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The resurgence and genetic implications of New World primates in biomedical research

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Abstract

There has been a recent resurgence of interest in New World monkeys within the biomedical research community, driven both by the sequencing of the common marmoset (*Callithrix jacchus*) genome as well as a growing demand for alternatives to Old World primates. New World monkeys offer attractive advantages over Old World species including cheaper and simpler husbandry while still maintaining a greater evolutionary proximity to humans than other animal models. Although numerous commonalities across primate species exist, there are also important genetic and reproductive differences that can and should play a critical role in selecting appropriate animal models. Common marmosets in particular have significantly reduced diversity at the major histocompatibility complex loci and are born as hematopoietic chimeras. New World primates can make ideal translational models for research, but scientists must necessarily incorporate complete understandings of their genetic and phenotypic differences from humans and other model organisms.

Keywords

Platyrrhines; Callitrichidae; *Callithrix jacchus*; *Saimiri* sp; *Saguinus oedipus*; Animal Models

Revisiting the New World primate model

Animal models are an important tool for biomedical research, but establishing animal models of human disease is inundated with challenges. Rodents, the most extensively used animal models, present difficulties both in accurately representing the disease under study as well as predicting the response to treatment in humans. This is particularly true for neuropsychiatric disorders [1,2] and infectious diseases [3,4]. Primate models, because of their greater genetic, behavioral, and physiological similarities to humans ameliorate some of these issues. Traditionally, Old World monkeys have been the primary non-human primate model, both for historical reasons of access as well as evolutionary proximity. The cost of maintaining non-human primate colonies is high, however, and available resources are strained under constant pressure by both the growing demands of scientists and increasingly restricted facilities and support. One potential solution to these shortages is increasing the availability of New World species. The most commonly used New World monkey species today, the common marmoset (*Callithrix jacchus*) and the squirrel monkey

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(*Saimiri* sp.), are smaller and easier to manage than their Old World brethren and have shorter generational times. We believe that with the recently released marmoset genome and pending release of the squirrel monkey genome, these and other New World monkeys will become more important and more commonly used in biomedical research.

Historically non-human primates, including the New World monkeys, have been used across a varied and complex field of research, encompassing infectious disease, neuroscience, drug development, reproductive biology, and behavioral sciences (Figure 1). Relative to Old World primates, the reduced body mass of New World monkeys brings particular advantages. In pharmacological research, smaller body sizes decrease the costs of compound synthesis. Their size also reduces feeding costs and lessens the square-footage required to house them, which lowers caging costs. A small body size also allows more easily for social group housing and makes the implementation of enrichment programs more manageable for researchers and facilities managers [5]. Generally, New World monkeys also have high reproductive efficiency and reach sexual maturity as early as 12 to 13 months [6], although squirrel monkeys do not sexually mature until 30 months [7]. Marmosets also have shorter lifespans, averaging about six years with a maximum of 15 years in captivity [6]. This helps enable the study of aging and age-related illness in these primate models and improves the feasibility of longitudinal studies [8]. In addition, New World monkeys do not naturally harbor herpes B virus (*Herpesvirus simiae*), alleviating some biosafety concerns relative to Old World species [9].

Although the suitability of New World monkeys as models will necessarily be dependent on the specifics of the study, there are many situations where the evolutionary proximity to humans holds advantages over rodents and the husbandry benefits offer advantages over Old World non-human primates. New World primates (platyrrhines) are found in the Americas and diverged from Old World primates (catarrhines) approximately 43 million years ago and saw widespread radiation 20–25 million years ago [10]. This has resulted in distinct differences across species, many of which are relevant to their use in biomedical research. One major barrier to the adoption New World monkeys as modern animal models was the lack of a reference genome, but the genome of the common marmoset (*Callithrix jacchus*) has been recently completed (Marmoset Genome Sequencing Consortium, Baylor College of Medicine – Human Genome Sequencing Center, personal communication), and the genome of the Bolivian squirrel monkey (*Saimiri boliviensis boliviensis*) is currently assembled (Vertebrate Genome Biology Group, Broad Institute, unpublished). Selecting capable animal models for translational studies must be done with an appreciation for the genetic and physiological differences that separate New and Old World primates and that separate various New World primate species from one another. This is especially true when considering the unique physiology of the callitrichids.

Hematopoietic chimerism in Callitrichidae

Callitrichids, tamarins, and marmosets are notable for their natural dizygotic twinning. Embryologists in the first half of the twentieth century observed that in early development, blastocysts of these twins fuse, giving rise to a single shared placenta [11,12]. This placental anastomosis results in the exchange of genetically distinct hematopoietic precursor cells during embryonic development [13,14]. This hematopoietic chimerism can cause challenges for genetics work in callitrichids. The most common and straightforward methods for gathering genomic DNA from blood result in effectively mixed samples, complicating attempts at genotyping and necessitating collection from other tissue sources. Even then, cryptic blood or lymphocytic infiltrates may complicate particularly sensitive molecular studies [15]. But although this chimerism may complicate genetic studies, it also allows for unique opportunities.

Historically, naturally occurring bone marrow-chimeric species have proven useful models for examining allotolerance, the regulation of reactivity toward the host environment [16–18]. In humans, placental anastomosis is extremely rare [19] and chimerism is seldom demonstrated [20–23], but callitrichids provide a natural primate model for studying transplantation biology. A study of skin grafts in tamarins (*Saguinus* spp.) demonstrated that intraspecies allografts were tolerated for extended periods of time (mean survival ranging between 38 and 70 days), and interspecies xenografts could also be well-tolerated (mean survival times between 14 and 23 days) [24]. As graft rejection is largely mediated by a major histocompatibility complex (MHC) class I response [25], this immunotolerance in callitrichids may reflect important genetic constraints. Indeed, it has been suggested that the bone marrow chimerism may be responsible for selective pressures on identity at the MHC class I loci in twins [26] and in turn suggests an important role for callitrichids in understanding MHC gene evolution.

MHC diversity and evolution in Callitrichidae

Today the forces that both generate and maintain the high MHC allelic diversity are of considerable debate [27,28]. Despite very common MHC class I polymorphisms across vertebrates, some callitrichids present limited MHC diversity. For example, *Saguinus oedipus* is restricted to 11 allelic products at only three MHC class I loci, [29]. Restriction fragment length polymorphism analysis has recently showed limited diversity of common marmoset MHC class I alleles [30]. In addition, the expressed MHC class I molecules of marmosets have been found to be 94% similar at the nucleotide level to those of *Saguinus oedipus* [31]. In comparison, over 5,518 distinct alleles at six class I loci have been identified in humans [32]. The limited MHC class I polymorphism of Callitrichidae species may contribute to their high susceptibility to a number of pathogens, leading researchers to explore their potential use as models of human disease. Up to 60% of captive *S. oedipus* are reported to spontaneously develop ulcerative colitis, of which 15% develop adenocarcinoma of the colon [33]. Additionally, *S. oedipus* develops fatal lymphoproliferative syndromes after infection with Epstein-Barr virus and *Herpesvirus saimiri*, as well as being highly susceptible to retrovirus-induced sarcomas and measle virus challenges [34,35]. This unusual immunogenetic profile, in addition to providing increased understanding of human disease, can also be studied to clarify both the mechanisms underlying the maintenance of bone marrow-chimerism and the evolution of restricted MHC class I gene products.

There are at least five potential explanations for the origin and maintenance of the unusually restricted MHC class I polymorphism found in callitrichids. A recent founder effect was first considered, but findings that demonstrate relatively polymorphic MHC class II loci have made this explanation unlikely [36]. Second, the geographic isolation of callitrichid species was thought to have contributed to low MHC class I diversity; however, other primates with restricted habitats such as the owl monkey (*Aotus* spp.) maintain polymorphic MHC class I loci, thus this explanation alone is insufficient [37]. Third, it may be possible that pressures in the natural habitat are driving down MHC class I loci diversity through event- or pathogen-driven selection. It is impossible to exclude event-driven selection without supporting evidence to the contrary; however, selective pressure for MHC class I identity between virally infected target cells and thymus-educated MHC-restricted cytotoxic T lymphocytes in these primates might play a role in the evolution of low levels of MHC class I polymorphism [29]. A fourth possibility, that the limited number of wild-caught animals in biomedical facilities may have created a founder effect in captivity, has been explored as an explanation for low MHC class I loci polymorphism. Although it is impossible to rule out this phenomenon completely, it has been suggested that the MHC class I profile of the over forty thousand *S. oedipus* exported from Columbia mirror that of *S. oedipus* genotyped directly from wild-caught primates [38]. The high frequency of twinning and bone marrow-

chimerism in callitrichids may provide a fifth potential explanation [26]. Relatively non-polymorphic MHC class I genes might be used as a mechanism by which MHC class I alleles can still be served with a minimum stimulation of alloreactivity [31]. If true, this finding would have implications on current research into the mediating role of MHC in reproductive success and spontaneous abortions. A definitive explanation for the restricted MHC class I polymorphism in callitrichidshas not yet been reached.

Expressed *S. oedipus* MHC class I genes are more closely related to the human non-classical HLA-G gene than they are to the genes of the classical HLA-A, -B, or -C loci, suggesting that these New World monkey MHC class I genes may have evolved from ancestral human non-classical homologues [39]. Because the species show normal CD8+ cytotoxic T lymphocyte responses, it suggests that their HLA-G-related MHC class I genes constitute the classical MHC class I genes of this primate [39]. If accepted, this finding would indicate that classical and non-classical MHC genes do not constitute mutually exclusive groups over evolutionary time.

Squirrel monkey provenance and genetics

Squirrel monkeys (*Saimiri* spp.) are another commonly used New World primate in biomedical research. They share many of the same advantages to researchers common to other New World monkeys, including small body mass, preference for grouped housing, and a relatively short time required to reach sexual maturity (2.5 to 3 years of age) [7]. Additionally, they have been reported to be more tolerant to some environmental stressors commonly associated with the modern research facility, particularly noise, than marmosets [40]. First formally elaborated upon as a research animal in 1968 [41], these monkeys have historically served as models for studying parasitic disease [42] as well as a host of other clinical and behavioral science research [43,44]. This utility and common usage was recognized in the decision to sequence the squirrel monkey genome and to introduce post-genomic tools to squirrel monkey research.

Unlike the callitrichids where genetic confounds arising from hematopoietic chimerism are found in individual animals, the main difficulty with squirrel monkey studies is cryptic, but significant, differences between populations. Squirrel monkeys in biomedical research tend to be an amalgam of at least three populations, *Saimiri sciureus sciureus*, *Saimiri boliviensis boliviensis*, and *Saimiri boliviensis peruviensis*, each of which is genetically distinct [45,46] and shows phenotypic variability [47]. Historically, the biomedical community using these resources has been ignorant of or ambivalent about these differences leading to hybridization within research colonies and calls for greater *a priori* characterization [48–50]. A number of PCR-based assays were developed for distinguishing among the populations [45,48,49,51] but generally these have only been implemented by savvy researchers already focused on squirrel monkey genetics and not among the more general community of behavioral and infectious disease researchers for whom the squirrel monkey is a valuable model.

More than two decades ago, Abee [50] reviewed some of the species differences in phenotype including those in physiology [52], behavior [53], and development [54]. Since that time additional differences have emerged, notably in susceptibility to the malarial vector *Plasmodium falciparum* [55], and these trait differences have been elaborated upon [47]. Given the likelihood that these phenotypic differences are driven in part, and likely large part given the similarities in husbandry between the squirrel monkey populations in captive colonies, by genetic differences, it is important that these be considered more explicitly in study design. These studies have, to date, been fairly limited and rarely extend into biomedical research. Even the most basic understanding of relationships and differences

within the *Saimiri* genera has been elusive, and although progress has been made towards it [56], many questions remain [57].

Even when the phenotype under study is not divergent between the populations, cryptic substructure can affect genetic studies. Differences in composition between "control" and "experimental" groups can lead to spurious genetic associations in much the same way as unaccounted for ethnic differences can impede human studies. Further, many of the squirrel monkey species can hybridize both in captivity and the wild [48]. Because of this, understanding the provenance and genetic heritage of these animals prior to use in study is imperative. Unfortunately it is all too common to see species or subspecies of squirrel monkeys unidentified in the literature or worse, misidentified.

Concluding remarks

Although there are many advantages to using New World primates, the genetic differences that separate them from Old World non-human primates need to be carefully considered when selecting the appropriate animal models across a host of research areas. For instance, certain research on infectious diseases, notably HIV, can only be studied in specific Old World monkey species. The publication of the *Callithrix jacchus* genome, combined with increasing demands from scientists, will mark a resurgence of New World monkeys in biomedical research that will only be furthered by the increasingly restrictive use of Old World primates [58] and the development of transgenic New World monkeys [59–61], perhaps aided by the species' natural tolerance for chimerism. This resurgence must be met by improved characterization and coordination of New World primate polymorphism data, providing researchers with a more definitive guide on whether the use of alternative primate species is both appropriate and translational for their research program. Another feature that should be considered is the unusually restricted MHC class I profile in callitrichids, which makes New World primates a likely candidate model for shedding light on the controversy surrounding the potential role of MHC-mediated behavior in both the maintenance of high MHC polymorphism and reproductive success.

New World monkey models have yet wide-spread enough to achieve the same level of collaboration and cross-fertilization that Old World primate research enjoys (Figure 2). However, the continued and renewed interest in these species necessitates a better and more complete understanding of their genetic structure and its implications for research. The technologies now available allow us to address these concerns, producing genetically-characterized, more translationally relevant New World monkey models of human disease.

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Text Box 1

A brief history of MHC

Research leading to the discovery of MHC genes dates to the early 20th century, when Little and Tyzzer discovered that tumors could be successfully transplanted among some strains of mice, but not in others [63]. Research on tissue rejection continued and, eleven years later, it was discovered that tissue transplants were not rejected if the donor and the recipient were identical twins [64]. This led many to believe that histocompatibility might be genetically controlled, and it was later suggested that immune responses may be the cause of tissue transplant rejection [65]. This was subsequently confirmed by the demonstration of an immune response attacking foreign tissue grafts in rabbits [66]. George Snell published more definitive evidence showing a genetic role in tissue graft compatibility beginning in the late 1940s. Snell's laboratory bred congenic strains of mice which differed at a single genetic region that controlled the rejection of foreign tissue. Snell coined these genes "histocompatibility (H) genes" [67], from which the contemporary name "major histocompatibility complex" is derived, modified due to later discoveries of the many genes present that are all found on the same chromosome. A better understanding of the immunological functions of the MHC gene products began about twenty years following Snell's naming of the H genes when Zinkernagel and Doherty demonstrated that T-cell responses were not only restricted to specific antigens, but also to specific MHC molecules [68]. Later, the understanding of the role of MHC genes in immune regulation was extended to antibody-mediated responses [69–71]. It was at this time that the codominant expression of MHC class I and class II gene products in an individual was first thought to confer a survival advantage to heterozygotes by increasing the variety of pathogens an immune system could interact with.

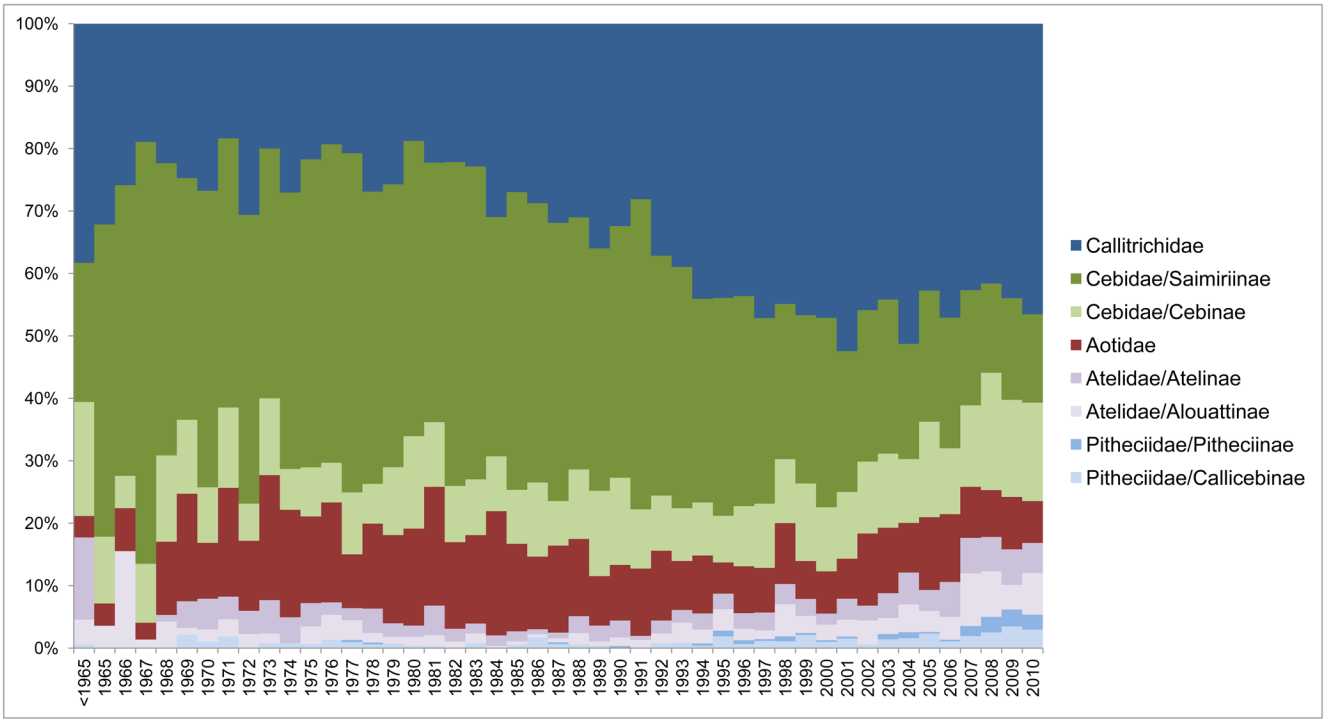

Figure 1.

Distribution timeline of New World monkey publications in the last fifty years. The percentage of total publications featuring New World monkeys is shown by year grouped by Family or Family/Subfamily following the taxonomy of Rylands and Mittermeier [62]: Callitrichidae, including marmosets and tamarins; Cebidae/Caimiriinae, including squirrel monkeys; Cebidae/Cebinae, including capuchin monkeys; Aotidae, including owl monkeys; Atelidae/Atelinae, including spider monkeys; Atelidae/Alouattinae, including howler monkeys; Pitheciidae/Pitheciinae, including sakis; and Pitheciidae/Callicebinae, including titi monkeys.

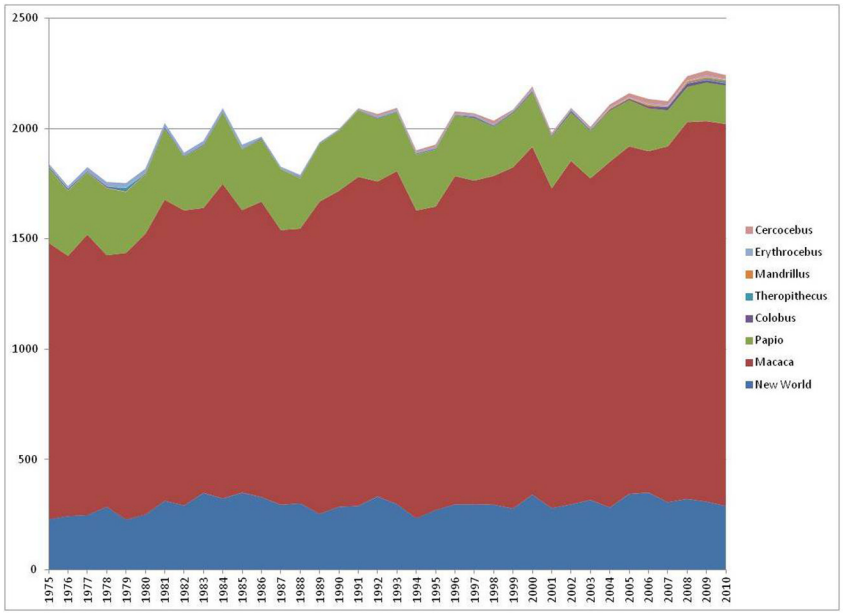

Figure 2.

New World monkey publications as a percentage of all non-human primate publications. PubMed was used as the source resource capture in order to standardize the publication calculation, which includes primarily literature relating to biomedical research. We anticipate a future surge in the use of New World primates as models for disease research in the coming years.