A phylogenetic protein-coding genome-phenome map of complex traits across 224 primate species

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Abstract.

Complex traits arise from networks of coding and regulatory loci, making their genetic basis difficult to resolve. Macroevolutionary studies leverage millions of years of divergence across species to uncover fixed genomic changes invisible to within-species approaches like GWAS. Studying variation in mammals and primates offers insights into the evolution of complex traits and provides a complementary framework for generating hypotheses in biomedical research. Here, we present the first phylogenetic protein-coding, primate-wide genome–phenome map (P3GMap), spanning 263 traits across 224 primate species, which we release through the Primate Genome-Phenome Archive (PGA, https://pgarchive.github.io). Using two complementary approaches, convergent amino acid substitutions and relative evolutionary rates, we link protein-coding variation to complex phenotypes and identify thousands of gene-trait associations, including lineage-specific adaptations in diet, immunity, and lifespan.

One sentence summary: Cross-species genome-phenome mapping in primates reveals thousands of protein-coding variants linked to complex trait evolution.

Authors Contributions

Author contributions were defined according to the CRediT taxonomy (https://credit.niso.org/). Alejandro Valenzuela (affiliations 1,2) led data curation, formal analysis, investigation, methodology, visualization, validation, and contributed to the original draft as first author. Fabio Barteri (1,4,9) contributed to investigation, methodology, visualization, and writing as co–first author. Claudia Vasallo (4) carried out investigation and validation. Lukas Kuderna (10) and Joseph Orkin (11) contributed to data curation. Jean Boubli (12), Amanda Melin (13), Hafid Laayouni (1), Kyle Farh (10), and Jeffrey Rogers (14) provided supervision. Tomàs Marquès-Bonet (1) contributed to funding acquisition and supervision. Gerard Muntané (5) contributed to conceptualization and methodology and served as co–corresponding author. Arcadi Navarro (1,2,3,5,6,7,8,9) contributed to conceptualization, funding acquisition, methodology, project administration, and resources, serving as co–corresponding author. David Juan (15) contributed to conceptualization and methodology and served as corresponding author. All authors participated in writing – review and editing.

1. Introduction.

Complex traits arise from the interplay of genetic and non-genetic factors. Genetic contributions are typically distributed across interacting coding and regulatory elements. This multilayered organization makes the genetic basis of phenotypic variation difficult to resolve. Much of our knowledge on the genetic architecture of complex traits originates from studies of model organisms (1–3) and human genome-wide association studies (GWAS) (4–7), which link genomic and phenotypic variation within populations. Although powerful, GWAS capture only segregating variation within contemporary populations and miss fixed substitutions along evolutionary lineages, changes that often underlie major phenotypic shifts and whose study may unveil loci of strong biological interest (8,9).

Macroevolutionary analyses address this gap by testing whether genetic elements are associated with traits across species. Phylogenetic Comparative Methods (PCMs) (9–12) exploit millions of years of divergence to reveal associations involving gene gain and loss, protein evolution rates, structural variants, and point mutations (13–16). PCMs have revealed the genetic architecture of key traits in human evolution, such as brain size (17,23,24) and maximum lifespan (25–28).

The growing availability of high-quality genomes now enables scalable, cross-species genome–phenome mapping. Leveraging high-quality assemblies from 224 primate species (29), we created the first phylogenetic protein-coding genome–phenome map (P3GMap), publicly available through the Primate Genome–Phenome Archive (PGA, https://pgarchive.github.io). This resource integrates 263 complex traits across primates and reveals thousands of coding variants associated with phenotypic evolution.

To illustrate the scope of the resource, we examined three case studies: insectivorous diet (30,118–120), white blood cell count (140,141), and maximum lifespan (25–28). For each of these traits, we defined phenotypic *Contrasts* as pairs of species from different lineages that show marked differences in trait values, and we used these to identify genes and individual substitutions consistently associated with the trait. These case studies exemplify how researchers can use the PGA to move from a trait of interest to candidate coding changes and pathways that may underlie its evolution.

2. Results

2.1 The Primate Phenomic Space

We compiled phenotypic data for 224 primate species by integrating the average species values of 263 quantitative and qualitative traits derived from over 800 measurements obtained from public sources (30–33). These traits were classified into five primary domains (behavior, 29 traits; ecology, 7; life history, 29; morphology, 93; and physiology, 67) and 15 secondary domains (Fig. 1, Methods, Table S1), thereby defining the primate phenomic space for comparative analyses. As data density varies across clades, comparisons should be constrained to sets of species with similar information. To do so, we applied supervised clustering to group traits into 13 categories based on phylogenetic sampling (Fig. 1, SM). Body mass-related traits were among the most consistently represented, explaining among 15–23% of the variance in the first component for clusters VIII–X (see Fig. 1A). To control for allometry (34–38), we corrected 74 morphological, 14 life history, and two physiology traits for *Adult Body Mass* (Data S1). The curated dataset is publicly available from the Primate Genome–Phenome Archive (PGA, https://github.com/pgarchive/data.2.2).

We conducted a genome-phenome analysis of protein-coding sequences to create the first P3GMap (also available on the PGA web). This resource catalogues associations between protein-coding genes and diverse phenotypes across primates. The map comprises alignments for 16,133 one-to-one orthologous genes, over 75% of which include more than 200 species (Fig. S1, SM). To detect genetic factors that correlate to phenotypic evolution, we applied two conceptually distinct approaches: Convergent Amino Acid Substitutions (CAAS) using CAAStools (40; SM CAAStools), and relative evolutionary rates (RERs) using RERconverge (39; SM RERconverge). These methods capture genome-phenome associations across a broad range of evolutionary scenarios, beyond classical positive selection signatures (9,11,13). To ensure consistency and scalability, we implemented a standardized strategy for cross-trait comparisons, providing a unified framework for mapping genome-phenome relationships in primates.

2.2.1 Convergent Amino Acid Substitutions Associated with Phenotypic Diversity

For each trait, we identified CAASs between species with diverging trait values. For continuous traits, we selected species with higher trait values (*Top*) and species with lower trait values (*Bottom*) (see Fig. 1B–C, Figs. S24–S27, Data S1, and for details SM A.1–A.4). For categorical traits, we compared species annotated with different labels (*e.g.*, *Diet*: gummivore vs insectivore). To ensure independence, the standard strategy emphasized *Contrasts* within families. Of the analyzed traits, 83 (37%) showed at least one intra-family

Contrast, and 63 showed at least one *Contrast* in two or more families. Traits in widely distributed clusters (WD) more frequently exhibited multiple *Contrasts (*~23%). In contrast, intermediately distributed (ID; ~60%) and Strepsirrhine-centered (STR; ~54%) clusters showed a high fraction of traits without *Contrasts*, reflecting both coverage limitations and the predominance of inter-family over intra-family variation in quantitative traits.

To apply CAAS and RER methods, we constructed a dataset of curated multiple sequence alignments of one-to-one orthologs extracted from a recently sequenced set of 233 primate genomes (29). Using CAAStools for these alignments with phylogenetic correction via permulations (41) and per-trait multiple testing (SM A.4), we detected 29,155 significant CAASs in 8,780 genes across 76 traits ($p_{permul\text{-}FDR} < 0.05$). This yielded in a median of 49 genes and 51 positions per trait (Fig. 2A, Figs. S28–S31, Data S2), providing a large-scale resource for studying candidate molecular convergence. These associations reflect fixed amino acid substitutions accumulated along evolutionary lineages rather than segregating variation within species.

We assessed the consistency of these discoveries using the set of primate species not involved in the discovery process, employing *PGLS* for quantitative traits and *phyloglm* for qualitative traits (see SM Internal phylogenetic test in primates; Fig. 2C, Fig. S39). This approach is conservative because it excludes extreme species from the consistency-checking step. As a quality control step, we focused on the ten traits with fewer than 100 validated associations, reducing the impact of non-specific associations ($p_{PGLS\text{-}FDR} < 0.05$, $p_{phyloglm\text{-}FDR} < 0.05$), recovering both known signals and novel candidate associations (Suppl. Table S3). Representative examples include associations between *Body Mass* and mitochondrial genes *NDUFS7* (substitutions Y223L, R230H, K231G, I232A; $p_{PGLS} = 1.37 \times 10^{-5}$–$3.57 \times 10^{-5}$) and *NOXO1* T/V223A ($p_{PGLS} = 2.06 \times 10^{-7}$); the immunoglobulin gene *ICAM1* R/V418M ($p_{PGLS} = 2.39 \times 10^{-5}$) (52); also the association of *Lactation Period Length* with *MEFV* K/R546Q ($p_{PGLS} = 1.66 \times 10^{-6}$), a regulator of innate immunity and familial Mediterranean fever (53–55). Additionally, we tested ten equivalent traits in non-primate mammals to determine whether their 4,968 CAASs exhibited consistent effects in the mammal phylogeny. Despite being highly conservative, this test yielded far more consistency than expected by chance ($p_{binomial}$: 4.07×10e−6, see SM, Suppl. Table S4). Representative cross-mammalian examples include *NELL1* Q176RN for *Lactation Period Length* ($p_{PGLS} = 1.09 \times 10^{-4}$), which has been previously associated with delayed milk production in goats (56) and to cranial bone development (57–59), and *MPDZ* H/P956Q for *Gestation Period Length* ($p_{PGLS} = 1.65 \times 10^{-5}$), a gene whose mutations cause congenital non-communicating hydrocephalus (60,61).

2.2.2 Relative Evolutionary Rates and Trait Associations

While CAASs detect genome–phenome associations independently of the underlying mechanism, relative evolutionary rates (RERs) identify genes whose evolutionary rates covary with trait changes, which is consistent with positive or purifying selection. We applied RERconverge to 16,109 the multiple sequence alignments of orthologous coding genes and 200 quantitative traits (see SM 3.1.1, RERconverge), assessing significance using permulations (41; SM 3.1.1.1). This analysis yielded 3,911 genes significantly associated with 194 different traits ($p_{permul\text{-}FDR} < 0.05$), with a median of 19 genes per trait, summarized across domains (Fig. 2A, Figs. S28–S31, Data S2). Because RERconverge applies less conservative corrections than CAAStools (SM 3.1.1), we also required FDR-corrected parametric p-values, which were broadly consistent with permulation statistics (SM 3.1.1.1).

RERconverge revealed biologically relevant signals (SM 3.1.1, Table S2), including *NKX6-2* for *Percentage of Time Moving* (Rho = 0.62; $p_{permul\text{-}FDR} < 10^{-3}$) which has been linked to spastic ataxia (42,43); *DEFA5* for *Percentage of Fauna Ingest* (Rho = –0.5; $p_{permul\text{-}FDR} < 10^{-3}$) which is a defensin gene associated with gastritis (44); and *DESI2* for *Mesencephalon Relative Size* (Rho = 0.69; $p_{permul\text{-}FDR} < 10^{-3}$), which is implicated in amyotrophic lateral sclerosis type 5 (47).

2.3 Functional analysis of the P3GMap

We performed over-representation analyses to evaluate biological functions associated with the discovered P3GMap genes. Genes with significant CAAS were associated with 199 unique enriched terms across 27 traits, each exhibiting at least one enrichment (Suppl. Data S3). Body mass–related traits were enriched for DNA repair categories, consistent with previous findings in *Carnivora* (87) and with the identification of DNA repair genes as anti-cancer targets in long-lived species (28,48,88–90) (Suppl. Table S5). The trait *Percentage of Time with Social Activity* showed enrichment for chromosome breakage (ER = 7.21; $p = 4.53 \times 10^{-7}$) and Fanconi anemia (ER = 4.73; $p = 3.03 \times 10^{-5}$), which are linked to developmental disorders (91,92) (Fig. 2D-E).

Across 48 traits, 94 enriched terms were found for significant RERconverge genes. These included *Long Philtrum* (distance >2SD between nasal base and upper lip) which is associated with *Pallidum* (ER = 3.35; $p = 2.97 \times 10^{-6}$) and *Subthalamus Size* (ER = 3.34; $p = 3.12 \times 10^{-6}$). Nose morphology is a key distinguishing feature between Strepsirrhines and Haplorhines (62,63) and has been linked to human syndromes involving cognitive, sensory, and craniofacial abnormalities (64–68). Traits under sexual selection also showed enrichment: *Hair Dimorphism* with the MHC complex ($p = 7.76 \times 10^{-6}$), which has long been proposed to affect mate choice (73–77), although this remains debated in some taxa (78–82); and *Body Mass Dimorphism* with mammary

neoplasms (ER = 2.16; $p = 4.65 \times 10^{-6}$), which is consistent with the effects of sex-dimorphism on cancer incidence (83–85).

Examining trait relationships further refined functional interpretation. Gene set overlaps across domains (Fig. 2F) revealed 16 significant pairs for CAAS ($p < 1 \times 10^{-50}$), concentrated in *Trichromatic Color Vision* and *Brain/Body Mass*, suggesting pleiotropic effects across sensory and morphological systems. Five overlaps involved life history traits, such as *Age of Female at First Reproduction* with *Trichromatic Color Vision* and with *Maximum Young Adult Weight*; and *Gestation Period Length* with *Maximum Young Adult Weight* (including sex-specific values). These reproductive overlaps were prominent in Atelidae, where Ateles and Lagothrix show polymorphic color vision and Alouatta displays routine trichromacy (117), pointing to coordinated evolution of vision, reproduction, and somatic traits under ecological and social pressures.

RERconverge overlaps (11 pairs, $p < 10^{-30}$) emphasized longevity-related traits. Genes for *Percentage of Infant Mortality* overlapped with *Maximum Male Longevity* and *Gamma-Glutamyl Transferase Levels* (GGT) ($p = 4.46 \times 10^{-74}$, $p = 7.13 \times 10^{-39}$), an antioxidant enzyme linked to cardiovascular and neurological disease (100–106), lung inflammation (107), cancers (108–110), and mortality prediction (111). Genes linked to *Cholesterol Levels* overlapped with *Median Male Longevity* ($p = 6.74 \times 10^{-48}$), although cholesterol–mortality links remain debated (112). Genes linked to *Serum Oxaloacetic Transaminase Levels* (AST) overlapped with *Median Female Longevity* ($p = 2.18 \times 10^{-38}$); elevated AST is associated with mortality in liver, neurological, and cardiovascular diseases (113–116).

Family-level analyses revealed lineage-specific patterns. *Cathemeral Activity* (sporadic intense activity periods during day and night) shared gene sets with *Dichromatic Color Vision* ($p = 7.72 \times 10^{-49}$) and *Seasonal Breeding* ($p = 2.34 \times 10^{-200}$), mainly in Lemuridae. The trait *Solitary Social System* overlapped with *Monochromatic Color Vision* ($p = 2.98 \times 10^{-41}$) in Lorisidae and Galagidae, and with *Dichromatic Color Vision* ($p = 9.85 \times 10^{-48}$) in Lepilemuridae, Microcebus, and Nycticebus. These results suggest co-evolution of vision, reproduction, and social behavior in response to nocturnality, seasonality, and mating strategies.

Finally, we asked whether P3GMap-associated genes overlap with human GWAS loci. No significant enrichment was found, consistent with limited overlap between cross-species and within-population variation (SM 6.1–6.2). Moreover, 86.16% of CAAS positions are fixed in humans. This suggests a decoupling between macroevolutionary divergence and microevolutionary variation, reinforcing the complementarity of cross- and within-species approaches to disentangle the architecture of complex traits.

2.4 Targeted Case Studies of Complex Primate Traits

While the general analysis in the P3GMap framework enables consistent cross-trait comparisons across hundreds of phenotypes with RERconverge, CAAS, and other methods, tailored lineage-specific CAAS analyses can reveal mechanisms obscured in large-scale scans. To demonstrate this, we examined three unrelated traits from different domains: *Insectivorous Diet*, *White Blood Cell Count*, and *Maximum Lifespan*. First, *Diet* (a widely distributed trait) displayed one *Contrast* for insectivory, reflecting the propensity of broadly distributed, often qualitative traits to capture intra-family extremes. Secondly, *White Blood Cell Count* (Strepsirrhine-focused trait) presented two *Contrasts*, providing an example within a cluster that generally yields fewer contrasting cases. By comparison, *Maximum Lifespan* showed no contrasts, providing an example of a quantitative trait whose variation tends to manifest between families rather than within them. By tailoring species *Contrasts* to the particular phylogenetic distribution of each one of these traits, we identified additional gene sets that refined the functional interpretation and highlighted recurrent adaptive pathways. Thus, the case studies (Fig. 3A–C) demonstrate the potential of the PGA for trait-focused exploration, which complements the global view of the general analysis presented above. Additionally, to leverage the biological relevance of our approach, we also performed a natural selection analysis on these positions, revealing directional selection toward the adaptative amino acids (SM 3.2)

2.4.1 *Insectivorous Diet*

Diet is closely associated with traits such as *Brain Size* (118–120) and *Dentition* (121,122) in primates, including Strepsirrhines (120). For insectivory, the standard *Contrasts* involved Lorisidae (slender *vs*. slow lorises) and *Daubentonia madagascariensis* (Daubentiidae) as insectivorous, compared with non-insectivorous species from other families. In the tailored design, we included Tarsiidae as an additional insectivorous lineage alongside alternative non-insectivorous selections (Fig. 3A). This approach identified 619 positions across 537 genes, all of which were significant by permulations (Fig. 3D). These were enriched in four categories (pFDR < 0.05): apical part of the cell (GO:0045177, 19 genes), cargo receptor activity (GO:0038024, 8 genes), lipase activity (GO:0016298, 7 genes), and endopeptidase activity (GO:0004175, 14 genes). These categories were not detected in alternative species selections separately. These enrichments suggest that the epithelial surface is a hub for nutrient absorption, which is consistent with structural changes implicated in nutritional and inflammatory disorders (123–128). Among candidate genes, *Sucrase–Isomaltase* (*SI*) carried CAASs A/R/T917K across all species sets and I627M in those including Tarsiidae, both under directional selection. *SI* is essential for carbohydrate digestion, and loss-of-function variants in Arctic human populations cause sucrose intolerance in childhood (129–131). Lipases also featured prominently, including *ASPG* (p.G374D), *HPSE* (A/F/L44V), *PLA2G3* (L432P), and *PNLIP* (K394R), all of them subject to directional selection (132,133). Of

the 27 genes and 14 positions shared across selections, DEFB113 V52I was the only site under selection in all comparisons. DEFB113, a β-defensin gene central to host defense, has undergone repeated gain and loss in mammals (134–136), with diet suggested as a driver of diversification (137–139).

2.4.2 *White Blood Cells Count*

White Blood Cell Count (WBC) metrics have rarely been explored in macroevolutionary analyses, though they correlate with mating systems and sexually dimorphic traits such as *Testis Size* (140,141). We contrasted species with extreme WBC counts from Hominidae and Lorisidae (standard strategy) and added Callitrichidae, which present outlier values. This identified 1,901 positions in 1,191 genes with significant permulation results. Enrichments included olfactory receptor activity (GO:0004984), also recovered in the general P3GMap analysis above, and two novel extracellular matrix (ECM) categories—ECM constituent (GO:0005201) and ECM–receptor interaction (hsa04512). These ECM categories partially overlapped with olfactory receptor genes (9 and 6 genes, respectively) but were only detected in the analysis tailored for the case study. Olfactory receptors (ORs), while canonical sensory genes, are also expressed in immune cells such as macrophages (142) and leukemia cell lines (143–145). Four ORs were particularly noteworthy: *OR4D5* (I48T) under directional selection in Hominidae; *OR10G9* with CAASs R89K and F/Y114L in Callitrichidae and Lorisidae (pPGLS $< 1 \times 10^{-3}$) plus four additional sites under selection; and OR52B6 and OR10AD1, the latter with L/M102I under directional selection. These findings suggest repeated co-option of ORs for immune as well as sensory roles. We also detected a xenobiotic metabolism cluster. *SULT1C3* carried four CAASs (K45R, H/R196Q, E227D, Q243Y) under directional selection in Callitrichidae and Hominidae, plus 19 further associations (pPGLS $< 1 \times 10^{-3}$). CES2 showed a CAAS (L599F) with directional selection and consistent phylogeny-wide association (pPGLS $= 5.46 \times 10^{-4}$). Both genes are central to detoxification and belong to neuro-immune pathways involved in xenobiotic avoidance, allergy, and immune dysregulation (146–148). Immune recognition genes also showed lineage-specific signals: LILRB3 under directional selection in Hominidae, LILRA6 under selection despite lacking CAASs, HLA-DQA1 with directional selection in Hominidae, and HLA-DPB1 with a CAAS (Q75R) in Callitrichidae and Lorisidae (pPGLS $= 1.67 \times 10^{-4}$). Collectively, these results underscore the interplay of immune function, environmental exposure, and lineage-specific adaptation in shaping WBC variation.

2.4.3 *Maximum Lifespan*

Longevity is a central focus of comparative genomics, with humans living markedly longer than their closest relatives (48,149–151). After correcting for *Body Mass*, the *Contrasts* used in the general analysis we performed for the P3GMap included humans (Hominidae), long-lived Cebidae, and several short-lived lineages. For the tailored use case, we refined these comparisons by adding Hylobatidae as another long-lived

clade and including additional short-lived species (Fig. 3C). This analysis identified 30,886 positions in 8,565 genes (Fig. 3D). However, because lifespan *Contrasts* often span entire families, detection can be noisy and inflated. To refine this, we assessed consistency. In primates, from 62.72% of informative positions (containing *Top* and *Bottom* states across more than five additional species), the analysis yielded 5,225 positions in 3,338 genes with consistent associations. In mammals, this figure was 30.71% of informative positions, yielding 1,061 positions in 921 genes with consistent associations across primates and non-primate mammals. These curated sets provided a robust basis for functional interpretation. First, among primate-consistent genes, enrichment analysis revealed four categories, including chromosome segregation (GO:0007059) and complement/coagulation cascades (hsa04610). Eight categories emerged for mammal-consistent genes, including interleukin-10 production (GO:0032613) and the regulation of multi-organism processes (GO:0043900). Across both clades, 139 amino acid positions in 136 genes were consistently associated and were enriched in cranial nerve paralysis (HP:0006824) and abnormal cranial nerve physiology (HP:0031910), conditions linked to diabetes (152,153), ischemic stroke (154), or aneurysm (155). From the gene sets linked to these terms in this case study, seven overlapped genes in the general strategy, highlighting the added value of examining overlaps across different selection configurations.

Studying the overlap between all strategies with the most phylogenetically restrictive set of consistent genes, six genes presented CAASs in all species selections. Notable examples include IL1B with CAAS L152M, a key regulator of immune and inflammatory responses (96,156,157), complemented with the detection of two other interleukines, IL12B and IL4I1. Additionally, we also recovered IL23R and IL5 in the directional selection analysis. A second example to highlight is *KLK4* Q227P (Kallikrein-related peptidase 4), known for exerting tumorigenic effects through activating growth factors like insulin-like growth factor (IGF), detected in comparative studies searching for genomic correlates of long-lived species (28,158). We also detected CAASs and directional selection in KLK1 P57R in Hylobatidae and Hominidae, though this site was not consistently associated across primates or mammals. Together, these results implicate immunity, inflammation, and growth factor pathways as recurrent contributors to lifespan evolution.

3. Discussion

This study presents the first P3GMap, which integrates 263 complex traits across 224 primate species. By combining CAAS (40) and RERs (39), we uncovered thousands of candidate associations linking coding variation to phenotypic evolution. The PGA and the associated P3GMap offer a unified resource for studying the genetic basis of traits relating to ecology, morphology, life history, and physiology. This kind of approach complements within-species studies such as GWAS (4–7) by capturing evolutionary signals that are fixed

along lineages (8,9), as illustrated by the observation that ≈86% of CAAS positions are fixed in humans. This reinforces the decoupling between macroevolutionary divergence, which establishes species-specific trait differences, and microevolutionary variation, which can be readily observed in within-species studies (28,48,88–90).

Our framework, has limitations. It focuses on single-copy protein-coding genes (29), excluding regulatory variation, gene duplications, and structural variants, all of which are also important for trait evolution (164). CAAS and RERconverge rely on distinct statistical and conceptual foundations, which can result in partially different gene–trait associations (39,40). Although permulation tests are rigorous (41), they are based on Brownian motion models and may not fully capture all evolutionary dynamics (11,159,160). These caveats highlight the need for future expansions that incorporate regulatory, structural, and expression data (164), as well as refined evolutionary models (11,159,160).

Despite these constraints, our results demonstrate the power of macroevolutionary analyses to illuminate the genetic architecture of complex traits (13–16). The P3GMap reveals recurrent pathways ranging from immunity, inflammation, and DNA repair, to growth factor signaling, linked to phenotypic change, echoing prior evidence from long-lived mammals (28,48,88–90) and other comparative frameworks (25–28,87). Our case studies connect genomic signatures to insectivory (118–122), immunity and WBC variation (140–145), and lifespan (25–28,149–151), illustrating the value of targeted *C*ontrasts for dissecting lineage-specific adaptations. As an open and scalable platform, the PGA provides a foundation for extending genome–phenome inference beyond protein-coding variation, strengthening the link between comparative genomics and human biomedical research.

4. Figures

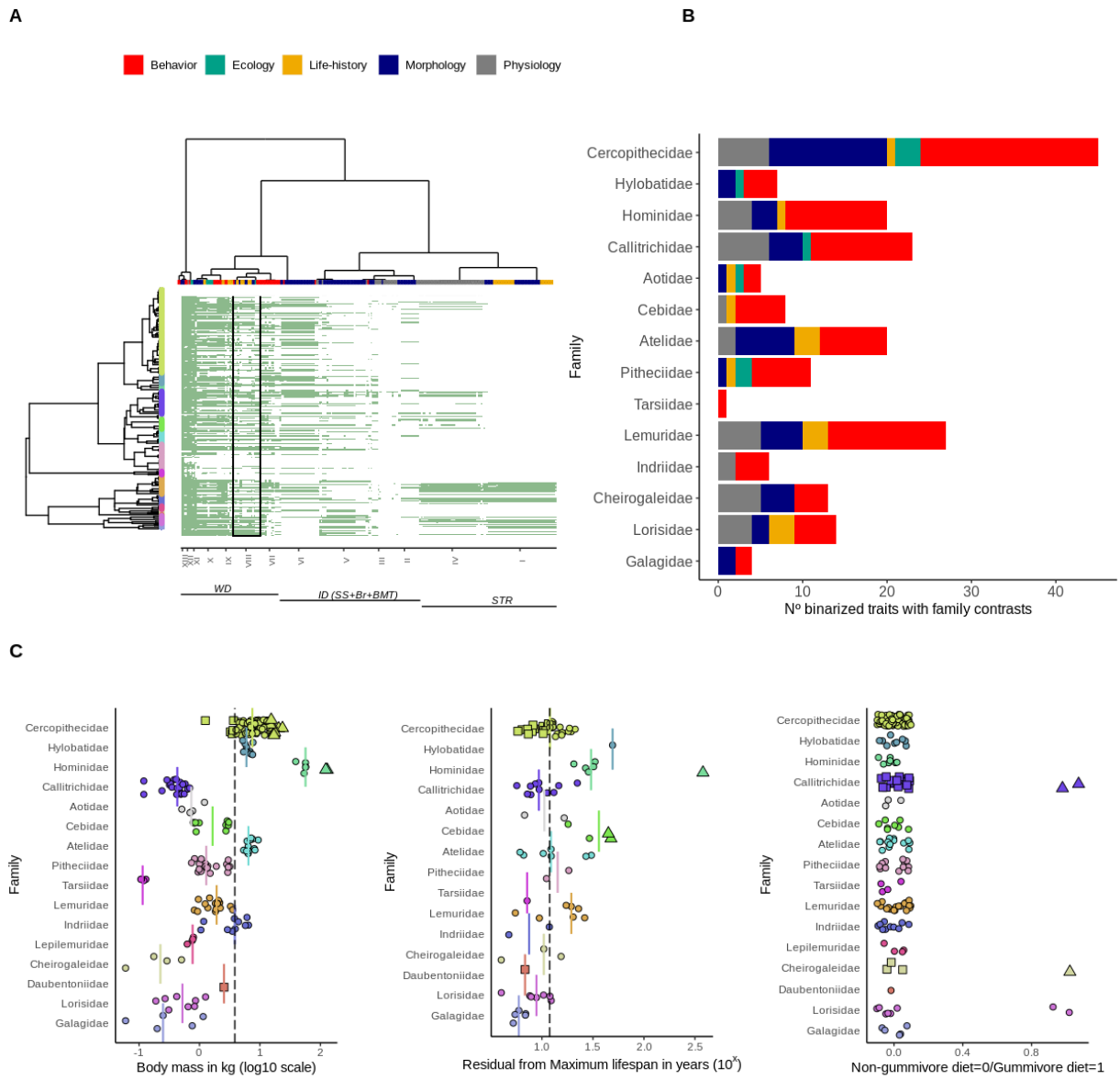

Figure 1. Overview of Primate Phenomic Data.

(**A**) Hierarchical clustering of phenomic data, mapped onto the primate phylogeny and grouped by the primate family. Based on data availability, the traits were classified into 13 data clusters [see Supplementary Material, Trait clustering by phylogenetic sampling]. The area within the square highlights traits from one of the clusters, Cluster VIII, which includes a broad range of ecological, life history, and morphological traits. (**B**) Total number of traits (x-axis) showing extreme phenotypic differences between species within the same family. Top and Bottom values refer to species with contrasting trait values (see text for definitions). (**C**) Examples

illustrating the distribution of values for three traits: Body Mass (left), Maximum Lifespan (center), and Gummivore, sap-eating, Diet (right). Each point represents a species. The vertical bars indicate median family values. Dashed lines correspond to the median global trait value. Species selected as Top and Bottom extremes (based on criteria explained in the text) are indicated by triangles and squares, respectively.

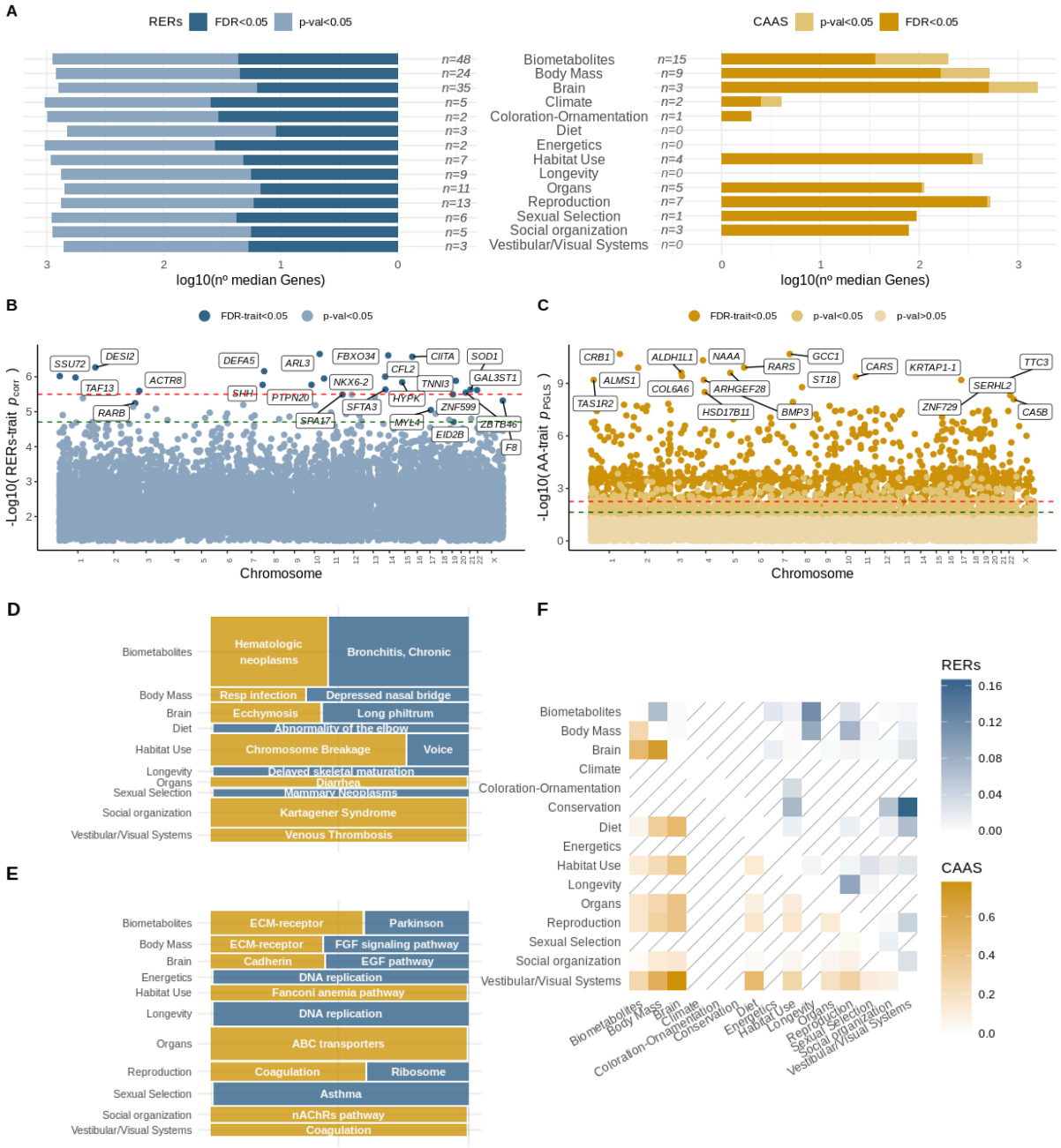

Figure 2. Exploring the Phylogenetic Protein-coding Genome–Phenome Map (P3GMap).

(**A**) Gene–trait associations recovered across secondary biological domains using RERs (left) and CAAS (right), showing the median number of significant genes per trait (log10 scale) and the number of traits with associations (center). (**B**, **C**) Manhattan plots highlighting top gene–trait associations detected by

RERconverge and CAAS, with significance thresholds indicated (green, FDR; red, Bonferroni). Genes surpassing strict thresholds are labeled. (**D & E**) Overlap of significant gene sets across secondary domains, with strip-lined boxes marking domain pairs without shared associations. . (**F**) Heatmap showing the overlap between functional enrichments identified by CAAS and RER across traits, highlighting pathways recurrently implicated by both approaches.

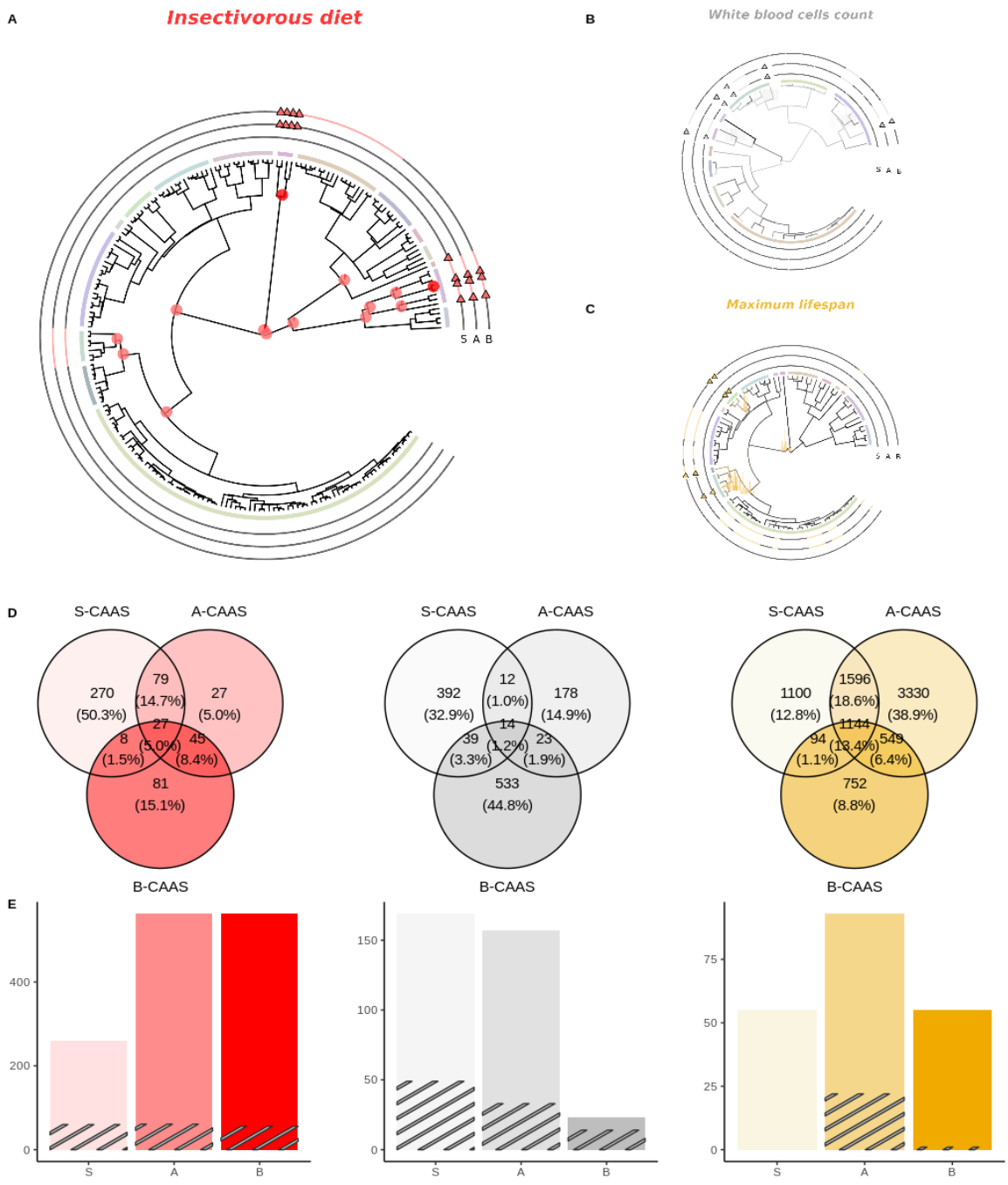

Figure 3. Case studies illustrating the CAAS selection approach for Insectivorous Diet, Maximum Lifespan, and White Blood Cell Count.

(**A–C**) Selection of Top species (triangles) and Bottom species (colored lines) using the standard genome–phenome strategy (*S*-) and two alternative approaches (*A*- and *B*-). Pie charts show ancestral states for qualitative traits, while internal nodes with strong quantitative shifts are depicted as posterior distributions (histograms). (**D**) Venn diagrams of gene overlap (p-perm < 0.05) between alternative family selections for

each trait. (**E**) Counts of sites under directional selection per trait; stray lines indicate CAAS positions also showing positive directional selection.

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