

Excerpt from *Animal Models in Light of Evolution* (p151-4):

In any given species, one or more of these cohesion mechanisms may be at work, but it may also be the case that mechanisms at work in one species may not be at work in another. Stabilizing selection, for example, might maintain the cohesion of an asexual bacterial population, while gene flow and developmental constraints might be at work in a sexual population. Some sexual populations are reproductively isolated from other such populations, while others hybridize. As Price [(Price 1996) p69] has noted, even hybridizing species usually retain distinctive species characteristics, with the hybrid zones where the hybrids flourish typically being narrow.

Evolutionary biologists have thus come to realize that the natural discontinuities that constitute species differences are the results of complex dynamical processes involving a multiplicity of mechanisms. How, then, do species differ? Where do new forms or morphologies come from? These questions will be deferred to a later chapter, where evolutionary developmental biology will be discussed. There is an issue that must be mentioned here, however, because of the way in which we have presented evolutionary biology from the standpoint of Mendelian genetics and population genetics. There is a growing consensus that evolutionary biology, as it emerged from the study of population genetics, is fundamentally incomplete. Currently, efforts are underway to incorporate into evolutionary biology insights derived for developmental genetics. In particular, as Gilbert and Burian have recently noted:

. . . the population genetics approach to evolution focuses primarily on genes that affect adults and their impact on competition for reproductive success, whereas the developmental genetics approach to evolution focuses on genes expressed during development, their interactions, and their impact on the ontogeny of the organism. [(Gilbert and Burian 2006) p71]

The incorporation of developmental genetics into evolutionary biology has resulted in considerable enrichment of an already fruitful branch of science. We explore some relevant details in the next chapter.

For the present, however, we note that the relationship between structural genes and the proteins they make has turned out to be somewhat complicated. The old idea of “one gene, one protein” no longer holds true. Alternative splicing of the primary RNA transcript has shown that different proteins can arise from the same DNA segment. Posttranscriptional modification of RNA transcripts (RNA editing, e. g., C to U conversions in an RNA transcript) also influence coding specificity [(Li 1997) p308]. It has recently been estimated by Szathmáry et al. (Szathmáry, Jordan, and Pal 2001) that in humans at least 35% of the gene transcripts undergo alternative splicing (see Figure 7.1). Theoretically, alternative splicing and RNA editing could generate 1,032,192 mRNA transcripts (each encoding a slightly different protein) from the *Drosophila para* gene (encoding a sodium channel) (Szathmáry, Jordan, and Pal 2001). Various spliceome projects are underway to study this phenomenon.

In a similar vein, according to Ledford:

Genome-wide surveys of gene expression in 15 different tissues and cell lines have revealed that up to 94% of human genes generate more than one product . . . Only about 6% of human genes are made from a single, linear piece of DNA. Most genes are made from sections of DNA found at different locations along a strand. The data encoded in these fragments are joined together into a functional messenger RNA (mRNA) molecule that can be used as a template to generate proteins. (Ledford 2008)

From the standpoint of human evolution, the role of alternative splicing in the evolution of the human brain has been of much interest. As observed by Bray:

. . . humans have just three genes encoding neuronal cell surface proteins called neuropins. However, through alternative promoters and alternative splicing, these three genes yield thousands of different isoforms expressed in distinct combinations on the surfaces of different neuronal cell types. Taken together with all other sources of molecular variation, it seems likely that each cell in an organism—even the estimated  $10^{11}$  nerve cells of the human nervous system—is chemically unique. (Bray 2003)

More recently, Lu et al. (Lu, Peng, and Su 2007) have shown that alternative splicing accounts for the existence of a human-specific, type II form of neuropsin, a protein involved in learning, memory and other aspects of human cognition.

Goldstein and Cavalleri (Goldstein and Cavalleri 2005) estimate that the human genome has around \$" million polymorphisms. Genes can vary because of numerous factors (see Figure 7.2). A gene can be deleted or inserted, can be inverted or a segment can be duplicated, the number of copies of a gene can vary. Genes can have single nucleotide polymorphisms (SNPs) where the usual nucleotide is substituted (adenine for cytosine, for example). These changes have consequences. Redon et al. (Redon et al. 2006) found a surprising number of copy number variants (CNVs) among humans. A copy number variant is exactly what it sounds like: a different number of copies of a given gene. For example you might have one copy of a gene that metabolizes a drug while your neighbor might have 10 copies. Depending on the nature of the copy number variant, your neighbor may likely metabolize the drug more rapidly than you will. Redon et al. discovered that at least 10 percent of genes in the human population can vary in the number of copies of DNA sequences they contain. These variations can greatly influence enzyme activity and a human's response to drugs and disease. For example, Gonzalez et al. (Gonzalez et al. 2005) studied genetic variation among African, European, Asian and American populations. They found that extra copies of the gene responsible for making CCL3L1, helped protect people against HIV-\$ and discovered that if people with extra copies became infected with HIV-\$, they progressed more slowly to AIDS.

As reported by Check, different patterns of copy number variation exist even between very closely related species and may indeed be medically significant:

And studies comparing us with our chimp cousins have already linked structural variation to our divergence from the apes. Last year, scientists from the University of Colorado in Denver and Stanford University found 1005 genes that differed in copy number among humans and four other primates. This month,

Eichler's group reported 651 likely structural rearrangements between chimps and humans. The group counted 245 genes contained in these variants, including some genes involved in reproduction and drug metabolism. Eichler's group has also found that segmental duplications have created much more of our genomic differences from chimps than single base-pair differences. There are 177 genes contained within the human-specific duplications. As such duplications are hotspots for evolution, those 177 genes could be partly responsible for creating the traits that make us human. These genetic differences could also be useful. Scherer's lab has just released a targeted analysis of inversions between the chimp and human genomes. The group found 1576 probable inversions, and confirmed 23; three of these differed among human individuals. Not only does this shed some light on primate evolution, but as inversions can often predispose DNA to harmful mutations, these inversions might be involved with human disease. (Check 2005)

We will have more to say about copy number variation when we focus our attention on matters generated by the metabolism of xenobiotics both from the standpoint of intraspecific variation and interspecific variation. It will turn out to be a complicating factor for the use of nonhuman species as *CAMs* of human biomedical phenomena.

ANIMAL MODELS IN THE LIGHT OF EVOLUTION

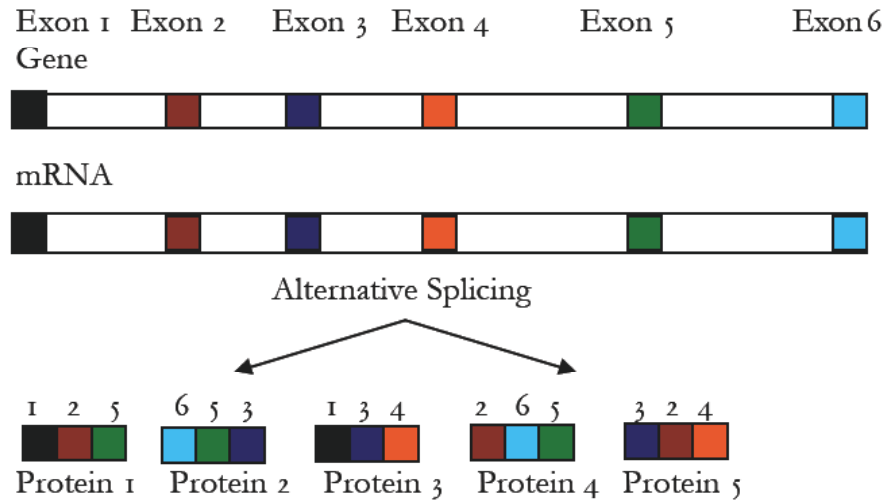


Figure 7.1. Alternative splicing

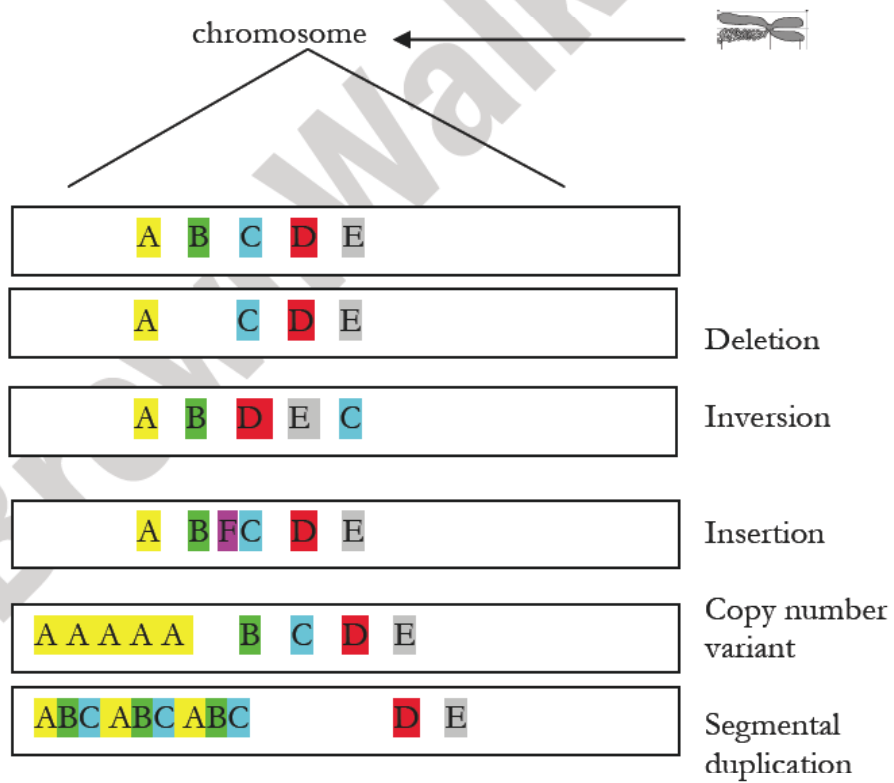


Figure 7.2. Gene variations