Conclusions: TSC-related renal involvement occurs since childhood, reinforcing the important role of the nephrologist in the care of these patients over lifetime. Only a low percentage of the study population were receiving the standard therapy, *i.e.* mTOR-i and renal-sparing surgical procedure, which might have contributed to the high rate of severe renal adverse events, as hemorrhage, loss of renal function and premature death. It is of paramount importance to enhance disease awareness for TSC to improve the medical care offered to these patients.

I have no potential conflict of interest to disclose.

WCN24-659

ARSENIC TRIOXIDE ATTENUATES MMP9/IL-17A EXPRESSION IN LUPUS NEPHRITIS – RESULTS FROM BIOINFORMATICS AND IN VITRO STUDIES

Desmond Yap[*1], Danting Zhang[2], Ka Ho Jason Sher[2], Litong Zhu[2], Ruiyan Xie[2]

[1]Hong Kong, Medicine, China, [2]Medicine, The University of Hong Kong, Hong Kong,

Introduction: Previous studies suggested that treatment with low-dose arsenic trioxide (ATO) might reduce the risk of flares in patients with active systemic lupus erythematosus (SLE), but the underlying pharmacological mechanisms have not been investigated.

Methods: The potential differentially expressed genes (DEGs) targets were identified using machine learning and network pharmacology analysis. The expression of characteristic genes and its association with immune cells was further examined and validated.

Results: Of twelve intersection DEGs, five immunoregulatory genes in SLE were identified by three machine learning models (RF, SVM and XGB), in which MMP9 demonstrated the highest ROC AUC (092) in predicting disease development (ROC AUC 0.942). KEGG analysis indicated strong associations with IL-17 signalling pathway (p=1.67E-18). MMP9 also showed positive correlations with macrophages and neutrophils in ssGSEA analysis (correlation coefficient 0.88 and 0.66 respectively). Our in vitro validation concurred with the bioinformatics results, which showed that ATO treatment in PBMC isolated from LN patients (n=5) could downregulate MMP9 and IL17A expression.

Conclusions: ATO could attenuate MMP/IL-17A pathways in PBMCs in LN patients and hence may serve as a novel therapeutic option.

I have no potential conflict of interest to disclose.

WCN24-700

GENOME WIDE ASSOCIATION STUDY IDENTIFIES NOVEL SNPS ASSOCIATED WITH ALBUMINURIA IN JAPANESE GENERAL POPULATION

Hiroshi Okuda[*1]

[1]Sendai, Tohoku Medical Megabank Organization, Japan,

Introduction: Urine albumin is one of the important indicators of renal failure. Generally, in high blood pressure, diabetes, urinary albumin excretion (UAE) tends to increase with poor control and renal dysfunction, but the difference between individuals is very large. This suggests that there are some genetic factors for UAE. We performed a genome-wide association study (GWAS) on urinary protein excretion using data from 10,000 Japanese people and reported 18 SNPs related to urinary albumin excretion. (Clin Exp Nephrol. 2020 Aug; 24 (8)). This time, we increased the number of samples and analyzed using the data of 67,000 Japanese people.

Methods: GWAS, for UAE, was performed using approximately 680,000 single nucleotide polymorphism

(SNP) data obtained from 67,000 TMM health survey participants collected from 2013 to 2020. The extreme outlier of UAE, outside ±4SD, was excluded for statistical reason. As covariates, age, gender, BMI, blood pressure, renal function (calculated by blood CysC), and HbA1c were used. Imputation was performed using a haplotype panel consisting of whole-genome sequence data of 2000 people, and further analysis was performed on the data, and allele frequency and INFO value after imputation were adjusted.

Results: The identified SNPs were found in regions associated with potassium metabolism.The analysis results were examined with $p < 5 \times 10^{-8}$ as the significance level, and novel SNPs related in urine protein excretion were identified on chromosome 6.

The SNP might be related in potassium metabolism.

Conclusions: The identified SNPs are considered to have some effect on urinary albumin excretion. It is necessary to consider the mechanism and further verify it.

I have no potential conflict of interest to disclose.

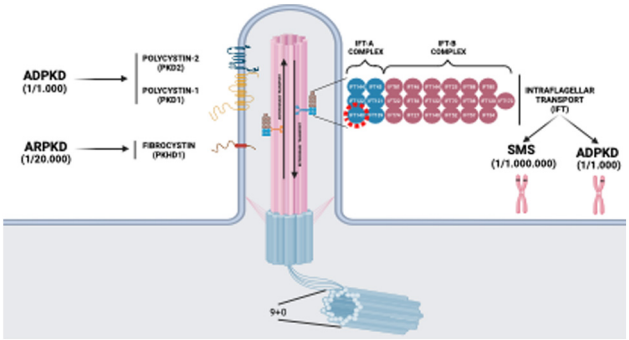
WCN24-850

A COMPLEX PEDIATRIC CASE WITH HOMOZYGOUS IFT140 VARIANTS INVOLVING RENAL CYSTS: A COMPREHENSIVE ANALYSIS TO GUIDE DIAGNOSIS AND PATIENT CARE

Paola Krall[*1], Esperanza Bayyad[2], Bárbara Poblete[3], Victor Faúndes[4], María Isabel González[5], Karen Orostica[6], Jorge Maturana[7], Ignacio Castro[7], Jerka Krstulovic[8], Jaime Tobar[8], Gastón Mendez[8], Jose Luis Guerrero[9]

[1]Valdivia, Instituto de Medicina, Chile; [2]Instituto de Medicina, Universidad Austral de Chile, Valdivia; [3]Escuela de Tecnología Médica, Universidad Austral de Chile, Valdivia; [4]Instituto de Nutrición y Tecnología de los Alimentos, Universidad de Chile, Santiago de Chile; [5]Servicio de Genética, Hospital Luis Calvo Mackenna, Santiago de Chile; [6]Instituto de Investigación Interdisciplinaria, Universidad de Talca, Talca; [7]Instituto de Informática, Universidad Austral de Chile, Valdivia; [8]Servicio de Pediatría, Hospital de Arica, Arica, [9]Servicio de Nefrología, Hospital Luis Calvo Mackenna, Santiago de Chile,

Introduction:

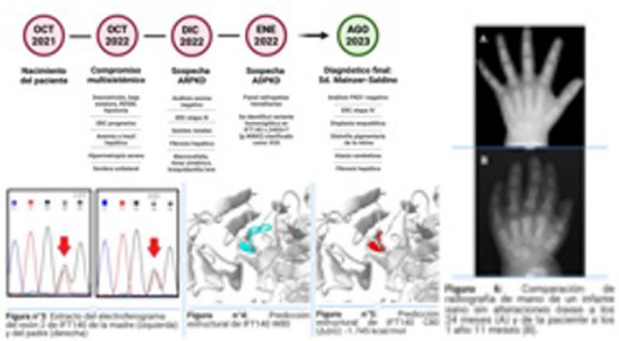


Polycystic kidney disease (PKD) is part of a genetically heterogeneous group of conditions called ciliopathies recognized as the most frequent inherited disorder leading to chronic kidney disease (CKD). The PKD1 and PKD2 genes are the main contributors to the autosomal dominant PKD (ADPKD) form typically observed in adults. In contrast, the PKHD1 gene is responsible for the autosomal recessive PKD form (ARPKD) that is generally diagnosed in utero or during the first months of life. Recently, mono-allelic, loss-of-function variants in IFT140, a core component required for retrograde transport in cilia, have been described as the third most common gene associated with the ADPKD spectrum with a mild phenotype. Notably, bi-allelic IFT140 variants are associated with another ciliopathy named Mainzer–Saldino Syndrome (MSS) characterized by skeletal abnormalities, ocular anomalies, kidney disease and additional findings such as hepatic fibrosis, intellectual disability, and short stature.

Methods: The clinical data were collected from both the patient's original hospital of admission and the referring hospital. The medical history, physical examination findings, laboratory test results, and radiological reports were thoroughly reviewed to compile a comprehensive clinical profile. Given the severe progression of CKD a targeted panel involving 400 genes associated with hereditary nephropathies was performed. ACMG guidelines were employed for preliminar variant classification, but Varsome, Internar, Missende 3d and mCSM were considered for variant reanalysis. Whole exome sequencing was performed to evaluate consanguinity.

Results: A 21-month-old female patient born from a Native Amerindian couple, exhibited chronic kidney disease stage IV, with malnutrition, short stature, severe hypermetropia, and developmental delay. Echographies exhibited renal cysts and hepatic fibrosis suggestive of ARPKD. Targeted gene panel revealed a homozygous novel variant of uncertain significance (VUS) IFT140 c.240G>T (p.W80C), confirmed to be

inherited from her parents (ages 35 and 43), who did not show echographic anomalies. PKD1 genetic analysis was negative. After re-analysis with diverse bioinformatic tools IFT140 W80C was reclassified as "likely pathogenic" with moderate and supporting evidence (PM1, PM2, PM3, and PP3) in an autosomal recessive inherited phenotype. The diagnosis of MSS was supported by the evidence of cone-shaped phalangeal epiphyses as well as short rib arches on an X-ray by the age of 2 years. During her last visit to the ophthalmologist, atypical retinitis was observed. The genetic data after a exome sequencing revealed a high rate of consanguinity in the patient.



Conclusions: This report highlights the role of genetic testing to elucidate diagnosis in severe phenotypes compromising kidney function that can be confused with PKD. Latin American populations are significantly underrepresented in genetic databases. As a result, variants from this population are often classified as VUS, but deserve re-analysis in benefit of the patient. MSS is an ultra-rare disease, with a frequency of less than 1 in 1,000,000. To the best of our knowledge, this is the first case of MSS diagnosed in Latin American. The content presented in this abstract was submitted for the Chilean Nephrological Meeting. Grant FICR 22-13.

I have no potential conflict of interest to disclose.

WCN24-859

JEJUNAL DIVERTICULOSIS AND ZEBRA BODIES IN FABRY DISEASE: A CASE REPORT

Facundo Graña[*1], Lucia Facal[2], Paula Parnizari[2], Alvaro Olivera[2], Jose Boggia[2], Gabriela Ottati[2], Maria Haydee Auchanya[2], Oscar Noboa[2]

[1]Montevideo, Montevideo, Uruguay, [2]Montevideo, Hospital de Clínicas Dr. Manuel Quintela, Montevideo,

Introduction: Fabry disease (FD) is an X-linked hereditary disorder caused by a deficiency of alphagalactosidase A, leading to intracellular deposition of glycosphingolipids in various tissues and organs.
Methods: Report the case of a patient with FD that presents with an atypical manifestation of the disease.
Results: A 58-year old male diagnosed with classical phenotype FD in 2016 was hospitalized because of abdominal pain. He had evidence of neurological, ophthalmological, and cutaneous involvement and markers of advanced disease: hypertrophic-ischemic cardiomyopathy, and stage IIIB-A3 chronic kidney disease. Following the FD diagnosis, enzyme replacement therapy (ERT) with Agalsidase alfa was initiated.The patient was admitted to the emergency department with diffuse abdominal pain accompanied by non-dysenteric diarrhea. Laboratory findings revealed leukopenia with lymphopenia, ESR 57 mm/h, serum creatinine 2.1 mg/dL, urea 66 mg/dL, K 4.2 mEq/L. Abdominal CT scan showed dilatation of the proximal left colon up to the rectosigmoid junction. Exploratory laparoscopy revealed complicated diverticulitis with perforation of a large diverticulum in the jejunum [Figure 1]. Resection and primary anastomosis were

performed. Following the surgery the patient developed worsening renal failure complicated with hypervolemia unresponsive to diuretic treatment, requiring initiation of hemodialysis (HD).Histopathological examination with electron microscopy (EM) of the resected intestinal segment showed glycosphingolipid deposits, characterized as "zebra bodies" which are typical of FD [Figure 2A]. These same lesions had been previously demonstrated in the renal biopsy performed in 2016 [Figures 2B and 2C].
Conclusions: Although gastrointestinal involvement is frequent in FD, it is often overlooked due to the nonspecific nature of symptoms, resulting in a delayed diagnosis. Abdominal pain, nausea, vomiting, diarrhea or constipation occur in approximately 20-70% of patients. These symptoms are caused by the deposition of glycosphingolipids in the autonomic intestinal ganglia and mesenteric blood vessels, leading to intestinal dysmotility, autonomic dysfunction, vasculopathy and myopathy.Small bowel diverticula are typically asymptomatic but can rarely lead to severe and life threatening complications. The location of diverticula has been observed in duodenum, jejunum and colon. The formation of diverticula results from prolonged intestinal dysmotility, causing increased intraluminal pressure and mucosal protrusion.We present a case of FD diagnosed at an advanced stage, that after 7 years of ERT developed a severe gastrointestinal complication, which precipitated the beginning of HD. We emphasize the presence of considerably large diverticula, promoted by the nature of FD. Supporting this hypothesis, "zebra bodies" were histologically documented in the diverticular lesions. This clinical case demonstrates the importance of a low threshold for the diagnosis of gastrointestinal complications in patients with FD and particularly in this patient the performance of laparoscopy was crucial for the timely diagnosis. This case report stands out for its rarity in revealing zebra bodies in jejunal diverticulum on EM.

I have no potential conflict of interest to disclose.

WCN24-864

ALPORT SYNDROME: GENETIC VARIANTS, PHENOTYPES OF KIDNEY DISEASE AND ASSOCIATION WITH END STAGE KIDNEY DISEASE IN A URUGUAYAN COHORT

Federico Yandian[*1], Lucía Spangenberg[2], Víctor Raggio[3], Nicolás DellOca[3], Lucía Urquiola[2], Santiago Fontenla[3], Fernanda Domínguez[3], Camila Simoes[3], Jessica Segarra[4], Lucía Facal[4], Paula Parnizari[4], Jimena Cabrera[5], José Tort[3], Óscar Noboa[4], Hugo Naya[2], José Boggia[4]

[1]Montevideo, Nephrology, Uruguay; [2]Bioinformatics Unit, Institut Pasteur, Montevideo; [3]Department of Genetics, Universidad de la República, Facultad de Medicina-UDeLaR, Montevideo; [4]Centro de Nefrología, Hospital de Clínicas "Dr. Manuel Quintela", Montevideo, [5]Sociedad Uruguaya de Nefrología Centro de Nefrología, Hospital de Clinicas "Dr. Manuel Quintela", Programa de prevención y tratamiento de las glomerulopatías (PPTG) de Uruguay, Montevideo,

Introduction: Alport syndrome (AS) is a genetic disorder responsible for up to 2.0% of kidney disease requiring renal replacement therapy. The classical phenotypic features and family history may not be present in many patients reaching ESKD (end stage kidney disease). We aim to explore kidney phenotypes, gene variants, and possible predictors of kidney failure in the genetically heterogeneous population of Uruguay.
Methods: Cross-sectional, observational study. Patients with CKD (chronic kidney disease) and a diagnosis of AS confirmed at molecular level referred to our clinic between October 2021 and April 2023 were included. Demographic, clinical, biochemical parameters and histologic characteristics of prognostic interest were collected from medical records and clinical encounters at the time of DNA extraction and in follow-up visits. The primary outcome was kidney failure.
Results: Data from 140 patients (58 families) was retrieved, 43 cases were AS. Genetic analysis confirmed a diagnosis of AS at the molecular level in 39 cases and 4 cases had potentially pathogenic heterozygous variants in COL4A3 gene. Mean (±SD) age was 38.0±14.5 years and 55.8% were women. The most frequently affected gene was COL4A5 (47%) followed by COL4A4 (33%) and COL4A3 (12%). Nearly half of patients presented hearing loss (49%) and visual alterations (51%), and 34.9% of the patients had eGFR $<$ 60 ml/min. Only 12 patients (27.9%) underwent a kidney biopsy, being FSGS (focal segmental glomerulosclerosis) the most common histopathological finding (18.6%). Of all patients, 12 (27.9%) reach ESKD, at a median age of 38 [IQR, 5] years. All patients who progressed to kidney failure had proteinuria (p=0.044) and a history of gross hematuria occurred more frequently (42%) in patients with ESKD (p=0.110) in comparison