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| Title of PhD project | **Characterising the genetic architecture of inherited cardiac conditions from whole-genome sequence data** | |
| Supervisor | Dr Yalda Jamshidi | SGUL |
| Co-Supervisor | Dr Hilary Martin | Wellcome Sanger Institute |
| Brief description of project | This project offers an outstanding opportunity to work with state-of-the-art genome sequencing technologies, apply and develop cutting edge statistical methods, and access WGS data sets including the UK 100,000 Genome Project to explore the contribution of more complex genetic architectures in rare inherited cardiac conditions, and the interplay between common and rare variants.<br><br>We have previously shown that common variants (SNPs) contribute to key determinants of cardiac muscle function and size in large population cohorts (PMID: 2765946, 300460336, 24952745, 23872634). Additionally, rare inherited and de novo mutations are known to play a role in congenital heart defects (e.g. PMID: 27479907) and later-onset cardiac disorders (25691538, 21887725), with rare inherited variants often being incompletely penetrant. It is becoming increasingly clear that oligogenic (28642161, 27058611) inheritance plays a major role in these disorders, and that same common SNPs that contribute to polygenic cardiac traits in the general population can also increase risk of rare cardiac disorders previously considered monogenic (25691538).<br><br>Whole genome sequencing (WGS) data allows us to assess the full spectrum of genetic variants in an individual. The UK 100,000 Genomes Project has conducted WGS on thousands of patients with cardiac defects (arrhythmias, cardiomyopathies, congenital heart defects) which will be the main focus of this PhD project, along with similar datasets from other projects. The student will investigate how rare and common variants interact to influence risk of these cardiac disorders and compare genetic architectures between disorders and between populations. The project will also involve querying electronic health records of 100,000 Genomes patients, UK Biobank and through collaboration with the Health Data Research UK Centres, to extract more detailed clinical information on heart phenotypes from | |

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| | patients referred for cardiac conditions and other disorders, to boost power for analyses.<br><br>As such data becomes more mainstream in clinical practice it will be important to find ways to define and characterise the influence of both common and non-coding alleles associated with increased or decreased risk for rare inherited conditions. The student will work on building risk scores for cardiac conditions incorporating both common and rare variants and collaborate with clinical geneticists at St George's to explore how best to communicate these findings to clinicians. |
| Skills we expect a student to develop/acquire whilst pursuing this project | • Programming in R and python/perl<br>• Bash scripting<br>• Knowledge of commonly used genetics software<br>• Familiarity with error modes in high-throughput sequencing data<br>• Knowledge of how to control for population structure in Genetic studies of disease<br>• Understanding of genetic architecture of common and rare diseases<br>• Ability to extract and clean data from electronic health records<br>• Statistical modelling in R |
| Particular prior educational requirements for a student undertaking this project | The student should have at least one of the following (preferably two or three!):<br>• Knowledge of human molecular and disease genetics<br>• Programming skills (e.g. R and python/perl)<br>• Basic statistical skills |