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# EXISTENCE OF A LATENT DEVELOPMENTAL PROGRAM: REVISITING THE UNIVERSAL GENOME MODEL OF EVOLUTION OF METAZOA

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**Abstract**

*In 2007, I published a hypothesis about mechanisms of evolution of large taxonomic groups of the Kingdom Animalia, which was based on advances in paleontology, genome analysis, genetics and embryology that are difficult to understand within Darwinian intuition. According to this model that I called a Universal Genome hypothesis: (a) the Universal Genome that encodes major developmental programs essential for various phyla of Metazoa emerged in a unicellular or a primitive multicellular common ancestral organism shortly before the Cambrian period; (b) The Metazoan phyla, all having similar gene sets, are nonetheless very morphologically distinct because each utilize specific combinations of developmental programs. A highly counterintuitive prediction of this idea, which strictly dissociates it from the classical evolutionary model, is that latent developmental programs should exist in genomes of lower Metazoan taxa. These latent programs control the development of organs and other morphologies that would emerge in evolutionary higher taxa. Potentially, such programs could be activated by mutations or application of signaling molecules, and thus be revealed in lower taxa. A paper on the embryology of fins published in the Cell journal provides an evidence for existence of such a latent developmental program. Here I comment of this discovery and its implication in our understanding of evolution.*

**Keywords**

*latent developmental programs • universal genome • evolutionary mechanics*

Major groups of facts described in the original publication (1) that led to formulation of the Universal Genome hypothesis are:

(A) Cambrian explosion – a seemingly simultaneous appearance of fossils of diverse Metazoan phyla in Cambrian period. There were attempts to suggest that evolution of these phyla took place before Cambrian period. They appeal to existence of unfossilizable forms, making these types of organism paleontologically 'invisible'. However, these attempts were generally refuted. Accordingly, it appears that there was no sequential evolution of Metazoa from simpler to more complex phyla, as would be predicted by the classical evolutionary model.

(B) Further surprises came from publication of full sequences of genomes from various animal groups. These publications highlighted that the emergence of Metazoa was associated with a burst of appearance of new genes that almost tripled in Metazoan genomes, compared to unicellular organisms to about 22,000–25,000. Appearance of novel gene families is somewhat expected since many of them are associated with formation of body plans, organ development and cell-cell communications, e.g., Hox, TGFb, Wnt, nuclear receptor systems, etc. Accordingly, Cambrian explosion known by fossilized remains was associated with emergence of a high number of new genes and gene families. The main surprise in the genome sequencing studies was that these new gene sets have very high similarities among animal phyla. Indeed, the majority of all human genes have direct orthologs in anemone (2). These data also indicate that after the Cambrian explosion associated with emergence of new genes, further evolution of all animal phyla was mostly unrelated to the appearance of new genes, and therefore new biochemical features (emphasis 'mostly' but not exclusively). Rather, it was associated with the raise of novel morphological structures, i.e., new developmental programs. Similarities between the genomes of very complex and relatively primitive groups have many implications in our understanding of evolution of Metazoa.

An important discovery was the presence in lower taxa of gene sets that define complex systems in more advanced taxa, like a set of bilateral symmetry associated Hox genes in taxa with radial symmetry, Cnidaria or Sponges. Surprisingly,

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such genes, e.g., orthologs of hox genes, are expressed in Cnidaria in an asymmetric (bilateral) manner, as if to define segments in these radial organisms (3). Whether bilateral taxa emerge from organisms with radial symmetry or these groups evolved independently, one does not expect to find genes responsible for development of bilateral symmetry in primitive Metazoa with radial symmetry. As noted in the original publication (4), the overall complexity of regulatory genes and signaling pathways in Cnidaria 'is paradoxical, given that this organism contains apparently few tissue types and the simplest extant nervous system consisting of a morphologically homogenous nerve net'. Thus, there appears to be a seemingly excessive complexity of genomes of lower taxa.

(C) Another surprising finding was similarities of genes that control functionally similar but morphologically and biochemically different developmental structures in various taxa, e.g., Chordata and Arthropoda. A classic example is development of limbs and limb-like structures in these and other taxa (e.g., tentacles in Mollusca), which is controlled by a set of switch genes that have to be activated in the right place of the embryo at the right time in a very specific order (5). Though structurally and biochemically limbs in these taxa are very dissimilar, functionally limbs are somewhat similar, and the genes that control the developmental programs are highly homologous and the order of their activation is nearly identical. The same phenomenon was reported for other functionally similar structures, including body segments, eyes, development of vocalization, and others. Therefore, more primitive and highly organized taxa deploy similar higher-level genetic modules to control structurally different lower-level programs, allowing to build functionally similar but structurally and biochemically dissimilar structures.

Similarities between the genes that control development of functionally similar but structurally dissimilar morphologies were extensively discussed in Shubin et al. (6), who coined the term 'deep homology'. The authors discuss the similarities in the control of development in different taxa of seemingly convergent eyes and appendages. They note that there should be a toolbox from which the system 'chooses' necessary tools to build the morphologies. They present a very in depth analysis of the 'deep homology', but in the final analysis, this idea practically is an integral part of the previously suggested model of the Universal Genome. The authors reiterate that the 'deep homology' goes in line with the Darwinian model, however it is difficult to explain why random mutations followed by selection may lead to a phenomenon of linking almost identical genetic modules to development of functionally similar but structurally dissimilar morphologies.

Notably, in its most basic form, the idea of the 'toolbox' is supported by multiple observations of 'multifunctional' proteins. For example, Ras-like proteins function both in transmitting signals in signal transduction pathways and regulating fusion of intracellular vesicles. In another example, p62/sequestosome protein functions both in cytokine signaling and in recruitment of substrates into the autophagosomes. However, similarities in regulation of development are incomparably 'deeper' and involve a sequential activation of 7–8 regulatory pathways that control all stages of development of specific morphologies. Not only these pathways in different taxa are similar, but also the sequence of their activation is almost identical. Such similarities are not naturally followed from the known biochemistry of the pathways themselves. Therefore, there appeared to be not a 'toolbox' to choose from but rather a set of complex developmental programs/modules that can be plugged to operate the development of different structures.

Another unexpected aspect of this phenomenon is that though the morphologies in different taxa controlled by a similar developmental program are structurally very different, they serve a similar function, e.g., eye or limb. Notably, Shubin et al. (6) gave an example of beetles' horns, which are controlled by the same program of limb development, though functionally the horns are different. This observation, however, does not refute that the major appendages in *Arthropod* are legs, which are functionally similar to *Vertebrate* legs or *Mollusca* tentacles. Therefore, surprisingly, the complex developmental programs are plugged to operate the development of morphologically different but functionally similar structures, which further complicates the ability to explain these phenomena in terms of random mutations/selection mechanism.

The existence and unusual activation of such latent programs may also explain a rare phenomenon of 'chimeric' animals. For example, Platypus combines morphologies normally do not coexist in one organism, e.g., a beak and eggs that are normal for reptiles and birds but are foreign for mammals, while hairs and milk feeding are common for mammals and are foreign for reptiles and birds. In another example, horns were found in certain unique extinct species of rodents (7) for which they are normally foreign but are common for artiodactyls and equids. Therefore, it appears that turning on latent developmental programs may lead to a sudden development of morphologies that are normal for other taxa.

(D) Further, in many cases (but not always) there is an absence of intermediate forms between sequentially evolving developmental programs, e.g., teeth and beak. Animal may have either teeth or beak but no intermediate form. Importantly,

beak appears in various groups in tetrapods multiple times independently, i.e., in turtles, dinosaurs, birds and platypus, suggesting that the developmental program of a beak exists in the Universal genome in a latent form, and waited to be 'turned on', in multiple subgroups independently.

These considerations together led to a hypothesis that Universal Genome that encodes genetic programs essential for development of organs, organ system and other major morphologies, emerged in the common ancestor of Metazoa shortly before the Cambrian period. Genomes of all Metazoan phyla represent slight variations of the Universal Genome, which is reflected in similarities of their genomes. In spite of the genome similarities, Metazoan phyla are nonetheless distinct because each utilize specific combinations of developmental programs. This idea predicts the existence of latent developmental programs in the genomes of lower taxa that control development of organs and major morphologies that show up only in higher taxa.

This prediction by itself may be problematic from the genetic prospective, since it requires effective preservation of these latent developmental programs in genomes, even though they are not expressed. However, we do have examples of such strict preservation of the developmental programs in the genomes, though we do not know the mechanisms. A good example is preservation of teeth development in chicken, which switched to beak and have not been using the 'teeth program' for about 300 million years. A mutant was isolated in chicken that develops the reptile-like teeth instead of beak (8). These teeth did not have enamel, however major morphological structures were preserved. Furthermore, identification of the regulating gene allowed artificial activation of the 'teeth program' in chicken embryo (8). Interestingly, genes responsible for the enamel making were lost in chicken (9), reiterating the notion that the higher-level genetic modules that control developmental programs are extremely conserved, while lower-level programs that define specific morphologies controlled by these genetic modules are less-preserved. It should be noted, however, there are examples of 'fluidity' of the developmental programs, e.g., in Arthropod, there is a diversity of morphogens that control the polarity (10, 11). Therefore, strong conservation of developmental programs is not at all universal, and in some taxa some developmental regulators are diverse.

Though above arguments to support the Universal Genome hypothesis could be appealing, they are indirect, and more importantly, retrospective. Accordingly, to support or disprove the model, a prospective experiment that tests the model's predictions is critical. A publication by Hawkins et al. (12) does exactly that, though the motivation of the authors was probably unrelated to testing evolutionary models. In this work, the authors identified a Zebrafish mutant called *rephaim* or *reph* with unusual fin structure that has a series of features of the tetrapod limb. Normally, the fin of Zebrafish and other teleost fish contains four proximal radial bones arranged side-by-side that are in contact with shoulder. These radial bones are followed by small nodular distal bones, and still more distal fin ray bones. In the *reph* mutant, new intermediate bones are formed between proximal radial bones and distal nodular bones. While proximal radials developmentally correspond to humerus (long bone of the upper arm) in tetrapods, intermediate bones correspond to ulna + radius (long bones of the forearm), and distal node bone + fin rays correspond to wrist + fingers. Therefore, in the *reph* mutant, a teleost fin plan is broken and a plan of the tetrapod limb is formed. The mode of ossification and cartilage segmentation in the *reph* mutant has not been found in the fins of teleosts, and resembles tetrapod limb development. Critically important is that new intermediate bones have epiphyses on both sides. Furthermore, similarly to synovial joints formed between long bones in tetrapods, in *reph* mutants, proximal and intermediate radials form a distinct joint pocket between them with specialized differentiation of mesenchyme shaping the interface. Joint markers are also expressed, which suggests that the joint differentiation program found in limbs of tetrapod is also activated in the *reph* intermediate bones. Amazingly, muscle development in this novel structure also resembles that in tetrapod. In Zebrafish muscles originate on the shoulder girdle and insert directly on the distal fin rays, bypassing the long proximal bones. In limbs of tetrapod, however, muscles originate from the shoulder as well as the long bones and insert on more distal positions along the limb. Importantly, intermediate bones in *reph* mutant have insertion points from muscles originating from the shoulder. Furthermore, different muscles originate on the intermediate bones and insert on the distal fin rays. Thus, conclude the authors, 'not only does the *reph* mutation reveal a capacity to make new, fully differentiated and patterned long bones, but these elements are morphologically integrated to form limb-like joints and muscle connections not seen in the fins of other teleosts'.

The *reph* mutation was mapped to Waslb gene that controls F-actin nucleation. The authors established a pathway that links this mutation to activation of Hox genes responsible for the embryonal patterning and demonstrated that the Hox11 gene family is responsible for the development of the intermediate bones in the *reph* mutant. Importantly, *Hox11* genes were previously shown to be responsible for the development of the forearm long bones radius and ulna in tetrapod. Therefore, not only the latent developmental program in Zebrafish provides for the development of a limb-like structures, this program is activated by the same

high-level regulatory genes that control limb development in tetrapods.

Overall, these findings strongly support the idea of latent developmental programs existing` in the genome whose evolution cannot be explained by classical evolutionary mechanisms.

As noted above, the discussed data indicate the existence of a latent developmental program that strongly supports the Universal Genome model in a prospective experiment. If additional latent developmental programs are uncovered, this will further support the model. Such latent programs potentially could be activated either by mutations, as in the case of the *rephaim* mutation, or by a specific application of the morphogens in the developing embryos, like activation of teeth in chicken. In such experiments, I would suggest to focus on latent programs that are 'easy' to activate. For example, activation of a beak development program in mammals or reptiles that do not originate from reptiles with a beak. Importantly, beaks appeared multiple times in the reptile lineage and therefore activation of the program should not be complicated. Similarly, activation of horns development program in mammals like rodents could also be a relatively uncomplicated since such chimeras previously existed, indicating the presence in rodents of the latent developmental program that can be activated.

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