



NEWSLETTER

Genetic Overgrowth PI3K Support

www.gopi3ks.com

December 2016 Issue 3

Welcome to the third newsletter for GoPI3Ks – Genetic Overgrowth PI3K Support. Here we will keep you informed of the current research, interesting news articles and stories from overgrowth patients.

Recent developments from the research team at Addenbrookes, Cambridge:

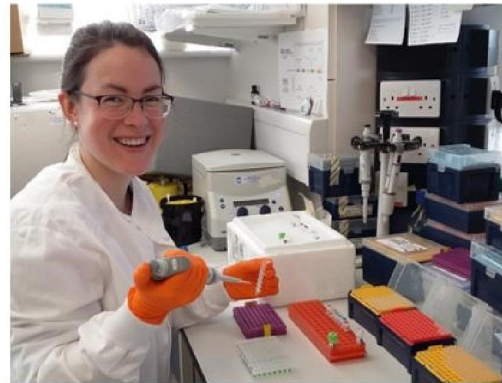
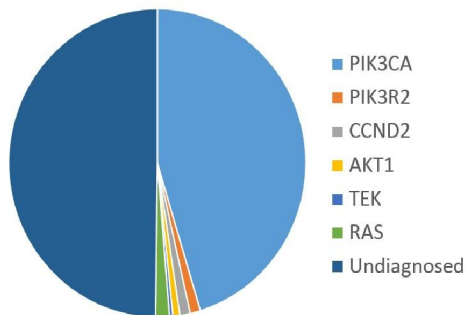


THE LATEST FROM ADDENBROOKES, THEIR RESEARCH & DRUG TRIALS

GENETIC TESTING – FROM RESEARCH LAB TO AN NHS SERVICE

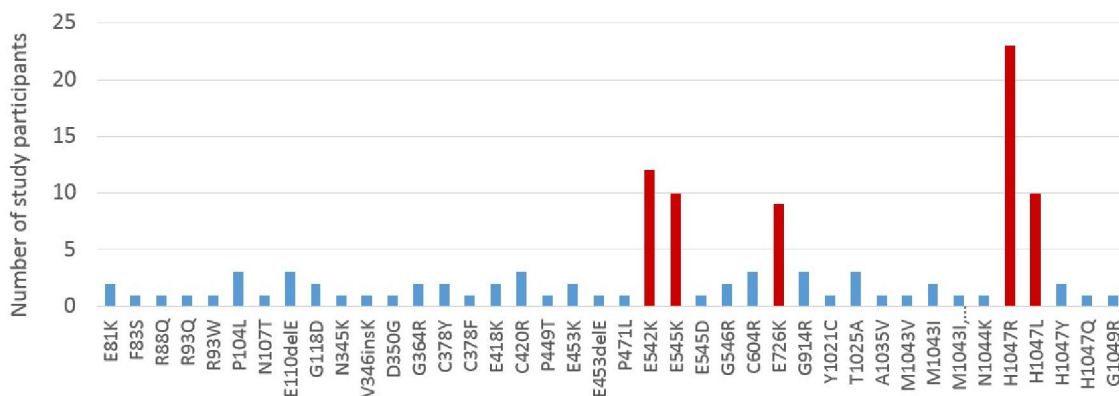
We have now tested over 300 people with segmental overgrowth, and have been able to genetically diagnose about half of them. Segmental overgrowth tends to be caused by mosaic (patchy) changes in a gene called *PIK3CA*, although in some cases, mutations in other related genes – such as *PIK3R2*, *CCND2*, or *AKT1* – are responsible instead. Having set up a diagnostic pipeline in our research lab over the past couple of years, we are now in the process of getting this genetic testing accredited as an NHS diagnostic service.

Genetic diagnoses of SOS study participants



Rachel Knox
Research Assistant

Genetic changes in the gene *PIK3CA* cause segmental overgrowth



About 40% of our study participants have genetic changes in a gene called *PIK3CA*, which controls growth. The changes are 'activating' – they switch on growth signals leading to excess growth in the affected parts of the body. *PIK3CA* codes for a protein which is made up of 1069 building blocks called amino acids.

The most common change causing segmental overgrowth is H1047R (the 1047th building block of the protein is changed from something called 'histidine' to an 'arginine'). The graph above shows the other changes which we have diagnosed in our study participants. Other common changes (shown in red) are E542K, E545K and H1047L. Several patients with MCAP/M-CM have the change E726K.

MODELLING OVERGROWTH IN STEM CELLS

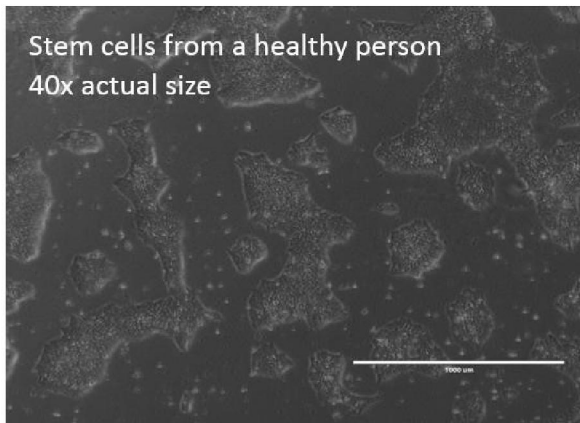
Until this year, we have been using skin cells grown from patient biopsies to study overgrowth in the lab. We are trying to work out why these genetic changes cause cells to divide faster than usual, and we have been testing a variety of drugs which might reverse this process. The disadvantage of studying skin cells (called fibroblasts) is that they age quickly when out of the body, and we can only perform certain types of experiments, being limited by

looking only at one type of cells (when in reality fat, bone and other tissue types are also affected).

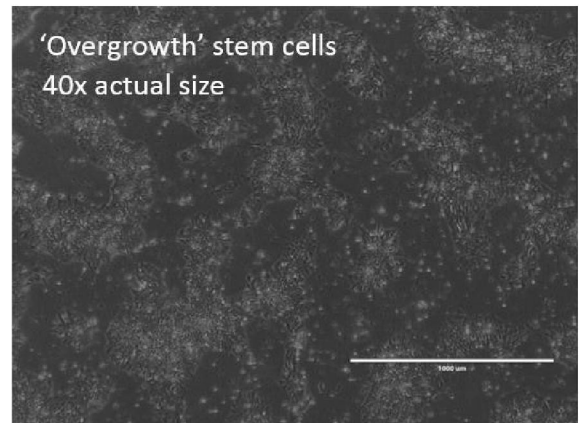


Ralitsa, a PhD student in our lab, is working with stem cells – cells which can develop into any cell type, given the right balance of nutrients. She has recently made a model of the most common genetic change in *PIK3CA* – H1047R – enabling us to study the effect of overgrowth during early differentiation, as when a baby develops in the womb. These ‘overgrowth’ stem cells mirror the characteristics of overgrowth syndromes – the cells divide faster and have a different morphology, making them a useful model in Ralitsa Madsen, which we can discover more about the biology PhD student of overgrowth, as well as test

potential treatments.



Stem cells made (‘re-programmed’) from a healthy person’s skin. We grow them in a jelly-coated plastic dishes, in which they form clumps called ‘colonies’. Cells at the edge of the colonies curl underneath, giving them a whitish rim.



‘Overgrowth’ stem cells containing the genetic change, *PIK3CA* H1047R. Cells divide more quickly, and colonies have a spikier appearance (without a white rim) – this can be reversed by giving the cells sirolimus, the drug used in our clinical trial.

CLINICAL TRIALS UPDATE

This year, after a long wait for many, and a considerable amount of planning, we finally started a clinical trial in *PIK3CA*-related overgrowth, testing whether or not sirolimus is an effective treatment for this condition. We have now completed enrolment and have been very grateful to the eleven children and adults from the UK and Ireland who have participated in the trial. We appreciate it is a huge amount of commitment from patients and their families, but it is equally an important step in identifying the best possible treatments for *PIK3CA*-related overgrowth. We have been running the trial in parallel with doctors in Dijon, France and Washington, USA and hope to get results in early summer 2017.



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We remain hugely grateful to all our study participants, as without you none of this work would be possible! For more information, please visit our website, Facebook page or follow us on Twitter:

<http://www.ovegrowthstudy.medschl.cam.ac.uk/> Twitter #overgrowthstudy
Facebook: <https://www.facebook.com/segmental.ovegrowthstudy>

OVERGROWTH FAMILY WEEKEND, BRACKNELL, OCTOBER 2016

In October this year we held an overgrowth family weekend along with the PSF (Proteus Syndrome Foundation) It was 5 years since the last gathering and so much has happened for many of the members, including myself, with now having the diagnosis of the PIK3CA mutation.



With Tracey from the PSF & Dr. Sue Husson from the Royal Manchester Hospital.

“Disability doesn’t make you exceptional, but questioning what you think you know about it does.” Stella Young

Our day started with a talk by Dr. Beisecker, who as well as focusing on Proteus Syndrome and it’s potential treatment, he is also working alongside Dr. Semple from Addenbrookes, Cambridge to help diagnose and possible treatment for those with a PIK mutation.

Following lunch, a talk by Dr. Semple focused on the research and drug trials around the PIK mutation that he and his team have been working on for a number of years. You can find more about the research at the beginning of this newsletter. From a personal point of view, it all seems very positive and more people are being given the chance to become part of the drug trial with what I hope will have a positive outcome. I feel that I am one of the lucky ones, as my mutation is found in my fat cells, which means I believe anyway, easier to treat as once the signal had been stopped from getting through to my mutated gene, it meant I stopped growing. My understanding is that this PIK mutation can occur in any cells which may mean treatment varies to its effectiveness. However, would I say don’t try the treatment? Not at all, I think if something has the possibility of working then what have you got to lose? I just hope that with time the medication that is currently being specifically designed to target just the PIK gene may help more people.

It was so nice to meet up with old friends like James who also has the PIK3CA mutation



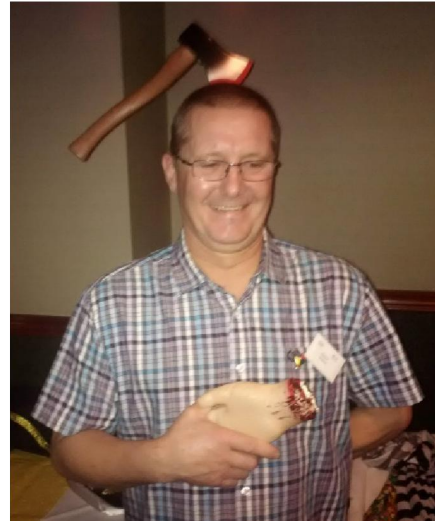
“As far as we’re concerned, *disability* means *possibility*.”

<http://media-cache-ec0.pinimg.com/736x/03/5f/89/035f891e8f4d563665993bc1c49248d2.jpg>

We also meet new families who are looking for answers which hopefully the doctors can provide, but also families which we (GOPI3Ks / PSF) can support now and throughout the years.

A little fun was had on the Saturday night with a photo booth, great way to wind down after an emotionally exhausting day.

Tracey from the PSF with Dr Biesecker



Brett Webster (ops now that's got to hurt)



Me & James Vincent (don't know who is the scariest!)

"Aerodynamically the bumblebee shouldn't be able to fly, but the bumblebee doesn't know that so it goes on flying anyway"

Mary Kay Ash

MY TIME AT THE FAMILY CONFERENCE WEEKEND

Here is Margaret Webster, one of our new members to GoPI3Ks talking about her first visit to a family weekend and what it was like for her:

When Mandy posted on the GoPI3Ks Facebook page that there was going to be a family conference weekend I jumped at the chance to go, I was so excited to be able to meet experts not only interested but doing research into it and other people with overgrowth issues, I'm 50 and never before met anyone.

On arriving at the Coppid Beach Hotel me and my hubby Brett went to our room which was brilliant, so spacious I could use my scooter in it. After a little while settling in and unpacking we went out to the lounge/bar area, Tracey came straight over to welcome us and took us over to where her son Jordan, Seana, Sue and Mandy were sitting and introduced us. We had a drink and quick chat before going back to our room, I had decided after the long drive with my legs down I put my legs up and rest them for the evening.

SATURDAY

The next morning after breakfast we went along to the Jupiter Room where Tracey and Mandy gave a short introduction and what was going to happen throughout the day. At this point I felt really chocked up, I couldn't believe after never meeting anyone similar to me my whole life I was in a room with people who had similar conditions.

Dr Les Biesecker was the first to speak about Proteus Syndrome, what mutation had caused it and how they were trailing a drug in America, he encouraged people to ask any questions at any time during his talk and enthusiastically answered them. Dr Veronica Kinsler then spoke on the work they were doing at Great Ormond Street Hospital. Jordan and Ross gave a fun and positive talk about living with Proteus, going to university and living independently they are both great guys.

After that we stopped for a break and lunch, at 1.30 we meet back up and Dr Semple gave his talk about the PIK3CA gene mutation, his study and research into it and the drug trail they are conducting at Cambridge. He then did a one on one question time with Mandy.

James Vincent stepped in when someone couldn't make it and spoke about his life and experiences, I could related James story it was very emotional. Well done James.

Then we stopped for a much needed break with coffee and cake, after the lunch we didn't really need cake but my favourite saying is there's always room for cake

We then went speed dating which was Dr Biesecker, Jordan, Ross and Paul Collins came round to each of our table and had 15 mins with each of them to ask any questions. I asked Dr Biesecker if someone could have both the Proteus and PIK3CA mutation together he said not and explained it and drew a little drawing to show the difference. Jordan and Ross were so open, I spoke to Ross about the difficulties having to have special shoes made. Paul spoke about the fundraising the PSF charity and what it does to help people with Proteus with the money that's raised.

After what I found an emotional day we went back to our room for a quick rest before getting ready for dinner, which was a 3 course sit down meal after which Jordan put on a slide show and spoke about his fun holiday adventures with his friend. We then had the opportunity to dress up for funny pictures.

SUNDAY

The next morning was informal, after breakfast we all sat round in the lounge area chatting exchanging funny experiences, and things like cars, shoes, wheelchairs, clothing things most people take for granted.

Everyone got the chance to have their own private one to one with Dr Biesecker. After a light lunch people started to leave on their journeys home. I didn't want to leave and hope to meet them all again one day.

I can't thank Tracey and Mandy enough for this experience.

P.A.G Patient Advisory Group

For a little while now James and I have been part of the NIHR Rare Diseases TRC P.A.G (Patient Advisory Group). The purpose of this group is, alongside other patients with rare conditions, to focus on how we as a rare condition group can help doctors understand more about rare diseases and the importance we bring to the medical field as a whole.

Our primary focus right now as it is a relatively new group, is to look at the best way for us to get information out there about rare diseases to the NHS. Looking at ways that data can be collected, stored and distributed that would benefit us as patients, but also doctors who very rarely, if at all, know anything about a majority of the rare diseases that they may come across in their working life.

We hope that in time we can help to create a database which will store essential information about various rare conditions that every doctor / GP / consultant can access.

This hopefully will limit the amount of traveling by patients and unnecessary appointments. The database can be used as frame of reference to understand more about a condition, any current and successful as well as unsuccessful treatment, plus contact details of relevant specialists in that area, which hopefully would enable slick referrals.

If anyone would like to be involved in this there are meetings every 6 months. These do take place in London, but I Skype in, so this is always another option for those who can't travel but still want to have their voice heard.

You can contact either Nicola West: nw303@medschl.cam.ac.uk

Or Kathryn Irons: ki260@medschl.cam.ac.uk

Rare Diseases Translational Research Collaboration

I know the title may sound daunting, but this is where the P.A.G grew from. *'The Rare Diseases Translational Research Collaboration (RD-TRC) is a collaboration between National Institute for Health Research (NIHR) Biomedical Research Centres, Biomedical Research Units and Clinical Research Facilities'*.

'Their focus is on the causes, impacts and treatment of rare diseases, of which there are about 7,000 inherited varieties, half of whose genetic basis is yet to be discovered'.

Despite these conditions being uncommon 1 in 17 of us will be diagnosed with one at some point during our lives.

'Three-quarters of these diseases affect children (30% of rare disease patients die before their fifth birthday)' this of course has a huge impact on those around, family members, partners and friends.

I will link to their website below, but in brief their work consists of: supporting research programs in to a variety of rare conditions by *'bringing together diverse centres of excellence with the facilities and expertise to lead programs of research'*.

Moreover, their outcome is to allow more patient involvement in research and this is very much central to their work, but also to develop a clearer understanding of what factors cause the underlying conditions of rare diseases and to become a nation that is the forerunner for this such type of research involvement. Their hope is that through patient as well as involvement from other research bodies that the lives of patients with rare conditions can be positively changed for the better. If you would like to know more you can visit their website by the following link: <http://rd.trc.nihr.ac.uk/>

NIHR 'THINK RESEARCH' RARE DISEASES PATIENT DAY

'The day was a joint collaboration between NIHR Rare Diseases Translational Research Collaboration (RD-TRC) and NIHR BioResource – Rare Diseases, and took place in mid-October at the Barbican Centre in London'

Please see this link for more information about the day: <http://rd.trc.nihr.ac.uk/think-research-patient-day2/> where you can view presentations by experts in the medical field and those patients living with a rare condition.

Rare Disease Day 2017– Pass it on! We're looking for patient quotes about Research

Rare Disease Day is on Tuesday 28 February 2017

Official website: <http://www.rarediseaseday.org/>

The Theme for 2017 is “**Research**” and Rare Disease- TRC will be holding events at different sites on the day, including an evening lecture in Cambridge.

For part of our social media promotion of Rare Disease Day, We'd love to get some quotes from patients, carers and patient groups along with a photograph, which we will run on

twitter. If you are camera shy, don't let it put you off simply send in your words. Please find some questions to get your ideas started:

Have you benefited from Research?

What does Research mean to you personally?

What would you like to see from Rare Disease Research in the future

If you are interested in telling us your story and can supply a picture to go along with your words (or a video for all the Spielbergs out there), please send details to Georgina Norris at gan23@medschl.cam.ac.uk

How Isolation Impacts Those Suffering With Rare Disease

- by Daniella Koren, Columnist, September 6, 2016, 2:32 PM <http://www.mediapost.com/publications/article/284073/how-isolation-impacts-those-suffering-with-rare-di.html>

There's little in life as jarring as being diagnosed with a serious disease like cancer or diabetes; the news irrevocably changes the lives of both the patient and their family. Yet as difficult as it is, there are many avenues to get information and connecting with others who are dealing with a similar challenge. But for those who learn that they have an illness that is so rare most people have never even heard of it, the scenario can be quite different.

The diagnosis itself is isolating, but when you consider that there may be few similar cases in the world, fewer physicians who recognize it, and fewer organizations for support, individuals with rare diseases face unique obstacles.

Little attention

Unlike diseases such as breast cancer and heart disease, which get significant media attention and garner massive support in the form of research and fundraisers, many rare diseases (those that affect fewer than 5 people in 10,000), are largely unknown or poorly understood. More common illnesses are supported by organizations that push for research funding and put together local and national awareness events, and many more individuals have been affected by those conditions.

In contrast, often only family members, a handful of caregivers, and those suffering with a rare illness are aware of what they are going through. According to Global Genes, approximately 50% of rare diseases [do not have a specific foundation](#) supporting or researching their condition.

The challenges: Delayed diagnosis, lack of support, and limited treatments

Many individuals with rare diseases find themselves in a world that doesn't recognize their pain or currently possess the knowledge to treat them. Despite the fact that there are a host of research and development efforts underway to find new medications, 95% of rare diseases [don't have](#) an FDA-approved drug treatment. And when you consider the fact that

new diseases continue to emerge frequently, both patient isolation and the pressing need for novel treatments will continue unless more attention can be drawn to these conditions.

An individual with Castleman's Disease, a disorder affecting the lymph nodes, [detailed](#) these challenges:

"The doctor I saw was perplexed by my condition so he sent me to get a couple dozen tests. A few days later while sitting outside the campus coffee shop, he told me in a calm, yet stern tone that I should see a cancer specialist in Houston. I was speechless ... After the tests, it was clear that I did not have cancer, instead I became part of the less than 1 in 100,000 cases of Castleman's Disease reported globally. I felt alone and isolated, like no one could help because no one knew what it was or how to treat it."

Solutions on the horizon

More organizations are being formed to address the medical and emotional needs of those with rare diseases. Jared Heyman, whose sister suffered with a rare illness, founded CrowdMed to bring together medical experts [to address some of the most complex cases](#). This platform allows patients to submit their information and get diagnostic and treatment suggestions within days. CrowdMed has become a viable resource that empowers patients.

As healthcare marketers, we can play a role in educating patients and healthcare providers about these conditions, as well as reaching out to sufferers to provide support resources. Avenues to achieve this goal include:

Supporting the efforts of individual disease advocacy groups and partnering with them to spread awareness and help generate R&D funding.

- Directing patients to resources that help them discover a support network, such as the [Rare Disease Clinical Research Network](#).
- Partnering with organizations like the [National Organization of Rare Disorders](#) and creating awareness of events like Rare Disease Day through social media and other channels.

The National Organization of Rare Disorders' motto:

"Alone we are rare, together we are strong,"

illustrates the value that healthcare marketers can bring to the effort, by spearheading campaigns that create awareness and action.



How studying a disease that affects hundreds of people could save millions of lives

A trio of rare diseases – two of which have fewer than 50 sufferers each worldwide – have advanced our understanding of 'bone turnover and remodelling' in the human body

- Adam Taylor Monday 19 September 2016: <http://www.independent.co.uk/life-style/health-and-families/health-news/how-studying-a-disease-that-affects-hundreds-of-people-could-save-millions-of-lives-a7316076.html>



A discovery of new bone formations in people with black bone disease may help treat osteoporosis AFP/Getty

A rare disease is one that affects fewer than [five in 10,000](#) people. You might wonder why anyone would dedicate their life to studying a disease when only a handful of people would benefit from a cure. Why not study one of the big killers, such as cancer, tuberculosis or malaria?

The significance of rare diseases is often not appreciated by people outside of the field. Rare diseases can provide valuable insights into the causes and progression of far more common diseases. The study of these diseases can also lead to the development of life-saving drugs. In fact, that's how statins were developed. The [cholesterol-lowering drug](#) is one of the most frequently prescribed medicines in the developed world and it has saved countless lives.

The journey to develop drugs that reduce cholesterol began in the late 1960s when a young Japanese biochemist named [Akira Endo](#) scoured thousands of strains of fungi looking for something that inhibited cholesterol production. He assumed that there are enzymes involved in producing cholesterol and something must inhibit one or more of these enzymes.

On discovering a product in fungi that did exactly this, tests moved to experiments in petri dishes. This was followed by clinical trials with participants who had dangerously high levels of cholesterol and were susceptible to heart attacks in their early years. The trial participants

suffered from [familial hypercholesterolemia](#), a rare but life threatening condition, the most severe form of which affects [one in 300,000](#) people.

Although Endo's drug, Mevastatin, didn't make it to the market, his study prompted further research into similar drugs, eventually culminating in the statins that are available on the market today and are used to treat more than [30m people](#) globally.

Insights into osteoporosis

Similarly, a trio of rare diseases – two of which have fewer than 50 sufferers each worldwide – have advanced our understanding of “bone turnover and remodelling” in the human body. Bone turnover and remodelling ensure we have just the right amount of bone for the things we do in life, whether working in an office, competing as a professional athlete or going into space. Whatever we do on a daily basis, the cells that make and break down bone need to ensure that the right amount is there – enough to keep us strong enough to function but not so much that it becomes too heavy and slows us down.

Understanding these rare diseases has also aided the development of therapies to help treat bone diseases including [osteoporosis](#). The first of the three diseases – [hypophosphatasia](#) – is an inherited disorder where sufferers struggle to make hard bones. It affects one in 100,000 people. [Van Buchem disease](#) and [sclerosteosis](#) have about 30 and 40 reported cases [respectively](#) and sufferers of these two conditions make so much bone that it traps nerves needed to control breathing, hearing and other essential functions.

Osteoporosis is often treated using a group of drugs called [bisphosphonates](#). These drugs mimic a molecule in the body which inhibits cells taking away bone; discovered from studies into understanding hypophosphatasia. The two rarer conditions have opened up our understanding of pathways that are involved in helping cells make new bone and this has potential for development of further treatment for osteoporosis and other conditions.

Black bone disease

More recently, another rare disease, alkaptonuria (“black bone disease”), has yielded clues about a very common condition: osteoarthritis.

People with alkaptonuria do not have enough of a particular enzyme, leading to a build-up of a chemical in the body called homogentisic acid. The build-up of this acid results in black and brittle bones. About one in every 250,000 people has this genetic disorder.

In my [own research](#), my colleagues and I examined bone samples from people with black bone disease and people with osteoarthritis. We discovered new bone formations that were common to both conditions. This finding helps us to understand a bit more about osteoarthritis and potentially offers new options to treat it. The new bone formations appear microscopically inside bones. Although we don't know exactly how they are formed, when we find out, we may be able to use this understanding to treat osteoporosis or help repair broken bones more quickly.

A [new mineralised structure](#) in cartilage that forms and contributes to joint damage has also been found in people with alkaptonuria. It is unusual to see hard mineralised structures in cartilage, which is very soft. The presence of these new mineralised structures in cartilage may help us to understand how cartilage is mechanically damaged in osteoarthritis. If we can understand how they are formed, we may be able to stop them damaging cartilage.

These recent discoveries offer new opportunities for understanding common diseases and highlight the significance of rare diseases to everyone.

Two British physicians understood the value of studying rare and unusual disorders many years ago. [William Harvey](#), discoverer of the circulatory system in the 17th century, said: "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease."

[William Bateson](#), an English biologist and coiner of the term "genetics", put it more succinctly: "Treasure your exceptions!"

DID YOU KNOW?

There are approximately 7,000 different types of rare diseases and disorders, with more being discovered each day

It is estimated that 350 million people worldwide suffer from rare diseases

If all of the people with rare diseases lived in one country, it would be the world's 3rd most populous country

In the UK, a disease is considered rare if it affects fewer than 50,000 citizens per disease

Approximately 50% of the people affected by rare diseases are children

30 million people in the United States are living with rare diseases. This equates to 1 in 10 Americans or 10% of the U.S. population

Approximately 50% of rare diseases do not have a disease specific foundation supporting or researching their rare disease

GoPI3Ks (THE CHARITY)

As some of you may know I am looking in to GoPI3Ks becoming a registered charity in the not too distant future. I have looked in to opening a bank account for us in the name of GoPI3Ks, this is taking a little longer than expected but should be up and running soon.

My intention is to build up enough funds (£5,000) that is needed to become a small registered charity. When this becomes a reality we will be able to help financially those living with the PIK3CA mutation. This could be for equipment such as bespoke clothing and shoes, wheelchairs, anything which makes your life easier and more independent.

I have also designed some lapel pins that people will be able to buy via our website, so once the bank account is up and running and if you would like a badge I can send you a link to pay and if you then email me at funnypaws2004@hotmail.com with your name and address I will send the badges out to you.

Here is what the badge looks like:



There is still a long way to go to become a registered small charity as we need £5,000 in the bank and this is what we are aiming for then we can really start to help people, but this takes time and fundraising. So if anyone has any ideas, or would like to go ahead and do some fundraising that would be fantastic.

I have also designed an information leaflet that I will be getting printed soon (I can also email them to you) should you want to pass this on to anyone you know, or if you would like to fundraise for the group, you can show this and hopefully it will help people understand more about the condition and also what a difference their money could make.

FINALLY

Merry Christmas

Here is to the start of a New Year and exciting things ahead for the GoPI3Ks group / charity. Let's make this a reality then we can really start to make a difference in everyone's life by helping people financially become more independent and live a fuller life.

Your GoPI3Ks team:

Mandy Sellars, Susan Harper,

Dr R Semple, Dr V Parker, Leena De'Silva,

and Rachel Knox.

