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the twisted way of things

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Imagine reading these words and not being able to pronounce them. Or reading them and not being able to grasp their meaning. These are just two of the drawbacks that many children – and adults – suffer from. In fact, we all know of someone who suffers from a reading disability, a common form of dyslexia. And that is because five to ten per cent of the population is afflicted by it. Because of its frequency, much progress has been made to try and understand why some children are simply not able to deal with words the way their classmates are, and yet they lack neither intelligence nor education. In the past years, it has become clear that dyslexia seems to have a hereditary component thus implying that a gene, or a collection of genes, could be at the heart of it. In the recent past, scientists have managed to track down at least one protein, with the appealing name of KIAA0319, which may well have a role in dyslexia and is involved in brain development.

Jazz, by Tak Salmastyan

Courtesy of the artist

The term "dyslexia" was coined at the end of the19th century, literally describing a person's disability to read text out aloud. James Hinshelwood, a British ophthalmologist who wrote a book about the disability in the early 1900s, actually referred to it as a congenital word blindness. Whereas, in the past, "stupidity" was the usual word used to qualify schoolchildren who could not cope with texts, today dyslexic pupils are no longer regarded as retarded but are – more often than not – granted special attention. Especially since, in our society, such a handicap can turn out to be a big disadvantage on the economic and social front.

The finding that dyslexia could be hereditary prompted scientists to find out which gene – or genes – could be involved. To date, scientists know of about a dozen which may all have some kind of role in dyslexia, although which is unknown. However, one gene in particular – KIAA0319 – is promising in that it seems to be involved in neuron adhesion and migration, i.e. in brain development. What is more, one of its isoforms has been found specifically in people suffering from dyslexia.

What exactly does KIAA0319 do? From a structural point of view, it hardly deserves to be mentioned. KIAA0319 is a pretty straight-forward transmembrane protein, found in the plasma membrane of neurons. It sports quite a large C-terminal end that sticks out in the extracellular space and a small N-terminal end that protrudes into the neuron's cytoplasm. The C-terminal end is highly glycosylated and carries five domains known as PKD (polycystic kidney disease) domains and one MANEC (motif at the N terminus with eight cysteines) domain.

Interestingly, PKD domains are known to be involved in cell to cell interactions or cell adhesion. In KIAA0319, the extracellular PKD

domains may mediate adhesion between neurons and glial cells – the cells which support and protect the brain's neurons. As such, KIAA0319 may play a part in neural outgrowth as well as neuron migration during brain development – thus linking dyslexia to a problem in neural development at an early age.

The most intriguing part of KIAA0319, however, is the way it behaves once it has seemingly served its purpose, i.e. ectodomain shedding and intramembrane cleavage, also known as RIP (…) short for regulated intramembrane proteolysis. Indeed, KIAA0319 literally falls apart, casting its proteic splinters either outside the neuron or within it. It is thought that at least five different cleavage events occur, four of which segment the C-terminal end into small peptides which are disseminated in the extracellular matrix. No one knows what their destiny is – if any at all – but they could trigger off other activities elsewhere in the brain. As for the intramembrane domain, it is released into the neuron's cytoplasm by way of endocytosis where it translocates to the nucleus. Could it be involved in gene regulation at this stage? Perhaps. What is sure, however, is that the collapse of KIAA0319 is one very effective way of regulating neuron migration.

People suffering from dyslexia carry a KIAA0319 isoform which causes the protein to be less expressed. As a consequence, less of it is available for neuron outgrowth and migration thus causing a mild malformation of part of the growing brain. As such, dyslexia is an intriguing handicap for biologists and neuroscientists alike. How is it that a part of the brain which is "malformed" can affect specific cognitive functions such as a reading disability while preserving intelligence on the whole? Another very interesting development is the notion that, as is the case for psychiatric illnesses, there could be a genetic predisposition to dyslexia. Indeed, people carrying the KIAA0319 isoform may not necessarily suffer from dyslexia. However, given a certain environment, the handicap may be triggered off.

In reality, though much progress has been made, dyslexia remains very much of a conundrum. It has been noted that many of the genes and their protein products are also involved in neuronal plasticity. Perhaps it is more this feature than neuron migration which has something to do with the affliction. What is more, it is not one sole gene, or protein, which is guilty of meddling with the brain but a network of molecules which interact. This said, such studies are great for shedding light on brain development as a whole, and understanding the effects of environment on disorders which can arise later on in age. In the long run, it may also shed some light onto why humans can read, and why their fellow apes cannot.

Cross-references to UniProt

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