

Concurrent Oral Presentations

Concurrent Oral Presentations 1: Clinical / Public Health: Diseases other than Osteoporosis

COP01

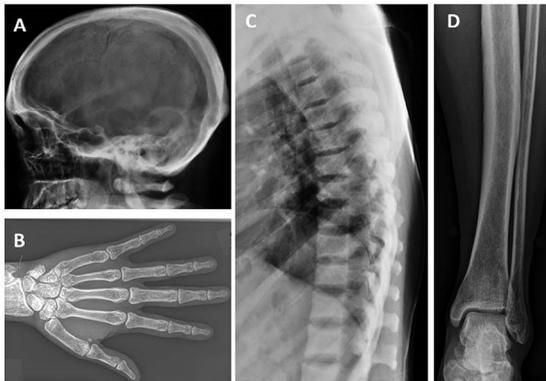
Identification of SLC4A2 as a new causal gene for osteopetrosis in human

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Background/Introduction: Osteopetrosis is a group of rare genetic disorders characterized by increased bone density.



Osteopetrosis is genetically heterogeneous and nine causal genes have been reported. Nevertheless, no mutation is found among these reported genes on some patients, suggesting unknown causal genes exist. Anion exchanger 2 (AE2, encoded by *SLC4A2*) exports carbonate ions and imports chloride ions to maintain the intracellular pH. AE2 is highly expressed in osteoclasts. *SLC4A2*-deficient mice and cattle display osteopetrosis associated with dysfunctional osteoclasts; however, no mutations in human *SLC4A2* have been reported to date in the context of osteopetrosis.

Purpose: To identify *SLC4A2*-associated osteopetrosis in human.

Methods: Whole exome sequencing and Sanger sequencing were used to detect the variant in the patient. Pathogenicity of the variants was assessed by a gene knockout-rescue system using mouse macrophage cell line, RAW 264.7.

Results: By whole exome sequencing, we identified novel compound heterozygous variants in *SLC4A2* (NM_003040.4: c.556G>A [p.A186T] and c.1658T>C [p.V553A]) in an osteopetrosis patient. Osteoclast differentiation induced by RANKL showed that osteoclastogenesis was impaired in *Slc4a2*-knockout RAW 264.7 cells. The impairment was rescued by wild-type *SLC4A2*, but not by mutant *SLC4A2*.

Conclusion(s): We discovered the first case of *SLC4A2*-associated osteopetrosis patient, which highlights the importance of AE2 in osteoclastogenesis in human.

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COP02

Femoral anteversion (FNA) in individuals with X-linked hypophosphatemia (XLH)

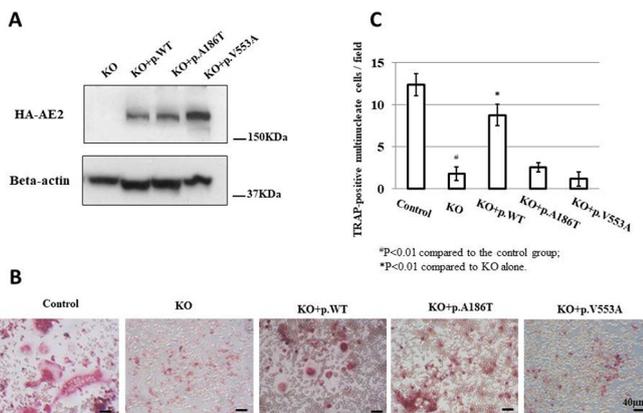
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Background/Introduction: XLH is a rare genetic condition which affects phosphate metabolism, resulting in osteomalacia. Individuals with XLH are also at risk of lower limb deformities and early onset of hip osteoarthritis. These two factors may be linked, as abnormal FNA (femoral torsion) is a risk factor for hip osteoarthritis. The contributions of regional femoral torsion e.g. intertrochanteric torsion (ITT), shaft torsion (ST) and condylar torsion(CT) to FNA

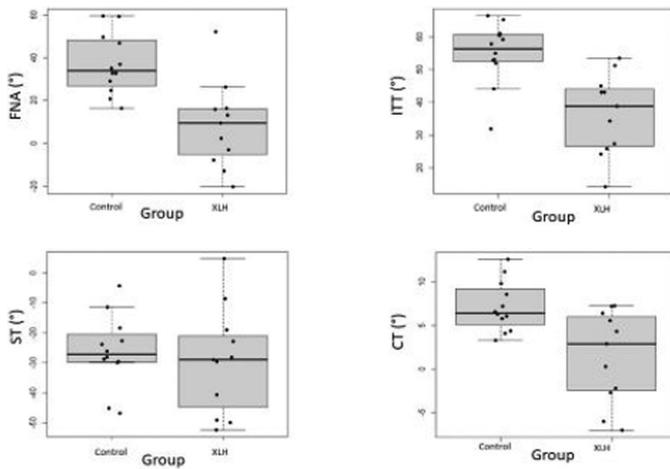


differ between clinical groups and are important when planning femoral osteotomies to correct FNA.

Purpose: This study aimed to compare FNA and regional femoral torsion of the femur between adults with XLH and controls.

Methods: 13 individuals with XLH (5 male, age 49 ± 9 y) and 12 age, sex and weight-matched control participants (7 male, age 49 ± 8 y) were recruited following ethical approval and informed consent. Magnetic resonance imaging (MRI) scans of the femur were obtained, from which FNA, ITT, ST and CT were measured. Data were normally distributed, therefore group differences were assessed using t-tests.

Results: FNA was 29° lower in individuals with XLH than controls ($p < 0.005$). This resulted mainly from lower ITT ($p < 0.001$) and in part CT ($p < 0.05$) whereas ST was similar in the two groups (Fig. 1).



Conclusion(s): We observed differences in FNA and region-specific femoral torsion in individuals with XLH compared to controls. These differences may contribute to clinical problems such as hip osteoarthritis common in XLH. Information on region-specific differences may be useful in planning corrective surgeries. Future work should examine how pharmacological and other interventions in this group affect FNA.

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COP03

Pregnancy-associated fracture risk in women with osteogenesis imperfecta, a nationwide register-based SCCS

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Background/Introduction: Osteogenesis imperfecta (OI) is a hereditary disorder of the connective tissue with a heterogeneous clinical presentation. A hallmark of OI is frequent fractures occurring with little or no trauma. Pregnancy and lactation are periods of increased fetal demand for calcium known to often result in an asymptomatic and fully reversible decrease in maternal Bone Mineral Density. Fracture risk associated with this bone loss among women with OI has not yet been evaluated.

Purpose: To evaluate the fracture rates and risk in the short and longer term associated with pregnancy.

Methods: Self-controlled case series 12- and 19- months prior to conception compared to a period of 12- and 19 months, respectively, postpartum among women with OI. The study is based on register data from the Danish National Patient Register. All women registered in the Danish National Patient Register with a WHO International Classification of Diseases 8th or 10th edition code for OI who gave birth one or more times in the period between 01.01.1995-31.12.2018 and who had a 12 or 19 months pre- and postpartum observation period were included.

Results: We found an incidence rate (IR) 12 months prior to conception of 59.9 [95%CI 22.8-97] per 1000 person years and an IR 12 months postpartum of 29.9 [95%CI 3.7-56.18]. Comparing pre- and post-pregnancy periods we found an incidence rate ratio (IRR) of 0.5 [95%CI 0.17-1.46]. Adjusting for parity and age at delivery did not significantly change in IRR. For the 19 months window the IR per 1000 person years pre-pregnancy was 58.28 [95%CI 36.16-87.77] and the IR postpartum 51.12 [95%CI 23.33-78.91], leading to an IRR of 0.87 [95%CI 0.40-1.82].

Conclusion(s): We found no evidence that the anticipated physiological decline in BMD during pregnancy and lactation leads to a higher risk of fractures in women with OI.

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COP04

Breast calcification chemistry as a biomarker for progression of in-situ breast cancer

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Background/Introduction: Breast microcalcifications are deposits of calcium oxalate, found mostly in benign tissue, or calcium phosphate in the form of hydroxyapatite, found in benign and malignant tissue. Differences in the crystallographic properties and chemical make-up of hydroxyapatite breast microcalcifications have previously been noted in differing breast pathologies.

Purpose: Ductal carcinoma in-situ (DCIS) is a precancerous breast lesion, which has the potential to form invasive breast cancer. Currently there are no definitive markers to determine DCIS invasiveness, therefore this work aims to elucidate differences in the calcification chemistry between invasive and non-invasive cases of DCIS, ultimately developing a novel biomarker for DCIS progression.

Methods: 75 formalin fixed paraffin embedded archive breast tissue samples were used subject to NHS REC approval (ref. 18/LO/0945). X-ray diffraction was carried out at 12keV on beamline i18 at Diamond Light Source, UK to determine crystallographic properties