Project Details	
Project Code	NMH27Ca Caseras
Title	Shared Genetic Architecture of Neuropsychiatric Disorders and Novel Brain Biomarkers: Towards Understanding Biological Processes
Research Theme	Neuroscience & Mental Health
Project Type	Dry lab
Summary	The field of imaging genetics has had limited success identifying shared common risk variants between mental disorders and brain phenotypes, this being key to understanding neurobiological mechanism for ill mental health. This is partly due to the lack of biological specificity of current available brain phenotypes. We plan to implement novel methods to enhance the resolution of diffusion weighted imaging in a very large cohort (UK Biobank) utilizing data from the unique Connectome scanner at CUBRIC. This will in turn allow generating novel MRI metrics closer to brain biology, to examine their genetic makeup and overlap with mental disorders.
Description	Recent large GWAS research is uncovering the importance of common genetic variants in increasing risk for severe mental disorder, and in shaping brain's neurodevelopment. However, the overlap between common variants influencing both the above remains elusive. This is key to understanding the neurobiological mechanisms of mental disorders and ultimately to develop strategies to stratify patients and develop new diagnostic and treatment strategies. We believe that one of the main limitations in identifying common genetic factors shaping brain's neurobiology and mental ill health is the lack of biological specificity of currently available MRI brain phenotypes. Brain phenotypes available in large cohorts of participants providing imaging and genetic data lack a link to any specific neurobiological process and can be affected by multiple factors (e.g. Fractional Anisotropy is affected by white matter tracts myelin content, density packing, axonal diameter, structural organisation, etc). In this project we plan to utilise the unique resolution provided by the ultra-high gradient Connectome scanner at CUBRIC, to enhance the resolution of existing MRI data in UK Biobank via a novel method (Image Quality Transfer), that our group has already implemented successfully in other datasets. Here, we will fine-tune existing IQT models to learn the mapping between high-quality Connectome data at CUBRIC and the 'standard' data acquired by UK Biobank. Through this we will increase signal-to-noise ratio (SNR), q-space sampling and spatial resolution; which will ultimately allow us to implement analytical methods producing brain phenotype metrics currently inaccessible in UK Biobank (e.g. cell body size and density in grey matter, or myelin sheet thickness in white matter). We will then use the statistical power provided by the large cohort that is UK Biobank (~100,000 participants with MRI and genotype data) to investigate the common genetic make-up of these phenotypes, further investigating the genetic overlap with mental disorders using different post-gwas methodologies such are LD score regression, MiXer, Genetic SEM, or polygenic scoring. Therefore, the main aim of this proposal is to identify common genetic variants that influence biologically specific MRI-derived brain phenotypes and determine how these genetic factors overlap with the

	genetic architecture of severe mental disorders, to examine potential neurobiological pathways into pathology. Breaking this down into specific objective, the student will work towards: 1. Enhance UK Biobank MRI data using Image Quality Transfer (IQT) and existing data from the Connectome scanner at CUBRIC 2. Derive novel and biologically specific MRI phenotypes for the UK Biobank cohort 3. Characterise the genetic architecture of the novel brain phenotypes 4. Investigate shared genetics between the brain phenotypes above and psychiatric disorders 5. Examine the potential neurobiological pathways existing within the above common genetic sets Due to the high level of specialisation of this project, and the need to access unique facilities (Connectome scanner/data) and UK Biobank genetic/imaging raw data exceptionally hosted at Cardiff University, the supervisory team is all located in Cardiff. The supervisory team, though, provides the student with access to a breadth of multidisciplinary expertise brought together from different schools/centres at Cardiff University, that is rarely available within a single institution. The student will work across internationally recognised centres spanning advanced neuroimaging, psychology, statistical genetics, and genomics, bringing together complementary disciplines that have traditionally operated independently. This interdisciplinary environment will allow the student to develop expertise in multimodal imaging, large-scale genomic analysis, quantitative data science, and big-data handling and use of supercomputing clusters while learning to integrate these approaches to address complex questions in brain biology. Exposure to researchers from different schools, methodological traditions, and scientific cultures will foster intellectual flexibility and collaborative working, providing many of the benefits typically associated with cross-institutional training. The student will therefore graduate with a broad, highly transferable skill set and the experience of working within a genuinely interdisciplinary research environment, positioning them strongly for future careers in academia, healthcare, or the life sciences sector. The proposed project is intentionally designed with a broad scope to provide the student with a flexible research framework within which a more focused PhD can be developed. This approach will enable the student to refine the research objectives by prioritising specific MRI-derived brain phenotypes that can be robustly quantified from the enhanced resolution data generated through the project. Furthermore, the student will have the opportunity to investigate the shared genetic architecture underlying selected neuropsychiatric disorders based on their own interests, employing a range of statistical genetic and biostatistical methodologies tailored to the specific hypotheses and research questions that emerge during the course of the project.
Can be completed part time?	No
Supervisory Team	
Lead Supervisor	
Name	Dr Xavier Caseras
Affiliation	Cardiff

College/Faculty	College of Biomedical and Life Sciences
Department/School	Division of Psychological Medicine and Clinical Neurosciences / Medicine
Email Address	caserasx@cardiff.ac.uk
Co-Supervisor 1	
Name	Dr Marco Palombo
Affiliation	Cardiff
College/Faculty	College of Physical Sciences and Engeneering
Department/School	School of computer Science and Informatics
Co-Supervisor 2	
Name	Professor Kevin Murphy
Affiliation	Cardiff
College/Faculty	College of Physical Sciences and Engineering
Department/School	School of Physics and Astronomy
Co-Supervisor 3	
Name	Dr Richard Anney
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	Cente for Neuropsychiatric Genetics and Genomics / School of Medicine