

Human diseases are a result of our genetic makeup and the environment we live in (pollution, social circle, etc.). However, for some diseases, it is only due to a mutation in a gene. The mutations in some genes can lead to an absent or defective protein that cannot do its normal function. For example, Dravet syndrome is a disease that causes childhood epilepsy in 1 of 20000-40000 births. Dravet syndrome is largely due to mutation in the SCN1A gene. Although some drugs can treat seizures in those children, such drugs cannot “repair” the mutated gene or replace the protein. Recently, scientists have found a way to solve this problem in animal models of Dravet syndrome. They performed this task with small pieces of DNA called antisense oligonucleotides (ASO). Using these ASO’s, they were able to restore the protein levels in the mice model of Dravet syndrome.

Although the ASO’s are promising, the question remains whether ASO’s can be used for all the mutated genes that confer various genetic diseases? A further complication is, some genes are like Matryoshka dolls. Inside such genes, they have small DNA regions that can be made into microRNA’s which in turn can control 100s of other genes. So, a burning question is what happens when ASO’s target these Matryoshka-like genes? What happens to these microRNAs in those genes? We want to solve a problem using ASO, but are we indirectly creating other problems because of this ASO? Now is the time to ask and test this question before ASO’s targeting such Matryoshka-like genes can reach patients.

During my postdoc, I was working on one such Matryoshka-like gene and I found out that ASO targeting that gene led to a serious problem that can be solved only by taking down the microRNA inside it. Luckily for me, I was working on a larval zebrafish that has a transparent brain and using advanced microscopy, I can see what problems can arise when ASO’s target such Matryoshka-like gene. However, before jumping to general conclusions that ASO’s targeting Matryoshka-like genes are problematic, we need to perform further rigorous research to confirm our observation. We expect that our studies in zebrafish will help other researchers and biotechnology companies to be vigilant when using ASO’s against such Matryoshka-like genes.