The Molecular Genetics of Depressive disorders pre- and post-puberty: where to from here?
Outline of presentation

1. Review of molecular genetic methods
2. Review of possible molecular genetic mechanisms
3. Review of key findings to date
4. Review of future directions

All of the above discussed within a developmental framework that suggests that the risk and resilience conferred by genes may differ from one developmental phase to another within the same individual and between individuals.
1. Review of molecular genetic methods

Linkage analyses

-test for co-inheritance within an extended family pedigree: inheritance of a particular trait (eg serious mood) ‘goes with’ a particular gene location

-main advantage is when a phenotype is well defined and the mode of inheritance is known

-affected relative pair strategies more readily applicable but have less statistical power because of relatively large distance covered by marker and the responsible gene for the particular phenotype

-a common approach: *transmission disequilibrium test (TDT)
1. Review of molecular genetic methods

Association studies

-test whether particular group of alleles most commonly associated with particular trait or disorder differs significantly from the mix found in a control group (usually representative of the general population)

-main advantage is when causative gene is selected for theoretical *a priori* reasons or a very dense map of markers is used

-main advantage over linkage analyses is the increased power to detect genes of small to moderate effect
1. Review of molecular genetic methods

Association studies (continued)

-functional polymorphisms of a candidate gene or region closely linked to highly polymorphic markers are the most useful approach:

a haplotype is the combination of alleles across a group of polymorphisms

-a common approach: *family-based control association study using the haplotype relative risk (HRR) statistic
OH NO! EVERYTHING HAS SUDDENLY TURNED NEO-CUBIST!

IT ALL STARTED WHEN CALVIN ENGAGED HIS DAD IN A MINOR DEBATE. SOON CALVIN COULD SEE BOTH SIDES OF THE ISSUE. THEN POOR CALVIN BEGAN TO SEE BOTH SIDES OF EVERYTHING!

THE TRADITIONAL SINGLE VIEWPOINT HAS BEEN ABANDONED! PERSPECTIVE HAS BEEN FRACTURED!

THE MULTIPLE VIEWS PROVIDE TOO MUCH INFORMATION! IT'S IMPOSSIBLE TO MOVE! CALVIN QUICKLY TRIES TO ELIMINATE ALL BUT ONE PERSPECTIVE!

IT WORKS! THE WORLD FALLS INTO A RECOGNIZABLE ORDER!

YOU'RE STILL WRONG, DAD.
2. Review of possible molecular genetic mechanisms

1. Genes exert a direct effect on depressive disorder

genes have their effects on proteins which in turn are implicated in the causal processes for depressive disorder

effects are probabilistic not determinative, that is expressed with respect to risk for disorder

eg: 5HT transporter polymorphism: dysthymic disorder (pre-) and major depressive disorder (post-puberty)?
2. Review of possible molecular genetic mechanisms

2. Genes exert a direct effect on part functions

these part functions when combined lead to depressive disorder

eg noradrenaline transporter polymorphism leads to
adrenergic hyper-reactivity which combined with irritability
and social skills difficulties leads to dysthymic disorder (pre-)
and major depressive disorder (post-puberty)?
2. Review of possible molecular genetic mechanisms

3. Genes exert a direct effect on temperament that does not compose a depressive disorder but increases its risk when combined with other risk factors. For example, the val/met polymorphism of COMT leads to impaired verbal and visuospatial working memory that is associated with intense reactions to new stimuli as a temperamental vulnerability that is a risk factor along with irritable mood, social skills difficulties and a non-empathic, insensitive, non-reciprocal caregiver relationship for the onset of dysthymic disorder (pre-) and major depressive disorder (post-puberty)?
2. Review of possible molecular genetic mechanisms

4. Genes exert a direct effect via increasing and/or decreasing environmental risk exposure termed ‘gene-environment’ correlation (rGE) for depressive disorder

passive rGE: genes exert a direct effect on parental phenotype that in turn forms a risk and/or resilience factor for the child eg empathic caregiver –resilience for depressive disorder?

active rGE: genes exert a direct effect on behaviour leading to selection or avoidance of certain environments eg noradrenaline transporter polymorphism leads to adrenergic hyper-reactivity which is associated with avoidance of social situations which is a risk for social skills deficits?
2. Review of possible molecular genetic mechanisms

4. Genes exert a direct effect via increasing and/or decreasing environmental risk exposure termed ‘gene-environment’ correlation (rGE) for depressive disorder

  evocative rGE: genes exert a direct effect on behaviour that elicits particular responses in people with whom the person interacts
eg serotonin transporter polymorphism leads to consistently calm behaviour that elicits warm empathic responses from peer group members leading to resilience for depressive disorder?
2. Review of possible molecular genetic mechanisms

5. Genes exert a direct effect through influencing susceptibility to environmental risks termed ‘gene-environment’ interaction (GxE) for depressive disorder

eg dopamine transporter polymorphism in the presence of punitive, non-empathic, insensitive caregiving leads to irritable mood and verbal and visuospatial working memory deficits that in turn lead to depressive disorder?

importantly the genes alone and the environment alone do not confer risk in these individuals: only the combination of these gene-environment factors confers risk

A/Prof A. Vance
please note all the examples given above are conjecture that awaits empirical confirmation

development adds another layer of complexity because gene alone, environment alone, and gene: environment correlation and/or interaction may be associated with different risk: resilience profiles at different developmental phases in the same individual and across individuals with/without specific disorders such as depressive disorders

eg developmental phase specific effect of hostile critical caregiver relationship
We have to contend with pleiotropic processes.....

Problems of Method (1960)

‘In reality, psychology teaches us at every step that though two types of activity can have the same external manifestation, whether in origin or essence, their nature may differ most profoundly.’

Vygotsky, Lev Semyonovich
Problems of Method (1960)

‘We believe that child development is a complex dialectical process characterised by periodicity, unevenness in the development of different functions, metamorphosis or qualitative transformation of one form into another, intertwining of external and internal factors, and adaptive processes which overcome impediments that the child encounters….most workers in child psychology ignore those turning points, those spasmodic and revolutionary changes that are so frequent in the history of child development.’

Vygotsky, Lev Semyonovich
"All right, Billy, you just go right ahead! . . . I've warned you enough times about playing under the anvil tree!"
"Hello, Emily. This is Gladys Murphy up the street. Fine, thanks ... Say, could you go to your window and describe what's in my front yard?"
"Well, well, King . . . looks like the new neighbors have brought a friend for you, too."
3. Review of key findings to date

Insights from pharmacotherapy have lead to the exploration of the following candidate genes:

1. Serotonin transporter polymorphisms

   TCA and SSRI site of action

   ins/del polymorphism-associated with ↑ physiological anxiety/ failure to habituate this response (part function/temperament effect?)

   VNTR polymorphism-associated with major depressive disorder (risk/resilience effect? pre-puberty effects?)
3. Review of key findings to date

2. COMT polymorphisms

22q11, COMT gene contains an evolutionarily recent G to A missense mutation that translates into a substitution of Met for Val at codon 108/158 (Val 108/158 Met polymorphism)

it is known that the Met allele is associated with 4x less dopamine catabolism than the Val allele

Val allele associated with significantly worse working memory performance than the Met allele

associated with rapid cycling bipolar disorder
(risk/resilience effect? pre-pubertal irritability/dysthymic disorder?)
3. Review of key findings to date

3. Monoamine oxidase A

VNTR and RFL polymorphisms associated with bipolar disorder (risk/resilience effect? pre-pubertal irritability/dysthymic disorder)

4. Tyrosine hydroxylase

RFL polymorphism associated with major depressive disorder (temperament/part function effect? risk/resilience effect)

5. Promising preliminary findings

ACE 1 ins/del polymorphism via substance P metabolism alteration
GABA(A) receptor alpha6 subunit variant (Pro385Ser) via neuroticism

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3. Review of key findings to date

Summary

- findings at the correlational level only
- longitudinal data across defined developmental physiological phases with excellent phenotyping and dense markers are needed to address risk/resilience? temperament/part function? direct?/gene-environment correlation/interaction? effects
4. Review of future directions

1. Refining of phenotypes

   dysthymic disorder and major depressive disorder versus symptoms (eg irritability) or syndromes (eg psychomotor retardation)

   addition of a neuropsychological/neurophysiological/neuroimaging signature(s)

   eg working memory-verbal and visuospatial
   eg visual memory-especially encoding phase
4. Review of future directions

1. Refining of phenotypes (continued)

   eg pro-saccadic function, anti-saccadic function
   eg fronto-parietal, fronto-temporal activation with a
defined neuropsychological probe using fMRI

2. Elucidation of genes regulating key physiological processes
   at different developmental phases
   eg working memory
   visual memory, especially the encoding phase
   saccadic function
   fMRI activation patterns
   (supported by Kandel’s work)
4. Review of future directions

2. Elucidation of genes regulating key physiological processes at different developmental phases

*HPAG axis investigations*

CRF:
high densities in hypothalamic PVN and central driver HPAG axis release stimulates ACTH (pituitary) which aids release glucocorticoids from adrenal cortex-metabolic / immune modulating effects via MR-hippocampus and GR widely distributed also high densities in amygdala suggesting a role in emotional mediation

-CRF and pre-pubertal trauma

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4. Review of future directions

2. Elucidation of genes regulating key physiological processes at different developmental phases

*HPAG axis investigations*

-glucocorticoid receptor function
MR: high affinity-control low basal levels circulating cortisol
GR: low affinity-control circadian and/or stress-related cortisol peaks
4. Review of future directions

2. Elucidation of genes regulating key physiological processes at different developmental phases

Adrenarche

-DHEA increase from 7 years in both sexes
-cognitive, behavioural and emotional correlates not systematically studied
Summary

-the available methods are improving through
more careful phenotyping
composite neuro-psychological/physiological/brain activation
phenotyping
improved candidate gene marker maps

-still unable to define specific mechanism of genetic effects on the
onset, progression and treatment responsiveness of
depressive disorders, pre- and post-puberty: longitudinal studies
required
Summary (continued)

- developmental phases influence genetic effects with respect to their risk and resilience potential

- findings to date are driven by pharmacotherapy and emerging aetiological models

- key physiological processes that are involved in the (1) primary pathophysiology of depressive disorders (2) secondary adaptive physiological processes are future goals of molecular genetic research