A novel PRKAR1A gene mutation with mild brachydactyly

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COI
We have nothing to disclose.

Take home message
PRKAR1A gene mutation carriers may show mild brachydactyly.

Background
Acrodysostosis is a rare skeletal dysplasia with severe brachydactyly, facial dysostosis and nasal hypoplasia. In 2012, PRKAR1A gene was identified as one of the responsible genes of Acrodysostosis with hormonal resistance (ADOHR).

Reported phenotypes of PRKAR1A gene mutations are severe brachydactyly and mild hormone resistance.

Objective
To report a novel heterozygous mutation of PRKAR1A gene in an ADOHR patient with mild brachydactyly.

Methods
This study protocol was approved by the Institutional Ethical Review Board of the Tokyo Metropolitan Children’s Medical Center and Keio University.

1. Mutational Analyses
Genomic DNA of the patient and his parents were extracted from the peripheral leukocytes or saliva by using standard techniques. We sequenced three genes of GNAS, PRKAR1A and PDE4D using the next generation sequence strategy. A PRKAR1A mutation indicated by the screening analysis was confirmed by Sanger sequencing.

2. Functional Assay
We generated PRKAR1A expression vectors containing wild type and mutant type. To compare the novel identified mutant type with previously reported one, we also generated R368X PRKAR1A expression vector, which is well characterized. Using HEK293 cells, we performed Forskolin induced CRE-Luciferase assay to analyse the Protein Kinase A activity.

Results

1. Gene analysis: PRKAR1A gene

2. Crystal structure modeling

3. Functional analysis

Discussion

• The facial appearance and mild brachydactyly with hormone resistance indicated PHP rather than ADOHR. But the response to PTH infusion indicated abnormality of downstream of the GNAS.

• MCPA analysis revealed that the severity of brachydactyly of the patient were similar to that of PHP, which reported to be milder than Acrodysostosis. [de Sancis et al., 2004].

• At present, he does not develop hypocalcemia or hypothyroid. It is considered that hormone resistance of this patient is mild as it has been reported [Linglart et al., 2011].

• Only one patient was reported to carry the misense mutation of cAMP binding domain [Nagasaki et al., 2012]. The reported patient presented typical ADOHR phenotypes including severe brachydactyly. The phenotype of mild brachydactyly may not associate with reduced function of this domain.

Conclusion
PRKAR1A gene mutation carriers may show mild brachydactyly.

Fig.1 Pedigree

Fig.2 Growth Chart

Fig.3 Radiograph of the left hand

Fig.4 MCPP analysis

Fig.5 Urinary P and cAMP response toPTH infusion of the patient and reported cases.

Fig.6 Partial sequences of the PCR products

Fig.7 PRKAR1A functional domains and the novel mutation of the patient.

Fig.8 Homology study

Fig.9 Crystal structure modeling of WT and G171R

Fig.10 PKA transcrational activity in cells stimulated with forskolin