# Clockwork Orangutan: microRNAs, thermoregulatory tradeoffs, and the evolution of brain size

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## SUMMARY

Models of the expansion of brain size relative to body size in the human lineage have not accounted for thermal homeostasis. We demonstrate that mammalian brain and liver sizes vary inversely relative to a thermoregulatory Core (kidney+heart+liver+brain). Since the advent of placentation and permanent homeothermy depended on faster metabolic rates (*MR*s) and coincided with increases in the number of microRNA families (*mirFam*), we rescaled *MR*/kg from log-based specific *MR*s to *mirFam*-based cellular *MR*s (*cMR*s). Liver *cMR* varied inversely with respect to body mass and the *cMR*s of kidney, heart and brain, recapitulating the downregulation of gluconeogenesis during developmental growth of the liver and whole body. With *mirFam* as a proxy for energy reliability, a logistic feedback model of relative brain size detected adaptation to a low-energy regime among the smallest primates and, among the largest primates, adaptation to the physiological limit on the rate of heat dissipation.

## INTRODUCTION

The diversification of mammalian orders is characterized by two long-term trends: increasing size[1] and decreasing body temperature[2]. Resting metabolic rates (*rMR*s) do not exhibit a long-term trend but, in coordination with thermal conductance ($C_{min}$), have allowed most orders of mammals to occupy nearly every climatic zone regardless of size[3-4], albeit with a narrower range of tolerance to heat than to cold[5-7]. These observations support the evolutionary relevance of a physiological limit on the rate of heat dissipation, initially elaborated by Speakman and Król (2010)[8]. Since current models of the evolution of brain size in the human lineage do not consider thermoregulatory constraints[9-10], there is no satisfactory physiological explanation for the brain's evolutionary expansion. We find that the divergence of Catarrhini was accompanied by a 15% increase in the median number of microRNA families (*mirFam*), similar to the earlier expansion of *mirFam* that coincided with faster metabolic rates (*MR*s), higher body temperatures, and the emergence of permanent homeothermy[11]. This adaptive shift to 24-h control of body temperature crossed a threshold of energy reliability relative to earlier-branching placentals and marsupials, among which many orders exhibit some degree of heterothermy[12-13], and set the stage for the subsequent ecological diversification of Boreoeutheria[14].

Orangutans are similar to humans in body size, but their brains are ⅔ smaller and generate heat at a rate of only 4W, compared to 15W in humans[15]. This thermogenesis raises the temperature of the brain's venous outflow, 15% of total blood volume per minute[19-20], by 0.2° - 0.3°C[16-18]. Evolving hominids could address this thermoregulatory challenge in two ways: a faster rate of heat dissipation,

or a tradeoff in energy expenditure with another metabolically expensive tissue, such as kidney, heart, liver or intestine[21-23]. Like chimpanzees[24], ancestral humans probably relied on behavioral thermoregulation in order to avoid hyperthermia which, however, would not have addressed the problem of internal heat generation. Uniquely human adaptations that promoted heat dissipation include hairlessness, bipedalism, and a 10-fold increase in the density of eccrine sweat glands relative to the densities found in chimpanzees and macaques[25]. The latter adaptation may have also increased the risk of dehydration[26] in a warmer and drier savannah environment[27-30].

Despite numerous attempts, the effort to detect the tradeoff predicted by the "expensive tissue hypothesis"[22] has been abandoned since the publication of a study encompassing 100 species, including 23 primates, that found no significant anticorrelations among the body mass-independent residuals of seven metabolically expensive organs[23]. Lande (1979)[31] first attributed the evolutionary increase in primate brain size to a genetic uncoupling of its dependence on body size. We postulated that thermal homeostasis could be achieved by relaxing the constraint imposed by body size not only on the size of the brain, but also on the sizes of the three other major thermogenic organs (kidney, heart and liver). In this case, the relevant standard for the sizes of the four most thermogenic organs would be the mass of a composite 4-organ "Core", analogous to the thermoregulatory core predicted by the biophysical model of Porter and Kearney (2009)[32]. Relative to this Core, we find that evolutionary increases in the proportion of the brain have been offset by decreases in the proportion of the liver, with a corresponding anticorrelation between their mass-independent residuals.

In order to compare of the evolution of the rates of thermogenesis among these four organs, we estimated their cellular *MR*s (*cMR*s) according to three criteria:

a) correlation with organ size and *mirFam* (physiological relevance)[11];
b) correspondence between the joint *cMR* of the four Core organs and the predicted rate of core thermogenesis, or ~ $\sqrt{M}$[32] (thermodynamic relevance);
c) utility for the unsupervised classification of major primate clades (phylogenetic relevance).

We find that liver *cMR*s are anticorrelated with body mass and the *cMR*s of kidney, heart and brain. Allometric scaling of a composite *mirFam*-based Core *cMR* matches the theoretical rate of core thermogenesis[32], unlike a log-based Core specific *MR* (*sMR*). Since the liver is the primary organ of gluconeogenesis during fasting or starvation, this liver-brain anticorrelation is consistent with an energy-limited, positive feedback model of brain size evolution[9-10].

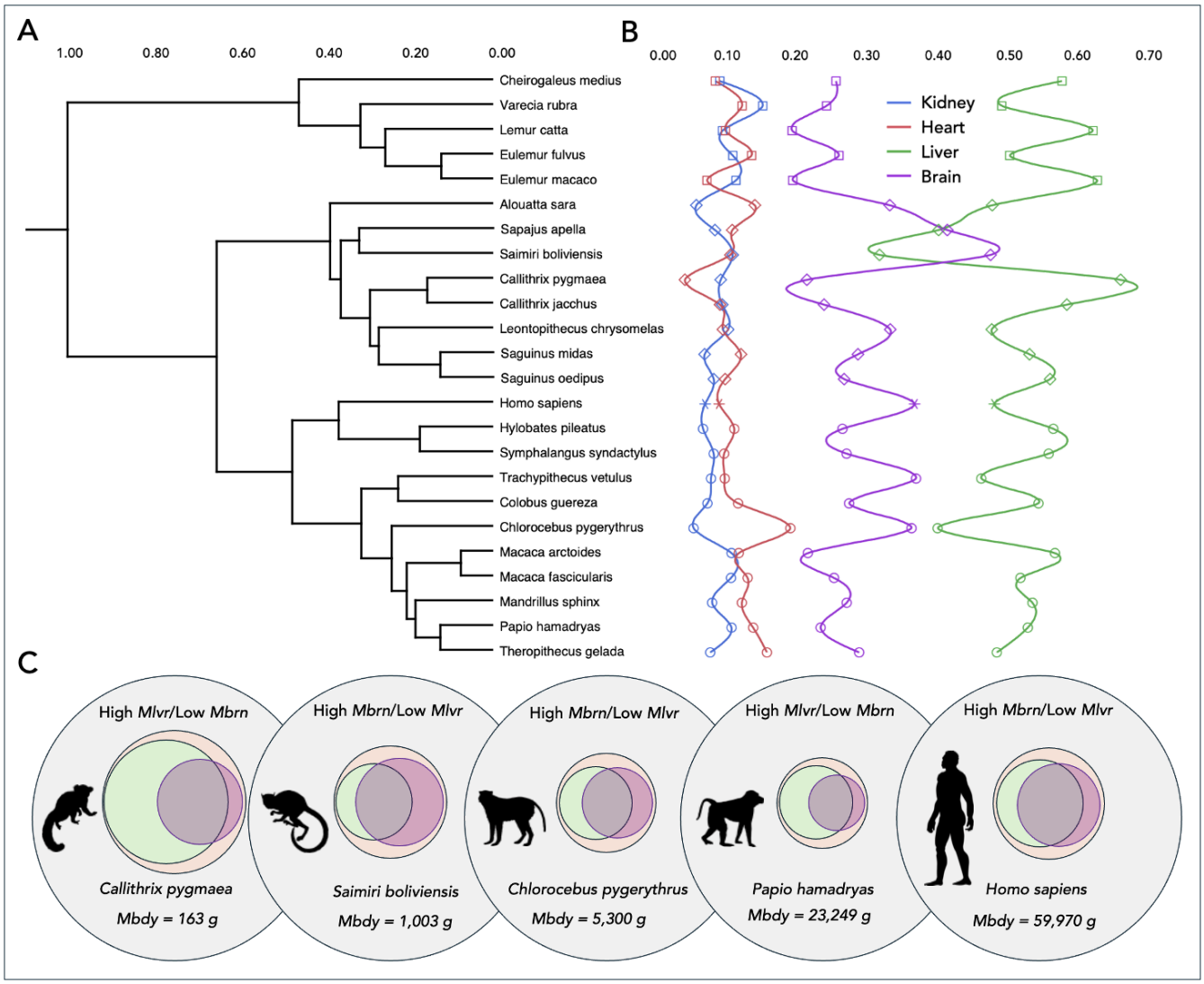


Figure 1. The proportion of brain mass in the Core varies reciprocally with that of the liver.
A. Time tree of 24 primates. The scale bar represents the relative time of divergence.
B. Mass proportion of each organ relative to the total Core mass.
C. Summary comparing representative species with relatively low or high ratios of brain/liver mass. The radius of each circle represents a spherical volume proportional to organ or Core mass. The relative sizes of liver and brain are represented by green and purple circles, respectively. Silhouttes: *Callithrix jacchus*, *Saimiri* (generic), *Erythrocebus patas*, *Papio* (generic), *Homo sapiens idaltu* (© Phylopic 2024, compiled by T. Michael Keesey).

## RESULTS

### *The proportion of brain mass in the Core varies reciprocally with that of liver*

Of six possible tradeoffs among four thermogenic organs, two occurred consistently in primate clades, that between brain and liver, and a dampened tradeoff between heart and kidney (Figure 1-B). Similar tradeoffs were observed among Glires, Laurasiatheria, Marsupialia, and an Afrotherian. (Supplementary Figures S1 and S2). The two species exhibiting the highest brain/Core mass ratios were the largest terrestrial mammal (*Elephas maximus*) and the smallest weasel (*Mustela nivalis*).

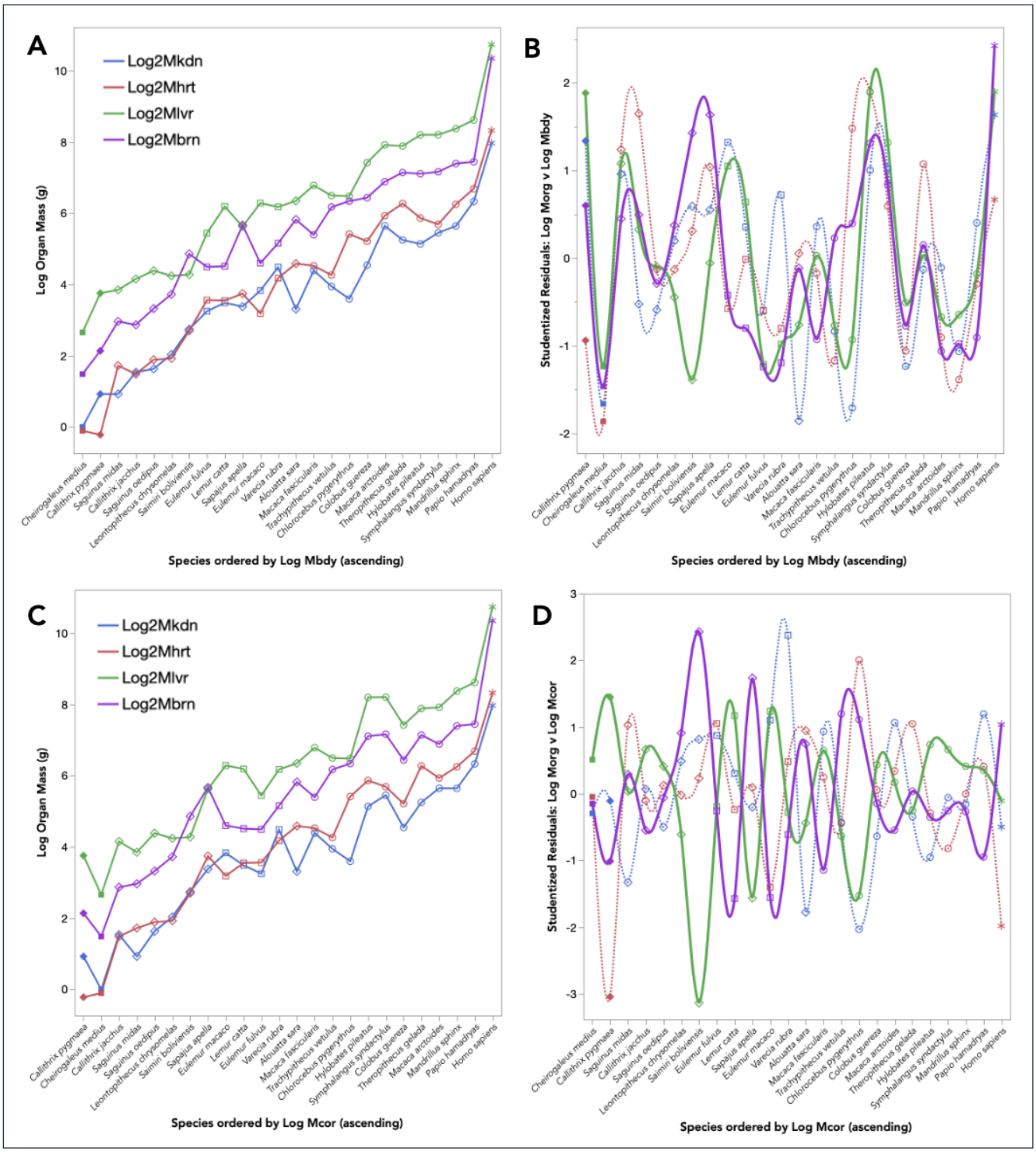


Figure 2. Variation of liver and brain mass relative to either the whole body or the four-organ Core.
A and C: Variation of organ size relative to body size and Core size in primates ($N$ = 24).
B and D: Mass-independent residual variation relative to body size and Core size in primates.
The line colors represent the same organs as in panels A and C.

A tradeoff between liver and brain mass was also readily demonstrable in log-transformed data, provided that they were ranked according to Core size (Figure 2-C), rather than body size (Figure 2-A).

Residuals of mass-independent regressions exhibited a periodic pattern of variation for each organ, corresponding to the relative proportion of body mass (Figure 2-B) or Core mass (Figure 2-D). Since the tradeoff between the residuals of brain and liver mass is apparent only when ranked according to Core mass, past standardization of log *Mbrn* with respect to log *Mbdy* has precluded its detection[23].

***Physiologically-based cMRs do not correspond to log-based sMRs***

Assuming power law models, we distinguish between:

specific *MR* (*sMR*): $sMR = m \times M^b$,

where *b* is the slope of log *rMR*/log *M*, and

cellular *MR* (*cMR*): $cMR = n \times M^c$,

where *c* is the allometric exponent obtained by maximum likelihood fitting of $rMR/M^c$ to the distribution of a physiologically-relevant trait, such as *mirFam*[11]. In the present report, "*rMR*" includes metabolic rates measured under basal conditions *i.e. bMR*s. As previously shown, *mirFam*-based cellular *MR*s (*cMR*s) are sensitive to body temperature and robust to variation in the range of mass, unlike log-based *sMR*s[11]. By definition, an *sMR* has a fixed value independent of size (Supplementary Figure S3-A); thus, the ratio of *sMR* to any trait that varies with size, such as *mirFam*, is uninformative (Supplementary Figure S4). Since a *mirFam*-based *cMR* increases or decreases as a function of size (Supplementary Figure S3-B), it yields a biologically informative and phylogenetically consistent rank order for *cMR*/*mirFam* ratios (Supplementary Figure S4). These observations raise a fundamental question, with implications for covariance models of trait evolution[33-36], of whether log transformation of *M* and *MR* provides the appropriate scale for the inference of *MR*/kg when there is only a narrow range of variation of any inferred *cMR*, and when the physical and ecological variables to which *cMR* has adapted, notably temperature and the availability of water, scale arithmetically.

***Estimation of thermogenic organ cMRs***

The context for our method is that the variation of mammalian *cMR* with respect to *mirFam* best fit a model of stabilizing selection when whole-body *cMR* was scaled to $M^{0.75}$ (hence "*cMR.75bdy*")[11]. In order to estimate a *mirFam*-based *cMR* for each thermogenic organ, we compared its dependence on both *mirFam* and organ mass in the range *cMR.60* - *cMR.90*, revealing opposite directions of correlation: increasing *P* values for kidney, heart and brain and decreasing *P* values for liver and whole body (Figure 3). Regression on *mirFam* or binned *mirFam* alone, without correction for organ mass, yielded essentially the same patterns, the only difference being a shift in the peak of the distribution of *P* values for *cMRbdy* from $M^{0.70}$ to $M^{0.75}$ (Supplementary Figure S5). *Assuming an operating range of*

$M^{0.70}$ - $M^{0.80}$, we estimated each organ *cMR* based on the lowest *P* value in this range, hence:

*cMR.**70**kdn*, *cMR.**70**hrt*, *cMR.**70**brn* and *cMR.**80**lvr*.

Inspection of Figure 3 reveals that the range $M^{0.70}$ - $M^{0.80}$ defines the limits of a zone of minimal correlation of Core *cMR* with Core mass and *mirFam*, centered at $M^{0.75}$.

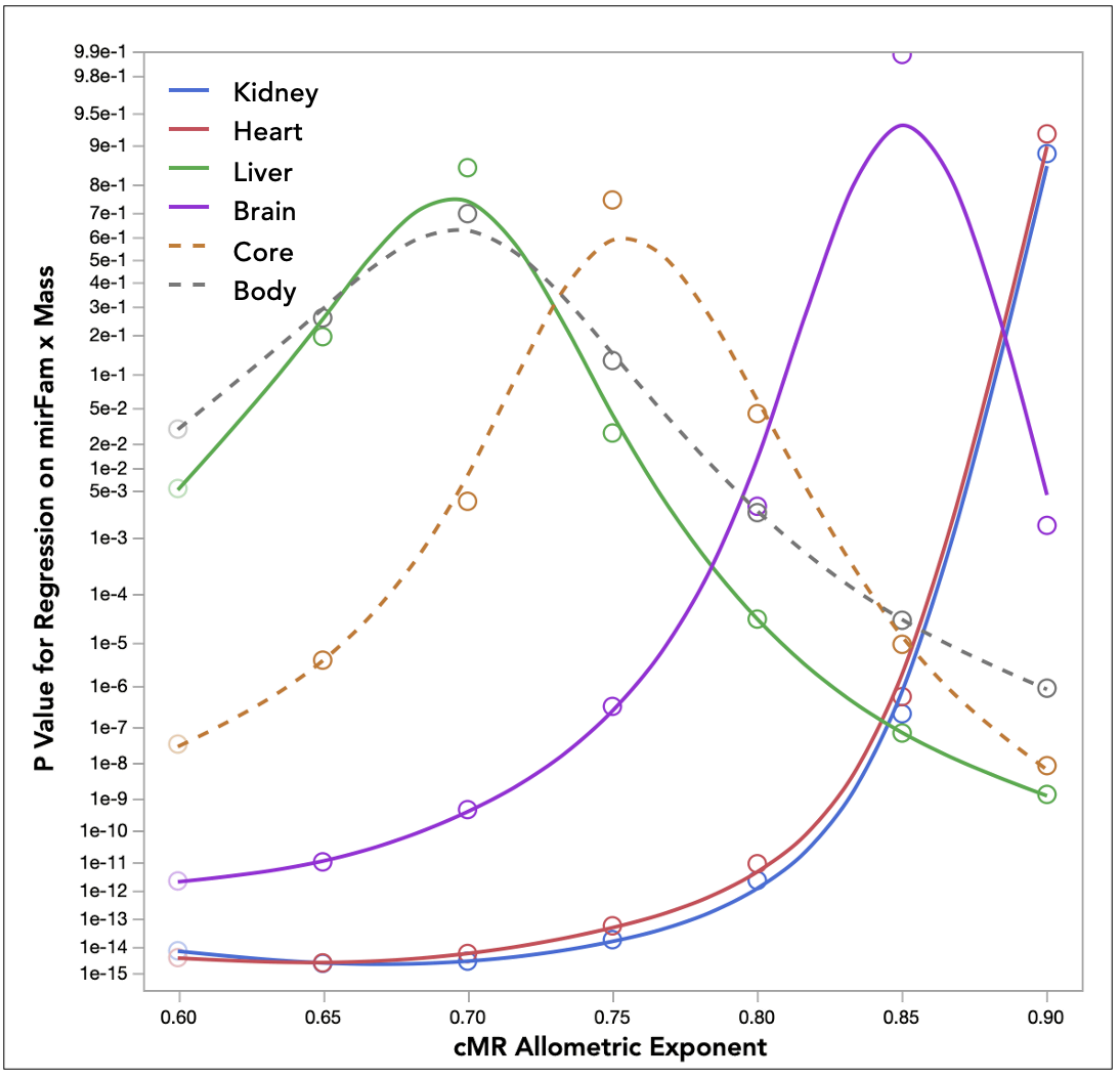


Figure 3. Dependence of *cMR* on *mirFam* and √*Morg* ($Morg^{0.5}$) (51 Euarchontoglires).
*P* values for regressions of organ *cMR* on √*Morg* and *mirFam* (binned – see Methods).
Regression on √*Morg* yielded *P* values several orders of magnitude lower than regression on log *Morg*.
Note that the minimal correlation for the Core *cMR* occurs when it is scaled to $M^{0.75}$.

For each organ, the log-based *sMR* corresponded to the crossover point for the inversion of the *cMR* slopes with respect to organ size *i.e.* the zone of greatest mass-independent variation (Figure 4). Again, there was an obvious distinction between the allometric exponent for slope inversions for kidney, heart and brain (~ *cMR.85*) (Figure 4-A) and the exponent corresponding to the slope inversions for liver and whole body (~ *cMR.70*) (Figure 4-B).

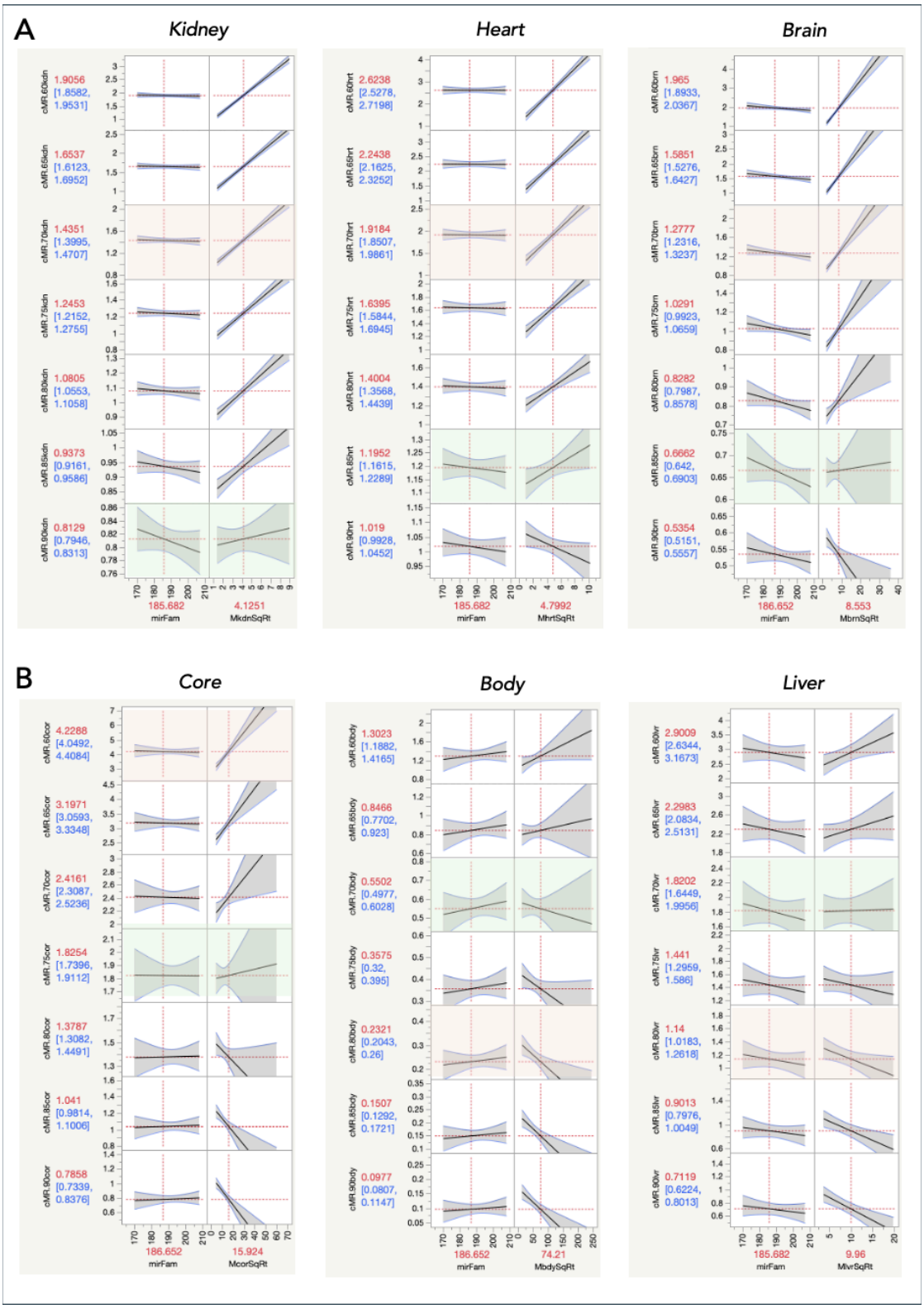


Figure 4. *cMR* slopes with respect to *mirFam* and $\sqrt{M}$, as a function of allometric exponent (22 primates). Estimated *cMR* slopes are shaded pink, log-based *sMR* slopes are shaded green. Grey bands represent CI. Note that log-based *sMR*s correspond to crossover points for the inversions of *cMR* slope with respect to $\sqrt{M}$.
A. Kidney, heart and brain *cMR*s exhibit similar patterns of slope inversion with respect to $\sqrt{M}$.
B. Liver and body *cMR*s exhibit similar slope inversions with respect to $\sqrt{M}$.
Only the Core *cMR* slopes invert at $M^{0.75}$. Values in red represent means ± CI (blue).

Only the Core *cMR* exhibited an intermediate slope inversion (~ $M^{0.75}$) and log-based *sMR* ($M^{0.756}$) corresponding to Kleiber's allometric exponent for mammalian *sMR* (Figure 4-B)[37]. $M^{0.75}$ was previously shown to be the optimal scaling for a model of stabilizing selection of mammalian *cMR* with respect to *mirFam*[11], suggesting that the highly conserved relationship between the whole body rate of energy expenditure and body size corresponds to a zone of minimal body size constraint on the Core *cMR*.

Plotting the estimated *cMR*s as a function of primate whole body size revealed a strict anticorrelation between liver *cMR.80 versus* body size and the *cMR.70*s of kidney, heart and brain (Figure 5-A). The slightly negative slope for *cMR.75bdy* with respect to log *Mbdy* was not significantly different from 0.0 ($P$ = 8.5e-02). The same ranking of slopes (heart > kidney > brain) and anticorrelation with liver *cMR.80* was obtained when organ *cMR*s were regressed on the thermal conductance ($C_{min}$) of 21 Boreoeuetheria (Figure 5-B), pointing to a common origin for these physiological and thermoregulatory relationships. $C_{min}$ is an extensive property that depends primarily on total body surface area and, secondarily, on the properties of the insulating layer[38]. Ranking Boreoeutheria according to log $C_{min}$ also revealed tradeoffs between the Core mass independent residuals of liver and brain (Supplementary Figure S6-A), and between *cMR.80lvr* and *cMR.70brn* (Supplementary Figure S6-B).

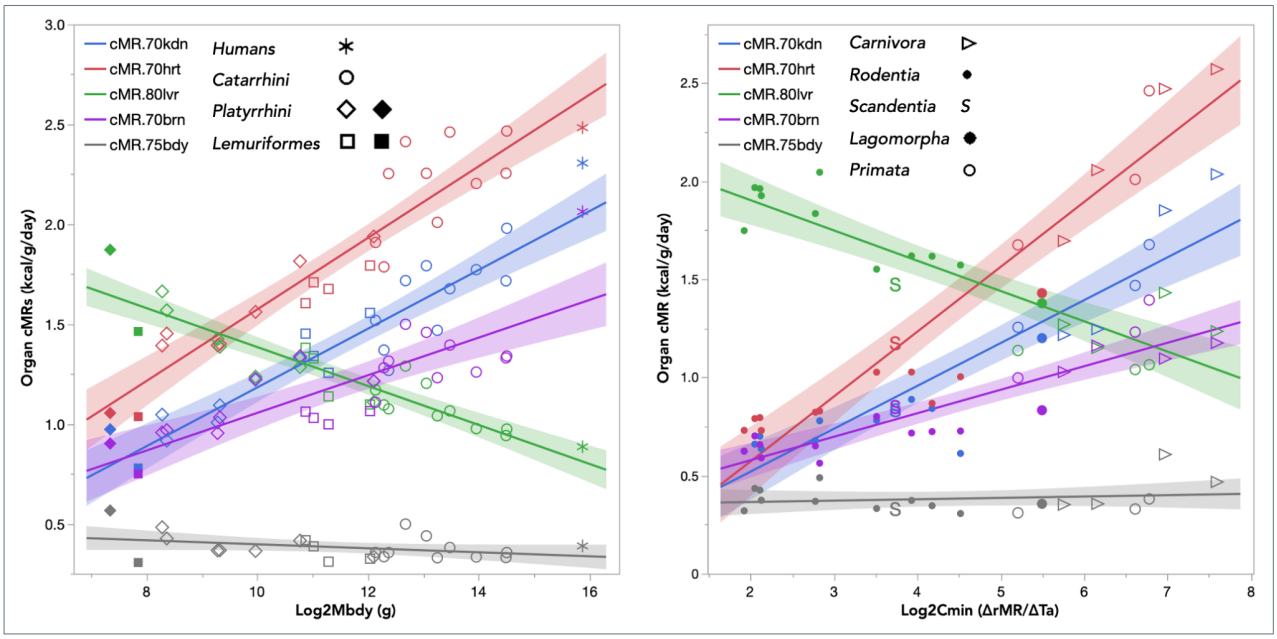


Figure 5. Core organ *cMR*s as a function of body size or thermal conductance.
A. Primates ($N$ = 24). Filled symbols represent likely heterotherms.
B. Boreoeutheria ($N$ = 21). $T_a$ = ambient temperature. Shaded bands: confidence intervals (CI).

### *Thermodynamic and phylogenetic relevance of Core organ cMRs*

For a steady state (whole animal) resting *MR* that scales as $M^{0.75}$, the rate of core thermogenesis is predicted to scale approximately as $\sqrt{M}$[32]. We applied partial least squares regression[39] in order to

predict the optimal scaling of a joint Core *cMR* composed of either *mirFam*-based *cMR*s:

$$cMR.Xcor = (rMRkdn + rMRhrt + rMRlvr + rMRbrn) / (Mkdn + Mhrt + Mlvr + Mbrn)^X$$

$$= (a \bullet cMR.\mathbf{70kdn}) + (b \bullet cMR.\mathbf{70hrt}) + (c \bullet cMR.\mathbf{80lvr}) + (d \bullet cMR.\mathbf{70brn})$$

*or* log-based *sMR*s:

$$sMR.Xcor = (rMRkdn + rMRhrt + rMRlvr + rMRbrn) / (Mkdn + Mhrt + Mlvr + Mbrn)^X$$

$$= (a' \bullet sMR.\mathbf{90kdn}) + (b' \bullet sMR.\mathbf{87hrt}) + (c' \bullet sMR.\mathbf{67lvr}) + (d' \bullet sMR.\mathbf{83brn})$$

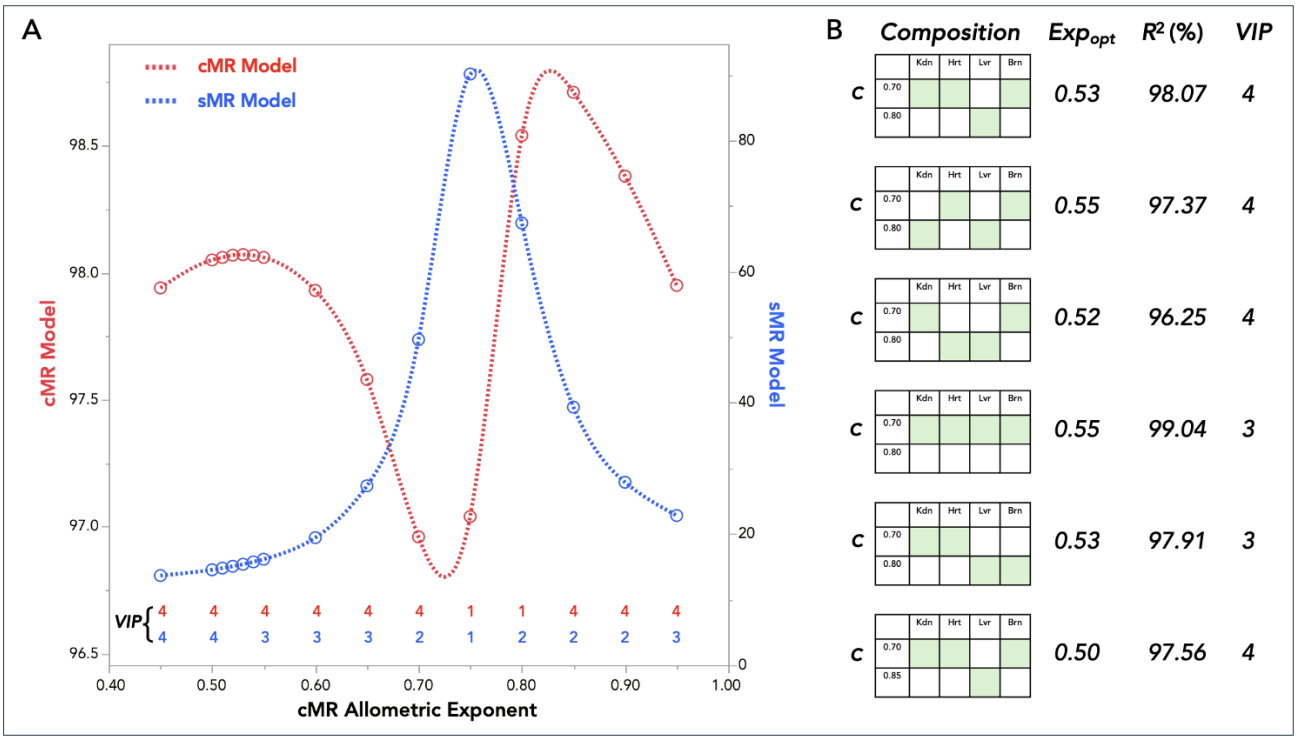


Figure 6. $R^2$ (% variation) for models of *cMRcor* predicted by linear combinations of the *mirFam*-based *cMR*s or log-based *sMR*s of the four thermogenic organs (note the difference between the scales) ($N$ = 22).
A. Comparison between *mirFam*-based organ *cMR*s and log-based organ *sMR*s. Below the plot, the table of values for *VIP* (*variable importance of projection*) indicates the number of organs upon which each model is significantly dependent[40].
B. Comparison of the joint *cMR* of combinations of *cMR.70* and *cMR.80* among the four thermogenic organs. "*c*" is the organ *cMR* allometric exponent. "$Exp_{opt}$" is the optimally fitting allometric exponent of the model.

In primates, the composite *cMR* model exhibited two peaks, one on either side of the inversion of Core *cMR* slopes with respect to √M: a broad peak centered at $M^{0.53}$, similar to that predicted by the biophysical model of core thermogenesis[32], and a second peak between $M^{0.80}$ - $M^{0.85}$ (Figure 6-A). The log-based joint *sMR* exhibited a single sharp peak at $M^{0.75}$, exactly that assumed for the whole animal and therefore consistent with a homogeneous mass, rather than a core-periphery model[32].

Importantly, the *cMR* and *sMR* models exhibited critical differences in *VIP* statistics (*Variable Importance of Projection*[40]), a measure of the number of variables constraining each model (Figure 6-A, bottom). In the range *cMR.55cor* - *cMR.70cor*, only the *cMR* models depended on all four organ *cMR*s (Figure 6-A, bottom). When scaled to $M^{0.75}$, both the *cMR* and *sMR* models of the Core were unconstrained by kidney, heart or brain, depending only on the *cMR* of the liver (Figure 6-A, bottom).

We applied an additional test of the relevance of the estimated organ *cMR*s by comparing the joint *cMR*s obtained by permuting the combinations of the estimated organ *cMR*s, yielding four models with *VIP* = 4 (Figure 6-B). Of these combinations, we found two that were able to resolve Platyrrhini from Lemuriformes in an unsupervised classification of major primate clades[41]: either *cMR.80* or *cMR.85* for liver, together with *cMR.70* for heart, kidney and brain. When liver *cMR* was varied between *cMR.75* - *cMR.85*, the lowest value for the Bayes information criterion (BIC) corresponded to the originally estimated set of *mirFam*-based *cMR*s (Supplementary Figure S7), yielding the following optimal primate model of thermogenesis by the defined, 4-organ Core:

$$\textbf{\textit{cMR.53}cor} = 0.53 \bullet \textbf{\textit{cMR.70kdn}} + 0.69 \bullet \textbf{\textit{cMR.70hrt}} + 0.37 \bullet \textbf{\textit{cMR.80lvr}} + 0.09 \bullet \textbf{\textit{cMR.70brn}}$$

In the context of the evolution of thermoregulation, the coefficient of each organ *cMR* in this model indicates its relative impact on the total rate of internal thermogenesis, from which one can infer the degree to which it has been constrained by natural selection *i.e.* the smaller its coefficient, the greater the degree of permitted evolutionary variation of the organ *cMR* since clade divergence.

***The Core model presents a new approach to investigate the evolution of thermoregulation***

The original biophysical model for thermoregulation assumed that metabolic heat emanates from the geometric center of an ellipsoid endotherm[32]. Depending on the wind condition or the presence of fur, the authors derived a single allometric exponent between 0.46 - 0.58 to scale the rate of core thermogenesis across the entire range of mammalian body size[32]. Since our Core model is delocalized among four thermogenic organs and makes no geometric assumptions, we expected lower allometric exponents ("c") and higher rates of thermogenesis ($rMR/M^c$) in smaller mammals with higher ratios of surface area/volume. Consistent with this expectation, the optimal allometric scaling of Core models developed in Carnivora, Primates and Glires were $M^{0.60}$, $M^{0.53}$ and $M^{0.40}$, respectively (Figure 7-A, -B).

The values of the model parameters in Glires present a striking contrast to those in the carnivore and primate models: a reversal in sign of the coefficient for brain *cMR* in Glires, and a reversal of the relative magnitudes of the coefficients for liver and brain (Figure 7-A). Since the median body size of

Glires was only 1/80th that of primates (Supplementary Table S3), the observation that the Glires model penalizes the *cMR* of the brain suggests an adaptation to a disproportionate reduction of body size relative to brain size. A converse pattern for the corresponding VIP values, reflecting the degree of constraint by each organ (Figure 7-B), was consistent with this interpretation.

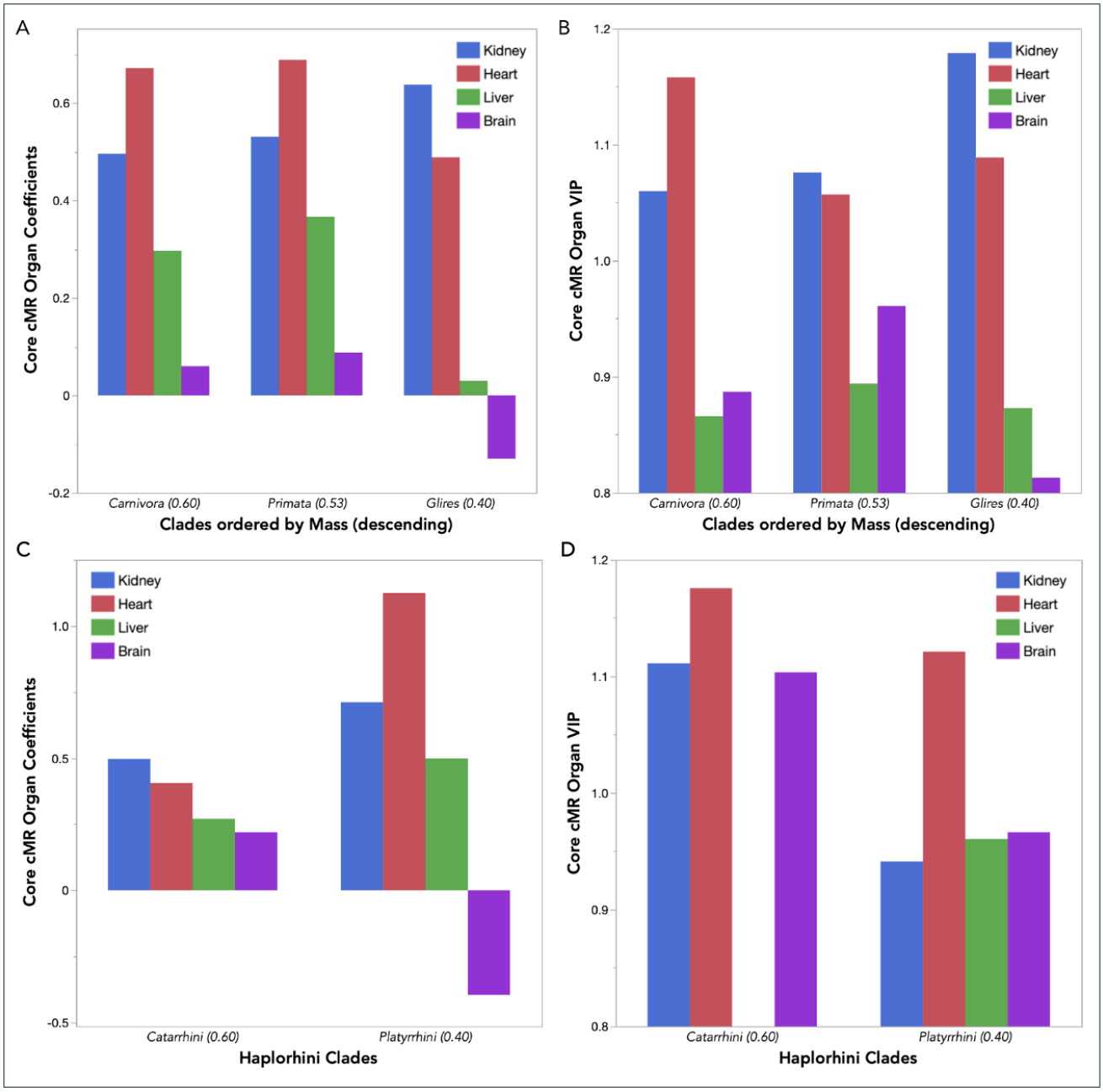


Figure 7. Organ cMR coefficients and VIP values for Core models in Boreoeutheria and Haplorhini.

Values in parentheses next to each clade indicate the optimal allometric exponent of the Core *cMR* model.
A. Organ coefficients for the optimal model for Carnivora ($N$ = 30), Primata ($N$ = 22) and Glires ($N$ = 26).
B. Organ VIP values above threshold of significance (0.80) for each model.
C. Organ coefficients of the optimal models for Catarrhini ($N$ = 10) and Platyrrhini ($N$ = 8).
D. Organ VIP values above threshold of significance (0.80) for each model.
Note that in Catarrhini, the VIP for liver (0.4070) has dropped below the threshold of significance.

Consequently, the median and average ratios of *Mbrn*/*Mbdy* have remained higher in Glires than in primates or carnivora ($P < 0.001$, analysis of means), contrary to the order of log *Mbrn*/log *Mbdy* (Supplementary Table S3). The same trends with respect to body size were recapitulated and magnified with the divergence of Platyrrhini from Catarrhini. The optimal Core *cMR* allometric exponent diverged from 0.53 for all primates to 0.60 for the larger Catarrhini and 0.40 for the smaller Platyrrhini, consistent with surface area considerations (Figure 7-C). As in the case of the divergence of Glires from primates, the Platyrrhini model penalized the coefficient for brain *cMR* (Figure 7-C), and the *Mbrn*/*Mbdy* ratio in Platyrrhini remained higher than in Catarrhini ($P < 0.001$, analysis of means). Among Catarrhini, the VIP for liver dropped to 0.4070, below the 0.8 threshold for significance, indicating a negligible contribution of the liver to the overall rate of Core model thermogenesis (Figure 7-D) (Supplementary Table S3).

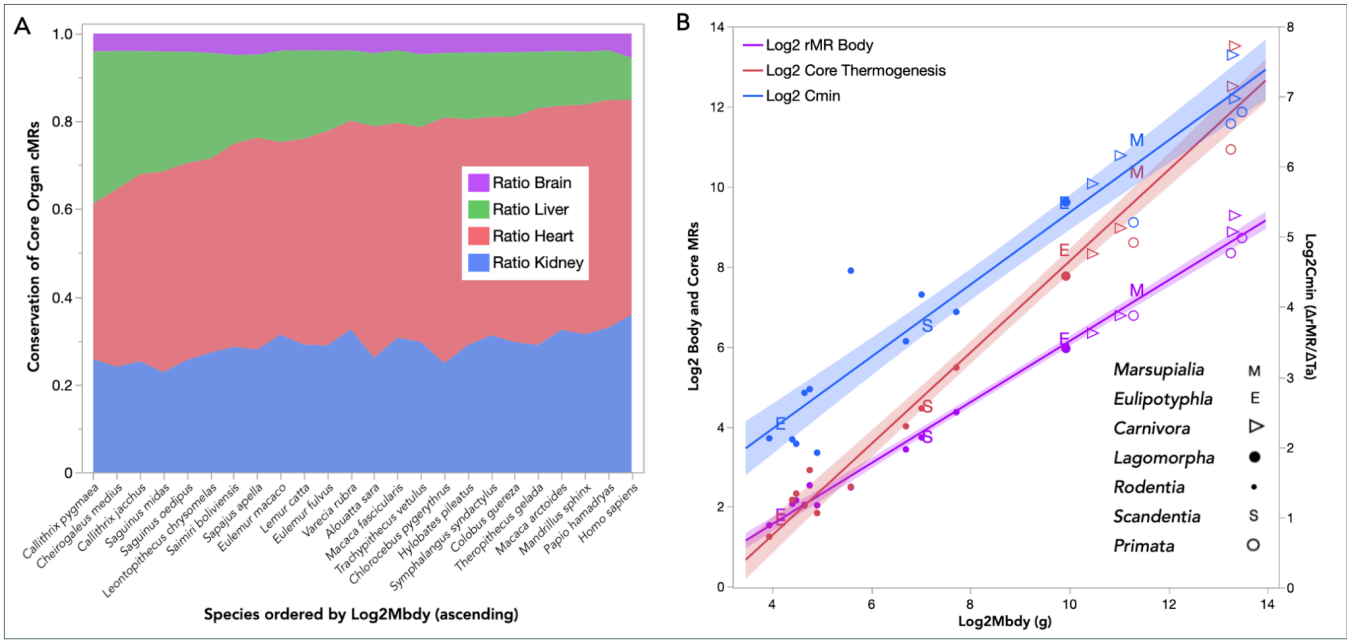


Figure 8. Summary of Predicted Thermoregulatory Adaptations in Mammals.
A. Each of the four terms of the linear model of *cMR.53cor* was expressed as a fraction of the sum ($N = 24$). Note that the contribution of *cMR.80lvr* exhibits the highest degree of evolutionary plasticity.
B. Variation of whole body *rMR* (*MRbdy*), Core thermogenesis (*MRcor* = *cMR.53cor•Mcor*) and thermal conductance (*Cmin*), relative to body mass. $T_a$ = ambient temperature. Bands represent CI.

Figure 8 summarizes the evidence of adaptations to thermoregulatory constraints. In the human lineage, apart from the brain-liver tradeoff in mass, there was a steady decline in the liver's contribution to the overall rate of Core thermogenesis (Figure 8-A). We also compared overall Core thermogenesis (*cMR53.cor · Mcor)* with whole body resting *MR* and thermal conductance (*Cmin*), all scaled to similar ranges. Among mammals with body mass < 500 g ($2^9$ g), Core thermogenesis

approached total body *rMR*, while with increasing size > 500 g, Core thermogenesis approached the maximal rate of thermal conductance (Figure 8-B).

### *The evolution of organ cMR tradeoffs validates the Core model of thermoregulation*

The preceding evidence suggests that Boreoeutheria have been able to maintain thermal homeostasis while diversifying in body mass by fine-tuning the relative sizes and rates of thermogenesis of the four Core organs, particularly in the case of liver. We applied Bayesian inference in order to investigate the historical timing of the resulting tradeoffs. In agreement with the differences predicted by Core *cMR* models (Figures 7 and 8), we found opposing directions of evolution between *cMR.80lvr* and body size, both between Haplorhini and Glires, as well as within each clade (Figure 9).

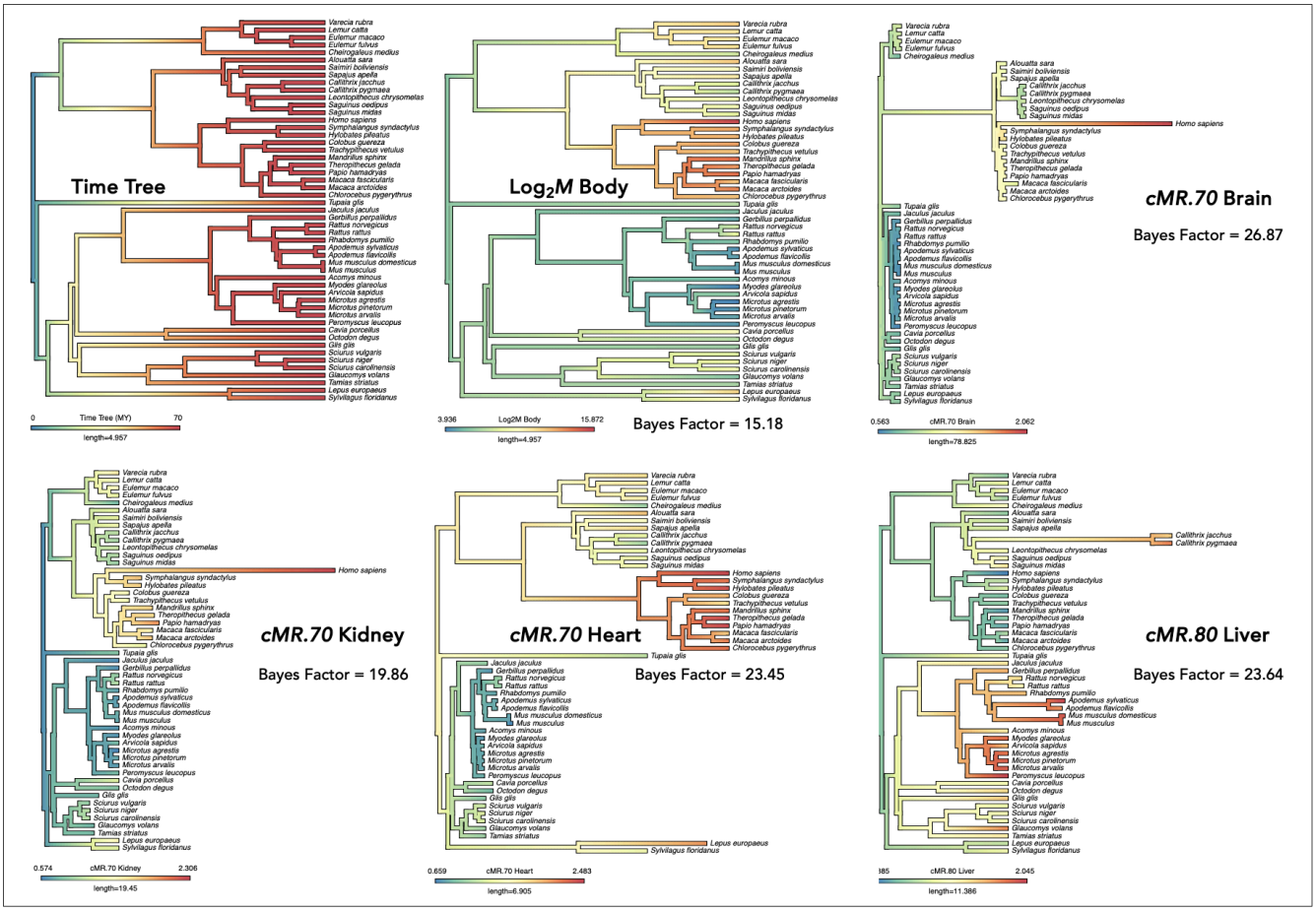


Figure 9. Variable rate phenograms of *Log$_2$Mbdy*, *cMR.80lvr*, and *cMR.70* of kidney, heart and brain.
The color values for the reference Time Tree depict the extent of underlying genomic evolution[8].
Bayes factors were computed from the difference between the median log likelihood (*Lh*) of the 1% most likely trees and the median *Lh* of the 1% of trees with the smallest non-zero sum of changes to branch length, *i.e.* those trees most similar to the reference time tree[11].

Among primates, an accelerated increase in liver *cMR* accompanied the decrease in size of two of the smallest Platyrrhini, one of which (*Callithrix pygmaea*) may be heterothermic[42]. All five of the smaller (<

1.0 kg) Platyrrhini exhibited an accelerated *decrease* in brain *cMR.70* paired with elevated levels of *cMR.80lvr*, consistent with adaptation to a low energy regime and greater reliance on gluconeogenesis. The evolution of brain *cMR.70* was arrested in Glires relative to Haplorhini, and those species that underwent the most severe reduction in size exhibited the greatest increases in liver *cMR.80*; conversely, the largest species (Lagomorpha) exhibited the lowest liver *cMR*s (Figure 9).

Brain *cMR.70* increased in intensity and its rate of evolution accelerated with the divergence of Haplorhini, and again with that of humans, in contrast to its relative stasis or decrease among Glires, Lemuriformes and smaller Platyrrhini (Figure 9). The relative levels of heart *cMR.70* generally tracked body size, with accelerated rates of heart evolution in the clades of the largest Glires (Lagomorpha) and primates (Catarrhini). The divergence of humans was marked by an exceptional increase in the rate of evolution of kidney *cMR.70*, in addition to that of *cMR.70brn* (Figure 9).

## DISCUSSION

### *Inferring cellular metabolic rates*

The recent publication of hundreds of primate genome sequences[43] has made possible ever more fine-grained analyses of the phylogenetic covariance of traits that may have fueled the evolutionary expansion of brain size in the hominid lineage[44]: diets richer in calories and protein[45-46], more efficient food acquisition and assimilation[47], greater adipose tissue reserves[15,23,48], and gains in the reliability of gestation, lactation and infant care[49-40]. However, the disposition of the internal heat generated by such larger brains has yet to be addressed: while the *bMR* of humans is 50% higher than that of similar-sized orangutans[15], primate whole-body *bMR*s account for only 35% of relative brain size[53] and *vice versa* (37% based on the 24 primates in the present dataset).

The conventional power law model allows the *rMR*s of species varying in mass over several orders of magnitude to be made a linear function of *M* by log transformation, regardless of phylogenetic order[37]. Phylogenetic comparative methods can then be applied to deconvolve inherited variation from variation that is random or adaptive[33-38]. However, the physical and ecological pressures to which organ and body *rMR*s have adapted, notably temperature and the availability of water, scale arithmetically, as do mass-adjusted *MR*s (*sMR*s or *cMR*s). Unlike the fixed *sMR* distribution derived from the slope of log *rMRorg*/log*Morg*, a *cMR* distribution can be matched to the distribution of a relevant physiological or thermodynamic variable without log transformation, while differences between phylogenetic orders can be resolved by standardization of the ranges of predictor and

response variables (see, for example, Supplementary Figures S4 and S9). The choice between *sMR* and *cMR* then reflects an assumption about which measure is the more proximate target of selection.

### ***Thermoregulatory* versus *body size constraints on organ size***

Since the seminal analysis by Lande (1979)[31], it has been the convention to base the allometry of brain size on whole body mass[23,52-53]. This approach has not detected significant anticorrelations among organ sizes[23], perhaps not surprisingly, given that organ sizes are developmentally programmed to track body mass[54]. We have previously shown in mammals that a model of stabilizing selection accounted better for the dependence on *mirFam* of whole-body *cMR* than did a Brownian motion process[11]. The optimal *cMR* scaling in this model of stabilizing selection was $M^{0.75}$, which we demonstrate in this study is the zone of minimal constraint by body size on the rate of Core thermogenesis. Moreover, additive models of both *cMR.75cor* and *sMR.75cor* were dependent only on the *cMR* of the liver, implying a degree of uncoupling of thermogenic organ mass from body size. Taken together, these observations suggest a hierarchy of organ size regulation: between clades, organ sizes have been developmentally programmed to track body size while within clades, the relative proportions of the Core organs have been adjusted in response to thermoregulatory demands.

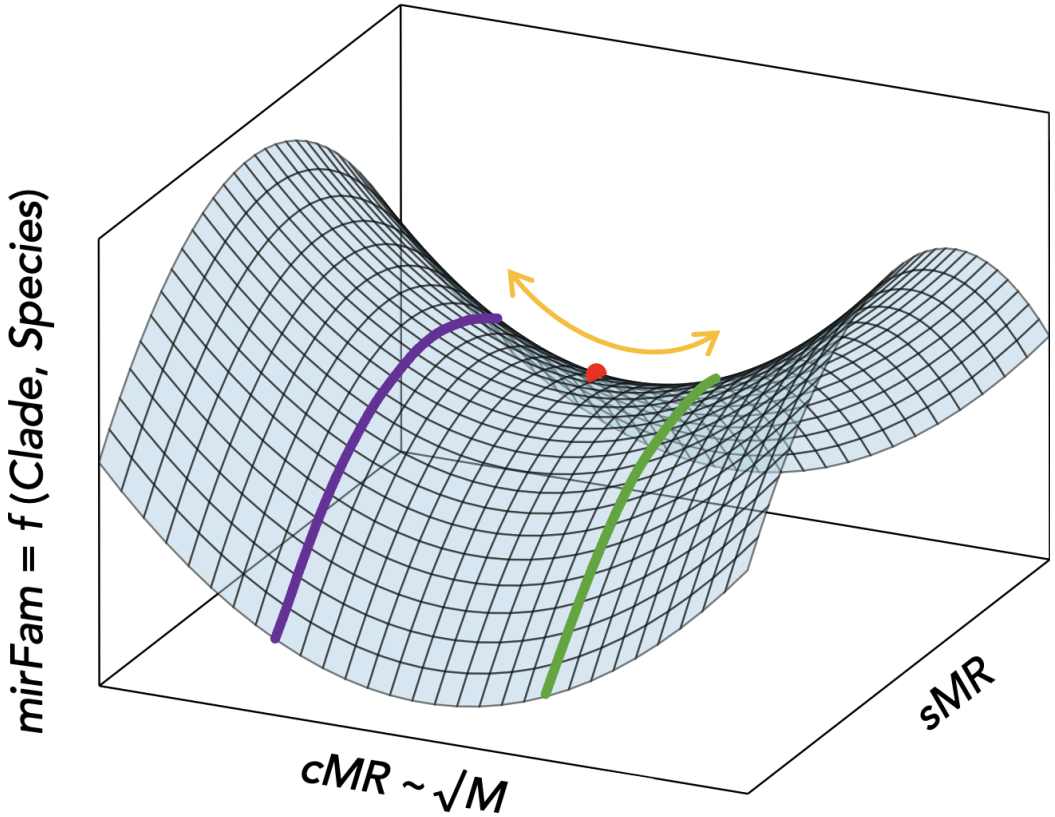


Figure 10. *mirFam*-based *cMR*s are displaced from the zone of minimal mass dependence defined by Core *sMR*. Brain (purple) and liver (green) *cMR*s exhibit opposite patterns of correlation with body size.

Figure 10 depicts the relationship between an organ *cMR*s and the Core *sMR* as a function of the evolution of the number of microRNA families. Since protein synthesis is the most costly biosynthetic process in mammalian cells, clade-wide expansions of the microRNA-target apparatus that have accompanied major increases in metabolic rates may have served to maintain metabolic efficiency by limiting the protein expression noise associated with faster rates of protein synthesis[11]. In this case, the saddle function may also be interpreted as a fitness landscape (Figure 10).

Lande (1979) attributed the enlargement of brain size in primates *versus* Glires to a genetic uncoupling of its dependence on body size[31]. Our thermodynamic models of Core *cMR* in carnivores, primates and Glires, together with Bayesian reconstruction of the evolutionary tradeoff between between liver and brain *cMR*s, suggest an inversion of this premise, namely, a disproportionate reduction of body size relative to brain size upon the divergence of Glires from primates, and Platyrrhini from Catarrhini (see also Smaers et al, 2021)[53]. Consequently, the average *Mbrn*/*Mbdy* ratios in Glires and Platyrrhini have remained significantly higher than the ratios in primates and non-human Catarrhini, respectively, in both cases contrary to the rank order of the ratio log *Mbrn*/log *Mbdy* (Supplementary Table S3). These examples illustrate how log transformation can alter the rank order of trait ratios, leading to different interpretations of evolutionary change, and returning to the fundamental question of the appropriate scale for comparison when there is a limited (<10-fold) range of phenotype variation, and when the physical and ecological variables to which the traits have adapted scale arithmetically.

***The developmental and phylogenetic plasticity of the liver***

Of the six possible *cMR* tradeoffs among four thermogenic organs, the brain - liver tradeoff is the most significant and most highly conserved. Since we detected the brain - liver tradeoff among all clades of Theria that we examined, this plasticity appears to be a property of the mammalian evolutionary toolkit. Upon depletion of glycogen in the fasting state, the liver serves as the primary organ of gluconeogenesis: the glucagon-dependent reduction of amino acid or glycerol carbons, fueled by free fatty acids released from adipose tissue. Gluconeogenesis contributes 40 - 60% of total glucose production after an overnight fast in humans, and greater than 90% after 48 hours of fasting[55]. Liver oxidation of fatty acids also generates ketone bodies that provide 60% of the human brain's energy during a prolonged fast, thereby sparing muscle protein[56]. Elevated levels of circulating fatty acids induce insulin resistance in liver and skeletal muscle[56], an additional mechanism to ensure an uninterrupted supply of glucose to the brain which, unlike these organs, cannot switch to fatty acid oxidation. Interestingly, specific microRNAs have been found to regulate many of the effectors

mediating the transition between the fed state/lipogenesis and the fasting state/lipolysis[57-59].

Brain glucose utilization peaks around age five in humans, early in the extended period between weaning and sexual maturity, which is also the period of slowest growth in body mass[60]. Based on the turnover of isotopically-labeled glucose, glucose production was proportional to brain mass over the entire lifespan, and therefore highest among young children[61]. Among prepubertal children (7 - 9 years of age), the rate of gluconeogenesis was still 50% higher than that found among adolescents[62-63]. The inverse relationship between developmental changes in the brain's glucose uptake and the rate of body mass growth[60] implicate the liver as the pivotal partner in this ontogenetic tradeoff.

Drawing on metabolite fluxes measured in humans, a computational model of the equivalent fluxes in mice found that following an overnight fast, the rates of liver gluconeogenesis, lipolysis and proteolysis were all elevated ~ 10-fold in mice, compared to the rates in humans[64]. These findings comport well with the opposite directions of evolution of *cMR.80lvr* that we found between Glires and primates, which are associated with divergent body size and life history strategies, notably population turnover[65-67]. The apparent evolutionary plasticity of the liver appears to have co-opted the liver's inherent mechanism of developmental plasticity: among mammalian organs, only the liver retains full regenerative potential[54]. If the evolution of liver size has adapted to both thermoregulatory constraints and the demand for glucose production, then a situation of high energy reliability/low dependence on gluconeogenesis in an incipient clade may have permitted reductions in relative liver size and/or thermogenesis, such as those associated with the divergences of Lagomorpha and Catarrhini. Conversely, smaller bodies and a tradeoff favoring the liver appear to signify adaptation to limited energy resources relative to population size, as exemplified by the divergence of Glires from Euarchontoglires, Strepsirrhini from primates, and Platyrrhini from Haplorhini.

Hippo-YAP, the bilaterian regulator of organ size[68], coordinates liver growth with the suppression of gluconeogenesis[69-72]. Significantly, the global underexpression of microRNAs that is frequently observed in tumor cells has been attributed to aberrant density-dependent regulation of the same Hippo-YAP signaling[73]: at low cell densities, Hippo signaling is normally suppressed, allowing YAP to localize in the nucleus and stimulate cellular proliferation, while at normal organ size and tissue density, YAP translocation and activity are inhibited by Hippo[68]. Constitutively active YAP suppresses microRNA levels in cells and tumors and post-transcriptionally induces oncogenic MYC protein[73-74]. Any resulting alteration in microRNA levels would be expected to cause dysregulation of gene

regulatory networks (GRNs), either by disrupting the timing of transient signals, such as transcription factors[75-76], or by shifting of the repression profile of targets regulated by multiple microRNAs[77]. By extension, the evolutionary plasticity of the liver implies a resetting of setpoints for liver size and activity with respect to body size and temperature; these, in turn, depend on the dynamic ranges for the interactions among Hippo-YAP signaling, organ size, and microRNA biogenesis.

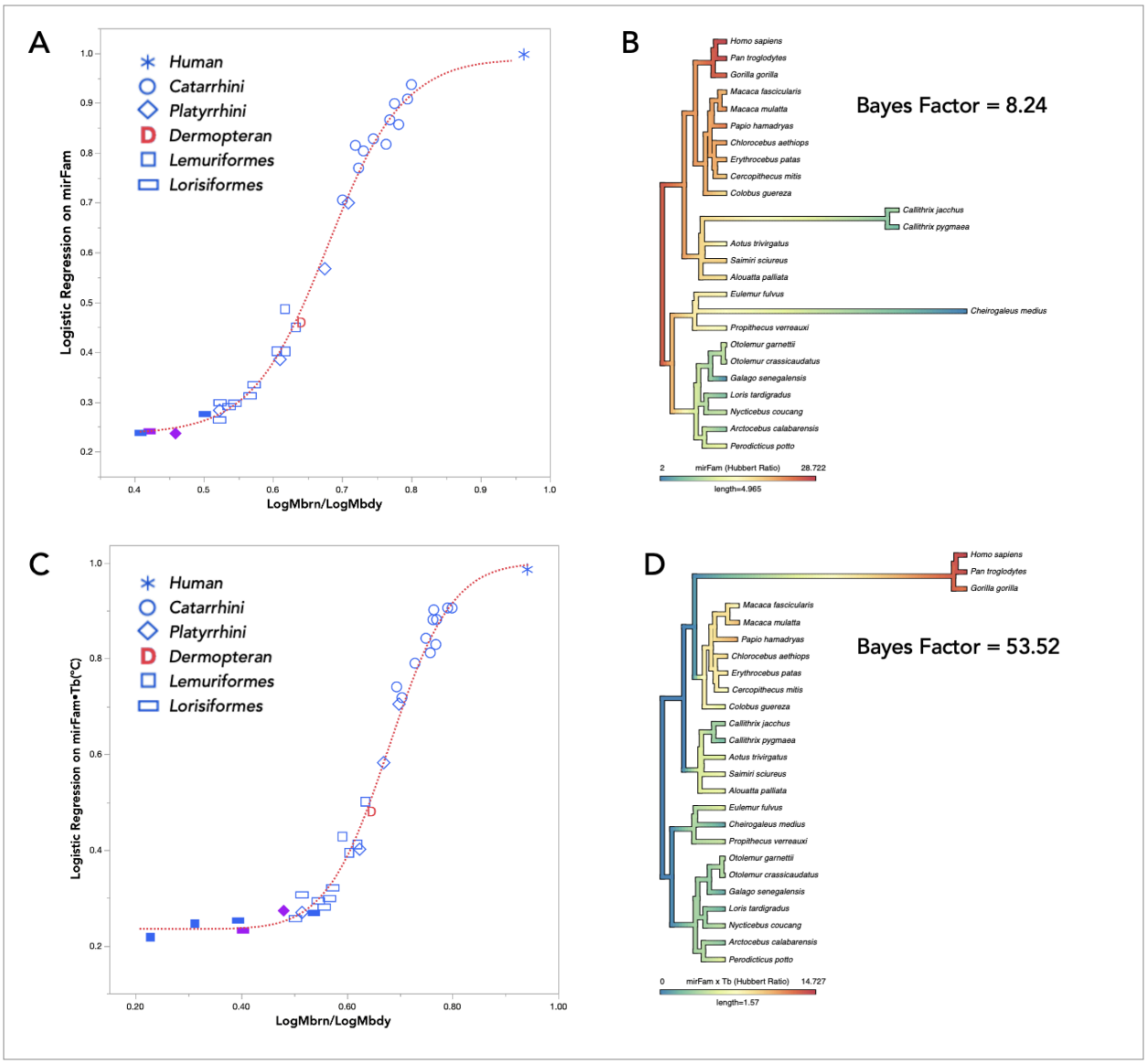


Figure 11. Logistic models of the evolution of relative brain size (data from Grabowski et al, 2023)[44].
A, C. For these idealized models, *mirFam* and *mirFam•*$T_b$ (°C) values were those predicted by the original logistic regression models, which excluded the small heterotherm *Cheirogaleus medius*:
$R^2$ = 1.00 (jitter applied) *versus* the original $R^2$ = 0.88 and 0.85, respectively.
By comparison, logistic regression of Log *Mbdy* on the ratio Log *Mbrn*/Log *Mbdy* yielded $R^2$ = 0.83.
B, D. Variable rate phenograms of the Hubbert linearization[78] of the corresponding logistic functions.
D = *Galeopterus variegatus*. Filled symbols: heterotherm (blue), suspected heterotherm (purple).

***A feedback model for brain size and energy reliability***

We modeled a simple feedback loop based on the association of larger brain size and *mirFam* with declining rates of liver thermogenesis, assuming that these reflect decreasing dependence on gluconeogenesis: energy reliability facilitates an increase in brain size which, in turn, facilitates improved energy reliability up to the limits imposed by anatomy and physiology, such as the diameter of the birth canal, or the physiological limit on the rate of heat dissipation[8]. Since the emergence of permanent homeothermy among Boreoeutheria was associated with a clade-wide increase in *mirFam*[11], we assigned *mirFam* to serve as a proxy for energy reliability. Using a logistic function, we fit *mirFam* to the primate brain size dataset of Grabowski et al (2023)[44]:

$$\frac{d\,(mirFam)}{d\,(\log M_{brn}/\log M_{bdy})} = r \bullet mirFam\,(1 - mirFam/mirFam_{max}),$$

where ***r*** is the growth rate, and the range of *mirFam* has been scaled to a range of 1.0.

As shown in Figure 11-A, log *Mbrn*/log *Mbdy* is a predictor of *mirFam,* rather than the converse, lending credence to the proposition that evolutionary increases in brain size were associated with greater energy reliability. Since *mirFam* can also be fit to the relative sizes of the other thermogenic organs (Supplementary Figure S8), the question arose as to which relationship might be the principal target of selection. However, the ranges of *mirFam* are highly clade-specific (Supplementary Figure S9-A), so that its variation relative to any trait is always secondary to phylogenetic distance. Since the dependence of whole body *cMR* on *mirFam* in mammals has evolved independently of phylogeny[11], we compared the dependence of individual organ *cMR*s on *mirFam*. In phylogenetic regressions on *mirFam* of organ *cMR*s ranging from *cMR.60* - *cMR.80*, all kidney and heart *cMR*s, and all but one liver *cMR* (*cMR.60lvr*), varied independently of phylogenetic distance (Pagel's *lambda* = 0.0) (Supplementary Table S4). In contrast, brain *cMR* variation with respect to *mirFam* was, in every case, secondary to phylogenetic distance (*lambda* = 1.0); thus, the evolutionary divergence of primate clades coincided with changes in the dynamic range of *mirFam* with respect to the relative size of the brain, in particular (Supplementary Table S4).

A variable rate phenogram corresponding to this logistic model was generated using the ratios from the Hubbert linearizations of the logistic functions (Figure 11-B)[78]; thus, the color scale represents rank order. The three smallest species, the heterothermic Lemuriform *Cheirogaleus medius* and two species of marmoset (*Callithrix*), exhibited an accelerated descent in rank, consistent with a previously reported observation on the evolution of brain size in Callitrichines[53]. *Callithrix pygmaea* may also be

heterothermic[42], and the *Callithrix* clade exhibited an adaptive increase of liver *cMR.80*, suggesting a regime of minimal energy reliability, perhaps related to low calorie-density folivory or insectivory[79].

Extending this logic, we postulated that the upper plateau of the logistic model, occupied by primates with the largest bodies and relative brain sizes, corresponds to a physiological limit on the rate of heat dissipation[8]. During exercise, human brain temperature increases in parallel with that of the body core, leading to hyperthermia and fatigue[16-18, 80]. Cooling of the brain, the only organ with its own exoskeleton, has been proposed as a benefit of the so-called "oxygen paradox" of neurovascular coupling *i.e.* the surplus blood flow in excess of oxygen demand, elicited by neuronal activation[81-83]. We find that, after correction for phylogeny, body temperatures ($T_b$) in primates are inversely correlated with *mirFam*, indicating that the product *mirFam* • $T_b$ is evolutionarily conserved. (Supplementary Figure S9-B). Since the highest *mirFam* are found in the largest primates (*Catarrhini*), this is reminiscent of the opposite trends, on a broad mammalian scale, between body size[1] and body temperature[2]. When Boreoeutheria were ordered by overall metabolic rate (*cMR.75bdy*), the values of *mirFam* • $T_b$ oscillated around the values of log $C_{min}$, further indicating that the product *mirFam* • $T_b$ tracks the physiological limit on the rate of heat dissipation (Supplementary Figure S10). Thus, the accelerated evolution detected among hominid apes near the plateau of the *mirFam* • $T_b$ logistic model (Figure 11-D) is consistent with adaptation to this limit[8].

In keeping with the long-range evolutionary patterns for mammalian body size[1] and temperature[2], Bayesian inference predicted opposite trends for *mirFam* and *mirFam* • $T_b$ with respect to relative brain size: descending in rank on the *mirFam* tree, except among Catarrhini, and ascending in rank on the tree for *mirFam* • $T_b$ (Figure 11-B and -D, respectively). Thus, our logistic model assigns the ancestral primate a high rank for energy reliability and a low rank relative to the heat dissipation limit, a propitious combination for the founder of a new order of mammals in a new fitness landscape[84]. In many respects this model, derived from the reparametrization of rates of organ energy consumption in terms of *mirFam*-based *cMR*s, fulfills the recent call for an explanation of the distinct pattern of brain size evolution in primates "in terms of the release of a constraint or an adaptive shift that initiated escalating feedback between brain and behavior"[10]. Together with the Core model of thermoregulation[32], it has allowed us to uncover a conserved energy tradeoff that was first proposed 40 years ago in order to account for the expansion of brain size in the human lineage[21]. Since this logistic model is agnostic regarding underlying mechanisms, it may also serve as a null hypothesis for comparison with the evolution of candidate mechanisms of adaptation.

***Implications for evolutionary medicine***

The reparametrization of *cMR*s also has far-reaching implications for evolutionary medicine[85]. For example, human kidney *cMR.70* underwent an adaptive increase to a level 30% higher than that found in other hominoid apes; by comparison, the value for the human was 10% *lower when scaled according to the slope (0.90) of log rMRkdn/log Mkdn*. Since the kidney is responsible for the homeostasis of pH, nitrogen, sodium, water and glucose, the rapid evolution *cMR.70kdn* in humans may represent adaptation to a diet enriched in lipid and protein[45-46], or to an altered landscape of opportunities for hydration *versus* risks of dehydration ("Savanna hypothesis")[27-30]. A related adaptation, a high density of eccrine sweat glands[25], may have enabled early humans to run down game in long distance pursuits[86], but may also have made them uniquely susceptible to dehydration[26], a marathon-enabling tradeoff. As it is, the kidneys of modern humans are quite susceptible to damage by heat stress: exposure to 40ºC for as little as one hour is sufficient to redirect blood flow to the skin, reduce blood flow to the kidney by one third[87] and trigger responses promoting water conservation that can eventually lead to acute kidney injury, such as activation of the renin-angiotensin-aldosterone system[88-89]. The kidneys of our hominid ancestors may have been even more vulnerable to heat and aridity, prior to this adaptive increase in *cMR.70kdn*.

Simulation of two million years of African and Eurasian climate and habitats supports the view that *H. sapiens* evolved from *H. heidelbergensis* in southern Africa during an unusually warm period that would have necessitated adaptation to hotter, drier conditions[30]. It is not generally appreciated[90] that maintenance of temperature homeostasis and water balance may have driven another uniquely human adaptation, the remarkable ability to store fat: adipose tissue was found to make up 41% of the body mass in adult women, compared to 9% in chimpanzee and 14% in gorilla females[15]. In addition to a prolonged the ability to release fatty acids, thereby sparing glucose for the brain, fatty acid oxidation generates a high molar ratio of water, which may appreciably affect overall water balance[94]: rats fed a high fat diet consumed less water following deprivation[95], and men who are obese manifested diminished thirst in response to dehydration[96]. Camels and fat-tailed sheep represent two other genera that manifest excess adiposity, relative to non-desert adapted ungulates[91-92]. Along with studies of aboriginal populations inhabiting the same arid regions for thousands of years, evidence of more rapid evolution and differential expression has been found among desert-adapted mammals for genes or gene families mediating lipid metabolism, insulin responsiveness, water and solute transport, as well as the activity of renin-angiotensin-aldosterone complex[93]. The permanent enlargement of breast tissue, in addition to providing nutrition during the extended infancy of humans, may have also served

a thermoregulatory function in a savanna environment that was hotter by day and cooler by night[97-98], as well as a portable buffer against infant dehydration. In sum, detection of the adaptive increase in human kidney *cMR* in the ancestors of modern humans prompts a reappraisal of other adaptations associated with the transition to a savanna ecosystem, some of which may represent overlapping nutritional and thermoregulatory functions.

**SYNTHESIS**

The adaptive value of repression by individual microRNAs operating in gene regulatory networks has been attributed to their ability to canalize phenotype expression by buffering the effects of environmental or allelic variation[99-100], to set thresholds for cell fate determination, and to maintain the identity of differentiated cells by defining ranges of protein expression[101-103]. Major stages in the diversification of animal cell types, morphologies and complexity of behavior have corresponded to significant expansions of microRNA and target repertoires[104-107]. For example, the appearance of 13 novel implantation-related microRNA families[108] marks the emergence of placental mammals, and the cognitive success of the genus *Octopus* has been linked to 34 novel microRNA families that are preferentially expressed in neural tissues[109]. However, these *post hoc* associations do not shed light on the conditions favoring repertoire expansion, nor on the relationship between the emergence of new traits and the number of families (*mirFam*), as opposed to the individual activities of new microRNAs[103].

The emergence of permanent homeothermy in the ancestral clade of Boreoeutheria and the attendant acceleration of metabolic rates was accompanied by a 15% expansion of the number of microRNA families[11], consistent with evidence that microRNAs are required to synchronize the timing of transient signals with metabolic rates[75-76]. A similar *mirFam* expansion accompanied the divergence of Catarrhini: in this study, we have been able to chart *mirFam* as a function of relative brain size, without reference to phylogeny, and link it to a reciprocal decline in thermogenesis by the liver, the primary organ of gluconeogenesis. These observations suggest that a high level of energy reliability, and presumably fitness, in an incipient clade may be a precondition for a significant expansion of the microRNA repertoire. What appear in the evolutionary record as clade-wide shifts to a higher number of microRNA families[110] and higher density of conserved target sites[11], would have necessitated a global reset of the dynamic ranges of microRNAs with respect to effector pathways, and of the repression profiles of targets that are regulated by multiple microRNAs[77]. While steady-state microRNA levels are stabilized by numerous homeostatic mechanisms[111-118], the robustness of such GRNs could have, in theory, facilitated rather than impeded the emergence of new or enhanced

phenotypes[119-121]. The two examples of microRNA repertoire expansion that we have considered here, the emergence of permanent homeothermy[11] and increasing brain size in Catarrhini, together with the observation that losses of microRNA families have occurred much less frequently than gains[122], suggest the operation of a ratchet mechanism, governed by selection for energy reliability, that pairs the diversification of microRNA regulatory networks with increasingly complex traits.

## DECLARATIONS

### *Limitations*

The three principal limitations of this study are:

i) the indirect origin of the mammalian organ *sMR*s in the main dataset (Supplementary Table S1). Apart from a single set of direct assays in humans[15], these have been inferred from organ masses measured in humans[16], rats, rabbits, cats and dogs (for references, see Wang et al 2012[1]).

ii) the small number and variable quality of the body temperature data in the AnAge database[5];

iii) underestimates of the number of conserved microRNA families by the MirMachine algorithm[6], relative to the reference, manually-curated database (currently MirGeneDB 3.0)[7].

These factors are not expected to affect the qualitative interpretation of our results.

### *Data Availability*

All original data with accompanying references are provided in Supplementary Tables S1 - S4.

### *Acknowledgment*

BF is supported by the Tromsø forskningsstiftelse (TFS) [20_SG_BF 'MIRevolution'].

### *Author Contributions*

Conceptualization: TS; Methodology: TS; Investigation: BF and TS; Writing – Original Draft: TS; Writing – Review & Editing: BF and TS; Visualization: TS; Funding Acquisition: BF.

### *Declaration of Interests*

The authors declare no competing interests.

### *Statement on the use of AI*

No part of this work was generated or edited using AI.

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**STAR METHODS - *Quantification and Statistical Analysis***

*Physiological Data*

The masses and *rMR*s of the four thermogenic organs were obtained from the dataset of Wang et al (2012)[1], originally derived from the compilation of Navarette et al (2011)[2] (Supplementary Table S1). Relative brain sizes for the logistic models were obtained from Grabowski et al (2023)[3].

Values for thermal conductance ($C_{min}$) were obtained from the dataset of Fristoe et al (2015)[4], with substitutions of congeneric species from the dataset of Wang et al (2012)[1]. Where $C_{min}$ was available for two or more congeneric species, we chose the one with the mass closest to the species in the Wang dataset. Body temperatures were obtained from the AnAge database[5].

*MicroRNA Families*, *Binning*

Complements of conserved microRNA families were obtained from the most complete assembly for each species using the covariance model MirMachine[6], trained on the manually-curated database of microRNA genes, MirGeneDB2.1[7] (Supplementary Tables S1 and S2). For Scandentia, Lagamorpha and Rodentia, *mirFam* refers to the number of families common to Euarchontoglires. For Lorisiformes, Lemuriformes and Platyrrhini, it refers to the number of families shared with Catarrhini. For the original regression of organ *cMR*s on *mirFam* and organ size (Figure 3), *mirFam* was binned according to natural divisions in its distribution: 141 - 161 (Scandentia and Glires), 165 - 181 (Glires, Lemuriformes and Platyrrhini), and 194 - 208 (Catarrhini).

*Phylogenetic Trees*

Using Mesquite © (2021) we derived ultrametric trees for 51 Euarchontoglires or 24 primates from the phylogenies of Alvarez-Carretero et al (2021)[8] and Shao et al (2023)[9] (Figures 8 and 9, respectively).

*Variable Rate Phenograms*

Variable rate trees and ancestral node values were inferred using BayesTraits.v4[10-11] (software available at www.evolution.rdg.ac.uk). Bayes factors for variable rate trees were computed from the difference between the median of the top 1% likelihoods and the median likelihood of the 1% of trees with the smallest non-zero sum of changes to branch length, *i.e.* those trees most similar to the reference time tree, as in Fromm and Sorger (2023)[12]. Phenograms were generated using Phytools[13].

*Statistics*

Linear, logistic and partial least squares regressions and normal mixture clustering were carried out and visualized using JMP16®. All $R^2$ values were adjusted for the number of predictors. Phylogenetic linear regressions were carried out using the R: CAPER package[14].

**STAR METHODS - *References***


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## SUPPLEMENTARY INFORMATION

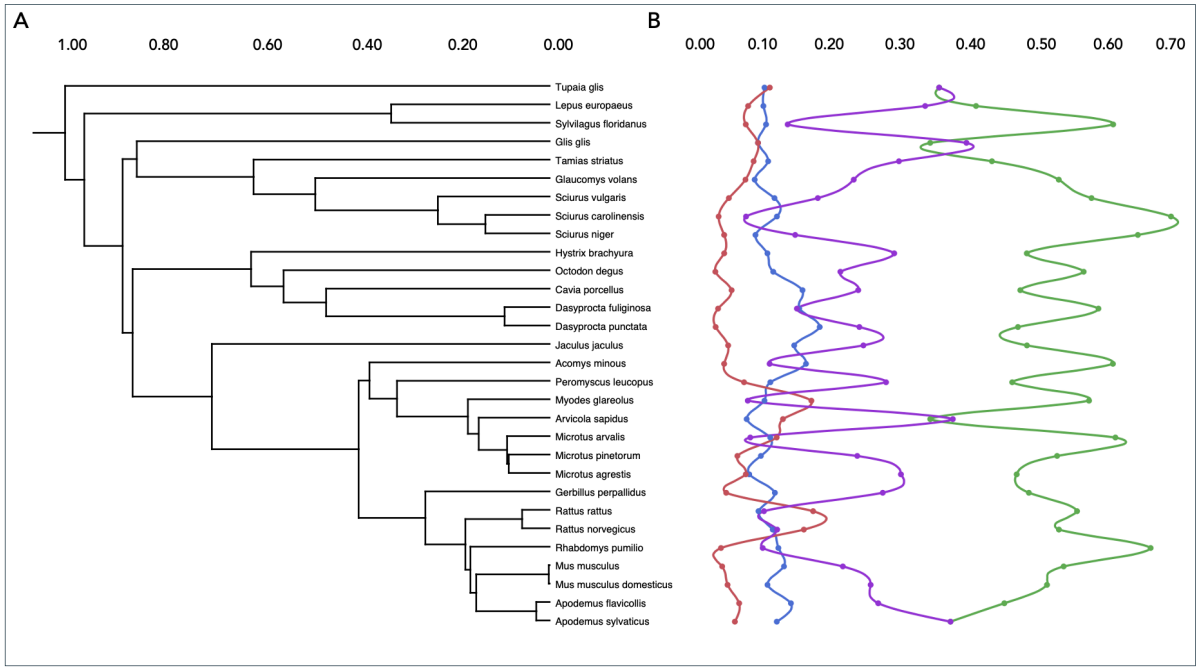


Figure S1. The proportions of brain and liver mass vary reciprocally in the Euarchontoglires Core. Species include one Scandentia, two Lagomorpha, and 27 Rodentia, including three Sciuridae.
A. Ultrametric phylogenetic tree[8]. The scale represents the relative time of divergence.
B. Mass proportion of each organ relative to total Core mass.

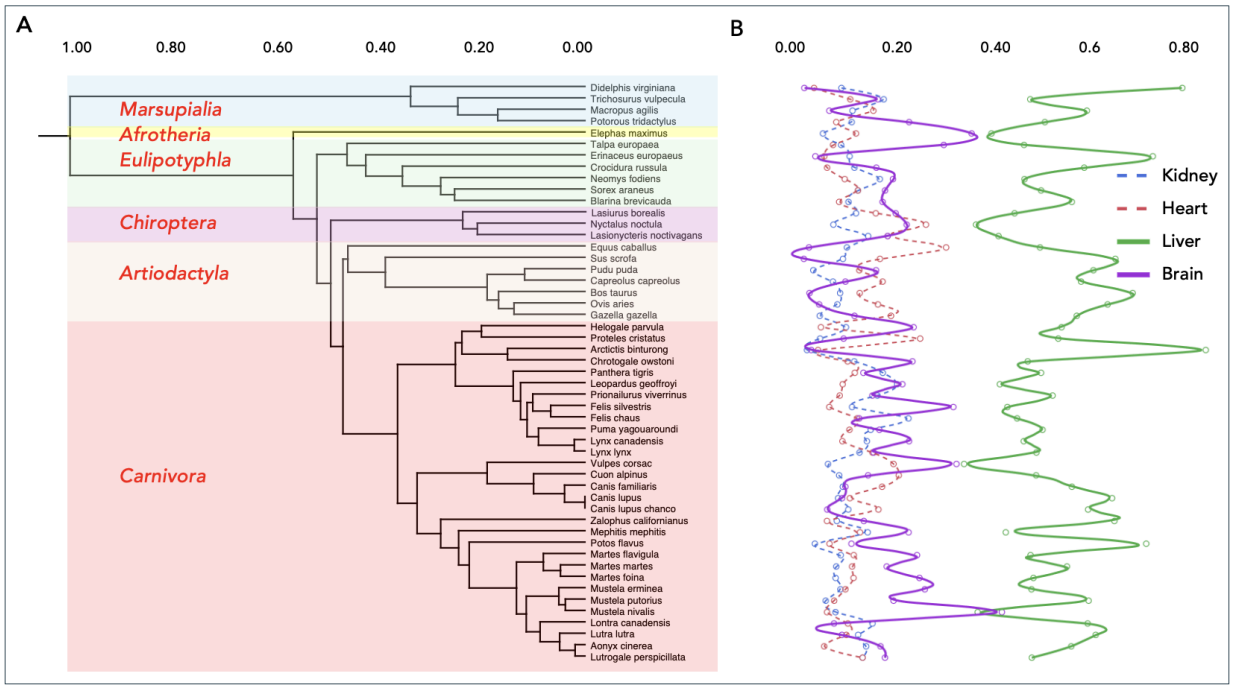


Figure S2. Core organ proportions in Metatheria, Afrotheria, and Laurasiatheria.
A. Ultrametric phylogenetic tree[8]. The scale represents the relative time of divergence.
B. Mass proportion of each organ relative to total Core mass. Note the difference in range, compared to Supplementary Figure S1-B.

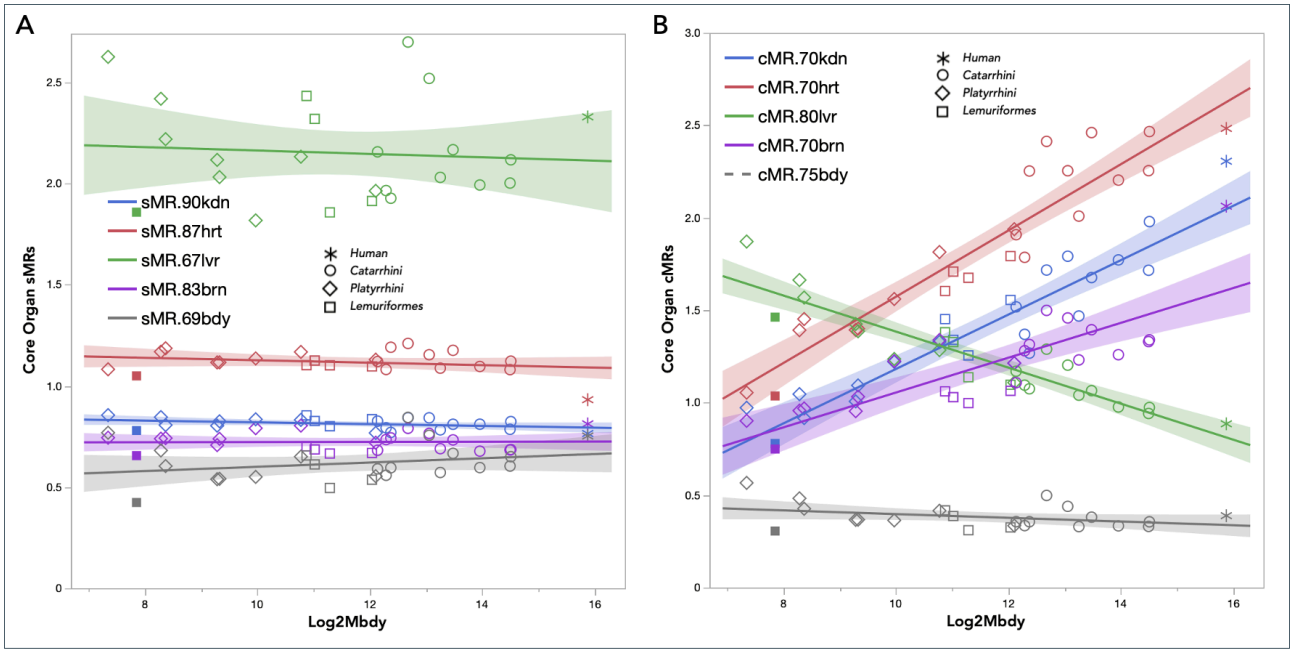


Figure S3. *sMR* slopes are independent of size while *cMR* slopes vary with size.
A. Log-based *sMR* slopes are independent of organ or body size (*N* = 24).
B. *cMR* slopes of Core organs, and whole-body *cMR* scaled to Kleiber's log-based allometric exponent[39].
Filled symbols represent the heterotherm *Cheirogaleus_medius*.
See the description of Figure 3 for details of the estimation of the Core organ *cMR*s.

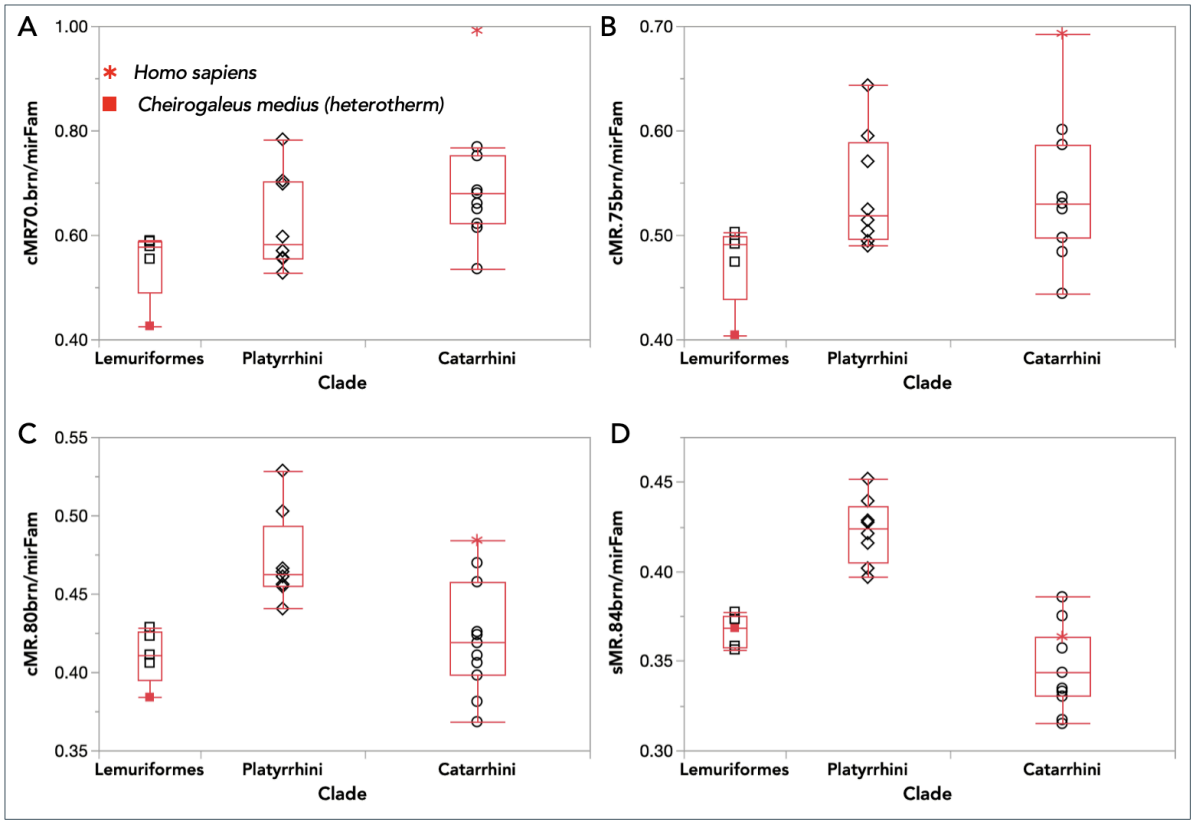


Figure S4. Distributions of the ratios of brain *cMR* or *sMR* to *mirFam* (*N* = 24).
A: ***cMR.70****brn/mirFam*. B: ***cMR.75****brn/mirFam*. C: ***cMR.80****brn/mirFam*. D: ***sMR.84****brn/mirFam*.
The slope of log *rMRbrn*/log *Mbrn* = 0.84, hence $sMRbrn = rMRbrn/M^{0.84}$.
Boxplots represent medians, quartiles, minima and maxima.

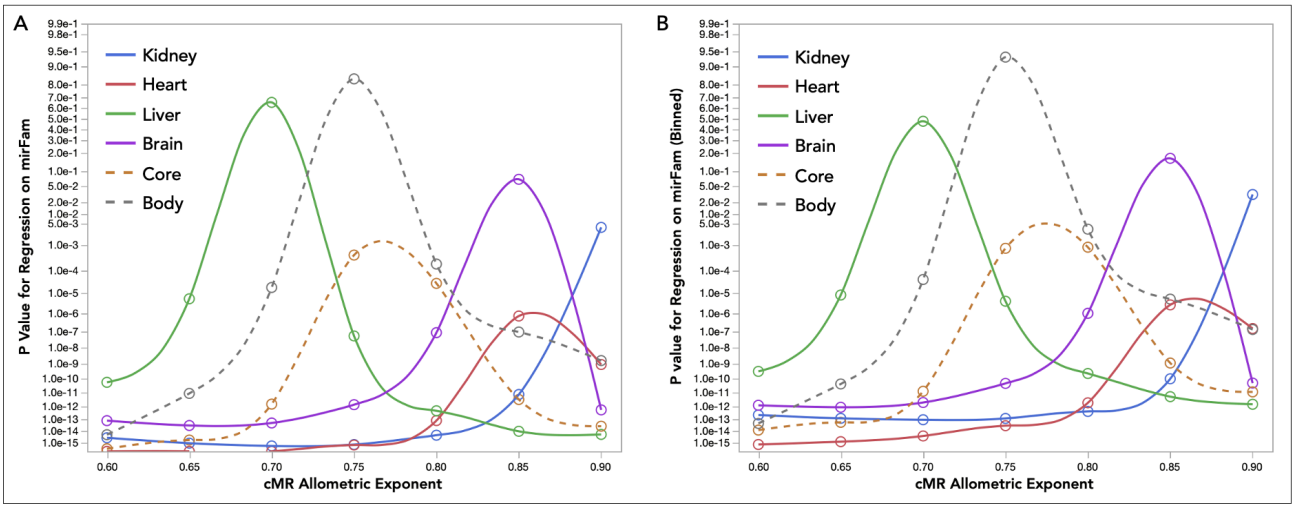


Figure S5. Dependence of *cMR* on *mirFam* or binned *mirFam* without mass correction (51 Euarchontoglires).
A. *P* values for the regression of each *cMR* on *mirFam*. Compare with Figure 3.
B. *P* values for the regression of each *cMR* on binned *mirFam*. *mirFam* was binned according to natural divisions in its distribution: 141 - 161 (Scandentia and Glires), 165 - 181 (Glires, Lemuriformes and Platyrrhini), and 194 - 208 (Catarrhini).

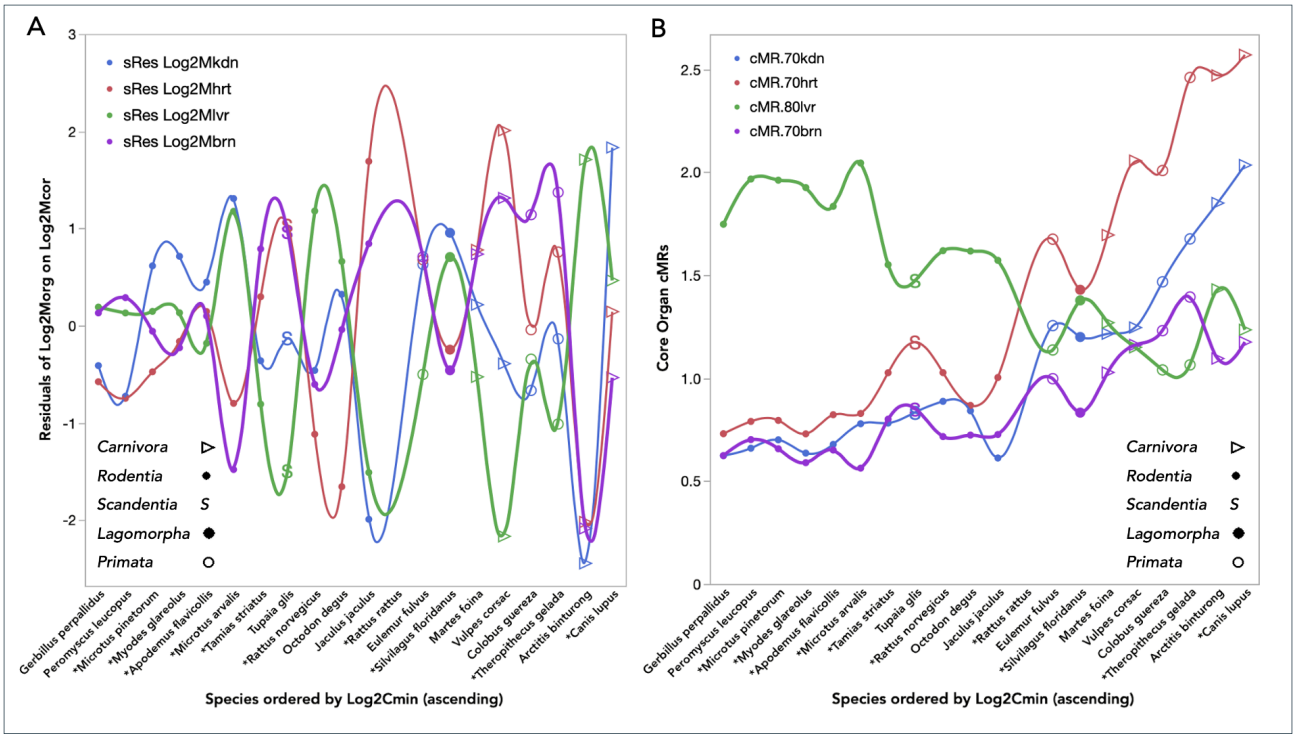


Figure S6. Core organ tradeoffs in Boreoeutheria ordered according to thermal conductance.
A. Reciprocal variation of studentized residuals of each $Log_2$*Morg* regressed on $Log_2$*Mcor.*
B. The tradeoff between *cMR.70brn* and *cMR.80lvr* is apparent except among the species with the lowest values of $C_{min}$. *Asterisks represent species in the 4-organ dataset of Wang et al (2012)[1] that have been substituted for congeneric species in the $C_{min}$ dataset of Fristoe et al (2015)[4].

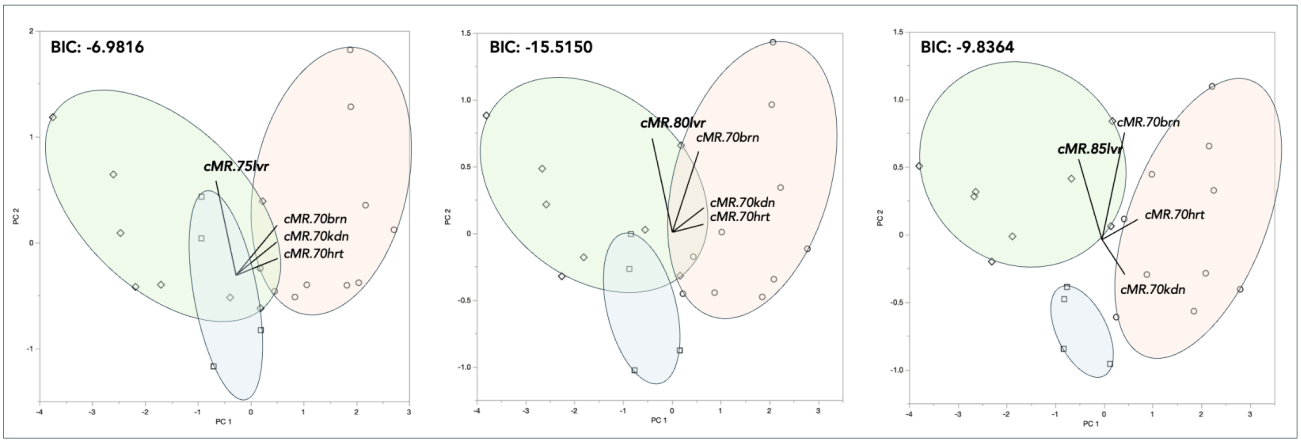


Figure S7. Unsupervised classification of primate clades based on Core *cMR* composition.
Of the four *cMR* models with *VIP* = 4 (Figure 6-B), only two (with *cMR.80lvr* and *cMR.85lvr*) resolved Platyrrhini from Lemuriformes. Principal components were calculated from each *cMR* correlation matrix, and membership in two clusters estimated by expectation maximization of their joint probability distributions (normal mixtures algorithm)[43]. BIC: Bayes Information Criterion.
Liver *cMR* was varied between *cMR.75lvr* - *cMR.85lvr* (***bold type***); kidney, heart and brain *cMR* = *cMR.70*. Ellipses were hand-drawn to encompass all members of each phylogenetic clade.

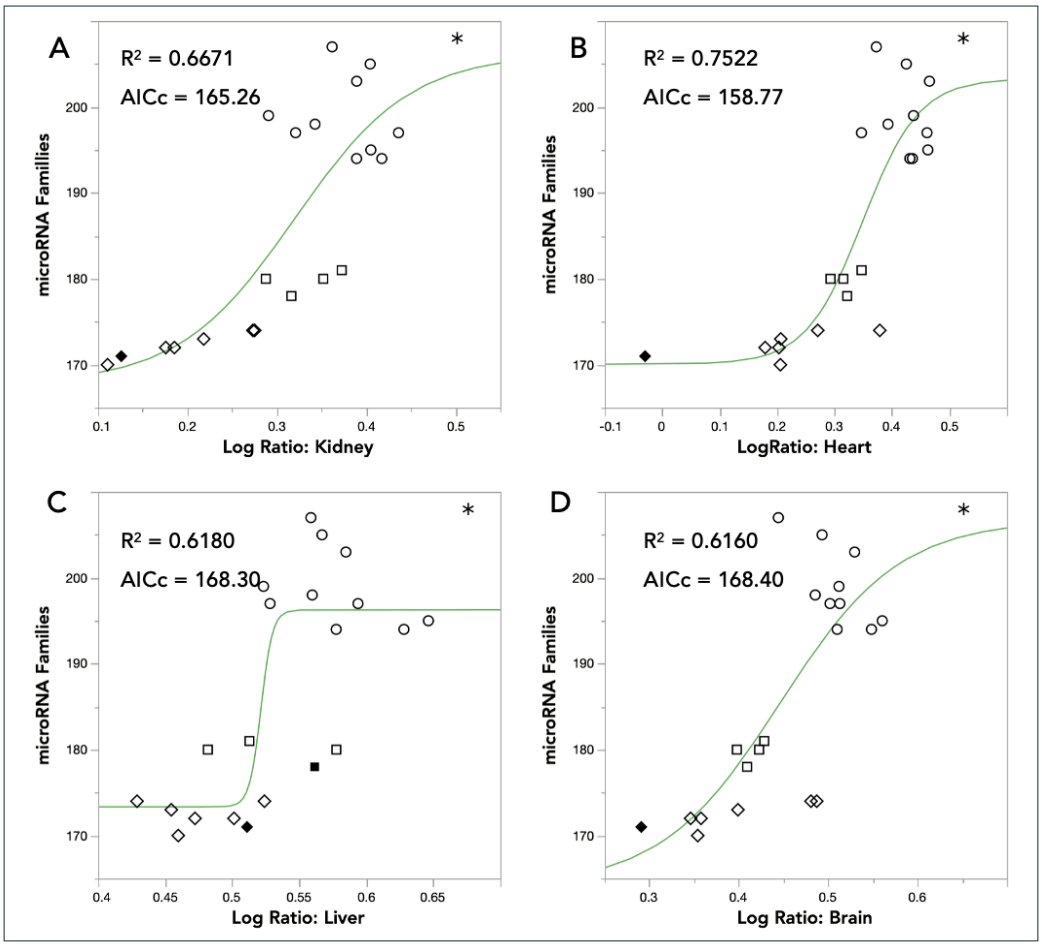


Figure S8. Logistic models for evolution of the relative size of the four thermogenic organs.
Symbols representing clades as in previous figures, with filled symbols representing heterotherms.

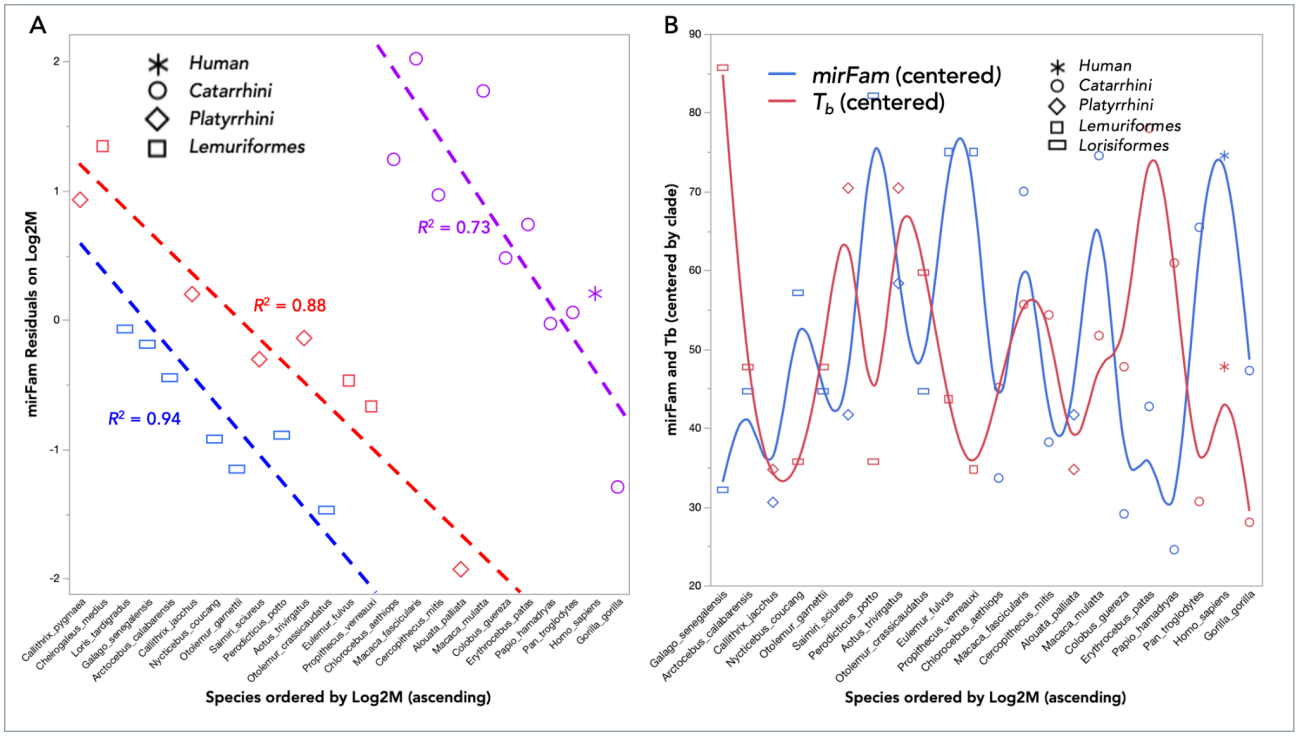


Figure S9. Conservation of *mirFam* and *mirFam* • $T_b$ (range-standardized by clade).
A. The *mirFam*-$\log_2 M$ relationship is least conserved among Catarrhini (purple).
B. Visualization of the reciprocal variation of *mirFam* and $T_b$. In order to control for phylogeny, the data were range-standardized and centered for Catarrhini, Lorisiformes, and Platyrrhini+Lemuriformes.

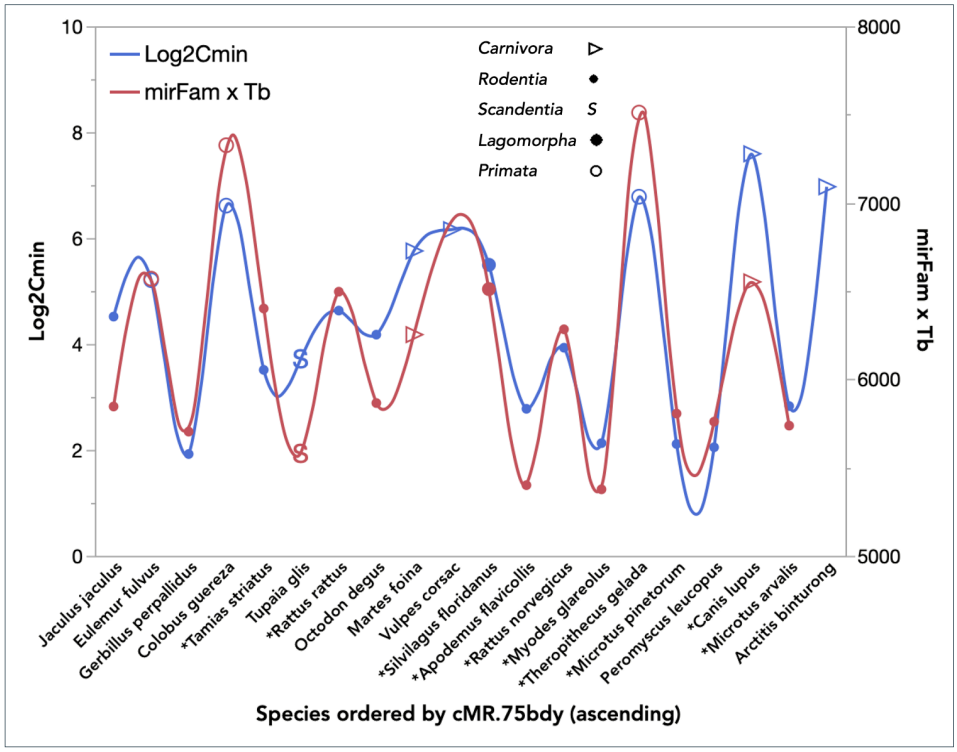


Figure S10. *mirFam* • $T_b$ tracks thermal conductance across Boreoeutheria.
*Asterisks represent species in the 4-organ dataset of Wang et al (2012)[1] that have been substituted for congeneric species in the $C_{min}$ dataset of Fristoe et al (2015)[4].
Note that *mirFam* • $T_b$ values are missing for two species.

Table S1. Summary of data for Euarchontoglires: *mirFam*, mass and resting *MR*s.
All physiological data were obtained from Wang et al (2012)[1], most of which had been compiled by Navarette et al (2011)[2]. The names of the indicated taxa were substituted with congeneric species on the phylogenies of Álvarez-Carretero et al (2022)[8] and Shao et al (2023)[9].

| Clade | Wang Taxon Names | Names on Phylogeny | *mirFam* | *Mkdn* (g) | *Mhrt* (g) | *Mlvr* (g) | *Mbrn* (g) | *Mcor* (g) | *Mbdy* (g) | *MRkdn* (W) | *MRhrt* (W) | *MRlvr* (W) | *MRbrn* (W) | *MRcor* (W) | *MRbdy* (W) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Primates | *Alouatta sara* | *Alouatta palliata* | 174 | 9.9 | 24 | 81.2 | 56.5 | 171.6 | 4399.6 | 13.7088 | 13.6112 | 33.6452 | 12.9948 | 73.96 | 169.5872 |
| Primates | | *Callithrix jacchus* | 172 | 2.9 | 2.8 | 17.8 | 7.3 | 30.8 | 311.8 | 6.039 | 17.928 | 37.352 | 20.453 | 81.772 | 180.7072 |
| Primates | *Cebualla pygmaea* | *Callithrix pygmaea* | 171 | 1.9 | 0.86 | 13.5 | 4.4 | 20.66 | 162.66 | 6.8432 | 11.1622 | 29.0377 | 20.9296 | 67.9727 | 112.3625 |
| Primates | | *Cheirogaleus medius* | 176 | 1 | 0.93 | 6.3 | 2.8 | 11.03 | 231.03 | 1.5238 | 0.94858 | 15.012 | 2.5432 | 20.02758 | 25.77858 |
| Primates | | *Chlorocebus pygerythrus* | 199 | 12.1 | 42.6 | 89 | 80.8 | 224.5 | 5300.5 | 2.204 | 2.8616 | 16.643 | 3.8471 | 25.5557 | 35.7841 |
| Primates | | *Colobus guereza* | 198 | 23.3 | 37 | 171 | 86.5 | 317.8 | 9749.8 | 2.9356 | 3.5644 | 14.553 | 6.2832 | 27.3362 | 46.7808 |
| Primates | | *Eulemur fulvus* | 180 | 9.5 | 11.8 | 43.4 | 22.5 | 87.2 | 2500.2 | 1.4364 | 3.3495 | 13.248 | 4.0794 | 22.1133 | 33.0213 |
| Primates | | *Eulemur macaco* | 180 | 14.2 | 9.1 | 77.8 | 24.2 | 125.3 | 1875.3 | 2.2227 | 3.4817 | 16.2184 | 4.78 | 26.7028 | 45.6892 |
| Primates | Human | *Homo sapiens* | 208 | 250 | 320 | 1700 | 1300 | 3570 | 59970 | 9.2862 | 14.1312 | 40.05 | 25.56 | 89.0274 | 199.0161 |
| Primates | *Hylobates concolor* | *Hylobates pileatus* | 195 | 35.2 | 58.2 | 293 | 137.8 | 524.2 | 6550.2 | 13.3043 | 25.16 | 63.612 | 27.9395 | 130.0158 | 323.3718 |
| Primates | | *Lemur catta* | 178 | 11.2 | 11.7 | 72.9 | 22.8 | 118.6 | 2074.6 | 12.789 | 17.135 | 50.27 | 15.162 | 95.356 | 195.6392 |
| Primates | | *Leontopithecus chrysomelas* | 173 | 4.1 | 3.8 | 18.9 | 13.2 | 40 | 642 | 27.4 | 39.162 | 78.566 | 35.518 | 180.646 | 471.706 |
| Primates | *Macaca nigra* | *Macaca arctoides* | 205 | 50 | 61 | 241 | 118 | 470 | 15870 | 42.6393 | 63.242 | 115.64 | 49.59 | 271.1113 | 669.3613 |
| Primates | Monkey | *Macaca fascicularis* | 207 | 21 | 23 | 110 | 42 | 196 | 4500 | 21.394 | 51.5696 | 84.252 | 44.5244 | 201.74 | 419.94 |
| Primates | | *Mandrillus sphinx* | 194 | 49.9 | 76 | 331 | 168 | 624.9 | 23024.9 | 0.8932 | 1.31274 | 3.9304 | 2.006 | 8.14234 | 13.62034 |
| Primates | | *Papio hamadryas* | 197 | 80.3 | 103 | 392 | 174 | 749.3 | 23249.3 | 2.229 | 2.4725 | 9.2769 | 3.8025 | 17.7809 | 31.2792 |
| Primates | *Saguinus lagonotus* | *Saguinus midas* | 170 | 1.9 | 3.3 | 14.4 | 7.8 | 27.4 | 330.4 | 0.2841 | 0.2094 | 2.2764 | 0.56832 | 3.33822 | 4.47022 |
| Primates | | *Saguinus oedipus* | 172 | 3.1 | 3.7 | 20.9 | 10 | 37.7 | 623.7 | 0.23424 | 0.1456 | 1.39829 | 0.2828 | 2.06093 | 2.90093 |
| Primates | | *Saimiri boliviensis* | 174 | 6.7 | 6.5 | 19.4 | 29 | 61.6 | 1002.6 | 0.609 | 0.34636 | 3.7466 | 0.7304 | 5.43236 | 8.15126 |
| Primates | | *Sapajus apella* | 171 | 10.4 | 13.4 | 49.3 | 50.8 | 123.9 | 1749.9 | 0.5126 | 0.25916 | 3.4181 | 0.29133 | 4.48119 | 5.79399 |
| Primates | | *Symphalangus syndactylus* | 194 | 43.7 | 51.5 | 294 | 143 | 532.2 | 8500.2 | 1.179 | 0.93177 | 9.5588 | 1.2834 | 12.95297 | 20.57737 |
| Primates | | *Theropithecus gelada* | 203 | 38 | 77.2 | 236 | 140.9 | 492.1 | 11402.1 | 0.27412 | 0.10241 | 1.43344 | 0.29232 | 2.10229 | 2.94789 |
| Primates | | *Trachypithecus vetulus* | 197 | 15.4 | 19.2 | 90 | 72 | 196.6 | 4999.6 | 0.47379 | 0.21728 | 3.2058 | 0.3715 | 4.26837 | 5.62837 |
| Primates | | *Varecia rubra* | 181 | 22.4 | 18.1 | 72.2 | 35.7 | 148.4 | 4200.4 | 0.25038 | 0.19992 | 2.1967 | 0.44973 | 3.09673 | 4.03113 |
| Scandentia | | *Tupaia glis* | 151 | 1.1 | 1.17 | 3.4 | 3.4 | 9.07 | 141.07 | 0.31892 | 0.24768 | 1.835 | 0.46055 | 2.86215 | 4.13635 |
| Glires | | *Acomys minous* | 157 | 0.32 | 0.18 | 0.9 | 0.9 | 2.3 | 42.3 | 0.779 | 0.98487 | 6.3756 | 1.54 | 9.67947 | 18.10547 |
| Glires | | *Apodemus flavicollis* | 141 | 0.34 | 0.18 | 1 | 0.61 | 2.13 | 25.13 | 7.2688 | 9.5589 | 41.0427 | 9.1884 | 67.0588 | 118.8928 |
| Glires | | *Apodemus sylvaticus* | 155 | 0.26 | 0.14 | 1.1 | 0.57 | 2.07 | 18.07 | 6.0705 | 9.4282 | 23.219 | 8.82 | 47.5377 | 109.5518 |
| Glires | | *Arvicola sapidus* | 149 | 0.7 | 0.28 | 2.6 | 1.1 | 4.68 | 61.68 | 9.301 | 7.5257 | 44.9684 | 9.8736 | 71.6687 | 118.9187 |
| Glires | Guinea Pig | *Cavia porcellus* | 174 | 5.6 | 2.3 | 27 | 4.7 | 39.6 | 799.6 | 4.623 | 5.785 | 13.2502 | 12.934 | 36.5922 | 64.7281 |
| Glires | | *Gerbillus perpallidus* | 147 | 0.27 | 0.13 | 1 | 0.58 | 1.98 | 29.98 | 110 | 140.8 | 340 | 312 | 902.8 | 1489.36 |
| Glires | | *Glaucomys volans* | 176 | 0.59 | 0.56 | 2.9 | 1.9 | 5.95 | 54.95 | 20.768 | 41.4966 | 121.302 | 47.1276 | 230.6942 | 362.6636 |
| Glires | | *Glis glis* | 168 | 0.68 | 0.48 | 3.2 | 1.5 | 5.86 | 83.86 | 25.2149 | 35.5865 | 113.484 | 47.047 | 221.3324 | 388.6604 |
| Glires | | *Jaculus jaculus* | 158 | 0.29 | 0.45 | 1.1 | 1.2 | 3.04 | 48.04 | 7.26 | 31.1406 | 38.982 | 28.4416 | 105.8242 | 221.0494 |
| Glires | | *Lepus europaeus* | 173 | 18.5 | 28.9 | 90.4 | 14.8 | 152.6 | 3338.6 | 26.4969 | 46.74 | 97.645 | 48.048 | 218.9299 | 617.6499 |
| Glires | | *Microtus agrestis* | 148 | 0.17 | 0.12 | 0.63 | 0.39 | 1.31 | 15.31 | 11.544 | 22.3108 | 44.748 | 5.5648 | 84.1676 | 162.2246 |
| Glires | | *Microtus arvalis* | 153 | 0.55 | 0.19 | 1.9 | 0.39 | 3.03 | 27.03 | 4.3533 | 4.2864 | 22.048 | 3.5392 | 34.2269 | 61.949 |
| Glires | | *Microtus pinetorum* | 154 | 0.36 | 0.15 | 1.1 | 0.58 | 2.19 | 21.19 | 0.57664 | 0.57312 | 4.256 | 0.954 | 6.35976 | 9.89316 |
| Glires | | *Mus musculus* | 167 | 0.28 | 0.07 | 0.68 | 0.36 | 1.39 | 15.39 | 0.67473 | 0.76758 | 3.6366 | 1.4784 | 6.55731 | 10.79621 |
| Glires | Mouse | *Mus musculus domesticus* | 167 | 0.51 | 0.16 | 1.8 | 0.5 | 2.97 | 27.97 | 0.51802 | 0.70224 | 4.3094 | 1.2825 | 6.81216 | 9.19356 |
| Glires | | *Myodes glareolus* | 143 | 0.24 | 0.1 | 0.67 | 0.35 | 1.36 | 15.36 | 1.3056 | 1.7629 | 5.3185 | 3.3831 | 11.7701 | 21.4049 |
| Glires | | *Octodon degus* | 156 | 1.1 | 0.41 | 4.8 | 1.9 | 8.21 | 129.21 | 2.304 | 2.6488 | 12.8904 | 3.6075 | 21.4507 | 39.9589 |
| Glires | | *Peromyscus leucopus* | 160 | 0.3 | 0.15 | 1.2 | 0.74 | 2.39 | 22.39 | 0.8998 | 0.46494 | 5.6736 | 1.1343 | 8.17264 | 13.26674 |
| Glires | | *Rattus norvegicus* | 168 | 1.5 | 0.87 | 9.2 | 2.3 | 13.87 | 209.87 | 3.9368 | 2.1022 | 19.602 | 2.1667 | 27.8077 | 51.4437 |
| Glires | Rat | *Rattus rattus* | 167 | 2.8 | 1.1 | 14.3 | 1.9 | 20.1 | 390.1 | 0.25752 | 0.57375 | 1.6973 | 0.8256 | 3.35417 | 5.59067 |
| Glires | | *Rhabdomys pumilio* | 161 | 0.41 | 0.21 | 1.8 | 0.6 | 3.02 | 50.02 | 0.28704 | 0.23274 | 1.4337 | 0.63 | 2.58348 | 4.61148 |
| Glires | | *Sciurus carolinensis* | 175 | 3.2 | 2.8 | 16.4 | 7.5 | 29.9 | 595.9 | 0.34272 | 0.21075 | 2.1175 | 0.44892 | 3.11989 | 4.20479 |
| Glires | | *Sciurus niger* | 165 | 3 | 2.5 | 10.7 | 7.5 | 23.7 | 412.7 | 0.16592 | 0.17472 | 1.31481 | 0.31512 | 1.97057 | 2.81057 |
| Glires | | *Sciurus vulgaris* | 175 | 1.7 | 1.7 | 5.5 | 6.3 | 15.2 | 274.2 | 0.24948 | 0.17511 | 1.748 | 0.4263 | 2.59889 | 4.10249 |
| Glires | | *Sylvilagus floridanus* | 170 | 6.3 | 4.8 | 32 | 7.9 | 51 | 972 | 2.0888 | 1.0945 | 12.584 | 0.9709 | 16.7382 | 29.7252 |
| Glires | | *Tamias striatus* | 173 | 0.81 | 0.66 | 2.9 | 2.4 | 6.77 | 103.77 | 0.36285 | 0.26607 | 2.7414 | 0.4098 | 3.78012 | 6.09722 |

Table S2. Primate microRNA families, brain volume, body mass and temperature.
Endocranial volume (ECV) and body mass were obtained from Grabowski et al (2023)[3].
Body temperatures were retrieved from the AnAge database (Magalhães et al, 2024)[5].

| Order | Species | *mirFam* | ECV | Mass (g) | $T_b$ (°C) |
|---|---|---|---|---|---|
| Catarrhini | *Homo sapiens* | 208 | 1252.00 | 50000 | 37.0 |
| Catarrhini | *Pan troglodytes* | 206 | 368.35 | 44967 | 35.7 |
| Catarrhini | *Gorilla gorilla* | 202 | 490.41 | 120950 | 35.5 |
| Catarrhini | *Macaca fascicularis* | 207 | 63.98 | 4251 | 37.6 |
| Catarrhini | *Macaca mulatta* | 208 | 88.98 | 6793 | 37.3 |
| Catarrhini | *Papio hamadryas* | 197 | 146.17 | 14150 | 38.0 |
| Catarrhini | *Chlorocebus aethiops* | 199 | 65.00 | 3720 | 36.8 |
| Catarrhini | *Erythrocebus patas* | 201 | 97.73 | 9450 | 39.3 |
| Catarrhini | *Cercopithecus mitis* | 200 | 71.33 | 6109 | 37.5 |
| Catarrhini | *Colobus guereza* | 198 | 74.39 | 8589 | 37.0 |
| Platyrrhini | *Callithrix jacchus* | 172 | 7.24 | 320 | 36.0 |
| Platyrrhini | *Callithrix pygmaea* | 171 | 4.17 | 116 | 35.2 |
| Platyrrhini | *Aotus trivirgatus* | 177 | 16.85 | 989 | 38.0 |
| Platyrrhini | *Saimiri sciureus* | 174 | 24.14 | 799 | 38.0 |
| Platyrrhini | *Alouata palliata* | 174 | 49.88 | 6250 | 36.0 |
| Lemuriformes | *Eulemur fulvus* | 180 | 25.77 | 2292 | 36.5 |
| Lemuriformes | *Cheirogaleus medius* | 176 | 2.60 | 140 | 38.0 |
| Lemuriformes | *Propithecus verreauxi* | 180 | 26.21 | 2955 | 36.0 |
| Lorisiformes | *Otolemur garnettii* | 166 | 11.50 | 764 | 36.0 |
| Lorisiformes | *Otolemur crassicaudatus* | 166 | 11.78 | 1150 | 36.6 |
| Lorisiformes | *Galago senegalensis* | 165 | 3.96 | 194 | 37.9 |
| Lorisiformes | *Loris tardigradus* | 166 | 5.87 | 193 | 35.5 |
| Lorisiformes | *Nycticebus coucang* | 167 | 10.13 | 653 | 35.4 |
| Lorisiformes | *Arctocebus calabarensis* | 166 | 6.92 | 309 | 36.0 |
| Lorisiformes | *Perodicticus potto* | 169 | 12.42 | 835 | 35.4 |

Table S3. Parameters of the thermodynamic Core *cMR* models for clades of Boreoeutheria.
Brain mass, body mass and *rMR* data were obtained from the dataset of Wang et al (2012)[1].
K = Kidney, H = Heart, L = Liver and B = Brain.
For the *median* ratios of Log *Mbrn*/Log *Mbdy*, mass was expressed in mg.
Three outliers were excluded: *Mustela nivalis* (carnivora); *Cheirogaleus medius* and *Homo sapiens* (primata).

| Clade | *N* | Mbdy(g) (median) | med.Mbrn /Mbdy | avg.Mbrn /Mbdy | Std Dvn | Log*Mbrn* /Log*Mbdy* | Core *cMR* Exponent | Core Model $R^2$ | Model Organ Coefficients | | | | Model Organ VIP Values | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | K | H | L | B | K | H | L | B |
| Carnivora | 29 | 5100 | 0.0083 | 0.0098 | 0.0048 | 0.6937 | 0.60 | 96.6015 | 0.496 | 0.672 | 0.297 | 0.060 | 1.060 | 1.158 | 0.866 | 0.887 |
| Primates | 22 | 4300 | 0.0136 | 0.0156 | 0.0072 | 0.7080 | 0.53 | 98.0708 | 0.531 | 0.689 | 0.367 | 0.088 | 1.076 | 1.057 | 0.894 | 0.961 |
| Catarrhini | 10 | 9125 | 0.0108 | 0.0120 | 0.0047 | 0.7182 | 0.60 | 99.3394 | 0.4965 | 0.4058 | 0.2703 | 0.2192 | 1.1111 | 1.1756 | 0.407 | 1.1035 |
| Platyrrhini | 8 | 632.85 | 0.0235 | 0.0227 | 0.0059 | 0.7074 | 0.40 | 90.7004 | 0.7111 | 1.1248 | 0.4986 | -0.396 | 0.9414 | 1.1213 | 0.9606 | 0.9663 |
| Glires | 26 | 52 | 0.0188 | 0.0190 | 0.0084 | 0.6387 | 0.40 | 99.0760 | 0.638 | 0.489 | 0.030 | -0.130 | 1.179 | 1.089 | 0.873 | 0.813 |

Table S4. Phylogenetic regressions[14] of primate organ *cMR*s on *mirFam* (*N* = 22).
The dataset excluded two outliers (the human and the heterotherm *Cheriogaleus medius*).
For reference, see the logistic regressions of *mirFam* on relative organ size (Supplementary Figure S8).

| | Allometric Exponent | Pagel's *lambda* | $R^2$ | *P* | *AICc* |
|---|---|---|---|---|---|
| KIDNEY | 0.80 | 0 | 0.5366 | 6.39E-05 | -42.7 |
| | 0.75 | 0 | 0.5834 | 2.14E-05 | -20.09 |
| | 0.70 | 0 | 0.5958 | 1.56E-05 | -0.93 |
| | 0.65 | 0 | 0.5946 | 1.61E-05 | 16.22 |
| | 0.60 | 0 | 0.5859 | 2.00E-05 | 32.13 |
| | | Pagel's *lambda* | $R^2$ | *P* | *AICc* |
| HEART | 0.80 | 0 | 0.4937 | 1.60E-04 | -38.02 |
| | 0.75 | 0 | 0.6476 | 3.83E-06 | -17.88 |
| | 0.70 | 0 | 0.6962 | 8.44E-07 | 0.63 |
| | 0.65 | 0 | 0.7133 | 4.69E-07 | 17.65 |
| | 0.60 | 0 | 0.7163 | 4.21E-07 | 33.66 |
| | | Pagel's *lambda* | $R^2$ | *P* | *AICc* |
| LIVER | 0.80 | 0 | 0.5724 | 2.79E-05 | -15.22 |
| | 0.75 | 0 | 0.4011 | 9.28E-04 | -10.98 |
| | 0.70 | 0 | 0.0854 | 1.01E-01 | -2.86 |
| | 0.65 | 0 | -0.0344 | 5.89E-01 | 10.24 |
| | 0.60 | 0.962 | 0.0145 | 2.66E-01 | 27.34 |
| | | Pagel's *lambda* | $R^2$ | *P* | *AICc* |
| BRAIN | 0.80 | 1 | 0.0329 | 2.05E-01 | -63.9 |
| | 0.75 | 1 | 0.107 | 7.55E-02 | -35.75 |
| | 0.70 | 1 | 0.1336 | 5.07E-02 | -10.58 |
| | 0.65 | 1 | 0.151 | 4.17E-02 | 11.76 |
| | 0.60 | 1 | 0.1596 | 3.71E-02 | 32.24 |