Immunodeficiency Genomics Research – Frequently asked questions.

Background information for patients and families.

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Genomics and the Human Genome Project are in the news and many people are interested to know what it is all about. Also PID patients may be approached to participate in research involving genomics.

This FAQ sheet is for your general information only and is not part of the consent process for any research project.

What is "genomics"?

Genomics is the science of genes, the code inside our cells that makes us who we are. We know a lot about how genes are built and how they are passed on from parents to children. We understand how some genes affect who we are and how we develop. Faults in some of these genes are known to cause specific inheritable diseases, including some types of immunodeficiency. But there are far more genes that we don't know anything about.

What does genomics research involve?

In order to learn more about diseases, we need to find out what makes people with conditions like immunodeficiency different from people who don't have this condition. Sometimes the answer lies in the genes. Medical genomics research looks at the DNA (the building block of genes) of people with a medical condition and compares these with healthy peoples' DNA. Differences may give clues to the causes of the disease.

How can I get involved?

There are two national research projects going on which will accept patients with immunodeficiency conditions. These are called the Bridge-PID study and the Genomics England (GeL) 100,000 genomes project. These studies may be linked eventually, so you should only sign up for one of them.

You can ask staff at your immunology centre whether they are currently participating in these projects. Eventually every centre will be able to recruit patients to the GeL 100,000 genomes project. Until then any centre can link up with other centres who are already actively recruiting patients.

If the genetic cause of your PID is known then you can't sign up for this research (examples include x-linked agammaglobulinaemia or Bruton's disease, some types of SCID and CGD). If you have had a bone marrow transplant then it is harder to contribute (your blood cells are from the donor), but there are ways round this.

If other members of your family are affected then the chances of finding a cause are higher.

What happens if I do sign up?

First you will be given a standard information sheet about the project. You should read this carefully and ask questions about anything you don't understand. When you are happy that you understand the project, you are invited to sign a consent form to say that you have had all the information you

need and that all your questions have been answered, and that you are willing to contribute to the study. You need to be absolutely sure that you are happy to take part. If you want more time to think about it or discuss it with your family, then say so.

If you are happy to participate, then a blood sample is taken and your details and details of your condition are recoded on a form. No name or other direct identifying information is included.

What happens to the blood sample?

The blood sample will be taken and sent to the laboratory that carries out the genetic test. Your name is not on the sample and only the staff at your immunodeficiency centre know which sample comes from which patient.

The test is called Whole Genome Sequencing. This means that the spelling of every single gene and all the other DNA in your chromosomes is deciphered. The genetic sequence (represented as a string of letters) is stored securely and confidentially on a large computer server. This is your genome. It can then be compared to other people's genomes to identify differences, some of which may genetic differences that made you ill.

What is the difference between "Whole Exome Sequencing" and "Whole Genome Sequencing"?

Genes are made of DNA. In between the genes themselves there is a lot of DNA that we don't understand very well. Some of this DNA may actually control how and when the genes are turned on and off, so we need to study this as well. Whole exome sequencing (or WES) only looks at the genes themselves. Whole genome sequencing (WGS) looks at all the DNA, both in and around the genes.

Will this give a definite cause for my PID?

Not necessarily. Every person is unique because of hundreds of thousands of tiny differences between our genomes. These are called "variants" and most of them are irrelevant for our health. The difficulty is to decide whether any of these variants has anything to do with a patient's condition.

When will I get a result?

The aim is eventually to make genomic testing results available within 6 months, although it is slower at the moment. That could be the point when your doctor can say "we have found the genetic change that caused your disease". However, it is also possible that doctors and scientists cannot see an obvious genetic reason for your illness, based on what we know at this moment. But they may be able learn more about your unique variants and how they link to your illness – this is research. When possible new genetic disorders are discovered then many further experiments are still needed to work out whether it is likely to be causing the immune problem. If other individuals with the same condition are found to have the same sorts of variants, then that could also increase confidence that this is a cause of the condition. Scientists need to be sure of such a link before feeding back to your doctor about a new diagnosis – we do not want to give wrong information. That is why reporting of this sort of result may take many years.

What happens if an unexpected abnormality is found?

This is an important question. You need to think about this before you join the study. Many people carry variants that are known to cause disease or make a disease more likely to occur. Examples

include genes associated with cancers or other conditions that don't occur till later in life. Sometimes people carry a genetic change which is silent in them, but can cause disease in a child they have with another person who also carries the same gene (cystic fibrosis is a common example). This is called a recessive condition and the parents are called “carriers”.

If such genes are found in your blood, then you may have an option to know this. The process is different between the Bridge-PID study and the GeL study, so you should make sure that you discuss it with your immunology team before you join.

Where can I find more information about genome research and testing?

http://www.genomicsengland.co.uk

https://www.eshg.org/fileadmin/eshg/documents/ESHG_Patient_leaflet_on_NGS.pdf

http://www.eurogentest.org/index.php?id=157

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