identical expression profile to the endogenous gene and the level of expression depends on the number of copies.

Results: While Pkd1TAG mice develop PKD in a severity proportional to the level of expression of the transgene, the Pkd1CC-CC lines are spared from PKD. These results demonstrate the importance of the coiled-coil motif in the development of the disease. To analyze Pkd1CC-transgene independently from the endogenous gene, the Pkd1CC mice where crossed on a Pkd1 genetic background that develop PKD and dies by birth. Interestingly, the resulting Pkd1C/C; Pkd1CC-mice survive past birth: these Pkd1C/C; Pkd1CC mice with one copy of the transgene show renal cysts and die at ~2 weeks, while the high-copy Pkd1C/C; Pkd1CC mice have no phenotype like the Pkd1CC mice on a Pkd1CC background. Because Pkd1C/C mice have no phenotype, these genetic complementation results suggest that Pce1CC is an hypomorphic allele. Biochemical characterization show that Pce1CC undergoes autoproteolytic cleavage at G protein-coupled receptor proteolytic site (GPS)/GAIN domain with similar cleavage efficiency as the native Pc-1. Intraacellular transport analysis of Pce1CC revealed a delay in maturation in the ER/Golgi network, consistent with a genetic hypomorph. Pce1CC secretion into exosomes both in vivo and in primary MEFS is also reduced. While Pc-1 and Pc-2 appear to interact in vitro through their expression pattern, the Pc-1 and Pc-2 appear to interact in vitro through their expression pattern.

Conclusions: Altogether, our results show that the coiled-coil motif in vivo is implicated in Pc-1 maturation independently of Pc-2 and highlight the existence of a critical partner in intracellular transport.

No conflict of interest

POS-433

MODELING PKD1 TARGETING STRATEGIES IN A PKD1 LOSS-OF-FUNCTION MOUSE MODEL

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Introduction: ADPKD is one of the most common inherited kidney diseases and cause of end stage renal disease. ADPKD is characterized by initiation and progression of multiple renal cysts. Most cases involve mutations in PKD1 gene, encoding Polycystin1(PC1). PKD1 gene dosage is supported as a pathogenic mechanism by studies in mouse models. Consistently, Pkd1 null mouse model develops severe renal cysts from E15.5 until neonatal death. With the aim of initiating studies for stable long-term effective correction of PKD, we propose a gene augmentation strategy by initiation and progression of multiple renal cysts. Most cases involve mutations in PKD1 gene, encoding Polycystin1(PC1). PKD1 gene dosage is supported as a pathogenic mechanism by studies in mouse models. Consistently, Pkd1 null mouse model develops severe renal cysts from E15.5 until neonatal death. With the aim of initiating studies for stable long-term effective correction of PKD, we propose a gene augmentation strategy.

Methods: Considering that microscopic cysts are likely initiated in utero in ADPKD kidneys, the severely cystic Pkd1 null mouse model was targeted at early renal stage with wild type Pkd1. Re-expression of Pce1 in Pkd1 null was targeted by three transgenic (tg) matings: a) a systemic Pkd1TAG (75kb;16 copy tg) b) 2 renal-specific SBPpkd1TAG (67kb; with 1Lo & 10Hi copy tg) c) a novel Tg mouse line targeting Pkd1 cDNA with SB renal-specific elements, SBP (15.8kb;16 copy tg). These bigenic mouse models were assessed for expression, morphologic and cellular longitudinal analysis.

Results: Pkd1+/— mice crossed into Pkd1TAG transgenic line escaped perinatal lethality and exhibit no renal or pancreatic phenotypes for several months. Thus, the Pkd1TAG transgene produced a functional protein with proper transgene regulation with 24kb upstream and 1.5kb downstream sequences. Pkd1TAG;Pkd1—/— mice at >8mo developed renal cysts but milder than the parental transgenic line consistent with their Pkd1 overexpression and a gene-dosage mechanism. Of significance, SBPpkd1TAGLo;Pkd1—/— kidneys express Pkd1 gene in 0.64-fold of the endogenous Pkd1 and Pce1 was equivalent to endogenous Pce1. These mice display delayed renal cysts, detectable at P3/P5 compatible with a significant increase of kidney to body weight (KBW) and with cystic surface area, and a life expectancy of P10-P15. The SBPpkd1TAGHl;Pkd1—/— mice overexpress Pkd1 and Pce1 by 7-fold relative to the endogenous gene. This overexpression led to retarded renal cysts that initiated from P15 (after developmental switch), a significantly elevated KBW and cystic surface area at P20 and survival up to ~3 months. The targeted genomic Pkd1 by the SBPpkd1TAGtg of the low or high expressers increased Pkd1 null life expectancy by 4- or 25-fold respectively. The third transgenic mating with the SBP;Pkd1+/— kidneys expressing Pkd1 at 0.87-fold the endogenous gene levels and equivalent to endogenous native Pce1, indicates that 16 copies of the cDNA reach similar levels as the single genomic SBPpkd1TAGLo;Pkd1—/—tg. Accordingly, SBP;Pkd1+/— kidneys displayed mild renal cyst formation at P0 and similarly extended lifespan to ~P15 or 4-fold over the Pkd1 null mice.

Conclusions: This study provides three crucial insights for Pkd1 gene targeting by identification of: 1 the largest referral Pkd1 gene segment of 24kb upstream sequences and 1.5kb downstream for total rescue of the phenotype by gene targeting; 2. the minimum SB regulatory of 0.9kb for substitution of the Pkd1 upstream region with appropriate epitelial cell targeting; 3. the key regulatory elements within the Pkd1 gene body.

No conflict of interest

POS-434

FISH-EYE DISEASE: A RARE CAUSE OF STEROID RESISTANT NEPHROTIC SYNDROME

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Introduction: Fish-eye disease is an extremely rare disease of cholesterol metabolism in which partial deficiency of lecithin–cholesterol acyl-transferase (LCAT) leads to very high serum free cholesterol levels. The characteristic clinical feature is corneal opacities, beginning in adolescence or early adulthood. Haemolytic anaemia and renal involvement are recognised features of complete LCAT deficiency. We report the first case of genetically confirmed Fish-Eye Disease in Sri Lanka.

Methods: A 5-year old boy born to second degree consanguineous parents presented with persistent proteinuria. He initially presented at the age of two years with nephrotic range proteinuria and was diagnosed to have steroid resistant nephrotic syndrome. He was treated with Cyclosporine and six cycles of Rituximab pulses although control of proteinuria was not optimal. Renal histological examination revealed focal segmental glomerulosclerosis (FSGS). He had very high total cholesterol (491 mg/dl) and LDL (331 mg/dl) levels and showed good response to statins, which reduced these values to 217mg/dl and 133mg/dl, respectively. His eye examination was normal. His serum creatinine was 64µmol/l (estimated Glomerular Filtration Rate (eGFR) - 78mL/min/1.73m²).

Given the course of progression and evolution of his nephrotic syndrome with very poor control despite being on multiple and strong immunosuppressants, genetic studies were performed. Genetic studies revealed a mutation in the lecithin: cholesterol acyl-transferase gene (LCAT, NM_000229.1, homozygous variant at position c.800A>G (p.Gln267Arg), not annotated in the gnomAD database of genetic variation). Based on supportive clinical features and confirmatory genetic studies, a diagnosis of Fish-Eye disease was made.

Results: Medical management of Fish-eye disease include supportive treatment, management of chronic kidney disease and renal transplantation in those with poorly controlled proteinuria and renal dysfunction, and corneal transplantation for those with significant corneal opacifications and reduced vision. However, in patients who had renal transplantation the disease can recur in the transplanted kidneys. Given that first-degree family members are at risk of and may offer genetic counselling. Enzyme (LCAT) replacement is an emerging promising therapy which will likely reduce the need for renal transplantation. Prenatal diagnosis is also possible in those with a known mutation within family.

Conclusions: Genetic mutations are commonly associated with steroid resistant nephrotic syndrome and are very valuable in the clinical
management. This case is unique given the very young age of the reported child and atypical presentation with steroid resistant nephrotic syndrome. Most children with Fish-eye disease do not manifest ophthalmological manifestations although vision gradually deteriorates as they grow into adolescence and adulthood. Therefore, it is paramount that children with normal vision are followed up regularly to screen for corneal opacifications.

No conflict of interest

POS-435
CHANGE IN EGFR BY CKD STAGE IN PRIMARY HYPEROXALURIA TYPE 1
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Introduction: The genetic disorder primary hyperoxaluria type 1 (PH1) is marked by an increased hepatic production of oxalate. The resulting hyperoxaluria leads to recurrent nephrolithiasis and nephrocalcinosis which are commonly observed in childhood. About 50% of PH1 patients develop end stage kidney disease (ESKD) by 33 years of age. Clinical trials of potential therapeutic agents are challenging due to disease rarity and time needed to reach hard clinical endpoints (such as ESKD). Thus, slope of eGFR over time is an attractive surrogate endpoint. However, clinical experience suggests that eGFR decline is not uniform across disease course. Thus we looked at the slope of change in eGFR during sequential stages of CKD in a PH1 cohort.

Methods: PH1 patients enrolled in the Rare Kidney Stone Consortium (RKSC) registry who were >2 years of age, did not have ESKD at diagnosis, and had ≥2 serum creatinine values between dx their last follow up prior to ESKD were studied. eGFR was estimated using the full age spectrum equation. ESKD was defined as the first occurrence of transplant, initiation of dialysis, or eGFR less than 15 ml/min/1.73m2. Absolute change in eGFR over time was estimated by linear regression within each CKD stage, and estimates across CKD stages were compared using GEE models.

Results: A total of 129 PH1 patients met inclusion criteria. Seventy (54.3%) were male and 99 (76.7%) were Caucasian. Median [IQR] age at PH1 dx was 8.6 [3.3, 21.6] years. There were 121 patients with follow-up in CKD stage 2; 72 in stage 3a; 41 in stage 3b; and 14 in CKD stage 4. (Table 1) Absolute annual change in eGFR increased with CKD stage (P=0.007 for trend). (Table 1).

Table 1. eGFR annual rates of absolute change (slope) during follow-up

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Follow-up late per patient</th>
<th>Annual absolute rate of change [ml/min/1.73m2/year]</th>
<th>Results from GEE model P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>3a (n=49) 72 787 180 [4,14] 5.13 [21] -2.04 (0.48) 0.24 (0.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>3b (n=41) 31 367 381 [4,31] -1.24 (0.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (n=14) 11 31 197 [4,12] -1.24 (0.40)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: As hypothesized, eGFR decline was not uniform across CKD stages in this PH1 population, with a higher rate of eGFR decline at CKD stages 3b and 4. Thus, absolute eGFR and CKD stage need to be accounted for when analyzing eGFR slope in this patient group. These data also suggest that measures to prevent GFR decline to < 45 ml/min/1.73m2 are particularly important, as the disease course accelerates thereafter.

No conflict of interest

POS-436
CLINICAL EFFECTIVENESS OF VARIOUS ANTI-RELAPSE THERAPY REGIMENS IN CHILDREN WITH PYELONEPHRITIS
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Introduction: Relevance: Currently, pyelonephritis (PN) remains one of the most common bacterial infections in children. Treatment of chronic PN (CP) should be based on the principles of staging, continuity and succession.

Purpose. Evaluation of the advisability of prescribing anti-relapse therapy, its tolerance and the effectiveness of various regimens to prevent relapse in children with acute and CP.

Methods: The study involved 167 children from 2 to 12 years old, including 139 (83.2%) girls and 28 boys (16.8%). Children were divided into the following groups: 1A (n=32) with the onset of acute PN, received cephalosporins (CS) of the third generation for 10-14 days; 1B (n=35) - with the onset of acute PN, received third-generation CS for 10-14 days, then for 1 month - a combination of standardized extracts of BNO 1040; group 2A (n=32) with recurrent CP received third generation CS for 10-14 days, then furazidin for 14 days; group 2B (n=34) with recurrent CP received third generation CS for 10-14 days, then furazidin for 14 days, then a combination of standardized extracts of BNO 1040 for 1 month; group 2C (n=34) with recurrent CP received third-generation CS for 10-14 days, then a combination of standardized extracts of BNO 1040 for 3 months.

Results: The tolerance of the drugs used for therapy was assessed on the basis of symptoms and subjective sensations reported by the patient or his parents throughout the entire period of their intake. Unsatisfactory tolerance of furazidin in the form of repeated vomiting after taking the drug was noted in 1 child, which required its cancellation. Among the adverse events and minor side effects in patients while taking furazidin were noted complaints of abdominal pain, nausea, episodic vomiting after taking the drug and the appearance of loose stools. We did not notice any undesirable effects that required the cancellation of the combination of standardized extracts BNO 1040 Centaurii herba, levistici radix, and Rosmarinus officinalis. On the background of taking the phytodrug the least number of adverse events was recorded in the form of short-term nausea, flatulence and a tendency to constipation (Figure 1).

During the prolonged therapy of the onset of acute pyelonephritis (group 1B) there was no change in the control urine tests in the first 6 months after the end of antibiotic therapy (Figure 2).

POSTER SESSION: INFLAMMATION, FIBROSIS, MATRIX BIOLOGY AND OXIDATIVE STRESS

POS19
15/04/2021
Poster Area
05:00 – 06:00