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Investigating the Genetic Basis for Hominoid Taillessness

Samantha M. Tickey-McCrane
University of Rhode Island, samanthatickey@my.uri.edu

Holly Dunsworth
University of Rhode Island, holly_dunsworth@uri.edu

Johanna E. Wegener
University of Rhode Island

Investigating the Genetic Basis for Hominoid Taillessness

SAMANTHA TICKEY-MCCRANE[1,2], JOHANNA E. WEGENER[2], HOLLY DUNSWORTH[1] | [1] Department of Sociology and Anthropology, [2] Department of Biological Sciences

Background

The exact mechanism via which hominoid tail loss occurred evolutionarily and those which maintain tail length variation among primates today, are currently unknown. Regarding skeletal data, there appears to be a tail length pattern where caudal vertebrae counts vary by factors of 3 or 4, possibly suggesting a segmental basis for the genetic elements involved. Based on known mechanisms of tail formation in embryos I identified genes that might be responsible for interruption of tail development, although non-coding, cis-regulatory elements are also likely involved in taillessness.

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Significance

If we can discover the underlying genetic mechanisms for taillessness, we can reconstruct the evolution of this significant feature that we share with apes, and that may have been a necessary precursor to bipedalism.

Methods

We used 4 developmental candidate genes to test for varying rates of evolution in regulatory elements between tailed and tailless primate species. Functional regulatory regions can be highly conserved and thus slow evolving even across distantly related taxa. Non-functional regions evolve with a neutral mutation rate thus reflect ancestry, rather than trait association. We used a Markov chain Monte Carlo (MCMC) phylogenetic footprinting approach implemented in the software package BigFoot v1.0 [9]. DNA sequences of the coding region and1000bp upstream were extracted from Ensembl Genome Browser 88 [10]. For each gene, we aligned tailless and tailed species separately and used 1000 cycles of burn-in followed by $2*10^5$ generations sampling every 2500 cycles. We then compared posterior probabilities at each nucleotide position in the alignment. High posterior probabilities suggest high degrees of conservation across taxa and are potential candidate regulatory elements. Furthermore, we used mVISTA to align the gene sequences, and the regulatory region 1000bp upstream, to visually identify areas of similarity and difference between species. Peaks represent conserved regions and valleys areas of genetic difference.

Our Sample Species

No tail	**Human**	*Homo sapiens*
	Chimpanzee	*Pan troglodytes*
	Gorilla	*Gorilla gorilla*
	Orangutan	*Pongo abelii*
	White Cheeked Gibbon	*Nomascus leucogenys*
Tail (medium)	**Indian/Chinese rhesus macaque**	*Macaca mulatta*
Tail (long)	**Olive baboon**	*Papio anubis*
	Western green monkey	*Chlorocebus sabaeus*
	White-tufted ear marmoset	*Callithrix jacchus*
	Gray mouse lemur	*Microcebus murinus*

Box 1: Macaques may hold the key…

Investigating the developmental and genetic bases of tail variation among *Macaca* holds great promise for reconstructing the evolutionary history of hominoid taillessness and its consequences. Future studies continuing to probe whole genomes and the expansion of available primate genomes will make this possible.

Jack Fooden proposes a scenario to account for the existing RTL patterning variation among *fascicularis*- group macaques (*M. fascicularis, M. cyclopis, and M. fuscata*) whereby tail lengths decrease with increasing latitudes, consistent with Allen's Rule.[2.]

Whatever the drivers of tail length variation among *Macaca,* they have great potential to serve as a natural experiment for investigating the genetic basis of tail loss and length variation, where closely related macaque species have vastly differing tail morphology, from absent to very long.

Identified Candidate Genes

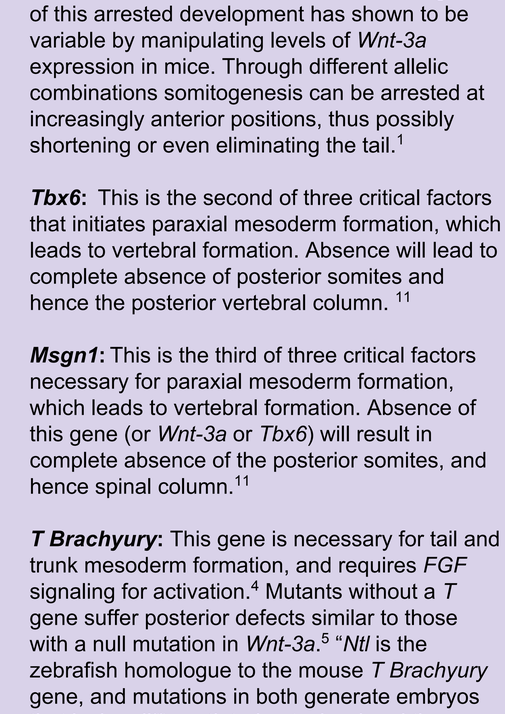
Wnt-3a	***Fgf24***
Tbx6	***Cdx1***
T Brachyury	***Hox10***
Tbx16	***Hox11***
Msgn1	***Hox13***
Ptf1a	***Cyp26a1***
CXCR2	***Ets ½***
Fgfr1	***Deltad* or *dld***
Fgf8	***ph2alpha* (gene group)**
Noggin* or *Nog	**(references below)**

***Wnt-3a*:** This is the first of three critical factors that initiate paraxial mesoderm formation, which leads to vertebral formation.[11] In mice with a null mutation of *Wnt-3a* the somites responsible for forming the posterior portion of the axial skeleton are not formed properly, causing complete absence of tail bud development, and a truncated axial skeleton. Moreover, the degree of this arrested development has shown to be variable by manipulating levels of *Wnt-3a* expression in mice. Through different allelic combinations somitogenesis can be arrested at increasingly anterior positions, thus possibly shortening or even eliminating the tail.[1]

***Tbx6*:** This is the second of three critical factors that initiates paraxial mesoderm formation, which leads to vertebral formation. Absence will lead to complete absence of posterior somites and hence the posterior vertebral column. [11]

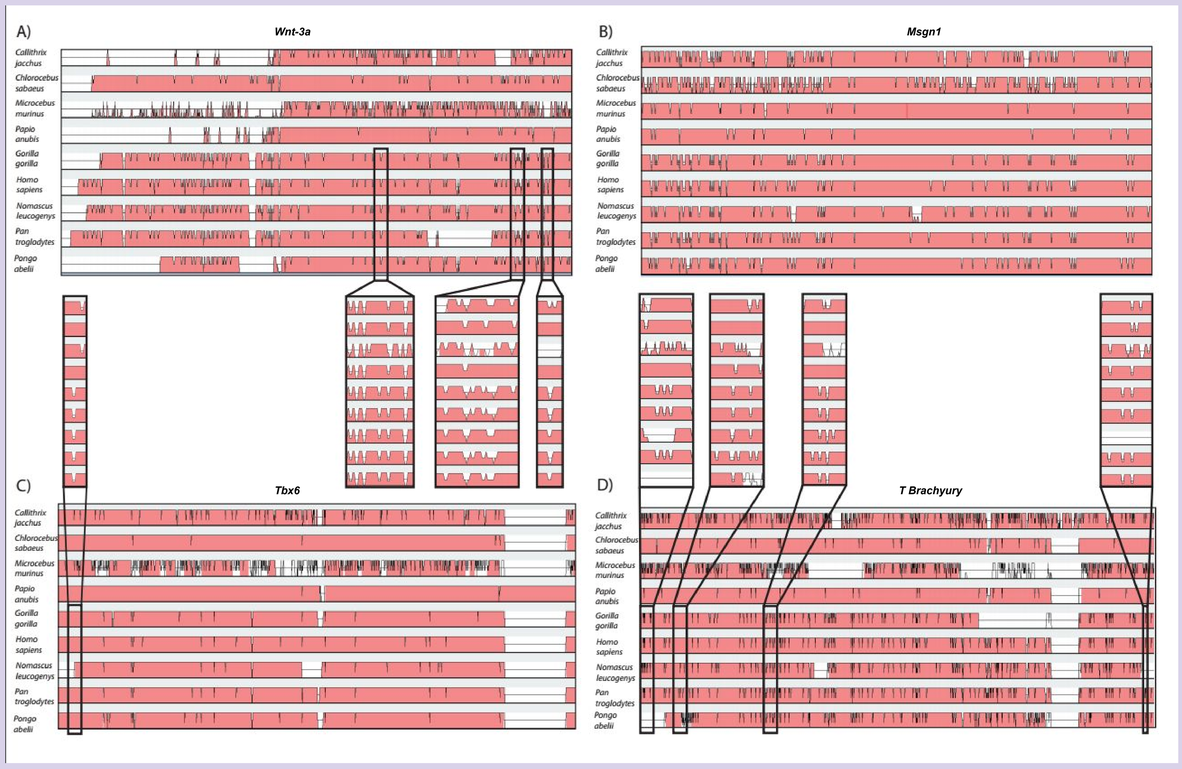
***Msgn1*:** This is the third of three critical factors necessary for paraxial mesoderm formation, which leads to vertebral formation. Absence of this gene (or *Wnt-3a* or *Tbx6*) will result in complete absence of the posterior somites, and hence spinal column.[11]

***T Brachyury*:** This gene is necessary for tail and trunk mesoderm formation, and requires *FGF* signaling for activation.[4] Mutants without a *T* gene suffer posterior defects similar to those with a null mutation in *Wnt-3a*.[5] "*Ntl* is the zebrafish homologue to the mouse *T Brachyury* gene, and mutations in both generate embryos that lack a differentiated notochord and the caudal region of their bodies"[6]

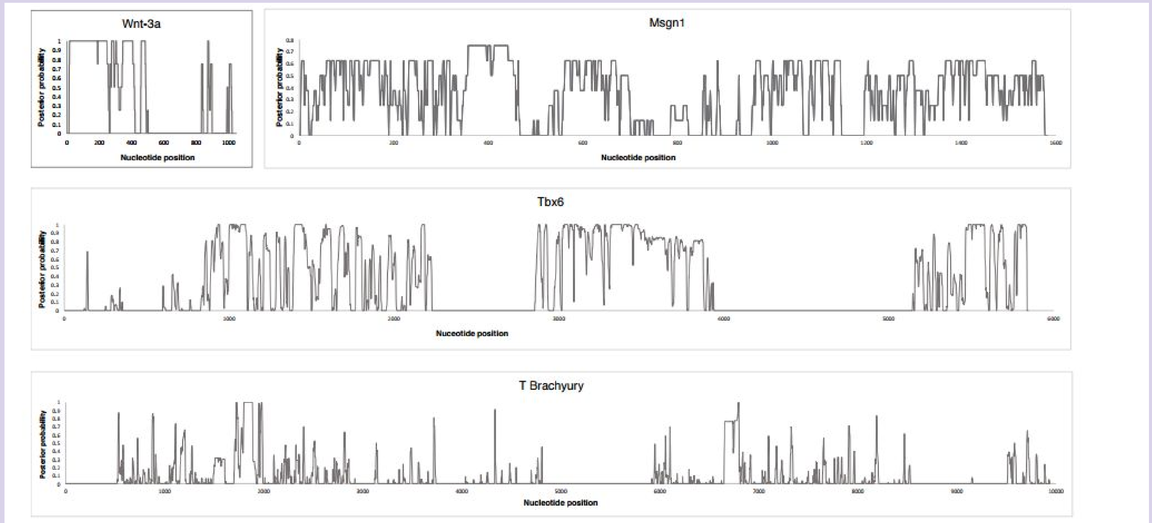


Molecular Phylogeny of Primates.
(34,927 bp sequenced from 54 genes; Perelman et al., 2011)

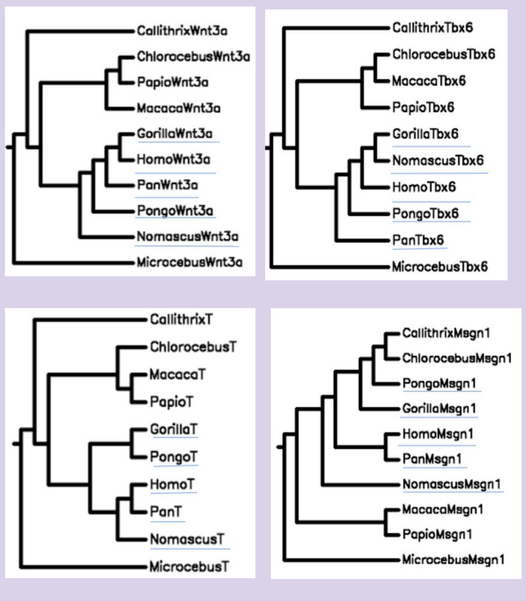
Results



mVISTA: The 1000bp region upstream of the developmental genes are highly conserved across taxa, which suggests presence of regulatory elements. From a preliminary visual analysis, we identified 8 regions in which the tailed species have conserved sequences that differ from the tailless species. Whether those regions are functional regulatory elements and whether mutations at those sites in the tailless species have regulatory effect will be the subject of future studies. Since the tailless species in our study are monophyletic, it is difficult to untangle synonymous mutations that have evolved under neutral conditions from non-synonymous ones that potentially have regulatory consequences. A more in depth analysis of the sequence alignment is needed to answer that question.



Phylogenetic Footprinting: The footprint analysis suggests the presence of potentially functional regulatory regions upstream of the developmental genes. Further analyses are needed to test whether the potential functional regions differ among tailed and tailless species, and whether mutations are synonymous or nonsynonymous.



Box 2: Do human "tails" hold any clues?

Cases of human infants being born with tails show that human tails do not contain vertebral structures like other primate tails. Rather true vestigial tails in humans contain only adipose and connective tissues, striated muscles, blood vessels, nerves, and a skin covering. [7]

Their formation may be linked to mutations in *Ets ½* . *Ets ½* codes for four daughter cells-the smaller, rostral daughter cells migrate to form a bilateral heart, while the larger, caudal descendants remain in the tail and form the proximal tail muscles.[8] Since human vestigial tails contain extra striated muscle, over-expression of this gene should be explored further as a possible causative mechanism.