Pseudo-pseudogenes: revealing further complexity in the genome

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By definition, pseudogenes are the remnants of former genes that are no longer functional. It is not that anyone has observed a functional gene become non-functional, but it is inferred based on comparisons with protein-coding genes. A pseudogene sequence is similar to that of known protein-coding genes, but lacks an obvious promoter or has 'disruptions' in the open reading frame (ORF) that are predicted to prevent translation into a functional protein.[1] Based on the assumption that they have no function, evolutionists had believed that pseudogenes could provide a record of DNA changes where natural selection is not acting.

Some evolutionists have promoted the idea that similar sequences in pseudogenes strongly support common ancestry, especially between humans and great apes. The alleged disruptions in the sequence are attributed to random copying errors. If two organisms appear to carry identical disruptions, then it is considered far more likely that they both inherited them from a common ancestor than that those errors occurred independently. While created genes might need to be identical in some regions to carry out their normal function, no-one would expect a creator to put the same error in two different organisms.[2]

An oft-cited example is the GULO gene. In many animals it produces an enzyme necessary for the final step in vitamin C synthesis. Yet in humans, primates, and some other animals, it is a pseudogene. By selectively presenting data, one can make a compelling sounding story that humans inherited the mistake from a common primate ancestor. However, investigations by Woodmorrape[3], Truman and Terborg[4], and Tomkins[5] all show that a more comprehensive view of the evidence reveals patterns that contradict evolutionary predictions. Despite this, some evolutionists have continued to promote the human GULO pseudogene as powerful evidence for common ancestry, ignoring inconvenient details (i.e. ones that do not fit their pre-conceived ideas).[6]

The whole concept that pseudogenes provide compelling evidence for universal common descent hinges on the idea that these sequences are truly *not* functional and that mutations are merely random events. Otherwise, creationists have a competing, plausible explanation for why these sequences exist.[7] That is, any particular pseudogene may be functional, as it was created to be. Alternatively, a pseudogene may have lost function in various lineages (as appears to be the case with the GULO gene), with the same mutations being attributable to the fact that those regions are predisposed to such mutations.

Despite superficial appearances, not all pseudogenes are functionless. Over a decade ago, it was recognized that most suitably investigated pseudogenes were found to play important functional roles.[8] Creationists have noted this.[9] Further scientific research continues to challenge the conventional view of pseudogenes.

Regulating genes

Even though most of the human genome does not code for proteins, at least 70% of the sequences are transcribed (copied to make RNA). Many different types of RNA are now known to regulate the expression of genes, insuring that the proper amount of gene product is expressed in the right place at the right time. Some of these RNA regulatory molecules are derived from pseudogenes.[10]

Several hundred pseudogenes are known to be transcribed in a variety of tissues and tumours. Some are transcribed in the sense direction, as is typical for genes; others are transcribed in the anti-sense (reverse) direction. Either way, the sequence is important for proper function. For example, some pseudogenes look very similar to an actual protein-coding gene. This sequence complementarity helps the pseudogene RNA target and bind the gene, which is essential for guiding in proteins to silence that gene. In some cases the pseudogene RNA can also function as a scaffold, providing a base on which molecular machinery is assembled.[10]

Of course, evolutionists still interpret the origin of these pseudogenes within their naturalistic paradigm. It is known that some protein-coding genes are also reverse transcribed (from 3' to 5', rather than 5' to 3'), and this antisense RNA product can help regulate the gene. Evolutionists have assumed that this bidirectional transcription of the protein-coding gene was the initial state. Then the gene was duplicated and damaged (where the pseudogene appears to have introns) or retrotransposed (where introns appear to be absent, as in processed pseudogenes), and the pseudogene now carries out this role.[11]

This explanation presupposes universal common ancestry. Additionally, it requires several highly unlikely events. Gene regulatory networks cannot just be randomly interrupted or changed without jeopardizing the organism. In the cases where overexpression of pseudogene RNA is associated with loss of cell-cycle control and cancer, additional antisense RNA copies are not tolerated.[10] Thus, the postulated intermediaries would not result in viable organisms.

Protein coding

The 'disruptions' that prevent pseudogenes from being translated into full length proteins are stop codons that appear amid the ORF sequence. Normally, such interruptions would stop the formation of the protein, because the mRNA translation machinery would terminate the addition of amino acids when it recognizes the stop codon. It was a great surprise, therefore, when a human pseudogene, which had several stop codons scattered across the ORF, was found to form a functional protein. It was observed that transcription of the pseudogene did not initiate from the predicted start codon. The resulting frameshift yielded an unusual, yet functional, olfactory receptor protein.[12]

It has been shown that over 100 pseudogene RNAs are translated into peptides.[1] Interestingly, 74% of the pseudogene peptides identified in humans had a similar transcript identified in the mouse, suggesting that they are functional.[13] Ironically, the sequence similarity between humans and other animals (both rodents and primates) is now being used to argue that these translated pseudogenes have function.[1]

A recent article has introduced a new term into the scientific literature: 'pseudo-pseudogenes'. The researchers found a clear case of a pseudogene being translated into a functional olfactory protein in *Drosophila sechellia*, a fruit fly that feeds almost exclusively on ripe fruit. In *Drosophila melanogaster* the intact gene detects acetic acid, a chemical found in the fermenting food which they, and most other *Drosophila* species, consume. It would be tempting to surmise that *D. sechellia* lost a gene it no longer needed, but the research showed, instead, that the pseudogene now codes for a protein with distinct odor-tuning properties.[14]

The olfactory receptor pseudogene found in *D. sechellia* differs from the one found earlier in humans in that the 'premature' stop codon is read through. Only recently has it been recognized that reading through a stop codon even occurs in eukaryotes, though it had been known to occur in bacteria.[15] In *D. sechellia*, the downstream sequence was shown to be the critical factor that allowed this readthrough to occur in neuronal tissue. Given the structure of other olfactory pseudogenes, the researchers suggest this may be a widespread phenomenon.[14]

Interestingly, decades ago creationist John Woodmorappe had predicted what now has been found in these so-called pseudo-pseudogenes: many pseudogenes are actually 'locked' genes, intended to be read only by readthrough of the premature stop codon, which may be limited to specific tissues. If the ability of readthrough is lost, the gene would become permanently 'locked', and then would truly be non-functional.[16] Thus, most pseudogenes were prematurely labelled as disabled genes because this and other design features were not understood.

Although the pseudogene in *D. sechellia* may have been derived from the similar gene found in other *Drosophila* species, this does not mean that the changes were merely due to naturalistic processes, such as random mutation, natural selection, and genetic drift. There are many well-recognized mechanisms in the genomes of all organisms to facilitate adaptive phenotypes.[17] DNA editing ability exists within our immune system, and it has been hypothesized DNA editing may play a role in adaptive mutations as well.[18] It should be self evident that adaptation, itself, does not turn one kind of organism into another; all *Drosophila* are still flies.

Figure 1. A gene that helps *Drosophila melanogaster* detect acetic acid in rotting fruit appears to have become a pseudogene in *D. sechellia;* yet when researchers investigated, they found this 'pseudogene' produces a functional protein with its own distinct odour-tuning properties.

Motivation for humility and trust

Despite mounting evidence for the functionality of pseudogenes, some evolutionists still promote them as compelling evidence of common ancestry of humans and primates. In reality it is an argument from ignorance, or at best from outdated beliefs. Their worldview, which assumes universal common ancestry, obliges them to see functional pseudogenes as the exception, and they boldly claim that pseudogene sequences

are non-functional until proven otherwise.[6] Such arguments repeatedly crumble as more scientific evidence comes to light.[19]

Previous conclusions about pseudogenes were based on knowledge of straightforward protein-coding genes. That knowledge was incomplete, as it is now recognized that stop codons do not universally stop the translation process and some promoters are not readily discernible by sequence alone. Many scientists underestimated the complexity necessary for the right protein to be expressed in the right place at the right time. It is understandable why the initial misconception existed, but now it should be recognized that the term 'pseudogene' is commonly a misnomer. This should engender humility in us all; no matter how much we learn about God's creation, there is always more to know. It should also encourage us to trust the One who was wise enough to place all the necessary components in place so the right things show up in the right place and at the right time.

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