Review Paper

The Ethical Aspects of Germline Gene Editing

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ABSTRACT

Globally, Germline Gene Editing is considered as a cheap, efficient and accurate innovative tool. Genome editing techniques in general have contributed to the therapy of challenging human diseases such as various types of cancer, neurodegenerative diseases, Duchenne muscular dystrophy, AIDS, Sickle cell anemia, Hemophilia, Autism spectrum disorder etc. But due to the various scientific achievements there is the need for regulations and ethical guidelines. Various ethical issues emerge which need to be addressed. In this review, the ethical aspects related to the new innovation are dealt with. Germline Gene Editing has associated advantages as well as disadvantages. It is observed that the advantages outweigh the disadvantages. Nevertheless, Germline Gene Editing is not considered practical enough and there is a need for stringent guidelines on the global level. The ethical guidelines taken by involvement of states, judiciary and public engagements will be necessary in future to decide whether somatic or germline gene editing is permissible. Gene editing in human somatic cells is conducted for therapeutic purposes but basic and clinical research is required. Germline Gene editing may pose health risks for the present and future generations. Therefore, requires in-depth research, debates and clarifications of regulations and guidelines. Thus, it is also imperative and important to understand the scope and future approach pertaining to this new innovative technique.

Keywords: germline, somatic, editing, genome, therapy

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Introduction

Rapid advances in the field of biotechnology have occurred such that even sci-fi possibilities have manifested as reality at times. Similarly, even in the case of genetic modification which alter the structural genetics of human -beings as well as their off springs too [1]. Recently, genetic engineering has evolved a new tool known as clustered regularly interspaced short palindromic repeats (CRISPR) which has resulted in human genome research globally; being cheaper, more efficient and having greater accuracy than traditional gene editing techniques [2].

In this technique, a CRISPR-associated protein 9 (Cas9) is guided by a short ribonucleic acid (RNA) sequence (guide RNAs) which act like molecular scissors when aimed at specific genomic loci. The DNA cleavage activates cellular repair mechanism (non-homologous end-joining) leading to insertions or deletions of genetic sequences. This may be applied to cell -culture and in-vivo applications for the manipulation of early human embryos [3].

The editing process takes place by first DNA recognition, cleavage and then repair phase of the molecule. The enzymes modified by human interference are a) mega nucleases b) zinc -finger nucleases c) transcription activator -like effector nucleases d) CRISPR-Cas 9. The editing processes utilizes the genetic characteristics in-situ to make the genetic modifications [4].

Since 2013, CRISPR -Cas 9 is a prominent gene editing method for its precision involved and its broad range of applications in life sciences which includes agriculture, food production and medical therapies. It has advantages in treatment and prevention of human diseases especially monogenic disorders and alter clinical implications of polygenic diseases [5].

Due to scientific achievements in gene editing there is an urgent requirement to develop ethical guidelines and regulations. Ethical issues such as justice, harm, culture, religion, beneficence, discrimination and governmental regulations emerge [6].

The three major ethical and legal issues being i) the risk and uncertainty related to the technology and its applications ii) intervention in the human germline and implications on future generations iii) legitimization of concepts of the technique and enhancement. Since these conceptual issues are not clarified, therefore germline gene editing in human beings cannot be justified [3].

Gene editing in human somatic cells is beneficial for the treatment of diseases but the basic and clinical research must be conducted to improve editing techniques. Somatic gene editing is promising therapeutic tool but the risks of germ cell editing is risky and considered unethical. Germline gene editing may result in risks which include random mutations occurring in modified genome dangerous consequences for the future generations [4].

In context to Germline gene editing, the health risks are posed not only to the current generation but the future ones too. The various types of adverse events include off-target, pleiotropic , genetic and epigenetic changes. Pre-clinical safety research which includes human (embryo) research which prove germline gene editing. But this requires further debates, research and clarifications. This also means that in future , there is potential for germline gene editing which would involve date collection of reproductive outcomes and long-term follow -up of the future generations. But lack of funding, invading privacy and confidentiality and the issues that may crop up [7].

Genome editing techniques have contributed towards the therapeutic potentiality in challenging human diseases such as various types of cancer, neurodegenerative diseases, Duchenne muscular dystrophy, AIDS, sickle Cell anaemia, Haemophilia, autism spectrum disorder etc [8].

In the present review the pros and cons applicable to Germline gene editing are considered. The ethical aspects associated with the new innovation are also dealt with. The scope and future prospects of Germline gene editing are also outlined post review of scientific literature available.

Advantages of Germline Gene Editing:

- Germline gene editing is helpful in the prevention of monogenic diseases like Huntington's or β- thalassemia. This would also permit people with heritable diseases to reproduce without hereditary impact of the concerned disease.
- Individuals with genetic risks depend on embryo selection, gamete donation or adoption. Embryo selection mostly through pre-genetic diagnostic testing (PGD) is applied to ensure that the genetic defect is not inherited. In such case Germline Gene Editing can be another option.
- Germline Gene Editing can also be an option in cases of infertility of both sexes and could be a potential treatment option for e.g. in non-obstructive azoospermia (NOA) in males and missense mutation in TUBB8 in oocytes.
- Gamete donation is legally prohibited in certain countries due to ethical and legal restraints. It is also possible that off springs are genetically related to the couple of potential parents of the child by germline gene editing, but it is a strong predictor of allowing genetic modifications by Germline Gene Editing.
- The genetic defects of the population will eventually disappear from the germline. Thus, the mutation is inhibited from spreading in the gene pool of the population concerned by Germline Gene Editing.
- Germline Gene Editing advocates public health benefits by improving the health outcomes for future generations. That means the cell for genome -wise program of Germline Gene Editing. Thereby reducing the health -care costs [9].
- Germline Gene Editing could improve the understanding of several genetic diseases by usage of embryonic stem cell lies in diseases for e.g. Parkinson's disease.

- Usage of Germline Gene Editing will help understand the mystery pertaining to early embryo development in case of humans.
- In cases where in both the parents carry the gene for the particular disease and wish to avoid its transition to their children. Hence such types of genes can be edited by Germline Gene Editing [10].
- Since, it is practically not possible that polygenic disorders such as diabetes, heart diseases, schizophrenia and some types of cancer by preimplantation genetic diagnosis (PGD) as many embryos will be required in IVF clinics. Hence Gene Editing offers multiple modifications in a single embryo. Though all is speculative it is not improbable.
- Germline gene editing has advantages over somatic gene editing since it is more efficient in the prevention of multiorgan disorders as well as potential multigenerational preventive effects.
- The umpteen number of times pre – implantation genetic diagnosis (PGD) is executed can be avoided provided Germline Gene Editing is implemented and is not underestimated [11].
- For moral and scientific causes preclinical research on Germline Gene Editing is required prior to any potential clinical applications of Germline Gene Editing. This may mean experimentation on both animal and human embryos but considering the specific sensitivity of Germline Gene Editing it should be implemented with considerable monitoring and societal oversight.
- In the process of Germline Gene Editing utilization, the issue of how to handle the possible incidental derivations regarding the genetics of gamete donors or embryos should be considered in the informed consent as per guidelines [7].
- Although, germline gene editing is designed to treat diseases; enhancement of gene and cellular therapies are possible. at least nine areas would be benefitted from the advances in these fields a) infectiology b) oncology c) haematology d) hepatology e) neurology f) dermatology g) ophthalmology h) pneumology and i) organ transplantation.
- Gene editing would help create isogenic and animal modified cell lines to be utilized in basic biomedical research. Isogenic cells have specific and standardized genetic profile whereas "chimeras" or modified animals have characteristics inherent to human body. Therefore, researchers have at their disposal experimental models of control that enable the generalization of empirical knowledge.
- The genes may be edited to affect the growth e.g., myostatin gene limits growth. Once the action of the gene is inhibited, the mass of the animals like pigs and cattle can increase significantly making them consumer friendly which will positively impact transgenic food industry.
- Germline Gene editing also has macroenvironmental effects. Gene drive mechanism facilitates release of genetically modified organisms into nature to disseminate a certain genetic variant, prevailing over the species already prevalent in the environment.
- It is important to mention that germline gene editing would also imply that enhancements of human capacities such as cognition, physical performance and longevity since theoretically gene manipulation would enable so and will be on demand if practically implemented [4].

Disadvantages of Germline Gene Editing:

- There are safety issues attached to Germline Gene Editing. Hence there should be safety guidelines outlined to be implemented globally.
- Due to Germline Gene Editing off- target mutations which may result in cancer or other diseases.
- Germline Gene Editing performed on human embryos that would be brought to term would therefore cause disease and disability.
- In the cases of usage of embryos for Germline Gene editing; they may be at risk of harm and it would be morally and ethically incorrect.

- To minimize the harm induced due to Germline Gene Editing, the ethical code of conduct for usage of embryos permits the 14- day rule or limits on embryo usage and not implanted to complete gestation period [10].
- Informed Consent Process should be implemented in Germline Gene Editing. But the authority of the current individuals involved to make decisions on the behalf of the future generations is questionable.
- Considering the long-term impacts even the consent of the future generation would be required but that being practically impossible and absurd to implement.
- Further, it also means reduction in the autonomy of the future generations. since Germline Gene Editing means domination, manipulation or controlling the futuristic genetic makeup.
- Germline Gene Editing may lead to inequality, discrimination and societal conflict since the genes (germline) are being manipulated.
- It would also mean that Germline Gene Editing would be utilized for biological enhancement, which would lead to problem worldwide. But regulations and restrictions levied would prevent the ethical and moral risks of attached with enhancement of biologic characteristics [6, 10].
- Germline gene editing maybe misused in multiple ways and lead to abuse of power, thus the entire human race maybe victimized.
- The eugenics associated with germline gene editing, should not be ignored enabling the fittest to survive, the possible rise of clones, designer babies and possible super humans cannot be ignored.

Scope and Future Approach

- The research pertaining to Gene editing especially Germline Gene editing needs to be regulated with appropriate guidelines.
- Private funds are common mode of funding which also form a motivation to disregard ethics and public opinion. This should not be the case.
- There is need of following certain guidelines which will ensure accountable norms and moral values.
- Disclosure of all the conflict of Interest with the media and scientific publication is necessary.
- Institutions not journals must be accountable for managing Conflict of Interest.
- Usage of sophisticated informed consent including use of quizzes to depict subject comprehension.
- Monitoring by institutional research board or committee to review methods, data and follow up plan on a public data base registry.
- No presentations at scientific meetings without prior publication or public posting of methods, data and ethical compliance.
- Boycotts of any nation's germline work not in conformance with ethical standards at meetings and conferences.
- Loss of access to government or taxpayer supported charity funding for ethical violations.
- Deny any citations by name of investigators or their institutions in peer -reviewed literature of any germline work done out of compliance.
- National and international statements outlining appropriate goals for Germline Gene Editing based on public inputs.
- Periodic mandatory training in ethical foe executing Germline Gene editing (13).
- Ensure that harmful effects of Germline Gene Editing are prevented by relevant guidelines and procedures.
- Protection of human rights and rights of future generations must be the foundation of legal viewpoints.

- In event of lack of legal interests, the right to life or attain the quality grade health as well as to preserve the human genome and right to genome identity- the legislator must opt for the owned that deserves highest protection.
- There is immense requirement for the process of deliberation and better governance in which all stakeholders of research participate and express their opinion prior to applying gene editing, enabling public empowerment too.
- In this manner it will be possible to unify scientific dev elopement with public viewpoints and social justice with the legal system to support in the decision that will eventually transform the future of mankind [14-15].
- Due to democratization of genetic tools required for gene editing, international scientific and legislative bodies are to develop guidelines. This will involve public engagement and basic principles of ethics.to respect the autonomy of the individuals and respect the diversity of the population. Human rights impact assessment should be done which involves public especially the vulnerable members of the society to express their opinions and concerns regarding Germline Gene Editing. Regulatory bodies and policy makers should adopt this assessment approach to enable a framework that is necessary for global protection of human rights [16].
- Precision medicine uses genetic tools in health-care model to make medicine more predictive, preventive and precise. The treatment plan can be customized as per individual characteristics of a patient by integrating multiple data sources with molecular analysis of disease.
- Gene editing applications extend to the prevention and treatment of disease, facilitated by cellular models of pathology of disease and novel therapeutic strategies. This widens the usage of gene editing in research and biomedical therapies [17].
- Vulnerability issue has a significant role towards Germline Gene Editing. Considering the instance of parent vulnerability but that of parent's autonomy is enhanced or respected by offspring by offering the intervention. But they are vulnerable if the informed consent does not state the purpose and the design of research conducted.
- The second group of vulnerable individuals are women of reproductive age. There is burden of care for the off springs healthy or with disability falls on the women in most societies and culture. The prospective children are vulnerable since they are highly susceptible and unable to prevent physical and moral harm done by these interventions. In Germline Gene Editing this means the many generations of children in future will be affected.
- Vulnerable are the weaker or poorer groups of people from the global viewpoint since the new innovation are unlikely to reach them which relates to allocation of research fundings too.
- The World Health Organization report emphasizes the centralization of values such as equity, social justice, moral values and global health justice in decision making policies pertaining to Germline Gene Editing. This will prevent discriminations and explicit policy commitments. A policy of thoroughly reviewing and monitoring the ethical code of conduct of research globally should be addressed [18].
- Precautionary principle will influence the decision-making in contexts where some human activity poses threat as in Germline Gene Editing. Hence it is required that a positive precautionary principle recommend the innovation but weighs on avoiding health, public welfare threat posed and other unresolved key questions [19].

Gene editing raises perplexing questions, and the issues need to be resolved. The Bioethics and Law Observatory was one of the first institutions to launch a Declaration that aims to analyze CRISPR from interdisciplinary viewpoints and promote ethically acceptable research and informed public discussions on this topic. Ethical concerns are hence raised globally. According to Bioethics and Law Observatory, the global discussion pertaining to Gene Editing is a requirement due to two main reasons. Primarily there is increased interest in the development of the innovative technique and its social impact. Secondly since there are both advantages and

disadvantages as aptly cited even in this review, thus further research is needed before its application globally. There are a wide range of opinions hence a mixed response regarding the ethical and legal framework in which this type of research needs to be conducted and in which case this innovation needs to be applied.

Conclusion

Germline Gene Editing is the type of Gene Editing which requires attention and consideration. The reason being considering that both the advantages and disadvantages it becomes rather difficult to decide. However, it is observed that the advantage outweighs the disadvantages. Nevertheless, it is not practical enough when it comes to Germline Gene Editing which requires stringent guidelines globally. There are futuristic scope but the underlying factor and the need of the present scenario is the involvement of states, governments , judiciary and public engagements in discussions. This will enable to arrive at the ethical guidelines and safety regulations needed in this direction for future clarity.

Such type of governance at the global level will facilitate a decision which has been facing the test of time. That is whether to proceed with implementation of stringent guidelines and regulations or not utilize the gene editing on germ cells and embryos but restrict only to somatic cells in future with ethical considerations.

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