Project Details	
Project Code	MRCNMH26Br Stergiakouli
Title	Using genetics to understand neurodevelopmental outcomes in children born with cleft from a clinical birth cohort
Research Theme	NMH
Project Type	Dry lab
Summary	This project will provide in-depth training in genetic epidemiology, neurodevelopmental disorders, cohort studies and cleft. The student will have the opportunity to develop into one of few experts globally with understanding across these areas. In this PhD you will investigate the genetic and non-genetic causes of neurodevelopmental and mental health outcomes in children born with one of the most common birth defects, cleft of the lip and/or palate. You will be based at the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol; a world-class research centre in the field of integrative epidemiology who has pioneered Mendelian randomisation.
Description	Cleft of the lip and/or palate is a common birth defect and occurs at a rate of one in 650 live births in the UK. Being born with cleft places a significant burden on children, their families and the health system as they require surgery (multiple times depending on cleft type), and other interventions to improve appearance, speech, hearing and dentition. They are also at increased risk of mental health and neurodevelopmental problems (Berman et al 2022). These problems may reflect the psychological, developmental and social impacts of clefting and its treatment. Alternatively, they may reflect genetic factors either as pleiotropic outcomes of genetic susceptibility to clefting or as independently inherited genetic risk. The UK-based Cleft Collective comprises the world's largest cohort study of children affected by cleft and their families (www.bristol.ac.uk/dental/cleft-collective/) with longitudinal information on mental health, parental, prenatal and early life factors as well as genetic data. The aetiology of both cleft and of mental health outcomes is complex, with common risk alleles (Cleynen et al 2021, Howe et al 2018) of individually small effects as well as rare genetic mutations of large effect and environmental factors playing roles. One group of rare mutations of large effect are Copy Number Variants (CNVs), referring to deletion or duplication of a part of the genome leading to differences between individuals in the number of copies of genes within the affected region. A number of CNVs are known to increase risk of neurodevelopmental disorders (ND-CNVs), such as ADHD and autism, as well as mental health disorders but the presence and the impact of ND-CNVs have not been studied in cleft (Chawner et al 2019). The PhD project will provide the first detailed description of neurodevelopmental and mental health outcomes in children with cleft and examine the contributions of genetic and environmental factors. We will use two unique genetically informative clinical cohorts of children; the University of Bristol Cleft Collective and the Cardiff University longitudinal ExperiencCes of people witH cOpy number variants (ECHO) study. Control samples will consist of the Avon Longitudinal Study of Parents and Children (ALPSAC) and the Millennium cohort which are deeply-phenotyped cohorts of typically developing children.

	The aims of the study are: To improve understanding of risk of neurodevelopmental and mental health problems in children born with cleft. This will be achieved by comparing children born with cleft to those at high genetic risk of neurodevelopmental and mental health problems but without cleft (children with ND-CNV from the ECHO study) and typically developing children. To improve understanding of the causes of neurodevelopmental and mental health problems in children born with cleft. This will be achieved by determining in children born with cleft the contribution of: a) composite genetic (polygenic) risk scores for neurodevelopmental and psychiatric disorders and b) rare genetic mutations. Causally informative designs will also be used to test the causal link between cleft and mental health problems. The student will be instrumental in determining the type of datasets and study designs that will be best suited to improve causal inference and will be encouraged to explore possible collaboration with the African Cleft Genetics consortium and/or use of publicly available data. To improve understanding of non-genetic factors, the project will also examine contributions of early developmental problems, family socio-economic status, family relationship quality, and traumatic experiences to risk of childhood psychiatric disorders in children born with cleft. The student will be able to take part in consultations with the Cleft Collective Patient and Public Involvement (PPI) group and steer the project towards non-genetic factors that they have identified as important for families affected by cleft.
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