Speedy the tortoise and altering the genetic code

August 5 2016, by Ricki Lewis, Phd

Speedy. Credit: PLOS Blogs

Last week my sister sent me a great article from Buzzfeed on "a reptile dysfunction". It's about stupid people who buy cute little baby tortoises that, after a few sweet months, enter a growth spurt and rapidly begin to

assume the dimensions of a dinosaur.

I did that.

An African Tortoise in Upstate New York

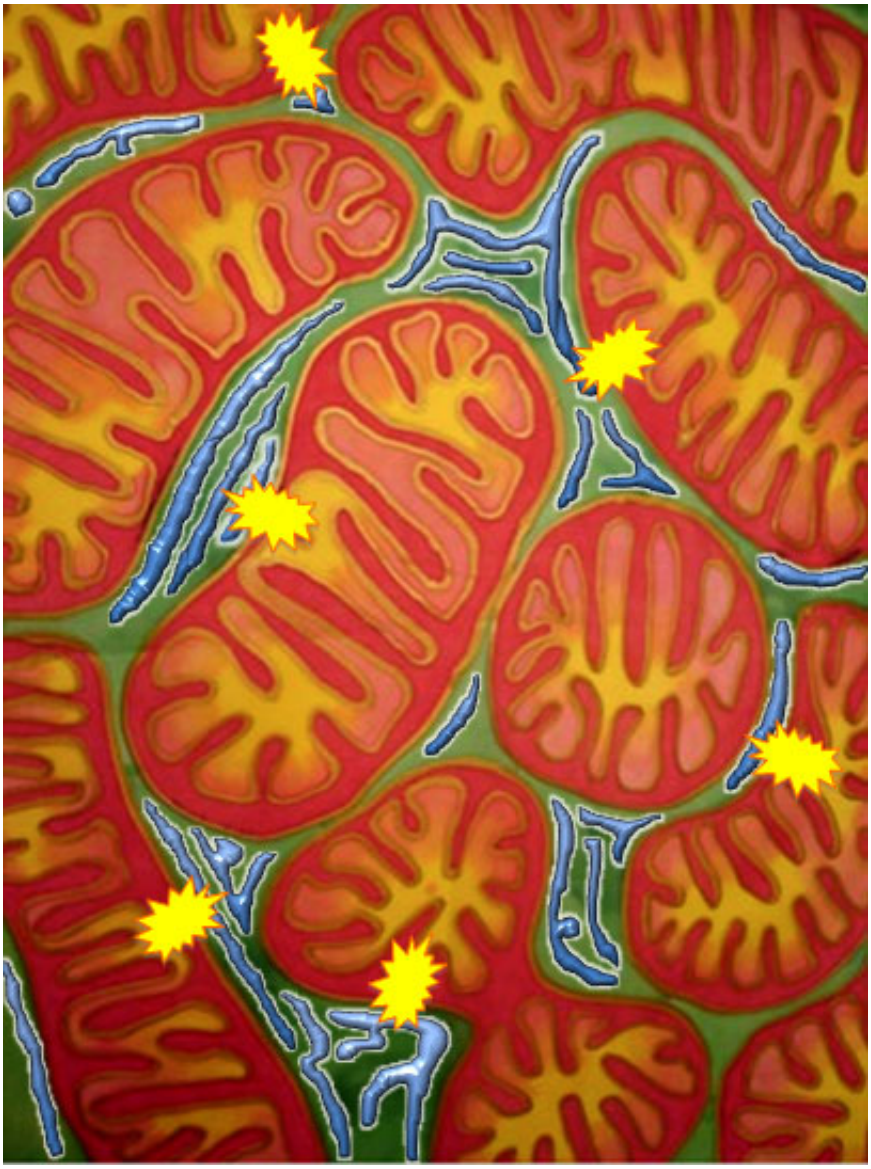
I got Speedy, an African spurred tortoise of species Centrochelys sulcata (they have their own closed Facebook group) at a reptile show when she was the size of an oreo. I should have realized that the fact that her natural habitat south of the Sahara was not exactly like that of the northeast US might be a limitation. But it was spring, and Speedy happily munched the lawn for months.

She grew. Fast.

By the time Speedy was three or so, she barely fit through my office doors, had taken to moving the furniture around at night, and her bi-monthly bowel movements had become an all-day affair requiring quarantine in the bathtub while I shoveled out the mess from my office. She was happy enough in my garden during the summer, but over the winter was clearly growing depressed.

I began reading about idiots who get baby tortoises and iguanas and then need to rehome them. So I found her a place at a tortoise ranch in Apple Valley, California, and found directions on the Internet on how to ship her. Only Airborne Express would take a live reptile, and her triple plastic crate contraption had to be festooned with "I am not a snake" stickers.

On a Monday at the end of summer, Speedy was all ready to go. I was so upset that I waited until the shipping store was about to close. Alas, I got there 5 minutes after the Airborne man had left.



Mitochondria have their own genomes, but the nuclear genome dwarfs it. Credit: PLOS Blogs

It was Monday, September 10, 2001.

Had Speedy shipped, she would have perished on a tarmac as the twin towers came down and airport traffic stalled for days.

Shaken, I held onto Speedy another month, and then off she went. The Airborne person in California let her sit in the passenger seat, freed from her packaging, and she eventually found love with a wealthy male Sulcata flown down by private jet, catapulted from his Napa Valley home due to his increasing size, and even laid an egg. Happy ending.

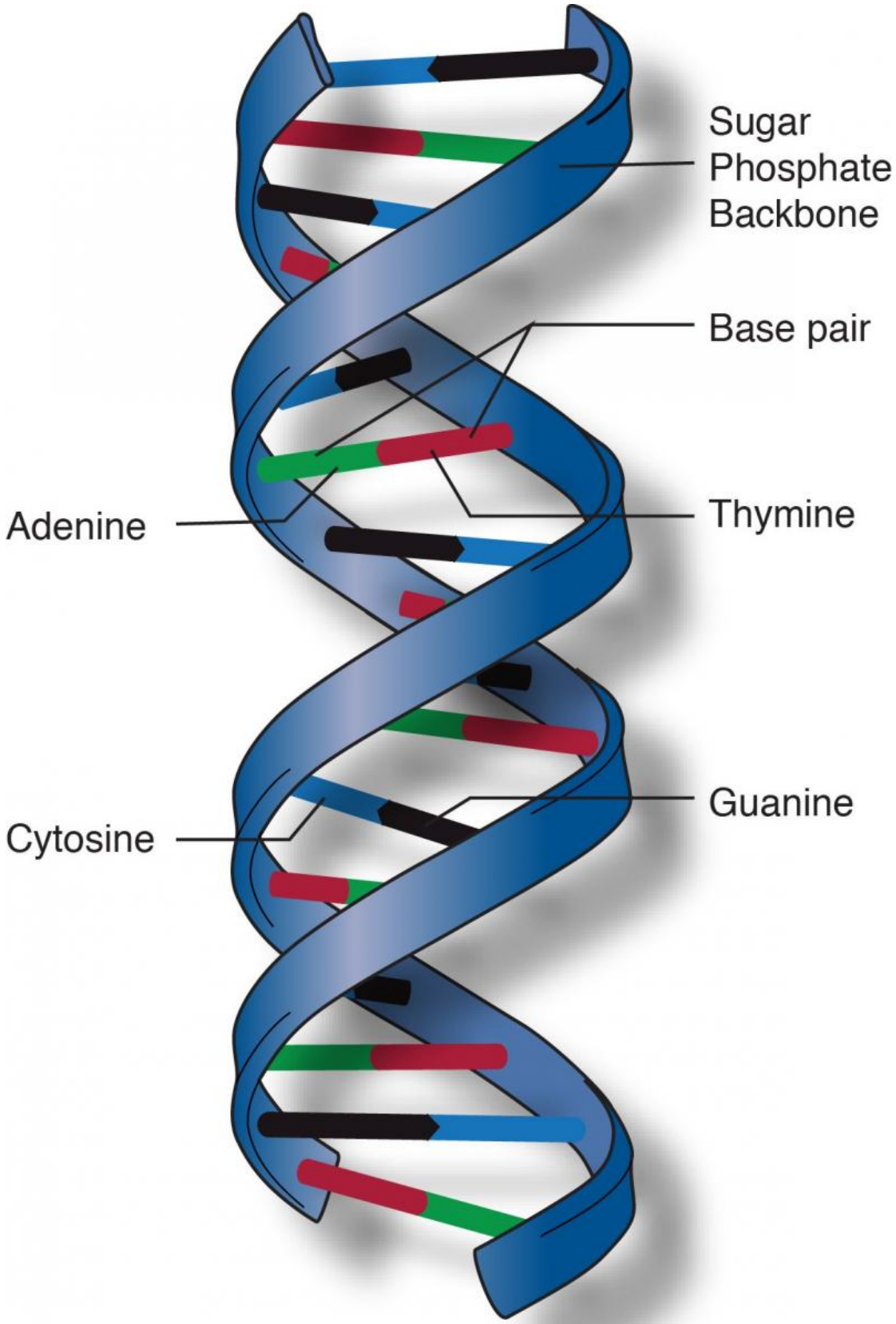
Bypassing Genetic Errors

I've always wanted to tell Speedy's story, so went in search of a genetics connection so I could do so here, at the DNA Science blog. And I found a great one! If I'd only known to look into her mitochondrial genome, I might have seen that Speedy and a few select other species can ignore certain devastating mutations.

According to a paper from 2008 in the *Journal of Molecular Evolution* by R. David Russell and Andrew T. Beckenbach, a few species of birds and turtles/tortoises, one genus of ants, the eastern oyster, and a glass sponge can bypass certain types of mutations in their mitochondrial genomes. (Mitochondria are the organelles that extract energy from nutrients, and they have their own tiny genomes).

Specifically, chickens, Parker's snake-neck turtles, the red-eared slider turtle, and sulcata tortoises like Speedy can survive a frameshift mutation that disrupts the 3-bases-in-a-row pattern of genetic information, or ignore inappropriate "stop" signals in a DNA base sequence.

An Aside on the Genetic Code: An Oft-Misused Term


Sugar
Phosphate
Backbone
Base pair
Adenine
Thymine
Guanine
Cytosine

The genetic code is universal. All species use the same DNA triplets to specify the same amino acids. Credit: PLOS Blogs

"Genetic code" refers to the correspondence of three-letter "words" in a sequence of DNA bases with three-letter words transcribed into the intermediate language of RNA (codons) that in turn are translated into the amino acids that build proteins.

The beauty of the genetic code is its universality – a DNA triplet of CCG encodes an RNA triplet of GGC, which encodes the amino acid proline, whether in a badger, a buttercup, or a bacterium. CRISPR-Cas9 genome editing, gene therapy, transgenics and knockouts, even the ancestral biotechnology of recombinant DNA, wouldn't exist without this universality. No, we don't have a "human genetic code", and no, National Geographic cover story, we're not trying to "change the genetic code of mosquitoes." To use "genetic code" and "DNA base (or genome) sequence" interchangeably, as the media so very often do, is to ignore the very basis of the existence and evolution of life on earth, the shared genetic code.

Frameshifts

A frameshift mutation is a particularly devastating sort of genetic glitch, often termed "catastrophic," because it alters that exquisite symmetry of three in the code by adding or removing one or two DNA bases. Imagine adding a "z" to the following sentence built of 3-letter words:

The big red dog ate the rat

Add an X and shift where the words form and the message becomes: The bXi gre ddo gat eth era t

The genetic gibberish of frameshifts may arise when DNA strands that have many short repeated sequences mispair during replication, like having difficulty finding your place in a page of text that repeats the same phrases in many places. The fact that frameshifts are rare compared to missense mutations, which swap one amino acid type for another, could reflect their severity. Organisms with them might not survive for long.

Still, frameshift mutations lie behind inherited diseases. The three "Ashkenazi mutations" for BRCA breast cancer, for example, are deletion of two bases or insertion of one in BRCA1 and deletion of one base in BRCA2.

Some glass sponges ignore frameshift mutations. Credit: PLOS Blogs

The strange collection of organisms examined in the 2008 paper have a "+1 frameshift insertion" in a gene called nad3, which has to do with the respiratory pathways in the mitochondria. I indeed found a +1 frameshift in the mitochondrial DNA of a family of humans in what may be the counterpart of the bird/turtle gene, but called the ND1 subunit of complex 1. The family members who have the mutation, all female, have early-onset dystonia (muscle spasms) and cataracts.

From Tortoises to Humans?

I pondered the possible utility of sulcata tortoises as an animal model, but the lifespan of a century, compared to two years for a mouse, was a definite negative. Owners have to put their sulcatas in their wills. A chicken model will have to do – birds and reptiles share a common ancestry that still echoes in today's shared DNA sequences.

I think we have something to learn from how the protein synthetic machinery of some birds, turtles, and tortoises can seemingly glide right over genetic errors. Conclude the researchers from 2008, "Turtles, for reasons that are not entirely clear, appear to exhibit a wide variety of the features requiring recoding of translation. Their mitochondrial genomes are evidently susceptible to both frameshifting and codon redefinition. Frameshift insertion mutations have now been documented at six separate sites, in three different genes." Maybe they're aliens.

A promising precedent for altering how proteins are made is the exon-skipping drugs now in clinical trials and nearing FDA approval for Duchenne muscular dystrophy (DMD). These drugs remove the parts of the dystrophin gene that harbor nonsense mutations, which otherwise insert a premature "stop" signal, resulting in a protein too puny, or absent altogether, in the muscles of affected boys. I summarized in Rare

Disease Report approaches for tackling DMD. Some birds and reptiles can ignore premature stop codons too.

It's nice to write about Speedy. But more importantly, finding that 2008 paper made me appreciate anew how valuable it is to understand the genetics of a variety of species. Thanks Buzzfeed!

More information: R. David Russell et al. Recoding of Translation in Turtle Mitochondrial Genomes: Programmed Frameshift Mutations and Evidence of a Modified Genetic Code, *Journal of Molecular Evolution* (2008). DOI: 10.1007/s00239-008-9179-0

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