ETHICAL ISSUES IN GENOMICS

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Abstract

Bioethics are usually associated with ethical issues that emerge from advances in medical sciences and practices. These basically include the ethical guidelines that should be followed during any research or medical procedure or practice that is to be conducted. The genetic material present in the form of DNA, which encodes guidelines for cellular life, is termed as genome. Genome of many organisms has been sequenced completely and with this genetic manipulation is possible. To characterize and manipulate the genome many techniques and procedures have been developed like Whole Genome Sequencing (WGS) and genome editing respectively. Some other techniques that come under the umbrella of functional genomics generate huge amount of data that can be characterized and manipulated according to the requirement. These new procedures and approaches have raised many ethical concerns and issues that are being addressed in this review.

Keywords: Bioethics, Functional genomics, Genomics, Genetic manipulation, Whole Genome sequencing

1. INTRODUCTION

Bioethics is defined as the study of the debatable issues that are promptly ascending due to rapid advancements and progressions in the fields of biotechnology, medicine and other fields of biology (Capron & Michel, 1993). The word bioethics was first used in the 20th century by Fritz Jahr (Lolas, 2008). However, in the 1970s, Van Rensselaer Potter who was an American botanist gave somewhat a more extensive connotation to the term bioethics as he included harmony

towards the biosphere as well thereby creating the concept of what can be called as *global ethics.* Global ethics served as link between different fields such as medicine, biology, ecology and incorporated human values to ensure the well-being and survival of the humans as well as animals and other species (Goldim, 2009; Lolas, 2008). Bioethics is a fundamental part of the research that cannot be neglected, and the importance is ever increasing. Bioethics deals with several issues ranging from organ transplant, abortion, surrogacy, gene therapy, cloning genetic engineering, recombinant DNA research and astroethics and life in space (Callahan, 1970; Gutiérrez-Samperio, 2001; Malcom, 1978; Mautner, 2009; Muzur, 2014). Different bioethicists may have a difference of opinion on how different situations and controversial matters should be handled. Principles of bioethics i.e. autonomy, non-malfeasance, beneficence and justice should be considered while conducting research, clinical studies or any experiments as these principles sets ethical guidelines which should be followed under all conditions for the aim of global benefit (McCormick, 2013).

Field of genomics is meticulously linked to bioethics. Genomics is defined as the complete study of genome of an organism by the application of various techniques (Organization, 2002, 2004). Genomics may be regarded as a discipline in genetics as both the fields are closely interlinked. Techniques in genomics may involve gel electrophoresis, PCR, blotting, microarrays, chromatin immuno precipitation, DNA and genome sequencing and sequence alignment assays (Bickel, Brown, Huang, & Li, 2009; Saraswathy & Ramalingam, 2011). Rapid advancement in genomics has elicited researches that allows us to understand systems as complex as brain (Kadakkuzha & Puthanveettil, 2013). Genomics studies determine the complete sequence of DNA of different organisms along with very fine and precise genetic mapping. The field of genomics may also comprise of studying different phenomenon like epistasis, heterosis, and pleiotropy. It may also cover the interaction and relation between the loci and alleles in the genome of an organism (Pevsner, 2015). Scientific studies and researches focused on studying single genes cannot be included under the umbrella of genomics until and unless the effect of gene on the entire genome is encompassed thus revealing the pathways in which this gene is involved and other analysis related to its function (Robinson, 2002). Genomics has widespread applications in various fields such as social sciences, biotechnology medicines

and anthropology (Barnes & Dupré, 2009). It also finds its pertinence in synthetic biology, bioengineering (Baker, 2011; Church & Regis, 2014). Genomics even has role in the conservation of species as conservationists utilize the genome information to appraise several genetic factors like to determine whether an organism is heterozygous or homozygous for a disorder or anomaly that is recessive in nature (Frankham, 2010). Evolutionary patterns and processes are also studied by bringing genomics into play (Allendorf, Hohenlohe, & Luikart, 2010).

With quick progression in genomics technology and techniques a number of ethical questions are being raised about what is ethically right and what is not as genomics actually involves playing and manipulating the genome. Is sequencing the genome of an individual right? Is it okay to know all the good and bad genes in it? Is it lawful to edit the genome even if it is only for the therapeutic purpose? Is the privacy maintained during survey analysis for genomics study? All these and many other questions are being faced by our society and addressing them is exceedingly important. A brief overview of ethical guidelines for genomic research consent is shown in Figure 1

Following are some of the communal ethical issues that arise with the genomics study

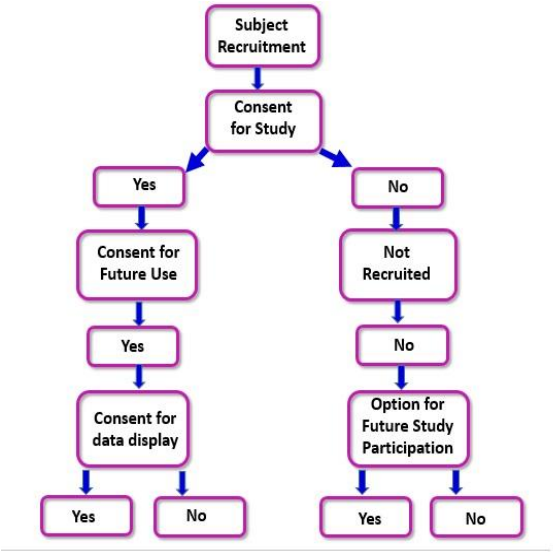

Figure1: Brief overview of ethical guidelines for genomic research

GENOME SEQUENCING

WGS (Whole Genome Sequencing) is the new powerful tool for genetic research and gene discovery in human. The diverse nature of WGS research is increasing the concern about the ethical issues related to it. Ethical considerations raised by WGS are somewhat like those raised by other applied genomic technologies in research. In every genetic research informed consent is an important requirement. The common rule makes it mandatory that researchers obtain informed consent for research that involves "a living individual". So, research permission be informed to the

person to sequence his/her genome. An informed consent must address the requirements of data protection and protection of human subject. WGS approaches should also be described in consent document but it is not necessary to explain the detail of a specific methodology. Goals of the research should be made clear to the participants in the informed consent procedure so that the patients may not expect direct therapeutic benefits from research. (Pinxten & Howard, 2014). Data obtained from genome sequencing of the research subject also possibly reveal information about DNA sequence of his/her close relatives, the consents of whom were not taken for participation in the research. This is a serious issue therefore, it is proposed that researcher conducting whole genome sequencing research should discuss this issue with the participant and encourage him/her to involve his/her close relatives in making decision about research participation. Also, the information generated about the third party, by the research activity, must be protected and kept confidential (McGuire, Caulfield, & Cho, 2008)

Sharing of data and samples for secondary use in other related researches may pose high risk to participant's privacy and autonomy if no mention of secondary uses was made in consent document. So, either the secondary user of data should stay within the primary study consent or re consent the participants for conducting further studies (Manasco, 2005).

WGS research usually reveals many results, which to return and share with participants is an important question as some people may assume these results to be helpful in making clinical decisions. The results obtained from lab research can never be used for this purpose unless results are confirmed in a clinical lab. If confirmed, researcher should notify physician and participant as these results may have an impact on treatment. If the results are of commercial benefit then it should be communicated to the participant and his/her consent should be taken before commercializing the results (Manasco, 2005). Results of unknown or no clinical significance are not returned to the participant (Wolf, 2013)and results of clinical validity but of no clinical utility (results that cannot be acted upon) are returned if the research subject prefer them(Wolf, 2013).

FUNCTIONAL GENOMICS

The development and application of global experimental approaches to assess gene function and interaction by using information provided by structural genomics is referred as Functional

genomics. It includes large-scale experimental methodologies or high-throughput combined with statistical or computational analysis of the results (Hieter & Boguski, 1997). Functional genomics as a mean of assessing phenotype is different from other approaches primarily with respect to the scale and automation of biological investigations. Modern functional genomics approaches would examine how 1,000 to 10,000 genes are expressed as a function of development in a single experiment. For years animals are used in research with modifications or manipulations for benefit of humans to identify human gene function, it represents a species modified to accommodate humanness, not just an animal enrolled in research. On the other hand, such experimentation imposes suffering to animals. According to epistemological theory gene sequences are same and doesn't matter in which specie they are present but from an ethical perspective gene sequences in different organisms is different (Hoeyer & Koch, 2006). Ethical issues regarding animal welfare can arise in all stages of genetically engineered animals such as invasiveness of procedures or methods, requirement of large number of animals and unpredicted welfare concerns. Other ethical issues include concerns over intellectual property, patents of genetically engineered animals and methods to create them (Caulfield & Gold, 2000).

CREATION OF BIOBANKS

Biological materials, an important tool in research and its associated databases for sample exchange among different organizations. Basic research on human biomaterials reveals structure, function, composition of cells, and sub cellular components, helps in molecular diagnostic of diseases and development in targeted therapies, pharmacogenetics and pharmacogenomics the way to personalized medicine also influenced by research. Apart from enormous benefits of research on samples taken from biobanks, ethical issues must be considered(Cambon-Thomsen,Ducournau , Gourraud, & Pontille, 2003). In the context of biobank, number of questions arises regarding the inform consent that when consent must be obtained and what information must be included in consent. With respect to biobanks privacy is another ethical issue. Different techniques are used to minimize these issues such as limit access to date, using privacy enhancing approaches. Another debating topic is intellectual property and ownership of participants, data, samples,

entire databases, and downstream products (Haga & Beskow, 2008)

GENOME EDITING

To amend any inherited genetic disorder gene editing is a potent tool which can either be done by using engineered nucleases like Zinc Finger Nucleases (ZNF), CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), TALEN (Transcription Activator like Effector Nuclease), Homing Endonuclease (HE) and Mega-TAL (Mega -Transcription activator like), induce double stranded breaks (DBS), which is repaired by DNA repair mechanism (Boissel et al., 2014; M Scharenberg, Duchateau, & Smith, 2013) or vectors like adeno-associated virus (AVV) and synthetic nucleotide templates(Khan, Hirata, & Russell, 2011). Genome editing is the modification in the genetic makeup, although it has emerged as a new therapeutic approach to cure disorders at genetic level as in case of hematopoietic diseases (Corrigan-Curay et al., 2015; Porteus, 2015)but there are several ethical concerns associated with germ line and somatic cell therapy. A committee regarding gene editing and ethical considerations related to it has been formed in conjunction with National Academy of Medicine (NAM), Royal Academy of Sciences, National Academy of Sciences (NAS) and Chinese Academy of Sciences (Moreno & Vaillancourt, 2016).

In germ line genome editing, intended or unintended, several ethical concerns arise. The spontaneous germ line alterations and hindrance in the normal functioning of the genes are attributed to the issues related to unintended genome editing. In case of intentional genome editing in which zygote is modified to correct genetic diseases but this may change the human gene pool or might re-create or create what exists or not naturally and usually a mosaic of edited zygote is formed which lead to practical limitations to germ line genome editing apart from ethical concerns(Kohn, Porteus, & Scharenberg, 2016).

There are no unique ethical concerns related to somatic cell modification through genome editing but these are associated with the nature, extent and applications of the gene editing process for example the clinical trials for HIV-1 were conducted using the cells edited using ZNF that disrupted the CCR5 HIV co-receptor (Tebas et al., 2014). There are ethical concerns regarding use of genome editing to enhance a function as in case of over expression of a therapeutic protein in resistance to HIV infection by

knocking out CCR5 or to modify HSC for the treatment of monochromatic leukodystrophy (Biffi et al., 2013) might lead to certain other cosmetic changes(Kohn et al., 2016) .

Gene editing poses serious genotoxic effects that need to be assessed and analyzed before any of the process is used. The integrating vectors might lead to uncontrolled integrations that may suppress the tumor suppressor genes or activate the proto-oncogenes while in case of nuclease mediated genome editing the DSBs may lead to the creation of an insertion or deletion and certain chromosomal aberrations due to wrong fusion of two DSBs. There are four limitations to the genome editing risk assessment;

1. The spontaneous mutagenesis in genome along with chromosomal rearrangements.
2. The current genotoxicity assays through sequencing has limit of detection 1: 10,000 thus there is a possibility that there could be undetected mutations and rearrangements in modified cells.
3. Whole genome sequencing can be used to assess genotoxicity but then it has low sensitivity and it might miss any oncogenic mutation.
4. There are many therapies that cause genotoxicity to cells that are not target to therapy, these should be recognized and assessed for risks. Functional genotoxic assays might be helpful, but no such tests have been established for human stem cells (Kohn et al., 2016). Although genome editing is a promising approach for treatment of various disorders but the raising ethical concerns and issues must be addressed and must be evaluated. At present there is no method efficient enough to evaluate the risks posed by the genome editing but protocols for safety assessment should be formed and issues like genotoxicity should be incorporated in them.

2. CONCLUSION

Genomics is promptly developing fields that will advent even more as the time progresses. Further research and insights in genomics holds great potential of saving lives, improving its standard and bringing a cure to diseases which are fatal at the present moment. As Spiderman says and we quote that with great power comes great responsibility so as studies in genomics advances more and more ethical issues will be raised these ethical issues must be addressed according to the need of time and ethical guidelines must be set and followed stringently for the greater good of humanity.

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