of Psychiatry, Columbia University, New York, NY.

Two recent studies have suggested that a schizophrenia susceptibility locus may lie on the proximal long arm of chromosome 5. Partial trisomy of a 20-30 centimorgan region of chromosome 5 (5q11.2-13.3) was found to cosegregate with schizophrenia in a Canadian family of Chinese descent. Moreover, DNA markers from proximal 5q (D5S39, D5S76) were found to be linked to schizophrenia and related disorders in seven British and Icelandic families. We now report an initial physical map of DNA markers relative to the partial trisomy chromosome 5, as well as preliminary evidence against linkage of this region to schizophrenia in four American families.

PMID: 2814374 [PubMed - indexed for MEDLINE]
Related Links

- Deletion mapping of DNA markers to a region of chromosome 5 that cosegregates with schizophrenia. [Genomics. 1989]
- No linkage of chromosome 5q11-q13 markers to schizophrenia in Scottish families. [Nature. 1989]
- New DNA markers with increased informativeness show diminished support for a chromosome 5q11-13 schizophrenia. [Ann Hum Genet. 1999]
- No evidence for linkage between chromosome 5 markers and schizophrenia. [Hum Hered. 1990]
- A genetic linkage study of schizophrenia to chromosome 5 markers in a northern Italian population. [Biol Psychiatry. 1992]

» See all Related Articles...
These studies have been plagued with methodological problems:

1. Failure to adequately define the trait under study
2. Bias in the selection of cases and controls
3. Inadequate sample sizes
4. Misuse of statistical methods

*(Who said: “lies, damn lies and statistics”?)*
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-HTT) 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-HTT 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.
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 147 s/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.
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.

(see also last page of this lecture)
Depression link revoked


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.

**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
BUT, there has been some (apparent) recent success in finding genetic variations that are involved in psychoses (such as schizophrenia) which have a strong inherited component –

http://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml

Schizophrenia is a debilitating neuropsychiatric illness with severe individual, family and societal burdens

- It has a worldwide prevalence of ~1%
- Illness typically arises in late adolescence or early adulthood
- Phenotype is heterogeneous and complex
- Multiple genetic and environmental components are likely to be involved
Genetic component

• *Family, twin and adoption studies all indicate a strong genetic component*

• *Patterns of inheritance are variable and not consistent with a simple monogenic trait*

• *Concordance between monozygotic twins is only 50% -- leaving plenty of room for non-genetic influences*
Non-genetic Factors affecting neurodevelopment:

- *prenatal environment including placental status, maternal infections, maternal nutritional status* can effect neurodevelopment
- *postnatal environment*

* For example, epidemiological investigations of 2 famines in the 20th century—the Nazi-induced 1944-1945 Dutch Hunger Winter and the Chinese famine of 1959-1961 following the failure of the Great Leap Forward—demonstrated an increased risk for schizophrenia among offspring conceived in famine conditions.

See also: *Maternal effects on Schizophrenia Risk*: Science 318:576 2007

Other issues complicating the search of predisposing alleles:

*The Brains of the Family*: does the difficulty in finding the genes responsible for mental illness reflect the complexity of the genetics or the *poor definitions of psychiatric disorders*? Nature 454: 154 2008
“Common disease-common allele” model

• Illness is caused by combinations of common alleles, each contributing a modest effect

Alternative model

• Some mutations predisposing to schizophrenia are highly penetrant, individually rare and of recent origin – even specific to single cases or families (Science 320:539 2008)

These are not mutually exclusive possibilities
Allelic variations of these candidate genes may confer susceptibility to schizophrenia
**DISC 1= disrupted in schizophrenia:** the product of the *DISC1* gene has been implicated in two major signal transduction pathways with roles in brain development and function.

Pedigree on next page shows that the chromosomal aberration* (reciprocal translocation) that disrupts the *DISC1* gene segregating with psychotic disturbance

**reciprocal translocation:** reciprocal exchange of chromosome segments between non-homologous chromosomes

![Chromosome Diagram]
Figure 1  Part of the family with a (1,11)(q42,q14.3) translocation. Karyotype analysis has been performed on 87 members of this family, and clinical psychiatric data were obtained from 69 of those family members. Shown are 58 of the family members for whom carrier status is known and whose psychiatric phenotype has been defined through follow-up by direct interview, general-practice contact, or hospital case-note review.

Major mental illnesses may be linked by a common cellular signaling mechanism. DISC1 is involved in at least two major signaling cascades that have been implicated in brain development and function: cAMP signaling and dynein-NUDEL signaling. Increases in cellular cAMP and protein kinase A activity disrupt DISC1-PDE4B interaction. This augments phosphodiesterase activity and increases the dynein signaling pathway, which have been linked to alterations in brain development, cognition, and mood behavior.
Box 2 | Some patterns of relative risk in gene–environment interactions

The table shows just three examples of different patterns of relative risk for three classical genetic diseases that have an environmental component, assuming dichotomous genetic susceptibility and environmental exposure (the data are from Refs 5,6).

In the first example, xeroderma pigmentosum (XP), exposure to ultraviolet light increases the risk of developing skin cancer in non-carriers of XP mutations, but the combination of these mutations and exposure to ultraviolet light vastly increases the risk of skin cancer. In theory, if individuals with XP mutations completely avoid ultraviolet light their risk of skin cancer becomes close to the background risk.

The example in the second column is that of phenylketonuria (PKU); only individuals with recessive mutations in the causative gene (phenylalanine hydroxylase) that are exposed to phenylalanine in the diet are susceptible to PKU.

In the third column, exemplified by a deficiency in the α-1 antitrysin gene, both non-smokers that are at genetic risk and smokers that are not at genetic risk have an increased risk of developing emphysema, and the combination (smokers that are at genetic risk) is associated with the highest risk.

There are many other patterns of gene–environment interactions, including ‘protective’ alleles and exposures.

<table>
<thead>
<tr>
<th>Gene variant</th>
<th>Environmental exposure</th>
<th>Relative risk (XP)</th>
<th>Relative risk (PKU)</th>
<th>Relative risk (emphysema)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Absent</td>
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<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
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