Gene-environment interplay

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Overview of talk

- Why gene-environment interaction is important and what it is
- Methods used to examine it
- Examples of research findings
- Implications and potential concerns

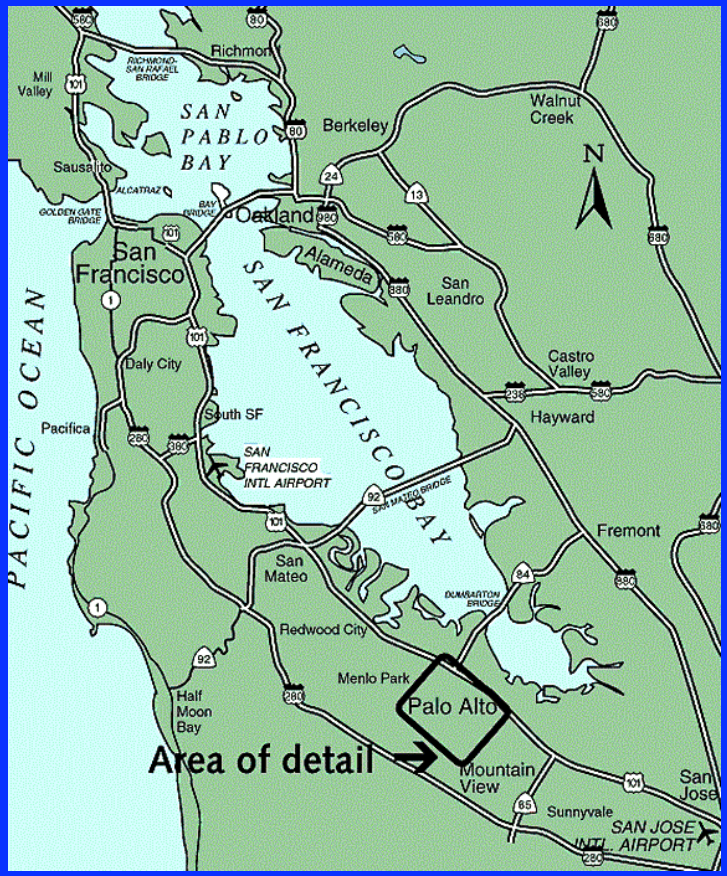
Why gene-environment interplay is important and what it is

The complex etiology of psychiatric disorder and behavior

What we know

- Psychiatric/behavior disorders are genetically influenced
- No psychiatric disorder/behavior is entirely attributable to genes
- Environmental factors contribute
- Gene-environment interplay is complex

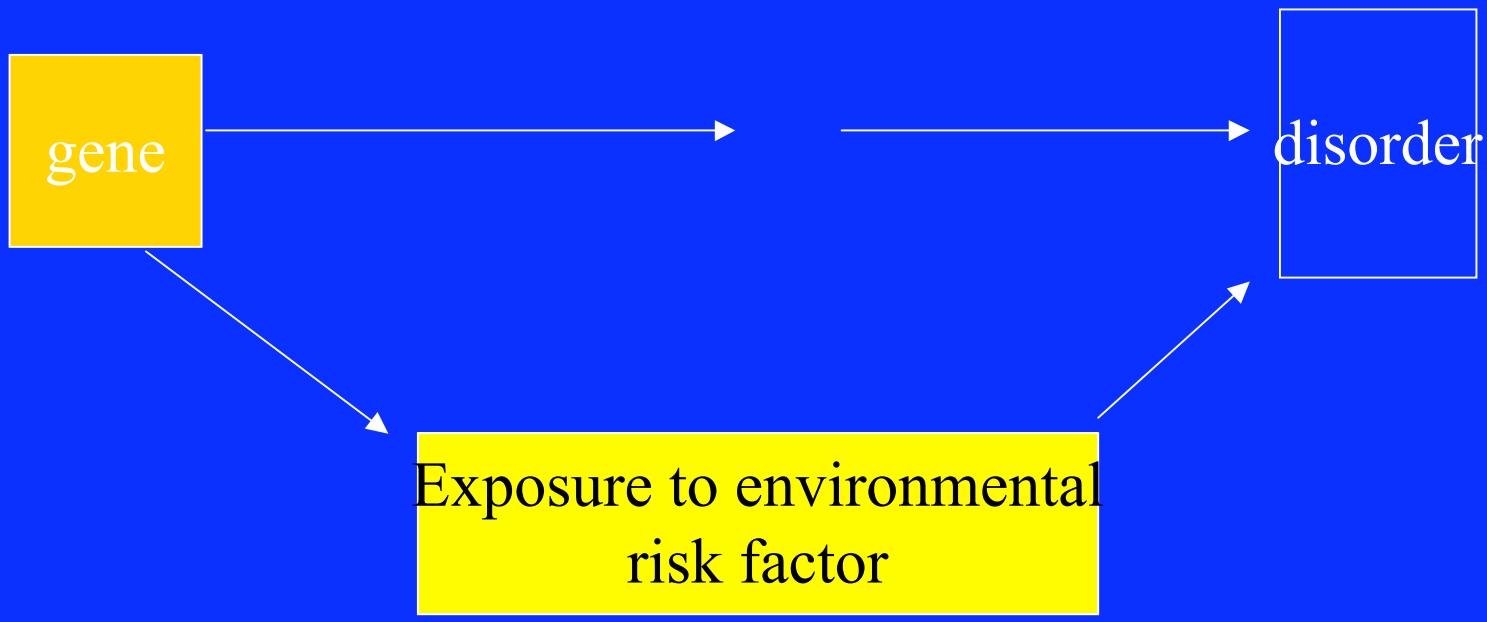
Multiple pathways to the same or similar outcomes



How genes and environment work together

- Co-act
- Environment can mediate genetic risks
- Gene-environment interaction*

Environmental factors may mediate genetic risk effects



Gene-environment interaction

- Same term-different meanings
- Genes influencing sensitivity/response to environmental adversity

Gene-environment interaction
What it means

- Those exposed to specific environmental factors do not all develop psychiatric disorder
- Those carrying a specific genetic variant (or having a specific genetic liability) do not all develop psychiatric disorder

Gene-environment interaction Emerging evidence

- Increasing evidence of importance in origins of medical, psychiatric disorders and behavior
- Can affect the course and manifestations of disorder
- Affects behavioral and brain responses to environmental stimuli (e.g. imaging)

Gene-environment interaction Pharmacogenetics

- Variability in response to medication
- Identifying genes influencing drug response, side effects

Methods used to examine gene-environment interaction

Methods used to examine G × E

1. Statistical inference of genetic liability

- Traditional designs where genetic susceptibility is inferred
- Effects of all genes

Twin studies
Testing for gene-environment interaction

- All methods are not the same

1. Test whether genetic variance differs according environmental risk exposure (heterogeneity)
2. Test whether risk of disorder varies according to genetic risk (affected co-twin) and environmental risk exposure

Molecular genetic studies

2. Measurement of a specific genetic risk factor

- Specific marker (variant) within a given gene
- Should ideally be a variant that is functional

Other methodological considerations

- Measured environmental factor-need accurate measures
- Main environmental effect, ideally causal
- Interaction ideally biologically plausible
- Problems of multiple testing
- Replication

Recent findings

Examples from psychiatric and behavioral genetics

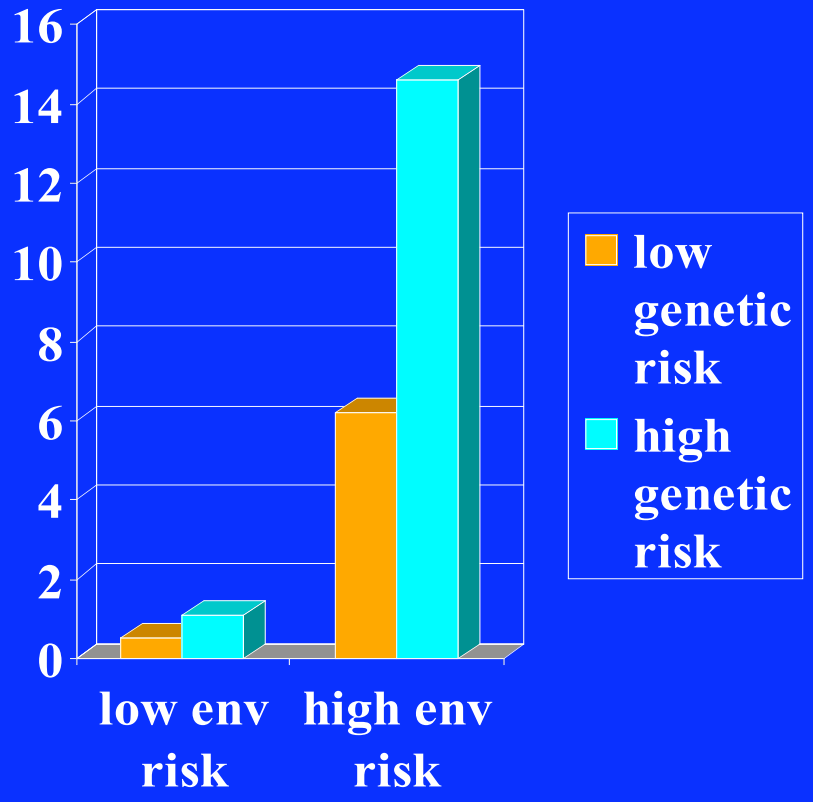
Twin studies

Testing for heterogeneity in genetic variance

- Cardiff Study of All Wales and North-West Twins
- Higher family conflict, lower genetic variance for adolescent depression

(Rice et al, 2006. Journal Am Acad. Child Adol Psych)

Twin study design 2.
Life events and adult depression
(Kendler et al, Am J Psych. 1995)



- MZ co-twin affected (high genetic risk), life events (high environment risk) increases risk of depression

Molecular genetic findings

Another example

- Early maltreatment and antisocial behavior

  (Caspi et al, Science, 2002)

Gene-environment interaction
Affecting course of disorder

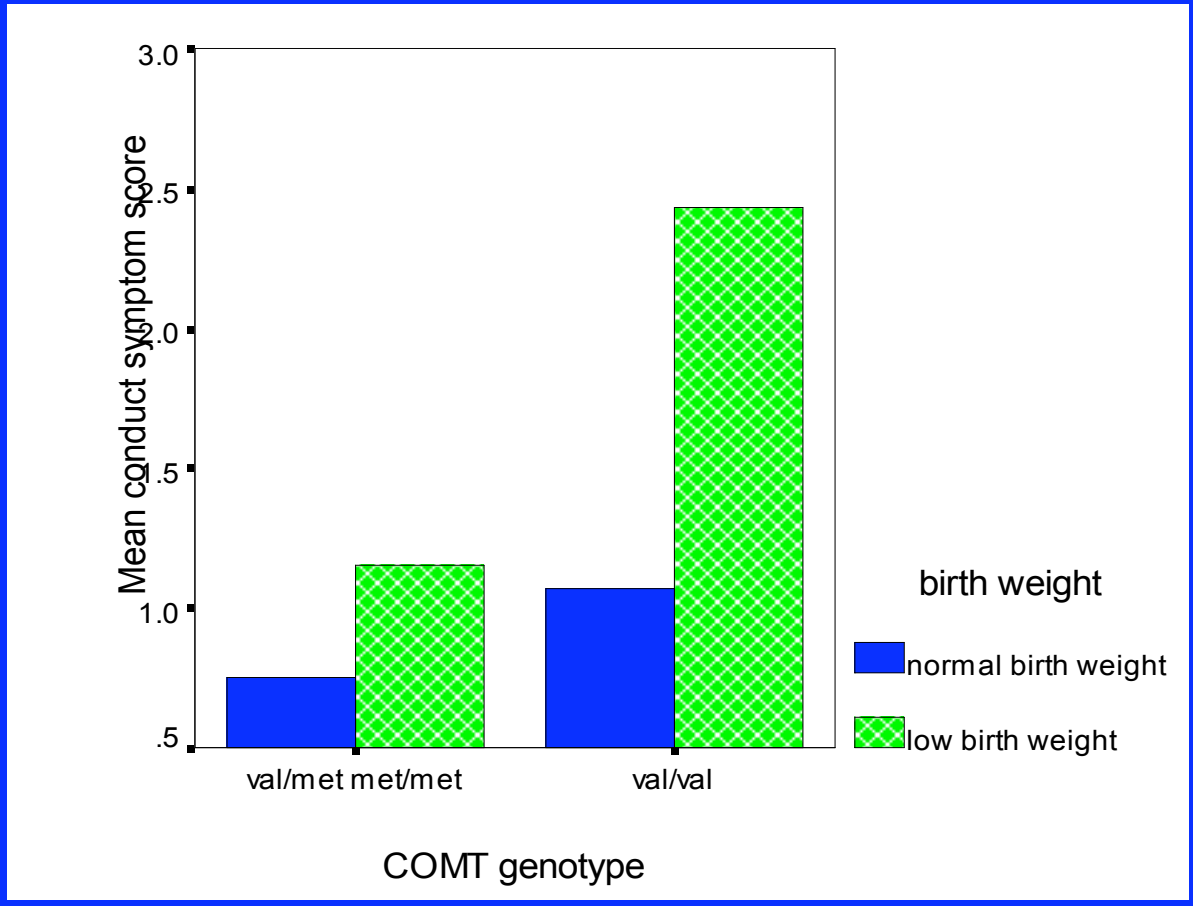
- Antisocial behaviour in children with ADHD

- Cardiff Longitudinal Study of ADHD

  240 children with ADHD

  Thapar et al, 2005, Archives of General Psychiatry

Figure 1
Mean number of DSM-IV conduct symptoms by genotype and birth weight



Considerations

- High genetic risk, high environmental risk increased likelihood of high levels of symptoms/disorder
- Multiple testing
- Replication
- Hypothesis-driven

Potential implications and concerns

Potential implications

- Improved understanding for families and clinicians
- Understand etiology, leading to new interventions and treatments
- Tailored medication/treatments
- Modifying genetic risks through environmental strategies
- Targeting services and interventions to highest risk

Potential concerns

- Misperceptions about determinism
- Misuse of information
- Genes and environment-double stigma and "blame" or perceptions of blame
- Stigma of having resources targeted
- Minority groups in research studies
- Exclusion of high-risk individuals

Awareness
A note of optimism

- Gene-environment interplay highlights that genes are not deterministic
- Pathways to disorder are complex
- Nuffield Council on Bioethics

Acknowledgements

- Cardiff Neuropsychiatric Genetics Group
- Frances Rice, Kate Langley, Tom Fowler, Gordon Harold
- Mike Owen, Michael O'Donovan
- Wellcome Trust Grant funding