P0051 **NOVEL AND KNOWN MUTATIONS IDENTIFIED BY CLINICAL EXOME SEQUENCING FOR THE DIAGNOSIS OF POLYCYSTIC KIDNEY DISEASE**

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**Background and Aims:** Autosomal dominant PKD determines formation of multiple cysts predominantly in the kidneys and usually becomes symptomatic during adulthood and can lead to renal failure. In contrast, in autosomal recessive PKD cysts occur in both the kidneys and the liver and usually presents an earlier onset. Obtaining genetic diagnosis is important to confirm clinical diagnosis and is required before treating with vasopressin 2 receptor blockers, which are the only drugs known to slow down the disease. Furthermore, in the case of kidney transplant from a living family member it is essential to exclude the presence of the mutation in the donor. We used clinical exome sequencing to provide genetic diagnosis to a cohort of patients with a clinical suspicion of PKD.

**Method:** 175 patients were referred to the Immunogenetics and Transplant Biology Service of the Turin University Hospital through a network of nephrology centers operating in the Piedmont region. Some patients were referred following genetic counseling. All patients signed an informed consent and the referring physicians provided relevant clinical data. DNA from eligible patients was extracted, checked for integrity, quantified and used for library preparation. A clinical exome sequencing (CES) kit by Illumina was used, allowing the analysis of 6,700 clinically relevant genes.

**Results:** Out of the 175 recruited patients eligible for CES, 38 (21.7%) had a clinical suspicion or diagnosis of PKD, with 50% of them presenting family history. The majority of the cohort was represented by male subjects (60.5%) and included both children (34.2%) and adults. The analytical approach was based on initial analysis of genes responsible for PKD (*PKD1*, *PKD2* and *PKHD1*). If no mutation could be identified, analysis was then extended to a panel of 99 genes responsible for ciliopathies. This approach led to the identification of causative variants in 33/38 (86.8%) of the PKD cohort, while no variant could be identified in 5/38 patients. In 5/33 (15.2%) patients, mutations were inconclusive as found in heterozygosity in genes known to have an autosomal recessive mode of inheritance, while 27/33 (81.8%) were in line with the initial clinical suspicion/diagnosis. Of these, the majority was represented by missense mutations (12), followed by frameshift and nonsense mutations (6 each) and 3 splicing variants. As expected, the majority of mutations were found in *PKD1* 17/27 (63%), *PKD2* 3/27 (11.1%) and *PKHD1* 2/27 (7.4%). In these two latter patients, variants were found as compound heterozygosity. We also found mutations in other genes known to cause cysts, including *TSC2* and *CPT2*. Of note, in 7 patients carrying *PKD1* mutations, we found a second variant in *PKD1* or *PKHD1*. Interestingly, when looking at patients characterized by kidney failure but lacking a clinical suspicion at recruitment or diagnosed with other phenotypes (66/175), we found variants in *PKD1* and in *PKD2* in 11 patients (9 and 2, respectively).

Of all identified variants in *PKD1*, *PKD2* and *PKHD1* genes, 17.6% were annotated as pathogenic (C5), 41.2% were likely pathogenic (C4) and 41.2% were variants of unknown significance (C3). 19 variants in these genes were not previously reported. All the variants found in genes responsible for PKD were validated and confirmed by Sanger sequencing. Family segregation studies are ongoing.

Finally, it is worth mentioning that in a portion of cases (5/38) with clinical and phenotypic features of PKD, supported also by a positive family history, we could not detect mutations in causative genes. These results may be explained by the presence of intronic variants, in line with data reported in literature.

**Conclusion:** These results demonstrate that CES may be applied to PKD patients to identify causative variants during their routine diagnostic flow. Furthermore, CES may be a useful tool to detect mutations in PKD-related genes in patients with undiagnosed diseases, considering its rapidly decreasing costs.