Journal of Advanced Medical and Dental Sciences

@Society of Scientific Research and Studies ***NLM ID:*** *101716117*

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Indian Citation Index (ICI) Index Copernicus value = 100

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Review Article

Hox genes and it's application in dentistry

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ABSTRACT:
The interruption of odontogenesis by any etiological factor may result in dental anomalies. Apart from the environmental factors, the impact of genetics in dental anomalies was found to be a factor in different levels. Many authors had questioned a common genetic defect resulting in different phenotypic conditions such as absent, malformed, malposed or ectopic teeth. Because the multidisciplinary treatment of these dental anomalies such as hypodontia, impaction etc., involves dentist's intervention, dental professional must be aware of the etiology and possible correlative conditions with dental anomalies.
Keywords Homeobox Genes; Homeotic Genes; Homeotic Mutation; Pattern Formation; dental anomalies.

Received: 16 February, 2023 Accepted: 19 March, 2023

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This article may be cited as: Senkumar L. Hox genes and it's application in dentistry. J Adv Med Dent Scie Res 2023;11(4):118-121.

INTRODUCTION

Hox genes are the homologs of the eight genes in the homeotic complex (Hom-C) of the fruit fly Drosophila. The Drosophila Hom-C genes were first identified through mutations that caused the transformation of a particular segment of the fly body into the likeness of another, hence the term homeotic from the Greek word homeo, which means similar. With the advent of molecular biology, these genes were isolated and found to encode related proteins that play fundamental roles in controlling the expression of many other genes. The Hox genes share a highly conserved DNA sequence called homeobox, which encodes a 60-amino acid DNA-binding motif, the homeodomain.[1,2] Through their ability to bind specific DNA sequences in association with cofactors, Hox proteins act as transcription factors to regulate programs of gene expression. In both vertebrate and invertebrate embryos, Hox genes encode key regulators that play fundamental roles in establishing the basic body plan of animals during development. Hox proteins provide a molecular code that specifies spatial and temporal information essential for establishing the unique properties of cells along the anteroposterior (A-P) body axis of all three germ layers. Today, we know that these homeobox (Hox) genes have been widely conserved during metazoan evolution, and they are present in organisms ranging from primitive chordates to humans. Hox genes are generally linked in chromosomal clusters as they arose by tandem duplication from a single gene. Within a cluster, all genes have the same 5′ to 3′ orientation with respect to transcription. In ancestral organisms such as amphioxus, there is a single cluster. The two rounds of genome-wide duplications in higher animals gave rise to four Hox clusters that encompass a total of 39 Hox genes present in most vertebrates, including chickens, mice, and humans. The exception are the ray-finned fishes that have seven to eight Hox clusters due to an additional round of duplication. These Hox genes are subdivided into 13 paralog groups based on the sequence similarities and position of genes in the clusters. Each cluster contains 9–11 Hox genes of different paralog groups.[3]

HOX GENE EXPRESSION PATTERN

A distinguishing hallmark of Hox clusters is the correlation between the physical arrangement of these genes along the chromosome and their temporal and spatial order of expression in the developing embryo. Genes located closer to the 3′ end of the chromosomal clusters will be expressed earlier and in more anterior domains than genes located closer to their 5′ ends. This property is known by the term temporal and

spatial colinearity and is thought to reflect the mechanisms that regulate the expression of these genes. Colinearity results in the establishment of nested domains of gene expression along the A-P body axis and generates a combinatorial Hox code used for specifying positional identities during development. In mice, transcription of Hox genes is sequentially initiated in the primitive streak and expanded anteriorly to reach rostral boundary in the neuroectoderm andmesodermduring gastrulation.[4,5] Initial establishment of Hox code is coupled with gastrulation and axial extension, which are controlled by major signaling pathways, such as fibroblast growth factor (FGF), retinoic acid (RA), and Wnt. The collinear expression of Hox genes in tissues such as the hindbrain and axial skeleton is in large part recapitulated by local cis-regulatory elements, often shared by neighboring genes. However, the precise control of the spatiotemporal domain of expression of some Hox genes may only be achieved in the context of the whole Hox cluster, indicating the presence of long-range or global regulation. For example, global control regions essential for ordered expression in limb and other tissues have been identified in the HoxD cluster. Similar global control regions for regulating expression of other clusters have not been identified. The chromatin structure and the nuclear organization of the clusters have also been implicated in the sequential activation of Hox genes. MicroRNAs have been detected in the Hox clusters, and there is evidence that they play roles in modulating the proper levels of expression of some Hox genes. Furthermore, there is evidence for translational control of Hox proteins. Hox genes and Hox proteins depend upon a wide variety of regulatory mechanisms to precisely control the spatial domains and levels of expression for their important regulatory roles in normal development.[6]

HOX GENE FUNCTION

Hox genes often act as a master regulator of developmental programs such as wing versus halter in Drosophila,but also regulate effector genes that control formation of particular tissues and organs. The DNA-binding homeodomain of Hox proteins recognizes relatively simple sequences containing an ATTA core on their target genes. This raises the issue of how specificity of target genes is achieved by different Hox proteins in a variety of developmental contexts. Some target genes have a cluster of monomer-binding sites to increase affinity and ensure proper regulation by Hox proteins. An additional layer of specificity is generated by the combinatorial interactions provided by Hox cofactors, such as Extradenticle/Pbx, Homothorax/Meis, and Prep. These cofactors physically interact with Hox proteins and cooperatively bind to unique bipartite recognition sites that allow activation of a specific set of target genes. Loss of Hox function in vertebrates and invertebrates can lead to homeotic transformations in a single tissue.[7] For example, Hoxb1 is required for the identity of rhombomere 4 (r4) and its inactivation results in transformation of r4 into an r2-like segment. However, studies using the mouse and other vertebrates as model systems have shown that genetic mutations in some of the Hox genes or changes in their expression patterns result in abnormalities in a large number of tissues. In the axial skeleton, mutations in Hox genes lead to skeletal defects such as abnormal vertebrae, fusions, and vertebral homeotic transformations. Additional abnormalities have been observed in limbs and many other organs in the mice with Hox mutations. Similar developmental defects have been observed by genetic or pharmacological manipulations that alter Hox gene expression. In some cases, the defects are much milder than expected, but genetic studies have shown that some of these Hox genes work together and can compensate for each other especially within the same paralog group. Hence, a defect in one gene may be corrected for or compensated by the activities of other Hox proteins. Consistent with the fundamental role of Hox genes in the A-P axis specification, alterations in Hox protein function or expression pattern have been linked to the evolution of animal body plans. In crustaceans, differential segmental expression of Ubx and abdA among different species is correlated with formation of different type of appendages in body segments. Furthermore, loss or misexpression of Ubx leads to homeotic transformations of segmental appendages.[8]

HOX GENES AND HUMAN DISEASES

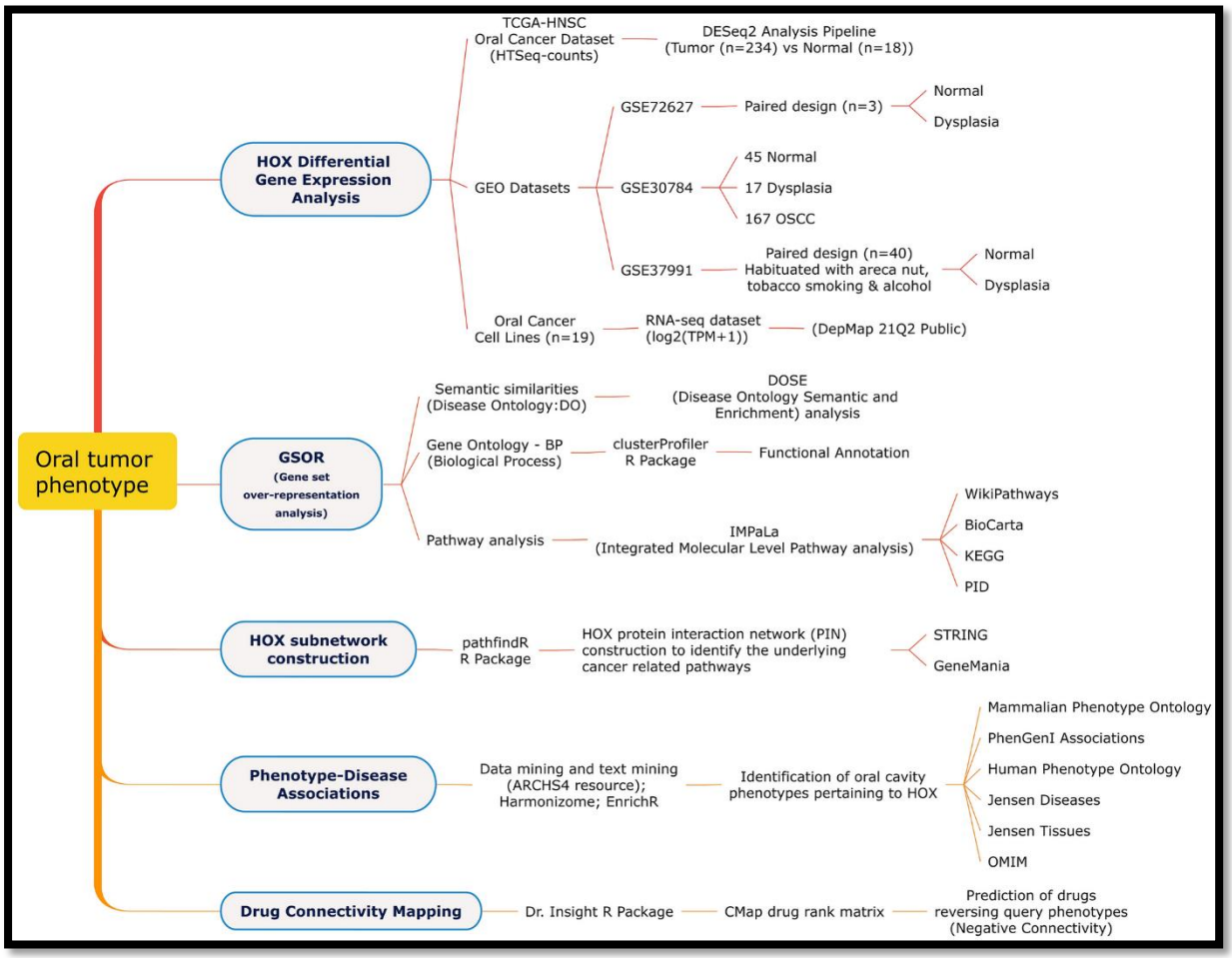
In humans, specific Hox genes have been implicated in genetic disorders affecting development of the limbs and the genitourinary tract. Several studies have suggested that Hox genes are also required for proper function of adult tissues. Specific Hox genes function together to control development of the mammary gland in response to pregnancy, whereas others may be involved in human endometrial development and implantation. In addition, genetic studies in mice have provided strong evidence for the role of Hox genes in normal hematopoiesis, such as hematopoietic stem cell renewal. In humans, deregulation of Hox genesis frequently observed in patients with leukemia. In addition, Hox genes have been found to be fused to the nucleoporin gene NUP98 in certain human leukemia, suggesting that altered transcription activity of Hox proteins underlies the pathogenesis of the fusion proteins.[9]

HOX GENES AND RELATION TO ORAL CANCER

HOX genes are well established in specifying the developmental states whose upregulation or downregulation has been noted to be involved in carcinogenesis. Our analysis showed that these deregulated HOX genes which have been described as being involved in developmental aberrations could lead to morphogenetic changes during oral

carcinogenesis. Moreover, HOX genes are epigenetically regulated via DNA methylation and altered histone modifications, which when dysregulated could potentially be driving the normal cell toward the neoplastic phenotype. Several studies have shown that deregulated HOX expression in oral cancer is either due to loss of tissue specificity or epigenetically-mediated loss of function. The regulatory role of HOX genes in determining tumor characteristics and factors contributing to oral cancer phenotype. In our analysis, HOXA2, HOXA5, HOXA7, HOXA10, HOXB2, HOXB7, HOXC6, HOXC10, HOXC13, HOXD10, and HOXD11 were differentially expressed in potentially malignant oral dysplastic lesions compared to the normal oral mucosa indicating their early involvement in the malignant transformation. (Figure 1)

Figure 1- Schematic diagram to identify the HOX genes involved with oral tumor phenotype.



HOX GENES IN ODONTOGENESIS AND TOOTH ANOMALIES

The process of odontogenesis is under the control of homeobox (HOX) genes; a number of different mesenchymal regulatory molecules and their receptors. HOX genes are classified as muscle segment (MSX1 and MSX2), distal-less (Dlx), orthodontical, goosecoid, paired box gene 9 (Pax9) and sonic hedgehog (Shh). Msx1 and Msx2 genes are responsible for the developmental position and further development of tooth buds, respectively. Dlx-1, Dlx-2 and Barx-1 genes are involved in development of molar teeth. Pax9 is a transcription factor required for tooth morphogenesis and plays a role in the establishment of the inductive capacity of the tooth mesenchyme as it is necessary for the mesenchymal expression of bone morphogenetic protein (Bmp4), MSX1 and Lefl genes. Tumor necrosis factor, fibroblast growth factor, Bmp, Shh and Wnt pathways are involved in signaling pathways of organogenesis on the 9th to 11th embryonic days to initiate tooth epithelium. Any mutation in these genes and any disruption of regulatory molecules may result in the anomaly of dental characteristics. The anteroposterior morphogenetic field concept, proposed by Butler in 1939, supports the current molecular investigations such as the determination of the interaction between a single gene and site specific orofacial expressivity. HOX genes, which play a role in oral and dental development are known to show site specific anteroposterior expression patterns. MSX1, regulator

gene in the third molar and lower second premolar agenesis, may be responsible for posterior site development. In addition to the other posterior area genes, which are Dlx-1, Dlx-2 and Barx-1, Pax9 also control the development of all of the molars. Furthermore, Neubüser et al., reported that there is an association between Pax9 transcription factor and repositioning of tooth buds on the mesenchymal level. This theory might give a clue to researchers about the genetic mechanisms of dental positional anomalies such as palatally displaced canines or different kind of transpositions. It appears that tooth agenesis, tooth size and position anomalies, which are often seen together, are the components of a complex, genetically controlled dental condition. Dental malpositions such as rotations, eruption failures and ankylosis are among other anomalies complicating this dental condition.[10,11] Currently, a dentist, probably the first to diagnose hereditary dental anomalies and malocclusion of an individual, will remain responsible for the detection of any additional defects in the same patient in order to provide the best treatment. The clinician should always keep in mind that some of those dental anomalies can coexist with certain syndromes and other family members might also have been affected. Whenever it seems necessary, a genetic consultation should be added as part of the orthodontic treatment. Finally, this interdisciplinary approach may help to reveal any risk of recurrence in subsequent generations.

CONCLUSION

Understanding the regulation and function of Hox genes and proteins will continue to provide valuable insight into how the animal body plan is established in normal development and modified during evolution and into ways of developing strategies for prevention, diagnosis, and treatment of genetic diseases. Further studies are required and the rapid progress in the field of genetics may help the clinicians to more accurately discern the environmental and genetic factors contributing to the development of dental anomalies.

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