

Chapter 9

Web Text Box 2

When a different amino acid will do: conservative mutations

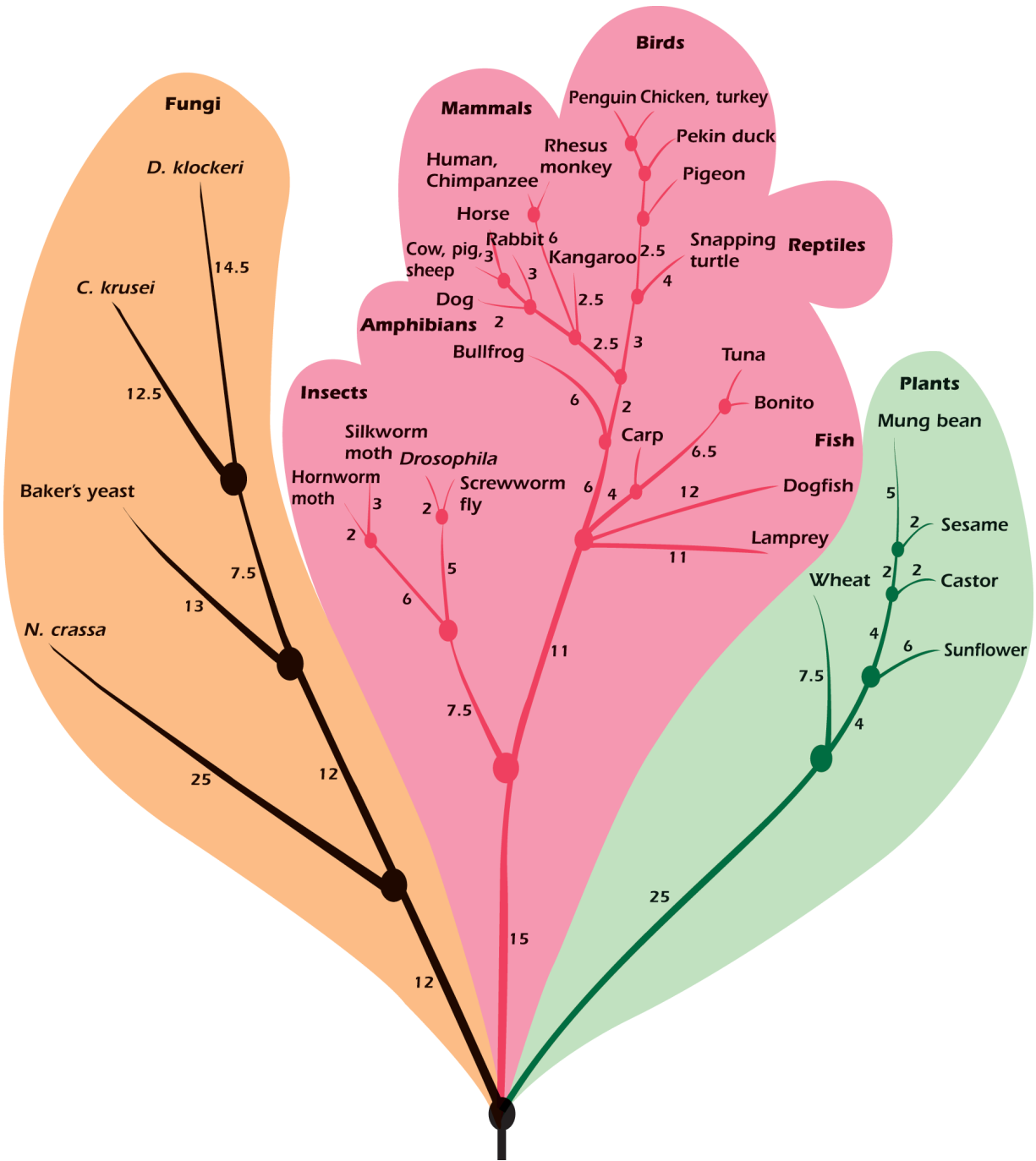
If a mutation results in a different amino acid being coded then the mutation is said to be missense (book page 64). Changes in side chains that are involved in binding substrates or cofactors, that interact with other proteins, or that participate in catalytic mechanisms are very likely to alter or destroy the protein's function. Evolution will weed out such deleterious mutations. However, mutations in other regions of the protein may be tolerated, as long as the change does not destroy or seriously alter the protein's function. Some missense mutations are said to be "conservative" as the changed amino acid residue has a similar property to the original residue (see Figure 9.2 on book page 139). For example an aspartic acid residue might be replaced by a glutamic acid residue without altering the function. Threonine may replace serine, asparagine may replace glutamine, and arginine may replace lysine. Although they are often involved in closely packed protein interiors, aliphatic nonpolar amino acids may sometimes be changed amongst themselves: alanine may sometimes replace leucine and isoleucine may replace valine without serious alteration of function. Change of an amino acid on the surface of a protein may be less deleterious than a change of one in the interior, given the caveats listed above. In some cases even a change of amino acid type (e.g. charged to uncharged) may be accepted on the protein surface.

Mutations will accumulate in a protein over millennia. The rate is constant for a single protein and each protein will have its own rate at which mutations are accrued, because each protein will have a different number of amino acid residues that are critical to its function. Histones (book page 57) are extremely highly conserved. It takes 600 million years from the time two species diverged for 1% of the amino acids in histones to differ. For comparison cytochrome c diverges to the same extent in 20 million years and

hemoglobin in 5.8 million. Comparisons of the sequences of the same protein in different species help to pinpoint those residues that are structurally or functionally vital as these will not change. Sequence data allows biologists to construct evolutionary trees.

Cytochrome *c* is a good example as it is small at 104 amino acids, and therefore less challenging to isolate and to sequence, but is a vital part of the electron transport chain in eukaryotes. The residues binding the haem are invariant. There are nine invariant glycines (where larger side chains would seriously distort the structure) and there are nine invariant lysines in a ring around the exposed edge of the haem. These positive charges probably allow binding to negative charges on complex III and complex IV (book page 197) to allow electron transfer to and from the cytochrome *c*. Preservation of these invariant amino acids has preserved the function of cytochrome *c* essentially unchanged, so that for example mammalian cytochrome *c* will function with components from yeast. Nevertheless mutation has occurred in the 1.5 to 2 billion years since cytochrome *c* evolved (when cells began respiring using oxygen). Over 100 species have had their cytochrome *c* sequenced and these differences used to construct the evolutionary tree on the next page.

Genetic engineers often introduce conservative mutations (called site directed mutagenesis) to study the role of particular amino acids. Replacement of a serine or threonine by an aspartate or glutamate introduces a negative charge that mimics the effect of phosphorylation of these residues (book page 142).



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