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ERA Long-Term Research Fellowship Project

G&K

Project's key info

Title of the project	Identifying new genes in ADPKD-like pedigrees
Working Group and ERA Committee involved in the project	Genes & Kidney (G&K) Working Group
Principal Investigator(s) of the project	Co-investigators: Emilie Cornec-Le Gall, Brest, (FRANCE) and John Sayer, Newcastle (UK)
Duration	12 months
Fellowship Grant	34.545,00 €
Start of the fellowship	Within 6 months after notification of the grant award to the fellow.

Receiving Institute

Name of receiving institute	INSERM UMR1078 Genetics Genomics and Biotechnologies - Brest (FRANCE)
Supervisor's name	Emilie Cornec-Le Gall Co-supervisor: John Sayer, Newcastle, UK
Supervisor's e-mail address	emilie.cornec-legall@chu-brest.fr

Project's detailed description

Project description

Autosomal dominant polycystic kidney disease (ADPKD) is predominantly caused by pathogenic variants in PKD1 and PKD2 involved in ~75% and ~18% of the families, respectively. In the past few years, several other genes have been associated with ADPKD-like phenotypes, including notably genes involved in the endoplasmic reticulum (ER) glycosylation machinery and/or ER folding pathway such as GANAB, DNAJB11, ALG8, ALG9 and more recently ALG5. In addition, monoallelic pathogenic variants to IFT140 were very recently shown to be associated with atypical, mild forms of polycystic kidney disease. Despite this recent expansion of the genetic spectrum of ADPKD and the increased awareness on differential diagnoses of cystic kidney diseases, ADPKD remains genetically unresolved in ~7% of the families.

The Genkyst cohort is an observational cohort of individuals with ADPKD and or autosomal dominant liver disease (ADPLD), aiming to describe the clinical and genetic spectrum of ADPKD, genotype-phenotype correlations and prognostic factors. More than 3400 individuals have been included, and genetic sequencing has been performed. In genetically unresolved individuals, further genetic studies including exome or larger genetic panels have led to the identification of new genes.

Currently, 50 genetically unresolved (GUR) pedigrees with ADPKD are being exome-sequenced.

Step 1: Analysis of exome data in ADPKD-like GUR pedigrees from the Genkyst cohort to identify new candidate genes.

In addition, to support evidence for association between candidate genes identified at step 1 and

to provide an adequate clinical description in a larger number of pedigrees, we will access to Genomics England 100,000 Genomes project (100kG).
All participants in the 100kG provided written consent to access their anonymized clinical and genomic data for research purposes.
Step 2: 100kG whole genome data will be analysed for monoallelic rare and predicted pathogenic variants in candidate genes identified at Step 1.
Upon identification of novel and candidate genes, in vitro models will be developed to characterize disease mechanisms, by obtaining urine derived epithelial cells (URECs) from patients with new forms of ADPKD, and by developing CRISPR-edited renal epithelial cells. This approach has been proven effective to identify new genes in ultra-rare diseases, such as recently ALG5 (Lemoine et al, AJHG 2022, PMID: 35896117).
Our two groups have developed an efficient and stimulating collaboration, resulting in other recent common projects (PMIDs: 34890546-32631624, and ongoing). All the genetic data to analyse during this 12-months project will be already generated before the beginning of the fellowship, to ensure feasibility in time.

Goals of the project

- Identify new candidate genes in ADPKD and or ADPLD-like pedigrees
- Describe the phenotype associated with new forms of ADPKD
- Assess variants and genes penetrance employing large cohorts of individuals with clinical and genetics information
- Identify new pathways relevant to renal and/or hepatic cystogenesis

Qualifications and/or expertise required to the fellow

- Biomedical or medical degree
- High level of motivation
- Communication skills, and a good level of English
- Desirable to have at least a master degree or equivalent in molecular genetics or in bioinformatics