The Causes of Variation

2016 International Workshop on Statistical Genetic Methods for Human Complex Traits
Boulder, CO.

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VIPBG, Richmond VA.
March 2016
GOALS – “Orientation”

• To outline some of the basic issues that we will address this week
• To set some of the issues in their historical context in the story of genetics and its application to human variation.
“Genetics”

The Study of

Variation and Heredity
“Variation”

“Why aren’t we all the same?”
“Heredity”

“Why do things run in families?”
“VARIATION”
Gregor Mendel (1822-1885)

1865: Experiments in Plant Hybridisation
Mendel

- Binary traits ("White vs Pink")
- Particulate ("Mendelian") Inheritance
- Simple mathematical and statistical laws
- Corresponded to behavior of chromosomes
- Explained inborn errors of metabolism -> Medical genetics, "gene-hunting"
- Provided Mechanism for Natural Selection
- Illuminated by structure of DNA
Continuous variation
Distribution of Stature in Virginia 30,000

0 if female, 1 if male

Height (in.)
The distribution of IQ among the 14,963 children born in Scotland on February 1, May 1, August 1, and November 1, 1926. The shaded histogram shows the percentages of the group with IQ's in various ranges of 10 points. This grouping is artificial and is done solely for ease of representation: it does not imply any discontinuity in the values of IQ that children can show. The continuous curve shows the ideal distribution calculated from the observations and representing the statistical population of which the children actually observed are regarded as forming a sample. (Data from MacMeekan; from Mather 1964.)
“Liberalism”
Categorical Outcomes

Often called “threshold traits” because people “affected” if they fall above some level (“threshold”) of a measured or hypothesized continuous trait.
Douglas Scott Falconer, FRS, FRSE (1913-2004)

FIGURE 9.5
Threshold model. All individuals with a value of $x$ greater than $T$ are affected. The proportion of affected individuals is the area under the distribution curve beyond $T$. 
Relationship between continuous normal “liability” and risk of “diagnosis” (see I.R.T.)
Question that bugs me:

How do you get from “liability” to “catastrophe”?
“HEREDITY”
Charles Darwin (1809-1882)

1865: On the Origin of Species
Francis Galton (1822-1911)

1869: Hereditary Genius
1883: Inquiries into Human Faculty and its Development
1884-5: Anthropometric Laboratory at “National Health Exhibition”
Galton's Other Work e.g. Meteorology
<table>
<thead>
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<td>Father</td>
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<td>33</td>
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<tr>
<td>Brother</td>
<td>35</td>
<td>39</td>
<td>50</td>
<td>42</td>
<td>47</td>
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<td>50</td>
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<td>Son</td>
<td>36</td>
<td>49</td>
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<td>51</td>
<td>60</td>
<td>45</td>
<td>89</td>
<td>40</td>
<td>48</td>
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<td>Grandfather</td>
<td>15</td>
<td>28</td>
<td>16</td>
<td>24</td>
<td>14</td>
<td>5</td>
<td>7</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Uncle</td>
<td>18</td>
<td>18</td>
<td>8</td>
<td>24</td>
<td>16</td>
<td>5</td>
<td>14</td>
<td>40</td>
<td>18</td>
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<tr>
<td>Nephew</td>
<td>19</td>
<td>18</td>
<td>35</td>
<td>24</td>
<td>23</td>
<td>50</td>
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<td>14</td>
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<tr>
<td>Grandson</td>
<td>19</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>14</td>
<td>5</td>
<td>18</td>
<td>16</td>
<td>14</td>
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<tr>
<td>Great-grandfather</td>
<td>2</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Great-uncle</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>5</td>
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<td>First cousin</td>
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<td>20</td>
<td>18</td>
<td>16</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Great-nephew</td>
<td>17</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>16</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Great-grandson</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All more remote</td>
<td>4</td>
<td>37</td>
<td>44</td>
<td>15</td>
<td>23</td>
<td>3</td>
<td>18</td>
<td>16</td>
<td>31</td>
</tr>
</tbody>
</table>

Hereditary Genius (1869, p 317)
ANTHROPOMETRIC LABORATORY

For the measurement in various ways of Human Form and Faculty.

Entered from the Science Collection of the S. Kensington Museum.

This laboratory is established by Mr. Francis Galton for the following purposes:

1. For the use of those who desire to be accurately measured in many ways, either to obtain timely warning of remediable faults in development, or to learn their powers.

2. For keeping a methodical register of the principal measurements of each person, of which he may at any future time obtain a copy under reasonable restrictions. His initials and date of birth will be entered in the register, but not his name. The names are indexed in a separate book.

3. For supplying information on the methods, practice, and uses of human measurement.

4. For anthropometric experiment and research, and for obtaining data for statistical discussion.

Charges for making the principal measurements:
THREEPENCE each to those who are already on the Register.
FOURPENCE each, to those who are not— one page of the Register will thenceforward be assigned to them, and a few extra measurements will be made, chiefly for future identification.

The Superintendent is charged with the control of the laboratory and with determining in each case, which, if any, of the extra measurements may be made, and under what conditions.
Francis Galton's First Anthropometric Laboratory at the International Health Exhibition, South Kensington, 1884-5.
Karl Pearson (1857-1936)

1903: On the Laws of Inheritance in Man: I Physical Characteristics (with Alice Lee)
1904: II Mental and Moral Characteristics
1914: The Life, Letters and Labours of Francis Galton
FAMILY MEASUREMENTS.

Professor Karl Pearson, of University College, London, would esteem it a great favour if any persons in a position to do so, would assist him by making one set (or if possible several sets) of anthropometric measurements on their own family, or on families with whom they are acquainted. The measurements are to be made use of for testing theories of heredity, no names, except that of the recorder, are required, but the Professor trusts to the bona fides of each recorder to send only correct results.

Each family should consist of a father, mother, and at least one son or daughter, not necessarily the eldest. The sons or daughters are to be at least 18 years of age, and measurements are to be made on not more than two sons and two daughters of the same family. If more than two sons or two daughters are easily accessible, then not the tallest but the eldest of those accessible should be selected.

To be of real service the whole series ought to contain 1000—2000 families, and therefore the Professor will be only too grateful if anyone will undertake several families for him.

Copies of this paper, together with cards for recording data, may be obtained from

or from the above-named Professor.
Pearson and Lee’s diagram for measurement of “span” (finger-tip to finger-tip distance)
**TABLE IV.**

*Coefficients of Heredity. Parents and Offspring.*

<table>
<thead>
<tr>
<th>Character</th>
<th>Father and</th>
<th>Mother and</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Son</td>
<td>Daughter</td>
</tr>
<tr>
<td>Stature</td>
<td>0.514 ± 0.015</td>
<td>0.510 ± 0.013</td>
</tr>
<tr>
<td>Span</td>
<td>0.454 ± 0.016</td>
<td>0.454 ± 0.014</td>
</tr>
<tr>
<td>Forearm</td>
<td>0.421 ± 0.017</td>
<td>0.422 ± 0.015</td>
</tr>
</tbody>
</table>

From Pearson and Lee (1903) p.378
**Correlation Coefficients for Direct Fraternal Heredity.**

<table>
<thead>
<tr>
<th>Character</th>
<th>Brother and Brother</th>
<th>Sister and Sister</th>
<th>Brother and Sister</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stature</td>
<td>$0.511 \pm 0.028$</td>
<td>$0.537 \pm 0.022$</td>
<td>$0.553 \pm 0.013$</td>
<td>$0.534$</td>
</tr>
<tr>
<td>Span</td>
<td>$0.549 \pm 0.026$</td>
<td>$0.555 \pm 0.021$</td>
<td>$0.525 \pm 0.013$</td>
<td>$0.543$</td>
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<tr>
<td>Forearm</td>
<td>$0.491 \pm 0.029$</td>
<td>$0.507 \pm 0.023$</td>
<td>$0.440 \pm 0.015$</td>
<td>$0.479$</td>
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<tr>
<td>Mean</td>
<td>$0.517$</td>
<td>$0.533$</td>
<td>$0.506$</td>
<td>$0.519$</td>
</tr>
<tr>
<td>Eye Colour*</td>
<td>$0.517 \pm 0.020$</td>
<td>$0.446 \pm 0.023$</td>
<td>$0.462 \pm 0.022$</td>
<td>$0.475$</td>
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<tr>
<td>Total mean</td>
<td>$0.517$</td>
<td>$0.511$</td>
<td>$0.495$</td>
<td>$0.508$</td>
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</table>

From Pearson and Lee (1903) p.387
**Assortative Mating. Based on 1000 to 1050 Cases of Husband and Wife.**

<table>
<thead>
<tr>
<th></th>
<th>Husband's Character</th>
<th>Wife's Character</th>
<th>Correlation and Probable Error</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td>Stature</td>
<td>Stature</td>
<td>( r_{12} )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Span</td>
<td>Span</td>
<td>( r_{34} )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Forearm</td>
<td>Forearm</td>
<td>( r_{56} )</td>
<td></td>
</tr>
</tbody>
</table>

From Pearson and Lee (1903) p. 373
Modern Data

The Virginia 30,000
(N=29691)

The Australia 22,000
(N=20480)
ANZUS 50K: Extended Kinships of Twins

Parents of Twins

Spouses of Twins

Twins

Offspring of Twins

Siblings of Twins

© Lindon Eaves, 2009
## Overall sample sizes

<table>
<thead>
<tr>
<th>Relationship</th>
<th># of pairs</th>
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<tbody>
<tr>
<td>Parent-offspring</td>
<td>25018</td>
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<tr>
<td>Siblings</td>
<td>18697</td>
</tr>
<tr>
<td>Spouses</td>
<td>8287</td>
</tr>
<tr>
<td>DZ Twins</td>
<td>5120</td>
</tr>
<tr>
<td>MZ Twins</td>
<td>4623</td>
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</tbody>
</table>
Nuclear Family Correlations for Stature
(Virginia 30,000 and OZ 22,000)
Nuclear Family Correlations for Stature and Liberalism/Conservatism (Virginia 30,000)
Nuclear Family Correlations for Liberalism/Conservatism
(Virginia 30,000 and Australia 22,000)
Nuclear Family Correlations for Stature and EPQ Neuroticism (Virginia 30,000)

- Spouses
- Mother-Dau
- Mother-Son
- Father-Dau
- Father-Son
- Male Sibs
- Female Sibs
- M-F Sibs

- Stature
- Neuroticism
Nuclear Family Correlations for Socially Significant Variables (Virginia 30,000)
Nuclear Family Correlations for Socially Significant Variables (Australia 22K)
The (Really!) BIG Problem

Families are a mixture of genetic and social factors
A Basic Model

Phenotype=Genotype+Environment

P=G+E \{+f(G,E)\}

f(G,E) = G-E “Interplay”

i.e. Genotype-environment interaction (GxE) and G-E correlation (rGE)
GxE Interaction and Correlation

- **GxE:** SENSITIVITY to E controlled by G

- **rGE:** EXPOSURE to E correlated with (“depends on”) G

Lots of good plant and animal models for both
Sources of rGE

• Environment is “caused by” (“selected by”) genetic characteristics of subject (“active/evocative” e.g. “niche selection”)

• Environment is “affected by” genetic characteristics of relatives (mothers, fathers, siblings, “passive”)

• Both are (may be) dynamic, temporal, developmental
Galton’s Solution:

Twins

(Though Augustine may have got there first – 5^{th} cent.)
One (≠ideal) solution

Twins separated at birth
Figure 2. Scatter diagram showing correlation between IQs of 122 sets of co-twins (A and B assigned at random). The obtained intraclass correlation ($r_i$) is 0.82. The diagonal line represents perfect correlation ($r_i = 1.00$).
But separated MZs are rare
An easier alternative:

Identical and non-identical twins reared together: Galton (Again!)
IDENTICAL TWINS

• MONOZYGOTIC: Have IDENTICAL genes (G)
• Come from the same family (C)
• Have unique experiences during life (E)
FRATERNAL TWINS

• DIZYGOTIC: Have DIFFERENT genes (G)
• Come from the same family (C)
• Have unique experiences during life (E)
Scatterplot for corrected MZ stature

Data from the Virginia Twin Study of Adolescent Behavioral Development
Scatterplot for age and sex corrected stature in DZ twins

Data from the Virginia Twin Study of Adolescent Behavioral Development
Twin Correlations for Adult Stature
(Virginia 30,000 and Australia 22,000)
Twin Correlations for Stature and Liberalism (Virginia 30,000 and Australia 22,000)
Twin Correlations for Stature and Liberalism
(Virginia 30,000 and Australia 22,000)
Twin Correlations for Socially Significant Variables
(Virginia 30,000)
Twin Correlations for Socially Significant Variables
(Australia 22,000)
Twin correlations for gene expression

A

Correlation (Fisher's Z)

density

Correlation (Fisher's Z)

B

Broad sense heritability

York et al.
Twin correlations for attitudes to gun control

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>r</th>
<th>s.e.</th>
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<tbody>
<tr>
<td>MZM</td>
<td>147</td>
<td>0.594</td>
<td>0.085</td>
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<tr>
<td>MZF</td>
<td>630</td>
<td>0.383</td>
<td>0.059</td>
</tr>
<tr>
<td>DZM</td>
<td>65</td>
<td>0.119</td>
<td>0.187</td>
</tr>
<tr>
<td>DZF</td>
<td>315</td>
<td>0.366</td>
<td>0.083</td>
</tr>
<tr>
<td>DZMF</td>
<td>215</td>
<td>0.137</td>
<td>0.105</td>
</tr>
</tbody>
</table>
Ronald Fisher (1890-1962)

1918: On the Correlation Between Relatives on the Supposition of Mendelian Inheritance
1921: Introduced concept of “likelihood”
1930: The Genetical Theory of Natural Selection
1935: The Design of Experiments
Fisher developed mathematical theory that reconciled Mendel’s work with Galton and Pearson’s correlations

(MS. received June 15, 1918. Read July 8, 1918. Issued separately October 1, 1918.)

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a. Distribution of scores produced by two genes
(N=1000 subjects)

b. The "smoothing" effect of the environment
(N=1000 subjects, 2 gene model)

c. Continuous distribution of polygenic trait
(100 genes with small cumulative effects)
Fisher (1918): Basic Ideas

- Continuous variation caused by lots of genes ("polygenic inheritance")
- Each gene followed Mendel’s laws
- Environment smoothed out genetic differences
- Genes may show different degrees of "dominance"
- Genes may have many forms ("multiple alleles")
- Mating may not be random ("assortative mating")
- Showed that correlations obtained by e.g. Pearson and Lee were explained well by polygenic inheritance
- Let to "Biometrical Genetics" (Mather, Jinks etc.)
Sewall Wright (1889-1988)

Path diagram for the effects of genes and environment on phenotype

- Genotype
- Environment

Latent variables: 
- $r$
- $h$
- $e$

Measured variable:
- $P$

Phenotype
Genetic AND Cultural inheritance?

Diagram:
- **Genes** from Parents to Offspring
- **Mother** and **Father** contribute to Offspring
- **Genes** from Parents to Offspring
- **Unique** factors in Offspring
- **Shared** factors in Offspring
- **Residual Environment** impact
Development
a. Genetic variation in developmental change: time series with common genes and time-specific environmental “innovations”
Attitudes over the life-span
Children of Twins ("COT")

Parents of Twins

Spouses of Twins

Twins

Offspring of Twins

Siblings of Twins
Gestational Age

Racial Differences in Genetic and Environmental Risk to Preterm Birth

Timothy P. York, Jerome F. Strauss, Michael C. Neale, Lindon J. Eaves

<table>
<thead>
<tr>
<th>Parental relationship</th>
<th>European American</th>
<th></th>
<th>African American</th>
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<tbody>
<tr>
<td></td>
<td>N. Families</td>
<td>N. Births</td>
<td>N. Families</td>
<td>N. Births</td>
</tr>
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<td>Sibship</td>
<td>284,446</td>
<td>575,709</td>
<td>66,983</td>
<td>119,791</td>
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<td>Maternal half-sibship</td>
<td>6,736</td>
<td>12,269</td>
<td>2,431</td>
<td>4,515</td>
</tr>
<tr>
<td>Paternal half-sibship</td>
<td>5,419</td>
<td>9,800</td>
<td>2,839</td>
<td>5,292</td>
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<tr>
<td>MZ male twin</td>
<td>595</td>
<td>1,092</td>
<td>69</td>
<td>99</td>
</tr>
<tr>
<td>MZ female twin</td>
<td>618</td>
<td>1,212</td>
<td>98</td>
<td>144</td>
</tr>
<tr>
<td>DZ male twin</td>
<td>393</td>
<td>700</td>
<td>52</td>
<td>77</td>
</tr>
<tr>
<td>DZ female twin</td>
<td>368</td>
<td>696</td>
<td>72</td>
<td>119</td>
</tr>
<tr>
<td>DZ male-female twin</td>
<td>936</td>
<td>1,614</td>
<td>139</td>
<td>210</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>299,511</strong></td>
<td><strong>603,092</strong></td>
<td><strong>72,683</strong></td>
<td><strong>130,247</strong></td>
</tr>
</tbody>
</table>
Table 1. Expected covariance of gestational age expressed as variance components between pregnancy outcomes as a function of relationship between offspring.

<table>
<thead>
<tr>
<th>Parental relationship</th>
<th>Fetal relationship</th>
<th>Expected covariance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ female twins</td>
<td>Half-sibling</td>
<td>$\frac{1}{4} f^2 + m^2$</td>
</tr>
<tr>
<td>DZ female twins</td>
<td>Cousin</td>
<td>$\frac{1}{8} f^2 + \frac{1}{2} m^2$</td>
</tr>
<tr>
<td>MZ male twins</td>
<td>Half-sibling</td>
<td>$\frac{1}{4} f^2$</td>
</tr>
<tr>
<td>DZ male twins</td>
<td>Cousin</td>
<td>$\frac{1}{8} f^2$</td>
</tr>
<tr>
<td>DZ male-female twins</td>
<td>Cousin</td>
<td>$\frac{1}{8} f^2$</td>
</tr>
<tr>
<td>Sibship</td>
<td>Sibling</td>
<td>$\frac{1}{2} f^2 + m^2 + c^2$</td>
</tr>
<tr>
<td>Maternal half-sibship</td>
<td>Half-sibling</td>
<td>$\frac{1}{4} f^2 + m^2 + hc^2$</td>
</tr>
<tr>
<td>Paternal half-sibship</td>
<td>Half-sibling</td>
<td>$\frac{1}{4} f^2 + hc^2$</td>
</tr>
</tbody>
</table>

$f^2$ = fetal genetic, $m^2$ = maternal genetic, $c^2$ = shared familial environment  
$h$ = parameter to allow for differences in half-sibling versus full-sibling shared environment ("fudge factor")
Table 4. Estimated variance components from model 2 with empirically derived 95% bootstrap confidence intervals adjusted for covariates (birth order, maternal age, fetal sex, source of care, smoking, maternal education).

<table>
<thead>
<tr>
<th>Source</th>
<th>Full Genetic Model (Model 2)</th>
<th>Reduced Genetic Model (Model 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal genetic</td>
<td>0.264</td>
<td>(0.0, 2.302)</td>
</tr>
<tr>
<td>Maternal genetic</td>
<td>0.976</td>
<td>(0.274, 1.357)</td>
</tr>
<tr>
<td>Shared environment</td>
<td>1.215</td>
<td>(0.499, 1.666)</td>
</tr>
<tr>
<td>Unique environment</td>
<td>4.642</td>
<td>(3.559, 4.899)</td>
</tr>
<tr>
<td><strong>European American</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal genetic</td>
<td>1.325</td>
<td>(0.640, 1.927)</td>
</tr>
<tr>
<td>Maternal genetic</td>
<td>0.503</td>
<td>(0.263, 0.767)</td>
</tr>
<tr>
<td>Shared environment</td>
<td>0.263</td>
<td>(0.006, 0.537)</td>
</tr>
<tr>
<td>Unique environment</td>
<td>1.673</td>
<td>(1.355, 2.024)</td>
</tr>
</tbody>
</table>
“Mating”
Spouses of Twins (“SPOT”)
“Twins and Spouses”
f(G,E)

Genotype x Environment Interaction ("GxE")
Genotype-Environment Correlation ("rGE")
(“Passive”) rGE
Twins and Parents
Twins and Parents ("TAP")

Parents of Twins

Spouses of Twins

Twins

Offspring of Twins

Siblings of Twins

© Lindon Eaves, 2009
Parental Neglect and Anti-Social Behavior

Eaves et al., 2010
Environmental pathways
GxE
Genetic Variance and Shared Life Events in Adolescent Females

![Bar chart showing the genetic variance for depression and anxiety in relation to the number of life events. The x-axis represents the number of life events (0, 1, 2+), and the y-axis represents genetic variance. The chart shows that as the number of life events increases, the genetic variance for anxiety increases significantly, while the genetic variance for depression remains relatively constant.](chart.png)
Putting it all together?
Multiple Genetic Pathways to Depression

Eaves et al. 2003