A Sporadic Case of Progressive Non-Fluent Aphasia (PNFA) Caused By A Novel Progranulin Mutation

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Introduction

According to the widely accepted consensus clinical criteria, Progressive Non-Fluent Aphasia (PNFA) is one of the 3 clinical types of Fronto-Temporal Lobar Degeneration (FTLD). Mutations in Progranulin (GRN) gene cause FTLD with Ubiquitin and TARDBP-43-positive neuronal inclusions, without evidence of hyperphosphorylated Tau-protein aggregates. The many mutations reported so far (>65) are associated with widely variable phenotypes and with both autosomal dominant familial and sporadic cases.

Aims

To further investigate the variability of GRN mutations in a Greek FTLD population

Methods

26 Greek and 300 Italian patients with clinically diagnosed FTLD, as well as 157 Italian controls, were scanned for GRN mutation. High-molecular weight DNA was isolated from whole blood using a Flexigene Kit (Qiagen, Hildren, Gemany), as described by the manufacturer. The amount of DNA for each sample was determined by measuring the optical density at 260 nm wavelength using a spectrophotometer (Eppendorf AG, Germany). DNA samples were aliquoted and stored at −20 °C until use. The entire GRN open reading frame,
including the noncoding exon 0 and exon-intron boundaries of exons 1-12 of the GRN gene, was sequenced using specific primers.

**Results**

No known mutations were found in our sample. Nonetheless, a new variant was found in a 62 year old Greek female patient with PNFA. The same variant was not found in the Italian FTLD patients (n=300) and controls (n=157), for a total of 914 chromosomes, suggesting it is a mutation rather than a benign polymorphism.

**Case Report**

*History:* 62 year old, right-handed, female, with a 15- month history of progressive language impairment of the PNFA type and only a mild functional impairment in her everyday activities. No medical history or known family history. Mother deceased at the age of 62, possibly from stroke.

*Language and cognition:* Effortful, dysarthric and agrammatic speech, markedly reduced semantic (animals) and phonemic (words beginning with letter K) fluency, phonemic paraphasias, severe naming and reading difficulties. Speech comprehension, visuospatial memory and ideomotor praxis relatively well preserved, but severely impaired global cognition and executive functioning (*Table 1*).

*Neurological examination:* Mild right-sided bradykinesia.

*Psychiatric examination:* Depressive mood and reduced interest for her previously beloved hobbies. No other behavioural disturbance.

*Neuroimaging:* Cerebral MRI: Bilateral fronto-parietal atrophy. SPECT scan: Bilateral frontal and left parieto-temporal hypoperfusion (*Figures 1, 2*).

*Genetic study:* GRN sequencing demonstrated a novel mutation in exon 12 (g.3208G>A), resulting in the Cys481Tyr substitution. The in-silico analysis (SIFT and Polyphen) predicted
that the aminoacid change occurs in a highly conserved region and it is damaging on the protein function (*Figure 3*).

**Discussion**

This variant hasn’t been reported yet, although in ex 12, close to this variant, many others have been described (including null mutations). Our case further demonstrates the variable clinical presentations of *GRN* mutations even in apparently sporadic cases with a clinical presentation of PNFA.
Table 1: Patient's raw scores

<table>
<thead>
<tr>
<th>Tests</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>MMSE</td>
<td>7/30</td>
</tr>
<tr>
<td>5 Objects- Immediate recall</td>
<td>5/5</td>
</tr>
<tr>
<td>5 Objects- Delayed recall</td>
<td>4/5</td>
</tr>
<tr>
<td>Semantic Fluency-Animals</td>
<td>1/1min</td>
</tr>
<tr>
<td>Ideomotor Praxis</td>
<td>15/18</td>
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<tr>
<td>Clock Drawing Test</td>
<td>0/7</td>
</tr>
<tr>
<td>Frontal Assessment Battery</td>
<td>4/18</td>
</tr>
</tbody>
</table>

Figure 1: axial MR-imaging

Figure 2: SPECT-HMAPO imaging
Figure 3

Contro       Greek Patient #