Molecular Biology Applications in Oral and Maxillofacial Surgery

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Abstract

Introduction
Genetics is now considered the most acknowledged field in studying human disease causes and considered a rich field in medical researches. Pharmacogenomics is a product of that researches and getting attention to personalize medicine to individuals through investing in the DNA based drug therapy [1,2]. Of all malignancies 1% is mainly caused by single-gene inheritance. Single gene, chromosomal, and multifactorial were used to describe hereditary conditions until the understanding of the interaction between different genes (polygenic inheritance) and including acquired somatic genetic disease category. About 5% of population after age of 25 years will have a disorder with a genetic basis [3].

Genetic Impact on Maxillofacial Surgery: Basic DNA Structure. DNA is a long polymer forming a chain of series of nucleotide molecules. Each nucleotide molecules has one molecule of deoxyribose sugar, one molecule of phosphoric acid and one nitrogenous base on the side of the sugar. There are four types of nucleotides in the DNA following the types of nitrogenous bases: Adenine (A), Thymine (T), Cytosine (C) and Guanine (G). The DNA helix model was first suggested by Watson and Crick in which the two polynucleotide chains run besides and opposite to each other. They are attached together by the nitrogen bases through hydrogen bonds with two types. The nitrogen base of the two attached stands of the DNA are paired in a constant arrangement in which Adenine always binds with Thymine and Cytosine always binds with Guanine. This will leads to stable hydrogen bonds between the pairs. The two DNA's stands are complementary twist around forming the double helix (Figure 1). A single turn of the helix is 3.4 nm in length with 10 base pairs and the helix diameter is 2 mm

Practical Genetic Methods
DNA sequencing:
It was first developed by Walter Gilbert then Frederick Sanger's on 1975 [6]. It is a process of accurately determining the nucleotide order in a strand of DNA. The initiation of rapid DNA sequencing methods has critically advances the medical researches. A great step proposed by a team of scientists in United State to lead an international program for sequencing the entire human genome in 1988 [7]. In 2000 the team completed the preliminary human DNA sequence of three billion base pairs and in 2004 the complete human DNA sequence was published. In addition they noted that many genes can have multiple functions. The ability to identify the gene that is responsible of an inherited single gene disorder and its diagnostic application will allow better understanding of diseases pathogenesis as well as possible therapeutic applications. This could be achieved through the identification of the human disease candidate gene by the use of animal models of disease or by homology. New disease genes can now be identified using genetic databases [8,9]. During 1980s recombinant DNA techniques allowed mapping through positional cloning which lead to purely identification of the gene by its location without knowing its function [10]. Sequencing technology developed to Exome sequencing which is the analysis of the coding regions of all known genes allowed direct identification of the causal mutation in a family within days to weeks instead of years [11]. Cystic fibrosis transmembrane regulatory gene (CFTR) is one of the early identified disease genes during 1980s [12].

Linkage analysis:
The adjacent loci on one chromosome are usually inherited together and are called linked alleles. These two close alleles are difficult to be separated during meiosis, crossover or recombination [7]. Linkage analysis was used largely before publication of the complete DNA sequence, development of next generation sequencing methods and microarrays with possibility to analyze multiple million single nucleotide polymorphisms (SNPs) [12].

The Human Genome Project (HGP):
Victor McKusick in 1969 proposed the idea of mapping the human genome. The Human Genome Project concept came in the meeting on 1986 and started in 1991. Its idea is to make a human genome organization which coordinates the individual national genome projects and harbor interaction between genetic scientists [13].

Polymerase Chain Reaction (PCR):
PCR facilitates DNA analysis using easily accessible sources such as saliva, buccal smear, blood, and pathological stored tissue. It can be used for detection of gene rearrangement, pathogenic mutation and also for the presence of infectious agent. The evolutionary techniques for analyzing an interesting DNA sequences are DNA sequencing, Southern and Northern blotting, mutation screening, microarray analysis, and real-time PCR. It is therefore resulted in advances in understanding the structure and function of normal gene besides exposing the inherited disease's molecular pathology which offers prenatal diagnosis, presymptomatic diagnosis of genetic diseases and detection of carrier cases that are difficult to detect clinically without symptoms [14-16].

Next-generation sequencing is called a clonal sequencing

provided by in vitro cloning using emulsion or bridge PCR to produce large amount of DNA molecules. It lets on concurrent testing of all monogenic disease causative genes having mutations. The specific gene can be targeted by hybridization or gene selected PCR, or by sequencing the entire exome while analyzing only limited genes in single gene [6, 13, 17]. In infectious diseases, the advancement of molecular biology shifted the conventional laboratory methods that depend on molecular methods providing rapid detection of infectious agents [18]. For example in virology the molecular methods provided ability for genotyping, resistance testing, and quantification of the virus load. In bacteriology in comparison to conventional methods molecular methods provided fast identification of serious bacterial infections, resistance testing, fastidious bacterial infection detection, and bacterial infection identification following antibiotics administration. More improvements are also found in fields of mycology and parasitology leading to fast diagnosis of fungal infection for example in cases of neutropenia. Additional applications of molecular biology involve biosecurity agents' identification, infection control and epidemiology [12,19-27].

Genetic counseling:
Genetic counseling is another field in molecular biology that has considerable importance and applications, it has been defined as "The use of genetic counseling to understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease including:

• Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
• Education about inheritance, testing, management, prevention, resources and research.

A gene transfer product
Ex-vivo investigations are done to provide a gene transfer product. They used keratinocytes mixed with retroviruses which can be delivered easily for treatment in oral mucosa or other sites [81].

Uses of gene therapy in head and neck cancer: Researches are directed to provide adenoviruses that are able to multiply and specifically the malignant cells containing mutated P 53 gene [82].

Uses of gene therapy in antibiotic resistant microorganisms: This resistance might be caused by definite genes activation that contributes to glycosyl transferase enzyme synthesis. This enzyme produces periplasmic glucans that provide resistance to antibiotics. Therefore, researchers found that the replication of the mutated definite gene makes the microorganisms susceptible to antibiotics [68].

Uses of gene therapy in host defense
The host defense can be supported by genes encoding antimicrobial protein. It can be supplemented in the host cell at the infection vulnerable sites [47].

Genetic in Special Conditions:
There are many inherited diseases commonly occur in families but does not follow the Mendelian inheritance and their occurrence among relatives is low. Those diseases have multifactorial inheritance ranging from mostly environmental to entirely genetic in causation. Examples: Cleft lip and palate, multiple sclerosis, psoriasis, rheumatoid arthritis, ankylosing spondylitis, osteogenesis imperfecta. Finding genetic susceptibility in common conditions:

Through twin studies, families share related genetics but also same environment, therefore to identify the susceptibility of a disorder that occur in a family whether it is caused by genetic or environmental is by comparing its frequency between identical and non-identical (dizygotic) twins. By heritability calculation: it gives the proportional contributions of environmental and genetic factors to a trait. It is symbolized as h^2
H2=ratio between proportion of a trait of a genetic cause and trait variation in a population
Also the estimation of familial clustering can be calculated by
λ2=ratio between sibling risk of affected individuals and incidence in general population

As per polymorphism association studies, about 10 million Single Nucleotide Polymorphisms (SNPs) have been identified in human genome. These studies provided the possibility to find disease susceptibility loci for many diseases [2,72,83-95].

Genetics in Personalized Medicine:
Drugs are shown to be more effective in some individuals than others, in addition, some individuals developed drug side effects more than others. Pharmacogenomics is the study of the interaction between people's genetic and drug response [96-102]. By the use of genome sequencing, it will be possible to provide personalized pharmacogenomics making optimum drug choice, dose, and estimating side effects [103-114]. Personalized medicine or precision medicine is aiming to provide treatment of a specific disease according to the individual genetic subtype [115-123]. An example of a drug response is malignant hyperthermia with muscle rigidity and raised body temperature occurred rarely as a complication of using halothane anesthesia and succinylcholine for muscle relaxant. Its prediction requires muscle biopsy to test the reaction with the anesthesia. The most likely cause is mutation in ryanodine receptor gene (RYR1).

References
Glodstein DB, Tate SK, Sisodiya SM (2003)

Pharmacogenetics goes genomic. Nat Rev Genet 4: 937-947.

William N, Katherine P (2008) Removing barriers to a clinical pharmacogenetics service. Pers Med 5: 471-480.

Albert FW, Kruglyak L (2015) The role of regulatory variation in complex traits and disease. Nature Rev Genet 16:197-212.