Causes of Color Blindness: Function and Failure of the Genes that Detect Color

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Abstract

Color blindness affects nearly 10% of the entire population, with multiple types of color blindness from various genetic mutations. In the following sections, the nature of light and how the human eye perceives light will be discussed. Afterward, the major forms of color blindness and their genetic causes will be considered. Once these genetic causes have been established, the current method for diagnosing color blindness will be investigated, followed by a discussion of the current treatments available to those with color blindness. Finally, a brief discussion will address possible future work for color blindness with the hope of finding better treatments and a future prevention.

Causes of Color Blindness: Function and Failure of the Genes that Detect Color

Introduction

Without the human eye's ability to detect color, the world would appear as dull as a black and white movie. However, despite our ability to detect color, not all humans perceive the same colors as one another. Some individuals may find it difficult to distinguish between particular colors of light while much of the population finds it relatively easy. This phenomenon is known as color blindness, and it has many different forms and causes. Color blindness affects nearly 8% of all males and about 0.5% of all females [1]. Color blindness was first reported by John Dalton in 1794 when he observed how he and his brother perceived color compared to other people. He concluded that the colors he and his brother perceived were different from other observers. Dalton went on to theorize that this unique color perception was due to a slight blue tint of his vitreous humor [2]. When Dalton died, his eyes were examined to find out that the specific type of color blindness he had experienced was called deuteranopia (making it difficult to distinguish reds from greens) [3]. It is known today that color blindness has nothing to do with the vitreous humor, but rather with the cones located on the retina of the inner eye. However, to understand the different forms and causes of color blindness, it is first essential to understand how light works.

What is Light?

The electromagnetic spectrum (EMS) is the term for the full range of electromagnetic waves (Figure 1). All forms of light, both visible and invisible, fall somewhere along this spectrum and can be further divided into seven main categories depending on wavelength (λ) and

frequency (ν). The category with the longest wavelengths and lowest frequencies are radio waves, followed by microwaves, infrared rays (IR), the visible spectrum, ultraviolet rays (UV), X-rays, and finally gamma rays. While the entire EMS spans nearly 10^{24} m, the visible light spectrum range is 400-700 nm ($4.0 \times 10^{-7} – 7.0 \times 10^{-7}$ nm), which accounts for only 300 nm (3.0×10^{-7} m) in total (Figure 2). It is in this small spectrum that all the colors that the human eye perceives are located.

Within this visible spectrum, all the colors of the rainbow can be found (red, orange, yellow, green, blue, indigo, and violet). As the wavelength of light increases, the color of light observed by the human eye changes. The human eye can detect a wavelength change as small as 2nm which gives rise to about 150 unique wavelengths of light [4]. These individual wavelengths can then be combined to create over 7,000,000 different, detectable colors [5]. Since both frequency and energy are inversely proportional to wavelength, as the wavelength of light changes, so does the frequency and energy. Starting at the highest wavelength and lowest frequency side, the color red is observed, followed by orange, yellow, green, blue, and finally violet. Therefore, of all the colors the human eye can detect, violet light has the highest frequency and thus the highest energy, and red light has the lowest frequency and thus the lowest energy.

Among all the different types of lights we have today, the sun is one of the only forms of natural light that exists (a few others would be fires, fireflies, etc.). The light rays that are emitted from the sun are white in color, which is the combination of all the colors of the visible light spectrum combined into one. According to NASA, as viewed from space, the sun is actually white in color, but due to our earth’s atmosphere, some of the light rays get scattered, leading to

the sun appearing yellow from earth [6]. When a beam of white light from the sun hits for example a blade of grass, all the colors of the visible light spectrum are absorbed into the blade of grass except for light rays around 570 nm in length. These light rays, which are seen by our human eye as green, get reflected onto our eyes and our brain uses these light rays to process an image. For objects such as a piece of paper that appear white, all the light rays are being reflected evenly into our eyes and none of them are being absorbed by the paper. On the other hand, objects that appear black absorb all the different wavelengths of light, leaving nothing to be reflected into the eye. In fact, in the truest definition, black is not defined as a color for this very reason, but rather the absence of color.

How the Human Eye Detects Light

When light from the outside world gets reflected into the eye of a normal functioning individual, the light passes through the pupil and hits the lens. The lens focuses this light onto the back of the eye which is composed of a layer of cells called the retina. The retina has 3 distinct layers – the photoreceptor layer, bipolar layer, and the ganglion layer – which transmit light from the retina into an action potential that gets sent to the optic nerve and eventually to the occipital lobe of the brain for processing [7, 8]. As light hits the retina, it first must pass through the ganglion cells located on the innermost part of the eye. The light then passes through the bipolar cells and finally to the photoreceptors where it gets detected (Figure 3). The photoreceptor layer of the retina is composed of rods which detect brightness and cones which detect color. The rods are distributed mainly along the outer edges of the retina which allows for better detection of images along the peripheral visual field. The cones are located mainly in the fovea centralis – a small

central spot positioned on the retina [9]. This allows for the greatest color detection/differentiation on the object being focused on by the eye.

Three different types of cones each have specific proteins that are highly sensitive to blue, green, or red light referred to as S-cones, M-cones, and L-cones respectively (Figure 4) [10]. These cones are similar to how a computer is designed with red, green, and blue light (RGB) that can individually be increased or decreased to display all the different colors of the visual spectrum. The specific proteins found in these cones are forms of a protein known as photopsin that are highly sensitive to a specific wavelength of light (short, medium, or long). It is this combination of cones that allow the human eye to detect light across the entire visual spectrum. Based on the relative levels of activity of the S-cones, M-cones, and L-cones, all the colors of the visual spectrum can be observed [11, 12]. However, if one of these cones becomes nonfunctional, much of the color observed in the visual field can become altered.

Three different genes provide the instructions for making the specific photopsin proteins found within each of the 3 different cones. These genes are opsin 1 short wave gene (OPN1SW) which makes the photopsin for short wave, blue/violet light, opsin 1 medium wave gene (OPN1MW) which makes the photopsin for medium wave, green light, and opsin 1 long wave gene (OPN1LW) which makes the photopsin for long wave, red light [13-15]. The OPN1SW gene is located on the long arm of chromosome 7 at position 32.1 (7q32.1) [13], while the locations of both the OPN1MW and the OPN1LW genes can be found on the long arm of the X chromosome at position 28 (Xq28) [14, 15].

As light is channeled onto the retina from the lens, both rods and cones absorb the photon energy and initiate nearly an identical chemical cascade that converts the light into an appropriate action potential (Figure 5). One of the only differences between these cascades in photoreceptors are the unique opsins that initially detect the light which were previously mentioned [10]. Interestingly, when light enters the eye, it stops the inhibition of the visual pathway, allowing the brain to detect the light. As light enters the eye and hits the retina, specific opsins (short, medium, or long) are activated according to the specific wavelengths of light hitting the retina. The S-cones will only activate its chemical cascade if short wavelength, blue/violet light is present. This is the same for both the M-cones and L-cones as well.

When a specific wavelength of light is present, it will travel into the respective cones and hit iodopsin. Iodopsin is composed of iodine and the specific light sensitive protein with retinal bound to the photopsin [16]. The light will convert 11-cis retinal into all-trans retinal which opens the binding site on photopsin. Photopsin then activates a protein called transducin which activates phosphodiesterase (PDE). Phosphodiesterase breaks down cGMP which causes cGMP gated channels transporting Na^+ and Ca^{2+} into the cell to close. This hyperpolarization of the cone causes voltage gated Ca^{2+} channels to close, which inhibits the release of a neurotransmitter known as glutamate to be released into the bipolar cells. Under normal conditions where no light is present, glutamate is continually being sent from the cones to the bipolar cells, acting as an inhibitor of an action potential. However, once light enters the cones, the glutamate being released from those cones becomes inhibited. This inhibition of glutamate into bipolar cells causes a stimulatory response in the bipolar cells which causes these cells to release large amount of glutamate into the ganglion cells. This increase of glutamate in ganglion cells

stimulates an increase in action potentials in the ganglion cells which gets sent to the optic nerve and finally up to the occipital lobe of the brain for processing [17].

Major Forms of Color Blindness

The two main categories that different forms of color blindness can be grouped into are referred to as red-green color blindness and blue-yellow color blindness. Between these two groups, red-green color blindness is far more common than blue-yellow color blindness. Individuals with red-green color blindness find it difficult to distinguish between reds and greens, while individuals with blue-yellow color blindness have difficulty distinguishing blues from greens, and yellows from reds [18]. In addition to these two main categories of color blindness, there is also a third, less common category known as complete color blindness which typically consists of no visual colors being observed and is extremely rare [18, 19].

Red-green Color Blindness

Deuteranomaly

Of all the varying forms of red-green color blindness – and color blindness in general – deuteranomaly is by far the most common. Deuteranomaly is a form of color blindness where greens appear redder (Figure 6). Deuteranomaly affects nearly 5% of all males and around 0.35% of all females [20]. Both the red photopsin gene and the green photopsin gene are located on the X chromosome and are positioned in a head-to-tail tandem array [21]. The proximity of these two genes, the fact that they are on the X chromosome, and the fact that color blindness is a recessive disorder are all factors that make deuteranomaly the most common form of color blindness; particularly among males.

This form of color blindness is caused by malfunctioning green cones that have their peak sensitivity shifted toward red cones [20]. This increased overlap between the red and green cones makes it difficult to distinguish hues of color that have excessive overlap (Figure 7B). Particularly with deuteranomaly, greens are harder to distinguish than reds. Therefore, when red hues of light enter the eye, they get detected by the normal functioning red photopsin cones, but some hues of red also get detected by some malfunctioning green cones. Alternatively, when hues of green light enter the eye, some of the cones are not activated since the peak sensitivity of green cones has been shifted toward the red cones. This creates an altered form of color since it is the ratio of cone activity that causes a signal to be sent to the brain for processing.

While both the red and green photopsins are created by head-to-tail tandem genes, research has indicated that these malfunctioning green cones are not caused by either the green photopsin gene or the red photopsin gene, but rather by a 5'-green – red-3' hybrid gene that becomes expressed in a particular way [21]. This 5'-green – red-3' hybrid gene is not necessarily the cause of deuteranomaly because it has also been found in individuals who have normal color vision (Figure 8A). However, the way in which this gene is expressed seems to indicate its efficacy in creating deuteranomaly.

In a study conducted by Hayashi, Motulsky, and Deeb, 10 male individuals with either deuteranomaly or deuteranopia (complete absence of green cones), were studied to determine if the position of the 5'-green – red-3' hybrid gene had any connection with deuteranomaly. These researchers discovered that out of all ten subjects, the 5'-green – red-3' hybrid gene was always located in the second position, while the first position was always occupied by the red photopsin gene (Figure 8B) [21]. In addition, 2 individuals with a 5'-green – red-3' hybrid gene in their

genotype with a normal phenotype had the 5'-green – red-3' hybrid gene located at the third position (Figure 8A). Therefore, Hayashi, Motulsky, and Deeb concluded that only the first two genes become expressed in humans, leaving the third gene inactivated. These findings are consistent with a previous research article that both Motulsky and Deeb were a part of where the researchers sought to determine the expression of both the red and green photopsin genes. It is known that there is a single red photopsin gene located upstream of multiple green photopsin genes which can be found on normal individuals [22]. However, it was unclear how many of these green photopsin genes were being expressed in individuals with normal color vision. Therefore, researchers analyzed sequences of mRNA from red- and green-specific photopsin genes and compared them with the respective genomic DNA sequences to find that only one green photopsin pigment gene was being expressed [23]. These researchers suggested that a control-like protein located around 3.8 kilobases upstream of the transcription start site (TSS) of the red photopsin gene controlled the transcription of a single mRNA from the multiple green photopsin genes present in the genome. The conclusion of the study showed that individuals with a 5'-green – red-3' hybrid gene do not necessarily develop deuteranomaly, but only when the 5'-green – red-3' hybrid gene is located just downstream of the red photopsin gene [23].

These findings support the observation made by Jørgensen, Deeb, and Motulsky that molecular abnormalities (e.g. the 5'-green – red-3' hybrid gene) were seen 2 times more than the phenotypic color vision defects in Caucasians. For African Americans, the largest molecular defect was the 5'-green – red-3' hybrid gene and these molecular defects were found the be 5 times more prevalent in individuals than the phenotypic color vision defects [24].

Further evidence supporting these findings show that individuals with normal color vision have been detected to have a 5'-green – red-3' hybrid gene located within the genome in addition to an individual with a point mutation on one of the green photopsin genes known to cause a form red green color blindness which had perfectly normal color vision [25, 26]. While unusual, these findings fall in line with the theory of only having a single red and a single green gene being expressed if the 5'-green – red-3' hybrid genes or the green photopsin gene with a point mutation were located downstream of the normal red gene and normal green gene coding for the respective photopsins.

Protanomaly

Another form or red-green color blindness is protanomaly, which is also referred to as "red-weakness". It is estimated that around 1.08% of males have protanomaly while only about 0.03% of females display protanomaly [27]. As the name may suggest, protanomaly causes individuals with this form of color blindness to have a difficult time detecting the saturation and brightness of red hues, thus leading to "red-weakness" [28]. This red-weakness found in protanomaly patients affects other colors of the color wheel such as yellow, yellow-green, and orange which all appear more green, and also more pale when compared to a normal vision individual since the red tones are harder to detect (Figure 6) [29]. In addition, individuals with protanomaly may also mistake reds for blacks since they have their visual field darkened at the red end of the spectrum [30].

Both Protanomaly and Deuteranomaly fall under the category of anomalous trichromats. This is because in both types of color blindness, all three types of cones are still present

(therefore receiving the name trichromats), but in each case, one of the three cones is mutated/defective (therefore the name anomalous is given). In the case of protanomaly, the long-wavelength, red photopsin gene is mutated, giving rise to the abnormalities found among individuals with protanomaly. In addition, as mentioned in the previous section, there is only a single OPN1LW gene and it is located on the long arm of the X chromosome at position 28 (Xq28) [15]. This location on the X chromosome makes protanomaly a sex-linked disorder and explains the increased prevalence of the disorder found among males compared to females.

Since Protanomaly is a relatively rare form of color blindness, details on the exact genetic cause remain difficult to determine. However, some evidence has pointed to the order in which the OPN1LW gene appears on the X chromosome. In a study conducted in 2006, two Japanese participants had a specific pattern of gene arrays that were unusual from what is normally observed in normal-color individuals [31]. Both participants had a green opsin (OPN1MW) gene as their first gene, followed by an OPN1LW gene located just downstream. In addition, both individuals also had an additional two OPN1MW genes located downstream from the OPN1LW gene [31]. While the OPN1LW gene was determined to be at the second position, normal color vision was still expected. However, both participants were identified as having protanomaly [31]. Among the vast research performed through the 1990s and early 2000s, this was the first time a green-red opsin gene order had been reported [31].

An additional finding from this research was that while no mutations were observed in the introns or exons of the OPN1LW gene, both participants had an A71C substitution in the promoter region of the gene [31].

An earlier article on genotype-phenotype relationships in red/green color defects conducted in 1992 mentions similar findings. These researchers observed that individuals who were carriers for a fused red-green gene, with additional normally functioning OPN1MW genes largely became protanomalous, with few exceptions [32]. Three participants in particular had only a single 5' red-green 3' hybrid gene. In each of the three subjects, the fusion of the OPN1LW and OPN1MW genes took place either at intron 2, 3, or 4 [32]. The results of their study helped show that the replacement of three hydroxyl-bearing amino acids on exon 5 from the OPN1LW gene (Tyr 277, Thr 285, and Tyr 309) with the corresponding hydrophobic amino acids in the OPN1MW gene (Phe 277, Ala 285, and Phe 309) were sufficient to create a photopsin protein that is spectrally similar to a normal OPN1MW gene in function, thus leading to protanomaly in these individuals [32]. These researchers hypothesize from their study that any individual with a single 5' red-green 3' (OPN1LW-OPN1MW) hybrid gene will develop as a protanomalous individual [32].

Protanopia

Protanopia is a form of red-green color blindness similar to protanomaly. However, instead of a malfunctioning red photopsin cone from the OPN1LW gene, individuals with protanopia completely lack the red photopsin cones from the OPN1LW gene. With no red photopsin cones, people diagnosed with protanopia are unable to see any 'red' light and are likely to confuse black for most hues of red [33]. Individuals with protanopia also may find difficulty distinguishing dark brown with dark green, mid-greens with hues of orange, and some purples with hues of dark pink (Figure 6) [33]. Protanopia is also classified as a deuteranope rather than a tritanope since there are only two cones functioning in these individuals compared to

normal color-vision subjects. This form of color blindness is prevalent to about 1.3% of all males and about 0.02% of all females [34]. As with the other red-green forms of color blindness, protanopia is a sex-linked disorder since the OPN1LW gene is located in the X chromosome.

The exact cause for the complete loss of functional red photopsin cones remains unclear. Some researchers believe that if the fusion of the OPN1MW and OPN1LW genes occurs upstream of exon 3, protanopia may develop since the gene will essentially code for a green photopsin cone [35].

Deuteranopia

Deuteranopia is an X-linked recessive disorder affecting the medium wavelength photopsin cones. This form of color blindness is like protanopia in that there is a complete deletion of one type of cone: in this case, the green photopsin cone from the OPN1MW gene. Individuals diagnosed with deuteranopia will see colors only through the lens of their other two cones (red and blue cones) and will be unable to detect hues of green which will drastically change the way in which they perceive colors. Individuals with deuteranopia will see a unique set of colors where normal red hues will appear brown and normal green hues appear more yellow (Figure 6). This alteration in color perception causes most of the world – from the eyes of a patient with deuteranopia – to appear as a combination of yellows and browns.

As with protanopia, deuteranopia falls under the category of deuteranopes since there are only two functional types of cones opposed to three in normal color-vision individuals. Deuteranopia is not very common in most individuals, accounting for only 1.2% of all males and around 0.01% of all females [34].

Deuteranopia is a condition caused by point mutations in the medium wavelength photopsin that is coded by the OPN1MW gene which produce non-functional M-cones [36]. Only one mutation has been directly linked to causing nonfunctional cones and that is C203R. This point mutation causes the replacement of arginine with cysteine at the 203rd amino acid. The specific point mutation most frequently observed is the substitution of a thymine with a cytosine [37]. However, little information is known about how exactly this mutation causes a non-functional medium wavelength photopsin.

One study suggests that the C203R mutation causes errors in the folding of the medium wavelength photopsin protein [38]. The study showed that photopsin possibly relies on a disulfide bond between the 3rd transmembrane helix and the 2nd extracellular loop which gets disrupted in the C203R mutation. This disruption in the disulfide bond leads to errors in the tertiary folding of the protein and may present problems in transportation of the medium wavelength photopsin from the endoplasmic reticulum to the Golgi apparatus. Also, this folding may affect the functionality of the protein [38]. This information is consistent with a protein found in rods called rhodopsin. Rhodopsin shares many similar characteristics with photopsin and has an amino acid structure that is nearly 44% similar [22]. In rhodopsin, 85% of people with retinal pigmentosa (a form of slow vision loss [39]) have had mutations that effect the transport of the rhodopsin from the endoplasmic reticulum to the Golgi apparatus [40].

Another study showed that the A70C mutation on the OPN1MW gene may be a source for the nonfunctional medium wave photopsin. In the study 32 out of 35 males with some form of green color blindness (deuteranopia or deuteranomaly) had a nucleotide substitution resulting in the replacement of alanine for cysteine (A70C) on the medium wavelength photopsin protein

at the second position of the promoter region [41]. While it remains unclear how this mutation specifically effects the medium wavelength photopsin protein, one idea is that the cytosine mutation is a source for DNA methylation which causes the gene to be suppressed, resulting in the lack of medium wavelength photopsin protein [42].

Blue-yellow Color Blindness

Blue-yellow color blindness is far less common than red-green color blindness due to the chromosome that the OPN1SW gene is located on. There are also only two different forms of blue-yellow color blindness and they are referred to as tritanomaly and tritanopia. As mentioned previously, while the OPN1MW gene and the OPN1LW gene are both located in a tandem array on the long arm of the X chromosome, the OPN1SW gene is located on the long arm of chromosome 7 at position 32.1 (7q32.1) [13]. The fact that the OPN1SW gene is not located on a sex chromosome indicates that the prevalence of blue-yellow color blindness should not necessarily be gender specific. And while there are varying statistics for the prevalence of blue-yellow color blindness worldwide, the average total percent population affected is along the lines of 0.05% of all humans [34].

Tritanomaly

Tritanomaly is the more common of the two types of blue-yellow color blindness and can be found in about 0.01% of men and about 0.01% of women [34]. Much like deuteranomaly and protanomaly, tritanomaly is not the absence of a specific type of cone, but rather a mutation/defect of a cone. The blue photopsin cone encoded by the OPN1SW gene is the malfunctioning cone in tritanomaly, and will cause individuals to see in the world around them in

varying hues of pink and turquoise in replacement of orange, yellow, red, blue, green and violet (Figure 6) [43]. Opposed to the other forms of color blindness previously discussed, this form of color blindness is also thought to be dominant rather than recessive in nature with incomplete penetrance [44].

Very few studies have been conducted to discover the genetic causes for tritanomaly. One possible explanation for this might be that the prevalence for this form of color blindness is extremely low compared to deuteranomaly or deuteranopia. While it is known that the mutation of the blue photopsin cone is the cause of tritanomaly, information regarding a defect in the OPN1SW gene, improper post-transcriptional modification of the blue photopsin cone, or errors in the transport of the photopsin protein all remain probable causes for this form of color blindness.

Tritanopia

Like the other forms of color blindness ending in "-opia" previously mentioned, tritanopia is the total absence of a particular cone, leaving the individual with only two functional types of cones. In tritanopia, the blue photopsin cone is completely missing, leaving the color detection of the eye solely to both the red and green photopsin cones. And just like in tritanomaly, tritanopia is an autosomal dominant disorder that has incomplete penetrance throughout the population [45].

Statistically, tritanopia is the only form of color blindness that is found slightly more frequently in women than in men. The percentage of the female population with tritanopia is about 0.03%, while only about 0.001% of males display tritanopia [34]. Individuals with tritanopia

see a more pronounced pink, while colors such as yellow are almost undetectable [43]. In addition, individuals with tritanopia may see gray in replacement of light blue, black rather than purple, red instead of orange, and some blue instead of medium green (Figure 6) [43].

Surprisingly, while tritanopia is the rarest form a dichromacy (having only two functional types of cones), there has been one research article published in 1992 that discusses a possible cause for this disease. However, it is important to note that this article refers to tritanopia as encompassing both a complete absence or a mutation in the number of blue photopsin cones, meaning that this information is relevant to both tritanopia and tritanomaly [46].

These researchers found that two specific amino acid substitutions took place in 4 out of the 9 tritanopia/tritanomaly individuals that were analyzed. These findings seem promising when compared to the 0 out of 43 individuals in control group 1 displayed these amino acid substitutions, and 0 out of the 84 individuals in control group 2 displayed the substitutions [46]. One of the two substitutions was the replacement of a glycine for an arginine at the 79th amino acid (G79R) in the OPN1SW gene of chromosome 7. The other mutation was the substitution of serine for proline at the 214th amino acid (S214P) in the OPN1SW gene [46].

While the mechanism of malfunction/deletion caused by these amino acid substitutions is still unknown, researchers hypothesize that the G79R substitution may affect the folding properties of the protein since arginine is a much larger amino acid than glycine and is also positively charged. An earlier research article supports this claim by showing that the substitution of a positively charged amino acid such as lysine, arginine, and histidine for a non-polar amino acid in rhodopsin (a similar protein to photopsin) lead to the complete loss of

function of rhodopsin in some cases [47]. It is also likely that the S214P substitution causes some form of folding/structural problem within the blue photopsin cones since proline is notorious for disrupting alpha-helical structures by putting a kink in the alpha-helix [47].

In addition to this article, other diseases/events have been linked to causing tritanopia. A few examples of this include exposure to ultraviolet light or even blunt trauma to the head region [48]. Furthermore, macular degeneration, which is associated with aging and diabetes, has been linked with causing tritanopia in affected individuals [48].

Complete Color Blindness

Finally, the last major category of color blindness is known as complete color blindness. Complete color blindness is also commonly referred to as monochromacy, but monochromacy is technically the term given to individuals with two malfunctioning cones, leaving them with only a one single functioning cone. However, while one cone remains functional in most forms of monochromacy, often monochromats remain completely color blind.

As the name suggests, individuals with complete color blindness have an inability to see colors at all. Complete color blindness is by far the rarest form of color blindness compared to both red-green color blindness and blue-yellow color blindness. Nearly all complete color blind individuals depend entirely on their rods to help them differentiate the world through different intensities of light [19]. While there are different subcategories of complete color blindness such as rod monochromacy, blue cone monochromacy, and cerebral achromatopsia, most differences are subtle, and have to do with the cause, rather than the effect of the total color blindness.

Rod Monochromacy

Rod Monochromacy is the most common of the three subcategories of monochromacy. However, only about 0.00001% of males and 0.00001% of females will have this form of color blindness [34]. As the name would suggest, individuals with rod monochromacy rely entirely on their rods to differentiate the world around them. This form of color blindness is an autosomal recessive disease and is also referred to as achromatopsia [19]. As for the cones of the eye, some cases show the cones to be absent, while other cases report that the cones are mutated in some way [19]. Individuals with rod monochromacy see colors through the lens of a black and white movie, only being able to distinguish colors on a grayscale (Figure 6).

Unlike other forms of color blindness previously mentioned, rod monochromacy is associated with other disorders such as photophobia (major sensitivity to light), reduced visual acuity, and nystagmus (repetitive, uncontrollable eye movements) [49]. The locus for this disorder has been identified to be on the long arm of chromosome 2 at position 11 (2q11) [50]. Research has shown that the gene causing rod monochromacy at this locus is the CNGA3 gene which encodes the alpha subunit of the cGMP-gated cation channel in the photopsin cones [49]. This is the first form of color blindness discussed that has not been caused by 1 of the 3 genes encoding the different photopsin cones found in the eye.

Of the five families with rod monochromacy that were investigated, a total of 8 different mutations were identified. These mutations include P163L, R283T, R283Q, T291R, R411T, V529M, P547L, and G557R. However, all 8 of these mutations only caused a missense amino acid substitution rather than a frameshift mutation. In addition, all individuals displayed

mutations on both alleles, verifying that rod monochromacy is a recessive disorder [49]. Since the CNGA3 gene encodes the alpha subunit of the cGMP-gated cation channel – a critical part of the visual cascade pathway – it is thought that in rod monochromacy, there is a complete loss of function in the cGMP-gated channel [49]. Researchers hypothesize that this impaired function is caused by the mutations found on individuals with rod monochromacy, which may lead to improper folding of the cGMP-gated channel in the plasma membrane. Another idea is that the mutations could cause the protein to become unable to be transported into the plasma membrane [49]. However, the exact cause for the impaired function has yet to be determined.

Blue-cone Monochromacy

The second subtype of complete color blindness is blue cone monochromacy. Blue-cone monochromacy is extremely rare, and with differing reports of individuals with this form of color blindness, it makes it very hard to distinguish from other forms of complete color blindness such as rod monochromacy [19]. Blue cone monochromacy is caused by a deletion or rearrangement of the OPN1MW and OPN1LW genes, leaving only the blue photopsin cones to perceive color. However, despite having a functioning cone type, most individuals remain totally colorblind [19].

While finding individuals with blue-cone monochromacy is difficult, a recent study published in 2019 identified a man with blue-cone monochromacy and investigated his genome for possible mutations [51]. Upon genetic analysis, researchers discovered that abnormal mutations were present on the NR2E3 gene (located on chromosome 15q23) known to cause enhanced S-cone syndrome in humans, and the OPN1LW gene which has been linked to blue-cone

monochromacy in the past [52, 53]. The mutation that took place on the NR2E3 gene was a substitution of a glycine for alanine at position 361 on the complementary DNA strand (c.G361A), and the mutation that took place on the OPN1LW gene was a substitution of an alanine for a glycine at position 244 on the complementary DNA strand (c. A244G) [51]. The location of the mutation on the OPN1LW gene was on exon 2, while all previous mutations identified for on this gene have been on exon 4 [51].

These findings of two novel mutations shown to cause blue cone monochromacy show a greater extent of complexity found within this subclass of total color blindness. Due to these complexities and the rareness of the disorder, there remains a large amount of information that is unknown about this disorder such as how these mutations lead to blue cone monochromacy.

Cerebral Achromatopsia

Cerebral achromatopsia is an extremely rare form of color blindness and very little is known about it. Only a few individuals have presented with this form of color blindness [54]. Researchers have discovered that while cerebral achromatopsia individuals see no colors in the visual spectrum, they have fully functional cones of all three forms. In addition, the rods function properly as well [19]. Cerebral achromatopsia is also unique in that it is the only form of color blindness identified that is not inherited from maternal and or paternal genes. It is thought that cerebral achromatopsia can be caused by trauma or blunt force to the head which leads to a disconnect somewhere along the signaling pathway from the eye to the brain [19].

Diagnosis

While there are many different categories and subcategories of color blindness to diagnose, there are also many ways to diagnose color blindness. However, the most common way of diagnosing color blindness is through the Ishihara Plate test. This test is designed mainly for detecting forms of red-green color blindness and can be taken online in about 5-10 minutes. The test is performed by presenting a colored circle with miniature colored circles located within the larger circle in the form of a mosaic (Figure 9). Within the larger circle is a number, and the smaller circles are different hues of the color of the wheel. Individuals that find it difficult to see the number within the circle may be subject to a specific form of color blindness which is determined by the specific colored circle they are observing. The current test utilizes 38 different circles before assessing the color vision of the test-taker [55].

While this test is free to take online, relatively fast, and used to diagnose the more common types of color blindness, many people question the accuracy of the test. A study conducted by Birch in 1997 investigated the different types of plates used and the accuracy of each group of plates. The researcher showed that out of 401 people with a form of red-green color blindness, the Hidden Digit plates (plates 18-21) were only accurate about 50% of the time when identifying color blindness, where the Transforming plates (plates 2-9) and the Vanishing plates (plates 10-17) were accurate 98.7% of the time in identifying individuals with red-green color blindness [56]. Another study conducted by Murat showed that more than 95% of ophthalmologists use Ishihara Plate Tests in their daily practice, yet 85% of the ophthalmologists agreed that the test did not meet their needs in full [57].

Color vision is interesting to diagnose since theoretically, one individual's interpretation of what a color looks like could be completely different from another individual's interpretation, and both people would still believe they are talking about the same color. Therefore, while the Ishihara Plate Test is beneficial as a basic indicator of color blindness, it should not be viewed as a confirmed diagnosis without the addition of other tests and a discussion with a licensed ophthalmologist.

Cures and Treatments

While it has been over 200 years since John Dalton first identified color blindness, there currently remains no known cure [58]. In addition, up until the last decade, there were no known treatments for color blindness either. However, in 2010 a pair of glasses made by Enchroma was invented to help treat certain types of color blindness [59].

This treatment involves the use of colored filters which filter out specific wavelengths of light that are commonly overlapped, which is common among many different types of color blindness such as deuteranomaly and protanomaly (Figure 7C) [59]. While the individuals using Enchroma glasses are still limited from seeing the full visible light spectrum, it enables the individual to discriminate between the different colors observed which were previously indistinguishable due to the overlapping signals found in some forms of color blindness [60]. Nonetheless, this treatment has limited success on patients with an absence of a particular cone such as deuteranopia and protanopia since they involve the loss of a functional cone, rather than the overlapping of cones [59]. In addition, the developers of Enchroma glasses have chosen to

focus on creating glasses specifically for red-green color blindness since it accounts for nearly 80% of all color-blind cases [59].

While this focus on red-green color blindness leaves individuals with blue-yellow color blindness (particularly tritanomaly) without a cure, the developers have been able to make great strides towards perfecting glasses for red-green color-blind individuals. In a new study that came out this year, researchers showed that red-green color-blind individuals who used Enchroma glasses were able to distinguish colors that they were not able to before, even without wearing the glasses [61]. One individual with deuteranomaly in particular stated that when wearing the Enchroma glasses he noticed his girlfriend's brown hair had red in it, and even without the glasses on, he was still able to see the difference [61]. While no research has been conducted as to the longevity of this "revived color-vision" post wearing Enchroma glasses, these findings are encouraging to color blind individuals who may be able to regain normal color vision without the daily use of Enchroma glasses.

Avenues of Hope

While there remains little information about some forms of color blindness such as protanopia, tritanomaly, and blue cone monochromacy, future work should continue to focus on the major forms of color blindness such as deuteranomaly, protanomaly, and deuteranopia since these forms of color blindness affect a larger number of individuals. By focusing on the more popular forms of color blindness, future discovers/breakthroughs will affect a larger population. In addition, there remains the potential that the future findings can be utilized in other, less common forms of color blindness.

One avenue of hope for the future would be to conduct experiments on mice that have a 5'-green-red-3' hybrid gene located just downstream of red photopsin gene, and a third, normal green photopsin gene present downstream of the hybrid gene. Crisper-Cas-9 could then be used to silence or remove the 5'-green-red-3' hybrid gene and studies could be conducted to determine if the colored vision of the mice returns to normal. Findings previously mentioned show strong support that only the first two photopsin genes are activated in humans. Therefore, if the 5'-green-red-3' hybrid gene could be removed prior to the formation of the eye in development, the activation of the downstream, normal green photopsin gene may become activated as a replacement. If these studies proved successful in mice, there could be a potential that a prescreening for this hybrid gene in humans could prevent patients from developing deuteranomaly, and possibly other forms of color blindness if the detection were early enough.

Another possible avenue for exploration would be to investigate how the supposed A70C mutation on the OPN1MW gene can cause the deletion of functional green photopsin cones. One suggestion supported by Ueyama H., et al. is that this mutation becomes a site for DNA methylation which could lead to the gene becoming silenced and thus not produce any green photopsin cones [41]. If this is the case, then future work could attempt to demethylate the mutated amino acid on the OPN1MW gene which may activate the production of the green photopsin cones in individuals with deuteranopia.

Conclusion

Color blindness has been shown to affect nearly 8-10% of all humans, with many different types of color blindness being identified within the last century. The scientific

understanding of color blindness and all its different forms has come a long way since John Dalton first theorized that the vitreous humor was the cause of color blindness in 1794. Within the major categories of color blindness such as red-green, blue-yellow, and complete color blindness, more than 8 different types of color blindess have been identified to date. Each of these forms of color blindness presents a unique world to the individual defined by limited patterns of detectable vision. In addition, each type of color blindness has been linked with one or more genetic defects that are unique to any other form of color blindness currently known.

Under normal physiological conditions, all three types of cones in the eye are produced from the OPN1SW, OPN1MW, and OPN1LW genes. However, while many defects that lead to color blindness take place on these genes, other genes such as the NR2E3 gene have also been linked to some forms of color blindness. This information demonstrates that we still have much to learn concerning the pathways associated with color detection.

In the last decade, Enchroma glasses have helped individuals with color blindness detect color more accurately. However, this treatment only works on limited types of color blindness and the glasses must be worn for enhanced color detection to be effective. Therefore, much more work needs to be done in the field to create better treatments and possible preventions for individuals who suffer from color blindness across the globe. One avenue of hope for the future is to investigate the silencing of 5'-green-red-3' hybrid genes on select individuals with color blindness. Silencing of the hybrid gene via Crisper-Cas-9 could lead to the activation of a normal green photopsin gene if it is located downstream of the hybrid gene. If successful, this procedure could be a potential prevention for specific types of color blindness if it were detected early enough.

References

1. Anonymous (2012). Map Accessibilty Survey for Colorblind People – Colblindor, https://www.color-blindness.com/2012/10/11/map-accessibilty-survey-for-colorblind-people/.

2. Fishman, G.A. (2008). John dalton: though in error, he still influenced our understanding of congenital color deficiency. Ophthalmic Genet. 29, 162-165.

3. Hunt, D.M., Dulai, K.S., Bowmaker, J.K., Mollon, J.D. (1995). The chemistry of John Dalton's color blindness. Science 267, 984-988.

4. Krudy, A., Ladunga, K. (2000). Measuring Wavelength Discrimination Threshold Along the Entire Visible Spectrum. Periodica Polytechnica 45, 41-48.

5. Anonymous Color & Vision Matters, https://www.colormatters.com/color-and-vision/color-and-vision-matters.

6. Garcia, M. (2018). Space to Ground: Color of the Sun: 04/27/2018, http://www.nasa.gov/mediacast/space-to-ground-color-of-the-sun-04272018.

7. Bedggood, P., Metha, A. (2013). Optical Imaging of Human Cone Photoreceptors Directly Following the Capture of Light. PLOS ONE 8, e79251.

8. Baden, T., Osorio, D. (2019). The Retinal Basis of Vertebrate Color Vision. Annu. Rev. Vis. Sci. 5, 177-200.

9. Watson, A.B. (2014). A formula for human retinal ganglion cell receptive field density as a function of visual field location. Journal of Vision 14, 15.

10. Purves, D., Augustine, G.J., Fitzpatrick, D., Katz, L.C., LaMantia, A., McNamara, J.O., Williams, S.M. (2001). Neuroscience. 2nd Edition (Sunderland (MA): Sinauer Associates).

11. Purves, D., Augustine, G.J., Fitzpatrick, D., Katz, L.C., LaMantia, A., McNamara, J.O., Williams, S.M. (2001). Neuroscience (Sunderland (MA): Sinauer Associates).

12. Gibson, J.S. (1898). On the Trichromatic Theory. Boston Society of Medical Sciences 2, 179-186.

13. Reference, G.H. (2020). OPN1SW Gene, https://ghr.nlm.nih.gov/gene/OPN1SW.

14. Anonymous (2019). OPN1MW Gene, https://ghr.nlm.nih.gov/gene/OPN1MW https://ghr.nlm.nih.gov/gene/OPN1MW https://ghr.nlm.nih.gov/gene/OPN1MW.

15. Reference, G.H. (2020). OPN1LW Gene, https://ghr.nlm.nih.gov/gene/OPN1LW.

16. Imamoto, Y., Yoshizawa, T., Shichida, Y. (1996). Chromophore configuration of iodopsin and its photoproducts formed at low temperatures. Biochemistry (N. Y.) 35, 14599-14607.

17. Kefalov, V. (2010). Phototransduction: Phototransduction in Cones. In, Anonymous , pp. 389-396.

18. Anonymous (2019). Types of Color Blindness, https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/color-blindness/types-color-blindness.

19. Anonymous (2007). Monochromacy – Complete Color Blindness – Colblindor, https://www.color-blindness.com/2007/07/20/monochromacy-complete-color-blindness/.

20. Anonymous Deuteranopia – Red-Green Color Blindness – Colblindor, https://www.color-blindness.com/deuteranopia-red-green-color-blindness/.

21. Hayashi, T., Motulsky, A.G., Deeb, S.S. (1999). Position of a 'green-red' hybrid gene in the visual pigment array determines colour-vision phenotype. Nature Genetics 22, 90.

22. Nathans, J., Thomas, D., Hogness, D.S. (1986). Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. Science 232, 193-202.

23. Winderickx, J., Battisti, L., Motulsky, A.G., Deeb, S.S. (1992). Selective expression of human X chromosome-linked green opsin genes. Proceedings of the National Academy of Sciences of the United States of America 89, 9710-9714.

24. Jørgensen, A.L., Deeb, S.S., Motulsky, A.G. (1990). Molecular genetics of X chromosome-linked color vision among populations of African and Japanese ancestry: high frequency of a shortened red pigment gene among Afro-Americans. Proc Natl Acad Sci U S A 87, 6512-6516.

25. Deeb, S.S., Alevarez, A., Malkki, M., Motulsky, A.G. (1995). Molecular patterns and sequence polymorphisms in the red and green visual pigment genes of Japanese men. Human Genetics 95, 501-506.

26. Deeb, S.S., Motulsky, A.G. (1996). Molecular genetics of human color vision. Behavior Genetics 26, 195-207.

27. Anonymous Protanopia – Red-Green Color Blindness – Colblindor, https://www.color-blindness.com/protanopia-red-green-color-blindness/.

28. Anonymous Anomalous Trichromats, https://www.testingcolorvision.com/tcv-anomalous-trichromacy.php#:~:text=Anomalous%20Trichromacy%20is%20the%20most,on%20which%20cone%20is%20altered.

29. Anonymous How Red-Green Colorblindness is Different from Other Types of Colorblindness?, https://iristech.co/how-red-green-colorblindness-is-different-from-other-types-of-colorblindness/.

30. Kalloniatis, M., Luu, C. (1995). The Perception of Color. In Webvision: The Organization of the Retina and Visual System, H. Kolb, E. Fernandez, R. Nelson, eds. (Salt Lake City (UT): University of Utah Health Sciences Center).

31. Ueyama Hisao, Tanabe Shoko, Muraki-Oda Sanae, Yamade Shinichi, Ohkubo Iwao. (2006). Protan color vision deficiency with a unique order of green–red as the first two genes of a visual pigment array. Journal of Human Genetics 51, 686-694.

32. Deeb, S.S., Lindsey, D.T., Hibiya, Y., Sanocki, E., Winderickx, J., Teller, D.Y., Motulsky, A.G. (1992). Genotype-phenotype relationships in human red/green color-vision defects: molecular and psychophysical studies. Am J Hum Genet 51, 687-700.

33. Anonymous Types of Colour Blindness, https://www.colourblindawareness.org/colour-blindness/types-of-colour-blindness/.

34. Anonymous Color Blindness Facts & Statistics: Prevalence, https://www.colour-blindness.com/general/prevalence/.

35. Wolfgang M. Jagla, Herbert Jägle, Takaaki Hayashi, Lindsay T. Sharpe, Samir S. Deeb. (2002). The molecular basis of dichromatic color vision in males with multiple red and green visual pigment genes. Human Molecular Genetics 11, 23-32.

36. Srinivasan, S., Fernández-Sampedro, M.A., Ramon, E., Garriga, P. (2017). Structural and functional alterations associated with deutan N94K and R330Q mutations of green cone opsin. BBA - Molecular Basis of Disease 1863, 1840-1847.

37. Carroll, J., Baraas, R.C., Wagner-Schuman, M., Rha, J., Siebe, C.A., Sloan, C., Tait, D.M., Thompson, S., Morgan, J.I.W., Neitz, J. et al. (2009). Cone photoreceptor mosaic disruption associated with Cys203Arg mutation in the M-cone opsin. Proc. Natl. Acad. Sci. USA 106, 20948-20953.

38. Kazmi, M.A., Sakmar, T.P., Ostrer, H. (1997). Mutation of a conserved cysteine in the X-linked cone opsins causes color vision deficiencies by disrupting protein folding and stability. Invest. Ophthalmol. Vis. Sci. 38, 1074-1081.

39. Hartong, D.T., Berson, E.L., Dryja, T.P. (2006). Retinitis pigmentosa. The Lancet 368, 1795-1809.

40. Sung, C.H., Makino, C., Baylor, D., Nathans, J. (1994). A rhodopsin gene mutation responsible for autosomal dominant retinitis pigmentosa results in a protein that is defective in localization to the photoreceptor outer segment. Journal of Neuroscience 14, 5818-5833.

41. Ueyama, H., Li, Y., Fu, G., Lertrit, P., Atchaneeyasakul, L., Oda, S., Tanabe, S., Nishida, Y., Yamade, S., Ohkubo, I. (2003). An A−71C substitution in a green gene at the second position in the red/green visual-pigment gene array is associated with deutan color-vision deficiency. PNAS 100, 3357-3362.

42. Ng, H., Adrian, B. (1999). DNA methylation and chromatin modification. Curr. Opin. Genet. Dev. 9, 158-163.

43. Anonymous Understanding Color Blindness | All About Eyes.

44. Neitz, M., Neitz, J. (2000). Molecular Genetics of Color Vision and Color Vision Defects. Archives of ophthalmology (1960) 118, 691-700.

45. Anonymous Colorblindness- Tritanopia, https://disorders.eyes.arizona.edu/handouts/colorblindness-tritanopia#:~:text=Genetics%3A,child%20with%20a%2050%25%20probability.

46. Weitz, C.J., Miyake, Y., Shinzato, K., Montag, E., Zrenner, E., Went, L.N., Nathans, J. (1992). Human tritanopia associated with two amino acid substitutions in the blue-sensitive opsin. Am J Hum Genet 50, 498-507.

47. Sakmar, T.P., Franke, R.R., Khorana, H.G. (1989). Glutamic acid-113 serves as the retinylidene Schiff base counterion in bovine rhodopsin. Proc. Natl. Acad. Sci. U. S. A. 86, 8309-8313.

48. Anonymous What is Tritanopia? Blue-Yellow Color Blindness, https://colormax.org/tritanopia/.

49. Kohl, S., Marx, T., Giddings, I., Jägle, H., Jacobson, S.G., Apfelstedt-Sylla, E., Zrenner, E., Sharpe, L.T., Wissinger, B. (1998). Total colourblindness is caused by mutations in the gene encoding the α-subunit of the cone photoreceptor cGMP-gated cation channel. Nature Genetics 19, 257.

50. Arbour, N.C., Zlotogora, J., Knowlton, R.G., Merin, S., Rosenmann, A., Kanis, A.B., Rokhlina, T., Stone, E.M., Sheffield, V.C. (1997). Homozygosity Mapping of Achromatopsia to Chromosome 2 Using DNA Pooling. Hum Mol Genet 6, 689-694.

51. Cai, B., Li, Z., Sun, S., Wang, L., Chen, L., Yang, J., Li, X. (2019). Novel mutations in the OPN1LW and NR2R3 genes in a patient with blue cone monochromacy. Ophthalmic Genetics 40, 43-48.

52. Chavala, S.H., Sari, A., Lewis, H., Pauer, G.J.T., Simpson, E., Hagstrom, S.A., Traboulsi, E.I. (2005). An Arg311Gln NR2E3 mutation in a family with classic Goldmann-Favre syndrome. Br J Ophthalmol 89, 1065-1066.

53. Nathans, J., Maumenee, I.H., Zrenner, E., Sadowski, B., Sharpe, L.T., Lewis, R.A., Hansen, E., Rosenberg, T., Schwartz, M., Heckenlively, J.R. (1993). Genetic heterogeneity among blue-cone monochromats. Am. J. Hum. Genet. 53, 987-1000.

54. Bartolomeo, P., Bachoud Lévi, A.C., Thiebaut De Schotten, M. (2013). The Anatomy of Cerebral Achromatopsia: A Reappraisal and Comparison of Two Case Reports, http://hdl.handle.net/10807/39500.

55. Anonymous Ishihara's Test for Colour Deficiency: 38 Plates Edition – Colblindor, https://www.color-blindness.com/ishiharas-test-for-colour-deficiency-38-plates-edition/.

56. Birch, J. (1997). Efficiency of the Ishihara test for identifying red-green colour deficiency. Ophthalmic Physiol Opt 17, 403-408.

57. Işik, M. (2019). How Reliable is the Ishihara Test? Retina-Vitreus/Journal of Retina-Vitreous 28, 251-258.

58. Badawy, A., Hassan, M.U., Elsherif, M., Ahmed, Z., Yetisen, A.K., Butt, H. (2018). Contact Lenses for Color Blindness. Advanced healthcare materials 7, e1800152.

59. Anonymous How EnChroma Glasses Work, https://enchroma.com/pages/how-enchroma-glasses-work.

60. Almutairi, N., Kundart, J., Muthuramalingam, N., Hayes, J., Citek, K., Alijohani, S. (2017). Assessment of Enchroma Filter for Correcting Color Vision Deficiency. College of Optometry.

61. Werner, J.S., Marsh-Armstrong, B., Knoblauch, K. (2020). Adaptive Changes in Color Vision from Long-Term Filter Usage in Anomalous but Not Normal Trichromacy. Current biology 30, 3011-3015.e4.

62. Anonymous (2016). Electromagnetic Spectrum, https://www.engineeringtoolbox.com/electromagnetic-spectrum-d_1929.html.

63. Anonymous Laser Safety - Laser Basics, https://www.pro-lite.co.uk/File/laser_safety_laser_basics.php.

64. Anonymous Simple Anatomy of the Retina by Helga Kolb – Webvision.

65. Anonymous The Color-Sensitive Cones, http://hyperphysics.phy-astr.gsu.edu/hbase/vision/colcon.html.

66. Anonymous (https://en.wikipedia.org/wiki/Color_blindness). Color Blindness.

67. H, D. (2018). ENCHROMA AND COLOR VISION DEFICIENCY.

68. Anonymous (2013). How to Interpret the Ishihara Color Plate Test, http://www.colorblindnessfacts.com/ishihara-test-interpretation/.

Appendix A

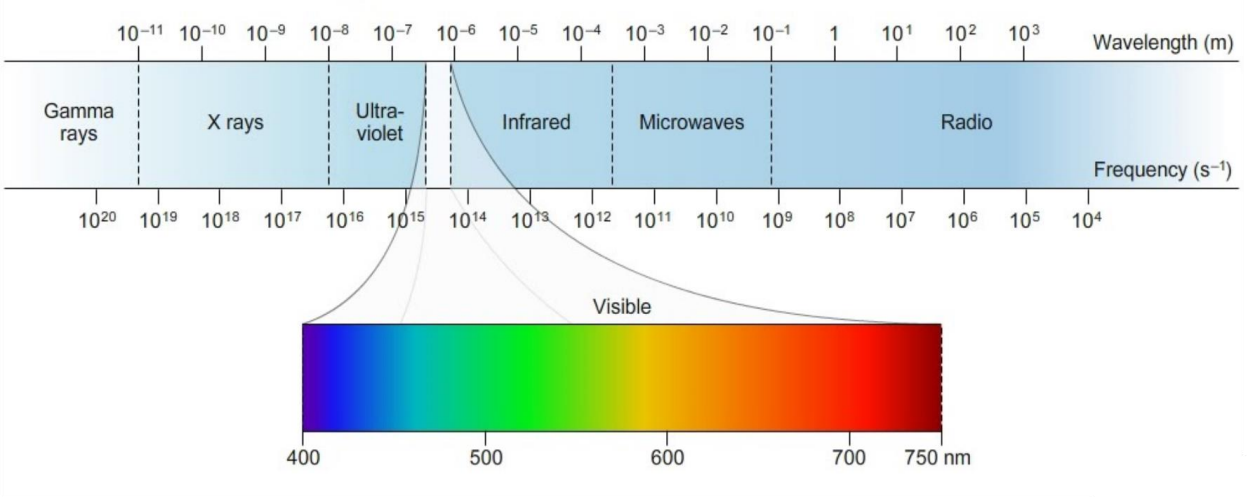

Figure 1. The electromagnetic spectrum showing the small portion of the visible light spectrum. The seven different categories of light separated by wavelength are known as radio, microwaves, infrared, visible, ultra-violet, X rays, and gamma rays. While the full electromagnetic spectrum spans nearly 10^{24} meters, the visible light spectrum is only from 300-700nm in length. Figure acquired from [62].

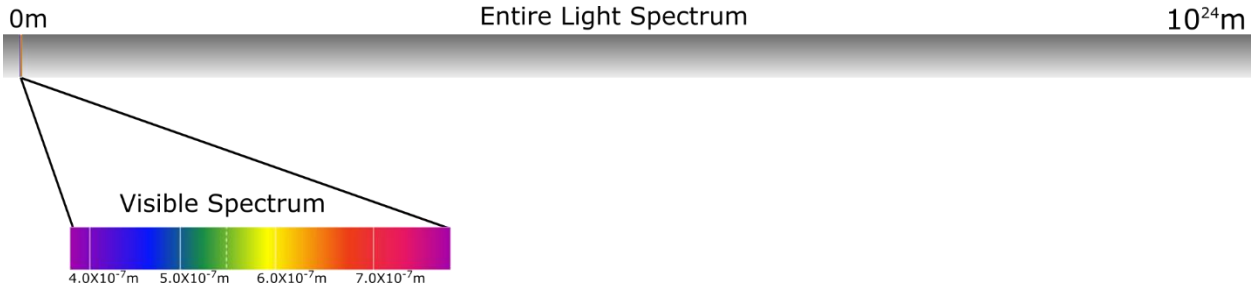

Figure 2. Visible light spectrum relative to the entire light spectrum. The entire spectrum of light spans nearly 10^{24} m in total. The small field of vision detectable to the human eye is at the highest energy, lowest frequency end of the spectrum found between 400-700 nm (4.0×10^{-7} – 7.0×10^{-7} m). It is within this small 300 nm range that all the colors detectable to the human eye are observed. Figure modified from [63].

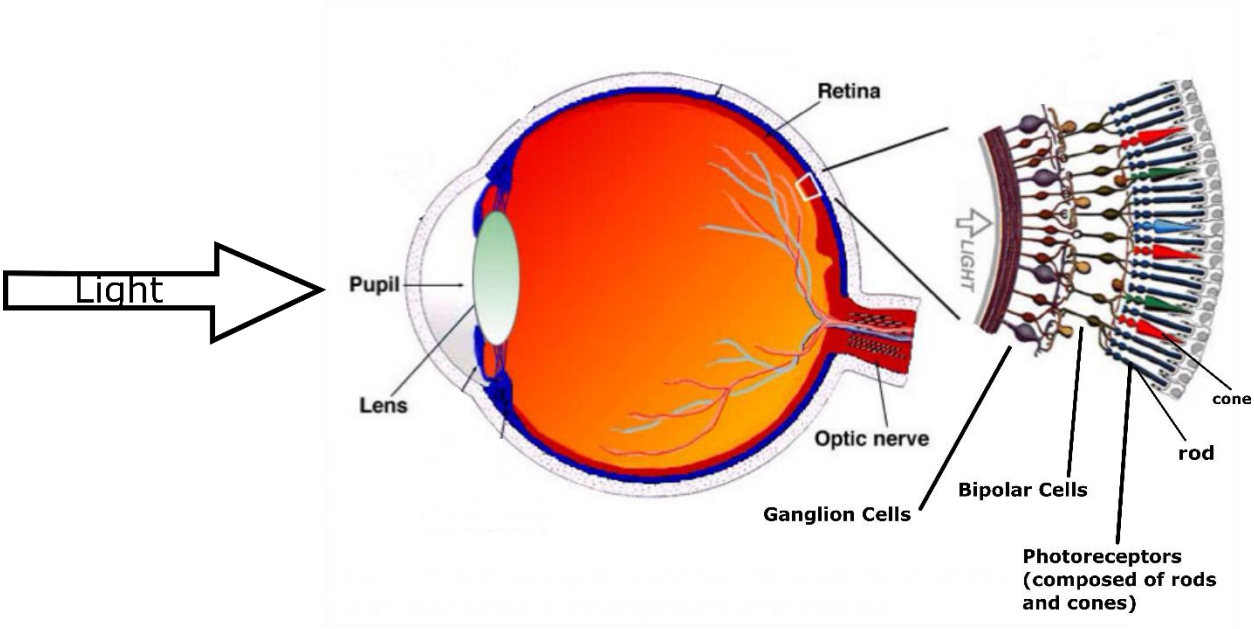

Figure 3. Diagram of how light enters the eye and the layers of the retina. Light enters through the pupil of the eye, then gets sent through the lens and onto the back of the retina. The light first passes through the ganglion cells, then through the bipolar cells to first get processed by the photoreceptor cells (rods and cones). The visual information is then sent backwards to the bipolar cells, then to the ganglion cells, and finally to the optic nerve where the information is sent to the brain for processing. Figure modified from [64].

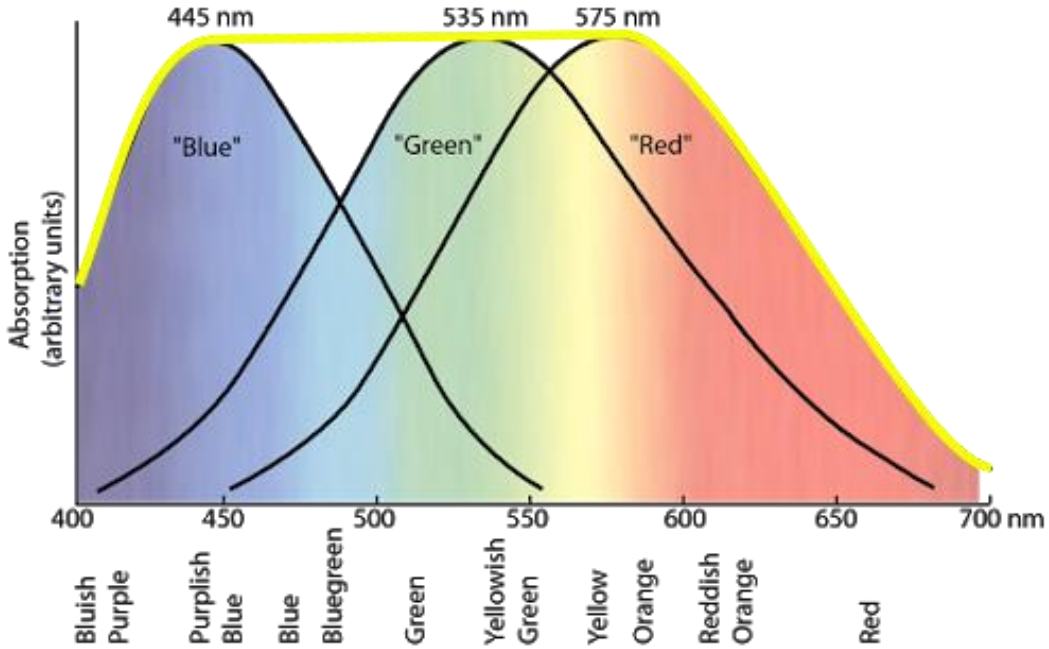

Figure 4. Absorption spectrums of the 3 different cones found within the eye. The yellow line indicates the visible light that humans can detect. It is this light that, depending on its wavelength, will get detected by a combination of three different cones found within the human eye. Blue photopsin cones (S-cones) detect light at the smallest wavelengths of the normal visual field, while green photopsin cones (M-cones) detect light in the middle of the visual field and red photopsin cones (L-cones) detect light at the largest wavelengths of the visual field. Normal vision results from the proper functioning of these 3 different cones. Figure modified from [65].

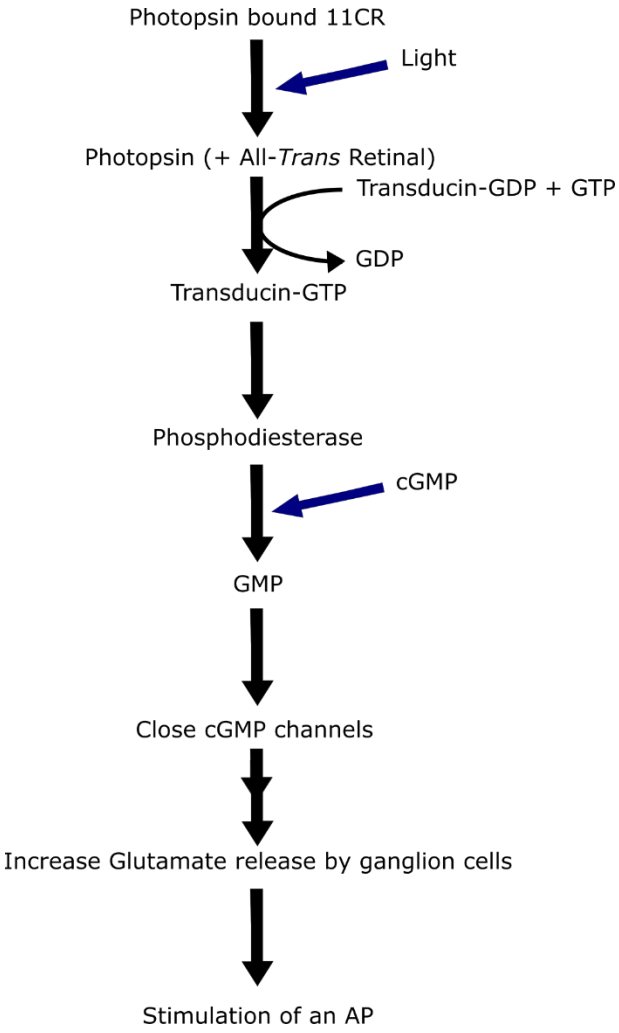

Figure 5. Theoretical phototransduction cascade of photopsin based off the known rhodopsin pathway. This phototransduction cascade has been partly identified while other parts have been taken from the known rhodopsin chemical transduction pathway. The apoprotein photopsin with bound 11-cis retinal separates upon specific light entering the cone allowing free photopsin to convert transducin-GDP to transducin-GTP which in turn activates PDE that breaks down cGMP. Subsequently, cGMP channels are closed, leading to a series of events that activate ganglion cells to release glutamate. The release of glutamate from ganglion cells stimulates an action potential that gets sent to the brain via the optic nerve for processing.

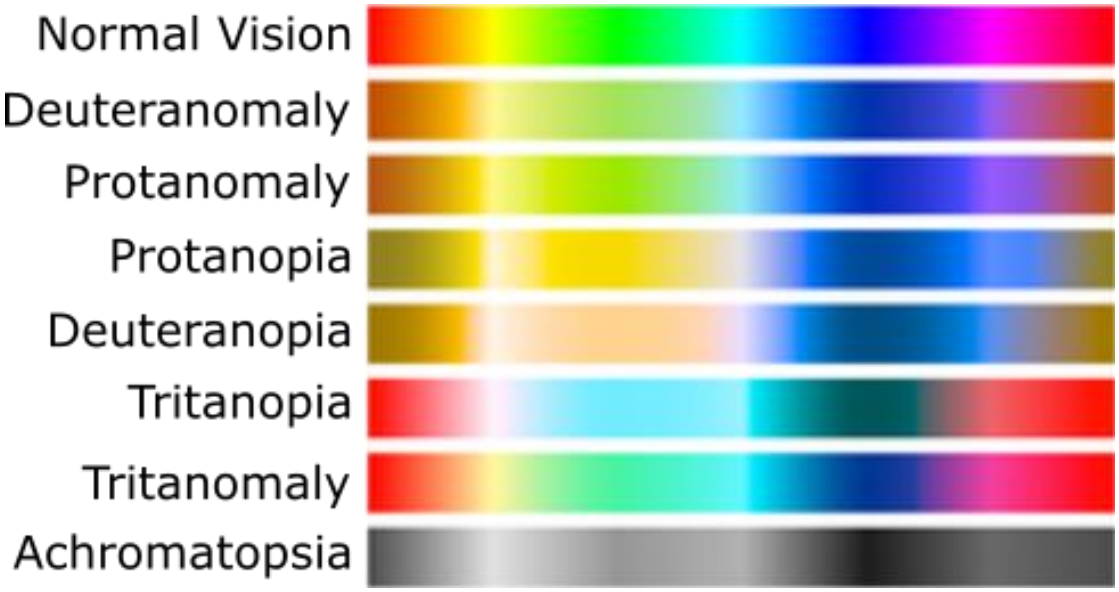

Figure 6. Visual electromagnetic spectrums for different forms of color blindness. Bar 1 represents the visual field of an individual with normal colored vision. Bar 2 represents the visual field of an individual with Deuteranomaly. Bar 3 represents the visual field of an individual with Protanomaly. Bar 4 represents the visual field of an individual with Protanopia. Bar 5 represents the visual field of an individual with Deuteranopia. Bar 6 represents the visual field of an individual with Tritanopia. Bar 7 represents the visual field of an individual with Tritanomaly. Bar 8 represents the visual field of an individual with Achromatopsia. Figure modified from [66].

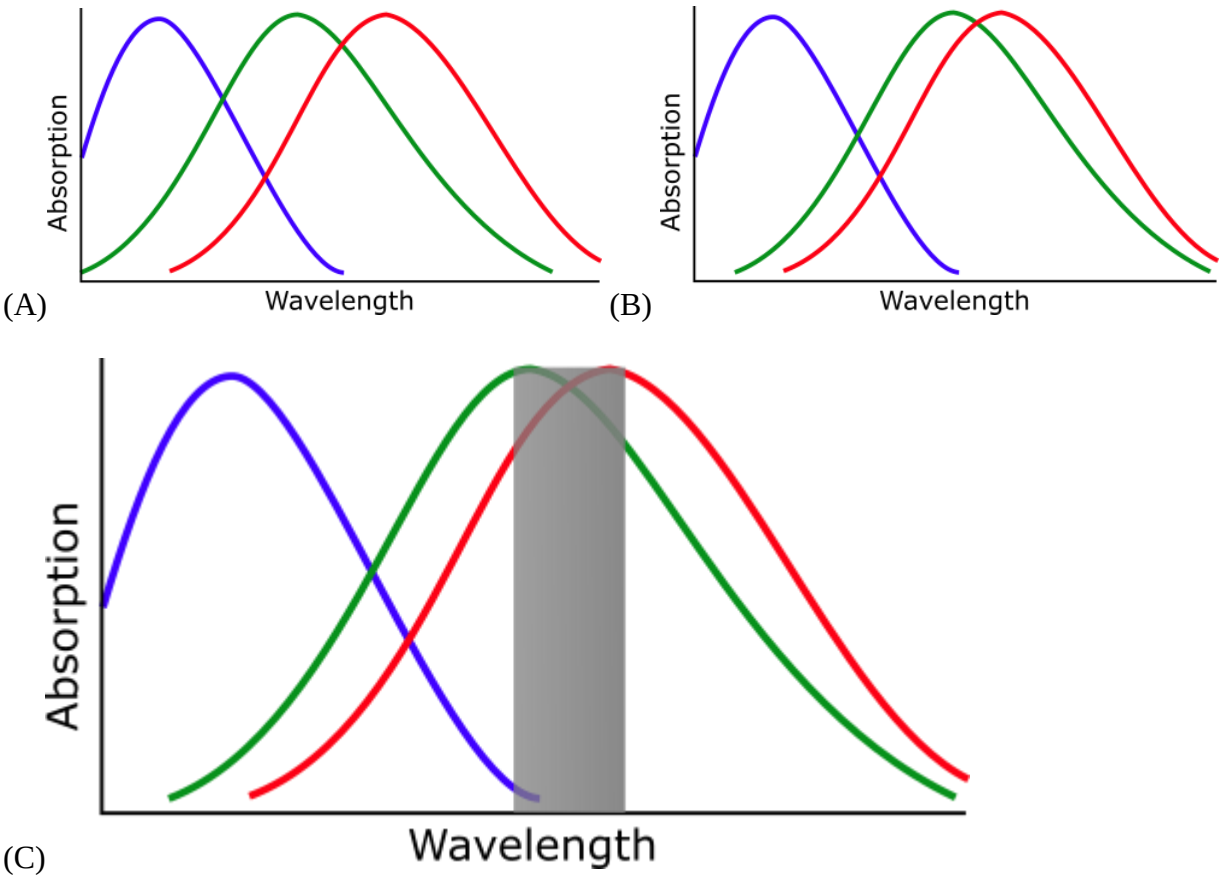

Figure 7. Simplified versions of cone overlap with normal and red-green color-blind individuals and how Enchroma glasses aid color blindness. (A) Simplified diagram of an individual with normal colored vision. The curves represent how each of the three cones overlap with each other normally. (B) Diagram of an individual with red-green color blindness. The image shows how the green cone is shifted over more of the red cone and causes an increased overlap between the two cones. (C) Diagram of an individual with red-green color blindness using Enchroma glasses. The image shows how Enchroma glasses block the part of the cones that have been overlapped in red-green color blindness. Figures modified from [67].

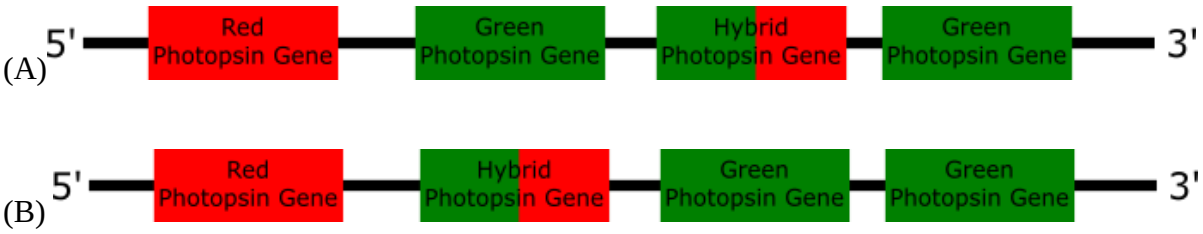

Figure 8. Order of red and green photopsin genes on Xq28 for normal color vision individuals and those with deuteranomaly. (A) One type of gene array for red and green photopsin genes found in individuals with normal color vision. For normal individuals, the first position is always the red photopsin gene and the second position is always the green photopsin gene. Downstream of these two genes, 5'-green-red-3' hybrid genes, as well as additional green photopsin genes have been found to be present in some individuals with normal color vision. (B) The gene array of individuals studied with deuteranomaly. For people with deuteranomaly, the first position was the red photopsin gene, and the second position was the 5'-green-red-3' hybrid gene. Downstream from these two genes, other normal green photopsin genes were found to be present in some individuals with deuteranomaly.

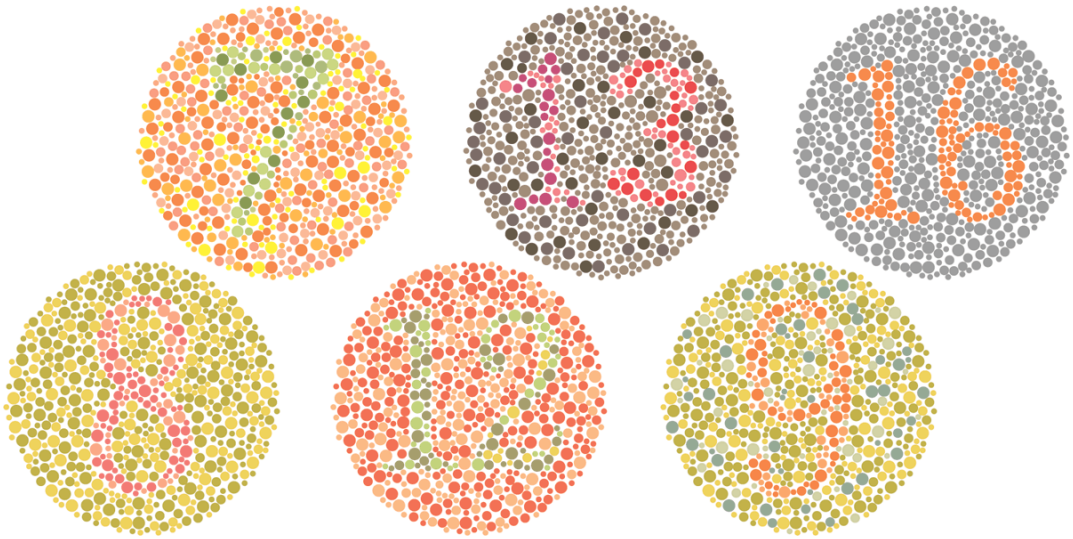

Figure 9. Plates from the Ishihara Plate test used to diagnose color blindness. Various plates such as the ones show here are used in the Ishihara plate test to diagnose color blindness. The test works by coloring a series of circles within a larger circle a specific color to determine an individual's ability to distinguish various color combinations. If the individual fails to see a specific number within the larger circle, this may be an indication that the individual has difficulty distinguishing between the colors presented on the plate, and can help diagnose the specific type of color blindness the individual suffers from. Figure acquired from [68].