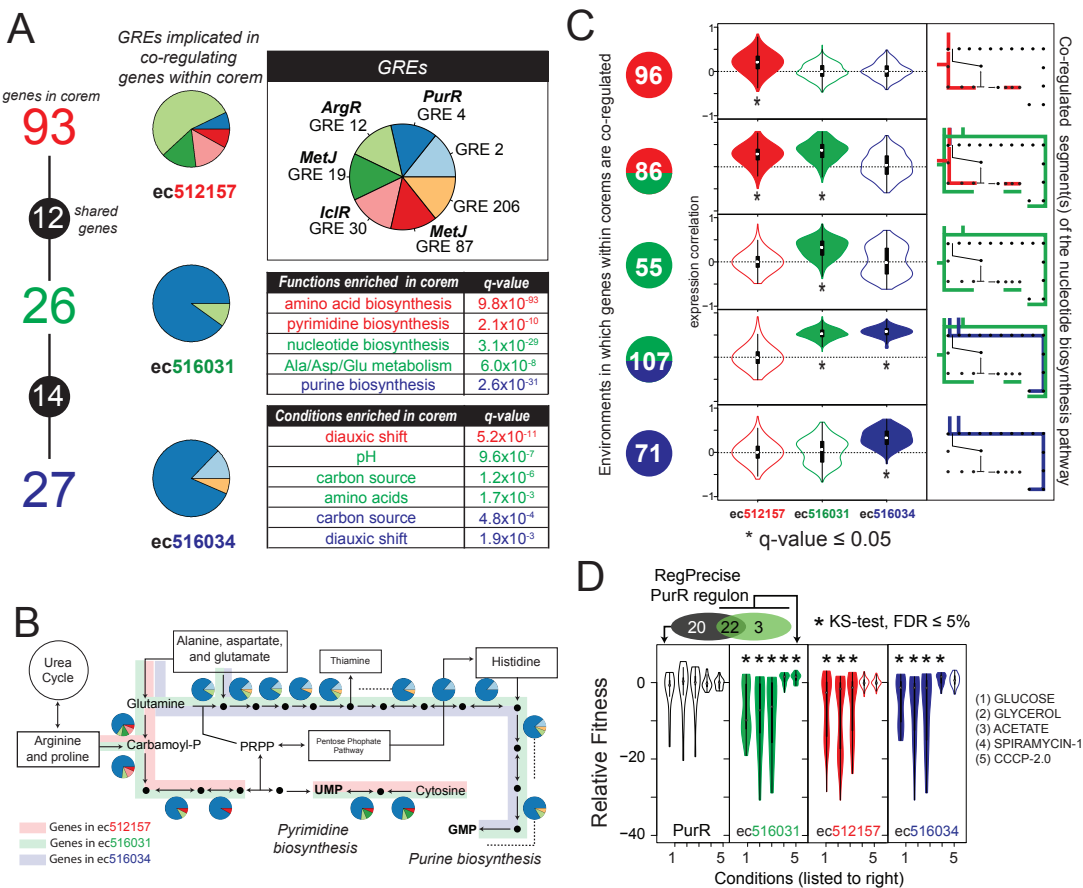


**Figure 4: Varying combinations of GREs act conditionally to subdivide and coordinate branches of the nucleotide biosynthesis pathway in an environment-dependent manner**



**Figure 4. Varying combinations of GREs act conditionally to subdivide and coordinate branches of the nucleotide biosynthesis pathway in an environment-dependent manner**

(A) Genes of nucleotide biosynthesis are distributed in overlapping combinations across three corems: purine (ec516034 – “purine corem”), pyrimidine (ec512157 – “pyrimidine corem”), or both pathways (ec516031 – “nucleotide corem”). (Left) Gene membership and overlap for the three corems as in Figure 3C. Pie charts indicate average GRE composition across all gene promoters in each corem (see Figure S3B for detail). (Top-Right Inset) GRE key for pie charts. Matches to TFs in RegulonDB noted above the GRE name. (Bottom-Right) Tables list enriched gene functions (40) and environmental conditions for each of the corems (see Supplementary Methods).

(B) A portion of the nucleotide biosynthetic pathways, near the branch point dividing purine (top) and pyrimidine (bottom) biosynthesis. Pie charts represent GRE composition in each gene promoter (Key in (A)). Operons denoted by dashed lines, with only the leader gene’s promoter architecture shown.

(C) Condition-specific co-expression of genes across the three corems. (Right) The active segments of nucleotide biosynthesis (as in B) are color-matched to corems. (Center) Violin plots show distributions of expression correlations between genes within each corem in relevant environmental conditions, when they are predicted to be co-regulated. Color fill and asterisks indicate corems with significantly low relative standard deviation (RSD;  $|\sigma/\mu|$ ; FDR  $\leq 0.05$ ). (Left) Colored circles indicate when genes within which corem(s) are predicted to be co-regulated (color) under how many conditions (number).

(D) Distributions of relative fitness values for gene deletions in the three corems, as well as 20 of the 42 PurR regulon genes not modeled by ec516031 (black) across 5 representative conditions (condition identifiers listed to right, additional conditions in Figure S6B). Asterisks denote conditions in which the distribution of fitness values is statistically significant (relative to the distribution of fitness values for all genes in that condition).

See also Figure S6A-B.