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POINT OF VIEW

"We are all mutants. But some of us are more mutant than others."
Armand Marie Leroi, Mutants: On Genetic Variety and the Human Body

Genetics of Atavism

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Abstract—Atavisms have attracted people's attention for a long time. First, atavisms excited their imagination and created fertile ground for myths and superstitions. With the development of science, atavisms became the subject of investigation, which soon provided evidence to support evolutionary theory. However, at the molecular level, the formation of atavisms remained insufficiently understood. Recent progress in comparative genomics and molecular developmental biology has helped in understanding the processes underlying the formation of one of the human atavisms: the vestigial tail.

Keywords: polythelia (supernumerary nipples), hypertrichosis, vestigial tail (*Brachyury*)

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INTRODUCTION

According Wilhelm Roux, the term "atavism" in biology defines the revival of a biological structure that was lost in ancestors during evolution (Correns et al., 1912). The term "atavism," coined in 1766 by French botanist Duchenne, comes from the Latin *atavis*, which roughly corresponds to the word "precursor" (Hall, 2010; Zanni and Opitz, 2013). We know several atavisms in humans: color blindness, extra nipples, enlarged teeth, an elongated coccyx ("tail"), excess hair, etc. The existence of atavisms is a big problem for creationists challenging evolution. Atavisms are the insurmountable argument of the theory of evolution, which contradicts the basic idea of creationism that animals and plants exist unchanged from the moment of their creation.

We should distinguish atavism from a vestige: a feature or organ that gradually loses the function that it performed in the ancestors in the process of evolution. Although structures called vestigial appear as underdeveloped features or organs, in contrast to atavism, they are common in individuals of the species. Examples of the vestigial structures are the so-called "wisdom teeth," the posterior molars, which do not perform a function for most of human life and lag in development; the body hair, varying from person to person in the population, which, in contrast to wool, does not carry the thermal insulation function; and the head muscles responsible for the movements of the auricles. All these organs and features were used by our ancestors but lost their function during human evolution. However, the term "vestige" is interpreted more broadly to mean any feature or organ that is underdeveloped and dysfunctional and not necessarily present in the norm. The term is used in this sense below.

We have already mentioned that atavisms are known not only in humans but also in plants and animals. Some authors believe that even cancer might be considered as a peculiar form of cellular atavism, since it represents the reversion of cells to their more primitive form of the ancestral quasi-unicellular phenotype (Lineweaver et al., 2021). In our opinion, this is a rather exotic idea, unfairly popular in modern scientific literature. As for publications on evolution at the cellular level, one can find among them a conceptually opposite point of view, according to which tumors act as a testing ground for the evolution of new genes (Kozlov, 2010; Matyunina et al., 2019). Nevertheless, we prefer to consider atavism from the developmental biology point of view. This approach has been studied by authors following in the footsteps of Wilhelm Roux, who defined atavism as "the emergence of a biological structure" (Zanni and Opitz, 2013; Tubbs et al., 2016).

Not all developmental anomalies, often called atavisms, are atavisms indeed. Hyperdontia, the appearance of an additional tooth or teeth, most often permanent, is a relevant example (Rallan et al., 2013; Belmehdi et al., 2018). However, the human ancestors did not have additional teeth, especially unpaired teeth. That is why this developmental anomaly, which is a consequence of the increased activity of growth factors in the dental plate, is not an example of the bio-

logical structure which has been lost during the evolution of the species, i.e., atavism.

The fact that a biological structure or function has been lost does not mean that the genes responsible for the formation of this structure have been lost as well. Loss of biological function is often associated with changes in the regulation of the gene's expression. Gene's expression can be completely or partially turned off by epigenetic effects on the regulatory region that determines the level of gene expression, for example, at the enhancer level or by inserting mobile genetic elements, such as transposons, into the regulatory regions of the genome. The famous American inventor T.A. Edison (1847–1931) once said: "To invent, you need a good imagination and a pile of junk." Obviously, nature had plenty of good imagination and had enough time to dig into a large pile of noncoding DNA (98.5% of the human genome), consisting mainly of transposons, regulatory and repetitive sequences, to find some of them useful from the evolutionary point of view. For example, one of the nonautonomous mobile elements, the *Alu*-element, is present in over 1 million copies, which is estimated to be 11% of the human genome. In this regard, it has been suggested that the multiplication of mobile elements in the genome plays an important role in speciation (Kazazian, 2004). In the process of evolution, many transposons have gained the functional role of regulatory elements. For example, they can act as enhancers (Oliver and Green, 2009).

After a detailed study of transposons, their isolation and modification, they have become effective vectors for DNA delivery into the genomes of model animals. This proves that Edison was right. Currently, transposons are widely used in creating transgenic animals and mutants. Integrating a transposon into the genome not only introduces new hereditary information. This process often disrupts the structure of DNA and the function of genes at the site of transposon insertion (Korzh, 2007, 2008; Kawakami, 2007; Sivasubbu et al., 2007). Excising of a transposon by active transposase (a protein responsible the transposition of a mobile element) or genomic stress often leads to the displacement (remobilization) of the transposon, which can restore the function of the gene lost because of insertion (Parinov et al., 2004; Urasaki et al., 2006; Kondrychyn et al., 2009). Such a remobilization could return cells, tissue, and organ to a state close to the state of the ancestral organism before integrating the transposon into the ancestor's genome that caused an altering of gene function and triggered evolutionary changes.

Hints of the causal relationships between atavisms and genes appeared even before the molecular nature of the gene became clear. It was worse with the understanding of molecular mechanisms. First, the number of atavisms is quite limited even in a relatively well-studied species such as human (Gaskill and Marlin, 1989). Second, modifications can occur in noncoding regions of the genome, which, in comparison with coding regions, are much less studied. Yet this situation is slowly changing, primarily because the number of species and individuals of the same species whose genomes have been sequenced is growing like an avalanche.

Considering Waddington's developmental concept of canalization, it is likely that atavistic phenotypes may arise because of changes in expression or mutations in more than one gene. For example, it is well known that a natural mutation or experimental inactivation of the function of several vertebrate and insect genes that regulate eye development (*Pax6, Eya, Six3, Hh*) leads to the same result—lack of eyes (Gehring, 2011; Shaham et al., 2012). Thus, the result of overexpression of the "master regulator" Pax6/eyeless, which causes the development of ectopic eyes in vertebrates and invertebrates (Holder et al., 1995; Chow et al., 1999), fits well into the proposed developmental scheme, according to which the expression of one gene can determine a set of regulatory interactions leading to the formation of a functional organ (the eye in this case). It is logical that loss of function mutations of such genes would lead to reduction or loss of an organ, while restoration of the function of a gene or genes would lead to at least partial restoration, if not complete recovery of the organ.

In development, the same result can be achieved by different ways. For example, an increase in the expression of the *Shh* gene may lead to blindness in cave fish during embryogenesis because of epigenetic regulation caused by increased methylation of regulatory regions of this gene (Yamamoto et al., 2004; Gore et al., 2018). It is known that an increase in *Shh* activity entails an increase in *Pax2* expression at expense of the expression of *Pax6,* a critically important master regulator of eye development (Macdonald and Wilson, 1996). In the blind naked mole-rat, the same result seems to be achieved by a combination of several inactivating mutations affecting other genes, e.g., *Cryba4* and *Crybb3* (Kim et al., 2011).

In order to give some order to the complex and very intricate web of molecular interactions responsible for the formation of specific tissues and organs, the concept of a gene regulation network (GRN) was proposed. The GRN consists "mainly of functional connections between regulatory genes that produce transcription factors and their target cis-regulatory modules in other regulatory genes together with genes that express spatially important signaling components" (Davidson and Erwin, 2006). *Pax6* belongs to one of these evolutionarily conservative GRNs: Pax-Six-Eya-Dach (PSEDN; Bessarab et al., 2004; Galli-Tsinopoulou et al., 2014). In all likelihood, the evolutionary loss in function of genes, on which GRN activity depends, may led to the formation of a vestige, i.e., to the reduction and subsequent disappearance of the

Fig. 1. Tail reduction has occurred several times in evolution, the first time in amphibians, and in rodents and great apes among mammals.

organ (Fig. 1), while the restoration of GRN activity may lead to the forming of an atavism.

This example illustrates that modern developmental biology has reached an important milestone. We have accumulated enough knowledge about various structures representing the atavisms and about the genes involved in the atavism's formation. Thank to this, researchers can not only guess which of the changes in gene expression can cause atavism but also test their assumptions in an experiment. Might the results of these experiments help to understand more deeply the molecular mechanisms underlying the atavisms? Might they provide a starting point for further analysis of the evolution of life on this planet? Or maybe they will provide additional arguments in the long dispute between evolutionists and creationists? Everyone can try to give the answers to these questions themselves. If we keep in mind the implications of Waddington's "canalization," then the testing of all candidate genes, even with today's use of high-throughput analysis techniques, may take considerable time. However, there has been recent progress in establishing causal relationships between atavisms and changes in the expression of some genes, which is the subject of further discussion on the example of three different atavisms.

POLYTHELIA (SUPERNUMERARY NIPPLES)

Unlike most mammals that have multiple nipples (up to 25–27 in opossums), primates, including humans, usually have only two nipples. Therefore, the appearance of additional nipples in humans is considered as a return to a more primitive evolutionary state, i.e., as an atavism. We should note that multiple nipples in humans are not so rare (from 0.2 to 5.6%; 31).

Boris Balinsky analyzed the early stages of mammary gland formation at Waddington's laboratory in the late 1940s (Balinsky, 1949–1950, 1950). The role of hereditary factors in this process was demonstrated by Little and McDonald (1965). In mice of the A/J line, the number of mammary glands (and nipples) differs from the five pairs canonical for mice. The genome locus responsible for this variation was named *scaramanga* (*Sca*, after one of the characters in the James Bond film: *The Man with the Golden Gun*). This locus was associated with the activity of the Erbb4–Nrg3 ligand, which acts as a cell differentiation signal for mammalian breast vestigial structures (Howard et al., 2005). Nrg3 and the components of the Nrg3-related signaling cascade might be considered as one set of factors regulating the development of human epithelium, but this has yet to be proven experimentally.

HYPERTRICHOSIS (EXCESSIVE AMOUNT OF HAIR)

People sometimes develop excess hair; this condition is known as hypertrichosis. Some individuals form ectopic areas of hair loss, others have hair covering the entire body so impressively that the image of one individual—Tognina Gonsalvus—was used as the first page of the popular book *Mutants* by A.M. Leroy, remade in 2004 into the BBC documentary *Human Mutants*. Leroy paraphrased George Orwell's famous aphorism "All animals are equal, but some of them are more equal than others" to show that all humans are mutants. Leroy's version, used as an epigraph to this review, reflects the role of mutations in the formation of the genetic heterogeneity of the human population.

Various hereditary factors can cause hypertrichosis, ranging from those responsible for abnormal neurulation (Pax3) to the preservation of rudimentary (embryonic) lanugo hair (Sales et al., 2021). Several genetic anomalies are associated with hypertrichosis, and large intrachromosomal insertions between 1.8×10^6 nucleotide pairs between the *FGF13* and *SOX3* genes on the X chromosome are among them (Zhu et al., 2011; DeStefano et al., 2013). Given that different inserts can cause the same phenotype, it is likely that the area of the insertion site and not the insertion itself is crucial for the occurrence of this particular phenotype. Given the sexual dimorphism on this trait in humans (male mustache, male beard, etc.), it seems logical that the elements regulating hairiness are located on the sex X chromosome. This region contains several genes encoding various proteins and microRNAs. Some of these genes (*SOX3, SPANXB1, SPANXC*) regulate the development of male germ cells, while others (*MCF2*) are associated with the development of granular skin cell tumors (https://www.uniprot.org/uniprot/).

In bony fish, the homologue of one of these genes, *zic3*, exists as a pair of genes with a related *zic6*, the loss of which in evolution illustrates the point of chromosome break between these two genes (Parinov et al., 2004; Kondrychyn et al., 2013; Winata et al., 2018). This may be one reason for the absence of *Zic6* in terrestrial animals. All these facts suggest that the region of the genome between *FGF13* and *SOX3* is a "hot spot" of chromosomal rearrangements, including intrachromosomal insertions, chromosomal divisions, and mergers. We should bear in mind that some genes in this interval play an important role in shaping the body plan or in maintaining physiological functions. FGF13 acts as a regulator of cardiac sodium channels Nav1.5 and Nav1.6 and probably takes part in regulating heart rhythm (Poon et al., 2016; Wang et al., 2017; Minhas et al., 2021), and ZIC3 regulates body asymmetry (Purandare et al., 2002; Bellchambers et al., 2021). How these functions combine with the regulation of the hair pattern is still unclear. Therefore, the nature of genes and the mechanism of their action that cause hypertrichosis remain mysterious.

RUDIMENTARY HUMAN TAIL

This article would not make sense if there was no place in it for an example that clearly proves the connection between the restoration of an evolutionarily archaic structure (or atavism) and genetic activity. Such an example is a vestigial (nonfunctional) human tail. New data on this atavism is about to be published. We should note that the connection with some genes in relation to the tail has long been quite obvious. However, it took the efforts of several generations of evolutionary biologists and the emergence of incredible opportunities provided by genomic sequencing of various species to prove this link.

This story began in 1921, when Nadezhda Dobrovolskaya-Zavadskaya (1878–1954) began working under the supervision of Professor Claude Regaud (1870–1940) at the Pasteur Laboratory of the Curie Institute in Paris. She conducted the first ever experiment on radiation mutagenesis of mammals (mice), in which several hereditary mutations with a certain phenotype were obtained. One of the mutations, represented by deletion, caused death in the homozygous state and a shortened tail formation in heterozygotes. Hence the name of the mutation: *Brachyury* (from Greek, "short tail"; Dobrovolskaïa-Zavadskaïa, 1927). The history of this discovery has been described in detail (Korzh, 2001; Korzh and Grunwald, 2001). When summing up her studies of *Brachyury* mutants, Dobrovolskaya-Zavadskaya wrote in 1934 that the analysis of the mutant allowed her to formulate the question of the genetic mechanism responsible for the development of the tail. Morphological studies of this deviation from the norm led her to assume the existence of genes responsible for the development of the tail. Such genes act as the key specific regulators of tail development, which instruct the process of formation of this organ. In the process of organogenesis, genes like *Brachyury* interact and cooperate with additional modifier genes (Dobrovolskaïa-Zavadskaïa et al., 1934). It is easy to see that, by replacing *Brachyury* in this statement with *Pax6*, we get a hypothesis about the role of Pax6 as the key regulatory gene of the eye development.

In conclusions drawn based on a series of *Brachyury* studies, Dobrovolskaya-Zavadskaya was significantly ahead of science at that time. How valuable the discovery of this mutant was for the formation of developmental biology as a scientific discipline can be judged from the following. It took another 10 years of further *Brachyury* research before the fundamental principles of developmental biology were formulated (Gluecksohn-Schoenheimer, 1944). Research of *Brachyury* has always been at the forefront of radiobiology, molecular biology, genetics, developmental biology, and crystallography. *Brachyury* was the first gene regulating mammalian development that was positionally cloned by Herrmann et al. (1990). Brachyury was one of the first mammalian transcription factors for which a spatial structure was determined using X-ray structural analysis (Müller and Herrmann, 1997). In the zebrafish, the first mutation for which it showed a connection with the gene was the deletion mutation *no tail* (*ntl*), which affects the zebrafish *tbxta* gene homologous to *Brachyury* (Schulte-Merker et al., 1994). *Brachyury* mutants were also identified in domestic animals, such as Manx cats (Buckingham et al., 2013), many dog breeds (bobbed-tailed dogs), for example, bobtail and corgi (Hytönen et al., 2009). Significant reduction or complete absence of the tail can be also found in wild animals, for example, tenrec (*Tenrec ecaudatus*), tailless fruit bat (*Megaerops ecaudatus*), and rodents:

capybara (*Hydrochoerus hydrochaeris*), agouti (*Dasyprocta*), hamsters (Cricetinae) and guinea pig (*Cavia porcellus*). One can expect the reason for the guinea pig's taillessness to be analyzed in detail soon since its genome has already been sequenced. We should also note that not all breeds of dogs with congenital tail shortening have a mutation in the *tbxt/Brachyury* gene (Hytönen et al., 2009). This confirms once again that the GRN is highly branched and that it is possible to reach a similar phenotype by mutating the different genes that compose the GRN.

Examining the formation of the caudal region of the spine in human development, developmental anatomists have shown that, the number of somites reaches a maximum at the 16th Carnegie stage, 39–41 pairs of somites, in human development. Later, their number decreases due to reduction of five somite pairs in the tail region by programmed cell death (apoptosis) (Tojima et al., 2018). Thus, there were grounds to link the biological prerequisites for the development of the tail in mammals with evolutionary theories and to back up these materials with molecular evidence. This paved the way for linking the biological prerequisites for tail development in mammals to evolutionary assumptions and supporting these findings with molecular evidence.

Let us imagine for a moment that a bioinformatics student is presently writing a diploma and studying all the genes associated with tail development disorders. This is relatively easy, given that we know many mutations that violate evolutionarily conservative elements of the molecular mechanism of tail development in model animals, such as the zebrafish and mouse. It turned out that such a student can easily identify all these genes (Tickey-McCrane et al., 2017). This list includes *Wnt3a, Tbx6, T/Brachyury* (*TBXT*)*, Msgn1, Tbx16, Hox10, Hox11, Hox13, Ptf1a, Cyp26a1, CXCR2, Ets1/2, Fgfr1, Fgf8, Fgf24, Cdx1, Dld, Ph2-alfa,* and *Noggin*. The first four genes are the most likely candidates for the role of genes whose function deficiency causes the absence of a tail. *Wnt3a*, *Tbx6*, and *Msgn1* are three key factors that initiate the formation of the paraxial mesoderm from which vertebrae develop, whereas *T* or *Brachyury* (renamed *TBXT* in 2018 for the convenience of bioinformatics) acts in inducing proliferation and differentiation of cells in the tail and trunk mesoderm. The mouse mutant *Wnt3a*, which phenocopies *Brachyury*, was even named *vestigial tail*, which gives a fairly accurate idea of what the author of this article thought about the role of the mutated gene in tail development (Heston, 1951). At that time, this gene was still hypothetical. *Wnt3a* was rediscovered as *int-4* (Nurse and Varmus, 1982) and cloned in the early 1990s (Roelink and Nurse, 1991; Krauss et al., 1992; Nusse and Varmus, 2012).

Apparently, the authors of the 2017 Tickey-McCrane diploma thesis were on the right track, referring to studies of monkey tails by Fooden (1997) and suggesting that "macaques may hold the key" to the mystery of the human tail. In the absence of reliable data linking the development of rudimentary human tails with genes involved in development, they conducted a somewhat speculative discussion in articles devoted to this topic about which of the tails are real (containing vertebrae) and which are pseudo-tails. Perhaps, in their analysis, the authors of the thesis followed the views of Dao and Netsky (1984) on the human tail, who believed that rudimentary human tails do not contain vertebral structures, unlike tails of caudate primates. A detailed morphological analysis showed that some vestigial human tails contain "additional vertebrae and are connected to the tip of the coccyx" (Sugamata et al., 1988). The strict definition of the "true" human tail has recently been revised, and it has been proposed that any tail is a true tail (Tubbs et al., 2016).

More recently it turned out that in order to answer the question of which of the genes handles the formation of a rudimentary tail in humans, it was necessary to compare the evolution of genes involved in the tail's development in tailed and tailless (anthropoid) monkeys. A recent preprint, which is likely to be published earlier than this text, linked the rudimentary human tail to evolutionary changes in *Tbxt* expression (*T, Brachyury*) caused by the insertion of *AluY,* one of the most common mobile elements in the human genome, into intron 6 between exons 6 and 7 *TBXT* of the ancestor of all great apes, including humans (Fig. 2). This event probably started the chain of evolutionary changes that led to the absence of a tail in great apes and humans (Xia et al., 2021). During transcription, *AluY* likely forms a pair with the second mobile element *AluSx1* in the opposite orientation, which is present in the neighboring fifth intron. This leads to the formation of a *TBXT* mRNA spatial complex comprising a stem and a loop. The loop encloses exon 6 *TBXT*, which causes the formation of an alternative transcript, *TBXT*-Δ*exon6*, with a partial loss of TBXT activity. After the *AluY* insert started the process of evolutionary adaptation, a short tail could, on the one hand, be an unfavorable factor for living in a three-dimensional environment, while, on the other hand, contribute to bipedal movement. Additional modifications of this mechanism probably caused not only the consolidation of this feature but also a further reduction of the tail.

Here, a comparison of dog-headed monkeys (Cercopithecoidea) and hominoid (Hominoidea) can shed light on the role of tail shortening in evolution. The separation of these groups likely occurred shortly before or immediately after the transition to a predominantly terrestrial lifestyle associated with the emergence of savannas and sparse forests instead of part of the jungles of Africa approximately 25 million years ago (Andrews, 1992; Senup, 2016). Dog-headed monkeys (for example, baboons) kept both the tail and

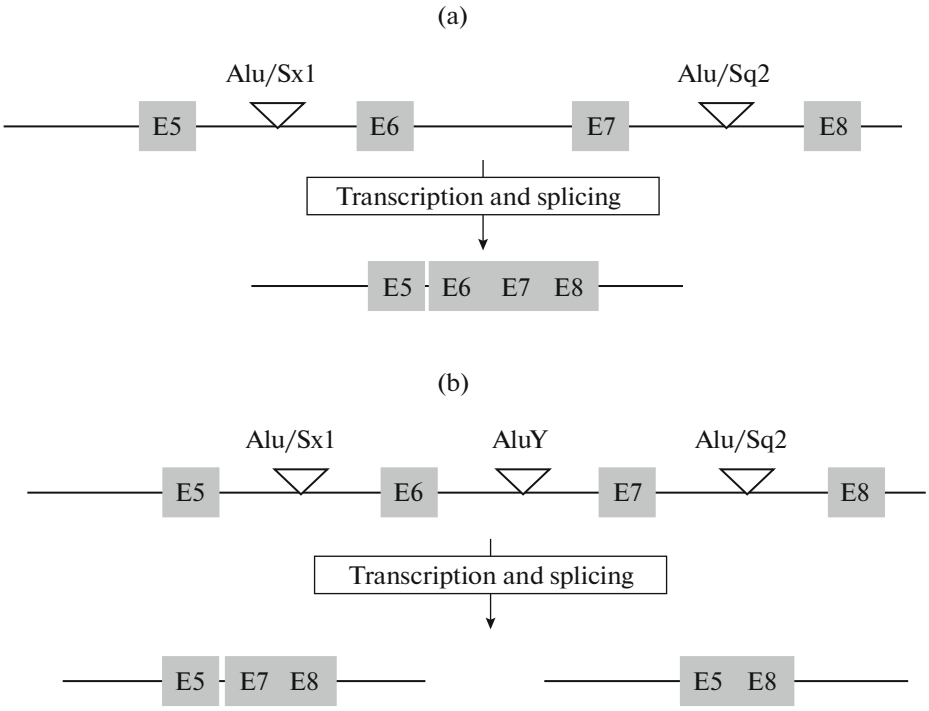

Fig. 2. Insertion of the mobile element *AluY* into the intron between 6 and 7 exons of the *BRACHYURY* (*TBXT*) gene in the ancestors of great apes caused a disruption of splicing and a decrease in the level of *TBXT* translation, which, in turn, triggered the process of tail reduction in the descendants of this group of animals, including humans. (a) Ancestral state, (b) hominids.

quadrupedal locomotion, whereas the anthropoids, even returning to a predominantly arboreal lifestyle (gibbons, chimpanzees, orangutans), use brachiation (climbing with the help of hands) and bear other signs of primary bipedality. It is likely, that the absence of a tail and bipedal walking are directly connected, having arisen in the line of anthropoids at the dawn of their formation. However, they are not a limitation for the arboreal lifestyle, only changing the locomotion used for this.

The proposed molecular mechanism of tail reduction is successfully reproduced in transgenic mice after the introduction of *AluY* into the mice *Brachyury* into the same position as in primates. This not only provided the experimental proof that integrating *AluY* into *TBXT* was involved into the tail reduction but also significantly expanded our understanding of the role of transposons in evolution. Thus, the research on *Brachyury*, the gene whose expression change probably triggered the evolutionary changes leading to a tail reduction in mammals, was again at the forefront of developmental biology, a science that arose largely because of the discovery of *Brachyury* in 1927 by Nadezhda Dobrovolskaya-Zavadskaya.

It is important to note that the study by Xia et al. (2021) suggests the role of other developmental factors, such as thyroid hormone (thyroid hormone, TG) and retinoic acid (RA) in the development of the posterior part of the body. To do this, it is necessary to consider several issues in a complex. It is possible that the role of *AluY* is not limited to the violation of splicing. Perhaps such mobile elements perform additional regulatory functions. It is known that TG causes tail resorption during metamorphosis in *Xenopus* (Tata, 1968, 2006), whereas RA is responsible for decrease in the expression of *Wnt-3a*, another potential regulator of tail development, mutations of which lead to shortening of the tail of mice, which resembles caudal regression syndrome (Padmanabhan et al., 1998; Iulianella et al., 1999; Shum et al., 1999). *Alu* repeats contain binding sites of transcription factors dependent on TG and RA (nuclear hormone receptors) (hormone-response elements, HRE). The canonical HRE for TG-RA is the nucleotide sequence AGGTCA, which is often present in *Alu* elements in two or more copies separated by a gap of two or four nucleotides. Many naturally occurring HRE differ from this motif by one or more nucleotides (Vansant et al., 1995; Piedrafita et al., 1996). It is possible that the insertion of *AluY* not only disrupts the splicing of *TBXT* but also, through additional regulation at the level of binding of nuclear receptors, changes the TG-RA-dependent developmental processes, for example, tissue resorption under the action of TG or expression of Wnt-3a in the *TBXT* area, which introduces an additional level of regulation of tail reduction.

The answers to the intriguing questions posed in this article will probably be given soon. Given the power of modern bioinformatics, it is easy to predict that this publication will launch a process of active revision of data in developmental biology related to mutant phenotypes resembling certain atavisms. In combination with comparative genomics, this will make it possible to decipher the molecular mechanisms of various atavisms. The study of the genetics of atavisms allows us, as can be seen from the examples above, to better understand the ways of species evolution, including the most interesting one for us, human. While the occurrence of atavisms is quite rare, it suggests that—although we are all mutants—some of us, a small minority, are morphologically slightly less mutant than the majority.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflicts of interest.

This paper does not contain information on any studies involving humans or animals performed by the authors.

AUTHOR CONTRIBUTIONS

V.P. Korzh proposed the concept and wrote the first version of the article. E.V. Gasanov substantially supplemented and developed the evolutionary aspect of the work. Both authors worked on the latest version and approved it.

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