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Variation in Eye Color of Human Beings

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ABSTRACT

A person's eye color results from pigmentation of a structure called the iris, which surrounds the small black hole in the center of the eye (the pupil) and helps control how much light can enter the eye. The color of the iris ranges on a continuum from very light blue to dark brown. Most of the time eye color is categorized as blue, green/ hazel, or brown. Brown is the most frequent eye color worldwide. Lighter eye colors, such as blue and green, are found almost exclusively among people of European ancestry.Eye color is determined by variations in a person's genes. Most of the genes associated with eye color are involved in the production, transport, or storage of a pigment called melanin. Eye color is directly related to the amount and quality of melanin in the front layers of the iris. People with brown eyes have a large amount of melanin in the iris, while people with blue eyes have much less of this pigment.A particular region on chromosome 15 plays a major role in eye color. Within this region, there are two genes located very close together: OCA2 *and* HERC2*. The protein produced from the* OCA2 *gene, known as the P protein, is involved in the maturation of melanosomes, which are cellular structures that produce and store melanin. The P protein therefore plays a crucial role in the amount and quality of melanin that is present in the iris. Several common variations (polymorphisms) in the* OCA2 *gene reduce the amount of functional P protein that is produced. Less P protein means that less melanin is present in the iris, leading to blue eyes instead of brown in people with a polymorphism in this gene.A region of the nearby* HERC2 *gene known as intron 86 contains a segment of DNA that controls the activity (expression) of the* OCA2 *gene, turning it on or off as needed. At least one polymorphism in this area of the* HERC2 *gene has been shown to reduce the expression of* OCA2*, which leads to less melanin in the iris and lighter-colored eyes.Several other genes play smaller roles in determining eye color. Some of these genes are also involved in skin and hair coloring.*

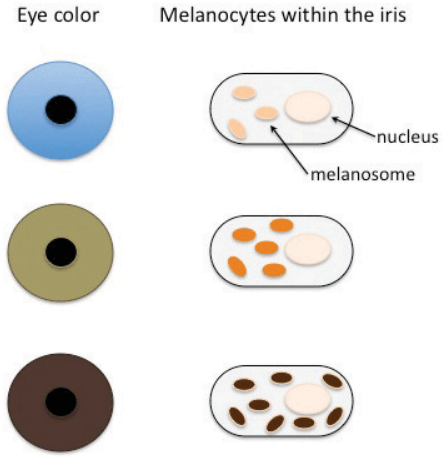
Genes with reported roles in eye color include ASIP, IRF4, SLC24A4, SLC24A5, SLC45A2, TPCN2, TYR, *and* TYRP1*. The effects of these genes likely combine with those of* OCA2 *and* HERC2 *to produce a continuum of eye colors in different people.*

Several disorders that affect eye color have been described. Ocular albinism is characterized by severely reduced pigmentation of the iris, which causes very light-colored eyes and significant problems with vision. Another condition called oculocutaneous albinism affects the pigmentation of the skin and hair in addition to the eyes. Affected individuals tend to have very light-colored irises, fair skin, and white or light-colored hair. Both ocular albinism and oculocutaneous albinism result from mutations in genes involved in the production and storage of melanin. Another condition called heterochromia is characterized by different-colored eyes in the same individual. Heterochromia can be caused by genetic changes or by a problem during eye development, or it can be acquired as a result of a disease or injury to the eye.

INTRODUCTION

DNA provides the set of recipes, or genes, used by cells to carry out daily functions and interact with the environment.Eye color was traditionally described as a single gene trait, with brown eyes being dominant over blue eyes.Today, scientists have discovered that at least eight genes influence the final color of eyes. The genes control the amount of melanin inside specialized cells of the iris.One gene, OCA2, controls nearly three-fourths of the blue-brown color spectrum. However, other genes can override the OCA2 instruction, albeit rarely. This multifactorial model for eye color explains most of the genetic factors that influence eye color. In 1907, Charles and Gertrude Davenport developed a model for the genetics of eye color. They suggested that brown eye color is always dominant over blue eye color. This would mean that two blue-eyed parents would always produce blue-eyed children, never ones with brown eyes.For most of the past 100 years, this version of eye color genetics has been taught in classrooms around the world. It's one of the few genetic concepts that adults often recall from their high school or college biology classes. Unfortunately, this model is overly simplistic and incorrect – eye color is actually controlled by several genes. Additionally, many of the genes involved in eye color also influence skin and hair tones. In this edition of Biotech Basics, we'll explore the science behind pigmentation and discuss the genetics of eye color. In a future edition, we'll discuss genetic factors that contribute to skin and hair color. The color of human eyes, skin and hair is primarily controlled by the amount and type of a pigment called melanin. Specialized cells known as melanocytes produce the melanin, storing it in intracellular compartments known as melanosomes. The overall number of melanocytes is roughly equivalent for all people, however the level of melanin inside each melanosome and the number of melanosomes inside a melanocyte varies. The total amount of melanin is what determines the range of hair, eye and skin colors.There are a number of genes involved in the production, processing and transport of melanin. Some genes play major roles while others contribute only slightly. To date, scientists have identified over 150 different genes that influence skin, hair and eye pigmentation. A number of these genes have been identified from studying genetic disorders in humans. Others were discovered through comparative genomic studies of coat color in mice and pigmentation patterns in fish.[1]

In humans, eye color is determined by the amount of light that reflects off the iris, a muscular structure that controls how much light enters the eye. The range in eye color, from blue to hazel to brown (see figure one), depends on the level of melanin pigment stored in the melanosome "packets" in the melanocytes of the iris. Blue eyes contain minimal amounts of pigment within a small number of melanosomes. Irises from green–hazel eyes show moderate pigment levels and melanosome number, while brown eyes are the result of high melanin levels stored across many melanosomes (see fig.1)



To date, eight genes have been identified which impact eye color. The *OCA2* gene, located on chromosome 15, appears to play a major role in controlling the brown/blue color spectrum. *OCA2* produces a protein called P-protein that is involved in the formation and processing of melanin. Individuals with *OCA2* mutations that prevent P-protein from being produced are born with a form of albinism. These individuals have very light colored hair, eyes and skin. Non-disease-causing *OCA2* variants (alleles) have also been identified. These alleles alter P-protein levels by controlling the amount of *OCA2* RNA that is generated. The allele that results in high levels of P-protein is linked to brown eyes. Another allele, associated with blue eye color, dramatically reduces the P-protein concentration.[2]

On the surface, this sounds like the dominant/recessive eye color model that has been taught in biology classes for decades. However, while about three-fourths of eye color variation can be explained by genetic changes in and around this gene, *OCA2* is not the only influence on color. A recent study that compared eye color

to *OCA2* status showed that 62 percent of individuals with two copies of the blue-eyed *OCA2* allele, as well as 7.5 percent of the individuals who had the brown-eyed *OCA2* alleles, had blue eyes. A number of other genes (such as *TYRP1*, *ASIP* and *ALC42A5*) also function in the melanin pathway and shift the total amount of melanin present in the iris. The combined efforts of these genes may boost melanin levels to produce hazel or brown eyes, or reduce total melanin resulting in blue eyes. [3]

DISCUSSION

Curiously enough, eye color variants for humans may have also started very recently (about 8,000 years ago), concurrent with sedentarism and domestication of plants and animals, and only (or mainly) in Europe. As of today, eye color variation in humans may be described as ***continuous***, with numerous shades from very light blues to very dark browns.[4]

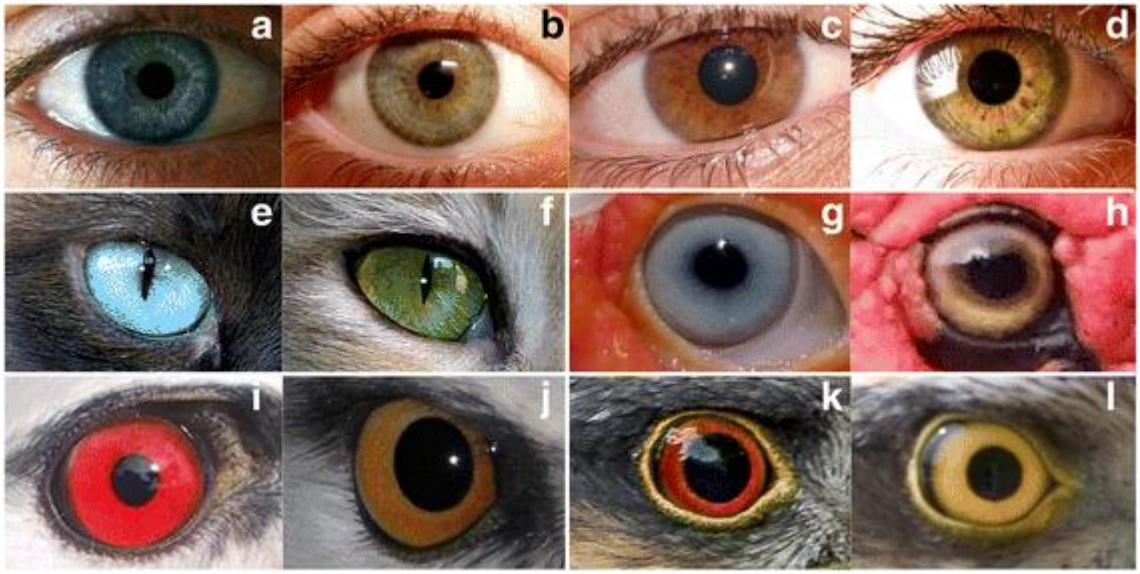


Fig.2-eye color classification

In the most elementary form, the inheritance of eye color is classified as a Mendelian trait.1 On the basis of the observation of more than two phenotypes, eye color has a more complex pattern of inheritance. Eye color ranges include varying shades of brown, hazel, green, blue, gray, and in rare cases, violet and red. The traditional view was correct in which an allele that codes for brown is dominant over green or blue, and green takes precedence over blue.[5]

Melanocytes in the stroma and anterior layers of the eye hold melanin in their cytoplasms. In the rest of the body, the melanin is secreted from the cells. This provides an explanation why some babies develop their eye color, but skin pigmentation changes constantly throughout life. Despite the color of the eye, the number of melanocytes does not differ. The quantity and quality of melanin in the cytoplasm determines the observed color of the eye. When light passes through a large amount of melanin, most of the visible light is absorbed, and the little that is reflected back appears brown. This same phenomenon is the reason why the pupil appears black. All visible light is absorbed by the retina. As the eye color lightens, less melanin is present in the cells, reflecting more of the visible spectrum. Red and violet eyes come from a lack of pigment. The red appearance is the reflection of the eye's blood vessels. When there is too little pigment to produce a strong blue color, the red reflections interact with the small amount of blue, producing a violet color.[6]

The biological process for producing melanin, melanogenesis, involves numerous protein interactions. In melanocyte-specific organelles known as melanosomes, two pathways for melanogenesis occur. One leads to eumelanin, a darker pigment (brown-black), and the other to pheomelanin, a light pigment (red-yellow). Tyrosinase (TYR), the enzyme responsible for pigment production in the body, starts the synthesis of both types of melanin by catalyzing a reaction between tyrosine and dopa, forming dopaquinone. In the presence of cysteine, the reaction will proceed to form pheomelanin. To form eumelanin, dopachrome tautomerase, TYR, and TYR-related protein 1 complete the chemical pathway from dopaquinone.[7]

Although the aforementioned proteins are responsible for the production of melanin, once it has been produced in the melanosomes, other proteins are responsible for melanin maturation.

Membrane-associated transporter protein and p protein oculocutaneous albinism II (OCA2) transport melanosomes for melanin maturation. Melanocortin 1 receptor (MC1R) instructs a melanocyte to switch production between eumelanin and pheomelanin.[3, 4, 5] Therefore, these two proteins affect the quality and quantity of the melanin in the cell. Other very minor genes are responsible for eye color production, such as agouti signaling protein, but they usually have miniscule effects.[5] Finally, two major genes are responsible for eye color: HERC2 and OCA2. During the first studies to classify genes for eye color, OCA2 was believed to be the dominating factor for eye color determination.[3, 6, 7, 8] Within the last couple of years, HERC2, an ubiquitin ligase-coding region, has been linked more strongly to eye color. Both genes are located on chromosome 15. OCA2 ranges from 15q11.2-12 and HERC 2 starts at 15q13. These genes are of the greatest importance for eye color.[8] Numerous ubiquitin ligases are coded for throughout the body. Chromosome 15 contains HERC1 and HERC2. Problems with just HERC2 lead to nerve tissue malfunctioning, small size and semi-sterility or sterility. They help with hormone secretion, which affects the pituitary and can lead to dysfunction of the hypothalamus and other protein complexes. The large *HERC2* gene requires 211 kb and 93 exons that codes for a 528 kDa protein made of 4834 residues. OCA2 codes for a major transmembrane protein in the melanosome maturation process: P protein. Similar to membrane-associated transporter protein, it transports melanosomes, but additionally, it controls their pH.[3, 13] Therefore, the P protein encoded by OCA2 affects the amount and quality of melanin that deposits in melanocytes. In mice and humans where the P protein is nonfunctional, albinism occurs, indicating its crucial role in pigmentation.[13, 14] The gene located 11.7 kb from HERC2 requires 345 kb, but it requires only 24 exons to produce a 110 kDa protein with 838 residues. These two seemingly unrelated genes have a major effect on eye color in humans.

The promoter region for OCA2 is located within the HERC2 gene. Although introns are usually viewed as superfluous DNA, intron 86 of HERC2 regulates the expression of OCA2. In studies with HERC2 functions, deletions caused hypopigmentation even though the protein has nothing to do with pigmentation. Further studies of this region and its sequence revealed that a change in one nucleotide, single-nucleotide polymorphism (SNP), regulates the binding site for the transcription of the OCA2 gene, altering its expression.[9] The base changes from a thymine to a cytosine. The SNP, rs12913832, causes a phenotype change from brown to blue eyes, respectively. In the case of the mutation within HERC2, the expression of the P protein encoded by OCA2 decreases, effectively decreasing its effects in pigmentation. This also explains why deletions within HERC2 would cause a decrease in melanin without interacting with the P protein itself.The *OCA2* gene also contains numerous regions for eye color expression. Over 300 SNPs for eye color have been identified on the gene, but classification of their results proved too arduous. The gene contains a main coding region for brown eyes (BEY2 15q11-15) and hazel eyes (BEY1).[3, 5] Other SNPs result in blue and green eyes. One SNP has been studied to show a large significance for eye color. Before the revelation of the effect of HERC2, rs1800407 in exon nine was thought to be the main factor for eye color. The change of this base from a C to a T causes a change from brown eyes to non-brown eyes (usually blue). In the P protein, the mutation causes residue 419 to change from an arginine to a glutamine. The possible changes in the DNA sequence are GCT to GTT and GCC to GTC. Although the crystal structure has not been published for the P protein coded by OCA2, residue 419 is predicted to face the cytoplasmic portion of the lipid bilayer in one of the several transmembrane domains. Therefore, the SNP change that results in R419Q most likely affects the P protein in conformation.Decreased expression of OCA2 affects the pathway for melanosome maturation. Melanin undergoes a packaging process and if large amounts of P protein are not available to process and transport it, the quality of the darker pigment is compromised and lighter shades will result.[10] Demonstrating epistasis, the HERC2 gene affects the results produced by the *OCA2* gene. Even if the *OCA2* gene contains the alleles for brown eyes, the SNP in intron 86 of HERC2 will prevent its expression. The decreased expression could account for incomplete dominance, as well. Lighter shades of brown and gray, a lighter shade of blue, show a mixture of two phenotypes where neither dominates completely.In the traditional view of eye color, it was taught that two blue-eyed individuals could only produce blue-eyed offspring. With the revelation of this epistatic relationship, it helps to prove that it can, and does, happen. A simple cross is provided in Figure 1: Blue-eyed Cross. ('H' represents the non-mutated HERC2 SNP, and 'O' represents the

OCA2 allele for brown eyes). The first parent contains the mutation in the HERC2 intron in both alleles but possesses an allele with the coding for brown eyes. The second parent has a non-mutated HERC2 allele but does not have the coding for brown eyes in the *OCA2* gene. More than likely, their offspring would have blue eyes, but a 25% chance stands that offspring would have brown eyes.

Table-1

hhOo x Hhoo

	hO	ho
Ho	Hh Oo	Hh oo
ho	hh Oo	hh oo

Blue-eyed Cross.

As mentioned previously, melanogenesis produces two different types of melanin and requires numerous proteins. TYR, located from 11q14-q21, begins the melanogenesis pathway. Dopachrome tautomerase (13q32) and TYR-related protein 1 (9p23) will continue the pathway to form eumelanin.15 Therefore, if any of these proteins are not coded for correctly, the eumelanin production may be hindered, producing lighter eyes. In the case of TYR, melanin production will halt entirely, resulting in albinism in the entire body. Although TYR does not code for color, a nonfunctioning TYR masks any other gene responsible for pigmentation.In the pheomelanin pathway, the presence of cysteine has a major role. Without cysteine, the synthesis cannot be carried out. Although cysteine is not an essential amino acid and its deficiency rarely occurs, the lack of it halts the production of pheomelanin. During pigment distribution in an infant, a diet low in cysteine or methionine, which it is synthesized from, would likely affect the color of the child's eyes until the amino acid is supplemented. In this case, pleiotropic effects change eye color.Aside from HERC2 and OCA2, the other genes involved in melanin production have some regions that correlate to other eye colors.5 MC1R contains regions that increase the probability of obtaining green eyes. This gene is often referred to as 'the red-headed gene' because of its prevalent expression in people with red hair and green eyes.4 Dopachrome tautomerase also contains regions for hazel and green eyes.5 Regions for brown eyes dominate the effects of these genes, though. Incomplete dominance shows in individuals with lighter shades of brown and hazel. A golden-brown iris indicates the mixture of both eumelanin and pheomelanin (produces the yellow color), and hazel is usually a mixture of brown and green or blue and green, depending on the shade.A few disorders are associated with eye color. The most common, which the *OCA2* gene is named for, is oculocutaneous albinism. An individual with this disorder produces little or no pigment in their ocular melanocytes. This condition is pronounced in people who produce little to no pigment throughout their entire body, but it can be localized to the eyes.2 When they produce no pigment at all, it is usually due to a nonfunctioning TYR.10 With this condition, a complete lack of pigment produces red eyes, and a small amount of pigment may produce violet eyes. Similar to a lack of TYR, other conditions cause ocular albinism. Disorders in the HERC regions of chromosome 15 cause Prader–Willi or Angelman's syndrome. Prader–Willi syndrome is inherited from the paternal side whereas Angelman's comes from the maternal side. These syndromes result in hypopigmentation, along with delayed development, seizures and child-like behavior patterns.10, Heterochromia, although not viewed as a severe disorder, affects many individuals. The disorder is characterized by different-colored irises or different colors within the iris. It is inherited or caused by somatic mutations within the cells.2 In addition, it can be caused by the inactivation of particular genes within the cells. As different genes may be transcribed in various cells, certain cells will produce more pigment or a different type of pigment than other adjacent cells. The eumelanin/pheomelanin switch triggered by the *MC1R* gene may account for some cases of this disorder.[9,10]

Table-2

Gene name	Effect on eye color
OCA2	Associated with melanin producing cells. Central importance to eye color.
HERC2	Affects function of OCA2, with a specific mutation strongly linked to blue eyes.
SLC24A4	Associated with differences between blue and green eyes.
TYR	Associated with differences between blue and green eyes.

CONCLUSION

Eye color is the result of variations in the amount of melanin, a pigment found in the front part of the iris of the eye. The lack of this pigment results in blue eyes, some pigment gives green and lots of pigment gives brown eyes.So light brown eyes just have a bit less melanin than darker brown eyes. All of the different shades of eye color happen the same way. Blue-green eyes have an amount of melanin between green and blue, hazel eyes have an amount of pigment between green and brown, etc. Some people have eyes that have different colored patches. For example, blue eyes with a green or brown circle around the pupil are pretty common. In these eyes, different parts of the iris make different amounts of melanin. What we don't have yet is a good handle on how this all happens genetically. Scientists have a pretty good model based on two genes that can help explain blue, green, and brown eyes. This is the model we based our eye color calculator on.Scientists have even found the key gene, OCA2, which can explain why some people have brown eyes and some people don't. Despite some work, scientists haven't been able to find the key gene involved in green eyes. This is most likely because there is more than one gene.A new study has identified three new genes that affect eye color.

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