Project Number: CC011

Title: A genome wide association study of mums of children born with a cleft

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Scientific Outline:

A better understanding of the causes of orofacial clefts will be essential to inform better prediction and prevention strategies. Although we know that around 30% of clefts arise as a result of genetic syndromes and follow a monogenic model of inheritance, the majority of clefts follow a multifactorial model with both genetic and prenatal environmental risk factors that are still largely unknown.

Some genetic risk factors (each conferring a small increase in risk of cleft) have been uncovered in Genome wide association studies (GWAS) (Yu et al, 2017, Beaty et al, 2010, Bohmer et al, 2013). As has been shown in other diseases, further GWAS in different populations are likely to uncover new variants. However, existing cleft GWAS have compared genes in people with a cleft to people without and it is maternal genes that will influence the prenatal environment, including placental size, structure and levels of nutrients, proteins, hormones and environmental pollutants (Traglia et al, 2017). In fact, a recent study showed that approximately 20% of the variability in fetal growth was tagged by common maternal genetic variants, and the fetal genome made a surprisingly minor contribution (Warrington et al, 2017). Fetal growth, as indicated by birth weight, appears to be correlated with severity of cleft, with children with more severe clefts tending to have a lower birth weight. It therefore follows that clefts may be influenced by some of the same factors that affect fetal growth, with a higher proportion of the variability in cleft being tagged by the maternal compared to the fetal genome.

The aim of this project is therefore to carry-out a GWAS of mothers of children with cleft to determine whether there are maternal genetic variants that increase the risk of having a child with a cleft
A GWAS of maternal DNA may prove to be more fruitful in uncovering genes for cleft than a GWAS of affected individuals. Such an analysis may also implicate biological pathways in the mother which are important in determining whether her offspring is born with a cleft. This will help to elucidate the biology and cleft and will highlight potential intervention targets. To our knowledge, such a GWAS has not yet been carried-out and this would be a completely novel analysis.

We plan to do this by comparing GWAS data from mothers of the cleft collective with GWAS data from 3 other population based births cohorts; ALSPAC, ALSPAC Generation2 and Born in Bradford. We will compare allele frequencies of the SNPs from the Illumina Global Screening array in Cleft mothers against mothers of children born without a cleft. Single nucleotide polymorphisms found to be associated with cleft in our cohort will be tested in 600 mothers from the Bonn II study a replication study of children born with a cleft and their mothers.

Beaty TH et al. A genome-wide association study of cleft lip with and without cleft palate identifies risk variants near MAFB and ABCA4. Nat Genet. 2010 Jun;42(6):525-9.

Böhmer AC et al. Analysis of susceptibility loci for nonsyndromic orofacial clefting in a European trio sample. Am J Med Genet A. 2013 Oct;161A(10):2545-9.

Traglia M et al. Independent Maternal and Fetal Genetic Effects on Midgestational Circulating Levels of Environmental Pollutants. Int J Obes. 2017 Oct 9. doi: 10.1038/ijo.2017.248. [Epub ahead of print]

Warrington NM et al. Maternal and fetal genetic contribution to gestational weight gain. Int J Obes (Lond). 2017 Oct 9. doi: 10.1038/ijo.2017.248. [Epub ahead of print]

Yu Y et al. Genome-wide analyses of non-syndromic cleft lip with palate identify 14 novel loci and genetic heterogeneity.Nat Commun. 2017 Feb 24;8:14364