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DIFFERENTIAL METHYLATION ANALYSIS IN CLEFT LIP AND PALATE AND ITS CONTRIBUTION TO PENETRANCE EFFECTS

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Cleft lip and/or palate (CL/P) is a common craniofacial congenital malformation, affecting 1 to 700 livebirth worldwide, with a multifactorial aetiology. Although several at-risk common alleles have been identified, they do not completely explain its high heritability (45% to 85%). We postulated that epigenetic factors as DNA methylation might contribute to this missing heritability. Using a methylome-wide association study in a Brazilian cohort (67 CL/P, 59 controls), we found 578 methylation variable positions (MVPs) significantly associated with CL/P and enriched in the "Regulation of Epithelial-to-mesenchymal transition" pathway. In an independent UK cohort (171 CL/P, 177 controls), we replicated 4 out of 11 tested MVPs. Epithelial-to-mesenchymal transition (EMT) is a key process during neural-crest cells formation as well as in palatal and lip fusion, in which cells from an epithelial state differentiate into a mesenchymal phenotype. *CDH1*, encoding E-cadherin, is a gene of importance during EMT and *CDH1* pathogenic mutations have been associated to CL/P, with incomplete penetrance (~50%). Next, we quantified *CDH1* promoter methylation levels in *CDH1* mutation-positive families with incomplete penetrance. We found methylation levels to be significantly higher in the penetrant individuals. Finally, aiming to identify individual methylation differences, we used a different approach in which we compared each CL/P vs. all controls (1 CL/P vs. 59 controls) at the promoter and gene body level. Very promising results were obtained with this analysis, which showed individual methylation variation in genes already associated to CL/P and in new candidate genes. We are now validating those results in an independent cohort and using a dcas*9-TET1* and dcas9-*DNMT3A* system for targeted demethylation and methylation respectively. Taken together, our results demonstrated the association of methylation at specific genomic sites and regions as contributing factors to CL/P and we suggest that altered DNA methylation may be a second hit contributing to penetrance.

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