Novel transmembrane protein c-Answer revealed by bioinformatic screening of genes present only in well regenerating animals

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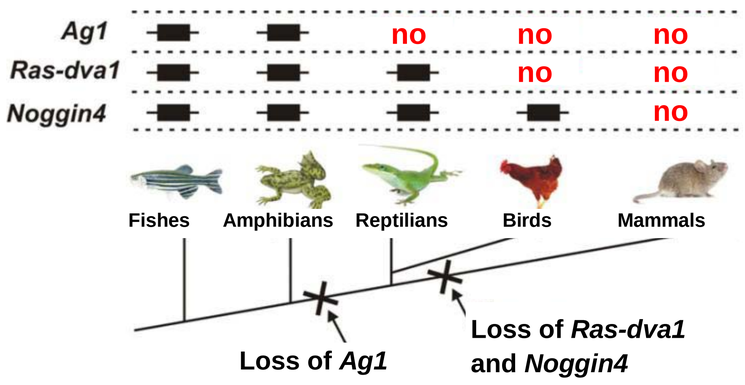


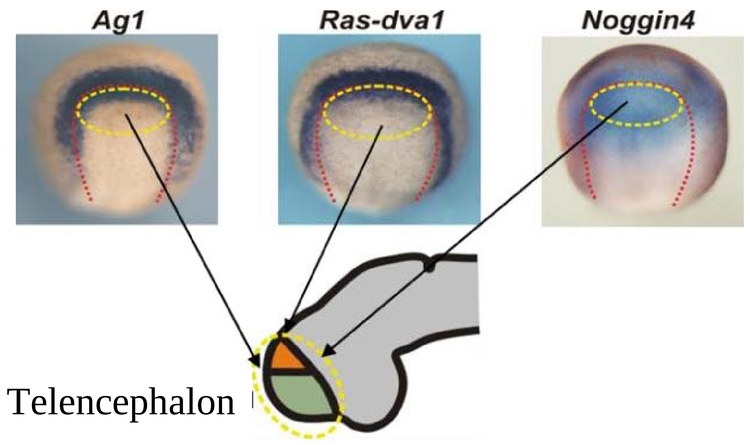
Example of genes lost in evolution:

Ag1 – secreted factor of the disulfide isomerase family

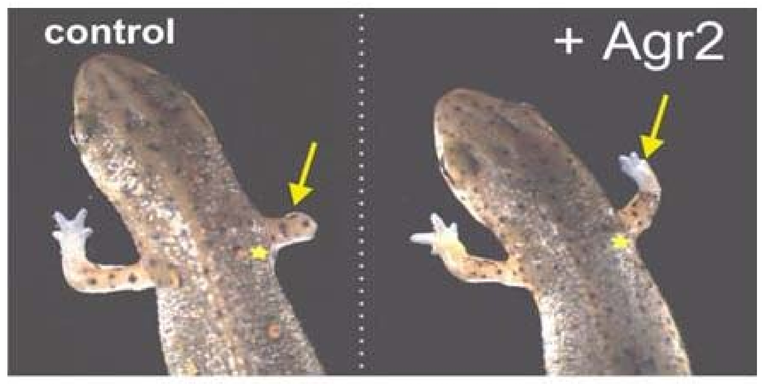
Ras-dva1 – Ras-like small GTPase

Noggin4 – secreted factor

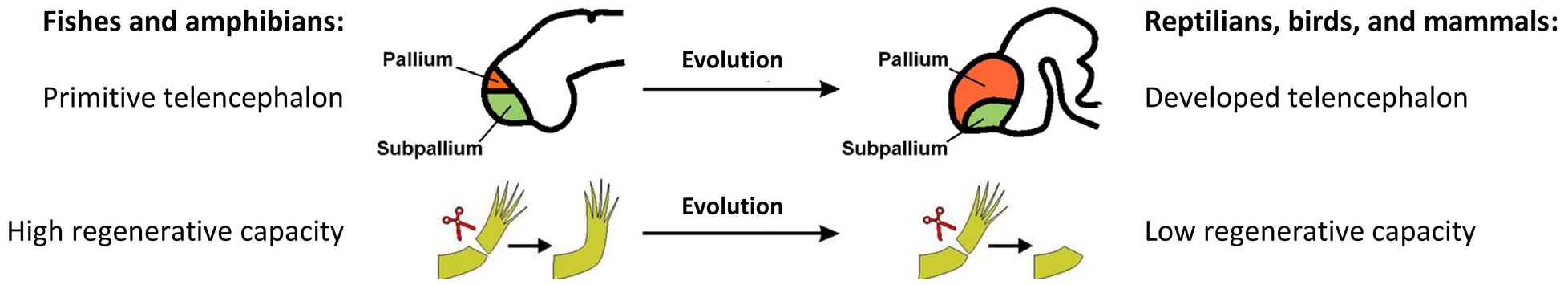
The *Ag1*, *Ras-dva1* and *Noggin4* genes are expressed in the frog primordial telencephalon.



The *Agr2* gene, an indirect homolog of *Ag1*, regulates regeneration in the newt.



(Kumar et al. 2007. *Science* 318, 772–777)



The genetic basis of higher regenerative capacity of fishes, amphibians and reptiles, comparing to birds and mammals, is still poorly understood. Usually, it is thought that this is a result of restructuring of the corresponding regulatory network, which consists of approximately the same set of genes. We hypothesized that another cause might be a loss of some genes which are essential for regeneration. We propose a bioinformatic approach for systematic search of such genes. Our method detects genes with local synteny disruption and, vice versa, appearance of genes with specific local synteny. The underlying algorithm operates with several megabases windows around protein-coding homologous genes simultaneously in many species. It relies on different definitions of gene homology and uses a consensus or voting scheme to reduce overprediction. The algorithm examines the co-localization of homologous genes and counts the number of their copies as well as the co-localization of CNEs. The method provides for flexible definition of detecting conditions and different forms of local synteny. Our algorithm outputs rather short gene lists, and quite similar lists for a wide range of parameters. Thus, we identified several genes that present only in fishes, amphibians and reptiles and revealed the genes, which demonstrated an increased expression during regeneration of tails and hindlimb buds in the model organisms, the *Xenopus laevis* tadpoles. We found out that one of these genes encodes a membrane protein, which is strongly up-regulated already at the 1st day of regeneration predominantly in the wound epithelium. As we demonstrated, this gene regulates the body appendages regeneration and also the telencephalic and eye development. We named the protein encoded by the revealed gene c-Answer, after cold-blooded Animals specific wound epithelium receptor-like protein. We suppose that the loss of c-Answer although resulted in a decrease of the regenerative capacity in birds and mammals, could be fixed by natural selection because the loss of this gene might provide new opportunities for the forebrain evolution. On the whole, local rearrangement of gene synteny is a likely driving force in many aspects of forebrain and species evolutions. Supported by the Russian Scientific Foundation project no. 14-50-00150.