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Background: Obesity is a heterogenous disease resulting from environmental and genetic factors and is characterized by disordered energy balance, regulated in part by the hypothalamic melanocortin-4 receptor (MC4R), including neuronal ciliary assembly and trafficking pathways.[1] Rare loss-of-function variants in genes encoding components of this pathway are associated with severe obesity and hyperphagia, with or without additional features.[2] However, such rare genetic disorders may be underestimated due to a lack of genetic screening in individuals with severe obesity.[3] Our objective was to identify and characterize rare genetic variants in a Spanish population from Madrid with childhood obesity. **Methods:** This analysis was conducted from a prospectively-collected cohort of children with obesity, generally with a BMI>+3DS. Participants were sequenced for 35 obesity-related genes, including 23 genes related to Bardet-Biedl (BBS) and Alström syndromes, plus an additional 12 genes associated with non-syndromic, monogenic causes of obesity, to identify individuals with rare (<1% frequency in gnomAD) potentially biallelic (homozygous and compound heterozygous) non-synonymous variants in protein-coding regions. **Results:** Of the 1019 Spanish patients with obesity, 493 (48.4%) were female and the mean age and BMI were 10.41 ± 3.38 years and 4.38 ± 1.76 SDS (79.8% above +3 SDS), respectively. We identified 26 rare potentially biallelic variants in 25 unique individuals, including 2 individuals with homozygous variants in *POMC*, 3 individuals with two variants in *SRC1*, one individual with two variants in *ADCY3*, and one individual with a homozygous mutation in *LEP*. In addition, we identified 18 individuals with biallelic mutations in one of 23 *BBS* or *ALMS1* genes, including two individuals with known pathogenic variants and clinically confirmed BBS. **Conclusions:** Rare and potentially biallelic sequence variants were identified in 25 individuals with childhood obesity. These results support the use of genetic testing for individuals with severe obesity who may be candidates for specific clinical interventions or additional targeted therapies.

Bone and Mineral Metabolism

PARATHYROID HORMONE TRANSLATIONAL AND CLINICAL ASPECTS

Investigating Analogues of Parathyroid Hormone (PTH) and PTH-Related Peptide (PTHrP) to Improve Anabolic: Catabolic Response Ratios Using UMR106-01 Osteocytic Cells.

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SAT-402

Osteoporosis, the most common bone disease in humans, is characterised by decreased bone mass and increased fracture risk[1]. Osteoporosis development is associated with an imbalance of bone resorption and deposition mediated by all three bone cell types; osteoblasts, osteocytes and osteoclasts[2]. Current treatments for osteoporosis either prevent further bone resorption (Bisphosphonates and anti-RANKL) or increase bone deposition through anabolism (Teriparatide and Abaloparatide)[3]. The two anabolic treatments are truncated analogues of endogenous peptides; parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP), respectively. Both are administered intermittently, act on PTH1R receptors on osteoblasts and osteocytes leading to an increase in bone mineral density and bone strength. However, both treatments also have side-effects of hypercalcemia and cortical bone porosity caused by osteoclast stimulation. We therefore compared an array of PTH and PTHrP analogues for potential stimulation of catabolic side effects and desired anabolic effects. Screening assays used are UMR106-01 osteocytic cells that have high levels of PTH1R to measure mRNAs involved in anabolic responses (suppression of WNT inhibitors SOST and Dkk1) and catabolic responses (stimulation of RANKL/OPG, IL6). Peptides were also analysed by real-time cellular impedance assays (xCELLigence) to measure unbiased receptor stimulation. xCELLigence assays showed PTH1-34, PTHrP1-34 and Abaloparatide had the highest potencies (3.7 nM,1.4 nM,1.7nM respectively) while Tyr^{1}PTH1-34 and PTH2-34 had significantly decreased potencies (64nM and 130nM), the β-arrestin biased agonist, D-$Trp^{12}Tyr^{34}$PTH7–34, had no effect. PTH1-34 potently inhibited SOST (IC_{50} 0.29nM), and catabolic genes (RANK/OPG EC_{50} 0.5nM, IL6 EC_{50} 2.5nM). PTHrP1-34 provided higher potencies for anabolic (inhibited SOST IC_{50} 0.08nM) and catabolic (RANKL/OPG EC_{50} 0.3nM, IL6 EC_{50} 1nM) genes. Altering the first amino acid to Tyrosine; Tyr^{1}PTH1-34 caused potent anabolic responses (SOST IC_{50} 0.97nM) yet showed decreased potency for catabolic responses (RANKL/OPG EC_{50} 20nM, IL6 EC_{50} > 100nM). Removing the first amino acid of PTH to PTH2-34 drastically decreases the effectiveness of the peptide (OPG, SOST and RANKL IC_{50} – no effect, IL6 EC_{50} > 100nM). These results indicate the importance of the N-terminal amino acid for PTH affinity and efficacy and suggest that Tyr^{1}PTH1-34 may offer the best combination of bone stimulation without causing hypercalcemia.

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Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

A Natural Antibody Against Oxidized Phospholipids Attenuates Age-Related Bone Loss and Prevents Age-Related Glucose Intolerance in Mice

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Lipid peroxidation produces oxidized phospholipids (OxPL) such as oxidized phosphatidylcholine. These compounds react with amino groups of proteins and lipids to form