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ORIGINAL ARTICLE

Ethical issues in human germline gene editing: a perspective from China

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Abstract

The ethical issues associated with germline gene modification and embryo research are some of the most contentious in current international science policy debates. In this paper, we argue that new genetic techniques, such as CRISPR, demonstrate that there is an urgent need for China to develop its own regulatory and ethical framework governing new developments in genetic and embryo research. While China has in place a regulatory framework, it needs to be strengthened to include better compliance oversight and explicit criteria for how different types of research should be reviewed by regulatory authorities. We also document a variety of opinions about the new technologies among the public, scholars, and policy makers. China needs to develop its own regulations in coordination with other countries; but it is unlikely that an international consensus will be achieved in this area, given the existing differences in regulations between countries. We should aim at harmonization, not necessarily complete consensus, and the perspective from China is vital when international norms are developed and harmonized. Chinese policy makers and researchers need to be aware of the international discussions, at the same time as the international community is aware of, and accommodates, Chinese positions on important policy options.

Keywords Germline · Gene editing · China · 14-Day rule · Human embryo

Abbreviations

CRISPR	Clustered regularly interspaced short palindromic repeats
HFEA	Human fertilization & embryology authority

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NHFPC	National health and family planning commission
MOST	Ministry of science and technology
NIH	National Institutes of Health
ISSCR	International society for stem cell research

1 Introduction

The ethical issues associated with germline gene modification and embryo research are some of the most contentious in current international science policy debates. These issues have received new attention with the introduction of the gene editing technology CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). Chinese scientists have been at the forefront of genetics research in general, and in the use of this technique for editing the genomes of human embryos in particular (Kang et al. 2016; Tang et al. 2017; Liang et al. 2015; Liu et al. 2018) and relevant Chinese research has been the center of attention in several recent international news reports. This began with Dr. Huang's research published in 2015 (Liang et al. 2015), and continued in November 2018 when Dr. He announced that two children had been born after their genomes had been edited using the CRISPR technique (CNN 2018). In both cases, criticism was swift that Chinese researchers had violated generally accepted ethical principles (Tatlow 2015). In Dr. Huang's case, it quickly became clear that his research, although controversial, was well within the boundary of acceptable practices. First, the embryos on which the research was done were all triploid, and discarded before 14 days. Second, the embryos were all left over from assisted reproduction clinics, and researchers obtained informed consent from couples who were told that their embryos would be used in certain types of research rather than for any reproductive purpose. Many scientists and bioethicists therefore agreed that Dr. Huang's research was ethically acceptable (Callaway 2016). This has been confirmed by the approvals in the UK by the Human Fertilization & Embryology Authority (HFEA) for such research in the beginning of 2016 (HFEA 2016) and by subsequent publications of such research in the US (Connor 2017; Belluck 2017).

Dr. He's research, however, seemed to confirm the worst fears of China's critics, that this was a country where "anything goes" and with rampant disregard for the ethics of research (CNN 2018). In general, there is considerable skepticism about China's ability to regulate the new technologies appropriately, and there are worries that China will permit research that is rejected by major international organizations, scientists, and bioethicists outside of China. In this paper, we present reasons why these worries are not warranted, by giving a short overview of relevant regulations of genetic technologies in China and the public discussion about the ethical issues raised by them in Chinese media. We shall also argue that China faces a considerable challenge to update current regulations, especially in light of the vigorous ethics debate that is also taking place within the country. China cannot simply copy international regulations or guidelines, but will have to adopt a regulatory framework that is both in line with existing Chinese legal traditions as well as in line with the diversity of attitudes and opinions within its population. Nevertheless, it seems clear that China will at some time in the future allow clinical applications of genetic

changes in human embryos, together with at least a few other countries. This position will likely still be controversial, with some countries continuing to prohibit any genetic changes in human embryos. We conclude the paper by arguing that international consensus is neither desirable nor feasible, and that we will have to accept that different countries will develop their own ways of regulating these new technologies. Different countries' regulations should be in harmony, but not necessarily identical.

2 The current regulatory and ethical framework in China

China has over the past few decades developed a regulatory framework for research on human subjects in general and genomic research in particular, including research using embryos and stem cells. There are basically two sets of rules that apply to research on embryos, including genome modification.

First, there are rules governing human subjects research (including research that involves human biological samples) promulgated by the China Food and Drug Administration (CFDA), the National Health and Family Planning Commission (NHFPC), and the Ministry of Science and Technology (MOST) (Regulations on ethical reviews of biomedical research involving human beings (trial implementation) (In Chinese) 2007; Regulations on ethical reviews of biomedical research involving human beings (In Chinese) 2016; Ethical guiding principles for ethical review of clinical trials for drugs (In Chinese) 2010). The first general human subjects regulation was introduced by the then Ministry of Health in 2007 and updated in 2016 by the NHFPC. There are special regulations for clinical research promulgated by the CFDA. These regulations include requirements for review by an independent institutional review board (IRB) as well as informed consent requirements. The 2016 rules strengthened oversight mechanisms. Researchers are required to get ethics approval before research starts. There are provincial level committees that are responsible for ensuring proper review by institutional committees in their provinces, and there is a national oversight committee. The regulations require that particular types of research are reviewed either by provincial-level committees or the national committee. There are penalties associated with violations. These are not specified, but individual researchers, chairs of ethics review committees and institutions can all be held liable for violations. However, the NHFPC can only regulate and supervise medical institutions, not universities or other research institutions, which are under MOST.

Second, there are regulations governing the use of Artificial Reproductive Technologies (ARTs) (Notice of the ministry of health on amending the technical specifications, basic standards, and ethical principles related to human-assisted reproductive technology and human sperm bank 2003). There is a licensing requirement for clinics where such procedures are performed. The Chinese government has the power to close clinics that are in violation of the regulations, and it has done so in the past (China Targets Reproductive Technology Abuse 2013).

In the case of Dr. He, a number of officials, both in the institutions involved in the research and the two relevant ministries, called for an investigation of possible violations of the regulations. Dr. He could himself have violated the human subjects

research regulations, and also general provisions in the criminal law. The institutions where he did his work could have violated regulations related to the licensing of ART clinics and the human subjects research regulations. There could thus be penalties both to Dr. He as an individual and to the institutions involved.

There is an additional document that is often mentioned in relation to the recent case. Partly in response to the research published on human-animal chimeras by the Chinese scientist Huizhen Sheng on a rabbit (Chen et al. 2003), which raised concerns both inside and outside of China about embryo research, the Ministry of Health and Ministry of Science and Technology jointly issued the "Ethical Guidelines for Human Embryonic Stem Cell Research" in 2003. (Ethical Guiding Principles for Human Embryonic Stem Cell Research (In Chinese) 2003) These Guidelines mandate that all human embryo research should comply with Chinese laws and regulations, and respect and observe "internationally recognized bioethics guidelines," without mentioning any specific international guidelines. It is illegal in China to manipulate the genome of the human gamete or embryo (including via mitochondrial transfer) for reproductive purposes, and forbidden to transfer the blastocysts which have been used for research into the reproductive systems of humans or any other animals. This implies that basic scientific research on germline gene editing is permissible but not research in clinical trials or clinical practice. The Chinese guidelines specify that: (1) Culture of embryos in vitro beyond 14 days after fertilization or nuclear transfer are not allowed, (2) Human-animal chimera embryo research and human-animal hybrids are forbidden, and (3) Research on human cloning for reproductive purposes is forbidden.

Even though the ban on germline genetic modification in China is called for in guidelines rather than laws or regulations, these guidelines do have some regulatory force. "Guidelines"(*指南*) or "guiding principles"(*指导原则*) in China do have legal consequences. (Ethical guiding principles for ethical review of clinical trials for drugs (In Chinese) 2010; Sipp and Pei 2016) For example, the "Ethical Guiding Principles for Human Embryonic Stem Cell Research" specifically state that "Any research activity involving human stem cells in China *must* follow these guidelines"; they give the relevant ministry agencies power to interpret and enforce the guidelines.(Ethical Guiding Principles for Human Embryonic Stem Cell Research (In Chinese) 2003) In China, people who do not follow guidelines may suffer financial penalties, loss of funding from the government, or even lose their job.(Sipp and Pei 2016).

In spite of these regulations, given the fast pace of research, worries are raised about the possibility that rogue scientists will carry out projects prematurely, without proper assessment, and thereby cause immediate and long-term harm to individuals and society. At the moment, there are no systematic and thorough reviews or quality assessment of decisions made by individual research ethics review committees. There are also no mandates that committees reviewing such research must use specific criteria. There is no *criminal* penalty for those who violate the guidelines and regulations; but there is now an attempt by some doctors, lawyers, and bioethicists to promote these to the level of law with associated criminal penalties. Chinese scientists have themselves issued appeals for the introduction of transparent regulations or guidelines that will regulate research of human germline gene editing, including determination of which kinds of research may or may not be done; and

they are concerned that appropriate basic research may fuel the ethical debate and thereby hinder research with good scientific and ethical quality.

Judging from the reaction of government officials and influential scientists to the case of Dr. He, it seems likely that the Chinese regulations of embryo research will be strengthened. This would include both enforcement mechanisms and criteria for the approval and prohibition of different types of research. However, as will be evident in the next section, it is at the moment not at all clear what the specific features this strengthening will have. There are considerable variations in attitudes towards embryo research among the public, scientists, and policy makers, making it difficult to predict what will emerge as a consensus about appropriate regulation in China.

3 Public opinion in China

It is sometimes claimed that Chinese people have especially liberal attitudes to reproductive health, genetic testing, and genetic modification. It is true that, for most Chinese people, generally, a human being starts from the birth of the baby, not the formation of the zygote or a time before birth (Xunzi, Ancient Chinese Philosopher.). It is unclear, however, that such beliefs will extend to agreement that all kinds of research on embryos can be permitted. When people become more aware of the stages of embryonic development, there may be a reluctance also in China to approve research on embryos that already display features recognized as human. Some empirical studies on Chinese doctors find that the majority of them hold that a human embryo is a kind of life that we should respect, and numerous doctors believe that human life begins at the zygote stage and destroying a zygote is thus the same as destroying a human life (Qiu et al. 2005; Qiu et al. 2010). The legal permissions to conduct basic scientific research on embryos do not translate into public acceptance of research or practices that involve germline gene editing, nor any research that involves synthetic embryo-like entities.

In the past, policy makers in China did not pay much attention to public opinion, but this has changed. Recently, for example, there has been extensive public discussion about the practice of organ donation in China (He 2015). Another example is the case of Zexi Wei and the scandal of stem cell research in general (Zhang 2016; Kiatpongsan 2009). This was a student who died after receiving an experimental treatment based on false advertising, after which the NHFPC suspended all clinical practice of cellular immunotherapy.(The national health and family planning commission held a picturephone meeting on normative management of medical institutions and medical technology management (In Chinese) 2016) The misuse of cellular immunotherapy under poor governance, together with sensational reporting about the "positive" effects by the media, has led to misconceptions about the development of immunotherapy among the public, but also to loss of trust in military and private hospitals in China. The scandal of stem cell therapy forced the NHFPC to stop all novel clinical research involving stem cells and to stop all research and clinical practice with experimental stem cell interventions (Han 2009). Although this action puts an immediate stop to the previous chaotic situation, it has also obstructed the development of stem cell research in China, and thereby ultimately the interests

of patients. It has therefore become increasingly clear among policy makers and researchers in China that they have to pay attention to the development of appropriate regulatory frameworks.

In spite of the generally positive attitudes among important groups in China to genetic research, the risk of human germline gene editing is still high; and for a country such as China, the lack of effective governance may lead to public opposition to research and science in general. Also, the lack of attention to fairness in the distribution of benefits, because of the low accessibility and affordability of gene editing technologies for the public, may increase the gap between different groups, and increase the effects of genetic differences between individuals. This may also lead to resentment towards genetics research.

There is currently a lively discussion about germline gene editing in China. First, there is still disagreement about whether we should do basic research on the human germline (such as embryos, gametes) in vitro. Some argue against basic research for the following reasons: germline gene editing has the power to destroy human genetic diversity, or even lead to extinctions of human beings; it will cause great harm to future generations; fear of designer babies, violation of the child's right to an open future; distributive injustice in access these kind of technologies; genetic discrimination; impact on the human gene pool (Ai 2016; Wang 2016; Li and Wang 2016). Others argue that basic research should be permissible: mainstream bioethicists in China agree that the embryo or fetus is not a human being, but its moral status is higher than other species, so we should not manipulate, discard, or destroy them without any sufficient and proper reason (Qiu 2015). Basic research on embryos is crucial for scientific development, but it should be for the purpose of health care and the welfare of future generations. In addition, it must be reviewed by IRBs and well regulated (Qiu 2016). Second, some worry about issues of designer babies, gene enhancement, and destruction of human genetic diversity that may happen if China does not adequately regulate the application of gene editing (Li and Wang 2016). Third, for germline genetic enhancement, most scholars think it should not be allowed, but a few argue that enhancement of health should be allowed in the future but under cautious evaluation (Qiu 2016). Fourth, some have argued that scientists and subjects should be responsible for their actions which relate to the development of human beings (Ai 2016). Fifth, there is an emphasis on the importance for having dialogue between scientists, bioethicists, sociologists, lawyers, policy makers, and the public (Li and Wang 2016; Zhang 2016).

There are few credible surveys in Chinese that address public attitudes on gene editing or modification, either for the purpose of health or enhancement (Qiu et al. 2005; Qiu et al. 2010). There is not enough evidence to show that most Chinese are more positive towards genetic enhancement than people in western countries. China does not accept eugenics defined as state controlled reproductive policies which violate an individual's autonomy, which also in China is regarded as unethical and unacceptable (Qiu and Zhang 2016).

The new issues raised by germline gene editing and embryo research may therefore provide a good opportunity for policy makers and research institutions in China to set up mechanisms for broad and deep public discussions. Unlike the situation a few decades ago, China now has its own expertise both in the required scientific

fields and in bioethics. The existence of strong genetics research in China is well recognized by the international community. What is less well recognized is also the presence of strong bioethics research groups in major universities in China. In addition to the debate going on in Chinese professional journals mentioned above, a vigorous debate about appropriate regulatory frameworks for the new technologies has started in China, involving researchers, bioethicists, and policy makers. For example, there is a regular forum organized by the Wuhan Sciences and Technologies University on research ethics for genetics research. At Peking Union Medical college, the premier medical university in China, scientists, doctors, bioethicists, and policy makers take part in national debates on gene therapy and stem cell therapy, that provide input to government policies in these areas. There are annual bioethics meetings in China, as well as regular meetings with researchers from major research intensive Asian countries, such as Japan, Korea, and Singapore.

In China, laws and regulations do not ban basic scientific research on human embryos, and Chinese people may show a liberal attitude both to research and practice for protecting babies from disease (Zhang and Zhang 2012; Hou et al. 2012; Han et al. 2007), partly because of China's population policy and lower social welfare protections than in developed countries. Even though there are no positive data demonstrating that Chinese people have more liberal attitudes than those found in countries such as the US, it is likely that the inclusion of the Chinese perspective will move the international opinion in a more liberal direction.

4 Governance and the international discussion

Even with the considerable debate about the appropriate use of new gene editing techniques in China, it is likely that a revised and improved regulatory framework is going to emerge. This is evident from the comments made by various government officials and individual scientists after Dr. He made his announcement (Wang et al. 2018; Zhang et al. 2018). Already, though, it is also clear that this framework will be closer to countries such as the UK and Sweden, rather than to countries such as Germany or even the US. China already allows research on non-viable embryos. The two ethical "boundaries" that have limited such embryo and genetic research during the past few decades, also in China, are now being questioned: embryo research should not be permitted after the first 14 days of development, and germline modification should be prohibited. The 14-day rule was introduced as a reasonable compromise, allowing important research to move forward at the same time as it set clear limits to research. It was always controversial, with some countries prohibiting embryo research altogether, and other countries, notably the US, with significant opposition (Reardon 2015). Nevertheless, it enjoyed considerable support not only among researchers but also within the bioethics community, particular in the US and UK, both of which, at that time, were leading in biomedical research as well as in bioethics research. Two papers in *Nature* and *Nature Cell Biology* report that they have sustained human embryos in vitro for 12–13 days before terminating them (Deglincerti et al. 2016; Shahbazi et al. 2016). Up until the publication of these papers, nobody had reported that embryos can be cultured beyond 9 days

(Carver et al. 2003). In the beginning of 2017, scientists from Harvard University published a paper arguing that advances in synthetic biology raise challenges to 14-day rule (Aach 2017). In some countries, regulations or guidelines require that research involving embryos cannot be cultured beyond 14 days or the appearance of the primitive streak if earlier than 14 days (Ethical Guiding Principles for Human Embryonic Stem Cell Research (In Chinese) 2003; Zi 2017). However, in the UK, the Nuffield Council on Bioethics is reconsidering the rule of 14 days since important scientific research could be done by maintaining embryo beyond 14 days.(Nuffield Council on Bioethics 2016) It is likely that China will follow the example of UK and consider a relaxation of the restriction of research to the first 14 days, and NHFPC has already considered revising the Guideline for Human Embryo Stem Cell Research which was released in 2003.

The prohibition against germline editing was challenged by the 2015 paper by Dr. Huang and co-workers (Liang et al. 2015). Although many countries still have restrictive policies governing embryo research and germline modification, some countries allow basic research or have mechanisms that permit such research, such as the UK, Sweden, and China (Callaway 2016; Ethical Guiding Principles for Human Embryonic Stem Cell Research (In Chinese) 2003; Zi 2017; Callaway 2016; China's Ministry of Health, Ministry of Finance, and ministry of Agriculture 2003; Isasi et al. 2016). In the US, the NIH has reiterated its ban on using federal funding for gene editing of human embryos, because of concerns about the moral status of human embryos (Reardon 2015). Such research is permitted without federal funding, and has already been done in US led by Shoukhrat Mitalipov of Oregon Health and Science University.(Connor 2017) The public also seems to have conservative views about germline gene editing in the US (Kolata 2016; Gaskell et al. 2017; Weisberg et al. 2017), and such research may face more restrictions in the US than in the UK and China.

Following the publication of Dr. Huang's work, a consensus summit was organized in Washington DC in December 2015, with representatives from, and jointly organized by, China, the UK, and the USA (International summit on human gene editing: A global discussion, in international summit on human gene editing: A global discussion, Olson 2016). The statement after the conference rejected an international moratorium of all human gene modification experiments, allowing basic research to go ahead, but agreed that any clinical application was premature. (Ma et al. 2017) In general, the ongoing debate about research on the human germline for non-reproductive purposes is mainly about concerns about the safety issues of gene editing, because based on current knowledge of biology, the risk/benefit ratio of human germline gene editing is extremely high.(International summit on human gene editing: A global discussion, in international summit on human gene editing: A global discussion, Olson 2016; Daley et al. 2016; Evitt et al. 2015) Gene editing still has a high rate of off-target alterations and other unintended consequences, which means that there is agreement that it is now premature do any clinical application on the human germline, or even clinical trials. But scientists are making progress on reducing the risk of germline gene editing, and there is an urgent need to think about how to regulate it. The consensus statement after the second international summit, held in Hong Kong in November 2018, did open up the possibility of developing a

pathway towards clinical application of gene editing in embryos (Statement from the organizing committee on reported human embryo genome editing 2018). China, being one of the organizers, likely therefore will join a country such as the UK and allow a regulatory pathway towards clinical use.

In spite of the consensus statements after these two international conferences, they clearly do not represent any international consensus. There are still sizable groups of people in many countries that would want to prohibit any research that involves human germline modification (Callaway 2016; Cyranoski and Reardon 2015). It is unlikely that many of these countries will change their prohibitions against any fetal research or genetic modification of embryos. It is extremely unlikely that any international consensus will emerge, and there are always questions about how representative the groups are that advocate particular positions. One problem is that although such groups typically include a number of prominent bioethicists from Western countries, they have not included any bioethicists from China, nor from any other non-Western countries. One example is the recent updates to the ISSCR (International Society for Stem Cell Research) Guidelines (ISSCR 2016). A task force of 25 members only included one stem cell scientist, but no bioethicist, from China. There were more than a handful of bioethicists on the task force from Western countries.

While the lack of a non-Western presence in international consensus development processes is clearly a problem, the solution is not simply to include more non-Western representatives in such processes, for two reasons. First, although such high international level events are clearly valuable, there is a limit to what can be achieved. They can only establish very general principles and, as has become quite evident, the new technologies raise difficult issues where there is no national or international consensus, and there is in any case, no effective enforcement available at the international level. Only at the country level is it possible to establish a regulatory framework that is acceptable to a specific national tradition and culture, and that has regulatory force within that country. Such regulatory frameworks are likely not to be identical; we can at the most expect them to be in broad agreement.

But even at a national level, another commission or consensus statement is also not likely to be useful at this stage, because of the large degree of uncertainty and apparent disagreement. At the moment, there needs to be a development of serious discussion fora for active researchers, bioethicists, and policy makers. This issue has recently been raised by a research group from Harvard with regard to ethical issues raised by Synthetic Human Entities with Embryo-like Features (Aach 2017). Rather than establishing a national commission to develop guidelines for such research, they propose.

> a set of exploratory inquiries into their moral and scientific issues rather than a commission for determining guidelines and research limits for them. Guidelines and research limits may ultimately be desirable and needed, but a commission will work best only when enough such groundwork has been done to provide it with systematic information, analyses, and alternative positions. Once this in hand, a commission could be assembled along the lines of prior embryo and stem cell commissions with the main goal of coming to a collective agreement on guidelines and research limits, as well as any needed non-

research limit guidelines (such as requirements for informed consent) (Aach 2017).

This process should happen both at the national and the international level. Similar to what is proposed by the Harvard group for the national debate, there also needs to be an ongoing debate among international scholars to lay a groundwork that can provide "systematic information, analyses, and alternative positions" that can be used to establish an international consensus about "guidelines and research limits" (Aach 2017).

Unfortunately, there are at the moment very few opportunities for engagement between Western and Chinese researchers and bioethicists. While there is intense interaction and debate within China, Western researchers and bioethicists are largely unaware of what issues and positions are regarded as important for the Chinese groups. The language barrier is an obvious reason for this, but so is the lack of institutional frameworks for sustained interactions on an international level between active Chinese researchers and bioethicists and their counterparts in the West. Major funders of international research, such as the European Commission, the US National Institutes of Health, and the Wellcome Trust, should consider funding for development of such institutional frameworks that will facilitate interactions between bioethicists, researchers, and policy makers. All of these institutions have successfully funded capacity building in research ethics, but mainly focused on human subjects research in general. Arguably, funding of these activities has now led to a saturation point, and there is little added value for continued funding of similar activities in the future. The more complex moral issues related to new technological developments in germline and embryo research are in urgent need of attention at this moment, precisely along the lines suggested by the Harvard group. This, however, needs to be not only at the national level, but has to involve interactions between international representatives.

5 Conclusion

The new technologies of gene editing are a step forward that will enable us to have the capacity to modify the human germline for the welfare of human beings. There have been rapid advances in such research lately, and China is an active participant in this research enterprise. As this field is developed, we need to have more dialogue between scientists, bioethicists, sociologists, religious figures, and the public, both within and between countries.(International summit on human gene editing: A global discussion, in international summit on human gene editing: A global discussion, Olson 2016; Baltimore 2015) It is clear that many of the regulations in China are outdated, and need to be modified in order to meet the challenges both of basic and clinical research. A further international dialogue is needed in order to harmonize, but not necessarily equalize, the regulations in different countries. A broad social consensus about what types of research should not be permitted anywhere should be achievable, even though individual countries may vary in what types of research they will approve.

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Compliance with ethical standards

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