

1 Polygenic adaptation and convergent evolution across
2 both growth and cardiac genetic pathways in African
3 and Asian rainforest hunter-gatherers

4 Christina M. Bergey^{1,2}, Marie Lopez^{3,4,5}, Genelle F. Harrison⁶, Etienne
5 Patin^{3,4,5}, Jacob Cohen², Lluís Quintana-Murci^{3,4,5,*}, Luis B. Barreiro^{6,*},
6 and George H. Perry^{1,2,7,*}

7 ¹Department of Anthropology, Pennsylvania State University, University Park, Pennsylvania,
8 U.S.A.

9 ²Department of Biology, Pennsylvania State University, University Park, Pennsylvania, U.S.A.

10 ³Unit of Human Evolutionary Genetics, Institut Pasteur, Paris, France.

11 ⁴Centre National de la Recherche Scientifique UMR 2000, Paris, France.

12 ⁵Center of Bioinformatics, Biostatistics and Integrative Biology, Institut Pasteur, Paris, France.

13 ⁶Université de Montréal, Centre de Recherche CHU Sainte-Justine, Montréal, Canada.

14 ⁷Huck Institutes of the Life Sciences, Pennsylvania State University, University Park,
15 Pennsylvania, U.S.A.

16 * *Co-senior authors*

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18 Corresponding authors: C.M.B. (cxb585@psu.edu) and G.H.P. (ghp3@psu.edu)

19 Abstract:

20

21 Different human populations facing similar environmental challenges have
22 sometimes evolved convergent biological adaptations, for example hypoxia re-
23 sistance at high altitudes and depigmented skin in northern latitudes on separate
24 continents. The pygmy phenotype (small adult body size), a characteristic of
25 hunter-gatherer populations inhabiting both African and Asian tropical rain-
26 forests, is often highlighted as another case of convergent adaptation in humans.
27 However, the degree to which phenotypic convergence in this polygenic trait is
28 due to convergent vs. population-specific genetic changes is unknown. To address
29 this question, we analyzed high-coverage sequence data from the protein-coding
30 portion of the genomes (exomes) of two pairs of populations, Batwa rainfor-
31 est hunter-gatherers and neighboring Bakiga agriculturalists from Uganda, and
32 Andamanese rainforest hunter-gatherers (Jarawa and Onge) and Brahmin agri-
33 culturalists from India. We observed signatures of convergent positive selection
34 between the Batwa and Andamanese rainforest hunter-gatherers across the set of
35 genes with annotated ‘growth factor binding’ functions ($p < 0.001$). Unexpect-
36 edly, for the rainforest groups we also observed convergent and population-specific
37 signatures of positive selection in pathways related to cardiac development (e.g.
38 ‘cardiac muscle tissue development’; $p = 0.001$). We hypothesize that the growth
39 hormone sub-responsiveness likely underlying the pygmy phenotype may have led
40 to compensatory changes in cardiac pathways, in which this hormone also plays
41 an essential role. Importantly, in the agriculturalist populations we did not ob-
42 serve similar patterns of positive selection on sets of genes associated with either
43 growth or cardiac development, indicating that our results most likely reflect

44 a history of convergent adaptation to the similar ecology of rainforest hunter-
45 gatherers rather than a more common or general evolutionary pattern for human
46 populations.

47 **Introduction**

48 Similar ecological challenges may repeatedly result in similar evolutionary outcomes, and
49 many instances of phenotypic convergence arising from parallel changes in the same genetic
50 loci have been uncovered (reviewed in [1–3]). Many examples of convergent genetic evolution
51 reported to date are for simple monogenic traits, for example depigmentation in independent
52 populations of Mexican cave fish living in lightless habitats [4, 5] and persistence of the abil-
53 ity to digest lactose in adulthood in both European and African agriculturalist/pastoralist
54 humans [6]. Most biological traits, however, are highly polygenic. Since the reliable detection
55 of positive selection in aggregate on multiple loci of individually small effect (i.e., polygenic
56 adaptation) is relatively difficult [7–11], the extent to which convergent genetic changes at
57 the same loci and functional pathways or changes affecting distinct genetic pathways may
58 underlie these complex traits is less clear.

59 Human height is a classic example of a polygenic trait with approximately 800 known
60 loci significantly associated with stature in Europeans collectively accounting for 27.4% of
61 the heritable portion of height variation in this population [12]. A stature phenotype also
62 represents one of most striking examples of convergent evolution in humans. Small body
63 size (or the “pygmy” phenotype, e.g. average adult male stature <155 cm) appears to have
64 evolved independently in rainforest hunter-gatherer populations from Africa, Asia, and South
65 America [13], as groups on different continents do not share common ancestry to the exclusion
66 of nearby agriculturalists [14, 15]. Positive correlations between stature and the degree of
67 admixture with neighboring agriculturalists have confirmed that the pygmy phenotype is,

68 at least in part, genetically mediated and therefore potentially subject to natural selection
69 [16–20].

70 Indeed, previous population genetic studies have identified signatures of strong positive
71 natural selection across the genomes of various worldwide rainforest hunter-gatherer groups
72 [15, 19, 21, 22]. In some cases, the candidate positive selection regions were significantly
73 enriched for genes involved in growth processes and pathways [15, 19]. However, in one rain-
74 forest hunter-gatherer population, the Batwa from Uganda, an admixture mapping approach
75 was used to identify 16 genetic loci specifically associated with the pygmy phenotype [17].
76 While these genomic regions were enriched for genes involved in the growth hormone path-
77 way and for variants associated with stature in Europeans, there was no significant overlap
78 between the pygmy phenotype-associated regions and the strongest signals of positive selec-
79 tion in the Batwa genome. Rather, subtle shifts in allele frequencies were observed across
80 these regions in aggregate, consistent with a history of polygenic adaptation for the Batwa
81 pygmy phenotype [17] and underscoring the importance of using different types of population
82 genetic approaches to study the evolutionary history of this trait. Similar studies focused on
83 other rainforest hunter-gatherer groups have found enrichment for signatures of selection on
84 genes involved in growth [15] and various growth factor signaling pathways [19], immunity
85 [19, 21, 22], metabolism [19, 21, 22], development [15, 22], and reproduction [19, 21, 22].

86 Here, we investigate population-specific and convergent patterns of positive selection in
87 African and Asian hunter-gatherer populations using genome-wide sequence data from two
88 sets of populations: the Batwa rainforest hunter-gatherers of Uganda in East Africa and the
89 nearby Bakiga agriculturalists [23], and the Jarawa and Onge rainforest hunter-gatherers of
90 the Andaman Islands in South Asia and the Uttar Pradesh Brahmin agriculturalists from
91 mainland India [24, 25]. We specifically test whether convergent or population-specific signa-
92 tures of positive selection, as detected both with ‘outlier’ tests designed to identify strong sig-
93 natures of positive selection and tests designed to identify signatures of polygenic adaptation,

94 are enriched for genes with growth-related functions. After studying patterns of convergent-
95 and population-specific evolution in the Batwa and Andamanese hunter-gatherers, we then
96 repeat these analyses in the paired Bakiga and Brahmin agriculturalists to evaluate whether
97 the evolutionary patterns most likely relate to adaptation to hunter-gatherer subsistence
98 in rainforest habitats, rather than being more generalized evolutionary patterns for human
99 populations.

100 Results

101 We sequenced the protein coding portions of the genomes (exomes) of 50 Batwa rainforest
102 hunter-gatherers and 50 Bakiga agriculturalists (dataset originally reported in [23]), identi-
103 fied single nucleotide polymorphisms (SNPs), and analyzed the resultant data alongside those
104 derived from published whole genome sequence data for 10 Andamanese rainforest hunter-
105 gatherers and 10 Brahmin agriculturalists (dataset from [25]). We restricted our analysis to
106 exonic SNPs, for comparable analysis of the Asian whole genome sequence data with the
107 African exome sequence data. To polarize allele frequency differences observed between each
108 pair of hunter-gatherer and agriculturalist populations, we merged these data with those from
109 outgroup comparison populations from the 1000 Genomes Project [26]: exome sequences of
110 30 unrelated British individuals from England and Scotland (GBR) for comparison with
111 the Batwa/Bakiga data, and exome sequences of 30 Luhya individuals from Webuye, Kenya
112 (LWK) for comparison with the Andamanese/Brahmin data. Outgroup populations were se-
113 lected for genetic equidistance from the test populations. While minor levels of introgression
114 from a population with European have been observed for the Batwa and Bakiga [23, 27],
115 PBS is relatively robust to low levels of admixture [28].

116 To identify regions of the genome that may have been affected by positive selection in
117 each of our test populations, we computed the population branch statistic (PBS; [29]) for

118 each exonic SNP identified among or between the Batwa and Bakiga, and Andamanese and
119 Brahmin populations (Fig. S1, S2; Table S15). PBS is an estimate of the magnitude of allele
120 frequency change that occurred along each population lineage following divergence of the
121 most closely related populations, with the allele frequency information from the outgroup
122 population used to polarize frequency changes to one or both branches. Larger PBS values
123 for a population reflect greater allele frequency change on that branch, which in some cases
124 could reflect a history of positive selection [29].

125 For each analyzed population, we computed a PBS selection index for each gene by
126 comparing the mean PBS for all SNPs located within that gene to a distribution of values
127 estimated by shuffling SNP-gene associations (without replacement) and re-computing the
128 mean PBS value for that gene 100,000 times (Table S17). The PBS selection index is the
129 percentage of permuted values that is higher than the actual (observed) mean PBS value
130 for that gene. Per-gene PBS selection index values were not significantly correlated with
131 gene size (linear regression of log adjusted selection indices against gene length: adjusted
132 $R^2 = -2.74 \times 10^{-5}$, F -statistic $p = 0.81$; Fig. S3), suggesting that this metric is not overtly
133 biased by gene size.

134 Convergent evolution can operate at different scales, including on the same mutation
135 or amino acid change, different genetic variants between populations but within the same
136 genes, or across a set of genes involved in the same biomolecular pathway or functional
137 annotation. Given that our motivating phenotype is a complex trait and signatures of
138 polygenic adaptation are expected to be relatively subtle and especially difficult to detect
139 at the individual mutation and gene levels, in this study we principally consider patterns of
140 convergence versus population specificity at the functional pathway/annotation level. We
141 do note that when we applied the same approaches described in this study to individual
142 SNPs, we identified several individual alleles with patterns of convergent allele frequency
143 evolution between the Batwa and Andamanese that may warrant further study (Table S16),

144 including a nonsynonymous SNP in the gene *FIG4*, which when disrupted in mice results
145 in a phenotype of small but proportional body size [30]. However, likely related to the
146 above-discussed challenges of identifying signatures of polygenic adaptation at the locus-
147 specific level, the results of our individual SNP and gene analyses were otherwise largely
148 unremarkable, and thus the remainder of our report and discussion focuses on pathway-level
149 analyses.

150 **Outlier signatures of strong convergent and population-specific se-** 151 **lection**

152 The set of genes with the lowest (outlier) PBS index values for each population may be
153 enriched for genes with histories of relatively strong positive natural selection. We used a
154 permutation-based analysis to test whether curated sets of genome-wide growth-associated
155 genes (4 lists tested separately ranging from 266-3,996 genes; 4,888 total genes; Suppl. Text)
156 or individual Gene Ontology (GO) annotated functional categories of genes (GO categories
157 with fewer than 50 genes were excluded) have significant convergent excesses of genes with
158 low PBS selection index values (< 0.01) in both of two cross-continental populations, for
159 example the Batwa and Andamanese. Specifically, we first used Fisher's exact tests to
160 estimate the probability that the number of genes with PBS selection index values < 0.01
161 was greater than that expected by chance, for each functional category set of genes and
162 population. We then reshuffled the PBS selection indices across all genes 1,000 different
163 times for each population to generate distributions of permuted enrichment p-values for
164 each functional category set of genes. We compared our observed Batwa and Andamanese
165 Fisher's exact test p-values to those from the randomly generated distributions as follows. We
166 computed the joint probability of the null hypotheses for both the Andamanese and Batwa
167 being false as $(1 - p_{Batwa})(1 - p_{Andamanese})$, where p_{Batwa} and $p_{Andamanese}$ are the p-values of

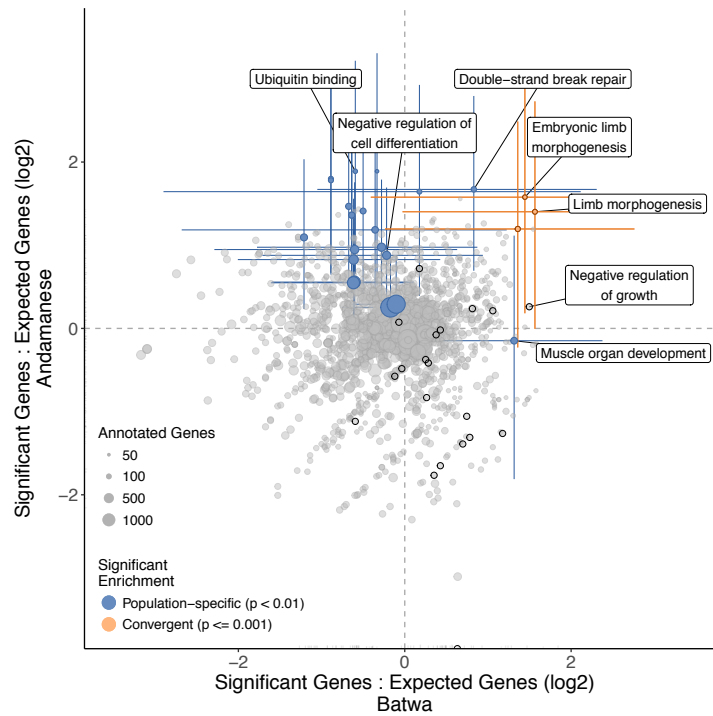
168 the Fisher’s exact test, and we compared this joint probability estimate to the same statistic
169 computed for the p-values from the random iterations. We then defined the p-value of our
170 empirical test for convergent evolution as the probability that this statistic was more extreme
171 (lower) for the observed values than for the randomly generated values. The resultant p-value
172 summarizes the test of the null hypothesis that both results could have been jointly generated
173 under random chance. While each individual population’s outlier-based test results are not
174 significant after multiple test correction, this joint approach provides increased power to
175 identify potential signatures of convergent selection by assessing the probability of obtaining
176 two false positives in these independent samples.

177 Several GO biological processes were significantly overrepresented—even when account-
178 ing for the number of tests performed—among the sets of genes with outlier signatures of
179 positive selection in both the Batwa and Andamanese hunter-gatherer populations (empiri-
180 cal test for convergence $p < 0.005$; Table S1; Fig. 1A). These GO categories include ‘limb
181 morphogenesis’ (GO:0035108; empirical test for convergence $p < 0.001$; $q < 0.001$; Batwa:
182 genes observed = 5, expected = 1.69, Fisher’s exact $p = 0.027$; Andamanese: observed = 6,
183 expected = 2.27, Fisher’s exact $p = 0.025$).

184 Other functional categories of genes were overrepresented in the sets of outlier loci for
185 one of these hunter-gatherer populations but not the other (Fig. 1A; Table S2, S24). The
186 top population-specific enrichments for genes with outlier PBS selection index values for
187 the Batwa were associated with growth and development: ‘muscle organ development’
188 (GO:0007517; observed genes: 10; expected genes: 4.02; $p = 0.007$) and ‘negative regu-
189 lation of growth’ (GO:0045926; observed = 7; expected = 2.48; $p = 0.012$). Significantly
190 overrepresented GO biological processes for the Andamanese included ‘negative regulation
191 of cell differentiation’ (GO:0045596; observed genes: 18; expected genes: 9.79; $p = 0.009$).
192 However, these population-specific enrichments were not significant following multiple test
193 correction (false discovery rate $q = 0.71$ for both Batwa terms and $q = 0.22$ for the An-

GO categories with significant enrichment for signatures of strong positive selection

A. Rainforest hunter-gatherers



B. Agriculturalists

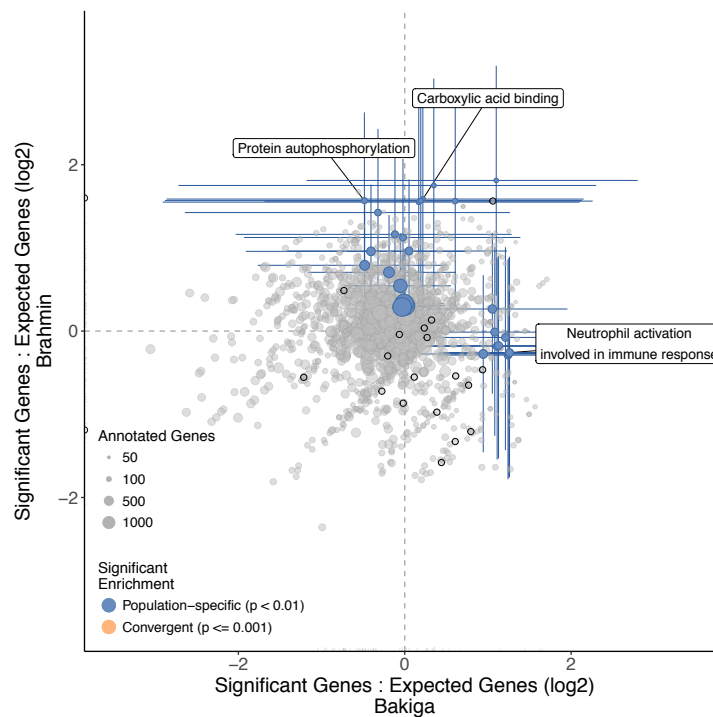


Figure 1: (Continued on the following page.)

Figure 1: Gene Ontology (GO) functional categories' ratios of expected to observed counts of outlier genes (with PBS selection index < 0.01) in the Batwa and Andamanese rainforest hunter-gatherers (A) and Bakiga and Brahmin agriculturalist control comparison (B). Results shown for GO biological processes and molecular functions. Point size is scaled to number of annotated genes in category. Terms that are significantly overrepresented for genes under positive selection (Fisher $p < 0.01$) in either population are shown in blue and for both populations convergently (empirical permutation-based $p \leq 0.001$) are shown in orange. Colored lines represent 95% CI for significant categories estimated by bootstrapping genes within pathways. Dark outlines indicate growth-associated terms: the 'growth' biological process (GO:0040007) and its descendant terms, or the molecular functions 'growth factor binding,' 'growth factor receptor binding,' 'growth hormone receptor activity,' and 'growth factor activity' and their sub-categories.

194 damanese result).

195 In contrast, no GO functional categories were observed to have similarly significant con-
196 vergent excesses of 'outlier' genes with signatures of positive selection across the two agri-
197 culturalist populations as that observed for the rainforest hunter-gatherer populations (Fig.
198 1B; Table S19), and the top ranked GO categories from both the convergent evolution anal-
199 ysis and the population-specific analyses were absent any obvious connections to skeletal
200 growth. The top-ranked functional categories with enrichments for genes with outlier PBS
201 selection index values for the individual agriculturalist populations included 'neutrophil acti-
202 vation involved in immune response' for the Bakiga (GO:0002283; observed = 13; expected =
203 5.43; $p = 0.003$; $q = 0.41$) and 'protein autophosphorylation' for the Brahmin (GO:0046777;
204 observed = 11; expected = 3.71; $p = 0.0012$; $q = 0.16$; Table S24).

205 **Signatures of convergent and population-specific polygenic adapta-** 206 **tion**

207 Outlier-based approaches such as that presented above are expected to have limited power
208 to identify signatures of polygenic adaptation [7–11], which is our expectation for the pygmy
209 phenotype [17]. Unlike the previous analyses in which we identified functional categories

210 with an enriched number of genes with outlier PBS selection index values, for our poly-
211 genic evolution analysis we computed a “distribution shift-based” statistic to instead identify
212 functionally-grouped sets of loci with relative shifts in their distributions of PBS selection
213 indices. Specifically, we used the Kolmogorov-Smirnov (KS) test to quantify the distance
214 between the distribution of PBS selection indices for the genes within a functional category
215 to that of the genome-wide distribution. Significantly positive shifts in the PBS selection
216 index distribution for a particular functional category may reflect individually subtle but
217 consistent allele frequency shifts across genes within the category, which could result from
218 either a relaxation of functional constraint or a history of polygenic adaptation. Our ap-
219 proach is similar to another recent method that was used to detect polygenic signatures
220 of pathogen-mediated adaptation in humans [31]. As above, we identified functional cate-
221 gories with convergently high KS values between cross-continental groups by repeating these
222 tests 1,000 times on permuted gene-PBS values and computing the joint probability of both
223 null hypotheses being false for the two populations. We then compared this value from the
224 random iterations to the same statistic computed with the observed KS p-values for each
225 functional category. For example, for the Batwa and Andamanese, we tallied the number
226 of random iterations for which the joint probability of both null hypotheses being false was
227 more extreme (lower) than those of the random iterations. In this way we tested the null
228 hypothesis that both of our observed p-values could have been jointly generated by random
229 chance.

230 The GO molecular function with the strongest signature of a convergent polygenic shift
231 in PBS selection indices across the Batwa and Andamanese populations was ‘growth fac-
232 tor binding’ (Table S3; Fig. 2A; GO:0019838; Batwa $p = 0.021$; Andamanese $p = 0.027$;
233 Fisher’s combined $p = 0.0048$; empirical test for convergence $p < 0.001$; $q < 0.001$), and the
234 top GO biological process was ‘organ growth’ (GO:0035265; Batwa $p = 0.028$; Andamanese
235 $p = 0.045$; Fisher’s combined $p = 0.0095$; empirical test for convergence $p = 0.001$; $q = 1$).

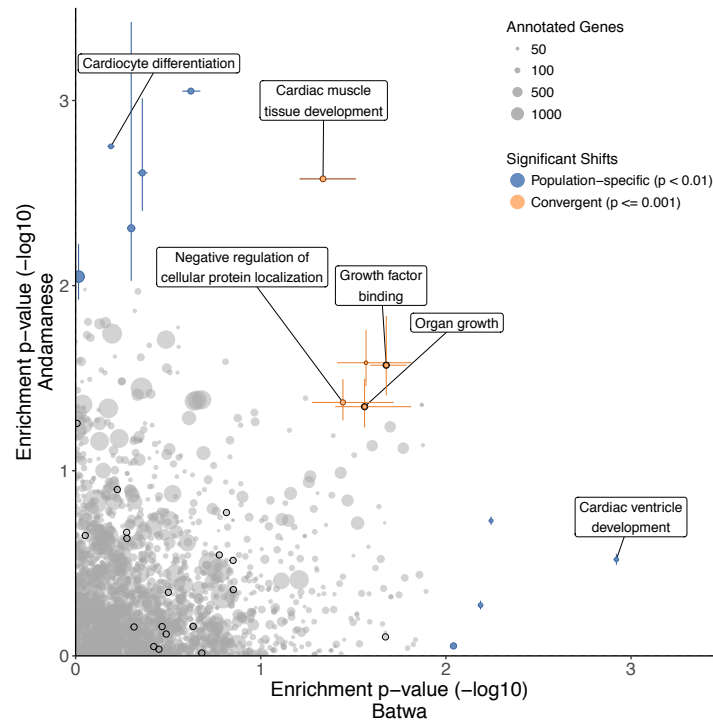
236 The other top Batwa-Andamanese convergent GO biological processes are not as obviously
237 related to growth, but instead involve muscles, particularly heart muscles. A significant
238 convergent shift in PBS selection indices across both hunter-gatherer populations was ob-
239 served for ‘cardiac muscle tissue development’ (GO:0048738; Batwa $p = 0.046$; Andamanese
240 $p = 0.003$; Fisher’s combined $p = 0.001$; empirical test for convergence $p = 0.001$; $q = 1$).

241 In contrast, when this analysis was repeated on the agriculturalist populations, no growth-
242 or muscle-related functional annotations were observed with significantly convergent shifts
243 in both populations (Fig. 2B; Table S26). The GO categories with evidence of potential
244 convergent evolution between the agriculturalists were the biological processes ‘leukocyte
245 differentiation’ (GO:0002521; Bakiga $p = 0.0086$; Brahmin $p = 0.0149$; Fisher’s combined
246 $p = 0.00128$; convergence empirical $p < 0.001$; $q < 0.001$) and ‘protein autophosphoryla-
247 tion’ (GO:0046777; Bakiga $p = 0.033$; Brahmin $p = 0.0099$; Fisher’s combined $p = 0.003$;
248 convergence empirical $p = 0.001$; $q = 1$).

249 We also used Bayenv, a Bayesian linear modeling method for identifying loci with allele
250 frequencies that covary with an ecological variable [9, 32], to assess the level of consistency
251 with our convergent polygenic PBS shift results. Specifically, we used Bayenv to test whether
252 the inclusion of a binary variable indicating subsistence strategy would increase the power
253 to explain patterns of genetic diversity for a given functional category of loci over a model
254 that only considered population history (as inferred from the covariance of genome-wide
255 allele frequencies in the dataset.) We converted Bayes factors into per-gene index values via
256 permutation of SNP-gene associations (Table S21) and identified GO terms with significant
257 shifts in the Bayenv Bayes factor index distribution [9, 32] (Table S27). The top results from
258 this analysis included ‘growth factor activity’ (GO:0008083; $p = 0.006$; $q = 0.11$), categories
259 related to enzyme regulation (e.g. ‘enzyme regulator activity’; GO:0030234; $p = 0.003$; $q =$
260 0.01), and categories related to muscle cell function (e.g. ‘microtubule binding’; GO:0008017;
261 $p = 0.003$; $q = 0.10$). There were more GO terms that were highly ranked ($p < 0.05$) in both

GO categories with significant enrichment for signatures of polygenic selection

A. Rainforest hunter-gatherers



B. Agriculturalists

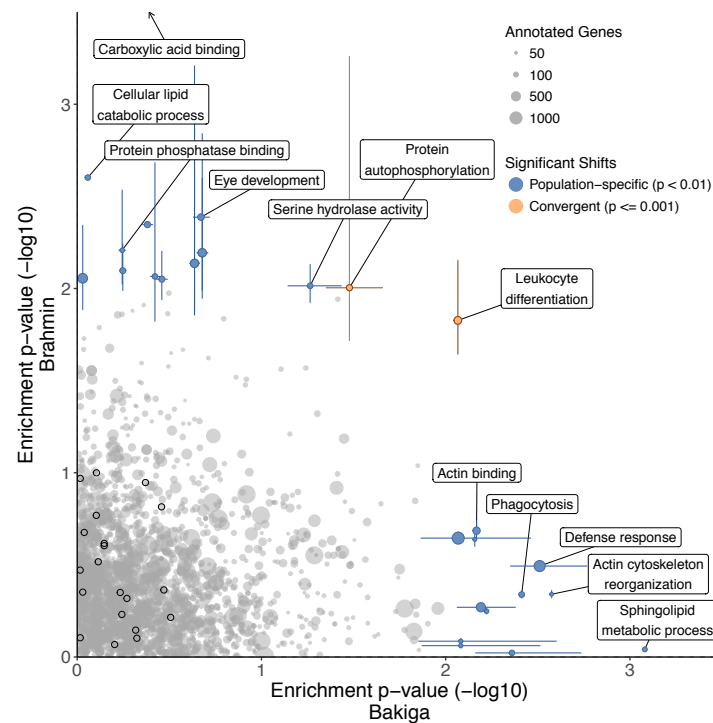


Figure 2: (Continued on the following page.)

Figure 2: Gene Ontology (GO) functional categories' distribution shift test p-values, indicating a shift in the PBS selection index values for these genes, in the Batwa and Andamanese rainforest hunter-gatherers (A) and Bakiga and Brahmin agriculturalist control comparison (B). Results shown for GO biological processes and molecular functions. Point size is scaled to number of annotated genes in category. Terms that are significantly enriched for genes under positive selection (Kolmogorov-Smirnov $p < 0.01$) in either population are shown in blue and for both populations convergently (empirical permutation-based $p \leq 0.001$) are shown in orange. Colored lines represent 95% CI for significant categories estimated by bootstrapping genes within pathways. Dark outlines indicate growth-associated terms: the 'growth' biological process (GO:0040007) and its descendant terms, or the molecular functions 'growth factor binding,' 'growth factor receptor binding,' 'growth hormone receptor activity,' and 'growth factor activity' and their sub-categories. One GO molecular function, "carboxylic acid binding" (GO:0031406; Brahmin $p = 7.3 \times 10^{-5}$; $q = 0.0050$) not shown, but indicated with arrow.

262 the hunter-gatherer PBS shift-based empirical test of convergence and the Bayenv analysis
263 than expected by chance (for biological processes GO terms: observed categories in common
264 = 13, expected = 8.03, Fisher's exact test $p = 9.67 \times 10^{-5}$; for molecular function GO terms:
265 observed categories in common = 4, expected = 1.45, Fisher's exact test $p = 0.045$).

266 While we did not observe any significant population-specific shifts in PBS selection index
267 values for growth-associated GO functional categories in any of our studied populations
268 (Table S4; Suppl. Text), for each individual rainforest hunter-gatherer population we did
269 observe nominal shifts in separate biological process categories involving the heart (Fig.
270 2A). For the Batwa, 'cardiac ventricle development' (GO:0003231) was the top population-
271 specific result (median PBS index = 0.272 vs. genome-wide median PBS index = 0.528;
272 $p = 0.001$; $q = 0.302$). For the Andamanese, 'cardiocyte differentiation' (GO:0035051) was
273 also ranked highly (median PBS index = 0.353 vs. genome-wide median PBS index = 0.552;
274 $p = 0.002$; $q = 0.232$). We note that while these are separate population-specific signatures,
275 17 genes are shared between the above two cardiac-related pathways (of 61 total 'cardiocyte
276 differentiation' genes total, 28%; of 71 total 'cardiac ventricle development' genes, 24%; Table
277 S28).

278 In contrast, cardiac development-related GO categories were not observed among those
279 with highly-ranked population-specific polygenic shifts in selection index values for either
280 the Bakiga or Brahmin agriculturalists (Fig. 2B; Table S29). The only GO term with a
281 significant population-specific shift in the agriculturalists after multiple test correction was
282 molecular function ‘carboxylic acid binding’ in the Brahmins (GO:0031406; $p = 7.30 \times 10^{-5}$;
283 $q = 0.005$).

284 To ensure that our results were robust to several possible biases, we repeated the above
285 analyses with several modifications. First, to control for potential biases related to varia-
286 tion in gene length and SNP minor allele frequency (MAF), we repeated all analyses after
287 computing the PBS selection index with binning of genes by length and SNPs by MAF,
288 respectively. Our results were not materially different (Tables S5-S12; Figs. S4-S8; Suppl.
289 Text). Second, to account for the effect of linkage disequilibrium among SNPs within a
290 gene, we re-computed the empirical test for convergence p-values by permuting gene-GO
291 relationships when generating the random null distributions for the PBS selection index val-
292 ues instead of gene-PBS relationships as in our original analysis. Again, downstream results
293 were largely unchanged (Table S13-S14; Suppl. Text). These additional analyses increase
294 our confidence that our results are not artifactual.

295 Discussion

296 The independent evolution of small adult body size in multiple different tropical rainforest
297 environments worldwide presents a natural human model for comparative study of the ge-
298 netic and evolutionary bases of growth and body size. Through an evolutionary genomic
299 comparison of African and Asian rainforest hunter-gatherer populations to one another and
300 with nearby agriculturalists, we have gained additional, indirect insight into the genetic
301 structure of body size, a fundamental biological trait. Specifically, we identified a signa-

302 ture of potential convergent positive selection on the growth factor binding pathway that
303 could partially underlie the independent evolution of small body size in African and Asian
304 rainforest hunter-gatherers.

305 Unexpectedly, we also observed signatures of potential polygenic selection across func-
306 tional categories of genes related to heart development in the rainforest hunter-gatherer
307 populations, both convergently and on a population-specific basis. To a minor extent, the
308 growth factor- and heart-related functional categories highlighted in our study do overlap: of
309 the 123 total genes annotated across the three heart-related categories (‘cardiac muscle tis-
310 sue development’ GO:0048738, ‘cardiac ventricle development’ GO:0003231, and ‘cardiocyte
311 differentiation’ GO:0035051), nine (7.3%) are also included among the 66 annotated genes
312 in the ‘growth factor binding’ category (GO:0019838). However, even after excluding these
313 nine genes from our dataset, we still observed similar polygenic PBS shifts in the Batwa and
314 Andamanese for both growth factor- and heart-related functional categories (Suppl. Text),
315 demonstrating that our observations are not driven solely by cross-annotated genes.

316 We hypothesize that the evolution of growth hormone sub-responsiveness, which appears
317 to at least partly underlie short stature in some rainforest hunter-gatherer populations [33–
318 37] may in turn have also resulted in strong selection pressure for compensatory adaptations
319 in cardiac pathways. The important roles of growth hormone (GH1) in the heart are evi-
320 dent from studies of patients deficient in the hormone. For example, patients with growth
321 hormone deficiency are known to be at an increased risk of atherosclerosis and mortality
322 from cardiovascular disease [38] and have worse cardiac function [39]. More broadly, shorter
323 people have elevated risk of coronary artery disease [40], likely due to the pleiotropic effects
324 of variants affecting height and atherosclerosis development [41]. Such health outcomes may
325 relate to the important roles that growth hormone plays in the development and function
326 in the myocardium [42, 43], which contains a relatively high concentration of receptors for
327 growth hormone [44]. We hypothesize that the adaptive evolution of growth hormone sub-

328 responsiveness underlying short stature in rainforest hunter-gatherers may have necessitated
329 compensatory adaptations in the cardiac pathways reliant on growth hormone.

330 An alternative explanation for our finding of potential convergent positive selection on
331 cardiac-related pathways relates to the nutritional stress of full-time human rainforest habi-
332 tation. Especially prior to the ability to trade forest products for cultivated goods with
333 agriculturalists, the diets of full-time rainforest hunter-gatherers may have been calorically
334 and nutritionally restricted on at least a seasonal basis [13]. Caloric restriction has a direct
335 functional impact on cardiac metabolism and function, with modest fasting in mice leading to
336 the depletion of myocardial phospholipids, which potentially act as a metabolic reserve to en-
337 sure energy to essential heart functions [45]. In human rainforest hunter-gatherers, selection
338 may have favored variants conferring cardiac phenotypes optimized to maintain myocardial
339 homeostasis during the nutritional stress that these populations may have experienced in
340 the past.

341 An important caveat to our study is the lack of statistical significance for our population-
342 specific analyses after controlling for the multiplicity of tests resulting from hierarchically
343 nested GO terms. The absence of strong signals of positive selection that are robust to
344 the multiple testing burden likely reflects both the expected subtlety of evolutionary sig-
345 nals of selection on polygenic traits and the restriction of our dataset to gene coding region
346 sequences. However, our comparative approach to identify signatures of convergent evo-
347 lution is more robust. Therefore, while we cannot yet accurately estimate the extent to
348 which signatures of positive selection that potentially underlie the evolution of the pygmy
349 phenotype occurred in the same versus distinct genetic pathways between the Batwa and
350 Andamanese, we do feel confident in our findings of convergent growth-related and cardiac-
351 related pathways evolution. The concurrent signatures of convergent evolution across these
352 two pathways in both African and Asian rainforest hunter-gatherers is an example of the in-
353 sight into a biomedically-relevant phenotype that can be gained from the comparative study

354 of human populations with non-pathological natural variation.

355 **Materials and Methods**

356 **Sample collection and dataset generation**

357 Sample collection, processing, and sequencing have been previously described [17, 23]. Briefly,
358 sampling of biomaterials (blood or saliva) from Batwa rainforest hunter-gatherers and Bakiga
359 agriculturalists of southwestern Uganda took place in 2010 [17]. The study was approved by
360 the Institutional Review Boards (IRBs) of both the University of Chicago (#16986A) and
361 Makerere University, Kampala, Uganda (#2009-137), and local community approval and
362 individual informed consent were obtained before collection. DNA samples of 50 Batwa
363 and 50 Bakiga adults were included in the present study. Exome capture, sequencing,
364 and variant calling were described previously [23]. Briefly, sequence reads were aligned
365 to the hg19/GRCh37 genome with BWA v.0.7.7 mem with default settings [46], PCR dupli-
366 cates were detected with Picard Tools v.1.94 (<http://broadinstitute.github.io/picard>), and
367 re-alignment around indels and base quality recalibration was done with GATK v3.5 [47]
368 using the known indel sites from the 1000 Genomes Project [26]. Variants were called indi-
369 vidually with GATK HaplotypeCaller [47], and variants were pooled together with GATK
370 GenotypeGVCF and filtered using VQSR. Only biallelic SNPs with a minimum depth of 5x
371 and less than 85% missingness that were polymorphic in the entire dataset were retained for
372 analyses.

373 Variant data for the Andamanese individuals (Jarawa and Onge) and an outgroup main-
374 land Indian population (Uttar Pradesh Brahmins) from [25] were downloaded in VCF file
375 format from a public website. To ensure the exome capture-derived African and whole
376 genome shotgun sequencing-derived Asian datasets were comparable, we restricted our anal-
377 yses of these data to exonic SNPs only.

378 **Merging with 1000 Genomes data**

379 We chose outgroup comparison populations from the 1000 Genomes Project [26] to be equally
380 distantly related to the ingroup populations: Reads from a random sample of 30 unrelated
381 individuals from British in England and Scotland (GBR) and Luhya in Webuye, Kenya
382 (LWK) were chosen for the Batwa/Bakiga and Andamanese/Brahmin datasets, respectively.
383 We re-called variants in each 1000 Genomes comparison population at loci that were variable
384 in the ingroup populations using GATK UnifiedGenotyper [47]. Variants were filtered to
385 exclude those with $QD < 2.0$, $MQ < 40.0$, $FS > 60.0$, $HaplotypeScore > 13.0$, $MQRankSum$
386 < -12.5 , or $ReadPosRankSum < -8.0$. We removed SNPs for which fewer than 10 of the 30
387 individuals from the 1000 Genomes datasets had genotypes.

388 **Computation of the Population Branch Statistic (PBS) and the** 389 **per-gene PBS index**

390 Using these merged datasets, we computed F_{ST} between population pairs using the unbiased
391 estimator of Weir and Cockerham [48], transformed it to a measure of population divergence
392 [$T = -\log(1 - F_{ST})$], and then calculated the Population Branch Statistic (PBS), after [29].
393 PBS was computed on a per-SNP basis. We computed an empirical p-value for each SNP,
394 simply the proportion of coding SNPs with PBS greater than the value for this SNP, which
395 we adjusted for FDR.

396 SNPs were annotated with gene-based information using ANNOVAR [49] with refGene
397 (Release 76) [50] and PolyPhen [51] data. As the Andamanese/Brahmin dataset spanned
398 the genome and the Batwa/Bakiga exome dataset included off target intronic sequences
399 as well as untranslated regions (UTRs), and microRNAs, we restricted our analysis to only
400 exonic SNPs. For both the Batwa/Bakiga and Andamanese/Brahmin datasets, we computed
401 a “PBS selection index” for each gene as follows. We compared the mean PBS for all

402 SNPs located within that gene to a distribution of values estimated by shuffling SNP-gene
403 associations (without replacement) and re-computing the mean PBS value for that gene
404 10,000 times. We defined the PBS selection index of the gene as the percentage of these
405 empirical mean values that is higher than its observed mean PBS value. When identifying
406 outlier genes, gene-based indices were adjusted for FDR.

407 In order to assess potential biases related to variation in gene length and SNP minor
408 allele frequencies (MAF), we repeated all analyses after computing the PBS selection index
409 with binning of genes by length or SNPs by MAF. Complete details of these methods are
410 included in the Supplemental Text.

411 To identify SNPs with allele frequencies correlated with subsistence strategy (hunter-
412 gatherer: Andamanese and Batwa; agriculturalists: Bakiga and Brahmin), we used Bayenv2.0
413 [32] to assess whether the addition of a binary variable denoting subsistence strategy im-
414 proved the Bayesian model that already took into account covariance between samples due
415 to ancestry. As with the PBS results, we computed an index for each gene by sampling
416 new values for each SNP from the distribution of all Bayes factors and comparing the actual
417 average for this gene to those of the bootstrapped replicates.

418 **Creation of *a priori* lists of growth-related genes**

419 To test the hypothesis that genes with known influence on growth would show increased
420 positive selection in rainforest hunter-gatherer populations, we curated *a priori* lists of
421 growth-related genes as described fully in the Supplemental Text. Briefly, we obtained
422 the following gene lists: i) 3,996 genes that affect growth or size in mice (MP:0005378) from
423 the Mouse/Human Orthology with Phenotype Annotations database [52]; ii) 266 genes as-
424 sociated with abnormal skeletal growth syndromes in the Online Mendelian Inheritance in
425 Man (OMIM) database (<https://omim.org>), as assembled by [53]; iii) 427 genes expressed
426 substantially more highly in the mouse growth plate, the cartilaginous region on the end of

427 long bones where bone elongation occurs, than in soft tissues [lung, kidney, heart; ≥ 2.0
428 fold change; [54]]; and iv) 955 genes annotated with the Gene Ontology “growth” biologi-
429 cal process (GO:0040007). As the GH/IGF1 pathway is a major regulator of growth and
430 disruptions to the pathway have been implicated in the pygmy phenotype, we also collected
431 lists of genes associated with GH1 and IGF1 respectively from the OPHID database of pro-
432 teinprotein interaction (PPI) networks [55]. Separately, we also used a list of genes found to
433 be associated with the pygmy phenotype in the Batwa [17].

434 **Statistical overrepresentation and distribution shift tests**

435 Using the PBS and Bayenv indices, we next tested for a statistical over-representation of
436 extreme values ($p < 0.01$) for the above *a priori* gene lists as well as all Gene Ontology
437 (GO) terms using the topGO package of Bioconductor [56], gene-to-GO mapping from the
438 org.Hs.eg.db package [57], and Fisher’s exact test in “classic” mode (i.e., without adjust-
439 ment for GO hierarchy). We similarly performed a statistical enrichment test using the
440 Kolmogorov-Smirnov test again in “classic” mode, which tested for a shift in the distribu-
441 tion of the PBS or Bayenv statistic, rather than an excess of extreme values. In all cases, we
442 pruned the GO hierarchy to exclude GO terms with fewer than 50 annotated genes to reduce
443 the number of tests, leaving 1,742 and 1,816 GO biological processes and 266 and 285 GO
444 molecular functions tested for the African and Asian datasets, respectively. To further reduce
445 the number of redundant tests, we also computed the semantic similarity between GO terms
446 to remove very similar terms. We computed the similarity metric of [58] as implemented
447 in the GoSemSim R package [59], a measure of the overlapping information content in each
448 term using the annotation statistics of their common ancestor terms, and then clustered
449 based on these pairwise distances between GO terms using Ward Hierarchical Clustering.
450 We then pruned GO terms by cutting the tree at a height of 0.5 and retaining the term in
451 each cluster with the lowest p-value. With this reduced set of GO overrepresentation and

452 distribution shift results, we adjusted the p-value for FDR.

453 **Identification of signatures of convergent evolution**

454 We used two methods to identify convergent evolution: i.) computation of simple com-
455 bined p-values for SNPs, genes, and GO overrepresentation and distribution shift tests using
456 Fisher’s and Edgington’s methods, and ii.) a permutation based approach to identify GO
457 pathways for which both the Batwa and Andamanese overrepresentation or distribution
458 shift test results are more extreme than is to be expected by chance (the “empirical test for
459 convergence”). These two approaches are summarized below.

460 We searched for convergence between Batwa and Andamanese individuals by computing
461 the joint p-value for PBS on a per-SNP, per-gene, and per-GO term basis. We calculated all
462 joint p-values using Fisher’s method (as the sum of the natural logarithms of the uncorrected
463 p-values for the Batwa and Andamanese tests [60]) as well as via Edgington’s method (based
464 on the sum of all p-values [61]). Meta-analysis of p-values was done via custom script and
465 the metap R package [62].

466 We also assessed the probability of getting two false positives in the Batwa and An-
467 damanese selection results by shuffling the genes’ PBS indices 1,000 times and performing
468 GO overrepresentation and distribution shift tests on these permuted values. We compared
469 the observed Batwa and Andamanese p-values to this generated distribution of p-values, as
470 described above. We computed the joint probability of both null hypotheses being false for
471 the Andamanese and Batwa as $(1 - p_{Batwa})(1 - p_{Andamanese})$, where p_{Batwa} and $p_{Andamanese}$ are
472 the p-values of the Fisher’s exact test or of the Kolmogorov-Smirnov test for the outlier- and
473 shift-based tests, respectively, and we compared the joint probability to the same statistic
474 computed for the p-values from the random iterations. The empirical test for convergence
475 p-value was simply the number of iterations for which this statistic was more extreme (lower)
476 for the observed values than for the randomly generated values.

477 We also performed a variation of this analysis, but to preserve patterns of linkage disequi-
478 librium among SNPs within a gene in the null distribution, instead of permuting gene-PBS
479 relationships to generate the random null distributions for the PBS selection index values
480 of the two populations considered jointly, we instead permuted the gene-GO relationships.
481 That is, to compute the PBS selection index, the one-to-many relationships between genes
482 and GO terms were shuffled when generating the null distribution, maintaining the groupings
483 of GO terms that were assigned together to an original gene. Full details of this analysis are
484 available in the Supplemental Text.

485 **Script and data availability**

486 All scripts used in the analysis are available at [https://github.com/bergeycm/rhg-convergence-](https://github.com/bergeycm/rhg-convergence-analysis)
487 [analysis](https://github.com/bergeycm/rhg-convergence-analysis) and released under the GNU General Public License v3. Exome data for the Batwa
488 and Bakiga populations have previously been deposited in the European Genome-phenome
489 Archive under accession code EGAS00001002457. Extended data tables are available at
490 <https://doi.org/10.18113/S1N63M>.

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642 **Competing interests statement**

643 The authors declare no competing interests.

1 Supplemental Material for: Polygenic adaptation and
2 convergent evolution across both growth and cardiac
3 genetic pathways in African and Asian rainforest
4 hunter-gatherers

5 Christina M. Bergey^{1,2}, Marie Lopez^{3,4,5}, Genelle F. Harrison⁶, Etienne
6 Patin^{3,4,5}, Jacob Cohen², Lluís Quintana-Murci^{3,4,5,*}, Luis B. Barreiro^{6,*},
7 and George H. Perry^{1,2,7,*}

8 ¹Department of Anthropology, Pennsylvania State University, Pennsylvania, U.S.A.

9 ²Department of Biology, Pennsylvania State University, Pennsylvania, U.S.A.

10 ³Unit of Human Evolutionary Genetics, Institut Pasteur, Paris, France.

11 ⁴Centre National de la Recherche Scientifique UMR 2000, Paris, France.

12 ⁵Center of Bioinformatics, Biostatistics and Integrative Biology, Institut Pasteur, Paris, France.

13 ⁶Université de Montréal, Centre de Recherche CHU Sainte-Justine, H3T 1C5 Montréal, Canada.

14 ⁷Huck Institutes of the Life Sciences, Pennsylvania State University, Pennsylvania, U.S.A.

15 * *Co-senior authors*

16 June 14, 2018

17 Corresponding authors: C.M.B. (cxb585@psu.edu) and G.H.P. (ghp3@psu.edu)

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63 1 Supplemental Text

64 **Positive selection signatures on growth-associated genes** We examined whether
65 gene-specific signatures of strong positive selection (using an “outlier-based” designation
66 of genes with PBS index values < 0.01) in the rainforest populations were enriched for
67 known functional associations with growth using *a priori* lists of 4,888 total growth-related
68 genes, consisting of (with some redundancy among individual categories, as expected): i)
69 3,996 genes that affect growth or size in mice (MP:0005378) from the Mouse/Human Or-
70 thology with Phenotype Annotations database [1]; ii) 266 genes associated with abnormal
71 skeletal growth syndromes in the Online Mendelian Inheritance in Man (OMIM) database
72 (<https://omim.org/>), as assembled by [2]; iii) 427 genes expressed substantially more highly
73 in the mouse growth plate, the cartilaginous region on the end of long bones where bone
74 elongation occurs, than in soft tissues (lung, kidney, heart; ≥ 2.0 fold change; [3]; and
75 iv) 955 genes annotated with the Gene Ontology “growth” biological process (GO:0040007).
76 Separately, we also considered in our analyses the set of 166 genes located within the 16
77 genomic regions previously associated with the pygmy phenotype in the Batwa, using an
78 admixture mapping approach [4], as well as GH1- and IGF1-associated genes using data
79 from OPHID database of proteinprotein interaction (PPI) networks [5].

80 We used each of the curated *a priori* growth-related gene lists for testing the hypothe-
81 sis that such loci are enriched for genes with signatures of strong positive selection (outlier
82 PBS selection index values) or have a shift in the distribution of PBS selection index val-
83 ues consistent with subtle polygenic adaptation in the Batwa and Andamanese rainforest
84 hunter-gatherer but not the Bakiga and Brahmin agriculturalist populations. We identi-
85 fied 202, 188, 291, and 252 outlier strong selection candidate genes (with PBS index values
86 < 0.01) in each of the Batwa, Bakiga, Andamanese, and Brahmin populations, respectively.
87 Genes in the *a priori* growth-related gene lists were not significantly overrepresented among

88 PBS outliers in any populations, except for those associated with mouse growth phenotype
89 in the Brahmin (68 observed, 47.7 expected; Fisher $p = 0.0179$) (Table S23). Though the
90 lack of over-representation of growth-related gene lists among loci with outlier signatures of
91 strong positive natural selection related to growth is perhaps unsurprising considering the
92 polygenic phenotype, our distribution shift-based test also showed no significant shifts in
93 the distribution of PBS indices for any population (Table S25). Genes in genomic regions
94 previously associated with the pygmy phenotype in the Batwa [4] were enriched for genes
95 with outlier PBS selection index values in the Batwa (outlier-based test: 5 observed, 1.39 ex-
96 pected; Fisher $p = 0.017$; Table S23) and the PBS distribution for the phenotype-associated
97 genes was shifted relative to the genome-wide distribution (distribution shift-based test:
98 Kolmogorov-Smirnov test $p = 0.056$; Table S25). We found no evidence that genes associ-
99 ated with GH1 and IGF1 were enriched for outlier or polygenic selection.

100 **Impact of cross-annotated genes between growth factor- and cardiac-related**
101 **pathways** To assess whether shared genes in GO categories relating to the heart and
102 growth factor binding were responsible for the significant shift in PBS selection index values
103 for genes in these annotations, we compared the distributions of PBS selection indices before
104 and after removing 9 genes common to heart pathways and growth factor binding. The
105 heart GO terms assessed were: ‘cardiocyte differentiation’ (GO:0035051), with a shift in the
106 Andamanese hunter-gatherers; ‘cardiac ventricle development’ (GO:0003231), with a shift in
107 the Batwa hunter-gatherers; and ‘cardiac muscle tissue development’ (GO:0048738) with a
108 convergent shift in the Batwa and Andamanese. Of the 123 heart related genes contained in
109 these pathways, 9 were also annotated to the GO molecular function ‘growth factor binding’
110 (GO:0019838): *ACVR1*, *EGFR*, *ENG*, *FGFR2*, *FGFRL1*, *LTBP1*, *SCN5A*, *TGFBR1*, and
111 *TGFBR3*.

112 After removing the 9 shared genes, the mean PBS selection index for the Andamanese

113 among genes annotated to ‘cardiocyte differentiation’ decreased slightly from 0.444 to 0.443
114 and the pre- and post-filtration distributions were not significantly different (Kolmogorov-
115 Smirnov $D = 0.023$, $p = 1$). Similarly, the mean PBS selection index for the Batwa for
116 genes in ‘cardiac ventricle development’ decreased slightly from 0.654 to 0.652, and the
117 distributions were not significantly different ($D = 0.044$, $p = 1$). Finally, for ‘cardiac muscle
118 tissue development’, the mean PBS selection index for the Andamanese increased from 0.450
119 to 0.453, and for the Batwa increased from 0.474 to 0.486. Again the pre- and post-filtering
120 distributions were not significantly different for the Andamanese ($D = 0.015$, $p = 1$) or
121 Batwa ($D = 0.015$, $p = 1$).

122 Similarly, after removing 9 shared genes, the mean PBS selection index for genes anno-
123 tated to ‘growth factor binding’ (GO:0019838) for the Batwa increased slightly from 0.437
124 to 0.440 and for the Andamanese decreased from 0.455 to 0.437. Again, the pairs of distri-
125 butions were not significantly different (Batwa: $D = 0.030$, $p = 1$; Andamanese: $D = 0.036$,
126 $p = 1$).

127 **Correcting for potential bias from differing gene size or global minor allele fre-**
128 **quency (MAF)** In order to assess the potential biases related to differences in gene length
129 (e.g. number of SNPs) or in SNP global minor allele frequencies (MAF), we repeated the
130 analysis after modifying how the PBS selection index was computed. As in the uncorrected
131 analysis, these corrected PBS selection index values were computed using 1,000 iterations.

132 First, to control for gene size, we sampled the PBS values for each SNP from only genes
133 with the same number of SNPs during the computation of the selection index. For larger
134 genes, gene sizes were binned to ensure sufficient SNPs from which to sample, using sets
135 $[11, 15]$, $[16, 20]$, and $[21, \infty)$.

136 Second, to control for differing MAF values for SNPs, we did the permutation-based
137 computation of the PBS selection index while matching SNPs on global MAF (computed

138 using the African or Asian datasets for within-continent analyses.) SNPs were grouped by
139 MAF into bins of size 0.01, and for each SNP in a gene, SNPs were sampled from only the
140 set in the MAF bin.

141 Neither modification to the PBS selection index computation algorithm majorly affected
142 the PBS selection index values nor the GO-based downstream analyses. Corrected and
143 uncorrected PBS selection index values were highly correlated ($R^2 = 0.993$ to 0.997 and
144 0.953 to 0.985 for the gene size- and MAF-corrections respectively; Fig. S4).

145 The GO biological processes and molecular functions with the strongest evidence of
146 enrichment for strong selection were similar for the convergent (Tables S5 and S6; Figs.
147 S5 and S6) and population-specific selection analyses (Tables S7 and S8; Figs. S5 and S6).
148 The only mentioned growth- or heart-associated pathway that was no longer significant after
149 correction was the biological process “negative regulation of growth,” which was significantly
150 enriched for genes with evidence of strong selection in the Batwa in the original analysis,
151 but its p-value rose to 0.0448 after correction for gene size. In contrast, “cardiac muscle
152 tissue development” (GO:0048738) which originally had a convergent empirical p-value of
153 0.025, was significantly enriched for strong positive selection convergently in the Batwa and
154 Andamanese after MAF-based filtration ($p = 0.001$).

155 Similarly, the top GO categories with evidence of polygenic selection were largely un-
156 changed for the convergent (Tables S9 and S10; Figs. S7 and S8) and population-specific
157 selection analyses (Tables S11 and S12; Figs. S7 and S8). Minor changes include “growth
158 factor binding” (GO:0019838) which rose to be no longer significant with the MAF-based
159 correction (original convergent empirical $p < 0.001$; MAF corrected $p = 0.005$).

160 **Modification of significance testing in empirical test for convergent evolution** We
161 also modified and repeated the analysis that computes the significance of the convergence
162 GO tests using a permutation-based approach. Whereas we originally permuted gene-PBS
163 relationships to generate the random null distributions of PBS selection index values for two
164 populations considered jointly, we instead permuted the gene-GO relationships to preserve
165 LD patterns. The one-to-many relationships between genes and GO terms were shuffled,
166 maintaining the groupings of GO terms that were assigned together to an original gene. We
167 repeated the GO-based analyses for enrichment of strong selection or polygenic selection
168 1,000 times with these randomized gene-GO annotations, and compared our actual observed
169 values to this randomly-generated null distribution. As before, we then defined the p-value
170 of our empirical test for convergent evolution as the probability that this statistic was more
171 extreme (lower) for the observed values than for the randomly generated values. The resul-
172 tant p-value summarizes the test of the null hypothesis that both results could have been
173 jointly generated under random chance. The results of the modified test were only slightly
174 different than the original for both convergence in strong outlier selection (Table S13) and
175 in a shifted PBS selection index (Table S14).

176 **2 Figures**

Fig. S1: Population Branch Statistic (PBS) schematic.

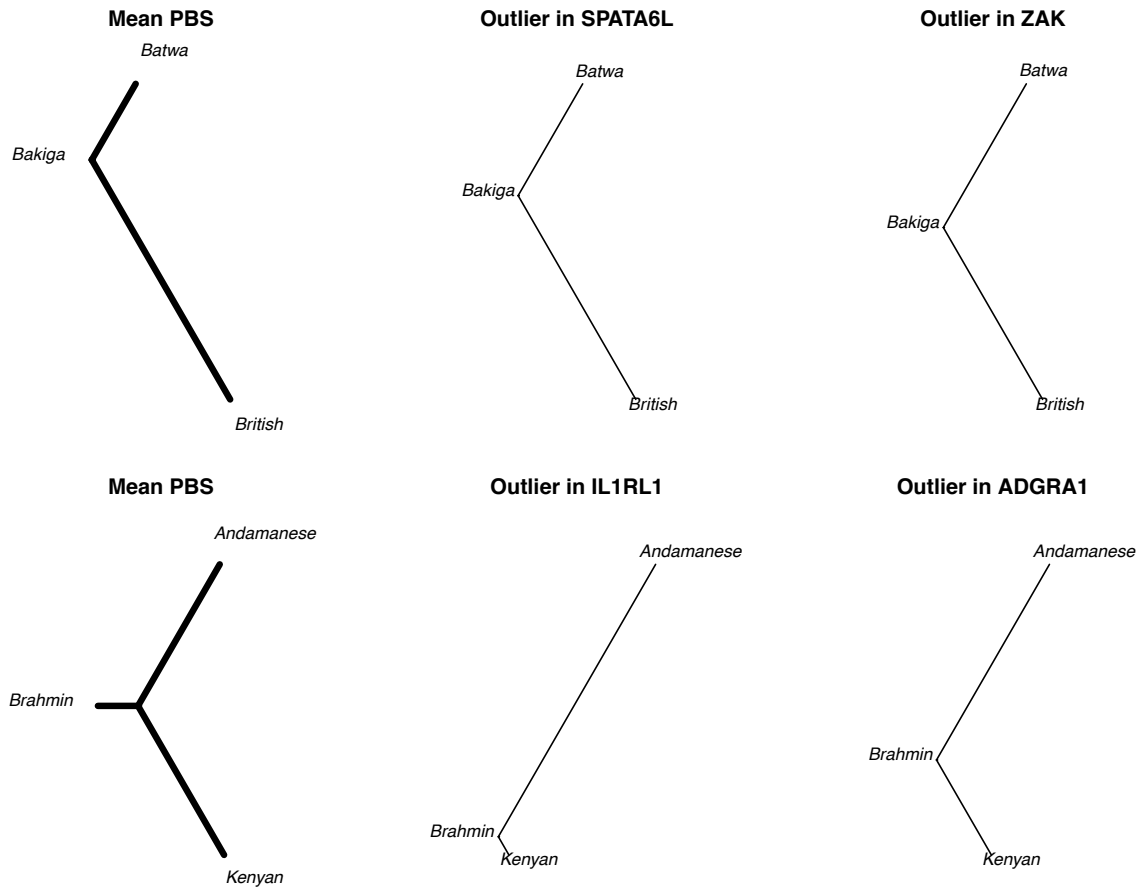


Figure S1: Mean values of the Population Branch Statistic (PBS; left) for the African dataset (Batwa, Bakiga, and outgroup British populations; upper row) and Asian dataset (Andamanese, Brahmin, and outgroup Kenyan populations; lower row). Middle and right columns contain PBS values for two outlier SNPs in each population.

Fig. S2: Population Branch Statistic (PBS) by SNP.

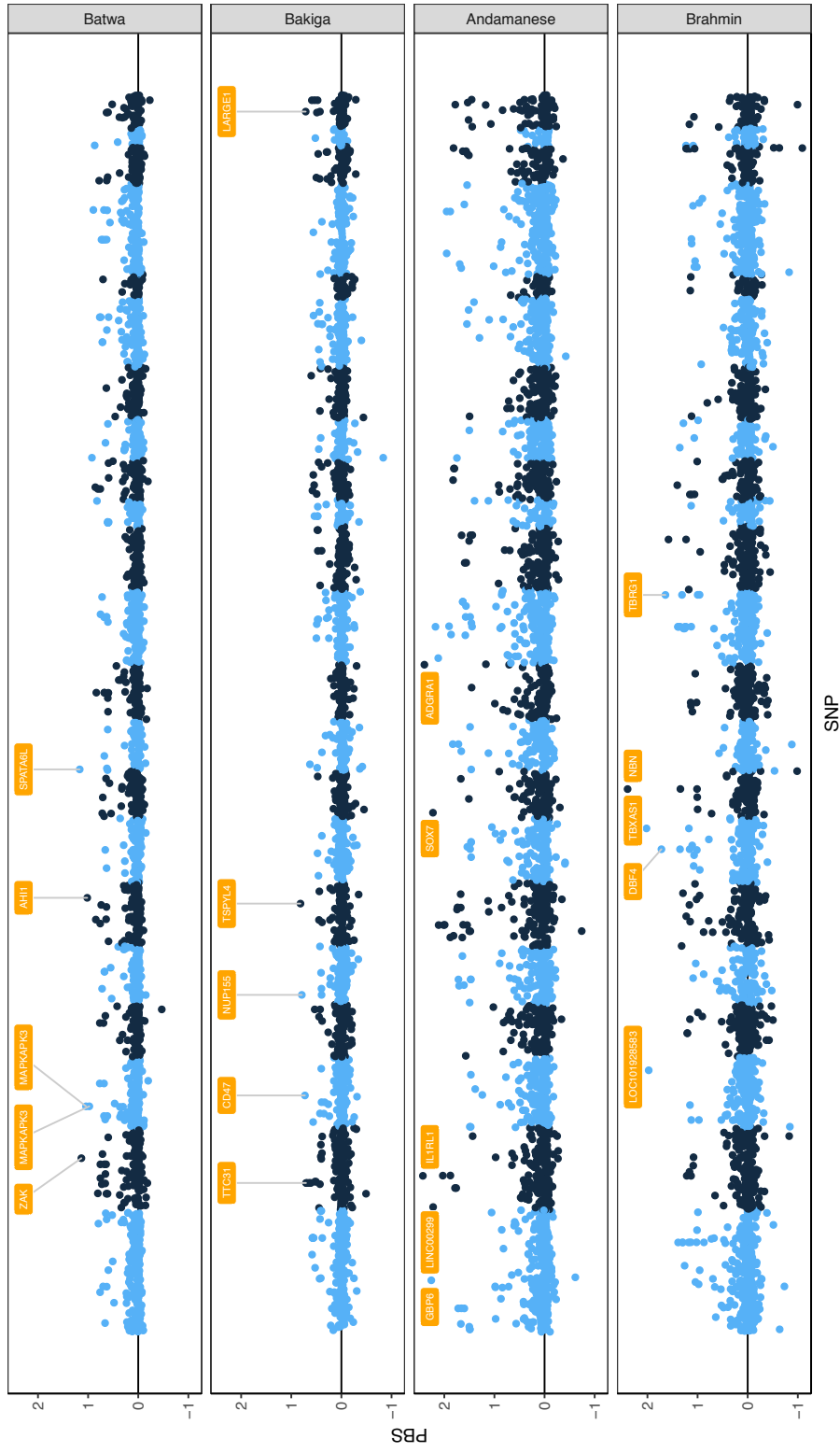


Figure S2: Population Branch Statistic (PBS) values plotted across the genome for the four focal populations. The genes containing the SNPs with the 5 highest PBS values in each population are labeled.

Fig. S3: Population Branch Statistic (PBS) by gene SNP count.

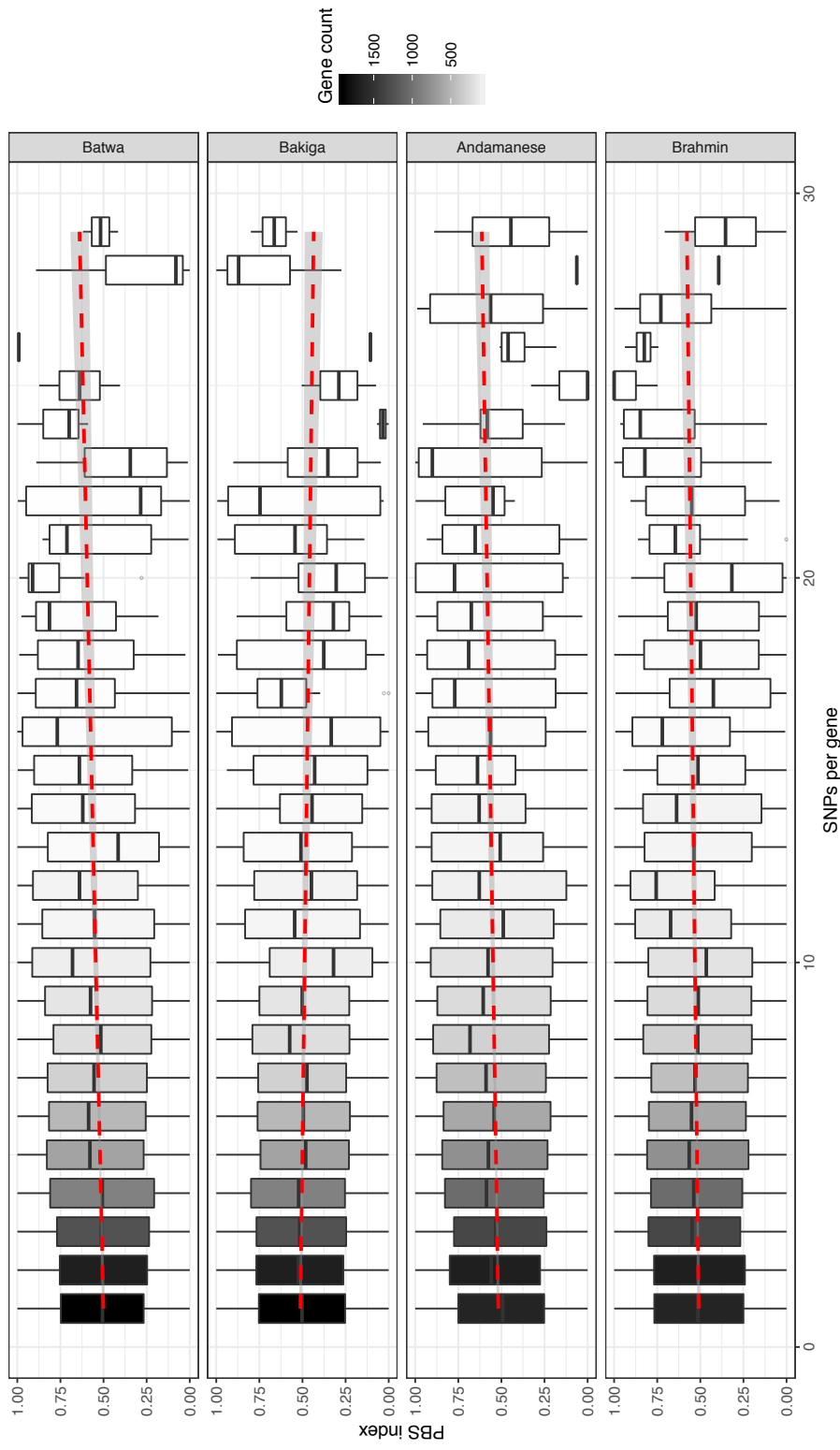


Figure S3: Population Branch Statistic (PBS) selection index values plotted by number of SNPs in gene. Color indicates number of genes with that SNP count. Only SNP counts from 1 to 30 shown.

Fig. S4: Gene size- and MAF-based corrections' impact on p-value.

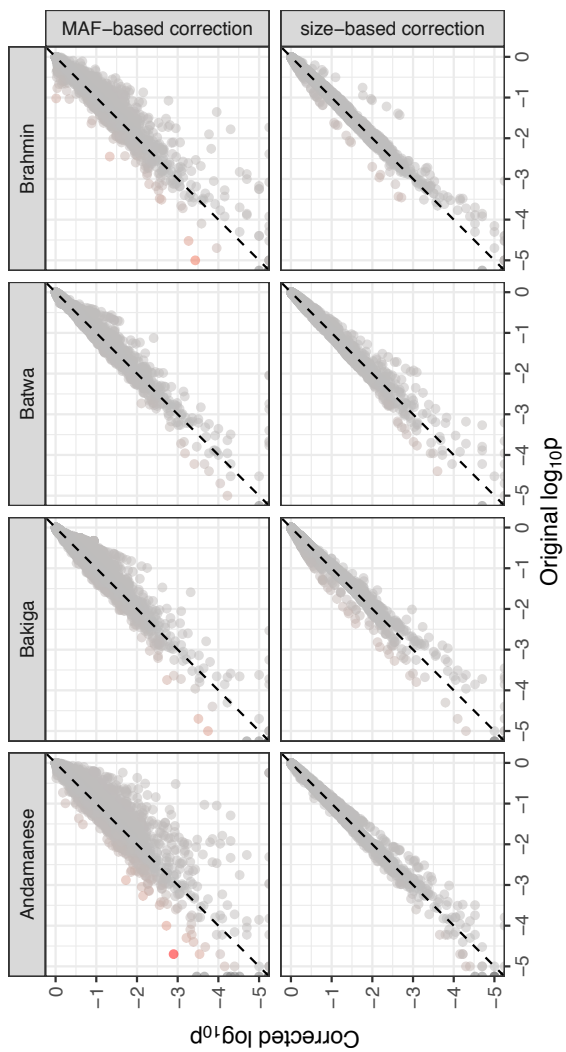
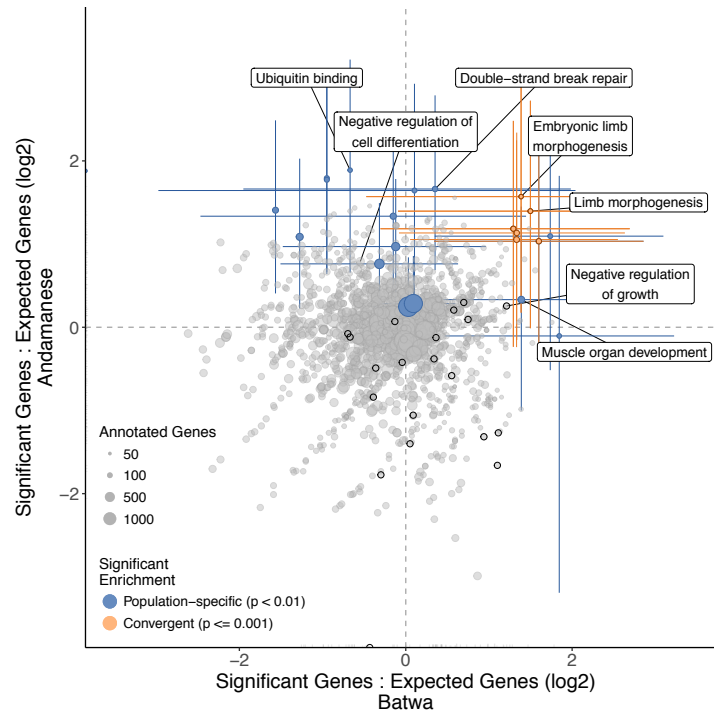


Figure S4: Plots of PBS selection index values for genes corrected for gene size and MAF shown compared to the original uncorrected values (with both plotted on a logarithmic scale). Red shading indicates higher percent difference from original value.

Fig. S5: Gene size-corrected strong positive selection enrichment results.

A. Rainforest hunter-gatherers



B. Agriculturalists

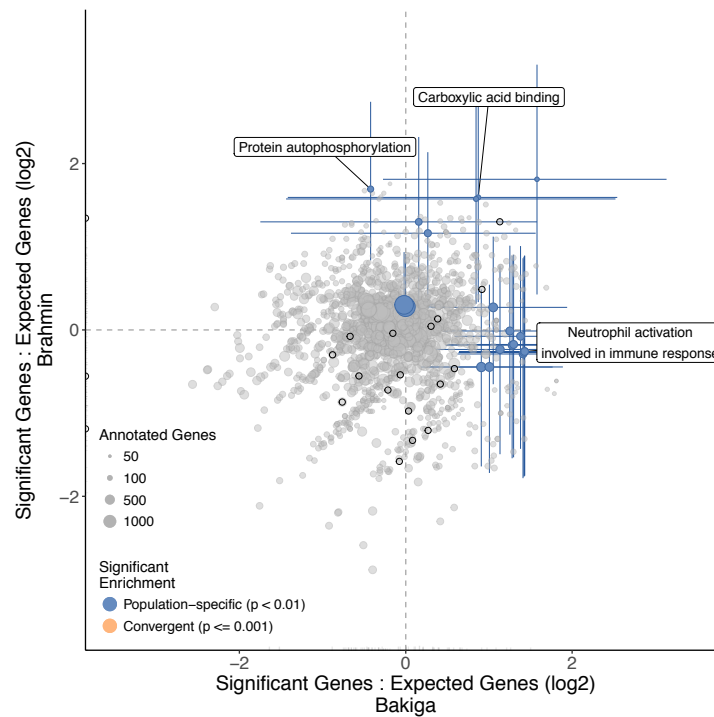
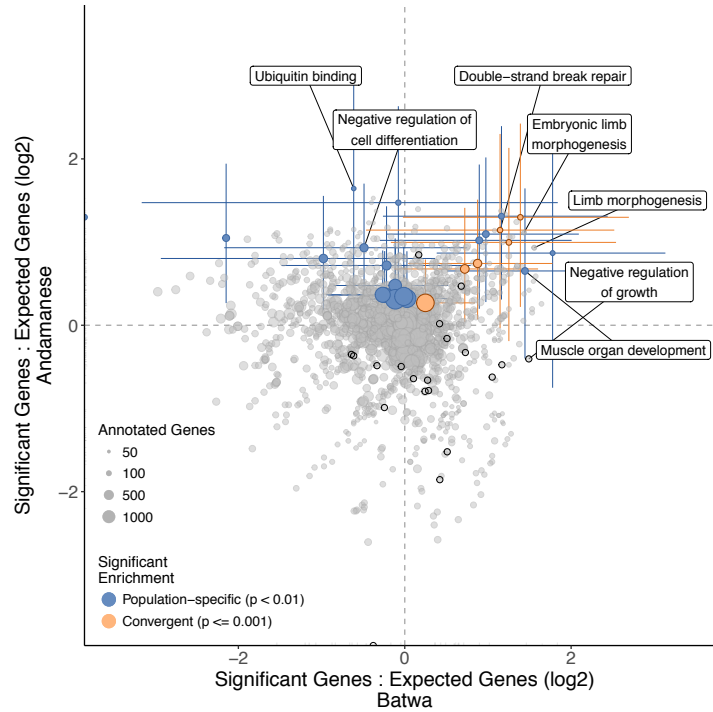


Figure S5: (Continued on the following page.)

Figure S5: After gene size-based correction, Gene Ontology (GO) functional categories' ratios of expected to observed counts of outlier genes (with PBS selection index < 0.01) in the Batwa and Andamanese rainforest hunter-gatherers (A) and Bakiga and Brahmin agriculturalist control (B). Results shown for GO biological processes and molecular functions. Point size is scaled to number of annotated genes in category. Terms that are significantly overrepresented for genes under positive selection (Fisher $p < 0.01$) in either population shown in blue and for both populations convergently (empirical permutation-based $p < 0.005$) shown in orange. Colored lines represent 95% CI for significant categories estimated by bootstrapping genes within pathways. Dark outlines indicate growth-associated terms: the 'growth' biological process (GO:0040007) and its descendant terms, or the molecular functions 'growth factor binding,' 'growth factor receptor binding,' 'growth hormone receptor activity,' and 'growth factor activity' and their sub-categories.

Fig. S6: MAF-corrected strong positive selection enrichment results.

A. Rainforest hunter-gatherers



B. Agriculturalists

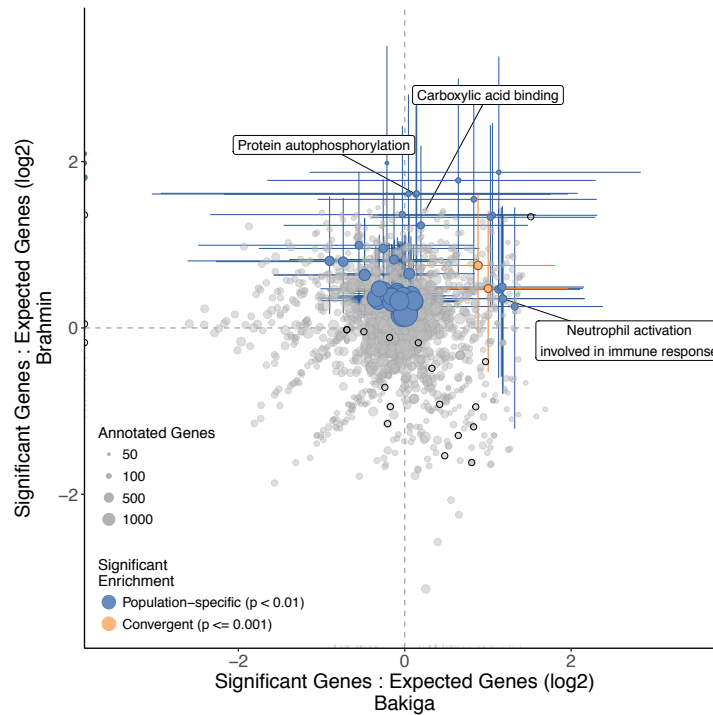
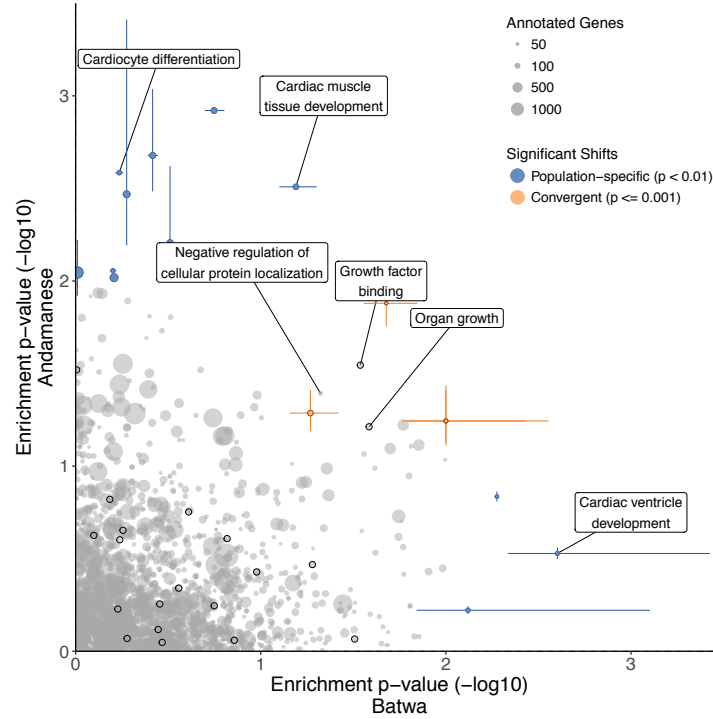


Figure S6: (Continued on the following page.)

Figure S6: After MAF-based correction, Gene Ontology (GO) functional categories' ratios of expected to observed counts of outlier genes (with PBS selection index < 0.01) in the Batwa and Andamanese rainforest hunter-gatherers (A) and Bakiga and Brahmin agriculturalist control (B). Results shown for GO biological processes and molecular functions. Point size is scaled to number of annotated genes in category. Terms that are significantly overrepresented for genes under positive selection (Fisher $p < 0.01$) in either population shown in blue and for both populations convergently (empirical permutation-based $p < 0.005$) shown in orange. Colored lines represent 95% CI for significant categories estimated by bootstrapping genes within pathways. Dark outlines indicate growth-associated terms: the 'growth' biological process (GO:0040007) and its descendant terms, or the molecular functions 'growth factor binding,' 'growth factor receptor binding,' 'growth hormone receptor activity,' and 'growth factor activity' and their sub-categories.

Fig. S7: Gene size-corrected polygenic distribution shift test results.

A. Rainforest hunter-gatherers



B. Agriculturalists

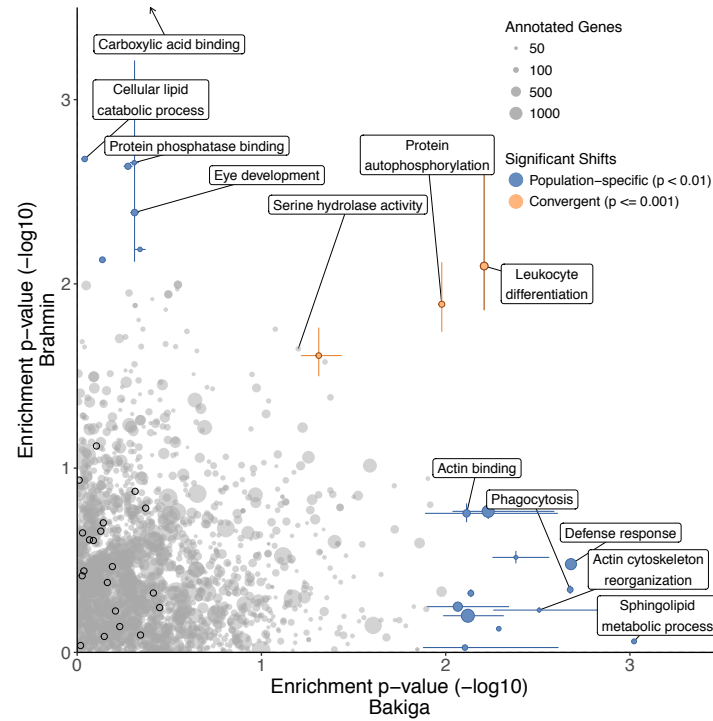
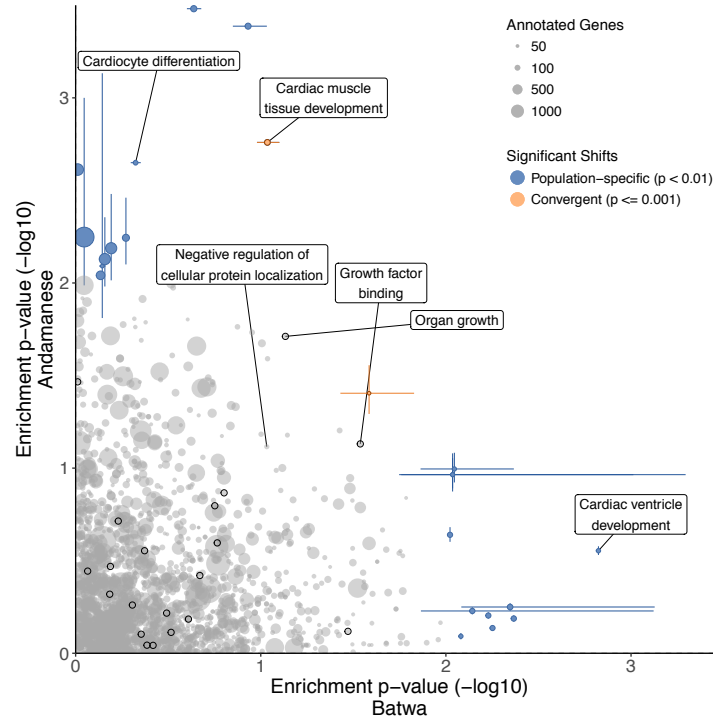


Figure S7: (Continued on the following page.)

Figure S7: After gene size-based correction, Gene Ontology (GO) functional categories' distribution shift test p-values, indicating a shift in the PBS selection index values for genes, in the Batwa and Andamanese rainforest hunter-gatherers (A) and Bakiga and Brahmin agriculturalist control (B). Results shown for GO biological processes and molecular functions. Point size is scaled to number of annotated genes in category. Terms that are significantly enriched for genes under positive selection (Kolmogorov-Smirnov $p < 0.01$) in either population shown in blue and for both populations convergently (empirical permutation-based $p < 0.005$) shown in orange. Colored lines represent 95% CI for significant categories estimated by bootstrapping genes within pathways. Dark outlines indicate growth-associated terms: the 'growth' biological process (GO:0040007) and its descendant terms, or the molecular functions 'growth factor binding,' 'growth factor receptor binding,' 'growth hormone receptor activity,' and 'growth factor activity' and their sub-categories. One GO molecular function, "carboxylic acid binding" (GO:0031406; Brahmin $p = 7.3 \times 10^{-5}$; $q = 0.0157$) not shown.

Fig. S8: Gene size-corrected polygenic distribution shift test results.

A. Rainforest hunter-gatherers



B. Agriculturalists

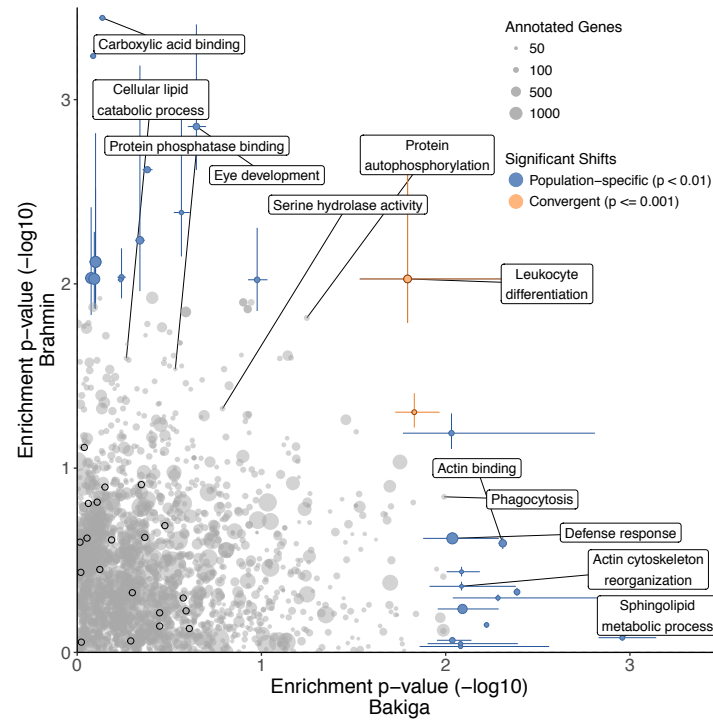


Figure S8: (Continued on the following page.)

Figure S8: After MAF-based correction, Gene Ontology (GO) functional categories' distribution shift test p-values, indicating a shift in the PBS selection index values for genes, in the Batwa and Andamanese rainforest hunter-gatherers (A) and Bakiga and Brahmin agriculturalist control (B). Results shown for GO biological processes and molecular functions. Point size is scaled to number of annotated genes in category. Terms that are significantly enriched for genes under positive selection (Kolmogorov-Smirnov $p < 0.01$) in either population shown in blue and for both populations convergently (empirical permutation-based $p < 0.005$) shown in orange. Colored lines represent 95% CI for significant categories estimated by bootstrapping genes within pathways. Dark outlines indicate growth-associated terms: the 'growth' biological process (GO:0040007) and its descendant terms, or the molecular functions 'growth factor binding,' 'growth factor receptor binding,' 'growth hormone receptor activity,' and 'growth factor activity' and their sub-categories.

3 Tables

177

Table S1: Gene Ontology (GO) biological processes with evidence of convergent enrichment for strong positive selection in the hunter-gatherer populations, as measured by outlier Population Branch Statistic (PBS) values. No molecular functions were found to be convergently enriched. Joint p -values were computed via a permutation-based method, and those with joint empirical $p < 0.005$ are shown.

GO Biological Process	Joint p	<i>Batwa:</i>			<i>Andamanese:</i>				
		Exp.	Obs.	p	adj. p	Exp.	Obs.	p	adj. p
GO:0030326 embryonic limb morphogenesis	0.000	1.47	4	0.0584	1	2.01	6	0.0147	0.901
GO:0035107 appendage morphogenesis	0.000	1.69	5	0.0267	1	2.27	6	0.0254	0.901
GO:0035108 limb morphogenesis	0.000	1.69	5	0.0267	1	2.27	6	0.0254	0.901
GO:0035113 embryonic appendage morphogenesis	0.000	1.47	4	0.0584	1	2.01	6	0.0147	0.901
GO:0048736 appendage development	0.001	1.95	5	0.0448	1	2.62	6	0.047	1.000
GO:0060173 limb development	0.001	1.95	5	0.0448	1	2.62	6	0.047	1.000
GO:0030048 actin filament-based movement	0.002	1.72	4	0.0927	1	2.33	5	0.0834	1.000
GO:0048705 skeletal system morphogenesis	0.002	2.20	5	0.0688	1	2.95	6	0.0743	1.000
GO:0007034 vacuolar transport	0.003	1.37	4	0.0470	1	1.75	4	0.0968	1.000

Table S2: Gene Ontology (GO) biological processes with evidence of population-specific enrichment for strong positive selection in the hunter-gatherer populations, as measured by outlier Population Branch Statistic (PBS) values. Results with $p < 0.01$ shown.

GO	Exp.	Obs.	p	adj. p
<i>Batwa RHG - Biological Processes:</i>				
GO:0007517 muscle organ development	10	4.02	0.0069	0.708
GO:0045926 negative regulation of growth	7	2.48	0.0118	0.708
<i>Andamanese RHG - Biological Processes:</i>				
GO:0006302 double-strand break repair	10	3.14	0.0011	0.171
GO:0070085 glycosylation	12	4.34	0.0013	0.171
GO:0000723 telomere maintenance	8	2.30	0.0020	0.175
GO:0033365 protein localization to organelle	25	14.09	0.0036	0.189
GO:1903827 regulation of cellular protein localization	19	9.66	0.0036	0.189
GO:0007569 cell aging	6	1.62	0.0052	0.208
GO:0009101 glycoprotein biosynthetic process	12	5.28	0.0065	0.208
GO:0034613 cellular protein localization	41	27.87	0.0067	0.208
GO:0051179 localization	116	97.30	0.0079	0.208
GO:0060249 anatomical structure homeostasis	13	6.09	0.0079	0.208
GO:0045596 negative regulation of cell differentiation	18	9.79	0.0090	0.215
<i>Batwa RHG - Molecular Functions:</i>				
GO:0003723 RNA binding	26	17.66	0.028	0.732
GO:0043167 ion binding	83	70.68	0.034	0.732
<i>Andamanese RHG - Molecular Functions:</i>				
GO:0043130 ubiquitin binding	7	1.89	0.0026	0.177
GO:0008233 peptidase activity	17	9.58	0.0153	0.383

Table S3: Gene Ontology (GO) biological processes (BP) and molecular functions (MF) with evidence of convergent distribution shifts in PBS selection index values in the hunter-gatherer populations. Joint p -values were computed via a permutation-based method, and those with joint empirical $p < 0.005$ are shown.

GO			Joint p	<i>Batwa:</i>		<i>Andamanese:</i>	
				p	adj. p	p	adj. p
BP	GO:0035265	organ growth	0.001	0.0275	0.997	0.04509	1.000
	GO:0048738	cardiac muscle tissue development	0.001	0.0461	0.997	0.00265	1.000
	GO:1903828	negative regulation of cellular protein localization	0.001	0.0360	0.997	0.04275	1.000
	GO:0016202	regulation of striated muscle tissue development	0.002	0.0135	0.997	0.04406	1.000
	GO:1901861	regulation of muscle tissue development	0.002	0.0135	0.997	0.04406	1.000
	GO:0045444	fat cell differentiation	0.004	0.0573	0.997	0.04058	1.000
MF	GO:0019199	transmembrane receptor protein kinase activity	0.000	0.027	0.817	0.0261	0.784
	GO:0019838	growth factor binding	0.000	0.021	0.817	0.0269	0.784
	GO:0032559	adenyl ribonucleotide binding	0.003	0.020	0.817	0.0579	0.877
	GO:0030554	adenyl nucleotide binding	0.004	0.017	0.817	0.0755	0.877

Table S4: Gene Ontology (GO) biological processes (BP) and molecular functions (MF) with evidence of population-specific distribution shifts in PBS selection index values in the hunter-gatherer populations. No molecular functions were found to be significantly shifted for the Batwa. Results with $p < 0.01$ are shown.

GO	p	adj. p
<i>Batwa RHG - Biological Processes:</i>		
GO:0003231 cardiac ventricle development	0.001	0.302
GO:0061351 neural precursor cell proliferation	0.007	0.348
GO:0034976 response to endoplasmic reticulum stress	0.009	0.348
<i>Andamanese RHG - Biological Processes:</i>		
GO:0016579 protein deubiquitination	0.001	0.232
GO:0035051 cardiocyte differentiation	0.002	0.232
GO:0048738 cardiac muscle tissue development	0.003	0.232
GO:1901800 positive regulation of proteasomal protein catabolic process	0.004	0.262
GO:0006508 proteolysis	0.009	0.453
<i>Andamanese RHG - Molecular Functions:</i>		
GO:0005085 guanyl-nucleotide exchange factor activity	0.005	0.278

Table S5: After gene size-based correction, Gene Ontology (GO) biological processes and molecular functions with evidence of convergent enrichment for strong positive selection in the hunter-gatherer populations, as measured by outlier Population Branch Statistic (PBS) values. Joint p -values were computed via a permutation-based method, and those with joint empirical $p < 0.005$ are shown.

GO Biological Process	Joint p	Batwa:			Andamanese:					
		Exp.	Obs.	p	Exp.	Obs.	p			
GO:0035107 appendage morphogenesis	0.000	1.77	5	0.0315	1	2.28	6	0.0258	0.966	
GO:0035108 limb morphogenesis	0.000	1.77	5	0.0315	1	2.28	6	0.0258	0.966	
GO:0048736 appendage development	0.000	2.04	5	0.0524	1	2.64	6	0.0478	1.000	
GO:0060173 limb development	0.000	2.04	5	0.0524	1	2.64	6	0.0478	1.000	
GO:1901617 organic hydroxy compound biosynthetic process	0.000	2.38	6	0.0314	1	3.19	7	0.0401	0.980	
GO:0030326 embryonic limb morphogenesis	0.001	1.53	4	0.0665	1	2.02	6	0.0150	0.966	
GO:0035113 embryonic appendage morphogenesis	0.001	1.53	4	0.0665	1	2.02	6	0.0150	0.966	
GO:0030048 actin filament-based movement	0.002	1.80	6	0.0089	1	2.34	5	0.0845	1.000	
GO:0007034 vacuolar transport	0.004	1.43	4	0.0537	1	1.76	4	0.0979	1.000	
		Batwa:			Andamanese:					
GO Molecular Function	Joint p	Exp.	Obs.	p	Exp.	Obs.	p	Exp.	Obs.	p
GO:0008514 organic anion transmembrane transporter activity	0.000	2.78	7	0.0212	0.6853	3.37	7	0.0515	0.902	
GO:0015081 sodium ion transmembrane transporter activity	0.000	2.31	7	0.0081	0.6853	2.93	6	0.0726	0.902	

Table S6: After MAF-based correction, Gene Ontology (GO) biological processes and molecular functions with evidence of convergent enrichment for strong positive selection in the hunter-gatherer populations, as measured by outlier Population Branch Statistic (PBS) values. Joint p -values were computed via a permutation-based method, and those with joint empirical $p < 0.005$ are shown.

GO Biological Process	Batwa:				Andamanese:			
	Exp.	Obs.	p	adj. p	Exp.	Obs.	p	adj. p
GO:0048522 positive regulation of cellular process	55.57	66	0.0534	1	87.93	106	0.01153	0.946
GO:1901617 organic hydroxy compound biosynthetic process	2.29	6	0.0267	1	3.66	9	0.01069	0.946
GO:0006302 double-strand break repair	2.26	5	0.0757	1	3.62	8	0.02808	0.946
GO:0006897 endocytosis	8.49	14	0.0447	1	13.76	22	0.01948	0.946
GO:0048738 cardiac muscle tissue development	2.52	6	0.0399	1	4.01	8	0.04694	0.946
GO:0080135 regulation of cellular response to stress	7.63	14	0.0203	1	11.95	20	0.01624	0.946
GO:0014706 striated muscle tissue development	4.07	8	0.0509	1	6.55	14	0.00585	0.946
GO:0070302 regulation of stress-activated protein kinase signaling cascade	2.52	6	0.0399	1	3.93	7	0.09815	0.946
GO:1901615 organic hydroxy compound metabolic process	5.70	9	0.1168	1	8.87	14	0.06046	0.946
GO:2001020 regulation of response to DNA damage stimulus	2.09	5	0.0572	1	3.35	7	0.04997	0.946
GO:0051592 response to calcium ion	1.75	6	0.0079	1	2.74	5	0.13789	0.946
GO:0015718 monocarboxylic acid transport	1.63	4	0.0793	1	2.39	5	0.08980	0.946
GO:0030048 actin filament-based movement	1.73	4	0.0942	1	2.78	7	0.02039	0.946
GO:0030326 embryonic limb morphogenesis	1.48	4	0.0594	1	2.31	5	0.08052	0.946
GO:0031098 stress-activated protein kinase signaling	3.15	7	0.0383	1	4.97	8	0.12454	0.946
GO:0035113 embryonic appendage morphogenesis	1.48	4	0.0594	1	2.31	5	0.08052	0.946
GO:0060537 muscle tissue development	4.30	8	0.0660	1	6.90	14	0.00910	0.946
GO Molecular Function	Batwa:				Andamanese:			
	Exp.	Obs.	p	adj. p	Exp.	Obs.	p	adj. p
GO:0008514 organic anion transmembrane transporter activity	2.68	6	0.051	0.798	4.03	10	0.0068	0.959
GO:0005342 organic acid transmembrane transporter activity	1.97	5	0.046	0.798	2.96	7	0.0282	1.000
GO:0015081 sodium ion transmembrane transporter activity	2.22	5	0.071	0.821	3.50	7	0.0600	1.000
GO:0046943 carboxylic acid transmembrane transporter activity	1.79	4	0.103	0.964	2.70	7	0.0177	1.000

Table S7: After gene size-based correction, Gene Ontology (GO) biological processes with evidence of population-specific enrichment for strong positive selection in the hunter-gatherer populations, as measured by outlier Population Branch Statistic (PBS) values. Results with $p < 0.01$ shown.

GO	Exp.	Obs.	p	adj. p
<i>Batwa RHG - Biological Processes:</i>				
GO:0007517 muscle organ development	11	4.20	0.0032	0.5650
GO:1903825 organic acid transmembrane transport	6	1.67	0.0061	0.5652
GO:0030048 actin filament-based movement	6	1.80	0.0061	0.5652
<i>Andamanese RHG - Biological Processes:</i>				
GO:0006302 double-strand break repair	10	3.16	0.0012	0.231
GO:0000723 telomere maintenance	8	2.31	0.0020	0.231
GO:1903827 regulation of cellular protein localization	19	9.70	0.0038	0.231
GO:0070085 glycosylation	11	4.36	0.0042	0.231
GO:1900180 regulation of protein localization to nucleus	10	3.77	0.0044	0.231
GO:0007569 cell aging	6	1.63	0.0053	0.232
GO:0060249 anatomical structure homeostasis	13	6.12	0.0082	0.299
GO:0051234 establishment of localization	99	81.24	0.0091	0.299
<i>Batwa RHG - Molecular Functions:</i>				
GO:0015081 sodium ion transmembrane transporter activity	7	2.31	0.0081	0.33245
<i>Andamanese RHG - Molecular Functions:</i>				
GO:0043130 ubiquitin binding	7	1.89	0.0026	0.177

Table S8: After MAF-based correction, Gene Ontology (GO) biological processes with evidence of population-specific enrichment for strong positive selection in the hunter-gatherer populations, as measured by outlier Population Branch Statistic (PBS) values. No molecular functions were found to be significantly shifted for the Batwa. Results with $p < 0.01$ shown.

GO	Exp.	Obs.	p	adj. p
<i>Batwa RHG - Biological Processes:</i>				
GO:0007517 muscle organ development	11	4.04	0.0023	0.492
GO:0051592 response to calcium ion	6	1.75	0.0079	0.492
<i>Andamanese RHG - Biological Processes:</i>				
GO:0051179 localization	142	114.34	0.00044	0.115
GO:0045596 negative regulation of cell differentiation	22	11.53	0.0026	0.266
GO:0071229 cellular response to acid chemical	9	3.24	0.0048	0.266
GO:0002460 adaptive immune response based on somatic recombination...	11	4.47	0.0050	0.266
GO:0014706 striated muscle tissue development	14	6.55	0.0059	0.266
GO:0048584 positive regulation of response to stimulus	53	38.05	0.0067	0.266
GO:0016337 single organismal cell-cell adhesion	22	12.61	0.0076	0.266
<i>Andamanese RHG - Molecular Functions:</i>				
GO:0043130 ubiquitin binding	7	2.24	0.0067	0.221
GO:0008514 organic anion transmembrane transporter activity	10	4.03	0.0068	0.221

Table S9: After gene size-based correction, Gene Ontology (GO) biological processes (BP) and molecular functions (MF) with evidence of convergent distribution shifts in PBS selection index values in the hunter-gatherer populations. Joint p -values were computed via a permutation-based method, and those with joint empirical $p < 0.005$ are shown.

GO			Joint p	<i>Batwa:</i>		<i>Andamanese:</i>	
				p	adj. p	p	adj. p
BP	GO:0016202	regulation of striated muscle tissue development	0.000	0.0100	0.994	0.0570	1.000
	GO:1901861	regulation of muscle tissue development	0.000	0.0100	0.994	0.0570	1.000
	GO:0045444	fat cell differentiation	0.001	0.0539	0.994	0.0517	1.000
	GO:0048634	regulation of muscle organ development	0.002	0.0101	0.994	0.0924	1.000
	GO:0035265	organ growth	0.003	0.0260	0.994	0.0613	1.000
	GO:0048738	cardiac muscle tissue development	0.003	0.0646	0.994	0.0031	1.000
	GO:0051147	regulation of muscle cell differentiation	0.003	0.0242	0.994	0.1026	1.000
	GO:1903828	negative regulation of cellular protein localization	0.003	0.0475	0.994	0.0405	1.000
	GO:0046434	organophosphate catabolic process	0.004	0.0154	0.994	0.0780	1.000
MF	GO:0019199	transmembrane receptor protein kinase activity	0.000	0.021	0.698	0.0132	0.736
	GO:0019838	growth factor binding	0.002	0.029	0.750	0.0285	0.736
	GO:0030554	adenyl nucleotide binding	0.002	0.014	0.698	0.0769	0.877
	GO:0032559	adenyl ribonucleotide binding	0.002	0.017	0.698	0.0599	0.877

Table S10: After MAF-based correction, Gene Ontology (GO) biological processes (BP) and molecular functions (MF) with evidence of convergent distribution shifts in PBS selection index values in the hunter-gatherer populations. Joint p -values were computed via a permutation-based method, and those with joint empirical $p < 0.005$ are shown.

GO			Joint p	<i>Batwa:</i>		<i>Andamanese:</i>	
				p	adj. p	p	adj. p
BP	GO:0048738	cardiac muscle tissue development	0.000	0.0921	0.993	0.00174	0.878
	GO:0033002	muscle cell proliferation	0.002	0.0919	0.993	0.02565	1.000
	GO:0035265	organ growth	0.003	0.0736	0.993	0.01943	1.000
	GO:0003007	heart morphogenesis	0.004	0.0375	0.993	0.06262	1.000
	GO:0016579	protein deubiquitination	0.004	0.1171	0.993	0.00041	0.369
MF	GO:0019199	transmembrane receptor protein kinase activity	0.001	0.026	0.675	0.039	0.874

Table S11: After gene size-based correction, Gene Ontology (GO) biological processes (BP) and molecular functions (MF) with evidence of population-specific distribution shifts in PBS selection index values in the hunter-gatherer populations. No molecular functions were found to be significantly shifted for the Batwa. Results with $p < 0.01$ are shown.

GO		p	adj. p
<i>Batwa RHG - Biological Processes:</i>			
GO:0003231	cardiac ventricle development	0.0025	0.371
GO:0061351	neural precursor cell proliferation	0.0080	0.371
<i>Andamanese RHG - Biological Processes:</i>			
GO:0016579	protein deubiquitination	0.001	0.273
GO:0035051	cardiocyte differentiation	0.003	0.273
GO:0048738	cardiac muscle tissue development	0.003	0.273
GO:1901800	positive regulation of proteasomal protein catabolic process	0.006	0.322
GO:0001936	regulation of endothelial cell proliferation	0.006	0.322
GO:0006508	proteolysis	0.009	0.396
<i>Andamanese RHG - Molecular Functions:</i>			
GO:0005085	guanyl-nucleotide exchange factor activity	0.0034	0.224
GO:0008134	transcription factor binding	0.0096	0.224

Table S12: After MAF-based correction, Gene Ontology (GO) biological processes (BP) and molecular functions (MF) with evidence of population-specific distribution shifts in PBS selection index values in the hunter-gatherer populations. No molecular functions were found to be significantly shifted for the Batwa. Results with $p < 0.01$ are shown.

GO		p	adj. p
<i>Batwa RHG - Biological Processes:</i>			
GO:0003231	cardiac ventricle development	0.0015	0.346
GO:0034284	response to monosaccharide	0.0043	0.346
GO:0008217	regulation of blood pressure	0.0056	0.346
GO:0050864	regulation of B cell activation	0.0083	0.346
GO:0048634	regulation of muscle organ development	0.0090	0.346
GO:1901861	regulation of muscle tissue development	0.0092	0.346
<i>Andamanese RHG - Biological Processes:</i>			
GO:0070646	protein modification by small protein removal	0.0003	0.087
GO:0048738	cardiac muscle tissue development	0.0017	0.160
GO:0035051	cardiocyte differentiation	0.0022	0.160
GO:0006508	proteolysis	0.0024	0.156
GO:0071840	cellular component organization or biogenesis	0.0057	0.283
GO:0007155	cell adhesion	0.0065	0.283
GO:0007169	transmembrane receptor protein tyrosine kinase signaling pathway	0.0091	0.298
<i>Andamanese RHG - Molecular Functions:</i>			
GO:0005085	guanyl-nucleotide exchange factor activity	0.0057	0.198
GO:0019783	ubiquitin-like protein-specific protease activity	0.0081	0.198

Table S13: Comparison of results of two methods for computing empirical test for convergence in strong outlier selection in both the Batwa and Andamanese RHGs. In the original method, genes and PBS selection index values are permuted to create an empirical null distribution. In the modified case, genes and their Gene Ontology (GO) annotations are instead permuted to create the null distribution. Biological processes (BP) with empirical test for convergence $p < 0.005$ in either method shown. No molecular functions were found to be significantly convergently enriched in both RHG populations.

	GO Biological Process	Original convergence p	Modified convergence p
GO:0035107	appendage morphogenesis	0.000	0.000
GO:0035108	limb morphogenesis	0.000	0.000
GO:0030326	embryonic limb morphogenesis	0.000	0.002
GO:0035113	embryonic appendage morphogenesis	0.000	0.002
GO:0048736	appendage development	0.001	0.003
GO:0060173	limb development	0.001	0.003
GO:0048705	skeletal system morphogenesis	0.002	0.003
GO:0048522	positive regulation of cellular process	0.006	0.003
GO:0080135	regulation of cellular response to stress	0.018	0.004
GO:0030048	actin filament-based movement	0.002	0.006
GO:0007034	vacuolar transport	0.003	-

Table S14: Comparison of results of two methods for computing empirical test for convergence in PBS selection index shift in both the Batwa and Andamanese RHGs. In the original method, genes and PBS selection index values are permuted to create an empirical null distribution. In the modified case, genes and their Gene Ontology (GO) annotations are instead permuted to create the null distribution. Biological processes (BP) and molecular functions (MF) with empirical test for convergence $p < 0.005$ in either method shown.

GO Biological Process		Original convergence p	Modified convergence p
GO:0016202	regulation of striated muscle tissue development	0.002	0.000
GO:1901861	regulation of muscle tissue development	0.002	0.000
GO:0048738	cardiac muscle tissue development	0.001	0.001
GO:0048634	regulation of muscle organ development	0.005	0.001
GO:0045444	fat cell differentiation	0.004	0.002
GO:0003007	heart morphogenesis	0.006	0.002
GO:0035265	organ growth	0.001	0.004
GO:0046434	organophosphate catabolic process	0.007	0.004
GO:1903828	negative regulation of cellular protein localization	0.001	0.006
GO Molecular Function		Original convergence p	Modified convergence p
GO:0019838	growth factor binding	0.000	0.001
GO:0019199	transmembrane receptor protein kinase activity	0.000	0.002
GO:0032559	adenyl ribonucleotide binding	0.003	0.004
GO:0030554	adenyl nucleotide binding	0.004	0.004
GO:0005524	ATP binding	0.005	0.004

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