Serotonin Transporter Gene Polymorphism and Family Caregiver Outcomes

Sandra B. Dunbar, RN, PhD, FAAN, FAHA, FPCNA
Senior Associate Dean
Candler Professor of Cardiovascular Nursing
Emory University Nell Hodgson Woodruff School of Nursing
Atlanta, GA

“Sometimes we learn by being told what to know. Sometimes we learn by being told what to do.

Sometimes by trying things out, by doing.

Mostly, we learn through a blend of both.”
What we will talk about

• Background: Family caregivers of persons with chronic conditions.
• Possible antecedent factors of demographic, social support and family context, caregiving demands, and overall health factors are associated with depressive symptoms in family caregivers of persons with heart failure.
• The serotonin transporter-linked polymorphic region (5-HTTLPR) genotypes (XL/L, LL, L/S, S/S).
• Data from study family caregivers of persons with heart failure as an exemplar of relationship of 5-HTTLPR with caregiving relationships.
• Issues in study of 5-HTTLPR in special populations defined by age, gender and race/ethnicity.
• Conclusions and implications for practice and future research
• Next steps for nursing science and practice.
Four kinds of people in the world

• Those who have been caregivers;
• Those who currently are caregivers;
• Those who will be caregivers;
• And those who will need caregivers.

Roslynn Carter
Former First Lady of the United States

I want you! For a family caregiver.....
Chronic Family Caregiving

• 44 million individuals in United States provide care for chronically ill, disabled or aged family member in any given year providing > 90% of informal caregiving in the U.S.

• Associated with multiple adverse outcomes compared to non-caregivers of same age
  • 63% higher mortality rate
  • Premature aging and shortened telomeres
  • Increased risk of caregiver also developing chronic illness

Family Caregiving for persons with Heart Failure

- HF FCGs contribute to HF self care.
- Caring for HF Patients is difficult, demanding, associated with increased CG stress and anxiety, and reduced QOL. Increases over time.
- Almost 30% of HF FCGs report depressive symptoms.
- Caregiver burden related to CG depression, Pt depression and QOL, and HF patient disease burden.
- Higher FCG strain associated with greater patient symptoms and lower patient quality of life.
- Caregivers have needs communication; Involvement with others; Information and education; sleep difficulties.
- Better mental health in HF FCG associated with absence of increased caregiver burden over time.
- Spousal FCGs may have comorbidities and at risk for poor health outcomes.

Greater understanding of associated factors with depressive symptoms is needed to inform interventions.
HF Family Caregiver Stress: Interventions to Promote Health and Wellbeing (NINR P01 NR011587)

• Aim: Using a PNI approach, promote health in family caregivers of persons with chronic illness

• Design: Randomization of HF and AD FCGs to
  • Usual Care Attention Control
  • Psychoeducational (PsychEd)
  • Psychoeducational + Exercise (PsychEd+EX)
Purposes

1) To examine individual factors, family context, and perceived caregiving demand as correlates of depressive symptoms in FCGs of persons with HF.

2) To explore the correlates of depressive symptoms within allele variation groups (XL/L, and any S - L/S, and S/S) of Serotonin Transporter Gene (5-HTTLPR).
Serotonin Transporter Gene

5-HTTLPR Gene *(aka SLC6A4, SERT, OCD1)*

[https://ghr.nlm.nih.gov/gene/SLC6A4#synonyms]

Chromosome 17

Allele Variants

Long allele

L

Short allele

S

transcriptional control region (TCR)

Possible Pairs: L/L  L/S  S/S
Importance of Serotonin Transporter Gene

• A functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele.
  • Caspi et.al. (2003)

• Genotype (presence of “S” allele) and depression were strongly associated and independent of age, gender, or family history of psychological problems.
  • In the PREDICT-Gene Study (Cervilla et.al, 2006),
  • Heart and Soul Study (Otte et.al, 2007)
Evidence for Importance of Serotonin Transporter Gene con’t

I. Observational studies about the serotonin transporter linked polymorphic region (5-HTTLPR), stress sensitivity, and depression in humans;

II. Experimental neuroscience studies about the 5-HTTLPR and biological phenotypes relevant to the human stress response;

III. Studies of 5-HTT variation and stress sensitivity in nonhuman primates; and

IV. Studies of stress sensitivity and genetically engineered 5-HTT mutations in rodents

• Caspi, et al. 2010
How the 5-HTTLPR Affects Neural Circuitry for Responding to Environmental Threat and Stress

Importance of Serotonin Transporter Gene con’t

• Moderates variation in response to childhood bullying distress.
  • Sugdon et al., J Am Acad Child Adolesc Psychiatry, 2010

• Caregiving of a family member with psychotic disorder with SS allele scored higher on Depression and anxiety.
  • Golimbet et al, 2009

• Genetic Moderators of the Impact of Physical Activity on Depressive Symptoms.
  • Dotson et al, J Frailty Aging, 2016

• Depressive symptoms in response to the stress of neighborhood crime.

• Cortisol stress responsiveness and Sleep quality.
  • van Dalfsen, et al Stress, 2018
Figure 1. Stress-related change in salivary cortisol (AUCi) as a function of sleep quality in S’/S’ and L’/L’ 5-HTTLPR genotype. Interaction: \(p<.01\).
Design and Methods

• Descriptive Correlational Cross-sectional Analysis;

• Sample (n=127) FCGs of persons with HF
  • Adults >21 years
  • Designated as primary FCG by HF patient
  • Living in same household or interacting with HF care recipient 4 X week for at least 1 hour regarding their HF treatment or care

• Measures:
  • Demographics
  • Family functioning – Global Family Function (GFF)
  • Social Support - ESSI
  • Oberst Caregiving Demands (difficulty and time)
  • Caregiver physical and mental strain
  • Sleep Quality (Pittsburgh Sleep Quality Index)
  • Depressive Symptoms (CES-D)
  • 5-HTTLPR genotype (n=92)
RESULTS
Participants (n=127)

- Age range 25-80 years  [mean 56.1 ± 11]
- 92% Women
- 58% African American
- 57% spouse, 19% adult child, 23.8% other
- 32% had >1 chronic condition
## Baseline Caregiver Burden, Depression, Stress, Sleep

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD [min – max]</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D (% ≥ 16)</td>
<td>15.2 ± 10.4 [0 – 46]</td>
<td>(n=53; 41.7%)</td>
</tr>
<tr>
<td>Oberst - Time</td>
<td>45.2 ± 12.5 [22 – 77]</td>
<td></td>
</tr>
<tr>
<td>Oberst - Difficulty</td>
<td>33.6 ± 14.7 [18 – 86]</td>
<td></td>
</tr>
<tr>
<td>Caregiver Strain Mental (some/a lot)</td>
<td>105 (82%)</td>
<td></td>
</tr>
<tr>
<td>Caregiver Physical Strain (some/a lot)</td>
<td>70 (54%)</td>
<td></td>
</tr>
<tr>
<td>Enriched Social Support Scale</td>
<td>24.3 ± 5.8 [11 – 34]</td>
<td></td>
</tr>
<tr>
<td>NYHA Class</td>
<td>50.4% Class I and II</td>
<td></td>
</tr>
<tr>
<td>Global Family Functioning (GFF)</td>
<td>2.09 ± 0.5 [1.00 – 3.55]</td>
<td></td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index (%&gt;5)</td>
<td>8.4 ± 4.4 [0 – 21]</td>
<td>67%</td>
</tr>
</tbody>
</table>
Multiple Regression Analysis to Predict Depressive Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
</tr>
<tr>
<td>(Constant)</td>
<td>-7.001</td>
<td>3.373</td>
<td></td>
</tr>
<tr>
<td>Total PSQI</td>
<td>.970</td>
<td>.179</td>
<td>.405</td>
</tr>
<tr>
<td>Oberst Difficulty</td>
<td>.153</td>
<td>.055</td>
<td>.215</td>
</tr>
<tr>
<td>Global Family</td>
<td>4.508</td>
<td>1.555</td>
<td>.222</td>
</tr>
<tr>
<td>Functioning</td>
<td>4.908</td>
<td>1.617</td>
<td>.227</td>
</tr>
<tr>
<td>Caring for Others?</td>
<td>-3.768</td>
<td>1.533</td>
<td>-.181</td>
</tr>
</tbody>
</table>

adj $R^2 = 0.427$

$F(5,106) = 17.55$, $p < .001$;
Serotonin Transporter Gene (Dunbar, P01-NR011587)
(5-HTTLPR Gene (aka SLC6A4, SERT, OCD1))

5-HTTLPR allele groups:
S/S – short/short
L/L – long/long
L/S = long/short

Possible Pairs: L/L, L/S, S/S
Multiple Regression Analysis to Predict Depressive Symptoms
5-HTTLPR (X/L and L/L)  n=42

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Sig.</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>(Constant)</td>
<td>-3.586</td>
<td>4.601</td>
<td>-.779</td>
<td>.440</td>
<td>-12.892 5.720</td>
</tr>
<tr>
<td>Total PSQI 0 (best) - 21 (worse)</td>
<td>.966</td>
<td>.253</td>
<td>.492</td>
<td>3.818</td>
<td>.000 .454 1.478</td>
</tr>
<tr>
<td>Global Family Functioning</td>
<td>4.477</td>
<td>2.040</td>
<td>.283</td>
<td>2.195</td>
<td>.034 .351 8.604</td>
</tr>
</tbody>
</table>

adj $R^2$=0.34
$F(2, 39)=11.527$, $p<.001$
Multiple Regression Analysis to Predict Depressive Symptoms
5-HTTLPR Any S (L/S or S/S)  n=50

<table>
<thead>
<tr>
<th></th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>95.0% Confidence Interval for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
</tr>
<tr>
<td>(Constant)</td>
<td>-4.280</td>
<td>2.800</td>
<td>-1.529</td>
</tr>
<tr>
<td>Mental Strain</td>
<td>7.522</td>
<td>1.441</td>
<td>.515</td>
</tr>
<tr>
<td>Family Member: NYHA Classification</td>
<td>3.456</td>
<td>1.005</td>
<td>.339</td>
</tr>
<tr>
<td>Caring for Others</td>
<td>6.967</td>
<td>2.042</td>
<td>.331</td>
</tr>
</tbody>
</table>

Adj R² = 0.54
F(3,46) = 20.160, p < 0.001

Caregiver demand and strain were associated with depressive symptoms in the any S allele group and not in the XL/L group.
Conclusions

Greater depressive symptoms in FCG of persons with HF were associated with:
- Worse sleep quality
- Greater perceived CG burden
- Worse family function
- Caucasian Race

In the 5-HTTLPR XL/L allele group, BL depressive symptoms were less affected by caregiver demand and strain than the any S (L/S or S/S) groups. Thus allele variants of the 5-HTTLPR may interact with caregiving differently and may help identify FCGs at greater risk for depressive symptoms.

Research directions to reduce depressive symptoms:
- Greater understanding and tailoring based on family context
- Improving FCG sleep
- Reducing caregiving demand
- Further study of allele variants of 5-HTTLPR with FCG burden/demand in HF
  - intervention response
Racial Differences in Phenotype Prevalence

HS = Heart and Soul Study (Kangelaris et.al, 2010);
COOL = P01 Caregiver Study
AA Depression & Caregiver Burden by gene type

Gene Phenotype
L/L or L/XL  L/S  S/S  L/L or L/XL  L/S  S/S

PROMIS Depression

Oberst Time (perceived)

Oberst Difficulty (perceived)

S/S Gene Type – much stronger association between higher perceived time caregiving and higher depression & anxiety levels – moderation by gene type

note: “dose” response unclear – more subjects needed
Clinical Applications – real and potential

• **Pharmacogenomics:** better response to selective serotonin reuptake inhibitors; genetic testing before prescribing antidepressant treatment may lead to better clinical outcomes, increased numbers patients experiencing remission early in treatment.
• **Preventive interventions** for FCGs with affinity for depression in response to stress. [RCT to test GxE effects]
• **Differential effects of caregiving stress-family context interactions** on FCGs outcomes of depression and anxiety.
• **Influence on healthy lifestyle behaviors** (physical activity, appetite and dietary intake, and sleep).
Lesson Learned: Things are not going to get simpler!

• Complexity is here to stay
  • Metabolomics
  • Genomics, Proteomics
  • Microbiome
  • Exposome, Glycomics
  • Social determinants of health
  • Symptom science; palliative care
  • Systems – family and environment
  • BIG DATA analytics
  • Artificial intelligence
What remains unknown: Toward Precision Nursing?

- Towards Precision Nursing
  - Better tailoring of Family focused interventions
  - Culture and traditions
  - Self management tailoring
- Right dose, right time, right cost
- Tailoring of FCG interventions based on the FCG phenotype?
Your thoughts and questions?