DO YOU SEE WHAT I SEE? A LOOK AT COLOR DEFICIENCIES IN KANSAS

An Honors Thesis

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The following faculty members have examined the final copy of this thesis for form and content, and recommend that it be accepted in partial fulfillment of the requirement for the degree of Honors Baccalaureate with concentration in Biology, Chemistry, and Health Sciences.

Mary Liz Jameson, Thesis Advisor

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ABSTRACT

Color vision deficiencies occur due to the modification or loss of function of one or more cone cells in the retina. Individuals with color vision deficiencies may face challenges related to color perception in everyday life. Various tests screen for and diagnose color vision deficiencies, and the Ishihara plate test is a common screening test for red/green color vision deficiencies. My research examined the visual transduction pathway and the genetics of color vision deficiencies. Additionally, I implemented a digital color vision survey to compare the frequency of color vision deficient adults in Kansas to the average global frequency. An Ishihara plate test was utilized to screen for dichromatic color vision deficiencies in a sample of adults in the state of Kansas. Subjects were presented with eleven digital plates from the official Ishihara plate test, and then they were asked to identify the figure on each plate. Of the 271 survey participants, 3.0% of female participants (n=199), 8.2% of male participants (n=61), and 0.0% of other gendered participants (n=11) demonstrated having a color vision deficiency. This is significant because, while the percentage of potentially color vision deficient males aligned with the global frequency (8.0%), the percentage of potentially color vision deficient females was much higher than the global frequency (0.5%). Although the sample size was only a small fraction of adults in Kansas, these results may indicate that color vision deficiencies are more prevalent in Kansas compared to the global frequency.

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INTRODUCTION

Almost nothing is ever completely black or white, and the realm of color vision is no exception. In most cases, when people think of color vision deficiencies, they often default to the idea of complete color blindness. However, the reality is that color vision deficiencies exist on a dynamic scale, in which many color vision deficient individuals still have the ability to perceive certain colors and hues. In a world where approximately 8% of males and 0.5% of females are color vision deficient to some degree (UC Davis 2020), many tools and environments are not easily accessible for such populations of people. Simple tasks such as differentiating the color of electrical wires, noticing color-coded text on displays, responding to traffic light signals, picking out clothing, and even selecting fresh produce are all common struggles that people with color vision deficiencies may face (Chaparro & Chaparro 2017). Many individuals with a color vision deficiency are still able to pursue careers in fields such a medicine, aviation, and other professions that may depend on the ability to differentiate colors, though it often comes with extra challenges. For instance, a doctor with a color vision deficiency may not be able to properly notice and diagnose ailments such as jaundice, redness of the skin, or other abnormal bodily colors. The ability to identify and respond to different colored signals and warnings is also a common hurdle that individuals with a color vision deficiency face in almost any career path. Individuals with color vision deficiencies must frequently use other means to interpret signals or signs that are most easily interpreted by color by the majority of the population (Stoianov et al. 2019). Redundant cues such as brightness, location, differences in text, shape, or size can often allow a color vision deficient individual to correctly interpret the sign or signal. However, solely depending on such redundant cues is not always reliable because relative brightness may vary and not all redundant cues are equally as effective at capturing the attention of a color vision deficient individual (Chaparro & Chaparro 2017).

In a world of color, there are four main types of general perceptual judgements that people use to differentiate and analyze colors, the first of which is comparative. Comparative judgement depends on a person's ability to determine

whether two or more colors match or go together, such as the task of evaluating whether two paint samples match or not. Denotative perception is used to organize an area such as in advertising to reduce visual clutter, guide the viewer's gaze, or separate different concepts. This can include using color to make something easier to find or representing certain things such as on a map. Connotative color use is the use of color to designate specific meanings such as danger. It can be used as identification of certain objects, indication of status such as with traffic lights, indication of magnitude such as with heat maps, or for the revealing of physical features such as the ripeness of fruit. Aesthetic color use is when color is used to elicit a certain emotional response or psychological response (Chaparro & Chaparro 2017). These four perceptual judgements shape the way each individual perceives and experiences the world, so it is imperative that we understand all the ways in which an individual may be impaired by having a color vision deficiency. However, people with color vision deficiencies are not widely understood or assisted. To further understand the complexities of color vision deficiencies, I synthesized an overview of the biochemistry and health sciences of color vision deficiencies. I also conducted a state-wide, digital survey to compare the frequency of color vision deficient adults in Kansas with the estimated global frequency of color vision deficient individuals.

1.2 MATERIALS & METHODS

To address color vision deficiencies and color perception, my research included two components: 1) A review of the biochemical and physiological basis for vision and color vision and 2) A color vision survey of Kansas residents.

The review on the biochemical pathway for vision, color vision, and color deficiencies is based on data collected from a variety of scholarly sources and peer-reviewed publications. To establish a foundation of knowledge before diving into the complexities of color vision, the initial subset of research focused on a detailed description of the biochemical pathway of the visual cycle. This was followed by a closer examination of the different types of color vision deficiencies and the gradient of variance that is associated with each type. Additional research was collected on the prevalence and genetics of color vision deficiencies since the majority of color vision deficiencies are inherited rather than acquired. The final portion of the literature review research process obtained during these first 16 weeks focused on the process of testing and diagnosing individuals with color vision deficiencies in a clinical setting. This is relevant because a significant proportion of the population has some degree of color vision deficiency with 1 in 12 males and 1 in 200 females of Northern European ancestry having some degree of color vision deficiency (MedlinePlus 2015). Even though there has yet to be a feasible cure or treatment plan for individuals with such deficiencies, many clinical trials and products are in the process of being tested to help aid in the ability of the individual to distinguish different colors.

The second component of my research was an online survey of adult, Kansas residents that utilized eleven plates from the Ishihara plate test (Shinobu n.d.). The original Ishihara test is composed of 38 unique plates to differentiate specific types of color deficiency, but other modified versions exist where fewer plates can be utilized to yield results of similar accuracy. This survey included 11 of the standard 38 plates, which is a sufficient number of plates to provide accurate results (**Figure 8**). The survey included the following: The first survey plate, Ishihara Plate #1, served as a control (**Figure 1, 8**). Individuals with normal color vision and color vision deficiencies could read the plate as "12." The next three survey plates 2-4 (Ishihara Plates #2, #6, and #8), were selected because they were designed to screen for red/green color deficiency. Individuals with normal color vision would interpret the number as "8," "5," and "15," respectively. Individuals with a red/green color vision deficiency would interpret the number on the plate as "3" and "2," and

"17,"respectively. Individuals with complete color blindness would not be able to distinguish any number on these plates. Survey plates 5-7 (Ishihara Plates #11, #15, and #16) were selected because even though they also screen for red/green color vision deficiencies, they do so by presenting a numeral figure for trichromats or no observable figure for individuals with a red/green color vision deficiency. Individuals with complete color blindness would not be able to distinguish any number on these plates. Survey plates 8-9 (Ishihara Plates #18 and #20) were selected because they screen for red/green color vision deficiency in a manner opposite to that of plates 5-7. For these two plates, individuals with red/green color vision deficiencies would see the numbers "5" and "45," respectively, while those with normal color vision or complete color blindness would not be able to discern any number (Shinobun.d.). Survey plates 10-11 (Ishihara Plates #22 and#23) were chosen for the survey because they aid in preliminary screening for the more specific types of color vision deficiency protanopia and deuteranopia. as well as severe cases of protanomaly an deuteranomaly. Individuals with normal color vision would interpret plate 10 as "26" and plate 11 as "42." Individuals with protanopia would only be expected to observe "6" and "2," respectively, while an individual with deuteranopia would only be expected to observe "2" and "4," respectively. Individuals with complete color blindness would not be able to interpret any number (Good-Lite n.d.).

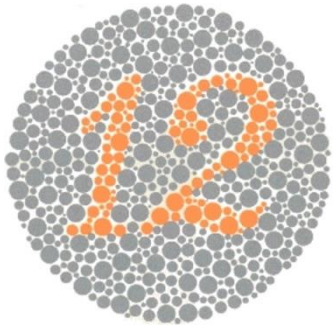

Figure 1. The demonstration plate from the original Ishihara color test. This plate served as the control that every individual taking the survey could see. This plate can be seen by individuals with normal color vision as well as individuals with a color vision deficiency. [Shinobu, CC-BY]

Prior to the public release of the survey, approval was granted from Wichita State University's Institutional Review Board (IRB) since the survey involved human subjects (Permit number 5308). The identity of survey participants remained anonymous throughout the duration of the research study, and all other IRB protocols were followed accordingly. Release of the survey occurred on January 20th, 2023, and remained open to the public for 16 consecutive days. Advertisements for the survey included a graphic with a hyperlink or QR code, which was distributed via the Honors' weekly email update, Shocker Blast, both personal and academic social media accounts, and physical flyers.

Upon entering the survey, participants were asked to verify their age, sex, and state of residence because this survey was designed to gain a general idea of adults within the state of Kansas. Given the selection of Ishihara plates, participants were asked to type in the figure they were able to see from each plate. Following completion of the survey, participants were provided with a web-based source for further information on color vision deficiencies if they had any personal concerns or curiosity. Responses were recorded within the Qualtrics system for later analysis and interpretation.

2.1 The Visual Transduction Pathway

To fully understand the science behind color vision deficiencies, one must first be familiarized with the mechanisms of the visual transduction pathway. Vision is dependent on the presence of light. For the brain to be able to process and make sense of the world, light that filters through the pupil of the eyes must be translated into an electrical signal for the brain to interpret. This phototransduction process is carried out by specialized cells called photoreceptors that are located in the retina of the eye (**Figure 2**). Photoreceptors are classified into two different categories: rods and cones. Rod cells are primarily responsible for low light scotopic vision, and in humans, they greatly outnumber the cone cells in a ratio of approximately 20:1 (von Lintig et al. 2010). On the other hand, cone cells, most notably found in the middle part of the eye known as the fovea, are responsible for detailed photopic vision, high visual acuity, and color perception (Sharpe et al. 1999). Another feature that differentiates rod cells from cone cells is the connectivity of the cells to bipolar cells and ganglia. While many rod cells are capable of sharing a single bipolar cell and ganglion, each

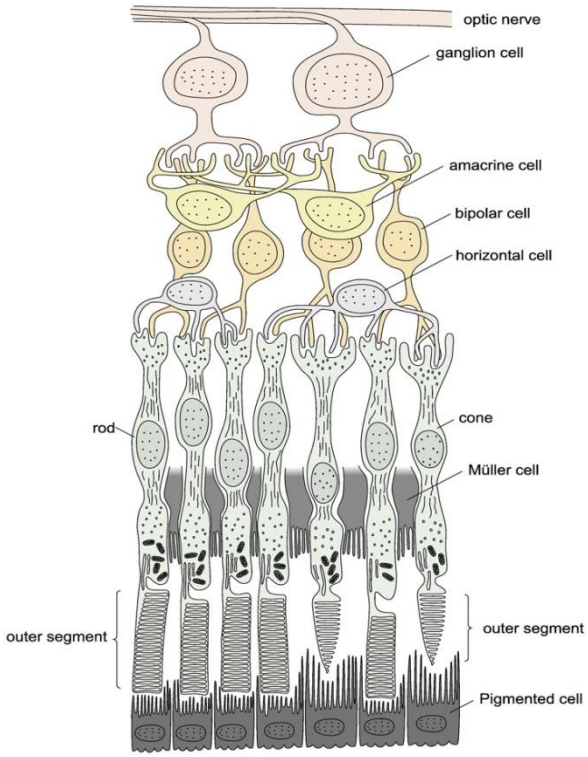

Figure 2. Schematic of the cells within the retina of most vertebrates. [Figure 1 from Imamoto & Shichida 2014 is reprinted with permission from Elsevier (© 2014)]

cone cell is designated to its own bipolar cell and ganglion. This makes sense because rods are tasked with collecting a large amount of light, resulting in less detailed vision. On the other hand, cone cells control the ability to see in high definition, so less sensory input prevents the neural pathway from being overstimulated. The method in which light energy can be translated into electrical signals is highly dependent on the anatomy of the rod and cone cells, most notably due to the presence of disks within the cells. Each cell houses a backbone called the cilium that runs along the length of the outer segment and connects it to the inner segment.

Perpendicularly attached to the cilium are folded disks that, in the cone cells, are continuous with each other and with the plasma membrane. This anatomical feature allows for a greater surface area for the rapid exchange of materials between the inner segment and the outer segment, such as the transportation of 11-cis-retinal for photopigment regeneration (Mustafi et al. 2009). While both types of photoreceptors follow similar phototransduction pathways, most of our knowledge is from extensive research on rod cells because many model organisms (such as rats) have rod-dominated retinas. Additionally, cone-dominated organisms are difficult to study, leaving many unknown aspects of the cone-specific phototransduction pathway (Imamoto & Shichida 2014).

Before the visual transduction pathway can even be set into motion, a specific visual chromophore must first be established. The chromophore 11-cis-retinal is the driving force for continuous vision— its absence would result in the inability to see anything (Kono et al. 2008). Its formation is the result of the natural oxidative cleavage of carotenoids (C40) to retinoids (C20). It can then be utilized to form 11-cis-retinal that is capable of binding to opsin and forming a complete visual pigment (von Lintig et al. 2010). Chromophore production, and ultimately the renewability of the visual cycle, is dependent on the uptake and oxidative cleavage of carotenoids, which utilize two different forms of vitamin A. Preformed vitamin A, most commonly found in animal products, is a retinyl ester known to be the active form of vitamin A since it can be hydrolyzed into retinol within the intestine. The other form of vitamin A— provitamin A— is most often found in plant-based food products and must be converted to preformed vitamin A to be most useful (MedlinePlus 2021). This process occurs by proteins that transform beta-carotene into all-trans-retinal, which is then reduced to all-trans-retinol (Kono et al. 2008). Acyltransferase enzymes can then produce retinyl esters (preformed vitamin A) by esterification of the all-trans-retinol. Retinyl esters can then be transported throughout the body with primary storage in the liver. Once the retinyl esters are taken up and re-secreted into the body as all-trans-retinol, visual chromophore production can finally take place (von Lintig et al.

2010).

The phototransduction pathway occurs within the outer segments (OS) of the photoreceptors and the retina's most outer layer, referred to as the retinal pigment epithelium (RPE) (Mustafi et al. 2009). In the case of rod cells, the key player of visual transduction is a G-protein-coupled receptor (GPCR) known as rhodopsin (von Lintig et al. 2010). Rhodopsin, a retinylidene protein, consists of an opsin protein bound to a chromophore, in this case 11-cis-retinal. When rhodopsin absorbs light photons that enter the eye, it acts as a catalyst that triggers a cascade of biochemical reactions that produce vision. The light absorption allows 11-cis-retinal to be photoisomerized into all-trans-retinal, which induces a conformational change in the opsin protein (Shichida & Matsuyama 2009). This opsin can then bind to the G-protein transducin, and guanosine diphosphate (GDP) is replaced with guanosine triphosphate (GTP). The activated transducin can then activate phosphodiesterase (PDE), which hydrolyzes cyclic guanosine monophosphate (cGMP), causing the photoreceptors' plasma membrane cation channels to promptly close. The change in electric potential causes the photoreceptor cell to become overall hyperpolarized (Mustafi et al. 2009). This change in electric potential allows for the all-trans-retinal to be reduced to all-trans-retinol by retinol dehydrogenases in the outer segments, which is transported to the retinal pigment epithelium where it undergoes an esterification process followed by the isomerization into 11-cis-retinol. The 11-cis-retinol is subsequently oxidized back into 11-cis-retinal and transported back to the outer segment of the photoreceptor where it binds back to opsin for the regeneration of rhodopsin (von Lintig et al. 2010). This completes the visual cycle, allowing for continuous vision (**Figure 3**).

Unlike rods, cone cells may not entirely depend on 11-cis-retinal from the retinal pigment epithelium (von Lintig et al. 2010). Even though cone cells follow a similar phototransduction pathway to rods, several studies centered around cone-dominant organisms provide evidence that supports the existence of a visual cycle unique to cone cells. In this proposed cone visual cycle (Mustafi et al. 2009), the newly reduced all-trans-retinol produced in the outer segments is isomerized within Müller cells, rather than the retinal pigment epithelium. These Müller cells, located in the retina, have the ability to regenerate the 11-cis-retinal chromophore for cone cells, which is key to continuous vision (Mustafi et al. 2009).

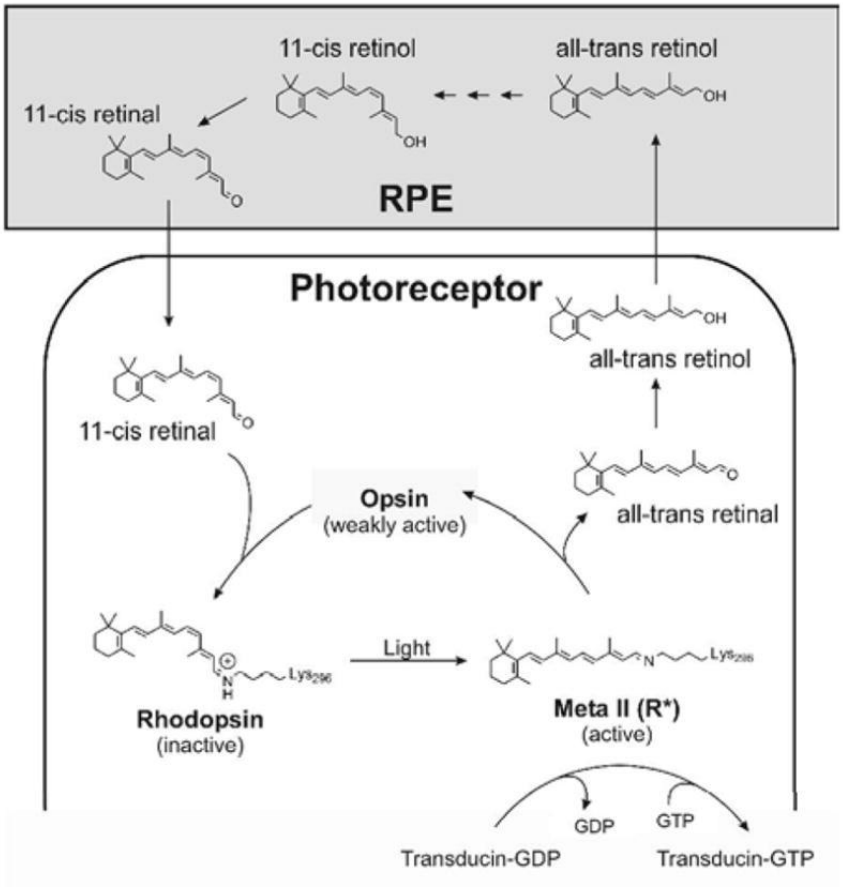

Figure 3. The biochemical phototransduction pathway as it cycles through the photoreceptor cell to the retinal pigment epithelium and back to the photoreceptor cell. [Figure 1 from Kono et al. 2008]

2.2 Genetics of Color Vision Deficiencies

At the surface level, color vision is the ability to differentiate wavelengths of light by comparing photon absorptions unique to different types of photopigments (Sharpe et al. 1999). In the case of light, any color can be produced from combinations of blue, green, and red light. Most of the human population has trichromatic vision in which color perception is possible due to three different varieties of cone cells, each with a specialized photopigment. S-cones can absorb light of short wavelengths of the visible spectrum, mostly the color blue. M-cones are capable of absorbing light of medium wavelengths, primarily greens. Lastly, L-cones can absorb longer wavelengths of light such as reds. However, it should be noted that cone cell photopigments do not actively register the wavelength of the light itself, but rather the rate at which photons are being absorbed by the photopigment. The absorbencies of these three photopigments function within a range of wavelengths that overlap with each other, but they possess a peak absorbency at differing locations within the visible light spectrum. M- and L-cone cells comprise the majority of present cone cells on the retina, clustered in the fovea, which allows for sharp visual acuity. S-cones are sprinkled around the outer portions of the retina in the

periphery of the fovea, and they are much less abundant than M- and L-cones (Sharpe et al. 1999).

Defects in any of the three types of cone cells may result in some form of color vision deficiency. Most cases of color vision deficiency are due to genetic mutations of the M- and L-cone cells, but S-cone-related color vision deficiencies do occur, though rarely (Neitz et al. 2011). Such genetic abnormalities can occur from point mutations when a single nucleotide is replaced by a different nucleotide. This can result in a silent mutation where the amino acid produced is not altered due to wobble nucleotides and the fact that mRNA codons are a degenerate code where more than one triplet arrangement can code for the same amino acid. Another category of point mutation is a missense mutation where the substituted nucleotide ends up coding for a different amino acid product. This can alter the protein folding process and either change the properties of the protein that affects its function or nullify the protein completely. However, more harmful point mutations have the power to terminate the genetic sequence altogether. This is known as a nonsense mutation, and it can have disastrous effects on the outcome of the protein being encoded if the genetic sequence is terminated too soon (Sharpe et al. 1999).

Nucleotide insertions or deletions may also arise within the coding regions or within the promoter sequence in which a section of the genetic sequence is added or removed. This has the potential to cause major disruptions in the genetic code because nucleotides are arranged in groups of three (termed codons) and the insertion or deletion of any number of nucleotides that are a multiple of one or two will cause a frameshift that can result in an early stop codon or an entirely unusable product that can have large implications (Neitz et al. 2011).

Another form of mutation that can influence color vision occurs during the process of crossing over during meiosis at the opsin gene locus on the X chromosome. Intragenic crossing over between the M-cone genes and L-cone genes can produce fused genes that contain coding sequences from both M- and L-cone genes, otherwise known as hybrids. Even though this crossing over event is more likely to take place between introns than exons, hybrids from exons crossing over can produce two different hybrids, depending on which gene's exon comes first. The first hybrid possibility is the 5'L-3'M (5'red-3'green) gene which is when the gene begins with L-cone exon. The second hybrid possibility is the 5'M-3'L (5'green-3'red) gene is when the gene begins with an M-cone exon (Sharpe et al. 1999).

2.3 Types of Color Deficiencies

In contrast to normal trichromacy with all three cone cells being present and functional, dichromacy is two-dimensional color vision in which one of the three photopigments is not fully functional. Further, monochromacy is one dimensional color vision that arises when only one photopigment is functional. With that in mind, it is important to remember that color vision deficiencies exist on a wide spectrum for each category, depending on a number of factors unique to each individual. For example, anomalous trichromats still possess all three cone photopigments. However, a deviation of function may be present in one of the photopigments, causing a slightly altered spectral sensitivity that may not even be noticeable if the cone photopigments function more similarly to a normal trichromat's. This is apparent when comparing the cone mosaic of an anomalous trichromat with a normal trichromat. An anomalous trichromat's cone mosaic should resemble a normal trichromat's cone mosaic, except that one of the cone photopigments is replaced by an anomalous photopigment. Other cases can more closely resemble the color vision of a dichromat, but while a true dichromat has a neutral zone of color perception, anomalous trichromats do not. The degree of the color vision deficiency has a strong dependence on hybrid photopigment genes because the replacement of a normal L-cone or M-cone photopigment gene can have significantly varying effects that depend on the position of the gene replacement. Anomalous trichromacy typically arises from unequal intragenic crossing over, but dichromatic disorders such as protanopia and deuteranopia are also possible outcomes (Sharpe et al. 1999).

Dichromacy encompasses a wide range of color vision deficiencies such as protanopia and deuteranopia, which are often coupled together because they both impact red/green color vision as a result of loss of function in the L-cones or M-cones, respectively (Sharpe et al. 1999). Red/green color deficiencies compose the greatest number of color vision deficiencies, most frequently affecting males due to the fact that red/green color deficiencies usually arise from recessive X-linked genetic mutations. This means that, in a heterozygous female with only one mutated X chromosome, the presence of the other normal X chromosome is enough to mask the mutated chromosome. However, if both X chromosomes were mutated, the female would exhibit the mutated trait. In the case of males, the one mutated X chromosome from the mother would be needed for the defective trait to be expressed (Neitz et al. 2011).

Protanopia and protanomaly, while similar in name and L-cone photopigment

dependance, differ because protanomaly is the deviation of L-cone function, and protanopia is the complete absence of L-cone photopigment function. Protanomals usually have a hue discrimination that is more shifted towards colors of shorter wavelengths, though the range varies from individual to individual. Individuals with protanopia (protanopes) often confuse reds, grays, and bluish blue/greens since they can only distinguish two hues and only about 21 different wavelengths. This is a rather small number of wavelengths, considering that the average trichromat can distinguish 7 hues (red, orange, yellow, green, cyan, blue, and violet) and approximately 150 different wavelengths. When unequal intragenic recombination in which crossing over occurs in the introns between L- and M-cone pigment genes, a 5'L-3'M hybrid gene is produced and protanomaly often occurs as a consequence. The replacement of a normal L-cone gene with a 5'M-3'L hybrid gene can also be a cause for protanopia in some cases.

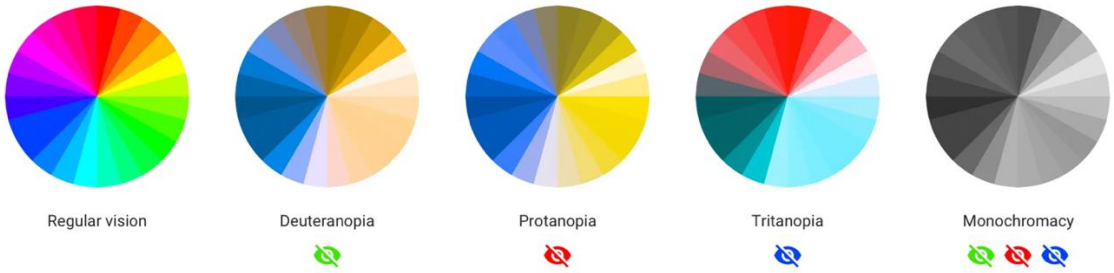

Figure 4. Comparison of the color spectra from the perspectives of an individual with normal trichromatic vision, deuteranopia, protanopia, tritanopia, and monochromacy. [Image from Tuchkov 2018, CC-BY].

(Sharpe et al. 1999).

The other common forms of dichromacy are deuteranopia and deuteranomaly (**Figure 4 & Figure 5**), which are often coupled with protanopia and protanomaly because they both impair red/green color vision in some manner. However, in the case of deuteranopia and deuteranomaly, it is the M-cone photopigments that are affected (Neitz et al. 2011). Deuteranomals have a hue discrimination that is shifted more towards longer wavelengths, and it can also vary from person to person. Individuals with deuteranopia (deuteranopes) are also only able to discriminate two hues, but they can usually discriminate up to 31 distinct wavelengths. Unequal intragenic recombination can also lead to deuteranopia when crossing over results in the formation of the 5'M-3'L hybrid gene (Sharpe et al. 1999).

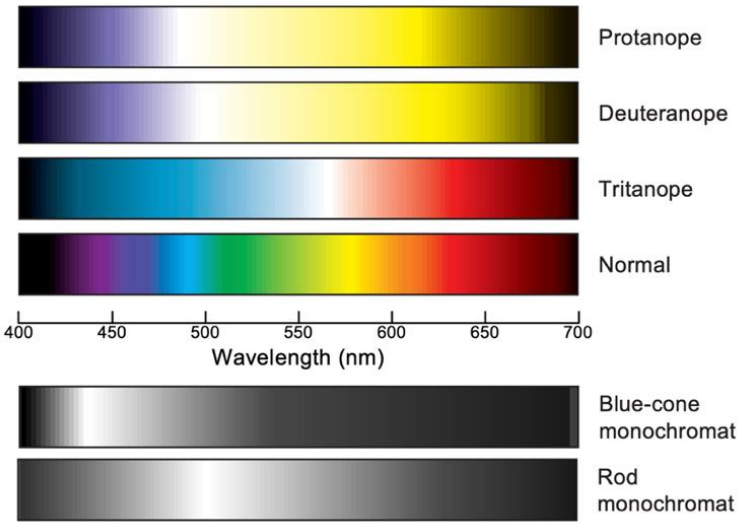

Figure 5. Color spectra from the perspective of an individual with protanopia, deuteranopia, tritanopia, normal trichromacy, blue cone monochromacy, and rod monochromacy. [Figure 1.13 from Sharpe et al. 1999]

Heterozygous carriers of protan and deutan effects are also worth mentioning because 15% of women inherit a mutated opsin gene in addition to a normal opsin gene (Sharpe et al. 1999). About 4% of that 15% are carriers for either protanopia or deuteranopia, while the other 11% are carriers for anomalous trichromacy (Sharpe et al. 1999). What sets heterozygotic carriers of dichromacy apart from heterozygotic carriers of anomalous trichromacy is that heterozygotic carriers of dichromacy possess molted, patchy cone mosaics with normal and abnormal cone distribution, while heterozygotic carriers of anomalous trichromacy have cone mosaics with normal M- and L-cones with additional hybrid cone photopigments present (Sharpe et al. 1999).

Even though most cases are X-linked in a way that leaves female, heterozygote carriers unaffected by the defective X chromosome, there are cases of heterozygous carriers having slightly abnormal color vision even though they are technically considered trichromatic. This is due to a genetic phenomenon known as X chromosome inactivation, which occurs during embryonic development when one of the two X chromosome in a female's somatic cells is transcriptionally silenced. Inactivation of one of the X chromosomes is random, but usually evens out with an equal number of maternal and paternal X chromosomes being inactivated. However, some individuals are subject to unequal X chromosome inactivation and may express color vision that more closely resembles one parent over the other (Lu et al. 2017).

Tetrachromacy is an extremely rare form of color vision abnormality that can arise from X chromosome inactivation, in which an individual possesses an additional fourth cone photopigment that allows them to see beyond the boundaries of the visible light spectrum.

Tetrachromacy is more often associated with the natural vision of birds and fish rather than humans (Imamoto & Shichida 2014). In humans, this extra cone photopigment is usually abnormal in some manner, and it can lead to the inability to process all four photopigment signals. Some tetrachromats are able to process all four photopigment signals independently, but this would be a very rare occurrence in humans (Marshall & Arikawa 2014).

Rarer forms of dichromacy known as tritanopia and tritanomaly are characterized by the complete or partial absence of function of the S-cone photopigments in low light conditions. This makes differentiating violets, blues, and blue/greens difficult for tritanopes (NEI… Types 2019). This color vision deficiency can arise due to genetic mutations such as a missense mutation of the S-cone opsin. In tritanopia, incomplete penetrance can occur, such that individuals with a mutated S-cone gene may or may not develop an abnormal vision phenotype. Even when mutations of the S-cones do occur, they do not usually alter an individual's visual acuity because most S-cones are not located in the fovea, but rather are dispersed around the fovea's periphery. Most tritanopes struggle to distinguish blues from greens and yellows from violets and grays. However, they still usually maintain the ability to differentiate yellows from blues, making tritanopia a less impairing condition than protanopia or deuteranopia because tritanopes are still able to distinguish reds, yellows, and greens. Unlike protan and deutan conditions, tritanopia can be difficult to diagnose (Neitz et al. 2011).

Aside from the many different forms of dichromatic color vision, monochromatic color vision deficiencies are possible too, though to a much less common degree. The frequency in males is 1 in every 100,000, and the frequency for females is 1 in every 10,000,000,000 (Sharpe et al. 1999). For instance, blue-cone monochromacy occurs when M- and L-cone cells are not present in the retina, causing little to no color vision and low visual acuity. Some blue cone monochromats may be able to see color in a way that more closely resembles a dichromat around the twilight hour when rods and S-cones are both active (Sharpe et al. 1999).

Similar to blue cone monochromacy is rod monochromacy. This is a rare congenital disorder characterized by total color blindness, photophobia, and low visual acuity. It arises from mutations in genes that influence all three types of cone cells. Rather than directly implicating the cone opsin genes themselves, rod monochromacy mutations target the gene that encodes the cGMP-gated cation channel in the cone photoreceptor, which plays a major role in the phototransduction pathway for all cone cells. This means that even if the cone cells are present in the retina, they will still not be able to properly function (Sharpe et al. 1999).

The stereotypical idea of color blindness that most people consider when they hear the words "color blind" is actually called complete achromatopsia, and it is extremely rare. It strongly resembles cone monochromacy, but with normal visual acuity. M- and L-cone cells can be affected, while S-cones are either inactive or absent from the retina (Neitz et al. 2011).

2.4 Color Vision Testing and Diagnosis

Color vision tests have been known to exist since before the early 1800s, but it was not until several unfortunate railroad accidents took place due to misinterpreting light signals that people began to realize the importance of color vision screenings (National Research Council Committee on Vision… Procedures 1981). Before that point, the extent of a color vision screening was asking the individual to identify a series of colors, the answers of which were subjective to the proctor's color perception. In 1837, a man of the name August Seebeck had participants sort colored pieces of paper, which proved to be a slightly less subjective method of color vision determination than previous methods of simply naming and describing the color (Melamud et al. 2004).

In today's world, a color vision test can fall into one or more of four different categories. A screening test is used to quickly diagnose color deficiencies. A grading/arrangement test is used to identify the degree of the color vision deficiency. The diagnostic test is used as a more precise measure to identify a color vision deficiency. Lastly, a vocational test is unlike the other three categories because it is not used to diagnose or screen for color vision deficiencies, but rather serve to simulate the typical work environment to see how an individual may perform in that work environment (Melamud et al. 2004).

In order for a color vision test to have widespread use and acceptance, it must have both reliability and validity. A test can be considered reliable if it is able to procure consistent results for a group, and it can be considered valid if results can be accurately compared to a set standard. To make sure that a test is reliable and valid, it is important to consider and control as many environmental factors as possible to ensure accurate results (Melamud et al. 2004). For instance, the type of illumination is important because different types of lights can potentially alter the hue of any given color. Many color vision tests will have an instruction manual that will specify the appropriate type of lighting, but most recommend using standard illuminant C lighting, which is an artificial light that mimics natural daylight. The intensity of the light is just as important as the type of light because too little light may result in difficulty distinguishing different colors, but too much light may create glare, which can decrease the perceived saturation of a color. Tests

will often suggest using anywhere from 250 lux to 600 lux, but never anything less than 100 lux (National Research Council Committee on Vision 1981).

Another factor to consider is the size of the field of view, which is influenced by the distance the participant is from the test, as well as the size of the test object, whether that be a plate or an image on a screen. This is an important aspect to a test's reliability and validity because too small of a field of view may result in an increased number of errors for any participant. Too large of a field of view may result in an increased number of people passing the test when they should not have (Melamud et al. 2004).

Efforts should also be made to control cognitive factors for each test subject because participants may experience test anxiety. Therefore, it is important to ensure that each participant is receiving the same treatment and the same set of directions as everyone else (National Research Council Committee on Vision 1981).

Plate tests are probably the most simple and popular methods for screening for color vision deficiencies. They are often inexpensive, durable, and easily accessible to the general population. They also have a 90-95% accuracy when used to screen for congenital red/green color deficiencies (National Research Council Committee on Vision 1981). The way these tests are typically conducted is with a multi-colored figure against a multi-colored background that is composed of small dots of various size and hue to make detecting the figure much more difficult by other means. The camouflaged figure is typically a simple symbol such as a number, letter, or basic shape. Pseudoisochromatic plate tests are usually used for screening, not diagnosis, and the results do not provide information on the severity or type of color deficiency. When administering a pseudoisochromatic plate test, it is important to have consistent lighting such as standard illuminant C. Participants should be shown each plate from the same distance (about an arm's length away), and the administrator should only allow the viewer about 4 seconds to report a figure. To reduce test anxiety, the administrator should make it clear to the participant that they may not see anything at any given plate, and that not seeing anything is not a bad thing. It is also important to make sure other environmental and cognitive factors are consistent with each participant in order to ensure accurate results (Melamud et al. 2004).

One of the most popular pseudoisochromatic plate tests is the Ishihara color plate test, developed in 1917 by Shinobu Ishihara from the University of Tokyo (Good-Lite n.d.). Consisting of 38 different plates, the Ishihara color test is most efficient in screening for red/green color deficiencies, but additional tests must be conducted to screen for both red/green and tritan defects (Birch 1997). Other versions of the test have been developed to include 24

plates or fewer. In the 38-plate edition, participants were allowed up to four errors before being considered potentially color vision deficient to some degree (Birch 1997). The first plate that participants are presented with is a test plate that can be interpreted by normal trichromats and individuals with color vision deficiencies. This allows participants to gain a sense of how the other plates will be portrayed. The Ishihara color plate test is comprised of four different types of plates, aside from the control plate (National Research Council Committee on Vision 1981). Vanishing plates (**Figure 6A**) are specific plates that are able to be interpreted by normal trichromats, but not by color deficient individuals. Qualitatively diagnostic plates (**Figure 6B**) use double digit numbers to differentiate a protan from a deutan. A protan would be able to see only one of the double digit's numbers, and the deutan would only be able to see the other. A normal trichromat would be able to report both numbers of the double digit. Transformation plates (**Figure 6C**) are similar in that they also contain two number figures, but their purpose to differentiate a normal trichromat from a color deficient individual. The fourth type of plate is the hidden digit plate (**Figure 6D**), and it serves the opposite function to the vanishing plate. With these plates, normal trichromats would not be able to distinguish any figure, while color deficient individuals would be able to see the figure (Birch 1997).

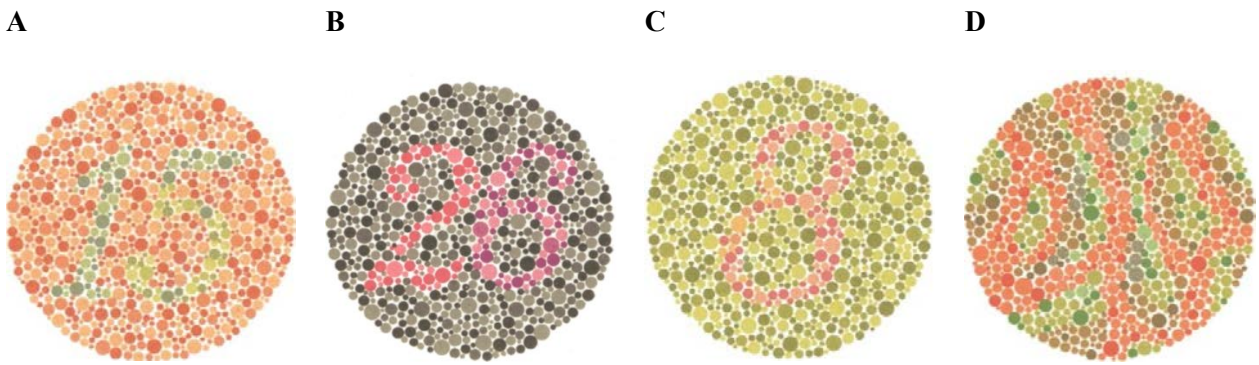

Figure 6 A-D. Four plates that represent each type of screening plate used in the Ishihara color test. From left to right: A: vanishing plate, B: qualitatively diagnostic plate, C: transformation plate, D: hidden digit plate. [Images from Shinobu, CC-BY].

In a time of digital operation and online accessibility, the question arises of whether an online Ishihara color test serves to screen for color vision deficiencies as accurately as a handbook plate test. A study conducted in South Africa put that question to the test in an experiment (n=120) of 18- to 25-year-old men and women (van Staden et al. 2018). In the

randomly selected online test group, nine or more errors was indicative of red/green color deficiency, though the online version did not specify whether color deficient individuals were protan or deutan. The handbook test group completed the 38-plate test under standard conditions (van Staden et al. 2018). In short, the experiment provided evidence that the online Ishihara color test was equally efficient in screening for color vision deficiencies as the original handbook version.

Another color vision test is the Farnsworth-Munsell 100-Hue (FM 100-Hue) Test, which tests a person's ability to differentiate colors based on hue by the accuracy in which they can sort and arrange four serieses of paper-covered caps (Melamud et al. 2004). Each collection of caps is provided in a box with two pilot caps with one at each end of the box. Participants are then required to arrange the 21-22 caps in the box based on color hue. Each of the four boxes are presented one at a time, and scores are calculated by comparing the participant's arrangements to the accepted correct arrangement. The higher the score, the greater the inability to differentiate colors based on hue.

A derivative of the Farnsworth Panel D-15 test, known as the City University Test, is a plate test that requires participants to match one of four peripheral colors to a central color on a given plate (National Research Council Committee on Vision 1981).

A similar test known as the Farnsworth dichotomous test for color blindness (also known as the Farnsworth Panel D-15) is primarily used to screen for red/green color vision deficiencies, but it can also be used to identify blue/yellow color vision deficiencies and cases of monochromacy. In this test, participants are presented with a box of 15 caps, each of which contains a different colored piece of paper. Participants are given a starting cap, and are then required to arrange the caps based on that starting cap. Participants are scored by comparing their arrangement to the set arrangement. While it is not the most effective screening test, it is often paired with the similar Lanthony Desaturated Panel D-15 Test. The test administration is the same as the Farnsworth Panel D-15, and scoring is almost the same as well. The key difference between the two tests is that individuals with anomalous trichromacy may be able to pass the Farnsworth Panel D-15, but they are not expected to pass the Desaturated Panel D-15 test (National Research Council Committee on Vision 1981).

The Lanthony New Color Test can be used to screen for acquired color vision deficiencies by testing neutral zones and color discrimination. The test consists of four boxes, each box containing 10 grey caps of variable lightness and 15 colored caps of the same hue but differing saturation. In the first part of the test, the participant is asked to sort the colored caps

from the gray caps. This allows for the identification of neutral zones, which are colors that may be confused with gray. The second part of the test is used to test for chromatic discrimination because participants are asked to arrange the colored pile of caps based on hue and the gray pile of caps based on lightness (Melamud et al. 2004).

Anomaloscopes are also commonly used to diagnose and classify congenital color vision deficiencies by utilizing color matching tasks. Two such models of anomaloscopes include the Nagel (model 1) to diagnose red/green color deficiencies and the Pickford-Nelson (Besancon) to diagnose blue color deficiencies. Anomaloscopes are extremely accurate in diagnosing color vision deficiencies, though they do require a trained individual for operation and maintenance (Melamud et al. 2004).

Lantern tests, while not used for screening or diagnosing purposes, can be used to assess an individual's ability to recognize color light signals such as traffic lights, railroad light signals, or other important operational light signals. The test administration is relatively simple, as one type of lantern presented only features a single-colored signal. A second type of lantern presented possess two colored signals (National Research Council Committee on Vision 1981).

The Holmgren Wool test is an older color vision screening test that requires participants to find a wool skein from a given pile that matches the presented wool skein. This test, while not commonly used to screen or diagnose color vision deficiencies these days, remains a mile marker for color vision testing since it was the first commercially available test for color vision (Melamud et al. 2004).

It is important to note that while a single color vision deficiency test can be enough to screen for color vision defects, multiple color vision deficiency tests are often needed to officially diagnose a color vision deficiency. Pseudoisochromatic plates have become common in screening for color vision deficiencies without the use of a second test.

2.5 Inherited Retinal Diseases

Affecting both rods and cones, inherited retinal diseases cause visual dysfunction and are the leading cause of blindness in the working age population (Brunet et al. 2022). With over 260 known heritable retinal diseases such as achromatopsia and retinitis pigmentosa, loss of cone cells can have severe effects on an individual's vision and lifestyle. This most often occurs due to primary cone cell death or secondary cone cell death. Primary cone cell death is the direct mutation of cone genes, such as with achromatopsia or other cone dystrophies. On the other

hand, secondary cone cell death starts with the degradation of rod cells, followed by the degradation of cone cells. One of the most notable conditions that arises due to secondary cone death is retinitis pigmentosa, which impacts 1 in 3,000 people worldwide (Newton & Megaw 2020). Such retinal dystrophies have an "estimated total worldwide economic burden of all visual impairments to global health systems is USD $3 trillion" (Brunet et al. 2022). Various treatments and cures such as gene replacement and genome editing are currently being developed with the hopes of restoring enough cone and rod function for an individual to live a better quality of life, but there is still a long way to go (Newton & Megaw 2020).

2.6 Life with Color Vision Deficiencies

While many sources go into detail about the challenges that color vision deficient individuals frequently face, it is important to mention the possible evolutionary advantages to color vision deficiencies. For instance, several studies have indicated that some dichromats may have more ease than trichromats when detecting camouflaged subjects (Morgan et al. 1992). Color can sometimes interfere with distinguishing textures or varying luminosities, but dichromats may sometimes have the advantage of filtering out the distractions that color can pose (Morgan et al. 1992). In most cases, dichromats can only differentiate about 10% of colors from the full visible light spectrum that trichromats can differentiate. However, because not every color within the full visible light spectrum appears equally in nature, dichromats may be able to perceive more color in a given scene of nature. For instance, tritanopes struggle to differentiate blues, violets, and blue/greens, so the percent of color they can perceive from the full visible spectrum would be much lower than the percent of color they could differentiate in a forest setting where blues and violets are much less commonly observed in comparison to greens and browns. One study tested this by presenting dichromats and trichromats with images of nature. On average, the dichromats were able to differentiate about 70% of the colors that the trichromats were able to differentiate (Pastilha et al. 2019).

Despite the additional challenges an individual with a color vision deficiency may face, a number of tools are being developed to assist color vision deficient individuals to better navigate this world of color.

For example, special filters for glasses are currently in the making for color vision deficient individuals (UC Davis 2020). Even digital color palettes are more accessible for color vision deficient individuals. The graphical software programs Photoshop and Illustrator have developed

functions that allow a creator to see how their digital project may appear to a color deficient individual. This allows for more accessible advertising and content creation (Chaparro & Chaparro 2017). In more recent years, specially designed mobile apps have developed a prototype to allow color vision deficient users to trace their finger along an image on the surface of their phone to transform a 2D image into something more distinguishable. The tracing of the image gradually increases the color contrast of the image using linear transformations that shear 3D data. Such an app has the potential to allow color vision deficient individuals to learn how to better differentiate similar colors, particularly in the case of protans, deutans, and tritans (Lau et al. 2015).

For the future development of potential technologies and perhaps even cures, it should be acknowledged that there are many different types of color vision deficiencies, and that the sense of color vision is unique to each individual. Despite the existence of slight differences among individuals' color vision, the lack of any component of color vision can often result in similar challenges in everyday life. A range of difficulties can arise in almost any environment or scenario, whether that be in the workplace, educational settings, social events, or even personal relationships.

RESULTS

A total of 302 responses were recorded by the digital survey, and 271 of these were complete, qualified responses (that is, the participant answered each prompt and met the survey qualifications of being a current Kansas resident of age 18 or older).

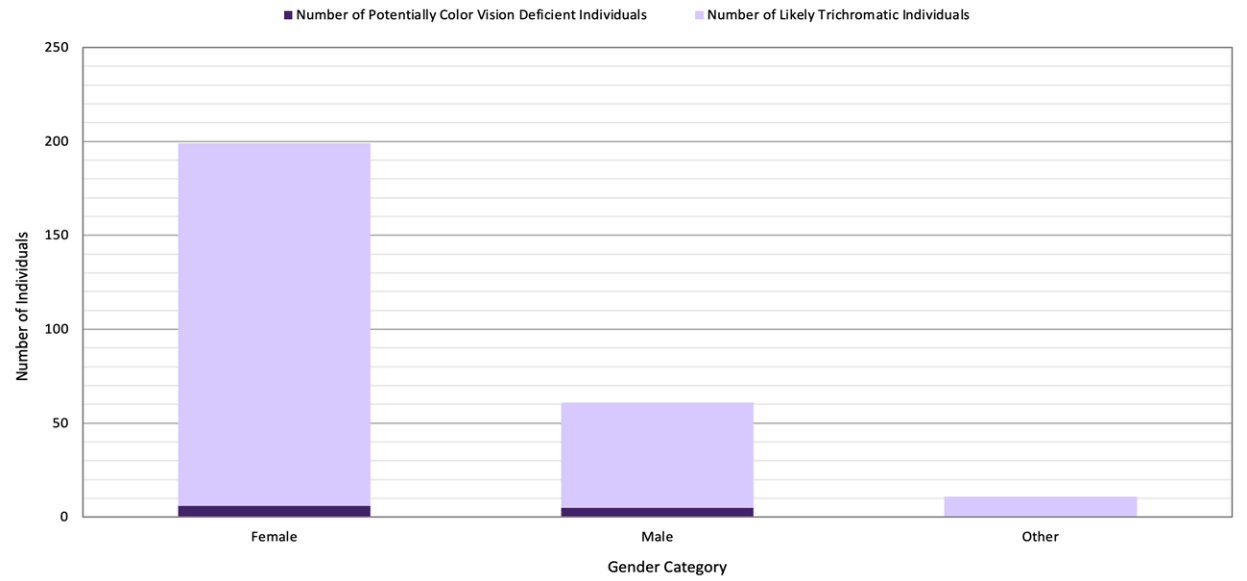

Figure 7. Results of the Kansas color vision survey based on 11 digital plates from the Ishihara color test. Respondents from each gender category demonstrated that 97% of females (n=199), 91.8% of males (n=61), and 100.0% of other genders (n=11) had trichromatic (normal) vision. Based on these results, 3.0% of females and 8.2% of males may exhibit a color vision deficiency.

Of those 271 responses, subject responses were further categorized into one of three categories based on their sex: Female, male, or non-binary/third gender/prefer not to say. It was observed that 97.0% of female participants (n=199), 91.8% of male participants (n=61), and 100.0% of other gendered participants (n=11) demonstrated trichromatic vision with fewer than 3 errors in this 11-plate test. Of those individuals, 78.9% of female participants, 75.4% of male participants, and 81.2% of other gendered participants completed the survey with 0 errors (**Figure 7**). A standard of 3 or more errors served as the trichromatic/color vision deficient determinative criterion based on protocols established by Birch (Birch 2010). In accord with that trichromatic/color vision deficient threshold, 3.0% of female participants and 8.2% of male participants could be considered to have a possible color vision deficiency. Further testing would need to be completed for an official diagnosis. Of the 11 plates, 1 plate served as the control, 9 plates served to screen for red/green color vision deficiency, and 2 plates served to

screen for protanopia and deuteranopia. There was an average of 9.9 errors for each plate, with a total of 109 errors over all 11 plates (**Figure 8**). Of those 109 errors, 32 of the errors were from plate #8. Only one error was reported for the control plate #1.

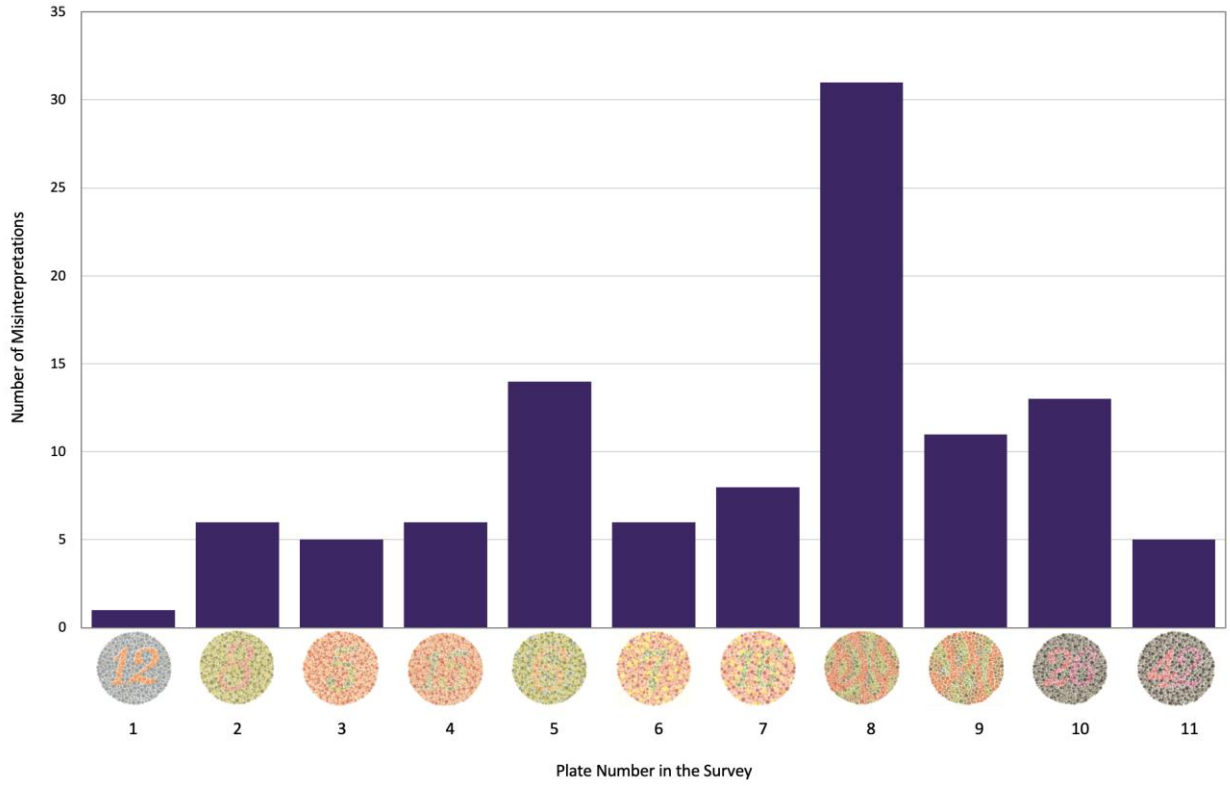

Figure 8. Number of misinterpretations associated with each Ishihara color used in the Kansas color vision survey. Plate 1 served as the control plate. Plates 2–9 screened for red/green color vision deficiency. Plates 10–11 screened for protanopia and deuteranopia (specific types of red/green color vision deficiency). Plate 8 represents the first plate in which a normal trichromat would not have been able to observe a number figure, but a red/green color vision deficient individual would have seen a number figure. Two frequently missed plates (plates 5 and 10) both featured the number "6" which was often mistaken for "8."

Even though the majority of participants demonstrated normal trichromatic vision, there were a handful of participants, both male and female, that displayed a red/green color vision deficiency. The survey results of one female indicated protanopia. Two participants, one male and one female, showed a milder indication of protanopia or deuteranopia. Further screening tests and diagnosis would be required to confirm these results.

Another result worth mentioning involves the two hidden digit plates, in which the presented figure could only be seen by individuals with a red/green color vision deficiency. The first of the two hidden digit plates, Plate #8, was the most missed plate of all 11 plates. A person with a red/green color deficiency would have observed the number "5" in the first plate and the

number “45” in the second plate. However, on Plate #8, a significant number of participants reported seeing a “4”, and 3 of the 271 participants reported seeing the number “45.” The second hidden digit plate, Plate #9, had no participant correctly identify the figure “45,” though several participants reported seeing the number “4.”

DISCUSSION

While the original Ishihara color test consists of 38 plates, other versions of the test exist in which as few as 10 plates were utilized as an initial screening tool for red/green color vision deficiency. My digital survey featured 11 of those 38 plates for brevity. With that in mind, establishing a trichromatic vision/color deficient vision threshold became somewhat subjective, as these plates were handpicked based on the 3:1 ratio of red/green deficiency screening plates to protanopia/deuteranopia screening plates in the original test. For example, only 9 of the 30 red/green color deficiency screening plates and only 2 of the 6 of protanopia/deuteranopia plates were utilized. This could have resulted in a margin of error in screening for a true color vision deficiency.

Results that were potential false positives or false negatives could be due to the fact that participants were permitted to complete the survey on their personal electronic device. There are no standards for brightness, contrast, saturation, and even hue for many electronic devices. These differences may have contributed to participants' visual perceptions.

Commonly confused numbers should also be taken into account because many individuals from each gender category (n=48) who otherwise demonstrated trichromatic vision misidentified one or two plates. Most commonly, the number "6" was mistaken for "8" in more than one plate, which may or may not be correlated to the individual's ability to distinguish colors.

The method for determining the trichromatic vision/color deficient vision threshold should also be taken into account when considering the validity of the screening survey. When evaluating the recorded responses for each participant, errors were considered to be any response that did not match the number a normal trichromat should have seen or not seen. This included commonly confused numbers, letters, the number a red/green color deficient individual would have reported, or not seeing any figure at all. This standard of assessment became especially important for the plates with hidden digits because some individuals reported seeing only one of the two numbers that were supposed to have been visible to a red/green color deficient individual. Such answers were not considered to be indicative of a red/green color deficiency. Other participants reported seeing figures such as animals, letters, or patterns. These responses, like the individuals who only saw part of the hidden digit figure, were deemed to be the equivalent of having not seen any figure at all because it can be assumed that many of the likely trichromatic participants were determined to find something in the nothing presented. The two

hidden digit plates were placed as the 8th and 9th plate in the series of 11 plates. All the previous plates should have contained visible figures to the typical trichromat, so it would make sense that the first hidden digit plate would have the most errors because participants likely became comfortable in assuming that they would be able to see a figure in each plate.

The results of the Kansas visual deficiency survey correlate with the national statistics for male participants, as the survey data revealed that 8.2% of male participants (n=61) may have a potential color vision deficiency, thus correlating with 8.0% of males in global research studies (Chaparro & Chaparro 2017). However, the survey data also revealed that 3.0% of female participants (n = 199) have a potential color vision deficiency, whereas 0.5% of females are reported in global research studies (Chaparro & Chaparro 2017). In other words, about 1 in 200 women have some form of color vision deficiency but in the Kansas sample, six times the number of females (6 out of 199) demonstrated having a potential color vision deficiency. This is interesting because the female sample size was over three times the size of the male sample size. This result may indicate that color vision deficiencies may be more prevalent in adults residing in the state of Kansas than previously assumed. A broader survey would be required to examine this possibility.

CONCLUSION

Nearly 10% of Kansans and the global population are color vision deficient in some way. Understanding the biochemistry behind color vision deficiencies in humans and the impact such deficiencies have is imperative for improving visual accessibility for all populations. Both inherited and acquired color vision deficiencies exist as a wide gradient. In almost every case, the root of the visual color deficiency can be attributed to the visual transduction pathway, which may result in a range of vision-related consequences. Cone cells are the foundation for color vision, and even slight modifications can lead to forms of dichromacy or monochromacy. Fortunately, a variety of tools and tests exist for the screening and diagnosis of the many types of color vision deficiencies in humans. The Ishihara plate test is often a go-to when screening for red/green color vision deficiencies and, with most color vision deficiencies being red/green, it serves an important role in helping people gain a sense of whether they may be color deficient. Even in this survey sample size of n=271, several color vision deficient individuals reported not being aware of having a potential color vision deficiency until participating in the survey. While further assessment from a vision professional is necessary for an official diagnosis, the awareness the Ishihara test provides is a good first step towards improving the lives of color vision deficient individuals.

Results of the color vision survey revealed a higher prevalence of color vision deficiencies in adult female Kansans at potentially 3.0%, compared to global prevalence of 0.5% (Chaparro & Chaparro 2017). Results for male Kansans at 8.2% with a potential color vision deficiency corroborates the global prevalence of 8.0%. Overall, this may mean that about 11.2% of adult Kansans exhibit some form of color vision deficiency, compared with the 10% global percentage. While more follow-up is necessary to confirm this observation, the greater-than-expected proportion of color vision deficient individuals in Kansas is a strong reason to encourage increased awareness of color vision and increased color accessibility for all populations.

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