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Atavistic Mutations Reflect the Long Life Span of Dispensable Genes

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A. Introduction

It looks as though the list of c-*onc* genes in the mammalian genome has been growing every month: some sharing the tyrosine kinase domain with growth factor receptors, others sharing the domain with steroid hormone receptors. Are they all essential to the development and well-being of the host? From their sheer redundancy alone, I suspect that most of them are not. If they are, more often than not, nonessential, why have they been persisting so long? The evolutionary antiquity of some of them has been well established.

In a previous paper [1], I pointed out that because of the low inherent error rate in vertebrate DNA replication estimated as 10^{-9}/ base pair per year, the average half-life of genes after they have become dispensable is as long as 45 million years. It would be recalled that the first placental mammals emerged only 75 million years ago. In another previous paper [2] and also in an accompanying paper to this one, I also pointed out the c-*onc* gene coding sequences are still constructed in the manner reminiscent of primordial coding sequences at the very beginning of life on this earth some 3.5 or more billion years ago, the possession of long unused open reading frames giving them a measure of immortality.

In this paper, I shall give an example of the primordial gene evolved before the division of eukaryotes from prokaryotes becoming dormant in various phylogenetic trees for very, very long time, only to be resurrected later. Before the advent of molecular biology, such resurrections were known as atavistic mutations. A few dramatic examples shall also be given.

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B. The Evolutionary Game of Hide- and Emerge Played by Hemoglobin Genes

The ultimate origin of hemoglobin genes is of extreme interest. In vertebrates, hemoglobins are encased in circulating erythrocytes, and the genome of certain teleost fish and upward contains two unlinked sets of genes; one set for α-chain and its allies, and the other for β-chain and its allies. Within vertebrates, hemoglobin polypeptide chains have been changing rather rapidly – a 1% amino acid sequence divergence every 8.3 million years. By contrast, glyceraldehyde 3-phosphate dehydrogenase, one of the sugar-metabolizing enzymes, has been undergoing a 1% amino acid sequence change every 40 million years. Reflecting the above noted rapid evolutionary changes, monomeric hemoglobins of lampreys are already intermediate between myoglobins on one hand and α- and β-chains of jawed vertebrates on the other [3]. Thus, within vertebrates, all the indications were that the gene duplication event that yielded the ancestral hemoglobin gene from a redundant copy of the myoglobin gene must have taken place at the onset of vertebrate evolution 300 million or so years ago. Indeed, at the rate of a 1% amino acid sequence divergence every 8.3 million

years, hemoglobins should have become totally unrecognizable in 830 million years: 100% amino acid sequence divergence.

Yet it had been known for a long time that hemoglobins appear sporadically not only among invertebrates (e.g., *Chinoromus* among dipteran insects, earthworms among the class *Polychaeta* of the phylum *Annelida*) but also among the plants (e.g., in nitrogen-fixing nodules of leguminous plants). A dimeric bacterial hemoglobin from *Vitreoscilla* has recently been sequenced [4]. It is comprised of 146 amino acid residues and is therefore of the same length as mammalian β-chains. Furthermore, all the functionally critical residues are present, e.g., a pair of histidine residues that hold a heme – 46th phenylalanine, which is invariant in all hemoglobins. This bacterial hemoglobin shows the greatest sequence homology (24%) with the pea leghemoglobin which is 153 residue long.

The fascinating evolutionary history of hemoglobins revealed above again confirms the view that most of the major innovations in evolution occurred at the very beginning of life on this earth before the division of eukaryotes from prokaryotes. In addition, it reveals yet another evolutionary principle often overlooked [2]. The gene once invented might remain dormant for a very, very long time, only to be resurrected in certain members. For example, insects as a rule do not express hemoglobin genes; even among dipteran insects, the familiar *Drosophila* and mosquitoes do not, while *Chyronomus* does. The gene that can be resurrected after a very long period of dormancy must necessarily be endowed with the immortal property, being impervious to normally function-depriving deleterious mutations that cause premature chain termination, reading frame shifts, etc. This is the inherent property of coding sequences endowed with long unused open reading frames capable of encoding amino acid sequences similar to that encoded by the used reading frame of that gene. Such was the property of primordial coding sequences of eons ago that were repeats of base oligomers, the number of bases in oligomeric units not being a multiple of three [2].

C. A Few of the More Dramatic Examples of Atavistic Mutations

A pair of horns adorning the poll is quite common among bovids (cattle, sheep, goats,

Fig. 1. A portrait of *Belmar*, the winner of the 1895 Belmont stakes, from a newspaper of the time [5]

and antelopes), cervids (deer), and even giraffids of the order *Artiodactyla*. Among members of the order *Perisodactyla*, however, such development apparently has never taken place, although extinct *Brontothelium* sported, and persisting rhinoceroses still sport, a horn or horns on the nose. Yet there have been two documented instances of modern horses growing a pair of horns on the poll. Records of racing thoroughbreds have been kept impeccably. *Marooned* was a popular gelding of the 1930 in the United States. He had small horns growing "pronouncedly" though not "conspicuously." Similarly, the horse who crossed the wire first in the 1895 Belmont Stakes boasted nobs above his forehead (Fig. 1). Belmar, a steel-gray runner of distinction also won the Preakness and Manhattan handicap [5]. It would be recalled that starting with the Kentucky Derby, the Preakness and the Belmont constitute 2nd and 3rd legs of the Triple Crown races for 3-year-olds in the United States.

The characteristic body shape of modern whales was already evident in an Eocene whale (*Zeuglodon*) of some 50 million years ago. This reversion of the body form of tetrapod mammals to the original fish-like body form of ancestral vertebrates was accomplished by transformation of front limbs to a pair of paddles, while pelvic bones became residual, and femur became an internal diminutive cartilaginous vestige, thus eliminating hind limbs. Yet Andrews [6] described a humpback whale, *Megaptera nodosa*, with hind limbs over a meter long. The femur of this whale was external and nearly complete. A number of sperm whales, *Physeter catodon*, have also been discovered which possessed not only the external femur but also partial phalanges [7]. These whales with hind limbs represent the case of an atavistic revision to the tetrapod body form from the previous atavistic reversion to the fish-like form.

D. Summary

Most of the major innovations in evolution occurred at the very beginning of life on this earth some 3.5 billion years ago before the division of eukaryotes from prokaryotes. This initial innovativeness was due, in no small part, to the peculiar construction of primordial coding sequences that were repeats of base oligomers, the number of bases in oligomeric units not being a multiple of three. Such coding sequences are conferred with a measure of immortality. Because of this initial immortality and of long life span of genes after becoming dispensable, the ancient gene may remain silenced in particular phylogenetic trees for a very long time, only to be resurrected later. Hemoglobin genes expressed in exceptional bacteria, plants, worms, insects, as well as in all vertebrates are a good example of this.

Atavistic mutations are more dramatic visible examples of such resurrection of long dormant genes. A few interesting examples are given.

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