# Exogenous Activation of BMP-2 Signaling Overcomes TGFbeta-Mediated Inhibition of Osteogenesis in Marfan Embryonic Stem Cells and Marfan Patient-Specific Induced Pluripotent Stem Cells.

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**Public Summary:**
Marfan syndrome (MFS) is a hereditary disease caused by mutations in the gene encoding Fibrillin-1 (FBN1) a large protein component of extracellular cell matrix. This syndrome is characterized by a number of skeletal abnormalities, including susceptibility to bone fracture, osteopenia and exaggerated growth of long bone and fingers. Severe forms of MFS give rise also cardio-vascular pathologies, such as aortic root dilatation and aneurysm. Sometimes this syndrome affects eyes as well, specifically the lens. We have previously demonstrated that unique skeletal defects observed in human embryonic stem cells derived from a Marfan embryo are faithfully recapitulated by stem cells derived independently from MFS adult patient fibroblasts. These types of cells are known as “induced pluripotent-stem cells” (iPSCs) and are obtained using a technique recently developed. In the current study we have moved a step forward gaining further insights into the pathology of Marfan syndrome. We have unveiled additional molecular and cellular mechanism(s) responsible of skeletal defects observed in Marfan cells. Our recent results demonstrate that alteration (elevated activation) of a biochemical signaling called TGF-beta occurring in Marfan cells inhibits another biochemical/cellular signaling known as BMP signaling which is a key regulator of bone growth and development. Our results shed new light on the signaling cross-talk occurring in Marfan cells. Indeed, this study is an important step towards determining the biological potency of clinically-relevant, functional cell types derived from Marfan embryonic stem cells and Marfan iPSCs. Our findings could contribute to development of effective novel therapeutic strategies targeting both, TGF-beta and BMP signaling pathways for treatment of MFS patients. Moreover, this study advances our understanding of molecular mechanisms underlying the pathogenesis of bone loss/abnormal skeletogenesis in human diseases caused by genetic mutations.

**Scientific Abstract:**
Marfan syndrome (MFS) is a hereditary disease caused by mutations in the gene encoding Fibrillin-1 (FBN1) and characterized by a number of skeletal abnormalities, aortic root dilatation, and sometimes ectopia lentis. Although the molecular pathogenesis of MFS was attributed initially to a structural weakness of the fibrillin-rich microfibrils within the extracellular matrix, more recent results have documented that many of the pathogenic abnormalities in MFS are the result of alterations in TGFbeta signaling. Mutations in FBN1 are therefore associated with increased activity and bioavailability of TGF-beta1, which is suspected to be the basis for phenotypical similarities of FBN1 mutations in MFS and mutations in the receptors for TGFbeta in Marfan syndrome-related diseases. We have previously demonstrated that unique skeletal phenotypes observed in human embryonic stem cells carrying the monogenic FBN1 mutation (MFS cells) are faithfully phenocopied by cells differentiated from induced pluripotent-stem cells (MFSiPS) derived independently from MFS patient fibroblasts. In this study, we aimed to determine further the biochemical features of transducing signaling(s) in MFS stem cells and MFSiPS cells highlighting a crosstalk between TGFbeta and BMP signaling. Our results revealed that enhanced activation of TGFbeta signaling observed in MFS cells decreased their endogenous BMP signaling. Moreover, exogenous BMP antagonized the enhanced TGFbeta signaling in both MFS stem cells and MFSiPS cells therefore, rescuing their ability to undergo osteogenic differentiation. This study advances our understanding of molecular mechanisms underlying the pathogenesis of bone loss/abnormal skeletogenesis in human diseases caused by mutations in FBN1. STEM CELLS 2012;30:2709-2719.