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Investigating ethnicity-related variability in the human L-cone spectral sensitivity function

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ABSTRACT

The human cone photoreceptor spectral sensitivities can differ between individuals. Large changes give rise to color vision deficiencies, but even among color-normals there is systematic individual variation. Characterizing the sources of this variation is important for understanding how well widely-used average spectral sensitivity functions represent diffferent observers. One contributor to individual differences in L-cone spectral sensitivity is the amino acid at position 180 of OPN1LW, which encodes the L-cone photopigment. Here, we examine group differences in the reported frequency of the L(S180) and L(A180) alleles using a combination of published reports and the genome sequencing database, gnomAD. We found the estimated allele frequencies differ across reported ethnicity categories. Thus, L-cone spectral sensitivity functions derived from historically available samples may not capture all population-level variation equally, particularly when applied to groups that were under-represented in the underlying datasets. We discuss how population-level variation of this kind relates to the interpretation and use of standard observer functions, and we outline recent promising work towards personalized cone fundamentals.

1. Introduction

1.1. Standard observer cone fundamentals and their limitations

At the very foundation of human color vision lies the spectral sensitivities of the long-wavelength sensitive (L), middle-wavelength sensitive (M), and short-wavelength sensitive (S) cone photoreceptors. Models of the human photoreceptor spectral sensitivities are typically focused on developing a generalized description across the human population. Such a "standard observer" model is widely used and has practical advantages and applications, such as in display design, where display manufacturers aim to reproduce real-world colors on a display, or in lighting design to create an indoor lighting environment to suit the average consumer. These models have been refined over the years (Smith & Pokorny, 1975; DeMarco et al. 1992; Stockman et al. 1993a; Stockman et al. 1993b; Stockman et al. 1999; Stockman & Sharpe, 2000). Since 2006, the Commission Internationale de l'Eclairage (CIE) has adopted the cone fundamentals of Stockman and Sharpe (Stockman & Sharpe, 2000) as physiologically-relevant standards, with the L, M, and S cone spectral sensitivities peaking at 570, 543, and 442 nm, respectively. While such standard observer models are useful tools in colorimetry, they do not account for the variation across individuals within the color normal population (Webster, 2015; Webster & MacLeod, 1988).

The cone spectral sensitivity functions are specified at the cornea, meaning there are individual differences at both pre-receptoral filtering stages in the eye and at the photoreceptor level. Before light even reaches the cones at the back of the retina, it is filtered by the lens and macular pigment, the optical densities of which, and thus the effective filtering of the incident light, can vary between observers (Asano, Fairchild, & Blondé, 2016; Asano, Fairchild, Blondé, et al., 2016; Emery & Webster, 2019; Pokorny et al., 1987; Webster & MacLeod, 1988). Then, when the light does reach the cones, differences in the optical density of the photopigment and in the wavelength of its peak sensitivity result in differences in the width and shift respectively of the cone spectral sensitivities between individuals (Stockman & Sharpe, 2000;

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Winderickx et al., 1993; Asenjo et al., 1994; Merbs & Nathans, 1992a; Neitz & Neitz, 1998; Shape et al., 1998; Elsner et al. 1993; CIE, 2006). Individual differences in the wavelengths of peak sensitivities of the photopigments can be traced to the genes that encode the photopigment opsins.

1.2. Genetics of individual variability in color vision

The L, M, and S opsins are coded for by the OPN1LW, OPN1MW, and OPN1SW genes. OPN1LW and OPN1MW lie in tandem on the X chromosome, while OPN1SW is found on chromosome 7 (Nathans, Piantanida et al., 1986). OPN1LW and OPN1MW are > 96% homologous, while both are only about 40% homologous to OPN1SW (Nathans, Thomas et al., 1986). This is thought to be due to the fact that the OPN1MW and OPN1LW distinction is a relatively recent divergence, evolutionary speaking (Nathans, Thomas et al., 1986, Neitz & Neitz, 2011). OPN1LW lies upstream of OPN1MW on the X chromosome, and it is typical for individuals to have one copy of OPN1LW, but multiple copies of OPN1MW (though the consensus is that only the first copy of OPN1MW is expressed) (Nathans, Thomas et al., 1986). OPN1LW and OPN1MW expression is controlled by a locus control region (LCR), which lies upstream of the opsin tandem on the X chromosome, and which binds transcription factors that enable it to interact with the OPN1LW or OPN1MW promoter, a process essential for L or M gene expression (Wang et al., 1992; Smallwood et al., 2002). It is believed that only one of the X-linked opsin genes, L or M, is expressed in any given cell (Baylor et al., 1987; Mollon, 1999). XX individuals have an extra copy of OPN1LW and OPN1MW compared to XY individuals, and inherited color vision deficiencies (CVDs) affecting the L- and M-cones are sex-linked (Birch, 2012; Delpero et al., 2005). In XX individuals, random X inactivation means that in any given cone cell only one of the two X chromosomes, and thus one of the OPN1LW/OPN1MW genes, is expressed (Lyon, 1961; Teplitz, 1965). Most single-nucleotide polymorphism (SNP) point mutations that occur in OPN1LW and OPN1MW, result in a functional hybrid gene, which codes an opsin with a different peak spectral sensitivity (λ_{max}) than the original opsin, with a λ_{max} between λ_{maxL} and λ_{maxM} (Mollon, 1997). There are several common SNPs that occur in one of the six exons in the OPN1LW and OPN1MW sequences that shift the λ_{maxL} and λ_{maxM} even within the color normal population (Stockman & Rider, 2023).

1.3. L(S180/A180) polymorphism

Of particular interest is the common SNP in exon3 of the OPN1LW gene that causes a serine (S180) to alanine (A180) substitution at codon 180, that changes the λ_{maxL} from ~ 559 nm to ~ 555.5 nm, resulting in a 2–7 nm shift in the peak wavelength of the L cone spectral sensitivity function (Asenjo et al., 1994; Neitz & Neitz, 1998; Sharpe et al, 1998; Merbs & Nathans, 1992b; Nathans et al., 1992). Individuals with L(S180) will have an L-cone spectral sensitivity shifted towards longer wavelengths i.e. greater separation between the L and M cone spectral sensitivities, while individuals who have the minor allele, L(A180), will have an L cone spectral sensitivity shifted towards shorter wavelengths, i.e. less separation between the L and M cone spectral sensitivities.

The reason for the special status of this polymorphism is two-fold. Firstly, it leads to a relatively large spectral shift in λ_{maxL}, and thus subsequently causes the L and M signals to be more or less correlated with each other (Asenjo et al., 1994; Neitz & Neitz, 1998; Sharpe et al, 1998; Merbs & Nathans, 1992b; Nathans et al., 1992). The L(S180) to L(A180) substitution is a sufficiently large spectral shift to cause measurable differences between individuals in performance on a psychophysical task such as differences in spatio-chromatic sensitivity (Dees et al., 2015). Additionally L(S180) and L(A180) individuals have two distinct matching ranges on the Rayleigh anomaloscope (Dees et al., 2015; Winderickx et al., 1992; Thomas & Mollon, 2004). Thus, while a 2–7 nm shift in the L-cone spectral sensitivity may not seem large, it represents a considerable change in the separation between the L and M cones and has a functional effect on the signal-to-noise ratio in discrimination along this color axis.

Secondly, this polymorphism is particularly common among the color normal population (Stockman & Sharpe, 2000; Winderickx et al. 1993; Neitz & Neitz, 1998; Sharpe et al., 1998), with a widely used estimate being 56% L(S180) and 44% L(A180). Other polymorphisms, which cause similarly large shifts, such as the corresponding M(A180) to M(S180) substitution, are reported to be much less prevalent, with only 6 − 7% of Caucasian XY individuals thought to have the minor allele (Winderickx et al., 1993; Neitz & Neitz, 1998). The high prevalence of the L(A180) minor allele is important because the standard observer L cone spectral sensitivity is defined to be the weighted average of the L(S180) cone spectral sensitivity and L(A180) cone spectral sensitivity, weighted by the estimated proportions of L(S180) and L(A180) in the population (Stockman & Sharpe, 2000).

Despite the long-held belief that the L(S180) vs L(A180) substitution is common, the generality of this characterization across ethnic groups is not yet well established. Much of the classic work on cone spectral sensitivities was conducted in American and UK laboratories from the 1980s to the 2000s, where participant pools were predominantly drawn from relatively homogeneous populations. As a result, reported frequencies may reflect the demographics of the samples studied and may not fully capture global population diversity.

1.4. Aims of this study

This study aims to (i) synthesize published estimates of L(S180)/L(A180) frequencies across ethnic groups, and (ii) extend coverage to underrepresented populations by analyzing allele-frequency summaries from the gnomAD database (Genome Aggregation Database v2.1.1; Karczewski et al., 2020).

We focus on relative differences across groups, and then discuss implications for the applicability of standard observer cone fundamentals and the motivation for personalized cone fundamental approaches.

2. Methods

2.1. Review of previous literature

We compiled published articles that provided either (i) L(S180)/L(A180) genotype frequencies or (ii) L-cone peak spectral sensitivity measures that could be used to infer L(S180) vs L(A180). When genotype was not explicitly reported, observers with L-cone peak sensitivity of 559 nm were classified as L(S180) and those of 555.5 nm as L(A180); observers with other peak sensitivities were excluded. Statistical comparisons referenced in the manuscript use the reported sample sizes and proportions.

2.2. Analysis of gnomAD dataset

To estimate allele frequencies in larger and more diverse cohorts, we analyzed the gnomAD v2.1.1 database (Karczewski et al., 2020), which aggregates exome and whole-genome sequences from multiple large-scale projects. gnomAD v2.1.1 contains 125,748 exomes and 15,708 genomes and reports allele-frequency summaries across major population labels (Latino/Admixed American, Ashkenazi Jewish, European (non-Finnish), European (Finnish), South Asian, East Asian, and African/African-American). Here, the term Caucasian is used to mean non-Finnish European as this most closely matches the populations that informed the estimate of L(S180) vs L(A180) allele frequency by Stockman and Sharpe (Stockman & Sharpe, 2000). Any individuals' sequences that do not classify clearly into one of the seven major groups are classified as Other.

The exome and genome sequencing projects incorporated in the gnomAD dataset use next-generation sequencing (NGS) technology.

Briefly, NGS works by breaking the genome into millions of small fragments of DNA, sequencing each small fragment, and then using computational techniques to reconstruct the full genome/exome sequence from these fragments with reference to a template sequence. gnomAD makes summary data publicly available, including population statistics of allele frequency, but full sequence data is not publicly available, except for a few examples. Here, the freely available data on OPN1LW were accessed and analyzed to extract the estimated frequencies of L(S180) vs L(A180) alleles in the OPN1LW aggregate population data, grouped by reported ethnicity.

3. Results

3.1. L(A180) frequency across ethnicities in prior literature

The widely cited estimate of 56% L(S180) and 44% L(A180) is derived from four cohorts totaling 304 observers, drawn predominantly from Caucasian XY individuals (Stockman & Sharpe, 2000; Winderickx et al., 1993; Neitz & Neitz, 1998; Sharpe et al., 1998).

Deeb et al. (1995) suggested that the L(A180) minor allele was significantly less frequent among Japanese XY individuals (16% L(A180), n=49, z=3.71, p<0.001, two-tailed, Cohen's h=0.63). Further evidence from Hayashi et al., (2001) in the early 2000s provides additional support to the observations of Deeb et al. (1995), that the L(S180A) substitution is significantly less frequent among Japanese XY individuals than Caucasian XY individuals (21% L(A180), n=119, z=4.39, p<0.001, two-tailed, Cohen's h=0.50).

Interestingly, it seems as though efforts to derive estimates of L(S180) vs L(A180) allele frequency ceased between the early 2000s and today, with very few papers reporting L(S180) and L(A180) frequencies, and those that do, doing so indirectly, when OPN1LW was sequenced as a means to improve estimates of L:M ratio from ERG/HFP settings (Bieber et al. 1998; Carroll, 2000). This is presumably partially driven by the infamous difficulty in sequencing OPN1LW, due to its high homogeneity with OPN1MW. Two studies from the mid 2000s that contain reports of L(S180) vs L(A180) allele frequency in Caucasian observers report a frequency that is not statistically significantly different from the 44% L(A180) estimate used for the Caucasian population (Carroll et al. (2002): 38% L(A180), n=50, z=0.79, p=0.43, two-tailed, Cohen's h=0.12; Sharpe et al. (2005): 42% L(A180), n=38, z=0.23, p=0.82, two-tailed, Cohen's h=0.04).

Estimates of L(S180) vs. L(A180) allele frequency in African/African-American observers can be inferred from data presented by McMahon et al. (2008), who investigated L:M cone ratios in African/African-American XY individuals. Although the frequency of L(S180) vs. L(A180) genotypes was not explicitly reported, McMahon et al. measured peak spectral sensitivity of the L cone—an indirect indicator of genotype—to refine L:M ratio estimates. Based on their findings, only one observer exhibited a peak sensitivity consistent with the L(A180) allele, while 26 showed sensitivity indicative of L(S180). Their results thus show that the frequency of L(A180) in African/African-American XY observers is significantly lower than the 44% L(A180) estimate from Caucasian XY individuals (4% L(A180), n=27, z=4.05, p<0.001, two-tailed, Cohen's h=1.05). The L(S180) vs L(A180) allele frequency derived from McMahon et al.'s cohort of African/African-American observers and its difference from the frequency in Caucasian observers has been previously noted by Hagen et al. (2019), who also report that in their sample of Caucasian Norwegian XY individuals L(A180) is more common than L(S180) (55% L(A180)), though this increase is not statistically significant from the reported 44% L(A180) in the Caucasian (American and Central European) XY population (55% L(A180), n=60, z=1.55, p=0.12, two-tailed, Cohen's h=0.22).

The frequencies reported above are summarized in Table 1. In addition to the comparisons made in previous literature, statistical comparisons across these datasets show that the L(S180) vs L(A180) allele frequency observed in the Japanese XY individuals, i.e. 20% L(A180) (n=168, pooling the observations from Deeb et al. (1995) and Hayashi et al. (2001) is significantly higher than the L(S180) vs L(A180) allele frequency in African/African-American individuals (4% L(A180), n=27, z=2.02, p=0.044, two-tailed, Cohen's h=0.52). Additionally, despite the considerable variability of the L(S180) vs L(A180) allele frequency across different samples of Caucasian observers, with estimates ranging from as low as 26% L(A180) (Sharpe et al., 1998) to as high as 55% L(A180) (Hagen et al., 2019), none of the L(A180) proportions within the Caucasian samples are significantly different from the 44% L(A180) estimate derived from the 304 Caucasian XY observers by Stockman and Sharpe (2000).

Table1
Table summarizing the L(S180) vs L(A180) allele frequency from past studies. The first column indicates the study, the second, the observers from whom the fraction L(A180) estimate was derived, the third, the number of observers from whom the L(S180) vs L(A180) allele frequency is estimated (i.e. the number of observers who met the inclusion criteria, see below), and the fourth the fraction of observers who had L(A180). The studies are listed chronologically in the table. In the two studies labelled with * the observers were not classified as L(S180) vs L(A180), but the peak wavelength sensitivity of their L pigment was reported. Observers who have a peak sensitivity of 559 nm were classified here as L(S180) and observers with a peak sensitivity of 555.5 nm as L(A180). Observers whose peak sensitivity was a wavelength other than 559 nm or 555.5 nm were excluded here (which led to the exclusion of n=12 observers in Carroll et al. (2002), and n=0 observers in McMahon et al. (2008)). Sharpe et al. (2005) were the only study to contain XX individuals, indicated by $^+$. Two additional XX individuals were included in their study but were heterozygous for L(S180) and L(A180) so are excluded here, leaving only XY individuals and XX who were homozygous included in the estimation of L(A180) proportion.

Study	Observers	n	Fraction L (A180)
Winderickx et al.,1993	Caucasian American XY individuals (74 color normals, 13 single-gene deuteranopes, 22 deutan defect)	109	0.44
Deeb et al., 1995	Japanese XY individuals	49	0.16
Neitz & Neitz,1998	Caucasian American color normal XY individuals	130	0.48
Sharpe et al., 1998	Caucasian Central European XY single-gene deuteranopes	27	0.26
Schmidt et al., as reported by Stockman and Sharpe, 2000	Caucasian Central European color normal XY individuals (36 color normals, 2 single-gene deuteranopes)	38	0.39
Hayashi et al., 2001	Japanese color normal XY individuals	119	0.21
Carroll et al., 2002	Caucasian American color normal XY individuals*	50	0.38
Sharpe et al., 2005	Caucasian Central European color normal XY (35) and XX(3) individuals who are homozygous for L(A180)$^+$	38	0.42
McMahon et al., 2008	African and African American color normal XY individuals*	27	0.04
Hagen et al., 2019	Caucasian (Norwegian) color normal XY individuals	60	0.55

Aggregating previously reported estimates across all ethnic groups yields an average weighting of 36% for L(A180), which is significantly different from the currently used value of 44% though the effect size is small (z=2.24, p=0.025, two-tailed, Cohen's h=0.15). Although this average may better reflect population-level diversity, it may not adequately capture the complexities of ethnic variability, as considered further in the Discussion.

The results of literature review suggest that, for the groups for which data are available, sample sizes are limited, particularly for African/African-American observers. Several major ethnicities, such as Latino and South Asian, are entirely unrepresented. East Asian observers are represented solely by Japanese individuals. These gaps will be addressed in the subsequent analyis of the gnomAD dataset.

3.2. gnomAD dataset

Table 2 presents the frequency of L(S180) and L(A180) alleles across eight ethnic categories from the gnomAD database. Frequencies are reported for the overall population within each ethnic group, as well as separately for XY and XX individuals. Additionally, the proportion of XX individuals who are homozygous for the L(A180) allele is provided. Within each ethnic group, allele frequencies differ minimally between XY and XX individuals. However, notable differences emerge between ethnic groups: approximately 1 in 4 Caucasian individuals carry the minor allele (L(A180)), compared to 1 in 10 East Asian individuals and just 1 in 20 African/African-American individuals. Pairwise comparisons were evaluated with a Bonferroni correction for 28 tests (corrected significance threshold, $\alpha = 0.05/28 = 0.0018$). Under this criterion, all pairwise comparisons between ethnicities are significant ($p<0.0018$), with the exception of the comparison between the Caucasian and "Other" categories. This lack of significant difference is not unexpected, as the "Other" category includes individuals who do not fit neatly into the defined groups and likely consists largely of individuals with mixed ethnic backgrounds. Given that most gnomAD datasets originate from U.S. laboratories, this group likely includes a substantial proportion of individuals with partial Caucasian ancestry.

Note, there are small but statistically significant differences between frequency estimates derived from genome and exome sequencing when considered separately, as compared to when pooled. The overall odds ratio for the frequency of the L(A180) allele in exome versus genome data is 1.25, with no single ethnicity exceeding an odds ratio of 1.26. This suggests a consistently small effect size across data types. Therefore, to maximize the sample size and statistical power, here we report the frequencies seen in the aggregated genome and exome database.

4. Discussion

4.1. Reliability of genome sequencing techniques

The gnomAD database estimate of the L(A180) allele frequency in Caucasian XY individuals is lower than traditional estimates based on more stringent sequencing methods with smaller sample sizes. Specifically, gnomAD reports a 26% frequency for L(A180) among 64,603 individuals, compared to 44% in a pooled sample of 304 observers (Stockman & Sharpe, 2000; z=7.13, $p<0.001$, two-tailed, Cohen's h=0.38). However, published estimates within "Caucasian/European" samples span a wide range (approximately 26–55% across the studies summarized in Table 1).

Sequencing the opsin gene array on the X chromosome is notoriously challenging due to the high sequence homology between the X-linked opsin genes (Haer-Wigman et al., 2022). Classical estimates have typically relied on long-range PCR to amplify OPN1LW and OPN1MW, usually spanning exons 2 to 5 (Dees et al., 2015; Neitz & Neitz, 2011). This approach differs considerably from next-generation sequencing (NGS), which typically uses short-read sequencing with the readouts aligned to a reference locus, and it remains unclear whether results obtained via NGS are consistent with those from long-range PCR. Thus, the absolute L(A180) frequency estimated from gnomAD should be interpreted cautiously.

This study used gnomAD v.2.1.1, but the choice of reference sequence for NGS can influence the interpretation of results. Nash et al. (2022) demonstrated that using the GRCh37 reference genome (used in gnomAD v.2.1.1) allows exon 3 of OPN1LW to be distinguished. It is worth noting that gnomAD v3.1 uses the GRCh38 reference genome, which cannot isolate exon 3 of OPN1LW as it contains only one canonical version of the OPN1LW/MW gene. Consequently, the L(S180A) variant is absent from GRCh38, and GRCh37 provides a more relevant reference genome as it enables separation between OPN1LW and OPN1MW by including their distinguishing polymorphisms.

Example reads from the publicly available gnomAD v2.1.1 dataset are consistent with expectations for OPN1LW. For instance, in the sample "hemi [exome 1]," the reads span two indicative codons known to differ between OPN1LW and OPN1MW. These reads show 100% concordance with OPN1LW, with codon 465 (amino acid position 155) showing a G (versus C in OPN1MW), and codon 457 (amino acid position 153) showing a C (versus A in OPN1MW). Similar patterns are observed in other samples, including "het [genome 1]," "hom [exome 3]," and "hemi [exome 2]." Moreover, reads containing a C at codon 465 are not contiguous with those showing a G at codon 538—the codon responsible for the alanine shift at position 180. This suggests that snippets responsible for C at codon 465 may originate from a separate gene, likely OPN1MW.

Importantly, even though GRCh37 should be able to distinguish exon 3 of OPN1LW from OPN1MW, cross-contamination remains a possibility. If misclassification were occurring, one might expect OPN1MW reads to be incorrectly attributed to OPN1LW due to the former's low coverage and the latter's high coverage. It is unlikely that OPN1LW reads are being misclassified as OPN1MW, as this would result in better apparent coverage for OPN1MW, which is not observed. If OPN1MW sequences were contaminating the OPN1LW dataset, we would expect a higher prevalence of alanine at codon 180, and thus a higher frequency of L(A180) than in previous sample estimates. However, our analysis reveals a lower prevalence of this minor allele. This observation runs counter to the contamination hypothesis and further supports the fidelity of the OPN1LW data in gnomAD v2.1.1.

The primary aim of this manuscript is to analyze the relative differences in L(S180) vs L(A180) allele frequencies across ethnicities, rather than the absolute proportions within any specific cohort. Therefore, as long as the sequencing method (NGS vs. long-range PCR) does not systematically interact with ethnicity, sequencing errors should not introduce ethnicity-specific biases, and relative allele frequencies of L(A180) can be meaningfully compared across groups. Because gnomAD

Table 2
Table summarizing the gnomAD OPN1LW L(S180) vs L(A180) allele frequency results. The columns (from left to right) show ethnicity, the number of exome sequences, the number of whole-genome sequences, the aggregate number of exome and genome sequences, the proportion of XY individuals in the sample, the frequency of L(A180) among all individuals in a given ethnicity, the frequency of L(A180) among XY individuals, the frequency of L(A180) among XX individuals, and finally, the proportion of the XX individuals with the L(A180) allele who are homozygous for L(A180) among all XX individuals. The frequency estimates have been rounded to 2 decimal places. Note, due to the low number (n=31) of South Asian genomes available indicated by *, the South Asian genome sequences are reported in the Other category in the gnomAD database.

Pop.	Exo.	Gen.	n	XY	A180	XY A180	XX A180	XX HOM
Latino/Ad-mixed American	17,296	424	17,720	0.23	0.34	0.33	0.35	0.27
Ashkenazi Jewish	5,040	145	5,185	0.32	0.30	0.30	0.29	0.26
European (non-Finnish)	56,885	7,718	64,603	0.32	0.26	0.25	0.27	0.24
Other	3,070	544	3,614	0.30	0.26	0.25	0.27	0.21
European (Finnish)	10,824	1,738	12,562	0.28	0.20	0.18	0.21	0.19
South Asian	15,308	*	15,308	0.59	0.11	0.11	0.11	0.16
East Asian	9,197	780	9,977	0.23	0.09	0.06	0.09	0.11
African/African-American	8,128	4,359	12,487	0.19	0.05	0.04	0.05	0.05

uses a unified mapping and variant-calling framework across cohorts and assigns population labels downstream from genome-wide variation, we expect any locus-specific callability effects to be largely shared across ethnic groups. Consistent with this, exome-versus-genome differences are small and similar across ethnic group (overall odds ratio = 1.25). Furthermore, the relative differences estimated from gnomAD align with prior reports, as summarized in Tables 1 and 2. For instance, Japanese samples (0.16–0.21) are around 1.5–3 times lower than Caucasian/European samples (0.26–0.55), while African/African-American samples (0.04) are approx. 6.5–12 times lower than Caucasian/European. GnomAD shows the same ordering: Relative to European (non-Finnish) (0.26), East Asian is approx. 3 times lower (0.09), and African/African-American is approx. 5 times lower (0.05). These suggest limited evidence for a strong ethnicity-by-method interaction in gnomAD data. A potential caveat is that if OPN1MW copy number varies by ethnicity, increased copy numbers could lead to greater misclassification of OPN1MW reads as OPN1LW, thereby underestimating L(A180) frequency in populations with more OPN1MW copies. However, there is currently no evidence that OPN1MW copy number does vary with ethnicity. Even if such variation were found, it is unlikely to fully account for the large inter-ethnic differences observed in L(A180) allele frequency in the gnomAD dataset.

4.2. Towards personalized cone fundamentals

This study highlights convergent evidence for notable ethnic differences in the frequency of the L(S180) and L(A180) alleles. Even based solely on long-range PCR data, significant variation is evident among African and African-American, Japanese, and Caucasian populations. This raises the important question of how such variability can be incorporated into the cone fundamentals.

Cone fundamentals are derived as linear transformations of color-matching functions (CMFs). For example, the widely used Stockman & Sharpe fundamentals are obtained by linearly transforming the Stiles & Burch 10-degree CMFs (Stiles & Burch, 1958, 1959). One pragmatic option is therefore to adjust the step in which L(S180) and L(A180) spectral sensitivities are incorporated. Stockman and Sharpe (2000) estimated L(S180) and L(A180) cone sensitivities by fitting linear transformations between CMFs and spectral-sensitivity measurements in observers of known genotype (single-gene deuteranopes). The current standard observer is based on a weighted average of these estimates, with weights reflecting the allele frequencies found in a sample of Caucasian XY individuals.

One might therefore wonder whether the Table 2 frequencies could be used to reweight the relative contributions of the L(S180) and L(A180) variants when constructing a standard observer. However, our gnomAD analysis is most informative about relative differences across groups, and the absolute frequency estimates at this locus should be interpreted cautiously given the known challenges of short-read sequencing in the highly homologous OPN1LW/OPN1MW gene cluster. Therefore, Table 2 does not, by itself, provide a sufficient basis for specifying revised weights for a standard observer; any reweighting would require additional validation of absolute allele-frequency estimates at this locus. In addition, given the discrete nature of the SNP and its effect on spectral tuning of the pigment, reweighting will not be optimal for any individual observer, who must have either one or other allele.

Although our analyses focus on the OPN1LW codon-180 polymorphism, in principle combinations of L- and M-opsin codon-180 variants could also contribute to individual differences in effective L–M spectral separation. To provide broader genetic context, we also examined the OPN1MW codon-180 variant in gnomAD v2.1.1. The M(S180) allele has a global frequency of 0.074, and its estimated frequency varies across ethnicity: Latino/Admixed American (0.187), Ashkenazi Jewish (0.176), East Asian (0.084), European (Finnish) (0.079), South Asian (0.076), Other (0.068), European (non-Finnish) (0.043), and African/African-American (0.041), spanning an overall approx. 4–5 times range (0.041–0.187). However, the between-group differences for this M−cone variant are smaller than those observed for OPN1LW codon-180, and its expected perceptual impact is likely smaller because the spectral difference between M(A180) and M(S180) is comparatively modest (~2 nm; Sharpe et al., 1998). Nevertheless, capturing the variation in cone fundamentals will ultimately require considering both OPN1LW and OPN1MW variation, as well as their combinations, rather than treating either locus in isolation.

More broadly, cone fundamentals and CMFs depend on additional sources of biological variability that are not captured by a two-allele model of L-cone spectral sensitivity. Although the L(S180/A180) polymorphism) is particularly significant, additional opsin variation beyond codon 180—including other SNPs and potentially structural variation within the opsin gene array—can further modulate spectral sensitivities (Stockman & Rider, 2023). In addition, prereceptoral filtering varies substantially across observers, including individual differences in lens and macular pigment optical density, which alter effective spectral sensitivities at the cornea and contribute to variability in color matches (Webster & MacLeod, 1988; Iannaccone et al., 2007; Howells et al., 2013).

Together, these considerations motivate renewed efforts to measure CMFs and cone spectral sensitivities in larger and more diverse samples (Stockman & Rider, 2023). The original Stiles & Burch CMFs, for example, were derived from participant pools whose demographic composition was not fully documented and may have been limited in diversity. New data will support personalized cone-fundamental estimation: direct or indirect measurement of observer-specific cone spectral sensitivities and/or individualized CMFs, potentially informed by genotype and combined with estimates of prereceptoral filtering. Recent work using LED-based multi-primary trichromators and observer-specific modeling provides scalable routes to estimating individual CMFs and cone spectral sensitivities in larger samples (Asano et al., 2016b; Shi et al., 2024a; Shi et al., 2024b; Shi et al., 2024c). These advances can complement standard-observer models by enabling more accurate prediction at both individual and population levels, benefiting vision science as well as a wide range of applied color technologies, where individual variation in cone fundamentals can produce substantial observer metamerism (Eissfeldt et al., 2021; Wu et al., 2021; Xie et al., 2020; Fairchild and Wyble, 2007). Ultimately, integrating large-scale, diverse measurements with individualized modeling may be desired for developing color standards and devices that are robust and equitable across a broader population.

5. Conclusion

This study presents findings on ethnic differences in L(S180)/L(A180) allele frequencies, drawing on prior literature and on analysis of the large-scale gnomAD database. The observed disparities in allele frequencies across ethnic groups are striking. Such ethnicity differences present a practical challenge for the use of standard observer models to describe the "average" human observer.

Data availability

All data accessed from gnomAD (Genome Aggregation Database v2.1.1) is available open access. https://gnomad.broadinstitute.org/.

CRediT authorship contribution statement

Allie C. Schneider: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Takuma Morimoto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Funding acquisition, Formal analysis, Data curation. **Michelle E. McClements:** Writing – review & editing. **Robert E.**

MacLaren: Writing – review & editing, Funding acquisition. **Hannah E. Smithson:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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