Gene x Environment Interaction in Depression

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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.

A Caspi et al. Science 2003;301:386-389

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   - Could there be G x E in depression?

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1. Plausibility for $G \times E$
Stress – Vulnerability Diathesis

• Individuals differ in their vulnerability to environmental stress
  – Some get depressed
  – Majority don’t

• Genotype may influence this vulnerability
Quantitative Genetics

• Dissociate G from E factors, and rGE, G x E

• Eg twin studies
  – MZ twins share all their genes, DZ twins share half their genes
  – If MZ twins more similar on a trait than DZ:
    • Genetic factors likely to contribute to phenotype
  – Can quantify:
    • Influence of genes
    • Influence of shared environment
    • Influence of unique environment
QG and G x E

• Take a twin sample with varying levels of an environment exposure of interest

• If there is G x E:
  – Genetic effects will be stronger at high levels of E

• Demonstrated in several studies
Disentangling gene-environment correlations and interactions on adolescent depressive symptoms
QG and G x E: Conclusion

• Genetic effects on depressive symptoms differ at different levels of environmental adversity

• G x E interaction operates in the aetiology of depression
2. 5-HTTLPR x Environment and Depression Risk
5-HTTLPR

- 5-hydroxytryptamine transporter-linked polymorphic region
  - (5-HT = serotonin)

- Also called hSERT

- Long form associated with higher 5-HTT activity than short form
  - So long probably has more efficient 5-HT transport
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.

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Fig. 1. Results of multiple regression analyses estimating the association between number of stressful life events (between ages 21 and 26 years) and depression outcomes at age 26 as a function of 5-HT T genotype.
Since Then?

- Caspi paper cited 3,402 times
  - Google scholar, 20 Sep 2011

- Karg et al meta-analysis, 2011 (Arch Gen Psych)
  - 54 studies
  - 40,749 individuals

- 4 main meta-analyses
  - Contrasting results
Munafò et al, 2009

• Interested in 14 studies
  – Only those with stressful life events

• 5 studies included
  – Could not get primary data on others

• 5-HTTLPR x E not significant:
  – OR 1.16, p = 0.27
Risch et al, 2009

- 14 studies included
  - Only those with stressful life events

- 5-HTTLPR x E not significant:
  - OR 1.01, 95% CI 0.94-1.10
Criticisms of Positive Studies

• Underpowered

• Inconsistencies of analysis:
  – Additive vs multiplicative models
  – Some do ss vs ls/ll; others do ss/sl vs ll

• Lack of main effects for 5-HTTLPR means there cannot be an interaction
Environmental Adversity

Risk of Depression

Environmental Adversity
Uher and McGuffin, 2008/2010

• Review of 34 studies
  – 17 full replications of significant 5-HTTLPR x E
  – 8 partial replications
  – 9 non-replications

• Positive findings more likely if interview or objective assessment of E used

• Large studies more likely to use questionnaires
Karg et al, 2011

• 54 studies

• 40,749 individuals

• Significant 5-HTTLPR x E: p = 0.00002
Stratified Analysis

• Type of environmental stressor:
  – Childhood maltreatment, $p = 0.00007$
  – Specific medical condition, $p = 0.0004$
  – Stressful life events, $p = 0.03$

• Method of measuring stress:
  – Objective measurement, $p = 0.000003$
  – Interview, $p = 0.0002$
  – Self-report questionnaire, $p = 0.042$
Further Analysis

• Results non-significant if only studies from the Munafò /Risch meta-analyses used
Environmental Adversity vs. Risk of Depression

- The graph shows a positive correlation between environmental adversity and the risk of depression.
- There are two data points indicating higher risk of depression for individuals exposed to greater environmental adversity.
Environmental Adversity

Risk of Depression

Environmental Adversity
Fig. 1. Results of multiple regression analyses estimating the association between number of stressful life events (between ages 21 and 26 years) and depression outcomes at age 26 as a function of 5-HT T genotype.
‘Plasticity Genes’ Belsky, 2009

- 5-HTTLPR is not a ‘vulnerability’ gene

- 5-HTTLPR leads to differential susceptibility to the environment

- ss are more adversely affected by adversity

- ss benefit more from positive environments
Biological Plausibility

• 5-HTTLPR may influence biological systems
  – These may affect how the brain reacts to stress

• Brain scanning:
  – s carriers have greater amygdala activation in an emotion-related task
  – s carriers have reduced anterior cingulate cortex-frontal cortex functional connectivity
  – 5-HTTLPR x E interaction in amygdala functional connectivity
• Hypothalamic-pituitary-adrenal axis
  – 5-HTTLPR x E interaction on:
    • Greater morning cortisol
    • Greater cortisol response to psychosocial stress test

• Cognitive styles
  – 5-HTTLPR associated with neuroticism
  – 5-HTTLPR x E on rumination
3. G x E for Other Genotypes
Other Genetic Polymorphisms With Significant G x E for Depression Risk

- BDNF
  - Brain Derived Neurotrophic Factor
- CRH1 Receptor
  - Corticotrophin-releasing hormone receptor, type 1
- CREB1
  - cAMP response element-binding protein 1
- NTRK2
  - Neurotrophic tyrosine kinase receptor, type 2
4. Research Implications
• G x E does operate in aetiology of ‘depression’
  – This may not necessarily be at 5-HTTLPR!

• GWAS studies need to take this into account rather than just looking for main effects

• We need good intermediate biological markers (endophenotypes) to help us in elucidating the genetics of depression

• We need to maximise accuracy of measurement of E
  – And probably depression as well
SUMMARY
• Effects of environmental adversity on depression risk are probably stronger in people with 5-HTTLPR short form

• Stronger effect of GxE for early adversity than recent life events

• Effects are stronger if more accurate measures of environment are used

• 5-HTTLPR may be a ‘plasticity’ gene, increasing susceptibility to positive and negative environments