

# Heritable genome editing: looking through the crystal ball



Dr Deepak Modi

Scientist F and Head Molecular and Cellular Biology laboratory

ICMR-National Institute for Research in Reproductive Health

Indian Council of Medical Research

Parel, Mumbai 400012

E-mail: [deepaknmodi@yahoo.com](mailto:deepaknmodi@yahoo.com)

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Wishing all the readers of "Polymorphism" a happy and productive 2020. On behalf of the editorial team, I thank you for supporting us and look forward for your continuous backing in the years to come. It is that time of the year when we look back and plan the future. Mankind witnessed a historic moment in the year 2018 in the area of genes and genomics. This is referring to the birth of the gene-edited babies on Nov. 25, 2018, announced by the Chinese scientist He Jiankui. This news sent shockwaves within and outside the scientific fraternity. It has been a year since then and in this 2020 opening issue of "Polymorphism", we thought it would be appropriate to discuss what happened in the last one year in the area of heritable genome editing through the crystal ball for a better tomorrow.

Amongst the several tools available for gene editing, the CRISPR is one of the most robust systems that allow accurate deletions, additions, or replacements of the nucleotides in the target genome. Since its invention, CRISPR technology has undergone several modifications and the present day CRISPR technology has been tested on a variety of cell types and organisms. It is now found to be very specific, robust and reproducible. With the promising results in other systems, scientists have applied CRISPR in human embryos to correct the beta thalassemia mutations, mutation causing cardiomyopathy and also deletion of the gene for CCR5 that aids HIV entry into the cells (Kang et al., 2016; Li et al., 2017; Liang et al., 2017; Ma et al., 2017). With a

steep learning curve, enough progress has been made to apply CRISPR in expanding our basic understanding of early human embryogenesis (Fogarty et al., 2017). While we still debate the nitty-gritties of the experiments and argue for and against its clinical applications (Lea and Niakan, 2019), He Jiankui announced two live births in which the babies have had their CCR5 gene deleted embryonically. Although this has not yet made it to any formal publication, based on non-peer reviewed reports, it presently appears that the editing is possibly incomplete, and the babies born are mosaics. This highlights the inadequacy of the technology or that of Jiankui. While it is impossible to verify any of the claims in the absence of data availability, the knee-jerk reaction of the scientific and the bioethics fraternity against this experiment was not unanticipated, leading to the suspension of all studies for embryo or heritable genome editing (Lander et al., 2019). However, some scientists view this moratorium as a self-imposed hurdle towards research on genome editing of human embryos that will delay the possibility of genome editing for a healthy tomorrow (Macintosh, 2019). Irrespective of the global debate, Russian scientists have already announced their plans for gene edited babies for the deafness gene GJB2, and CCR5 (Cyranoski, 2019).

While the debates on the bioethics aspects of the heritable genome editing continue, several new experiments on primate embryos and embryonic stem cells using CRISPR have been

published (Zeng et al., 2018; Kumita et al., 2019; Rath et al., 2019; Zhang et al., 2019). The studies largely addressed if CRISPR technique can edit the gene in every cell, preventing mosaicism and avoid the off-target effects in human embryos. While the technology is evolving and methods are being optimized, the results published are quite assuring; the following points need to be borne in mind while considering CRISPR technology in human assisted reproduction for producing genome-edited children: 1) Embryonic genomes can be edited with minimal off-target effects, 2) The precise mechanism by which the editing has been achieved is yet unclear, 3) The editing is most reliable only when applied in oocytes just before fertilization. Editing after pronuclear fusion leads to mosaicism.

Therefore, for practical use, one will need to apply pre-implantation genetic testing (PGT) to identify the embryos that will need preimplantation genetic correction (PGC). However, the present day PGT is reliable at the blastocyst stage while PGC needs to be applied at fertilization. Thus, at present CRISPR technology can be applied only to maternally inherited genetic conditions, making the scope of its applications very limited.

Regardless of these limitations, I see the glass as half full. Technically, we have overcome many hurdles and progressed considerably. Interestingly, there is a perceived demand of germline genome editing to being with for autosomal dominant and mitochondrial disorders (Cohen et al., 2019; Viotti et al., 2019).

It is a matter of time that the assisted reproduction clinics will not just make embryos but will also diagnose them and even correct them before initiating the pregnancy. The realms assisted reproduction clinics to occupy will magnify beyond fertility management.

Like any other technology, concerns are raised on the misuse of CRISPR technology in human embryos. In the light of eugenics, issues such as editing of mutations for treatable conditions and correction of mutations of late onset disease or those with incomplete or low penetrance (e.g., schizophrenia and autism mutations, the heritable cancer mutations) are being heavily debated. The concern of "positive eugenics" of "desired traits" (e.g. intelligence, physical appearance) and "social genetics" (HLA matched embryos) is growing amongst the circles of social scientists and bioethicists. However, the assisted reproduction fraternity is not new to such concerns of "slippery slope" and "designer baby." The society had already faced similar dilemmas and knee jerk reactions when In Vitro Fertilization (IVF) was first demonstrated and PGT was first applied clinically.

The ordeals faced by Bob Edward and Siddharth Mukherjee are infamous, and we all have witnessed the hostility of the system. However, today the technology has heightened to a point where we not only offer fertility to couples with involuntary childlessness but also give the joy of biological parenthood to couples with other sexual preferences and even singles. It is the time to

learn from these examples and not let history repeat itself. Let us admit that the heritable genome editing is a reality and beneficial to society at large. Outlawing it will only push it under the carpet, will only lead to its further abuse and cause more harm than good. It will only delay the scientific progress and have long term social implications, including stigmatization of children born with modified genomes. Instead, I urge that we all work together and set up the guidelines to define steps that will be required to appropriately use heritable genome editing without distinguishing between beneficial and augmenting modifications.

The medical and scientific fraternity is accountable to take the appropriate steps and establish progressive guidelines to make sure that the human embryo genome editing is placed in responsible hands and not judged by unadorned morality. We are and should be the torch bearers in developing the strategies for heritable genome editing and making a positive impact for the benefit of mankind.

**Note:** The views expressed in the article (OTH/885/12-2019) are of the author and not necessary of those of ICMR or NIRRH.

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