Figure 2: Evolutionary conservation in different contexts. Evolutionary conservation can be inferred via sequence comparison in different contexts. (A) The examination of sequence conservation in orthologous sequences *across multiple species* looks at a longer evolutionary timescale. (B) The examination of the enrichment of rare variants (or depletion of common variants) in the same genomic element *across multiple individuals within a single species or population* looks at a shorter evolutionary timescale. Here, the red diamonds denote variants that are rare in a single human population (found in only one or a small number of individuals) and the blue diamonds denote variants that are commonly found in multiple individuals in the population. (C) The examination of sequence conservation in *similar protein domain sequences within a single genome* can reveal species- and domain-specific conservation that might be important to the structure or function of the domain family. (D) To illustrate (C), we use ankyrin protein domains as an example. We translate the DNA sequence of each ankyrin domain into its amino acid sequence. In order to relate the positions of the linear sequence of an ankyrin repeat domain to their structural locations, we then specifically paint each of the six ankyrin domains found in the structure of the human Notch 1 ankyrin domain (PDB ID: 1YYH) similar to the sequence profile in (E). (E) The top plot in this panel is the sequence profile of an ankyrin repeat domain with 30 amino acids, colored by position left to right, from green to yellow, corresponding to the coloring of the motifs of the human Notch 1 PDB structure in (D). In the sequence profile, the height of the amino acid letters connotes the degree of conservation of a particular residue at a specific location along the ankyrin repeat; the degree of conservation is computed using relative entropy in bits of information. To examine evolutionary conservation in more detail, the sequence profile can be further analysed with genomic variant profiles. For example, for each of the position along the ankyrin motif, the second plot shows the absolute numbers of variants binned into four categories: cyan bars show the number of variants that are common (c) and synonymous (s); blue bars for variants that are common and non-synonymous (ns); pink bars, rare (r) and synonymous; red bars, rare and non-synonymous. Subsequently, we can derive log ratios from these numbers to demonstrate an enrichment (or depletion) of categories of variants, in order to gain further biological insights. Here, the third subplot displays a general enrichment of rare variants relative to common variants across the entire motif, suggesting a uniform evolutionary importance of the ankyrin domain in the human population. However, the fourth subplot exhibits a depletion of nonsynonymous variants relative to the synonymous variants at more conserved motif positions (in the sequence profile), hinting at only a *subset* of positions being of particular functional importance to the ankyrin domain family.