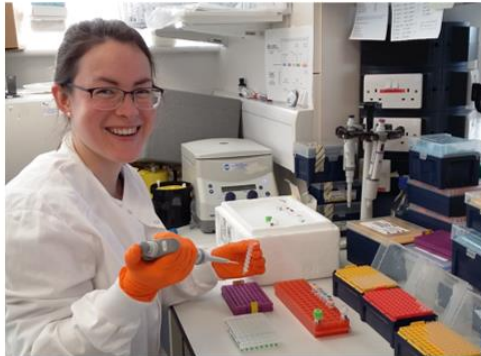


## SPEEDING UP DIAGNOSIS- NEWS FROM THE LAB

We have now recruited over 240 study participants, and so far we have been able to give a definite genetic diagnosis to 80. For many others we are eagerly awaiting the next round of



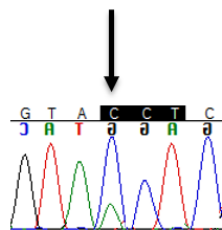
Rachel Knox  
Research Assistant

gene sequencing, and from this we hope to make many more new diagnoses. One of the most important pieces of work we are doing in the lab at the moment is to try to increase the speed of this process, which is challenging because the gene changes that drive the overgrowth are only found in some cells and tissues in the body.

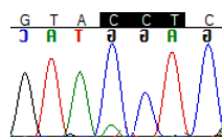
Our approach is first to look for a panel of the eight commonest genetic causes, mostly in the gene called *PIK3CA*. We usually have these results within a month of

a person being recruited. If we don't find the answer doing this, we then broaden the search to look at 60 different genes which control growth. This has taken 3-6 months, as we have to run samples in batches, but we are now in the process of changing to a new method of gene sequencing (called MiSeq) which will allow us to run many more samples at the same time, making things a lot faster. If after this we still don't find a genetic diagnosis, we review all available information and either recommend analysis of a second tissue sample (for example, from a skin biopsy) or else we go on to read all genes simultaneously in a final attempt to identify new, rare causes of overgrowth.

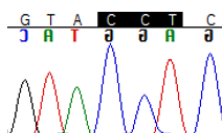
Tooth DNA



Saliva DNA



Healthy volunteer



### Genetic diagnosis from a baby tooth!

Many thanks to study participants who have sent us their baby teeth!

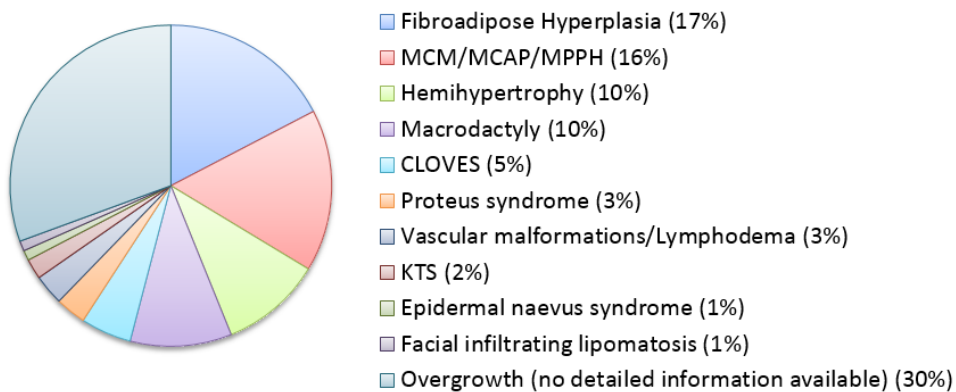


For MCAP/M-CM patients, we have been using saliva as 'affected' DNA to make a genetic diagnosis. However, baby teeth (which have already fallen out) are also a good source of DNA, and often carry the overgrowth-causing mutation, as Professor Clayton-Smith's group in Manchester recently discovered.

We tried this out for one participant who we had previously diagnosed from saliva. As you can see from the DNA sequencing opposite, the small green peak indicating a mosaic mutation is higher in tooth DNA than saliva DNA!

So step aside, tooth fairy! We may have a better use for baby teeth than you...

## Clinical diagnoses of our participants upon recruitment



## IMPROVING UNDERSTANDING OF LONG TERM OUTLOOK

Perhaps the first critical questions about any medical problem for patients and their families is what the future holds. Answering that question is particularly complex in the rare overgrowth disorders that we study, where not all parts of the body are affected. This means that different people can have very different severities of problem even with the very same gene change. A key aim of our studies is to draw information about the long term outlook so that we can offer the most accurate advice to families, and so we can target new treatments to those who need them most. There is no quick way to answer this need. Instead it relies on gathering information from as many patients as we possibly can, on continuing to follow their progress as time passes, and on swapping notes with



Thanks to our second grant from the National Institute for Health Research, our new research co-ordinator, Leena de Silva, joined our team in May 2015. Some of you may have met her already during your visits to the Clinical Research Facility. We see 1-2 study participants each week in Cambridge, as well as doing genetic testing on samples sent to us from all over the world!

researchers and doctors in other countries who see many similar patients.

It is incredibly important that we register any major medical events

that happen to patients who are part of our study in between visits, so we are always grateful for being kept in the loop by our participants and their doctors.

## TURNING RESEARCH INTO AN NHS SERVICE

All our studies to date have been funded by research grants. However in our view it is critical that we use the new information we have learnt about overgrowth syndromes and



Dr Robert Semple  
Wellcome Trust Senior  
Research Fellow  
Honorary Consultant  
Endocrinologist

the challenges they pose for patients and their families to improve the dedicated services that can be offered as part of NHS care. In June this year, we met with teams of specialised doctors from Great Ormond Street, St George's, and the Royal Free Hospitals in London as well as specialists from Manchester to discuss a bid to persuade the Department of Health to set up an NHS highly specialised service for segmental overgrowth. The aim of this bid will be to strengthen the "joining up" and co-ordination of care, so there is always a known National Expert Centre and freely accessible advice to both families and their doctors. If successful, this will include 'one-stop-shop' clinics in Cambridge, Manchester and London to see a team of overgrowth specialists for reviews as regularly as needed. Financial times are

challenging in the NHS, and this bid will be multi-step, slow process which can't lead to new funding any earlier than April 2017, but the first stage will be submitted shortly and we will keep you informed as to progress.

## CLINICAL TRIALS UPDATE



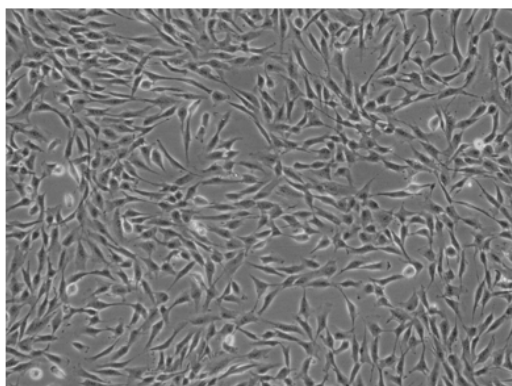
Dr Victoria Parker  
Registrar in Endocrinology

We are about to start a clinical trial with a drug called sirolimus or rapamycin in 30 patients with some of the more severe growth problems. 10 patients in the UK with progressive overgrowth and confirmed mutations in the gene *PIK3CA* are going to take this as a tablet once a day for 6 months, along with others in France and the USA. They will have regular MRI and DXA scans to measure growth before and after taking the tablet and will be monitored for side effects.

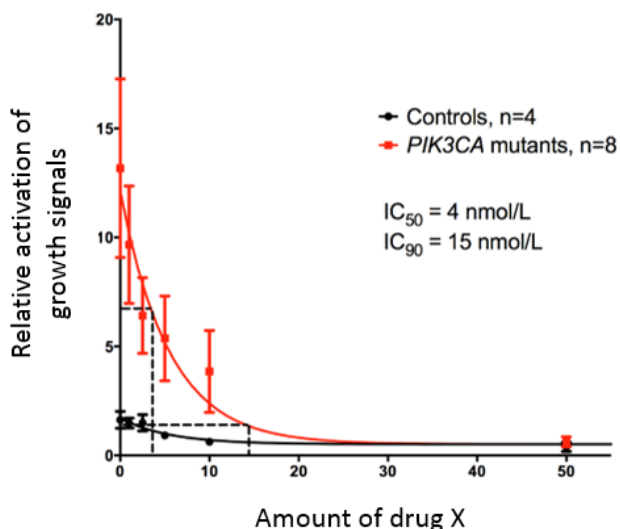
In the lab, we have also tested other promising experimental drugs. We are discussing with pharmaceutical companies possible future studies using their drugs, and we foresee a series of clinical trials in the next few years with the potential to transform treatment of overgrowth syndromes.

#### Testing new inhibitors in the lab

We have been testing new medicines on cells grown from skin biopsies from our study participants. Skin cells from affected parts of the body have more growth signals (activation of certain proteins) than cells from unaffected parts of the body. When we add certain inhibitors, we can 'switch off' these over-active growth signals. The drugs which work well in cells, all of which are already approved for use in patients, may help to slow down segmental overgrowth in patients.



Patient fibroblast cells grown from a skin biopsy (100x magnification)



Julie Harris  
Research Sister

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.overgrowthstudy.medschl.cam.ac.uk>

Twitter #overgrowthstudy

Facebook: <https://www.facebook.com/segmental.overgrowthstudy>