Advances in genetic sequencing diagnose Paralympic hopeful's rare condition

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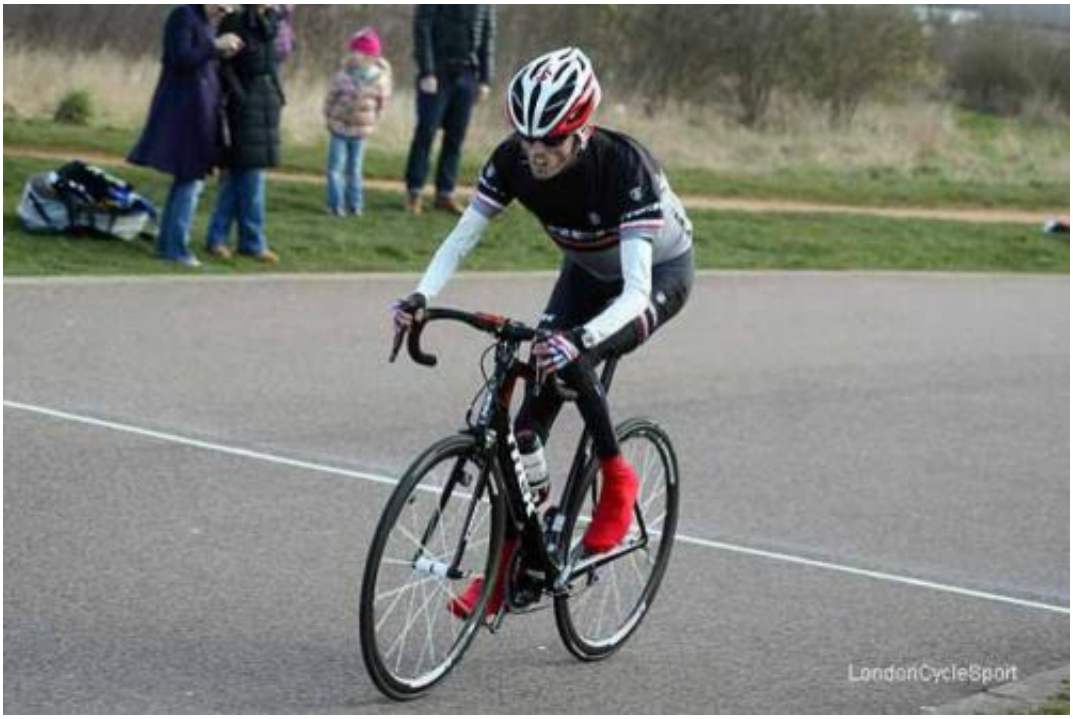


Researchers identify the single genetic mutation responsible for rare condition in UK Paracycling Champion, Tom Staniford. Credit: Tom Staniford

National Paracycling Champion Tom Staniford has an extremely rare condition which, until now, has puzzled his doctors. He is unable to store fat under his skin – yet has type 2 diabetes – and suffered hearing loss as a child. Now, thanks to advances in genome sequencing, an international research team led by the University of Exeter Medical School has

identified Tom's condition and pinpointed the single genetic mutation that causes it.

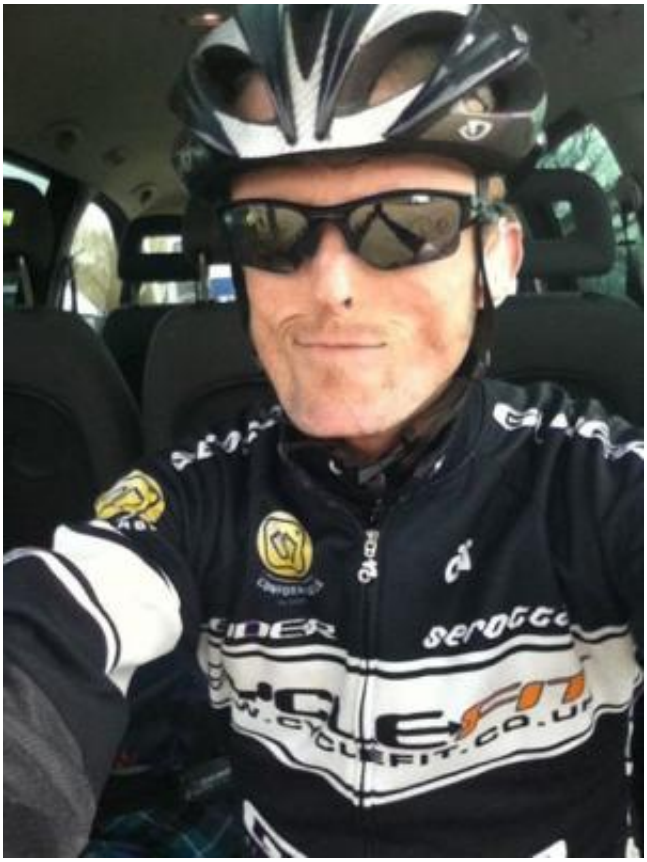
As well as allowing a better understanding of Tom's condition, the discovery may have implications for his bid to participate in the Rio 2016 Paralympic Games. He hopes this new diagnosis will allow him to be more accurately classified in paracycling competitions; a more accurate classification could help him become a world champion.

In a study published in today's *Nature Genetics*, researchers funded in part by the Wellcome Trust and the National Institute for Health Research have identified the genetic mutation behind MDP Syndrome, a condition thought to affect as few as eight people in the world, including 23-year-old Tom.

"In some ways, identifying the syndrome behind my symptoms shouldn't be important – a name is just a name, after all – but it is reassuring to know that there are other people with the condition and that we can lead relatively normal lives," says Tom Staniford. "What could prove crucial, though, is enabling me to be properly classified in competitions so that I am not competing at an unfair disadvantage against others. I hope to be able to compete for Great Britain in the 2016 Paralympics and this finding could make a real difference to my chances."

In 2011, Tom became the youngest solo cyclist ever to become British National Paracycling Circuit Race Champion. He had previously won both a Sports Scholarship and a Vice Chancellor's Excellence Scholarship at the University of Exeter, and graduated from his double degree in Law and French Law last year.

He was born a normal weight, but throughout his childhood and teenage years lost all the fat around his face and limbs. His hearing deteriorated throughout his childhood, and he now wears hearing aids.



Researchers identify the single genetic mutation responsible for rare condition in UK Paracycling Champion, Tom Staniford. Credit: Tom Staniford

Tom's condition means he has no natural cushioning on his body, and suffers extremely sore feet and a higher risk of breaking bones if he falls from his bike. He has to take extra measures to protect himself from the cold, particularly when he races, and he boosts his energy levels through a special diet.

Unusually, Tom's body thinks he is obese because of the higher fat levels in his blood, and he has type 2 diabetes; his diabetes is managed using metformin and a carefully controlled diet. However, when training, Tom is able to reduce his use of metformin as the intense exercise acts as

form of self-medication, controlling his insulin levels.

Professor Andrew Hattersley, a Wellcome Trust Senior Investigator at the University of Exeter Medical School, has been working with Tom for several years, to help manage and understand his condition. He led an international team of researchers in a study of four unrelated patients in the UK, US and India, all with the same symptoms. None of the patients had any family history of a similar condition, suggesting that their condition may have been caused by individual genetic mutations – spontaneous changes in their DNA, rather than inherited mutations.

By sequencing and comparing the entire genomes of the patients and their families – the complete map of DNA in their bodies – Professor Hattersley and colleagues were able to pinpoint the exact mutation responsible – an abnormality in the POLD1 gene on chromosome 19. They found that a single amino acid was missing from an enzyme which is crucial to DNA replication. Recent studies have shown that a different type of mutation in the same gene is associated with a predisposition to colorectal and endometrial cancer.

Professor Hattersley says: "Tom's condition has been a puzzle to us for many years. We could see the symptoms, including the very unusual case of type 2 diabetes in someone with no obvious body fat, but did not know what was causing them.

"We had to look at thirty million base pairs in Tom's DNA, and similar numbers in his family members and the other patients, to identify the single mutation. This would not have been feasible even a couple of years ago, but new sequencing technology makes it possible for even patients with a rare genetic disorder to receive a diagnosis.

"Identifying the gene responsible has implications both for predicting the long term impact of the condition on Tom's health and – equally

importantly to him – on his sporting career."

The diagnosis of MDP Syndrome has been as important to Tom for identifying what the disease is not as to what it is: he had previously been told by a specialist that he may have progeria, a rare genetic disorder of extreme premature ageing, associated with high risk of dementia. The new diagnosis will reassure Tom that this is not the case.

Professor Hattersley and colleagues hope that the genetic discovery will help scientists identify therapies that could make a significant difference for people with this rare and complex syndrome. It could also have wider implications for understanding obesity and related conditions; knowing how the body works when no fat is stored in key places can provide meaningful clues about why and how too much fat is stored.

Dr Michael Dunn, Head of Genetic and Molecular Sciences at the Wellcome Trust, adds: "This is a great example of genome sequencing coming of age. Where previously sequencing a patient's entire genome was prohibitively expensive, it is now far more cost effective. As we've seen here, it is no longer just about identifying genes implicated in common diseases, but is about informing diagnoses and prognoses of rare diseases – and, in Tom's case, helping inform his sporting performance."

More information: Weedon, MN et al. An in-frame deletion at the polymerase active site of POLD1 causes a multisystem disorder with lipodystrophy. *Nature Genetics*; 16 Jun 2013. DOI: 10.1038/ng.2670

Provided by Wellcome Trust