Clinical history

• 58-year-old man with a four-year history of bilateral essential tremor, right hand greater than left, for which thalamic deep brain stimulators were placed. Subsequent MR imaging noted a 0.6 cm, non-enhancing, T2-hyperintense lesion in the left cerebellar hemisphere.

• MRI surveillance of the lesion documented a tripling in size. MRI report stated: “...contiguous involvement of the left middle cerebellar peduncle and brainstem, including the pons, extending across the midline.”

• Concomitant with the lesion growth, the patient’s tremors returned and became refractory to DBS.

• Patient was referred to neurosurgery for biopsy of left cerebellar mass.
Discussion

• Differential diagnosis
• Ancillary studies?
Ubiquitin
Diagnosis:

• Findings suggestive of fragile X-associated tremor ataxia syndrome (FXTAS)
Tissue molecular testing

• SNP-copy number microarray and 500-gene NGS panel failed to detect any abnormalities in the biopsied tissue.
Clinical follow-up

- Based on the biopsy results, the patient was referred to medical genetics, where peripheral blood was drawn for germline testing.

### Results: PREMUTATION ALLELE

<table>
<thead>
<tr>
<th>GENE</th>
<th>MODE OF INHERITANCE</th>
<th>VARIANT</th>
<th>ZYGOSITY</th>
<th>CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR1</td>
<td>X-Linked</td>
<td>Repeat Number: 97, METHYL: NONE</td>
<td>Hemizygous</td>
<td>Premutation</td>
</tr>
</tbody>
</table>

**Reference Range**

<table>
<thead>
<tr>
<th>Classification</th>
<th>CGG Repeat Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>less than 45</td>
</tr>
<tr>
<td>Intermediate (&quot;gray zone&quot;)</td>
<td>45-54</td>
</tr>
<tr>
<td>Premutation</td>
<td>55-200</td>
</tr>
<tr>
<td>Full mutation</td>
<td>greater than 200</td>
</tr>
</tbody>
</table>

97 CGG repeats in *FMR1* gene
Fragile X-associated tremor ataxia syndrome (FXTAS)

• Trinucleotide $\text{CGG}$ repeat expansion in $\text{FMR1}$ gene on X chromosome
  • Fragile X syndrome: $\geq 200$ repeats, diagnosed around age 3
  • FXTAS: 55-200 repeats (premutation carrier) onset in 50s or older
  • Primary ovarian insufficiency: female with premutation, $< 40$ years

• Clinical features (major diagnostic criteria):
  • Essential tremor and/or ataxia. May show parkinsonism, neuropathies, executive function and memory deficits.
  • MRI: Increased $\text{T2}$ FLAIR signal in middle cerebellar peduncle
    • Also cerebral white matter lesions and mild generalized atrophy
  • $\text{FMR1}$ sequencing showing 55-200 repeats
Fragile X-associated tremor ataxia syndrome (FXTAS)

• Gross spongiosis and discoloration of cerebellar white matter is present in the vast majority of FXTAS cases
  • May also be focal cerebral WM lesions and subcortical WM discoloration
• Histopathology:
  • Presence of intranuclear inclusions in astrocytes and neurons positive for ubiquitin, p62, αB-crystallin and FMR1 mRNA.
  • Inclusions are widespread: frontal cortex, cerebellum, hippocampus, basal ganglia, brainstem and PNS.
  • White matter lesions demonstrate a loss of myelin, as well as axonal degeneration and gliosis.
  • Perivascular iron deposition and patchy astrogliosis


