Shedding light on the 'dark matter' of the genome

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Most of the time, Stefano Torriani is a plant pathologist. His most recent research project revolved around the fungus *Mycosphaerella graminicola* where he analyzed a special class of genes that encode cell wall degrading enzymes. A virulent fungus relies heavily on these enzymes when attacking a plant. But while investigating these genes, Torriani came across something odd; one gene came in different sizes in different individuals.

To further explore and better understand this phenomenon, the researcher deviated from his original plan and drew in other experts, including Daniel Croll, Patrick Brunner and Eva Stukenbrock from the research group led by Bruce McDonald, Professor of Plant Pathology, ETH Zurich. What they discovered after a year of feverish research throws new light on genome evolution - but still leaves many questions unanswered.

The intron makes the difference

The plant pathologists quickly answered the question of why the same gene came in different lengths in different individuals. In some strains the gene, "ID-60105", which encodes for a cell wall-digesting enzyme, had an intron, in other strains the same gene did not have an intron.

Thus, the researchers stepped into a relatively young field in biology. So-called "spliceosomal introns" were discovered only 30 years ago.

Because they are non-coding regions of a gene, they provide no information on the structure of the encoded protein. Introns are separated by the coding regions, called exons. A gene, including both exons and introns, is read by the cellular machinery and transcribed into a messenger RNA. In a next step, the noncoding introns are cut away and the coding exons are spliced together. This creates the blueprint for the corresponding protein encoded by a gene.

Biologists still do not understand the function of introns and why they are present in such large numbers in most eukaryotes, the higher organisms, including humans. Prokaryotes, ie bacteria, lack introns. "About 30 percent of human DNA consists of introns, which constitute a major fraction of what is often called junk DNA because it does not encode a protein sequence," says McDonald, "it is the dark matter of the genome. We know it is there, but we don't know why it is there or how it came into existence".

Intron polymorphisms: sometimes there, sometimes not

Up until now, biologists believed that within a species, an intron is either fixed or not present at a particular point in a gene. The plant pathologists were surprised, therefore, to discover that *M. graminicola* deviated from the conventional model. The intron was present in some individuals and absent in others. "The idea that introns can exhibit presence/absence polymorphisms within a species is quite new and very few reports exist in the literature up until now," says Torriani.

The first reports of intron presence-absence polymorphisms include one gene found in the fruit fly *Drosophila* and a handful of genes in the water flea *Daphnia*. In their paper, which has just appeared in *Current Biology*, the group led by Professor McDonald added three new species that

showed a multitude of intron polymorphisms.

Younger species in transition

In their work, the researchers compared not only genes from different individuals of *M. graminicola*, but also the same genes in other closely related fungal species. In some cases the evolutionarily older species had no intron in a gene, while the younger species *M. graminicola* was in a transitional stage where some individuals carried an intron while it was absent in others. "It is these rare transitional stages that will allow us to understand the evolutionary processes that lead to intron gains and losses in genomes," concludes co-author Daniel Croll. "Once the intron is present in every individual, it is fixed in the gene and we don't know how it came into existence."

The comparison of the genes and their introns revealed a unique example that may shed some light on these evolutionary processes: compared with its sister species, one of the studied genes of *M. graminicola* acquired an intron only recently and this intron then rapidly increased in frequency to near fixation. Why a new intron could so rapidly become fixed in this gene in *M. graminicola* is a mystery. "Maybe individuals carrying this intron have a fitness advantage compared to individuals without the intron," Croll muses, "this is our first evidence that natural selection may play a role in intron fixation".

Effects on fitness remain unclear

Researcher can still only speculate whether introns offer any general advantages to eukaryotes. Many more experiments will be needed to confirm or discard current ideas regarding the role of introns in genome evolution. "For example, do introns affect the fitness of a species, does the loss or gain of an intron increase fitness, decrease fitness or have

neutral consequences for an individual or a species? We simply do not know", says the ETH professor.

As a result of their comparison across several fungal genomes and individual genes, the ETH Zurich researchers also found the first concrete examples illustrating that introns can multiply and insert themselves elsewhere in the genome. The researchers were able to identify whole families of closely related introns, and then determine the frequency with which a particular intron family was present in the genome.

Analysing human introns next?

The researchers are convinced that their work will lead to a better understanding of intron evolution for all eukaryotes. Following their example, one can perform similar gene or genome analysis in other organisms, especially due to the rapid development of ever faster and cheaper sequencing technologies. Fungi have relatively small genomes, which makes these studies easier compared to organisms with much larger genomes such as humans. But McDonald is convinced that similar studies will be carried out in human populations soon, and then we will learn if the presence or absence of introns has any clinical relevance connected to human health. But for now, these plant doctors next want to figure out whether the diversity of intron patterns found in their pathogens affects the expression of disease on their host plants.

Provided by ETH Zurich

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