KITLG Gene: *Why Am I Blonde?*

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Hair color differences are a clear example of phenotypic variation in humans. While many factors impact hair color, the human gene KITLG is associated with blonde hair. KITLG encodes a KIT ligand, a growth factor, for the KIT tyrosine kinase receptor. The KIT ligand binds to melanocytes, which play a fundamental role in pigmentation by producing melanin, a pigment that gives skin, eyes, and hair their color. Previous research has identified an upstream single-nucleotide polymorphism, a nucleotide A-to-G substitution, as associated with blonde hair using transgenic mice and comparing fur color between ANC-Kitl/+ (ancestral A allele) and BLD-Kitl/+ (blonde-associated G allele), which displayed lighter fur. However, the polygenic character of blonde hair is poorly understood. Therefore, the proposed experiment will investigate how multiple, blonde-associated genes interact, specifically KITLG and SLC24A4, under four experimental conditions: BLD-Kitl/+; BLD-Slc24a4/+; BLD-Kitl/+, BLD-Slc24a4/+; and +/+ (wild-type control).

THE PHENOTYPE

Why am I blonde? Hair color differences are a clear example of phenotypic variation in humans (Guenther et al., 2014). My family is an example of this variation: I am the only blonde, while my parents and siblings have dark hair. Growing up, I questioned this difference and was accused of dying my hair because of it. The familial difference inspired me to research blonde hair, searching for genetic factors that contribute to this variation. Research studies have demonstrated the association between the human gene *KITLG* and blonde hair.

Beyond my personal curiosity, blonde hair plays a culturally significant role worldwide. Contemporary popular culture has stereotyped blonde women as more attractive and having more fun, suggesting that blonde women, specifically, are happier and more popular (HandWiki, 2022; Dechter, 2015). This stereotype extends to ancient Greece, and ancient texts suggest that blonde hair was associated with youth and beauty. In both modern and ancient cultures, blonde hair has been imitated using bleaches, dyes, and wigs (Guenther et al., 2014). However, a 2011 study in Russia found that brunettes are considered more attractive, and a study in Brazil found that blonde women are looked down upon (Dechter, 2015). Therefore, geographical location contributes to how hair colors, specifically blonde hair, are perceived. In some cultures, blonde hair is associated with negative stereotypes: ghost-like abnormality, promiscuity, or unusual ancestry (Guenther et al., 2014). Furthermore, “blonde moment,” “dumb blonde,” and the “blonde myth” are stereotypes that portray blonde-haired women as attractive but scatterbrained and unintelligent (Dechter, 2015). Women face stereotypes due to their hair color, demonstrating societal pressure and expectations based on outward appearance. Therefore, the human gene *KITLG*, which is associated with blonde hair, plays a role for my family as well as women across the globe.

Fundamentally, hair color is determined by the amount of melanin, a type of pigment, in the hair. There are two types of melanin: eumelanin, associated with black and brown hair, and pheomelanin, associated with blonde and red hair. The type and amount of melanin in hair are determined by many genes (U.S. National Library of Medicine, n.d.). Melanin pigment is produced by melanocytes, specialized cells found in skin, eyes, hair, and other tissues that synthesize melanin. *KITLG* plays an essential role in the development, migration, and differentiation of many cell types, including melanocytes (Guenther et al., 2014). Specifically, *KITLG* encodes the *KIT* ligand, a crucial growth factor that binds to the *KIT* receptor tyrosine kinase located on melanocytes, the cells responsible for producing melanin (Guenther et al., 2014). Due to *KITLG’s* crucial role in melanocyte production and, consequently, melanin synthesis, it is associated with blonde hair color.

Not only does *KITLG* play a role in skin, eye, and hair pigmentation (melanogenesis), but it also has molecular roles in blood cell production (hematopoiesis) and gamete production (gametogenesis). (Allen et al., 2014; Guenther et al., 2014). Focusing specifically on melanogenesis, two associated disorders include Familial Progressive Hyper- and Hypopigmentation and Waardenburg syndrome type 2F.

Familial Progressive Hyper- and Hypopigmentation (FPHH) is a pigmentary disorder characterized by a mix of dark (hyperpigmentation) and light (hypopigmentation) spots on the skin (Wang et al., 2009; Xiao-Kai et al., 2017). FPHH is an autosomal dominant disorder associated with a heterozygous mutation in *KITLG*; therefore, only one copy of the gene is required to express the phenotype, meaning that only one parent needs to carry the gene. The skin spots are typically present at birth or develop during infancy but progress with age, with hyperpigmented patches increasing in size and number (Weizmann Institute of Science, n.d.-a). Research demonstrates that a gain-of-function mutation increases the melanin content by 109% compared to the wild-type *KIT* ligand. Mutations in *KITLG* can disrupt normal signaling pathways involved in melanocyte regulation, potentially leading to both overproduction of melanin in some areas (hyperpigmentation) and deficiency in others (hypopigmentation) (Johns Hopkins University, n.d.).

Waardenburg syndrome type 2F (WS2F) is an auditory-pigmentary disorder characterized by sensorineural hearing loss, hypopigmentation of the skin and hair, and heterochromia iridis. Sensorineural hearing loss refers to hearing loss of the inner ear or the auditory nerve, which connects the inner ear to the brain. WS2F is an autosomal recessive disorder associated with a homozygous mutation in *KITLG*; therefore, two copies of the gene are required to express the phenotype, meaning both parents must carry the gene. Symptoms present with congenital or neonatal onset (Weizmann Institute of Science, n.d.-b). Sensorineural hearing loss is often caused by damage to the hair cells in the inner ear, which convert vibrations into electrical signals that the brain can interpret. In addition to its role in melanogenesis, *KITLG* also regulates neural crest migration, during which embryonic cells derived from the neural tube move from their original location to various regions of the embryo to form diverse tissues (Vona et al., 2022). Therefore, mutations in *KITLG* can disrupt ear and hair formation, cause hypopigmentation of skin and hair, and result in heterochromatic eyes due to its role in melanocyte regulation.

Previous research has established an association between *KITLG* and blonde hair color, particularly in Northern European populations (Guenther et al., 2014). However, the interplay between *KITLG* and other genetic factors is poorly understood. Future experiments should address this limitation by examining how multiple genes influence blonde hair and its shades.

MOLECULAR FUNCTION OF THE GENE PRODUCT(S) AND MOUSE MODEL

The human gene *KITLG*, located on chromosome 12, encodes the *KIT* ligand, which binds the *KIT* tyrosine kinase receptor. The *KIT* ligand acts as a growth factor and binds to *KIT* receptors on cell surfaces, initiating signaling pathways involved in development and function (Guenther et al., 2014; Hoekstra, 2014).

The *KIT* ligand has been associated with melanocyte development, survival, proliferation, and migration, indicating its crucial role in pigmentation. As a growth factor expressed by various cell types, including those in the hair follicle, the *KIT* ligand interacts with the *KIT* receptor, which is primarily expressed on the surface of melanocytes (Hu et al., 2022). Melanocytes play a fundamental role in pigmentation by producing melanin. At the molecular level, ligand-receptor binding

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between the *KIT* ligand and receptor initiates intracellular signaling cascades that involve the phosphorylation of tyrosine residues on the *KIT* receptor and downstream effector molecules (Yarden & Ullrich, 1988). The signaling pathways regulate cellular processes in melanocytes, such as their differentiation and melanin synthesis, and are essential for maintaining a normal population of melanocytes and, consequently, pigmentation (D'Mello et al., 2016). Therefore, dysregulation of this signaling, often due to mutations in *KITLG* or *KIT*, can disrupt melanocyte homeostasis and lead to pigmentary disorders like Familial Progressive Hyper- and Hypopigmentation and Waardenburg syndrome type 2F.

KITLG, the human gene that encodes the *KIT* ligand, plays multiple roles in hematopoiesis (blood cell production), melanogenesis (melanocyte production), and gametogenesis (gamete production) (Allen et al., 2014; Guenther et al., 2014). Melanin plays a fundamental role in hair color and is produced by melanocytes; *KITLG* has a molecular role in this process (Hu et al., 2022). Specifically, *KITLG* is associated with blonde hair color due to a non-coding single-nucleotide polymorphism (SNP) (rs12821256), which substitutes nucleotide A to G, located over 350 kb upstream of the *KITLG* transcription start site, and is associated with blonde hair color (Guenther et al., 2014). The SNP affects *KITLG* expression in hair follicles, leading to reduced pigment production without altering expression in the rest of the body (Conger, 2014).

A transgenic mouse model was used to examine a regulatory region of *KITLG* that encodes the *KIT* ligand and is associated with blonde hair color in Northern Europeans. Specifically, the region contains a nucleotide A-to-G SNP (rs12821256) 350 kb upstream of the transcription start site. The results demonstrated that the blonde-associated *KITLG SNP, BLD-Kitl/+*, resulted in significantly lighter hair pigmentation than in control mice. Thus, a single-base change in the *KITLG* regulatory sequence is sufficient to significantly alter the activity of the functional hair follicle enhancer (Guenther et al., 2014).

To explore the functional impact of the regulatory variant, Guenter et al. (2014) used the Steel panda mutation (Slpan), an X-ray-induced Kitl (mouse gene homologous to human *KITLG*) allele caused by an upstream chromosome inversion, which reduces pigmentation. While mice homozygous for the allele were completely white, heterozygous mice had noticeably lighter hair color than the control mice, indicating that a single copy of the upstream displacement is sufficient to lighten hair color by reducing *Kitl* expression.

To determine the specific base-pair changes associated with blonde hair, three segments of human DNA spanning the 17.1 kb blonde-associated regions, as determined by a previous genome-wide association study, were separately cloned upstream of a minimal promoter and *lacZ* reporter gene: H1, H2, and H3. Only H2 drove consistent reporter expression in transgenic mouse embryos; thus, two subclones, H2b (kidney) and HFE (hair follicle enhancer), were examined. HFE drove consistent expression in developing hair follicles, and histological analysis confirmed that expression corresponded to a site of endogenous *Kitl* expression in the epithelial cells of developing hair and skin. Thus, the site of *Kitlg* expression attracts melanocytes to the developing epidermis and hair follicles.

Guenther et al. (2014) demonstrated the genetic basis of blonde hair color by examining a regulatory variant upstream of the *KITLG* transcription start site. Due to the lighter fur resulting from the heterozygous Slpan mutation, an upstream chromosome inversion, the study indicated that a single copy of the upstream displacement is sufficient to lighten hair color by reducing *Kitl* expression. Furthermore, using a *lacZ* reporter gene, the HFE region was determined to drive constant expression in hair growth follicles at a site of endogenous *Kitl* expression.

One specific aspect of the mouse model was the in vivo investigation of the effects of the rs12821256 SNP, a nucleotide A-to-G substitution. Guenther et al. (2014) generated matched lines of transgenic mice that expressed *Kitl* cDNA of either the ancestral (A; ANC-Kitl) or blonde-associated (G; BLD-*Kitl*) hair enhancer. To minimize differences due to transgene copy number, orientation, or integration site, the ϕC31 integrase system was used to generate single-copy integrants at the H11P3 locus on mouse chromosome 11. To prepare the mouse embryos, the HE-Kitl site-specific insertion plasmids were individually mixed with ϕC31 RNA and injected into the pronuclei of H11P3 mouse (FVB) embryos. Integration occurred at the same position in both transgenic lines, indicating that the phenotypic differences are due to the base pair present: A for the ancestral hair enhancer or G for the blonde-associated hair enhancer. Eight days postnatal, dorsal skin samples were analyzed using quantitative RT-PCR, and the *Kitl* mRNA expression revealed that the BLD-*Kitlg* enhancer drove a 21% lower expression of *Kitl* compared to the ANC-*Kitl* enhancer. Furthermore, the coats of the BLD-*Kitl*/+ mice appeared significantly lighter than the coats of the ANC-*Kitl*/+ mice and had lower pigmentation density in hair shafts. Thus, a single-base change in the *KITLG* regulatory sequence is sufficient to significantly alter the activity of a functional hair follicle enhancer.

Therefore, previous research has established a significant association between *KITLG* and blonde hair color, particularly in Northern European populations (Guenther et al., 2014). However, the polygenic character of blonde hair is poorly understood. Therefore, the proposed future experiment will investigate how multiple, blonde-associated genes interact, specifically focusing on *KITLG* and *SLC24A4*.

EXPERIMENT FOR THE FUTURE

Specific Aims

Previous research has established a significant association between rs12821256, a non-coding single-nucleotide polymorphism (SNP) that substitutes nucleotide A for G over 350 kb upstream of the *KITLG* transcription start site, and blonde hair color, particularly in Northern European populations (Guenther et al., 2014). However, the polygenic nature of blonde hair color and the interplay of additional regulatory elements remain poorly understood. To address this gap, the research study aims to investigate the polygenic contributions of *KITLG* and *SLC24A4* to the blonde hair color phenotype. The association of rs12896399, a SNP in the region that contains the first exons of *SLC24A4*, has recently been implicated in blonde hair (Han et al., 2008; Sulem et al., 2007). Specifically, the research study examines how variations in both genes, represented by the blonde-associated *KITLG* enhancer SNP and specific *SLC24A4* alleles, interact to influence hair pigmentation. The hypothesis of the research study is that mouse models carrying the blonde-associated alleles of both *KITLG* and *SLC24A4* will exhibit more pronounced blonde hair color than those with only one or neither of the alleles, indicating a polygenic effect on blonde hair color. To examine the hypothesis, hair pigmentation characteristics across four experimental groups will be compared: BLD-*Kitl*/+, BLD-*Slc24a4*/+, BLD-*Kitl*/+, BLD-*Slc24a4*/+, and +/+ (wild-type control).

Experimental Protocol

The experiment relies on transgenic mice generated using the protocol described by Guenther et al. (2014). The wild-type control mice are FVB/C57Bl/6J F1 hybrids that have not undergone genetic modification, as described by Guenther et al. (2014).

First, to begin the transgenic process, the allele lines are established. Both the *KITLG* and *SLC24A4* insertions are performed using the following protocol, adapted from Guenther et al. (2014), in which *Kitl* and *Slc24a4* are the mouse genes for *KITLG* and *SLC24A4*, respectively. First, the HE-*Kitl* site-specific insertion plasmid, containing the blonde-hair rs12821256 SNP, will be mixed with ϕC31 RNA and injected into the pronuclei of H11P3 FVB embryos. These are embryos from the FVB-H11P3 mouse strain, which align with wild-type control mice and provide a well-characterized genetic background that allows site-specific integration at the attP sites at the H11 locus. Therefore, this method allows for insertion at the H11P3 locus.

Following the insertion, genomic DNA from the ancestor and offspring mice will be analyzed with primer pairs PR387/PR425, PR522/Kg1576, and

Kg1580/Kg1581 to screen for site-specific and random integrations. HE-*Kitl* mice with confirmed site-specific insertions will be bred with wild-type controls to establish the BLD-*Kitl*/+ line. The process was then repeated using the HE-*Scl24a4* site-specific insertion plasmid (rs12896399) and *Scl24a4*-specific primers. HE-*Scl24a4* mice with confirmed site-specific insertions will be bred with wild-type controls to establish the BLD-*Scl24a4*/+ line. Lastly, HE-*Kitl* and HE-*Scl24a4* mice, with confirmed site-specific insertions, will be bred to establish the BLD-*Kitl/Slc24a4* line.

Breeding between the genetically modified mouse lines and wild-type control mice will lead to experimental groups. The BLD-*Kitl*/+ is heterozygous for the *Kitl* blonde allele. Therefore, they are the offspring of a homozygous wild-type control, +/+, and a homozygous *Kitl* blonde allele, BLD-*Kitl/Kitl*. Similarly, the BLD-*Slc24a4*/+ is heterozygous for the *Slc24a4* blonde allele, BLD-*Slc24a4/Slc24a4*. Therefore, they are the offspring of a homozygous wild-type control, +/+, and homozygous *Slc24a4* blonde allele, BLD-*Slc24a4/Slc24a4*. Lastly, the BLD-*Kitl*/+, BLD-*Slc24a4*/+ are heterozygous for the *Kitl* blonde allele and *Slc24a4* blonde allele. Therefore, they are the offspring of a homozygous *Kitl* blonde allele, BLD-*Kitl/Kitl*, and a homozygous *Slc24a4* blonde allele, BLD-*Slc24a4*/*Slc24a4*. These breeding pairs constitute the three experimental groups, which will be compared to the wild-type control FVB/C57Bl/6J F1 hybrids.

Phenotypic analysis will be performed by assessing the coat color by three methods: visual assessment, spectrophotometry, and histological analysis. First, the coat color of the mice in each group will be visually assessed at different developmental stages: postnatal at 3 weeks, adolescence at 2 months, and adulthood at 6 months. Representative mice exhibiting the hair-color phenotypes associated with the respective genes will be analyzed. Once visually assessed, the hair pigmentation will be quantified. Specifically, using reflective spectrophotometry, a technique that measures the amount of light reflected by a sample, the pigmentation of shaved fur will be quantified (Vaughn et al., 2009). Samples will be taken from each experimental group and from different body locations (head, ventral, and dorsal). Reflective spectrophotometry will provide quantitative data on lightness and darkness, and potentially on pheomelanin (light melanin) and eumelanin (dark melanin). Lastly, histological analysis will examine hair follicle morphology and melanin distribution (pheomelanin and eumelanin) in skin biopsies from each group. Tissue samples measuring 4 to 10 µm will be fixed, dehydrated, embedded, and sectioned over 2 days (Meng et al., 2022). This process will reveal potential differences in melanocyte number, size, and melanosome number, size, and pigment production.

Statistical analysis will determine whether the differences in hair pigmentation are statistically significant. Since there are four groups, ANOVA, which tests differences in the means of two or more groups, will be used. The coat color measurements will be compared using ANOVA for each method: visual scores, reflective spectrophotometry, and histology. Furthermore, histological data will be analyzed to identify any qualitative or quantitative differences in melanocyte characteristics. This will be conducted via visual scores. To verify visual accuracy, analysis will be conducted using machine learning techniques that process image data and pixel patterns to identify color (Komura et al., 2025).

The research study will provide insight into the interaction between *Kitl* and *Slc24a4* in influencing mouse coat color. The findings will promote a better understanding of the polygenic basis of blonde hair color, providing a model for human pigmentation.

Controls

The control for the research study is the wild-type FVB/C57BL6/J F1 hybrids, +/+. The control group possesses the wild-type alleles for both the *Kitl* and *Slc24a4* genes. The purpose of the wild-type control group is to establish the baseline coat color phenotype in the absence of the blonde-associated alleles, *Kitl* and *Slc24a4* genes. This will allow direct comparison with the experimental groups using the *Kitl*, *Slc42a4*, and both the *Kitl* and *Slc24a4* genes. Since the wild-type control group provides a baseline coat color, any deviations observed can be attributed to the presence and potential interaction of the gene variants.

Predicted Outcomes

It is expected that the wild-type control group (+/+) will exhibit the baseline coat color of FVB/C57BL6/J F1 hybrids. As demonstrated by Guenther et al. (2014), mice with the *Kitl* blonde allele, BLD-*Kitl*/+, exhibit a lighter coat color than wild-type control mice. Furthermore, it would be expected that the mice with the *Slc24a4* light-hair allele, BLD-*Slc24a4*/+, will also exhibit a lighter coat color compared to the wild-type control mice. These results would support previous research implicating *KITLG* and *SLC24A4* in blonde hair color.

However, the goal of the research study is to examine the polygenic influences on blonde hair color, focusing on the interplay between *KITLG* and *SLC24A4*. It is expected that mice with the *Kitl* and *Slc24a4* alleles will exhibit lighter hair color than those with either gene alone. If a lighter coat color is observed when both *Kitl* and *Slc24a4* alleles are present, it can be concluded that the alleles exhibit an additive effect in support of polygenic influence on blonde hair color, promoting lighter hair than a single-gene modification alone. However, if no difference is observed between the experimental group with both *Kitl* and *Slc24a4* genes and the groups with either *Kitl* or *Slc24a4* alone, then it can be concluded that there is no polygenic effect, and further research can be conducted to determine the most influential alleles.

Considerations

Regarding phenotypic variability, *KITLG* and *SLC24A4* are not comprehensive of the genes implicated in blonde hair color. Therefore, further research should be conducted, using a scientific basis from genome-wide association studies (GWAS) to examine other genes implicated. By generating and analyzing additional heterozygous combinations, the interaction could be examined more fully. Furthermore, epistatic interactions, where one gene masks the effect of another, should be considered. In addition, environmental factors may play a role in blonde hair color, which is not considered in the research study. Since the environmental factors were kept constant in the research study, a similar study could be conducted with various environmental factors, such as diet and housing conditions.

Lastly, homology to human blond alleles is a challenge of the research study. While robust research has established homology between *KITLG* and *Kitl*, less is known about *SLC24A4* and *Slc24a4*. However, when conducting studies in mouse models with potential implications for humans, it is important to ensure that the regions have the same functional impact in both mice and humans. Therefore, targeting conserved regulatory and coding regions between human and mouse genomes should be prioritized. In addition, in vitro functional assays could be conducted to assess the potential impact on gene expression.

CONCLUSION

KITLG and its gene product, *KIT* ligand, are associated with blonde hair color due to the *KIT* ligand's role in melanocyte development, the specialized cells that produce melanin, the pigment that gives color to skin, eyes, and hair. Previous research has demonstrated, using transgenic mice, that a nucleotide A-to-G SNP (rs12821256) 350 kb upstream of the *KITLG* transcription start site is associated with blonde hair color. However, there is a limited understanding of the polygenic character of blonde hair color.

The proposed future experiment examines the polygenic character of blonde hair, analyzing the relationships and, potentially, the compounding, inhibitory, or unchanged effects of *KITLG* and *SLC24A4*. To determine if the presence of both genes results in lighter fur color, the proposed experiment uses four experimental groups: BLD-*Kitl*/+; BLD-*Slc24a4*/+; BLD-*Kitl*/+, BLD-*Slc24a4*/+; and +/+ (wild-type control). While the experiment may not fully capture the complexity of polygenic inheritance, it provides an initial step toward understanding the interactions

among multiple genes contributing to hair color, an essential step toward moving beyond single-gene explanations. Polygenic effects are crucial for understanding how common traits are inherited when multiple genes are involved, and the proposed experiment can be extended to other polygenic traits and complex traits that involve environmental influences as well.

Artificial Intelligence Use Statement

I did not use artificial intelligence to augment my writing or my paper. Using the class discussion, both in general and specifically related to the paper "A molecular basis for classic blond hair color in Europeans" by Guenther et al. (2014), I became familiar with the paper and had an idea for a future experiment: a polygenic character. I appreciate Dr. Karen Kirk's assistance in better understanding the complex protocols presented in the primary literature.

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