Appraising of Genetic Inheritance in Craniofacial Complex- An Asset to Orthodontists

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Abstract

Nowadays there is an increase in number of people undergoing orthodontic treatment as their main concern is related to the discrepancy of craniofacial complex which is hampering facial aesthetics along with other functional and structural issues. As orthodontists play a vital role in transforming craniofacial complex and successful treatment depends on appropriate diagnosis of the cause. Genomics is the science associated with identification of various discrepancies in craniofacial complex and allows orthodontists to better understand the genetic inheritance and its pattern which is affecting the development of craniofacial complex. A scrupulous knowledge of underlying genes also helps in determining phenotype-genotype relation which in turn aids in diagnosing craniofacial biology and evolution. Hence, this review aims to provide contemporary correlation between genetics and its importance in orthodontics.

Keywords Craniofacial anomalies, malocclusion, genetic inheritance, orthodontics

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INTRODUCTION

Craniofacial anomalies and dental malocclusions are conditions which include derangement leading to disproportion of facial structures and functions. Orthodontic treatment plays a significant role in correction of different anomalies related to craniofacial complex.

As there is high existing frequency of various craniofacial discrepancies around one-third of population needs treatment. It is important to consider genetic inheritance and its pattern to understand the cause of underlying aetiology. Genomics is the science which is concerned with role of genes associated with structure and function in development of an individual and also helps in identifying inheritance pattern of growth involved in development of a complex.[1]

Genetic inheritance is transmission of characters from parents to offspring which

consists of genes or alleles to control a trait or a character. The 'father of modern genetics', Gregor John Mendel described different modes of inheritance and put forward the basic law of genetics. The changes in the physical-chemical nature of genes was studied by Thomas Hunt Morgan known as gene mutations. On the basis of these ingenuity different modes of inheritance have been introduced include monogenic, polygenic and multifactorial.

The studies showing hereditary patterns reveal the DNA sequence found within the genes are involved in controlling of craniofacial development. Further, Familial studies/pedigree studies and Twin studies have been carried out which explains the contribution of genetic factors in growth and development. A study by Grant Townsend et al., revealed that genes have more influence on tooth size, shape, arch width length and dental traits. Based on population studies Familial and Twin studies it is evident that genes play an important role in craniofacial complex and also involved in dental malocclusion[2]

A study by Young et al reported that underlying aetiology depends not only on genotype but also on the final phenotype which is established based on interaction between environmental, epigenetic and genetic factors. Hence this enhances the genotype-phenotype relation which further helps in enhancing contributing factors to observe various changes in craniofacial complex.[3]

Understanding the importance of genetics for treatment planning in orthodontics practice is necessary. Once the inheritance factors are determined, the dentist can differentiate environmental and epigenetic factors and plan the treatment accordingly. An insight of several studies have been presented below which contributes to different genetic factors essential for orthodontists to plan treatment.[4]

EFFECT OF GENETIC INHERITANCE

Craniofacial anomalies are developmental problems. Rapid advances in molecular genetics have helped in providing evidence based information especially through hereditary factors. There has been substantial literature regarding Familial and monozygotic/dizygotic twin study samples showing interlinkage between the genetics and craniofacial complex. It is well known that many craniofacial abnormalities including dental malocclusion are results of genes interaction with environmental factors.[5]

The studies concerned with heritability pattern showed that DNA sequence found within the genes involved in craniofacial development are called homeobox genes, these genes includes homeotic gene group(HOX)-(HOXA-D), muscle segment (MSX-1 and MSX-2), distal less genes, sonic hedgehog genes(SHH), orthodenticle gene (OTX), PTHR genes, and T-box transcription factor genes. These homeobox genes will act during embryonic development and helps in regulation of craniofacial development.[6]

Craniofacial discrepancies are often accompanied by alteration in genes during developmental process. Chromosomal aberrations or deficiencies lead to different types of deformities. These craniofacial disturbances include Dysostosis, Treachers Collin syndrome, Pierre Robin syndrome, Osteogenesis Imperfecta, Amelogenesis Imperfecta, Dentinogensis Imperfecta, Hemifacial Microsomia, Apert Syndrome, Pagets Disease, Cherubism and Cleft lip and Palate. The complexity of aetiology depends upon the fundamental understanding of the genomics. The following is a brief assessment of various craniofacial anomalies and dental malocclusions.[7]

CRANIOFACIAL ANOMALIES

The alteration of genes during the process of genetic inheritance and development of a complex leads to craniofacial discrepancies. The abnormal development

of brachial arches results in deformities and deficiencies. Genetic syndromes with different inheritance pattern associated with craniofacial complex are:

Treachers Collin Syndrome

It is also known as mandibulofacial dysostosis. It shows autosomal dominant transmission caused treacle gene(TCOF1). It includes underdeveloped zygoma, absence cheek bones, ear anomalies and micrognathia.

Pierre-Robin Syndrome

It shows autosomal recessive inheritance and caused by deficiency of TGFB3-transforming growth factor. It is characterised by micrognathia. A study showed that X-linked form is also existing.

Osteogenesis Imperfecta

It is an autosomal dominant inheritance and also known as Brittle bone diseases or Lobstein syndrome. It is due to deficiency of COL1A1 and COL1A2(type 1 collagen). It is characterised by blue sclera and multiple fractures.

Amelogenesis Imperfecta

Autosomal dominant disorder caused by AMELX, ENAM, and MMP20 genes. It includes mottled or pitted enamel with teeth easily prone to breakage.

Dentinogenesis Imperfecta

It shows autosomal dominant inheritance caused by DSPP type-1 gene, it affects both primary and permanent dentition. It characterised by discoloured or opalescent teeth with wear of dentin in teeth.

Hemifacial macrosomia

It exhibits autosomal dominant or recessive pattern. It includes facial asymmetry, hypoplasia, ear anomalies and mandibular deficiency. It is concerned with defect in brachial arches.

Cleft lip and cleft palate

It is associated with multifactorial inheritance trait, many developmental and environmental factors are concerned with the cause of cleft lip and palate. Around 10-15% cases are familial and 80% are isolated cases. It was found that transforming growth factor alpha(TGFA) is also associated with cleft lip and palate. Another study, showed the cause of cleft lip and palate is due to mutations in MSX1, MSX2 and BMP4 genes. However, nonsyndromic cleft lip and palate is associated with autosomal dominant inheritance and X-linked recessive forms. It is characterized non fusion of maxillary and lateral nasal processes hampering with delayed eruption, delayed tooth and face development and problems with speech, feeding and aesthetics.

Other craniofacial malformations including Cliedocranial Dysplasia, Apert, Pfeiffer and Crouzon syndromes shows autosomal dominant mode of inheritance caused by mutation in RUNX-2(core binding factor) and fibroblast growth factor receptor(FGFR-2) which are characterized by craniosynostosis, hypoplasia and mandibular prognathism.[8,9,10]

DENTAL MALOCCLUSIONS

Malocclusion is deviation from what is defined as normal occlusion. These can be skeletal or dental which can be detected by analytical methods which include morphological and genotypic analysis. There are evidences from familial and twin studies that genes and environmental factors contribute significantly for the establishment of malocclusions.

CLASS II

Heritability studies have been carried out to investigate the role of inheritance in class II malocclusion, based on exclusive studies it is observed that class II follows polygenic and multifactorial inheritance pattern in which there is a correlation between immediate family members and siblings. Although class II division 1 and class II division 2 are different clinically but they follow almost same pattern of inheritance. The study by Marcovic et al,gave strong

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genetic evidence for class II where he determined concordance-disconcordance rates of monozygotic and dizygotic twins, he demonstrated intra and inter pair comparison of 114 class II division 2 malocclusions and 48 twin pair and 6 triplets were formed from which he concluded that 100% monozygotes were concordant and 90% dizygotes were disconcordant. Cephalometric and longitudinal studies have showed that class II can appear in primary dentition, which exhibits retruded mandible and severe overjet than class I. Recent studies have also shown that class II malocclusions are influenced by muscular and neuromuscular system. Several published reports have shown the familial occurrence of class II including twin studies and family pedigrees.[11]

CLASS III

Class III malocclusion is characterised by short maxilla and long mandible also known as mandibular prognathism. Many studies have shown that primary cause of mandibular prognathism is based on polygenic hypothesis. The study by Schulze and Weise demonstrated the concordance in monozygotic twins was six times more than dizygotic twins for class III malocclusion, later a polygenic multifactorial threshold model was put forward by Edward to explain the mode of inheritance in class III. The imbalance between the skeletal structures result in deficiency of maxilla and excessive growth of mandible which depends on the wide range of genetic and environmental factors contributing to the development of class III malocclusion.[12]

Though the famous pedigree study of Hungarian/Austrian dual monarchy by Strohmayeret alobserved the detailed analysis of Hapsburg family line and concluded that mandibular prognathism was based on autosomal dominant trait, this study did not provide sufficient information, hence considered as an exceptional study. After this many familial studies have been suggested to demonstrate autosomal dominant trait with incomplete penetrance. Litton et al. studied analysis of the literature and analysed group of family members and siblings with class III, both autosomal dominant and autosomal recessive traits were ruled out. However, after the introduction of polygenic model with explanation of familial distribution it has been suggested that different mode of inheritance might be present in different populations resulting in Class III malocclusion.[13]

PHENOTYPE-GENOTYPE CORRELATION FOR CRANIOFACIAL DEVELOPMENT

To determine the inheritance pattern it is important to apprehend the relation between phenotype and genotype as the development of craniofacial complex depends on interaction between genetic, environmental and epigenetic factors. The role of these factors are further explained by advances in phenomics and genomics.

Phenomics is concerned with the quantification of phenotypes produced over the course of development in response to other genetic mutation and environmental factors. Phenotyping can be done by various morphometric analysis which includes facial morphology, tooth morphology (size and shape), two-dimensional digital imaging, three dimensional imaging, etc. these approaches has provided an insight to determine the evolutionary changes in phenotype of an individual.[14]

On the other hand, genotype is regulated by different levels, depends on genetic variation and epigenetic factors. Genome wide association studies(GWAS) includes analytical framework for identifying the genetic variation responsible for craniofacial development. Linkage analysis in families also helps in identification of the underlying trait**.** Adhikari et al. showed

association of four different genomic traits with three nose related and with chin retrusion in 6000 subjects of latin American descent.[15]Lesile et al. identified functional variants for 1409 cleft lip and palate trios in three genes: NOG, FGFR2 and PAX7, these variants contributed an insight on genetics using targeted sequencing and functional analysis.[16] Although GWAS are useful in identification of various gene variants, there are few limitations associated with statistical analysis. Further, gene or allele can be detected through association studies, population genetic studies, linkage analysis studies, animal model experiments and functional genomics studies. To retrieve full information from genome studies underlying molecular analysis should be combined at genetic and epigenetic levels.[17] The elucidation of phenotype-genotype is dependent on many different levels, in addition to genetic variation, distance and epigenetic regulators. Moreover, gene has more significant effect on craniofacial growth and development which also plays a major role in leading to changes on phenotypic level. While progress has been made in establishing noteworthy phenotypic methods to anthropology and to detect the pattern of inheritance.[18]

Phenotype-genotype correlation is challenging because of complexities in craniofacial morphology arising due to genetic factors as these factors are dependent on the interaction between gene-gene and gene-environment. Further multidisciplinary investigations have been carried out in context to genetic variation and facial or dental phenomics in human population and animal models to overcome the complexities present in phenotype-genotype relation.

CONCLUSION

As reviewed by the article, the growth and development of craniofacial complex is dependent on genetic and environmental factors. The discrepancies seen are mostly related to polygenic and multifactorial inheritance, hence it is important to understand the genetic behaviour for appropriate diagnosis of aetiology which has direct effect on the outcome of the treatment. There has been tremendous progress in genomics in orthodontics, however there are many complexities associated with the genetic architecture and to date, many multidisciplinary models/studies are helping in determining gene variations and environmental factors in process of controlling craniofacial anomalies and malocclusions for improvement in treatment planning. The field of genomics link research findings to the clinical applications and the alliance between orthodontists and researchers will further help in advancement in this field.

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