School of Life Sciences

Seminar Series

No. 2019-30

Thu., **28 November**, 4:00pm

Jukhyun Bio Auditorium(RM.121)

Korean

Identification of novel gene variants leading to skeletal dysplasia

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광주과학기술원 생명과학부

Gwangju Institute of Science and Technology School of Life Sciences

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Younghwan Kim, Ph.D.

Education/Experience

1994-1998	B.S., Seoul National University, Seoul, Korea
1998-2000	M.S., Seoul National University, Seoul, Korea
2004-2009	Ph.D., The University of Texas at Austin, TX, USA
2010-2013	PostDoc, The Rockefeller University, NY, USA
2014-present	Associate Professor, Dept. of Biological Sciences, Sookmyung Women's University

Abstract

Fibrodysplasia ossificans progressive (FOP) is a rare autosomal dominant human skeletal disorder characterized by progressive heterotopic ossification within soft connective tissues. All the patients presented with clinical features of FOP so far have been found to carry heterozygous mutations in the activin A type I receptor (ACVR1) gene, a bone morphogenetic protein (BMP) type 1 receptor. Here, we report for the first time a de novo heterozygous N334T mutation in BMPR2, one of the BMP type 2 receptors, in a patient with FOP phenotype. A 16-year-old boy had subcutaneous migrating nodules at the scalp at age 3 years, and flare-ups and stiffness of the neck and back since 6 years of age. Physical examination revealed completely fixed neck, back, and right shoulder. Radiographic examination showed heterotopic ossifications at the back muscles, periscapular muscles, upper and thigh muscles. Interestingly, anomaly of the great toe is detected. No AVCR1 variants were determined. Whole exome sequencing revealed a de novo and heterozygous mutation of BMPR2, c.981G>A (p.N334T). Constitutive activation of Smad signaling was determined in the patient cells, which is down-regulated upon CRISPR-Cas9 mediated BMPR2 silencing. At the cytological levels, patient-derived cells were positive for the APL expression and calcium accumulation, both of which are abolished by treatment of Dorsomorphin, a Samd signaling inhibitor. The N334T mutation is located in the kinase domain of BMPR2, which is highly conserved among species. Expression of the BMPR2-N334T in HEK293T cells induces Smad1/5/9 phosphorylation even in the absence of BMPs. Consistently, significant enhancement of BMP responsive gene expression is observed from the BRE reporter assay. In addition, BMPR2-N334T expression in C2C12 myoblasts leads to Smad1/5/9 phosphorylation and increased expression of the downstream signaling targets including ID1, ID3, ALP, RUNX2 and Osteocalcin, all of which are required for extensive bone formation. All the results described above provide evidences in support of BMPR2 as a causative gene for the FOP phenotype of this patient.