# An enzyme keeps the parasites of the genome in check and turns them into an evolutionary advantage

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Jumping genes are double-edged sword: By copying and integrating themselves into other parts of the genome these so-called transposons can lead to a variety of genetic disorders such as haemophilia or breast cancer. On the other hand the mobile DNA bits can create new genes

and new gene expression programs. This is crucial for maintaining high genetic variability and adaptability to environmental changes. Scientists from the Max Planck Institute of Immunobiology and Epigenetics Freiburg in collaboration with the University of Freiburg have now found that an enzyme called DHX9 can neutralize the harmful structures formed by transposons and effectively increase the tolerance of the genome to include these jumping genes. By understanding this process better scientists can devise better therapies for diseases caused by transposons while retaining their evolutionary advantage.

Geneticists have long focused only on a very small part of DNA that contains blueprints for proteins. The non-coding remainder, around 97 percent in humans, was often dismissed as junk. But what was damned as junk before turned out to be the key regulator of genes determining where and how much protein should be synthesized. However, an even closer look into the "junk" revealed that it is also home for many more actors in the genome. One of these are the so-called transposons or jumping genes. Jumping genes are DNA sequences which are able to copy themselves and then insinuate the copies into distant sections of the genome.

"Our work revolves around a family of human transposons called Alu elements, which with more than 1.1 million copies, compose more than ten percent of our entire genome" says Tuğçe Aktaş, co-first author of the study. To copy themselves, Alu elements are transcribed into RNA, reverse transcribed and then reintegrated into the genomic DNA at a different location. Once reintegrated, the short Alu elements have a vast amount of effects on the genome. "Depending on their site of insertion they can cause problematic mutations if they, for instance, jump into essential genes. Interestingly, Alu elements can cause a variety of genetic disorders such as haemophilia, breast cancer or familial hypercholesterolaemia, thus our work has to be explored further for therapeutic potential," says İbrahim Avşar Ilık, co-first author of the

study.

## Jumping genes in evolution

Alu elements, are often referred to as "invaders" or "parasites" harming the genome stability. But at the same time Alu elements are also important drivers of evolution. Studies comparing primates and humans showed that more than five thousand Alu elements were newly inserted into the human genome during the past six million years. Scientists suggest that they act as a "creative destroyer" by separating parts of the genome into functional pieces that can be copied, moved around and re-used in other contexts. This ability to modify the DNA by more than 1.1 million Alu elements at the same time increases the possibility to create new genes as well as gene expression programs that probably allowed faster adaptation to the environment.

"We wondered how our genome deals with the outcome of this continuous copy-pasting and still avoids potentially fatal threats. Our discovery that DHX9 as the enzyme responsible for neutralizing harmful RNA structures produced during expression of our genes is very exciting as it opens a new angle to look into the complex biology hidden behind this abundant RNA helicase," says Asifa Akhtar, Max Planck Director and the lead investigator.

## Untie the knot

DHX9 has the ability to unwind DNA and RNA duplexes and plays a central role in many processes in the cell like DNA replication, transcription or RNA processing. The Akhtar team in collaboration with Daniel Maticzka and Rolf Backofen from the bioinformatics research group of the University of Freiburg was able to show that in mice and humans DHX9 finds and removes disruptive RNA structures formed by

dense Alu insertions. "If the distance between Alu elements in our genome is not large enough they interact with each other and form massive tangled RNA pieces", says İbrahim Avşar Ilık. These huge cluttered structures can have fatal consequences, because essential RNA processing signals can be masked by them. DHX9 resolves the clutter and hands the now-untangled RNA over to further processing. "So without DHX9, our RNA turns into an entangled yarn that is no good for knitting," adds Tuğçe Aktaş (see Fig. 1).

DHX9 does not do all the work by itself but has a "partner in crime" called ADAR, another enzyme that was previously shown to also be involved in the handling of tangled RNA structures especially during viral infections. "We suggest that this clearing unit evolved originally to fight against viral invasions. Their untangling activities were later reassigned and put into use in cells that are not under viral invasion, but are experiencing a surge in Alu element insertions", explains Asifa Akhtar the evolutionary implications of the data.

The great collaborative effort between the Max Planck Institute and the University of Freiburg leads the team to propose that DHX9 allowed the insertion of excessive amounts of Alu elements in our genome by simply counteracting harmful consequences of having too many of them side-by-side. Even though harboring so many disturbing jumping genes may seem like a waste of our cellular resources it pays for itself in the long run with genomic innovations that would otherwise be impossible. In other words, what is seen as a waste in our genome has never really been a waste, it is essentially a long, expensive road to complexity.

**More information:** Tuğçe Aktaş et al. DHX9 suppresses RNA processing defects originating from the Alu invasion of the human genome, *Nature* (2017). DOI: 10.1038/nature21715