Project Details	
Project Code	MRCPHS25Ex Frontini
Title	Integrative analysis of whole genomes and transcriptomes from multiple cell types in rare disease patients.
Research Theme	Population Health Sciences
Summary	Comprehensive genetic analysis using whole genome sequencing (WGS) still fails to identify the genetic cause of diseases in about 50% of patients with rare diseases. To increase this yield, the NIHR BioResource for Rare Disorders launched the RNA phenotyping initiative, which combines RNA-sequencing and proteomic data with WGS for 1000 patients with rare diseases. This PhD project will develop new approaches to integrate these data to identify new causes of disease.
Description	The use of Whole-Genome Sequencing has dramatically increased the diagnostic yield and shortened the time to diagnosis for individuals affected by rare diseases. However, WGS still fails to identify the underlying genetic cause in about 50% of patients. This is due to several factors, mainly: (i) lack of statistical power due to small sets of cases with different genetic aetiology, (ii) difficulty in predicting the consequences of a number of causal genetic variants, and lastly, (iii) challenges with identifying structural variants using current WGS techniques. To increase the percentage of individuals receiving a diagnosis the NIHR National BioResource for Rare Diseases launched the RNA phenotyping initiative. Here, WGS is supplemented with RNA-sequencing from four highly purified blood cell types and proteomic data from the same cells and plasma. This unique dataset provides an exciting opportunity to complement genome analysis with functional measurements of gene expression at the messenger RNA and protein level. Understanding how gene expression varies with genotype and disease status will allow the identification of novel genetic aetiologies for rare disorders. It will enhance our understanding of human biology, improve the diagnostic yield of clinical genetic analyses, improve prognostication, and inform the development of treatments. The candidate will join a group with an extensive track record of studying blood disorders and they will be part of a multi-disciplinary collaborative research environment that includes clinicians, biologists, statisticians and bioinformaticians. The aim of the project is to develop approaches for integrating and exploiting the novel collected data and apply these to discover new causes of disease in a unique cohort of one thousand rare disease patients, boosting the diagnostic power of genetic testing and broadening access to precision medicine. The candidate will take ownership of identifying relevant computational methods, applying them and subsequently developing new methodology where necessary, to integrate genotype and gene expression data. To focus the studentship, the candidate will work with data from a selected group of patients enrolled with bleeding secondary to a platelet function disorder and unresolved genetic cause. In addition to the initial sequencing and proteomic data, the student will have access to laboratory data generated using recall by genotype studies. Employing this, they will lead the analyses and with the direction of the supervisory team, will coordinate the assembly of evidence to support the publication of their findings in peer-reviewed journals. Focusing on blood

	disorders in general, and platelet function disorders in particular, will enable to student to make the most from the specialist knowledge of the project supervisors in this area. However, the methodologies developed will be relevant to a broad range of disease areas. Furthermore, many genes implicated in platelet function are also implicated in the development and function of other cell types, such as neurons, immune cells hepatocytes and melanocytes. Depending on the student's interests and the loci investigated, it will be possible to investigate broader non-haematological phenotypes within the study cohort.
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