Continuous heterogeneity

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Boulder Twin Workshop
March 2006
Ways to Model Heterogeneity in Twin Data

- Multiple Group Models
  - Sex Effects
  - Young/Old cohorts
Problem:

• Many variables of interest do not fall into groups
  – Age
  – Socioeconomic status
  – Regional alcohol sales
  – Parental warmth
  – Parental monitoring

• Grouping these variables into high/low categories loses a lot of information
‘Definition variables’ in Mx

• **General definition**: Definition variables are variables that may vary per subject and that are not dependent variables.

• **In Mx**: The specific value of the def var for a specific individual is read into a matrix in Mx when analyzing the data of that particular individual.
‘Definition variables’ in Mx

create dynamic var/cov structure

• **Common uses:**

1. As covariates/effects on the means (e.g., age and sex)

2. To model changes in variance components as function of some variable (e.g., age, SES, etc)
Cautionary note about definition variables

• Def var should not be missing if dependent is not missing

• Def var should not have the same missing value as dependent variable (e.g., use -2.00 for def var, -1.00 for dep var)
Definition variables used as covariates

General model with age and sex as covariates:

\[ y_i = \alpha + \beta_1 (\text{age}_i) + \beta_2 (\text{sex}_i) + \varepsilon \]

Where \( y_i \) is the observed score of individual \( i \), \( \alpha \) is the intercept or grand mean, \( \beta_1 \) is the regression weight of age, \( \text{age}_i \) is the age of individual \( i \), \( \beta_2 \) is the deviation of males (if sex is coded 0 = female; 1 = male), \( \text{sex}_i \) is the sex of individual \( i \), and \( \varepsilon \) is the residual that is not explained by the covariates (and can be decomposed further into ACE etc).
Standard model

- Means vector

\[
\begin{pmatrix}
m \\ m
\end{pmatrix}
\]

- Covariance matrix

\[
\begin{pmatrix}
a^2 + c^2 + e^2 \\ Za^2 + c^2 \\ a^2 + c^2 + e^2
\end{pmatrix}
\]
Allowing for a main effect of $X$

- Means vector

$$
\begin{pmatrix}
m + \beta X_{1i} & m + \beta X_{2i} \\
\end{pmatrix}
$$

- Covariance matrix

$$
\begin{pmatrix}
a^2 + c^2 + e^2 \\
Za^2 + c^2 & a^2 + c^2 + e^2 \\
\end{pmatrix}
$$
! Basic model + main effect of a definition variable

G1: Define Matrices
Data Calc NGroups=3
Begin Matrices;
X full 1 1 free ! genetic influences
Y full 1 1 free ! common environmental influences
Z full 1 1 free ! unique environmental influences
M full 1 1 free ! grand mean
B full 1 1 free ! moderator-linked means model
H full 1 1 ! coefficient for DZ genetic relatedness
R full 1 1 ! twin 1 moderator (definition variable)
S full 1 1 ! twin 2 moderator (definition variable)
End Matrices;
Ma M 0
Ma B 0
Ma X 1
Ma Y 1
Ma Z 1
Matrix H .5
Options NO_Output
End
G2: MZ
Data NInput_vars=6 NObservations=0
Missing = -999
RE File=f1.dat
Labels id zyg p1 p2 m1 m2
Select if zyg = 1 /
Select p1 p2 m1 m2 /
Definition m1 m2 /
Matrices = Group 1
Means M + B*R | M + B*S /
Covariance
X*X' + Y*Y' + Z*Z' | X*X' + Y*Y' _
X*X' + Y*Y' | X*X' + Y*Y' + Z*Z' /

!twin 1 moderator variable
Specify R -1
!twin 2 moderator variable
Specify S -2
End
G2: MZ
Data NInput_vars=6 NObservations=0
Missing =-999
RE File=f1.dat
Labels id zyg p1 p2 m1 m2
Select if zyg = 1 /
Select p1 p2 m1 m2 /
Definition m1 m2 /
Matrices = Group 1
Means M + B*R | M + B*S /
Covariance
X*X' + Y*Y' + Z*Z' | X*X' + Y*Y' 
X*X' + Y*Y' | X*X' + Y*Y' + Z*Z' /

!twin 1 moderator variable
Specify R -1
!twin 2 moderator variable
Specify S -2
End

Tell MX modTw1, modTw2 are Definition Variables
G2: MZ
Data NInput_vars=6 NObservations=0
Missing =-999
RE File=f1.dat
Labels id zyg p1 p2 m1 m2
Select if zyg = 1 /
Select p1 p2 m1 m2 /
Definition m1 m2 /
Matrices = Group 1
Means M + B*R | M + B*S /
Covariance
X*X' + Y*Y' + Z*Z' | X*X' + Y*Y' _
X*X' + Y*Y' | X*X' + Y*Y' + Z*Z' /

!twin 1 moderator variable
Specify R -1
!twin 2 moderator variable
Specify S -2
End
G3: DZ
Data NInput_vars=6 NObservations=0
Missing =-999
RE File=f1.dat
Labels id zyg p1 p2 m1 m2
Select if zyg = 2 /
Select p1 p2 m1 m2 /
Definition m1 m2 /
Matrices = Group 1
Means M + B*R | M + B*S /
Covariance
X*X' + Y*Y' + Z*Z' | H@X*X' + Y*Y' _
H@X*X' + Y*Y' | X*X' + Y*Y' + Z*Z' /
!twin 1 moderator variable
Specify R -1
!twin 2 moderator variable
Specify S -2
End
MATRIX X
This is a FULL matrix of order 1 by 1

1
1 1.3228

MATRIX B
This is a FULL matrix of order 1 by 1

1
1 0.3381

MATRIX Y
This is a FULL matrix of order 1 by 1

1
1 1.1051

MATRIX Z
This is a FULL matrix of order 1 by 1

1
1 0.9728

MATRIX M
This is a FULL matrix of order 1 by 1

1
1 0.1035

Your model has 5 estimated parameters and 800 Observed statistics

-2 times log-likelihood of data >>> 3123.925
Degrees of freedom >>>>>>>>>>>>>>>>>> 795
MATRIX X
This is a FULL matrix of order 1 by 1
1
1  1.3078

MATRIX B
This is a FULL matrix of order 1 by 1
1
1  0.0000

MATRIX Y
This is a FULL matrix of order 1 by 1
1
1  1.1733

MATRIX Z
This is a FULL matrix of order 1 by 1
1
1  0.9749

MATRIX M
This is a FULL matrix of order 1 by 1
1
1  0.1069

Your model has 4 estimated parameters and 800 Observed statistics

-2 times log-likelihood of data >>> 3138.157
Degrees of freedom >>>>>>>>>>>>>>>>> 796
Model-fitting approach to GxE
Adding Covariates to Means Model
‘Definition variables’ in Mx

create dynamic var/cov structure

• **Common uses:**

1. As covariates/effects on the means (e.g. age and sex)

2. To model changes in variance components as function of some variable (e.g., age, SES, etc)
Model-fitting approach to GxE
Individual specific moderators

A

C

E

Twin 1

Twin 2

A

C

E

m + βM M1

m + βM M2

M

Twin 1

Twin 2

a + βx M1

c e
c e

a + βx M2

c e
c e
E x E interactions
Main effects and moderating effects
Definition Variables in Mx GUI

1.0 (MZ) / .5 (DZ)  1.0

A1  C1  E1  A2  C2  E2

βx  a

Mod  Twin 1  Mod

Dick et al., 2001
• Classic Twin Model:
\[ \text{Var} (P) = a^2 + c^2 + e^2 \]

• Moderation Model:
\[ \text{Var} (P) = (a + \beta_X M)^2 + (c + \beta_Y M)^2 + (e + \beta_Z M)^2 \]

Purcell 2002,
Twin Research
Var (T) = \( (a + \beta_X M)^2 + (c + \beta_Y M)^2 (e + \beta_Z M)^2 \)

*Where M is the value of the moderator and*

Significance of \( \beta_X \) indicates genetic moderation
Significance of \( \beta_Y \) indicates common environmental moderation
Significance of \( \beta_Z \) indicates unique environmental moderation

\( B_M \) indicates a main effect of the moderator on the mean
Plotting VCs as Function of Moderator

- For the additive genetic VC, for example
  - Given $a$, $\beta$ (estimated in Mx model) and a range of values for the moderator variable

- For example,
  
  $a = 0.5$, $\beta = -0.2$ and $M$ ranges from -2 to +2

<table>
<thead>
<tr>
<th>$M$</th>
<th>$(a+\beta M)^2$</th>
<th>$(a+\beta M)^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>$(0.5+(-0.2\times-2))^2$</td>
<td>0.81</td>
</tr>
<tr>
<td>-1.5</td>
<td>$(0.5+(-0.2\times-1.5))^2$</td>
<td>0.73</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+2</td>
<td>$(0.5+(-0.2\times2))^2$</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Model-fitting approach to GxE

![Graph showing the component of variance vs. moderator variable]

- **C** represents the Component of variance
- **E** represents the Moderator variable
- **A** represents another component or variable
Matrix Letters as Specified in Mx Script

A

C

E

A

C

E

M

Twin 1

Twin 2

M

\(a + \beta_x M_1\)

\(c + \beta_y M_1\)

\(e + \beta_z M_1\)

\(X + T*R\)

\(Y + U*R\)

\(Z + V*R\)

\(a + \beta_x M_2\)

\(c + \beta_y M_2\)

\(e + \beta_z M_2\)

\(X + T*S\)

\(Y + U*S\)

\(Z + V*S\)

\(m + \beta_M M_1\)

\(m + \beta_M M_2\)

\(M + B*R\)

\(M + B*S\)
! GxE - Basic model
G1: Define Matrices
Data Calc NGroups=3
Begin Matrices;
X full 1 1 free
Y full 1 1 free
Z full 1 1 free
T full 1 1 free  ! moderator-linked A component
U full 1 1 free  ! moderator-linked C component
V full 1 1 free  ! moderator-linked E component
M full 1 1 free  ! grand mean
B full 1 1 free  ! moderator-linked means model
H full 1 1
R full 1 1  ! twin 1 moderator (definition variable)
S full 1 1  ! twin 2 moderator (definition variable)
End Matrices;
Ma T 0
Ma U 0
Ma V 0
Ma M 0
Ma B 0
Ma X 1
Ma Y 1
Ma Z 1
Matrix H .5
Options NO_Output
End
G2: MZ
Data NInput_vars=6 NObservations=0
Missing =-999
RE File=f1.dat
Labels id zyg p1 p2 m1 m2
Select if zyg = 1 /
Select p1 p2 m1 m2 /
Definition m1 m2 /
Matrices = Group 1
Means M + B*R | M + B*S /
Covariance
(X+T*R) * (X+T*R) + (Y+U*R) * (Y+U*R) + (Z+V*R) * (Z+V*R) | 
(X+T*R) * (X+T*S) + (Y+U*R) * (Y+U*S) _
(X+T*S) * (X+T*R) + (Y+U*S) * (Y+U*S) | 
(X+T*S) * (X+T*S) + (Y+U*S) * (Y+U*S) + (Z+V*S) * (Z+V*S) /
!
twin 1 moderator variable
Specify R -1
!
twin 2 moderator variable
Specify S -2
Options NO_Output
End
G2: DZ
Data NInput_vars=6 NObservations=0
Missing =-999
RE File=f1.dat
Labels id zyg p1 p2 m1 m2
Select if zyg = 1 /
Select p1 p2 m1 m2 /
Definition m1 m2 /
Matrices = Group 1
Means M + B*R | M + B*S /
Covariance
(X+T*R)*(X+T*R) + (Y+U*R)*(Y+U*R) + (Z+V*R)*(Z+V*R) | 
H@(X+T*R)*(X+T*S) + (Y+U*R)*(Y+U*S) |
H@(X+T*S)*(X+T*R) + (Y+U*S)*(Y+U*S) |
(X+T*S)*(X+T*S) + (Y+U*S)*(Y+U*S) + (Z+V*S)*(Z+V*S) /

!twin 1 moderator variable
Specify R -1
!twin 2 moderator variable
Specify S -2
Options NO_Output
End
Practical

• Cohort (young/old) model using definition variables (coded 0/1)

• Extension to continuous age
Cohort Moderation

Younger Cohort

Older Cohort
Cohort Moderation

Same fit as 4 group script

\[-2 \text{ times log-likelihood of data} \ggg 3760.830\]

\[\text{Degrees of freedom} \ggg 1761\]
Your task

• Add tests to age_mod.mx to test
  – the significant of age moderation on A
  – the significant of age moderation on E
  – the significant of age moderation on both A and E jointly
Age Moderation

17 years old 83 years old
Comparing Results

<table>
<thead>
<tr>
<th>Model</th>
<th>-2LL</th>
<th>df</th>
<th>chi-sq</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 group cohort</td>
<td>3760.030</td>
<td>1761</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort mod.</td>
<td>3760.030</td>
<td>1761</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age mod.</td>
<td>3764.448</td>
<td>1761</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drop A mod.</td>
<td>3764.873</td>
<td>1762</td>
<td>0.426</td>
<td>0.514</td>
</tr>
<tr>
<td>Drop E. mod.</td>
<td>3768.636</td>
<td>1762</td>
<td>4.189</td>
<td>0.041</td>
</tr>
<tr>
<td>No mod.</td>
<td>3768.680</td>
<td>1763</td>
<td>4.232</td>
<td>0.120</td>
</tr>
</tbody>
</table>
Why is the fit worse using the continuous moderator?

- Artefact – was the GxE due to the arbitrary cut-point?
- Confound – is there a second modifier involved?
- Non-linear – would we expect the effect of age on BMI in adults to be linear?
Nonlinear Moderation can be modeled with the addition of a quadratic term

\[ a + \beta_X M + \beta_{X2} M^2 \]
\[ c + \beta_Y M + \beta_{Y2} M^2 \]
\[ e + \beta_Z M + \beta_{Z2} M^2 \]

Purcell 2002
Non-linear Age Moderation

17 years old 83 years old
## Comparing Results

<table>
<thead>
<tr>
<th>Model</th>
<th>-2LL</th>
<th>df</th>
<th>chi-sq</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age + Age² mod.</td>
<td>3698.365</td>
<td>1758</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drop both A mod.</td>
<td>3701.449</td>
<td>1760</td>
<td>3.084</td>
<td>0.214</td>
</tr>
<tr>
<td>Drop both E mod.</td>
<td>3702.907</td>
<td>1760</td>
<td>4.543</td>
<td>0.103</td>
</tr>
<tr>
<td>Age mod. No Age² terms.</td>
<td>3764.448</td>
<td>1761</td>
<td>66.083</td>
<td>.000000 etc</td>
</tr>
<tr>
<td>No mod.</td>
<td>3768.680</td>
<td>1763</td>
<td>70.315</td>
<td>.000000 etc</td>
</tr>
</tbody>
</table>
Age Effects

Young

Old

\[ a_Y = a_O ? \quad c_Y = c_O ? \quad e_Y = e_O ? \]
GxE Effects

Urban

Rural

\[ a_U = a_R \ ? \]
\[ c_U = c_R \ ? \]
\[ e_U = e_R \ ? \]
Gene-Environment Interaction

• Genetic control of sensitivity to the environment

• Environmental control of gene expression

• **Bottom line**: nature of genetic effects differs among environments
Gene-Environment Interaction

• *First observed by plant breeders:*
  – Sensitive strains – did great under ideal conditions (soil type, sunlight, rainfall), but very poorly under less than ideal circumstances
  
  – Insensitive strains – did OK regardless of the condition; did worse under ideal conditions but better under poor conditions
Conceptualizing Gene-Environment Interaction

![Graph showing gene-environment interaction with produce yield on the y-axis and environmental conditions on the x-axis. The graph illustrates different strains (sensitive and insensitive) and their response to varying environmental conditions.]
Standard Univariate Model

\[ P = A + C + E \]
\[ \text{Var}(P) = a^2 + c^2 + e^2 \]
## Contributions of Genetic, Shared Environment, Genotype x Environment Interaction Effects to Twin/Sib Resemblance

<table>
<thead>
<tr>
<th></th>
<th>Shared Environment</th>
<th>Additive Genetic Effects</th>
<th>Genotype x Shared Environment Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ Pairs</td>
<td>1</td>
<td>1</td>
<td>(1 \times 1 = 1)</td>
</tr>
<tr>
<td>DZ Pairs/Full Sibs</td>
<td>1</td>
<td>(\frac{1}{2})</td>
<td>(1 \times \frac{1}{2} = \frac{1}{2})</td>
</tr>
</tbody>
</table>
Contributions of Genetic, Shared Environment, Genotype x Environment Interaction Effects to Twin/Sib Resemblance

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<td>1</td>
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<td>$1 \times \frac{1}{2} = \frac{1}{2}$</td>
</tr>
</tbody>
</table>

*In other words—if gene-(shared) environment interaction is not explicitly modeled, it will be subsumed into the A term in the classic twin model.*
Contributions of Genetic, Unshared Environment, Genotype x Unshared Environment Interaction Effects to Twin/Sib Resemblance

<table>
<thead>
<tr>
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<th>Unshared (Unique) Environment</th>
<th>Additive Genetic Effects</th>
<th>Genotype x Unshared Environment Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ Pairs</td>
<td>0</td>
<td>1</td>
<td>0 x 1 = 0</td>
</tr>
<tr>
<td>DZ Pairs/Full Sibs</td>
<td>0</td>
<td>$\frac{1}{2}$</td>
<td>0 x $\frac{1}{2}$ = 0</td>
</tr>
</tbody>
</table>
Contributions of Genetic, Unshared Environment, Genotype x Unshared Environment Interaction Effects to Twin/Sib Resemblance

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<tr>
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<td>0</td>
<td>1</td>
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</tr>
<tr>
<td>DZ Pairs/Full Sibs</td>
<td>0</td>
<td>$\frac{1}{2}$</td>
<td>$0 \times \frac{1}{2} = 0$</td>
</tr>
</tbody>
</table>

*If gene-(unshared) environment interaction is not explicitly modeled, it will be subsumed into the E term in the classic twin model.*
ACE - XYZ - M

Main effects and moderating effects
**Gene x (Quasi-Continuous) Environment Models**

<table>
<thead>
<tr>
<th></th>
<th>$a^2$</th>
<th>$c^2$</th>
<th>$e^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fewest 20-24 yr olds</td>
<td>0.11</td>
<td>0.57</td>
<td>0.32</td>
</tr>
<tr>
<td>Most 20-24 yr olds</td>
<td>0.61</td>
<td>0.01</td>
<td>0.38</td>
</tr>
<tr>
<td>Lowest migration</td>
<td>0.17</td>
<td>0.48</td>
<td>0.35</td>
</tr>
<tr>
<td>Highest migration</td>
<td>0.64</td>
<td>0.01</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Dick et al., 2001
Testing for GxE Moderation

- Continuous data
  - Moderation of means and variance

- Ordinal data
  - Moderation of thresholds and variance
Expanding the Model

• Nonlinear Interaction
• Gene-Environment Correlation
Nonlinear Moderation

Moderator

AA
Aa
aa
Nonlinear Moderation can be modeled with the addition of a quadratic term.

\[ a + \beta_X M + \beta_{X2} M^2 \]
\[ c + \beta_Y M + \beta_{Y2} M^2 \]
\[ e + \beta_Z M + \beta_{Z2} M^2 \]

\[ \mu + \beta_M M \]
Gene-environment Interaction

• Genetic control of sensitivity to the environment
• Environmental control of gene expression

Gene-environment Correlation

• Genetic control of exposure to the environment
• Environmental control of gene frequency
This complicates interpretation of GxE effects

- If there is a correlation between the moderator (environment) of interest and the outcome, and you find a GxE effect, it’s not clear if:
  - The environment is moderating the effects of genes or
  - Trait-influencing genes are simply more likely to be present in that environment
Ways to deal with rGE

- Limit study to moderators that aren’t correlated with outcome
  - Pro: easy
  - Con: not very satisfying

- Moderator in means model will remove from the covariance genetic effects shared by trait and moderator
  - Pro: Any interaction detected will be moderation of the trait specific genetic effects
  - Con: Will fail to detect GxE interaction if the moderated genetic component is shared by the outcome and moderator

- Explicitly model rGE using a bivariate framework
\(a_M\)  
\(a_S + \beta_{XS}M\)  
\(a_U + \beta_{XUM}\)

\(\beta_{XS}\) indicates moderation of shared genetic effects

\(B_{XU}\) indicates moderation of unique genetic effects on trait of interest
Ways to deal with rGE

• Limit study to moderators that aren’t correlated with outcome
  – Pro: easy
  – Con: not very satisfying

• Moderator in means model will remove from the covariance genetic effects shared by trait and moderator
  – Pro: Any interaction detected will be moderation of the trait specific genetic effects
  – Con: Will fail to detect GxE interaction if the moderated genetic component is shared by the outcome and moderator

• Explicitly model rGE using a bivariate framework
  – Pro: explicitly models rGE
  – Con: Power to detect $B_{XU}$ decreases with increasing rGE; difficulty converging
  – NOTE: THIS MODEL IS NOT INFORMATIVE FOR FAMILY-LEVEL VARIABLES (E.G., SES, PARENTING, ETC)
## Final Things to Consider

### Unstandardized versus standardized effects

<table>
<thead>
<tr>
<th></th>
<th>ENVIRONMENT 1</th>
<th>ENVIRONMENT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstandardized Variance</td>
<td>Standardized Variance</td>
</tr>
<tr>
<td>Genetic</td>
<td>60</td>
<td>0.60</td>
</tr>
<tr>
<td>Common environmental</td>
<td>35</td>
<td>0.35</td>
</tr>
<tr>
<td>Unique environmental</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>Total variance</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
Final Things to Consider

• Unstandardized versus standardized effects

• Don’t forget about theory!
Final Things to Consider

- Unstandardized versus standardized effects

- Don’t forget about theory!
  - “Moderation in all things….including moderation”
  - Mike Neale
http://pngu.mgh.harvard.edu/%7Epurcell/gxe/
Confidence intervals

• Easy to get CIs for individual parameters

• Additionally, CIs on the moderated VCs are useful for interpretation

• e.g. a 95% CI for \((a+\beta M)^2\), for a specific \(M\)
• Define two extra vectors in Group 1

P full 1 13
O Unit 1 13
Matrix P -3 -2.5 -2 -1.5 -1 -0.5 0 0.5 1 1.5 2 2.5 3

• Add a 4th group to calculate the CIs

CI
Calc
Matrices = Group 1
Begin Algebra;
F= ( A@O + T@P ) . ( A@O + T@P ) /
G= ( C@O + U@P ) . ( C@O + U@P ) /
I= ( E@O + V@P ) . ( E@O + V@P ) /
End Algebra;
Interval @ 95 F 1 1 to F 1 13
Interval @ 95 G 1 1 to G 1 13
Interval @ 95 I 1 1 to I 1 13
End;
Calculation of CIs

\( F = (A \oplus O + T \oplus P) \cdot (A \oplus O + T \oplus P) \div \)

- E.g. if \( P \) were \((0\ 1\ 2)\)

  then \((A \oplus O + T \oplus P)\) equals

  \( (a \otimes (1\ 1\ 1) + x \otimes (0\ 1\ 2)) \)
  
or \( (a\ a\ a) + (0\ x\ 2x) \)
  
or \( (a\ a+x\ a+2x) \)

Finally, the dot-product squares all elements to give \( \left( a^2\ (a + x)^2\ (a + 2x)^2 \right) \)
Confidence intervals on VCs
Plotting VCs

- For the additive genetic VC, for example
  - Given $a$, $\beta$ and a range of values for the moderator variable

- For example,
  
  $a = 0.5$, $\beta = -0.2$ and $M$ ranges from -2 to +2

<table>
<thead>
<tr>
<th>$M$</th>
<th>$(a+\beta M)^2$</th>
<th>$(a+\beta M)^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>$(0.5+(-0.2\times-2))^2$</td>
<td>0.81</td>
</tr>
<tr>
<td>-1.5</td>
<td>$(0.5+(-0.2\times-1.5))^2$</td>
<td>0.73</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+2</td>
<td>$(0.5+(-0.2\times2))^2$</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Sample Gene-Environment Interaction

- Trait
  - +a
  - 0
  - -a

- AA
- Aa
- aa

Moderator