

Use of the Zebrafish model to study a new transposon-derived gene family involved in the development of the vertebrate nervous system

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New gene formation is one of the major sources of evolutionary innovations for organisms. These events can arise *de novo*, by gene duplication or by transposable element (TEs) co-option or “molecular domestication”, which makes TEs crucial actors of evolutionary innovations. The global impact of new gene formation through TE molecular domestication on the emergence and early evolution of Vertebrates is probably still underestimated. The cases of *rag1* and *rag2*, at the basis of the adaptive immune system, and the *syncytins*, involved in placental development, have already highlighted the role TEs can have on gene formation. Further investigating this aspect, we have identified, by comparing human proteins to TE databases, an entire family of genes deriving from the Myb-like protein of *Harbinger* DNA transposons. The results suggest the formation of five genes from independent *Harbinger* transposon molecular domestications in a common ancestor of jawed Vertebrates around 500 Mya. We also identified one gene that arose from the duplication of a *Harbinger*-deriving gene in sarcopterygians (around 400 Mya), and one retropseudogene in simians (around 60 Mya) expressed as a long non-coding RNA and positioned in a cluster of 40 non-coding RNA genes. The functional and evolutionary analysis of this gene family originating from recurrent and concomitant molecular domestications of *Harbinger* transposons is particularly interesting to give more insights into the impact of TE molecular domestication on the organismal innovations associated with the emergence and diversification of the vertebrate lineage.

Using the zebrafish model, we have observed that these genes are expressed during development but also in brain and testes. Most genes of this family show also a major expression in the human brain, particularly during fetal development. In order to analyze at the functional level, the genes of this family, we used a protocol of CRISPR-Cas9 allowing to obtain direct knockout in G0 in zebrafish (adapted from Wu et al. 2018). This allowed us to select a particularly promising gene, called *MSANTD2*. Indeed, zebrafish mutants for this gene present developmental delay including head, tail and nervous system malformation at 1day post fertilization (dpf). Moreover, the apparition of jaw malformations at 4dpf suggests the implication of this gene in neural crest cell migration or differentiation. Further investigations of *MSANTD2* – which has been associated to neurodevelopmental diseases such as autism spectrum disorders and schizophrenia in human – will allow us to better understand the genetic innovations having driven the evolution of the nervous system in vertebrates.