Genetics Clinical Medicine and Dentistry

Anju Singh[1], Konark[2], Abhas Kumar[3], A Rajan[4], Namrata Singh[5], Amarendra KR[6]

ABSTRACT

William bateson, coined the terms genetics, genes and alleles[3] Genetics can be defined as the study of genes and of the statistical law that govern the passage of genes from one generation to next. New insights into genetic basis of disease are being generated at an ever increasing rate. The explosion of information was ignited by technological advances, such as the polymerase chain reaction (PCR) and antomated DNA sequencing and is fueled by rapid progress in the human genome project (HGP).

Although its promise is great, the intergration of genetics into the everyday practice of medicine remains challenging. The great change occurring in medical genetics is that genetic testing may soon be used to test for disease risk/susceptibility to such common diseases as cardiovascular disease, diabetes, and chronic periodontitis.

Keywords: Genetics Clinical Medicine, Dentistry

INTRODUCTION

During the past few decades, the health care professional have become increasingly aware that genetic factors play an important role in clinical medicine and dentistry[1]. William bateson, coined the terms genetics, genes and alleles[3]. Genetics can be defined as the study of genes and of the statistical law that govern the passage of genes from one generation to next[2]. Genetics abnormalities comprises of disorders due to defect in the genetic system comprising of the genes and the chromosome. Gene in the genetic material DNA, that controls the production of a single protein.[3-5] New insights into genetic basis of disease are being generated at an ever increasing rate. The explosion of information was ignited by technological advances, such as the polymerase chain reaction (PCR) and antomated DNA sequencing and is fueled by rapid progress in the human genome project (HGP). Although its promise is great, the intergration of genetics into the everyday practice of medicine remains challenging.[6]

The great change occurring in medical genetics is that genetic testing may soon be used to test for disease risk/susceptibility to such common diseases as cardiovascular disease, diabetes, and chronic periodontitis. It may also be practical to determine individual risk for orofacial developmental anomalies such as clefting, as well as for some forms of cancer such as oral squamous cell carcinoma. Clearly, the expansion of genetic testing to the arena of predictive testing of disease risk, prognosis, and resp Tomorrow's faculty will need a good grounding in genetics to pursue teaching and research careers[11]. once to therapy will be an important component of health care in the future.[10]

HISTORY

The word genetics is derived from the Greek word "Gun" which means "to become" or "to grow into". Discernible pattern of heredity transmission were recognized first in the 18th and 19th centuries.

In 1750's Maupertius described the autosomal dominant inheritance of polydacytly. First real step in understanding of transmission of the genetic blue print was made by an Augustinian Monk, Gregor Johann Mendel, in 1864.

Conduction hybridization experiment in garden pea (pisum sativum) between 1856 and 1863, he cultivated and tester some 29,000 oea plants from these experiments he deducted some generalizations, which later become known as Medel's principles of heredity.

Mendle's conclusions were largely ignored, In 1900, however his work was rediscovered by there European scientists Hugo de Veries, Canal correns and Eaich Von Tschemark.

Normal Variation

Individual uniqueness is founded on variation in the sequences of a person's DNA. Some genetic variation is sufficiently common to constitute a polymorphism in the observed phenotype

Example: ABO blood group, HLA systems

Much of this 'expressed' variation arises from single base changes in the DNA encoding biosynthetic enzymes or structural proteins in the cell.

Silent variation: huge amount of pleomorphism in introns and in the tracts of DNA that lie between genes.

Variable Number of Tandem Repeats

Type of polymorphism where the number of units in a repetitive sequence varies between individuals.This is the basis for the science of Genetic Fingerprinting.

Pathological Variation

When DNA change has pathological consequences it is known as Mutation. Mutations are the result of a single base pair changes in the exon sequence of a gene, so that there is an amino acid substitution in encoded protein.

A new type of mutation recently discovered is caused by a sudden and often gross expansion in the number of trinucleotide repeat units in a repetitive sequence.

Special feature of mutation that distinguishes it from normal variation is that the function and/or quantity of encoded proteins is usually substantially disturbed.

Patterns of Inheritance

The most common classification of disorders of inheritance in

[1]Senior Resident, P.M.C.H, [2]Senior Lecturer, Department of Conservative Dentistry and Endodontics, P.D.C.H, [3]Maxillofacial Surgeon, P.D.C.H, [6]Associate Professor, Department of Surgery, N.M.C.H, Patna Bihar, [4]Diploma DTMH, R.I.M.S, Rachi, [5]M.B.B.S (D.G.O), Noble Hospital, Pune, India

Corresponding author: Dr Anju Singh, (MDS), Senior Resident, P.M.C.H, Patna, Bihar, India

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man is:
Mendelian or single gene inheritance
1. Autosomal dominant
2. Autosomal recessive
3. X-linked dominant
4. X-linked recessive.
5. Chromosomal inheritance
6. Polygenic or multifactorial inheritance

Human genetics deals with the variations between humans. Variations are, in part, reflections of differences that exist at the DNA level. Variations that influence gene function are usually referred to as Mutations. Other variations that do not affect health or functioning of an organism are called *Polymorphisms*. Mutations may arise in somatic cells or germ cells, but only germ cell changes are heritable.

The ever ongoing gene 'experiments of nature' have resulted in a wide variety of mutant phenotypes, which might have remained unknown in lab conditions.

Disorders caused by the transmission of a single mutant gene show either autosomal or sex linked inheritance.

In reality, genes are never dominant or recessive. It is only their protein products that produce clinical patterns called as “Dominant" or “Recessive".

There are approximately 1200 single gene disorders and account for more than 5% of all hospital admissions. Single gene disorders can be classified into autosomal and sex chromosome linked disorders.

Genetic Counselling

Genetic counseling concern with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in the family”[6] In most cases, the individual seeking counseling will already have child or other relative or will himself be affected.

Proper counseling may be given only after correct diagnosis has been established.

For example, after thorough history taking and pedigree analysis a disorder may be shown to be inherited as an autosomal dominant trait in a particular family; the recurrence risk may them be quoted as 50% even though the exact diagnosis is unknown.

The counselor should be able to import information to the patient and his family in language capable of comprehension. The counselor should try to dispel any notions of guilt, which parents may have after the birth of child with a congenital disorder

PROCEDURES FOR PRENATAL DIAGNOSIS

1. Visualization of fetus

Ultrasonography: With this technique it is now possible *to* visualize embryo as early as 5 1/2 to 6 weeks of pregnancy and cardiac activity is detectable at 7-8 weeks.

It has now become a routine procedure for verification of viable embryo, determination of gestational age, diagnosis of multiple gestations, determination of placental and fetal positions, diagnosis of fetal anomalies, detection of uterine malformations and a guide for passage of instruments for invasive procedures.

Radiography: Although mineralization of fetal skeleton at 11 weeks *of* gestation is adequate *to* permit radiographic examination, this procedure has been discarded due *to* safety reasons

Fetoscopy: It has been employed for cannulation of umbilical vessels and for blood sampling, transfusion and fetal tissue biopsies

2. Analysis of fetal tissue

Amniocentesis

- Optimum time: 16-18 weeks *of* gestation
- Under strict aseptic conditions and local anesthesia, 20-30 ml of fluid is aspirated.
- In less than 0.1% of patients amnionitis (inflammation of amniotic membrane) occurs.
- About 90% of all amniocentesis are performed for cytogenetic analysis. The rest 10% is used for biochemical investigation.
- The fibroblast like cells obtained at amniocentesis can be cultured in a variety of tissue culture media enriched with fetal bovine serum for 1-3 weeks permitting accumulation of sufficient dividing cells for karyotyping.
- A minimum of 15 cells are examined and the modal chromosome number is established.
- Sex determination of fetus is 99% accurate by this method

Chorionic villus sampling

- Optimal time: 9-12 weeks
- the Chorion frondosum contains the mitotically active villus cells and is, therefore, the area to be biopsied.
- At 9-12 weeks of gestational age villi float freely within the intervillous space
- attached only loosely to the underlying decidua, which explains why aspiration sampling at the stage is usually only minimally traumatic
- CVS sampling: 10-25 mg of chorionic villi is collected.
- Because the langerhans cells of the cytotrophoblast are in dividing phase, it is possible to perform a "direct" chromosome analysis, immediately after sampling, or alternately after 24 hours of incubation in a tissue culture medium.
- Direct analysis has the great advantage of permitting a fetal chromosome analysis within 24-48 hou

Fetal and Maternal blood analysis

- Its non-invasive way of prenatal diagnosis. Flow cytometric test of maternal blood with anti gamma globin Mab (Monoclonal antibody to gamma chain of haemoglobin molecule) is highly specific for examining fetal cells irrespective of its gender because the amount of gamma hemoglobin chain produced per cell is significantly higher in fetus in comparison to that of adults.
- This procedure greatly reduces the total number of candidate fetal cell to be sorted by increasing fetal cell purity in the test sample. It has been estimated that a 20 ml sample of maternal blood contains 0.20 fetal cells
- To utilize these rare cells for a prenatal diagnosis of chromosome abnormalities, enrichment techniques are being improvised to make it a standard non-invasive procedure.

Fetal Liver Biopsy

- A variety of enzymes of intermediary metabolism are expressed only in the liver.
- The prenatal diagnosis of disorders associated with

abnormalities of these enzymes cannot be accomplished by enzyme assay of amniotic fluid or chorionic villi cells.
- Thus, fetal liver biopsy is useful in conditions like Type I Glycogen Storage disease etc.

Fetal skin biopsy
- This approach is used only in those disorders where skin is involved eg. Epidermolytic hyperkerations.
- Definitive prenatal diagnosis requires that the histological appearance of the skin be pathognomonic at 20 weeks of gestation.

Pre-implantation diagnosis
- In this procedure, 1 or 2 cells are removed from cleavage stage embryos from the patients.
- Affected embryos are identified by using molecular genetic techniques.
- Subsequently, healthy embryos are re-implanted in the uterine cavity enabling further development till full term.
- By doing preimplantation diagnosis, first and second trimester abortions are avoided.
- The couples can decide whether to attempt a pregnancy instead of aborting the fetus at a later stage, thus offering minimal risk to the mother.
- The major problem with this technique at present is low pregnancy success rate

A number of strategies developed to design optimal procedures for the preimplantation diagnosis of genetic defects are:
- Polar Body biopsy
- Multicell biopsy
- Blastocyst biopsy
- Polar Body biopsy

The chromatin of polar body is virtually the "mirror image" of the chromatin of the oocyte. Since the first polar body does not contribute to the development of the embryo it can be removed with minimal adverse effects on the oocyte.

Multicell biopsy: Prior to the late 8-cell stage, 1-3 blastomeres of the pre-embryo are dissociated with pipetting after boring a small hole in zona pellucida, that heals rapidly afterwards.

Blastocyst biopsy: From trophoblast (which later forms placenta) of the blastocyst a number of cells can be safely removed for analysis without adversely affecting the fetus.

BASIC INFORMATION REQUIRED FOR GENETIC COUNSELLING

A genetic counsellor must have:
1. Precise and fully confirmed diagnosis of the disease
2. Accurate pedigree of the family
3. Knowledge of the mode of inheritance of the condition

INDICATIONS FOR PRENATAL DIAGNOSIS

1. Advanced maternal age (e.g; Down syndrome)
2. Previous child with chromosome aberration
3. Intrauterine growth delay
4. Biochemical disorder
5. Congenital anomaly
6. Previous history of Neural tube defect in the family
7. Structural anomalies found on the ultrasonography
8. Person with mental retardation or developmental delay (e.g. fragile X syndrome)
9. Couples with a history of recurrent miscarriages

LATEST ADVANCES IN GENETICS

DNA vaccination

DNA vaccination is performed by directly injecting the plasmid DNA encoding an antigenic protein intramuscularly or intra-dermally.

The amount of protein produced and expressed in the cell leads to surprisingly a strong immune responses.

Advantages of DNA vaccines
1. They can be easily manufactured at an industrial scale.
2. Different DNA vaccines can be combined and delivered at once.
3. DNA vaccines are more stable and resistant to temperature fluctuations. Thus they can be easily stored and transported.
4. Antigens retain their native form to express potentially. So number of effective doses can be substantially reduced

Disadvantages
1. In spite of its universal acceptance, vaccination is not always an 100% success e.g. Hepatitis B
2. It is very necessary to understand the mechanisms by which DNA induce immune response.
3. There is as yet no way to control excess plasmid that fails to find a way inside the cell.
4. There is a possibility of plasmid disrupting a vital DNA sequence in the host cell.

DNA Chip
- DNA chip is an array of DNA sequences embedded in a gel that layers over a silicon surface.
- It provides a medium for matching the known and unknown DNA samples based on base-pairing rules to identifying the unknowns.
- It may be manual or make use of robotics.

A DNA chip also referred to as DNA array.

Types

Macroarray contain sample sizes of about 300 microns or larger and can be easily imaged by existing gel and blot scanners.

Microarray contain sample spot sizes in less than 200 microns in diameter and require specialized robotics and imaging equipment that generally are not commercially available

Formats of Gene Chips

Format I: probe DNA is immobilized on a solid surface such as a glass using robot spotting and exposed to a set of targets either separately or in a mixture.

Format II: an array of peptide nucleic acid (PNA) probes is synthesized either on-chip The array is exposed to a labeled sample DNA which is hybridized

Applications of DNA chip
1. Drug and receptor discovery in Pharmacogenomics that is therapeutic responses to drugs and the genetic profiles is compared.
2. Toxicological research in Toxicogenomics
   It correlates between toxic responses to toxicants and changes in the genetic profiles.
3. In diagnostic human pathology
4. Used to study the aging process in mice.
5. In the analysis of thousands of genes simultaneously.

At present, such chips are available only from a single company,

Affymetrix chips USA. of cost $2,500.

CONCLUSION

As we all know genetics play an important role in health disease. Now with advancement in science its importance in dentistry has become clearer. Its well own by now that genes are the one which determines the genotypic and phenotypic nature of any human being.

Improved method in diagnosis, treatment and prevention has enabled the investigators to focus more of their attention on the role of genetic in oral disorder.

Timely, genetic counseling and better availability of various diagnostic and treatment approach, can lead to attain better oral health.

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