THE DOUBLE HELIX, A DOUBLE EDGED SWORD: ETHICAL ISSUES IN GENETIC TESTING AND RESEARCH

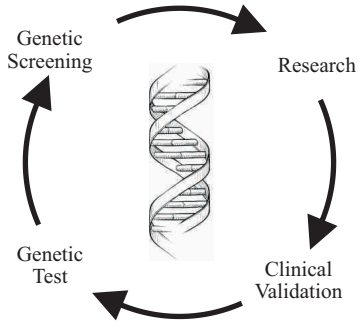
Natasha Anwar

This editorial may be cited as: Anwar N. The double helix, a double edged sword: Ethical issues in genetic testing and research. J Postgrad Med Inst 2013; 27(2):117-21.

The DNA genome is unique in each one of us. It can tell us about our ancestors, our susceptibility to disease, response to treatment and prognosis. Such complex information needs careful handling. How it translates into clinical practice and who has the right to access this information, is proving to be a challenge. It is very important to educate researchers on the impact of genetic research and its consequences for patients and for society as a whole[1].

The Ethical, Legal and Social Implications (ELSI) Research Program has identified three pivotal factors currently shaping genomic research, its clinical translation, and its societal implications: (1) the increasingly blurred boundary between research and treatment; (2) uncertainty - that is, the indefinite, indeterminate, and incomplete nature of much genomic information and the challenges that arise from making meaning and use of it; and (3) the role of negotiations between multiple scientific and non-scientific stakeholders in setting the priorities for and direction of biomedical research, as it is increasingly conducted "in the public square"[2].

Figure 1: Relationship between the Process of Genetic Research, Testing and Screening



One of the most important things to remember is that ethical research begins at the planning stage when study design, reliability and sensitivity of the method, sample collection and informed consent documents are developed. Researchers must be aware of important aspects of the informed consent process, including details of what exactly will be tested, how long the samples will be stored and what will happen to the sample after the study is complete.

Genetic information is personal and unique, however it does not define an individual completely. With a growing knowledge of the regulation of gene expression in eukaryotic organisms, it is becoming increasingly evident that the sequence is just part of the puzzle. The genome is permanent; researchers are trying to find ways to change it. Information in the genome is said to be predictive but not confirmative. So, even a relative risk of a disease, no matter how low, creates an element of discrimination.

Address for Correspondence:
Dr. Natasha Anwar,
Associate Professor,
Department of Biological Sciences,
Forman Christian Medical College (A Chartered University), Lahore - Pakistan
E-mail: nat_nabi@yahoo.co.uk

Individual and community beliefs, values and morals as well as religion may influence the perception of disability and raise a number of issues, including the use of genetic tests in prenatal screening. Some argue that genetic testing be restricted only to conditions that have a significant health impact. BRCA1 and BRCA2 for screening in newborns, for example. The genetic test results will

certainly reveal the sex of the child but different cultures place different values on the sex of a child. If no genetic abnormalities are found, what should be the view if the parents want to terminate the pregnancy[3].

Another critical aspect of genetic testing is how to communicate results to patients. After confirming positive results on fresh samples, genetic counseling service must be available to help patients understand and interpret their risk of disease.

Genetic tests are no longer confined to clinical use now. Direct-to- consumer genetic testing (DTC-GTs) are now commercially available to the general public. An exploration of genetic health professionals' experience with DTC-GTs in their clinical practice concluded that the majority of genetic health professionals not confident about interpreting and explaining DTC-GTs[4].

In addition, these tests provide a probability of risk. Although this is important but it should not be the only basis for informing choice of treatment or choices that might relate to future disease risk. If you carry a BRCA1/2 mutation you are at a higher risk of developing breast cancer, but will you definitely get it? The interpretation and significance of a positive result remains challenging. You carry an altered form of a gene that encodes a protein that is essential for the action of a particular drug, you have a 40% chance of responding, should you be given the drug which has side effects when your chances or response are low? What about when resources are limited? Who should get the drug - the person who has 45% probability of responding or someone who has 50%? This challenges the ethical principal of justice as there should be equity of access to services and information, ideally[5].

Participants involved in the genetic testing or genetic research need to feel that researchers and doctors are capable of dealing fairly with those who entrust them with the intimate physical and medical information about themselves[6]. Outrage and betrayal frequently result when expectations are not met, especially among patient populations with a strong stake in the outcome of the research in question, leading to avoidance of further research participation[7,8].

In the 1990s, researchers from Arizona State University collected blood samples from over one hundred members of the Havasupai Tribe of Indians in Arizona. The researchers hoped to find a genetic link to Type 2 diabetes, a disease that afflicts over half the tribe. While, many of the tribe members signed a consent form allowing the use of their blood to “study the causes of behavioural/medical disorders”, they maintain the belief that the blood would be used only for diabetes research. After researchers were unable to identify any genes related to diabetes, they used the blood samples to study inbreeding in the tribe, the genetic causes of schizophrenia, as well as the ancestral origin of the Havasupai. The results were embarrassing to the tribe and contradicted the tribe's oral history and the tribe then took legal action against the university[9].

The ownership of information from genetic studies remains a legal and public policy issue. From the perspective of the company filing patients for different genes, acquiring these patents prevents other companies from taking a more protective stance towards the same[10,11]. The Bayh-Dole Act in the US, encourages publicly-funded research institutions to commercialize inventions that originate from federally funded research. The act also grants the intellectual property to the research institution rather than the funding agency with an idea that the revenue from successful commercialization will, in turn, fund future lifesaving research[12].

PRIVACY & CONFIDENTIALITY

Whatsoever things I see or hear, in my attendance on the sick or even apart there from, which on no account one must spread abroad, I will keep to myself holding such things as sacred secrets (Hippocratic Oath, 4th Century B.C.).

A researcher's obligation to protect confidentiality is higher than that of a clinician. Research often does not provide benefit to the participant and provides no compelling reason to become involved in the research. Therefore those involved in designing, approving, and carrying out research must determine how to conduct research that maintains participants' confidentiality. To avoid unintentional review by an employer any consent form should not be placed in the medical record.

Investigators must be clear about what how genetic samples or data will be identified. How will the identity of patients be protected? What kinds of information will be revealed to whom, at what point in the course of research? In 2009, USA has passed legislation that prohibits discrimination and harassment of individuals on the basis of their genetic information. The Genetic Information Nondiscrimination Act (GINA) also prohibits the release of genetic information by any company or institution involved in

conducting testing. We, at present, have no such legal governance in Pakistan.

Genetic and genomic research now involves aggregating data and samples from multiple research projects or from clinical sources into a central database and biorepository for future research use. In addition, there are a growing number of biobanks built by directly collecting data and samples from a population or subpopulation to assemble a large-scale research resource. Both of these sources are important to genetic and genomic research. The large size of many of these collections facilitates the analysis of genetic variants that are rare, have modest association with phenotypic traits, or reveal such an association only when combined with other genetic variants.

An individual inherits from their parents half of their father's genes and half of their mother's. Similarly, we share a proportion of our genes with our relatives: family members are genetically related. The closer the family relationship (brothers, sisters) the more likely it is that they have genes in common. Therefore it is likely that a family relationship will be identified when samples are sent for genetic analysis. These are termed incidental findings. An incidental finding is a finding "concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting the research but is beyond the aims of that research[13]". In a genetic family study, for example, a researcher may identify misattributed parentage of a study participant[13], or while surveying the genetic variation of a specific population for one disease (e.g., diabetes), a researcher may find an allelic variation in some individuals that puts them at risk for a different disease (e.g., cardiovascular disease) than the one under investigation. For the most part, the clinical significance of a finding may be unclear or negligible; however, some findings may necessitate follow-up clinical consultation[14,15]. Therefore if your proposal or consent form has no provision of results, there might be certain compelling circumstances under which results will need to be given to patients. A number of guidelines and recommendations had been published recently to manage such findings[16,17].

Genetic conditions are family health problems. A diagnosis or a finding of an inherited predisposition has implications for other family members. Again as well as providing valuable information on hereditary nature of the gene and disease it can also stir up some difficult family issues too. This is more of a concern when some members of a family refuse to take part and do not want their information or contact details to be shared. They may also be reluctant in talking to other family members about their status and participation in the study.

Responsibility and obligation however need to be balanced with the right of an individual to choose to know their personal genetic information or, equally, not to know. The emphasis needs to be on the right of the person to choose. Genetic counseling is essential both before and after genetic testing so that all the implications of undertaking testing including having information which might be of interest to others can be understood. It is a good idea to have a proposed recruiting strategy for family members to also protect those relatives from coercion or undue influence. The researcher must also protect against the release of information about family members to each other. Counseling before testing is essential to help avoid such situations.

GENETIC TESTING AND RESEARCH IN PAKISTAN

In Pakistan, a number of very important and significant studies have been conducted to identify the genetic basis of deafness, blindness, microcephaly, β-thalassemia, hereditary breast cancer, etc[18-22]. There is now also some evidence for a European origin for a small proportion of the Pathan Y chromosomes[23]. Routine prenatal genetic testing is also available for certain genetic disorders, and is offered in several laboratories. However, unlike other countries, we do not have a system to register or accredit laboratories that provide such services. We are also beginning to understand the religious and social consequences of such screening[24].

Clearly we are a mixture of diverse ethnicities with unique familial and social characteristics that enable far more informative genetic studies to be conducted. As genetic research is growing in Pakistan, we may see more studies especially relating to the correlation between genes and treatment outcome in this era of personalized predictive medicine which seems to be very alluring as a means to be more cost effective and rational with limited resources.

CONCLUSION

Ethical concerns in genetic research mostly relate to informed consent issues such as future use of genetic samples, individual and community rights, ownership of tissues and genetic information; and

signing over any property rights. To avoid complications it is important to have a properly qualified genetic counselor on board to provide appropriate notification of results and the risk assignment as a result of the test carried out. We need to further understand genetic susceptibility to realize the utility of personalized genomic medicine. As our access to genetic information is becoming more frequent, it will clearly have an impact on the way people feel about genes, disease and identity.

In the context of a developing country, there are often no institution or judicial policies that address the use of genetic information or the ethical conduct of genetic research. It is a very new field of research for many developing countries. Therefore, until we are able to strengthen policies, we must educate researchers and it should be incumbent on the researchers to ensure the protection of the patients. Hence education and awareness of such issues must be highlighted for researchers in order to sensitize them and enable them to be prepared when handling this double edged sword. As is often the case with medical issues in Pakistan, we have so much to learn and prepare for. However, with little legislation and lack of political and social will, it becomes more incumbent on the researchers whether medical or not to ensure good conduct of project. With this new era of molecular medicine we also need a new era of responsible conduct of medicine and research in this country. The question is, are we willing to take responsibility and implement measures or will we wait for our own scandals to hit the headlines?

DNA neither cares nor knows

DNA just is

and we dance to its music

[Richard Dawkins, River Out of Eden: A Darwinian View of Life;1995. p. 133.]

REFERENCES

1. Green ED, Guyer MS. National Human Genome Research Institute. Charting a course for genomic medicine from base pairs to bedside. Nature 2011:470;204-13.
2. Henderson GE, Juengst ET, King NM, Kuczynski K, Michie M. What research ethics should learn from genomics and society research: lessons from the elsi congress of 2011? J Law Med Ethics 2012;40:1008-24.
3. Malek J. Use or refuse reproductive genetic technologies: which would a 'good parent' do? Bioethics 2013;27:59-64.
4. Brett GR, Metcalfe SA, Amor DJ, Halliday JL. An exploration of genetic health professionals' experience with direct-to-consumer genetic testing in their clinical practice. Eur J Hum Genet 2012;20:825-30.
5. Barlow-Stewart K, Parasivam G. The Australasian genetics resource book: a source of current and accurate information for health professionals, individuals and families, teachers and students. 8th ed. St. Leonards, N.S.W.: Centre for Genetics Education; 2007.
6. Kass NE, Sugarman J, Faden R, Schoch-Spana M. Trust the fragile foundation of contemporary biomedical research. Hastings Cent Rep 1996;26:25-9.
7. Greenfield DL. Greenberg v. Miami Children's Hospital: unjust enrichment and the patenting of human genetic material. Ann Health Law 2006;15:213.
8. Tarini BA. Storage and use of residual newborn screening blood spots: a public policy emergency. Genet Med 2011;13:619-20.
9. Mello MM, Wolf LE. The Havasupai Indian tribe case-lessons for research involving stored biologic samples. N Engl J Med 2010;363:204-7.
10. Cho M. Patently unpatentable: implications of the myriad court decision on genetic diagnostics. Trends Biotechnol 2010;28:548-51.
11. Allyse M. 23 and Me, We, and You: direct-to-consumer genetics, intellectual property, and informed consent. Trends Biotechnol 2013;31:68-9.
12. Mowery DC, Nelson RR, Sampat BN, Ziedonis AA. The growth of patenting and licensing by US universities: an assessment of the effects of the Bayh-Dole act of 1980. Res Policy 2001;30:99-119.

13. Parker LS. The future of incidental findings: should they be viewed as benefits? J Law Med Ethics 2008;36:341-51.

14. Shalowitz DI, Miller FG. The search for clarity in communicating research results to study participants. J Med Ethics 2008;34:e17.

15. Kaufman D, Murphy J, Scott J, Hudson K. Subjects matter: a survey of public opinions about a large genetic cohort study. Genet Med 2008;10:831-9.

16. Rehder CW, David KL, Hirsch B, Toriello HV, Wilson CM, Kearney HM. American College of Medical Genetics and Genomics: standards and guidelines for documenting suspected consanguinity as an incidental finding of genomic testing. Genet Med 2013;15:150-2.

17. Wolf SM, Crock BN, Van Ness B, Lawrenz F, Kahn JP, Beskow LM, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Geneti Med 2012;14:361-84.

18. Khan M, Ajmal M, Micheal S, Azam M, Hussain A, Shahzad A, et al. Homozygosity mapping identifies genetic defects in four consanguineous families with retinal dystrophy from Pakistan. Clin Genet 2012;[Epub ahead of print].

19. Bashir ZE, Latief N, Belyantseva IA, Iqbal F, Amer Riazuddin S, Khan SN, et al. Phenotypic variability of CLDN14 mutations causing DFNB29 hearing loss in the Pakistani population. J Hum Genet 2012;[Epub ahead of print].

20. Kakar N, Goebel I, Daud S, Nürnberg G, Agha N, Ahmad A, et al. A homozygous splice site mutation in TRAPPC9 causes intellectual disability and microcephaly. Eur J Med Genet 2012; 55:727-31.

21. Ansari SH, Shamsi TS, Ashraf M, Farzana T, Bohray M, Perveen K, et al. Molecular epidemiology of β-thalassemia in Pakistan: far reaching implications. Indian J Hum Genet 2012;18:193-7.

22. Farooq A, Naveed AK, Azeem Z, Ahmad T. Breast and ovarian cancer risk due to prevalence of BRCA1 and BRCA2 variants in Pakistani population: a Pakistani database report. J Oncol 2011;2011:632870.

23. Firasat S, Khaliq S, Mohyuddin A, Papaioannou M, Tyler-Smith C, Underhill PA, et al. Y-chromosomal evidence for a limited Greek contribution to the Pathan population of Pakistan. Eur J Hum Genet 2007;15:121-6.

24. Jafri H, Ahmed S, Ahmed M, Hewison J, Raashid Y, Sheridan E. Islam and termination of pregnancy for genetic conditions in Pakistan: implications for Pakistani health care providers. Prenat Diagn 2012;32:1218-20.