Ethical and Social Issues in the Genome Research of A-Bomb Survivors

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Abstract. The Radiation Effects Research Foundation (RERF), located in Hiroshima city, is a research institute dedicated to the examination of the health of A-bomb survivors and their children. The children are known as "second-generation A-bomb survivors." RERF has investigated the correlation between the health problems of second-generation A-bomb survivors and their parents' radiation exposure, but no definitive correlation has been found with the methods used to date. However, some A-bomb survivors and second-generation A-bomb survivors are concerned about the inherited effects of radiation exposure on their offspring. RERF is currently planning the parents/child "trio genome study" to decode and compare the genomes (whole genome information) of A-bomb survivors and their children. It is expected that this research project will reveal whether or not the effects of A-bomb radiation exposure are inherited to descendants at the genomic level. However, genomic information can also be shared with their families. Furthermore, A-bomb survivors have faced discrimination in marriage and other matters. Therefore, strict ethical considerations are necessary for this research project, and RERF scientists have continued to consider how to address these issues. This research examines the ethical and social issues involved in the trio genome study through semi-structured interviews with RERF scientists, participant observations at public events that RERF organised, and document collection and analysis. As a result, the concept of "individual genomic diversity" emerged with profound implications.

Keywords: Atomic Bomb Survivors, Trio Genome Study, Individual Genomic Diversity.

1 Introduction

At 8:15 am on 6 August 1945, an atomic bomb was dropped on Hiroshima by the US military, the first in the world. The precise death toll remains unknown; by December 1945, it was estimated that 140,000 individuals had perished. Subsequently, another atomic bomb was deployed on Nagasaki. Numerous A-bomb survivors (Hibakusha) and their offspring reside not only in Hiroshima and Nagasaki but also throughout Japan. According to the Ministry of Health, Labour, and Welfare (MHLW), there are currently approximately 120,000 A-bomb survivors (first-generation). It is said that

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there are sometimes 200,000 their children (second-generation A-bomb survivors) in Japan, sometimes as many as 500,000.

In 1947, the United States founded the Atomic Bomb Casualty Commission (ABCC) to examine the health consequences of the atomic bombings. The ABCC engaged in collaborative research with Japan until 1975, when it was reconstituted as the Radiation Effects Research Foundation (RERF). The RERF instituted a system under which both nations jointly managed its operations and shared the funding of the research. RERF has continued to investigate the health of A-bomb survivors and second-generation survivors. It has conducted health check-ups of many A-bomb survivors and their children and keeps blood and other samples.

RERF presently has a research project to decode (sequence) the whole genomes of A-bomb survivors and second-generation survivors. This project is occasionally called the "trio genome study."

The trio genome study is a study project that focus on victims of war and their offspring. As experts in public health ethics stated, scientists should be aware of the histories of communities investigated and the "risks and burdens" they are asked to undertake by participation, as well as the "risks of stigma" associated with findings. Furthermore, "researchers have an obligation to provide whatever benefit can be derived from the study to those who participate in the research [1] ." The results of genomic studies can be shared with the families of the subjects. Additionally, A-bomb survivors have faced discrimination in marriage and other aspects of life. Therefore, strict ethical considerations must be taken into account in this study. RERF scientists are also concerned about such issues and organised an online meeting in 2020 to discuss the ethical issues of the project. The author participated in it and the results of the discussions were published in a paper [2].

This trio genome study has the potential to reveal critical results for A-bomb survivors and second-generation survivors. The paper employs sociological methods such as interviews and participant observations to further explore the ethical and social issues specific to this study project.

2 Background: The "trio genome study" project by RERF

In 1927, H. Muller discovered that exposing the parents to X-rays induced mutations (variants) in their offspring in experiments with *Drosophila*. During the same period, a similar phenomenon was observed in plants. Since these findings, there has been ongoing concern about the possibility that the effects of radiation exposure from the use of nuclear weapons or accidents at nuclear power plants could be inherited by subsequent generations.

RERF has been investigating the health conditions of A-bomb survivors and their children (second-generation survivors) for many years, from the era of its predecessor, ABCC. They have examined various aspects, such as sex ratio [3], chromosome abnormalities [4], mortality [5], multifactorial diseases [6], and congenital disabilities [7] in the children. However, to date, no correlation has been found between parental radiation dose and health problems in their children.

On the other hand, several surveys indicate that some A-bomb survivors and second-generation survivors are apprehensive about the potential inheritance of radiation

exposure effects. Additionally, some second-generation survivors have faced discrimination and prejudice or are concerned about the possibility of such treatment [8–11].

This implies that the accumulated research findings of RERF may not be adequately communicated to atomic bomb survivors, their second-generation descendants, and society at large. Alternatively, RERF's research results may not be trusted by the public.

On the other hand, advancements in genomic science have facilitated studies on the genetic effects of the atomic bombings on second-generation survivors at the genetic level. Accordingly, it is anticipated that sequencing the whole genomes of parents, one of whom is an A-bomb survivor, and their children (i.e., the trio genome study) will clarify whether the effects of the exposure are inherited or not at the genome level. For instance, RERF's Stakeholder Committee stated, "We hope that this study's findings will bring closure to the studies on the genetic effects of radiation that have been ongoing since the 1950s [12]."

As previously noted, RERF organised an international online workshop on 10-11 December 2020 to explore the ethical, legal, and social issues (ELSI) associated with the trio genome research, in which the author also participated [13].

The workshop confirmed that as an ELSI for the trio genome study, there are issues such as how and with whom the results of whole genome sequencing should be shared, how the risks of genetic effects should be accounted for, and how to protect the ultimate personal information of the genome. Genetic counselling, how to return genome sequencing results, and how to make data public were presented as discussion points. Several prerequisites were also reconfirmed. For example, the target population of the trio genome study is A-bomb survivors and second-generation survivors. They are not selected as subjects because they are patients with a specific disease or because they are healthy volunteers. In other words, "Studies on atomic bomb survivors have a characteristic of victim research" [14]. The results of the trio genome study also include the third generation of atomic bomb survivors and beyond. "The results of trio GS [genome sequencing] may affect the future of all survivors' offspring, comprising between 300,000 to 500,000 people all over Japan [15]". Furthermore, the results could impact not only the second-generation A-bomb survivors, but also the survivors and their children of the Chernobyl nuclear power plant accident (1986) and the Fukushima Daiichi nuclear power plant accident (2011).

The workshop affirmed, through the above discussions, the need to reach a common understanding through dialogue with the community of A-bomb survivors and second-generation survivors who are not necessarily the subjects of the trio genome research. "Community engagement beyond individual subjects in the ELSI of genome research" is crucial [16], and it "may be an important and useful approach [17]."

As previously mentioned, the research findings by RERF to date may not have been sufficiently communicated to A-bomb survivors, second-generation survivors, and to society at large. Also, as discussed below, the results of the trio genome study may be difficult to comprehend. Will variants derived from parental exposure be found or not? If found, are they 'many' or 'few'? Even if results are obtained, their interpretation may not always be straightforward.

Given the above, one can see how challenging the trio genome study is. So, how do the scientists involved in the trio genome study feel about the project, and how do they explore to build relationships with the subjects (A-bomb survivors and second-

generation survivors) and the public? This paper aims to reveal the conflicts faced by the scientists engaged in the trio genome study, particularly their conflicts with heredity and variation, and argues that these conflicts also embody the ethical and social challenges inherent to this project.

3 Method

In the research for the paper, to elucidate the conflicts and gropings faced by the scientists, (1) semi-structured interviews were conducted with two RERF scientists (five interviews totalling 8 hours and 33 minutes) and one journalist (1 hour and 44 minutes) covering second-generation atomic bomb survivor issues (Table 1), (2) participant observations were made at eight public events organised by RERF, documented through field notes (Table 1), and (3) relevant documents were collected to complement these interviews and participant observations.

The research was conducted in accordance with the Guidelines for Research Based on the Code of Ethics of the Japan Sociological Association. In the interviews, the consent of the subjects was obtained in written form. Additionally, permission was granted by the participants to appear under their own names in the subsequent results.

Table 1. Fieldwork (interviews, participant observation)

Date	Interview/ Participant observation	Interviewee/Event title
6 August 2023	Participant observation	Participated in a public tour of RERF Hiroshima Laboratory, together with other visitors.
7 August 2023	Participant observation	[RERF de Live Streaming] “RERF's Basic Research” (online)
9 August 2023	Participant observation	[RERF de Live Streaming] “About RERF's Population Surveys” (online) “Introduction to the Nagasaki Institute” (online)
10 August 2023	Participant observation	[RERF de Live Streaming] “Research Resources from the Perspective of Information Technology” (online) “I am an interpreter for RERF!” (online)
2 October 2023	Interview	Dr. Asao Noda (1 hour 44 minutes)

13 October 2023	Participant observation	1st study meeting on “Genetic effects research by genome analysis” (RERF Hiroshima Laboratory)
27 October 2023	Participant observation	2nd study meeting on “Genetic effects research by genome analysis” (online, delivered by RERF Nagasaki Laboratory)
13 November 2023	Interview	Dr. Asao Noda (1 hour 34 minutes)
15 January 2024	Interview	Dr. Asao Noda (1 hour 58 minutes)
13 February 2024	Interview	Dr. Arikuni Uchimura (1 hour 45 minutes)
13 April 2024	Participant observation	“Parental Exposure and Children’s Health: Public Seminar in Hiroshima” (Hiroshima Peace Memorial Museum)
6 August 2024	Participant observation	Open House in Hiroshima “Parental Exposure to Radiation and Children’s Health: Information Session on RERF’s New Research”, etc. (RERF Hiroshima Laboratory)
11 September 2024	Interview	Dr. Arikuni Uchimura (1 hour 32 minutes)
26 September 2024	Interview	Ms. Misa Koyama (1 hour 44 minutes)

4 Results and Discussion: How to interpret variants?

4.1 'Traces' or stigma?

When listening to the scientists at RERF, what the author heard were words rather familiar to sociologists, such as 'traces (≈stigma)' and '(genetic) diversity.'

In 2020, RERF published the result of a study conducted as part of the preparation of the trio genome study. The researchers sequenced the whole genome of offspring mice born to parents exposed to 4 Gy of radiation and found that about 10 mutations (variants) of two types were newly caused by parental radiation exposure [18]. However, their interpretation requires utmost caution.

According to the paper and an interview with Dr. Arikuni Uchimura, Department of Molecular Biosciences in RERF, who conducted the study and is the leader of the trio genome research, most mutations (variants) such as insertions, deletions, replacements, and others are only a few base pairs in length, with the longest being about 10 bases. The length of the whole genome is approximately 2.7 billion bases in mice and 3.1 billion bases in humans. Only about 1% of this is called a genes - the part of the genome that contains the information needed to make proteins. It is estimated that there are between 19,000 and 25,000 genes in humans - depending on how they are defined. Of these, experts have so far listed about 4,600 genes that, if mutated, could lead to diseases and other health problems. Also, the American College of Clinical Genetics and Genomics (ACMG) has listed 81 gene variants that, if found, should be reported to the patient for appropriate action [19]. The length of a single gene ranges from a few thousand to 15,000 bases. Moreover, the function of the gene is not significantly affected unless variants occur in important parts of that gene. Even if the parents are not exposed to radiation, around 70 variants can occur in the children. The number is known to increase with the age of the father. The radiation dose of 4 Gy is based on the highest radiation dose among the survivors. In fact, half of those exposed to 4 Gy of radiation die soon afterwards; Uchimura explains that most of the survivors covered by the trio genome study were exposed to doses of 1 to 2 Gy [20].

Of course, the results of experiments on mice do not apply to humans. But if they did, the possibility of about 10 very small mutations occurring selectively in locations on the DNA that could cause health problems is very low [21].

When the author asked, "Couldn't it be that we are worrying too much and that, once the study was carried out, most people received the results calmly?" Uchimura said.

> I would like it to be like that, but... this is just my own opinion, I do feel that this is a 'heavy' thing indeed. Even if we explain to them that "multi-site mutations (variants) will occur in this way," some second-generation people may think that "the 'trace (Konseki)' of their parent's exposure to the atomic bomb will remain in their future." There are such implications in finding variants. About 70 new variants can occur in children even if their parents were not exposed to radiation. Moreover, it is known, for example, that the number of variants occurs more frequently in children born to older parents. If parents have a child a year older, approximately two extra variants will occur. I have never seen anyone worried that the second son, who is two years younger than the first son, would suffer any health problems due

> to the increased number of mutations. In that sense, even if an increase in the number of mutations is observed due to radiation, I think there is a possibility that it will be accepted calmly. But it may happen that a feeling like "(I am) a child of someone who was exposed to the atomic bomb" will remain in the mind of a second-generation survivor for a long time. So I think that if the story is told emotionally, it might shock A-bomb survivors and second-generation A-bomb survivors. I fear and worry about that [22].

The 'traces' Uchimura refers to may correspond to what sociologists call 'stigma' (especially self-stigma). 'Stigma', according to sociologist Irving Goffman, refers to "the situation of the individual who is disqualified from full social acceptance" or "an attribute that is deeply discrediting" [23]. In Japanese, it is sometimes translated as 'Rakuin', 'Omei', or 'Henken', but in academic settings, it is often stated in English as 'stigma'. It can mean 'attribute' or it can mean 'situation' or 'relationship'. According to Goffman, we exercise discrimination on the assumption that stigmatised people are not human [24]. In other words, stigma induces discrimination. To make a strict distinction, stigma is a negative gaze towards someone, while discrimination is a negative action against someone. In many cases, however, stigma and discrimination may be interchangeable concepts.

It is important to note that, as Goffman points out [25], people are not always stigmatised by others. People can also internalise the negative gaze of others and stigmatise themselves. This type of stigma is called "self-stigma" in the field of psychiatry [26].

Perhaps in Hiroshima, everyone has made efforts to reduce the stigma that A-bomb survivors and second-generation A-bomb survivors have carried with them for some 80 years since the end of the war. However, it is undeniable that the results of the trio genome study may evoke such stigma. Uchimura said.

> I think those things are really difficult after all. We may need to think about it separately from the issue of the health effects of radiation that are assumed scientifically and medically. Moreover, it is already certain in my mind that there should never be any discrimination based on variants caused by radiation exposure [27].

It is of course unclear whether the results of the trio genome study will promote or eliminate existing discrimination and stigma, or neither. In Japan, the Law for the Promotion of Genome Medicine came into force in June 2023. The law clearly states the prevention of discrimination based on genetic information. However, there are no penalties. In one survey, approximately 3% of respondents stated that they or their family members had been treated in a discriminatory manner based on genetic information. In addition, about 70% of respondents stated that legislation with penalties is needed [28].

4.2 Genomic diversity

However, we may be able to consider parental exposure-derived variants (if they are found) in the second-generation not as 'traces' or 'stigma', but as 'diversity.'

On 13 April 2024, the Radiation Effects Research Foundation (RERF) organised a public seminar entitled “Parental Exposure and Children’s Health: Public Seminar in Hiroshima.” Drs. Asao Noda, Department Chief (then), and Arikuni Uchimura, Laboratory Chief of the Department of Molecular Biosciences, explained about the parents/child trio genome study that is being planned. Around 200 people, including A-bomb survivors and second-generation A-bomb survivors, attended the seminar, listened to RERF’s explanations, and asked questions enthusiastically.

In this public seminar, the word ‘genomic diversity’ was used several times.

Noda explained the history of research on the second-generation survivors of radiation exposure and emphasised that, to date, no studies have shown that parental exposure has affected the health of their children (no genetic effects have been observed with the methods used so far), but research is still ongoing. Noda also explained that several whole genome analysis studies of large numbers of people have been carried out worldwide, and their results have shown that we all carry a huge number of variants. Noda said, “Then we are now in an era where the differences in DNA base sequences among people are no longer called ‘mutations (Totsuzen heni)’, but rather genetic or genomic ‘diversity (Tayosei)’ [29].”

> It would be important to create a society that accepts the diversity of each individual’s genome, wouldn’t it? It’s the society that we can say that even if changes are found, humans are living in the fluctuations of their genomes. And then the genetic effects of radiation exposure need to be discussed with an understanding of this situation [30].

At the press conference after the public seminar, the following conversation took place between the author (Kayukawa) and Noda.

> Kayukawa: One of the keywords today was ‘genomic diversity.’ Does this mean that RERF predicts that variants will be found in second-generation A-bomb survivors at a level that is not expressed in the form of disease or other symptoms?
> Noda: No, I mean that we do not deny it. I wouldn't go so far as to say that we predict it. I mean that it is possible. The most significant change among variants is the loss of the function of the gene. But there are variants where the DNA sequence changes but the function remains unchanged. I think we should call all of them, including such variants in genomic diversity.
> Kayukawa: Are you concerned about the social trend of not recognising such genomic diversity?
> Noda: I don’t want society to become a place where the words “genetic mutations (variants) have been seen” are used with prejudice and strike out on their own. I hope that there is a shared understanding in society that changes that are not expressed in the form of disease, if any, do not exceed the range of diversity that would normally occur [31].

There is a change in DNA but no change in function. This means that with the current situation where no correlation has been found between the radiation exposure of the A-bomb survivors (first generation) and the diseases and disorders of the second-generation survivors, it may be difficult for us, the general public, to accurately

understand the subtle implications if any variants are found in the second-generation survivors that are thought to be derived from the radiation exposure (Table 2). How do RERF scientists explain it? That difficulty is exactly one of the ethical and social issues of the trio genome research. Indeed, how the results are returned to the subjects has often been discussed as an ethical issue in human genome research [32]. However, it is neither possible nor justifiable to impose scientists all accountability on their participants and society. Understanding the subtle implications of such variants—if any—would be a challenge for the public and society as well.

Table 2. Difficulties in understanding trio genome study results

	A strong correlation is found between the radiation dose of A-bomb survivors and the diseases and disorders of the second generation of A-bomb survivors.	A weak correlation is found between the radiation dose of A-bomb survivors and the diseases and disorders of the second generation of A-bomb survivors.	No correlation was found between the radiation dose of A-bomb survivors and the diseases and disabilities of the second-generation A-bomb survivors (current situation).
A large number of variants that might be derived from A-bomb exposure are found in the second-generation survivors.	It is easy to understand the reason for it.	It is difficult to understand the reason for it.	It is very difficult to understand the reason for it.
A small number of variants that might be derived from A-bomb exposure are found in the second-generation survivors.	It is difficult to understand the reason for it.	It is easy to understand the reason for it.	It might fall within the scope of human diversity; however, it may be difficult for society to understand this.
No variants that might be derived from A-bomb exposure are found in the second-generation survivors.	It is very difficult to understand the reason for it.	It is difficult to understand the reason for it.	It is easy to understand the reason for it.

(Created by the author with help from Noda)

4.3 'Support' to prevent adverse health effects

On the other hand, at the press conference after the public seminar, Misa Koyama, a freelance journalist covering the second-generation survivors, was listening to the conversation between the author and Noda. Koyama said.

> I also think that a society that can accept diversity is wonderful. However, I think it is not right to simply say 'let's accept diversity' to those who have been affected by the 'diversity' that neither came from their lifestyle nor was inherited from their

parents or ancestors but was brought about because of their parent's exposure to the atomic bomb.
You mean that it might be possible to find out that the number of variants is significantly high or that the location of the variants is a place that functions as a cancer suppressor. The A-bomb survivors and second-generation A-bomb survivors who want their genomes examined want to know whether the children have been affected by their parents' radiation exposure, but also if they have been affected, they want to use what the research has found as 'support (Sasae)' to prevent any adverse effects on their health, don't they? [33]

As far as the author understands, RERF scientists have grasped the issues raised by Koyama. As of October 2024, RERF has not initiated the trio genome study. As the Stakeholder Committee on Usage of RERF's Stored Biosamples also said, it will be a major challenge not only to return the study results to the participants but also to set up a system of genetic counselling and follow-up [34].

5 Conclusion

The scientific method to date has not demonstrated that the exposure of parents (A-bomb survivors) has impacted the health of their children (second-generation survivors). Nonetheless, some A-bomb survivors and second-generation survivors remain concerned about the effects on their offspring. The ethical issue of how the results of human genome research are returned to participants is frequently discussed in the field. If the results of the trio genome study found, for instance, parental exposure-derived variants in the DNA of second-generation survivors, it could be challenging for scientists to explain how this is consistent with previous findings that no health effects of parental exposure have been found for second-generation survivors. For A-bomb survivors, second-generation survivors, and the public, it could be difficult to comprehend it. How RERF scientists explain the nuanced implications of these findings and how second-generation survivors and others understand them can itself be an ethical and social challenge. This paper points out both that interpreting 'mutation/variant' as 'diversity' rather than as 'trace' or 'stigma' could offer a potential path toward resolution. Conversely, it also highlights potential issues, such as the risk of obscuring responsibility for the act of perpetration, in accepting the consequences of parental radiation exposure in such a manner. Furthermore, and needless to say, RERF scientists refused to use exposure-derived variants as a justification for discrimination, even if such variants were identified. In addition to determining how to return the results of the trio genome studies to the participants, establishing a system of genetic counselling and follow-up will be a significant challenge.

This is an interim result. The perspectives of A-survivors and second-generation survivors ought to be examined as well.

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