Epigenetics could help diagnose different types of cleft

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Cleft lip and/or palate are common birth defects and affect around 15 in every 10,000 births in Europe. New research by the University of Bristol from the largest study of cleft lip and/or palate in the world, the Cleft Collective, has found epigenetics could help diagnose different types of cleft.

A child born with a cleft may face difficulties with feeding, speech, dental development, hearing and social adjustment and often undergo surgery in the first year of life. Many children need additional surgery later in life and may experience low self-esteem, psychosocial problems, poor educational attainment, and the condition can harm the emotional wellbeing of the whole family.

The majority of cases are caused by a complex interplay of genetic and environmental factors, although the precise mechanism is unknown. Epigenetic processes, such as DNA methylation, when methyl groups attach to DNA and change the way it is read, can be influenced by genetic and environmental factors, so it is hypothesised that DNA methylation might either be involved in causing clefts or might be a useful tool to diagnose clefts. As a first step in exploring the role of epigenetic mechanisms in cleft, the research team were interested in whether children with different types of cleft: cleft lip only (CLO); cleft palate only (CPO) and cleft lip with cleft palate (CLP) had different DNA methylation profiles.

This is the first study to use DNA samples collected as part of the Cleft Collective cohort, and one of the first studies to look at the role of epigenetic mechanisms in cleft lip and/or palate.

The research team measured methylation from 150 children in the Cleft Collective cohort study at over 450,000 sites on their blood cell DNA. They then tested whether methylation was different in children with different types of cleft: CLO, CPO and CLP. Next the researchers compared methylation in blood to methylation in lip or palate tissue samples that were collected during surgery to repair the cleft.

The researchers found multiple regions of the genome where children with CLO, CPO and CLP showed differences in their blood methylation levels. The biggest differences were seen between children with CPO

and children with CLO. At some regions, blood DNA methylation correlated highly with DNA methylation in lip/palate tissue.

There are three possible reasons why children with different types of cleft might have different DNA methylation profiles. Firstly, DNA methylation might be a biological mechanism that causes different types of cleft to form. Secondly, DNA methylation might not play a causal role itself, but might reflect genetic and/or environmental factors that do. Thirdly, the direction of effect might actually be reversed, with different types of cleft causing changes to DNA methylation.

Dr Gemma Sharp, Lecturer in Molecular Epidemiology in the School of Oral & Dental Sciences and a member of the Cleft Collective team, said: "This study supports the idea that different types of cleft are not necessarily caused by the same things. This is important because research studies often treat people with different cleft types as a single group with the same anomaly. This study suggests that they should be considered separately according to the type of cleft they have.

"Our study is a promising first step in exploring the potential role of epigenetics in causing clefts. It also highlights that epigenetic data might be useful in diagnosing different types of cleft. Cleft palate rarely shows up on ultrasound and can be difficult to diagnose after birth, so better diagnosis could help to reduce the rate of poor outcomes associated with late diagnosis of CPO."

The research team are following the children in the study as they grow up, so in future studies we hope to explore whether methylation in infancy is associated with later surgical, health, developmental and psychological outcomes. If so, DNA methylation might be useful for identifying individuals with a cleft who might develop poorer outcomes and benefit from more intensive monitoring and/or therapy.

More information: Gemma C. Sharp et al. Distinct DNA methylation profiles in subtypes of orofacial cleft, *Clinical Epigenetics* (2017). DOI: 10.1186/s13148-017-0362-2