

Heterozygous Disruption of $G_{s\alpha}$ in Osteocytes Decreases Peripheral Fat without Affecting Bone Mass

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The stimulatory α -subunit, $G_{s\alpha}$, of a heterotrimeric G-protein is a ubiquitously expressed protein that mediates signals from various hormone and neurotransmitter receptors to the generation of cAMP. Heterozygous loss-of-function mutations of $G_{s\alpha}$ lead to Albright hereditary osteodystrophy characterized by skeletal defects and, in case of the mutation on maternal allele, results in obesity. To define $G_{s\alpha}$ actions in osteocytes *in-vivo*, we engineered homozygous (DMP1- $G_{s\alpha}$ KO) or heterozygous (DMP1- $G_{s\alpha}$ Het) mice lacking $G_{s\alpha}$ in osteocytes. DXA analysis of 21-week old DMP1- $G_{s\alpha}$ KO mice showed significantly decreased total body BMD (19%) and BMC (21%) ($p < 0.01$, $n \geq 6$) whereas, microCT analysis of the distal femur showed an 86% decrease in trabecular bone volume. Histomorphometry analysis of femurs from 7-week old DMP1- $G_{s\alpha}$ KO mice showed a significant decrease in the number of osteoblasts, BFR, MAR, and the number of osteoclasts indicating a state of low turnover ($p < 0.05$, $n \geq 3$). Sclerostin expression in tibia of DMP1- $G_{s\alpha}$ KO mice was increased 3-fold indicating possible inhibition of Wnt signaling in osteoblasts. Additionally, DMP1- $G_{s\alpha}$ KO, but not DMP1- $G_{s\alpha}$ Het, mice showed hematopoietic abnormalities. Neither micro-CT nor DXA bone parameters differed between control and DMP1- $G_{s\alpha}$ Het. Interestingly, both DMP1- $G_{s\alpha}$ KO and DMP1- $G_{s\alpha}$ Het mice showed a significant decrease (>40%) in peripheral fat at 21-weeks of age as analyzed by DEXA ($p < 0.01$, $n \geq 6$). Preliminary analysis showed hypoglycemia, decrease in adipocyte size, and decrease in adiponectin and leptin expression in fat tissue in both DMP1- $G_{s\alpha}$ KO and DMP1- $G_{s\alpha}$ Het mice compared to controls. These results suggest a possible direct role of $G_{s\alpha}$ signaling in osteocytes in regulating not only bone metabolism, but also peripheral adiposity.