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 lifetime.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, 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 genomics 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."8
- 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.

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**Table 1: Summary of Candidate Genes associated with Resilience**

<table>
<thead>
<tr>
<th>Sample (N)</th>
<th>Adversity Measure</th>
<th>Resilience Measure</th>
<th>Genes Investigated</th>
<th>Findings</th>
<th>Resilient Genotype</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents (218)</td>
<td>Childhood Trauma Questionnaire-Short Form</td>
<td>Behavioral Indicator of Resiliency to Distress</td>
<td>5-HTTLPR, COMT</td>
<td>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</td>
<td>5-HTTLPR: L</td>
<td>8</td>
</tr>
<tr>
<td>Malnourished and malnourished adolescents from low socioeconomic backgrounds (339)</td>
<td>Abuse / neglect</td>
<td>Anxious / depressed symptoms</td>
<td>5-HTTLPR, MAOA</td>
<td>S allele of 5-HTTLPR predicted higher depression, anxiety, and somatic symptoms; adolescents with low MAOA activity exhibited heightened depressive symptoms</td>
<td>5-HTTLPR: L</td>
<td>9</td>
</tr>
<tr>
<td>Children exposed to Hurricane Ike (116)</td>
<td>Hurricane Related Traumatic Experiences-Revised</td>
<td>Posttraumatic Stress Disorder-Reaction Index for Children- Revised</td>
<td>5-HTTLPR, BDNF</td>
<td>No significant findings for 5-HTTLPR; the effect of social support on PTSD symptoms was stronger among children with the Met allele</td>
<td>5-HTTLPR: ?</td>
<td>10</td>
</tr>
<tr>
<td>Adolescents (1032)</td>
<td>Perinatal risks; Childhood events; Long-term difficulties</td>
<td>Early Adolescent Temperament Questionnaire (Effortful control)</td>
<td>5-HTTLPR, BDNF</td>
<td>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</td>
<td>5-HTTLPR: L</td>
<td>11</td>
</tr>
<tr>
<td>South African adults (150)</td>
<td>Traumatic Life Events Checklist</td>
<td>Davidson Trauma Scale (DTS)</td>
<td>5-HTTLPR, BDNF, DRD2</td>
<td>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</td>
<td>5-HTTLPR: S</td>
<td>12</td>
</tr>
<tr>
<td>African American adolescents (576)</td>
<td>Environmental, familial, and interpersonal stresses</td>
<td>Physical health, mental health, trouble with the law, and social relationships</td>
<td>5-HTTLPR, DRD4</td>
<td>Individuals with the risk alleles (S of 5-HTTLPR, 7R of DRD4) were associated with less resilience</td>
<td>5-HTTLPR: L</td>
<td>13</td>
</tr>
<tr>
<td>Children diagnosed with ODD or ADHD (ODD = 148, ADHD = 309)</td>
<td>Children’s Perception of Inter-parental Conflict Scale; Alabama Parenting Questionnaire</td>
<td>California Children Q-Sort; ODD / ADHD symptoms</td>
<td>5-HTTLPR, DRD4</td>
<td>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</td>
<td>5-HTTLPR: L</td>
<td>14</td>
</tr>
<tr>
<td>Maltreated and nonmaltreated children from low socioeconomic backgrounds (595)</td>
<td>Abuse / neglect</td>
<td>Resilient Functioning (prosocial, disruptive-aggressive, and withdrawn composites)</td>
<td>5-HTTLPR, DRD4, CRHR1, OXTR</td>
<td>Significant G x E (maladaptation) interactions were observed for each gene</td>
<td>5-HTTLPR: L</td>
<td>15</td>
</tr>
</tbody>
</table>

*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.