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Exploring the links between evolution and development 29

In order to achieve a modification in adult form, evolution must modify the embryological processes responsible for that form. Therefore an understanding of evolution requires an understanding of development.
T. J. HORDER, 1989

Animal life is extraordinarily diverse. Roughly 35 major groups ('phyla') of animals can be distinguished, mostly on the basis of the profound differences between them. How did such diversity emerge? One intriguing fact is that while adults can be very different from one phylum to another, this is less true of their earlier developmental stages – the egg, embryo and juvenile. At first, all eggs and embryos are very similar, and the different organisms only achieve their distinctiveness as development proceeds.

The relationship between development and evolution has a long history of study. Darwin used embryology as one of the five principal pillars of evidence on which he based his argument that evolution had occurred and also that all organisms were related by genealogical descent.

In the later 19th century, the German biologist Ernst Haeckel interpreted this phenomenon of diverging embryologies as organisms recapitulating their individual evolutionary histories during their embryology, with each stage of development representing a sequential step in evolution. However, this theory has long since been discarded, primarily because of evidence that any step in an organism's embryology can evolve, not just the final one. And rather than recapitulating evolution, variations in embryology are viewed as the raw material, not the record, of evolution.

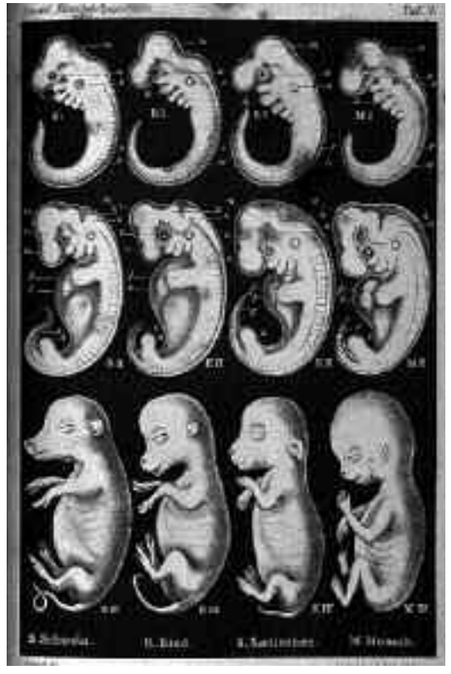


Plate from Ernst Haeckel's Anthropogenie *(first edition 1874) comparing different embryos – pig, cow, rabbit and human – demonstrating the principle that animals become distinct as embryology proceeds.*

Regulatory genes

Given the importance of embryology in evolutionary change it is perhaps surprising that it does not feature in standard syntheses of evolutionary theory. It was not until the discovery of specific genes that regulate development, as well as technological advances that facilitated their study, that embryology was integrated into mainstream evolutionary biology. This was heralded by the analysis in fruitflies (*Drosophila*) of the effects of mutations in developmental genes, specifically of members of the *Hox* gene cluster. Mutations of these genes lead to dramatic changes in the specification of parts of the fly's anatomy, producing legs in place of antennae, and extra pairs of wings.

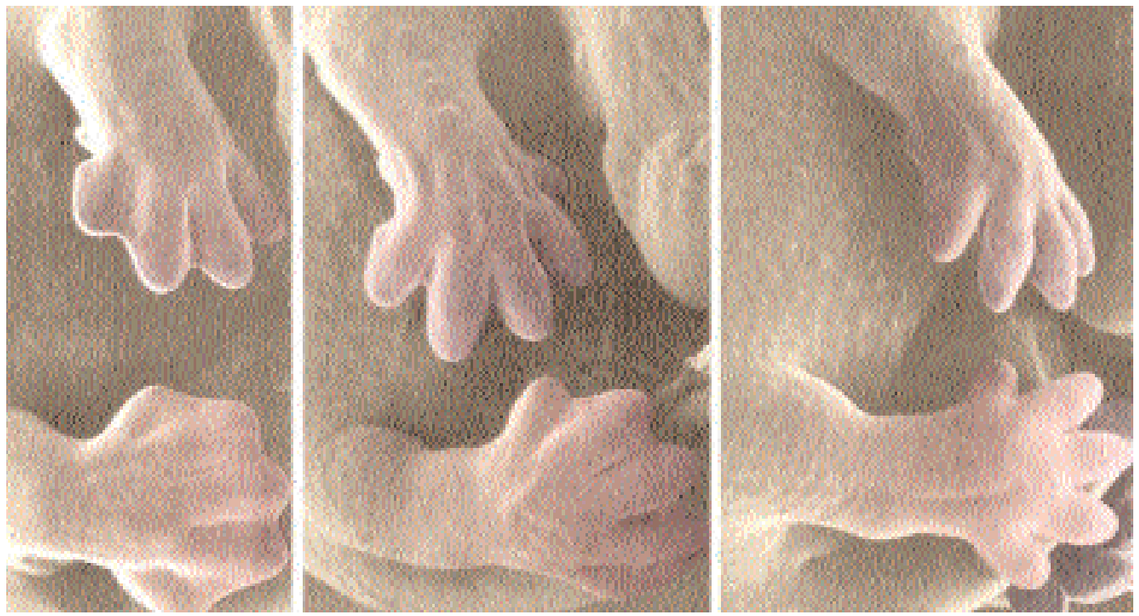
Opposite above *Development of the limbs in a mouse embryo showing the gradual emergence of the digits from a homogenous rudimentary limb.*

Right *A normal fruitfly,* Drosophila melanogaster *(left),with two wings, and a bithorax mutant, with four, the result of failure of expression of the Ultrabithorax transcription factor.*

The discovery of regulatory genes brought a new perspective to developmental biology, most especially in understanding the mechanics of embryology. It also revealed that not only are these genes shared by almost the full range of animal diversity, but that they are so structurally and functionally conservative that the same gene from a mouse could be used to rescue induced genetic deficiencies in as distant an evolutionary relative as a fruitfly.

Developmental regulatory genes perform multiple roles, and for the vast majority of them these roles are still being worked out. By far the most completely understood are the *Hox* genes, which most especially perform the role of establishing the main head–tail axis within the developing embryo, as well as positions along it. The areas of expression (where the gene is being transcribed) of individual *Hox* genes can be much greater than their areas of influence. This is because more posterior *Hox* genes suppress the influence of their more anterior counterparts. Where they do have influence, they perform the role of a transcription factor, encoding a protein that binds to other genes, regulating their activity, either positively or negatively. Effectively, they act as traffic wardens within developing embryos, promoting the activity of genes in one cell but not another.

If *Hox* genes can confer the identity of specific body parts, it is easy to see how mutations in these genes can lead to the transformation of one body part into another (homeosis): if a posterior gene is not expressed, then its role is overtaken by its more anterior counterpart. Mutant fruitflies with two pairs of wings, rather than one, have long been known to occur naturally. This happens when the *Hox* gene in the segment posterior to the standard wings, which would normally suppress wing development, is not expressed. Thus, the second segment also produces wings. Perturbation (disturbance?) of other *Hox* genes can lead to changing the identity of limbs, such as legs in place of antennae. Similar phenomena are encountered in distantly related animals. For instance, in vertebrates, variations can occur in the relative numbers of different classes of vertebrae, such as lumbar and cervical. However, while these are clear cut examples of the relationship between genes and morphology, it should be



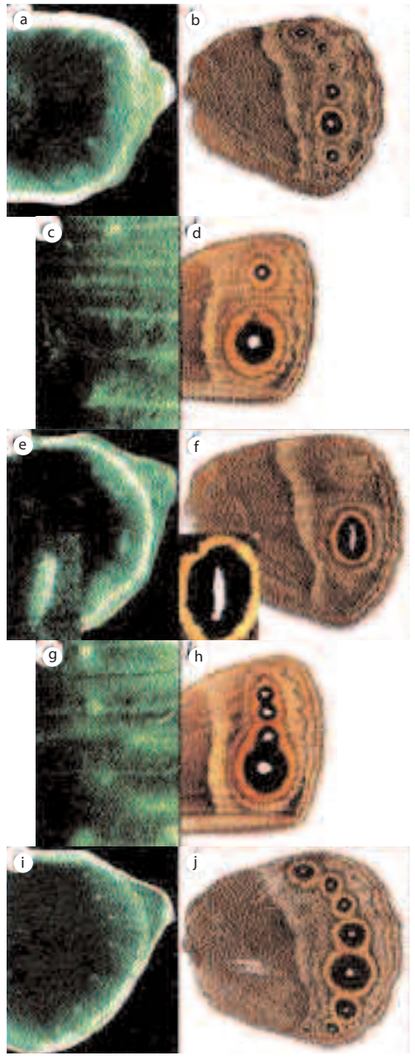
remembered that the role of these genes is indirect and there are many intermediate steps. Thus, the effects of changing *Hox* gene expression is often less obvious.

Few other classes of regulatory genes are as well characterized in terms of function and evolution as the *Hox* gene. What we do know, however, is that there is a toolkit of regulatory genes common to all animals, from sponges to worms, humans and fruitflies, and that these genes are more often than not deployed in the same way in disparate organisms. For example, the gene *Pax6* is so tightly linked to the specification of eye development that in experiments it is possible to initiate eye development in areas of the embryo where eyes should not normally occur by introducing the *Pax6* protein. Other regulatory genes that have been directly connected with anatomical development include *Tinman* and heart development, *Caudal* and gut development, *Distalless* and limb development.

Regulatory genes and evolution

The connection between regulatory genes and the specification of anatomical features led to the idea that the diversity of complex, bilaterally symmetrical animals (bilaterians) may be explained by the evolutionary origin of this genetic toolkit. However, analysis of simpler animals such as sponges and jellyfish has revealed that they, too, possess the genetic toolkit. Indeed, they share with humans a number of genes that fruitflies do not, indicating, somewhat ironically, that there has been significant gene loss among some bila-

Above *A stage 16 chick embryo, removed form its egg sack, using a molecular label to show where the Hoxa-2 gene is being transcribed into messenger RNA.*



Right *Expression of the transcription factor* Distalless *(Dll) in the wing of the butterfly* Bicylcus anyana. *The first pair (a–b) show the natural pattern of Dll expression and eyespot phenotype; the other pairs are a variety of mutants*

Far right *Two forms of the stickleback fish with (top) and without (bottom) pelvic fins and a fin girdle, resulting from different alleles in the transcription factor Pitx1.*

terians, most especially along the lineage leading to fruitflies. It also indicates that the genetic toolkit cannot explain the complexity of animal diversity.

So it appears that animals are more than the sum of their genetic parts – but not too much more. Much of the complexity of organisms is effected within the embryo through the interaction of cascades of regulatory genes in complex genetic circuits. Discovering the architecture of these circuits is extremely labour intensive – the function of every component interaction (not merely every gene) has to be validated experimentally. Nonetheless, from what little is already known it is clear that there is a significant amount of evolutionary conservation of the circuit architecture, even among the most distantly related complex animals.

It is tempting to think of these regulatory gene circuits as key innovations that facilitated new thresholds of complexity in animal evolution, but our understanding of their own evolution is extremely scant and certainly insufficient to contemplate stages in their evolution. It is far more likely that complexity in organisms evolved gradually through selection acting on developmental variation. So far, however, the role of developmental variation in models of selection has not been widely considered, although there have been pioneering studies on specific traits like eye spot patterns on butterfly wings, pigment patterns in fruitflies, and fin skeletons in stickleback fishes. These have revealed that developmental variation is not limitless – the same patterns are converged upon, but this is because certain alleles (one of a pair of alternative genes that occur at a specific locations on a chromosome) within highly conserved genes act as hot spots for the recurrent evolution of those features.

As we are learning more about the genes that direct development, it becomes increasingly clear that genetic conservation is the rule, not the exception. Indeed, the surprising fact is that so much organismal diversity could have emerged in the face of so much genetic conservatism.