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REVIEW ARTICLE

Genetics in an orthodontic perspective

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Abstract

Genetics is the science concerned with the structure and function of all genes in different organisms. Malocclusion is a manifestation of genetic and environmental interaction on the development of the orofacial region. It is important to consider genetic factors to understand the cause of existing problems, which has influence the outcome of treatment. The review aims to provide information to the dental practitioner and orthodontist on basics of genetics and common disorders with gene impairments. These genetic factors in turn have an impact on outcome of orthodontic treatment.

Introduction to Basics of Genetics

Growth is the combined result of interaction between several genetic and environmental factors overtime.[1] Malocclusion is a manifestation of genetic and environmental interaction on the development of the orofacial region. It is important to consider genetic factors to understand the cause of existing problems, which influences the outcome of treatment.[2] Genetics is the science concerned with the structure and function of all genes. Austrian monk, Gregor John Mendel was known as "father of modern genetics." The studies by Mendel, on garden pea, he put forward basic laws of genetics, namely law of segregation, law of independent assortment, and law of dominance. In 1903, Sulton and Boveri proposed the "Chromosomal Theory of Inheritance."[2] Thomas Hunt Morgan studied the arrangement of genes along chromosomes. In 1953, Watson and Crick demonstrated the structure of DNA molecule. Solenoid model of chromosome was proposed by Finch and Klung.[2,3]

The cell is the basic unit of any living body. It is made of organelles such as cell wall cytoplasm, endoplasmic reticulum, ribosomes, mitochondria, and nucleus. The nucleus has threadlike structures of different length and shapes called chromosomes. The number of chromosomes in every cell of an organism is constant, and it changes from one species to another. All humans normally have 23 pairs of chromosomes as 22 pairs of autosomes and one pair of sex chromosomes. Females have two X chromosomes, while male has one X- and one Y-chromosome. Gene is the smallest structural and functional unit of inheritance. Segment contains information required for the synthesis of a polypeptide. Genes have the ability to determine traits and undergo identical replication and mutation. Genome is the entire genetic content of a set of chromosomes present within a cell or organism. The genome varies from one individual to another in terms of single base changes of DNA as single-nucleotide polymorphisms (SNPs). The main use of human SNP map will be to determine the contribution of genes to diseases. Transcription is the process by which information is transmitted from DNA to the messenger RNA at the initial stages of replication and translation is the process in which the genetic information is actually converted into proteins. Transcription

to protein synthesis is the basic function in genetics. Patterns of genetic transmission may be as repetitive, discontinuous, and variable.[2-5]

Gene mutations are known as a change induced by certain agents in the composition of base pairs of DNA which results in altered protein synthesis and altered expression of certain traits. Mutagens are ionizing radiation, chemicals, certain viruses, and high temperature. On the basis of genes involved, these may be point mutations or chromosomal mutations which are inherited or transmitted by different modes of inheritance as monogenic, polygenic, and mmultifactorial. In monogenic pattern traits develop due to the influence of a single gene. This monogenic inheritance will occur by autosomal dominant, recessive, and X-linked recessive transmission.[4-6]

Heritability patterns are studied by familial studies/pedigree studies and twin studies. Twin studies revealed that genetic factors have more influence on occlusal traits, on arch width length tooth size, shape, and genetic contribution in growth and development. Genetic disorders may be numerical and structural. A homeobox is a DNA sequence found within the genes which is involved in the regulation of development of craniofacial development. These are called as homeobox genes and these will play a major role in embryonic development. The differences between organisms can be explained by the different modes of action of the homeobox genes. Those particular interest in craniofacial development includes muscle segment (MSX1) and MSX2, distal-less genes, homeotic (HOX) gene group - (HOXA-D), bar class homeobox genes, paired box genes, sonic hedgehog genes, orthodenticle gene (OTX), goosecoid gene, PTHR genes, and T-box transcription factor genes. Homeobox genes have the properties such as transcription factors and DNA-binding homeodomine as these will act in sequential zones of the embryo in the same order that they occur on the chromosome.[2,4-7]

In 1836, Kussel studies revealed that both skeletal and dental malocclusions can be transmitted. Different dentofacial disturbances of genetic origin include dysostosis of craniofacial structures, osteogenesis imperfect, amelogenesis imperfect, dentinogenesis imperfecta, micrognathia, macrognathia, Paget's disease of bones, cleft lip and cleft palate, dental and skeletal malocclusions, Marfan's syndrome, Gardner syndrome, Down's syndrome, Cherubism delayed eruption of teeth, hypodontia, macrodontia, bimaxillary protrusion, bimaxillary atresia, and abnormal overjet and overbite. Dysostosis is a defective normal ossification of fetal cartilage. This condition includes craniofacial dysostosis, mandibulofacial dysostosis, cleidocranial dysostosis, and orodigitofacial dysostosis.[6-11] Some of the important genetic disorders with orthodontic implications are discussed in brief.

Craniofacial Dysostosis

It is also known as Crouzon syndrome which is first branchial arch syndrome, and it is transmitted by autosomal dominant inheritance. Clinical features include hypoplastic maxilla with relative mandibular prognathism, low-set ears, hearing loss, exophthalmos, and hypoplastic maxilla. A cause may be a mutation in fibroblast growth factor receptor gene (FGFR2 and FGFR3) and deletions of the short arm of chromosome 11.[12]

Treacher Collins Syndrome

It is also known as mandibulofacial dysostosis and is characterized by a generalized lack of mesenchymal tissue. It shows autosomal dominant transmission. The clinical features include absence of cheekbones downward slanting of eyes, micrognathia, ear anomalies, underdeveloped zygoma, and left palate. Causes may be mutations in specific genes - TCOF1 (POLR1C and POLR1D). TCOF1 gene codes for treacle protein which controls neural crest cell migration during craniofacial development.[13]

Cleidocranial Dysplasia

It is also known as cleidocranial dysostosis and mutational dysostosis. It shows autosomal dominant mode. Clinical features include missing of clavicles, prognathic mandible with hypoplasia of maxilla, delayed ossification of midline structures, delayed closure of fontanelle, bones and jaws which are underdeveloped, supernumerary teeth, failure to the eruption of permanent teeth, and bulging of the forehead. It is caused by mutation in core-binding factor of *RUNX2* gene (subunit alpha-1 located in short arm of chromosome 6) which encodes transcription factor required for osteoblastic differentiation, leading to the above clinical features.[14]

Hemifacial Microsomia

In this condition, tissues which seem to have been derived from the first branchial arch are deficient. Duplication of the gene OTX2 induces hemifacial microsomia. There may be a hemorrhage from the stapedial artery around the 6th week of intrauterine development, and tissues that were in development at that time are damaged by the hemorrhage and the subsequent reorganization so that tissues are smaller or fail to develop completely. Clinical features show hypoplasia or absence of the mandibular condyle, and a part of the ramus of the mandible and the masticatory muscles is deficient, and the external, middle, and inner ear may fail to develop.[2,4,15]

Apert Syndrome

The syndrome is characterized by malformations of the skull, face, hands and legs. It is a first branchial arch syndrome, affecting the maxilla and mandible. Disturbances in the development of the branchial arches in fetal development create widespread effects. Clinical features include craniosynostosis, syndactyly, high-arched palate, and crowded teeth. Apert syndrome is due to autosomal dominant pattern due to a defect on the FGFR2 gene on chromosome 10.[4,15]

Orodigitofacial Dysostosis

It is an inherited syndrome including defects of oral cavity, hands, and face. Clinical features show bifid tongue, missing or malpositioned teeth, depressed nasal bridge, anomalies of hands and mental retardation. Mode of inheritance is Type I - X-linked dominant and Type II - autosomal recessive. This shows female predominance.[1,2,7,15]

Pierre Robin's Syndrome

This syndrome is characterized by micrognathia and bird face. It is caused by deficiency of transforming growth factor – TGFB.3 and due to environmental factors like extreme flexion of neck during fetal life.[2,4,16]

Osteogenesis imperfecta

It is also known as brittle bone disease or Lobstein syndrome. The inheritance pattern is autosomal dominant mode. Clinical features include blue sclera, multiple fractures, bones prone to fracture, hearing loss, and bulging of eyes. Defective connective tissue formation and deficiency of Type-1 collagen can be seen. Due to mutation in COL1A1 and COL1A2 genes.[4,5,16]

Amelogenesis Imperfecta

It is a disorder of tooth development caused by mutations in AMELX, ENAM and MMP20 genes. Clinical features show discolored pitted or grooved enamel often, prone to rapid wear and breakage of teeth.[5,16]

Dentinogenesis imperfecta

It is a genetic disorder of bone development, caused by mutation in DSPP Type I gene and shows autosomal dominant mode of transmission. Clinical features include discolored teeth and wear of teeth. Both primary and permanent teeth are affected. It is caused by mutation in DSPP gene – Type II and III. Type I is associated with osteogenesis imperfecta.[5,17]

Micrognathia

It is abnormality featuring a small-sized lower jaw due to underdevelopment of mandible in infants. Clinical features shown are chin deformity, dyspnea, and abnormal teeth alignment. It is notable in due totrysomy.[13,18] Turner syndrome and Treacher Collins syndrome.[17,18]

Macrognathia

Macrognathia or megagnathia is a condition wherein abnormally large jaws are found. Clinical features include mandibular protrusion when the mandible is affected, and gummy smile when maxilla is affected. The ramus of mandible forms steep angle with body along with excessive condylar growth causes chin to appear prominent. Macrognathia is seen in pituitary gigantism, and acromegaly.[17,18]

Paget's Disease of Bone

It is a disorganized bone remodeling with excessive bone resorption and formation. Clinical features show affected bone to be weaken resulting in pain, misshapen bones, fractures, and arthritis in the joints. Causes are mutations in SQSTM1 and receptor activator of nuclear factor (RANK): SQSTM1 protein for the regulation of osteoclast and RANK Kb membrane protein for the activation of osteoclasts.[4,17-19]

Cleft Lip and Cleft Palate

It is a non-fusion of body's natural structures that form before birth and is isolated or associated with syndromes. Non-fusion of maxillary and lateral nasal process leads to clefting in the lip while non-fusion of median palatine processes leads to clefted palate. Clinical features include delayed tooth development and delayed eruption, hypodontia or hyperdontia, smaller facial dimensions, problems with feeding, speech, and socialization. Causes are mutations in MSX1, MSX2, FGFR1, FGFR2, and BMP4. MSX1 and MSX2 genes involved in both syndromic and non-syndromic clefts.[20,21]

Dental and Skeletal Malocclusions

Most of the malocclusions occur due to the discrepancy between skeletal and dental dimensions in the jaws. Studies showed that arch size dimensions have a familial tendency. Tooth variations are influenced by environmental factors. A heritable pattern of malocclusion was supported by Peck *et al*. Class II Division 1 malocclusion shows polygenic and multifactorial inheritance. By Harris (1975) cephalometric studies, it is revealed that mandible is significantly more retruded than in Class I patients, and length of the body and overall mandibular length reduced with a higher correlation between the patient and his immediate family.[8,16,17,19,22]

Class II Division 2 malocclusion shows autosomal dominant inheritance with simultaneous and synergistic influence of genetic and environment. Class III malocclusion runs in families with a famous example - "Habsburg jaw." Clinical features show retrognathic maxilla. Autosomal dominant mode of inheritance as well as eenvironmental factors also causes this malocclusion.[1,23] Genetic factors include vascular endothelial growth factor, insulin-like growth factor-1, collagen Type II, growth hormone receptor, and transforming growth factor. Environmental factors include hypoxia, ionizing radiation, nutrition deficiency, metabolic and hormonal disorders, enlarged tonsils, nasal blockage, and posture.[24,25]

Syndromes Linked to Malocclusion

The common Syndromes or genetic disorders associated with delayed tooth eruption are amelogenesis imperfecta, osteogenesis imperfect, cherubism, down's syndrome, cleidocranial dysplasia, Gardner's syndrome, and dentin dysplasia. Gene, parathyroid hormone receptor 1 mutation is a causative factor for primary

failure of eruption. Tooth number, size, and position are also genetically influenced which is revealed by different studies.[9-11,26,27] The down's syndrome is due to trisomy 21. Clinical features include physical growth delays, erruption characteristic facial features, and intellectual disability.[1,19,21,28]

Gardner's syndrome also known as familial colorectal polyposis which shows autosomal dominant mode of transmission and clinical features includes multiple impacted teeth, multiple supernumerary teeth, multiple jaw osteomas with cotton-wool appearance, and odontomas. The syndrome is caused by mutation in the APC gene located in q arm of chromosome 5.[1,2,4,11,28]

A genetic role for orthodontic tooth movement, influencing the remodeling, is a clear possibility. The potential for relapse exists when the functional and developmental aspects of growth clinically altered to a physiologically imbalanced state. Studies revealed that local osteoprotegerin transfer inhibits the relapse of orthodontic tooth movement.[18,29]

Root resorption is the result of contribution by multiple genetic and environmental factors. Genetic enhancement of fracture repair and healing of an experimental segmental defect by gene therapy (adenoviral transfer of the BMP-2 gene) are proved. Human genome project was initiated in the mid-1980 s to characterize the human genome and to reveal complete DNA sequence.[28,30]

Genome mapping is the process of finding the location of genes on each chromosome. It is a critical step in identifying the genes involved in a genetic disease. Once a disease gene is accurately located, we can determine its DNA sequence and study its protein product. Gene cloning and therapy have been underway since the latter portion of the 20th century which is useful for medical field.[28]

Conclusion

The pattern of growth and development is typically the result of an interaction between multiple genetic and environmental factors over time. Thus, the malocclusion seen in most of the instances is of polygenic/multifactorial cause. It is important to consider genetic factors in orthodontics, to understand the cause of existing problem, which may have influence on the outcome of treatment. Malocclusions with a genetic cause are less amenable to treatment.

Although most of the above conditions require the multidisciplinary team management, dental malformations such as cross-bites, crowding, underdeveloped maxilla, mandibluar retro and prognathism, and missing and impacted teeth, patients may initially present to dental clinic for their primary care and relief. An understanding of these abnormalities is necessary for the dental team to make the appropriate referrals to insure that the patient receives the best available care. The orthodontist can be an integral part of the multidisciplinary team.

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