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Epigenetics and Orofacial Clefts: A Brief Introduction

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The term “epigenetics” is used liberally as a possible explanation for traits and conditions that do not appear to be solely genetic in origin. Since orofacial clefts (OFCs) fall into that large category, it is not surprising that the scientific literature in this area has also pointed to a potential etiologic role for epigenetics (Dixon et al., 2011).

WHAT IS EPIGENETICS?

Whereas genetic influences on our traits involve variation in our DNA sequence, epigenetic influences involve changes in how DNA is packaged, expressed, and turned into protein. The underlying DNA remains the same, but chemical modifications change levels of gene activity. These modifications can attach to the DNA itself or to the histone proteins the DNA is wrapped around. In DNA methylation, which is the most commonly studied epigenetic mechanism, methyl groups attach to DNA and may influence expression of nearby genes—often switching them off.

Although every cell in every tissue has essentially the same DNA sequence, epigenetic processes differ between cells. They play a large role in cellular differentiation by enabling a cell to express only the genes that are necessary for its function. Epigenetic modifications can last for the whole of a cell’s life and survive division, but they can also change in response to external influences. Together, this means that environmental factors might trigger long-term changes in gene activity, which in turn might influence health and disease over an individual’s life (Godfrey et al., 2011). Some evidence also suggests that epigenetic modifications to gamete DNA might enable these traits to be passed to the next generation. Although most of the DNA is stripped of methylation in early development, experiments have shown that marks can remain on certain parts of the DNA that cause aberrant methylation patterns to be reestablished during development (Greer et al., 2014). Another way in which epigenetics can be passed between generations is during pregnancy, when a mother’s environment can influence the epigenome (all of the epigenetic modifications in the genome) of her developing baby in utero.

IS EPIGENETICS RELEVANT TO OROFACIAL CLEFTS?

Epigenetic processes, particularly DNA methylation, are important in determining the structure and function of the developing embryonic tissues, so it is plausible that aberrant epigenetic mechanisms may contribute to OFCs. Although human evidence is lacking, evidence from mouse models suggests an important role for DNA methylation and other epigenetic processes in orofacial development and OFCs (Kuriyama et al., 2008; Seelan et al., 2013; Juriloff et al., 2014).

Additionally, in humans, large observational epigenome-wide studies and meta-analyses have found consistent associations between putative risk factors for OFCs and differential methylation in DNA of babies of exposed mothers. For example, maternal obesity (Sharp et al., 2015) and folate deficiency (Joubert et al., 2016a) have been linked to changes in the methylation of neonatal cord blood DNA. Through its role as a coenzyme of one-carbon metabolism, folate is directly involved in methyl group transfer in DNA methylation, which might support evidence for folate deficiency and impaired folate metabolism as risk factors for OFCs. Prenatal tobacco smoke exposure has a particularly large effect on offspring DNA methylation. A recent meta-analysis of epigenome-wide association studies from 13 cohorts (n=6685) identified more than 6000 sites near 3620 genes that were differentially methylated in relation to maternal smoking (Joubert et al., 2016b). Twenty-seven of these genes have previously been linked to OFCs, including VAX1, NOG, BMP4, and MSX1. This suggests that maternal smoking may influence offspring risk of OFC through a mechanism involving DNA methylation.
Although we are unaware of any studies investigating this, it seems plausible that epigenetic modifications associated with the development of OFCs could also directly influence longer-term outcomes; that is, the downstream consequences of having an OFC may be mediated by changes to the epigenome, and these changes may be independent of the factors that caused the OFC (Fig. 1). Observational studies have found associations between early-life exposures and differential methylation that persists in later life (Simpkin et al., 2015) as well as associations between early-life methylation and later-life OFC-associated outcomes, such as cancer (Verma, 2012).

**WHAT ARE THE IMPLICATIONS OF EPIGENETICS FOR CLINICAL PRACTICE?**

As technologies to measure epigenetic phenomena become less expensive, and the statistical tools to analyze these become more refined, the potential to use epigenetic analysis in the clinic is increasing. In line with this, two main clinical applications are emerging: (1) development of epigenetic biomarkers to predict or classify disease and (2) exploitation of epigenetic mechanisms to prevent or treat disease.

**EPIGENETIC BIOMARKERS FOR PREDICTION OR CLASSIFICATION**

Most notably in cancer research, aberrant DNA methylation is being explored as a biomarker of tumor progression for both diagnosis and prognosis (Delpu et al., 2013). One advantage of an epigenetic biomarker over a genetic one is that aberrant methylation is more common than genetic mutation. However, the unique features of epigenetic processes also present challenges in developing accurate biomarkers: (1) some epigenetic changes are cell-specific and may not be detectable in diagnostic tissues such as blood; (2) some epigenetic changes are reversible, so the timing of measurement is important; and (3) epigenetic changes can occur in response to a wide range of environmental factors and are influenced by the underlying genetic sequence, so factors such as age, sex, diet, smoking, and genotype may affect biomarker efficacy. Nevertheless, epigenetic biomarkers are showing some success as predictive tools, and it is possible that such tools may be useful in predicting or classifying OFCs or downstream consequences of OFCs. For example, if a biomarker can be measured in an accessible tissue, such as amniotic fluid, maternal blood, or chorionic villus blood, it might be a useful tool for antenatal diagnosis or classification of OFCs. Additionally, if measured at birth or early childhood, a biomarker might be useful in predicting surgical success, likelihood of scarring, or longer-term health outcomes, thus identifying groups of patients who might benefit from extra monitoring.

**EPIGENETIC MECHANISMS FOR TREATMENT OR PREVENTION**

Epigenetic studies in relevant tissue, such as lip/palate tissue collected during cleft surgery, can be combined with causal inference techniques to offer valuable insights into causation of disease and therefore biological mechanisms. Ultimately, this will help to inform intervention and prevention. As mentioned previously, epigenetic changes are reversible and can be influenced by external factors. Thus, disease-causing epigenetic mechanisms could potentially be manipulated to treat or prevent disease. For example, demethylating agents have shown some success in cancer chemotherapy, and there are current efforts to develop drugs that target epigenetic changes in specific genes (Stein, 2014). If epigenetic mechanisms are shown to have a strong causal role in OFCs, then developing prenatal therapies to alter or halt epigenetic changes may be effective in reducing incidence.

**SUMMARY**

It is biologically plausible that epigenetic changes might be involved in the development of OFCs and in OFC outcomes. Despite this, there has been very little investigation of such changes in humans. This presents exciting and promising opportunities for further research that could inform better prediction, prevention, and management strategies for clinical use.
REFERENCES


