A systematic review of progranulin concentrations in biofluids in over 7,000 people - assessing the pathogenicity of GRN mutations and other influencing factors

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Background

- Heterozygous mutations in the GRN gene are a major cause of genetic frontotemporal dementia (FTD), causing an estimated 5-10% of all FTD cases (1).
- GRN encodes for progranulin (PGRN) and mutations lead to haploinsufficiency.
- Mutations are associated with significantly lower concentrations of PGRN in biofluids in mutation carriers compared to controls (2,3).

Methods

- We contacted all authors who have published data on PGRN concentrations in serum, plasma or CSF (in any medical condition) up to December 2019.
- We asked if they were able to share anonymised data including PGRN concentrations and clinical data such as specific mutation if present, clinical diagnosis, age at onset of dementia, sex, and GRN rs5848 polymorphism.
- Data from 7,071 people was collated and analysed, including PGRN measured with a range of assays and in different fluid types (Table 1).

Results

- We also found that females have significantly higher PGRN levels than males.

Table 1: Number of PGRN measurements across different assay and fluid types

<table>
<thead>
<tr>
<th>Assay</th>
<th>Adipogen</th>
<th>Behinder</th>
<th>Metagenost</th>
<th>IBD</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (GRN mutation carriers)</strong></td>
<td>149 (7)</td>
<td>506 (8)</td>
<td>56 (3)</td>
<td>59 (3)</td>
<td>1441 (5)</td>
</tr>
<tr>
<td><strong>Plasma (GRN mutation carriers)</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Serum (GRN mutation carriers)</strong></td>
<td>149 (7)</td>
<td>756 (12)</td>
<td>59 (3)</td>
<td>49 (3)</td>
<td>605 (4)</td>
</tr>
<tr>
<td><strong>CSF (GRN mutation carriers)</strong></td>
<td>0 (0)</td>
<td>135 (7)</td>
<td>30 (2)</td>
<td>56 (3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 2. Mean levels (ng/µL) and standard deviation of PGRN concentrations measured with different assays across different fluid types

<table>
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</thead>
<tbody>
<tr>
<td><strong>Total (GRN mutation carriers)</strong></td>
<td>61.55 ± 1.53</td>
<td>71.00 ± 1.48</td>
<td>75.95 ± 1.32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Plasma PGRN concentrations measured with the Adipogen assay spanning the GRN gene. Dotted lines indicate suggested cut-offs of 61.55ng/µL, 71.00ng/µL and 75.95ng/µL, as defined in (1), (2) and this dataset, respectively. Exonic mutations are in light grey and intronic mutations are in dark grey.

Figure 2. Differential plasma PGRN concentrations across six different mutation groups and compared to non GRN mutation carriers. P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, two-tailed Mann-Whitney test.

Figure 3. GRN polymorphism rs5848 influences plasma PGRN concentrations in this data set.

Figure 4. Sex differences in plasma PGRN concentrations in this data set.

Conclusions

- Missense variants outside the signal peptide have significantly higher levels compared to other groups (figure 2).
- This suggests that these mutations are less likely to be pathogenic.
- Based on this, we defined a cut-off of 75.95ng/µL with a Youden's index of 0.92.

Figure 2. Differential plasma PGRN concentrations across six different mutation groups and compared to non GRN mutation carriers. P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, two-tailed Mann-Whitney test.

Figure 3. GRN polymorphism rs5848 influences plasma PGRN concentrations in this data set.

Figure 4. Sex differences in plasma PGRN concentrations in this data set.

- These findings highlight the variable pathogenicity of different GRN mutations and the importance of considering other factors when looking at biofluid concentrations of PGRN.
- This is important for upcoming clinical trials of progranulin-associated FTD where PGRN levels are being used as outcome measures.

References