Red Hair: A Mutation, A Royal Trait, and Sometimes a Curse

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Of all the races on this earth, the Celtic are extremely well known for having one of the most captivating hair colors known to man, red. From mysterious and alluring, to fiery and powerful, this hair color captures the attention of people all over the world. Until about a decade ago, we did not know what exactly caused this hair color to emerge into our society however, this did not keep us from wondering why. From the artwork of Michelangelo, to the present day media attention of redheaded British Royalty, red hair color always had a significant position in our society. Thanks to the work of Roger Cone, Jonathan Rees, and other distinguished scientists, we now know that the physical manifestation of this hair color is because of a mutation in a gene on chromosome sixteen, and not having originated from the Neanderthals.

Generally, hair color is determined by a substance called melanin. This is produced by melanocytes, a group of specialized cells near the hair bulb (Sustaita). There are two types of melanin, eumelanin and phaeomelanin, and the ratios of these pigments are what determine hair color. Brown to black hair color is produced by a high amount of eumelanin pigment and a little amount of phaeomelanin. Red hair color is produced by a high amount of phaeomelanin, and a little amount of eumelanin pigment, while blond hair is produced by little amounts of both pigments (Red Hair Genetics).

There are two genes responsible for the production of hair color, the melanocortin-1 receptor gene (*MC1R* gene) and the pro-opimelanocortin gene (*POMC* gene). The *MC1R* gene is located on chromosome 16, the long arm, section 24, subsection 3, and it provides instructions for creating a gene product, the receptor for the alpha-melanocyte-stimulating hormone (α-MSH) (Genetics Home Reference). The *POMC* (pro-opiomelanocortin) gene

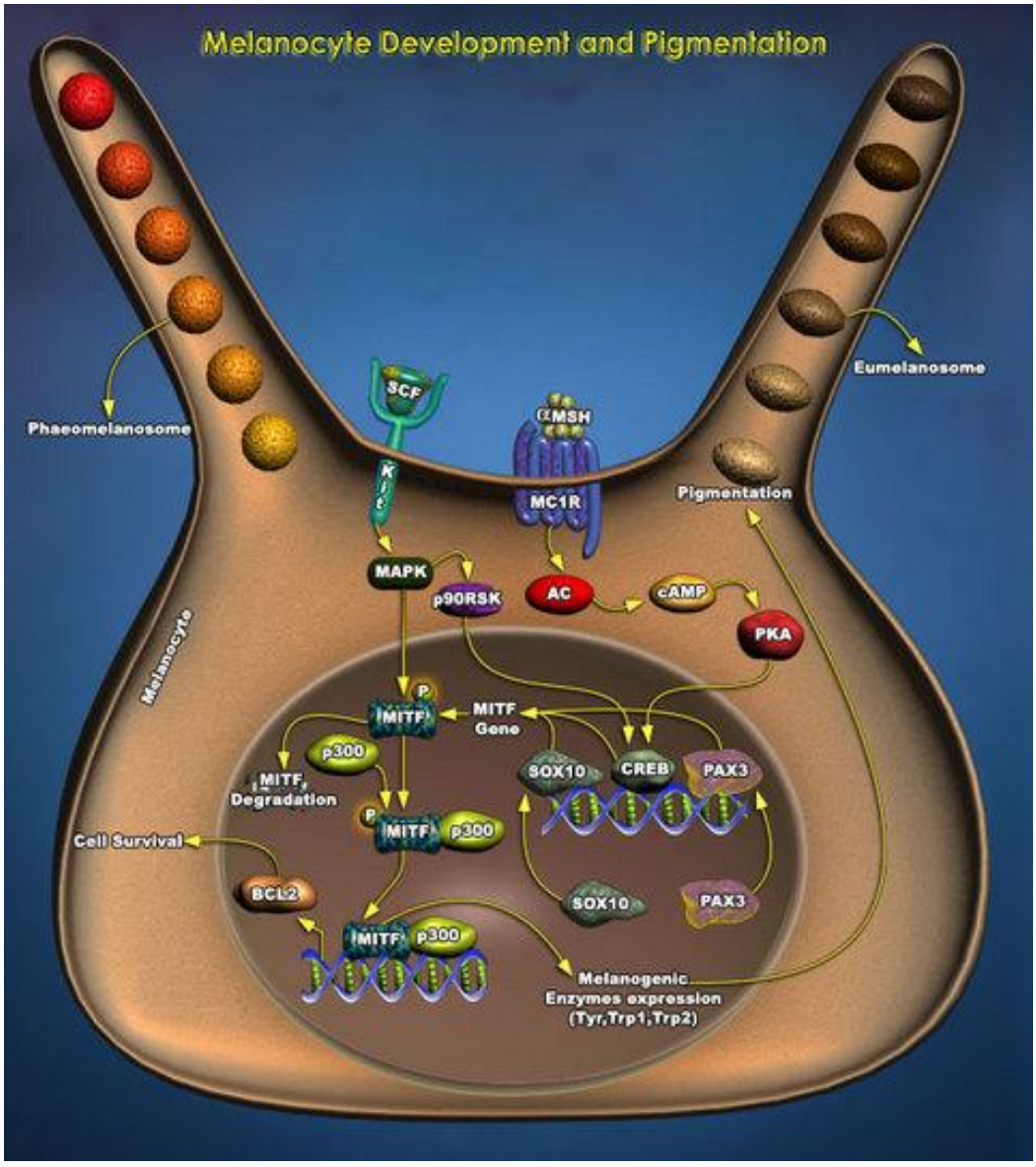
produces peptide products yielding a few hormones, one of which is the α-MSH. This α-MSH is produced in the pituitary gland of the brain and binds to an extracellular melanocortin-1 receptor which is located in the plasma membrane. By the binding of this hormone to the outside of the receptor, the receptor becomes activated and its result shows up in the melanocytes. Although the MC1R is one of 5 possible receptors, the MC1R is the main receptor for α-MSH (Millington).

The melanocortin-1 receptor belongs to a class of protein receptors known as the G-protein-coupled receptors (GPCRs). These receptors make up the largest and most diverse families of proteins (Kroeze, Sheffler and Roth). They are located on the plasma membrane and communicate between the external and internal environments of the cell. Each receptor is activated by the binding of its specific ligand to the receptor's active site. This causes the protein to become activated and release some specific components inside the cell for the activation of a specific cellular mechanism (Filmore). According to an article from the *Journal of Cell Science*, scientists claim that "Depending on the type of G protein to which the receptor is coupled, a variety of downstream signaling pathways can be activated…" (Kroeze, Sheffler and Roth). This family of proteins is so incredibly diverse because each receptor has to stay independent in order to prevent conflicting signals with other receptors.

In a properly functioning *MC1R* gene, the melanocortin-1 receptor receives the α-MSH and sends signals to stimulate chemical reactions inside the melanocytes that produce the dark pigment, eumelanin (Genetics Home Reference). The general chemical pathway for the production of the eumelanin pigment is as follows: α-MSH, MC1R, cAMP, Tyrosine,

Dopaquinone, and then either the chemicals for phaeomelanin or eumelanin (Rees and Ha M.D, Melanocortin-1 receptor: What's red got to do with it?).

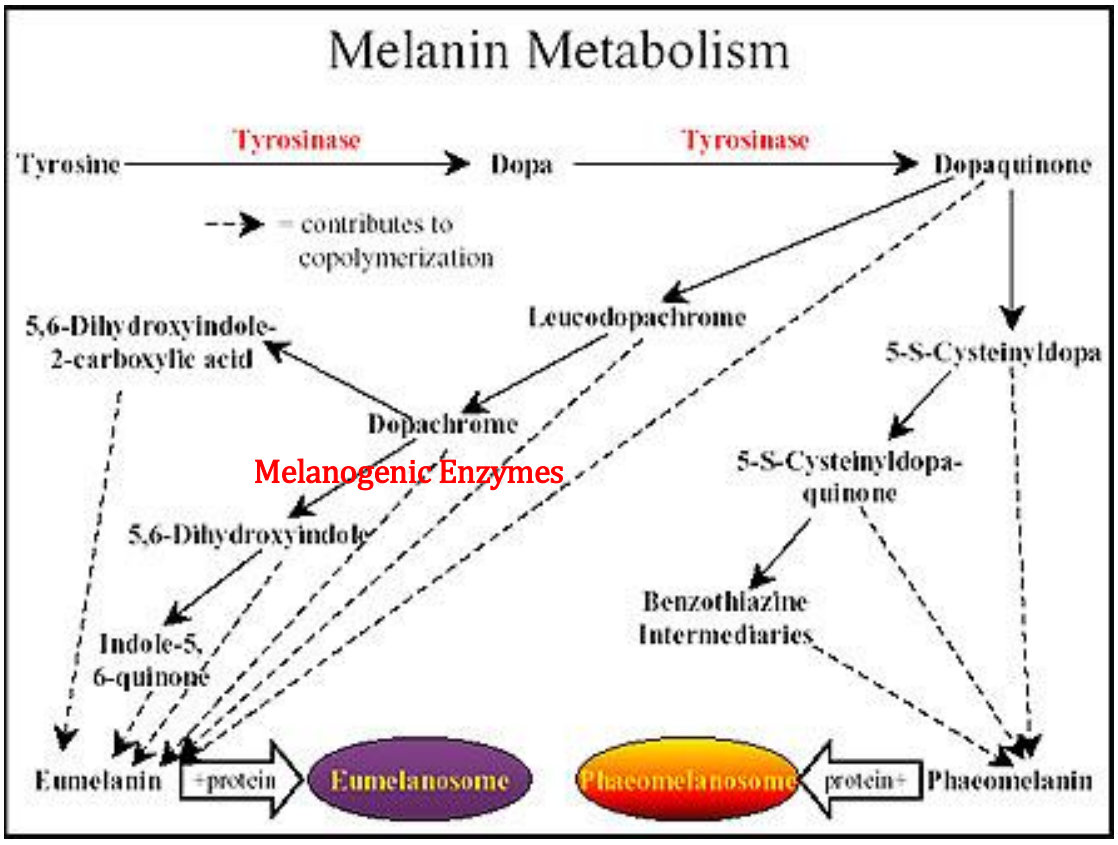
When the melanocortin-1 receptor is activated, the cyclic adenosine monophosphate (cAMP) concentration inside the melanocytes is elevated, resulting in the activation of the eumelanin pathway (Figure 1). Specifically, the synthesis of eumelanin producing enzymes is elevated due to the increased levels of cAMP inside the melanocytes. The dark or black pigments that are synthesized by the enzymes are then combined with proteins forming eumelanosomes. Then, these eumelanosomes get deposited in the hair as dark or black pellets (Filmore; Figure 2). In a mutated melanocortin-1 receptor, the α-MSH is unable to bind to the receptor resulting in the activation of the default phaeomelanin pathway. In heterozygotes, one allele is active and the other allele is inactive. Because of this, half of the receptors are activated for the production of eumelanin pigments and the other half undergo activation for the default phaeomelanin pigments. Therefore, both pigments are found. Although the *MC1R* gene is a key gene in human pigmentation, researchers also believe that there are other genes that contribute to the outcome of a person's hair and skin color (Genetics Home Reference). Therefore, it is important to keep in mind that *MC1R* is the main determining factor of producing red hair, but it is not the only one.



Source: Gene Assist Pathway Atlas.

Figure 1: The signal transduction pathways for the production of hair color. Activation of MC1R by α-MSH elevates cyclic-AMP levels in the melanocytes. With the presence of cyclic-AMP, the transcription and translation of the enzyme required for the production of eumelanin pigment are enhanced. Therefore, the melanogenic enzymes synthesize

eumelanin. However, when the receptor is mutated and not activated, the phaeomelanin pigment is produced by default.



Source: University of Alabama.

Figure 2: In the presence of the melanogenic enzymes, the biochemical pathway for synthesis of eumelanin is activated. Without these enzymes, the default pathway for the synthesis of phaeomelanin is preferred.

In 1995, this *MC1R* gene in humans was discovered by Jonathan L. Rees, professor at the University of Edinburgh, *et al*. However before Jonathan L. Rees *et al*., Roger Cone *et al*. were first to clone the *MC1R* gene in mice in 1993. From their work, they concluded that some of the mutations concerned meant that MC1R did not work. Since these mice served

as models for human red hair, scientists were able to apply Cone's research to human genetics. (Rees and Ha M.D, Melanocortin-1 receptor: What's red got to do with it?) From this, scientists concluded that the receptor did not work in humans as well, in order for the red hair phenotype to develop.

Specifically, the red hair color is caused by loss of function mutations for the melanocortin-1 receptor gene (*MC1R* gene). This gene has an autosomal recessive mode of inheritance and in order for one to develop the red hair phenotype, one needs to have both copies of the *MC1R* gene to be mutated (Rees, Healy and Jordan). There are five mutations that are the most commonly associated with red hair: Asp84Glu, Arg142His, Arg151, Arg160Trp, and Asp294His (Mumm and Draznin M.D). Each mutation is referred to as a variant and, for example, Asp84Glu means that the amino acid aspartate is replaced by the amino acid glutamate at codon 84. Each codon is a triplet of nucleotide bases in the messenger RNA (messenger ribonucleic acid). If the receptor is mutated, it produces an alternative version of the protein and cannot bind to the α-MSH. From this mechanism, the eumelanin pathway is still slightly activated to produce a very low concentration of eumelanin pigment. However, since the receptor is mainly not active, the default phaeomelanin pathway is greatly activated to produce phaeomelanin pigment at a higher concentration, thus producing red hair. It is the ratio of the higher amount of phaeomelanin pigment to eumelanin pigment that produces red hair color and not black.

Melanocytes have a way of recycling the receptor that is activated and bound to α-MSH. This occurs by the cytoplasmic protein β-arrestin binding to the activated receptor, which ends up "turning off" the G-protein-coupled receptor. This arrestin-receptor complex

enters the cell via endocytosis which in turn causes the ligand to be removed, and the receptor to be recycled back to the membrane (Filmore). However, if the receptor is not activated, there will be no recycling of the receptor back to the membrane because there will be no ligand to be removed.

From the development of red hair comes the fear of developing skin cancer as well. Because of the mutations in the *MC1R* gene, the production of phaeomelanin can aid in the development of skin cancer. Jonathan L. Rees, *et al.* showed that most redheads are homozygous for many loss of function mutations. In addition, there also seemed to be a clear dosage effect for heterozygotes, being intermediate between homozygous and wild-type individuals for skin type, freckling, and shades of hair. In the case of skin, the carriers (heterozygotes) can be at more of a risk of developing skin cancer, even if they do not have red hair. Overall, the *MC1R* gene mutations are largely responsible for the most common cancer in Caucasians (Rees and Ha M.D, Melanocortin-1 receptor: What's red got to do with it?).

There are two theories behind why *MC1R* gene mutations have a higher probability of leading to skin cancer. The first one is that eumelanin may be a better sunblock than phaeomelanin. If there is less eumelanin, then the ultraviolet radiation photons may not be blocked and will harmfully affect the epidermal cells. Another theory is that not necessarily the absence of eumelanin, but the presence of phaeomelanin is directly harmful because it is an ineffective sunblock and may produce dangerous effects when exposed to radiation. Maria Teresa Landi, M.D., Ph.D., the lead study investigator at the National Cancer Institute offers the following possibility: “One possibility is that people with *MC1R* variant forms and

variable pigmentation generate more reactive chemicals in their cells as a result of the ultraviolet exposure in sunlight. These reactive chemicals can induce mutations, like those in the *BRAF* gene, which may lead to cancer" (National Cancer Institute). *BRAF* genes, or cancer-causing genes, are mutated when exposed to UV radiation and result in melanomas, or tumors from cells which produce skin pigment, which can develop anywhere on the body where these cells are present (National Cancer Institute).

Historically, because of the high amounts of sun exposure in Africa, having light skin posed as a great threat to those living there so it was harder for this trait to emerge. '"We don't know with certainty when the first redheads walked the earth,' Rees says. 'But we believe these changes arose in less time than we thought, maybe 20,000 to 40,000 years ago'" (Derbyshire). From comparisons between chimpanzee and the human DNA sequences, it was clarified that there was a large degree of functional constraints on the *MC1R* gene until migration out of Africa. Concepts like migration patterns are a part of Population Genetics, "the subdiscipline that studies heredity in groups of individuals for traits that are determined by one or only a few genes" (Russell). In general, there was evidence of strong selection against skin lightening or red hair color, therefore mutations of the gene were not "allowed to occur by evolution." This way, it was very hard to see the accumulations of these mutations. Then, the human population spread out of Africa and caused the selective force against the redheads to be removed. From this, there were more individuals with lighter hair color, eye color, and skin color. In the non-African populations, especially in Europe, there was rapid development of mutations in this gene. Therefore, this was because of many different significant changes, not just from a small group of

mutated individuals (Rees and Ha M.D, Melanocortin-1 receptor: What's red got to do with it?).

Rees *et al*. also explained that the importance of being a redhead may have stemmed from the "biologically materialistic position" concept, which is the conscious choice of mate based upon appearance, status, or other similar perceptions. Overall, this may have affected human evolution (Rees and Ha M.D, Melanocortin-1 receptor: What's red got to do with it?). Conceptually, the phenotype of red hair was like that of a peacock's tail. In the way of attracting mates, these features were considered to be beautiful and at the time, red hair was also quite a rare feature, hence the reason why it was considered to be such a desirable trait.

In addition, it is believed that the redheads were selected against in Africa because of the high levels of UV radiation, therefore causing a genetic drift to occur to Europe. In a new genetic study, lead author Carles Lalueza-Fox, of the University of Barcelona stated that, "In the cases of both Neanderthals and modern Europeans, the gene mutation that caused fairer complexions spread only after the respective populations migrated from Africa" (Handywerk). From this genetic drift, countries such as Scotland and Ireland are known for the highest percentages of redheads in Europe.

It is difficult to narrow down when the mutations actually arose, but evolutionary experts have argued that these mutations arose after ancestors of white Europeans moved northward from Africa around 20,000 to 40,000 years ago. However, there is also a theory that the red hair gene originated in the Neanderthals. "The idea was based on a claim that the gene was at least 100,000 years old and so may have been present before modern man

left Africa. To pass into our DNA, our ancestors would have had to have interbred with Neanderthals, an unfashionable theory among experts" (Nic & the Neanderthals). Although, there are many theories, the more accepted one is that this trait did not come from Neanderthals. From multiple studies, there is evidence that both modern humans and Neanderthals both had mutations for the *MC1R* gene for red hair; however we did not inherit this from Neanderthals. Scientist Holger Römpler of Harvard University discussed their study: "'The two Neanderthal individuals we studied showed a point mutation not seen in modern humans'" (Harvard University). To make sure their point mutation was legitimately from the Neanderthals they were studying, they checked about 3,700 people for a specific point mutation of the *MC1R* gene. "None showed the mutation, suggesting that Neanderthals and *Homo sapiens* followed different evolutionary paths to the same redheaded appearance" (Harvard University). Therefore, although about one percent of Neanderthals may have had red hair, we did not get this mutation from them.

Currently, Scotland holds the highest percentage of thirteen percent of redheads on earth. Under Scotland is Ireland with ten percent, however, redheads are seen all over the earth, even in Asia. Although Scotland and Ireland hold the highest percentages of redheads, there are theories that red hair is not originally a Celtic trait, but that it came from the Vikings. In about 795 A.D., the Vikings raided near Dublin and their red hair color was passed down the generations when they started mating with the Irish (BBC). Eric the Red was known for his red hair and so were many other Scandinavians. However, this is not to say that the Scandinavians were the only reason for the Irish having their red hair. They could have already had the mutation in their population, but in a small amount and so when the Vikings invaded, the presence of redheads in the population increased

dramatically as a result of interbreeding. In the *2006 European Journal of Genetics*, there was a study on Scandinavians and their impact on Irish genetics. From this, they found that "…there is scant evidence of Scandinavian Y-chromosome introgression in a general Irish population sample" (McEvoy, Brady and Moore). Although this study was based on forty-seven Irish men, this is still quite accurate because "…the findings are consistent with a relatively small number of Norse settlers (and descendants) migrating to Ireland during the Viking period (ca. AD 800-1200)" (McEvoy, Brady and Moore). Therefore, the rumor that the Irish owe their vibrant red hair to the Viking invasion seems false. The Vikings may have had an impact on the number of redheads, but they are not the sole reason for the emergence of red hair in Ireland.

From my own background, I have many relatives of Polish descent who have or had red hair and it made me wonder why. In the past, I thought that the Celts were the ones with red hair, so I wondered as to why my Polish relatives have red hair as well. From my research, I found out that Poland was heavily populated with the Ashkenazic Jews, who are also known for their red hair. In a 1990 article titled "Polish Jewish History," the author stated that "During the eighteenth century, at least, about half of the urban population of Poland was Jewish" (Hundert). Therefore, it seems safe to say that they were Ashkenazic Jews and not Sephardic Jews because they were from Poland. In an article titled, "On the Racial Characteristics of Modern Jews," researchers found that there were "…thrice as many red-haired individuals as either Poles, Russians, or Austrians, and half as many again as Germans." Although this is quite an old article from 1886, it suggests to us the high amount of red haired Jews in Europe. In addition, the article also makes the connection between the Ashkenazic Jews and red hair. "…when it does occur among Ashkenazim of

North Europe, it is found more among Jews than in the indigenous population…" (Jacobs). Therefore, the Ashkenazic Jews of Northern Europe, and especially in Poland, are unique because of the high prevalence of red haired individuals in its population.

In many of these articles, red haired people were grouped together as being a part of erythrism. This is a term describing those as having "exceptional prevalence of red pigmentation" (as in skin or hair) (Merriam-Webster). In another article titled, "Anthropology of the Jews," the researchers claimed that erythrism is a characteristic of European Jews. In addition, they claimed that red hair is not considered to be of recent origin, and that "…it was not unknown among the ancient Hebrews, for Esau was said to have been 'red all over like a hairy garment'" (Fishberg). Thus, it seems that red hair has been in our population for centuries and that the Celts are not the only ones known for having this beautiful characteristic.

So far, many understand that the Celts could have inherited some of their red hair color from the Vikings, but it seems that those of Jewish descent may also have contributed to the accumulation of redheads, even in Scotland. According to the article titled "On the Racial Characteristics of Modern Jews", the researchers speculate that the Scottish could have inherited their red hair from the European Jews. "Indeed, but for the abundant presence of red hair among Scotchmen [*sic*] it might be more open to explain the origin of red hair among Europeans as due to an infusion of Jewish blood than to account for it among Jews by assuming intermixture with Aryans" (Jacobs). To say that this is possible helps explain how Scotland is the country today that has the highest percentage of red haired individuals, although the country is mainly Christian. However, there is also the

possibility of Jewish people changing their religion to Christianity, and the fact that there might be Jewish heritage in the backgrounds of the Scots, but they just do not know it yet. The whole topic of Ashkenazic Jews still requires more research and study, but this does not falsify the archived research on the redheads of Europe.

Interestingly enough, there was a time where people in England tried to emulate the redheaded royalty. Queen Elizabeth I had natural red hair and in the Elizabethan era, many of the nobility tried to emulate her red hair (Alchin). It was considered fashionable to have red hair and many women tried to make their hair just like that of Queen Elizabeth I. In fact, the members of the English Royal family of the House of Tudor were all redheads and the color red was tied to royal ceremonies (Douglas).

Like in Europe, the color red was also valued in Asia. In India, red symbolizes fertility and purity, which is usually why Indian brides have red saris and lenghas (Smith). Often, red is paired with gold in clothing because gold refers to wealth, therefore adding importance to the red color. Also in Indian weddings, the women use henna on their skin for mendhi art which produces a dark red color. Henna is a plant, that when crushed and added to water can produce various shades of red on skin and hair. Nevertheless, natural red hair is rarely, yet still found in Pakistan and other parts of Asia.

Also from my own background, my relatives and I use henna on our skin for weddings and religious ceremonies. Years ago, I learned that henna can be added to hair as well. The practice of adding henna to hair came later and it was primarily considered for practical use, not necessarily as a fashion statement. Often when older people lose their hair color, they use henna to dye their hair. Yet now, henna is often used as a fun and

natural way of adding red color to hair. It is a semi-permanent dye, but it is used because it is a cheaper and more natural way of adding color. These traditions of mendhi art and henna use in hair spread to Pakistan and are now often a part of wedding ceremonies and religious holidays in the Indo-Pakistan area.

From fiery and determined, to romantic and passionate, redheads always seemed to have captured the attention of others, but not always good attention. In the United Kingdom, there is a term known as "gingerism" that refers to the bullying or harassment of redheads. Even in British royalty, no one is ever safe from this gingerism. Prince Harry claims that he was bullied ever since he was a child (Sky News). Some even consider gingerism to be almost as bad as racism. This has gone even to the extent of causing a family to move twice in order to avoid persecution because of their red hair (Rohrer). In the past, redheads were known to be untrustworthy and evil. Red was the color of the devil and women with red hair and green eyes were often killed because they were considered to be witches in Germanic folk culture (Johansen). Often, there were redheads with green eyes because the phaeomelanin responsible for the red hair is also responsible for green eyes. Therefore, the electric combination of bright red hair and stunning green eyes were often viewed as evil and demonic.

In famous paintings, red hair was also symbolic of sin. In Michelangelo's Temptation, Eve is depicted as having brown hair and she is being handed a red apple from a red haired serpent woman. Then, Adam and Eve are thrown out of the Garden of Eden and Eve is wearing red hair instead of brown (Johansen). In addition, at St. Paul's Cathedral, Eve has blonde hair beforehand. Then, Adam and Eve are driven from the Garden of Eden and it is

shown that she now has red hair and is cowering (Johansen). The red color in the apple, the serpent woman, and Eve in the second fresco are all symbolic of evil and sin. Therefore, it is not surprising that Michelangelo used this red color in his paintings because of the obvious association of red and the devil.

Although there are articles that document high percentages of redheads, many people are worried if they are here to stay because it is a recessive trait. Recently, there has been a rumor about redheads becoming extinct in the future. Many news articles are starting to make people wonder and in the *Seattle Times*, they claim that there will be no more redheaded individuals by the year 2100. "The reason, according to scientists at the independent institute in England…is that just 4 percent of the world's population carries the red-hair gene. The gene is recessive and therefore diluted when carriers produce children with people who have the dominant brown-hair gene" (Flanigan). Genetically, this just does not make sense. As long as there are individuals who have the mutation to show the red hair phenotype, or individuals as carriers of the mutation, there will be no extinction of the red hair color. The only way one could think that this color will disappear is if all of those with the red hair, or the carriers, stop breeding completely with others who either have red hair, or are carriers of the mutation. Ethically, this would just not be possible because humans will continue to breed with whomever they choose, and no one would be able to control this aspect of our lives. Therefore, although these news articles do provide scientists with more attention from the general public, this scare is just that and nothing more. However, it is important to realize that it is definitely possible that there may be a decrease in the number of redheaded progeny. Nevertheless, the vibrant, bold, and fiery red color is here to stay in our human population.

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