Request for your understanding and cooperation on the study of genetic analysis

Saitama Medical Center, Department of Laboratory Medicine, Department of Endocrinology & Diabetes

We have obtained permission by the institutional review board and the president of Saitama Medical Center to conduct the study entitled ''Genetic analysis of thyroid stimulating hormone receptor gene in the patients of gestational transient hyperthyroidism", and have initiated the study.

In this study, we will investigate whether gene structure and function can be related to a "gestational transient hyperthyroidism" onset, and make clear whether the gene is involved in the disease or not.
We ask for your kind cooperation to conduct the study, after reading and understanding the following explanation.

What is "gestational transient hyperthyroidism(GTH)" ?

"Hyperthyroidism" is the condition due to excessive production of thyroid hormone by the thyroid gland. Graves' disease is the most common cause of this condition. Graves' disease is caused by thyroid-stimulating antibody in the patient's body. Another hyperthyroidism status: "gestational transient hyperthyroidism(GTH)" is caused by human chorionic gonadotropin(hCG) which stimulates the thyroid of pregnant woman. Thyroid function is normally regulated by thyroid stimulating hormone(TSH). hCG resembles TSH in structure and function, so the thyroid of pregnant woman may be stimulated by hCG during early pregnancy period when hCG level is very high.
This condition is likely to occur in approximately 1-5% of all pregnancy, especially in twin pregnancy or other conditions causing abnormally high level of hCG. This condition is self-limiting and needs no therapy in moderate cases, but in severe cases therapeutic intervention is necessary. After the transient hyperthyroidism, hCG level gradually decreases during pregnancy and normalizes after delivery; thyroid function also normalizes accordingly. Thus, this condition is called "gestational transient hyperthyroidism".

In recent years, some patients with GTH are reported to receive excessive thyroid-stimulation signal by hCG due to the specific mutations in TSH receptor gene. Althogh pregnant women who have such mutations seem to be susceptible to GTH, their thyroid functions are normal in the period of nonpregnancy. If they need therapeutic intervention during pregnancy, they would receive the identical therapy to the usual GTH patients who do not have such TSH receptor gene mutations.

What is "gene" ?

The term "gene" means "a small unit which determines inheritance". In human, about 30-40 thousands of genes are working. The constituent of gene is DNA. Gene plays two important roles. First, gene is the accurate "design drawing of human body". One fertilized egg devides and devides repeatedly, and as the number of cell increases, each cell is determined to become "cell of eye" or "cell of gut" and so on, finally 6 thousand billion cells make up the human body, and all of the design drawings of human body are contained in genes. Second, gene plays an important role of "conservation of species". Children and their parents are similar to each other because of the action of gene.

Gene and disease

Genes play important roles for human body like this, but the variation in genes may result in various diseases. The term "mutation" is the permanent alteration of the gene of the cells consisting human body (somatic mutation). Some diseases may occur with the focus on the mutant cells, which is not hereditary. On the other hand, genetic mutation may result in hereditary desease. Although you may think that altenation of gene must result in desease, in fact, it rarely results in disease. Genes varies each other as well as faces or fingerprints are, most of the variations of genes are unrelated to any diseases. In 6 thousand billion cells consisting human body, alternation of genes occurs frequently, but most of them are unrelated to any diseases, and are non-hereditary. Only small propotion of the mutation of gene is related to disease, and hereditary.

Charactaristics of the study of genetic analysis of responsible gene for hereditary diseases

Genes play two important roles, "design drawing of the human body" and "conservation of species", as mentioned above. In case of inborn mutation of the responsible gene for the disease, the genetic analysis may be relevant according to the two roles of genes. First, for the person who have the mutation of the responsible gene, it becomes possible to predict the future development of the disease, and based on the information found out,

to early diagnose or prevent it. Second, it will become possible to discover the potential patients among the relatives of the patient, and prevent the onset of the disease, or diagnose it early, then start the adequate therapy early. However, the notification of the potential disease to someone who is currently healthy or the prediction of a genetic disease for the relatives of the patient based on the genetic analysis has not been seen in conventional medicine. Thus, it may generate various ethical, legal, and social problems; anxiety of onset of the disease, and may affect employment, marriage,or taking out an insurance policy.

Cooperation to the study of genetic analysis

This study aims to analyse the structure and function of your TSH receptor gene, and investigate the relation between the possible mutation in your TSH receptor gene and "gestational transient hyperthyroidism" from which you are now suffering or have been suffered. As mentioned previously, it becomes clear that certain mutations in TSH receptor gene may cause "gestational transient hyperthyroidism". So, if susceptible mutation of the genes is pointed out by analysis of your TSH receptor gene, the information is available for early diagnosis and treatment in your future pregnancy. In addition, the information may be available for early diagnosis for other persons with the same disease. However, this diagnostic procedure is not completely sure, so we will continue to make effort to improve the diagnostic procedure and discover other responsible mutations for the disease through this study.

You are suffering from "gestational transient hyperthyroidism", so we would like to ask you to permit us to utilize your blood as well as your medical record for this study. Small amount of blood sampling (about 2 mL) is conducted together with a blood sampling for usual clinical examination, so there is no harm or burden for your body. Now, we ask you to cooperate in this study, we are going to give you specific explanations of the procedure first before the consent, including the contents of this study. If you can understand these explanations and then agree to cooperate on this study, please sign the"consent form for cooperation on the study of genetic analysis" as an expression of your approval.

Premise of Consent

(1) Voluntariness of cooperation on this study and freedom of withdrawal

You can agree or not to cooperate on this study of your own free will. You will have no disadvantage at all when you disagree. If you want to withdraw the consent after you have already consented, you can withdraw the consent with no disadvantage. In such case, your blood sample and result of genetic analysis will be disposed, and your medical record will not be used for study after that time. However, if the articles of the study have already published before your withdrawal, the results of the test of blood or genetic analysis and so on cannot be deleted from the publication.

(2) Reserch Program

Subject for the study : Genetic analysis of the thyroid stimulating hormone receptor gene in patients with gestational transient hyperthyroidism.

Name of reserch institute and principle investigator :

Reserch institute and principle investigator is shown as following.
Research insutitute : Saitama Medical Center　Department of Laboratory Medicine, Department of Endocrinology and Diabetes
Principle investigator : Pr Mitshashi Tomoaki, Professor of Department of Laboratory Medicine, and Director of Central Clinical Laboratory

Aim of the study :

This study aims to make more accurate diagnosis of inborn susceptibility to gestational transient hyperthyroidism by genetic analysis of the TSH receptor gene using blood sample.

Research method :

Blood sampling (about 2 mL) is conducted together with a blood sampling for usual clinical examination. There is only negligible risk for your body with blood sampling. Genomic DNA will be extracted from white blood cells in your blood sample and DNA sequence of the TSH receptor gene will be determined. We will examine the differences of DNA sequence and the functions of TSH receptor between you and the other, and its relationship to your symptom.

Duration of the study :

This study will be conducted untill January 31, 2020 in the plan.

Disclosure of the study plan, etc :

You have access to the contents of the study plan and documents in relation with the method of genetic analysis, etc, if you want.

(3) **Advantage and disadvantage of the participants of this study:**

Since you have already been diagnosed to gestational transient hyperthyroidism, your treatment plan may not change significantly by the genetic analysis. However, if some mutation of the gene which may cause susceptibility to the disease is detected, early discovery and treatment in your future pregnancy becomes possible, and the screening of similar disease among your relatives and kids becomes easy with similar examination. However, in case of positive diagnosis and susceptibility to develop the disease, you may suffer on an unexpected disadvantage in case of employment, marriage, or taking out an insurance policy, and so on. Even in the case of negative diagnosis, your family might feel uneasy or be worried. For this reason, you can receive genetic counseling in the hospital, or be introduced to another genetic counseling division. In addition, it should be mentioned that gestational transient hyperthyroidism is relatively frequent disorder occurring only during pregnancy, and its therapy is identical regardless of the presence or absence of mutations of the gene.

(4) Protectoin of private information

The results of genetic analysis, which may cause various troubles, need to be carefully handled and be protected from any leakage. Preceding the study, your address, name and date of birth, etc. will be deleted from your blood sample and all medical records that we will use, and a new code will be assigned to them. The table which connects you and this code is securely managed and stored by Pr Muroya Takashi, The chief of the Department of Laboratory Medicine, who is assistant manager of private information, under the supervition of Pr Tamaru Jun-itchi, Professor of Department of Pathology, who is the chief manager of private information. In such a way, the researchers who will analyze your gene can not identify who is the holder of the genetic analysis data. However, if necessary, when we explain the result of genetic analysis of your gene to

you, decoding procedure is made by assistant manager of private information, so, at this moment, you can get the result of genetic analysis of your gene.

(5) Disclosure of the result of genetic analysis

We will explain the result of genetic analysis of your gene only for you on your request, and we will not inform the result even to your family, unless you approve or request to do so. However, the samples and the data will be stored until three years after January 31, 2020 that is the expected end of the study period, then all samples and data will be disposed after anonymization. Thus after that, you can not receive, in any way, explanation of the result.

(6) **Publication of reseach results**

The research results thanks to your cooperation may be published on conference presentation, on scientific journal, or on database, and so on, after blotting out of your name or your family name.

(7) Holders of the intellectual property rights arising out of the study

If some patent rights arise in result of the study of genetic analysis, the rights do not pertain to you but the Research Institute or the investigators, etc. Further, if some economic income arise based on the patent, you have no right to ask for.

(8) Plan of handling of samples, etc, after the end of the study on genetic analysis

The samples of your blood,etc, will be used only for this study. The samples and the data for the study will be stored until three years after January 31, 2020 that is expected the end of the study period, and are all anonymized and disposed. But, if you agree to preserve the samples after then, we will keep your samples preserved for future research as precious resource. In the future, in the case of usage of your sample for reseach, we will get approval of the research plan from Ethical Review Board, and you again, before starting the reseach.

(9) Matters regarding cost allocation

All of the cost necessary for this study of genetic analysis are paid by research funds of Department of Internal Medicine, Endocrinology & Diabetes and Department of Laboratory Medicine, so you will never be charged any extra fee for this study. However, if the susceptibility of disease is revealed by the study, diagnosis or treatment will be needed. Also, the is no financial support or compensation for your transportation fee, etc.

(10) Genetic counseling

Genetic counseling division is installed in the hospital, in preparation for your needs to consult on your disease or the result of the study of genetic analysis. There you can receive a consultation by the doctor in charge of genetic counseling. Please notify physician in charge of medical examination, staffs in charge of informed consent or staffs of Medical Affairs Division.

/ /2016

Research institute : Saitama Medical Center Department of Laboratory Medicine, Department of Internal Medicine of Endocrinology & Diabetes
Principle investigator : Pr. Mitshashi Tomoaki, Professor of Department of Laboratory Medicine,and Director of Central Clinical Laboratory

Phone number : 049-228-3491(room of Director of Central Clinical Laboratory)

Informed Consent form for the study of genetic analysis

Saitama Medical Center, Department of Laboratory Medicine, Department of Endocrinology & Diabetes
"Genetic analysis of thyroid-stimulating-hormone-receptor in gestational transient hyper-thyroidism"

Saitama Medical Center　President Tsutsumi Haruhiko
Saitama Medical Center　Principal Researcher Pr. Mitsuhashi Tomoaki

I have received an explanation from the physician in charge of recruiting potential volunteer research subject of the study "Genetic analysis of thyroid-stimulating-hormone-receptor in gestational transient hyper-thyroidism"
The explanation was clear and sufficient, and I understand the following articles marked ☑.

☐ Analysis of gene
☐ Your freedom of participation and withdrawal
☐ Aim of the study
☐ Plan of the study
☐ Method of the study
☐ Benefit and disadvantage for you
☐ Protection of personal information
☐ Disclosuer of the result of genetic analysis
☐ Publication of achievement of the study
☐ Proprietary right of intellectual property derived from the study
☐ Policy of handling of the sample after the end of the study
☐ About cost allocation
☐ The system of genetic counseling

Now, I agree about the following articles marked ☑, and disagree with the following articles marked ☒.

☐ I allow Saitama Medical Center, Department of Laboratory Medicine, Department of Endocrinology & Diabetes to use my blood sample for the genetic analysis study.

☐ I allow Saitama Medical Center, Department of Laboratory Medicine, Department of Endocrinology & Diabetes to preserve my blood sample after the end of the study, and to use it for other medical studies including newly planned and performed genetic analysis.

Date:　　/　　/2016
Adress:
Name:

【for Physician】
I clearly explained above the study to the patient.
Date:　　/　　/2016
Department:
Name:

Withdrawal of Informed Consent

Saitama Medical Center, Department of Laboratory Medicine, Department of Endocrinology & Diabetes
"Genetic analysis of thyroid-stimulating-hormone-receptor in gestational transient hyper-thyroidism"

Saitama Medical Center　President Tsutsumi Haruhiko
Saitama Medical Center　Principal Researcher Pr. Mitsuhashi Tomoaki

I withdraw my consent for the study above, and the following article(s) marked ☑.

☐ To use my blood sample for the genetic analysis study.
☐ To preserve my blood sample after the end of the study, and to use it for other medical studies including newly planned genetic analysis.

Date:　　/　　/2016
Adress:
Name:

【for Physician】
I received the Withdrowal of Informed Consent for the study

Date:　　/　　/2016
Department:
Name: