



TAILOR MADE

A medical research study examining the possibility that your genes might know where your IBD is heading could help doctors to offer the best treatment programme

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Rupert Edcombe had been a healthy boy all his young life. Then two years ago, when he was nine years old and on holiday in France with his parents, he was struck down with severe stomach aches. “It came out of the blue,” says his mother, Amanda. “We visited three chemists, a local doctor and then a more senior doctor, who suggested stomach ulcers. Rupert was very weak, and ordinary medicine was having no effect. We were in a complete state, not knowing how to help him.”

Back home in Yoxford, Suffolk, Rupert’s condition grew worse. “He was bleeding by that stage, and clearly very unwell,” says his father, Chris. “He had to rush to the loo 10 times a day. It was full-on and scary, to say the least.”

Overwhelmed by anxiety, Amanda shared her concerns about the severity of Rupert’s condition with the family GP, who acted quickly. “I was as sure as I could be it was not food poisoning or a bug, but something far more serious,” she says. “We were referred straight away to Addenbrooke’s, for which I am so grateful. Some families have to wait years to find out what is going on.”

Addenbrooke’s Hospital in Cambridge is a specialist centre for the investigation and treatment of Inflammatory Bowel Disease (IBD) in children, serving the east of England.



Dr Matthias Zilbauer is leading the epigenetic research project

Here, Rupert underwent clinical investigations that led to a diagnosis of Ulcerative Colitis.

“There had been no precedent in either of our families, as far as we know, so it came as a complete shock,” says Amanda. “As a parent, you start to blame yourself, thinking ‘Is it something I have done? Did I use the wrong cleaning products, could it be because of something in the environment?’ I constantly wonder what the trigger was.”

The same questions occupy a growing number of parents with children who are affected by IBD. And researchers based at Addenbrooke’s are on a scientific quest to hunt down the answers.

A two-year research project entitled ‘Epigenetics in Paediatric IBD – Investigating Intestinal Epithelial DNA Methylation and its Role as a Clinical Biomarker’ has just started. Funded by a grant of £115,000 from Crohn’s and Colitis UK, the lead researcher is University of Cambridge lecturer, and honorary consultant in paediatric gastroenterology at Addenbrooke’s, Dr Matthias Zilbauer.

“We know that cases of IBD have been rising fast over the past 50 years, and that the incidence is highest in the developed world: in northern Europe, for instance, some reports suggest that numbers have almost doubled,” he says. “In the developing world, IBD is pretty much unheard of. But in ▶



Rupert, 11, is helping improve IBD care by participating in the study

RESEARCH

- ◀ countries such as China, Japan and India, which are adopting a western lifestyle, we are starting to see incidence pick up. That would suggest there is something in the way we live that is contributing to the development of these conditions.”

The theory is that while human DNA – our fundamental genetic code – has not changed much over the past 50 years, the way individual cell types respond to changes in the environment may cause alterations, and possibly malfunction of cells, leading to disease. In principal, epigenetic mechanisms are able to switch genes on or off, and this may happen in response to environmental factors.

“The intestinal epithelium is the inner lining of the gut, and there is lots of evidence to suggest that the function of that cell layer is impaired in people with IBD,” says Matthias. “Our hypothesis is that malfunction of the gut epithelium might be at least in part due to alterations in the epigenetic programming – specifically the DNA methylation profile – possibly caused by changes in our environment. Our aim is to prove that hypothesis, and to see if we can use that information to improve the management and treatment of IBD.”

The increase in childhood-onset IBD is particularly marked, and until now it has proved impossible to accurately predict the course of disease progression in individual patients. “Any child diagnosed with IBD can have a range of severity,” says Matthias. “Some are affected relatively mildly, require very little treatment and spend very little time in hospital. For others no treatment works, they have to undergo surgery including gut re-section, spend a lot of time in hospital, fail to thrive and may suffer severe psychological as well as physical consequences.

“Right now there’s no way to tell which patient will go which way at the beginning of their journey. We are hoping that by looking at their gut layer and their epigenetic profile, we will be able to identify which



Matthias hopes the samples will be revealing



child will fall into which category, to allow us to better target their treatment.”

To that end, Matthias and his research team have been collecting blood and tissue samples from young patients who attend the Addenbrooke’s paediatric IBD clinic. The process usually involves endoscopy and

colonoscopy, during which small tissue samples called biopsies are taken from the upper and lower digestive tract via a flexible tube. For children, this painless procedure takes place under general anaesthetic.

“Samples are taken for clinical needs first, and then extra ones are taken for research,” says Matthias. “There is no added risk to the patient, only added benefit.”

The research samples are immediately processed in a laboratory within the hospital, where the epithelial cells are purified before being analysed using extremely sophisticated epigenetic profiling arrays. This generates information consisting of around half a million epigenetic data points that allows comparison of the epigenetic profile between the gut epithelium of patients with IBDs and disease-free controls.

“The theory is that this will allow us to match a patient’s tissue to a particular type of disease, and help us to predict whether they will



SAMPLES ARE TAKEN FOR CLINICAL NEEDS FIRST, AND THEN EXTRA ONES ARE TAKEN FOR RESEARCH

be affected mildly, moderately or severely,” says Matthias.

“That would be a breakthrough.”

It takes the efforts of the whole Addenbrooke’s gastroenterology paediatrics team – more than 30 people, including a dedicated research nurse, pathologists, surgeons, anaesthetists, laboratory scientists and data analysts – to gather and process this vital information. “We have all worked hard to collect the samples, but we were waiting for the funding to allow us to do the analysis,” says Matthias. “Thanks to Crohn’s and Colitis UK, we are now ready to roll.”

Matthias is optimistic that, given the modern tools at his team’s disposal, progress will be made in clinical understanding of childhood IBD and in improving ways of targeting treatment.

“If we can come up with biomarkers, then we will have made great strides,” he says. “The encouraging thing is, epigenetic changes are potentially reversible. There are new epigenetic drugs being developed, and the more we discover about the complex interplay between the different factors affecting IBD, the better it will be for patients and their families.”

That is music to the ears of Chris, Amanda and young Rupert Edgcombe. The family regularly makes the 100-mile round trip from their home to the Cambridge hospital for check-ups, and the Addenbrooke’s team is on hand any time they are needed.

“When Rupert was first referred there, they asked if we wanted to take part in the research project,” says Amanda. “We were determined to do anything and everything we could to help, so we said ‘yes’. It feels important and useful, and we are very glad to be involved.”

Now 11, Rupert has just started secondary school, and for the moment his IBD is under control. “It’s terribly tough for him when there are flare-ups, and at the best of times he has stomach aches once or twice a day,” says Amanda. “We are all learning to live with IBD, but I do get anxious about what the future might hold for him. I hate not knowing how severe his IBD might be. It makes me feel totally powerless.”

“I am one of those people who wants answers, and I hope that they will come soon.”

Matthias can understand how that feels. Three months ago he became a father for the first time with the birth of a daughter, Angelina. “That has certainly given me a different perspective on my work,” he says. “I now feel even more empathy with the parents of our patients – it is the hardest thing in the world to see your own child suffer. I am more resolved than ever before to do what I can to help.”

TAKING PART IN RESEARCH AND CLINICAL TRIALS

Great breakthroughs in IBD treatment and care wouldn’t be possible without a lot of willing volunteers, but getting involved can be a daunting prospect, and you may have many questions.

● Where do I start?

Your doctor is usually the best person to talk to first. He or she may know of research being carried out and can advise on what would be suitable for you.

● What will happen?

In a clinical trial, this depends on what phase the treatment is at – rest assured that a lot of work is done in the lab before human trials begin. You may be given a dosage of a new drug or a placebo, and researchers will monitor you carefully for improvements to your condition or any side effects.

● How long will the study last?

This depends on the trial, and you should be sure to find out all the details before you get involved.

● Is it dangerous?

While there is some risk in clinical trials, there are very strict scientific guidelines and ethical and legal codes. Clinical trials happen all the time, and horror stories are very rare. If there are any signs that the treatment is unsafe, the research team will stop testing.

● How do I know if a trial is right for me? What if I change my mind?

Discuss the decision with your doctor, look at the eligibility criteria, and consider the benefits and risks for you personally. Get a second opinion if you are still unsure. You can choose to leave a trial at any point, even if you signed paperwork.