

NEWS AND COMMENTARY

Evolutionary genetics

When duplicated genes don't stick to the rules

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Heredity (2006) 96, 204–205. doi:10.1038/sj.hdy.6800771; published online 16 November 2005

A common assumption among biologists, and one that we teach our students, is that orthologous genes (ie homologous genes in two different species) have identical or highly similar functions, while paralogs (ie genes created by duplication within a species) will evolve different functions. However, in a recent paper in *Current Biology*, Causier *et al* (2005) describe exceptions to this pattern, which provide a challenge to our understanding of the evolution of multigene families.

Recent analyses of genome sequences have revealed that gene duplication has been rampant. The creation of extra gene copies can occur by unequal crossing over, reverse transcription, or even the duplication of entire genomes. It has now been generally accepted that such duplication events have been crucial for adaptive radiations of species and the general increase of genetic and biological complexity (Maere *et al*, 2005).

The consequence of all these duplications is that, in many eukaryotes, the majority of genes occur in more than one copy and so form gene families, some comprising tens or even hundreds of genes. It is important to decide on the correct homology relationships when comparing gene families in different species. In simple models of gene family evolution, after a duplication event, one of the gene copies is assumed to be redundant and freed from functional constraints, and therefore able to evolve a new function (Ohno, 1970). So whereas orthologs tend to have the same function in different species, paralogs can evolve different functions (see Figure 1a).

An exception to this rule, described in this new paper, comes from C-function genes in two model plants: the thale cress, *Arabidopsis thaliana*, and the snapdragon, *Antirrhinum majus*. In the generally accepted ABC model of flower development (Coen and Meyerowitz, 1991), the C-function genes are responsible for the specification of male and female reproductive organs. Mutants in the C-function genes cause reproductive

organs to develop into nonreproductive perianth organs.

In *Arabidopsis*, the classical C-function gene encodes a homeotic MADS-box transcription factor called AGAMOUS (AG). Previous analyses based on phylogenetic tree construction have shown that a gene called FARINELLI (FAR) is the ortholog of AGAMOUS in *Antirrhinum*. The orthologous relationship between both genes was again confirmed in this new study based on genome colinearity, that is, by comparing the gene content and order of the two genomes. However, although both genes are unambiguously orthologs, they have clearly different functions.

Nevertheless, a functional homolog of AGAMOUS in *Antirrhinum* does exist; a

gene called PLENA (PLE), which is actually a paralog of FARINELLI that originated through a gene duplication event that occurred about 125 million years ago in a common ancestor of *Arabidopsis* and *Antirrhinum*. In turn, PLE has an ortholog in *Arabidopsis*, called SHATTERPROOF (SHP) (Figure 1b), which, like FAR, has a different function from its ortholog. Thus, although FAR is the ortholog of AG, and SHP is the ortholog of PLE, the functional homolog of AG is PLE, and not, as would be expected, FAR.

Duplicated genes can diverge in function in at least two different ways. The first way is through the accumulation of amino-acid changes in the protein-coding domain itself. Although such changes can indeed lead to genes with new functions or subfunctions, clear examples of such functional divergence are still quite rare. A second way is through changes in the noncoding regulatory elements of the duplicate.

One model that describes such changes and that has become increasingly popular in the last few years is the subfunctionalization model proposed by Force *et al* (1999). This model starts

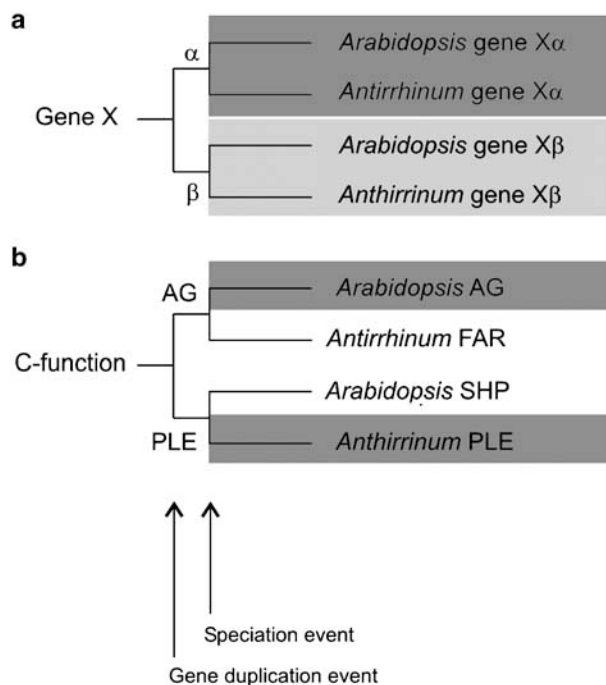


Figure 1 Phylogenetic trees depicting the relationships between orthologous (originated by speciation) and paralogous (originated by duplication) genes. (a) The generally accepted view is that orthologous genes have identical or highly similar functions in different organisms (indicated by similar colours), while duplicates in the same organisms have diverse functions (indicated by different colours). (b) The situation for the C-function genes in *Arabidopsis* and *Antirrhinum*. The *Arabidopsis* AG and the *Antirrhinum* PLE genes have almost identical functions, but have not been derived from the same ancestral gene. The SHP and FAR genes have obtained new functions in *Arabidopsis* and *Antirrhinum*, respectively.

from the assumption that a gene usually performs several different functions. For example, different DNA regulatory elements can control the expression of genes in different tissues and at different times during development. If a gene, including its regulatory elements, becomes duplicated, it is possible for each copy to lose different regulatory subfunctions. Each copy will then show different spatial and/or temporal gene expression patterns, but the two gene copies will then complement each other by jointly retaining the full set of subfunctions that were present in the ancestral gene.

The subfunctionalization model is attractive because it suggests a mechanism through which duplicates can be preserved in the genome, and seems to fit well with the large number of duplicated genes present in most eukaryotic genomes. Furthermore, experiments are uncovering an ever-increasing number of examples of subfunctionalized genes (Prince and Pickett, 2002).

The genes that Causier *et al* studied seem to have experienced both kinds of

functional divergence. AG, FAR, and PLE all display very similar expression patterns in the developing male and female reproductive organs, whereas the SHP genes are only expressed in the fourth whorl of the flower, indicating subfunctionalization (or at least loss of some subfunctions). At the protein level, ectopic expression in transgenic *Antirrhinum* of FAR and PLE clearly showed that both paralogs have developed differential abilities to promote the formation of female and male reproductive organs, in contrast to the genes AG and SHP, which proved functionally equivalent. Furthermore, the authors show that, even in *Arabidopsis*, the separate pathways leading to specification of male and female reproductive organs can be triggered jointly by one protein, AG, or individually by two proteins, PLE and FAR, which thus seem to have subdivided their ancestral function.

In conclusion, Causier *et al* have provided one of the first examples where different members of a duplicated gene pair have retained identical functions in different lineages, contradicting the dogmatic view of the evolu-

tion of gene duplicates. However, it is possible to envisage a scenario leading to this outcome. If duplication preceded speciation, and both duplicates maintained overlapping (or identical) functions through the speciation event, it would not matter which gene subsequently changed its function: it could be the paralog, or, as in this case, one of the orthologs. So these new findings clearly illustrate that essential developmental functions can be randomly assigned to either product of a gene-duplication event.

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