Collaboration Projects

Initiative toward Prevention and Early Detection of Disease Using Healthcare Data and Genome Analysis

Research Laboratories

Daisuke Ochi† Takafumi Yamauchi† Satoshi Hiyama

With the aim of achieving the "ultimate smart life" that can prevent the onset and progression of disease, NTT DOCOMO has begun joint research focusing on diseases and changes in physical condition related to pregnancy as an initial target. This research will analyze information that combines the three elements of genome information, biological substances in blood, and daily healthcare data on a scale of several hundred pregnant women. Through this initiative, NTT DOCOMO expects to establish the world's first methods for the prevention and early detection of diseases that many pregnant women experience but whose causes has so far been unclear. This research is being conducted jointly with the Tohoku Medical Megabank Organization of Tohoku University (Executive Director Masayuki Yamamoto, Professor Masao Nagasaki, and others).

1. Introduction

As declared in "New Initiatives toward Delivery of Medium-term Targets" announced in April 2015, NTT DOCOMO plans to collaborate with new partners for the creation of value including solutions to social issues such as health and medical care [1]. To this end, NTT DOCOMO is promoting research and development toward the "ultimate smart life" that can prevent the onset and progression of diseases affecting many people.

Disease is thought to develop as a

complex intertwining of genetic factors that an individual is born with and acquired environmental factors such as lifestyle and living environment. Since 2003 when the entire human genome*1 was first sequenced [2], great strides have been made in the analysis of genetic factors owing to advances in genome analysis technology. In contrast, environmental factors have traditionally been analyzed on the basis of questionnaires targeting a person's lifestyle, so accuracy and frequency of administering these questionnaires have been issues of concern. Against this background, the NTT DOCOMO Group has constructed and deployed a healthcare data collection platform that can determine an individual's lifestyle practices in part with high accuracy and high frequency. This is accomplished by leveraging NTT DOCOMO's core competence in mobile terminals and network operation to enable the daily measurement of healthcare data such as blood pressure and physical activity. We expect the use of this platform to enhance the analysis of environmental factors.

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^{*1} Genome: All genetic information associated with the entire base sequence of DNA (see *2 below) making up an organism's chromosomes.

A major issue in modern medicine is that fundamental methods for preventing and treating many diseases related to pregnancy have not yet been found. NTT DOCOMO has therefore set pregnancy-related diseases as its first research target with the aim of establishing disease-prevention and early-detection methods for diseases related to pregnancy. It plans to accomplish this by being the first in the world to perform integrated analysis that combines genome information with biological substances in blood obtained by periodic blood sampling and daily healthcare data obtained using the healthcare data collection platform.

In this article, we explain disease factors, precision medicine and prevention and NTT DOCOMO's approach, the method of joint research targeting pregnancy-related diseases, and expected results from this research.

This joint-research initiative commenced in November 2014 in partnership with the Tohoku Medical Megabank Organization (ToMMo) of Tohoku University, a leading genome analysis center in Japan [3].

2. Background to Research: Disease Risk Factors

As stated above, the aim of this research is to establish methods for prevention and early detection of diseases, but we first examine the causes of disease to provide some background. Many diseases are thought to develop through an intertwining of genetic factors and environmental factors. It is therefore essential that both types of factors be analyzed in detail to prevent the onset and progression of those diseases (**Figure 1**).



2.1 Genetic Factors

Among the causes of disease, genetic factors originate in inherent genetic information passed from parent to child. This information is determined by the sequencing of a substance called DeoxyriboNucleic Acid (DNA)^{*2} found in human cells. Human DNA consists of four types of bases in a double helix structure—there are approximately 3 billion base pairs in DNA.

The arrangement of bases (base sequence) in DNA includes information that acts as a template for biological substances in blood such as protein. Part of this base sequence is copied as messenger RNA (mRNA)*3 that preserves this information and serves as a basis for synthesizing protein and other important biological substances. Protein can provide key functions for maintaining biological activities. These include a function for generating muscles and internal organs, a function for digesting and absorbing food, an immune function, and a function for regulating organ functions. The base sequence in DNA differs in part from person to person and the functions of protein generated from this base sequence likewise depend on the individual. As a result, protein that does not function normally can be generated depending on the person and it is that protein that can trigger disease. For example, a specific biological substance is needed to stabilize blood pressure, but if an abnormality exists in the base sequence of the protein involved in the

generation of that biological substance, the quantity of that biological substance cannot be correctly controlled. This turns out to be a genetic factor for a disease like high blood pressure.

2.2 Environmental Factors

The body contains a wide variety of substances such as protein and metabolic products, the latter of which includes lipids and amino acids that are generated by chemical reactions in the production and consumption of energy. It is said that several thousand types of metabolic products exist within the body.

Such metabolic products appear and disappear daily in the body, but their concentrations are controlled within a certain range so as not to hinder biological activities. At the same time, the types and concentrations of these biological substances can vary according to environmental factors. A good example of such an environmental factor is an individual's lifestyle including diet, exercise, and sleep, which, if erratic and disordered, can cause the balance among biological substances to collapse. This condition can lead to a change in physical condition and eventually to disease. The natural environment in which one lives including weather and temperature is likewise an environmental factor that can induce changes in one's physical condition. For example, it is known that blood pressure during pregnancy can vary according to the expected date of delivery [4].

In the above way, our biological activities are governed not just by genetic factors but also by a variety of environmental factors. These two types of factors make their contribution in a complex manner. They bring about changes in the functions, types, and concentrations of biological substances such as protein and can induce changes in a person's physical condition. Such small changes that are out of the ordinary can be an "omen," and if they worsen, they can eventually lead to disease. A correct assessment of these factors that differ from person to person should help promote the development of precision medicine and prevention tailored to one's own physical constitution.

3. Precision Medicine and Prevention and NTT DOCOMO's Approach

The analysis of genetic factors has made great progress thanks to advances in genome analysis. However, the analysis of environmental factors has so far been mostly based on a self-reporting system consisting of lifestyle questionnaires administered once or twice a year. This format has raised issues with respect to analysis accuracy and frequency.

NTT DOCOMO can determine some of an individual's lifestyle practices with high accuracy and high frequency by using its healthcare data collection platform via mobile terminals and the network to measure and acquire healthcare

- *2 DNA: A substance carrying genetic information in an organism and consisting of four types of nucleobases: adenine, guanine, cytosine, and thymine.
- *3 **mRNA:** A substance generated from part of the DNA base sequence for synthesizing protein.

data on a daily basis. These data include blood pressure and ambient temperature, weight, body temperature, active mass, quality of sleep, etc. For example, a person making measurements with a weight and body composition analyzer need only touch the analyzer with his or her smartphone to register the measurement data on the healthcare data collection platform through Near Field Communication (NFC)*4. This enables centralized management of the user's healthcare data on a daily basis. In short, NTT DOCOMO's approach makes it possible to determine a user's biological information and lifestyle behavior day in and day out, which has been difficult to do by conventional approaches.

Information obtained via the healthcare data collection platform can be analyzed in a comprehensive manner with information on biological substances obtained by periodic blood sampling and genetic information obtained by genome analysis. We expect such comprehensive analysis to bring about new discoveries in relation to disease prevention and early detection.

4. Research Target

While there are countless diseases in the world, there are those that, while accounting for many patients, have not yet been fully explained owing to the difficulty of analyzing the environmental factors affecting each patient. These include diseases related to pregnant women such as pregnancy-induced hyper-

NFC: A short-range wireless communication

technology including FeliCa and other systems.

tension syndrome, diabetes, and premature delivery. Approximately 200,000 out of one million pregnant women suffer from these diseases each year in Japan. However, due in part to limitations applied to medication and examinations so as not to affect the unborn child, little progress is being made in explaining the causes of these diseases or developing fundamental methods of treatment. Yet, it is known that health conditions during pregnancy can have a profound effect on the future health of the mother and child. For example, it is known that maternal obesity during pregnancy magnifies the risk of premature mortality in adult offspring [5].

NTT DOCOMO aims to establish methods for the prevention and early detection of pregnancy-induced diseases as its initial research target. It will adopt an integrated approach to information analysis that targets not only genome information but also biological substances obtained by periodic blood sampling and daily healthcare data.

5. Joint Research

To resolve the issues described above in relation to pregnancy-induced diseases, NTT DOCOMO commenced a joint research project with ToMMo in November 2014. This project is scheduled to run approximately four and a half years.

5.1 ToMMo

ToMMo was founded to establish

advanced forms of medical care and support reconstruction in the wake of the Great East Japan Earthquake. It is a leading genome analysis center in Japan having biobank facilities for collecting and storing genome information on a scale of 150,000 individuals. It also features Japan's largest genome-analysis facility using cutting-edge genome-analysis techniques. ToMMo is conducting a large-scale survey called a "three-generation cohort study*5" [6] of mainly healthy pregnant women but also targeting the child to be born and the child's father, siblings, and grandparents. The study will analyze genetic factors and environmental factors through blood sampling and questionnaires.

5.2 Overview of Joint Research

This joint research aims to enhance the comprehensive analysis of genetic factors and environmental factors by combining ToMMo's genome analysis facility and NTT DOCOMO's mobile healthcare data collection platform. The ultimate goal is to establish new methods of prevention and early detection of diseases and to contribute to the health of the mother and child and the development of advanced medical care. NTT DOCOMO has also obtained approval from the ethics review committee established by Tohoku University School of Medicine to perform a "maternity log study" as an addition to the three-generation cohort study. This study will target pregnant women receiving

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^{*5} Cohort study: Research that examines health changes in a group of people and studies the relation between body conditions, lifestyle, etc. and the onset of diseases.

obstetric care at Tohoku University Hospital. It will include blood sampling as a supplement to the blood sampling conducted under the three-generation cohort study and daily measurement of healthcare data. The plan is to target several hundred pregnant women for this study and to have them participate from the first stage of pregnancy to approximately one month after giving birth.

In the study, the subjects will use specific devices to make daily measurements of blood pressure and ambient temperature, weight, body temperature, amount of physical activity, etc. and will register measured values with NTT DOCOMO's healthcare data collection platform using smartphones (**Figure 2**). They will also be asked to give blood samples several times during the course of their participation.

Data obtained from blood samples

and other healthcare data constitute sensitive information for the pregnant women participating in this study. In this joint research, we are setting up a security system based on ToMMo security guidelines and managing personal information with strict controls. Bloodsample data and other healthcare data are immediately turned into anonymous data at ToMMo so that study participants cannot be identified in the analysis process.

5.3 Challenges in Joint Research

Observational studies that target people involve many concerned parties starting with the subjects and medical practitioners. It is essential in studies of this type to design and share detailed research procedures, test them in advance, and construct a support system for the subjects.

Moreover, considering that the pregnant women acting as subjects in our research will be asked to measure and register healthcare data regularly over a long period of approximately 10 months, maintaining a subject's motivation to register that data is also a challenge. It is important that some means be developed to encourage a subject to take interest in the growth of her unborn child and in the change of her own physical condition. One way would be to develop a smartphone application especially for joint research and incorporate gamelike elements according to the rate of data registration.

5.4 Expected Results

There have been past studies targeting pregnant women and analyzing metabolic products [7], but the joint research introduced in this article is the world's



first comprehensive analysis combining daily healthcare data with periodic blood sampling, genome information, biological substances, etc. The plan here is to observe how biological substances such as protein and metabolic products change over time and to clarify how that change relates to daily healthcare data, the onset of disease, and genome information. We also aim to shed light on the causal relationship between lifestyle and physical changes, between physical changes and blood pressure, etc. and to establish methods for prevention and early detection of diseases related to pregnant women.

Prevention and early detection of diseases affecting pregnant women can bring about positive effects not only during pregnancy, at childbirth, and after childbirth, but also in the pre-pregnancy and child-development periods (Figure 3). It has been pointed out that health management before pregnancy can have an effect on the health of the mother and unborn child during pregnancy. It is therefore expected that the development of a pre-pregnancy health management method tailored to the individual should reduce the risk of pregnancy-related diseases and promote a healthy pregnancy. Likewise, the development of health-management and disease-prevention methods to be applied during pregnancy should lead to childbirth without incident and increase the number of mothers that can maintain their health after giving birth. For example, it is known that the occurrence of pregnancy-induced hypertension syndrome and diabetes can increase the risk of high blood pressure and diabetes after childbirth. The disease attack rate

after childbirth can therefore be expected to drop by controlling the onset of such diseases during pregnancy. In addition, improving conditions in the womb should make for healthy development of the unborn child and have a positive effect not only on the mother but also on the child's development after birth. In this way, establishing technology for the prevention and early detection of diseases particular to pregnant women can protect the health of the mother and child over a broad range of time from the pre-pregnancy stage to the child development period.

6. Conclusion

This article described factors contributing to disease, issues in precision medicine and prevention, NTT DOCOMO's research target, the method adopted for



joint research, and expected results. Going forward, we expect to apply the knowledge gained from this exploratory research on diseases targeting pregnant women and their prevention and early detection to prevention of diseases in other target groups. NTT DOCOMO wants to contribute its expertise to achieving a healthy long life for everyone.

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Collaboration Projects

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