The Interaction between Genotypic and Inflammatory Grief Disorder
Is Associated with Elevated Circulating Levels of IL-6
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Background
• Spousal bereavement is associated with increased morbidity and mortality in the surviving spouse. Although most widow(er)s are resilient, a minority experience a chronic debilitating condition called Complicated Grief disorder¹, showing increased morbidity rates².
• However, the mechanism linking Complicated Grief disorder and adverse health outcomes has not been clarified.
• Prior research has identified a G x E interaction between a variation in an inflammatory genotype (IL-6) and bereavement on circulating levels of inflammation³ (Figure 1).
• Genetic variability may interact with Complicated Grief disorder in the expression of inflammatory markers.

Methods
• Sixty-four older adults were recruited from the Los Angeles area (widowed = 36; married/partnered = 28) with an average time since spousal loss of 2 years.
• Inventory of Complicated Grief-Revised (ICG-R)⁴ + 19 items; assesses indicators of pathological grief, such as anger, disbelief, and hallucinations, on a 5-point scale.
• The Complicated Grief group was determined by a score of 30 or higher on the ICG-R.
• Genomic DNA was extracted from peripheral blood monocytes, and the IL-6 -174 SNP was determined for each participant.
• Genotype frequencies met Hardy–Weinberg equilibrium and were consistent with the literature.
• High sensitivity ELISA for circulating levels of IL-6 was performed on plasma.

Objective
• The present study compared Complicated Grief, Non-Complicated Grief, and Non-Bereaved married/partnered older adults to examine whether a single nucleotide polymorphism (SNP) in the human IL-6 gene promoter region (rs1800795 G/C) might influence vulnerability for increased inflammation following spousal loss.

Genotype Frequencies

<table>
<thead>
<tr>
<th></th>
<th>ICG-R (n=28)</th>
<th>Non-Complicated Grief (n=23)</th>
<th>Complicated Grief (n=13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 -174GG (High)</td>
<td>13</td>
<td>40%</td>
<td>52%</td>
<td>0.26</td>
</tr>
<tr>
<td>IL-6 -174GC (Low)</td>
<td>15</td>
<td>54%</td>
<td>47%</td>
<td>0.48</td>
</tr>
<tr>
<td>IL-6 -174CC</td>
<td>15</td>
<td>23%</td>
<td>10%</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th></th>
<th>Mean/SD</th>
<th>Mean/SD</th>
<th>Mean/SD</th>
<th>P-value</th>
<th>F-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.39/4.15</td>
<td>72.83/4.01</td>
<td>73.08/5.52</td>
<td>0.01</td>
<td>0.21</td>
<td>0.94</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>15/8</td>
<td>54%/57%</td>
<td>10/77%</td>
<td>0.03</td>
<td>0.03</td>
<td>0.56</td>
</tr>
<tr>
<td>Ethnicity (non-Caucasian)</td>
<td>5/22</td>
<td>39%/39%</td>
<td>29%/15%</td>
<td>0.21</td>
<td>0.11</td>
<td>0.73</td>
</tr>
<tr>
<td>Employment (retired)</td>
<td>15/12</td>
<td>75%/78%</td>
<td>78%/82%</td>
<td>0.96</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>Education (postgraduate)</td>
<td>13/65</td>
<td>40%/39%</td>
<td>45%/36%</td>
<td>0.57</td>
<td>0.57</td>
<td>0.57</td>
</tr>
<tr>
<td>Years married/partnered</td>
<td>41.18/11.24</td>
<td>31.46/16.22</td>
<td>18.22/12.60</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.35/5.63</td>
<td>27.01/5.61</td>
<td>26.88/5.68</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
</tr>
<tr>
<td>Alcohol (drinks per week)</td>
<td>11/15</td>
<td>6.00/6.00</td>
<td>6.00/6.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Results
• There was a dose-dependent increase in circulating levels of IL-6 across the three groups (NB: 1.9 ± 0.9 pg/ml; NCG: 2.3 ± 1.7 pg/ml; and CG: 3.7 ± 2.7 pg/ml).
• In a regression controlling for age and BMI, group (β = 0.61) and group x genotype (β = -0.44) were both predictive of circulating IL-6 [F(5,57) = 3.58, p = 0.007].
• All IL-6 -174C allele carriers had similar levels of circulating IL-6.
• However, levels of circulating IL-6 were twice as high in Complicated Grief IL-6 -174G homozygotes compared to Non-Complicated Grief and Non-bereaved IL-6 -174G homozygotes (Figure 2).

Conclusion
• The present study found elevated levels of IL-6 in the Complicated Grief group, explained by the interaction between IL-6 -174 SNP and Complicated Grief disorder such that Complicated Grief G homozygotes showed a two-fold increase in IL-6 compared to Complicated Grief C allele carriers.
• The results suggest a possible mechanism for increased morbidity and mortality in widow(er)s suffering from Complicated Grief.
• With future replication, these data might indicate clinical follow up for this group.

Acknowledgements
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References