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The lemur revolution starts now: The genomic coming of age for a non-model organism

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ABSTRACT

Morris Goodman was a revolutionary. Together with a mere handful of like-minded scientists, Morris established himself as a leader in the molecular phylogenetic revolution of the 1960s. The effects of this revolution are most evident in this journal, which he founded in 1992. Happily for lemur biologists, one of Morris Goodman's primary interests was in reconstructing the phylogeny of the primates, including the tooth-combed Lorisifomes of Africa and Asia, and the Lemuriformes of Madagascar (collectively referred to as the suborder Strepsirrhini). This paper traces the development of molecular phylogenetic and evolutionary genetic trends and methods over the 50-year expanse of Morris Goodman's career, particularly as they apply to our understanding of lemuriform phylogeny, biogeography, and biology. Notably, this perspective reveals that the lemuriform genome is sufficiently rich in phylogenetic signal such that the very earliest molecular phylogenetic studies – many of which were conducted by Goodman himself – have been validated by contemporary studies that have exploited advanced computational methods applied to phylogenomic scale data; studies that were beyond imagining in the earliest days of phylogeny reconstruction. Nonetheless, the frontier still beckons. New technologies for gathering and analyzing genomic data will allow investigators to build upon what can now be considered a nearly-known phylogeny of the Lemuriformes in order to ask innovative questions about the evolutionary mechanisms that generate and maintain the extraordinary breadth and depth of biological diversity within this remarkable clade of primates.

Where you work and where you play
Where you lay your money down
What you do and what you say
The revolution starts now
STEVE EARLE – THE REVOLUTION STARTS NOW LYRICS

1. Introduction

Phylogeneticists of all stripes glory in the fact that Darwin chose to illustrate a phylogeny as the sole figure in *The Origin of Species*. It is also well established that Darwin ended his days without ever knowing what is the biological mechanism of heritable variability (though see a very thoughtful essay by Charlesworth and Charlesworth, 2009 on what Darwin did and did not surmise about heritability). Copious books, essays, and empirical accounts have been written on the first meeting of Mendelian genetics and macroevolutionary thought, yielding the great evolutionary synthesis of the 1930s and 1940s. It was then, finally, that Darwinian perspectives on phylogeny began to take an indelible hold on biological thought. From that moment onwards, it has been the unrelenting goal of phylogeneticists to assemble this grand Tree of Life.

Beginning in the 1950s with protein electrophoresis, molecular biologists started to tinker with the idea that measures of genetic distance among and between organisms could be interpreted as a proxy for their evolutionary relatedness. The obvious thought was that organisms that share the most recent ancestry will show the greatest similarity of genetic material. Pioneering work by Walter Fitch, Emile Zuckerkandl, and Linus Pauling laid the groundwork for the molecular phylogenetic revolution, led principally by Allan Wilson, and by Morris Goodman, to whom this special volume is dedicated. Although the first decade or so of this revolution relied upon indirect measures of genetic distance such as DNA–DNA hybridization, numerous breakthroughs in our understanding of evolutionary relationships were achieved, such as the (very controversial, at the time) finding that chimpanzees are more closely related to humans than to gorillas (Sibley and Ahlquist, 1984). Several authors took exception to these results in particular, both in terms of the obvious incongruence with the morphological details shared by chimpanzees and gorillas (reviewed in Holmquist et al., 1988), but also due to various subtleties of statistical analysis (Farris, 1985; Templeton, 1985).

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The dispute was for many settled decisively by Felsenstein (1987) who employed a maximum likelihood mixed model analysis of variance method to show that there was indeed significant support for the human-chimp clade contained within the DNA–DNA hybridization data published by Sibley and Ahlquist, 1984. Felsenstein pursued the matter further by exploring the question of just how many base pairs of DNA sequence data would convey the same degree of statistical power as the vast amount of genetic material being compared by hybridizing the single-copy regions of whole genomes. His answer was very precise: 4472 base pairs of DNA sequence data would convey equivalent power. This result would have come as no surprise to Morris Goodman and the other molecular phylogenetic revolutionaries who had long been utilizing amino acid sequence data for resolving questions of evolutionary relatedness (Goodman et al., 1972, 1974; Matsuda et al., 1973; Moore et al., 1973).

The molecular phylogenetics field moved rapidly and nearly uniformly to the analysis of DNA sequence data coincident with the PCR revolution launched by Kary Mullis (Mullis et al., 1986), and for many years, the field has been driven nearly exclusively by PCR and Sanger sequencing based methods. Studies have evolved from sampling strategies in which only a few taxa were sequenced for only one organellar or nuclear locus, to combined analysis of representative loci from both genomes, to whole mitochondria (i.e., mitogenomics) to large-scale samples of nuclear loci (i.e., phylogenomics). Founded by Morris Goodman in 1992, the journal *Molecular Phylogenetics and Evolution* was created specifically to "disseminate the results of these molecular studies" (Goodman, 1992). This dream has been more than fulfilled, and indeed, a backwards glance at the content of the journal can be viewed as a mirror of the developing molecular phylogenetic field (Table 1) which is today undergoing its latest and perhaps greatest revolution. Although in the year of its founding, the field was comprised by phylogenetic information that was "miniscule compared to the huge reservoirs that remain[ed] to be tapped" (Goodman, 1992), the progress of the past few years is truly astounding. Table 1, which is a tabulation of basic information from each year of the journal, clearly illustrates this progress. Whereas studies of 20 years ago tended to rely on parsimony or distance-based analysis of small subsets of genetic data and OTUs (operational taxonomic units), there has been a steadily increasing trend towards more loci, more OTUs, and increasingly sophisticated statistical analysis of the data (Table 2). Most notably, the journal has had to increase the number of published papers by more than a factor of ten to keep up with the outpouring of empirical and methodological studies. Clearly, each technological advance in data generation has been quickly followed by studies with increasing amounts of data, which in turn have necessitated analytical methods and tools of increasing statistical and computational power. We see a version of the Red Queen Hypothesis played out in the pages of *Molecular Phylogenetics* and *Evolution*.

With the advent of "next generation" sequencing methods first introduced in 2005 (see Egan et al., 2012 for a detailed history of these technologies), it is now possible to generate millions of bases at a fraction of the cost of traditional Sanger methods. Accordingly, the field is starting to move rapidly in the direction of whole genome sequencing, not only for the purposes of resolving evolutionary relationships, but for any conceivable application of genomic data to fields as disparate as molecular ecology and cancer biology. Happily, Morris Goodman not only lived to see these advances, he was fully immersed in their applications (Goodman and Sterner, 2010; Goodman et al., 2009, 2010; Jameson et al., 2011; Sterner et al., 2010).

2. Phylogeny of the lemurs: Nearly known

Lemurs have been the focus of molecular phylogenetic study from the earliest days of the field's emergence. The suborder Lemuriformes is comprised entirely of primate species endemic

Table 1
MPE publication trends.

Year	Data				# of OTUs			Phylogenetic analysis				Journal statistics		
	organell only (mtDNA or cpDNA)	nDNA only	Organelle & nDNA	Whole mtDNA genomes	Minimum #	Maximum#	Mean #	Parsimony	Distance	Likelihood	Bayesian	# of volumes	# of issues	# of papers
1992	7	3	0	0	5	14	10	7	3	3	0	1	4	31
1993	2	8	0	0	4	47	23	5	8	1	0	1	4	35
1994	6	3	0	0	5	36	15	6	4	0	0	1	4	40
1995	5	3	2	0	7	56	21	8	8	3	0	1	4	43
1996	3	6	0	1	8	34	20	8	5	2	0	2	6	84
1997	6	3	1	0	8	42	25	9	8	1	0	2	6	72
1998	4	5	1	0	10	60	28	9	8	3	0	2	6	101
1999	6	4	0	0	7	49	28	9	8	6	0	3	9	123
2000	4	5	1	0	14	49	31	9	5	6	0	4	12	167
2001	7	0	3	0	14	67	37	10	6	10	0	4	12	166
2002	7	2	1	0	12	78	39	10	3	4	0	4	12	162
2003	8	1	1	0	13	165	45	10	1	7	1	4	12	189
2004	6	4	0	0	20	100	46	9	1	6	6	4	12	332
2005	4	2	3	1	21	142	66	8	3	8	8	4	12	234
2006	5	1	3	1	13	834	131	8	2	6	8	4	12	276
2007	3	1	5	1	15	76	42	9	1	5	5	4	12	345
2008	3	3	3	1	23	136	70	9	3	4	8	4	12	387
2009	0	2	7	1	22	161	78	7	1	4	8	4	12	297
2010	1	3	6	0	42	102	69	5	1	3	9	4	12	431
2011	0	1	8	1	18	282	88	6	1	7	8	4	12	248
2012	1	3	6	0	8	241	98	5	2	8	8	TBD	TBD	TBD

Represents sample of first 10 empirical studies (regardless of organismal focus) from each journal year. Data type, # of OTUs and phylogenetic methods were tabulated from empirical studies only (i.e., simulation or method development studies were not considered); symposium proceedings were also not considered in tabulation of these statistics due to potential bias; the majority of empirical studies used multiple optimality criteria, and thus do not sum to 10; # of papers does not include editorial remarks, book reviews or eratta. The author does not claim precise accuracy of the data, but stands by the observable trends described in the body of the paper.

Table 2
Phylogenetic software employed in studies referenced in Table 1.

Year	Phylogenetic software
1992	PAUP (4); HENNING86 (1); PHYLIP (4); other (1)
1993	PAUP (5); PHYLIP (3); MUST (1); MEGA (1); GCG (2); other (1)
1994	PAUP (6); PHYLIP (4); MUST (1); HENNING86 (1)
1995	PAUP (7); HENNING86 (1); PHYLIP (7); MEGA (2)
1996	PAUP (6); PHYLIP (4);MEGA (3)
1997	PAUP (5); PHYLIP (3); MEGA (5); MUST (1)
1998	PAUP (8); PAUP* (2); PHYLIP (3); MEGA (2); TREECON (1)
1999	PAUP (6); PAUP* (3); PHYLIP (5); PUZZLE (1); MOLPHY (1); MEGA (2); fastDNAML (1)
2000	PAUP (4); PAUP* (5); PHYLIP (2); MUST (1); PUZZLE (1)
2001	PAUP (3); PAUP* (7); PHYLIP (2); MEGA (1); PUZZLE (3)
2002	PAUP (1); PAUP* (7); PHYLIP (1); MEGA (1); HENNING86 (1); PUZZLE (1)
2003	PAUP (1); PAUP* (9); MrBayes (1); PHYLIP (1); PUZZLE (1)
2004	PAUP* (9); MrBayes (6); MEGA (1)
2005	PAUP* (9); MrBayes (8); PHYLIP (2); MEGA (1)
2006	PAUP* (8); MrBayes (8); PHYML (1); MEGA (1); POY (1)
2007	PAUP* (10); MrBayes (5)
2008	PAUP* (8); MrBayes (8); GARLI (1); NONA (1); Other (1)
2009	PAUP* (7);MrBayes (9); GARLI (1); PHYML (2); TNT (1)
2010	PAUP* (6); MrBayes (9); GARLI (3)
2011	PAUP* (5); MrBayes (8); RAxML (4); MEGA (2); TreeFinder (1)
2012	PAUP* (4); MrBayes (8); RAxML (5); PHYML (1); GARLI (2); MEGA (1); TNT (1)

Software employed for the purpose of phylogeny estimation is represented; software employed for other purposes such as sequence alignment, suitability for concatenation; molecular evolutionary statistics (such as tests for positive selection), model testing or divergence time estimation is not referenced; "other" indicates software designed by the authors and singularly employed in their studies. Numbers in parentheses indicate the number of papers in which the programs were employed. Given that the majority of studies employ multiple programs and optimality criteria, the numbers per year do not sum to ten.

to the island of Madagascar. Given that Madagascar has been separated from the rest of the world and surrounded by a formidable ocean barrier for at least the past 88 million years (Agrawal et al., 1992; De Wit, 2003; Rabinowitz et al., 1983), and that the oldest plausible age estimates of the primate clade are considerably younger (e.g., Dos Reis et al., 2012), how lemurs came to occupy their island home has been a continuing puzzle. Although their unique fidelity to Madagascar has long served to create the sense that they must be a unique evolutionary lineage, this intuition has been frequently challenged. Indeed, in the early to mid-1980s, nearly all primate classifications (Fleagle, 1988; Schwartz, 1986; Szalay and Delson, 1979) placed one of the lemuriform groups, the dwarf and mouse lemurs (family, Cheirogaleidae), into the Lorisiformes due to their shared and otherwise unique condition of the cranial blood supply (Cartmill, 1975; Szalay and Katz, 1973). Similarly, the bizarre morphological specializations of the aye–aye (genus, *Daubentonia*) have inspired widespread speculation about its placement in streprirrhine primate phylogeny (Groves, 1989; Oxnard, 1981; Pocock, 1918). In both cases, that of the dwarf lemurs and of the aye–aye, a paraphyletic Lemuriformes would necessitate at least two crossings of the Mozambique Channel (Yoder, 1996; Yoder et al., 1996a).

2.1. The early years (1900–1990)

A surprising amount was known about lemur diversity and evolutionary relations as early as the first part of the 20th Century (e.g., Beddard, 1908; Gregory, 1915; Major, 1896; Pocock, 1916, 1918; Smith, 1907; Standing, 1907, 1908). Focus on areas of lemur biology such as behavior and ecology became prominent in the 1960s and 1970s with the vanguard of specialists such as Alison Jolly, Jean Jaques Petter, Alison Richard, Robert Sussman and Ian Tattersall leading the charge. A second wave of long-term field studies in Madagascar began in the 1980s led by behavioral ecologists, including Joerg Ganzhorn, Peter Kapeller, and Patricia Wright. All of these remarkable biologists have dedicated years of their lives to the study and protection of lemurs in their native Madagascar. Simultaneously, Yves Rumpler began his pioneering quest to decipher evolutionary relationships from karyotypic patterns while integrative biologists and paleontologists such as Robert Martin, Elwyn Simons and Alan Walker sought to frame the morphological characteristics of lemurs in an evolutionary context.

Molecular phylogenetic analysis of lemurs and lorises enters the picture in the 1970s, producing results that have withstood the test of time (Dene et al., 1980, 1976). Although focused on measures of genetic distance via immunodiffusion analysis, the results of these studies are remarkably congruent with the DNA sequence studies that have come in subsequent years, many of which have employed multiple loci and sophisticated methods of phylogenetic analysis. Early immunodiffusion analysis showed clear support for the monophyly of the lemuriforms, including both the dwarf and mouse lemur clade, as well as the enigmatic aye–aye (Dene et al., 1976, p. 53, Fig. 2). Succeeding years have been rich with detailed molecular phylogenetic investigation of the evolutionary relationships among lemurs, and their close relatives, the lorises. As seen in Fig. 1 (linked to Table 3), these studies have essentially served to confirm the findings of the first forays into molecular phylogenetic analysis of lemurs.

2.2. The PCR revolution

Molecular phylogenetic analysis of lemurs (and virtually all organismal groups) enjoyed a remarkable boost in activity as a consequence of the relative ease in collecting DNA sequence data subsequent to the development of the Polymerase Chain Reaction. Within less than a decade post-PCR, molecular phylogenetic analyses of the lemurs and other primates began to emerge with increasing frequency. The earliest PCR-based studies tended to focus on mitochondrial loci (e.g., Adkins and Honeycutt, 1994; Delpero et al., 1995, 2001; Pastorini, 2000; Pastorini et al., 2000, 2001a,b, 2002, 2003; Stanger-Hall and Cunningham, 1998; Wyner et al., 2000; Yoder, 1994; Yoder and Irwin, 1999; Yoder et al., 1996b), though the Goodman lab was leading the way in investigation of nuclear loci, particularly those associated with the

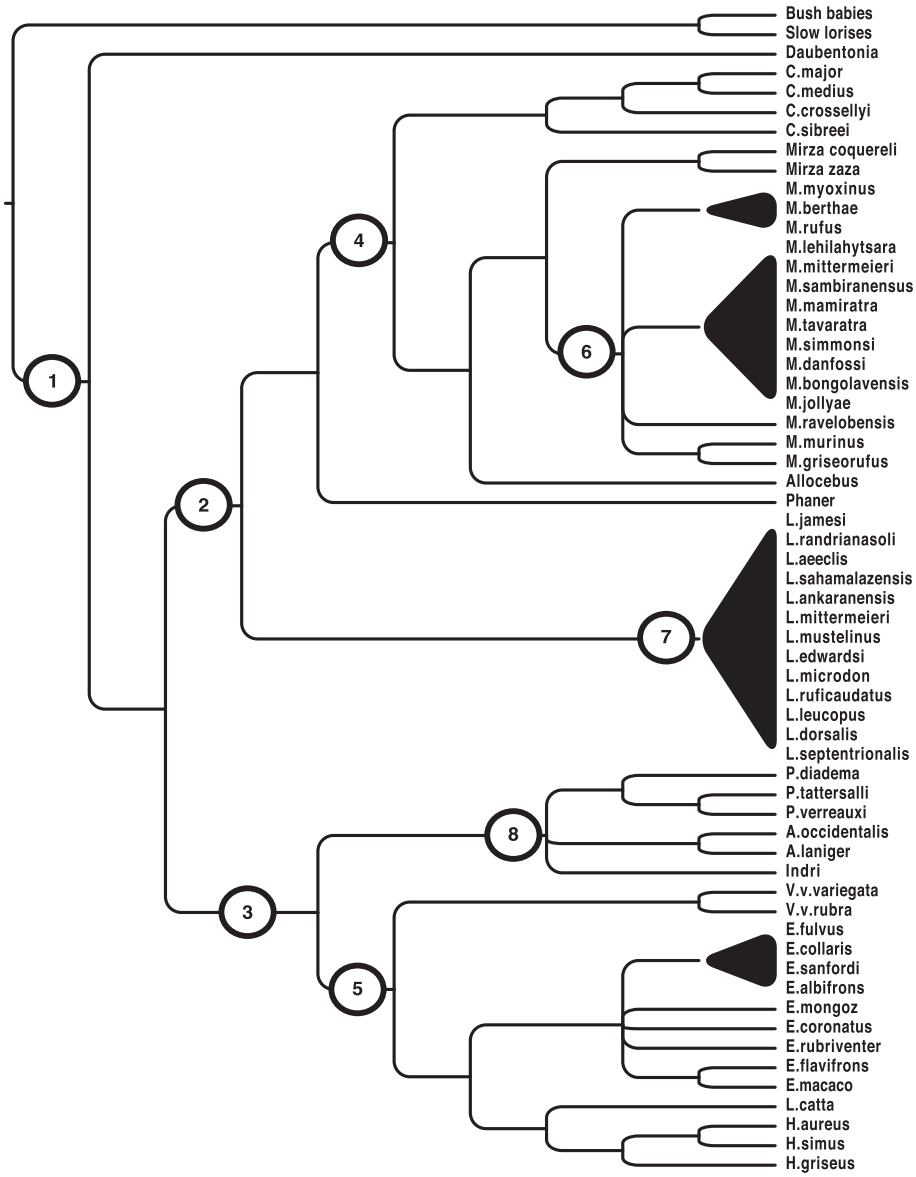

Fig. 1. Composite phylogeny of the Lemuriformes summarizing more than 35 years of molecular phylogenetic research. Numbered nodes on tree refer to references in Table 3. Each referenced study pertains to the clade identified by the node number. Species level taxonomy is not exhaustive. Nomenclature follows Mittermeier et al. (2010) where possible.

hemoglobin complex (Goodman et al., 1994, 1998; Koop et al., 1989b; Porter et al., 1997, 1995; Stanhope et al., 1996). Indeed, the remarkable power of PCR allowed investigators for the first time to examine and compare mitochondrial loci from the extinct subfossil lemurs along with homologous material from living lemurs (Karanth et al., 2005; Orlando et al., 2008; Yoder, 2001; Yoder et al., 1999). Though only tangentially related to the PCR revolution, Rumpler and colleagues have all along been contributing significant results using karyotype data (Rumpler, 2002; Rumpler et al., 2004, 2011, 2008; Warter et al., 2000). Others have tried their hand at genomic character-state data such as SINEs (McLain et al., 2012; Roos et al., 2004; Zietkiewicz et al., 1998) and restriction fragment data (Crovella et al., 1993, 1995; Jung et al., 1992; Montagnon et al., 1993; Razafindraibe et al., 1997), the latter with somewhat mixed results.

2.3. Nuclear DNA and phylogenomics

The most recent trend to emerge in lemur molecular phylogenetics has been the steady increase in investigations that are generating nuclear data for analysis. Though the first few studies tend to focus on single (or only a few) nuclear loci, often in conjunction with mitochondrial markers (Delpero et al., 2006; Goodman et al., 1994; Heckman et al., 2007; Porter et al., 1997; Poux and Douzery, 2004; Rumpler et al., 2011; Yoder and Irwin, 1999), emerging technologies have rapidly transformed the field of molecular phylogenetics into a sampling framework typically referred to as "phylogenomics", with an explicit focus on generating megabases of nuclear DNA rather than kilobases. Lemuriform phylogenetics have reaped the benefits (Horvath et al., 2008; Horvath and Willard, 2007; Jameson et al., 2011; Liu et al., 2009; Matsui et al., 2009; Perelman et al., 2011), and accordingly, we have now reached the position where we can reflect back over the progressive development of molecular phylogentic studies of lemurs, and ask "Are we there yet?". The most honest answer is "nearly". Although the combination of data diversity and congruence has yielded what might be called a nearly-known phylogeny of lemurs, there are two regions of the lemuriform evolutionary tree that remain problematic; one with regard to understanding the number of species in the mouse (genus *Microcebus*) and sportive (genus

Table 3
Molecular phylogenetic studies.

Node 1: Lemuriform Monophyly	Node 2: Lepilemur plus Cheirogaleidae	Node 3: Lemuridae plus Indriidae	Node 4: Cheirogaleidae	Node 5: Lemuridae	Node 6: Microcebus (species diversity)	Node 7: Lepilemur (species diversity)	Node 8: Indriidae
Dene et al. (1976)	DelPero et al. (2006)	DelPero et al. (2001)	Pastorini et al. (2001b)	Crovella et al. (1993)	Yoder et al. (2000)	Rumpler et al. (2001)	Razafindraibe et al. (1997)
Adkins & Honeycutt (1994)	Horvath et al. (2008)	McLain et al. (2012)	Hapke et al. (2005)	Yoder & Irwin, (1999)	Louis et al. (2006)	Ravaoarimanana et al. (2004)	Warter et al. (2000)
Yoder (1994), Yoder et al. (1996a)	Perelman et al. (2011)		Groeneveld et al. (2009), (2010)	Wyner et al. (2000)	Heckman et al. (2007)	Andriaholinirina et al. (2006)	Pastorini et al. (2001a)
Porter et al. (1995), (1997)	McLain et al. (2012)		Weisrock et al. (2012)	Pastorini et al. (2000)	Olivieri et al. (2007)	Craul et al. (2007)	Rumpler et al. (2004), (2011)
Stanger-Hall & Cunningham (1998)				McLain et al. (2012)	Weisrock et al. (2010), (2012)	Rumpler et al. (2008)	
DelPero et al. (2001), (2006)							
Rumpler (2002)							
Pastorini et al. (2003)							
Roos et al. (2004)							
Poux & Douzery (2004)							
Horvath et al. (2008)							
Perelman et al. (2011)							
McLain et al. (2012)							

Molecular phylogenetic studies that bear directly on the node numbering system in Fig. 1. References are representative, though not exhaustive.

Lepilemur) lemurs and their patterns of hierarchical divergence (Weisrock et al., 2012), and the other regarding the hierarchical ordering of the deepest internal nodes of the phylogeny, namely, the interrelationships of the lemurid, cheirogaleid, indriid, and lepilemurid lineages. Some progress has recently been made in this regard – namely, a study reporting the use of *Alu* insertions as phylogenetic markers (McLain et al., 2012). This study finds sistergroup relationships between the indriid and lemurid lineages, and the cheirogaleid and lepilemurid lineages, respectively. With regard to the latter result, it is therefore in accord with the two other studies that have employed broadly dispersed loci from across the genome to address lemuriform interrelationships (Horvath et al., 2008; Perelman et al., 2011). As the field moves forward, with ever increasing species-level sampling and genome-wide sampling of loci, we can hope that both the deep and the shallow nodes of the phylogeny will gain statistical confidence. In both cases, however, it will be the combination of more data analyzed with appropriate methods (e.g., those that explicitly consider the complexities of the coalescent process) (Rannala and Yang, 2003) that offer the greatest hope for confident resolution.

3. Why should we care?

Lemurs are recognized as one of the most remarkably diverse radiations of primates alive today (Kamilar and Muldoon, 2010; Kamilar et al., 2012; Martin, 1972, 2000; Thalmann, 2007; Vences et al., 2009). Over the course of the past two decades, the number of recognized species has increased from slightly more than 30 (Mittermeier et al., 1994) to more than 100 (Mittermeier et al., 2010). Though this breathtaking inflation in recognized species numbers has rightly called for circumspection (Markolf et al., 2011; Tattersall, 2007), it can nonetheless be said that the explosion in numbers primarily mirrors the result of increased field activity (Mittermeier et al., 2008) as well as an enhanced appreciation for the biodiversity among the several radiations of nocturnal and "cryptic" lemuriform lineages, primarily the genus *Lepilemur* (Andriaholinirina et al., 2006; Craul et al., 2007; Mendez-Cardenas et al., 2008; Ravaoarimanana et al., 2004; Rumpler et al., 2001) and the dwarf and mouse lemurs, family Cheirogaleidae (Groeneveld et al., 2010, 2011, 2009; Louis et al., 2006; Olivieri et al., 2007; Rasoloarison et al., 2000; Schmid and Kappeler, 1994; Weisrock et al., 2010; Yoder et al., 2000; Zimmermann et al., 1998).

The puzzle of lemuriform evolution thus becomes bewitching. Knowing, as we do, that Madagascar was geographically isolated before primates evolved, we are compelled to question how lemurs came to inhabit Madagascar. Where did their ancestors originate? When did they arrive? How did they get there? And given their extraordinary diversity, what have been the ecological, behavioral and climatological forces that have driven their diversification? Molecular phylogenetic approaches can help answer all of these questions, and more.

3.1. Lemuriform biogeography

The mode and timing of lemuriform origins have been repeatedly questioned over the years (reviewed in Martin, 2000; Tattersall, 2006), though it now seems that sufficient data have accumulated to conclusively support the Dene et al. (1976) finding of lemuriform monophyly. The tree topology illustrated in Fig. 1 makes it clear that the breadth and depth of lemuriform diversity originate from a common ancestral lineage, thus implying that lemurs colonized Madagascar only once. Moreover, the well-defined sistergroup relationship to the Afro-Asian lorisiforms indicates that Africa was almost certainly the ancestral home of the stem lemuriform lineage (Yoder and Nowak, 2006). In order to ask *how* lemurs arrived in Madagascar, however, we first need to understand *when*.

Given that Madagascar has been surrounded by an oceanic barrier for at least 88 my, we must conclude that dispersal, not vicariance, would have been the mode of their arrival. This leaves two potential mechanisms of dispersal: either lemurs and other Malagasy mammals were able to exploit subaerial (and thus, partially terrestrial) routes, or they must have endured overwater dispersal via what G.G. Simpson referred to as "sweepstakes" mechanisms. The plausibility of subaerial exposures connecting Madagascar to South America and/or India via Antarctica have periodically been suggested via the Gunnerus Ridge and Kerguelen Plateau, both on geological and conjectural grounds, though recent palaeogeographical modeling appears to have soundly refuted this idea (Ali and Krause, 2011). Similarly, it has been suggested that an island chain spanning the distance from Africa to Madagascar via the Davie Ridge may have offered opportunities for at least partially-terrestrial dispersal routes (Mccall, 1997). The temporal window for this putative island chain was quite explicit, however, and has been found to be inconsistent with molecular phylogenetic hypotheses of lemuriform (and Malagasy carnivoran) origins (Yoder et al., 2003). With these terrestrial routes rejected, we are left with one remaining alternative: implausible as it may seem (Stankiewicz et al., 2006), lemurs must have dispersed via rafting across a formidable oceanic barrier, perhaps aided by an ancestral capacity for heterothermia (Kappeler, 2000).

The estimated timing of such an event is of increasing relevance to the debate. A recent study to employ palaeogeographic reconstructions and palaeo-oceanographic modeling concludes that for the period spanning the early-Eocene through the mid-Miocene, ocean currents would have flowed from west to east (in contrast to their present-day east to west flow) and at periodically high rates, thus strongly promoting the overwater dispersal of small-bodied mammals from Africa to Madagascar (Ali and Huber, 2010; Samonds et al., 2012) thus yielding a pattern wherein obligate rafters show a decrease in the probability of transoceanic dispersal from the Paleocene onward, reaching the lowest levels after the mid-Miocene (Samonds et al., 2012). This is precisely the same pattern favored by molecular phylogenetic studies of divergence times in lemurs and in other endemic Malagasy mammals (Poux et al., 2005; Yoder et al., 2003; Yoder and Yang, 2004).

3.2. Timing is everything

The previous section illustrates the importance of placing phylogenetic results within a temporal framework in order to move beyond pattern to explore process. Divergence time estimation is far from a trivial process, however, and for every advance made in theory and methodology, new studies emerge that either support or refute the results of the work that has come before. In the case of lemuriform phylogeny reconstruction, it is actually rather remarkable that the most recent phylogenomic studies can in some ways be seen as merely confirmatory of the immunodiffusion work of 35 years ago. Such agreement is not the case with the recent literature focused on estimating the timing of the lemuriform radiation. Estimated ages range from the late-Cretaceous (Arnason et al., 2008), to the early- to middle-Paleocene (Perelman et al., 2011; Roos et al., 2004; Yoder et al., 2003, 1996a; Yoder and Yang, 2004) to the early- to middle-Eocene (Dos Reis et al., 2012; Yoder et al., 1996a). Thus, these estimates encompass a range of more than 30 million years, a geological period that spans one of the most dynamic and revolutionary events to ever affect the earth, the Cretaceous/Tertiary (K–T) boundary. It is not a trivial matter, therefore, to determine when in this geological period of global upheaval the origin of lemurs occurred. But how do we decide which estimate is best supported?

The answer is not at all obvious. The perennial obstacle in divergence time estimation is the fact that phylogenetic branch lengths (which are the currency by which divergence times are estimated) are the product of evolutionary rate and time. They are inextricably linked, and in order to know one, you must know (or have a good approximation of) the other. Copious literature exists on the subject of rate/time interdependence (succinctly articulated in Thorne et al., 1998)), though it is beyond the scope of this review to summarize the relevant issues, which also include routine violations of a molecular clock, the necessity to incorporate realistic models of genetic change over time, the problematic nature of the fossil record for purposes of calibration, and the need for adequate amounts of data. These issues are universally challenging. In the specific case of lemurs, however, the issues of rate calculation and temporal calibration are especially daunting. The terrestrial fossil record for the Tertiary of Madagascar is a vacuum (Krause et al., 1997), and thus there are no known fossil lemurs, and of all primate groups, issues of rate calculation are particularly problematic in the Strepsirrhini.

Our first glimpse of the potential oddities of molecular rate behavior in lemurs came in 1980 with the report from DNA–DNA hybridization data that the rate of "evolution of DNA of primates from Madagascar is significantly less than that of all other groups of living primates" (Bonner et al., 1980), including the sistergroup to the lemurs, the lorisiform primates. This initial observation was further elaborated in subsequent studies measuring degrees of immunological cross-reaction of protein antigens (Schreiber and Bauer, 1998) and in more targeted genetic regions such as globin genes (Koop et al., 1989a; Porter et al., 1995). Most recently, genomic-scale studies have verified the observation of slow evolutionary rates relative to other primates (Perry et al., 2012b). Fluctuations in rate variation across and within lineages is not a new problem, and indeed, such violations of the molecular clock have spurred many of the most important methodological developments in the field of divergence time estimation (Drummond et al., 2006; Heath et al., 2012; Ho et al., 2007; Kishino et al., 2001; Rannala and Yang, 2007; Sanderson, 2002; Thorne and Kishino, 2002; Thorne et al., 1998; Yang and Rannala, 2006). Nonetheless, the observation that rates of molecular evolution appear to be markedly different between the lorisiform and lemuriform lineages is bound to create challenges for even the most sophisticated methods of analysis. The difficulty intensifies with the possibility that molecular evolutionary rates change not only across phylogenetic lineages, but also within them though time, a phenomenon sometimes referred to as heterotachy. The so-called "hominoid rate slowdown" is a classic example of this hypothesized phenomenon (Sarich and Wilson, 1973). Most recently, convergent heterotachy across the primate phylogeny has been evoked to explain primate divergence times that are estimated to be considerably more recent than those found in previous molecular phylogenetic studies (Steiper and Seiffert, 2012). Compound this problem with the fact that although there are some remarkable fossils within the lorisiform lineage for purposes of calibration (Seiffert et al., 2003), there are none within the lemuriform portion of the phylogeny.

The challenges for divergence time estimation notwithstanding, the anomalies of rate variation within the strepsirrhine primates are of interest in and of themselves. For example, lemurs have been suggested to manifest the lowest mitochondrial transition rate of any primate (Hasegawa et al., 1990), though this result was later overturned via increased species sampling within the lemuriforms (Yang and Yoder, 1999). Copious theories postulating the causes for rate variation among lineages have been erected (often to be promptly torn down) in the general literature. These include differential generation times, selection pressures, body size, metabolic rates, ancestral population size, climate, social organization, and diversification rates, to name only a subset (Bromham and Leys, 2005; Bromham and Woolfit, 2004; Gillooly et al., 2005; Lanfear

et al., 2007, 2010; Martin and Palumbi, 1993; Mooers and Harvey, 1994; Ohta, 1972; Sarich and Wilson, 1973; Tsantes and Steiper, 2009). Thus, despite the problematic nature of rate variation for divergence time estimation (and for phylogeny reconstruction), these theories present fascinating hypotheses to be tested empirically. Putatively, given the extraordinary range of biological and life-history diversity across the lemuriform clade, we should be able to directly test the idea that a small mammal with a rapid generation time (e.g., a mouse lemur) will show higher rates of molecular evolution than a larger mammal with longer generation times (e.g., the indri). At present, existing molecular data within lemurs do not support a generation-time effect, though this could relate more to limited data than to lack of biological actuality. This is one of the many areas in which the opportunities offered by "next-generation" sequencing technologies offer promise.

4. The lemur revolution starts now

The latest revolution in molecular evolutionary studies has been enabled by what most investigators refer to as "next-generation" sequencing technologies. The designation is a bit misleading in that rather than refer to a single technology, next-generation methods actually represent an array of technologies that yield the same essential result: massive amounts of DNA sequence data that can be rapidly generated in a fraction of the time and at a fraction of the cost of traditional Sanger sequencing methods. For the most part, these technologies generate a very large number of sequencing reads, though virtually all of them quite short ($\leqslant$ 400 bp, depending upon the sequencing platform). Despite the indisputable advantage of being able to generate hundreds of thousands of nucleotide sequences in a single run, new technologies bring with them new challenges. In the case of "next-gen" methods, the overlap among sequences tends to be very short, making assembly problematic, and the error rate is typically much higher than with Sanger methods (for superb reviews of the various short-read "next-generation" technologies, see Egan et al. (2012) and Ekblom and Galindo (2011). Perhaps most challenging of all will be "keeping researchers from drowning in this data flood" (Ekblom and Galindo, 2011). The need to keep afloat will become even more challenging as we move into what is sometimes referred to as 3rd-generation technologies wherein single molecules are sequenced and the need for DNA amplification obviated during the sequencing reaction. These technologies offer the promise of even more rapid and less expensive data generation, making the $1000 genome (Mardis, 2006) – something that not long ago seemed like science fiction – a reality.

4.1. Phylogenomics: only the beginning

An implicit message in the increasing number of phylogenetic studies to employ a megabase "phylogenomic" approach is that due to the sheer volume of data, and the fact that these data are generated from across the breadth of the genome, there is safety in numbers. That is, phylogeneticists have to some degree been "mesmerized" by the idea that whole genome representation in phylogenetic studies will be the sole solution to problems of incongruence and uncertainty (Philippe et al., 2011). Although phylogenetic analysis of multi-megabase datasets is still in its infancy, cautionary flags are already going up (e.g., Jeffroy et al., 2006; Philippe et al., 2011; Philippe and Roure, 2011; Yang and Rannala, 2012). The majority of phylogenomic studies aim to sample as broadly as possible across the genome, with an increased reliance on data that are available in public databases. This approach is certainly well justified, yet due to the fact that the amount of data and degree of orthology will vary widely among taxa, the maximal data approach will lead to inevitable gaps in data representation when species sampling is broad. In other words, whereas some taxa will have enormous amounts of data, others will have only a subset of those data. The discussion relating to the difficulties incurred by missing data in phylogenetic analysis is ongoing (Camargo et al., 2012; Crawley and Hilu, 2012; Nabhan and Sarkar, 2012) with consensus yet to be reached. Moreover, with the very enormity of genetic loci in a given study, many investigators are either reluctant or ill-equipped to employ the models of nucleotide substitution that have proven to be of such tremendous value to phylogenetic analysis (Felsenstein, 2004; Yang, 2006). This is due both to the computational expense of models, as well as to potential uncertainty as how best to partition the data for model fitting. The fear therefore is that so-called "supermatrix" approaches to phylogenetic analysis are proving to be somewhat anachronistic and descriptive in their computational approach. The challenge moving forward will be to handle analysis of these enormous data sets with the same degree of statistical sophistication that has rightfully become standard for smaller, more tractable data sets.

4.2. Revolutionary opportunities for understanding lemur biology

Though resolving the Tree of Life remains a consummate goal, the power of new sequencing and gene-expression technologies goes far beyond the promise of phylogenetic resolution. New technologies offer the power to connect genotype to phenotype in non-model organisms (such as lemurs) in ways that were beyond imagining even a few years ago. Until recently, if one's study organism was only distantly related to organisms for which genomic scale data were available, and/or was an organism unsuited for terminal or invasive experimentation, studies were by necessity limited to descriptive genetic or observational experimentation. This for the most part has meant that explorations of gene expression and regulation as they relate to phenotype were beyond reach. Now, however, the comparison of multiple whole genomes of known evolutionary relationships offers an enormous step forward for addressing the difficulties of connecting genotypes to phenotypes. These comparisons can be deployed for phenotype discovery most easily at the cellular level, especially for biochemical and physiological characteristics, given that the pathways from gene changes to cellular changes are more direct than those from gene to the whole organism (Preuss, 2012). For example, an early transcriptome study has revealed tantalizing suggestions of a substantial enrichment of peroxisomal genes likely to have evolved under directional selection in the ancestral primate lineage (Perry et al., 2012a). And increasingly, comparative genomics – especially among primates – is having direct impacts on our understanding of human health. As put succinctly by Ganten and Nesse (2012): "Evolution comes to medicine, genomics comes to evolution".

For example, within the past year alone, one study was able to non-invasively examine the effects of social status on patterns of gene regulation in macaques, finding that expression patterns in a suite of immune system genes could be tracked closely enough to observe the effect of dominance rank over the lifetime of single individuals (Tung et al., 2012). And as a tour de force example of the power of comparative genomic methods to reveal phenotypic effects, three studies were simultaneously published, all showing strong genomic correlations to the autism phenotype in humans (Neale, 2012; O'Roak, 2012; Sanders, 2012). In one of these studies, the authors were even able to pinpoint specific paternal effects on the expression of *de novo* point mutations associated with autism risk factors in offspring (O'Roak, 2012).

The studies above succeeded because of a well-characterized organism-specific genome sequence. Such data are not yet available for lemurs, but the time draws ever closer when these non-model primates will be richly characterized at the genome

level. With the increasing richness of genomic resources among the phylogenetically and phenotypically diverse species that comprise the lemuriform clade, investigators will be able to conduct studies of increasing depth and biological illumination. As an example from another organismal group, a recent study employed comparative population genomic data to identify probable mechanisms driving speciation among freshwater and marine sticklebacks by detecting areas of the genome involved in parallel adaptation to their respective aquatic environments (Jones et al., 2012). The comparison of whole genomes among closely related species and/or individuals can also reveal surprising patterns of the interrelatedness of genes, irrespective of the species phylogeny (Gibbs and Rogers, 2012; Scally et al., 2012). Mechanisms such as introgression via hybridization and/or incomplete lineage sorting can produce patterns wherein two orthologous genes can be either more or less-closely related than the species that carry them. Within the realm of population ecology and conservation genetics, we will thus be able to identify the geographic regions in Madagascar that harbor the most genetically robust as well as the most threatened populations of lemurs, and moreover, to identify those regions of the genome that most succinctly reveal the deleterious effects of inbreeding.

As of this writing, the mouse lemur (*Microcebus murinus*) genome has been sequenced to 100× coverage at the Baylor College of Medicine genome center, using the Illumina Hi-Seq platform (J. Rogers, pers. comm.). Assembly, annotation and analysis of this genome are anticipated in the coming months, soon giving lemur biologists access to a draft genome that will serve as a valuable resource for subsequent genetic and genomic analyses, and an important new tool for a variety of studies that build on that information. Other members of the lemuriform radiation have been characterized at courser levels, which will be of increasing benefit to the nascent field of lemur comparative genomics (e.g., Perry et al., 2012b). Thus, we can at last begin to ask specific questions about the genetic mechanisms driving and maintaining species boundaries among those groups of lemurs such as mouse and sportive lemurs who appear to have undergone remarkable and recent episodes of rapid diversification. Those of us who have long desired to understand the genetic mechanisms governing the expression of extreme phenotypes in lemurs (e.g., hibernation in dwarf and mouse lemurs; cyanide resistance in *Hapalemur*; exquisite neuromotor control in sifakas; ecolocation abilities in aye–ayes – the list goes on and on) will finally have our day. And perhaps most fundamentally, with regard to the origins of this extraordinary group of primates, we can begin to explore what might have been the specific adaptive advantage that allowed lemurs to endure what must have been a treacherous journey from Africa to Madagascar, and potentially, the genetic advantages that allowed them to cement their survival and diversification upon arrival. These are questions of longstanding interest and illusive appeal. At last, the time has arrived for answering them.

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