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Identification of Candidate Genes for Psychological Resilience to Develop an Additive Genetic Resilience Index: An Integrative Review

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Problem

- Most individuals experience at least one potentially traumatic event (PTE) in their life time[1]
- Following exposure to PTEs, some individuals are more vulnerable to develop psychopathology, such as PTSD, whereas others are less adversely affected, who are often described as "resilient"[2]
- It is estimated that the heritability of resilience is .52 to .77 in men and .38 to .70 in women[3,4]
- Resilience is influenced by multiple genes[5], which have been studied using candidate gene approach and genome-wide association study (GWAS)
- The Serotonin-Transporter-Linked Polymorphic Region (5-HTTLPR) has been studied the most, but other genes are also related to resilience[6]
- The purpose of the integrative review was to identify genes that may contribute to individual differences in resilience to PTEs in order to develop an Additive Genetic Resilience Index (AGRI)

Significance

- The nurse scientists are encouraged to build the evidence base to inform integration of genomics into nursing practice[7]
- AGRI will facilitate the integration of genetics into studies about resilience

Search Strategy

- PubMed, EMBASE, PsychINFO, and CINAHL databases were searched in October 2014
- The keywords included "resilience", "serotonin transporter gene", and "5-HTTLPR"
- Inclusion criteria were:
  1. Human subjects approved research
  2. Published in English
  3. Peer-reviewed research article
  4. Both genotypes and resilience measured
  5. 5-HTTLPR and additional gene(s) investigated

Results of Literature Search

- 94 manuscripts were initially identified
- 8 studies that met inclusion criteria were selected
- Level of evidence was IV (*i.e.* well-designed case-control and cohort studies)
- Findings are summarized in Table 1

Table 1: Summary of Candidate Genes associated with Resilience

Sample (N)	Adversity Measure	Resilience Measure	Genes Investigated	Findings	Resilient Genotype	Ref.
Adolescents (218)	Childhood Trauma Questionnaire-Short Form	Behavioral Indicator of Resiliency to Distress	• 5-HTTLPR • COMT	S allele carriers of 5-HTTLPR were more likely to perform poorly on the task (*i.e.* choose to quit) than L allele carriers; Val allele carriers of COMT were more likely to quit the task than Met allele carriers	• 5-HTTLPR: L • COMT: Met	8
Maltreated and nonmaltreated adolescents from low socioeconomic backgrounds (339)	Abuse / neglect	Anxious / depressed symptoms	• 5-HTTLPR • MAOA	S allele of 5-HTTLPR predicted higher depression, anxiety, and somatic symptoms; adolescents with low MAOA activity exhibited heightened depressive symptoms	• 5-HTTLPR: L • MAOA: 3.5/4R	9
Children exposed to Hurricane Ike (116)	Hurricane Related Traumatic Experiences-Revised	Posttraumatic Stress Disorder-Reaction Index for Children-Revised	• 5-HTTLPR • BDNF	No significant findings for 5-HTTLPR; the effect of social support on PTSD symptoms was stronger among children with the Met allele	• 5-HTTLPR: ? • BDNF: Val	10
Adolescents (1032)	Perinatal risks; Childhood events; Long-term difficulties	Early Adolescent Temperament Questionnaire (Effortful control)	• 5-HTTLPR • BDNF	The L/L–Val/Val genotype was unaffected by childhood events whereas L/L-Met-Carrier, L/S-Val/Val, and S/S-Val/Val genotypes showed greatest plasticity	• 5-HTTLPR: L • BDNF: Val	11
South African adults (150)	Traumatic Life Events Checklist	Davidson Trauma Scale (DTS)	• 5-HTTLPR • BDNF • DRD2	L allele of 5-HTTLPR was associated with a non-zero DTS score; a significant epistatic interaction effect between BDNF and DRD2 variants on DTS scores	• 5-HTTLPR: S • BDNF (Met) x DRD2 (A1)	12
African American adolescents (576)	Environmental, familial, and interpersonal stresses	Physical health, mental health, trouble with the law, and social relationships	• 5-HTTLPR • DRD4	Individuals with the risk alleles (S of 5-HTTLPR, 7R [L] of DRD4) were associated with less resilience	• 5-HTTLPR: L • DRD4: S	13
Children diagnosed with ODD or ADHD (ODD = 148, ADHD = 309)	Children's Perception of Inter-parental Conflict Scale; Alabama Parenting Questionnaire	California Children Q-Sort; ODD / ADHD symptoms	• 5-HTTLPR • DRD4	For ODD, S allele of 5-HTTLPR was associated with higher neuroticism and ODD symptoms; For ADHD, children with S allele of DRD4 were more resilient to effects of inconsistent discipline on conscientiousness	• 5-HTTLPR: L • DRD4: S	14
Maltreated and nonmaltreated children from low socioeconomic backgrounds (595)	Abuse / neglect	Resilient Functioning (prosocial, disruptive-aggressive, and withdrawn composites)	• 5-HTTLPR • DRD4 • CRHR1 • OXTR	Significant G x E (maltreatment) interactions were observed for each gene	• 5-HTTLPR: L • DRD4: C • CRHR1: 1 or 2R • OXTR: G	15

* Abbreviations: COMT = Catechol-O-MethylTransferase; MAOA = Monoamine Oxidase A; BDNF = Brain-Derived Neurotrophic Factor; DRD2 = Dopamine Receptor D2; DRD4 = Dopamine Receptor D4; CRHR1 = Corticotropin-Releasing Hormone Receptor 1; OXTR = Oxytocin Receptor; ODD = Oppositional Defiant Disorder; ADHD = Attention Deficit Hyperactivity Disorder; G x E = Gene by Environment

Synthesis of Evidence

- Candidate genes associated with resilience include 5-HTTLPR, COMT, MAOA, BDNF, DRD2, DRD4, CRHR1, and OXTR
- To construct an AGRI, each allele is assigned a number based on its relationship to resilience
- Ex. 5-HTTLPR: 1 = S/S, 2 = L/S, 3 = L/L; BDNF: 1 = Met/Met, 2 = Val/Met, 3 = Val/Val, so an AGRI for L/L of 5-HTTLPR and Val/Val of BDNF would be 6
- Both G x E and G x G interactions have been observed, which may complicate developing AGRI
- A notable gap is the lack of adult samples

Implications for Practice

- AGRI will be used to examine the association between multiple candidate genes and resilience
- A validated AGRI will help to identify individuals at greater heritable risk for psychological problems after exposure to PTEs
- AGRI may help to develop more precise (*e.g.* genotype-informed) nursing interventions to promote resilience among individuals exposed to PTEs