Project Number: CC013

Title: A genome wide association (GWAS) study of cleft with stratification by cleft subtype.

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Approval Date: November 2018

Scientific Outline:

There are two aims to this study to:

1) Carry-out a GWAS to determine whether there are further common variants (not so far detected) associated with cleft lip and/or cleft palate and to confirm whether the previously identified variants are risk factors for cleft in the UK population
2) Stratify by subtype and severity of cleft to look for subtype-specific genetic variants

Some genetic risk factors (each conferring a small increase in risk of cleft) have been uncovered in GWAS (Yu et al, 2017, Bohmer et al, 2013). As has been shown in other diseases, further GWAS in different populations are likely to uncover new variants. In addition, meta-analysis of the results from Previous cleft GWAS and many studies of the environmental risk factors for cleft have grouped different subtypes of cleft (for example, cleft lip only and cleft lip with cleft palate) as a single disorder. We therefore plan to carry-out a GWAS analysis of the Cleft Collective using population based birth cohorts which have also been genotyped in Bristol as controls.

Increasing evidence suggests that the different subtypes of cleft have different risk factors. For example, Kutbi et al (2017) recently showed that maternal obesity was associated with having a child with a cleft palate (with or without a cleft lip), but there was no evidence to show that maternal obesity was associated with having a cleft lip alone. In support of this we have shown that DNA methylation patterns (which are indicators of both exposures and biological pathways) are different between subtypes in the cleft collective (Sharp et al, 2017). Therefore, we will explore potentially distinct aetiologies in different subtypes of cleft, defined using both the location (lip, palate), laterality (uni- or bilateral) and completeness (incomplete, complete) by carrying out GWAS analyses for each of these cleft subtypes.