Discover

SCIENCE FOR THE CURIOUS

Recently, Cartault's team spotted the signs of a previously unnoticed disease. Babies who have it start suffering from extreme anorexia before their first birthday. They refuse to eat and they vomit uncontrollably. The white matter that connects different parts of their brain gradually vanish. Their brainstems, which control automatic processes like breathing and heartbeats, start to wither. It's an understandably fatal condition, and some Réunion parents have lost several children to it.

The team named the disease Ravine encephalopathy, after the region it's most common in. It's rare, affecting around one in every 10,000 to 15,000 people. But when it appears, it tends to run in families. "It became obvious that it was an inherited disease," says Alexandra Henrion-Caude, who led the study.

To find the gene responsible, the team scoured the genomes of nine families, including 15 people with the disease and 17 siblings without it. Their search revealed a single genetic change that was found in everyone with the disease, and no one else. It lay within a gene SLC7A2, which is deployed in the developing brain. In the affected babies, a single DNA 'letter' within this gene had changed from an A into a G. This mutation – the equivalent of a lone typo in a book – seemed to be responsible for the debilitating symptoms. If people inherited one copy of the G version, they were fine. No disease. If they inherited the double whammy, one from each parent, they developed Ravine encephalopathy.

There's a similar story behind many genetic diseases, but this one had a twist: the mutation was nestled within three layers of junk. Cartault found that it lay inside a jumping gene called a LINE element. These bits of DNA can copy themselves and paste the duplicates elsewhere in the genome. They're so good at multiplying that they make up around 17 per cent of our genome. This particular LINE element was stranded. It had degenerated to the point where it could no longer jump.

But that wasn't all. The LINE element was embedded within another stranded jumping gene called a SINE element. These are similar in character but shorter. They make up 11 per cent of our genome.

And the SINE element, in turn, lay inside an intron – the part of a gene that's eventually thrown away. When genes are activated, their DNA is converted into a related molecule called RNA. At this point, several introns are snipped out. The remaining segments – the exons – are glued together, and they're the ones that contain instructions for making proteins.

So, here was a mutation that caused a fatal brain disease, lying in the genetic equivalent of Russian nesting dolls. Clearly, these sequences aren't junk. If they were, changing that A to a G would have no effect. So what are they doing?

It turns out that the brain retains most of the discarded intron as a piece of "non-coding RNA", which never goes on to produce a protein. It is, however, still important. When the team neutralised this RNA in laboratory cells, those cells started to die.

They now think that the RNA somehow helps to keep neurons stable. The mutation means that a baby's brain produces less of the RNA, and its neurons start to self-destruct. That fits with the vanishing white matter and disappearing brainstems of babies with Ravine encephalopathy. Indeed, compared to these ill-fated infants, normal people have 8 times more of this precious RNA in their brains.

The details still need to be worked out, but Cartault's study shows that this piece of "junk" plays an important part in the growing brain. It's one of many such studies. "I think that examples like this will become more and more apparent as we sequence more people," says Alysson Muotri from University of California San Diego.

Muotri was involved in a similar example herself, which I wrote about last year. He found that a fault in the MECP2 gene unleashes a wave of LINE elements, which coincides with another genetic brain disorder called Rett syndrome. Others have suggested that non-coding RNAs can broadly affect the odds of various diseases, or that some of them might have spurred the rise of our vaunted intelligence.

The big question now is: how much of the supposed junk is actually useful? Some says it's a "large fraction". Others point out that the onion has five times more of this non-coding DNA than we do. If it's all useful, why does the onion need that much more of it?

Reference: Cartault, Muniera, Benkoc, Desguerred, Haneinb, Boddaerte, Bandiera, Vellayoudoma, Krejbich-Trotot, Bintner, Hoarau, Girard, Génin, de Lonlay, Fourmaintraux, Naville, Rodriguez, Feingold, Renouil, Munnich, Westhof, Fähling, Lyonnet, and Henrion-Caude. 2012. Mutation in a primate-conserved retrotransposon reveals a noncoding RNA as a mediator of infantile encephalopathy. PNAS
http://dx.doi.org/10.1073/pnas.1111596109