

How to understand a gene involved in neurodevelopment. First step: phylogenetics!

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As humans we share a great deal of similarity with other vertebrates, which are a group of animals that include mammals, amphibians, reptiles, birds and fish. These similarities become even more evident when we look at genes, the heritable pieces of DNA carrying the information that shapes the traits of an organism. Because of this likeness, researchers use animal models to understand genetic and molecular mechanisms in our species. The gene called quaking, the main character of this project, is a very good example.

It was found in mice that mutations of the quaking gene cause either death at embryonic stage or, in adults, legs tremor and problems in brain development. It's also known that the gene is expressed in certain type of cells in the nervous system, starting early in development. Humans also have the quaking gene, and that's why research groups are interested in the gene.

Zebrafish, a small fish, is an excellent animal model for studying genes during development. By researching gene databases, we found not one but three copies of the quaking gene in zebrafish, called *qkia*, *qkib* and *qki2*. This was not surprising, as gene duplication events are common in the evolution of vertebrates. Of the copies of the zebrafish quaking gene, at least one is expected to be more closely related to the human quaking gene, assuming the copies originated at different times. The goal of this study was to identify which quaking gene in zebrafish is the more closely related to the human version of the gene. This would allow researchers to make predictions on the function of the human quaking gene using zebrafish as animal model.

For this investigation I used the tools of phylogenetics, which is the science that unveils the evolutionary relationships among organisms. It does so by inferring evolutionary trees, the graphic representation of the evolution of organisms based on genetic differences. Evolutionary trees are a bit like family trees.

Through online databases I collected both DNA and protein sequences of the quaking genes from different species. This is the first fundamental step to construct the phylogenetic trees. Amphioxus, a fascinating invertebrate that is found close to the vertebrate group in the "family tree of animals", was one of the species included. Another species was the coelacanth, considered a living fossil and the fish closest to tetrapods (all vertebrates with four limbs). Sequences from a number of other animals were also added in the study. These include chicken, frog, mouse, human and, of course, zebrafish. The sequences of these species were aligned to find the differences among them.

By comparing the quaking gene in all of these animals I created an evolutionary tree showing how the gene evolved and how it is related among the animals.

By looking at the resulting tree I could infer that the quaking gene duplicated early in evolution of vertebrates, since the invertebrate amphioxus had one copy, while coelacanth had two copies (*qkia*-like and *qkib*-like). All tetrapods had just one copy (*qkib*-like), so it was safe to assume that one copy (the *qkia*-like) was lost at the root of our lineage. Zebrafish retained those copies and probably because it was involved in another known duplication event, has a third copy of the gene (*qki2*). The zebrafish *qkib* and *qki2* clustered together with the one quaking copy of tetrapods in the tree, so we concluded that those two are more closely related to the human quaking gene.