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

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Abstract

Leveraging 60 million years of primate evolutionary diversity, we conducted a large-scale cross-species genome-phenome analysis of protein-coding genes across 224 primate species and 263 phenotypic traits spanning five domains: behavior, ecology, life history, morphology, and physiology. Using phylogenetic comparative methods, we generated the Primate Protein-coding Genome-Phenome Map (P3GMap), available in the Primate Genome-phenome Archive (PGA https://pgarchive.github.io), identifying over 29,000 convergent amino acid substitutions (CAASs) and 3,900 gene-trait associations. As case studies, we applied targeted analyses to insectivorous diet, white blood cell count, and maximum lifespan, uncovering lineage-specific adaptations and signatures of directional selection. We show that traits undergoing greater phylogenetic divergence were linked to more extensive genetic change, and that most CAASs were fixed in humans, suggesting a decoupling of macro- and microevolutionary processes. Notable specific findings include associations between mitochondrial metabolism genes and body mass, immune-related loci and lactation, and olfactory and xenobiotic-processing genes with white blood cell counts. Together, our results establish a scalable framework to explore the molecular basis of complex traits across evolutionary time and demonstrate the value of integrating intra- and interspecies data to understand the genetic foundations of human biology.

One-Sentence Summary: We conducted a comprehensive cross-species genome-phenome analysis of protein-coding genes across 224 primate species, uncovering thousands of candidate causal amino-acid changes linked with 263 phenotypes and demonstrating the value of integrating evolutionary perspectives to understand the genetic architecture of complex human traits.

Introduction.

For decades, our understanding of the genetic basis of complex traits has been largely derived from both experimentation with model organisms (1–3) and analyses of genomic and phenotypic variation within populations, primarily through GWAS in humans (4–7). Although these intra-species approaches are powerful and successful, they are limited by the variation present in extant populations, and so they cannot detect genetic variants fixed in the lineage of the species under study (8,9). In contrast, complementary approaches like Phylogenetic Comparative Methods (PCMs) (9–12), can help unveiling phenotypic associations across a broad spectrum of genomic variations accumulated over millions of years, including gene gain and loss, protein evolution rates, structural variations, and point mutations (13–16). Even when applied to a limited set of traits or focused on candidate genes and episodes of positive or purifying selection (17–22), *PCMs* have advanced our understanding of the genetic architecture of key traits in human evolution such as brain size (17,23,24) and maximum lifespan (25–28), to mention only two.

Scaling up PCMs, we introduce the Primate Genome-Phenome Archive (PGA), a comprehensive resource containing high-quality phenotypic data for 225 traits across 224 sequenced primate species (29), aimed to elucidate the genetic underpinnings of complex traits. Applying different PCMs to the PGA, our analysis identified thousands of genome-phenome relationships in protein-coding genes, providing unprecedented insights into the evolutionary dynamics and genetic underpinnings of many complex traits [...].

The Primate Phenomic Space

We selected representative trait values for 225 non-redundant primate species- from a pool of 263 high-quality quantitative and qualitative measurements curated from over 800 phenotypes available from public sources (30–33). We categorized these 225 traits into five primary biological domains: behavior (29 traits), ecology (7 traits), life history (29 traits), morphology (93 traits), and physiology (67 traits), and 15 secondary biological domains (See Fig. 1, Methods and Table S1) that constitute the the Primate Phenomic Space.

This phenotypic dataset was compiled from diverse studies with varying sampling depths and strategies, which resulted in heterogeneous data densities across species (see also Supplementary Material). To characterize the sampling structure and facilitate comparisons of traits with similar data coverage across clades, we clustered them into 13 groups highlighting differences in phylogenetic sampling (Figures S2-S22, see also SM). Some traits in clusters I and II, such as *Median Longevity* (N=24) and *Maximum Litter Size* (N=24), were more thoroughly sampled within *strepsirrhines*. Notably, *Strepsirrhine* families, such as *Lemuridae* and *Indriidae*, contributed, on average, more than 90% of the traits across all primary biological domains. In contrast, traits such as *Body Mass* (N=214), *Locomotion* (N=220), and *Diel Activity* (N=220) were densely represented across the phylogeny (clusters XI-XIII), including in under-studied families such as *Lepilemuridae* and *Tarsiidae*, which contributed data for fewer than 50% of traits on average. Mass-related traits were among the best represented in the most densely

populated clusters, explaining XX% of the variance in the first component of the Factor Analysis of Mixed Data (FAMD) for clusters VIII, IX, and X (Figure 1A).

Influence of allometry on trait variation is a well established phenomenon (34–38), thus we controlled allometric effects in 74 morphological, 14 life history, and two physiology traits known to scale with body size (Data S1). This resulted in a curated phenotypic dataset that is made publicly available to support further research on primate phenotypic evolution (https://pgarchive.github.io).

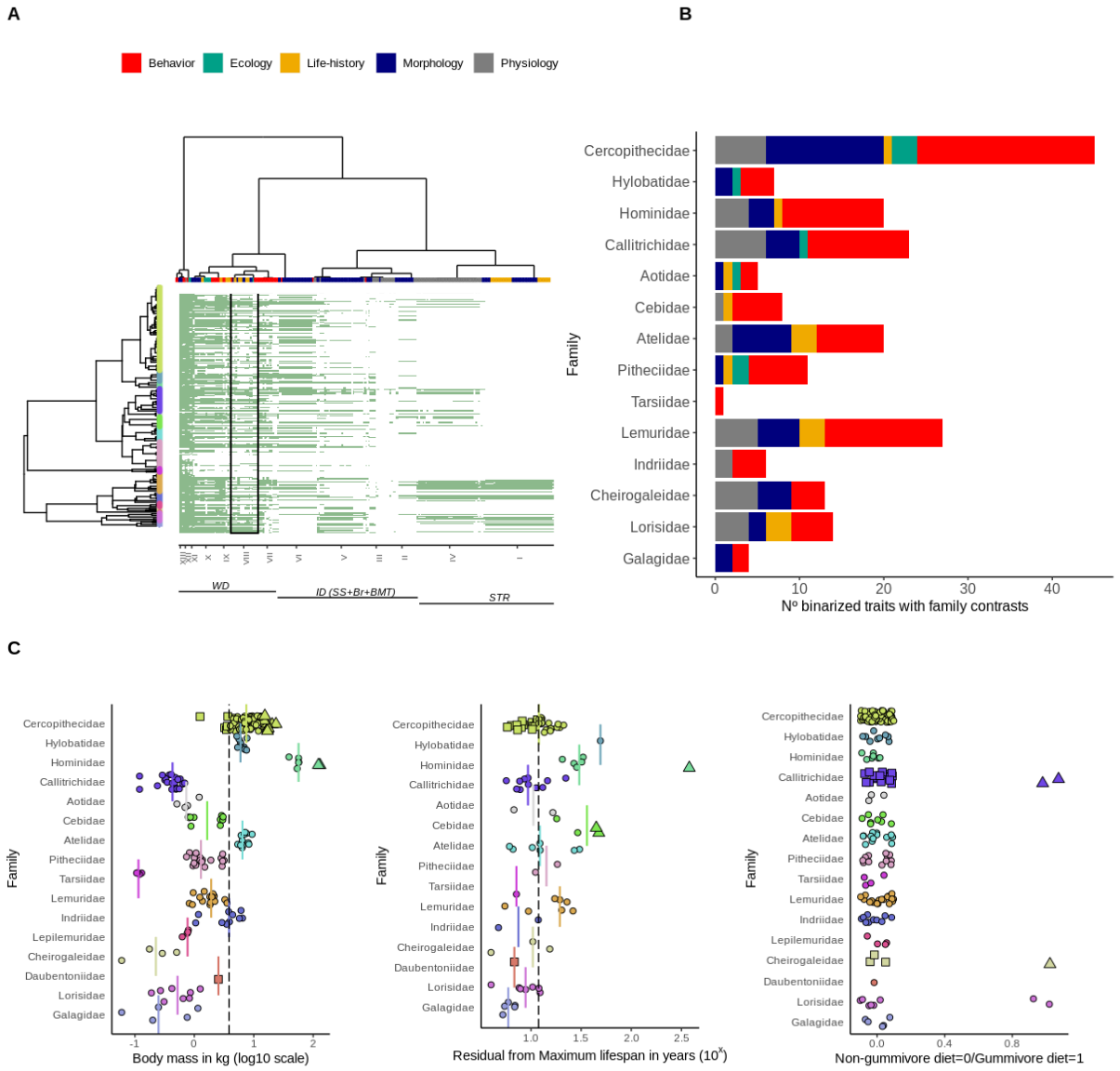


Figure 1. Overview of the *Primate Traits Database (PDB)* (A) Hierarchical clustering of phenomic data, mapped onto the primate phylogeny and grouped by primate family. Based on data availability, the traits were classified into 13 data clusters [see SM]~~, categorized as *WD* (widely distributed), *ID* (intermediately distributed), and *STR* (strepsirrhine-focused)~~. 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.

The Phylogenetic Protein-coding Genome-Phenome Map (P3GMap)

We conducted a genome-phenome analysis of protein-coding sequences to build the first phylogenetic protein-coding genome-phenome map (P3GMap) to be uploaded in the PGA. This resource catalogs the phylogenetic associations between protein-coding genes and a broad array of phenotypes across the primate lineage.

The P3GMap consists of multiple sequence alignments for 16,133 one-to-one orthologous protein-coding genes across the primate phylogeny. Over 75% of the alignments included more than 200 species (see Figure S1 and SM). To identify genomic factors associated with phenotype evolution, we applied two complementary strategies. First, we identified Convergent Amino Acid Substitutions (CAAS) between species with divergent phenotypes using CAASTools (40, see SM "CAAStools") . Second, we linked gene-specific relative evolutionary rates (RERs) to phenotypic rate of change across the phylogeny, using RERconverge (39) (see SM "RERconverge"). These methods capture genomic-phenotypic associations across a broad range of evolutionary scenarios bypassing the need to detect classical signatures of strong positive selection [REF paper Guojie].

To enable systematic cross-trait comparisons, we developed a *standard strategy* that prioritizes consistency and scalability across hundreds of traits, rather than tailoring parameters to optimize fine-tuned detection for individual traits or groups of traits. We must note that the P3GMap focuses only on single-copy protein-coding genes, and so it is not intended to fully resolve the genetic architecture of each trait. However, it offers for the first time a comprehensive panoramic view of the genome-phenome relationship in primates, and provides a framework for identifying genetic signatures underlying key evolutionary transitions.

Convergent amino acid substitutions linked to primate traits

For each trait we identified CAASs between groups of species with extremely different quantitative phenotypic values (or contrasting qualitative values). To do so, for each phenotype we classified species with high trait values (or arbitrary qualitative states) as *Top* species, and species with low values (or complementary qualitative states) as *Bottom* species (See Fig. 1B-C, Figure S24-S27, Data S1, and SM sections A.1-A.4). These pairwise comparisons are named *Contrasts*. The remaining species, which were not classified as *Top* or *Bottom*, were not used in the first phase of the analysis. For the *standard strategy* we focused on *contrasts* within the same family. This design increases the likelihood that phenotypic differences observed in different families represent independent cases of convergence.

Among our set of traits, 83 (37%) exhibited at least one intra-family phenotypic *contrast*, out of which 63 showed *contrasts* in two or more families, unveiling a considerable amount of

independent convergent evolution in primate traits. We applied CAAStools on these 83 traits and controlled for phylogenetic effects using a permulations (41). Then, we performed a per-trait multiple testing correction (see SM A.4). Altogether, 29,155 unique significant CAASs were identified in 8,780 genes across 76 traits ($p_{\text{permul-FDR}} < 0.05$), corresponding to a median of 49 genes and 51 positions across the primary biological domains (Fig. 2A, Figure S28-S31 and Data S2). To our knowledge, this represents the largest set of candidate causal amino acid substitutions ever identified in association with such a comprehensive and diverse array of phenotypic traits, providing an unprecedented resource for the study of convergent molecular evolution.

To evaluate the consistency of these associations, we validated the recovered CAASs in the species not included in the original groups (the *Top* and *Bottom* groups) by means of phylogenetic generalized least squares (PGLS) for quantitative traits and phylogenetic logistic regression (phyloglm) for qualitative traits (See SM Internal phylogenetic test in primates) (Fig. 2C and Figure S39). This a highly conservative sanity check, since power was drastically reduced by removing species with extreme values and since intermediate species do not necessarily share the *Top* or *Bottom* amino-acid residues. We obtained a median of 7,14% nominally significant positions ¿per trait? (Figure S40-S44 and Data S2).

For a more targeted investigation, we focused on 10 traits with <100 validated and significant phylogeny-wide associations ($p_{PGLS\text{-}FDR} < 0.05$, and $p_{phyloglm\text{-}FDR} < 0.05$). These analyses revealed both, previously known and novel gene-trait associations (Suppl. Table S3). Notable examples include associations between *Body Mass* and mitochondrial metabolism genes (50,51): *NDUFS7* (NADH:ubiquinone oxidoreductase core subunit S7) with substitutions Y223L ($p_{PGLS} = 1.37 \times 10^{-5}$), R230H ($p_{PGLS} = 3.57 \times 10^{-5}$), K231G ($p_{PGLS} = 1.37 \times 10^{-5}$), and I232A ($p_{PGLS} = 1.37 \times 10^{-5}$) and *NOXO1* T/V223A (NADPH Oxidase Organizer 1) ($p_{PGLS} = 2.06 \times 10^{-7}$); as well as genes in the immunoglobulin protein superfamily (52), including *ICAM1* R/V418M ($p_{PGLS} = 2.39 \times 10^{-5}$). For *Lactation Period Length*, we found associations with genes linked to familial Mediterranean fever (FMF)(53–55), such as *MEFV* K/R546Q ($p_{PGLS} = 1.66 \times 10^{-6}$), a key regulator of innate immunity.

To further validate our results, we gathered a set of 10 equivalent species-specific trait values from non primate mammals and tested whether the XX CAASs presented a consistent and significant direction of the effects. This test is even more conservative, since changes in the trait in distant species are not likely to be mediated by the same amino-acid change. Still, the test yielded a median of 7,28% nominally significant positions ($p_{PGLS} < 0.05$) (Figure S45-S47). Eight CAAS remained significant after FDR correction ($p_{PGLS\text{-FDR}} < 0.05$) (See also Supp. Table S4). Notable examples include position Q176RN *in ELL1* for *Lactation Period Length* ($p_{PGLS} = 1.09 \times 10^{-4}$), previously linked to late milk production in dairy goats (56) and to bone formation, regeneration, and craniosynostosis (57–59), and *MPDZ* H/P956Q for *Gestation Period Length* ($p_{PGLS} = 1.65 \times 10^{-5}$), a gene with germline mutations associated with congenital non-communicating hydrocephalus (60,61).

Correlations between rates of gene evolution and traits

While the CAAS approach can detect genome-phenome associations regardless of the underlying evolutionary mechanism, complementary insights can be gained by identifying genes whose rates of evolution correlate with trait changes across the phylogeny. Such associations may reflect episodes of accelerated or constrained protein evolution (potential signatures of positive or purifying selection). To carry-out such analysis, we used RERconverge in 16,109 alignments of orthologous protein-coding genes and 200 quantitative traits (See also SM: RERconverge). Gene-trait correlation significance was assessed via permulations (41) (see also SM B.2). Five qualitative traits (*Extinction Risk*, *Natal Dispersal, Female Ranging Patterns*, *Infanticide* and *Stable Groups*) were excluded because of the high computational cost of permulations (see Supplementary Materials and Methods (SM)).

We identified significant gene-trait correlations involving 3,911 genes and 194 traits ($p_{\text{permul-FDR}} < 0.05$), with a median of 19 associated genes per trait (Fig. 2A, Figure S28-S31 and data S2). RERconverge applies a more permissive correction than CAASTools (see SM), which may lead to inflated significance. To address this, in the selection of specific gene-trait associations, we additionally required significance based on FDR correction of alternative parametric p-values (p_{corr}). RERconverge provides p_{corr} as a high-resolution, computationally efficient, but phylogeny-agnostic alternative to $p_{\text{permul,}}$, with both statistics showing similar values across our dataset (see SM).

RERconverge allowed identifying genes with functions linked to the associated traits (Fig. 2B and Fig, S38; see also SM RERconverge B.1 and Suppl. Table S2). Examples include *NKX6-2* for *Percentage of Time Moving* (*Rho* = 0.62; $p_{\text{permul-FDR}} < 10^{-3}$), implicated in spastic ataxia in humans (42,43), *DEFA5* for *Percentage of Fauna Ingest* (*Rho* = -0.5, $p_{\text{permul-FDR}} < 10^{-3}$), a defensin family gene associated with gastritis (44), and *DESI2* for *Mesencephalon Relative Size* (*Rho* = 0.69, $p_{\text{permul-FDR}} < 10^{-3}$), linked to amyotrophic lateral sclerosis type 5 (47).

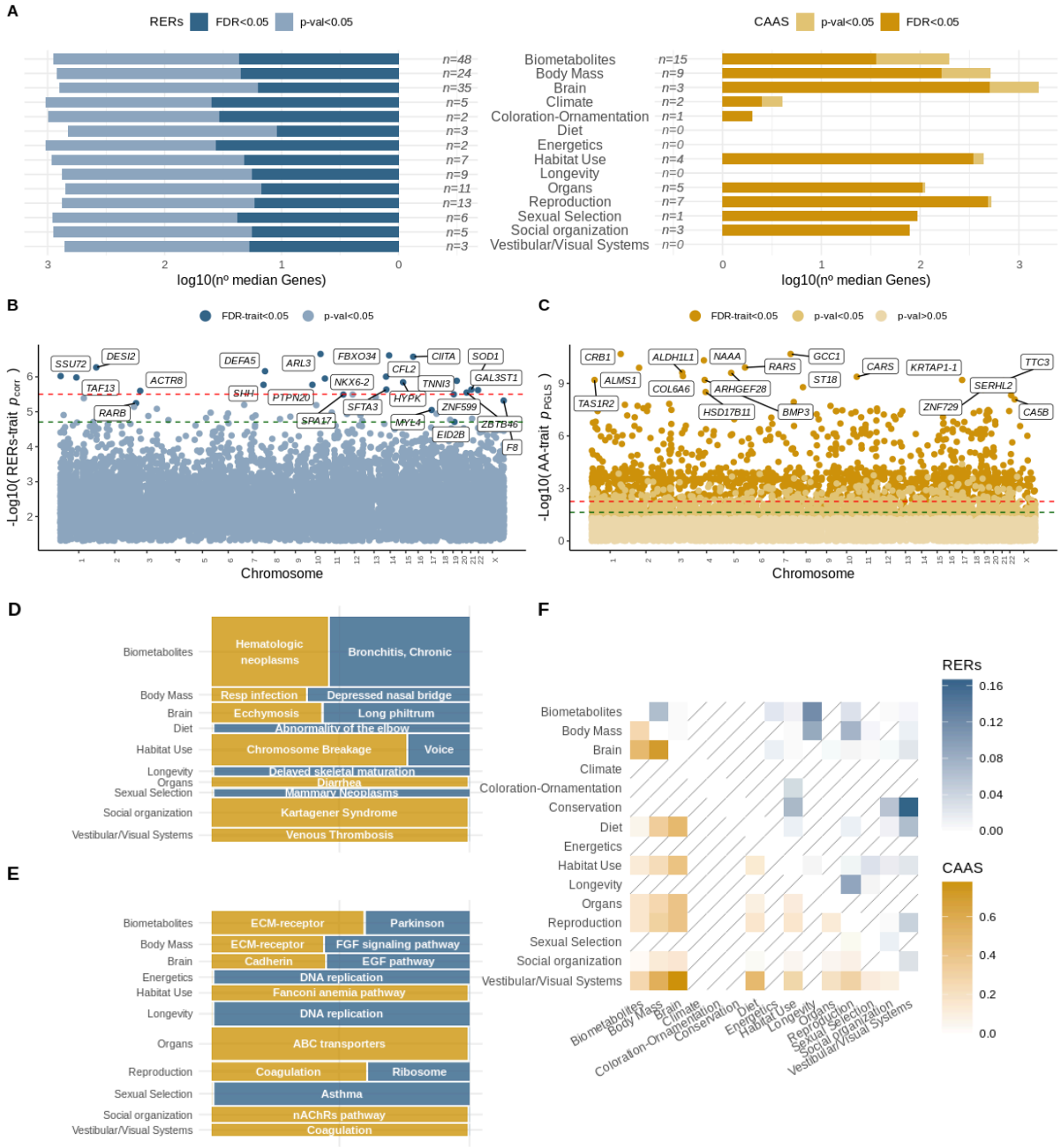


Figure 2. Phylogenetic Protein-coding Genome-Phenome Map (P3GMap) exploration. (A) Median number of genes after multiple-gene test correction ($p_{\text{Permul-FDR}} < 0.05$) for permulation of each quantitative trait, reporting the log10 scale of the median gene count on RERs (left) and CAAS (right) for each secondary biological domain. The *n* counts (middle) indicate the number of traits with associations per secondary biological domain. **(B and C)** Manhattan plot with correlation p-values for RERs (left) and PGLS p-values for CAAS (right) showing the lowest quantitative RERs-trait p-value and lowest AA-trait p-value for each gene, respectively. The dashed green line corresponds to the FDR threshold and the dashed red line corresponds to the strict Bonferroni threshold. Genes labeled with their corresponding gene names for RERs ($p_{\text{bonf-trait}} < 0.05$) and CAAS ($p_{\text{PGLS-trait}} < 1e\text{-}8$). **D)** Heatmap with the proportion of significant pairs of traits ($p_{\text{FDR}} < 0.05$) obtained from the hypergeometric test of gene set overlap between secondary biological domains. Boxes with strip lines represent pairs of secondary biological domains with no significant gene set overlap for each PCM methodology.

Our analysis also uncovered hundreds of novel gene-trait associations potentially relevant to both biomedicine and evolutionary biology (Fig. 2). Notably, traits that exhibited greater evolutionary divergence across the primate phylogeny were more likely to be linked across with a higher number of genomic associations, consistent with the expectation that extensive phenotypic change is often accompanied by widespread molecular adaptation. These findings reinforce the utility of phylogenetic rate analyses for capturing evolutionary signatures that may escape detection in traditional within-species approaches.

A first functional exploration analysis of the standard P3GMap

We evaluated the biological terms linked to our results using over-representation analysis (ORA) (Suppl. Tables XXX). For significant CAAS genes, we identified 199 unique enriched terms across the 27 traits analyzed (Suppl. Data S3). Body mass-related traits were enriched with DNA repair-related categories (Fig. XX or Suppl. Table XX), consistent with recent findings for the order *Carnivora* (87). Additionally, DNA repair genes have been highlighted in several studies as targets of positive selection for anti-cancer mechanisms in long-lived species (28,48,88–90). Two other notable cases involved the trait *Percentage of Time with Social Activity*, with associated genes enriched with the terms *chromosome breakage* (*ER* = 7.21; $p = 4.53 \times 10^{-7}$) and *Fanconi anemia* (ER = 4.73; $p = 3.03 \times 10^{-5}$). These genes are associated with developmental and congenital disorders (91,92).

Focusing on significant genes from RERconverge (P<0.05), we found 94 functionally enriched terms across XXX traits (*p*FDR < 0.05; hypergeometric test). Among these, we identified enrichments of the term *Long philtrum* (defined as a distance >2SD between the nasal base and the midline of the upper lip), associated with the relative sizes of the brain regions *Pallidum* (ER = 3.35; $p = 2.97\times10^{-6}$) and *Subthalamus* (ER = 3.34; $p = 3.12\times10^{-6}$). These results highlight nose morphology as a key phenotypic distinction among primates, reflecting one of the most characteristic differences between *strepsirrhines* and *haplorhines* (62,63), and a trait that has been implicated in numerous human syndromes involving cognitive, sensory, and communication disabilities, as well as facial abnormalities (64–68). Two additional significant enrichments were associated with traits under sexual selection. *Hair Dimorphism* was linked with the MHC protein complex ($p = 7.76\times10^{-6}$), a relationship proposed in several studies as relevant for mate choice in mammals, birds, and fish (73–77), although some studies have disputed this association in specific taxa (78–82). Likewise, *Mass Dimorphism* was associated with *mammary neoplasms* (*ER* = 2.16; $p = 4.65 \times 10^{-6}$), which is supported by studies linking sex-based dimorphisms to differential cancer incidence in humans (83–85).

Functional interpretation of the gene sets obtained for each biological domain may also be enhanced by examining their relationships with other biological categories (97–99). Gene set overlap was evaluated through hypergeometric tests between all pairs of traits across the primary and secondary biological domains (Fig. 2D). First, focusing on gene sets containing significant CAAS-trait associations, we obtained gene overlaps for 16 trait pairs ($p < 1 \times 10^{-50}$),. These overlaps were concentrated in *Trichromatic Color Vision* and brain and body mass domains, suggesting that gene sets involved in sensory perception and morphological development may contribute pleiotropically to multiple complex traits across evolutionary contexts. In addition, we found five overlaps involving life-history traits above this threshold: *Age of Female At First*

Reproduction with both *Trichromatic Color Vision* and with *Maximum Young Adult Weight*; *Maximum Possible Reproductive Success Under Optimal Conditions* with *Trichromatic Color Vision*; and *Gestation Period Length* with both *Maximum Young Adult Weight* and *Maximum Young Adult Weight in Males*. Several of these reproductive traits are shared among families that have undergone recent phenotypic changes in color vision, particularly within the *Atelidae* family. Notably, genera within the *Atelinae* subfamily, such as *Ateles* and *Lagotricha*, exhibit polymorphic color vision, whereas the *genus Alouatta* displays routine trichromatic vision (117). These findings suggest that recent evolutionary shifts in visual perception may have co-occurred with changes in reproductive and somatic traits, pointing to coordinated molecular adaptations linked to ecological or social pressures.

Second, focusing on the RERconverge results, we identified robust gene overlaps for 11 trait pair combinations ($p < 10^{-30}$; hypergeometric test). Notably, four of these associations involved longevity-related traits. For example, genes associated with *Percentage of Infant Mortality* overlapped with *Maximum Male Longevity* and *Gamma-Glutamyl Transferase (GGT) levels* ($p = 4{,}46 \times 10^{-74}$ and $p = 7{,}13 \times 10^{-39}$, respectively). *GGT* is an important antioxidant enzyme involved in glutathione metabolism, previously associated with cardiovascular and neurological diseases (100–106), lung inflammation (107), and various cancers (108–110) in humans. It has also been proposed as a predictor of mortality in the general population (111). We also found a robust significant overlap between genes linked to *Cholesterol Levels* and *Median Male Longevity* ($p = 6{,}74 \times 10^{-48}$), although the relationship between cholesterol, lipid metabolites, and human mortality remains complex and sometimes contradictory (112). Additionally, genes associated with *Serum Oxaloacetic Transaminase Levels*, also known as aspartate transaminase (AST), overlapped significantly with those linked to *Median Female Longevity* ($p = 2{,}18 \times 10^{-38}$). Elevated AST levels have been associated with mortality in patients with liver, neurological, and cardiovascular diseases (113–116).

Focusing on traits associated with specific primate families provides an opportunity to detect lineage-specific evolutionary patterns that may be masked in broader analyses. Such comparisons can reveal coordinated molecular adaptations shaped by shared ecological niches, social structures, or historical constraints within particular clades. In this context, we found that *Cathemeral Activity* shared enriched gene sets with both *Dichromatic Color Vision* ($p = 7{,}72 \times 10^{-49}$) and *Seasonal Breeding* ($p = 2{,}34 \times 10^{-200}$) associations mainly driven by members of the *Lemuridae* family. Similarly, *Solitary Social System* showed robust overlap with genes linked to *Monochromatic Color Vision* ($p = 2{,}98 \times 10^{-41}$), involving *Lorisidae* and *Galagidae*, and with *Dichromatic Color Vision* ($p = 9{,}85 \times 10^{-48}$), associated with *Lepilemuridae, Microcebus*, and *Nycticebus*. These family-level patterns highlight potential co-evolution between visual systems, reproductive timing, and social behavior, traits that may have jointly responded to nocturnal lifestyles, seasonal environments, or mating strategies in these lineages.

Finally, we assessed whether the genes or pathways associated with traits across the primate phylogeny were enriched for heritability in corresponding human traits based on GWAS data. No significant trend was detected, suggesting limited overlap between phylogenetically inferred associations and loci contributing to current within-population variation in humans. Furthermore, among the full set of genomic positions underlying CAASs, the vast majority (86,16%) were

fixed in human populations for traits included in the P3GMap. This highlights a potential decoupling between macroevolutionary changes, which shape long-term phenotypic divergence across species, and microevolutionary processes, which govern variation within species. Such divergence reinforces the central notion of our finding: the complementary nature of cross-species and population-based approaches for understanding trait architecture

Three case studies: the genomic architecture of traits with complex phylogenetic histories

The *standard strategy* for the selection of species to be compared to detect CAAS applied above is designed to provide a consistent and scalable framework for constructing the P3GMap across a highly heterogeneous set of phenotypes, enabling broad cross-trait comparisons while preserving phylogenetic representativeness. Beyond this general strategy, more targeted selections of contrasting phenotypes within specific clades can uncover lineage-specific evolutionary mechanisms. To demonstrate this potential, we examined three case studies spanning distinct biological domains—Insectivorous Diet, White Blood Cell Count, and Maximum Lifespan. By refining species selection based on the particular phylogenetic distribution of each trait, we identified additional gene sets that improved downstream functional interpretation and revealed shared molecular pathways driving trait evolution. Importantly, the structure of the PGA enables researchers to perform similar clade-specific or trait-focused analyses, expanding the utility of the resource beyond the standardized genome-phenome map.

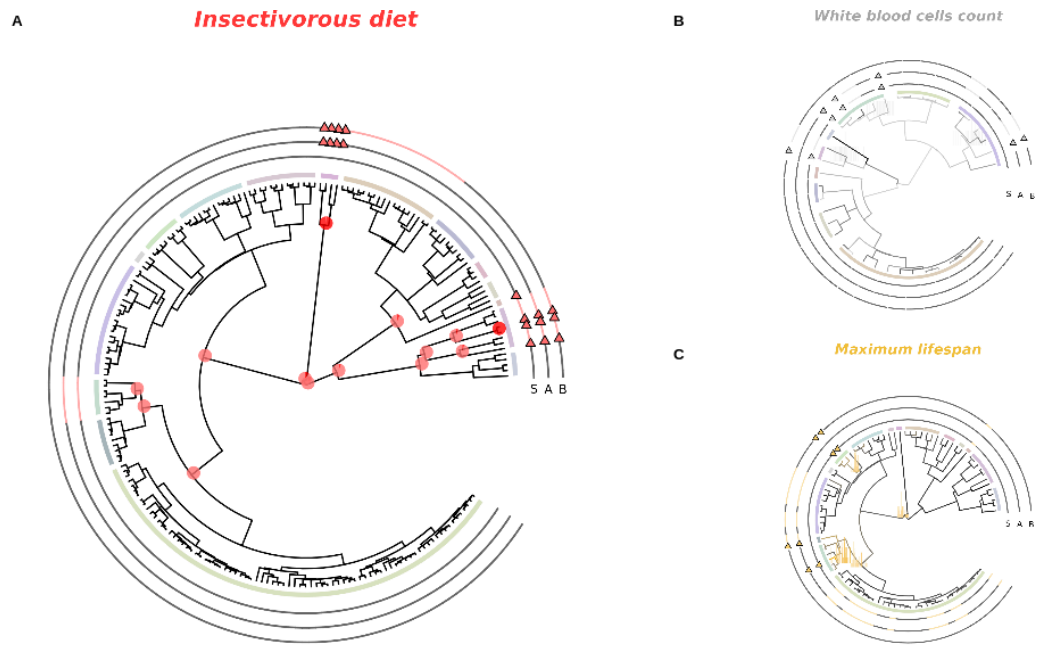
The case studies of *Insectivorous Diet* and *White Blood Cell Count* (Fig. 3A & 3B) illustrate how targeted analyses can uncover deeper biological insights. We also examined Maximum Lifespan (Fig. 3C), a trait whose phenotypic contrasts occur primarily across families rather than within them, often aligning with common species groupings in the alignments and leading to more permissive associations. To better understand the mechanisms behind these associations, we performed a focused analysis of the evolutionary relevance of the implicated amino acid changes, including natural selection analysis. By identifying sites under positive selection, we were able to assess whether these substitutions reflect adaptive pressures. This combined approach demonstrates the added value of the PGA/P3GMap when integrated with selection-based methods to dissect the molecular basis of complex traits.

Insectivorous diet

Diet interacts closely with other morphological traits, including brain (118–120) and dental adaptations (121,122), both across the entire evolutionary history of primates and within specific clades such as strepsirrhines (120). We focused on the *Insectivorous Diet*, for which our *standard strategy* selected contrasting insectivorous and non-insectivorous species within the family *Lorisidae* (slender lorises show greater insect dependence than slow lorises) and included *Daubentonia madagascariensis* (the only extant *Daubentiidae*) as an insectivorous species, along with non-insectivorous species from different families. For this targeted analysis, we included *Tarsiidae* as an additional insectivorous lineage using alternative selections of non-insectivorous species (Fig. 3A).

In doing so, we identified 619 amino acid positions in 537 genes, all of them showing significant permulation results (Fig. 3D) and were enriched in four biological categories (pFDR < 0.05, hypergeometric test). Of course, many of these genes were also detected by the *standard strategy*, including 19 genes associated with the apical part of the cell (GO:0045177), eight linked to cargo receptor activity (GO:0038024), seven to lipase activity (GO:0016298), and 14 to endopeptidase activity (GO:0004175). However, none of these enrichments were detected without the selection of alternative species. The role of the epithelial cell surface in nutrition and metabolism has been extensively studied, particularly in the context of small intestine function (123–125). Structural changes such as villus blunting or flattening of the epithelial surface are known to contribute to inflammatory and nutritional disorders (126–128).

A notable gene linked to this category is Sucrase-Isomaltase (SI), for which we identified CAASs A/R/T917K across all species selections and I627M in those including *Tarsiidae,* with directional selection detected. Sucrase-Isomaltase is an essential gene for carbohydrate digestion, and loss-of-function (LoF) mutations in Arctic human populations have been associated with gastrointestinal symptoms upon sucrose introduction in childhood diets (129–131).



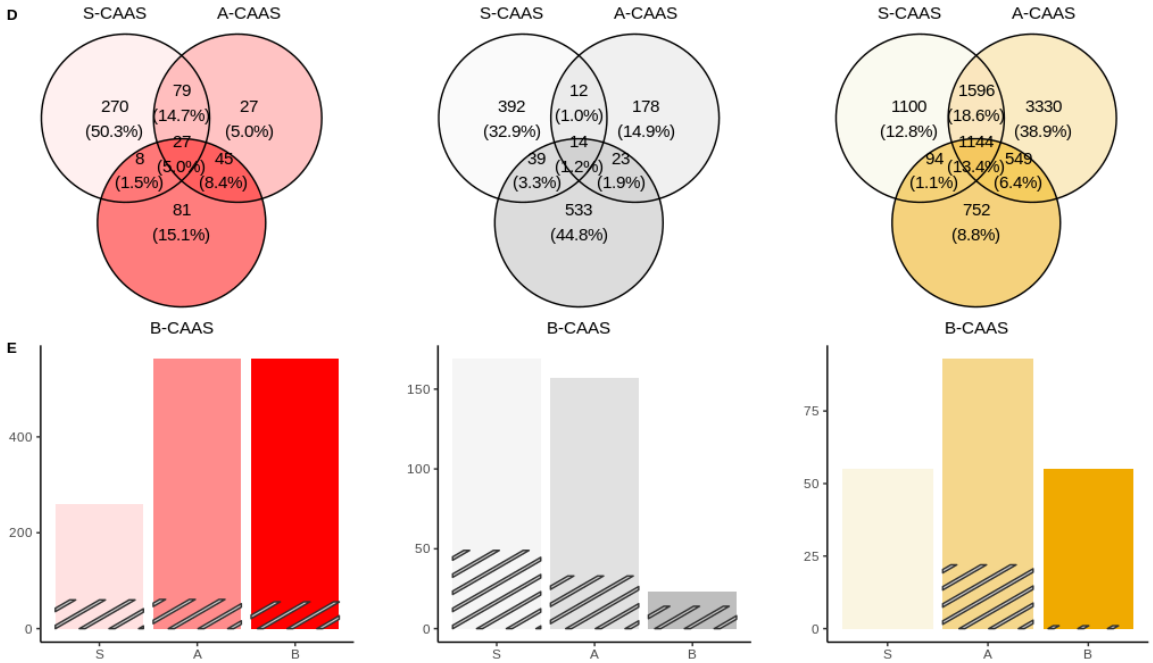


Figure 3. Study cases: The potential of the CAAS selection approach applied to *Insectivorous Diet*, *Maximum Lifespan* and *White Blood Cells Count*. A, B, and C) Selection of *Top* (triangle) and *Bottom* (colored line) species for each trait using the *standard strategy* for the complete genome-phenome map (S), and two alternative selection approaches (A and B). Pie charts represent ancestral states for the qualitative trait, whereas internal nodes with strong trait shifts are represented by continuous posterior distributions in the shape of histograms for the quantitative traits. **D)** Venn diagram representing gene overlap (*p-perm* < 0.05) between alternative family selections for each trait studied **E)** Directional selection counts for each phenotype studied. Stray lines indicate the number of positions detected with CAAS, which show positive directional selection.

Lipases also play a critical role in fat digestion and intestinal absorption (132,133). Consistent with this category, we detected CAASs in *ASPG* p.G374D (Asparaginase), *HPSE* A/F/L44V (Heparanase), *PLA2G3* L432P (Phospholipase A2 Group III), and *PNLIP* K394R (Pancreatic lipase) in the species selection, including *Tarsiidae*, with directional selection also being detected.

Interestingly, among the 27 genes and 14 amino acid positions shared across all species selections, *DEFB113* V52I (Defensin Beta 113) was the only CAAS with directional selection detected in all comparisons. A member of the β-defensin family mainly involved in host defense, *DEFB113* has undergone multiple gene gain and loss events throughout mammalian evolution (134–136), with diet proposed as an external force influencing gene family diversification (137–139).

White Blood Cells

Although white blood cell (WBC) metrics have not been extensively studied from a macroevolutionary perspective, several studies in primates have explored the associations between immune and mating systems, as well as correlations with sexually dimorphic traits, such as testis size (140,141). For this analysis, we included species with contrasting WBC from the

two families used in our *standard strategy* (*Hominidae and Lorisidae*) and added *Callitrichidae*, since they present extreme values. We identified 2,829 positions in 1,659 genes, including 1,901 positions in 1,191 genes with significant permulation results. These were enriched for olfactory receptor activity (GO:0004984), which was also observed in the *standard* P3GMap analysis, and for two extracellular matrix (ECM)-related categories, ECM constituent (GO:0005201) and ECM-receptor interaction (hsa04512). These ECM-related functions showed partial gene overlap with olfactory receptor activity (nine and six, respectively), but were not detected using the standard P3GMap. Olfactory receptors (ORs), a highly conserved sensory system in mammals, are also expressed in immune cells such as macrophages (142) and in human leukemia cell lines (143–145). Across all species selections, we identified four OR genes of particular interest. OR4D5 (I48T) showed directional selection in Hominidae. OR10G9 displayed CAASs (R89K and F/Y114L) in Callitrichidae and Lorisidae, with consistent associations across the primate phylogeny (pPGLS $< 1 \times 10^{-3}$); four additional positions in this gene also showed signs of directional selection. OR52B6 and OR10AD1 carried CAASs as well, with OR10AD1 presenting a substitution (L/M102I) in *Hominidae* and *Lorisidae* under directional selection. These findings suggest that OR genes may have been recurrently co-opted during primate evolution to mediate not only chemosensory functions but also immune-related processes, potentially linking environmental sensing with host defense.

We also identified a cluster of genes involved in xenobiotic metabolism, highlighting potential evolutionary adaptations to environmental exposures. SULT1C3 (Sulfotransferase Family 1C Member 3) showed four CAASs (K45R, H/R196Q, E227D, Q243Y) under directional selection in *Callitrichidae* and *Hominidae*, along with 19 additional significant associations (pPGLS $< 1 \times 10^{-3}$) in *Callitrichidae*-inclusive sets of species. Similarly, CES2 (Carboxylesterase 2) exhibited a CAAS (L599F) with directional selection and a consistent association across primates (pPGLS = 5.46×10^{-4}). These genes play key roles in detoxification and are part of neuro-immune pathways implicated in xenobiotic avoidance behaviors, allergy susceptibility, and immune dysregulation (146-148).

In addition, we detected directional selection in key immune-related genes, particularly within the Leukocyte Immunoglobulin-Like Receptor family, LILRB3 in *Hominidae*, and LILRA6 under selection despite lacking CAASs. Within the Major Histocompatibility Complex (MHC), HLA-DQA1 showed directional selection in *Hominidae*, while HLA-DPB1 exhibited a CAAS (Q75R) in *Callitrichidae* and *Lorisidae*, with significant phylogeny-wide association (pPGLS = 1.67×10^{-4}). Again, these findings illustrate the role of immune system genes in lineage-specific adaptations and point to the evolutionary shaping of immune recognition mechanisms in response to environmental and pathogenic pressures.

Maximum lifespan

Longevity-related traits are key targets for identifying molecular convergence across primate and mammalian phylogenies, and for understanding their implications in human biology. For instance, within the great apes, humans have evolved markedly longer lifespans than their closest relatives (48,149–151). In the case of Maximum Lifespan (after correcting for Body Mass), in addition to the species included in the *standard strategy* (humans within *Hominidae*, other long-lived *Cebidae*, and several short-lived species from different families), we specifically

targeted *Hylobatidae* as another long-lived lineage and included additional short-lived species across the phylogeny (Fig. 3C).

We identified 30,886 positions in 8,565 genes showing significant permulation results (Fig. 3D). As explained above, the phylogenetic distribution of *Maximum Lifespan* in primates does not meet our standard criteria for recovering intra-family groups of contrasting species, leading to noisier and potentially overestimated CAAS detection. To address this, we assessed association consistency in both primates and mammals. In primates, we evaluated 62,72% of the positions where more than five additional species carried amino-acids found in both the *Top* and *Bottom* groups. This refinement yielded 5,225 positions in 3,338 genes with significantly consistent associations across the primate phylogeny. We then applied the same criteria to the mammalian alignments, testing the association consistency in mammals for 30,71% of the positions. This analysis identified 1,061 positions in 921 genes, with significantly consistent associations across both primates and non-primate mammals. This bespoken phylogenetic curation enabled us to derive a more informative gene set for investigating the genetic basis of *Maximum Lifespan*.

We identified four enriched functional categories among the genes carrying CAASs with significantly consistent associations across primates, including chromosome segregation (GO:0007059), which was also detected in our standard species selection, and the complement and coagulation cascades (hsa04610). Among the genes with significantly consistent associations across mammalian phylogeny, we found eight enriched categories, including interleukin-10 production (GO:0032613) and regulation of multi-organism processes (GO:0043900). Additionally, we identified 139 amino acid positions in 136 genes that showed consistent associations in both primates and mammals. These genes were significantly enriched in two human phenotypes: cranial nerve paralysis (HP:0006824) and abnormal cranial nerve physiology (HP:0031910). The human brain contains 12 cranial nerves, and paralysis typically arises from congenital, traumatic, or vascular disorders, including life-shortening conditions, such as diabetes (152,153), ischemic strokes (154), or aneurysms (155). Seven overlapping genes were also found in the standard species selection, and six of them correspond to CAASs in all species selections. A notable example is *IL1B* (Interleukin 1 Beta), where we identified the CAAS L152M, a variant in a gene that plays a central role in cytokine-induced immune and inflammatory responses (96,156,157). We also identified CAASs in two other interleukins from the same gene set, *IL12B* and *IL4I1*, and detected directional selection in *IL23R* and *IL5*.

Another example is *KLK4* Q227P (Kallikrein-related peptidase 4), which promotes tumorigenesis by activating growth factors, including insulin-like growth factor (*IGF*). The insulin-like growth factor 1 (*IGF-1*) signaling pathway has been repeatedly highlighted in comparative studies of longevity across species (28,158). In addition, we detected both directional selection and CAASs in *KLK1* (Kallikrein 1) P57R, in the selection of *Hylobatidae* and *Hominidae*. *KLK1* is known to degrade insulin-like growth factor-binding protein-3, although this particular amino acid position is not consistently associated across primates or mammals.

Concluding remarks and limitations

In this study, we leveraged the most comprehensive catalog of primate genomic and phenotypic variation to date to develop a standardized, cross-trait comparative framework for mapping

protein-coding genomic variation onto phenotypic diversity. By integrating this framework with phylogenetic comparative methods, we generated the Primate Protein-coding Genome-Phenome Map (P3GMap), made available through the Primate Genome-Phenome Archive (PGA). This resource revealed widespread associations between protein-coding variation and 263 complex traits across 224 primate species. Our results highlight how macroevolutionary analyses can complement within-species approaches to better understand the genetic architecture of traits with both evolutionary and biomedical relevance. The primate gene-trait associations uncovered here provide a foundation for exploring their functional implications in human health, especially through future comparative multi-omics studies that can illuminate the conservation and divergence of relevant genes and pathways.

While this broad strategy offers a panoramic view of phenotypic evolution, it also enables trait-focused exploration, as illustrated in our case studies on Insectivorous Diet, White Blood Cells, and Maximum Lifespan. These examples show how targeted species selections, informed by phylogenetic trait distributions, can uncover lineage-specific signatures and deepen our understanding of convergent molecular evolution (11,159,160).

Nonetheless, our approach has limitations. The use of permulation-based methods grounded in Brownian motion models offers a rigorous control for phylogenetic structure but may not fully capture the complexity of evolutionary dynamics. Additionally, differences between the two analytical methods (RERconverge and CAASTools), reflect distinct conceptual and statistical foundations, which introduce some variability in the gene-trait associations recovered. Rather than being a drawback, this highlights the value of complementary approaches for capturing a broader spectrum of evolutionary relationships between genomes and phenome. Moreover, by focusing on protein-coding sequences, we did not account for regulatory variants, structural variation, or gene expression dynamics—key contributors to trait architecture (164). Finally, most CAAS positions were found to be fixed in human populations, which expands our understanding of the molecular basis of these traits and is a substantial addition to lists of actionable genes and individual variants. Importantly, while our analyses identified thousands of such candidate protein-altering variants, many with potential functional relevance, experimental validation will be essential to confirm causality.

Despite these limitations, the scope and resolution of our analysis compare favorably with large-scale GWAS, which typically identify far fewer loci with limited causal interpretability. In contrast, our phylogenetic approach implicates thousands of protein-coding variants directly linked to phenotypic changes. These findings lay the groundwork for future efforts to functionally characterize the evolutionary and biomedical roles of the implicated loci. As phenotypic datasets become richer, more classes of genomic variants are explored and statistical models more refined, PGA can serve as a platform for expanding genome-phenome inference beyond coding regions, ultimately helping to bridge comparative genomics and human medical genetics.

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