Cleft Lip/Palate and Cancer: a True Connection

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Fissura Labiopalatina e Câncer: uma Conexão Verdadeira

Labio Leporino/Paladar Hendido y Cáncer: una Conexión Verdadera

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INTRODUCTION

Cleft lip and palate occurs as often as in one in every 500 to 700 livebirths. Individuals born with these craniofacial conditions appeared to have a shorter lifespan of approximately 10 years, likely due to cancer[1]. When the association between clefts and cancer was investigated, it seemed that individuals born with clefts were more often diagnosed with cancer than the general population[2,3], their unaffected parents were more likely to have cancer (particularly lymphomas and leukemia)[4], and their families were more presumably to report cancer in comparison to other families not segregating cleft lip and palate[5-8]. When the inverse relationship was investigated, it was shown that individuals who survived cancer or were being treated after a cancer diagnosis were more probable to have a family history of cleft lip and palate[9,10]. Individuals born with clefts appeared to be at least six times more seemingly to develop cancer, and their first- and second-degree relatives three times more possibly[3].

These associations are not coincidence. The likely explanation for the elevated instances of cancer in individuals born with clefts and their families is that the same gene alterations that might impact the development of the facial structures may predispose individuals later in life to cancer. The identification of these alterations is therefore of interest.

DEVELOPMENT

Mutations in the tumor suppressor gene epithelial cadherin (*CDH1*), which are correlated with gastric, breast, colorectal, thyroid, and ovarian cancers, were shown to be present in individuals born with cleft lip and palate from families segregating hereditary diffuse gastric cancer[11-15]. *CDH1* mutations have also been reported in families segregating cleft lip and palate in an autosomal dominant fashion without any history of cancer[16,17], and the accumulation of common variants in *CDH1* and two additional cell adhesion genes (*ACTN1* or actinin alpha 1, and *CTNNB1* or catenin beta 1) has been associated with cleft lip and palate[18]. *CDH1* promotes adhesion between adjacent cells during development, tissue maintenance, and tumor suppression[19]. Cell proliferation, both during development *in utero* or when cancer has started, likely is promoted by an interaction between anaphase-promoting complex/cyclosome (APC/C) and *CDH1*, which controls the expression of isocitrate dehydrogenase 3β (IDH3β). Accumulation of IDH3β accelerates G_1/S (growth/DNA synthesis) transition of the cell cycle[20]. This is important during embryology, but a problem when a tumor is growing.

When *CDH1* mutations were analyzed, their likely pathogenesis and location in the protein differed between cases of hereditary diffuse gastric cancer and cleft lip and palate. Mutations causing cleft lip and palate clustered within the linker regions between the extracellular domains of *CDH1*[21]. Differential methylation of *CDH1* in carriers of *CDH1* mutations from families segregating cleft lip and palate also suggested that altered methylation at specific genomic locations may be a second hit contributing to penetrance[22]. Another approach that have been used to study *CDH1* was to test for overrepresentation of alleles of common variants in the population in cases born with cleft lip and palate. This work unveiled that associations could be detected when more detailed clinical descriptions were used. *CDH1* was associated with unilateral right cleft lip with tooth agenesis[23]. These findings hold the promise that specific *CDH1* mutations will allow for risk assessments for hereditary diffuse gastric cancer or cleft lip and palate.

Aside from the APC/C-CDH1-IDH3β, another pathway of interest involves responses to endoplasmic reticulum-based stress signals (ER stress), typically the unfolded protein response. Serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1 (IRE1) when activated, modifies the transcription of the X-box binding protein 1 (XBP1), and XBP1 then

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upregulates ER chaperones and endoplasmic reticulum associated degradation (*ERAD*) genes to allow recovery from ER stress[24]. A common *IRE1* variant (rs196929) in a recessive form was shown to be found more often among individuals born with cleft lip and palate that had positive family history of cancer, including families reporting a specific type of cancer or multiple ones, cancer affecting females (breast or reproductive tract), or cancer affecting structures of the gastro-intestinal tract[25]. These findings suggest that a common *IRE1* variant in the population may be a marker for increased cancer susceptibility.

CONCLUSION

The ability to predict cancer continues to be of great interest and associations such as the one described here between cleft lip and palate and cancer in the same families provide new opportunities for understanding the etiology of both conditions. It also demonstrates that careful clinical descriptions and more comprehensive family histories need to be incorporated in the studies involving cancer, as well as cleft lip and palate and other craniofacial anomalies.

CONTRIBUTIONS

The author participated of all the phases of the manuscript and approved the final version to be published.

DECLARATION OF CONFLICT OF INTEREST

There is no conflict of interest to declare.

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