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Association between bone mineral density and genetic polymorphisms of Wnt signaling pathway among older adults in Taiwan

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Background: Osteoporosis is one of the chronic diseases of the elderly, which is commonly found in the elderly population, and the prevalence rate of osteoporosis increases with age. The cause of osteoporosis is complex, and bone mineral density(BMD) is generally lost with age, some factors will cause loss of bone such as lack of exercise, smoking, drinking, lack of calcium diet, lack of sunbathing. Especially genetic factors may play an important role.

Objective: To explore the association between BMD and the polymorphism of Wnt signaling pathway, and to test the gene-environment interaction. Provide early prevention strategies for high risk groups of bone deficiency.

Material and methods: We performed a case-control study and recruited 764 participants who received health examination at Health Management Center of Tri-Service General Hospital from March 2017to August 2018. Demographic data were obtained by structured questionnaire, and bone mass density was measured by Dual-Energy X-ray Absorptiometry (DEXA). DNA was extracted from a peripheral blood sample, and the genotypes were determined using polymerase chain reaction and iPLEX Gold SNP genotyping methods.Subjects with T-score < -1 was classified as osteopenia case group, t-score ≧-1 was classified as healthy control group. All data analyses were done by using R software version 3.4.2.

Results: In female, after adjusted age and BMI, the frequencies of rs2707466 (WNT16) CT genotype were decreased risk of T-score< -1 than CC genotype (OR=0.60, 95% CI=0.38 - 0.93). T allele were decreased risk of T-score< -1 than C allele (OR=0.60, 95% CI=0.42 - 0.87). CT+TT genotype were decreased risk of T-score< -1 than CC genotype (OR=0.57, 95% CI=0.37 - 0.87).

Conclusion: We found that rs2707466 (WNT16) in female were associated with T-score< -1.

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Glucocorticoid receptor promotes osteoblast and adipocyte differentiation by recruiting and being recruited to lineage selective enhancers

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The glucocorticoid receptor (GR) is a ligand activated hormone nuclear receptor targeted in the treatment of immune and auto-inflammatory disorders. While frequently prescribed, glucocorticoid therapy is associated with several adverse side effects including osteoporosis. In glucocorticoid-induced osteoporosis numbers of bone-forming osteoblast cells are reduced and marrow adipose volume is increased, suggesting that altered differentiation from the common precursor (MSCs) underlies glucocorticoid-induced osteoporosis.

Dexamethasone (dex) is a potent agonist of GR and a common component of both the osteogenic and adipogenic differentiation cocktail when differentiating MSCs *in vitro*. We studied the role of GR in lineage speciation of human telomerase-immortalized mesenchymal stem cells from bone marrow (hMSC-TERT cells) by loss-of-function experiments and withdrawal of dex. By employing global profiling of gene expression, enhancer activity and GR binding early after osteogenic and adipogenic stimulation we identified cell-type selective and common GR dependent programs (Figure A). Importantly, only activation of enhancers was associated with GR binding (Figure B) while lineage context and GR binding intensity were equally important for GR dependent enhancer activity (Figure C). Machine learning algorithms identified known GR interactors such as C/EBP-beta but also novel transcription factors that affect lineage speciation of MSC. Knockdown of either *CEBPB* or *NR3C1* had similar effects on early transcriptional changes due to interaction of C/EBP-beta and GR on the chromatin level with GR recruiting C/EBP-beta to osteoblast-specific and common activated enhancers and vice versa for adipocyte-specific enhancer activation.

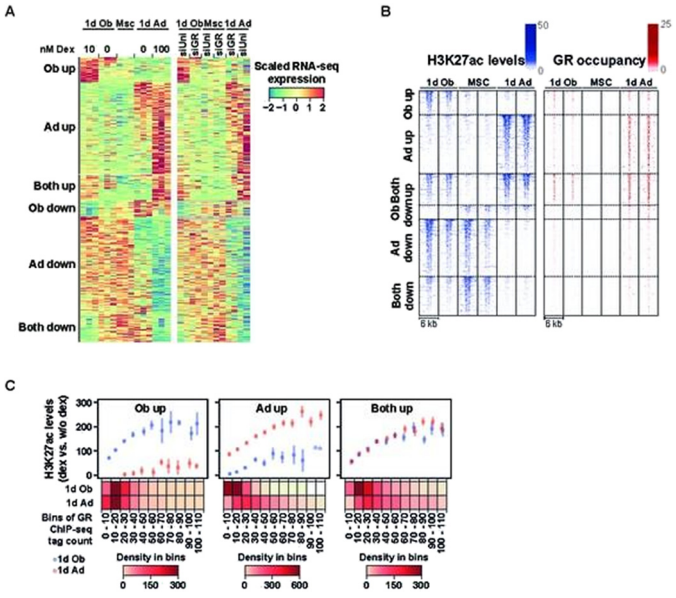

Fig.

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RUNX2 T-1025C variant is associated with bone-related biochemical parameters and fracture risk in Maltese postmenopausal women

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Background & objectives: Runt-related transcription factor 2 (RUNX2) is a major transcription factor involved in osteoblast and chondrocyte differentiation, skeletogenesis and fracture repair. Transactivation of *RUNX2* is under tight regulatory control particularly via promoter 2 (P2). The study aimed to assess the effect of the P2 *RUNX2* T-1025C variant in relation to bone mineral density (BMD) at different anatomical sites, fracture risk and levels of biochemical parameters in the Maltese population.

Methods: Genotyping was performed in 1,045 Maltese postmenopausal women from the Malta Osteoporotic Fracture Study using the TaqMan® fluoregenic 5' nuclease allelic discrimination assay. Genotype-phenotype associations were analysed using the Mann-Whitney statistic whereas odds ratios with 95% confidence intervals were computed using logistic regression analysis adjusted for confounders.

Results: Genotyping was successful in 1,043 samples, with the reference T and alternative C alleles observed at a frequency of 0.92 and 0.08 respectively. Women aged >60 years with the TC genotype had higher total serum calcium (p=0.029) and lower total serum alkaline phosphatase (ALP) levels (p=0.046) relative to women with the TT genotype. Additionally, carriers of the C allele showed higher femoral neck BMD than homozygous carriers of the T allele. Nonetheless, the latter did not reach statistical significance (p>0.05). Homozygosity for the C allele was associated with an almost 5-fold increased fracture risk compared to homozygosity for the T allele, which was not attenuated after adjusting for BMD (adjusted OR: 4.9 [1.2-19.6], p=0.025). This is the first study to report an association with fractures. No association was seen with lumbar spine or total hip BMD.

Conclusion: Results indicate that the *RUNX2* T-1025C is a possible genetic determinant of fracture risk in the Maltese population, as well as calcium and ALP control. This functional variant alters the binding of several transcriptional activators and repressors, possibly affecting bone composition and strength.

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Phosphate, BMI and body composition in the Rotterdam Study: Mendelian randomization analysis suggests a causal effect of BMI on serum phosphate level

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Objectives: Observational studies have reported associations between serum phosphate (P) and body mass index (BMI) in specific clinical settings (such as morbid obesity and hypertension) but the nature of this relation in the general population is unclear. This study aimed to investigate whether P and BMI and body composition are related and to explore evidence of causality through bidirectional one-sample Mendelian Randomization (MR).

Methods: 9633 subjects from three cohorts from the population-based Rotterdam Study were included for phenotypic analyses and 8378 subjects were included for MR analyses. Age-adjusted results were meta-analyzed. Outcomes were BMI, waist-to-hip ratio, fat mass, lean mass and fat%, estimated by DXA. Subgroup analysis adjusted for leptin levels was performed. For MR, allele scores with 6 single nucleotide polymorphisms (SNPs) for P and 905 SNPs for BMI were constructed.

Results: An inverse association between P (mg/dL) and BMI was found in both genders (β (95% CI): men: -0.40 (-0.72 to -0.07), p=0.02; women: -1.94 (-2.21 to -1.66), p< 0.001), with a significant sex-interaction (p< 0.05). Results were not explained by potential confounders. Adjustment for leptin attenuated but did not abolish this relation in women. There was a negative relation with fat percentage and fat mass in both sexes, but the latter was abolished in men after adjusting for estradiol and testosterone. Age and sex adjusted MR analyses suggests a causal effect of genetically determined BMI on phosphate (β (95% CI):-0.01 (-0.02 to 0.00), p=0.05), but not vice versa.

Conclusion: In a population-based setting, P was negatively associated with BMI and fat percentage with a stronger effect in women compared to men. Leptin partially explained this relation in women. MR analysis suggests a causal effect of BMI on P and not vice versa. Our results suggest an underlying sex dimorphism in P homeostasis that should be further explored.

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Short stature and microcephaly in two siblings due to a novel *de novo* IGF1R variant

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Introduction: Heterozygous mutations in the type 1 insulin like growth factor receptor gene (*IGF1R*) cause pre- and postnatal growth failure, microcephaly and IGF-1 resistance.

Case presentation: The, proband is a 3.8 year old girl with SS (height -2.3 SD) (3 SD under MPH), microcephaly (HC -2.5 SD), delayed BA -1.5 years and a history of SGA (BW -2.2 SD, BL -3.2 SD, HC -2.3 SD) without catch-up growth. Her karyotype was normal 46XX. Her brother was also born SGA (GA 40, BW -2.6 SD, BL -2.9 SD, HC -2.2 SD) without catch-up growth. At the age of 1.5 years old his height was -1.2 SD (2 SD under MPH) with relative microcephaly (HC -2.1 SD). Father and mother were unrelated, healthy with normal heights of -0 SD and +2.3 SD (MPH +1.2 SD), respectively. Both siblings presented biochemical signs of IGF-1 resistance, which, together with their clinical characteristics led to suspicion of an *IGF1R* mutation.

Results: A *de novo*, heterozygous, non-synonymous, missense *IGF1R* variant c.3595>G (p.Gly1199Arg) was first detected by Sanger sequencing in the proband and then the same variant was detected in the brother, but in none of the parents. Maternity and paternity was confirmed by SNP arrays.

This variant was not present in Genome Aggregation Database (GnomAD n>120.000 exomes and >15.000 genomes). Finally the variant is predicted to be damaging by all *in silico* tools used.

Conclusions: We detected a novel, heterozygous, *de novo* variant in *IGF1R* associated with short stature, SGA without catch-up growth, microcephaly, and biochemical signs of IGF-1 resistance in two siblings. Gonadal mosaicism is the most likely explanation for the recurrence of this variant in the younger brother.

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Bone transcriptome sequencing reveals local tissue determinants of bone mineral density

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