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Metabolic phenotyping in people with common genetic variants associated with weight gain or tendency to develop late onset diabetes.

Participant Information Sheet (Protocol 1 v3 July 2007)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of the study and what will happen if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1

What is the purpose of the study?

We all have genes, which control things about us like hair colour, eye colour, weight etc. We also have lots of variation in our genes, which is why we all look different. Such genetic variants are very common. Scientists have thought for some time now that these common genetic variants might contribute to inherited differences in people's susceptibility to weight gain and diabetes. However, this idea has been very difficult to prove. Very recently scientists have identified common genetic variants in a number of genes, which appear to have an effect on body weight and tendency to develop diabetes later in life. How these genetic changes alter the tendency to gain weight and risk of diabetes is currently unknown. The purpose of this study is to improve our understanding of how genetic variants alter body weight regulation and diabetes risk. Specifically we would like to measure how much you eat and how much energy your body uses up under carefully controlled conditions. The reason for wanting to understand this issue better is to try to identify more effective ways of preventing weight gain and reducing the incidence of diabetes.

Why have I been chosen?

You previously gave a blood or saliva sample as part of the Cambridge BioResource study. Genetic material (DNA) was isolated from that sample and we are now able to check your DNA for genetic variants. In themselves, the variants we are studying have very small effects on your metabolism. We are now inviting people from the Cambridge BioResource study for more detailed studies of their metabolic state so we can better understand how common genetic variants alter the tendency to gain weight and to develop diabetes later in life.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and will be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. **You are also free to decline particular parts of the study - for example you can elect not to have the biopsies.**

What will happen to me if I take part?

1. Participating in this study requires one 3-day visit to the Wellcome Trust Clinical Research Facility (WTCRF) at Addenbrooke's Hospital.
2. Your visit would last from the late afternoon of Day 1 until the morning of Day 3. It will involve spending two nights in the WTCRF.
3. During your stay we would provide all meals.
4. At the start of your visit we would ask for your written consent to participate in the study. We would also appreciate your consent to write to your GP to tell him/her that you are participating in the study. We would not seek any medical information from your GP.
5. During the afternoon of the first day we would make measurements of your body composition – the amount of lean (mostly muscle), fat and bone in your body. These measurements are made in two ways. The first uses a DXA scanner. The measurement involves a very small amount of X-ray, no more than the amount you receive from the atmosphere in 3 hours. A measurement takes between 5 and 10 minutes, during which you would lie on the scanner bed as the scanner arm passes over you. The second measurement is made by the BOD POD. This is an egg-shaped capsule in which you would sit for about 5 minutes whilst we measure the volume of your body. Results of the measurements are available immediately and we would share these with you.
6. We will ask you to collect all your urine in a bottle for a 24 hour period starting on the first evening, from which we will analyse the amount of protein your body uses, and the levels of catecholamines - chemicals involved in the control of energy expenditure.
7. Whilst you are asleep at night and for seven days thereafter, we would like you to wear a heart rate and movement monitor. This is a small disk, about the size of a 50p coin, which attaches to two self-adhesive electrodes placed on your chest. An additional movement sensor is worn like a small wristwatch.
8. In the morning we would wake you between 7h00 and 8h30. We would ask you to lie still on the bed, but to remain awake, whilst we measure your Basal Metabolic Rate (BMR). We would place a transparent canopy over your head and shoulders and draw the air you breathe out away from this. We analyse this air and calculate the amount of energy your body uses up in the resting, "basal" state.
9. After measuring your BMR we would measure your body temperature.
10. Finally, before you rise, we would place a cannula in a vein in your arm to enable us to take a sample of blood. A cannula is a little plastic tube that does require a needle to insert but once it is in place it can be used for taking blood without the need for further needles. The blood we take will be analysed for chemicals and hormones related to your metabolism, such as blood sugar, blood fats, cholesterol, insulin and thyroid hormones.
11. We will then give you a standardised meal consisting of regular breakfast foodstuffs (cereal, toast, juice etc.). We would ask you to eat everything provided within a set period of time. At set times during the meal and after the meal we will take blood samples from the cannula we placed at the start of the study. The total amount of blood drawn will be less than a cup (200 mls). We will ask you to tell us how full/ hungry you feel at set points during the meal.
12. At lunch time we will provide a range of standard foodstuffs and you will be free to eat as much as you wish. Dinner will again be a standardised meal.

13. We will ask you to spend the second night of your visit in a special calorimetry room. We would measure your energy expenditure overnight. The room is like a small bed-sitting room, comfortably furnished and with TV, DVD, Video, and Computer to pass the time. By measuring changes in oxygen and carbon dioxide in the air you breathe out in the room, we are able to calculate how much energy your body is using whilst you sleep.
14. Glucose tolerance test: On the following morning we will again place a cannula in your arm for blood sampling. We will then ask you to drink a glass of water with glucose dissolved in it. The drink is very sweet and is designed to test your body's response to a glucose challenge. We will take 6 blood samples over two hours. Total blood volume will be less than half a cup (100 mls).
15. After the glucose tolerance test we plan to get a small sample of muscle from your leg and fat from under the skin on your stomach. You are free to choose not to have the biopsies.

MUSCLE BIOPSY PROCEDURE

The muscle biopsy is done under local anaesthetic on the outer side of your thigh and involves the use of a blunt hollow needle to get a piece of muscle tissue from your leg. **The local anaesthetic injection is associated with stinging pain, but the remainder of the procedure is usually painless. If you do feel any pain, we will give additional anaesthetic or abandon the procedure if you'd prefer us to stop.** Following the biopsy the cut (approximately 0.5cm) will be closed with steristrips. The cut will leave a small scar at the site of the biopsy.

FAT BIOPSY PROCEDURE

The fat biopsy is taken under local anaesthetic from the superficial fat on the abdomen or buttocks/ thigh, and involves the use of either a blunt hollow needle or a small cut to get a small piece of fat. **The local anaesthetic injection is associated with stinging pain, but the remainder of the procedure is usually painless. If you do feel any pain, we will give additional anaesthetic or abandon the procedure if you'd prefer us to stop.** Following the biopsy the cut (approximately 0.8cm for hollow needle biopsies or 3 cm for surgical cut biopsies) will be closed with steristrips and/ or sutures. The cut will leave a small scar at the site of the biopsy.

Biopsies carry a small risk of infection and bruising but you will be checked for this by the doctor. **You can expect to feel some discomfort for 2-3 days after the procedure but we will supply you with suitable painkillers if you require them**.

16. Finally we would perform a MRI/S scan to measure abdominal ("tummy") fat and muscle or liver glycogen or fat. MRI/S stands for magnetic resonance imaging/ spectroscopy. It involves lying in a tube like structure for up to 50 minutes. It carries no health risks, but some people may feel claustrophobic in the scanner. As with all our tests you are free to decline this test if troubled by claustrophobia. The scanner is very noisy, so you will be given ear-phones to wear during the scan. MRI/S has no known long term adverse health effects.
17. You should also know that we are organising additional more detailed studies in order to assess how people with genetic variants respond to short-term (3day) overfeeding, underfeeding or long term weight loss diets. You may be invited to participate in those studies too, but will be provided with a separate information sheet and consent form.

Expenses and Payments - We would reimburse you for your travelling expenses and on completion of the study we well arrange for you to receive a "thank you" payment of £100.

What do I have to do?

We would like you to visit the Clinical Research Facility before agreeing to participate so you can see the area where you would stay and meet some of the staff, so we can describe the research in more detail, and so we can answer any questions. We would then like you to come to the Clinical Research Facility for a study visit on the day and at the time we agree. We would ask you to eat normally and avoid alcohol during the 24 hours before your visit. During your visit we would like you to remain within the Clinical Research Facility. We would like you to eat the meals that we provide (we would discuss your food preferences before you come, and would try to accommodate them). We would provide drinks when you wish, but these would be free from caffeine.

What are the possible disadvantages and risks of taking part?

Risks associated with blood sampling and tissue biopsies include local bruising, local pain and infection. All of these are very unlikely as the procedures are done under sterile conditions by experienced doctors and nurses.

Ionising Radiation

During the DXA scan, the total amount of X-ray given would be no more than you normally receive from the atmosphere in three hours and is comparable to the extra radiation received during a European air flight.

For Women

When you attend for the study we would ask you to confirm that you are not pregnant. If you are in any doubt we would offer a pregnancy test. We are not permitted to make any investigation using X-ray, however small the dose, if a woman is pregnant.

What are the possible benefits of taking part?

There are no direct benefits to you from taking part, though we will happily share with you the results of measurements made during your stay.

What if there is a problem?

Any concerns or complaints which arise from your taking part in the study will be addressed. Detailed information on this is given in part 2.

Will my taking part in the study be kept confidential?

Yes. All information about your participation in this study will be kept confidential. The details are included in Part 2

Contact Details

If you would like any further information before or during the study please contact Dr Savage at the Wellcome Trust Clinical Research Facility. The direct telephone number is 01223 596055. There is an answer phone if you call out of hours.

This completes Part 1 of the Information Sheet.

Thank you for reading about this study. If the information in Part 1 interests you and you are considering participation then please continue to read the additional information in part 2 before making any decision.

Part 2

What will happen if I don't want to carry on with the study?

If you withdraw from the study we would like to retain any useable data and sample analyses that we have obtained up to the time of your withdrawal. We will confirm with you that you are happy for us to do this. If you are not, we will destroy the data and samples.

What if there is a problem?

Complaints:

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. You can contact the researchers on 01223 596055. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from Addenbrooke's Hospital Patient Liaison Service on 01223 216756.

Harm:

In the event that something does go wrong during the research study, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Cambridge/ Addenbrooke's Hospital but may have to pay your legal costs. The study is insured for negligent and non-negligent harm under the University's Clinical Trials policy. The University's insurers are Royal & Sun Alliance, the insurance policy reference is GA00329253 and the Limit of Indemnity under the policy is £10m. The normal National Health Service complaints mechanisms will also be available to you.

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records may be looked at and the data collected for the study will be looked at by authorised persons involved in running and analysing the research. They may also be looked at by authorised persons from the Addenbrooke's Hospital Research and Development Department to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

Procedures for handling, processing and storage and destruction of data are compliant with the Data Protection Act 1998.

Data will be stored securely in the WTCRF. Data will be held, processed and reported anonymously through an identity code.

Data will be retained for a period of up to 15 years.

MRI/ MRS scans will also be stored in the Wolfson Brian Imaging Centre (WBIC) where we do the scans. These scans will be stored for 10 years and your identity will be linked to the scans and accessible to WBIC staff.

Will my GP be informed of my taking part?

With your consent, we will advise your GP that you are taking part in this study. We will not ask your GP for any information. With your permission, we will inform your GP of any concerns about your health which come to light during the study.

What will happen to any samples I give?

Blood samples will be analysed shortly after your study visit for chemicals related to your metabolism. Any residual samples will be securely stored by the research team. **We would also like to get your permission to use these samples in other ethically approved studies**. If any results are outside the normal range we will advise you and discuss the implications with you, and will then advise your GP.

The biopsy material will be frozen or preserved immediately and then stored in the Addenbrooke's Tissue Bank, a nationally registered tissue bank. **Samples may be stored for up to 15 years.** Samples will be used for histological, biochemical and molecular analysis. If any results are outside the normal range we will advise you, discuss the implications with you, and will ask your permission to then advise your GP.

Procedures for handling, processing and storage and destruction of samples are compliant with the Human Tissue Act 2004.

What will happen to the results of the research study?

The results will be published in scientific journals and/or presented at scientific meetings. When data are published or presented they will be completely anonymous.

Who is organising and funding the research?

The study is organised by medical doctors and researchers at Addenbrooke's Hospital. It is funded by research grants from the Wellcome Trust and is sponsored by Addenbrooke's Research and Development Department.

Who has reviewed the study?

This study has been given a favourable ethical opinion for conduct in the NHS by the Cambridgeshire 3 Research Ethics Committee, an advisory committee to the East of England Strategic Health Authority.

Thank you.

We would like to thank you for considering taking part in our research and for taking the time to read about this study. If you now go on to participate in the study you will be given a copy of this information sheet and of your signed consent form to keep.

(Protocol 1 v3 July 2007)