The heritability of malocclusion

Why is genetics important?

- Medicine – understand the genetic basis of thousands of genetic disorders (cancer, heart disease etc.).
- Bioscience research – molecular genetics techniques are used to understand the molecular basis of numerous cellular mechanisms.
- Biotech/pharma- molecular genetic/biology techniques used to create new drugs.

Introduction and terminology

What is genetics?

- **Genome**

Individual's genome is the full amount of genetic information inherited from both parents. Typically, it is distributed among the haploid set of chromosomes in the cell nucleus. Humans are diploid organisms (2N) having 46 chromosome (two genomes), with one haploid (N) set of chromosome (23 chromosome: one genome) coming from the egg and another haploid set coming from the sperm. This information is encoded by ~3.2 billion nucleotide base pairs (bps), comprised of adenine (A), thymine (T), Cytosine (C) and guanine (G).

- **Chromosome**

Chromosome is the vehicles of genetic information, which consist of DNA and associated proteins; localised in the nucleus of eukaryotic cells. One of the two arms of a chromosome is labelled by the letter p and the other arm is labelled by q. The cells of each species have a characteristic number of chromosomes, bacterial cells normally possess a single chromosome; potatoes have 48 chromosomes; fruit flies have eight chromosomes; pigeon cells possess 80 chromosomes; human cells possess 46 chromosomes constituting 23 homologous pairs: 22 pairs of autosomal chromosomes and 1 pair of sex chromosome (XX or XY). The two chromosomes of a homologous pair are usually alike in structure and size, and each carries genetic information for the same set of hereditary characteristics (An exception is the sex chromosomes). Most cells that carry two sets of genetic information are called diploid. However, not all eukaryotic cells are diploid: for example, reproductive cells (eggs, sperm) have a single set of chromosomes and called haploid. A haploid cell has only one copy of each gene.

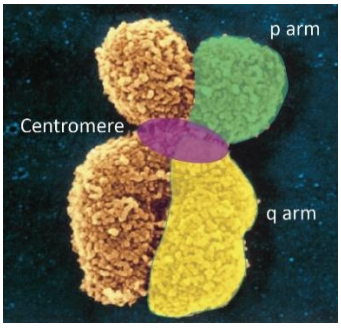

Figure 1: Chromosome parts.

- **Deoxyribonucleic acid (DNA)**

DNA is a hereditary molecule where genetic information is encoded. It consists of two polynucleotide chains wound around each other in clockwise direction. The two chains are antiparallel (opposite polarity); the two strands are oriented in opposite direction.

Nucleotides DNA is typically a very long molecule and is therefore termed a macromolecule. Within each human chromosome is a single DNA molecule that, if stretched out straight, would be several centimetres in length. In spite of its large size, DNA has a quite simple structure: it is a polymer chain made up of many repeating units linked together. The repeating units of DNA are called nucleotides, each comprising three parts: (1) a sugar, (2) a phosphate, and (3) a nitrogen-containing base. DNA contains four nitrogenous bases: adenine (A), cytosine (C), guanine (G), and thymine (T), and the sequence of these bases encodes genetic information. The sugar-phosphate backbones are on the outside and the bases oriented toward the central axis. A always bonds with T and G bonds with C. The specific pairing, A-T and G-C, called complementary base pair; the nucleotides sequence in one strand dictates that of the other. If one chain has the sequence 5'-TATTCCGA-3', then the opposite antiparallel chain must bear the sequence 3'-ATAAGGCT-5'

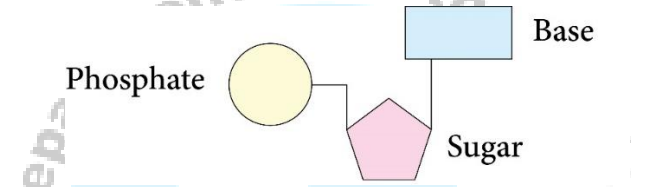

Figure 2: DNA chemical structure.

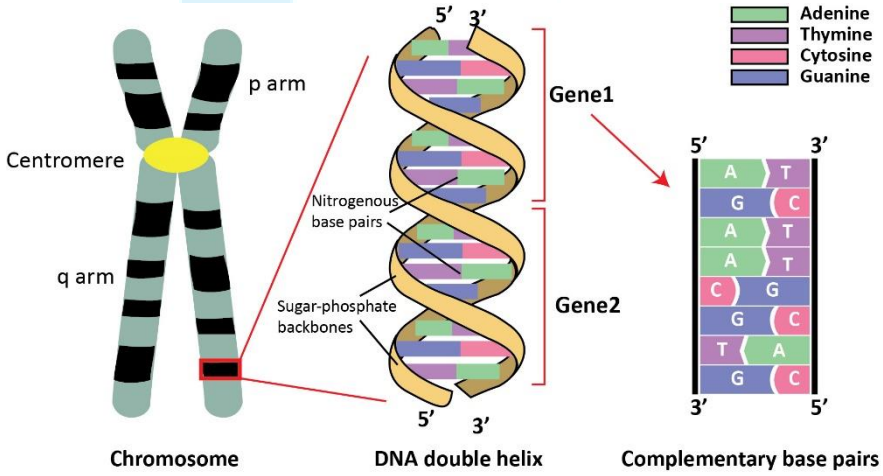

Figure 3: Double helix model for DNA.

- **Gene**

Gene is the functional unit of heredity; consist of specific sequence of information that provides the instruction for making a unique protein or a set of proteins. It is located at specific part of a chromosome, the location or address for any gene within a geneome is called its locus (plural loci, referring to the physical location of more than one gene). Human genome is comprised of 25,000 genes (accounting only ~ 2% of the entire genome), average gene length ~ 3000 bps of information.

- **Gene vs allele**

Alleles are different forms for the same gene, via specific natural variation in DNA sequence; they occupy the same locus or position on the chromosome. Accordingly, specific gene at a locus can vary among individuals or homologous chromosomes in the same individual.

For example, if a gene on a particular chromosome encodes a characteristic such as hair colour, another copy of the gene at the same position on that chromosome's homolog also encodes hair colour (each copy is called an allele). One of them might encode red hair and the other might encode blond hair. Thus, most cells carry two sets of genetic information.

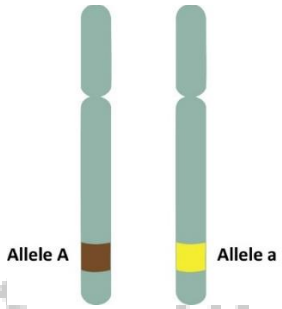

Figure 4: Alleles.

What is Genotype

Genotype is defined as the genetic constitution of an individual. It may refer to specified gene locus or to all loci in general. It refers to the alleles for both copies of a given gene; It is considered homozygous when composed of identical alleles (e.g. INS^{A}/INS^{A}**)** and heterozygous if of different alleles (e.g. INS^{A}/INS^{B}**)**.

What is Phenotype

Phenotype is an observable trait or set of traits (structural and functional) of an individual produced by the interaction between its genotype and the environment. A phenotype may be visible or not readily visible but measurable such as blood type and enzymes (molecular characteristic). The contribution of environment varies. Sometimes it is great, but in others it is non-existent. Individuals with the same genotype can have different phenotypes and individuals with the same phenotype may have different genotypes.

Pedigree analysis

One technique used by geneticists to study human inheritance is the analysis of pedigrees. A pedigree is a pictorial representation of a family history, essentially a family tree that outlines the inheritance of one or more characteristics, dominant or recessive and to show the chance of being affected or carrier.

When a particular genetic trait or a disease is observed in a person, a geneticist often studies the family of this affected person by drawing a pedigree and the affected individual is called a proband. Males in a pedigree are represented by squares, females by circles. A horizontal line drawn between two symbols representing a man and a woman indicates a mating; children are connected to their parents by vertical lines extending below the parents. Persons who exhibit the trait of interest are represented by filled circles. A Roman numeral identifies each

generation in a pedigree; within each generation, family members are assigned Arabic numerals, and children in each family are listed in birth order from left to right.

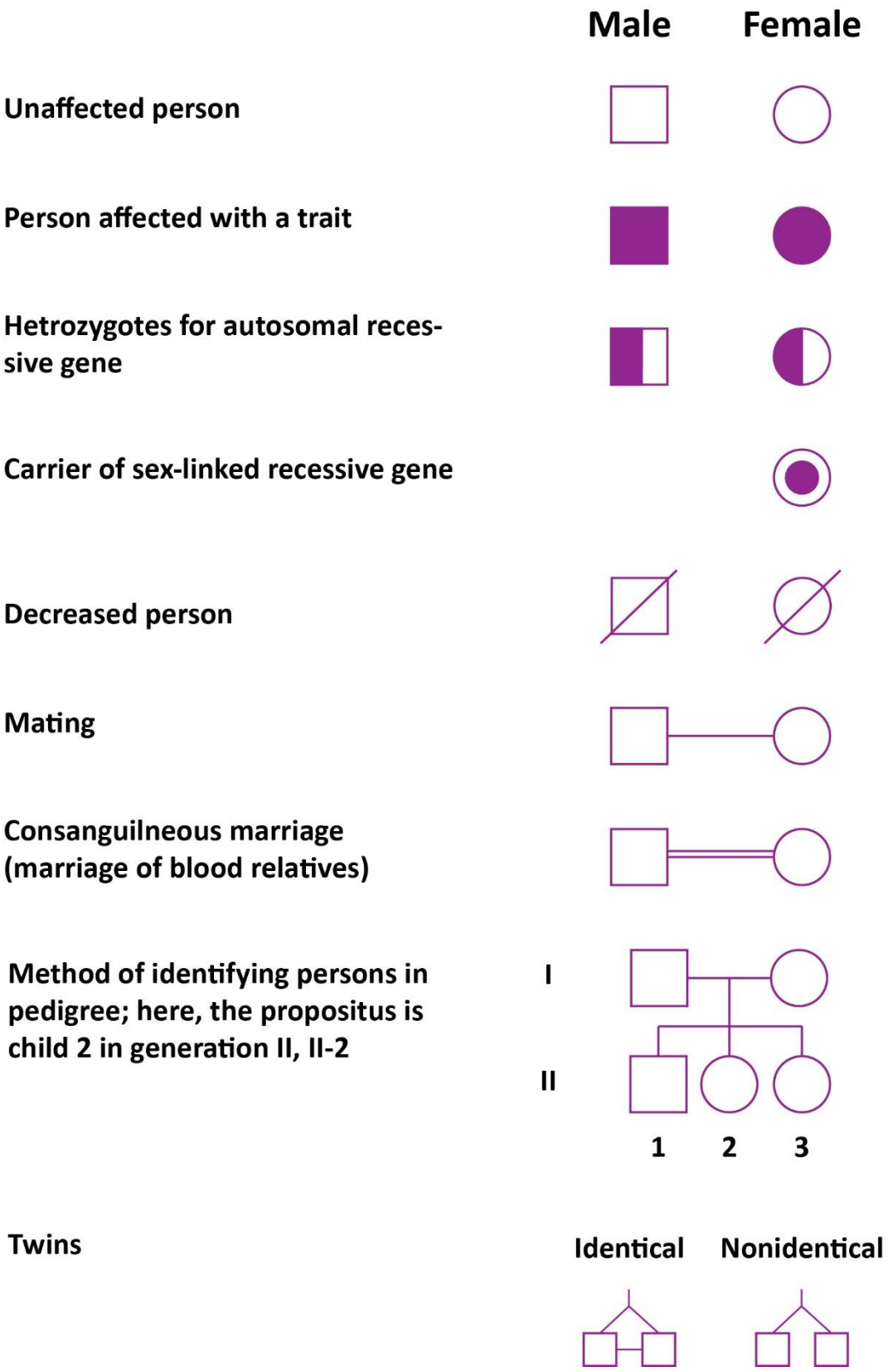

Figure 5: The symbols commonly used in pedigrees.

Heritability of malocclusion

Describes how the genetic information is passed down one generation to the next.

The trait is a particular aspect or character of phenotype, e.g. number of teeth, arch length and arch width. Syndrome is a combination of traits that occur together in non-random pattern that is different from the usual pattern. Depending on the genetic influence on traits, the traits can be considered to be of three types:

i. Monogenic traits (Mendelian). Traits that develop because of the influence of a single gene locus.

ii. Polygenic traits (complex or common). Traits that are resulted from complex interaction of multiple genes.

iii. Multifactorial traits. When polygenic traits are influenced by environmental factors along with multiple genetic factors, meaning they are influenced by the interaction of multiple genes, as well as environmental factors.

Autosomal dominant trait or syndrome – if the gene locus is located on one of 22 autosomal chromosome pairs and the trait or disease manifests itself when the affected person carries only one copy of the gene responsible, along with one normal allele, then the individual is heterozygous for that allele. However, the affected individual could be homozygous for the responsible gene allele. The mode of inheritance of the trait is called autosomal dominant.

Autosomal recessive trait or syndrome – if the production of the trait or syndrome does not occur when only one copy of a particular allele is present at the locus on a pair of autosomes, but does occur when two copies of that particular allele are present at the locus of a pair set of autosomes. Two copies of the defective gene are required for expression of the trait. The parents are heterozygous.

X-linked (recessive) trait – recessive genes on X chromosome. Express themselves phenotypically in males as if they were dominant genes because a male usually only has one X chromosome (hemizygous). A male with the genotype is affected in the pedigree.

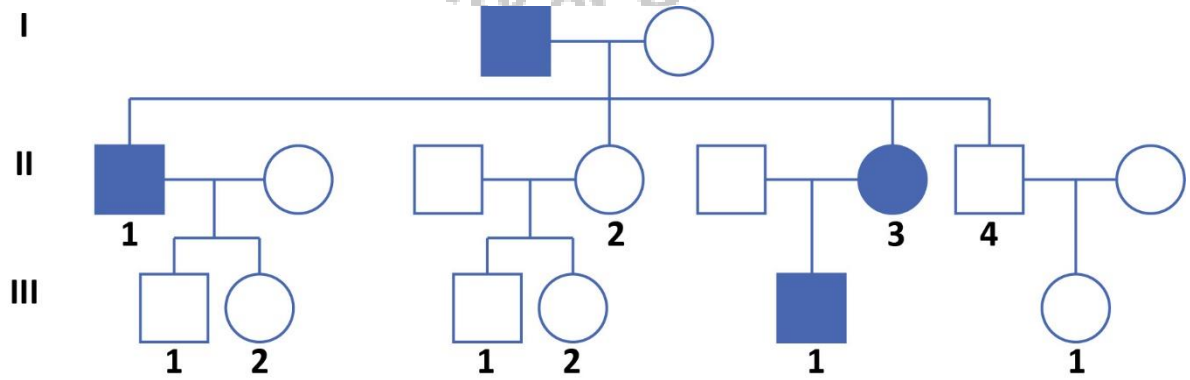

Figure 6: Autosomal dominant trait

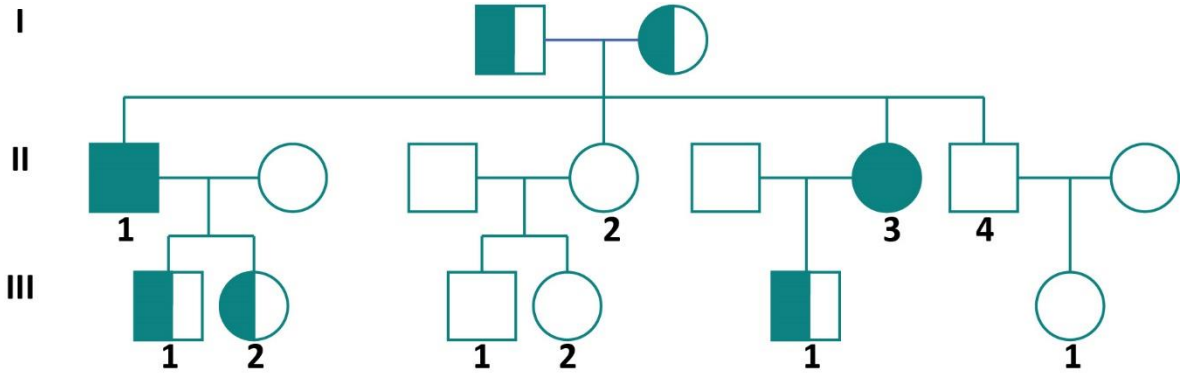

Figure 7: Autosomal recessive trait.

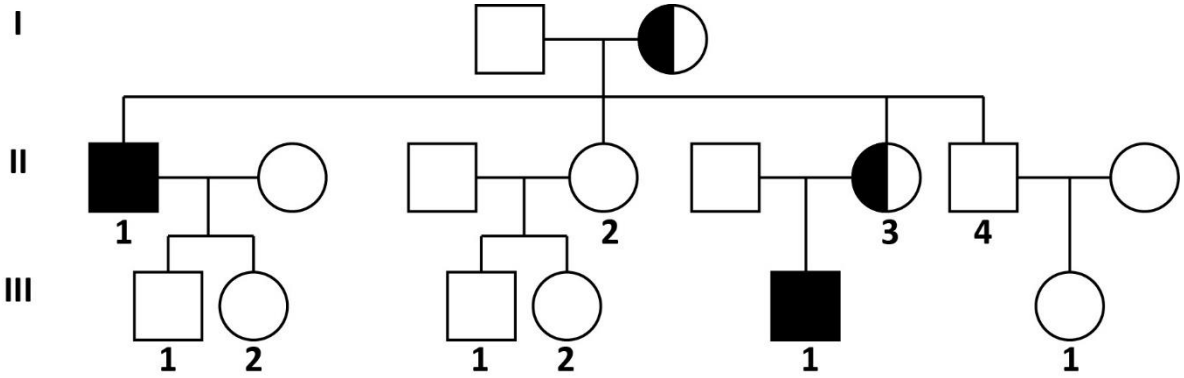

Figure 8: X-linked recessive trait.

Genetic Influence on Skeletal and Dental Malocclusion

Studies have shown that skeletal malocclusions are more influenced by genetics whereas dental malocclusions are more often due to environmental factors. Malocclusion is a trait that can be greatly influenced by environmental factors. Yet it should not be forgotten that genome might influence the response to environmental factors.

Most problems in orthodontics are not strictly the result of only genetic or only environmental factors, unless trauma, but a combination of both. It is important to understand the cause of the problem before attempting treatment.

- **Class II div 1**

Class II division I malocclusion appears to have a polygenic/multifactorial inheritance.

Environmental factors can also contribute to the aetiology of class II division 1 malocclusions such us digit sucking. Soft tissues can exert an influence on the position and inclination of upper and lower incisors and the need to achieve lip/tongue contact for anterior oral seal during swallowing can encourage the lower lip to retrocline the lower incisors and the protruding tongue to procline the uppers, influencing the severity of the overjet.

- **Class II div 2 (have strong genetic component)**

Class II division 2 malocclusion exhibits high genetic influence and is often considered as a genetic trait. Results of many studies suggest the possibility of autosomal dominant inheritance. Class II div 2 is a multifactorial (polygenic complex) trait; a number of genes

(acting additively) rather than being the effect of a single controlling gene for the entire occlusal malformation. High lip line, lip morphology and behaviour are also considered to be causing Class II division 2 malocclusion. Furthermore, the presence of strong masticatory muscle pattern in Class II division 2 cases is explained by the genetically determined muscular and neuromuscular system.

- **Class III (have strong genetic component)**

Class III malocclusion with mandibular prognathism often 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 family". This was the famous mandibular prognathism demonstrated by several generations of the Hungarian/Austrian dual monarchy. Many studies had suggested a strong genetic basis for mandibular prognathism (autosomal dominant trait). The genetic factors appear to be heterogeneous with monogenic influence in some families and multifactorial (polygenic complex) influence in others.

Although wide range of environmental factors have also been suggested as a contributor to the development of mandibular prognathism. Among these are enlarged tonsils, nasal blockage, posture, hormonal disturbances, endocrine imbalances and trauma/disease. Soft tissues do not play a part in the aetiology of class III.

Malocclusion associated with genetic syndromes

Craniofacial disorders and genetic aetiology with malocclusion

- Facial clefts, cleft lip and cleft palate.
- Cleidocranial dysplasia.
- Gardner's syndrome.
- Down's syndrome.
- Osteogenesis imperfecta.

Butler's Field Theory

According to this theory, mammalian dentition can be divided into several developmental fields. The developmental fields include molar/premolar field, the canine field and the incisor field. Within each developmental field, there is a key tooth, which is more stable developmentally and on either side of this key tooth, the remaining teeth within the field become progressively less stable.

Within Molar/Premolar Field: Within molar/ maximum variability will be seen for the third molars. Third molars are the most common teeth to be congenitally absent and to be impacted. When premolars are congenitally absent, the second premolars are more commonly affected than the first premolars.

Within Incisor Field: Within incisor field, according to Butler's field theory, the maximum variability will be seen for the lateral incisor. Variabilities of lateral incisor include:

a. Peg-shaped lateral incisor

b. Congenitally missing laterals

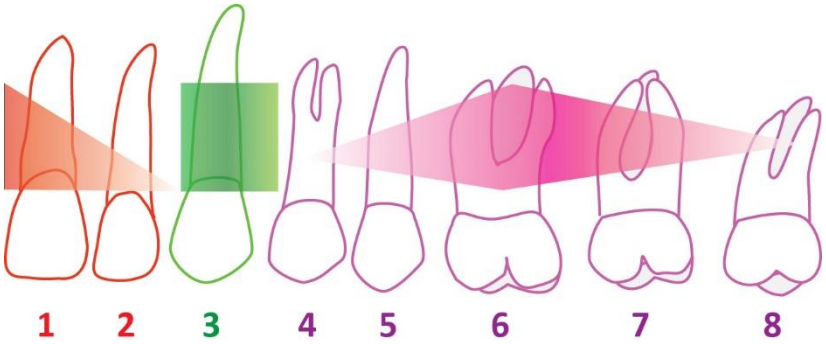

Figure 9: Butler's fields.

Local occlusal variables

- **Hypodontia**

Hypodontia has a hereditary nature. Maxillary lateral incisor is the most common tooth to be congenitally missing next to third molars followed by the second premolar. Hypodontia often exhibits familial occurrence and fits polygenic models of inheritance.

Congenital absence of teeth and reduction in tooth size are associated, hypodontia and hypoplasia of maxillary lateral incisors frequently present simultaneously. Hypodontia and the reduction in tooth size are in fact controlled by the same or related gene loci.

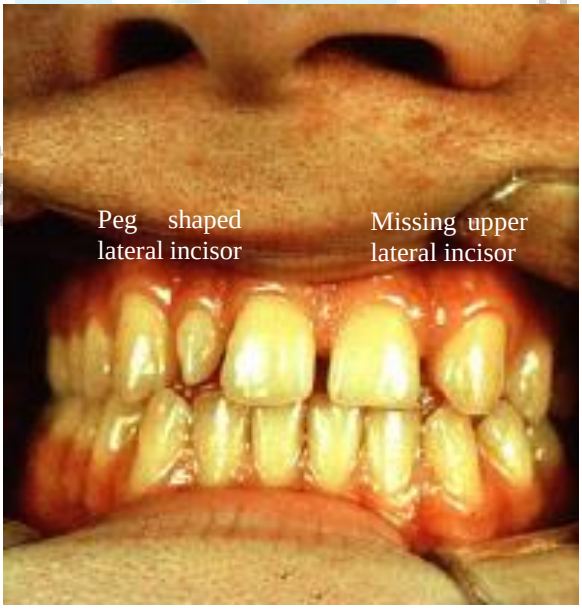

Figure 10: Hypodontia and hypoplasia.

- **Supernumerary**

Supernumerary teeth, most frequently seen on premaxillary region, also appears to be genetically determined. Mesiodens are more commonly present in parents and siblings of the patients who exhibit them. The mode of transmission could be explained by a single autosomal dominant gene.

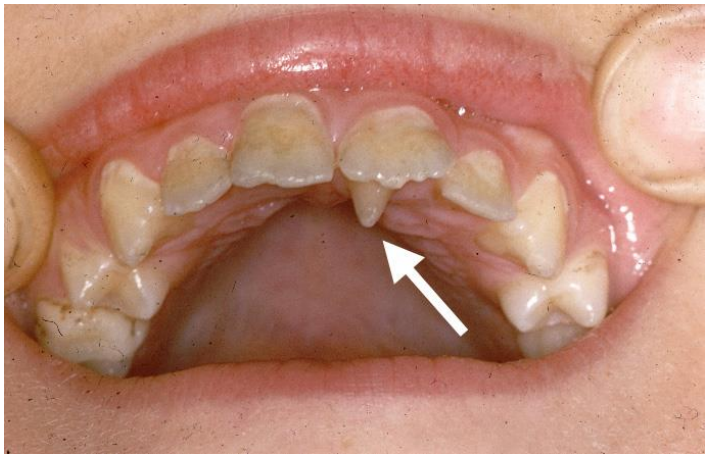

Figure 11: Mesodense.

- **Tooth size and shape**

Studies have shown that tooth crown dimensions are strongly determined by heredity. As dietary habits in humans adapt from a hunter/gatherer to a defined food culture, evolutionary selection pressures are tending to reduce tooth volume, which is manifested in third molar, second premolar and lateral incisor "fields."

- **Ectopic maxillary canine**

Various studies have indicated a genetic tendency for ectopic maxillary canine. Palatally ectopic canines have an inherited trait, being one of the anomalies in a complex and genetically related dental disturbances, often occurring in combination with missing teeth, microdontia, supernumerary teeth and other ectopically positioned teeth. Studies have also shown an association between ectopic maxillary canines and class II malocclusion, which has a strong basis. In addition, tooth transposition most commonly affects maxillary canine/first premolar class position and shows a familial occurrence.

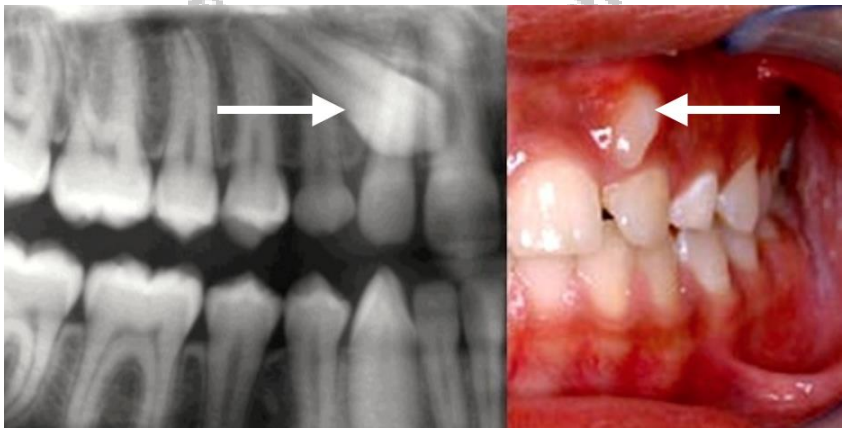

Figure 12: Ectopic maxillary canine.

Clinical Implications of Genetics in Orthodontics

Malocclusion with a "genetic cause" is generally thought to be less responsive to treatment than those with an "environmental cause". The greater the genetic component, the worse the prognosis for a successful outcome by means of orthodontic intervention. However, knowing exactly the relative contribution of genetic and environmental factors is not always possible. Malocclusions of genetic origin (skeletal discrepancies) when detected in growing period, are being successfully treated using orthopaedic and functional appliances, except in extreme cases where surgical intervention is required. When malocclusion is primarily of genetic origin, for example, severe mandibular prognathism then treatment will be palliative or surgical. Examination of parents and older siblings can give information regarding the treatment need for a child and treatment can be begun at an early age.