Project Details	
Project Code	MRCPHS24Ex Frontini
Title	Integrative analysis of whole genomes and transcriptomes from multiple cell types in rare disease patients.
Research Theme	Population Health Sciences
Summary	The use of Whole-Genome Sequencing increased the diagnostic yield for rare diseases. However, even WGS fails to identify the genetic cause in about 50% of patients. To increase this yield, the NIHR National BioResource launched the RNA phenotyping initiative which adds RNA-seq and proteomic to WGS. The project aims to develop approaches for integrating these data to discover new causes of disease in a unique cohort of a thousand rare disease patients.
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 including: (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) the current technology used in WGS cannot detect certain types of causal variants. In an effort 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 blood cell types and proteomic data from the same cells and plasma. This unique dataset provides an exciting opportunity to identify novel genetic aetiologies and 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 be part of a multi disciplinary group that includes medics, biologists, statisticians and bioinformaticians. The aim of the project is to develop approaches for integrating and exploiting such data, and apply these to discover new causes of disease in a unique cohort of a thousand rare disease patients, boosting the diagnostic power of genetic testing and broadening access to precision medicine. The candidate will take ownership of developing some of the methods, whilst applying them, and those developed by others, to a selected group of patients presenting with platelet and bleeding disorders akin to storage pool disorder but with a still unresolved genetic cause. They will lead the analyses and will, with the direction of the supervisory team, coordinate the assembly of enough evidence, including now data generated using recall by genotype studies, to support the publication of their findings in peer-reviewed journals.
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