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GENETIC TESTING OF FAMILIES WITH VERY EARLY ONSET POLYCISTIC KIDNEY DISEASE REVEALS THE FUNCTIONAL SIGNIFICANCE OF HYPOMORPHIC VARIANTS
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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is generally an adult onset disorder; however rare very early onset (VEO) cases under the age of 2 years are reported and have a high recurrence risk in subsequent pregnancies. Elucidation of the underling mechanism causing the early onset phenotype has significant benefits for genetic and reproductive counselling.

Methods: We performed an audit of all ADPKD diagnostic referrals with age of onset less than 2 years referred for diagnostic genetic testing of PKD1 and PKD2 from 2010-2018. Testing was performed by long-range PCR with Sanger sequencing of all coding exons and/or next-generation sequencing (from 2016 onwards) and MLPA.

Results: A total of 28 cases with reported age of disease onset under 2 years were identified. 5 patients with a clinical history not suggestive of ADPKD and no mutation detected in PKD1 and PKD2 were subsequently excluded. Of the remaining 23 patients, 15 (65%) had at least 2 variants detected, including one likely hypomorphic variant; 4 (22%) had one pathogenic PKD1 mutation and 3 (13%) had no mutation detected in PKD1 or PKD2. Parental analysis from 12 families confirmed biallelic inheritance in 9 (75%) cases and 4 (33%) cases with a de novo mutation. Biallelic inheritance of PKD1 and PKD2 variants was found in 2 cases and biallelic PKD2 mutations in 1 case. Of the 15 patients with multiple variants, 13 had a likely or definitely pathogenic mutation as well as a likely hypomorphic variant; whilst 2 patients had 2 likely hypomorphic variants confirmed in trans. 10 (43%) cases had no previous family history of ADPKD.

Conclusions: This study highlights a high incidence of hypomorphic variants inherited in trans with a pathogenic mutation or another hypomorphic variant in children with a VEO phenotype. The previously reported and experimentally validated p.[Arg3277Cys] hypomorphic PKD1 variant was detected in 3 families. The minor allele frequency of the hypomorphic variants detected ranged from 0-0.2% which is higher than expected for a disease-causing variant. These variants require careful consideration in the context of early onset disease and parental segregation analysis to determine phase. Our study also demonstrates a high incidence of de novo mutations and high incidence of cases with no previous family history. A model of reduced gene dosage during embryonic kidney maturation is the simplest molecular mechanism underlying the VEO phenotype.

POSTER SESSION: ‘ONCONEPHROLOGY’, URINARY TRACT MALIGNANCY AND CHEMOTHERAPY

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PEMETEREXED AS A RENAL-FRIENDLY ANTICANCER AGENT IN LUNG CANCER WITH RENAL FAILURE
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Introduction: Pemetrexed is an anticancer agent with low toxicity which is commonly used in non-squamous, non-small cell lung cancer(NSCLC). However, there is not much research on the optimal dose according to the renal fuction and whether the treatment response varies with the renal function. We retrospectively examined whether pre-treatment renal function affects progression free survival and renal survival in patients used pemetrexed.

Methods: We reviewed the medical records of 124 patients with non-small cell lung cancer who used pemetrexed at Jeju National University Hospital from 2009 to 2017. Cases with combination (multi-drug) chemotherapy were excluded from the study to confirm the effect of pemetrexed alone. Pemetrexed alone was used in 71 patients. We investigated the patient’s gender, age, histology, progression free survival, and estimated GFR (eGFR, by MDRD equation). The baseline eGFR was divided into two groups: fair eGFR (more than 60ml / min / 1.73m2) and lower eGFR (59ml/min or less). eGFR at 3 months (GFR3) was also investigated.

Results: Median age of patients were 69.8 years old (range, 41.8-84.6). Of the total 71 patients, 37(52.1%) were male. 47(66.2%) were performance status (ECOG) 0 and 1. All patients were non-squamous NSCLC in histology and were treated with standard dose (500mg/m2) of pemetrexed. 43(60.6%) were fair eGFR and 28 (39.4%) patients were lower eGFR. 46(64.8%) were fair GFR3 and 25(35.2%) were lower GFR3. No patient needed renal replacement therapy till 3months after pemetrexed. Median PFS of fair eGFR and lower eGFR were 2.7(95%CI, 2.3-3.1) months and 4.7 (95%CI, 3.3-6.0) months, respectively, which was not significantly different (p=0.096).

Conclusions: None of the renal function variables was associated with clinical outcomes such as progression free survival and renal survival. Pemetrexed is considered an anticancer agent that can be used actively without dose reduction in non-squamous NSCLC patients even with poor renal function.

SAT-336
NON-NEOPLASTIC RENAL DISEASES ARE COMMON AND UNDERDIAGNOSED IN NEPHROURETERECTOMY SPECIMENS
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Introduction: The relationship between chronic kidney disease and renal malignancies is increasingly being recognized. Non-neoplastic kidney diseases can be diagnosed in up to 15% of tumor nephrectomy specimens from kidney cancer patients. We conducted this study to evaluate the non-neoplastic renal parenchyma of nephroureterectomy specimens of urothelial neoplasia of the renal pelvis.

Methods: We retrospectively reviewed our Pathology database from 2014-2018 and identified 63 nephroureterectomy specimens in adults. The non-neoplastic renal parenchyma was reviewed and clinical data was obtained through electronic medical record review, including age, sex, race, and co-morbidities.

Results: The average age of the cohort was 72 years (22-94 years) with 41 males (65%) and 22 females (35%). Ethnically, there were 54 Caucasians (86%), 5 African-Americans (8%), and 4 other (6%). 13 patients (21%) had a clinical diagnosis of diabetes. After review of the H&E and PAS slides, 7 cases (11%) had diffuse and/or nodular mesangial sclerosis that was consistent with diabetic nephropathy (Figure). In 5 cases (71%), the diabetic nephropathy had not been originally diagnosed, and of these 5 patients, 4 did not have nephrology consultation.