EDITORIAL

Ethical Controversies and Challenges in Human Genome Editing

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ABSTRACT

Human genome editing consists of human somatic cells editing and human germ layer editing. Somatic cell editing utilizes all human cells except reproductive cells. Germ layer editing includes reproductive cells. Any changes made by germline editing is passed through generations. Arrival of CRISPR technology and its increasing utilization has also raised concern and controversies in ethical areas. Somatic cell editing enables cells causing heritable disease to be replaced by normal somatic cells and elimination of heritable disease. Further basic and clinical research for somatic cell editing have increased for therapeutic purposes, and are considered an asset for the elimination of heritable disease in the future. At present, the ethical needs in somatic cell editing are safety, risk-benefit calculation, protection of vulnerable subjects, informed consent and equity of access. The ethical concerns and controversies surrounding germline editing are: whether potential benefits outweigh the potential risks, therapeutic need, affordability and equity. The most important controversy lies in intergenerational effects and raises the question as to whether the benefits outweigh the risks of utilizing germline editing. Further, this type of research and clinical process violates fundamental values, ethical governance and societal safety. The ethics of embryo research is also in need of revision because of controversial research conducted by Dr. H.E. Jiankui. Slippery slope concerns, for example, 1. allowing basic research in human embryos with germline editing 2. risk of moving from basic research to therapeutic stage and 3. allowing basic and clinical research with genome editing of somatic cells may open the door to basic and clinical research on germline editing. Thus, safety and beyond safety concerns, with lack of good governance, pose: danger of potential harm to the child who was unable to give consent to this process, potential for any state to impose eugenic application, commodification of children, social inequality and criminal use of this technique, are still to be resolved. In spite of the benefit of resolving human illness, ethical questions, controversies and challenges remain, particularly from human germline editing.

KEY WORDS

human genome editing, ethical controversies, human germ layer editing, human somatic cell editing, basic and clinical research

INTRODUCTION

In 1993 Francisco Mojica *et al*.[1,5] discovered what is now known as "clustered regularly interspaced short palindromic repeats" (CRISPR). Jinek *et al*.[2,5] in 2012 combined crRNA and tracRNA molecules into a sole molecule of single RNA. This facilitated successful genome editing in mammalian cells by CRISPER-Cas9 system[3,5]. In the human genome, this system was repeated successfully in 2013[3-5]. Liang *et al*.[6] in 2015 announced that the CRISPR-Cas9 gene editing technique was used to modify the DNA sequences on human embryo for the first time[6,7].

CRISPR-Cas9 has become a game changer[8,9] in the field of human engineering. This system has superior efficacy, superior safety, is more precise, popular, has economic benefits and has markedly easy accessibility for obtaining results. This technique uses enzymes[7] rather than virus to alter DNA. As utilization of CRISPR-Cas9 rapidly increased, it brought high levels of disruption for gene editing[8-12] research and the ethical landscape. Concern, controversy and challenges arose across the ethical landscape in human genome editing.

Human genome editing consists of 1. Human somatic cell editing and 2. Human germline editing (GGE). Human somatic cell editing utilizes all human cells except reproductive cells. This enables somatic cell editing to replace monogenetic heritable disease cells, to be replaced by normal somatic cells, thus eliminating monogenetic diseases and disorders[8]. GGE includes reproductive cells and early embryos. Any changes by GGE are passed through generations[7,8]. GGE potentially enables targeting the editing of genes responsible for monogenic and polygenic diseases and disorders, and to spread resistance of infectious diseases[7-9,12,13].

SOMATIC GENOME EDITING AND ITS ETHICAL ISSUES AND CONCERNS

The ethical appraisal of somatic genome editing falls into two opposing groups. The majority of supporting groups include: 1.) The

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Organizing Committee of the 2015 International Summit of Human Genome Editing[14,17,18] and 2.) The 2017 US National Academies of Science, Engineering and Medicine (NASEM)[15,16,19]. These groups along with other ethicists and researchers suggestions, places CRISPR somatic genome editing to be governed by existing ethics for gene therapy. The view of the above groups of researchers and ethicists is that CRISPR somatic genome editing does not cause any concerns and challenges. Thus, the gene therapy ethical committee will be sufficient to appropriately and rigorously evaluate potential safety, harm, and benefits of somatic cell editing. NAS-NAM reports have also suggested that gene therapy committee is sufficient enough to manage somatic genome editing with a strong and rigid ethical safeguard[8,14,15]. According to this group, the gene therapy regulatory mechanism has been very successful in preventing unauthorized uses of research in the area of gene therapy research.

The opposing groups[22-24] indicate that CRISPR somatic genome editing is novel, unprecedented and questions whether the sufficiency of existing gene therapy regulation is able to govern efficiently for the extension of their new responsibility. The lack of capability and the lack of coordination across jurisdictions, will hamper the evaluation of safety, efficacy and utility. High variability of biological manufacturing processes for the individual focus need, protection of the vulnerable patient, informed consent, and above all stakeholders for further conversation requires separate ethical regulatory mechanism for the somatic genome editing.

However, majority views are that human somatic genome editing should be allowed to treat or prevent diseases and disability, by the Food and Drug Administration's (FDA) gene therapy mechanism. Clinical trial with CRISPR human somatic genome editing have been allowed (including by FDA) and these trials have been started[25-29]. The specificity of approved product regulation may limit the use and special requirements are in place to ensure that somatic genome editing may not inadvertently involve the germline genome editing studies. Expansion in future of genome editing for other purposes should be based on the inclusive stakeholders' conversation.

GGE ETHICAL CONTROVERSIES, CONCERNS AND CHALLENGES

In 2015, heightened concern and controversies arose after a study by a Chinese scientist was published describing the use of CRISPR-Cas9 for modifying the DNA of a non viable human embryo[6]. In 2018, Chinese scientist Dr. He Jiankui edited the genome of two embryos for making them resistant to human HIV by disabling the gene CCR5[30,31] and resulted in producing two baby girls. One baby has both copies of gene modified making her resistant to HIV while the other baby has only one which makes her still susceptible to HIV[31-33]. This research news magnified the concern of ethicists and scientists throughout the world.

Before considering any ethical issues and heightened concern, the important question is to find whether there is need for humans to utilize the CRISPR-Cas9 germline genome editing, when other similar technologies are available. Scientists and researchers in favour of using GGE point out the need of harmful mutation in embryos and gametes responsible for monogenetical disorders, for preventing harmful genetic disorders. Most scientists in favour also argue the medical need for GGE is so compelling that GGE is a moral imperative and using it will lighten the burden of human existence[8,34].

IVF and preimplantation genetic diagnosis (PGD) can also provide similar help. However, supporting groups in favour of GGE point out that by GGE, the risk of passing genetic disorder is eliminated for future generations. Further, they also argue that PGD and IVF are similar technologies, and are approved for research and clinical use, hence, GGE should also be allowed.

Use of GGE means to have genetically related children for couples affected by disorders for which PGD is ineffective, particularly in cases where no unaffected embryo can be created. A more vital question for these couples who want genetically related children, but that present technologies cannot provide, is to consider GGE. This is a normative consideration and important one in favour of GGE. There are many cases (several hundred) worldwide where GGE would be the only option to create unaffected embryo. Thus, GGE has the potential to: 1. prevent the transmission of genetic variants known to be associated with serious illness and conditions[12,44] 2. lessen the chances of developing serious illness or disabilities 3. enhance human function[16] and 4. use of GGE justified because it can improve clinical use of IVF and also shed light on causes of early miscarriage.

BASIC RESEARCH WITH GGE

GGE deals with: 1. the importance of increased knowledge 2. research activities involving human embryo, and 3. questions about oocyte donation and increased new information[8,20]. Thus, basic research with GGE on human embryo will bring: a) increased efficiency and precision which may help to understand differences between human and animal developmental biology[8,20,35] and b) the preliminary data obtained from research will help in improving somatic genome editing, thereby improving the understanding and knowledge of genetic disease and mechanism of early human development[35,36]. Information obtained from research will also improve the therapeutic benefit of IVF by reducing incident of early miscarriage[20].

RESEARCH INVOLVING HUMAN EMBRYOS

Research activities require destruction of human embryo which is opposed by many ethicists and clinicians alike[16,20,27,37,38]. Scientists also have brought another important issue of extending the statutory limit of research beyond 14 days limit to 16 or 17 days[38-40] and will also help to understand the mechanism of gastrulation which takes place on 16th -17th day after fertilization[38].

The women's oocytes for GGE need protection from risk of coercion and exploitation. Lastly, slippery slope concerns also have become very important[20,41-43]. Slippery slope concerns are: 1. allowing basic research in human embryos with GGE may lend to future clinical research which at present time is ethically very troubling 2. allowing basic and clinical research with genome editing on human somatic cells may lead the way eventually to bring basic and clinical research on GGE and 3. the risk of moving from therapeutic stage to enhancing in GGE. Thus, the ethical concern about above are important for new ethical considerations.

SAFETY OF CRISPR TECHNOLOGY

The safety of CRISPR technology is a very important part of the ethical debate. In spite of being described as a very safe and novel technique, this technique still has several limitations like other technologies for genome editing. The limitations are: a) limited on-target efficiency

b) incomplete editing may result in mosaicism and c) inaccurate both on-target and off-target editing[8,37].

Intergenerational long-term effects on future generations[20] and moving from pre-clinical to clinical research areas, are two vital considerations for ethical issues[20,45,46].

Pre-clinical research activities can give a great deal of direction towards safety but still many scientists and ethicists believe that even safety based on scientific pre-clinical research is not safe enough. In other words, particularly knowing the benefit of technology and "how safe is safe enough", so that acceptance will become real[20].

Another debated issue is "violation of future generations' (children) capacity to live as autonomous agents when their makeup are designated genetically without their consent"[46-48]. Harris in his article[13] has rejected the above views. UNESCO panel experts have raised related issues and suggested GGE threatens "equal and inherent dignity of all human beings"[49] whereas a famous legal expert[50] has rejected these claims and described it as "genomic metaphysics"[50,55] and essentialist vision[50,54]. In relation to respecting dignity by not altering the human germline, is the idea of protecting the human gene pool as a distinct collective heritage.

GGE can cause social inequalities and shifting of social norms particularly if it is available in selected countries or selected people[15,51,52]. The present acceptable norm of reproductive settings can be changed by GGE and prospective parents can be under pressure and expectation to avoid conception of embryos and fetuses that carry harmful genetic mutation[20,51].

Supporters of GGE suggest on the contrary, that GGE will address the natural inequalities[51,52]. An important concern about GGE is that it causes negative exacerbating views of people living with disabilities, which GGE will correct[51,52]. Nuffield Council[51] in 2018 reported and suggested that adopting the principle of "social justice and solidarity" will prevent GGE creating the above concern.

Other various criticisms of GGE include that it brings: 1. disrespect of DNA as human heritage 2. challenges of God's role 3. lack of informed consent by children of future generations affected[4] 4. negative impact on individual with disabilities 5. perception of parental negligence for deciding against GGE 6. unknown and unpredictable risks of creating novel genome mutation 7. commodification of children[8]. 8 danger of state imposed eugenic application and 9. potential for criminal activities[16].

The complicated and tricky concern of enhancement by GGE is another important point to consider. The longstanding debate on the distinction between treatment and enhancement should be considered[15,51] and GGE should be employed only to edit harmful mutation for the welfare of persons[12].

However, on a scientific thinking basis, every treatment improves disabilities and brings a better and more successful life, but also has some degree of enhancement (for example, plastic surgery and cosmetic surgery), which are at present approved. Supporters of GGE have answered the above various criticisms but very little agreement has been reached between supporters and opposers (either side). However, one should remember genome is not static and every generation like the generation before has gone through series of mutations in one life-time. Scientists and ethicists still have time to compromise but both sides should agree to have strict, regulated, effective, and controlling governance of genome editing. This is a vital step to bring basic research and future possibilities for therapeutic uses and increased clinical research activities. Socially just mechanism for GGE with a goal to serve public interest, based on broad and inclusive social debate will be a satisfactory answer. Various organizations including the WHO expert advisory panel[8], NCBI[56], ASHB[25] (American Society of Human Genetics Board), Nuffield Council on Bioethics[51], European Ovidio Convention[53], NAS/NAM[16] and many others have suggestions and comments on GGE, an unprecedented, novel, CRISPR technology.

The majority of organizations have accepted basic research and therapeutic activities on GGE provided there is good governance of GGE, which should be based on following guidance: 1. to promote well being of human kind 2. responsible science 3. transparency in all action and steps in research or therapeutic activities 4. due care of patients participating in the research study, that is careful, deliberate, and based on sufficient scientific evidence 5. respect for patients participating, which requires recognition of dignity, integrity, acceptance of choice, and respect for individual decisions 6. transnational cooperation, support of commitment to a collaborative approach, and respecting different cultural contexts 7. fairness-equitable distribution of the burden and benefit of research taking into account the risk/benefit evaluation.

GGE research should only proceed when: 1. reliable oversight mechanism exists to prevent extension to use it other than for preventing serious disease or conditions 2. there is an absence of reasonable alternatives and compelling medical rationale 3. evidence based that supports clinical use 4. maximal transparency consistent with patients privacy 5. limiting to converting such genes that has been convincingly demonstrated to cause or predispose to that disease 6. ethical justification and approval with REB and obtain informed consent 7. comprehensive plan for long-term multi-generational follow-up that also respect personal autonomy 8. credible pre-clinical or clinical data on risk and potential health benefit from GGE 9. converting genes to version that are prevalent in general population and reliable to ordinary health and benefit or no evidence of serious adverse reaction 10. ongoing vigorous oversight during clinical trial of GGE for safety and efficacy 11. clear and continuing public process to solicit and incorporate stakeholders' input 12. continued reassessment health and societal benefit and risk with public participation 13. balancing individual level of benefit and societal level of risk.

CONCLUSION

Present analysis shows that the main concern in human somatic cell editing (genome) is whether existing research ethics of gene therapy and oversight mechanism are sufficient enough or needs further enhancement or revised ethics, and oversight mechanism. Majority of opinions agree that existing gene therapy ethics and oversight mechanism should be revised to include the above suggestions provided by various panels, committees and experts, as described above.

The oversight mechanism should have enhanced additional power and means to supervise the basic research, pre-clinical and clinical area of research activities of human somatic cell editing.

There should be international agreement and that should be followed hopefully worldwide. Above should meet in balanced form of the individual benefit and societal level of risk.

Human genome germline editing (GGE) is the area of worrisome changes in future babies. If new ethical guidelines as described above are not prepared with very strict governance, then it should be taken into account before ethical decision is taken for GGE. If it requires new governance, that should again consider all the guidance above and should seek researcher to keep their activities within its boundary rigidly.

At this stage, only basic research on GGE should be allowed to proceed based on data coming out of these basic research studies. Plans for restricted, therapeutic, clinical trials with the new ethical guidelines, and governance with strong oversight mechanism should be considered. The fact remains that GGE for therapeutic purposes should be endeavoured with caution and under new ethical and governance guidelines. Caution does not mean prohibition of appropriate therapeutic uses of clinical trials, results of which are for the betterment of human health. Fears of GGE taking steps beyond the above described ethical and governance regulations should be stopped by strong, strict and rigid oversight mechanism. As a famous scientist said "ethics is the study of what we ought to do; science is the study of how the world works"[31]. The hope is that both ethics and science in combination will bring the best outcomes for any research activities including somatic genome editing and germline genome editing (GGE).

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