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ERA Long-Term Research Fellowship Project

Genes and Kidney

Project's key info

Title of the project	Deciphering the contribution of non-coding variation to Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT)
Working Group involved in the project	Genes & Kidney
Principal Investigator(s) of the project	Melanie Chan
Duration	12 months
Fellowship Grant	37.050,00 €
Start of the fellowship	Within 6 months after notification of the grant award to the fellow

Receiving Institute

Name of receiving institute	Imperial College London
Supervisor's name	Melanie Chan
Supervisor's e-mail address	m.chan@lms.mrc.ac.uk

Project's detailed description

Project description
Congenital anomalies of the kidney and urinary tract (CAKUT) comprise a heterogeneous group of developmental malformations affecting the kidneys and urinary system and represent the leading cause of kidney failure in children and young people. Although CAKUT affects approximately 1 in 500 births, a monogenic cause is identified in fewer than 20% of cases, leaving the majority of genetic risk unexplained. The genetic complexity of CAKUT, including variable expressivity and incomplete penetrance, suggests that disease risk cannot be explained solely by rare, highly penetrant coding variants. Increasing evidence indicates that **rare non-coding regulatory variants** play a significant role in congenital and developmental disorders by disrupting gene regulation during organ development. This project hypothesises that rare non-coding variants—both single-nucleotide/indel and structural variants—affect gene regulatory mechanisms during kidney development and account for a substantial proportion of the missing heritability of CAKUT. Using whole-genome sequencing data from over 1,000 individuals with CAKUT from Genomics England, combined with high-resolution human embryonic kidney epigenomic datasets (single-nucleus ATAC-seq and RNA-seq), the project will systematically identify and prioritise rare non-coding variants in cis-regulatory elements, non-coding RNAs, and untranslated regions. Variants will be assessed for conservation, predicted functional impact, and segregation, and integrated with clinical phenotypes. Advanced machine learning models trained on embryonic kidney epigenomic data will be used to predict how prioritised variants disrupt gene regulation, including effects on chromatin accessibility, transcription factor binding, and three-dimensional genome organisation. In

parallel, genome-wide rare variant association analyses within kidney-development regulatory regions will be conducted to identify regulatory networks contributing to CAKUT pathogenesis, with replication sought in independent cohorts.
Overall, this project aims to uncover novel regulatory mechanisms underlying CAKUT, improve genetic diagnosis, and advance understanding of kidney developmental biology.

Goals of the project

The project aims at:

1. Providing a comprehensive overview of the contribution of non-coding regulatory variation to CAKUT, increasing our understanding of how transcriptional networks are disrupted during development
2. Enhancing the diagnostic yield for CAKUT patients using epigenomic data and machine learning to facilitate the interpretation of non-coding variation.

Qualifications and/or expertise required to the fellow

The fellow should:

- have a good fundamental understanding of genetics and statistics.
- be competent in written and spoken medical/scientific English.
- experience in bioinformatics (e.g. R, python) would be beneficial.
- have proven research experience.