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Color Blindness and the Role of Sex-Influenced Genes

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Abstract — Sex linkage is defined as the pattern of allele expression and inheritance associated with an individual's sex chromosomes. Sex-linked genes are genes located on the sex chromosomes. Genes associated with the X chromosome are referred to as X-linked genes or X chromosome genes. Color blindness is a condition in which a person is unable to distinguish certain wavelengths of light that can be differentiated by normal vision. The ratio of the index finger length (2D) compared to the ring finger length (4D) is an inherited trait influenced by sex-influenced gene expression. Patterns of baldness in humans, or androgenetic alopecia (AGA), are age-related conditions characterized by hair thinning, miniaturization, and hair loss. The objective of the research titled "*Color Blindness and the Role of Sex-Influenced Genes*" is to determine whether a person is color blind and to identify the genotype of each individual in a group based on the size of their index finger. The methods used include an online Ishihara test for color blindness, conducted by each subject using a prepared website. For the sex-influenced gene experiment, participants made patterns of their index, ring, and middle fingers on both hands on HVS paper, and the finger lengths were observed. The results showed that all participants were not color blind (normal), and some participants had longer index fingers, longer ring fingers, or equal lengths of the index and ring fingers.

Keywords — *Baldness; Color Blindness; Finger Length Ratio; Sex Linkage; Sex-Linked Genes*.

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INTRODUCTION

Sex-linked inheritance refers to the pattern of allele expression and transmission associated with an individual's sex chromosomes. A phenotype is classified as sex-linked if the gene responsible for that trait is located on a sex chromosome. In humans, the term "*sex-linked phenotype*" generally denotes traits influenced by genes on either the X or Y chromosome. The inheritance of sex-linked traits is governed by genes situated on the sex chromosomes, with the majority of sex-linked inheritance occurring due to the X chromosome rather than the Y chromosome. Similar to autosomes, sex chromosomes contain various genes essential for normal biological functions. Mutations in these genes can lead to sex-linked disorders, such as color blindness, hemophilia, and Rett syndrome. The impact of sex on sexual selection is influenced by evolutionary rates and directions since sex chromosomes and autosomes experience distinct selective pressures depending on the sex of the individual [1-2].

Sex-linked genes are those located on sex chromosomes. Genes associated with the X chromosome are termed X-linked genes, while those on the Y chromosome are known as Y-linked genes. The inheritance pattern of X-linked genes influences the resulting phenotype [3]. The determination of biological sex depends on the presence of the Y chromosome, specifically the sex-determining region of the Y chromosome. In humans, Y-linked genes are inherited exclusively from fathers to sons, while X-linked genes are passed down from both parents [1]. Various molecular mechanisms contribute to sexual development, involving not only sex chromosome-linked genes but also autosomal genes that regulate hormone balance [2]. The X chromosome contains 867 identified genes, many of which are responsible for the development of tissues such as bones, nerves, blood, liver, kidneys, retina, ears, heart, skin, and teeth. At least 533 disorders are linked to genetic anomalies on the X chromosome. Traits or disorders determined by X chromosome genes follow X-linked inheritance patterns [4].

Sex-influenced inheritance is exemplified by conditions such as male pattern baldness in humans, horn development in specific sheep breeds (e.g., Dorset Horn sheep), and certain coat patterns in cattle. In such cases, autosomal genes are responsible for phenotypic differences, but their expression is influenced by an individual's hormonal profile. Consequently, a heterozygous genotype may result in one phenotype in males and a contrasting phenotype in females [5]. Like autosomes, sex chromosomes contain multiple genes necessary for normal function, and mutations in these genes can result in sex-linked disorders.

Autosomal genes refer to those located on non-sex chromosomes, whereas gonosomal genes are associated with sex chromosomes [6]. Autosomal traits differ in inheritance patterns from sex-linked traits [7]. Human traits linked to autosomes may be determined by either dominant or recessive genes. Recessive inheritance is characterized by generational skipping of a trait, whereas dominant inheritance is marked by the continuous expression of a trait without generational gaps [8].

Autosomal inheritance follows a pattern where an individual inherits one gene from each parent, forming a unique gene pair. If one parent carries two different alleles, the offspring has an equal probability of inheriting either allele. Autosomal genes are classified into three types: autosomal dominant lethal (AA: lethal, Aa: normal, aa: normal), autosomal dominant non-lethal (AA: normal, Aa: normal, aa: affected), and autosomal recessive lethal (AA: normal, Aa: affected, aa: lethal) [9].

Color blindness is a condition where an individual cannot distinguish certain wavelengths of light, typically due to alterations in the sensitivity of cone cell photoreceptors in the retina. This disorder is primarily inherited but can also result from excessive chemical exposure. Data indicates that color blindness affects approximately 8% of men and 0.4% of women [13]. The condition is caused by mutations in the OPN1LW, OPN1MW, and OPN1SW genes [10]. As an X-linked disorder, color blindness manifests in three forms: monochromacy (total color blindness), dichromacy (partial color blindness), and anomalous trichromacy [11].

Monochromats possess only rods or a single type of cone, leading to an inability to perceive colors. Dichromats lack one of the three cone types, causing difficulty in distinguishing specific wavelengths of light. Dichromacy is further categorized into three types: (a) Protanopia, characterized by the absence of red-sensitive photoreceptors, impairing vision in the 560–670 nm wavelength range; (b) Deuteranopia, marked by the absence of green-sensitive photoreceptors, affecting perception of hues around 530 nm; and (c) Tritanopia, defined by the absence of short-wavelength cones, which impairs blue-yellow color discrimination in the 420–500 nm range. Anomalous trichromats possess three types of cones but with altered spectral sensitivity, leading to three subtypes: (a) Protanomaly, involving reduced sensitivity to red light due to long-wavelength pigment defects; (b) Deuteranomaly, caused by defects in the middle-wavelength (green) pigment; and (c) Tritanomaly, involving shifts in blue pigment sensitivity towards the green spectrum [12-13].

The digit ratio (2D:4D) in individuals, defined by the length of the index finger (2D) compared to the ring finger (4D), is a genetically inherited trait influenced by sex. Generally, men exhibit a lower 2D:4D ratio than women. Prenatal exposure to sex hormones, particularly testosterone and estrogen, regulates finger length by influencing the activity of HOXA and HOXD genes, which are critical for finger development. Higher prenatal testosterone levels result in a shorter index finger relative to the ring finger, whereas elevated prenatal estrogen levels lead to a longer index finger [14]. Male pattern baldness (androgenetic alopecia, AGA) is another example of sex-influenced inheritance [5].

AGA is an age-related condition characterized by hair thinning, miniaturization, and loss. This condition follows an inherited pattern associated with genetic markers on the X chromosome, suggesting a link to variations in the androgen receptor (AR) gene [7]. Factors contributing to AGA include genetic predisposition and hormonal influences, particularly the role of dihydrotestosterone (DHT), which is synthesized from testosterone by the enzyme 5-alpha reductase type II. This enzyme is more prevalent in men, explaining why AGA is significantly more common in males than females [16].

Although female pattern baldness exists, it is much rarer than in men. When women inherit the BB genotype for baldness, they exhibit milder symptoms, which appear later in life compared to males [5]. The practical study "*Color Blindness and the Role of Sex-Influenced Genes*" aims to determine an individual's color vision status and identify their genotype.

MATERIALS AND METHOD

Tools and Materials

The tools used in the research "Color Blindness and the Role of Genes Influenced by Sex" include the Ishihara test website, white HVS paper, a pen, and a ruler. The materials used are the practitioners as subjects.

Work Procedure

A color blindness test was conducted for each proband online using the prepared Ishihara test website. Then, the test results were documented and the error percentage was calculated. If the error percentage is less than 50%, then the practitioner is declared normal, and if the error percentage is more than 50%, then the practitioner is declared color blind. Next, the work procedure begins with drawing a horizontal line on the practical HVS paper, then placing the left hand on the paper with the tip of the index finger touching or in contact with the horizontal line. Then, the pattern is made with a pencil or pen following the shape of the fingers. Then, the genotype and phenotype are determined, and class data is created to prove the gene frequency in the population of male and female individuals (practitioners).

RESULTS AND DISCUSSION

Ishihara Test

Table 1. Results of the Ishihara Test

No.	Name	% True	% False	Fenotip	Genotip
1	Sari Ayu Sagita	100%	0%	Normal	XX / $X^{cb}X$
2	Anisah Zakiyyah	92%	8%	Normal	XX / $X^{cb}X$
3	Syarifah Al Aini	100%	0%	Normal	XX / $X^{cb}X$
4	Muhammad Alif Ramadhani	100%	0%	Normal	XY
5	Zufar Azarial Azmi	96%	4%	Normal	XY
6	Naurah Rizki Fajrinia	92.10%	7.9%	Normal	XX / $X^{cb}X$
7	Shafannisa Febrina Irwandi	100%	0%	Normal	XX / $X^{cb}X$
8	Aisyah Dhuha Nita Sari	100%	0%	Normal	XX / $X^{cb}X$
9	Anjaliya Salma Putri	89.47%	10.53%	Normal	XX / $X^{cb}X$
10	Shelly Damayanti	92.11%	7.89%	Normal	XX / $X^{cb}X$
11	Aprilantia Wilatikta	89.47%	10.53%	Normal	XX / $X^{cb}X$
12	Andini	100%	0%	Normal	XX / $X^{cb}X$
13	Salma Argya Rasmi	100%	0%	Normal	XX / $X^{cb}X$
14	Yunita Maulida Rohmawati	100%	0%	Normal	XX / $X^{cb}X$
15	Azizah Izzah Maharani	89.47%	10.53%	Normal	XX / $X^{cb}X$
16	Kintan Alifia Novebriyanti	92.10%	7.90%	Normal	XX / $X^{cb}X$

Based on the Ishihara test results table in **Table 1**, the following results were obtained. All probands in the data are classified as normal. Of the 16 probands, there are 8 probands who have a Correctness Percentage of 100%, with a Wrongness

Percentage of 0%, namely Sari Ayu Sagita, Syarifah Al Aini, Muhammad Alif Ramadhani, Shafannisa Febrina Irwandi, Aisyah Dhuha Nita Sari, Andini, Salma Argya Rasmi, and Yunita Maulida Rohmawati. With that percentage, the phenotype of those 8 probandus is classified as normal. Then, out of all 16 probandus, there were also errors in answering during the test, resulting in a percentage of correct answers not being 100%. There is one practitioner with a correctness percentage of 96% and an error percentage of 4%, whose phenotype is classified as normal, namely Zufar Azarial Azmi. Then there are 4 practitioners, namely Anisah Zakiyyah, Naurah Rizki Fajrinia, Shelly Damayanti, and Kintan Alifia Novebriyanti, who have a Correct percentage of 92.10% with a Wrong percentage of 7.9%. With that percentage, the phenotypes of the four probands are classified as Normal. Then, there are 3 probands, namely Anjaliya Salma Putri, Aprilantia Wilatikta, and Azizah Izzah Maharani, who have a Correct Percentage of 89.47% with a Wrong Percentage of 10.53%. With that percentage, the phenotypes of the three practitioners are classified as normal. In the female proband with a normal phenotype, the genotype is XX / $X^{cb}X$, where $X^{cb}X$ represents a carrier female of color blindness. In the male proband with a normal phenotype, the genotype is XY.

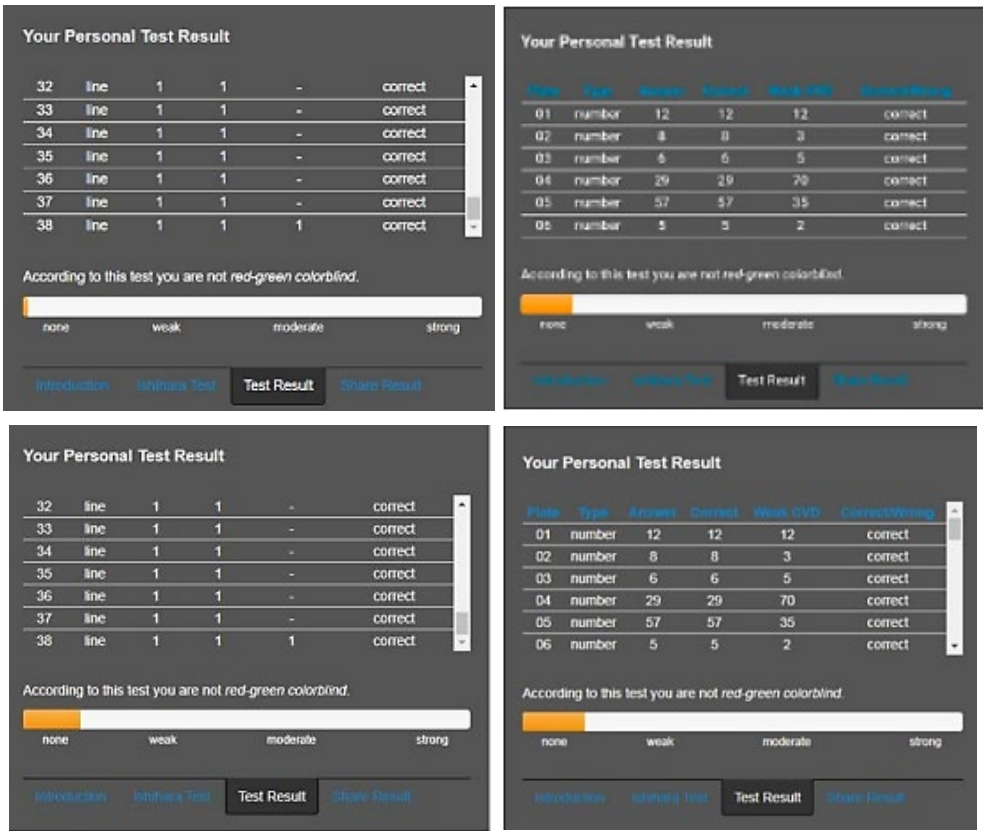

Fig. 1. Ishihara test result.

Finger Length Ratio Test

Table 2. Results of the comparison observation between the length of the index finger and the length of the ring finger on the probandus.

	Gender	Long Index Finger	Short Index Finger	Same	% Long Finger	% Short Finger	% Same
Right	Male	1	1	0	50.00%	50.00%	0%
	Female	3	10	1	21.43%	71.43%	7.14%
	Total	4	11	1	25.00%	68.75%	6.25%
	Gender	**Long Index Finger**	**Short Index Finger**	**Same**	**% Long Finger**	**% Short Finger**	**% Same**
Left	Male	1	1	0	50.00%	50.00%	0%
	Female	6	8	0	21.43%	71.43%	7.14%
	Total	7	9	0	25.00%	68.75%	6.25%

From the table, it can be seen that out of 16 probands, 4 of them have a longer index finger on their right hand. 1 of the 4 people is male, while the other 3 are female. 11 out of the total 16 probandus have shorter index fingers on their right hands. 1 out of those 11 people is male, while the other 10 are female. It is known that the number of probandus with the length of the right index finger equal to the length of the right ring finger is one person of female gender. This results in 50% of the males having a right index finger longer than their right ring finger, while 21.43% of the females have a right index finger longer than their right ring finger.

This results in 25% of the probands having a right index finger longer than their right ring finger, and only 6.25% of the total probands having equal lengths for their right index and right ring fingers. In the table, it can be seen that out of 16 probands, 7 of them have a left index finger longer than their left ring finger. 1 out of those 7 people is male and the other 6 are female. 9 out of the total 16 probandus have a left index finger shorter than their left ring finger. 1 out of those 9 people is a man, while the other 8 are women. In addition, it is known that out of the 16 probandus, none have a left index finger length equal to their left ring finger length.

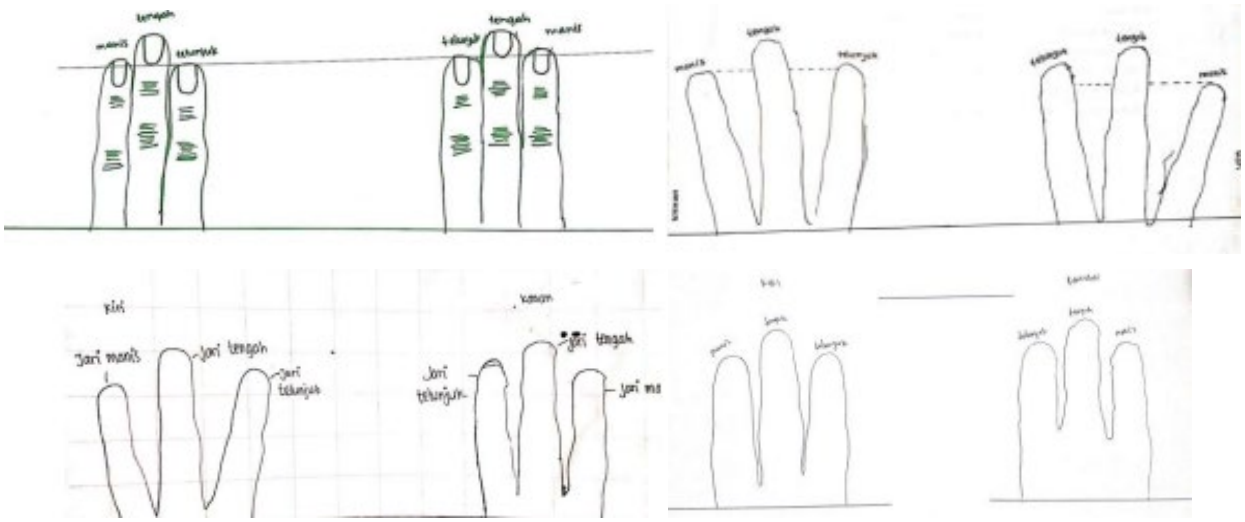

Fig. 2. Result length of the index finger and the length of the ring finger on the probandus.

This shows that 50% of the total 2 male probandus have a left index finger longer than their left ring finger, while the remaining 50% have a left index finger shorter than their left ring finger. 43% of the total 14 female probands have a left index finger longer than their left ring finger, whereas 57% of the total 14 female probands have a left index finger shorter than their left ring finger. When observed as a whole, 43.75% of the subjects have a left index finger longer than their left ring finger, and 56.25% of the subjects have a left index finger shorter than their left ring finger. There is no population where the left index finger and left ring finger are of equal length at all.

Expanding the discussion to encompass the effects of color blindness on social interactions and occupational choices offers a comprehensive understanding of its impact. Individuals with color vision deficiencies often face challenges in daily activities, which can lead to social misunderstandings and feelings of exclusion. For instance, difficulties in distinguishing colors may affect participation in certain social or cultural activities, potentially leading to social isolation. Professionally, color blindness can limit career options, especially in fields where color discrimination is crucial, such as graphic design, electrical work, and healthcare diagnostics. Color vision deficiencies can significantly influence an individual's professional choices and quality of life [33]. Therefore, acknowledging and accommodating color blindness in social and occupational contexts is essential to mitigate its adverse effects [32].

The findings on color blindness and the role of sex-influenced genes have significant implications in clinical settings, particularly in genetic counseling and educational strategies for affected individuals. Genetic counseling can provide valuable insights into the hereditary nature of color blindness, enabling individuals and families to make informed reproductive and lifestyle decisions. Early genetic screening can help identify individuals at risk, allowing for tailored interventions and adaptive learning strategies. In the educational domain, incorporating specialized learning tools, such as color-adjusted teaching materials and digital assistive technologies, can enhance accessibility for colorblind students. Additionally, workplace accommodations, including modified visual cues and color-friendly design strategies, can improve employment opportunities for those with color vision deficiencies. By integrating these clinical and educational approaches, the impact of color blindness can be mitigated, ensuring a more inclusive environment for affected individuals.

Color blindness is a condition caused by the inability of the cone cells in the eyes to capture a certain spectrum of colors due to genetic factors. Color blindness is a condition inherited from parents to their children, carried by the X chromosome because the gene that produces the photo pigment is linked to the X chromosome [18]. Color blindness can be inherited or acquired due to a condition. Inherited color blindness cannot be cured, and the percentage of inherited color blindness in men is higher compared to women. This is because men only carry one X chromosome. whereas when the X chromosome carries the color blindness gene (cb), the man will experience color blindness. Meanwhile, women have two X chromosomes, resulting in two possibilities: the woman is a color vision carrier ($X^{cb}X$) or a color vision deficient (XX). Thus, there is a study that states that color blindness affects about 8% of men and 0.5% of women [19]. In normal humans, there are three types of cone cells that have sensitivity to different colors. Normal color vision is created from the combination of three types of photoreceptors [20]. The weakening of one type of cone cell or even the absence of one type of cone cell results in a color vision deficiency. According to [18]. Color blindness disorders are divided into three types: Trichromatic anomaly, Dichromat, and Monochromat. Anomalous trichromacy is a condition where three types of cone cells remain, but one of them is not normal or does not function properly, causing the sufferer to have difficulty distinguishing certain shades of color. There are three types of color blindness that are commonly experienced, namely anomalous trichromacy, dichromacy, and monochromacy [18].

Anomalous trichromacy is a condition where three types of cone cells remain, but one of them is not normal or does not function properly, causing the sufferer to have difficulty distinguishing certain shades of color. There are three types of color blindness that are commonly experienced, namely anomalous trichromacy, dichromacy, and monochromacy [18].

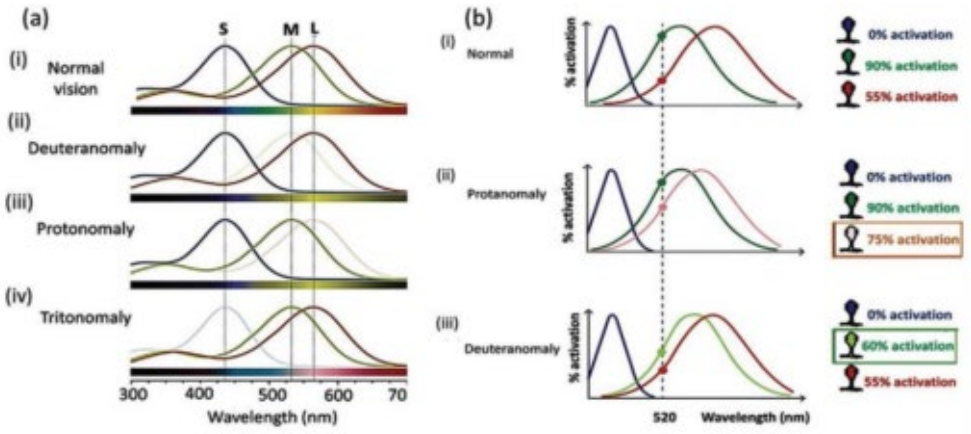

Fig. 3. (a) Trichromatic anomaly color blindness graph (b) The visualization graph if someone with color blindness perceives a wavelength of 520 nm [21].

In image a(i), it shows the vision graph of a normal person, where the red, blue, and green wavelengths are clearly observed. Figure a(ii) shows the Deuteranomaly graph, which is a condition where the green cone cells do not function properly,

making the sufferer less sensitive to recognizing the color green. Therefore, the interpretation of the graph in figure a shows the green color fading. Deuteranomaly affects 4.63% of males and 0.36% of females. In image b(iii), the green wave captured is only 60%. Next, in image a(iii), there is the color blindness condition known as Protonomaly, which is a state where the red cone cells do not function properly, making the sufferer less sensitive to recognizing the color red. Therefore, the interpretation of the red color fading in graph a(iii) indicates that, according to studies, the protonomaly condition affects 1.08% of men and 0.03% of women. Figure 1(iv) shows the Tritanomaly condition, which is a state where blue cone cells do not function properly, making the sufferer less sensitive to recognizing the color blue. Therefore, the interpretation of the graph shows a fading blue color [18,21].

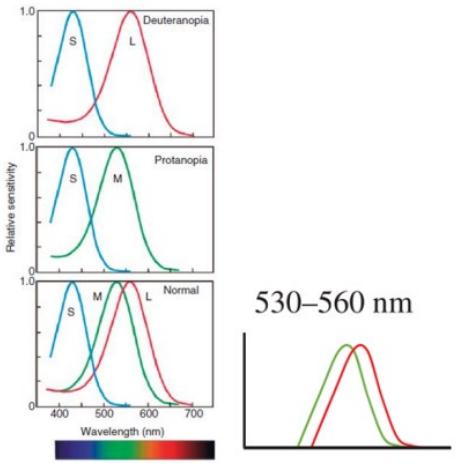

Fig. 4. Color blindness disorder Dikhorimat [22][23].

The next color blindness disorder is Dichromatism, which is a condition where one of the three cone cells is absent. Thus, it is divided into three categories of dichromacy: Deuteranopia, protanopia, and tritanopia. Deuteranopia is shown in the first graph where this anomaly occurs because the green cone cells are absent, resulting in a decrease in the brightness or combination of green colors. Therefore, in the first graph, the green color graph is not visible. The next condition is protanopia, which is caused by the absence of red cone cells, resulting in reduced brightness or intensity of red colors. Protanopia is shown in the second graph with the interpretation of the absence of a red-colored graph. Then there is Tritanopia, which is an eye disorder caused by the absence of blue cone cells, resulting in reduced brightness of blue colors. Therefore, the interpretation of the graph does not include a blue-colored graph [18,22].

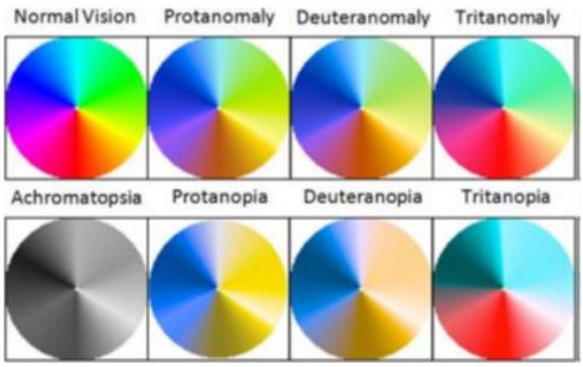

Fig. 5. Comparison of color spectrum in normal and abnormal eyes [22].

The next eye disorder is monochromat, which is a condition of the retina that experiences total damage in responding to color. This condition is characterized by a reduction in all color vision, so that only black and white are visible [18]. From the presence of these abnormalities, it is linked to the results of the color blindness practical test conducted on 16 practitioners, consisting of 14 female practitioners and 2 male practitioners. From the test results, it was found that all practitioners had a normal phenotype. Where all practitioners can recognize the numbers or lines present on the pseudoisochromic sheet of the Ishihara test, and the final result of the test is declared normal [24].

Length of the Index Finger

The digit ratio of finger length is the ratio of the lengths of different finger digits and is usually measured from the midpoint of the lower crease where the fingers join the hand to the fingertip. Most commonly, the digit ratio only shows the 2D (index finger):4D (ring finger) ratio [25]. The ratio of the length of the index finger to the ring finger in an individual is a character or trait inherited through genes whose expression is influenced by sex (sex influence gene). The length of the second finger or index finger (2D) and the fourth finger or ring finger (4D) is related to sex differences, where the 2D to 4D ratio for most males is found to be smaller than that for females [14]. The ratio of the second to fourth digit (2D:4D) is influenced by the end of the first trimester of pregnancy (from week 1 to the end of week 12 of pregnancy) and is believed to be a biomarker of the balance between prenatal testosterone and prenatal estrogen hormones. After that, the ratio of the index finger to the ring finger (2D:4D) may remain unchanged throughout life. Testosterone affects the growth of the ring finger (4D), while exposure to estrogen stimulates the growth of the index finger (2D). Specifically, males show a lower ratio on the index finger due to increased prenatal testosterone exposure [26].

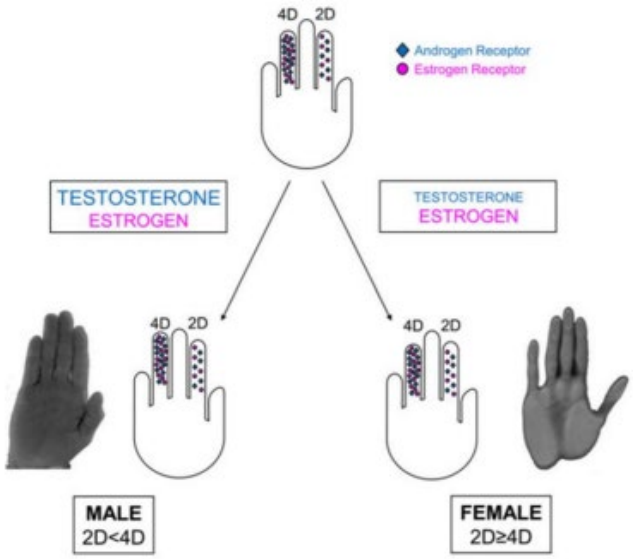

Fig. 6. The difference in finger digit ratio between women and men [27].

This sexual dimorphism is already evident since the individual is still a fetus. There are several factors that influence finger size, one of which is sex hormones, namely testosterone and estrogen. These hormones will affect the function of two genes, namely HOXA and HOXD (homeobox A (HOX A) and homeobox D (HOX D)), which play a role in controlling the length of a person's fingers. These genes are influenced by prenatal androgens, which also contribute to the formation of reproductive organs in the womb. Low levels of testosterone or androgens and high levels of prenatal estrogen will cause the index finger to be longer than the ring finger, or conversely, high levels of testosterone or androgens and low levels of prenatal estrogen will cause the

index finger to be shorter than the ring finger. Additionally, it has also been reported that the 2D:4D ratio can be used as a fairly significant biological marker. A high 2D:4D ratio (where the index finger is longer than the ring finger) in women is associated with lower cellular immunity (T cells) compared to men with a lower ratio. This is related to the role of androgens as immunosuppressants [14]. The 2D:4D ratio is also influenced by the increased replication of Cysteine-Adenine-Guanine (CAG) DNA in the androgen receptor gene. If the alleles in the Androgen Receptor (AR) gene have more CAG repeats, then the AR gene becomes insensitive to testosterone [25].

Related to the research results, data was obtained showing that women's index fingers are mostly shorter than their ring fingers, at 71.43% on the left hand and 57% on the right hand, while men have the same percentage. It is known that the lower the 2D:4D ratio obtained (the index finger is shorter than the ring finger), the higher the prenatal testosterone exposure, which stimulates the central nervous system to enhance the ability to make certain visual-spatial decisions, thereby increasing physical abilities. High prenatal testosterone levels also help represent dominance and may activate masculine characteristics during puberty [26]. A low digit ratio is associated with certain characteristics such as aggression in men and assertiveness in women. In addition, data differences are also known due to variations that have been reported in different ethnic and geographical groups. The finger ratio varies between different ethnic groups, and this is suspected to have a greater influence than the differences between genders [25]. The 2D:4D ratio can be used as an indicator of prenatal sex hormone exposure, whereas in adulthood, there is no significant relationship between sex hormone levels and the 2D:4D ratio, both in men and women [14].

In genes linked to the X chromosome, they exhibit Criss-Cross Inheritance or are also referred to as a cross inheritance pattern. A father's gene will be inherited by his daughter, and a mother's gene will be inherited by her son. This trait is closely related to its connection to color blindness, which is more commonly expressed in males than in females. This is because men only have one X chromosome. In males, the terms dominant or recessive are not recognized, so the trait of color blindness in males is more easily expressed. Meanwhile, women have two X chromosomes, so color blindness in women only occurs in a homozygous recessive state. Women who are heterozygous (carriers) do not experience color blindness, but they have the potential to pass the color blindness trait to their offspring. Therefore, color blindness is caused by the presence of a recessive allele c (color blind) linked to the X chromosome [28].

CONCLUSION

Based on the research that has been conducted, it can be determined whether the probandus has color blindness or not. By conducting the Ishihara test on the probands, it was found that 8 probands had a Correctness percentage of 100%, with an Error percentage of 0%, 1 proband had a Correctness percentage of 96% with an Error percentage of 4%, 4 probands had a Correctness percentage of 92.10% with an Error percentage of 7.9%, and 3 probands had a Correctness percentage of 89.47% with an Error percentage of 10.53%. With those percentages of Correct and Incorrect, all probands have a normal phenotype and the genotype XX / $X^{cb}X$ for female probands and the genotype XY for male probands. In addition, it is also known that 4 probands have a right index finger longer than their right ring finger. One of them is male. As many as 11 probands have a right index finger shorter than their ring finger, one of whom is male. One probandus has a right index finger that is the same length as his right ring finger. It is known that 7 probandus were found to have a left index finger longer than their left ring finger. One of them is a male probandus. As many as 9 probandus have a left index finger that is longer than their left ring finger. One of them is a female probandus. No probandus was found to have the same length of the left index finger and the left ring finger.

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