Understanding genetic testing

A review

Our understanding of human genes and of the genetic basis of disease has grown dramatically in the last decade. Currently, more than 4,000 diseases are known to be genetic and are passed on in families. Moreover, it is now known that alterations in our genes play a role in such common conditions as heart disease, diabetes, and many types of cancer. The identification of disease-related genes has led to an increase in the number of available genetic tests that detect / diagnose the disease or an individual's risk of disease.

Our genetic material

Every human cell contains 46 molecules of genetic material called 'Chromosomes" in its nucleus. These chromosomes are made of a double-stranded helical structure called DNA (Deoxy ribose Nucleic Acid). The DNA in each chromosome constitutes many genes. The genes encode instructions for different proteins that are required by the body to function normally. Current science suggests that human chromosomes carry from 25,000 to 35,000 genes and every gene is made up of thousands, even hundreds of thousands, of chemical bases.

Human cells contain two sets of chromosomes, one set inherited from the mother and one from the father. 22 pairs (1-22) are called autosomes and 23rd pair is called sex chromosome pair (XX for female and XY for male). Although each cell contains a full complement of DNA, cells use genes selectively. Many genes encode proteins that are unique to a particular kind of cell and that gives the cell its character - making a brain cell, say, different from a bone cell. A normal cell activates just the genes it needs at the moment and actively suppresses the rest.

Genotype is all the genes the individual carries, whether they show as characteristics or not. Phenotype describes the way these genes are actually expressed in the person like physical appearance, morphology, behavior and body functions. When genes are working properly, our bodies develop and function smoothly. But should a single gene, even a tiny segment of a single gene gets altered (mutated), the effect can be dramatic: deformities and disease, even death. Many, if not most, diseases have their roots in our genes. More than 4,000 diseases are thought to stem from mutated genes inherited from either or both the parents. Common disorders such as heart disease and most cancers arise from a complex interplay among multiple genes and between genes and factors in the environment.

Types of genetic testing

Cytogenetics

Genetic testing involves examining a person's genetic material taken from cells in a sample of blood or, occasionally, from other body fluids or tissues. Genetic tests use a variety of laboratory techniques to determine if a person has a genetic condition or disease or is likely to get the disease. The genetic change can be relatively large: a missing or added piece of a chromosome, a change in position of a part or the entire chromosome - that is visible under a microscope. Such a study of chromosomes is called as **Cytogenetics**. The general procedure includes staining of the chromosomes with specific dyes and arranging them in a specific order (1-23). This type of organized arrangement of chromosomes is called a Karypotype and it is usually done with the help of automated image analysis system. The karyotype is examined by genetics experts and the chromosomal defects are interpreted.

Several hundreds of conditions are a result of chromosomal defects. For example the condition Down Syndrome is diagnosed as a numerical defect of chromosome 21. That is, instead of two 21 chromosomes there are 3 (one extra). The presence of this extra chromosome results in mental retardation, dysmorphology and several other physical defects in the child. Another common example is Turner syndrome in which there is loss of one X chromosome in females resulting in Amenorrhea and other growth related problem.

A substantial percentage of common gynecology and obstetric conditions like recurrent abortions, bad obstetric history, molar pregnancies and infertility are due to chromosomal defects. Some of the pediatric conditions like dysmorphology, growth and mental retardation, delayed milestones are also associated with chromosomal abnormalities.

Molecular Genetics

If the genetic change is extremely small, as little as one extra, missing, or altered chemical base at the level of single gene it is called a molecular defect. The testing of such disorders is called Molecular genetics or DNA testing.

Thousands of human diseases are caused by defects in single genes. They are rare disorders with simple inheritance patterns in family pedigrees. Single gene disorders can be divided into a number of different categories according to how they are transmitted from generation to generation. Some are described as dominant diseases because only one mutant gene is required, and such diseases tend to crop up in every generation. Polycystic Kidney disease, few forms of muscular dystrophies, Achondroplasia (dwarfism) is some of the examples of autosomal Dominantly inherited diseases. Other diseases are described as autosomal recessive because both copies of the gene must be defective in order for the disease to occur. These recessive diseases often skip generations. Some of the examples of recessively inherited diseases are Thalassemia (severe anemia condition), Sickle cell Anemia and congenital deafness.

Many single gene disorders affect both sexes equally. However, where the relevant gene is present on the X-chromosome, the associated disease tends to be more common in males. Examples of such disorders are Duchene muscular dystrophies, haemophilia (blood clotting disorder) and Fragile X (most common cause of mental retardation).

Individuals are tested if there is a family history of one specific disease, show symptoms of a genetic disorder or if parents want to diagnose a specific genetic problem in their children. Sometimes testing requires additional genetic material from other family members for comparison. Tests also vary in *sensitivity*, that is, their ability to detect mutations or to detect all patients who have or will get the disease. Interpretation of test results is often complex and should be done by expert medical geneticists

A highly sophisticated method called Polymerase chain reaction (PCR) is used to diagnose single gene disorders. PCR makes a huge number of copies of a gene with a small of quantity of DNA as the starting material. This is done on an automated PCR thermal cycler or PCR machine. After PCR the mutations are visualized on agarose gel for reporting. Experienced molecular biologists and medical geneticists interpret the results to provide highly useful information for physicians and doctors. The technique is also used for the detection of Viral DNA like HIV and in determining the number of viral copies (Viral load).

Metabolic Disorders

In addition to studying chromosomes and single genes, genetic testing also includes biochemical tests for the presence or absence of key proteins that signal aberrant genes.

Inborn errors of metabolism are a rare group of genetic disorders that can have serious clinical consequences for an affected neonate or young infant. If undiagnosed and untreated, these disorders can cause irreversible mental retardation (ranging from mild to severe), physical disability, neurological damage and even fatality. Early detection (soon after birth) and an accurate diagnosis are very important for expediting the treatment or interventions. Neonatal screening is gaining great importance and rapid momentum in many countries in view of its considerable public health significance

Some of the common disorders for which newborn infants are screened are congenital hypothyroidism, Congenital adrenal hyperplasia, Galactosemia and Phenylketonuria Time

resolved flourimetry, Elisa, Tandem Mass spectrometry, hplc and Gas chromatography are different technologies used to diagnose metabolic disorders.

Newborn screening to detect treatable metabolic and other disorders is now an accepted part of routine neonatal health care in almost all countries with well-developed medical services, and is becoming established in many countries in less well-developed regions It is a preventative health care measure and has clear benefit to the newborn because treatment is available for the disorders diagnosed.

Prenatal Screening

Each year, more than 4 million babies are born all over the world with birth defects. Prevention of birth defects has an important role in reducing the impact 0f birth defects. Prenatal screening is one such affordable and effective program available to reduce the impact of certain genetic conditions.

These tests are usually done early in a pregnancy, in first 4 months. A 'screening' test does not tell for sure that the developing baby has a certain problem, but it does tell us if it is more likely. When a screening test is positive, further investigation is usually recommended.

Prenatal screening tests can help to find certain problems and they can also reassure you if these problems are very unlikely. However it should be remembered that no such prenatal screening test can identify all the possible health problems that any baby might have. The most common prenatal screening tests check for a higher chance of numerical chromosome problems, like Down syndrome and open neural tube defects like spina bifida.

Prenatal Diagnosis

Prenatal Diagnosis is genetic testing of a fetus. This is done when there is a risk of bearing a child with defective genes. Congenital anomalies account for 20 to 25% of perinatal deaths and prenatal diagnosis employs a variety of techniques to determine the health and condition of an unborn fetus. Prenatal diagnosis helps in determining the outcome of the pregnancy, managing the remaining weeks of the pregnancy, planning for possible complications with the birth process, planning for problems that may occur in the newborn infant, deciding whether to continue the pregnancy and in finding conditions that may affect future pregnancies

Depending on the gestation age during which the invasive prenatal procedure is done different types of fetal samples can be studied. *Chorionic Villus sampling* (CVS) is performed around 10 weeks of gestation by removing a small sample of the placenta (nourishment for the baby) from the uterus. It is removed with either a catheter (a thin tube) or a needle. Local anesthesia is used for this test. *Amniocentesis* is done around 16 weeks of gestation during which a sample of amniotic fluid (the fluid around the baby) is removed from the uterus. *Cordocentesis* is done around 20 weeks of gestation to remove blood from the cord that connects the fetus to the mother. The invasive procedures although carry a small risk, they are generally safe if performed under ultrasound guidance, in sterile environment by experienced radiologist or obstetrician.

The samples (CVS, amniotic fluid or cord blood) are cultured in the lab and relevant evaluations are done. For example if amniotic fluid is sent to a lab for prenatal diagnosis of Thalassemia DNA test is done and if the diagnosis is for Down syndrome karyotyping is done by the laboratory.

Preimplantation genetics

Preimplantation genetic diagnosis (PGD) is a test that screens for genetic flaws among embryos used in in vitro fertilization. With PGD, DNA samples from embryos created in-vitro by the combination of a mother's egg and a father's sperm are analyzed for gene abnormalities that can cause disorders. Fertility specialists can use the results of this analysis to select only mutation-free embryos for implantation into the mother's uterus. PGD

technology has been actively developed for many genetic disorders including cystic fibrosis, beta thalassemia, haemophilia, muscular dystrophy etc. Although PGD has been practiced for years, only a few specialized centers worldwide offer this procedure.

Cancer genetics

Genetic testing plays a very important role in cancer diagnosis, management and treatment. For example in case of leukemia, genetic testing helps in classification of the tumor, confirmation of diagnosis and is indicative of the prognosis. Treatment planning and ongoing monitoring of the cancer requires genetic testing. Chromosomal analysis, DNA based PCR and gene expression studies are the tests that help oncologists in case management. Cancer predisposition testing is done for certain hereditary cancers like breast, ovarian and colon cancer.

Genetic Counseling

Genetic counseling is an interactive session with medical genetics expert which helps analyze and convey information about genetic testing to affected individuals and their families. Genetic counselors work as members of a healthcare team, providing information and support to families who have members with birth defects or genetic disorders and to families who may be at risk for a variety of inherited conditions. They identify families at risk, investigate the problem present in the family, interpret information about the disorder, analyze inheritance patterns and risks of recurrence, and review available options with the family and the doctor.

Examples of problems seen by genetic counselors include recurrent pregnancy loss, infertility, unidentified fetal birth defect, and mothers with late maternal age, children with delayed milestones, growth and mental retardation, familial disorders, haemoglobinopathies, muscular dystrophies, neurodegenerative disorders, leukemia, breast cancer and so on.

Conclusion

Gene testing already has dramatically improved lives. Some tests are used to clarify a diagnosis and direct a physician toward appropriate treatments, while others allow families to avoid having children with devastating diseases or identify people at high risk for conditions that may be preventable. Aggressive monitoring in those inheriting a gene for familial cancers, for example, has saved many lives. Substantial research is on going on late-onset disorders, cancers and heart disease that are complex in nature and have both genetic and environmental causes. Genetic tests may indicate a susceptibility or *predisposition* for these diseases. While Gene Therapy holds great promise for complete cure the present application of genetic testing is primarily prevention