Genetic and environmental contributions to callous-unemotional traits and conduct problems

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Background

• A growing evidence base indicates that children with high vs. low CU traits:
  – Differ in the severity and variety of antisocial behaviour they display
  – Have different neurocognitive profiles

• What can genetically informative studies tell us about the origin of CU and CP?
Overview

- Twin Method
- Twin Studies of AB and CU traits
- Molecular Genetic Research
- Environment
- Implications
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Probing the aetiology: Classical twin design

Identical
Monozygotic (produced by the splitting of a single zygote)
MZ

Nonidentical
Fraternal
Dizygotic (produced by two zygotes)
DZ
**Twin method**

- Genetic influence (A) = identical twins > fraternal twins
- The greater resemblance would be expected based on MZ twins sharing all their polymorphic genes

**Twin method**

- Shared environmental influence (C) = environmental influence that makes family members similar to each other
- Non-identical twins more similar than expected by genetic relatedness
Twin method

- Non-shared environmental influence (E) = environmental influences that make family members different from each other
- Identical twins not 100% identical
  - Measurement error

Heritability and environmental estimates in twin studies

- Apply to a particular population at a particular time
- A, C, and E estimates are likely to partially reflect gene-environment correlation (e.g. rAE) or interaction (e.g. AxE)
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Twin and adoption studies of antisocial behaviour

- Antisocial behavior (AB)
  - Moderate heritability
  - Some shared environmental influence
  - Moderate non-shared environmental influence

Rhee & Waldman, 2002
Aetiology of callous-unemotional traits in children and young people

(reviewed in Viding & McCrory, 2012, Development & Psychopathology)

• 15 published twin studies at the time of review
• From U.S., U.K., and Sweden
• Sample sizes moderate (398 pairs) to large (3687 pairs)
• A wide age range across studies (7-24 years)
• A variety of measures

Viding & McCrory (2012)

• CU traits have moderate to strong heritability
• Shared environmental influences do not play a role in driving individual differences in CU traits in adolescents
  – Environmental influences making members of the twin pair similar to each other do not, as a rule, account for individual differences in psychopathic personality in children/adolescent
• Findings in line with adult data on psychopathic and other personality traits
  – Non-shared environmental influences important
Sex differences?

• Qualitative sex differences?
  – Different genes and environments influencing phenotypic variance in males and females
  – Can be tested with twin studies that include opposite sex DZ twins

• Larsson et al., 2006; Viding et al., 2007; Fontaine et al., 2011
  – No support for qualitative sex differences

Sex differences?

• Quantitative sex differences?
  – Do the same genetic and environmental influences affect males and females to a different degree?
  – Can be studied by comparing a model where A, C, E can be different to a model where A, C, E are fixed to be the same between sexes.
Fontaine, Rijsdijk, McCrory & Viding (2010), JAACAP

Four trajectories of CU identified through general growth mixture modeling: stable high, increasing, decreasing, and stable low.

Elevated CU associated with:
- increased levels of behavioral difficulties and family risk factors at 4 years old
- higher levels of conduct problems and hyperactivity at 12 years old

These associations were strongest for the stable high group.

Some evidence for potential quantitative sex differences

<table>
<thead>
<tr>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>$h^2$</td>
<td>$c^2$</td>
</tr>
<tr>
<td>Stable High CU</td>
<td>0.78</td>
</tr>
<tr>
<td>(0.42 – 0.88)</td>
<td>(0.00 – 0.35)</td>
</tr>
</tbody>
</table>
Origins of stability of CU traits across development

• Blonigen et al. (2006); Forsman et al. (2008)
  – Heritability estimates remain similar across time-points
  – CU: phenotypic stability mostly due to genetic influences; change environmentally influenced

Is there a difference in the origin of conduct problems between children with high vs. low CU traits?

Early-onset conduct problems (SDQ Conduct Problems scale)

High CU

Low CU

DeFries-Fulker analysis: Top 10% CP, Top 10% +/- CU
Summary

• CU traits are heritable; possibly more heritable for boys than for girls

• Stability of CU traits in childhood/adolescence largely driven by genetic influences
  – Change environmental?

• CP more heritable in children with CU traits than in their non-CU counterparts

Viding, Blair, Moffitt, & Plomin, 2005; Viding, Jones, Frick, Moffitt, & Plomin, 2008; Dev Sci

Heritability/environmental estimates after controlling for variance shared with hyperactivity
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Molecular genetics

- Twin and adoption studies do not tell us about actual genes
  - However important in establishing, e.g.:
    - whether a trait/disorder is heritable
    - whether the genetic effects are stable throughout development
    - whether there is heterogeneity in aetiology between different subtypes
    - help focus molecular genetic investigations

- Molecular genetic studies of behaviour and psychiatric illness attempt to understand the specific genetic influences on a trait/disorder
Genes

- The genome comprises the entire set of chromosomes for the organism

- Every chromosome is made up of DNA, each strand of which contains many genes

Genes

- Genes are the particles on chromosomes that carry the genetic information that is passed from parents to their offspring
• A gene is a unit of DNA that codes for a protein.

• The genome has start and stop signals to define a gene.

• The genome has also got regions that regulate whether gene is expressed or not (or how much it is expressed) – the expression can be responsive to environmental conditions (epigenetics)

• GATC nucleobase (guanine, adenine, thymine, cytosine) code can vary between individuals – a gene that has more than one variant is called a polymorphism

• Variants are called alleles (many in each gene). We have two copies of every gene (which may be different alleles)
  – Exceptions, e.g. X-linked genes, males have only one copy

• Alleles can cause:
  – Different shaped proteins
  – Different amounts of protein
‘Allelic variation’ in mini coopers

Better for sunny days - Miserable on rainy days.  
Better for rainy days - Too hot on sunny days.

Two alternative forms of the same gene are good for different purposes.

May increase likelihood of one behaviour/disorder, but decrease likelihood of another.

• There are several types of DNA variation, e.g.:
  – variable number of tandem repeats of a particular stretch of DNA
    • ATTCGATTCGATTCGC
    • ATTCGATTCGC
  – single nucleotide polymorphisms
    • GTTTGT
    • GTTTGT
SNPs

- 90% of DNA sequence variability is **single-nucleotide polymorphisms (SNPs)**: single base pair positions in genomic DNA at which different sequence alternatives (alleles) exist.

\[
\begin{align*}
\text{SNP} & \quad \text{GATATCGCA} \\
\text{A allele} & \quad \text{G} \\
\text{Genotype} & \quad \text{GG, GA, AA} \\
\text{A part of two chromosomes}
\end{align*}
\]

- Abundant (millions in the human genome)

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- More than 99% of human DNA sequences are the same across the population
  - the 1% accounts for individual differences

- Variations in the genome (such as a single nucleotide polymorphism – SNP) are found about every 1000th bp

- These polymorphisms account for much of individual differences in the risk for psychiatric disorders
The one-gene one-disability (OGOD) model does not seem to apply to most psychiatric disorders/behaviours; there have been very few ‘big hits’ in psychiatric genetics.

The quantitative trait locus (QTL) model for common complex disorders.
The puzzle of complex psychiatric genetics

- Polygenic, heterogeneous disorders
- Generally weak risk effects
- Gene-gene and gene-environment interactions?

Molecular genetic studies of psychiatric disorders and traits have produced very few ‘big hits’

- Genetic effects small and probabilistic, most studies lack sufficient power to detect such effects
- Genetic effects may be conditional on environmental risk exposure or the presence of other risk genes
What genes for antisocial behaviour?

- Most molecular genetic research into antisocial behaviour has not differentiated between CU subtypes
  - Several serotonin and dopamine system genes implicated (+ some other ‘hits’)
    - variable success in replication

- ‘MAOA-antisocial behaviour’ association, especially when GxE accounted for
  - But does this relate to threat reactive, low CU aggression?

What genes for CU?

- Those conferring low emotional reactivity/arousal? (Viding & Jones, 2008; Glenn, 2010)
• Certain genetic variants, for example serotonin transporter polymorphism, can bias the functioning of brain circuits important for emotional processing.

• Different alleles associated with increased (s) / decreased (l) risk for heightened emotional reactivity (neuroticism/anxiety).

• In the absence of risk factors, outcomes similar for s and l allele carriers.

Significantly more likely to develop CU traits

‘Risk’ genotype

Sadeh et al., 2010; see also Sadeh et al., 2012
What genes for CU?

- **Neurodevelopmental genes?**

  Size matters: Increased grey matter in boys with conduct problems and callous-unemotional traits

  Stephane A. De Brito, Andrea Mechelli, Martin Will, Kristin R. Laurens, Alice P. Jones, Gareth J. Barker, Sheilagh Hodges and Essi Viding

  Heritable Variations in Gray Matter Concentration as a Potential Endophenotype for Psychopathic Traits

  Fruhling V. Rijsdijk, PhD; Essi Viding, PhD; Ste ´phane De Brito, PhD; Matteo Forgiarini, BSc; Andrea Mechelli, PhD; Alice P. Jones, PhD; Zavien McCorry, BScPsych, PhD

  Molecular Psychiatry (2011) 6, 478-477; doi:10.1038/ mspp2010.74; published online 10 June 2010

  A De Brito*, E. McCreery*, A. Mechelli*, M. Wilks*, A. Jones*, S. Hodges* and E Viding*

  Small, but not perfectly formed: decreased white matter concentration in boys with psychopathic tendencies

  Some tentative hits near neurodevelopmental genes for CP/HCU (Viding et al., 2010)
  - Not replicated in our own genome-wide association study of CU traits (Viding et al., 2013)
  - One of the ‘tentative hits’, a SNP near ROBO2, replicated by an Australian group – but associated with CP (rather than CU; Dadds et al., 2013)
What genes for CU?

• Those promoting affiliation/attachment?

• Oxytocin is thought to have a role in promoting empathic and affiliative behaviors, which children with CU lack.

• Beitman et al. (2012) found an association between OXTR rs237885 single nucleotide polymorphism (SNP) of the oxytocin receptor gene and CU in a sample of aggressive children.

• Malik et al. (2012 - the same research group), on an overlapping sample, failed to find any association between CU and a different set of oxytocin receptor SNPs.

Summary

• Molecular genetic work in its infancy
  – Different risk genes for HCU and LCU?
  – Rare variants?

• Genes act in a probabilistic manner and in concert with environmental factors

• No genes FOR CP or CU!
  – Genetic factors may 'bias' information processing, which can predispose individuals to be at risk for developing antisocial behaviour and psychopathic personality
Psychological Behavioural Environment

Conduct Problems without CU

- Mainly environmentally driven
- Genes predisposing to high emotional reactivity? Extra sensitive to environmental threat?

Conduct Problems with CU

- Strongly heritable
- Genes predisposing to low emotional reactivity and atypical attachment?

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All this behavioural genetic talk seems to ignore the environment...

- High heritability and atypical neural activity do not equal immutability
- Both twin and molecular genetic studies demonstrate that environment matters
- Longitudinal data suggest that CU traits can both increase or decrease across development
- We also know that brain development is not fixed

HCU - Environments

- We need to understand gene-environment interplay, in particular gene-environment correlation
  - Do associations between parenting and child outcome reflect an environmental process or genetic vulnerability?
  - What does the child bring into the parenting dynamic?
- We need to distinguish between ‘what is’ and ‘what can be’
  - Not untreatable

Wootton et al., 1997; Viding et al., 2009; Waller et al., 2013; Dadds et al., in press
- Waller, Gardner, & Hyde (2013) - Parenting focused interventions can be effective for children with high levels of CU
- 'Warm' parenting associated with reduced CP in children with CU

Outcomes, moderators, and mediators of empathic-emotion recognition training for complex conduct problems in childhood

Mark Richard Dadds a, Avril Jessica Cauchi a, Subodha Wimalaweera a, David John Hawes b, John R. Rose c

- Reduced behavioural problems, increased parent reported empathy following treatment – most pronounced for children with high CU

LCU - Environments

- Environmental main effects and gene-environment interplay
- Dose – response relationship between harsh/inconsistent parenting and conduct problems
- Parenting interventions work well

Wootton et al., 1997; Viding et al., 2009; Waller et al., 2013
Conduct Problems with CU

- May get better with “warm” parenting and emotion training
- Do not respond to all existing treatments

Conduct Problems without CU

- Associated with harsh and incompetent parenting
- Respond to existing treatment approaches!

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SUMMARY

• Conduct Problems:
  • Similar outward behaviour by different mechanisms (equifinality)

• CU traits designate a subgroup of children who:
  – are genetically vulnerable to CP
  – have low amygdala response to other people's distress
  – lack ability to resonate with other people's emotions

Implications?

• Pro-sociality, but by slightly different means depending on the child’s level of CU traits?

• High CU:
  – Support for positive parenting.
  – Emphasise what is in it for the child? How may his/her good behaviour guarantee access to rewards and privileges?
  – Attention to other people's emotions? Anchoring to own emotional experience?

• Low CU:
  – Existing CP interventions work well:
    • Sanctions and rewards
    • Empathy induction
Future research targets to broaden evidence base

• More gene-environment interplay studies
• Neuroimaging studies using a wider array of tasks
• Behavioural studies investigating different types of rewards
• More treatment studies
  – Different settings: clinic, school, community
• Longitudinal studies combining multiple levels of analyses

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