The role of genetic/inherited factors in the craniofacial abnormalities

What is genetics?

Genetics is defined as the science concerning with the inheritance of a trait, whether normal or abnormal and if there is any environmental interaction with its inheritance.

What is genome?

Genome is the entire genetic content of the set of chromosomes present within a cell of an organism or it is a genetic mapping of an organism having genetic information contained in the deoxyribonucleic acid (DNA).

The human body is formed from billions of cells each contains 46 chromosomes. It was found that the human genome is made up of a double helix of DNA comprising 3.3 billion linearly arranged chemical nucleotide base pairs named adenine (A), thymine (T), cytosine (C), and guanine (G) bases. Base A was found to pair with T in the DNA double helical structure while C base pairs with G.

Moreover, there are about 30000 gene codes for protein synthesis that perform most body functions (Figure 1).

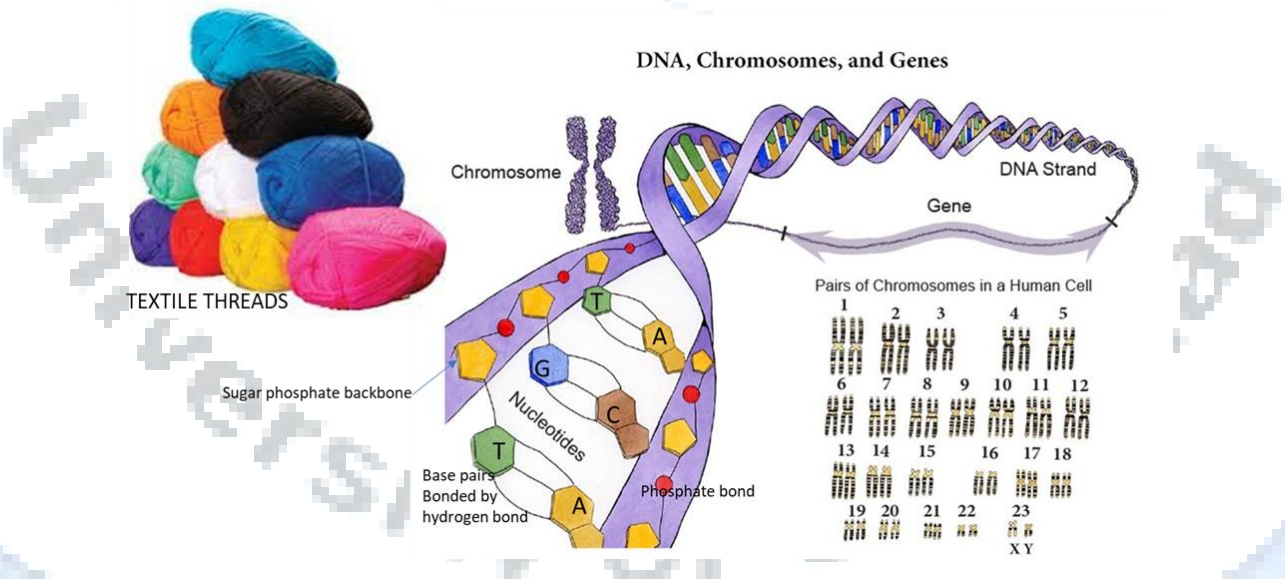


Figure 1: Human genome protein base pairs (A=T, C=G) bonded by weak hydrogen bond, sugar molecules form backbone on both sides attached by phosphate bonds forming a structure resembling a step ladder which undergoes a condensed and multiple complex coiling to form a chromosome.

Chromatin is the macromolecule comprising the DNA, RNA and protein which result in formation of chromosomes within the nucleus.

Genes are segments on the DNA encoding the hereditary information necessary to code the formation of proteins. Proteins are necessary to determine the characteristic features of an organism.

The functions of the genes are: 1- maintaining the specificity of the trait, 2- transmission of the characters from parents to offspring and 3- synthesis of proteins.

Therefore, genes are considered as the smallest structural functional units of inheritance or the most basic and functional unit of heredity. Each gene has a specific position (locus) on the chromosomal map (Figure 2).

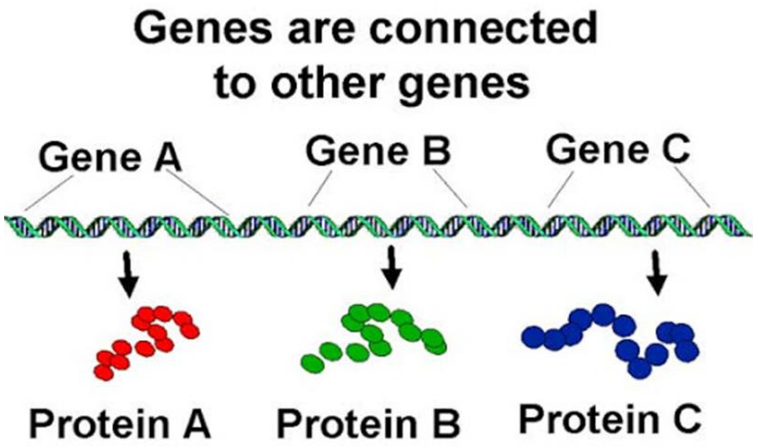


Figure 2: Different genes function in production of polypeptide chains that express different traits.

Alleles

Are defined as genes at the same locus on a pair of homologous chromosomes. Then, one allele is carried out from each parent. These alleles are responsible for the variations and uniqueness of every individual. When both members of a pair of alleles are identical, the individual is homozygous for that locus (TT or tt), whereas if the two alleles at a specific locus are different, then the individual is referred to as heterozygous for that locus (Tt) (Figure 3).

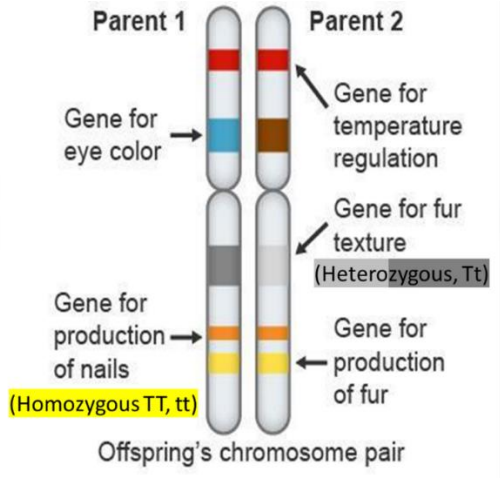


Figure 3: Homo- and heterozygous alleles

Locus/Loci

Within the human genome, every gene resides in a specific location referred to as a locus. The term locus/loci is used when describing a single genetic region or location.

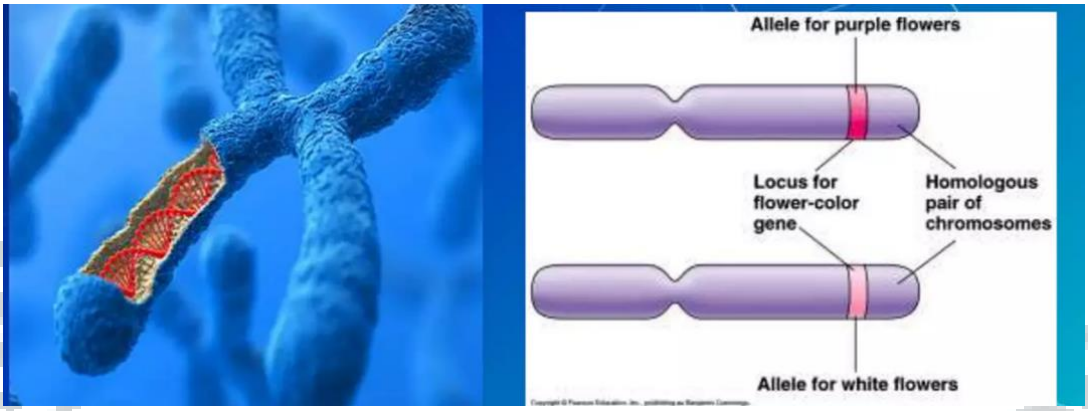


Figure 4: Locus or loci of color trait

Autosomes and sex chromosomes

Human cell normally has 22 homologous pairs of autosomal chromosomes. Each pair comprises one from mother (***maternal***) and the other from father (***paternal***) chromosomes called autosomes (Figure 5).

In addition, one pair of sex chromosomes is present. Females have 2 X (XX) chromosomes while males have one X and one Y chromosome (XY).

Chromosomes are different in lengths having 50 to 250 million base pairs in each.

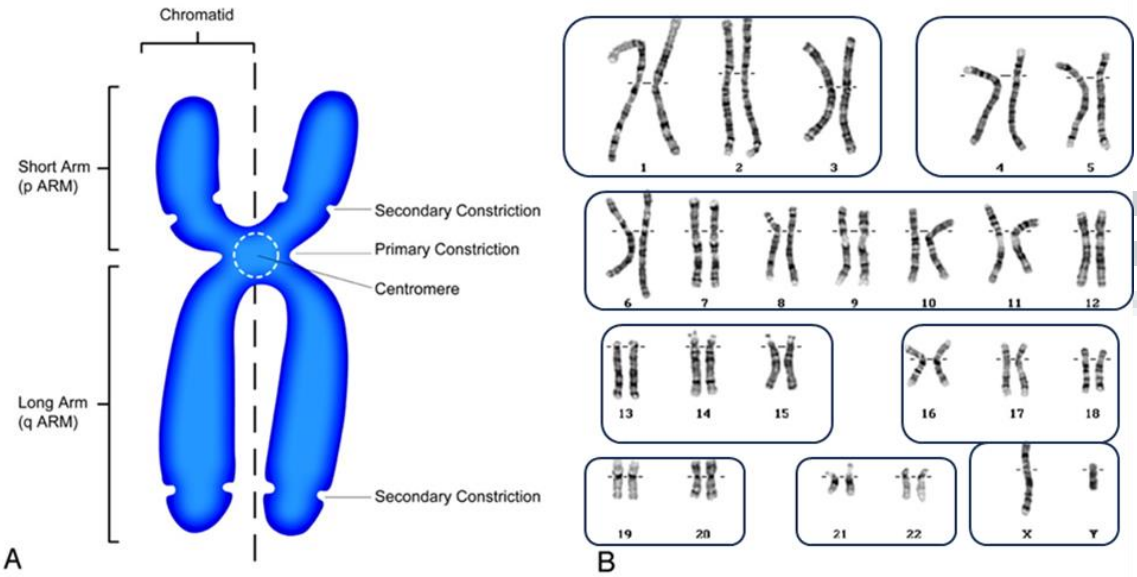


Figure 5: A, Schematic drawing of a human chromosome in metaphase of the cell cycle. Note the shorter arm p and the longer arm q joined at centromere. B, Normal male karyotype showing the 23 pairs (22 autosomes and 1 pair sex chromosomes) forming a total of 46 arranged in decreasing order in 8 groups based on size and shape.

Karyotype

Is the laboratory photographic image to look for numbers or structural abnormalities of chromosome complement of an individual.

Genotype

Is the set of genes of an individual that does not change in individual lifetime in general. Genotype can also be defined as the genetic constitution of an individual and may refer to specified gene locus or to all loci in general (Figure 6).

Phenotype

Is the sum of all the observable physical characteristics of an individual. The characteristics of an individual have developed because of the interaction of the

individual`s genotype and epigenetic or environmental factors in or around the individual over a period of time.

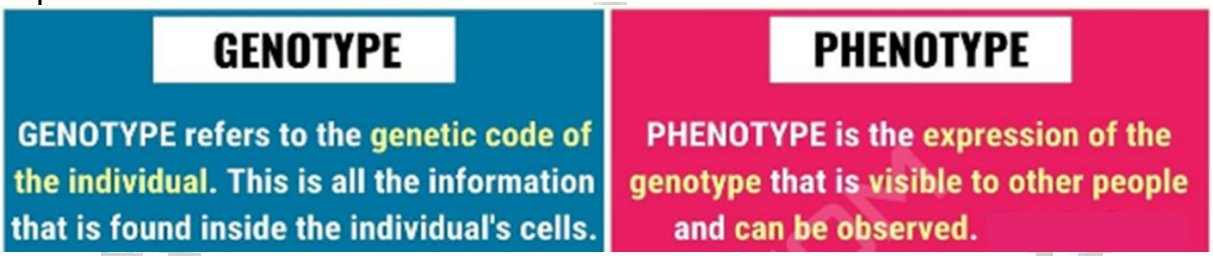


Figure 6: Genotype vs phenotype

These factors include diet, diseases, drugs, smoking, stress, impaired nasal respiration or tongue dysfunction.

The individual`s phenotype is not only morphological but also physiological and psychological characteristics and properties.

Epigenetic factors

These are environmental factors which have the ability to result in the same genes being expressed differently in different organisms. Therefore, the change in DNA will not be in the linear sequence but in the expression and properties of gene products of proteins.

E.g. obesity is determined genetically but can be expressed differently in different individuals, if some of them have diet control regimes and other have not.

How is genetics implicated in malocclusion?

A phenotype is generated by the summation of the effects arising from an individual's genotype and the environment in which the individual develops over a period of time. For this reason, in the presence of any anomaly, the morphological characteristics, such as skull structure, jaw length and volume and sagittal jaw relationships are assessed. Therefore, the aim of orthodontic treatment is to exert a therapeutic influence on the phenotype.

Hence, the greater the genetic proportion of the anomaly, the more difficult is to achieve therapeutic influence. Whereas, the more environmental factors are involved in

the anomaly, the easier it is to treat it. An example is the skeletal class III where genetics plays the major role in its development.

The severity of the phenotype depends not only on the presence of genetic, epigenetic, and environmental factors, but also on their interaction over time. For the above example the treatment of skeletal class III might be easier in children than in adults.

How is malocclusion inherited?

Malocclusion characteristics could be inherited as a trait.

A trait is a particular aspect or characteristic of the phenotype, e.g., number of teeth, arch length and arch width. The traits can be of three types:

i. ***Monogenic traits*** develop because of the influence of a single gene locus. It is either autosomal dominant type, autosomal recessive type, or X-linked traits.

ii. ***Polygenic traits*** that result from complex interaction of multiple genes.

iii. ***Multifactorial traits result*** from interaction of multiple genes, as well as environmental factors.

How can malocclusion trait be transmitted?

Malocclusion can be transmitted by one of the following modes:

(i) Repetitive traits

The recurrence of a single dentofacial deviation within the immediate family and in the progenitors. The same is repeatedly seen generation after generation, e.g. long mandible in Hapsburg Royal Family (Figure 7)

(ii) Discontinuous traits

Is the recurrence of malocclusion trait reappearing within the family over several generations but not continuously. This trait is seen in the family tree but not in all generations. E.g. facial clefts

Figure 7: Repeatedly inherited long mandible in Hapsburg Royal Family

(iii) Variable traits

The occurrence of variable expression of different but selected types of malocclusion within several generations of the same family. E.g. Missing lateral incisor in some siblings but not in others.

Penetrance vs Expressivity

Penetrance is the frequency of gene effect. Incomplete penetrant gene shows an expected phenotype in a proportion of individuals (appears in some people but not in others). Whereas, when a gene is completely penetrant, it is always expressed.

However, expressivity refers to the severity of gene expression in different individuals that could be in varying degrees (Figure 8). So, the affected persons in a single family may show varying degree of disease severity. E.g., osteogenesis imperfecta shows varying degrees of severity in different persons within the same family extending from only multiple bony fractures, bony fractures combined with dentinogenesis imperfecta or in severe cases even associated with hearing loss.

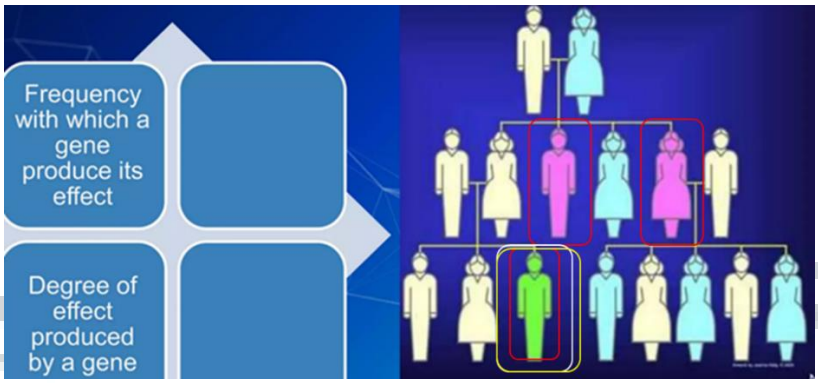


Figure 8: Penetrance vs expressivity. Incomplete penetrant gene and highly expressive resulting in changing the phenotype totally.

Gene expression (Transcription + Translation)

In order genotype to be exhibited as a phenotype, information from DNA inside the nucleus is transmitted via mRNA through a process called transcription at initial stage of replication, then from the mRNA to the factory of the proteins in the ribosomes where the information is actually translated into protein synthesis which appear as a phenotype such as structure or function (Figure 9).

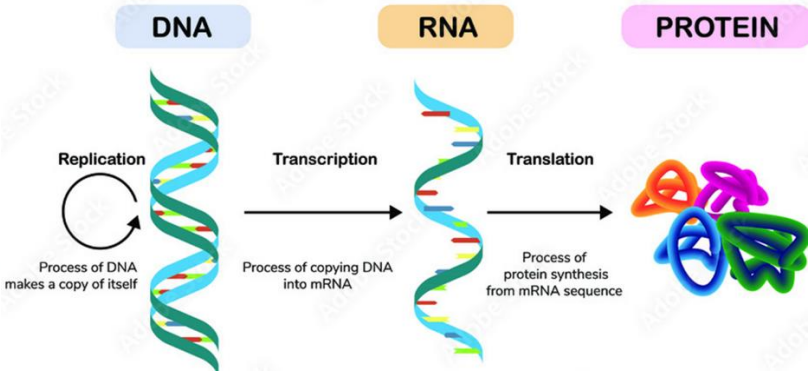


Figure 9: Gene expression by transcription vs translation

Methods of Studying Heritability of Malocclusion

The best evidence in establishing the relative contribution of genes and environment in the development of malocclusion can be offered by the following studies:

1- Twin studies (Figure 10)

A- Monozygotic twins: The identical twins develop from single fertilized ovum. They are identical in genetic makeup and sex, i.e. genotype is identical, then their difference is only attributed to environment.

B- Dizygotic Twin: develop from two separately fertilized ova at the same time. Dizygotic twins share only 50% of their total gene complement, then the differences between them are due to both environment and genetic makeup.

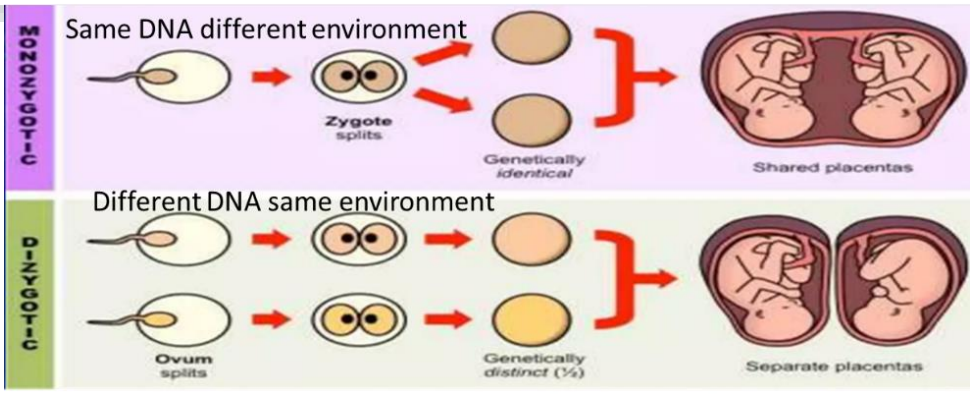


Figure 10: Monozygotic and dizygotic twins

2- Familial Studies/Pedigree Studies

This is by constructing family trees to study the nature of heritability of traits in which males are denoted by squares and females by circles and by noting dominant and recessive traits in the family (Figure 11).

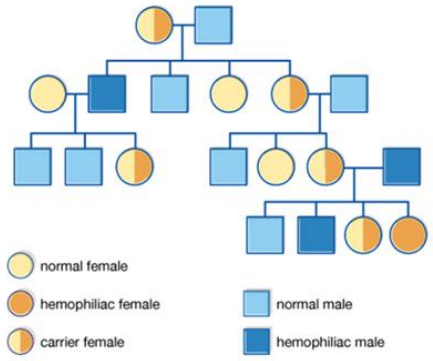


Figure 11: Family tree of hemophilic patient

3- Inbreeding studies

Studying the recessive and dominant traits with families who experience marriages of relatives.

Concordance and discordance

If a particular character is present in both members of twin pairs, they are said to be concordant. However, if only one member expresses the trait, they are said to be discordant. E.g., in cleft lip and palate (CLP) (Figure 12), studies found that the monozygotic twins have concordance rate 35%, whereas dizygotic twins have only 5%.

This could reflect the role of genetic factors in this craniofacial anomaly. The higher the concordance rate, the more significant the genetic contribution and the higher the heritability of the cleft.

A B

Figure 12: (A) Concordant pair with CLP phenotype. (B) Discordant twin one with CLP and another with cleft lip only.

Gene mutation

Is any structural or numerical alteration in the DNA base pairs leading to change in protein synthesis and hence resulting in body structural and functional anomalies (Table 1). Therefore, mutation could be visible, detrimental, or lethal.

Mutagens are the factors inducing the mutation. They could be ionizing radiation, chemicals, drugs, or viruses.

Table 1: Examples of mutation in gene numbers

Mutation	Cause
Polyploidy	Additional set of chromosomes
Monosomy	Missing single autosome
Trisomy	Additional single autosome
Klinefelter syndrome	Additional X (XXY) (Figure 13)
Turner syndrome	Missing X (X0Y) (Figure 13)

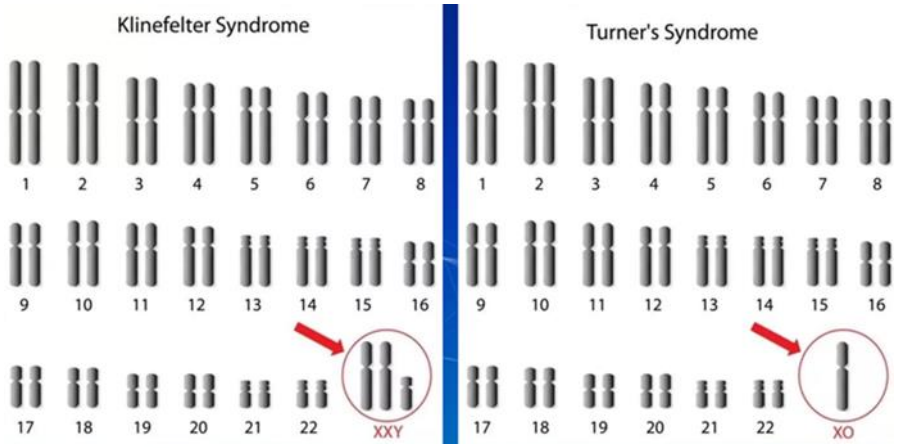


Figure13: Klinefelter and Turner syndromes

Moreover, a structural disorder in the basic composition of the chromosome is called structural mutation. It is either deletion, duplication, translocation, or inversion of a portion of chromosome.

Genome Wide Association Study (GWAS)

This is an approach used in genetics research to associate specific genetic variations with particular diseases. The method involves scanning the genomes from many different diseased people and looking for genetic markers that can be used to predict the presence of a disease.

Single nucleotide polymorphisms, frequently called SNPs (pronounced /snips/), are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block (nucleotide). In Figure 14, a SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T).

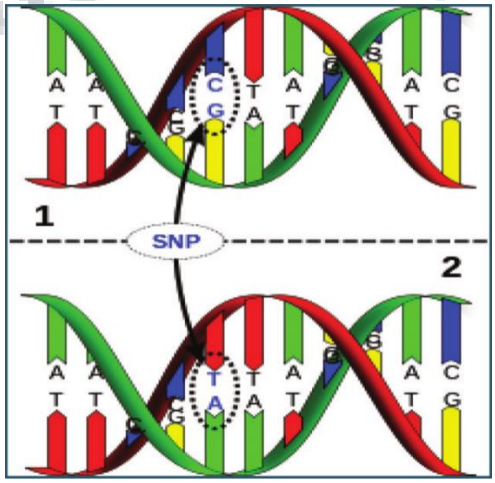


Figure 14: Replacement of protein bases at a SNP may represent presence of a particular disease.

Heritability of malocclusion

Several studies have shown that skeletal malocclusions are more influenced by genetics whereas dental malocclusions are more often due to environmental factors.

This is because the genetic estimate of skeletal anomalies is higher than those of dental such as tooth position, number, and size. Various familial and twin studies indicate that class II division 1 and class II division 2 malocclusions are multifactorial (interaction of both genetic and environmental factors) while class III malocclusion is heavily influenced by genetic.

Heritability of class II

Class II division I malocclusion (Figure 15)

appears to have a polygenic/multifactorial inheritance.

- A smaller mandible than class I and overall mandibular length reduced.
- A higher correlation between the parents and their immediate family (grandparent, ground children and siblings).

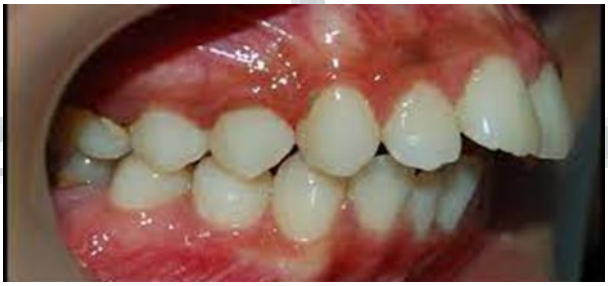


Figure 15: Class II div1 malocclusion

However, environmental factors, such as tongue pressure, digit sucking habit can also contribute to Class II division 1 malocclusion.

Class II Division 2 Malocclusion (Figure 16)

- Exhibits high genetic influence and is often considered as a genetic trait.
- Familial occurrence has been evidenced in twin and triplet studies and in family pedigrees.

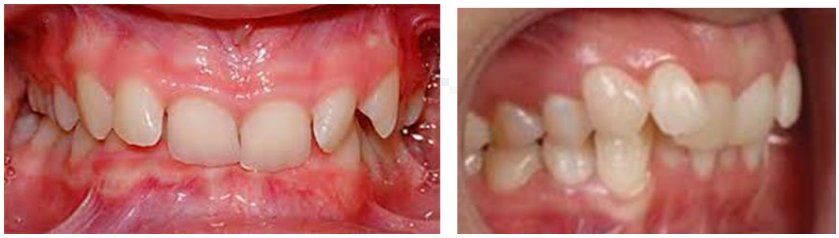


Figure 16: Class II div2

Heritability of class III

A true skeletal Class III (Figure17) with mandibular prognathism often genetically runs in families. The most famous example of a genetic trait in humans passing through several generations is probably the pedigree of the so-called "Hapsburg" This was the famous mandibular prognathism demonstrated by several generations of the Hungarian/Austrian Empire.

Figure 17: Class III malocclusion

However, environmental factors, such as enlarged tonsils, nasal blockage, premature loss of permanent molars, and trauma can also cause a habitual Class III. This means that the genetic factors appear to be monogenic influence in some families and multifactorial in others (polygenic complex).

Heritability of local dental anomalies

Tooth Size

- Twin studies have shown that tooth crown dimensions are strongly determined by heredity.
- Hypodontia of the third molar, second premolar and lateral incisors show a familial tendency and fits polygenic models of inheritance (Figure 18).

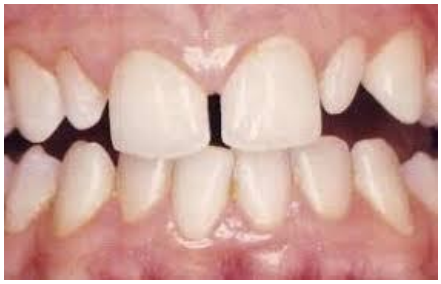


Figure 18: Hypodontia of lateral incisors

Teeth number

Supernumerary teeth, most frequently seen in premaxillary regions, also appears to be genetically determined. E.g. mesiodens are more commonly present in parents and siblings (Figure 19).

Missing maxillary lateral incisor which is next to third molars often exhibits familial occurrence.

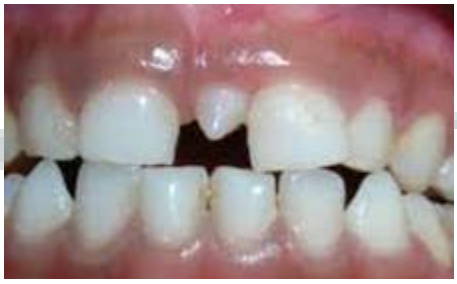


Figure19: Mesiodense

Abnormal Tooth Shape

Abnormalities in lateral incisor region varies from peg shaped to microdontia to missing teeth, all of which have familial trends, female preponderance and association with other dental anomalies (such as missing teeth, ectopic canines, transposition), suggesting a polygenic aetiology. Carabelli trait also appears to be strongly influenced by genes (Figure 20).

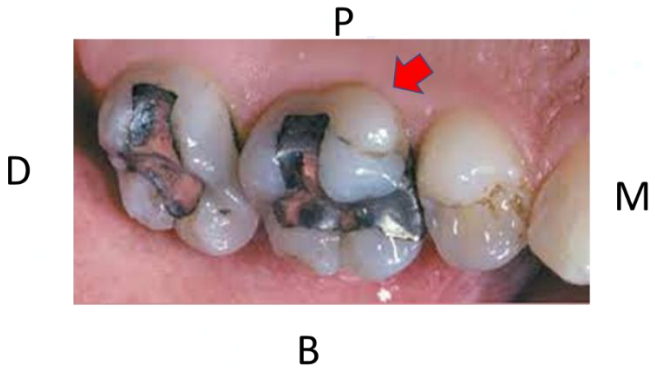


Figure20: Cusp of Carabelli

Ectopic Maxillary Canine

Palataly ectopic canines (Figure 21) have an inherited trait, being one of the anomalies in a complex and genetically related dental disturbances, often occurring in a combination with missing teeth, microdontia, supernumerary teeth and other ectopically positioned teeth.

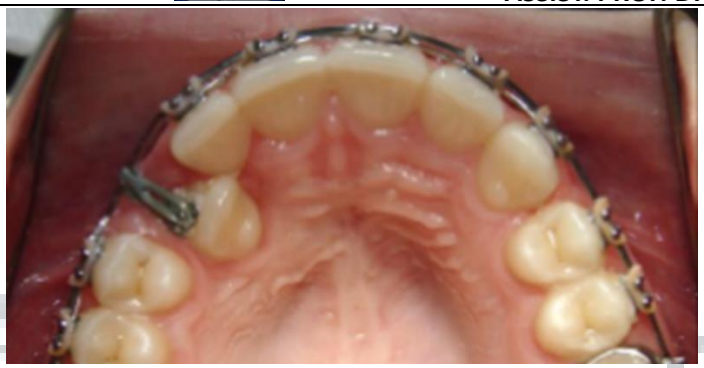


Figure 21: Palataly erupted canine

Submerged Primary Molars

Primary molars, commonly submerged teeth, especially in mandibular arch are genetically determined (Figure 22).

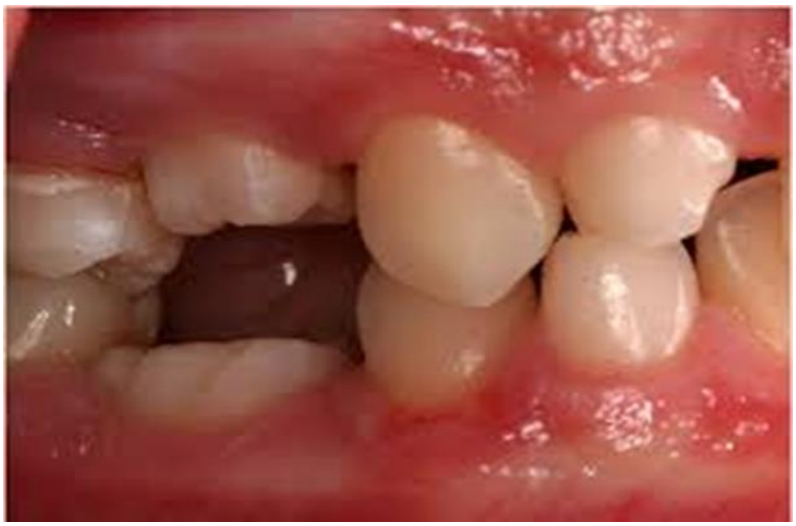


Figure 22: Submerged upper and lower primary right molars

Soft tissue heritability

Soft tissue morphology and behavior have a genetic component and they have a significant influence on the dentoalveolar morphology.

For example, in class II division 1, a short upper lip and high lip level with flaccid lip tone will favour proclination of upper incisors Figure 23).

Figure 23: Lip incompetence due to short and flaccid upper lip

It is thought that the external matrix (lip and cheek morphology and behavior are strongly genetically determined, while internal matrix (tongue posture and behavior) can be influenced by both genetic and environmental factors.

Genetic basis of Relapse in orthodontic

Heredity of the occlusal characteristics, jaw size and positioning, soft tissue structure and abnormal habits may contribute to unwanted forces that tend to move back the treated dental arches into the original malocclusion.

Heredity of External Apical Root Resorption

External Apical Root Resorption (EARR) (Figure 24) is defined as a 1-3mm spontaneous reduction in root length even without undergoing orthodontic treatment. There is evidence that 7-13% of people have EARR of maxillary central incisors as a multifactorial trait due to genetic and environmental factors.

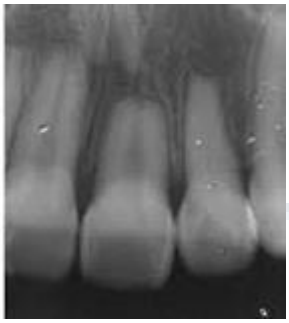


Figure 24: External apical root resorption of maxillary incisors

Butler's Field Theory in heritability of malocclusion

Butler stated that mammalian dentition can be divided into several developmental fields including molar/premolar field, canine field, and incisor field.

Within each developmental field, there is a key tooth, which is more developmentally stable and on the distal side of this key tooth, teeth within the field become

progressively variable. This means that dental variability manifests itself strongly in distal than mesial direction.

Examples:

Within molar/premolar field, third molar is more prone to variation than first molar (Figure 25 A), while in premolar field there is a higher frequently congenital missing/agenesis of second premolar than first premolar (Figure 25 B).

In the canine field, especially in maxillary arch, canine can be impacted or ectopically erupted (Figure 25 C). However, in the incisor field the lateral incisor is considered less developmentally stable than central as it could be in peg-shape or even congenitally missing (Figure 25 D).

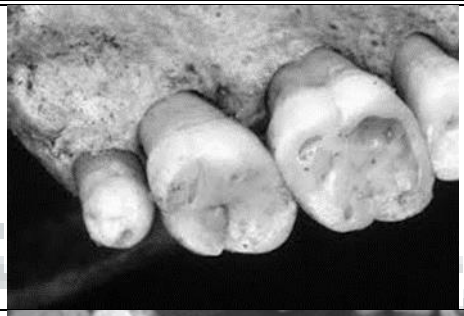
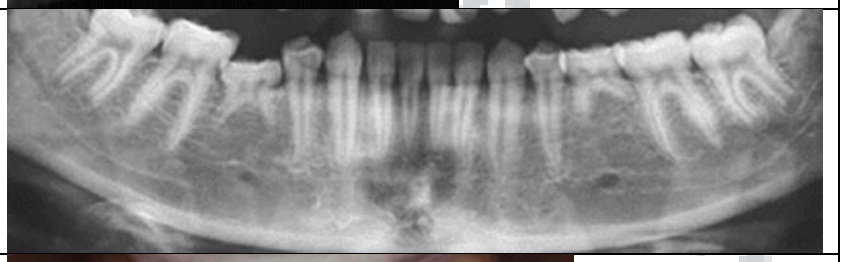
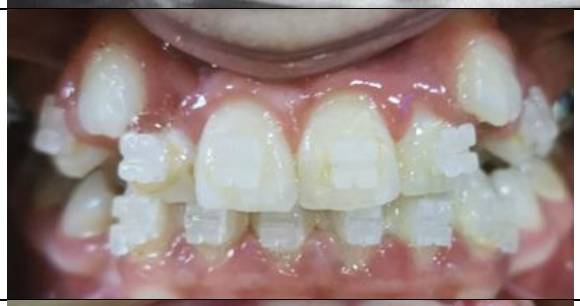
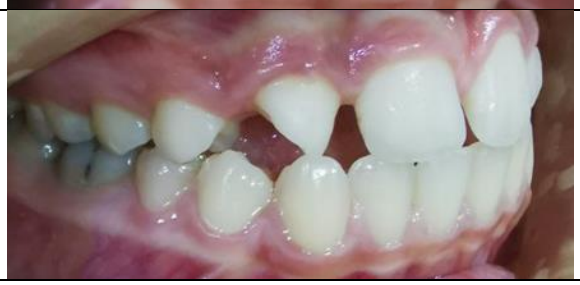
A. Third molar is more prone to variation than first and second molars	
B. Agenesis of lower second premolar	
C. Buccally malposed/ ectopic canines	
D. Agenesis of lateral incisor	

Figure 25: Field theory of Butler, who claimed that there are 4 developmental fields: molar, premolar, canine and incisor fields. Within each filed dental variability manifests itself stronger in distal than mesial direction.