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PID UK
Supporting families affected by primary immunodeficiencies

Celebrating Rare Disease Day 2017

Dear PID UK members,

Welcome to a special edition of our newsletter celebrating Rare Disease Day.

This year's theme is 'With research, possibilities are limitless'.

Research is crucial to providing patients with the answers and solutions they need, whether it's a treatment, cure or improved care. With this in mind we invited researchers and clinicians to give updates on the latest advances for people affected by PID.

Patients play such a crucial role in research so we have a guide to encourage you to ask about research and a patient perspective of being involved in a research project.

We hope you enjoy reading what is being done to make the future brighter for the PID community.

With best wishes,

The PID UK team.

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A guide to patients taking part in research

Being part of a research project may mean you get better treatment at the same time as helping other people with your condition. So what's involved and how can you sign up? This guide below has some answers.

Who does research into PID and why?

Many hospitals, universities, drug companies and some charities are involved in PID related research. Doctors, scientists, research nurses and patients all help in this. The research aims to

- Improve the understanding of PID, including identifying the different genes and pathways that go wrong in these conditions
- Develop better treatments and cures for PID
- Improve people's quality of life.

Why should I take part in research?

Healthcare breakthroughs can only happen if evidence shows that a new prevention, treatment or cure is safe and beneficial. This evidence is collected by carrying out research studies that involve patients.

There are lots of reasons to be involved in research. Some of these might benefit you personally:

- You might benefit from a better treatment
- Your condition might be monitored more closely
- You and your doctor might learn more about your condition and be able to tailor treatment more appropriately
- You might meet people with the same condition.

There are also broader reasons to get involved:

- You might be helping to develop better ways to look after people who have the same condition as you
- You might be helping to give a better future for people with PID.

What sort of research can I take part in?

There are three main types of research you might take part in:

Observational

An observational study helps researchers understand your condition better or a group of people with the same condition better. It will not directly affect your health, as no new treatments may be given. One example is allowing your medical information to be entered into the UK PID registry. Others might include:

- Samples being taken such as blood, sputum and lung fluids
- Measurements being taken, such as lung function tests
- An interview or questionnaire

Interventional

An interventional study is when a new treatment, for example physiotherapy or new drug, is given. Every drug that is prescribed to treat PID has been through research studies to make sure that it works and is safe to use.

Qualitative

Qualitative research aims to understand more about people's experience of living with a condition. In this type of research you might be asked about your experiences of anxiety, pain, doing day-today activities, for example. The research team will try to identify patterns that will help them to understand the issues faced by people living with a PID, and ways to improve these issues.

How do I know that the study is a good one?

Most studies are reviewed by an independent scientific panel to make sure that they are well-designed and meet quality standards. Research carried out in the NHS must follow guidelines set out by the Research Governance Framework for Health and Social Care.

Once this scientific review has taken place, the research team then has to find money to fund the study. During this process, another independent review is carried out by the organisation considering awarding the money. Only the highest quality studies will be funded.

Do I have to get involved in research?

No one has to take part in research and your doctors and research team will understand if you do not want to. The care you receive will not otherwise be affected by your decision to take part or not take part in research.

If you are interested but you have some questions or concerns about what's involved, how it might affect your condition, how much time it will take and how you'll get to the research venue, speak to your health care or research team. They will be able to help answer your questions so that you can give informed consent to take part.

Will I get paid for participating in research?

Participating in medical research will usually involve travelling to the place where the research is being carried out, such as a hospital or clinic. Volunteers who take part in a medical research study will often have their travel expenses paid. Before committing to taking part, it's worthwhile asking the research team exactly what expenses will be covered and what financial compensation will be offered.

How can I find out more about taking part in research?

Your health care team might ask you about taking part in a research study or you might want to look for a study yourself. There are lots of ways to find out more. Do ask your health care team.

Useful links

- The organisation People in Research supports public involvement in medical research.
- The NHS choices website has more information about clinical trials.

  Visit http://www.nhs.uk/Conditions/Clinical-trials/Pages/Introduction.aspx
- The UK Clinical Trials Gateway helps you make informed choices about clinical trials. They offer useful guidance on how trials work and help connect you to researchers running trials you might be interested in.

Prion Surveillance in Primary Immunodeficiency Patients

Chief Investigator Dr Anna Molesworth, PhD of the National CJD Research & Surveillance Unit gives an update on this important research monitoring prion infection in PID patients.

Extended funding for Creutzfeldt–Jakob disease (CJD) project

We're really pleased to the extension of funding for our project, 'Prion surveillance in primary immunodeficiency patients', from the Department of Health (UK) Policy Research Programme.

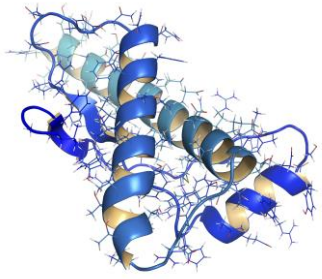
With the extension, which runs until 2022, we will:

- Continue to work with our current study participants, taking a blood sample once every two years and giving them an annual telephone call in between. We will continue to test any available tissue (for example, the tissue left over from biopsies) for abnormal prion protein and seek consent in life from all participants for post-mortem examination and removal of tissue samples for prion testing following their death.
- Invite currently non-participating immunology centres throughout the UK to take part in the study.

- Invite anybody who is interested, but is not currently participating in the study, to contact us if they think they would like to take part. Our new research nurse, Kudzai Karekwaivanane (left), is very happy to talk to you!

About the project

The prion surveillance study started in 2006. Prion diseases are associated with a naturally occurring protein (the prion protein) that has changed into an abnormal form. Sometimes infection can be detected in certain body tissues even before the person becomes ill. The prion surveillance study aims to find out whether any evidence of prion infection could be found in antibody-deficient patients who received certain UK-sourced immunoglobulin products between 1996 and 2000. The products were made from plasma from UK donors and have been infected with a particular type of prion that causes variant Creutzfeldt–Jakob Disease (vCJD) – a very rare disease that causes degeneration of nerve cells in the brain and spinal cord.



The importance of monitoring

To date, no patients have shown symptoms of prion disease, nor is there any evidence of prion infection in the tissues tested. These results are reassuring but it is very important that we continue to monitor patients over the long term as we know that prion disease may take many decades to develop after exposure.

There is no blood test that can reliably tell us if someone is infected before they develop symptoms of disease. All study participants have agreed to donate blood for storage for future testing when such a test becomes available.

Approximately 175 immunodeficiency patients are thought to have been exposed to UK-sourced immunoglobulin between 1996 and 2000. Of these, 77 from 16 immunology centres across Britain have been involved in the study. We are very grateful to these people, their families and carers for their participation, and we look forward to having more people join us this year.

Why is it important to take part in the study?

By participating in this research, you will be helping us better understand the risk of CJD being linked with medical treatment and it may mean that public health precautions can be taken in order to help prevent infecting others.

If you are not already part of this study, or if you would like to find out more, please contact your local immunology team or Kudzai at the surveillance unit on 0131 537 2128 or 07464 677118.

Taking part in the CJD project – a participant's perspective

'I agreed to take part in the prion study in 2006. This was not a decision I made lightly, and it was made while attending my annual immunology appointment. I felt that agreeing to take part in the study was a sensible course of action.

Why? I believe patients who benefit from regular medical treatment have a duty to support the medical profession that allows them to lead a "normal" life. Also, I have always been conscious of the fact that the medical treatment I rely on, immunoglobulin therapy, has required people to dedicate their time and body to give plasma to help people like me who are affected by a primary immunodeficiency. It is only correct I do the same.

Being part of the study could not be more simple. I had a brief meeting with my immunology nurse, who explained the aims of the study and why it is important. I also signed a consent form, which was a formal document to confirm my willingness to take part in the research. It was also reassuring to know that I could withdraw from the project at any point should I change my mind, although this is unlikely in my case.

I donated blood (I am certainly used to that procedure!) and will continue to do so every two years; while I am attending an appointment that would be taking place in any case. Although I receive no detailed information about the research my blood is being used for, I know it is being used to develop an understanding of the risk of CJD being linked to my medical treatment.

One of the most reassuring aspects of the study is that all information is confidential. I have no concern about my name or personal details being published in any journals or conference papers. I am a participant in an important study, but do not have to dedicate any time or have any concern about my details.'

Research and the UKPID/ESID registries

This article by Dr Matthew Buckland, Chair of our Medical Advisory Panel and Consultant immunologist at Great Ormond Street Hospital and the Royal Free Hospital NHS Foundation Trusts, gives an insight into how patient data in the UKPID and ESID registries are being used to help drive forward better health care for the PID community.

Patient registries provide important clinical data on medical disorders or interventions. The primary immunodeficiency (PID) registries in the UK and Europe are driven by a need to understand the patterns, causes and effects of PID (known as epidemiology); how patients are diagnosed and managed; and how diagnosis and management affect outcomes for patients. Knowing and understanding this information is important because it helps shape policy decisions about health care going forward.

Two years ago the structure of the registries was altered across Europe. The purpose was to improve data collection and the quality of information gathered, and to align the information with the questions we wanted to ask.

Using the data to ask research questions

The first stage was to create what are referred to as 'level 1 data sets' and then use the information to answer research questions, such as:

- What are the percentages of different PIDs across Europe?
- What percentage of PID patients come from consanguineous families?
- What percentage of PID patients have affected family members?
- Does the sex of the patient have an impact on the age he/she is when symptoms first appear?
- Are there some disorders with a genetic basis that are commoner in certain places?
- Are neonatal diagnoses increasing over time?
- Does diagnostic delay decrease over time?
  What are the most frequent presenting symptoms of PID?
- Are asymptomatic diagnoses increasing over time?
- What percentage of patients in different subcategories undergo haematopoietic stem cell transplant or gene therapy, and is that increasing over time?

The level 1 data required to support this information are relatively small, but the questions above are clearly very important in helping us to understand how we are performing as a community in recognising, diagnosing and treating patients at an early time point.

Delving deeper

The next question we want to ask is how our approach to antibody replacement is impacting on patients with a range of antibody deficiency disorders, including CVID. This considerably larger level 2 data set focuses much more on how different treatments help and the disease-related outcomes.

Bespoke research

There is a third level of data collection, which is driven by a much more bespoke research question. The level 3 data set currently in use is for APDS (activated PI3 kinase delta syndrome) and will help us to look at the role of specific therapies in this rare disorder.

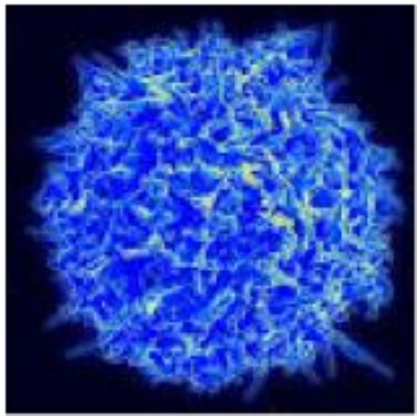
The vital importance of your data

The research registries are an invaluable resource that over time will enrich our understanding of PID and how best to treat patients. Many publications already in circulation are based on data collected from the UK and across Europe, and these have been used to improve the quality of care. The other incredibly useful benefit of the registries is that we can use the data to have more informed discussions with newly diagnosed patients and their families. By collating outcomes across Europe over time, we will be able to give a clearer picture to people who want to understand what the future may hold for them. After all, knowledge really is power!

Advances in haematopoietic stem cell transplantation

Huge advances in haematopoietic stem cell transplantation for people affected by PID have been made over the last ten years.

This article written by Dr Andrew Gennery, Consultant in Paediatric Immunology at the Great North Children's Hospital, highlights a new technique that will help more families with PID benefit from this curative treatment.



T-cell depletion

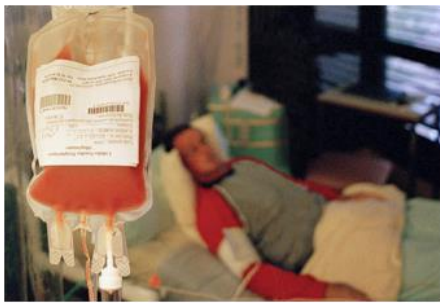
T-cells, a type of white blood cell, are the cells that cause graft versus host disease (GVHD) after a haematopoietic stem cell transplant (HSCT, also known as bone marrow transplant). The T-cells are removed when there is a strong possibility that GVHD may occur after an HSCT. The removal process is called T-cell depletion.

Tissue matching and graft versus host disease

A possible side effect of an HSCT occurs when the donated cells do not recognise that they should be in the patient and try to reject the patient's cells, resulting in GVHD. GVHD can be fatal. Doctors try to prevent it by choosing a donor who is an identical tissue type match, because an exact tissue match makes GVHD unlikely. They generally also prescribe medication (commonly cyclosporin) to patients, to further guard against GVHD. However, despite these interventions, GVHD may still occur. It is usually after about four months that the donated cells become tolerant of the patient and the risk of GVHD passes.

T-cell depletion is used when a good match cannot be found

Occasionally it is not possible to find a donor whose tissue type matches that of the recipient exactly, and so doctors may consider using a parent as a donor. Parents are generally a 50% tissue type match to their children. When a parent donor is used, it is highly likely that GVHD will occur. To prevent GVHD, it is possible to remove the T-cells. After the transplant, the patient produces his or her own T-cells that do not cause GVHD.



Balancing the risks and benefits of T-cell depletion

T-cells are important for fighting viral infections, and so the drawback with T-cell depleted transplants is that patients are extremely vulnerable to viral infections until their own T-cells develop, which is about four months after HSCT, even though the risk of GVHD is reduced.

Outlook for the future

Historically the outcome of T-cell depleted transplants has been much worse than transplants using matched donors. Newly available techniques have been developed that remove the T-cells but leave behind cells that will fight viral infection. Results using these techniques are remarkable, with success rates of over 90%. Even more refined techniques are likely to become available in the future, meaning that there should almost always be an option for stem cell therapy for patients with PID.

Update on genome sequencing projects in PID

In this article Professor Sophie Hambleton, Professor of Paediatrics & Immunology at the Great North Children's Hospital in Newcastle, brings us up to date with latest news on the use of genomics to help diagnose PID.

Many of you have already taken part in research projects involving sequencing of your DNA (and possibly that of your family members). The idea behind this is that most PID is written in our genes, and reading this code might help us understand and manage PID. If you already have a genetic diagnosis then genome sequencing is not usually needed.

What are researchers looking for in my genome?

Researchers are looking for genetic changes that caused your immunodeficiency. Sometimes spelling mistakes in a single gene are enough to cause illness. We already recognize a lot of these PIDs in children, linked to particular genes that are important for the immune system. These genes are the first to be screened for spelling mistakes when a new patient's DNA sequence is analysed. If changes are found, and the pattern of disease fits with the known role of that gene, a diagnosis can be made. The genetic change needs to be confirmed within the NHS before it is reported back as a definite finding.

At present most patients with PID do not have recognizable single gene disorders. Researchers therefore need to look outside the known PID genes for answers. There may be new single-gene PIDs to discover. We may find DNA changes outside genes that influence how nearby genes are turned on and off. Other patients – especially adults with infection-only CVID – may not have a truly genetic disorder. On the other hand, they may have a collection of genetic risk factors that set the scene for CVID when triggered, for instance by infection. By comparing the DNA fingerprint of different individuals with the same immune problem, researchers are trying to discover genetic patterns that predict CVID.

Why does this matter?

Knowing your precise diagnosis might help you. It might help to predict what your medical future holds, or which different treatments might work better (or worse). Since genes run in families, it may help predict whether close family members (including your own children, siblings, cousins) might be at risk of the same illness or of passing the gene on to their children. Genetic counseling will be on hand with information and support if needed. In this way, knowing your precise diagnosis might help your family members. The more we learn about PID in general, the better for everybody affected. When researchers find a new PID gene it can speed up the diagnostic process for future patients with the same condition and might lead to them getting earlier treatment.

What has been happening so far?

Two major national projects have been the BRIDGE-PID project (part of the NIHR Bioresource) and the 100,000 Genomes Project (run by Genomics England). These are both research projects designed to help establish the place of genome sequencing in clinical care, as well as for scientific advance. Until now the two projects have functioned in parallel, with different procedures for recruitment and reporting. But they are now in the process of merging into a single pathway. This coincides with thousands of genome sequences starting to come back through the pipeline. Researchers, clinical scientists and clinicians are combining their efforts to analyse these genomes and feed back results as effectively as possible. There is a lot of work to do.

Over 160 patients with immune and blood disorders have now been sequenced by Genomics England (out of a total of almost 23,000 people with rare disease or their relatives). In early successes, new genetic diagnoses have been made for two children with PID in different parts of the UK leading to changes in their management. We are confident that genome sequencing will help us make diagnoses in a larger proportion of PID patients than ever before.

How can I get my genome sequenced?

New patients will be enrolled only through the 100,000 Genomes Project and Genomic Medicine Centres, which are spread around the country to ensure access for all. Patients in the devolved nations are included, not just those in England. If you are interested in taking part, talk to your immunology team as they will be able to refer you to your local Genomic Medicine Centre. The 100,000 Genomes Project will continue well into 2018 but will then be replaced by an NHS-commissioned genomic service. We are lobbying for PIDs to be among the conditions for which genome sequencing will be available within the NHS.

Want to find out more?

You can find details about the 100,000 Genomes Project here: https://www.genomicsengland.co.uk/the-100000-genomes-project/

and information about taking part here: https://www.genomicsengland.co.uk/taking-part/.

Beyond DNA

Dr William Rae, from the University Hospital Southampton NHS Foundation Trust, looks at a new genetic approach to increasing the diagnosis rate for PID through studying RNA, the sister molecule to DNA.

Genetic testing and DNA

The number of genes known to cause primary immunodeficiency (PID) has increased rapidly to more than 300 over the last few years (*Figure 1*). This is owing to the introduction of 'next-generation' sequencing technologies and improved tools for analysing the vast amount of data they generate. This has meant that more accurate, faster and cheaper genetic testing is now possible for patients and for research purposes.

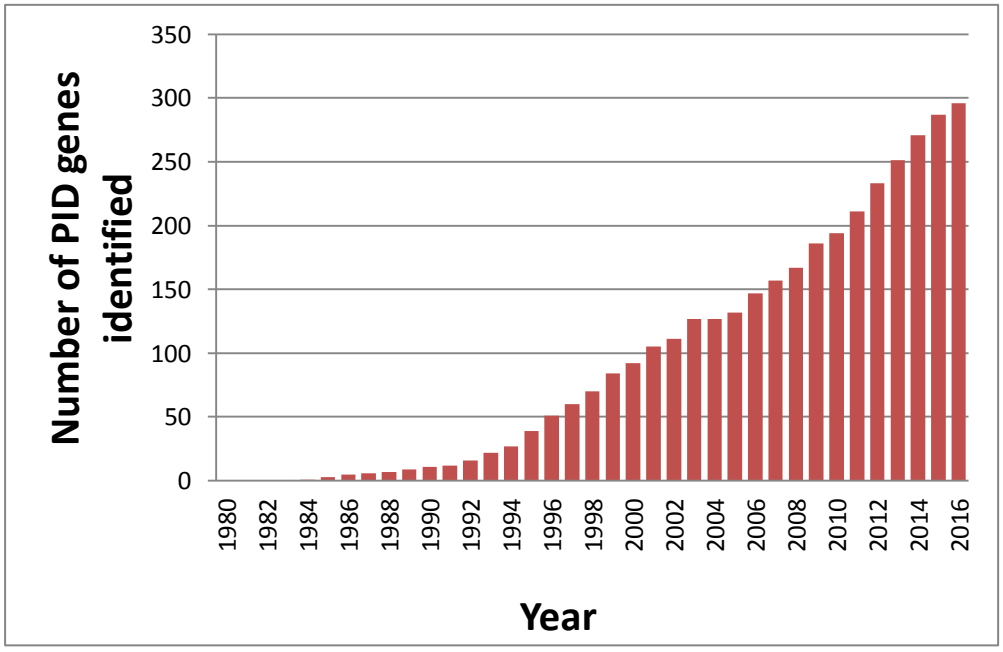


Figure 1

Adapted from *Meyts, I et al., J Allergy Clin Immunol. 2016 Oct;138(4);957-969*

Large-scale projects, such as the 100,000 Genomes Project, provide opportunities for patients and their families to have genetic investigation for the causes of PID, and many PID centres in the UK now also offer genetic testing for patients from the clinic. However, despite these advances, only approximately 25–50% of patients receive a genetic diagnosis. Partly this is due to the challenges in analysing large volumes of data, and the lack of understanding about the function that regions of unknown DNA, so-called non-coding DNA regions, have in controlling how cells work. Non-coding DNA has in the past been referred to as 'junk' DNA but we now know it plays an important role.

From DNA, to RNA, to proteins

In other rare diseases an additional test looking at ribonucleic acid (RNA) has been shown to increase the number of genetic diagnoses found for patients. RNA is the molecule that is initially made by creating a copy of DNA, by a process known as transcription (see Figure 2 on the next page). Many different factors can influence this process of RNA transcription from DNA and these may result from alterations in non-coding DNA regions.

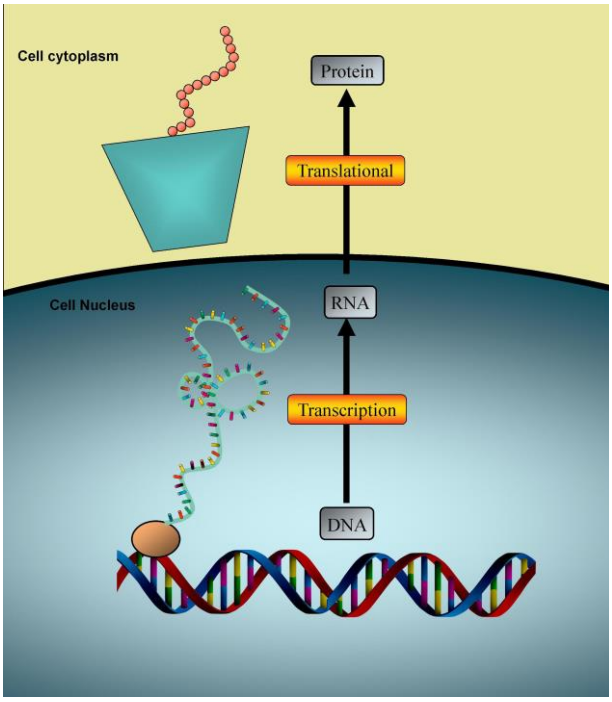


Figure 2

The RNA is then used as instructions for cells to make proteins by a mechanism known as translation (Figure 2). In fact, without RNA, proteins would never be made. These proteins then go on to perform jobs within the cell, including a vast range of functions in immune cells.

In summary, defects anywhere in this process from DNA to protein can result in impaired cell functions.

The potential of studying RNA

By studying RNA it is possible to detect defects in the process of transcription, both of individual genes and also within broader immune cell pathways. Knowledge of abnormal or absent RNA can then help researchers to carefully study these non-coding regions of DNA to finally identify genetic changes that may have been overlooked during the initial genetic analysis. By this process we hope to increase the number of patients who will receive a genetic diagnosis for their condition.

Our new study

We plan to perform a research study to look at the RNA within immune cells (known as the cell's transcriptome) in patients with PID. By careful analysis of these data, we will determine which specific pathways within immune cells are not working correctly. This will mean we can specifically target genetic analysis to these regions. The aim is to use this approach to provide more genetic diagnoses for patients with PID and their families, and allow them to receive the best possible care.

For the project we will ask patients, who have consented to take part in the study, to give 10ml (2 teaspoons) of blood, from which immune cell transcriptomes will be analysed. We plan to offer enrolment into this study to all PID patients and share protocols with other PID services throughout the UK.

Dr Will Rae is NIHR RD-TRC Immunology Fellow and Clinical Research Fellow, NIHR/Wellcome Trust Clinical Research Facility, University Hospital Southampton, UK. *will.rae@uhs.nhs.uk*

About Primary Immunodeficiency UK

Primary Immunodeficiency UK (PID UK) is a national organisation supporting individuals and families affected by primary immunodeficiencies.

Our website at www.piduk.org provides useful information on a range of conditions and topics, and explains the work we do to ensure the voice of PID patients is heard.

If we can be of help, please contact us at hello@piduk.org or on 0800 987 8986 where you can leave a message.