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ARTÍCULO

Ethical issues related to gen editing using CRISPR-Cas9 technology

Cuestiones éticas de la edición genética mediante la tecnología CRISPR-Cas9

Qüestions ètiques de l'edició genètica mitjançant la tecnología CRISPR-Cas9

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Abstract

Immersed already in the 4th industrial revolution, clearly the digital age has invaded our lives. People tend to celebrate every technological and scientific advance without thinking properly about the possible undesired side effects or unexpected consequences. One of the most outstanding achievements of the last years has been the CRISPR/Cas9 technique. It seems to be the magic wand to solve whatever. In this article I propose to think critically about the ethical issues related to this incredible technique. I will focus this work on 3 ethical aspects of gene editing: 1. The link between gene editing and the old concept of eugenics; 2. Aspects related to the idea of modifying human genetics in order to conquer other planets and 3. The ethical implications of uploading all these data to the web. Finally, I suggest focusing on interdisciplinary ethical discussion, the dialogue between professionals, institutions and government which must ensure the protection of the autonomy of patients and the safeguarding of their rights. To conclude, the suggestion of considering the role of Universities in ethical education of the future professionals with a practical rather than a theoretical approach is considered, with special attention to the integration of cybernetics in medicine.

Keywords: CRISPR/Cas9; bioethics; eugenics; Mars mission; big data; human enhancement; gene editing.

Resumen

Inmersos ya en la 4ª revolución industrial, claramente la era digital ha invadido nuestras vidas. La gente tiende a celebrar cada avance tecnológico y científico sin pensar adecuadamente en los posibles efectos secundarios no deseados o las consecuencias inesperadas. Uno de los logros más destacados de los últimos años ha sido la técnica CRISPR/Cas9. Parece ser la varita mágica para resolver lo que sea. En este artículo me propongo pensar críticamente sobre las cuestiones éticas relacionadas con esta increíble técnica. Centraré este trabajo en 3 aspectos éticos de la edición de genes: 1. El vínculo entre la edición de genes y el antiguo concepto de eugenesia; 2. Aspectos relacionados con la idea de modificar la genética humana para conquistar otros planetas y 3. Las implicancias éticas de subir todos estos datos a la web. Finalmente, sugiero enfocarse en la discusión ética interdisciplinaria, el diálogo entre profesionales, instituciones y gobierno que debe asegurar la protección de la autonomía de los pacientes y la salvaguarda de sus derechos. Para concluir, se plantea la sugerencia de considerar el papel de las Universidades en la educación ética de los futuros profesionales con un enfoque más práctico que teórico, con especial atención a la integración de la cibernética en la medicina.

Palabras clave: CRISPR/Cas9; bioética; eugenesia; misión a Marte; big data; mejora humana, edición genética.

Resum

Immersos ja en la 4a revolució industrial, clarament l'era digital ha envaït les nostres vides. La gent tendeix a celebrar cada avanç tecnològic i científic sense pensar adequadament en els possibles efectes secundaris no desitjats o les conseqüències inesperades. Un dels assoliments més destacats dels últims anys ha estat la tècnica CRISPR/*Cas9. Sembla ser la vareta màgica per a resoldre el que sigui. En aquest article em proposo pensar críticament sobre les qüestions ètiques relacionades amb aquesta increïble tècnica. Centraré aquest treball en 3 aspectes ètics de l'edició de gens: 1. El vincle entre l'edició de gens i l'antic concepte d'eugenèsia; 2. Aspectes relacionats amb la idea de modificar la genètica humana per a conquistar altres planetes i 3. Les implicancias ètiques de pujar totes aquestes dades a la web. Finalment, suggereixo enfocar-se en la discussió ètica interdisciplinària, el diàleg entre professionals, institucions i govern que ha d'assegurar la protecció de l'autonomia dels pacients i la salvaguarda dels seus drets. Per a concloure, es planteja el suggeriment de considerar el paper de les Universitats en l'educació ètica dels futurs professionals amb un enfocament més pràctic que teòric, amb especial atenció a la integració de la cibernètica en la medicina.

Paraules clau: CRISPR/Cas9; bioètica; eugenèsia; missió a Mart; big data; millora humana, edició genètica.

1. Introduction

We have crossed the thresholds of the 4th industrial revolution, there are no doubts. The irruption of computer media, the exponential expansion of social networks and the technological scientific advance in the area of computing shows that the digital age invaded our lives. And we were the ones who allowed that to happen with each click on accepting terms and conditions, without even stopping to think whether it was correct or not. We have celebrated each update of cell phones to models with more and more connection possibilities, without realizing that these new smartphones were going to handle learning algorithms that feed on our tastes.

In this digital universe, all areas have their potential enhanced. One of the areas where it was most rooted was in Medicine. During 2020, in addition to the lockdown caused by the SARS-CoV-2 pandemic, the world set its eyes on medicine and the horizon of Artificial Intelligence was magnified in an epic way. And then, without realizing it, we were rudely pushed into the era of the GNR Revolution, namely: Genetics, Nanotechnology and Robotics. Gene editing using the CRISPR-Cas9 technique was the theme of the year and it was also the theme chosen for the Nobel Prize in Chemistry. Genetic editing is framed within this GNR Revolution, and every minute that passes, more and more advances.

2. Genetic revolution and gene editing

The Genetic Revolution includes all the knowledge acquired from the discovery of the structure of DNA (1) and the Human Genome Project (2) that achieved, thanks to the concomitant advancement of computing, to be completed in less time than projected. A complete timeline analyzing the events that led to the sequencing of the human genome can be accessed from the project site (3). These molecular insights paved the way for the discovery of the genetic and molecular bases of various diseases. Advances in molecular techniques made it possible to propose genetic editing to repair genetic errors and thus avoid suffering from the disease in question. Health expenditures would also be avoided to sustain a respectable quality of life for sick people and a human resource would be gained in the labor production chain (4). It is no coincidence that the 2020 Nobel Prize in Chemistry have been won by the researchers Emmanuelle Charpentier and Jennifer Doudna, for their contributions in the genetic editing technique using CRISPR-Cas9 (5). Let us remember that this same technique was applied in the controversial case of twins in China, whose genome was redesigned to be allegedly resistant to HIV infection (6).

3. CRISPR technique

It was in 2007 when the scientist Francisco Mojica first discovered Clustered Regularly Interspaced Short Palindromic Repeats, from where a CRISPR acronym is obtained. The key piece in this system in an enzyme called Cas9, which can recognize and cut specific sequences of virus DNA. This system is a kind of immune system for bacteria. CRISPR is the bacteria's mechanism against some viruses. When a virus infects the bacteria, part of the CRISPR system processes and keeps a piece of genetic code from that virus. From this moment, the bacteria can recognize the virus and attack the virus more efficiently (7).

After intense research scientists could modify the Cas9 enzyme to snip pieces of the target cell's DNA, allowing them to study gene function. The process operates much like a "cut and paste" technique, exactly like you do when writing a text and want to replace words or a whole sentence. Once the CRISPR sequence is cut with Cas9, scientists can then "guide" the CRISPR sequence to replace specific sequences in the DNA. Then, for some genetic diseases, where specific sequences are mutated, it is possible through CRISPR/Cas9 to remove the wrong genetic sequence and replace it with an unaffected sequence. This method can cure many genetic disorders.

With the CRISPR technique, genes can be edited in somatic cells, which would not generate major complications in the person who undergoes the editing process and does not affect future generations. This characteristic can be either positive or negative. Positive in the sense it respects the autonomy principle referred to the modified person but negative in the sense that this modification must be repeated in each generation when the genetic defect is passed to the offspring. On the other hand, genes can be altered in germ cells, resulting in the inheritance of these editions, that is, future generations inherit the genetic change. Genetic modification of germ cells involves the manipulation of embryos, with the possibility of having to discharge many of them. For these reasons, germline gene editing is an ethical controversial topic (7).

The technique is not free of side effects and can also replace unwanted genes or affect sequences in fragments of a different size than originally intended, or even generate a mix of cells with different modifications (or with no modifications at all) in the same organism (mosaicism). Given that the edition is heritable, we do not know what problems may be caused in the future in the individuals of that family line. If there are collateral effects, many individuals will be affected. And there is no way to know unpredictable side effects, even when the first generation does not present problems (7).

Having presented these concepts as a conceptual framework, I will focus my work on 3 ethical aspects of gene editing:

(1) The link between gene editing and the old concept of eugenics

(2) Aspects related to the idea of modifying human genetics in order to conquer other planets

(3) The ethical implications of uploading all these data to the web

4. New eugenics

Eugenics is an old ethical issue. Arguments in favor of this practice are based on the concept that "the practice of encouraging the birth of children to parents having qualities considered desirable to the community is the right thing to do". Arguments opposite the practice are based on the concept that the human genome is sacred and it has to be protected. This sacredness of the human genome proceeds from its assimilation to nature, and even more so, to human being essence. It also has a strong genetic determinism burden (8).

Societies have always favored traits that have good qualities such as being tall, running faster, having a higher IQ, or possessing keener senses. But now CRISPR/Cas9 introduces the possibility of choosing these qualities on purpose. The choice, however, inevitably comes at the cost of favoring one trait over another. It has been suggested that such a system could create a "biological class system" tantamount to the world's previous race-based classifications.

So the main situation here is the Germline editing, in opposition to somatic cell treatments with CRISPR/Cas9. Germline editing creates permanent changes not only for the affected newborn but for the newborn's future children and for all subsequent generations.

Why is it important to find a solution to this issue? Germline gene editing was not the own decision of the new born, but his/her parents, and he/she will never be able to remove this gene editing or its consequences. So, should we think and seriously discuss about the rights and liberties that should be protect in future, when parents decide to modify the genome of their kids? Or, should we think seriously about prohibiting the Germline editing in humans in case that the germline editing practice using donated embryos could prosper in the hired womb of an extremely poor woman unaware of the whole situation?

Many of the therapeutic interventions aimed at reducing people's suffering and ensuring a dignified and healthy life, without the occurrence of diseases that can be preventable and are socially acceptable because they do not have serious negative consequences, can be considered as

a form of eugenics. Gene editing to avoid certain diseases could generate genetically advantaged individuals, who would enjoy better health, better quality of life and probably an extension of life expectancy. This situation will generate social injustices caused by the intervention of human hands. From a Kantian point of view, it would not be correct to modify the genome of a few, generating inequities in a great majority (9). At this point, I would like to stress the idea that inequity is what should be fight, not genome editing itself, which has many advantages for human health as already mentioned.

5. Modification of Human genome in order to conquer other planets

It is no news that public and private agencies are preparing a human mission to Mars. As the project is growing, little attention is being paid to the philosophers, ethicists, and social scientists. There are a lot of ethical issues related with the Mars missions. I would like to focus on the idea of human enhancements for space missions. Given that the space environment is hazardous for humans, it can be expected that new ethical issues concerning the value of human life may appear (10).

It has already been said how ethically controversial could be the human enhancement technologies. We should consider that maybe human enhancement may become a necessary procedure. In this case we realize that ethical challenges may appear not on Mars, but on Earth, with the decisions related to human enhancement. The main ethical issues are related to the risk of social inequality, the risk (or the advantage) of passing genetic modifications to next generations, the risk of emergence of new illnesses, the risk of terrestrial bacteria and virus evolving in Mars. What is going to happen if life on Earth is not possible anymore and only few "modified" people could live in Mars? Should we genetically prepare next generation just in case? Should we start first discussing this possibility in order to ask for consent? (11).

So the most important issue is related to encourage direct stakeholders to engage in a broad discussion on the ethical challenges of a human mission to Mars. Main ethical questions would be those like: Is all this effort worth the risk and the cost, for the sake of the humanity? How can we make sure that we are making the right decisions? How can we begin a public discussion to analyze all the angles of such important topic, especially about human health and biology? How much risk is too much risk? Which kind of new ethical conflicts could emerge in the outer space? Is it possible that the genetic enhancement could modify the moral values? Or the stressful situation of living in a completely different environment will damage main values in an irreversible way?

There is a very good guide and introduction to the ethics of space missions and space in general in "The Ethics of Space Exploration" edited by Schwartz and Milligan. The authors mention many ethical issues in space, such as the rationale for large expenditures on space exploration, risks to human health and life in space, the issue of contamination and care for pristine space environments, the responsibility for cleaning up space debris, the issue of property and mining rights with regard to space resources, the right to terraform planets, and the question of appropriate space governments (12).

One of the top issues is that of environmental protection in relation to the putative status of hypothetical microbial life on Mars. Is it ethical to contaminate space with our own microbes, or is it ethical to contaminate the Earth with Martian microbes? What could happen if they combined and create a new supermicrobe?

Another critical issue is the technological implementation called "brain-computer interface" (BCI) which could generate complex and controversial ethical concerns because this type of human enhancement may create threats to human privacy or the risk of discrimination. On the other hand, some authors argue that cognitive enhancement may lead to reaching desirable properties that increase human autonomy (10). Enhanced astronauts may be better adapted to hazardous factors in space but the question arises if mission planners should apply any radical enhancement procedures that may affect human freedom. Another argument often proposed to justify these exploring missions is the important push they represent to develop new cutting edge technology that could represent an unquestionable benefit for the whole society. This argument is hand by hand with the idea that human beings modify the environment much more than the environment changes human genetic burden. We are now realizing that human biological evolution is limited by the products of the human mind. (13).

6. Big Data and Gene Editing

Nevertheless, so the situation been explained, future implementation of germline gene editing is a reality, even when extremely controversial. Many policy documents, professional recommendations, and groups of authors seem to imply that germline gene editing for specific purposes could be acceptable if certain conditions are met. Requirements specified most often include adequate safety and efficacy of the method, societal debate and/or societal consensus, and appropriate governance (14).

The European Group on Ethics in Science and New Technologies (EGE) states that germline gene editing should be subject of careful examination, due to the potentiality and depth that the consequences of this research may have for humanity (15).

All these daily researches produce tons of sensitive information that flow apparently freely through the web. Handling all this health big data is made relatively easy, using the suitable software, the appropriate algorithm and with the opportunity of having many issues solved with just one click and even better, in the palm of the hand, with everyday more powerful smartphones.

Recently the Observatory of Bioethics and Law published two important documents with specific recommendations about the use of Big data in health (16) and guidelines about the evaluation of projects encompassing new health technologies and personal data (17).

In the recently released document "Guidelines for reviewing health research and innovation projects that use emergent technologies and personal data" it is remarked that "Scientific and technological changes are occurring at a dizzying rate, in an exacerbated market society where health is being increasingly commodified, and in which personal data are monetized. Although it is true that lawmaking processes and knowledge creation and transfer rates are not the same, there is a certain paralysis in the application of laws, due basically to a lack of understanding of the digital phenomenon that we are facing. It is therefore considered that RECs [Research Ethical Committees] are willing and able to act as guarantees that research, and the innovation that goes with it, comply with ethical principles and meet the established legal requirements" (17). The same document clearly sets that "The digital society, data driven, based, therefore, on the intensive exploitation of datasets, including personal data, has clearly shown that the current review model – a child of the second half of the 20th century – for analysing research projects in which humans take part and/or their data personal is used, is outdated and ineffective, due to the technical, ethical and legal challenges posed by personal data processing in the 21st century".

Because of this reason, it is emphasized the accountability of the Research Ethical Committees for safeguarding individuals and specially their personal data, assuring the privacy and confidentiality of the owners.

The document also affirms that "Thus, personal data are the gold of our time, and health, biometric and socio-demographic data, especially, are considered by law to be special categories of data that require the highest protection because they say everything about us; and because they could be used for unwanted purposes and give rise to covert discrimination, with profound implications for people's freedom and that of future generations. The possession of personal datasets by third parties, whether private or public initiatives, could affect our rights depending on the uses, giving these third parties extraordinary power over us, a situation that goes unnoticed

by the great majority of people. The decisions taken in the field of health research and innovation, and in highly digitized contexts will mark the lives of people, groups and societies" (17).

Many questions must be address to this relevant topic. Does the right to privacy include the editing of offspring DNA? Does it violate the future child's autonomy? Does the individual at least retain a substantive due process right to access medicine from private sources? Who is supposed to be the owner of the digital data circulating though the web? Do we have the right to change future human DNA forever? Can we guarantee same health solutions for all? How can we safeguard for hackers all the sensitive digital data? (7, 18).

7. Concluding remarks

Bioethics, understood as interdisciplinary ethics linked to issues of life, including all living beings and the environment and in particular, reduced to issues of human health and the practice of medicine, should be redefined at this time to take into account, the foreseeable consequences or not of the GNR Revolution.

We could conceive bioethics as the science of interstices, understanding that the interstice is the space between cells where intercellular communication mechanisms occur, it is also the space where cells understand their own limits and recognize the existence of another cell. Nature is wise enough to teach us that the same respect between cells should exist between humans as well. When this respect is broken, such as in cancer disease, in the aforementioned analogy, every reasonable mechanism finishes and death is close. The same for human interactions occurs when no respect between people starts and destruction is near.

Among the main concerns of Bioethics in the XXI century are: What would be the main regulations that each country should discuss and make available to the population to guarantee equitable access to health for the population? Is germ cell gene editing ethical? Is it ethical to modify human genetics to conquer other planets? Is it ethical to lose our privacy and give our sensitive data to the web? Are we enough sure that gene editing will not produce negative side effects and provoke new and worse illnesses? Will modifying genetics, inserting a nanodevice into the brain and linking it to a computer make us superhumans? Are we playing God, will we stop being Homo sapiens to be Homo Deus? (19).

Finally, we must appeal to responsibility, which concerns health professionals, the institutions that decide to incorporate the most revolutionary advances in science into their services, and the governments that will ultimately be the ones to regulate and control their use.

For this reason, the dialogue between these three actors: professionals - institutions - government must ensure the protection of the autonomy of patients and the safeguarding of their rights (20).

Much of all these aspects can be improved if we work from the continuous education in terms of ethics and reflective dialogue on the problems mentioned. A challenge for scientific societies is the inclusion of bioethical dialogue and the generation of consensus or guidelines to orient the correct performance in future situations. This education should be continuous and more visible for the general population.

It is also urgent to establish dialogues with people, especially with those who may be exposed to more vulnerable conditions. It is important in these dialogues to work from sincerity and common sense. New technologies go through all of us equally and it is good to establish good communication practices within the doctor-patient relationship to face contingencies from a relationship of mutual recognition and respect. This dialogue will be beneficial to advance later in the informed consent process, with a better predisposition of people to consent these new technologies (21). It looks like we need bioethical recommendations more than expected (22).

It remains to propose to the Universities to incorporate into their curricula the integration of all these new technologies in medicine, or at least, to warn students about the immediate future with other modes of the medical act. It is necessary to rethink the curricula of medical schools and colleges to properly prepare future professionals, which are also part of the accountability of the institutions. It would be very helpful warning the students not only about the technique itself or the biomedical advances but specially, about all the bioethical concerns.

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