| Project Details | |
|---|---|
| Project Code | MRC23IIARCa Fraser |
| Title | Tracking the genetic link between neurodevelopmental conditions, inflammation and kidney disease |
| Research Theme | Infection, Immunity, Antimicrobial Resistance and Repair |
| Summary | Population studies have identified genetic traits linked with neurodevelopmental disorders. Patients with these conditions often display an increased risk of kidney disease. The genetic and molecular basis for this joint susceptibility profile is unknown. Combining training in genetic epidemiology with immune pathology and molecular cell biology studies, the successful applicant will investigate the regulatory mechanisms responsible. |
| Description | Copy Number Variants (CNVs) occur where the number of copies of a specific segment of DNA varies in individuals. They are a common and important source of genetic difference. Some CNVs have a devastating impact on people carrying them, often across multiple organs or body systems including brain (neurodevelopmental disorders such as intellectual disability, ADHD and autism) and kidneys, whilst also increasing risk of immunological problems. An example is deletion of region 11.2 on chromosome 22q, causing 22q11.2 Deletion Syndrome.. The specific genes and mechanisms responsible for these problems are poorly understood. Key research question: why there is a strong risk of kidney disorders and dysregulated inflammation in people carrying CNVs linked to neurodevelopmental disorders? The student will be trained by experts in, genetic epidemiology of CNVs, kidney disease and inflammation biology, brain and behaviour. The student will be supported and encouraged to lead all aspects of the project, guided by the supervisory team. Aim One: Study the role of high-risk CNVs in kidney-and inflammation-related phenotypes by analysis in cohort studies. First, analysis will be conducted comparing kidney and immune-related disorders and associated risk phenotypes in adults with and without 54 high-risk CNVs in a large-scale longitudinal population-based sample of adults with linked electronic health records (including the UK Biobank cohort, ~500,000 participants). We have already called the CNVs in these cohorts. Second, in our cohort of patients recruited because they have a genetic diagnosis of one of these CNVs (n~900) we will examine their linked secondary care electronic health records to learn more about their kidney and immunological phenotypes. Aim Two: Evaluate gene expression in mouse models of CNVs For the second part of the project, the student will focus on three CNVs which are common and of high impact (1q21.1, 22q11.2, 16p11.2). The student will study kidney tissue, blood and other samples from mice exhibiting CNVs at these loci. These samples are available because of an extensive MRC-funded programme of behavioural and neuropsychiatric studies in mice (collaboration Cardiff, led by van den Bree, and Bristol Universities, collaborator Prof M Jones) providing the opportunity to relate findings with respect to kidney phenotype and inflammation regulation to brain function. The student will evaluate kidney dysplasia using standard molecular biology approaches and will evaluate gene expression at the level of individual kidney cells using single nuclear RNA sequencing (snRNAseq). The overall aim is to uncover phenotypic change linked to |

| | |
|---|---|
| | CNVs and to identify and quantify candidate genes responsible. Preliminary analyses of our snRNAseq datasets for 25 genes directly involved in the 22q11.2 mouse model have identified 5 candidate genes, namely Prodh, Gnb1, Dgcr8, Tango2 and Comt. The student will extend this analysis to other genes affected by the three CNVs under study. They will evaluate gene expression through postnatal mouse growth, evaluating normal versus CNV-heterozygous animals. Aim Three: Evaluate gene function in vitro using gain- and loss-of function In the final part of the project, the student will use their data from genetic studies in humans and expression and phenotyping data in mice to predict key genes responsible for renal dysplasia. They will evaluate gene function in vitro, using enforced expression by adenoviral transfection, and repression using siRNA transfection, in the range of in vitro kidney models established across the collaborating renal laboratories in Cardiff (Fraser) and Bristol (Coward). |
| Supervisory Team | |
| Lead Supervisor | |
| Name | Professor Donald Fraser |
| Affiliation | Cardiff |
| College/Faculty | Biomedical and Life Sciences |
| Department/School | MEDIC |
| Email Address | fraserdj@cf.ac.uk |
| Co-Supervisor 1 | |
| Name | Professor Marianne van den Bree |
| Affiliation | Cardiff |
| College/Faculty | Biomedical and Life Sciences |
| Department/School | Psychological Medicine and Clinical Neurosciences |
| Co-Supervisor 2 | |
| Name | Professor Richard Coward |
| Affiliation | Bristol |
| College/Faculty | |
| Department/School | Medicine |
| Co-Supervisor 3 | |
| Name | Professor Simon Jones |
| Affiliation | Cardiff |
| College/Faculty | Biomedical and Life Sciences |
| Department/School | MEDIC |