TITLE

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.

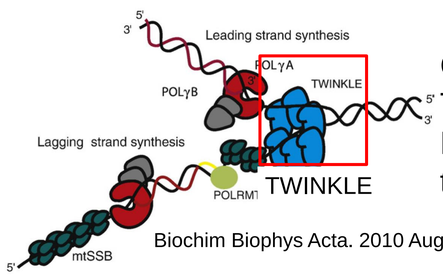
1951年 Perrault *et al*. described 2 sisters

2010年 *HSD17B4* (Pierce B et al.)

2011年 *HARS2* (Pierce SB et al.)

2013年 *LARS2* (Pierce SB et al.)
CLPP (Jenkinson EM et al.)

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



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

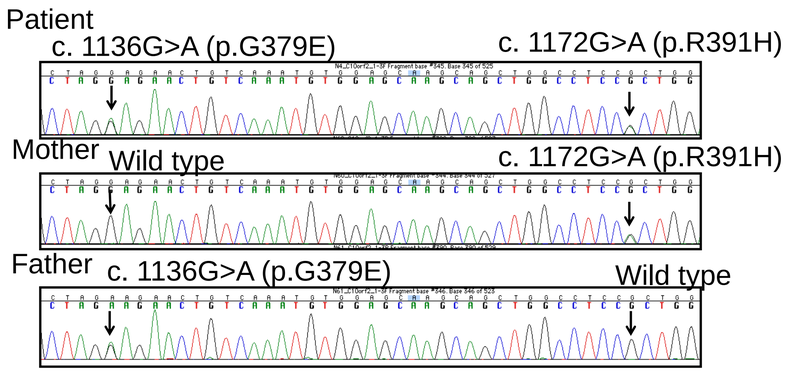
Biochim Biophys Acta. 2010 Aug;1797(8):1378-88.

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

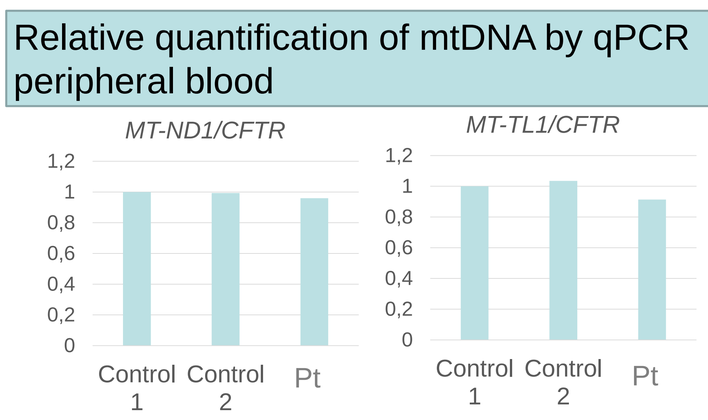
Molecular analysis

Sequence analyses (PCR-direct method)

- No mutations of *HARS2, LARS2, or CLPP*
- *C10orf2* sequence：compound heterozygous mutations, c.[1136G>A];[1172G>A]



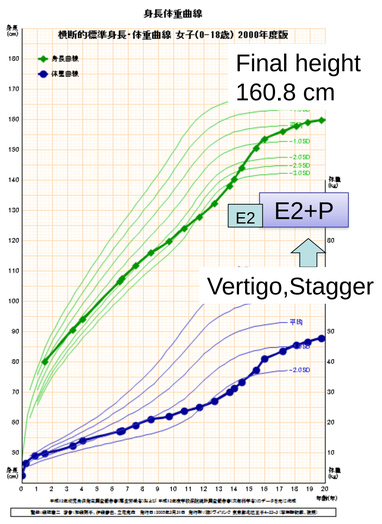
Relative quantification of mtDNA by qPCR in peripheral blood



mtDNA depletion was not detected in peripheral blood.

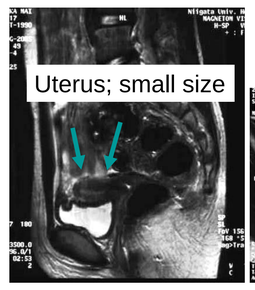
Case presentation: 13-year-old Japanese girl

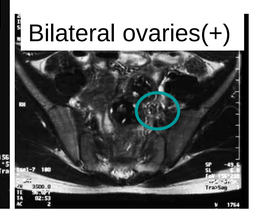
Chief complaint: short stature
Family history: no consanguinity, her parents were clinically normal
History of present illness: The patient was referred to our hospital due to short stature at the age of 12 years.
Physical examination at 13 years of age:
Body height (BH); 138.2 cm (-3.2 SD), Body weight (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		Reference
LH (mIU/mL)	37.1	<0.7
FSH (mIU/mL)	163.2	0.6-5.3
E2 (pg/mL)	<10	<10
TSH (mU/L)	2.6	0.5-5.0
FT4 (ng/dL)	1.2	0.9-1.6
IGF-1 (ng/mL)	330	193-643
Chromosome (G-banding) 46,XX		





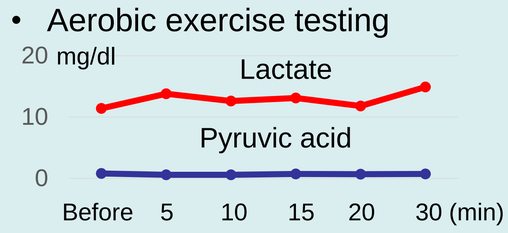
Diagnosis
- 46,XX ovarian failure
- Sensorineural deafness
  - ➢ Perrault syndrome

Neurological findings at 24 years of age

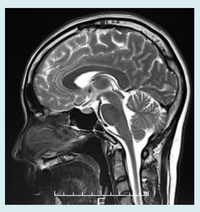
- Physical exam; Nystagmus, intention tremor, loss of deep tendon reflexes, incapable of standing with closed eyes
- nerve conduction study
  - ✓ Motor nerve：normal velocity and amplitude
  - ✓ Sensory nerve：poor amplitude

➢Cerebellum ataxia
➢Peripheral sensory neuropathy of the extremities

- Aerobic exercise testing

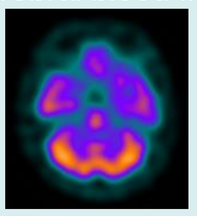


Brain MRI T2W1

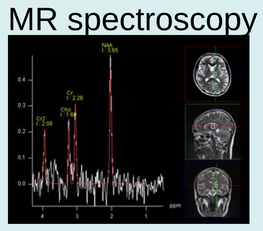


Mild atrophy of upper cerebellum

SPECT imaging of cerebral blood flow

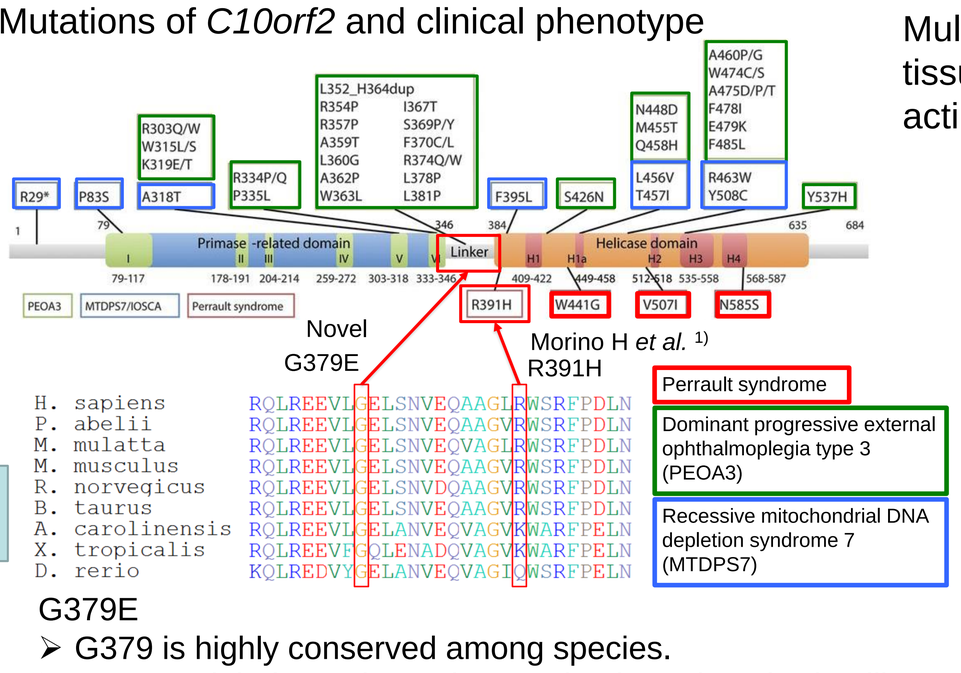


MR spectroscopy



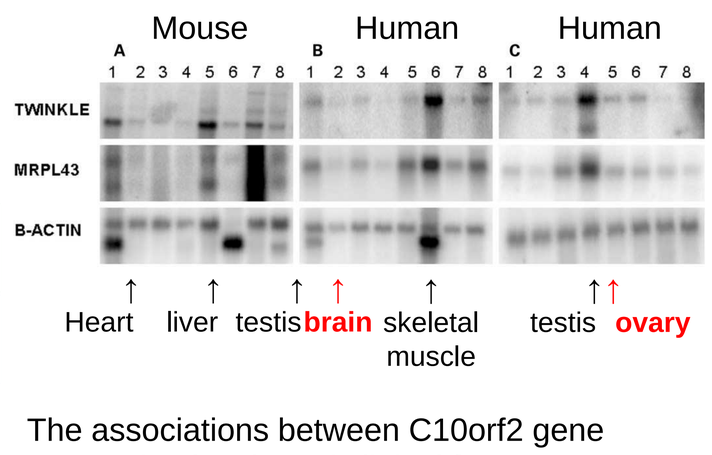
No lactate peak

Mutations of *C10orf2* and clinical phenotype



G379E
- ➢ G379 is highly conserved among species.
- ➢ G379E might be pathogenic mutation based on the *in-silico analyses. (*PolyPhen-2: damage score 0.48, POSSIBLY DAMAGING; Mutation Tester: disease causing)
- This mutation, which is located in the linker domain, was the first reported for Perrault syndrome.

Multiple northern blots of mouse and human tissues probed with Twinkle, MrpL43 and β-actin cDNAs. (Hum Mol Genet. 2004 Dec 15;13(24):3219-27.)



The associations between C10orf2 gene expression levels and clinical features are poor.

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

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55ESPE 373--P1
Gonads & DSD
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DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS
PosterSessionOnline.com