Hox Genes: The Blueprint for All Living Creatures

Urantia Foundation, Science Symposium IV

November 6-8, 2025

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Introduction

In 1984,[1] a Hox gene mutation was observed in a fruit fly in which an entire leg appendage, normally located on the thoracic segment, was on the fly's head replacing an antenna. This became known as the famous Antennapedia mutant. This unique phenotypic result of a Hox gene mutation, known as a homeotic transformation, alerted geneticists to the existence of Hox genes.

The left upper image is a normal fly's head. In the right upper image, a leg appendage is growing at the normal location of its right antenna. In the lower pictures, on the left, there is a whole normal fruit fly, whereas on the right a bithoracic mutant is shown with two complete thoracic segments with two pairs of wings.

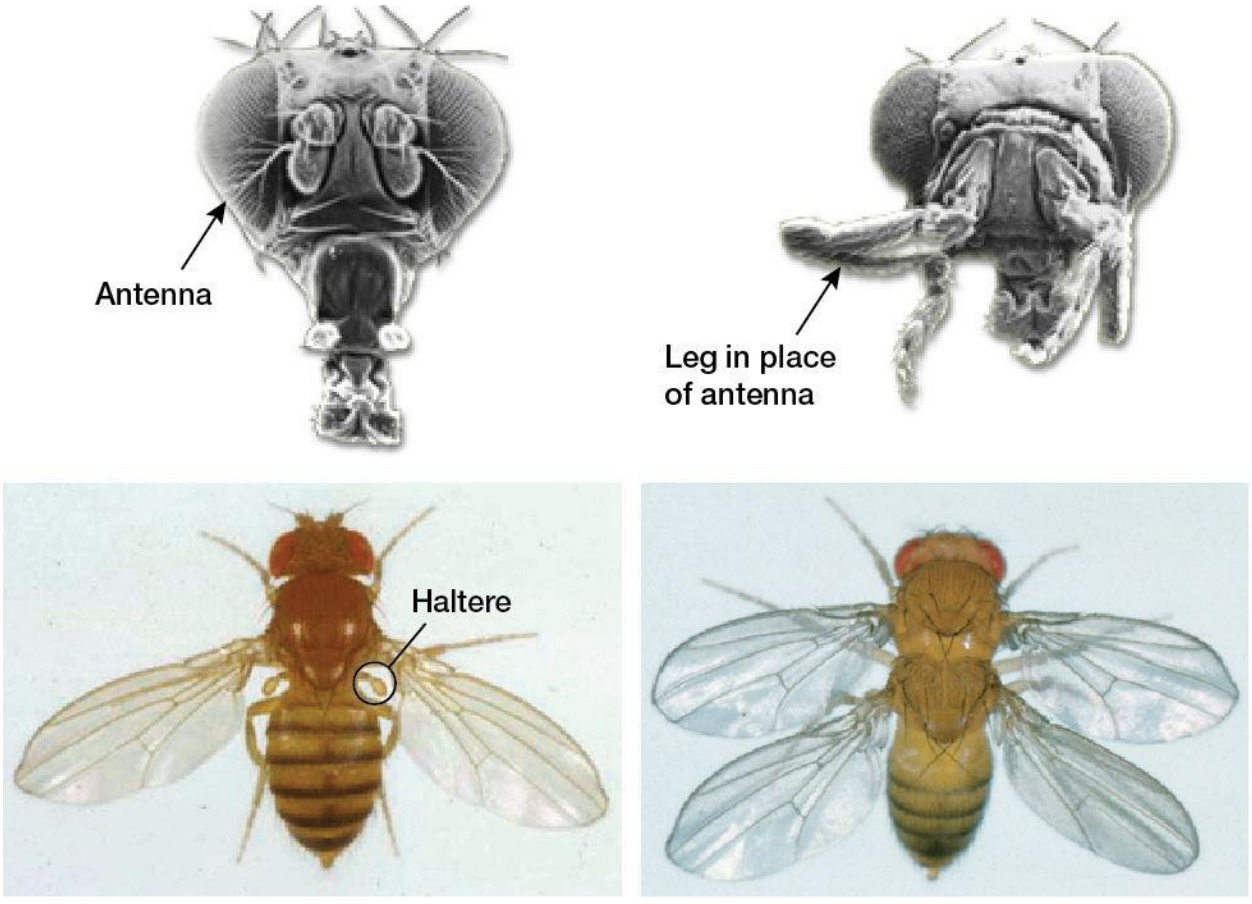

Figure 1. Picture of fruit flies (Drosophila melanogaster) with antennapedic and bithoracic mutants. Credit: Bottom images courtesy of the Archives, California Institute of Technology

Such homeotic transformations, hence the name Hox genes, immediately captivated the interest of evolutionary biologists and geneticists. The chief function of Hox genes is to regulate other genes including the location of major body parts. They have been referred to as “master genes” in that they control whole clusters of genes. They accomplish this by repressing or activating genes in a variety of tissues especially during embryonic development.

Two major Hox gene complexes in Drosophila

There are two major Hox gene complexes in Drosophila known as Antennapedia and Bithoracic Complexes consisting of a total of eight Hox genes as listed below.

- Antennapedia Complex (Ant-C)
  - *Labial (lab)*
  - *Proboscipedia (pb)*
  - *Deformed (Dfd)*
  - *Sex combs reduced (Scr)*
  - *Antennapedia (Antp)*
- Bithoracic Complex (BX-C):
  - *Ultrabithorax (Ubx)*
  - *Abdominal (Abd-A)*
  - *Abdominal (Abd-B)*

Figure 2. List of eight Hox genes, with abbreviations, in the Drosophila melanogaster genome

The Helix turn Helix Molecule, the Homeodomain, is a Transcription Molecule.

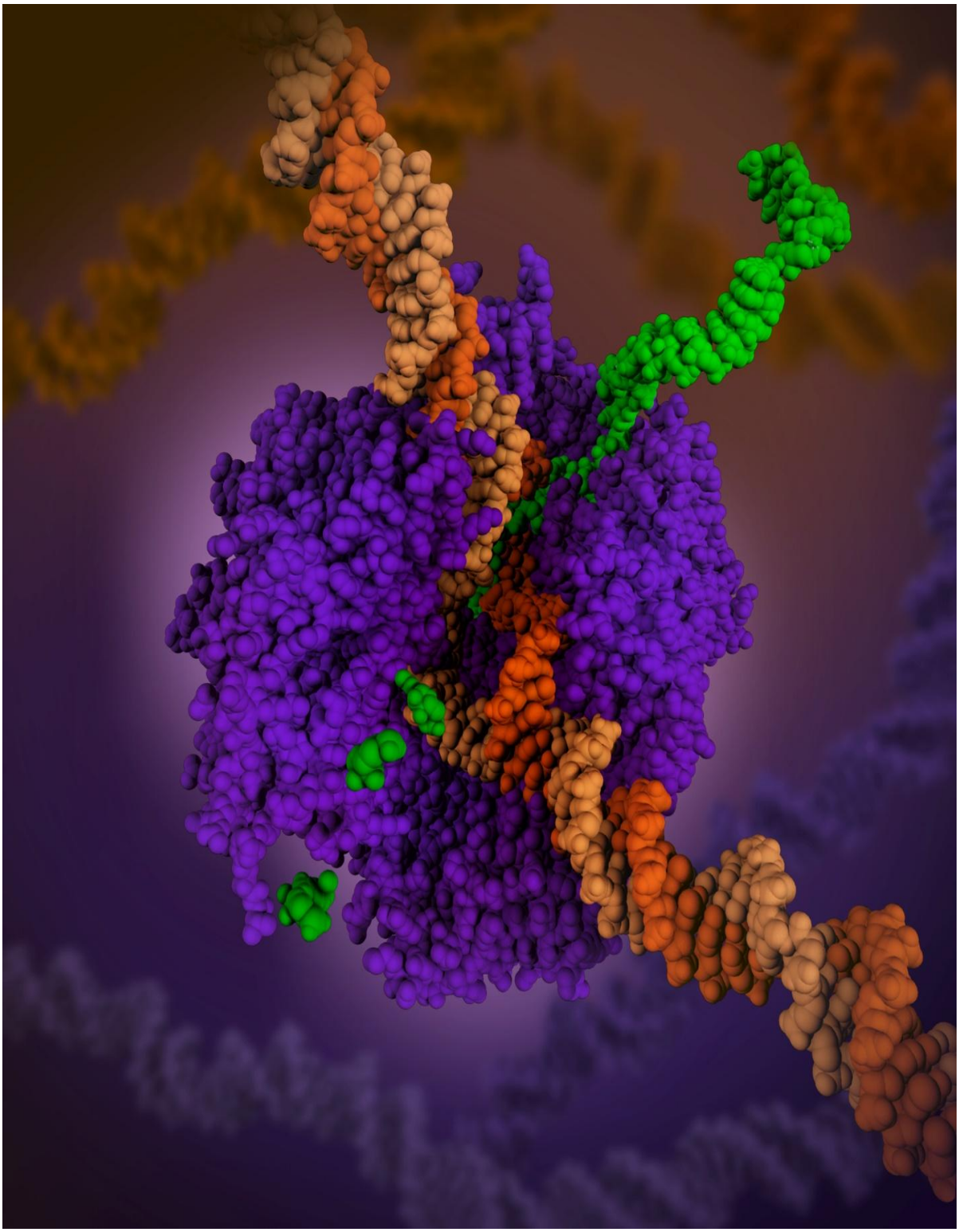

Figure 3. RNA Polymerase II during active Transcription. Credit: Maria Voigt and PDB-101 CC-BY-4.0, via Wikimedia Commons

This image of RNA polymerase II represents what is considered the heart of molecular biology. Following the discovery of the structure of the DNA molecule in 1953, great strides in molecular biology led to the discovery of how DNA synthesizes mRNA, which in turn carries the molecular information to ribosomes that produce proteins.

The transfer of information from its repository in DNA to the intracellular nano-machinery where it is interpreted and translated into living action, has become known as the **central dogma of molecular biology.** In other words, it represents a widely accepted tenet or code expressive of the authoritative opinion of molecular biologists. The transcriptive action performed by the homeodomain in the homeotic genetic system is on par with the information transfer process expressed by central dogma.

This image shows RNA polymerase II (purple), in molecular detail, during transcription. The double-stranded DNA is held in the jaws of the RNA polymerase in which the two strands, the bright orange and yellow orange, have been separated, or unzipped. The sense strand, (bright orange) is actively being transcribed. It is being copied onto a single strand of RNA (green).

Homeobox sequences all have a distinctive structure and configuration. They all contain a sequence of approximately 180 nucleotides forming 60 amino acids, known as the homeobox sequence. The homeobox sequence contains the Hox genes that bind to specific segments of the DNA molecule while it is functioning as a **transcription** molecule. Transcription molecules initiate transcription of genetic information to RNA molecules that function as messengers. This mRNA carries information from the cell nucleus to the ribosome, directing it to produce a specific protein or specific molecule required for growth and development of a normal embryo. Transcription is the process by which genes are turned on and off.

The "helix turn helix" (HTH) moiety performs a unique, essential, step in the transcription process of Hox genes.

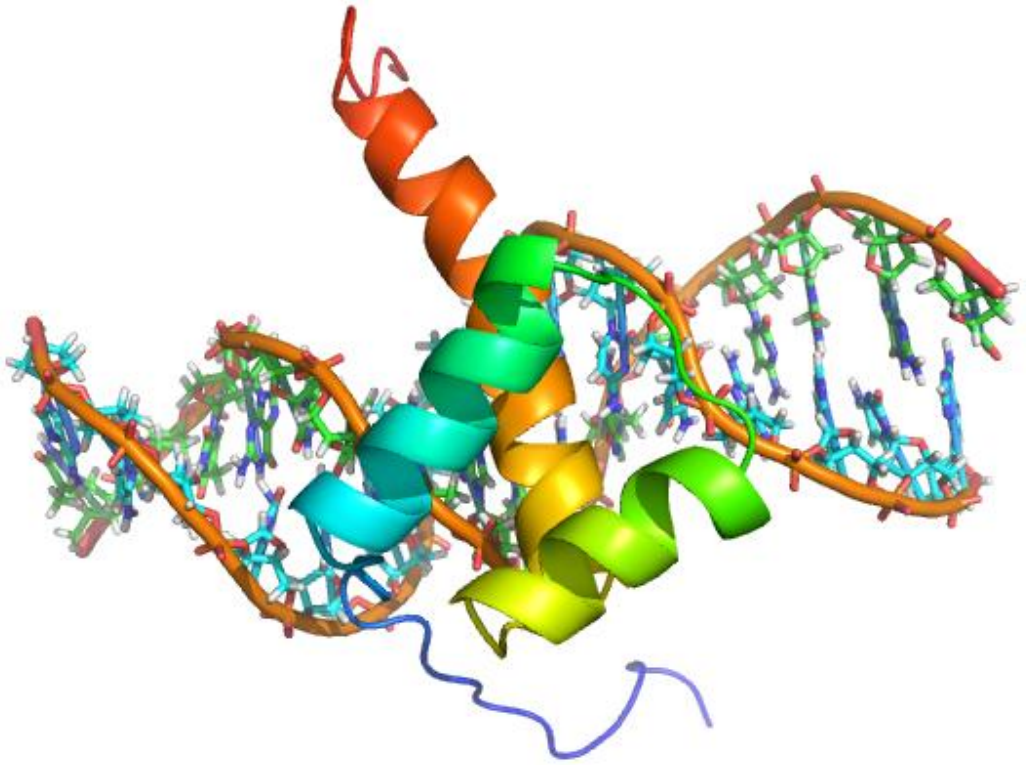

Figure 4. The Helix turn Helix Molecule, the Homeodomain, is a Transcription Molecule. Credit: Takuma-sa - Own work, CC0

A unique feature of each homeodomain sequence is a region that contains two or three alpha helices forming a precise molecular configuration enabling it to attach to specific regions of the DNA molecule. This configuration is widely recognized as the HTH in which two of the three alpha helices are turned abruptly on one another with an interconnecting amino acid chain. In the molecular illustration above, the three alpha helixes are differentiated by different colors and sizes. The largest red ribbon motif represents alpha helix number three, the contact helix; number two is represented by the shortest spiral ribbon colored yellowish green; and number one is represented by the greenish blue intermediate size alpha helix that is antiparallel to number two and perpendicular to number three. The three alpha helices are tightly packed together by hydrophobic interactions, forming a homeodomain. The C-terminal of the

contacting alpha helix makes direct contact with the major groove of the DNA double helical molecule, specifically with asparagine, arginine, and serine, and the N-terminal arm contacts the minor groove, completing the “key in lock” molecular interaction. In this manner the homeotic system turns a gene on or off in the correct order and at the correct time, resulting in the transcription of genetic information essential to the growing embryo or living organism.

The acquisition, storage, distribution, and dissemination of accurate information is absolutely essential in all living organisms.

Spatial Collinearity

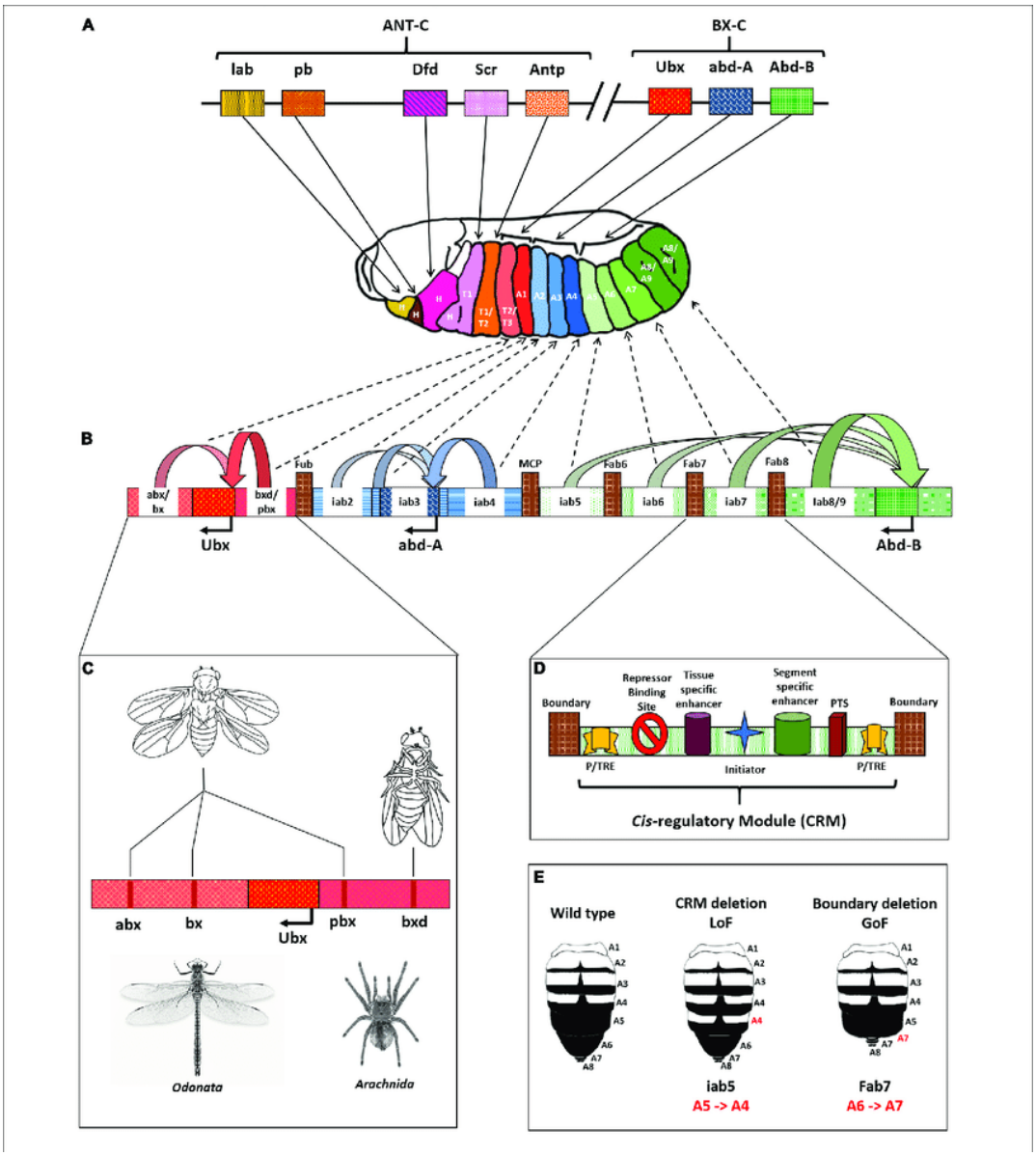

Figure 5. Spatial collinearity illustrated Credit: Hajirnis, Nikhil & Mishra, Rakesh. (2021). Homeotic Genes: Clustering, Modularity, and Diversity. Frontiers in Cell and Developmental Biology. 9. 718308. 10.3389/fcell.2021.718308. CCA 4.0 International

Spatial collinearity is a unique feature of homeotic genes. Generally, non-Hox genes appear scattered throughout chromosomes with no conceptual pattern or predictable location. In contrast, Hox genes are like “islands of compatible comprehensible structure.”[2] Spatial collinearity refers to the organized location of the Hox gene clusters on a given chromosome. The location of the gene on the chromosome is essential to its normal function. Its location

represents an actual portion of the transcriptional message carried by the gene. If there is disruption or rearrangement of the chromosomal location, abnormalities frequently result that are incompatible with life. The chromosomal locational integrity of a gene, as an essential part of the transcriptional message, is a unique feature of homeotic genes.

A normal function of Hox genes is to provide regional identification of the normal locations of body structures. They provide the information needed by new cells, enabling them to undergo differentiation to produce the specific features and structures at the right time in the correct locations along the anterior-posterior axis of the developing embryo. For example, in insects, different Hox genes are primarily responsible for the head, thorax, and abdomen.

The schematic drawings above illustrate spatial collinearity. In (A), the color-coding indicates that the location and relative positions of the eight Hox genes on the chromosome of the fruit fly correspond to the region of control on a specific segment in the larvae as well as in the corresponding segment of the adult. This is known as spatial collinearity and is a unique feature of Hox genes as compared to other genes. Not only is the spatial relationship of the genes on the chromosome related to their spatial activity in the larval and adult stages during development, but the timing of their action also sequentially controls the developmental progress from the head toward the tail resulting in the Hox genes controlling the entire body plan anatomically and sequentially. This is known as morphogenesis.

In (B), the broad curved arrows indicate functioning cis-regulatory molecules that can influence dynamics of gene expression. Multiple transcription binding sites are located near the various homeotic genes that provide multiple sites for cis-regulatory modules to function.

(C) and (D) illustrate specific and extensive phenotypic alterations that may result from cis-regulatory molecular changes resulting mainly from deletion mutations. Extreme examples indicate that the deletion mutations can transform a fruit fly into a dragonfly-like or a spider-like insect.

(E) illustrates that cis-regulatory molecular gene deletions can result in the addition or elimination of entire abdominal segments.

Conservation of Hox Genes

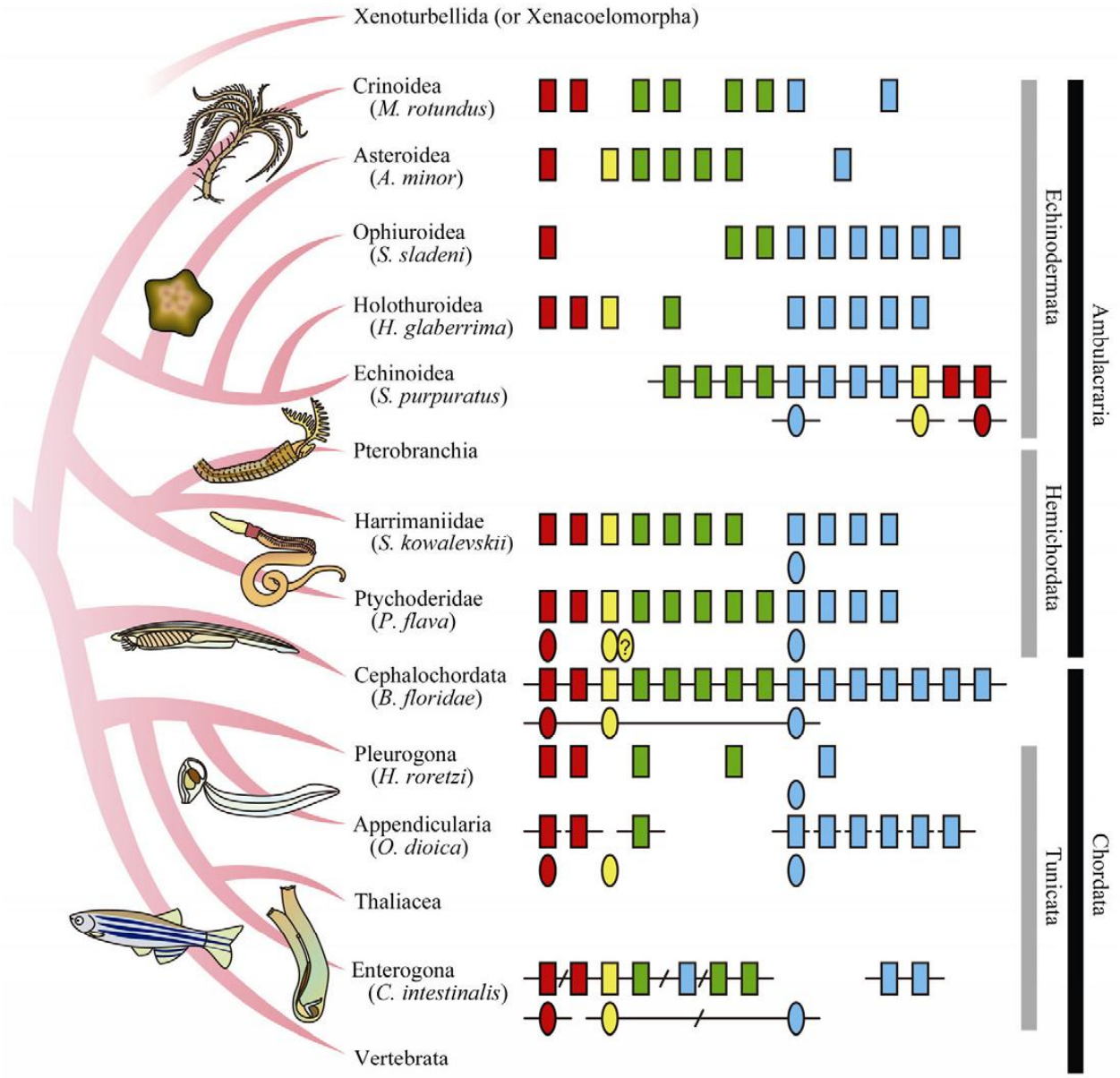

Figure 6. Hox gene conservation throughout invertebrates including Echinodermata, Hemichordata, and Chordata Credit: Tetsuro Ikuta, Evolution of Invertebrate Deuterostomes and Hox/ParaHox Genes, Genomics, Proteomics & Bioinformatics, Volume 9, Issue 3, 2011, CC-By-NC-SA 30

There is an extensive distribution of Hox genes throughout the studied invertebrates, indicated by the color-coded Hox and ParaHox genes listed with each organism. Although Hox genes are not pictured in this display for Pterobranchia and Thaliacea, further analysis indicates active homeotic genes in both species. The number of Hox and ParaHox genes associated with each of

the other listed organisms ranges from 5 to 15, with the largest number associated with Cephalochordata.

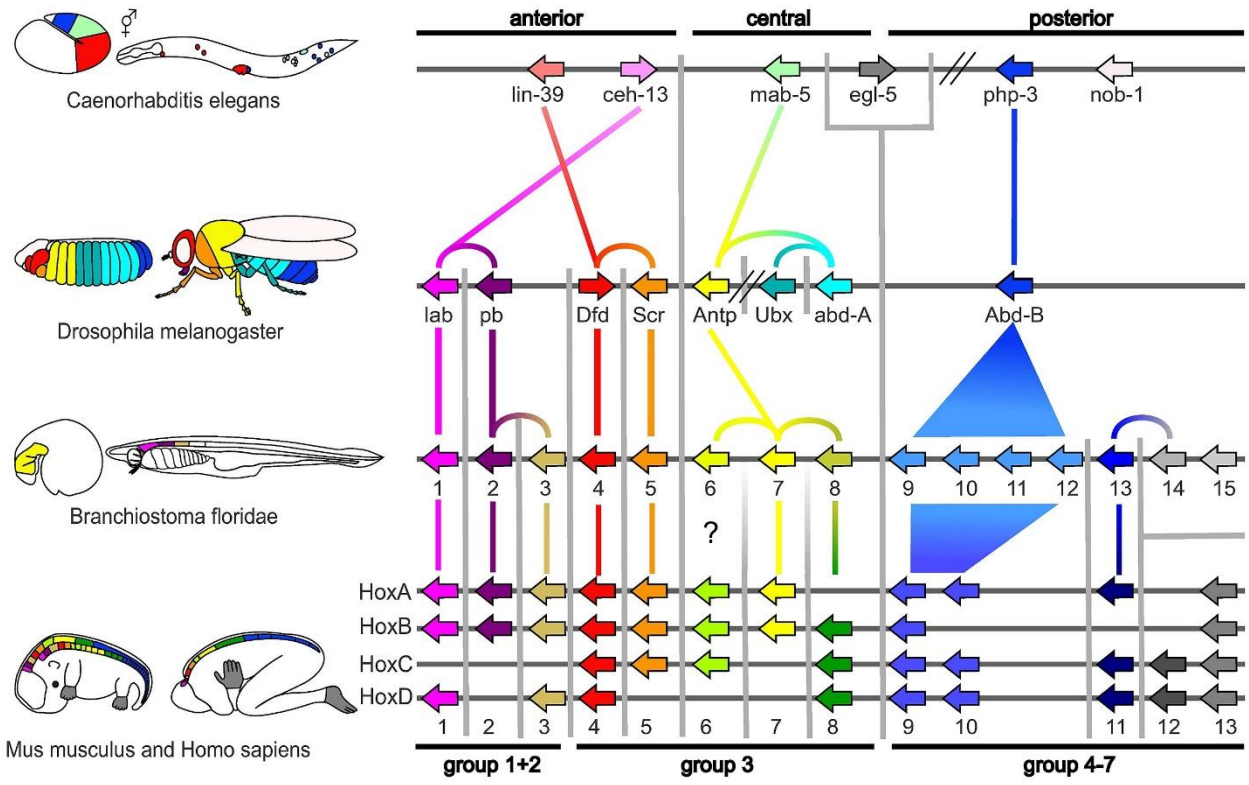

Figure 7. The conservation of Hox genes is unsurpassed throughout the entire genome. Credit: Stefanie D. Hueber, Georg F. Weiller, Michael A. Djordjevic, Tancred Frickey, CC by A 4.0 International

Figure 7 illustrates the remarkable degree to which Hox genes are conserved across multiple evolutionary levels. On the left there are samples of different organisms along the evolutionary tree of life.

First is C. elegans which is a primitive roundworm measuring approximately 1 mm in length and is a member of phylum Nematoda. It is bisexual, non-segmental, often lives in decomposing vegetative soil, and has been extensively analyzed scientifically. It has been described as "about as primitive an organism that exists which nonetheless shares many of the essential biological characteristics that are central problems to human biology"[3] including homeotic system gene function.

Next in the evolutionary lineup is Drosophila melanogaster, commonly known as the fruit fly. The fruit fly is an outstanding model for scientific investigation, particularly homeotic genetic

studies. It has four chromosomes containing eight Hox genes all located in one chromosome, a short lifecycle, striking genetically-controlled eye colors, a rapid life cycle with large numbers of offspring, and can be economically maintained in a laboratory. It is a most useful model for studying genetically transmitted human diseases because approximately 75% of homeotic genes that induce human diseases are shared by fruit flies.

The third organism is the Florida lancelet, a representative of the invertebrate subphylum Cephalochordata. Cephalochordata display the same basic body plan as vertebrates in which structural integrity is maintained by a notochord that extends the entire length of their body occupying the anatomical location of vertebral bodies which subsequently developed in vertebrates. They are histologically and anatomically much simpler than vertebrates. They have 14 Hox genes with no duplications which are considered a full complement.

The fourth evolutionary stage is represented by two mammalian vertebrates, the Mus musculus (common house mouse) and Homo sapiens, both of which share four identical clusters of Hox genes. They are located on four separate chromosomes designated Hox A, Hox B, Hox C, and Hox D. The vertical red and green lines indicate experimentally documented functional equivalents between genes in the different clusters on the different chromosomes. This provides significant redundancy in the homeotic genetic system, potentially providing significant conservation stability. Once again this characterizes the remarkable degree of conservation of Hox genes throughout the entire genome.

The homeobox genetic system is highly conserved throughout the entire genome.

The homeobox gene sequences are highly conserved throughout the entire genome including plants, animals, fungi, and in many single cell eukaryotes[4] indicating their widespread activity in four of the five kingdoms of living organisms. The term conserved refers to both their widespread distribution throughout all living organisms and their history of having been accurately copied from generation to generation since near the beginning if not at the beginning of life. They remain essentially unchanged in chemical composition and function since the earliest forms of life, more than 500 million years ago. The level of conservation is unique and unsurpassed by any other group of genes.

Five kingdom classification system of all living creatures

In 1969[5] Robert Whittaker proposed a five-kingdom system for the classification of all living organisms that has become generally accepted throughout the scientific community and is used in this paper.

To more fully grasp the comprehensive scope of the of living organisms in which the homeotic system exercises master control we will briefly address reasons why we have been unable to identify any homeotic activity within the Monera and then review the numerous single celled eukaryotes in the Protista kingdom in which homeotic activity occurs, followed by the kingdoms of fungi, plants and animals .

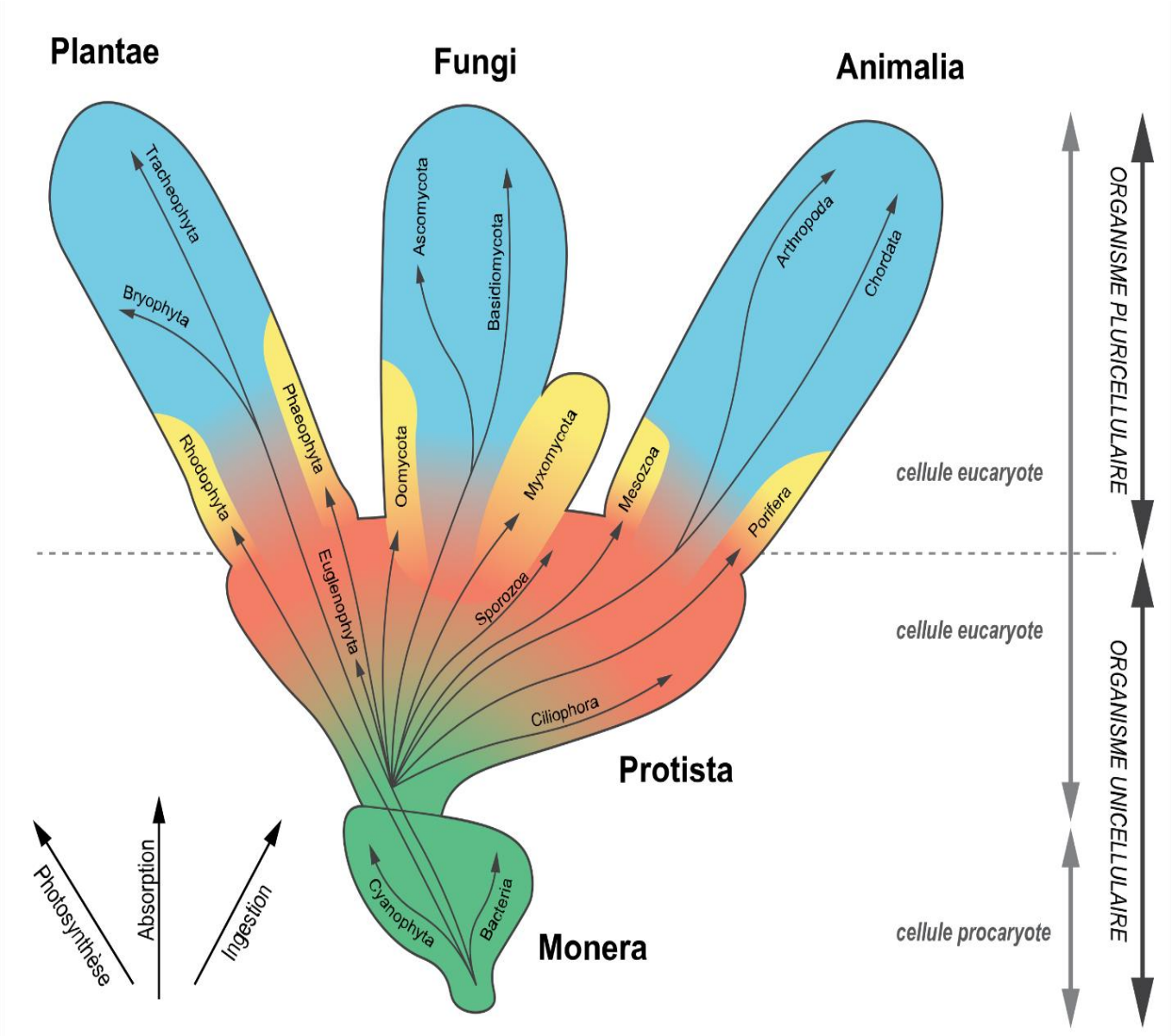

Figure 8. Robert Whittaker's Five kingdom classification system of all living creatures *Credit: PBrieux, CC BY-SA 4.0, via Wikimedia Commons*

The Monera kingdom

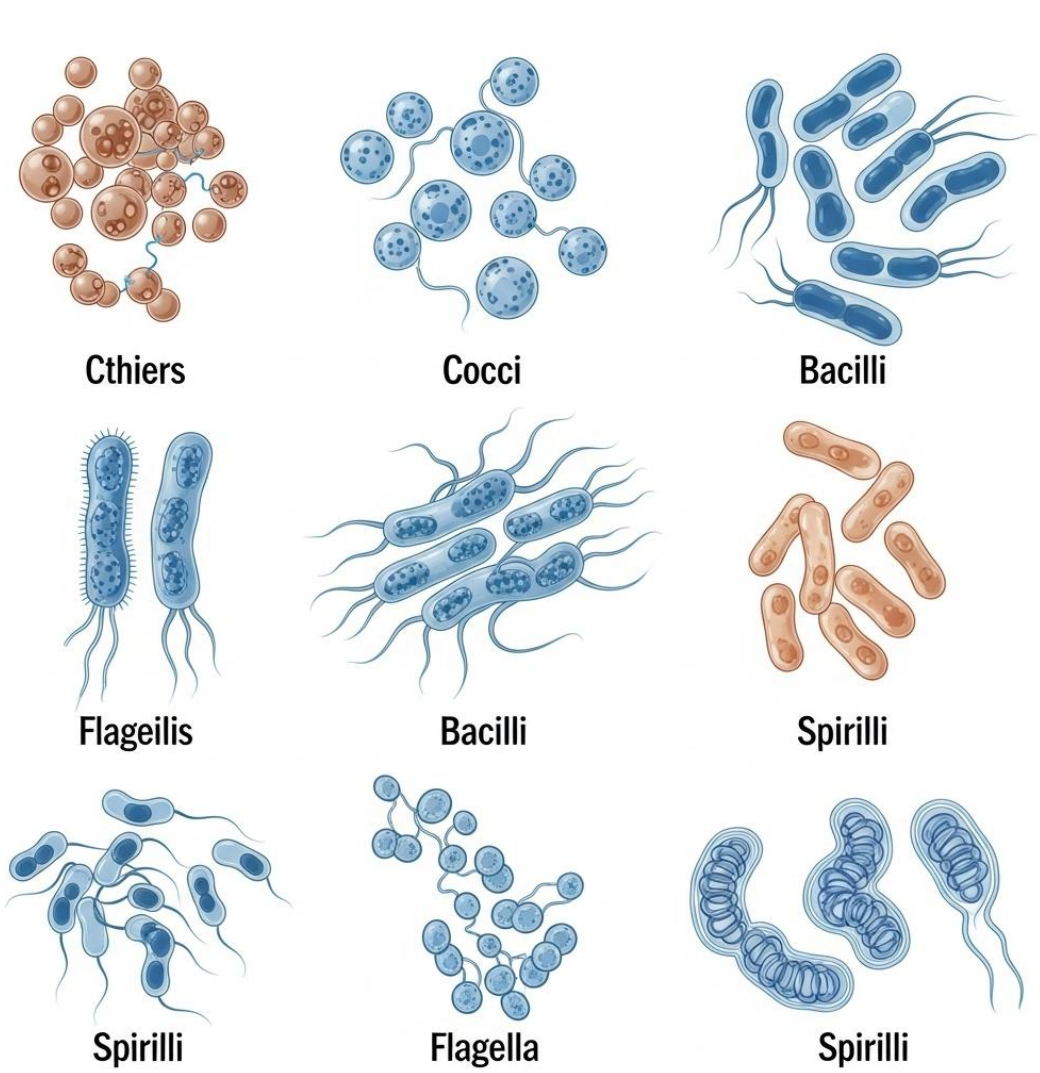

Figure 9. The Monera kingdom. Credit: Easy Peasy AI CC by A 4.0 International

The Monera kingdom is entirely composed of prokaryotic cells which are non-nucleated cells in which the genetic material is not enclosed within a nuclear membrane but exists within the cytoplasm frequently as strands or clusters. The complete absence of the distinctive characteristics of homeodomains may render it impossible to identify or confirm homeotic genetic function.

Retrograde evolution of bacteria may also be responsible for obscuring homeotic genetic function throughout the primitive Monera kingdom. Their homeotic genetic system may have been decommissioned.

How did parasitic bacteria evolve prior to the existence of their host organisms? There are many examples throughout evolutionary history in which massive groups of organisms have undergone retrograde functional capacity resulting in extinction. The food source of the whole fungal kingdom is dependent primarily on organic sources. Retrograde evolution with loss of chloroplast function could explain the parasitic dilemma of bacteria. Many bacteria are responsible for causing serious infectious diseases in humans and animals that have changed the course of human history and at the same time are extremely beneficial in other situations.

A recently discovered potentially highly beneficial function of marine bacteria is the large number of plastic eating bacteria thriving under extreme conditions of darkness and cold in the deepest regions of the ocean such as the Mariana Trench. They can synthesize enzymes capable of breaking down and actually consuming polyethylene materials in plastics as their food source.

They occur in multiple shapes and sizes. Spherical shaped bacteria called cocci are common. Examples of diseases they cause include pneumococcal pneumonia, strep-throat, and multidrug-resistant organism (MDRO) infections. Spiral shaped organisms known as spirochetes are responsible for causing syphilis and a rod-shaped bacterium known as Mycobacterium tuberculosis causes the common form of human tuberculosis as well as tuberculosis in many animals. Mycobacterium leprae, a closely related bacterium, causes leprosy in humans. Escherichia coli is a widespread bacterium with large numbers representing the normal flora of the colon. Another taxon in this kingdom is the RTO bacterium, a single celled prokaryote capable of living under extreme temperature conditions such as hot vents in the ocean floor. Another unusual member of this kingdom is cyanobacteria which contain chloroplasts enabling them to extract carbon dioxide from the atmosphere and produce oxygen by photosynthesis.

While Monera are very primitive organisms, it is important to recognize that they make up the majority of the cells in our bodies. The estimated number of bacteria representing the normal flora in an average human, as well as the estimated number of human cells in the average human body have been revised upward significantly, now calculated at 38 trillion and 30 trillion respectively.[6]

The Protista kingdom

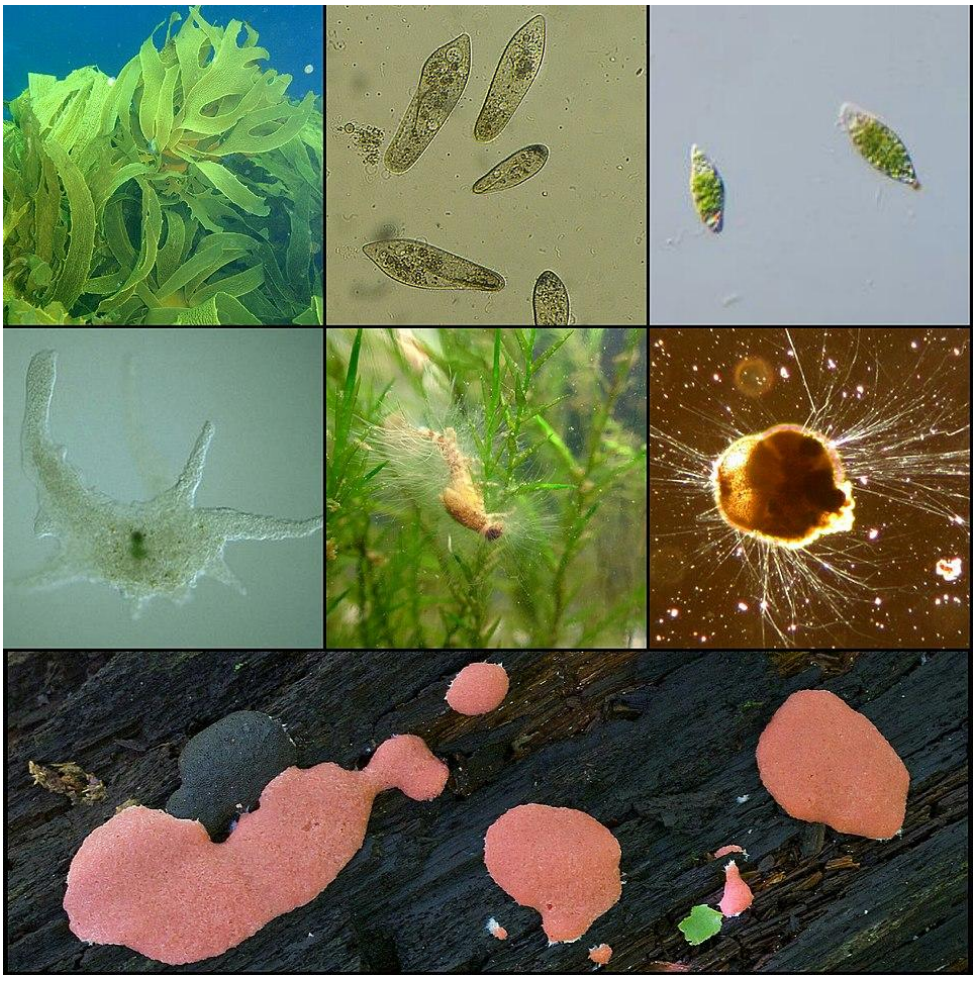

Figure 10. The Protista kingdom Credit: 148LENIN, CC BY-SA 4.0 via Wikimedia Commons

The Protista kingdom includes a wide variety of mainly single-celled organisms with characteristics of both animals and plants. All are eukaryotic cells, ranging from photosynthetic algae which provide their energy, amoebae which can engulf their food by phagocytosis, heterotrophic organisms that consume organic compounds as food, slime molds, kelp, and protozoans including Trypanosomes that are parasitic in many mammals including humans. They cause Trypanosomiasis commonly known as African sleeping sickness that is exclusively spread by a biting insect vector, the tsetse fly, distributed across a wide band of equatorial Africa. Volvox forms colonies representing multicellular organisms. Many members of this group are ciliated such as Paramecium or have flagella capable of individual locomotion. It is of note that the amoeba, is mentioned in *The Urantia Book* as representing "survival of the first early steps in life differentiation together with failure of subsequent development." [7]

The Fungi kingdom

Figure 11. 19 different edible mushrooms, Credit: CCO

The kingdom of fungi includes a large group of multicellular organisms that do not possess chloroplasts and therefore incapable of photosynthesizing their food. Fungi consist entirely of eukaryotic cells. Their cell walls consist of chitin. Fungi are heterotrophs, feeding primarily on food sources such as plant debris. They produce digestive enzymes that can be absorbed providing nutrition for growth and reproduction. Fungi display a large variety of colors, shapes, and sizes, some of which are food sources such as portobello mushrooms and truffles. Unicellular forms such as yeast are widely distributed. Fungi also cause extensive diseases in humans and animals and are widely distributed plant pathogens. This image includes 19 edible mushrooms recognized in French cuisine.

The Plantae kingdom

Figure 12. Composite image to illustrate the diversity of plants. Credit: Ryan Kitko, Creative Commons Attribution-Share Alike 4.0 International, 3.0 Unported, 2.5 Generic, 2.0 Generic and 1.0 Generic license.

The plant kingdom is comprised of photosynthetic eukaryotic life forms ranging in size from unicellular algae to the mighty Sequoia trees in the redwood forests of California. The most prevalent group in this kingdom consists of angiosperms including flowering plants and seed

producers. Many of the resulting seeds are encased in protective coverings such as the great variety of delicious fruits. The gymnosperms include plants that produce naked seeds such as conifers. The cell walls of plants are composed of cellulose which provide structural support in lumber, widely used commercially as building material.

Photosynthesis provides the oxygen essential to all animal life and maintains a healthy level of carbon dioxide in the atmosphere. Photosynthesis is essential for life on this planet. Its ability to convert electromagnetic radiation energy from the sun into chemical energy in the form of sugar and starch is an amazing feat accomplished by an unimaginable host of chloroplasts. Human life is dependent on plants for food, fuel, and medicines.

The Animalia kingdom

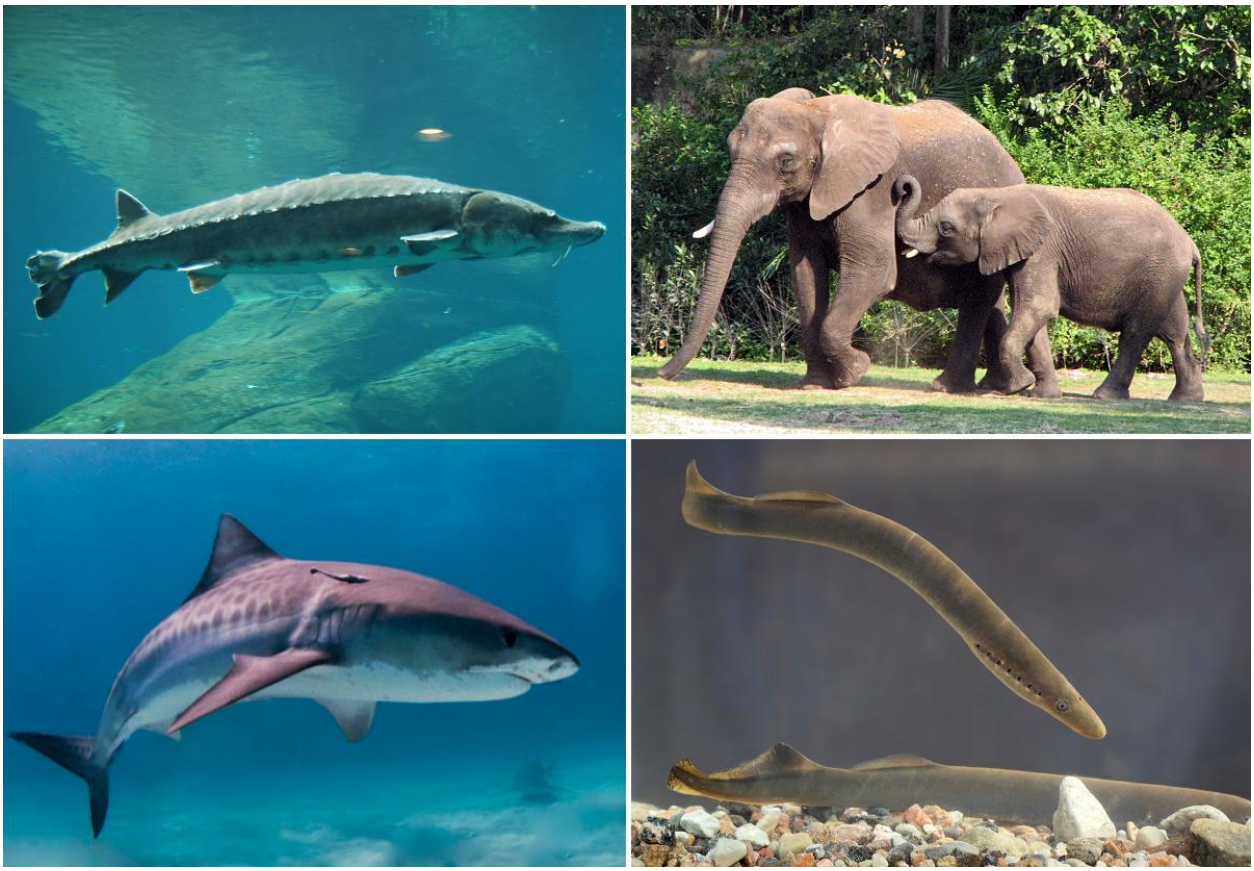

Figure 13. Four examples of vertebrates : *Acipenser oxyrinchus*, African Elephants, Tiger Shark and a River Lamprey. Credit: Wikimedia, Creative Commons Attribution-Share Alike 4.0 International

The members of the animal kingdom are essentially all mobile organisms consisting exclusively of eukaryotic cells (excepting red blood cells which are a special case of eukaryotes as they lose their nuclei and organelles upon maturity). Animal cell walls are flexible and pliable accommodating mobility. They contain many specialized tissues such as muscle cells, nerve

cells, heart muscle cells, skin cells, fat cells, and bone cells to name a few. They are genetically diploid resulting from the union of haploid gametes produced by sexual reproduction. The sexual reproductive cells such as the egg and sperm are genetically haploid, that is they have half the normal number of chromosomes in somatic cells, having undergone a reduction division known as meiosis. Recombination of the haploid genetic input from each parent provides offspring that are genetically different from each parent as well as significant diversity among siblings. This contrasts with asexual reproduction in which the offspring are genetically identical. A far greater potential for complexity results from a lengthy embryonic development period controlled by Hox genes. Hox genes occur exclusively in animals. The vertebrates possess internal skeletal support.

There is extensive conservation of the homeotic genetic system throughout all living organisms.

This review of the five-kingdom system of classification of living organisms indicates the extensive control exercised by the homeotic genes.

Nearly every animal and plant composed of eukaryotic cells that has been studied has homeobox sequences in its DNA, indicating that the homeotic genetic system functions very early if not at the very beginning of planetary life. The presence of homeotic gene sequences in animals as different as jellyfish, insects, and mammals suggests that these genes have a crucial function in nearly every living organism, having descended from an ancient common ancestor.

The similarities among Hox genes, especially in the shared homeobox sequence, strongly supports the generally held idea that they all arose from a single ancestral genetic source that was then duplicated multiple times. After each duplication event, the genes gradually changed, taking on slightly different functions. This process is known as "duplication and divergence"[8] enabling genes to add new features and functions.

Duplication and divergence initiates evolution of new genes and new metabolic pathways.

Duplication and divergence cause:

Multiple copies of the same genes – paralogs

Hox gene redundancy

New and different genetic functional capacity

Neo-functionalization initiation

"Over 35 years ago, Susumu Ohno stated that gene duplication was the single most important factor in evolution. He reiterated this point a few years later in proposing that without duplicated genes the creation of metazoans, vertebrates, and mammals from unicellular organisms would have been impossible. Such big leaps in evolution, he argued, required the creation of new gene loci with previously nonexistent functions."[9]

The homeotic genetic system, including the remarkable duplications that have occurred during past genetic history, particularly in vertebrates and mammals, provided precisely the "new gene loci" that Susumu Ohno predicted, approximately 50 years ago, was required to enable the dramatic evolution that we now observe in retrospect.

Duplication represents a de novo evolutionary event

Although there are multiple metabolic pathways whereby duplication of genetic material can occur, most appear to be entirely spontaneous and frequently deleterious to the individual. From our vantage point, the genetic duplications of entire or nearly entire Hox gene clusters such as the two relatively complete duplications known to have occurred in vertebrates and the resulting four associated Hox gene clusters, and the prominent degree of their conservation throughout the entire genome and across evolutionary history, all suggest that Hox gene duplications represent de novo evolutionary events.

It is difficult to predict or to document the evolutionary progress resulting from divergence that accompanies duplications. The redundancy resulting from Hox gene duplication makes possible new and different functions of the multiple gene copies a process known as neo-functionalization.

Additional duplication events happened in some branches of the animal family tree. In insects, for example, a gene near the right end of the cluster was duplicated. In certain types of fish, up to eight duplications have occurred.

Hox genes share not only DNA sequences, but also share functions. Mouse Hox genes can substitute for their homologues in flies. And when activated in other segments, the mouse genes can cause homeotic transformations in flies.

Like other genes, Hox genes are more similar in closely related species and less similar in more distantly related species. By comparing sequence similarity, scientists can determine when in evolutionary history certain duplication events happened, and where some Hox genes were lost along the way.

Hox genes code for proteins that attach to molecular switches on DNA, turning other genes on and off. The DNA-binding piece of a Hox protein that is encoded by the homeobox. The homeodomains in different Hox proteins are similar but not identical—they bind to different

DNA sequences. So different Hox proteins regulate different sets of genes, and combinations of Hox proteins working together regulate still other sets of genes.

Hox gene knockout of long-range genetic effects

As regulators of other genes, Hox proteins are very powerful. A single Hox protein can regulate the activity of many genes. And sets of genes work together to carry out "programs" during embryonic development—programs for building a leg or an antenna, for example—much like computer programs carry out specific tasks.

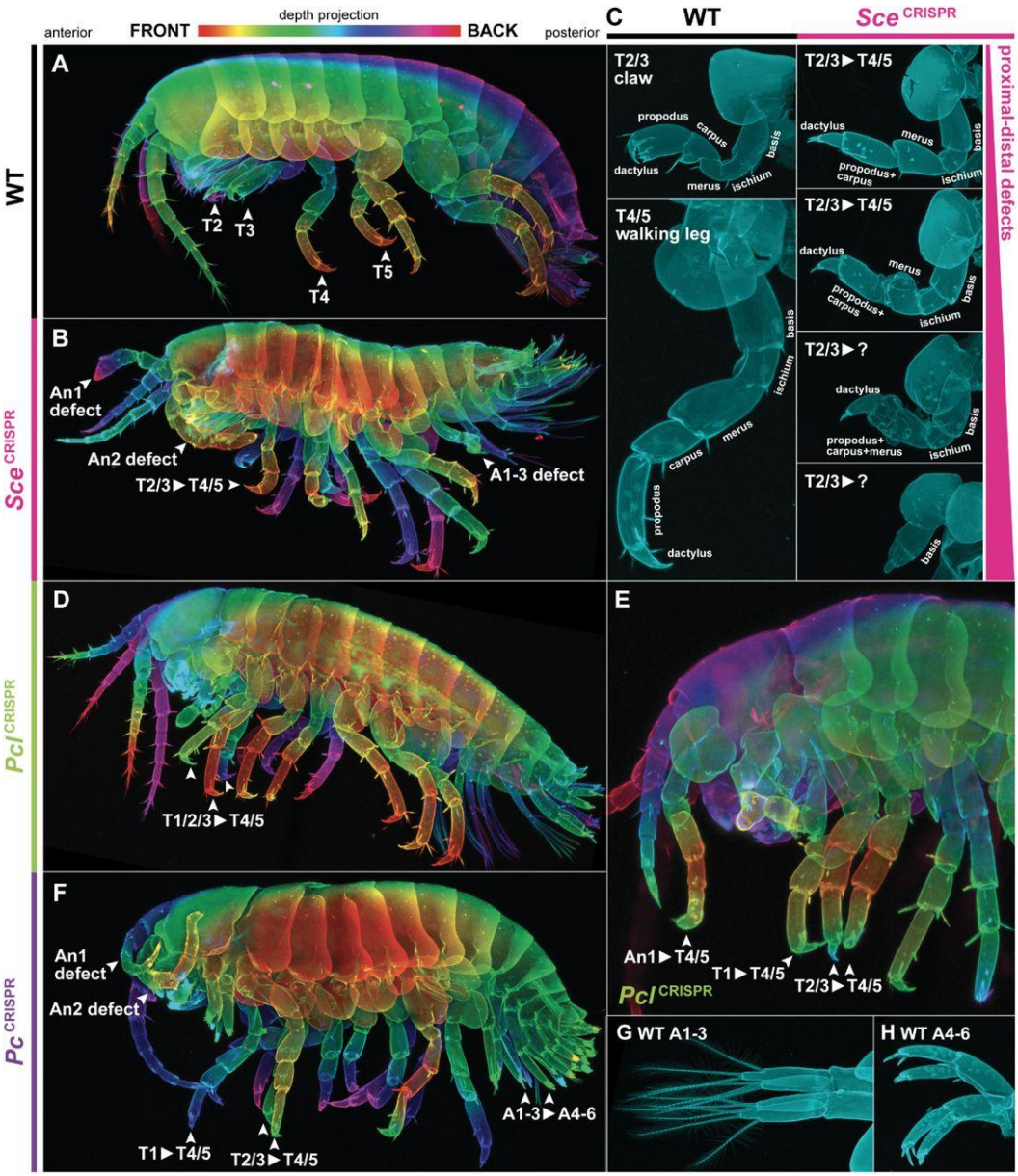

Figure 14. Hox gene knockout of long-range genetic effects in shrimp. Credit: Dennis A Sun, Yuri Takahashi, Rebecca J Chang, Nipam H Patel CC-BY-NC-ND 4.0 International license.

These images were obtained during various stages of a research project on a non-insect arthropod, a crustacean, Parhyale hawaiensis, a shrimp species in which knockouts were performed on three Hox genes, Ultrabithorax (Ubx), abdominal-A (abd-A), and abdominal-B (abd-B) which control three consecutive segments in the anterior abdomen. A series of gene knockouts were performed with each individual gene as well as combinations of consecutive genes. The study was focused on their effects on distant segments. These genetic influences contrast with the "all or nothing" phenotypic effects caused by of the Antennapedia mutant and Bithoracic mutant observed on the fruit fly head and thorax respectively.

In the right upper area on Figure 14, a series of images display progressive defects in the claws and legs at T2-3 and T4-5 thoracic segments and there are additional genetic defects involving the antennae arising from the anterior head segment caused by the knockouts of the Hox genes that primarily control the anterior abdominal segments.

Geneticists are aware of the phenomenon known as "posterior dominance" in which Hox genes primarily controlling posterior segments, display a mild suppression effect on Hox genes controlling anterior segments. It is illustrated in this image by the vertically oriented pink graft in the right upper corner that becomes progressively thicker as one moves from anterior to posterior location in the organism.

Hox genes control somatic tissues in vertebrates.

The similarities between Hox gene functionality in vertebrates compared with what we have observed in fruit flies and other more primitive forms of life, are most remarkable. Although the segments, such as head, thorax, and abdomen, that dominate the regional organization that make up the basic body plans of insects, are absent in vertebrates, there are clustered somatic tissues located along the vertebral spinal column bilaterally corresponding to each vertebral level, representing a subtle segmental body plan.

A research project performed by M. R. Capecchi and colleagues at the University of Utah on mouse forelegs clearly established the possibility of paralogs replacing blocked genes. Paralogs are nearly identical genes that resulted from previous Hox gene duplications providing redundancy of genetic expression. They found that where multiple paralog genes occurred, to produce a mutation anomaly of a given gene, all the paralog genes needed to be blocked simultaneously for the most severe anomaly to occur.[10]

Experiments like this and others establish functional similarities between Hox genes in mice and fruit flies. The control by homeotic genes of the segmentation observed in arthropods is much less apparent in vertebrates. In arthropods they direct the growth of eyes, mouthparts, and

antennae on head segments, legs and wings on thoracic segments, and repetition of multiple abdominal segments. Hox genes in vertebrates direct vertebral bodies in multiple areas to develop distinctively different anatomical features such as highly mobile vertebrae in the upper neck, ribs in the thoracic area, larger bulkier vertebral bodies in the weight-bearing lumbar region, fusion of vertebrae throughout the pelvic area and highly mobile vertebrae throughout the tail. The limited segmentation throughout the vertebral spine is also matched with a mild degree of segmentation in the associated soft tissue structures in the form of somites during embryonic development. These widespread features of the homeotic genetic system exemplify the remarkable conservation of Hox genes.

"Therefore, *Drosophila* NK (and related) genes have remained a tight gene cluster since the origin of these genes >500 million years (Myr) ago, which implies the existence of a selective reason for the gene clustering in *Drosophila*."[11]

M. R. Capecchi, further states that, "It is apparent that the order of hox genes on the chromosomes of these two species has not altered significantly since the lineages of insects and vertebrates diverged approximately 530 Myr ago."[12]

These findings provide reliable empirical evidence for the early appearance of the homeotic genetic system functioning during the earliest stages of evolution followed by highly conserved continuous control throughout evolutionary history.

Punctuated equilibrium

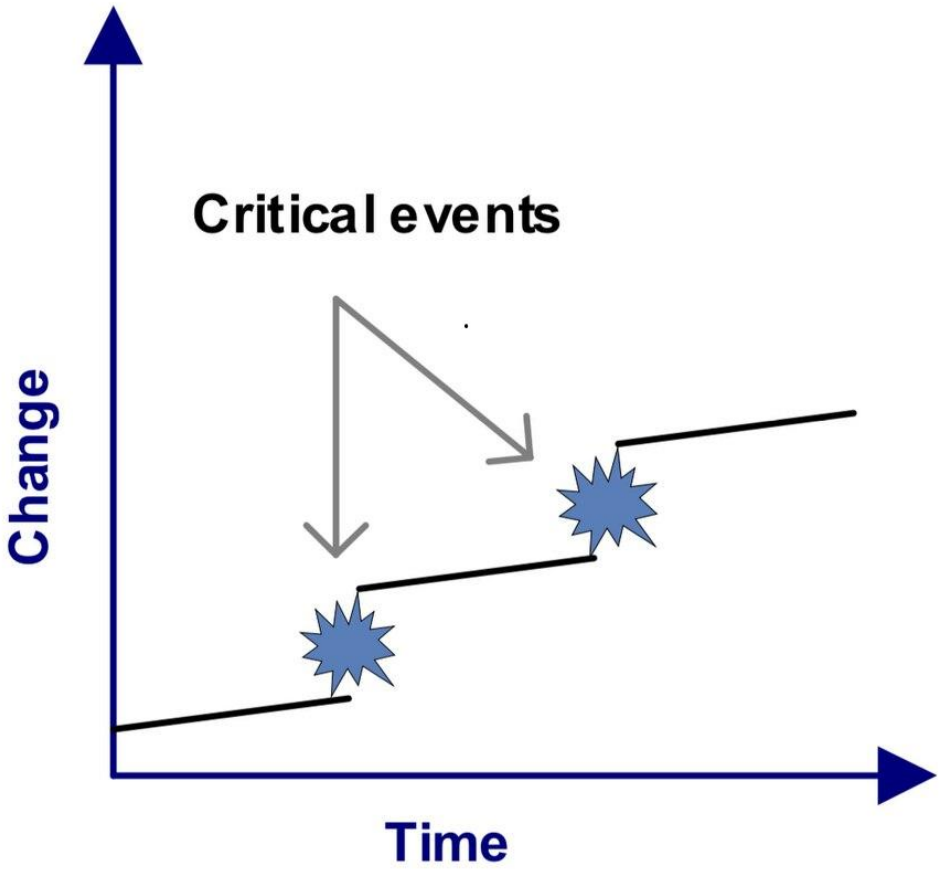

Figure 15. Representation of Punctuated Equilibrium, illustrating sudden changes in the rate of evolution. Credit: Isaiisas, via Wikimedia, Creative Commons Attribution-Share Alike 4.0 International

The unique characteristics of Hox genes capable of bringing about extensive reorganizations of body plans rapidly because of their control of large numbers of other genes, explain and support the hypothesis of **punctuated equilibrium.** It has gained significant attention and acceptance as an advancing empirical explanation of the many gaps in the fossil records.

The Urantia Book description of a crucial stage during the final step in human evolution exemplifies the theory of punctuated equilibrium in action as follows:

"A little over a million years ago the dawn-mammals . . . *suddenly* appeared. These were active little creatures, about 3 feet tall that could easily stand erect. . . .They had a primitive opposable thumb as well as a highly useful grasping great toe. From this point onward the prehuman

species successively developed the opposable thumb while they progressively lost the grasping power of the great toe."[13]

"These aggressive little animals spread over the Mesopotamian peninsula for more than 1000 years, constantly improving in physical type and general intelligence. This new tribe had taken origin from the highest type of lemur ancestor. The next epoch-making development occurred-the sudden differentiation of the ancestors of the next vital step in the evolution of human beings." [14]

We will now examine a series of *sudden* major evolutionary developments recorded in *The Urantia Book* in which Hox genes exercised control.

The age of the trilobites and the Cambrian explosion occurred suddenly in geological time.

"*Suddenly* and without gradation ancestry the first multicellular animals make their appearance. The trilobites have evolved and for ages they dominate the seas. From the standpoint of marine life this is the trilobite age."[15]

The appearance of trilobites in the fossil records of the Cambrian explosion 521 million years ago is one of the most remarkable success stories of our entire biological evolutionary history. Trilobites ware particularly suited to fossilization, having a calcified exoskeleton and existing primarily as an aquatic organism.

"Trilobites were among the most successful of all early animals, existing in oceans for almost 270 million years, with over 22,000 species having been described. . . . They reached a large size measuring more than 70 cm and probably weighed as much as 4.5 kg."[16]

The most reasonable terminology to characterize the biological progress that happened during the Cambrian era is an explosion and the geological evidence indicates that the homeotic genetic system was a major controlling factor.

Trilobites and the Cambrian explosion

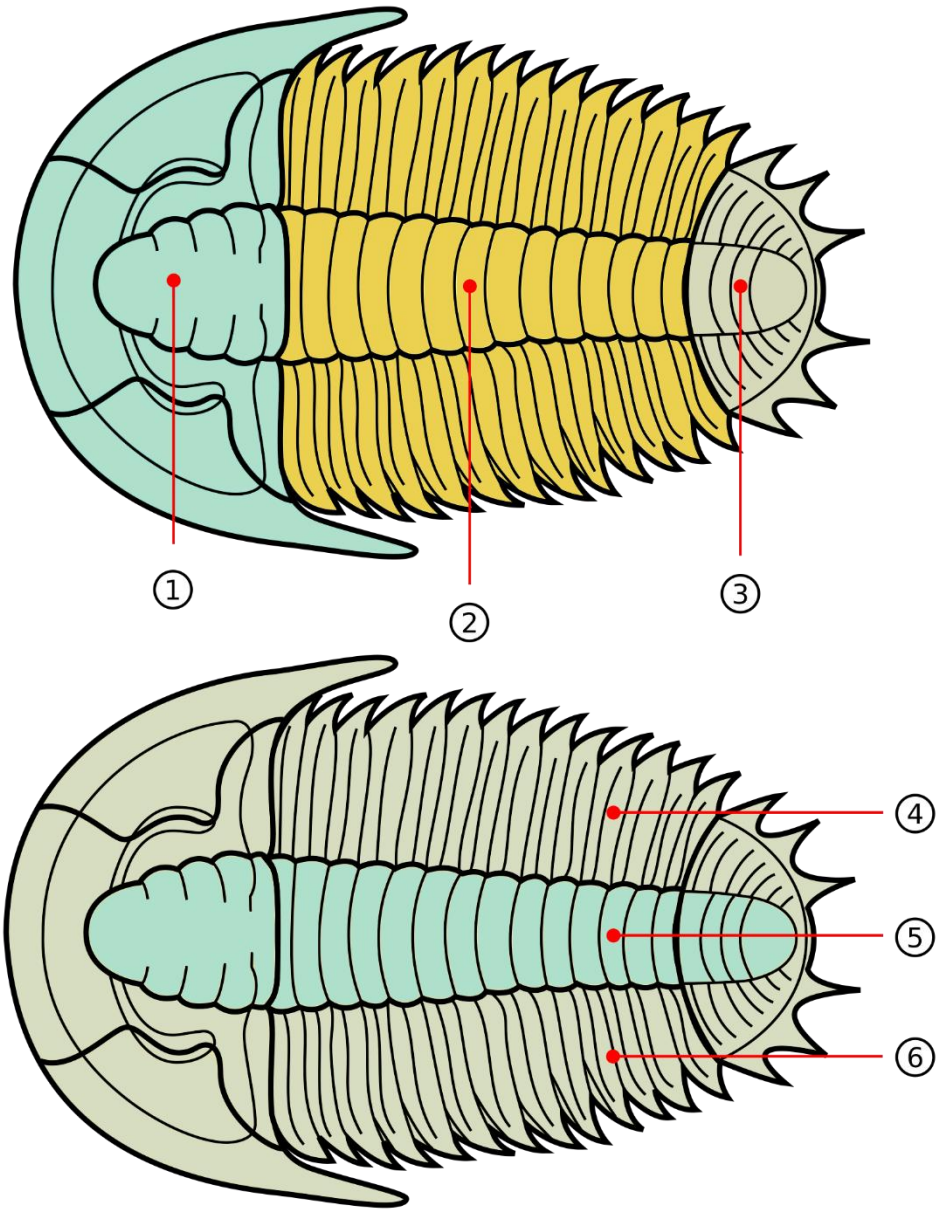

Figure 16. Trilobites. Credit: Sam Gon III, derivative by Obsidian Soul, CC0, via Wikimedia Commons

The trilobite body is divided into three major sections: 1 – cephalon; 2 – thorax; 3 – pygidium. Trilobites are so named for the three longitudinal lobes: 4 – right pleural lobe; 5 – axial lobe; 6 – left pleural lobe; the antennae and legs are not shown in these diagrams.

Hox genes are widely recognized as playing an important role in embryonic development particularly in controlling the correct location, timing, and function of each segment of various animals such as arthropods and metazoans. Paleontologists recognize the importance that Hox

genes have played in evolutionary development of many organisms. A phylogenetic analysis used to recognize homeotic evolution in trilobites reached the conclusion that homeotic evolution commonly occurred among Cambrian trilobites. The trilobite body plan contains eight body regions or segments. The cephalon contains the frontal lobe, glabellar, and occipital ring regions; the thorax contains the anterior thoracic and posterior thoracic segments, the pygidium contains the articulating ring, axial, and terminal piece regions. “Trilobites, being arthropods, probably contained eight major Hox genes that controlled their segment types.”[17]

Mollusks and cephalopods

“The larger mollusks, or cephalopods . . . grew to fifteen feet long and one foot in diameter. This species of animal appeared *suddenly* and assumed dominance of sea life.”[18]

Following the disappearance of the trilobites, the oceans were rapidly taken over by the larger mollusks and cephalopods. They consist of a large diverse group of marine animals including octopi, squid, bivalves, snails, clams, oysters, conches, sea slugs and periwinkles.

Studies of homeotic genes in mollusks “revealed an overall number of 11 Hox genes in seven out of eight molluscan class level taxa.”[19]

Homeotic gene studies performed on one of three prominent bivalve subclass members of the phylum Mollusca, Acanthochitona crinita*,* reveals extensive transcribing activity throughout the larval stage. The active transcription process is documented by the yellow fluorescence throughout major portions of the larval embryo which is displayed in orthogonal sections. This is a common method of tracing Hox gene activity, typically as it is directing the body plan, segmentation, timing, and location of gene activity along the anterior-posterior axis of the embryo.[20]

Phylum Mollusca is widely recognized as one of the most diverse organismal groups having populated the Ediacaran oceans around 550 million years ago.[21] Pin Huan et al., reported dorsal-ventral decoupling of Hox gene expression which they suggested contributed significantly to the extensive diversification observed in mollusks.[22] Once again, we observe a developmental phenomenon of amazingly rapid evolutionary progress in which the impetus was the work of an ancient highly conserved homeotic genetic system.

Mollusca and cephalopods

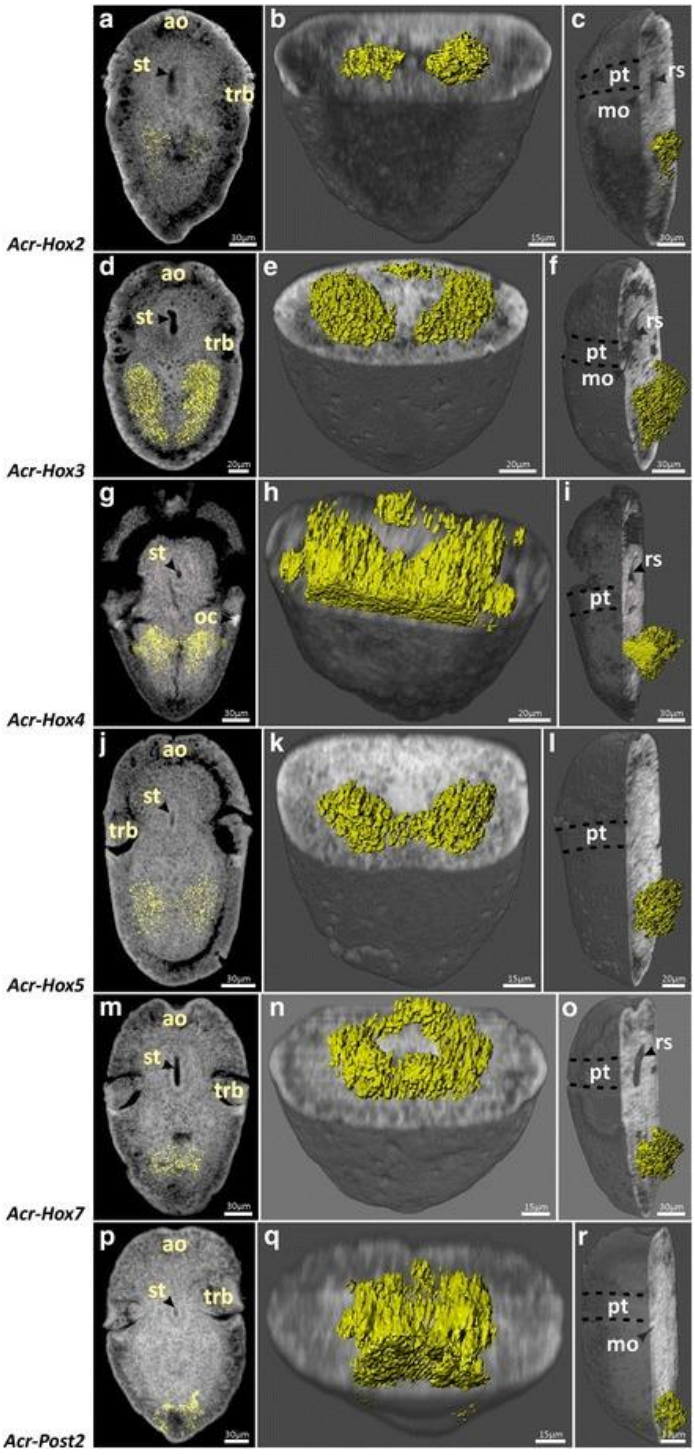

Figure 17. Mollusca and cephalopods. Credit: Fritsch et al. Creative Commons Attribution 4.0 International License

Figure 17 displays a three-dimensional image with sections through the larvae in orthogonal planes. The Hox gene transcription process is documented in extensive areas throughout the larvae by a yellow flourescence label that is mainly distributed in the sub-epidermal regions. The transverse images displayed in the left column document areas controlled by Hox2-5 and hox7. Various anatomical structures of the larvae are labeled. These findings indicate a high level of homeotic genetic activity associated with the rapid proliferation of Mollusca during the late Cambrian explosion.

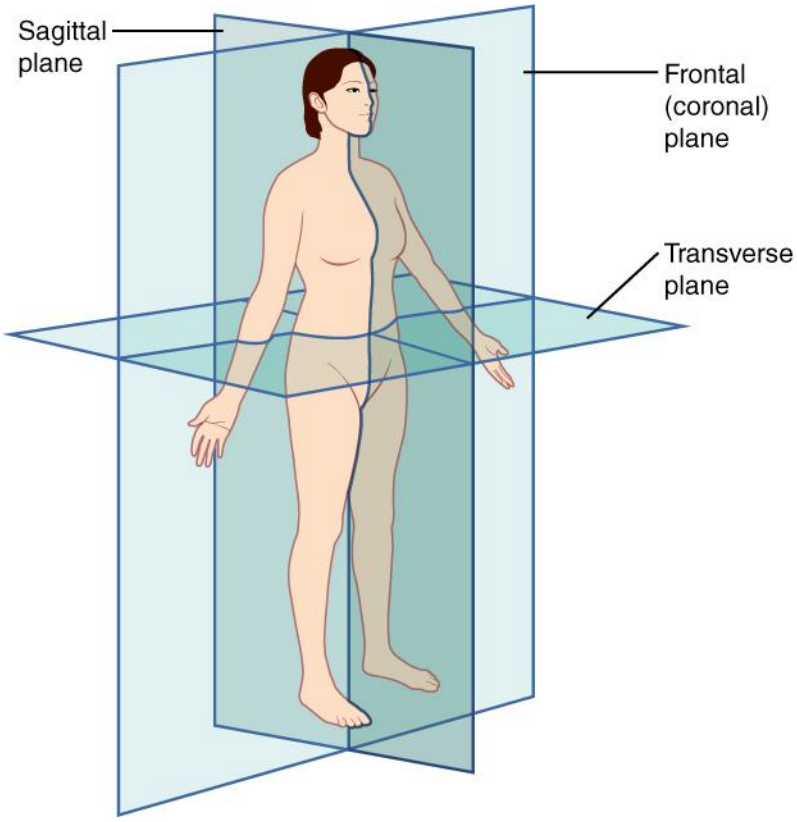

Figure 18. Illustration of orthogonal planes. Credit: OpenStax College. Anatomy & Physiology, Connexions Website. http://cnx.org/content/col11496/1.6/, Jun 19, 2013.

Air-breathers

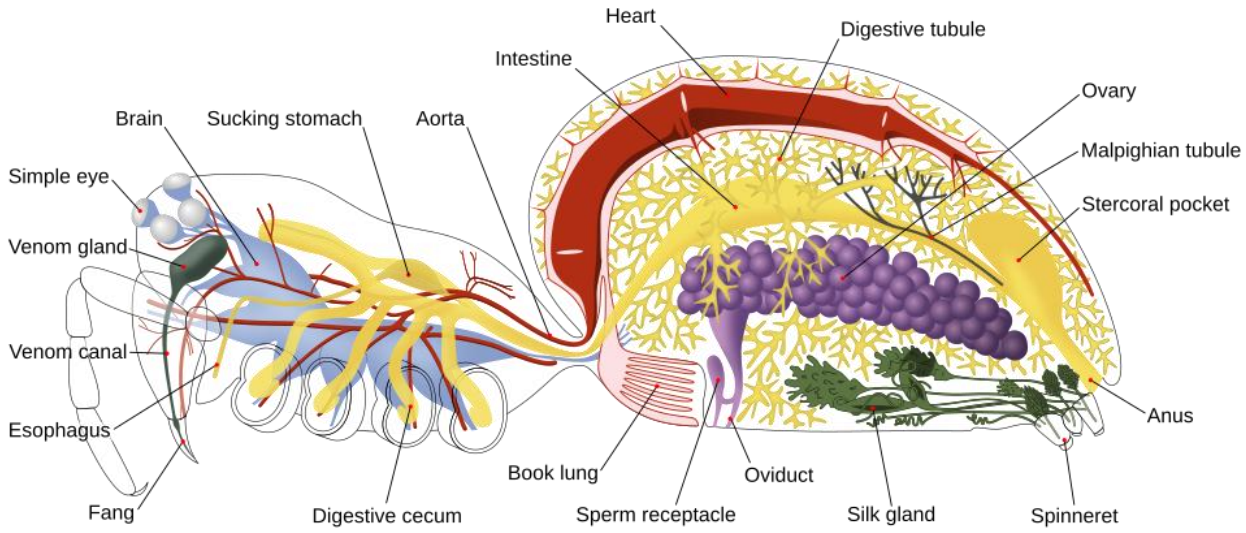

Figure 19. Anatomical diagram of a scorpion illustrating its book lung along with remarkable detailed internal anatomy, has resulted from the good fortune of having discovered this well-preserved fossil in Scotland. Credit: The Spider Book (1912, 1920) by John Henry Comstock, Creative Commons Attribution 3.0 Unported

"Toward the close of the final Silurian submergence there is a great increase in the echinoderms – the stone lilies – as is evidenced by the crinoid limestone deposits. Soon thereafter, and suddenly, the true scorpions – actual air breathers – make their appearance."[23]

Relatively recently, discovery of an ancient whole genome duplication (WGD) event occurred in an ancestor of spiders and scorpions. As a result, two Hox clusters appear to have been fully retained in families and clusters in Arachnoid pulmonates. "Overall, our results show a high level of retention of homeobox genes in spiders and scorpions post – WGD, which is likely to have made a major contribution to their developmental evolution and diversification through pervasive sub--functionalization and neofunctionalization and paralleling the outcomes of WGD in vertebrates."[24]

Scorpions represent a transitional form bridging the gap between marine and land-based animals. This required the development of respiratory organs known as book lungs. In scorpions these consist of four pairs of plates or sheets of highly vascular tissue arranged like pages in a book. These are exposed to the exterior providing a large surface area for oxygen and carbon dioxide exchange. There are two pairs similarly arranged like pages in a book.

Book lungs have been studied in an exceptionally well-preserved fossil arachnid (Trigonotarbida) from the early Devonian period located in Scotland dated approximately 410 million years ago during the late Cambrian explosion. Using nondestructive imaging methods, the study identified

fossil trabeculae for the first time, establishing a permanent airspace for respiration, “thus show[ing] unequivocally that trigonotarbids were fully terrestrial and that the microanatomy of the earliest known lungs is indistinguishable from that in modern Arachnida.“[25]

Suddenly the prolific fern family made its appearance.

“The earth was being overrun by new orders of land vegetation. Heretofore few plants grew on land except about the water’s edge. Now, and suddenly, the prolific fern family appeared and quickly spread over the face of the rapidly rising land in all parts of the world.”[26]

Figure 20: Ferns. Credit: Japanese Painted Fern Athyrium nipponicum, Credit: Derek Ramsey (Ram-Man), Creative Commons Attribution-Share Alike 2.5 Generic

Ferns are highly prolific, rapidly growing vascular plants that are widely distributed in all climatic zones and environmental conditions around the world. They are notorious for hosting large genomes. Ceratopteris richardii has recently undergone completion of decoding its massive

genome consisting of 720 pairs of chromosomes and 7.46 GB of DNA, more than double the size of the human genome.

“The large size and complexity of most fern genomes have hampered efforts to elucidate fundamental aspects of fern biology and land plant evolution through genome-enabled research. Here we present a chromosomal genome assembly and associated methylome, transcriptome and metabolome analyses for the model fern species *Ceratopteris richardii*. The assembly reveals a history of remarkably dynamic genome evolution including rapid changes in genome content and structure following the last whole-genome duplication approximately 60 million years ago. These changes included massive gene loss, rampant tandem duplications and multiple horizontal gene transfers from bacteria, contributing to the diversification of defence-related gene families.”[27] The role of Hox genes as a major factor contributing to the rapid evolution and worldwide spread of ferns is indeterminate, due to the genome disrupting events of 60 million years ago.

An invasion of land animals occurred about 210 million years ago.

“When the seas were at their height, a new evolutionary development *suddenly* occurred. Abruptly, the first of the land animals appeared. These air-breathing amphibians developed from the arthropods whose swim bladders had evolved into lungs.”[28]

Figure 21. Carboniferous labyrinthodonts. Credit: Tom Page (CC BY-SA 2.0)

Suddenly large numbers of amphibians permanently abandoned their marine existence. The plants and grasses were spreading rapidly over the land providing food for the animal invasion

taking place at this time. The homeotic genetic system was well established resulting in rapid growth and development, mobilization of animals in general, and rapid expansion of vertebrates everywhere.

The first forests began developing. Plant life was luxurious providing nourishment for the newly arrived land animals. Many of these amphibians had already evolved lungs from their swim bladders. Climatically, this was a relatively warm period. The level of atmospheric carbon dioxide was dropping rapidly as the oxygen level was increasing from widespread photosynthesis by extensive plantlife, particularly the ferns. These atmospheric changes greatly benefited the rapidly expanding terrestrial invasion of land animals.[29]

Reptiles suddenly appeared 140 million years ago

"140 million years ago *suddenly* and with only the hint of the two reptilian ancestors that developed in Africa during the preceding epoch, the reptiles appeared in full-fledged form. They developed rapidly, soon yielding crocodiles, scaled reptiles . . . ."[30]

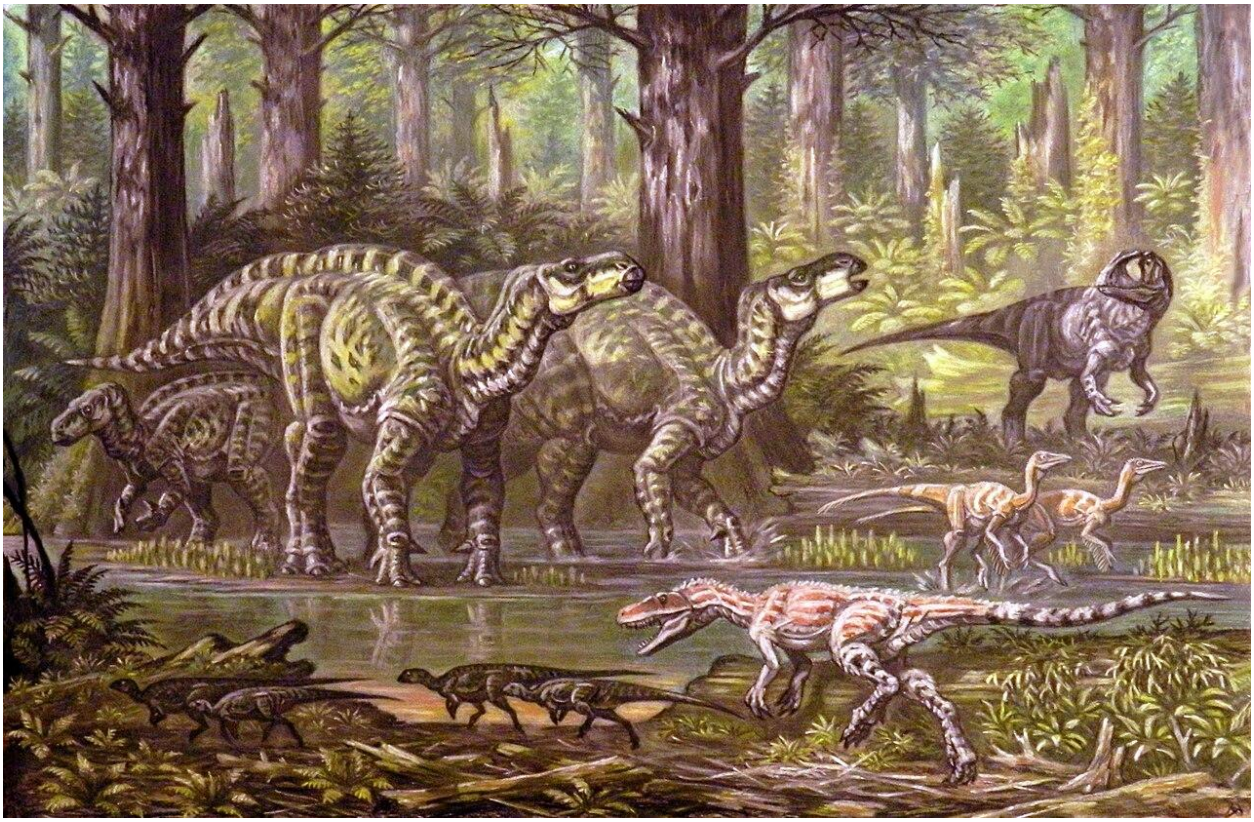

Figure 22. Credit: ABelov2014 (https://abelov2014.deviantart.com/), Creative Commons Attribution-Share Alike 3.0 Unported

During the Triassic period, reptiles were recovering from the Permian – Triassic mass extinction, thought to have resulted from dramatic climatic changes from an arid period to an extremely wet climate known as the Carnian Pluvial Episode (CPE) dated 234-232 million years ago. consisting of perhaps 1 million years of constant rain, after which once again it became arid. Recently, M. Bernardi, et et al., have shown that the dating of this "Triassic reptilian" explosion, followed promptly after the CPE suggesting that the sudden reversal of the climate to more favorable conditions resulted in the sudden recovery of reptiles.[31]

Another example of rapid expansion of the reptilian population occurred during the Jurassic period, known as the Mesozoic, which followed the Triassic period, extending from 201.3 million years to 145 million years extending for more than 56 million years. This is generally known as the "age of dinosaurs." During this period the largest land animals ever to have lived on earth hatched from eggs, roamed the Western states, fed largely on foliage, grew to enormous sizes, died and were then encased in the sand and mud of the Morrison formation and subsequently fossilized. One of the most concentrated displays is located at Dinosaur National Monument in Utah in which a large cluster of fossilized dinosaurs are located, housed in a spectacular hillside display. The combination of aridity, the action of the rivers (the Green River now meanders through this region) creating a giant floodplain, the wind activity causing rock outcroppings, all contributed to creating this unique preservation environment . More than 50 species of dinosaurs have been identified in the Morrison Formation ranging in size from numerous small, agile, largely carnivorous dinosaurs which hunted in large herds, to the huge solitary herbivorous camarasaurus reaching up to 23 meters in length and 42 metric tons weight.

The number of Hox genes varies only slightly across the entire subphylum Vertebrata. There is no scientific evidence to suggest that the homeotic genetic system was less active among dinosaurs but we do know that dinosaurs possessed extremely small brains compared to their massive bodies which, no doubt, was a factor in their rapid extinction.

Certain amphibians and reptiles displayed a unique ability to regenerate various structures such as eyes, limbs, hearts, upper and lower jaws, and spinal cords. This is particularly true of Hox A and Hox B genes. If this process could be reverse engineered in humans, it might be possible to heal serious spinal cord and brain injuries. It may also have applications in healing processes following surgery in reducing fibrosis. Studies have shown that a factor as small as a single base pair in human Hox analogs can be significant. Studies of newts have shown that cells at the site of injury can rapidly reproduce undifferentiated cells with the potential to differentiate, resulting in the production of a new limb or a new organ.[32]

"90 million years ago the angiosperms emerge from these early Cretaceous seas and soon overran the continents. These land plants *suddenly* appeared along with fig trees, magnolias, and tulip trees."[33]

Angiosperms

Angiosperms are known to be the most highly developed and the most advanced plants on earth. They are by far the largest groups of plants making up 70 to 80% of the various species. They are generally referred to as flowering and seed plants. More than 300,000 species of angiosperms have been identified and are classified into 8000 genera. They are capable of living in all the climatic zones and have adapted to a wide range of habitats. To date, approximately 5% have undergone analysis of their genome.[34]

Based on their homeobox genes they are classified into 14 classes, corresponding to the 14 classes of land plants. It is difficult to over-emphasize the importance of the sudden explosive arrival of angiosperms which rapidly covered the entire earth. "All 14 classes are found only in land plants, including moss and vascular plants, suggesting that homeobox genes have proliferated within each class particularly in flowering plants, indicating that all classes had already differentiated in the common ancestor of moss and vascular plants. In different land plants, including moss and flowering plants, multiple gene copies are observed for most classes, suggesting that proliferation and fundamental differentiation of gene paralogues within the original classes reflects the increasing complexity of plant development and architecture."[35] They quickly became the major food source for the rapidly expanding animal population. Seeds, based on sexual reproduction in which the male and female gametes combine to produce a diploid type organism, greatly expanded the angiosperms' adaptability to different environmental conditions and climatic changes. In addition, the seeds themselves became a major food source. The sexual means of reproduction is far more efficient and provides far greater variation and competition between plant species than the asexual form of reproduction based on spores relied upon by ferns.

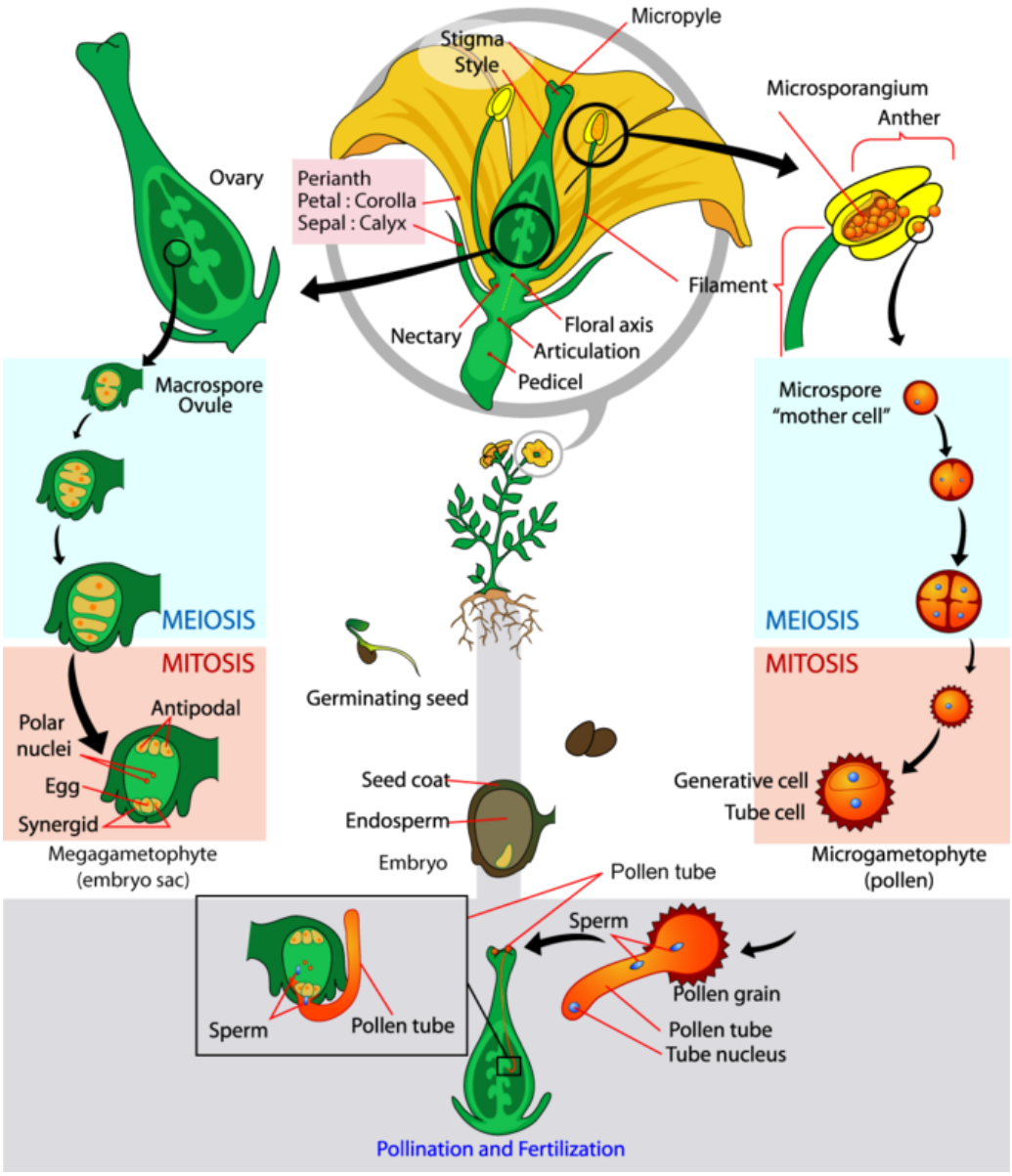

Figure 23. The Life Cycle of an Angiosperm. Credit Boundless, CC BY-SA 4.0

The figure above illustrates the most common reproductive scenario in angiosperms. The male gametophytes result from microspores that have developed from pollen grains. Female gametophytes form from an ovule that formed from macrospores. The macrospore in the ovule undergoes meiosis, generating four megaspores in which three are small and do not survive. The one large macrospore survives and produces the female gametophyte. As the grain of pollen contacts the stigma it results in an extension of the pollen tube enabling the pollen to reach the ovule where two sperm cells are deposited in the embryo sac. One fertilizes the

ovum, producing a diploid zygote whereas the other produces a triploid cell that later becomes a food source for the resulting embryo.

Fifty million years ago placental type mammals suddenly appeared directly from a reptilian ancestor that had survived the long reptilian descent.

Figure 24. Diversity of Neoplacentalia, Credit: Christopher Bland, 2020 Creative Commons Attribution-Share Alike 4.0 International

"50 million years ago…. the placental type of mammals suddenly appeared, and they constituted the most important evolutionary development up to this time."[36]

A functioning placenta offers a great advantage in that it provides for a relatively mature and well-developed newborn infant and mammary glands provide excellent nourishment. The superior brain power of mammals' large brains provide much greater ability to avoid predation as well as to adjust to changing environmental conditions and emergencies.

Much of our information and understanding of how Hox genes control and contribute to growth and development of mammals is derived from our extensive experimentation with mice. Because of their small size, ease of growth and rapid reproduction, mice have been the experimental mammalian animal of choice for decades of homeotic system experimentation. Since the Hox gene complement in the mammalian genomes are uniform throughout, data derived from the mouse gene research is equally applicable to all other mammals.

M. R. Capecchi at the Department of Human Genetics, University of Utah School of Medicine, has performed extensive studies on the role of Hox genes in mice. He has achieved disruptions of 37 of the 39 Hox genes.[37] He not only described the individual functions of Hox genes during development but also explored the interaction among them by introducing multiple mutations into the same mouse. From this analysis he has concluded that in mammals Hox genes function not only as individual entities but also as members of a highly integrated network with

paralogous genes, adjacent genes in the same linkage group, and even with non-paralogous genes.

Collinearity in humans

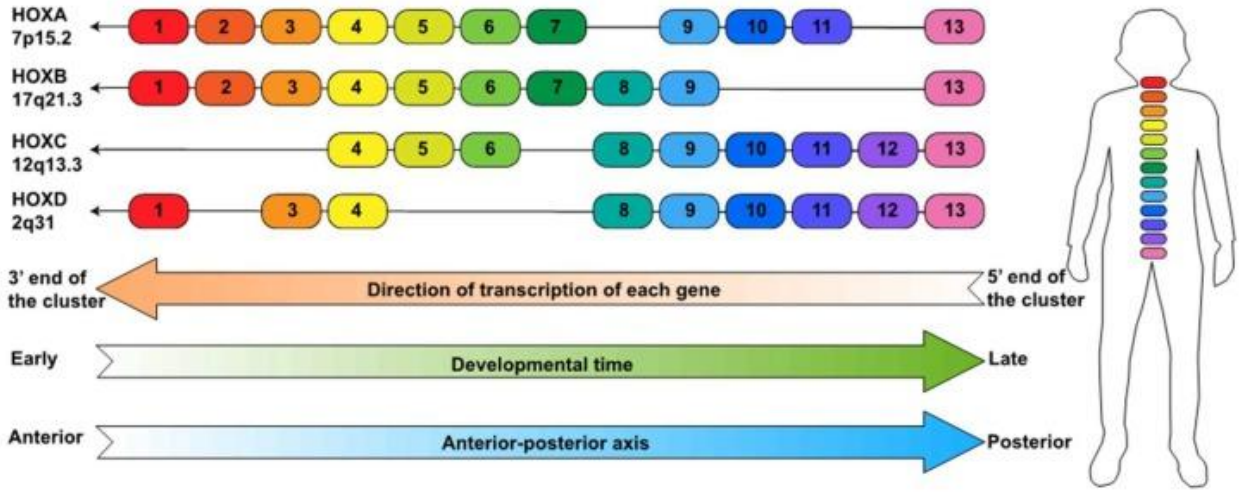

Figure 25. Credit: 2019 Zhifei Luo,Suhn K. Rhie, and Peggy J. Farnham, Licensee MDPI, Basel, Switzerland, by Creative Commons Attribution (CC BY) license.

In humans, as in all other mammals and vertebrates, there are a total of 39 Hox genes, located in four separate chromosomes; (7p15.2, 17q 21.3, 12q13.3, and 2q31). The four clusters represent duplications in which there are slight variations in the number of genes in each family group designated Hox A, Hox B, Hox C, and Hox D.

Figure 25 shows the Hox family members present in each of the four loci, along with the direction of individual gene transcription and the directions of the spatial and temporal waves of transcription of the genes in each cluster. On the right is a schematic indicating the relative positions in the human body at which the Hox paralogs are expressed during development.[38]

Hox genes play an expanded role in humans' growth and develop from early pattering to permanent control of neurotransmitter identity.

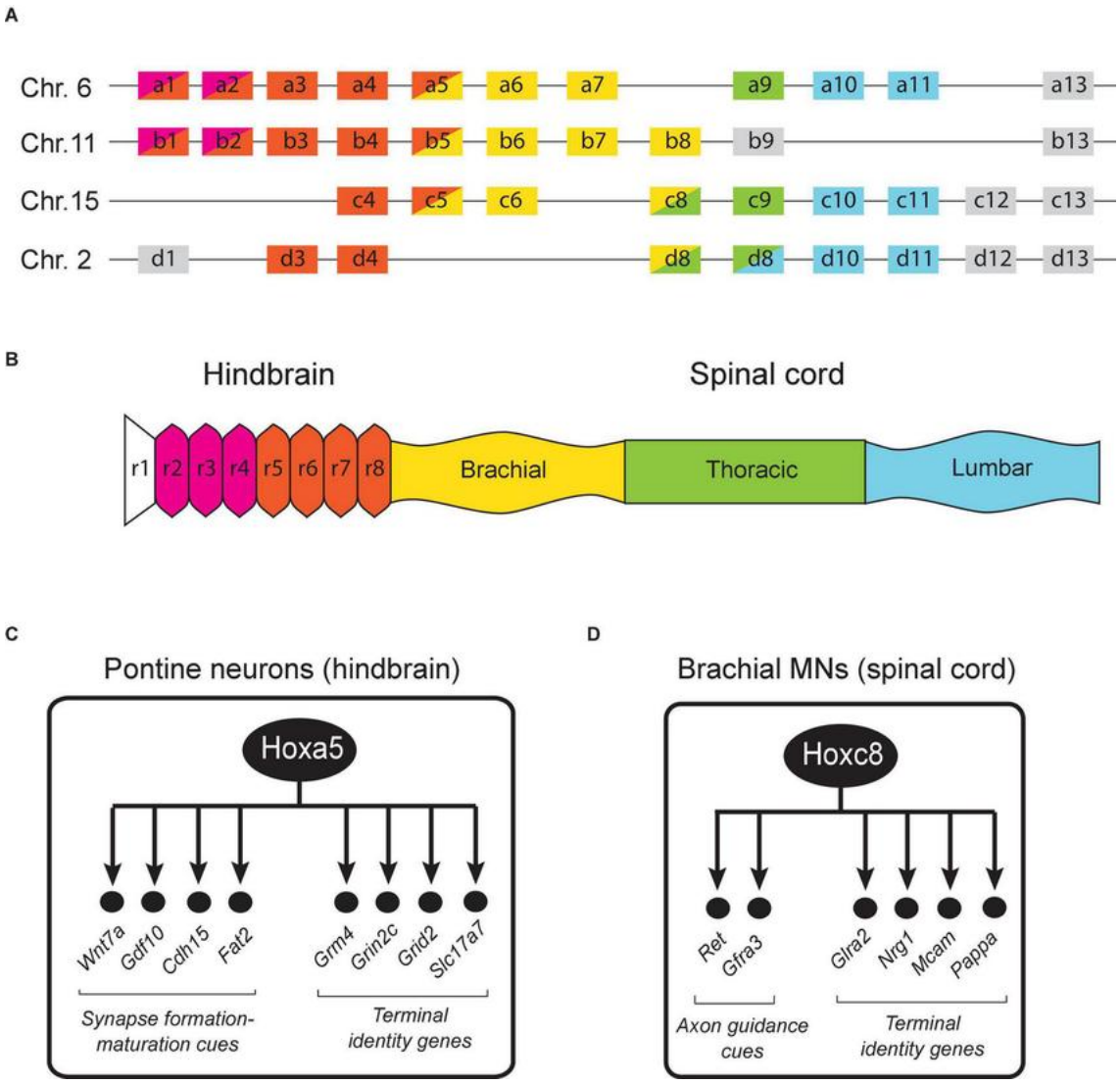

Figure 26: Hox genes in humans' expanded role from early pattering to permanent control of neurotransmitter identity. Credit: Feng, Weidong & Li, Yinan & Kratsios, Paschalis, CC BY 4.0

Section (A), illustrates a standard display of Hox genes that exists throughout the entire vertebrate genome.

In (B), Hox gene collinearity is expressed along the anterior-posterior axis of the embryonic nervous system, starting with the hindbrain and extending the length of the spinal cord.

In (C), the focus is on Pontine neurons in the hindbrain, resulting from Hoxa5 activity.

In (D), control of motor neurons by Hoxc8 genes are studied. Motor neurons control motor activity such as muscle function. They send signals to muscle cells initiating muscle activity enabling walking, running, swimming, throwing, and tackling.

Hoxa2 genes perform a significant role in guiding neuron migration and neural connections at synapses during embryonic brain formation. In addition, they maintain an ongoing function as providers of neurotransmitter identity, an important ongoing core element of neuronal function throughout adulthood. "These findings uncover a noncanonical role for Hox proteins during post-embryonic life, critically broadening their functional repertoire from early patterning to the control of neurotransmitter identity."[39]

Human cancers caused by Hox genes mutants.

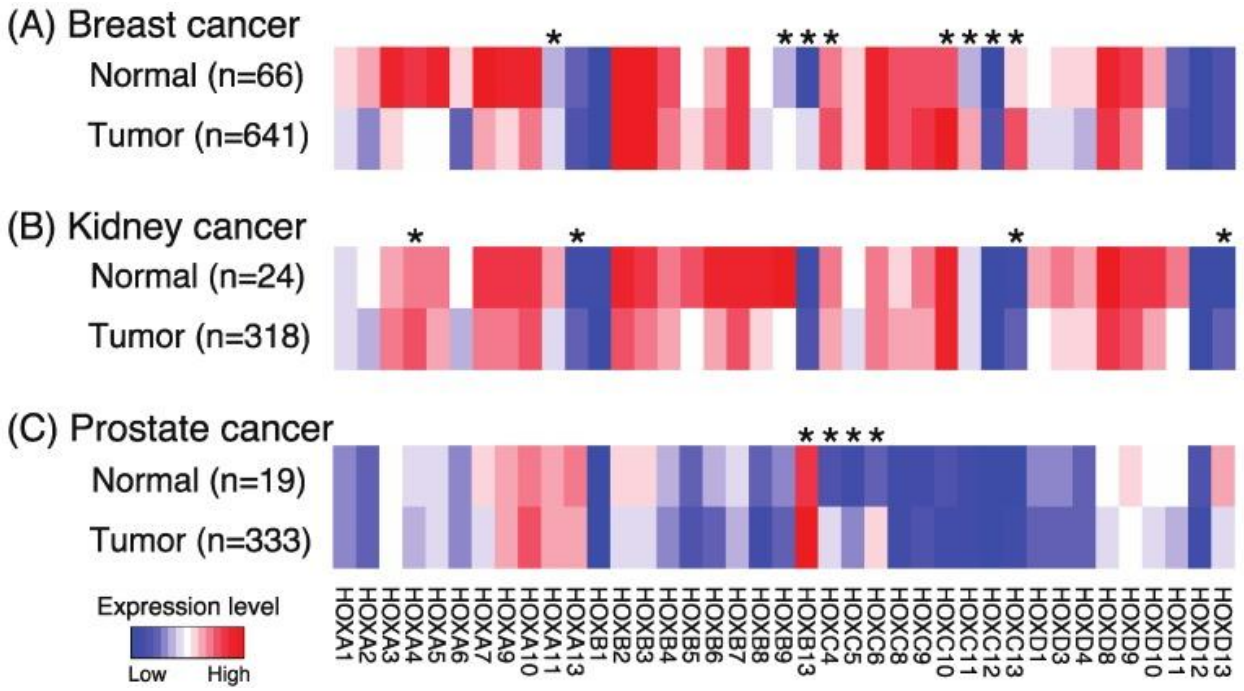

Figure 27. Human cancers caused by Hox genes mutants. Credit: Zhifei Luo, Suhn K. Rhie, and Peggy J. Farnham, Licensee MDPI, Basel, Switzerland, by Creative Commons Attribution (CC BY) license.

Figure 27 shows expression of the 39 human Hox genes in normal vs tumor samples. Shown are heatmaps indicating relative expression levels of the human Hox genes in normal and tumor samples from breast (A), kidney (B), and prostate (C) TCGA RNA-seq datasets. RNA-seq data were normalized as previously described [23]. Wilcoxon rank sum tests were performed between normal and tumor groups, and *p* values were adjusted using the Holm method. An asterisk indicates genes showing a significant upregulation in the tumor samples as compared to the normal samples (adjusted p value < 0.01).[40]

In this study by Z. Luo, et al., entitled, "The Enigmatic Hox genes: Can We Crack Their Code?" the authors measured the relative levels of expression by each of the 39 Hox genes in 641 breast cancers, 318 kidney cancers and 333 prostate cancers compared with normal tissues.

Levels of influence by Hox genes were greatest in breast cancer in which eight Hox genes displayed a significant upregulation in the tumor samples as compared to the normal samples; the number showing a similar increased levels of involvement for kidney tumors and prostate tumors were four each.

Hox genes are known to be associated with lung cancer, primarily lung cancer in nonsmokers. About 80% of all lung cancers occur in patients with significant smoking history. The lung cancers in which Hox genes are thought to be a causative factor are genomically different from lung cancer in smokers. Studies performed at NIH in the National Cancer Institute (NCI) under the direction of Maria Teresa Landi have shown that lung cancer in non-smokers is genomically significantly different than lung cancer resulting from smoking and will probably require a different mode of therapy.[41]

There are 10 commonly recognized Hox gene mutations. There are over 6000 recognized genetic disorders in humans. Hox genes are primarily concerned with organizing the body plan and orientation along the anterior-posterior axis. Limb development anomalies have been associated with Hox gene mutations such as synpolydactyly and hand foot genital syndrome resulting from mutations of HoxD13 and HoxA13.[42]

Finally, Hox genes are also known to play a role in adipogenesis and differentiate between white and brown adipose tissue.

Conclusions:

Hox genes, known as master genes, control the development of body plans of essentially all living organisms particularly along the long axis starting from head to tail as well as the symmetry in all bilaterians.

Hox genes cause sudden genetic advances in phenotypic development resulting in large gaps in the fossil records, the so-called “missing links.”

Hox gene function appears to have begun at or near the beginning of evolutionary life on this planet, approximately 500-600 million years ago. Recent research on Cnidaria has established that Hox genes are extremely ancient, probably having been derived from an extinct protohox gene cluster.

Hox genes have had a prominent role in all the “*sudden*” advances of evolutionary development extending from unicellular organisms to the emergence of Homo sapiens.

Hox genes possess the unique characteristic of spatial collinearity in which their position on the chromosome represents an integral part of the transcriptional message transmitted to mRNA.

Hox genes possess a unique structural configuration known as the homeobox (Hox) in which approximately 180 base pairs are associated with each Hox gene.

Hox genes possess a uniquely high level of conservation throughout the entire genome, that is they are widely distributed, accurately reproduced from generation to generation, and have consistently controlled body plans, from anterior to posterior throughout all biological evolutionary history.

Hox genes are organized into Hox clusters. There are four clusters of Hox genes in all vertebrates including humans. Each cluster is located on a different, chromosome and are designated as Hox A, Hox B, Hox C, and Hox D gene clusters.

The four clusters of Hox genes in all vertebrates have arisen from two separate ancient Hox gene duplications that have been conserved to the present.

Duplication of the Hox gene clusters provided the new gene loci predicted by Susumu Ohno approximately 55 years ago to promote rapid evolutionary development – a distinct form of **punctuated equilibrium.** The rapid evolutionary progress of vertebrates and mammals confirm Ohno's prediction.

Many gene duplications appear spontaneously and are frequently deleterious to the individual. The complete Hox gene distributions of the past appear to be both **de novo and beneficial**.

M. R. Capecchi states that, "It is apparent that the order of hox genes on the chromosomes of these two species has not altered significantly since the lineages of insects and vertebrates diverged approximately 530 Myr ago."[43]

Extensive research into the role of Hox genes has established their fundamental involvement in the *sudden* evolutionary transformations of record in *The Urantia Book*.

"From era to era, radically new species of animal life arise. They do not evolve as the result of the gradual accumulation of small variations. They appear as full-fledged and new orders of life, and they appear *suddenly*."[44]

Our best scientific understanding of the origin of Hox genes is consistent with *The Urantia Book* statement, ". . . [I]n cooperation with superphysical forces we organized and initiated the **original life patterns** of this world and planted them in the hospitable waters of the realm. . . . All planetary life . . . had its origin in our three . . . marine-life implantations."[45] (Emphasis added)

Acknowledgments:

I offer my deepest heartfelt gratitude to my loving wife, Betty, for her patient support and encouragement during the many hours required to complete this project.

I am most grateful to our son Michael Zehr, for his extensive technical assistance, including selecting illustrations, citations, and formatting this paper.

I am most grateful to our daughter, Joyce Anderson, who performed the final comprehensive editorial review.

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