Compound heterozygous C10orf2 mutations in a Japanese patient with 46, XX ovarian failure and deafness

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Background

Perrault syndrome is a rare autosomal recessive disorder characterized by sensorineural deafness in both sexes and primary ovarian failure in 46, XX karyotype females. HSD17B4, HARS2, LARS2, CLPP and C10orf2, which are associated mitochondrial function, have been reported as causative genes.

1951
Perrault et al. described 2 sisters

2010
HSD17B4 (Pierce B et al.)

2011
HARS2 (Pierce SB et al.)

2013
LARS2 (Pierce SB et al.)

2014
C10orf2 (Morino H, Pierce SB et al.)

C10orf2, encoding the TWINKLE protein, a DNA helicase acting in the mitochondria.

Objective and hypotheses: Here we report a Japanese patient who was identified with C10orf2 mutation with the fourth case in Perrault syndrome.

Case presentation: 13-year-old Japanese girl

Chief complaint: short stature

Family history: no consanguinity, her parents were clinically normal

History of present illness: The patient was referred to our hospital due to short stature at the age of 12 years.

Physical examination at 13 years of age:
Body height (BH): 138.2 cm (-3.2 SD). Body weight (BW): 30.2 kg, %tile BMI: 3.1. Tanner stage: Breast: 1; Pubic hair: 1; No genital anomaly

No neurologic findings

Hearing test: 30~40 dB bilateral sensorineural hearing loss

Bone age (TW2 methods; J-RUS): 9 years and one month

Endocrinological data

<table>
<thead>
<tr>
<th>Reference</th>
<th>LH (mIU/mL)</th>
<th>FSH (mIU/mL)</th>
<th>E2 (pg/mL)</th>
<th>TSH (mIU/L)</th>
<th>FT4 (ng/dL)</th>
<th>IGF-1 (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>37.1</td>
<td>163.2</td>
<td>&lt;10</td>
<td>2.6</td>
<td>1.2</td>
<td>330</td>
</tr>
<tr>
<td>Control</td>
<td>0.7</td>
<td>0.9-5.3</td>
<td>&lt;10</td>
<td>0.5-5.0</td>
<td>0.9-1.6</td>
<td>193-643</td>
</tr>
</tbody>
</table>

Chromosome (G-banding) 46,XX

Mutations of C10orf2 and clinical phenotype


Neurological findings at 24 years of age

- Physical exam: Nystagmus, intention tremor, loss of deep tendon reflexes, incapable of standing with closed eyes
- Nerve conduction study
  - Motor nerve: normal velocity and amplitude
  - Sensory nerve: poor amplitude

- Cerebellum ataxia
- Peripheral sensory neuropathy of the extremities

Molecular analysis

Sequence analyses (PCR-direct method)
- No mutations of HARS2, LARS2, or CLPP
- C10orf2 sequence: compound heterozygous mutations, c.[1136G>A];[1172G>A]

Patient
- c.1136G>A (p.G379E)
- c.1172G>A (p.R391H)

Mother
- Wild type
- c.1172G>A (p.R391H)

Father
- c.1136G>A (p.G379E)
- Wild type

Relative quantification of mtDNA by qPCR in peripheral blood

<table>
<thead>
<tr>
<th>MT-ND1/CFTR</th>
<th>MT-TL1/CFTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Control</td>
</tr>
<tr>
<td>Pt</td>
<td>Pt</td>
</tr>
</tbody>
</table>

mtDNA depletion was not detected in peripheral blood.

CONCLUSIONS

- C10orf2 mutations should be considered in patients with ovarian failure and sensorineural deafness.
- This is the first report of a mutation in the linker domain in a patient with Perrault syndrome.

References


Poster presented at: 373-P1