

Regular Article

Throwing the Baby Out with the Bathwater: The Debate on Heritable Human Genome Editing in Japan in the Aftermath of the He Jiankui Affair

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Abstract

This article advocates for a bolder stance on the part of scientists and other academics in Japan on the issue of therapeutic heritable human genome editing (HHGE). The article's contention is that the current moratorium on HHGE science is unlikely to be broken until the moral scruples that the public has on this subject are addressed and resolved. After reviewing literature that highlights the untenability of the popular objections to HHGE, the article goes on to describe the bold pronouncements made in the aftermath of the 2018 He Jiankui affair by Western scientists and contrast these with the silence, or half-hearted endorsement of HHGE, on the part of the Japanese scholarly elite. The article then ends with a discussion on the role that society and social debate have to play in guiding the advancements in technology and science. Drawing parallels with technological developments in other areas, I finish with an urging towards Japan's scientific elite to play a more proactive role in educating the public on this matter.

Keywords: heritable human genome editing; Japan; debate; He Jiankui; reproductive therapy; science

1. Introduction

Although this is not popularly known, Japan is the place where the idea was born that led to the United States (US)-led Human Genome Project. As has been described in a number of academic publications (Cook-Deegan 1994; Ito 2005; Kishi 2004; Sasaki 2019), it was a University of Tokyo molecular biologist, Akiyoshi Wada, who pioneered in the 1970s the idea of developing technology to allow the rapid sequencing of deoxyribonucleic acid (DNA). Indeed, in 1975, having the vision of an automated rapid DNA sequencing machine, he applied for government funding to try to establish a project whereby he could build one. Alas, this

visionary's contemporaries in Japan lacked the prescience to see the value of what he was proposing. Wada's initial request for funding was rejected, and even when some funding was granted to him a while after his initial application, the sum was so insignificant that he decided the next best way to proceed in order to see his vision realized was to try to set up an international collaborative project, with his foreign academic counterparts bringing the necessary funds. Crossing the Pacific, he went to the US to talk to James Watson—one of the scientists who had been credited in 1962 with the Nobel Prize for the discovery of the structure of the DNA. By that time, under the auspices of Wada's minor national

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project at home, two other Japanese scientists, Yuzuru Fushimi and Hideki Kambara, had invented technologies that would later become critical to the success of the Human Genome Project. Regrettably for Wada and his team, however, since Japan and the US were in the midst of a trade war, Wada's initiative would be misinterpreted by the Americans as a threat, with the upshot being that the government there would refuse Wada funding, only to expend the most generous sum of \$120 million to Watson to lead his own version of the project of sequencing a human's entire genome. Ultimately, as has been opined many a times in Japanese science circles, when a draft of the first human genome sequenced was published in 2001, merely 6% of it was done by Japanese scientists, whilst the contribution to it by the US and the UK was 59% and 31% respectively. The idea started from Japan, but in the end the fanfare over success happened in the US and the UK, with Wada, Fushimi and Kambara becoming the "unsung heroes" of the Human Genome Project.

Against the background of how cutting-edge Japan had been in the field of molecular biology in the 1970s/1980s and how a lesson was contained therein for the country to advance research ideas generated domestically, it is conspicuous that, as of today, no Japanese research exists that seeks to wield control over the genome—such research seems still very much neglected here. In particular, it stands out that the number of scientific papers reporting experimental work on heritable human genome editing (HHGE) is at zero. As a search on databases such as Google Scholar, PubMed, and Researchmap (which is operated by the Japanese government), would reveal, as of 17 March 2023, science seeking to manipulate the human genome, even only for

research purposes, is virtually non-existent here. Given that the country continues to be a powerhouse for research and innovation in many other areas, this failure to engage with HHGE is quite notable.

With regards to HHGE, what ought to be noted is that on a normative level the debate has greatly advanced in recent times, with a great many bioethicists and legal scholars advancing the argument that using HHGE, at least in the case of reproductive therapy, is justifiable. Although a number of works can be cited that do this (e.g., Gyngell et al. 2019, Johnson 2021, and Thaldar 2022), it is perhaps worth singling out the argument developed by the Stanford University's Henry Greely, who refutes the fundamental premises of the objections made to HHGE. Greely explains, for example, that there is no such thing as "the human germline genome", which is sacred and in need of preservation for posterity; in fact, he points out, there are 7.3 billion human germline genomes, because every living person has a 'germline genome' and "each one is different" (Greely 2021: 209). Furthermore, ad hoc genomic changes, he highlights, occur all the time anyway, both inadvertently and as a result of deliberate actions on our part. To cite one of Greely's examples that illustrate this point, the use of synthetic insulin has boosted over time the number of people with DNA variations leading to diabetes, since those with this condition who would have died as a child in the past now live long enough to reproduce. Similarly, the transition from hunting to farming centuries ago resulted in a greater number of copies in our gene pool of starch-digesting genes.

To return the focus on HHGE in Japan, with a view to pushing this country to play its part in the development of a responsible path for therapeutic HHGE, the

present article seeks to put the spotlight on this regrettable state of affairs. Some discussion already exists that sees the absence of HHGE science in Japan as a result of confusing and contradictory regulatory rules in this area. In particular, as it will be elaborated on later in the article, the Hokkaido University scholar Tetsuya Ishii has pointed out how the Japanese situation is regulated by a multitude of administrative guidelines, as opposed to by a clear single law, and that although some people might interpret this bureaucratically drawn framework to permit genome editing of human embryos, as long as it is at the laboratory level and not for use in reproduction, it is also possible to come to a conclusion from certain earlier-installed rules that this is not the case (Ishii 2020). Even though, since Ishii's submission of his manuscript, it is also possible to point to the instalment in 2019 of the "Guidelines for Research Using Gene-altering Technologies on Human Fertilized Embryos", which permits genome editing on surplus embryos, and the revision in 2021 of the "Ethical Guidelines for Assisted Reproductive Technology Research that Involves the Generation of Human Embryos", which permits genome editing on new embryos), the existence of these earlier-dating regulations Ishii mentions could be said to make HHGE still a grey area in Japan. Against this backdrop, the present article seeks to advocate for a bolder and more proactive stance by the scholarly community here, just as has been the case elsewhere, in interacting and communicating with the citizenry about what the science involves and what issues are at stake. In seeking to advance this agenda, the article joins Nakazawa et al. in arguing for a vibrant grassroots-level domestic discussion on this subject, with social scientists and humanities specialists taking the leadership

role (Nakazawa et al. 2018). Whilst promulgating clear rules would also be beneficial, ultimately, I argue, the way to break the stalemate in Japan's HHGE science is through helping the public overcome the moral scruples it has about it.

2. The global state of HHGE debate after the He Jiankui storm

In May 2015, precisely 17 months since China claimed the monkey in the global race to gene-edit mammals (Niu et al. 2014), a team of 16 Chinese scientists reported the first experimental work of this kind in human embryos. Although the embryos used in this experiment were non-viable, since the world was far from having reached a consensus that clinical HHGE would be morally acceptable, the authors had found it difficult to take their manuscript to print. Indeed, prior to being accepted by *Protein and Cell*—a journal established in 2010 with an editorial board comprising predominantly of China-based scientists—they had received rejections from both *Nature* and *Science*. As for the results presented by the paper, they demonstrated an astonishing lack of fidelity: of the 71 embryos that survived intervention with the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 to correct the mutation causing the lethal heritable blood disorder beta thalassemia, 28 were cleaved, and only 4 contained the replacement genetic material, but with regards to these 4 embryos, a great many off-target mutations were found, and still more were envisioned (Liang et al. 2015).

Two years after this paper, another manuscript of this nature emerged, this time making it to *Nature*, from within the American community of scientists. In this

second study, the team of the developmental biologist Shoukhrat Mitalipov at the Oregon Health and Science University in Portland made the landmark claim that his team had managed to rid human embryos of the disease mutation giving rise to the deadly condition known as hypertrophic cardiomyopathy. “By modulating the cell cycle stage at which the DSB [double-strand break] was induced”, the team stated, “we were able to avoid mosaicism in cleaving embryos and achieve a high yield of homozygous embryos carrying the wild-type MYBPC3 gene without evidence of off-target mutations” (Ma et al. 2017). Asserting in this way that they have corrected the pathogenic gene mutation whilst avoiding problems such as mosaicism, Ma et al. advocated the use of HHGE as a complementary therapeutic measure to pre-implantation genetic diagnosis (PGD), only to be immediately thereafter challenged to provide a validation of their conclusions (Egli et al. 2017).

With little else being reported in the way of research on applying CRISPR/Cas9 for human reproduction at the time of the Second International Summit on Human Genome Editing in 2018 in Hong Kong, the announcement by the Chinese biophysicist He Jinkui came as a shock that he had gone on to apply this technique clinically. Although, as elaborated by Stanford University legal scholar Henry Greely (Greely 2019), there are numerous other levels at which He’s action was condemned, the criticism of his decision to employ in humans a tool for which there was no demonstrable unequivocal evidence that it is safe and effective was overwhelming. The resulting furore, which has been widely covered in the media and academic circles, saw calls for a moratorium coming from various directions, including from leading scientists (Lander et al. 2019; Wolinetz &

Collins 2019; Getz & Dellaire 2019; Baylis 2019; see also Wellcome Sanger Institute 2019; Royal Society 2019; SCIMEX 2019).

As the dust was settling from the He announcement, however, the voice was raised from within the Western academic community that the missteps committed by a few rogue scientists should not divert us from the goal of acquiring technical competency in HHGE so as to respond to the unmet medical need of certain patients. Although all of Harris 2018a & 2018b, Steffann et al. 2018, Gyngell et al. 2019, Brokowski & Adli 2019, Hammerstein et al. 2019, Lovell-Badge 2019, Rasnich 2020, and Greely 2021 could be cited as expressions of this idea that there is a moral imperative to act upon HHGE science, one particularly strong exposition of it is found in a 2019 essay entitled *After the Storm—A Responsible Path for Genome Editing* and penned by the influential trio of geneticists George Q. Daley of the Harvard Medical School and the Boston Children’s Hospital, Robin Lovell-Badge of the United Kingdom (UK)’s flagship for discovery research in biomedicine—the Francis Crick Institute, and Julie Steffann of Paris University and the Necker-Enfants Malades Hospital (Daley et al. 2019). Daley, it is worth noting, had previously individually gone as far as outlining what a responsible pathway for clinical translation of HHGE would look like (Daley 2018; also cited in Daley 2020). Included in this outline were both: a list of safeguards for ensuring faithful implementation, with a special focus on the chief concern about mosaicism, and a hierarchy, developed on principles of medical triage, of “disease indications that might represent a gradation of medical necessity, and thus permissibility” (Daley 2020: 8). However, it was here in this joint essay that Daley argued most forcefully

against making a reflex reaction to He, citing the extent to which patients stand to benefit from HHGE. Apart from the couples where both partners carry homozygous recessive disease alleles, or those where one of the members is homozygous for an autosomal dominant disease allele such as that for Huntington's disease, there are all those couples, a significant majority, the trio of authors argued, who are affected by an autosomal recessive or dominant genetic disease and whom pre-implantation genetic diagnosis (PGD) has failed (Daley et al. 2019: 899).

Today, whilst caution is still very much the watchword when it comes to HHGE, a moratorium on it has increasingly come to be seen as too extreme a measure. To elaborate, as evident from the analysis of the wealth of ethics reports and statements issued on HHGE by 2018 by various national and international bioethics bodies (Brokowski 2018), there is a consensus that clinical HHGE should be banned at present. On the other hand, however, the common conclusion of the three arguably highest profile national bodies that have issued documents on HHGE—namely, those of the US, the UK and Germany—was that no categorical ethical barriers exist for its use for reproductive purposes. To illustrate the tenor of one of these texts, the US National Academies of Sciences, Engineering and Medicine (NAS), for example, states that:

Heritable genome-editing trials must be approached with caution, but caution does not mean they must be prohibited. If the technical challenges were overcome and potential benefits were reasonable in light of the risks, clinical trials could be initiated if limited to the most compelling circumstances, if

subject to a comprehensive oversight framework that would protect the research subjects and their descendants, and if sufficient safeguards were in place to protect against inappropriate expansion to uses that are less compelling or less well understood. (NAS 2017: 134)

To go back to George Daley—the Dean of Harvard Medical School—though, even at the 2018 Summit where He Jiankui made the revelation that provoke widespread immediate outrage, he made the step of asking for HHGE not to be ruled out in principle. Daley, who, by his own admission, had been involved in reviewing the above-mentioned first HHGE scientific papers, stressed that the feasibility for HHGE is here and that the ethical considerations can no longer be put off. To quote him:

... a number of groups have applied gene editing now to human embryos in the context of in vitro fertilization and attempting to determine variations of a protocol that would enhance the fidelity and reduce mosaicism. I think there has been an emerging consensus that the off-target problem is manageable, and in some cases even infinitesimal. There are some interesting proofs of principles, like diseases such as beta-thalassemia that could potentially be approached with this strategy (Daley 2018).

This was followed by him laying down the details of the procedure through which embryos can be effectively assessed for what he calls “fidelity of genome editing safety” (Ibid.). Included in this outline were both: a list of safeguards for ensuring faithful implementation, with

a special focus on the chief concern about mosaicism, and a hierarchy, developed on principles of medical triage, of ‘disease indications that might represent a gradation of medical necessity, and thus permissibility’ (Daley 2020, 8).

3. The current state of the debate in Japan: Too limited

Whilst strong admonitions, such as the ones by Daley, Lovell-Badge and Steffann mentioned above, were made in the West against knee-jerk reactions to He Jiankui, in Japan, by contrast, the atmosphere was one of complete condemnation of HHGE, even as an idea. Nobody was seen to argue here the case for a responsible path forward for HHGE or to uphold the principle that if it were technically possible for us to change our germline genome safely and effectively, there might be cases where it would be compelling to do so. Nor did anyone take the challenge of pointing out the flaws that underpin the common objections to HHGE and highlighting the responsibility to continue pursuing mastery of the technique for the sake of those currently without a therapeutic reproductive option. Even today, the difference is striking between the record of firm affirmations made in the aftermath of the He announcement by scientists and bioethicists in other countries of the prospective value of prudently implemented HHGE, and the silence, on the other hand, that remains in Japan on this subject.

In the midst of this silence on the part of the academic community, it is no wonder that public support for HHGE was found to drop in the aftermath of the He Jiankui fiasco. Indeed, in the absence of counterforces, the episode of the botched HHGE experiment in China

only damaged the populace’s view of this procedure in a way that further inhibits debate. To cite concrete evidence of this, through a sequence of questionnaires from the three years of 2016, 2018 and 2019, it was shown in the context specifically of Japan that the widely publicised 2018 HHGE scandal led to a significant decline in the acceptance of the use of the genome editing technology in general, and particularly so for human reproduction (Watanabe et al. 2020). More specifically, the surveys, which asked questions about the acceptability of genome editing in a range of fields, from fishery to agricultural breeding, to human reproduction, revealed in the final sample year a stark rise in disapproval of the technology’s utilization of fertilized human eggs—from 12% in 2018 to 29% in 2019. Moreover, respondents on whom use in fertilized human eggs made the strongest impression were found to have risen from 15.9% in 2018 to 20.4% in 2019, with this being interpreted by the trio of scientists that had conducted these surveys as “suggesting the news of the twin babies in China had a substantial influence on the Japanese public,” raising public awareness of the genome editing methods, but also damaging their reputation. Whilst this is merely a speculation, it is possible to consider that this documented change in public opinion in Japan will make leading public figures, including politicians, and prominent scientists more hesitant when it comes to discussing HHGE. Ultimately, this can only restrict the public debate, meaning that the ethical challenges surrounding the technology would remain unexamined, with the moratorium in science continuing to the detriment of those who need HHGE.

Recently, an attempt was made by Hokkaido University’s bioethicist Tetsuya Ishii to create momentum

for the enactment of a law on HHGE, which he saw as the most appropriate approach to breaking the moratorium on this science. In particular, lamenting the virtually non-existent HHGE science, Ishii pointed to is the confusion and uncertainty that must exist amongst Japanese scientists as to whether they are free, i.e. without the threat of being penalized, to engage in such work. “When it comes to research involving human germline genome modification”, he elaborated, “the Japanese regulatory framework [as created by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Health, Labour and Welfare (MHLW)], is characterized by gaps and inconsistencies” (Ishii 2020: 442), with the definitions used in it “often [being] at odds with scientific understanding” (Ibid.: 448). “What Japan needs [he concluded] is a coherent, up-to-date, fundamental law that governs both basic research and medical use of human germ cells as well as embryos, one that is discussed in and approved by the Diet, Japan’s bicameral legislature, instead of by a Cabinet Committee, to ensure broad social understanding of, and support for, scientifically important research on human germline (Ibid.: 463).

Apart from this discussion by Ishii, what needs to be added is that following the approval to use human embryos in genome editing research in China and the United Kingdom in 2015 and 2016 respectively, the Japanese community of scientists and other academics, or more specifically the Science Council of Japan (SCJ)—an organization of over 2,200 members representing Japan’s academic community—issued a call to the government to enact legislation. The SCJ stated in its call that HHGE science is acceptable if the goal is to learn about the natural reproductive process (pursuing it for

the purpose of developing a therapy for people with intractable diseases was deemed unacceptable), and it wanted to see a law promulgated to this effect (SCJ 2017). In the meantime, at the government level, deliberations had already begun as to whether regulatory action is needed. In particular, an investigative committee set up within the Council for Science, Technology and Innovation (CSTI) operating under the Cabinet Office had been discussing the ethical issues since 2016. With the academics’ recommendations being issued, the further step was taken of establishing a Task Force under the CSTI to review the policy on handling of embryos. During the deliberations within this Task Force, the view was expressed by a number of Japanese scientific Societies (e.g., the Japan Medical Association, the Japan Society for Gene and Cell Therapy, the Japan Society of Human Genetics, the Japan Society of Obstetrics and Gynecology, and the Japan Society of Reproductive Medicine) that there is a limit to which they can self-regulate and that the promulgation of a law on HHGE is necessary in order to prevent misuse of the technology (Nakazawa et al. 2018; Kato 2020). However, when the CSTI released draft guidelines for HHGE research, it became clear that the SCJ’s and various Societies’ plea for a law would not be granted, and that, if anything is done at all, then that would be a revision of the existing ministerial-level guidelines. Indeed, rather than making a higher-level policy recommendation, the report simply urged the two bureaucratic bodies with jurisdiction over this matter, namely the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Health, Labour and Welfare (MHLW) to update their existing guidelines (CSTI 2018, 2019 & 2021). As for the content of the update, this also departed from the

SCJ recommendations in that approval for basic HHGE research was proposed, albeit in two separate stages, for both—the acquisition of knowledge about embryogenesis and for reproductive therapy—with so far only the former being acted upon jointly by the ministries (MEXT & MHLW 2019).

Disapproving of both of these departures from its suggested policy, the SCJ felt compelled to issue in 2020 another set of recommendations (SCJ 2020). In it, it stated unambiguously that ‘basic research aimed at clinical application should also be prohibited’ (Ibid., 7). Three justifications that were offered in the way of explaining this stance were that: 1) the message might be sent ‘to the people presently living with disabilities or with intractable diseases that they should not have been born’; 2) ‘a woman who accepts the pregnancy and childbirth could be [sic.] persuaded into not giving birth to a child with a disease or disability’, with this ‘result[ing] in an unacceptable endorsement of eugenics and a pattern of thinking that is the same as in the old [coercive] eugenics’; and 3) the right to self-determination of future generations would be violated (Ibid., 5-6).

Despite this tone of the SCJ with regards to HHGE research for reproduction, they clearly expected the science to happen for the purpose of understanding embryogenesis. That this is the case could be gauged from a chapter on Japan by Ishii, who served on both scholars’ committees, which was included in the above-mentioned 2020 volume *Human Germline Genome Modification and the Right to Science*. To discuss again with focus on Ishii, whilst his proposal for a reinvigoration of the parliamentary debate is valid and goes some way in the direction of addressing the glaring absence of discussions on the subject, Ishii only goes half the distance.

This is because, firstly, he falls short of advocating HHGE for reproductive therapy, arguing that the science should be conducted only insofar as to open the “black box” of conception, full stop. Secondly, he advocates for the criminalization of Japanese nationals who might in the future go and seek HHGE abroad. In an effort to motivate the politicians to enact a law in this area, Ishii suggests that the latter is necessary as a deterrent to Japanese patients who might want to flee for treatment abroad. “[I]n the era of cross-border reproductive medicine”, he seems to write in alarm, “some prospective parents might choose to go abroad to seek germline modification as the last-resort remedy for their infertility problems, or to treat a genetic disease in their offspring” (Ibid.: 465). To prevent this from happening, he argues, “[a] national law is needed, one with extraterritorial reach”, because ministerial guidelines would not be enough to stop such patients (Ibid.: 465).

Although this issue is tangential to the main one discussed in this article, it is worth arguing that the criminal sanctions that Ishii has in mind in such a scenario would be best directed at charlatan service providers and not the patients who act out of desperation. Indeed, condemnation of couples to domestic reproductive exile, which a law that promises to penalize a national who returns from HHGE therapy on foreign soil is, would perhaps be too much of a draconian measure to have.

4. A call for a bolder stance by Japanese scientists and other academics

How many people in Japan share the knowledge, with Greely above, that there is no such a thing as “the human germline genome” that passes unaltered from generation to generation? And, how many people share

the knowledge that each of our genomes changes, as a result of what we do as well? And how many people realize that the proposed CRISPR-induced changes for reproductive therapy simply change the frequency with which a particular, already common gene variant, is seen in the population?

Instead of urging reflection on such questions, whatever limited debate there exists in Japan on this subject stops at the level of the dogmatic, unquestioning acceptance of the view that HHGE is a line that should never be crossed. This situation seems regrettable. Japan has a lot to contribute technologically to the therapeutic HHGE project, and a societal debate here is a necessary precondition for science to happen. Society indeed has a key role to play in the development of such a technology, impacting the path that science takes. Feeding into policy decisions as it does, societal debate potentially serves as a powerful factor in guiding science, and the two need to march hand in hand. There exist numerous examples where this has hitherto been the case. Take, for example, the way society directed the development of nuclear technology. If it were not for political and war considerations in the US in the 1940s, the so-called Manhattan Project would have never been launched to develop the nuclear bomb. True, nuclear technology might well have developed independently of that Project at some later point in time. However, to say that those scientists operated in a void, taking an initiative of their own, would be a gross misrepresentation. To make the same point with an example where the reverse has happened (i.e., the lack of social support for a technology making the associated science stagnate), it must be remembered what happened with human embryonic stem cell research in the late 1990s and the 2000s. In the

US—arguably the leading global scientific powerhouse, the ban during the era of the Bush Administration on the use of federal funding for research using human embryonic stem cells on all but a limited number of cell lines already in existence led to many opportunities for developing cures of intractable illnesses being lost, as scientists had no choice but to choose alternative directions in which to spend their time and efforts. In Japan too, the work involving the manipulation of embryonic stem cells that began at the turn of the century never took off, precisely because the widely held public view of this as a taboo precluded the debate from deepening. Ultimately, in this jurisdiction, resources became focused on using induced pluripotent stem cells, despite the apparent short-term technical advantages, for the development of therapeutics at least, of embryonic stem cells.

As these examples suggest, HHGE science cannot progress in an ethical emptiness. A vibrant public debate is needed to direct it. It is time that Japanese scientists and other academics stepped up and fulfilled their role of enlightening the public.

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