Charles Darwin was a brilliant naturalist who recognized many biological connections through his observations of the natural world. Darwin would no doubt revel in our ability to draw biological inferences from DNA sequences. Of course, we also know that biological inference and biological content are easily conflated and that genomics can only take us so far without proper authentication via empirical biology. Here, I will discuss some recent efforts in my lab in which unique features of genomes provided insight into problems such as the emergence of adaptive immunity, the vertebrate aquatic-to-terrestrial transition, and noncanonical roles for the glycopolymer, chitin. My thesis is that, while comparisons of the “known” genetic components between species are important and necessary, many salient biological insights will be gleaned only when specifically looking for, and investigating, the differences among lineages. I shall discuss broad implications from our work and how these have led to empirical inquiries at multiple biological levels (genes, cells, tissues, organisms, ecosystems).