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# Genetics in medicine

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Nature magazine's 10 people who mattered in the year 2015 included Junjiu Huang of China as "Embryo Editor", a modest biologist who sparked global debate with an experiment to edit the genes of human embryos[1]. Junjiu Huang published the world's first report of human embryos altered by gene editing using a powerful technique known as CRISPR-Cas9, to modify the gene responsible for the blood disorder thalassemia[2]. The paper invited a lot of ethical debate on genetic modification of humans, but also established the possibility of eradicating disease causing mutations in families. What was only a theory some years ago now seems to be a possibility.

The role of genetics in medicine has largely been academic and not considered a vital part of treatment in the past. Genetic disorders in populations are known to be rare and restricted to some single gene or chromosomal disorders, making them a low priority class of diseases for the practicing physician. The application of genetics to medical practice has traditionally involved a taking of family history and alerting the members of the risk. With the completion of the sequencing of the human genome in 2003, genetics is gradually becoming an integral part of clinical practice. With the information of inestimable diagnostic and therapeutic importance that The Human Genome has made available, the medical profession now must rise to both the opportunities and challenges that this wealth of information presents[3].

The global burden of congenital anomalies is estimated to be 7.94% of which disorders with a significant genetic component comprise 5.32%[4]. Most diseases involve many genes in complex interaction, in addition to environmental influence. An individual may not be born with a genetic disease but be at a high risk of acquiring it (genetic predisposition). A sequential acquisition of genetic mutations in various genes that are involved in cell multiplication and repair triggers cancer. Most of the common diseases have also been found to have a genetic component. For example, Diabetes mellitus is attributed to mutations in genes as varied as those of the Major Histocompatibility Complex to genes that code for calcium transporters. Genes coding a metalloproteinase, Human Leucocyte Antigen (HLA-G) and collagen type IV amongst several others have been implicated in Asthma. Similarly, many genes have been associated with cardiovascular disease including those for methylenetetrahydrofolate reductase, coagulation factor III, a $K^+$ channel, fatty acid binding protein and estrogen receptor. Other genetic diseases are monogenic, where mutation in a single gene results in disease. The Online Mendelian Inheritance in Man (OMIM) database contains a complete catalog of these genes and genetic disorders (http://omim.org/). Genome Wide Association Studies (GWAS) and next generation sequencing (NGS) are already being applied clinically for the molecular characterization of tumors, diagnosis of rare disorders, development of targeted therapies, identification of pharmacogenetic variants and elucidation of the genetic basis of common diseases.

Genetic syndromes are suspected on noticing dysmorphic features that are evident on physical examination, multiple anomalies in one patient, unexplained neurocognitive impairment and a family history that is suggestive of a hereditary disease. Geneticists can assist in diagnosis, suggest additional testing and referrals if warranted, help direct medical care and provide counseling for affected patients and their families. Many genetic conditions are suspected or confirmed by commonly ordered tests such as radiography, blood count or a basic metabolic panel. Genetic tests can be performed to diagnose or confirm a disorder using microarrays, Sanger's sequencing, Fluoresce in-situ Hybridization (FISH), karyotyping and NGS. Genetic testing is also offered for identifying mutations in genes that code for drug metabolizing proteins. Individual genetic variation in genes associated with metabolism and targets of commonly used drugs can be responsible for variability in treatment outcome and toxicity. For example, drugs that target Epidermal

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growth factor receptor (EGFR) are commonly used for treating colon cancer, but show reduced response in people who have mutations in the KRAS, BRAF or PTEN genes. The occurrence of a mutation in these genes guide the oncologist into selecting an alternative drug. The list of important pharmacogenes and their variants has been compiled by various organizations and can be found at http://www.pharmaadme.org/ and http://www.pharmgkb.org .

Gene therapy aims to treat a genetic disease at its roots. Remarkable evidence of safety and efficacy of gene therapy for the treatment of severe inherited disorders of the blood, immune and nervous systems as well as cancers, exist. In March 2017,a successful gene therapy breakthrough for sickle cell disease by incorporating DNA containing an anti-sickling variant into a boy's hematopoietic stem cells was reported. The "corrected" stem cells were then transplanted into his bone marrow keeping the boy sickling free for a reported 2 years[5]. Gene therapy has also found success in Severe Combined Immunodeficiency Syndrome (SCID) and cancer. Gene editing, mentioned at the beginning of the article, is also a form of gene therapy that might become applicable to many common inherited conditions like sickle cell anemia, congenital heart disease, Inborn Errors of Metabolism and hereditary cancers in future, opening the prospects of a complete prevention of inherited disease within a family.

The task of incorporating genetic information into the diagnosis and treatment of disorders is carried out by a medical geneticist, a specialization of medicine introduced in the 1980s in the US. Medical genetics has evolved from a research oriented science to a service oriented speciality since then. In the USA, the Residency Review Committee for Medical Genetics accredits medical genetics programs and requires these programs to "provide education in the basic sciences and clinical areas pertinent to medical genetics, including mendelian genetics, cytogenetics, diagnosis and treatment of inborn errors of metabolism, molecular diagnosis, syndrome indentification and dysmorphology, teratology, reproductive genetics, congenital malformations, multifactorial disorder, mental retardation and developmental disabilities, genetic screening, social and ethical issues in medical genetics, genetic counseling and quantitative human genetics"[6]. For implementation, either the practicing physician needs to be trained in all of the above, or should have the above expertise available to him/her at all times.

Many hospitals in Nepal have now initiated capacity building for diagnosis of inherited genetic disorders as well as inherited cancers and targeted therapy for the same. Genetic counseling, genetic testing and screening protocols have been started in various hospitals. The significance of genetic aspects in treatment and prevention however, are not widely acknowledged amongst practicing physicians. A lack of therapeutic options to offer to families with genetic disease might have been one of the main reasons. Nevertheless, the importance of knowing the type of mutations and screening procedures to check for the inception of the associated disease needs to be appreciated. For example, many patients with family histories of hereditary colon cancers in Nepal have been tested for germline mutations. Accordingly, the family can now follow a screening procedure to apprehend cancer in its initial stage with a high probability of a successful therapeutic outcome. Families are also willing to explore their options of genetic editing during Pre-Implantation Genetic diagnosis in order to eradicate the disease from the genomes of their offspring.

In order to incorporate genetics into mainstream practice, education on genetic basis of disease, human genomics and phenotypes, genetic counseling, genetic testing and targeted therapy should be incorporated in medical education. Medical and clinical genetics should be made available as specialization courses for students who wish to become experts in this dynamic and important burgeoning field of medicine.

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