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The Genetic and Evolutionary Drives behind Primate Color Vision

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Primate color vision is based on two to three cone types in the retina, each expressing a different class of visual pigment, making them the only mammals that possess trichromacy. These pigment classes are the short wavelength-sensitive (SWS1) pigment and the long wavelength-sensitive (LWS) pigment, orthologues of the same pigments found in many other vertebrates, as well as the middle wavelength-sensitive (MWS) pigment, a paralogue to the LWS pigment. Trichromacy was achieved differently in Old World and New World primates. In Old World primates, a duplication of the LWS opsin gene occurred giving rise to a "red-sensitive" or *L* pigment and a "green-sensitive" or *M* pigment. Their corresponding *L* and *M* genes are adjacent on the X chromosome which, together with their high sequence homology, is the underlying cause for the high frequency of red-green color blindness seen in humans. In New World primates and prosimians, however, the mechanism leading to trichromacy, with one exception, is based on a single polymorphic LWS gene, from which different allelic variants encode pigments with differing spectral peaks. X chromosome inactivation limits expression to just one gene per photoreceptor meaning that trichromacy is only seen in females; while all male are red-green color blind. Despite several leading hypotheses, the reasons for the different evolutionary paths taken by Old and New World primates for trichromacy are still unclear and remain to be confirmed.

Keywords: trichromacy, dichromacy, visual pigments, ecology, visual opsins, evolution

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INTRODUCTION

Color vision arose in early agnathan vertebrates over 540 mya (Xian-Guang et al., 2002; Shu et al., 2003) as a tetrachomatic system based on the presence of four spectrally different types of cone photoreceptors (Collin et al., 2003; Davies et al., 2007b). These cones are defined by which type of visual pigment they express that, in turn, are described by their peak absorbance (λ_{max}) as longwave-sensitive (LWS) with λ_{max} 500–570 nm, middlewave-sensitive (MWS or RH2) with λ_{max} 480–530 nm, and shortwave-sensitive, with two pigments, SWS2 with λ_{max} 400–470 nm and SWS1 with λ_{max} 355–445 nm. Located in the vertebrate retina alongside rod photoreceptors, cones are usually responsible for color vision at normal light levels, while rods are responsible for monochromatic vision in dim light, although rods might also play a role in color vision (Blackwell and Blackwell, 1961; Paramei et al., 1998; Freitag and Pessoa, 2012).

Structurally, visual pigments are members of the GPCR family and consist of a polypeptide chain of 340–370 amino acids that forms seven α-helical transmembrane (TM) domains connected by

cytoplasmic and luminal loops, plus an extracellular N-terminus and an intracellular C-terminus, the latter containing phosphorylation sites important in opsin deactivation. In all vertebrate opsins, the TM regions form a cavity in which a retinal chromophore is covalently linked to a conserved Lys residue on the opsin protein via a Schiff base (SB). In mammals, the chromophore is invariably 11-*cis*-retinal derived from vitamin A1; spectral tuning is determined solely by the amino acid sequence of the opsin protein, with specific residues playing a major role in defining the spectral sensitivity of each pigment. In pigments with a λ_{max} value above 385 nm, the SB is protonated, with a negatively-charged residue at site 113 (usually Glu113) acting as a counterion to stabilize the proton of the SB (Nathans, 1990). An unprotonated SB, on the other hand, is found in SWS1 pigments that show ultraviolet-sensitivity with λ_{max} values around 360 nm (Fasick et al., 2002; Hunt and Peichl, 2014).

Orthologues of the four pigment classes found in cone photoreceptors survived the split between the agnathans and gnathostomes and have been retained by most vertebrate classes, although in many cases, one or more pigments have been lost, with the ancestral tetrachromatic color vision being reduced to trichromacy, dichromacy, or monochromacy. Mammals, in general, fall into the dichromacy category, in which RH2 and SWS1 pigments in monotremes (Davies et al., 2007a; Wakefield et al., 2008), or RH2 and SWS2 pigments in marsupials and placental mammals (Jacobs, 1993), have become non-functional.

EVOLUTION OF COLOR VISION IN PRIMATES

It is assumed that at the base of the primate lineage, the ancestral species possessed only the SWS1 and LWS pigments and were dichromats (Hunt et al., 1998). The trichromacy seen in some primate species has been achieved therefore not by the retention of SWS2 or RH2 pigments found in other vertebrate groups but by a duplication of the LWS pigment. This duplication allowed for a mutational drift between the two copies generating two spectrally distinct isoforms maximally sensitive at around 530 nm (*M* pigment) or 560 nm (*L* pigment). Interestingly, the three major primate groups, prosimians, New World primates and Old World primates achieved trichromacy via different molecular mechanisms after the New World and Old World landmasses split during the Middle Cretaceous around 65 million years ago (Kious and Tilling, 1994).

TRICHROMACY IN OLD WORLD PRIMATES

Amongst mammals, primates are the only ones that possess true trichromatic color vision. In Old World primates, or catarrhines, from Africa and Asia (including humans), this was achieved by a ∼40 kb duplication of the X-linked *LWS* gene that is thought to have occurred at the base of the Old World primate lineage (Nathans et al., 1986b; Hunt et al., 1998; Dulai et al., 1999). Part of this duplicated region comprises the entire coding regions of the *LWS* opsin gene (Hanna et al., 1997; Dulai et al., 1999), giving rise to a head-to-tail tandem array of *LWS* genes (**Figure 1**). The duplicated *LWS* genes have subsequently diverged to give an upstream copy (*OPN1LW*) encoding a long wavelength-sensitive (LWS) pigment with λ_{max} around 560 nm and a downstream copy (*OPN1MW*) encoding a middle wavelength-sensitive (M) pigment with λ_{max} around 535 nm. Trichromacy is therefore achieved by individual cones expressing just one copy of either the *L* or *M* pigments together with S cones expressing the autosomal *SWS1* gene (*OPN1SW*). The coding regions of *L* and *M* opsin genes have a 98% homology compared to only 40% with the *S* opsin gene sequence; this is largely the result of the original duplication but maintained by processes, such as gene conversion (Zhou and Li, 1996; Zhao et al., 1998; Hiwatashi et al., 2011). This high level of identity also extends to the introns.

Since the duplicated opsin gene array is present on the X chromosome, the process of X chromosome inactivation (Lyon, 1974) in females is necessary to guarantee that only one array is active in any given cone cell. However, a second mechanism must also be present to ensure that only one gene, either *L* or *M*, is expressed, since the gene array is comprised of a single *L* pigment gene followed by one or more *M* pigment genes. This is thought to be the role of the locus control region (*LCR*) located, in humans, between 3.1 and 3.7 kb upstream of the opsin gene array. The *LCR* is a highly conserved region across vertebrates and acts as a regulatory and enhancer element controlling expression of linked genes. It is not only present in the Old World primate species but also in species where only a single X-linked opsin gene is present (Dulai et al., 1999). Gene activation and regulation is nonetheless thought to require interaction between the *LCR* and the promoter region immediately upstream of the coding region and that the distance between the two influences the frequency of promoter activation (Shaaban and Deeb, 1998). Since each *L* and *M* genes possess a minimal promoter immediately upstream of exon 1, it is thought that the *LCR* interacts with only one of these gene-specific promoter regions, thereby activating only the downstream gene (Shaaban and Deeb, 1998). Indeed, in a study where transgenic mice carried the human *LCR* and *L* and *M* promoters driving different reporter genes (Smallwood et al., 2002), expression from the proximal *L* promoter was higher than from the distal *M* promoter (**Figure 2A**), and the addition of a 9 kb spacer between the *L* and *M* genes resulted in a further decrease in *M* promoter expression, whereas an *LCR* duplication resulted in a more equal expression from both promoters. In contrast, placement of the *M* promoter upstream of the *L* promoter resulted in a total lack of expression from the *L* promoter, indicating that distance of the *L* and *M* promoters from the *LCR* affects their level of activity and that the *M* promoter is the stronger of the two promoters. This may be therefore the mechanism whereby the *M* promoter compensates for its greater distance from the *LCR*. The interaction of the *LCR* with either the *L* or *M* promoter is considered to be a stochastic process (**Figure 2B**); differing strengths of promoter interaction may explain the different *L* and *M* cones ratios seen in the retinae of different human individuals that range from a 4:1 ratio in most individuals to a 30:1 ratio in some rare cases (Carroll et al., 2002). In a number of Old World monkey species, however, a 1:1 ratio was found

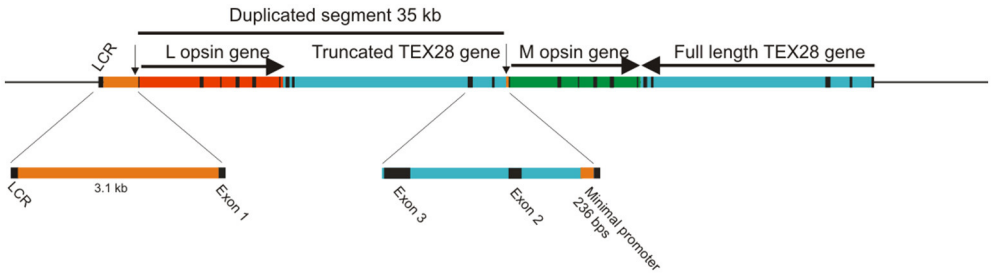

FIGURE 1 | Origin of opsin gene duplication on the X chromosome of Old World primates. The exons for the *L* and *M* opsin genes and for the *TEX28* gene are shown as black bars. Arrows indicate the direction of transcription. The positions of the upstream *LCR* and the minimal promoters for the *L* and *M* opsin genes (vertical arrows) are shown.

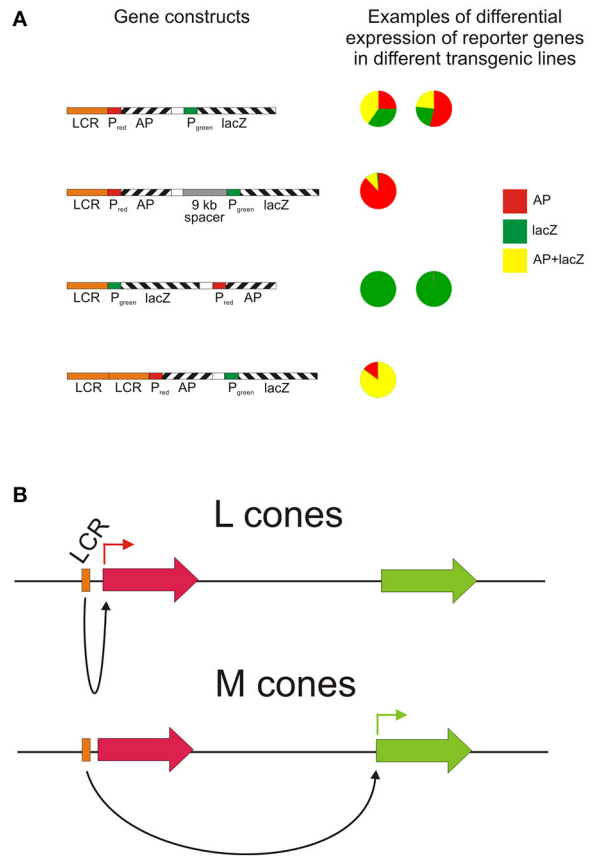

FIGURE 2 | The role of the LCR in directing reporter gene expression from *L* and *M* opsin gene promoters. (A) The relative activity of the *L* and *M* promoters in four different transgene arrays assessed in a number of transgenic mouse lines by scoring individual cone cells for the expression of the reporter genes. P_L, human *L* opsin gene promoter; P_M, human *M* opsin gene promoter; AP, human placental alkaline phosphatase; lacZ, *E. coli* β-galactosidase. Re-drawn from Smallwood et al. (2002). **(B)** Potential mechanism for the stochastic expression of *L* or *M* opsin genes via LCR-opsin gene promoter interaction.

(Bowmaker et al., 1991), and this may again be attributable to the more equal strengths of the respective *L* and *M* opsin gene promoters.

The extremely close sequence homology between the *L* and *M* pigment genes in primates (Nathans et al., 1986b) has allowed the spectral shifts between the two pigments to be largely driven by substitutions at three amino acid sites, 180 (found in exon 3) and 277 and 285 (both found in exon 5) (Neitz et al., 1991). Amongst the catarrhines, the polar residues Ser, Tyr, and Thr are present at these sites in the *L* variants of the LWS pigment, respectively, whereas, the non-polar residues Ala, Phe, and Ala are present in the *M* variants, respectively (Nathans et al., 1986b; Ibbotson et al., 1992). These amino acid differences account for most of the spectral separation of the *L* pigment at 560 nm and the *M* pigment at 535 nm and are mostly conserved across Old World primates, including humans (Ibbotson et al., 1992; Dulai et al., 1994). Site 180 is polymorphic in humans; Ser180 is the more common residue in the *L* pigment but Ala180 is present at a significant frequency to give a slight short wavelength-shift in the *L* pigment of between 2.6 and 4.3 nm in some individuals (Sanocki et al., 1993).

The close proximity of the *L* and *M* genes and their close sequence homology is thought to promote mispairing during meiosis. Where this has been followed by intragenic and intergenic crossing-over within and between the *L* and *M* genes in the array, gene loss, gene duplication, and the production of hybrid genes has resulted; it is these latter two events that are responsible for the high frequency of red-green color vision deficiencies in humans (Nathans et al., 1986a; Neitz and Neitz, 2000), and the presence of extra downstream copies of *M* genes in the array, with copy numbers ranging from one to five and a modal value of two (Nathans et al., 1986a; Drummond-Borg et al., 1989; Feil et al., 1990; Jorgensen et al., 1990). As mentioned above, the *L* and *M* gene array is present in an essentially identical form throughout Old World primates, yet red-green color vision deficiencies are extremely rare in non-human primates; genetic defects in the opsin gene array have been detected in just two studies (Jacobs and Williams, 2001; Verrelli et al., 2008). In the first, three male monkeys were found to have a hybrid *L/M* gene in a colony of 744 male long-tailed macaques (Onishi et al., 1999, 2002), giving a frequency of anomalous trichromacy of only 0.4%, and in the second, an *L/M* hybrid was identified in a single animal amongst 58 male chimpanzees (Terao et al., 2005); the protanomaly in this animal was confirmed by behavioral tests (Saito et al., 2003). Multiple *M* opsin genes have been identified

in gibbons, with an average incidence of 23.5% across all species studied (Hiwatashi et al., 2011). However, no cases of gene loss from the array or the presence of hybrid genes were noted in 152 individual animals genotyped. Overall therefore, there would appear to be strong evidence that red-green color vision deficiencies are highly detrimental to survival within non-human Old World primate communities and are removed by natural selection.

TRICHROMACY IN NEW WORLD PRIMATES

The genetic mechanism underlying trichromacy in New World primates, or platyrrhines from Central and South America, is, with one exception, not based on a duplication event, but on the presence of polymorphic copies of the *LWS* gene (Neitz et al., 1991; Williams et al., 1992), with the different allelic copies giving rise to pigments with λ_{max} values ranging from 535 to 565 nm (**Table 1**). Since only females can have two X chromosomes, full trichromacy is limited to heterozygous females with different allelic forms of the gene on each chromosome, while all males are dichromats (Mollon et al., 1984). The only exception is found in the howler monkey, *Alouatta* spp. where full trichromacy in present in both sexes. This is due to a similar, but independent, duplication of the *LWS* gene as seen in Old World primates (Jacobs et al., 1996a; Dulai et al., 1999), giving rise to separate *L* and *M* genes encoding pigments with λ_{max} values of 530 and 558 nm, respectively (Saito et al., 2004; Silveira et al., 2014). This duplication is limited to the *Alouatta* genus and thought to have happened more recently than the catarrhine event, as demonstrated by the lower rate of substitutions of only 2.7% between the *L* and *M* genes (Hunt et al., 1998). The presence of a separate LCR upstream of each opsin gene, indicating that the duplication included both the opsin gene and its upstream LCR (Dulai et al., 1999). The spectral tuning of the howler monkey's *L/M* pigments however does parallel the mechanism seen in the catarrhine monkeys with identical substitution in sites 180, 277, and 285 defining the λ_{max} values of the *L* and *M* pigments (Saito et al., 2004).

Apart from the trichromacy in the howler monkey, most other New World monkeys seem to have evolved along two lines and this split is particularly noticeable between the two major subfamilies of the Cebidea family, the Cebinae and the Callitrichinae. In the Cebinae family, which includes the capuchin and squirrel monkeys, all three sites, 180, 277 and 285, are polymorphic with either Ser/Ala, Tyr/Phe, and Thr/Ala present, respectively (**Table 1**). The triad Ser-Tyr-Thr accounts for a λ_{max} of 563 nm, Ala-Phe-Thr for a λ_{max} of 550 nm and Ala-Phe-Ala for a λ_{max} of 535 nm. In contrast, in the family Callitrichinae, which includes marmosets and tamarins, site 277 is not polymorphic with only Tyr found, so the λ_{max} values for *L* and *M* pigments differ by a maximum of only 19–20 nm. In this family branch the triad combination and respective λ_{max} are as follows: Ser-Tyr-Thr for 563, Ala-Tyr-Thr for 556, and Ala-Tyr-Ala for 543 nm. However, it is important to notice that, in many cases, different combinations of residues across the three sites (**Table 1**) can produce three or more different spectral variants with intermediate λ_{max} values (Jacobs and Deegan, 2003a). In the other two families that form the New World monkey parvorder,

TABLE 1 | The allelic variation found in the *LWS/MWS* (*L/M* cone opsin) genes of New World monkeys and prosimians.

	Family	Genus	Common name	Number of *L/M* genes	Variants per gene	Estimated λ_{max} (nm)
Platyrrhini	Atelidae	*Alouatta*	Howler monkey	2	1	558, 530
		Ateles	Spider monkey	1	2	563, 550
		Lagothrix	Wooly monkey	1	3	562, 550, 530
	Pitheciidae	*Callicebus*	Brown Titi monkey	1	3	562, 550, 535
		Pithecia	Saki monkey	1	3	562, 550, 535
		Cacajao	Bald uakari	1	6	562, 556, 550, 543, 535
	Cebidae	*Cebus*	Capuchin monkey	1	3	563, 549, 535
		Samiri	Squirrel monkey	1	3	564, 550, 536
		Aotus	Owl monkey	1	1	545
		Leontopithecus	Lion tamarin	1	3	563, 555, 543
			Saddle back tamarin	1	3	563, 557, 545
		Callithrix	Marmoset	1	3	565, 559, 543
Prosimians Prosimians	Lemuroidea	*Varecia*	Red-ruffed lemur	1	2	558, 543
		Eulemur	Blue-eyed black lemur	1	2	558, 543
			Red-bellied lemur	1	1	558
	Cheirogaleidae	*Cheirogaleus*	Greater dwarf lemur	1	2	558, 543
	Indriidae	*Propithecus*	Coquerel's sifaka	1	2	558, 543

Data taken from Mollon et al. (1984), Travis et al. (1988), Boissinot et al. (1998), Tan and Li (1999), Jacobs and Deegan (2001, 2003a,b, 2005), Saito et al. (2004), Talebi et al. (2006), Veilleux and Bolnick (2009), Bunce et al. (2011), Corso et al. (2016), and Jacobs and Bradley (2016).

Atelidae, and Pitheciidae (Perelman et al., 2011), trichromacy appears to have followed the same evolutionary process seen in the Cebinae family (Riba-Hernandez et al., 2004); however, the bald uakari (*C. calvus*) found in the Pitheciidae family, has recently been reported to have six functional polymorphic *L* opsin alleles with different combinations of residues at sites 180, 277 and 285, although two of these are estimated to have the λ_{max} at 550 nm (Corso et al., 2016).

TRICHROMACY IN PROSIMIANS

Polymorphism is also the mechanism of trichromacy in prosimians (Tan and Li, 1999), the lorises and galagos from Africa and Asia, the lemurs from Madagascar and the tarsiers from Southeast Asia, which form the most basal branch of the primate phylogeny. A polymorphic *LWS* gene has been reported in three diurnal prosimian species, the red ruffed lemur, *Varecia variegata rubra*, Coquerel's sifaka, *Propithecus verreauxi coquereli*, and the blue-eyed black lemur, *Eulemur macaco flavifrons*, and in a nocturnal species, the greater dwarf lemur, *Cheirogaleus major* (Tan and Li, 1999; Jacobs et al., 2002; Veilleux and Bolnick, 2009). However, in these species, the spectral shifts between pigments arise from substitution at just site 285, with Thr present in the *L* pigment gene and Ala in the *M* pigment gene, encoding pigments with λ_{max} of 558 and 543–545 nm, respectively (Tan and Li, 1999; Jacobs et al., 2002; Veilleux and Bolnick, 2009). In the majority of non-polymorphic species, an *M* pigment (with Ala285) is present, with *L* pigments (with Thr285) found in only three species. Sites 180 and 277 seem so far to be conserved across all prosimians with Ala and Tyr present, respectively (Tan and Li, 1999). Although polymorphism has been reported in just four species, it is possible that this may be an underestimate of the number of trichromatic prosimian species since many of the studies have been restricted to small cohorts of animals. However, a recent study using a large sample group of the red-bellied lemurs (*Eulemur rubriventer*) showed that this species has a 100% frequency of the *L* allele with Thr at site 285, probably due to a genetic bottle neck event in the studied population (Jacobs and Bradley, 2016). Indeed this same group later demonstrated that amongst lemur species, the presence of *M* or *L* pigments is highly variable (Jacobs et al., 2016).

The presence of trichromacy mediated by the same mechanism of polymorphic *LWS* genes in New World monkeys and different present-day species of the separate prosimian branches of tarsiers and strepsirhines suggests that the ancestral primate may have been a trichromat with polymorphic *LWS* genes (Melin et al., 2013b). Indeed when comparing the sequences of primate *LWS* genes, including several prosimian species, the most parsimonious conclusion is that the ancestral primate carried polymorphic copies of the *LWS* gene (Tan et al., 2005).

SPECTRAL TUNING OF THE SWS1 PIGMENT

The SWS1 opsin is subdivided into two categories; ultraviolet sensitive (UVS), with $\lambda_{max} < 390$ nm (355–390 nm), and violet sensitive (VS), with $\lambda_{max} > 390$ nm (390–450 nm). It is found throughout all vertebrate groups. The UVS SWS1 pigments almost certainly represent the ancestral form of the pigment (Hunt et al., 2004, 2009) and within mammals, they are relatively common in marsupials but are restricted in eutherians to just a sub-set of species from the Orders Rodentia, Chiroptera, and Insectivora (Hunt and Peichl, 2014). In mammalian SWS1 pigments, the tuning mechanism between UVS and VS pigments is defined by site 86. Substitutions at this site have been shown to produce complete shifts from VS to UVS and *vice-versa* in several species. Phe86 is generally associated with a UVS pigment (Hunt et al., 2004) and it is the replacement of this residue by either Tyr, Ser, or Val (Cowing et al., 2002; Parry et al., 2004; Yokoyama et al., 2005) that is responsible for the loss of UVS in a number of non-primate species (Hunt et al., 2007).

In primates, all species possess a violet-sensitive (VS) pigment (Bowmaker et al., 1991; Hunt et al., 1995) but the tuning method used to change from the ancestral UV state to current violet sensitivity remains uncertain. It was initially proposed from mutagenesis studies of the mouse UVS pigment, that tuning from UV to violet requires the simultaneous replacement of residues at three sites, Phe86Leu, Thr93Pro, and Ser118Thr (Yokoyama and Shi, 2000; Shi et al., 2001). However, other residue changes at these sites are found in some species of New World primates and prosimians, which all seem to have a VS SWS1 pigment (**Figure 3**). Interestingly, Phe86 is present in one species, the aye-aye, a prosimian endemic to Madagascar (Carvalho et al., 2012), but expression of the aye-aye pigment showed peak sensitivity in the violet region at 409 nm (Carvalho et al., 2012). This eliminated the possibility of a major role of Phe86 in conferring UVS in primate pigments. Analysis of several primate SWS1 sequences showed that the only residue that is consistently conserved in primate VS pigments is Pro93. Since Pro93 is also found in the VS pigment of the clawed frog (Starace and Knox, 1998), it is not surprising that when a Pro93Thr substitution was introduced into the aye-aye pigment, it was capable of causing a dramatic shortwave shift of 38 nm, resulting in a UVS pigment with $\lambda_{max}$of 371 nm (Carvalho et al., 2012). This does not however rule out a role for site 86 in the initial shift to violet sensitivity at the base of the primate lineage, especially since Tyr86 is found in the SWS1 gene of the tree shrew and colugo (Moritz et al., 2013), close relatives of the primates. The most parsimonious scenario is that Phe86 was present at the base of the primate lineage but underwent a series of substitutions in the various primate lineages where replacement of Phe by either Leu, Tyr, Asn, Val, Ser, or Cys occurred (Carvalho et al., 2012). A subset of these changes (Ser, Tyr, and Val) have been shown to generate shifts into the violet region (Hunt et al., 2007) but if a Thr93 Pro substitution also occurred at the base of the primates, this might have removed constraints on the residue at site 86, thereby allowing different substitutions at this site (Carvalho et al., 2012).

MONOCHROMACY IN PRIMATES

The basic requirement for color vision is the presence of at least two spectrally distinct cone types in the retina. Most mammals

possess a dichromatic color system, so the loss of one spectral cone type is thought to preclude cone-based color vision. Within mammals, the loss of the S cones seems to be the rule in most marine species but has also been observed in a few terrestrial species, with examples in most major mammalian groups like carnivores, rodents and primates (Peichl and Moutairou, 1998; Peichl et al., 2001; Newman and Robinson, 2005; Jacobs, 2013). In many of these species, a *SWS1* opsin pseudogene is still present in the genome (Peichl, 2005). In the primate group (**Table 2**), the owl monkey, and several species of lorises, galagos and tarsiers (part of the prosimian branch) have been shown to carry a *SWS1* pseudogene (Jacobs et al., 1996b; Kawamura and Kubotera, 2004; Tan et al., 2005); since these species do not possess a polymorphic or duplicated *LWS* gene, they are considered to have monochromatic vision (Jacobs et al., 1993, 1996b; Tan and Li, 1999; Levenson et al., 2007; Mundy et al., 2016).

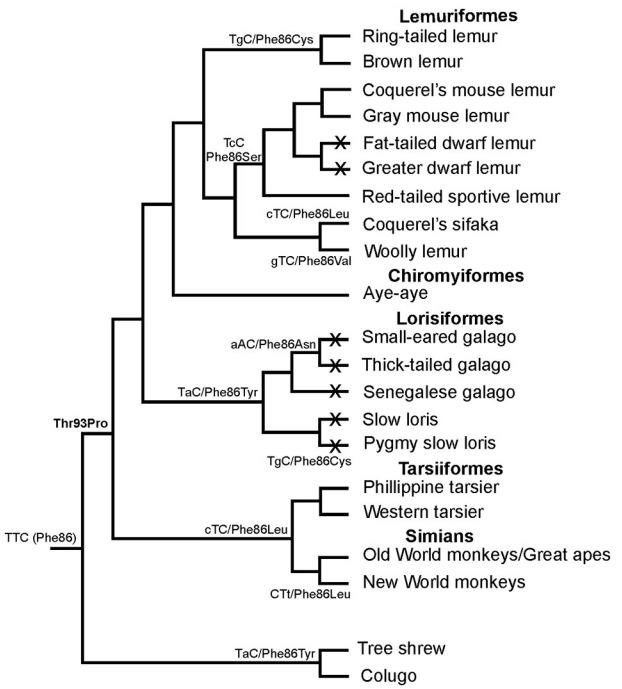

FIGURE 3 | Phylogenetic relationships of different primate species showing the different residues found at site 86 in S cone opsins, together with the corresponding codon sequences. Under the scenario presented, Phe86 was present in the ancestral primate and retained by the aye-aye. Replacement of Phe by either Leu, Cys, Asn, Val, Ser, or Cys then occurred by single nucleotide changes at each step to generate the amino acid changes. Crosses on lineages indicate species where SWS1 pseudogenes are present. Based on data from Carvalho et al. (2012).

It was initially thought that the last common ancestor of extant primates was nocturnal since this trait was carried on in most extant species of prosimians. Since the loss of a functional SWS1 pigment amongst terrestrial mammals is restricted to nocturnal species, it is not surprising that the only primates to have lost the SWS1 pigment are also nocturnal (Jacobs, 2013). However, the nocturnal ancestral primate hypothesis has been challenged by a study that evaluated the selective constraints on the *SWS1* gene across several species of prosimians (Tan et al., 2005). They were able to demonstrate that in prosimians carrying a non-functional *S* opsin gene, different levels of functional relaxation were found in the three major prosimian clades (tarsiers, lemurs and bushbabies/lorises) where each one accumulated completely different mutations generating separate pseudogenes. This indicates that nocturnality, and subsequent loss of the *SWS1* gene, most likely occurred as separate events in each prosimian clade, rejecting the claim that the ancestral primate was nocturnal (Tan et al., 2005).

The only other nocturnal primates are found in the *Aotus* genus of the platyrrhine monkeys. They have been shown to possess, in addition to the rod pigment, only an *M* cone pigment with λ_{max} of 543 nm (Jacobs et al., 1993). A number of nucleotide deletions, insertions and nonsense mutations were found in the *SWS1* gene in three species of *Aotus,* rendering it non-functional (Jacobs et al., 1996b; Levenson et al., 2007), that seem to have occurred at the base of the lineage. Interestingly, although most *Aotus* species are considered strictly nocturnal (**Figure 4**), one of the three species analyzed, *A. azarai*, displays a cathemeral activity pattern (active both during daylight and night time)

TABLE 2 | Loss of short-wavelength cone function in primates as a result of opsin gene mutations.

Genus	Common name	Species	Type of evidence	References
Aotus	Owl monkey	*A. azarai*	Staining/genetics/ERG/behavior	Wikler and Rakic, 1990; Jacobs et al., 1993, 1996b; Levenson et al., 2007
		A. nancymaae		
		A. trivirgatus		
Otolemur	Greater galago	*O. crassicaudatus*	ERG/genetics	Deegan and Jacobs, 1996; Jacobs et al., 1996b; Kawamura and Kubotera, 2004
Galago	Lesser galago	*G. senegalensis*	Genetics	Kawamura and Kubotera, 2004
Nycticebus	Loris	*N. coucang*	Genetics	Kawamura and Kubotera, 2004; Tan et al., 2005
		N. pygmaeus		
Cheirogaleus	Dwarf lemur	*C. major*	Genetics	Tan et al., 2005
		C. medius		

Modified From Jacobs (2013).

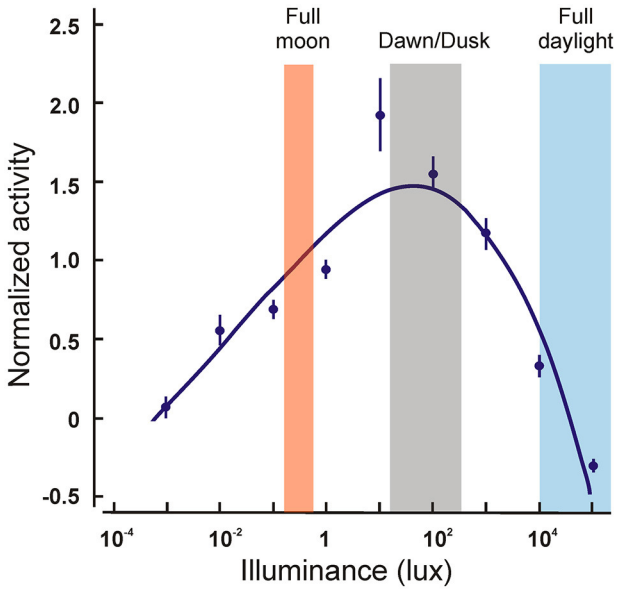

FIGURE 4 | Locomotor activity levels of wild *Aotus azarai* as a function of ambient illuminance levels. The points represent the averaged activity levels for nine animals. Note that the greatest activity occurs at dawn and dusk, and that some activity is still present at very dim or at very bright light levels. Data replotted from Fernandez-Duque et al. (2010).

(Fernandez-Duque et al., 2010). Since the phylogenetic analysis strongly implies that the loss of the *SWS1* gene occurred at the base of this genus, this shift to a cathemeral lifestyle would have been acquired after these species diverged; monochromatic vision does not appear therefore to have hindered this shift in lifestyle.

EVOLUTIONARY DRIVES BEHIND TRICHROMACY IN PRIMATES

The diversity of color vision phenotypes found amongst primates has stimulated a prolific discussion over the past three decades about the implications of color vision for primate foraging behaviors, predation avoidance, social behavior, mate choice, and group dynamics (**Figure 5**; Buchanan-Smith, 2005). Nevertheless, the selective forces and relative benefits influencing the evolution of color vision in primates are still under debate.

Since the nineteenth century, fruit coloration has been understood as a trait that evolved in parallel with animal color vision (Jacobs, 2007), where the primary advantage of color vision would be to allow the detection of conspicuously colored targets against a green dappled background foliage, in which lightness would vary randomly (Mollon, 1989). In line with this, visual modeling studies have predicted that trichromats should have improved discrimination in the green-red part of the spectrum, since they express two *M/L* opsins, giving them an advantage for conspicuous fruit detection (Osorio and Vorobyev, 1996; Regan et al., 2001; Perini et al., 2009). Therefore, the poly-allelic X-linked polymorphism of New World primates and prosimians could be seen as resulting from a heterotic process (Mollon et al., 1984). Evidence from behavioral experiments has provided some support for this frugivory hypothesis (Caine and Mundy, 2000; Smith et al., 2003; Leonhardt et al., 2009; Bompas et al., 2013), although indications of a clear trichromatic advantage for fruit foraging under natural conditions (Melin et al., 2009; Veilleux et al., 2016) and of a heterozygote superiority (Fedigan et al., 2014) are still not fully resolved. So how could the frugivory hypothesis explain the difference in color vision found between Old World and New World primates? Apparently, fruits from Africa (Uganda), which darken when ripe, are smaller than South American (French Guiana) fruits that lighten during ripening (Sumner and Mollon, 2000). Since dichromats might enhance their color vision capacities when target size is augmented (Gomes et al., 2005; Melin et al., 2013a), the diet of platyrrhines should be easier to detect against a foliage background, when compared to catarrhines' diet, reducing the selective advantage of trichromacy over dichromacy in New World primates.

Two decades ago, however, the frugivory hypothesis was challenged by an alternative hypothesis (Lucas et al., 1998; Dominy and Lucas, 2001), which proposed that young edible leaves, but not ripe edible fruits, would be systematically selected by trichromatic primates based on their redness (Lucas et al., 2003). Supporters of the folivory hypothesis also suggested that the abundance of cryptically colored keystone fruits in the New World and Madagascar might not favor the evolution of routine trichromacy, since young leaves never became a critical fall-back food in these places, as they did in areas inhabited by Old World primates (Dominy et al., 2003). This hypothesis seems to hold true when we recall that the most folivorous New World primates, the howler monkey (*Alouatta* spp.), are also the only platyrrhines to express full trichromacy (Jacobs et al., 1996a; Dominy and Lucas, 2001). However, wooly spider monkeys (*Brachyteles arachnoides*), a platyrrhine with a high leaf content in their diet, have been shown to be a polymorphic species with a relatively low frequency of trichromatic individuals in their populations (Talebi et al., 2006), greatly weakening the folivory hypothesis.

Alternatively, given their inferior performance in relation to trichromats in detecting conspicuous food items, dichromats may compensate their disadvantage by identifying cryptic/camouflaged food (Mollon, 1989) since neural processing of information on color and shape/texture occurs concurrently and competitively (Liebe et al., 2009). Thus, individuals with greater dependence on color cues (e.g., trichromats) would be hindered by chromatic noise, while those with poorer color vision (e.g., dichromats) would benefit by assessing achromatic cues, important for the identification of shapes, outlines and textures (Regan et al., 2001). Several behavioral studies have supported the idea that the visual polymorphism of New World primates balances the advantages of dichromats in recognizing camouflaged objects (Morgan et al., 1992; Saito et al., 2005) or insects (Melin et al., 2007; Smith et al., 2012), and of trichromats in detecting conspicuous food targets (Caine and Mundy, 2000; Smith et al., 2003; Leonhardt et al., 2009; Bompas et al., 2013). In fact, recent molecular evidence has shown that the visual polymorphism of New World primates has been maintained by balancing selection (Hiwatashi et al., 2010). Additionally, it

FIGURE 5 | Examples of evolutionary drives that might have influenced the evolution of primate color vision. Original pictures (left column) and simulations of dichromatic (middle column) and monochromatic (right column) vision are shown.

has been shown that under certain circumstances (e.g., lower luminosities), dichromats may improve their color perception (Freitag and Pessoa, 2012), matching the performances of trichromats in conspicuous food detection tasks (Caine et al., 2010).

Unfortunately, progress in our understanding of the evolutionary drive behind trichromacy has been limited by an inordinate focus on a single hypothesis, the importance of trichromacy for food selection, while ignoring other sensory challenges that might impact on fitness. In fact, a few studies suggest that color may not even play an essential role in primate short distance food detection (Hiramatsu et al., 2008, 2009; Bompas et al., 2013), so other selective forces (e.g., detection of predators; sexual selection and social dynamics) should be examined. Color modeling studies have predicted that trichromats should outperform dichromats when discriminating socio-sexual signals (Sumner and Mollon, 2003; Changizi et al., 2006) and predators (Pessoa et al., 2014). The influence of color vision on sexual selection and social dynamics have been studied in Old World primates (Waitt et al., 2003; Changizi et al., 2006; Setchell et al., 2009; Gerald et al., 2010) and, to a lesser extent, in prosimians (Clough et al., 2009) and New World primates (Smith et al., 2005; Surridge et al., 2005; Moreira et al., 2015). However, many studies may have overestimated animal color variation, by using subjective human perception when investigating other primate socio-reproductive signals (Higham et al., 2010). The few visual modeling studies that have considered the visual system of certain primate species indicate that chromatic cues might not be essential for socio-reproductive signaling, and that dichromacy should be sufficient (Higham et al., 2010; Moreira et al., 2015).

Since color can either be used to camouflage an object from its background, through chromatic noise, or improve visual recognition of a target (Li and Lennie, 2001), two non-excluding hypotheses might be drawn in relation to the advantages and disadvantages of color vision to camouflaged predator detection. In other words, the color pattern of some predators (e.g., yellow black spotted cats) may interact with the background pattern of dappled green foliage in a way that produces chromatic noise and only allows predator identification by achromatic cues, favoring dichromats. On the other hand, the same yellow-coated predators may also contrast with the green foliage background, enabling their detection by chromatic information, favoring trichromats. Through color vision modeling and behavioral experiments, the only study to test the predator detection hypothesis to date demonstrated that trichromats excel over dichromats when searching for camouflaged predators (Pessoa et al., 2014). This study suggests that the diversity and distribution of color vision in extant anthropoid taxa could reflect the selective advantages of trichromats and dichromats in detecting predators (Pessoa et al., 2014) and cryptic insects (Melin et al., 2007), respectively. The color vision polymorphism of New World primates would

be expected therefore to have developed in small anthropoids, since these small bodied primates tend to include more insects and fewer leaves in their diets (Fleagle, 1999). Predation pressure is also much higher (Stanford, 2002), so the presence of both trichromatic and dichromatic individuals may be beneficial. Howler monkeys (*Alouatta* spp.), on the other hand, that are folivorous and do not rely on insects, are subjected to a disproportionately high predation risk (Terborgh, 1983; Calleia et al., 2009) that might have selected for their full trichromacy, without the need for unnecessary dichromatic individuals.

CONCLUSION

In primates, trichromacy arose from an ancestral dichromatic state. In Old World (catarrhine) primates, this was achieved through a gene duplication that expanded the *L/M* array on the X chromosome. By contrast, trichromacy in New World (platyrrhine) primates and prosimians (with the exception of the howler monkey that evolved a similar mechanism to the catarrhines) is mediated by allelic variants of the *L* cone opsin gene that encodes spectrally distinct photopigments.

All primates express an SWS1 photopigment that is VS and in all cases except one, the residue present at site 86 is consistent with a VS pigment. The one exception is the pigment in the prosimian aye-aye where Phe86 is present; the presence of Phe at site 86 confers UVS in all non-avian vertebrates but in the aye-aye, the pigment remains VS but with a spectral peak short-wavelength shifted to a value that is near the UVS/VS boundary. In other species, such as the owl monkey and a number of prosimians, the *SWS1* gene has become pseudogenized; these species are therefore considered to be cone monochromats. Thus, it is possible that the single cone type in these species has been conserved for achromatic discrimination. It is also possible that under mesopic (twilight) conditions, where both rod and cones are active, a state of rudimentary or conditional dichromacy exists.

The nature of the selection pressures and advantages (or disadvantages) behind the evolution of trichromatic vision in primates continues to be the subject of debate, with projected roles in the foraging of ripe fruit, the detection of more nutritious young leaves, and in the breaking of predator camouflage. As yet however, no single hypothesis has been shown to explain convincingly the evolution and conservation of trichromacy in all cases, so it may be that different combinations all these factors may be active in different species.

AUTHOR CONTRIBUTIONS

DH was responsible along with WD for conceiving the review and in outlining the initial contents. This was subsequently extended and modified by DH, LC, and DP. DH prepared the early drafts and the final submitted version, as well as **Figures 1**–**4**. LC was responsible for extending the section of the review that covers primate genetics, DP with the section of the review that covers evolutionary drive, plus **Figure 5**, and JM with the section of the review that deals with human color vision defects. All authors were involved in the final editing and review of the paper.

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