No Conflicts to Report

Background
• Women experience clusters of symptoms during the menopausal transition, not only hot flashes
• Participants in the Seattle Midlife Women’s Health Study experienced three symptom clusters during the menopausal transition

Acknowledgements
• Research was supported by grants from the National Institute of Nursing Research NiNR: R21NR012218 Menopause Symptom Clusters: Refocusing Therapeutics and
• R01NR 04141 Menopausal Transition: Biobehavioral Dimensions
• P50 NR02323 and P30 NR04001 Center for Women’s Health Research

Estrogen Synthesizing Gene Polymorphisms and Symptom Clusters during the Menopausal Transition and Early Postmenopause: Toward Personalized Menopause Care
Nancy Fugate Woods
Lori Cray
Ellen Sullivan Mitchell
Fred Farren
Jerald Herting
Symptom Clusters during the Menopausal Transition and Early Postmenopause

Cluster 1
Cluster 2
Cluster 3
Cray et al, 2012

Symptom Clusters: Correlates

- Cluster 1 was associated with the late menopausal transition stage and early postmenopause (Cray et al, 2012) and with lower urinary estrone and higher FSH levels (Woods et al, 2013)
- Gene polymorphisms associated with estrogen synthesis genes (CYP 19, 17 HSDB1) are of interest as biomarkers, e.g. CYP 19 11r associated with higher estrone levels (Woods 2007)

Sex Steroid Pathways: Estrogens

Figure 1. Six genes in the sex steroid pathway (in grayed areas) with measured circulating hormone concentrations (shown in shadowed boxes).

- Estrogen Synthesis: CYP 19 – aromatase gene 17 HSDs
- Estrogen Metabolizing: CYP1A1, CYP 1B1
- Estrogen Receptors: ESR1, ESR2

Gene Polymorphisms and Symptom Clusters
Aim

Assess the associations between estrogen synthesis gene (CYP 19 & 17 HSD) polymorphisms and the three symptom clusters

- CYP 19 repeats (TTTA)n – 7r, 7r-3, 11r (tetranucleotide repeat polymorphisms) and rs 10046 (C/T)
- 17HSDB1 rs2830 (A/G), rs592389 (G/T), rs 615942 (T/G)

Methods: Seattle Midlife Women’s Health Study

Study Design – Seattle Midlife Women’s Health Study

- Longitudinal study with 508 women interviewed between 1990-1992 (screened over 11,000 households from multi-ethnic census tracts)
- Annual follow-up since enrollment with 390 women starting longitudinal study in 1992
- Cohort included 243 participants in 1996 when monthly urine samples were added to study and in 2000 193 provided buccal swabs for genotyping
- Women had 16 years of education, 85-91% employed, 75-89% white, and 68-69% partnered

Genotyping

- Buccal swab samples were genotyped by the Center for Ecogenetics and Environmental Health at the University of Washington using polymerase chain reaction primers and allele specific probes
- CYP 19 7r, 7r-3, 11r TTTA(n) and rs 10046 (C/T)
- 17 HSD (rs2830 (A/G, GG), rs592389 (G/T, TT), rs615942 (C/A, AA)
Identifying Symptom Clusters: Latent Class Analysis

- Latent class (or latent mixture) model empirically determines whether there are distinct clusters (latent classes) of symptoms
- Does not assume linearity, normally distributed data, or homogeneity of variances
- LCA (Mplus v. 5) was used to find clusters (latent classes) of MT symptoms
- Gene polymorphisms include as covariates to assess effect on symptom cluster membership

Polymorphisms and Symptom Clusters: Cluster 1 vs 3

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>b</th>
<th>SE</th>
<th>Wald(1)/ OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 19 rs 10046 (C/T)</td>
<td>.138</td>
<td>.800</td>
<td>0.17</td>
</tr>
<tr>
<td>17 HSDB1 615942 (T/G)</td>
<td>1.92</td>
<td>0.54</td>
<td>3.55**</td>
</tr>
<tr>
<td>17 HSDB1 2830 (A/G)</td>
<td>-0.059</td>
<td>0.58</td>
<td>-1.02</td>
</tr>
<tr>
<td>17 HSDB1 592389 (G/T)</td>
<td>2.30</td>
<td>0.49</td>
<td>4.72**</td>
</tr>
</tbody>
</table>

Results

- 17 HSD rs 592389 (G/T) and rs 615942 (T/G) were associated with lower likelihood of having cluster 1 vs 3
- 17 HSD rs 592389 (G/T) and rs 615942 (T/G) were also associated with higher estrone levels (p<.05, .10)
- CYP 19 repeat/deletion and rs 10046 (C/T) polymorphisms had no significant effects on symptom cluster membership
- None of the estrogen synthesis polymorphisms differentiated symptom clusters 2 and 3
Discussion and Conclusions

- Women with Symptom Cluster 1 (high hot flash group) were less likely to have the polymorphisms for \textit{17 HSDB1 rs2389 (G/T) and rs 615942 (T/G)} polymorphisms than those in Cluster 3 (low severity symptoms)
- Association of the \textit{17 HSDB1 rs 592389 and rs 615942} genotypes with higher estrone levels makes the relationship plausible
- No other polymorphisms were significantly related to Symptom Clusters

Conclusions

- Based on our studies, Symptom Clusters 1 and 3 can be distinguished by:
  - Menopausal transition stages, E1G and FSH
  - Perceived stress
  - Epinephrine and norepinephrine
  - Gene polymorphisms related to estrogen synthesis (17 \textit{HSDB1 rs 592389 and rs 615942})
- Replication of findings relating symptom clusters to estrogen synthesizing genes needed in larger and ethnically diverse populations

Thank you for your interest in women’s health!