Chapter 1
Demystifying Skin Color and "Race"

Keith C. Cheng

Abstract Historical confusion in thinking about skin color and race derives from the state of science at the time human classifications were proposed, and from our incomplete understanding of the genetics of human pigmentation and human ancestry. The pervasiveness of racism reflects the universal human desire for kinship, in settings of competition for resources, where it is common to devalue and harm other groups for the benefit of the group with which one identifies. To gain insight into the biological basis of skin color, scientists have studied the structure of pigmented tissues, hundreds of pigment variants in vertebrates, and a range of enzymes and molecules that affect melanin formation. We have learned that most population-specific traits can be explained by evolutionary chance, and that a small minority of traits, including skin color, have exerted a selective advantage during evolution. The selective advantages of dark and light skin color in the equatorial and more polar geographic regions, respectively, antedate sun screen and Vitamin D supplementation. Since modern technology has largely rendered these evolutionary advantages irrelevant, skin color has become a sociological issue that is amenable to reason. Education can play a central role in work toward a society free of racism, as long as that education is firmly grounded in critically evaluated science and is free of tribalism.

This work is written from my perspective as a geneticist and physician whose curiosity led to unexpected insight into the genetic basis of skin color. Until our discovery of the zebrafish *golden* gene, I had no professional intent to study either skin color or race. The presented considerations are informed and motivated by issues faced by minorities.

K.C. Cheng
Jake Gittlen Cancer Research Foundation, Division of Experimental Pathology, Pennsylvania State University College of Medicine, Hershey, PA, USA
e-mail: kcheng76@gmail.com

R.E. Hall (ed.), *Racism in the 21st Century*, DOI: 10.1007/978-0-387-79097-8_1,

Introduction

Scientific advances profoundly affect our worldviews. Advances in physics allowed us to realize that the earth is not flat. The discovery of microbes allowed us to abandon beliefs in spirits and humors as the cause of human disease. Similarly, as argued in this chapter, knowledge of the biological and genetic basis of skin color and ancestry will allow humanity to correct misconceptions about skin color and race that have contributed to some of the greatest injustices in human history.

In deciding upon specifics to include in this chapter, I asked what aspects of scientific understanding and thinking about the concept of race might, most likely, suggest solutions to the problems of racism. It was clearly important to address the concerns of today's scientists about even using the term "race." This concern is based on the poorly defined sociological components and violence-laden history of race (Marks 1995, Sankar & Cho 2002, Bamshad et al.2004, Mountain & Risch 2004, Sternberg et al. 2005, Gould & Lewontin 1979). Awareness of the historical, anthropological, and philosophical aspects of "race" and racism are also essential to attain any real understanding of the complexities of race and racism.

After a brief historical overview of human classifications and racism, we will cover some of the basic cell biology, genetics and medical implications of skin color as it affects our thinking about ancestry and race. In order to add insight into the mechanisms of modern science, I will share the story of the recent discovery of a likely genetic mechanism underlying the evolution of light skin in peoples of European ancestry (Lamason et al. 2005). I will then explain how the issues raised by this discovery, combined with the awareness of issues associated with being part of an ethnic minority, led me to believe that scientists, while justified in their avoidance of the use of race in scientific investigation, do not need to avoid the issue of race. A main point of this chapter is that a healing process is critical to diminishing racism, that scientists can help this process by active engagement in calm, logical and scientifically accurate discussions of race and ancestry with the lay public.

Historical Context

Much of the confusion in thinking about skin color and race derives from the state of science at the time human classifications were proposed and from our incomplete understanding of the genetics of human pigmentation and human ancestry. Classifications of humans from the 18th and 19th centuries were created by physicians with minimal knowledge about the biology of skin color. The practice of medicine was based more on humors and spirits than current concepts of pathophysiology. The idea that all living things are composed of cells was only beginning to be understood. The idea that cells

contained organelles (such as those containing pigment) would only be possible with advances in microscopy that came in the 20th century. Although thoughts about inheritance were postulated, DNA and genes were unknown concepts. The first classifications of humans were based on the available small samples of people. Within this context, it is not surprising that the founder of today's form of biological taxonomy, Carolus Linnaeus (Linné 1767), and the founder of anthropology, Johann Friedrich Blumenbach (1865) wrote classifications that contained concepts typical of their era, but known to be incorrect today. Linnaeus succumbed to the assignment of negative personality features to human groups. Blumenbach, despite his prominent and positive role in the Enlightenment, unscientifically assigned aesthetic value to the physical features of skulls. These mistakes, which fed ethnocentric assumptions about intelligence, carried on through Western scientific history even into the 20th century and were unfortunately used to justify bad science (reviewed by Gould 1996) and centuries of human atrocities across the globe.

Modern scientists, armed with modern knowledge and education in modern philosophies of equality, are finally able to distance themselves from the evils of racism. However, we still have a large distance to travel. Even in this modern day, many people, including at times notable scientists, forget that there are two primary and separate determinants of the state of any living thing: the genetic and the environmental, otherwise known as "nature" and "nurture". Whenever both roles are not simultaneously considered, or distinctions clouded, erroneous conclusions are drawn. Hence today's continuing struggle with race and racism.

Whence Racism?

Racism has been a pervasive form of tribalism in human societies of all times and places. Why this is the case is the subject of abundant and vociferous debate. To provide a starting point for discussion, I offer a personal perspective on this question that is based on reading of scientific literature, personal experience, and discussions with psychologists and anthropologists. The pervasiveness of racism is consistent with the human desire for kinship that, in settings of competition for resources, leads to the practice of actively devaluing and harming other groups for the benefit of the group with which one identifies. Tribalism is associated with all manner of distinctions, ranging from skin color to religion to regional/ethnic groups to sport team allegiance. Since parts of tribalism have evolutionary benefit, it is also reflected in other animals (Lorenz 1966). Any solution to racism must therefore acknowledge our instincts, and use the power of reason to teach ourselves how related we actually all are. There is reason to believe that greater understanding of skin color, ancestry, genetics, and the sociology of race will lead to greater tolerance and equality.

A conclusion of overriding importance for public policy is that the *social environment*, *not the genetics*, of underprivileged peoples must be the relentless focus of successful governments and societies—good societies will provide opportunity for every human regardless of ancestry, thereby allowing everyone in their society the opportunity to reach his or her full potential. It is the *social environment*—not the genetics—that is the primary variable that determines human achievement and development of intelligence by learning. What we now know about what it takes to achieve excellence, together with what we now know about the neurobiology of learning, converge on this conclusion. If this writing accomplishes its purpose, it will contribute in some manner to increasing acceptance between peoples regardless of color, thereby facilitating the equitable distribution of opportunity.

The Cell Biology of Pigmentation

In all humans, regardless of "race," skin is colored by a mixture of pigments called melanin (Jablonski 2004, 2006, Sturm 2006, Barsh 2003). The predominant form of melanin is black eumelanin, and the body's factories for generating melanin are pigmented cells called melanocytes—G. *melas*, black; G. *kytos*, cell. The study of pigmented tissues under the electron microscope showed that melanin is packaged within melanocytes in membrane-bound subcellular structures called melanosomes—G. *soma*, body. As more melanin is generated by the cell, the number, size, pigment density, and elongation of these melanosomes increase. The melanocytes of human skin, which are approximately equal in number regardless of the degree of skin pigmentation, are responsible for generating all of the melanosomes in human skin. Most of human skin is comprised of keratinocytes—G. *keras*, horn. The melanocytes deliver melanosomes to the keratinocytes by packing their fingerlike cellular projections with melanosomes, and then "feeding" them to the keratinocytes. The melanosomes we see in keratinocytes thus derive from melanocytes, rather than the keratinocytes themselves. For reasons we do not yet understand, the greater melanin production seen in darker skin is associated with larger, darker, longer, and more numerous melanosomes. A key point to learn here is that the most common differences in pigmentation appear to be due to differences in the level of activity of the involved genes or proteins, rather than their presence or absence.

To gain insight into the biological and genetic basis of pigmentation, scientists have studied the structure of pigmented tissues, hundreds of pigment variants in mice and other organisms, dozens of genetic abnormalities that diminish pigmentation in all vertebrates (including humans), and a range of enzymes and molecules that affect melanin formation (Sturm 2006). The cellular and molecular mechanisms of biological processes, including pigmentation, have shown remarkable conservation in evolution. Despite vast amounts of

work, the genes determining the key skin color differences between races had been elusive (Barsh 2003). In the last decade, we have begun to identify genes underlying the largest difference in human skin color—that between peoples of African versus European descent. The discovery of this key to understanding skin color differences between people of West African and European ancestry came from the study of a light-skinned variant of a popular pet, the zebrafish (Lamason et al. 2005, Sturm 2006).

Zebrafish and the Genetics of Human Skin Color

Our new insight into the genetics of human skin color was serendipitous, coming from two seemingly unlikely sources—cancer research (Lamason et al. 2005) and zebrafish, a common pet store fish that has become a favorite of researchers interested in the biology of vertebrates (Lieschke & Currie 2007). In brief, since mutations in body cells are responsible for turning normal cells into cancer cells, we were interested in finding genes involved in the process of mutation. We used a powerful scientific tool for finding genes that are involved in any biological process—making and studying mutants in the context of what are called genetic screens. For our genetic screen in zebrafish, we used a lightly colored variant of zebrafish, called *golden*, which the founder of the field, George Streisinger, had found in a pet store in Oregon. What Dr. Streisinger did was to develop a visual test to detect mutation in which mutant cells appear as light cells on a dark background in the eye (Streisinger 1984)—figuratively "stars in the sky." We used that test in our genetic screen to find genes involved in susceptibility to cancer (Moore et al. 2006). Now that we have indicated our original reason for our use of *golden* fish, we can focus back on the nature of the variation itself. The populations of zebrafish from pet stores are derived from companies in warm parts of the country, such as Florida, that raise them by the tens of thousands—in populations that represent to some degree the variation in nature. We know from a multitude of DNA studies and photographic studies that humans vary in a multitude of subtle ways. The fact is that the continent with, by far, the greatest variation of any population is Africa. That variation includes variation in a large number of characteristics, such as shapes and lengths of noses, ears, limbs, and pigmentation. Zebrafish populations also vary in many ways, including patterns of pigmented cells, lengths of fins, and pigmentation; *golden* zebrafish may be viewed as one might view a lighter-skinned individual in Africa. For our research, we wanted to find the sequence of the *golden* gene because it would potentially help us to characterize the mutants we had derived from our cancer project. But beyond cancer research, this work would yield an unexpected insight into the evolution of human skin color variation.

The central finding leading to our discovery about human skin color derived from curiosity about the *cellular process* affected in *golden* zebrafish. To satisfy

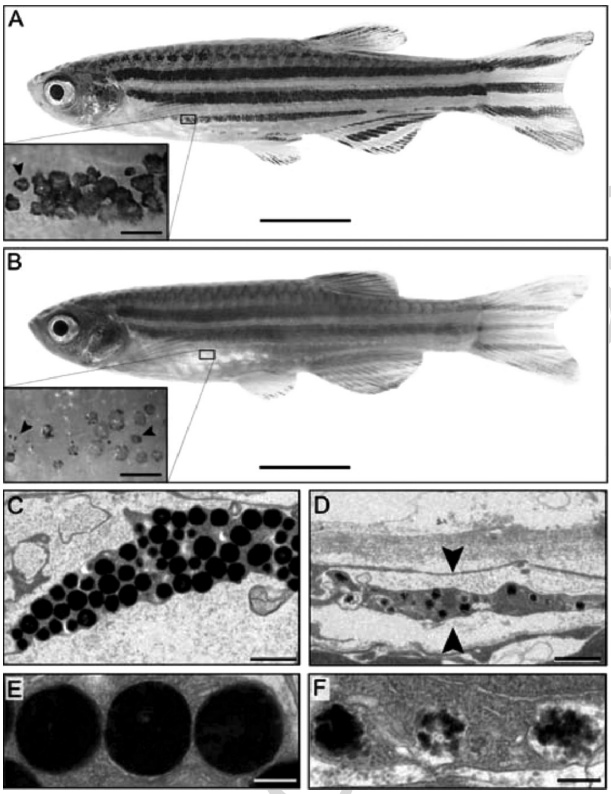

Fig. 1.1 Phenotype of *Golden* Zebrafish
Lateral views of adult wild-type (**A**) and *golden* (**B**) zebrafish. Insets show melanophores (arrowheads). Scale bars: 5 mm (inset 0.5 mm). gol^{b1} mutants have smaller melanophores with fewer, dysmorphic melanosomes. Transmission electron micrographs of skin melanophore from 55 hpf wild-type (**C and E**) and gol^{b1} (**D** and **F**) larvae. gol^{b1} skin melanophores (arrowheads show edges) are thinner and contain fewer melanosomes than wild-type. Melanosomes of gol^{b1} larvae are smaller, less pigmented and irregular compared to wild-type. Scale bars: (**C**, **D**) 1000 nm; (**E**, **F**) 200 nm. (Reprinted with permission from *Science* magazine.)

that curiosity, we first studied adult *golden* fish under a light microscope to look closely at their skin. We noted that the pigmented *cells* in the dark stripes are present in the most common number and pattern, but lighter in color and often smaller in size (Fig. 1.1, A and B)—the pigmented cells were just smaller in size and lighter in color. But why were the pigment cells lighter in color? We used the electron microscope to determine what might have happened to the melanosomes (Fig. 1.1, C and E) in the skin cells of *golden* fish. The light color of *golden* pigmented cells could be due to one or more of three changes—a reduction in the number of melanosomes per cell, in the average size of the melanosomes, or in the amount of pigment deposited in the average melanosome. As a rule of

thumb in biology, individual gene functions are frequently quite specific, so we expected only *one* feature (number *or* size *or* pigment intensity) of melanosomes to be changed in *golden* fish. Thus, it was to my great surprise that *all three* of these features were diminished in the melanosomes of *golden* zebrafish (Fig. 1.1, C–F). Nothing in my entire career in science was more striking than the moment in which I came to understand that these *same three qualitative changes* had long been known to be associated with the differences between light and dark *human* skin (Bolognia & Orlow 2003)! This finding directly suggested that whatever gene or mechanism is involved in causing the light skin of golden zebrafish would also prove to be important in humans—this motivated our subsequent studies.

In everyday life, the lay public has historically developed its views of the world based on single types of "evidence"—if a source we consider authoritative tells us that the sun goes around the earth, or that the earth is flat, we are apt to accept the contention as fact without looking at alternative explanations that are just as or even more possible, especially if it is said to dictate our fate or otherwise serves our interests. If we are taught that everyone in another "race" or political party is inferior we tend to accept that too. If we are taught that humans have nothing to do with global warming we may listen more to individuals with no scientific training and clear conflicts of interest. We must even look harder at falsified documents by politicians and non-scientists than at evidence generated by scientists who understand the dangerous trends and who suggest positive and responsible courses of action. In good science, however, we make models based on evidence, and then test as many predictions of those models as possible in such a way that the evidence can *support or contradict* each model. As applied to skin color, we began from an observation—that cellular changes associated with light skin in both zebrafish and humans are similar, I asked what multiple forms of evidence could be found that support or eliminate the idea that a mutation in the human gene corresponding to the zebrafish *golden* gene played an important role in the light skin of one or more human populations. That would first require finding the zebrafish gene and then the human gene.

We identified the gene responsible for the color of *golden* zebrafish after years of molecular analyses, whose specifics are not important to this discussion. What you do need to know, however, is that genes can be thought of as segments of DNA that, from bacteria to humans, most frequently encode the sequences of amino acid subunits in the corresponding proteins (which include the structural units that hold us together, make up our hair, and facilitate all of the biochemical reactions that make life possible). After finding the sequence of the zebrafish gene, we searched on-line databases, and found a single human gene whose amino acid sequence was 68% identical to that of the zebrafish gene. Similar genes *within* a species, molecular cousins, if you will, are called members of gene families, or *paralogs*. Genes of similar structure and function *between* different species, typically of the most identical function, are called "*orthologues*." The 500 amino-acid human *golden* gene, also called *SLC24A5*, encodes what is called a "sodium, calcium exchanger," based upon similarity

with its similarly named paralogs. The presence of one corresponding human orthologue to the zebrafish *golden* gene reflects its strong evolutionary conservation in at least all vertebrates. The next task was to find evidence for or against conserved function of the human protein in pigmentation. Since there is a large evolutionary distance between fish and humans, a stringent test would be to determine whether the human protein could function in zebrafish. The *golden* mutant in this gene allowed us to test that possibility. To do this test, we could inject the RNA or DNA that would be expected to be made into protein, and see whether the pigmented cells in *golden* embryos would become as dark as those in zebrafish without the mutation in the *golden* gene. Strikingly, we found that the human homologue can cause the light *golden* cells of zebrafish to darken. In fact, *both* European and African versions of the gene caused *golden* cells to darken. Upon studying the new "HapMap" database (HapMap 2007) of human genetic variation (a catalogue of single letter changes commonly found in human DNA), we discovered in a particular place in this gene, a guanine, or "G" is present in nearly all African and East Asian (Chinese and Japanese) sample populations, and that adenine, or "A" was present in every individual in the European HapMap population (from Utah, derived from northwestern Europe). Among the ten places where there was known variation between populations in this gene, this change was the *only* one causing a change in the genetic code resulting in a change in amino acid in the corresponding gene—the 111th amino acid, alanine, which is invariant in vertebrate evolution, was changed into a threonine in all of the European individuals tested (Lamason et al. 2005). Since *Ala* is the abbreviation for alanine (pronounced "al′—a—neen") and *Thr* the abbreviation for threonine (prounounced "three—o—neen"), this amino acid change is abbreviated *Ala111Thr*. This nomenclature is common in genetics.

A Key Role for SLC24A5 in the Lightening of Skin Color in Europeans

Using the zebrafish, we had discovered an important gene that affects the number, size, and depth of staining of melanosomes. We also found that the human gene could contribute to pigmentation by replacing the corresponding gene's function in zebrafish. After noting the similarity between the skin of *golden* zebrafish and the skin of Europeans, we searched for and found a one-letter change in the DNA sequence in the human version of the zebrafish gene that changed amino acid 111. But for what fraction of measured skin color differences between Africans and Europeans does the *Ala111Thr* change in *SLC24A5* account? In our collaboration, anthropologist Mark Shriver and colleagues used DNA and quantitative machine-based measurements of skin color to correlate the presence of this change in people with so-called "admixed" European-African ancestry to corresponding skin color measurements. To have admixed European-African ancestry is to have both European and

African parentage. From this work, we were able to calculate that the *Ala111Thr* change accounts for 25–38% of the skin color difference between West African and northern European skin (Lamason et al. 2005). This range of effect was subsequently confirmed by studying the skin and DNA of populations from South Asia (the Indian subcontinent) (Stokowski et al. 2007).

We then looked for specific evidence of selection for light skin in the population of European ancestry by studying the patterns of variation across the pages of our genetic code book—our DNA. Here, we are looking to see whether evidence exists for biological selection for a DNA change corresponding to lighter skin color conveyed by a variation in a very specific point in a specific gene on a specific chromosome. We know that most variation in DNA is due to genetic variation within groups, and has no biological effect (Collins 2004). In the case of the *Ala111Thr* change in *SLC24A5* in Europeans, however, we have a very rare situation—a wide constellation of evidence consistent with selection. To understand this evidence you need to know that we have one set of chromosomes from our mothers and a second set from our fathers. In the case of the *golden* gene, for both zebrafish and humans, two copies of the mutant chromosome are necessary for the lighter skin color. If we expect that there is selection for light skin color, *both* copies of the gene will be mutant, and *nearby variations* present on the original mutated chromosome will be indirectly selected for—a genetic "hitch-hiking," if you will. This leads directly to less variation in the region around *SLC24A5*. The size of the region showing decreased variation around *SLC24A5* is larger than anywhere else in the genome, and only for the European population. This is the strongest evidence one could have expected, in support of the idea that there was *selection* for light skin color in the northern latitudes of Europe.

If there is selection for lighter skin as humans move to northerly latitudes, there has to be some *biological reason* for having light skin in those regions. There exist two types of complementary evidence that have to do with essential nutrients and sunlight (Jablonski 2004, 2006). Sunlight is needed for one essential nutrient (vitamin D). However, sunlight is less intense and less lengthy in northern latitudes—it would therefore be predicted that light skin is favored in those latitudes. But why is there darker skin in Africa? Since intense sunlight destroys another nutrient (folate) that is essential for proper fetal development, darker skin is favored for survival in equatorial regions. If there is selection for light skin, the European allele of *SLC24A5* should also be found across all of Europe. That is indeed the case and is consistent with selection for light skin within Europeans peoples (Lamason et al. 2005, Norton et al. 2007), perhaps after the last glacial retreat some 15,000 years ago (Fig. 1.2). *When* the mutation arose is an open question—existing evidence is consistent with a model in which the mutation was present in Africa long before humans migrated into Europe. The mutation in the human *golden* gene may have been a naturally occurring variant in Africa. Similarly, in zebrafish, we find *golden* mixed in with populations of zebrafish. In humans there was selective pressure for the lighter variant, but not in zebrafish.

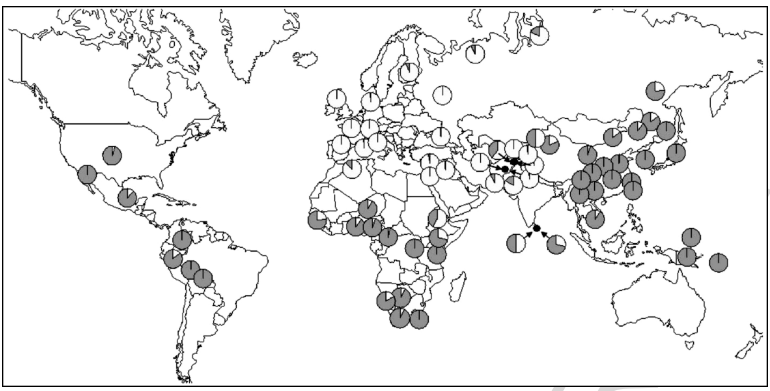

Fig. 1.2 World Distribution of the *Ala111Thr* Allele of *SLC24A5*
World distribution of the *Ala111Thr* allele of *SLC24A5*. This representation is derived from data from a collaboration with Ken Kidd (Yale University), combined with data from Norton et al. (2007), and from Soejima & Koda (2007). The proportion of alleles in each population is represented by a pie chart in which the ancestral allele is represented in grey, and the new, derived allele is represented in white. It is readily apparent that the *Ala111Thr* derived allele of *SLC24A5* becomes more predominant in Europe as the population is further northwest. Notably, the derived allele is nearly absent in East Asia, where the evolution of light skin was derived by other genetic mechanisms, in a process called convergent evolution. The small proportion of this allele in Mexican and Vietnamese populations might be accounted for by admixture with European (Spanish/Portuguese and French populations, respectively). When the DNA variations associated with light skin color in East Asians are found, we expect the corresponding diagram to show white circles in East Asia and the Americas, grey circles in Africa, and unpredicted proportions among European populations. Figure generated with Jason Mest and Victor Canfield. (Figure courtesy of the author.)

What other genetic variations are associated with light skin color in Europeans? Pigment variants in animals helped scientists to find another gene important in the evolution of human light skin: *MATP* ("membrane-associated transporter protein," also called *SLC45A2* or *AIM1*—"antigen in melanoma 1"). Among the animals informing us about the pigmentary function of this gene were the so-called *underwhite* mutation in mice (Newton et al. 2001) and the "b" mutation in the medaka fish (Fukamachi et al. 2001). In humans, a specific mutation in this gene, *Leu374Phe* mutation (the ancestral amino acid leucine is replaced in the variant by phenylalanine at amino acid 374) is present in most but not all Europeans (less frequent than the *SLC24A5* mutation) and contributes about an equal amount to skin color as the European *Ala111Thr* variant in *SLC24A5*. But what relative contribution did the variations in *golden* and *MATP* play in selection for skin color? Compared with the 150,000 base-pair region of diminished variation in *SLC24A5*, *MATP* is associated with a smaller, 40,000 base-pair region of diminished variation in Europeans. This smaller region may be evidence of lesser selection for this mutation in *MATP* compared with that in *SLC24A5*, or simply that the *golden* variant is necessary

to see a significant effect on skin color mediated by *MATP*. This question remains to be resolved. Nonetheless, the single-letter changes in *SLC24A5* and *MATP* alone are estimated to contribute to half or more of the difference in skin color between Africans and Europeans—two single-letter changes among the three billion in our DNA. These changes influence skin color, but have no other known implications—in particular, implications about intelligence.

At the time of publication of our work with *golden*, there were no published data on the frequency of the European allele among individuals on the Indian subcontinent. In their pursuit of genetic markers of European versus Sri Lankan populations, however, Soejima and Koda showed that the European allele of *SLC24A5* can be found at frequencies of about 50 and 30% in the lighter Sinhalese and darker Tamil populations, respectively (Soejima & Koda 2007). The focus of their chapter was on the fact that the northern European allele of *MATP* discussed below is nearly absent in Sri Lankans. Their work suggests the possibility that Europeans originated in South Asia, becoming lighter in skin color through adaptive mutations such as that in MATP, as descendants moved into the more northerly latitudes. A monumental study of thousands of Icelanders published late in 2007 identified other mutations, presumably subsequent to that in *SLC24A5* that seem to have contributed to the extra-light skin of Scandinavian peoples (Sulem et al. 2007). Together the data suggest the possibility that the gradation of light skin toward that of Scandinavians required a genetic foundation laid by *SLC24A5,* upon which additional mutations may be added to further lighten the skin.

We have learned from the above that when a trait is selected for, it can be expected that the amount of genetic variation around the selected variation will show less change around it. While this diminished variation applies to *SLC24A5* in Europeans, there is no diminished variation in the region around *SLC24A5* in the light-skinned East Asians of Beijing and Tokyo, both of whom are light peoples. This indicates that variation in *SLC24A5* has nothing to do with their lighter skin color. East Asians (Chinese, Japanese, and Koreans) evolved light skin independently from Europeans, via mutations in different genes that remain to be identified (Lamason *et al.* 2005, Norton *et al.* 2007). This finding of "convergent evolution" for light skin color in northern latitudes by different genetic mechanisms comprises compelling evidence that, during the migration of humans into northerly latitudes, light skin color is biologically necessary.

Health Implications of Light Skin Color

Light skin in Europeans is associated with skin cancer susceptibility (SEER 2004). Skin cancer is of several types corresponding to the cell types normally present in the epidermis—the layer of skin covering our entire bodies.

Squamous cell carcinoma of the skin arises from its predominant cell type, the keratinocytes. Basal cell carcinoma arises from the cells at the bottom layer of the epidermis, the basal cells. Melanoma arises from the cells making all the pigment of skin, the melanocytes. The incidence of all of these types of skin cancers is increased in Europeans. All are thought to arise from lack of protection of the DNA of the skin cells from the sun, which is known to cause specific types of mutations. The cancer of pigmented cells, melanoma, is one of the most deadly human cancers. After it spreads, it kills four out of five patients within five years due to a dearth of effective treatments (Terando et al. 2007). One of the greatest hopes in melanoma treatment is immunotherapy, in which antibodies or specialized "killer" cells are directed to attack proteins on the cancer cell (Terando et al. 2007). Once development from the egg to adult is complete, pigmented cells are no longer essential for life (other than for protection from the sun and to enhance vision). Proteins that are particularly abundant in pigmented cells are potentially good targets for immunotherapy. In support of the use of this protein for targeting, we were able to show that the *SLC24A5* protein is expressed primarily in pigmented cells and at levels thousands of times higher in melanoma than in non-pigmented cells (Lamason et al. 2005). By attaching fluorescent "flags" into the protein, we determined that it likely sits in the melanosome membrane or its precursor. Work primarily by others has since revealed that some 1500 other proteins are associated with melanosomes (Chi et al. 2006). Which of these are specific to melanosomes and common in most or all melanomas will have to be determined to help choose the best target. An important unanswered question is why East Asians (e.g. Chinese, Japanese, and Koreans) have lighter skin but do not show the degree of increase in the risk of skin cancer that is characteristic of people of European ancestry. Finding the genes underlying the light color of East Asian skin, and comparing the mechanisms of decreased pigmentation with that of Europeans, will be key to understanding skin cancer susceptibility. We might also mention that European ancestry is associated with the most common form of acquired blindness in humans, age-related macular degeneration (Yates & Moore 2000), suggesting that *SLC24A5* might contribute to this disease (Cheng & Canfield 2006).

The field of pharmacogenomics studies how variations in our DNA cause variations in our responsiveness to drugs. The Race, Ethnicity, and Genetics Working Group (2005) is part of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health, dedicated to ensuring proper consideration of the connections between race, ethnicity, and genetics (Race, Ethnicity, and Genetics Working Group 2005), such as those associated with the finding of the *golden* gene. At the time of publication of our work in 2005, we met them in part to discuss the question of whether the group agreed or disagreed with the idea that discussing the finding about *golden* with the public would derive the best societal benefit by presenting it as *demystifying* skin color and race (primarily associated with skin color). In short, the committee agreed. Now for the details.

Part of the inspiration for our discussion was the publicity around BiDil, the first medication tailored for a specific racial group—in this case African Americans with heart failure. BiDil had been approved because black patients frequently respond inadequately to beta-blockers and ACE inhibitors, both of which are used to treat heart disease (Kahn 2005). However, the drug may work better in African Americans not because of skin color but because, it is said, heart failure is more commonly due to hypertension in African Americans, while, in people of European ancestry, ischemic damage associated with atherosclerosis is more frequently responsible. It has thus been argued that the drug should be prescribed for heart failure secondary to hypertension, regardless of skin color. It is of course important to develop drugs that work most effectively in subpopulations. In Africans, or any subpopulation, genetic variations affecting specific disease susceptibility or drug responsiveness variations may be unique or common. It is important to note that African Americans are partly European in genetic background. The fraction of European ancestry in African Americans can be estimated to be between 9 and 27%, as suggested by the frequency of European alleles of *SLC24A5* or *MATP* in three African American populations in the Single Nucleotide Polymorphism database (dbSNP) database found in the HapMap website (http://www.hapmap.org/). Gene variations associated with drug responsiveness have no reason to be particularly associated with skin-color genes. Rather, such traits would be expected, most of the time, to be inherited independently from skin-color genes, making skin color, and therefore race, an unreliable substitute for knowing the real gene variations that correlate with drug responsiveness. Only after we know what specific sequences correlate with drug responsiveness can we begin to measure the strength of correlations between skin color and drug responsiveness. Unless a skin-color gene variant is directly responsible for drug responsiveness, skin color will never be a guarantee of such an association. These arguments apply to variations associated with disease susceptibility as well. A similar view has been stated by *New England Journal of Medicine* editor Robert Schwartz (Schwartz 2001).

Psychological and psychiatric issues are also associated with skin color. Lighter skin color has become so desirable among non-European peoples that self-esteem and social behavior are significantly impacted by skin color (Hall 1995, Butts 2003). This phenomenon is so strong that in essentially all non-European societies, and particularly among women, the use of skin-lightening creams has become commonplace, even when such use is known to be harmful to both the skin, and also to other organs (Ntambwe 2004). For example, more than half of women in Nigeria and Senegal have been reported to use harmful skin-lightening creams (Ofili et al. 2006, Ajose 2005, Mahé et al. 2003). Even more tragic is the fact that darker-skinned individuals *within* families are *not* given the same respect or opportunities as siblings who are born with lighter skin (Rangel 2007).

Perhaps the most important health implications of skin color have to do with race-associated health care disparities. These disparities are in turn related

largely to income, education, job opportunity and access to health care, and are well-known to be associated with skin color (James et al. 2007). The relationship between skin color, race, and racism is discussed elsewhere in this book. The complex interplay between demographics, generations of racism, socioeconomics, and human behavior are separate issues that require additional study, long-term planning, and implementation if we are to ameliorate race-determined health care disparities. We should take pause to realize that the social consequences of negative attitudes toward skin color *alone* have had, and will continue to have, a huge and largely adverse global impact on human health.

Sociology of the SLC24A5 Story

Discussion of any gene change that helps to define the light skin color of Europeans can be expected to elicit controversy. Accordingly, before the *golden* story even appeared, several scientific colleagues warned me that discussing race would amount to walking a minefield—that I should stick with the science and avoid discussions of race. Many expressed the viewpoint that race is a social construct with no scientific merit (Tishkoff & Williams 2002, Bamshad et al. 2004, Sternberg et al. 2005, Gould & Lewontin 1979).

Ancestry is a much more specific and useful scientific term than race. As confirmed by continuing work on human variation (HapMap 2007), there exists far more variation between individuals within most populations than between traditional major population groups. However, there is no denying that variation is greatly diminished in small inbred populations, or that *SLC24A5* is a gene clearly associated with a key physical feature associated with the traditional concept of race. I felt it would not be helpful to deny a direct answer to the public's most frequently asked question—the implications of the finding with regard to race an area in which society must have help from scientists.

Given that discussion of race is inherently controversial, there is wisdom in avoiding hurtful controversy. However, as a member of an ethnic minority affected by racism, were I to deny discussion of the relevance of the new science to race I would be disingenuous—denying inherently social implications of this knowledge in order to stay comfortable in my ivory tower. Furthermore, I strongly sensed that this was an unusual opportunity for the public to gain a deeper understanding of the problems of thinking and acting in terms of "race." At best, a positive new perspective and even a redefinition of race could then be shared with others and possibly contribute to increasing understanding and diminishing racism. Initially, a convincing way of dealing with the issue of race and skin color was not evident. In my search for the best path to follow, I was fortunate to find the work of Stephen Oppenheimer, who is known for his scholarly exposition of the scientific basis of human origins in Africa (Oppenheimer 2004). Dr. Oppenheimer kindly corresponded with me by email

as a complete stranger. He validated my discomfort about denial, saying that, in his opinion, self-censure is often worse than addressing difficult issues. He shared an approach that had worked well for him: Before engaging in a discussion about human differences, determine the purpose of the discussion. Enhancing understanding of diversity is acceptable; whereas racism, which devalues a group by being competitive, exclusive, or derogatory, is unacceptable (Oppenheimer 2004). Melanoma researcher John Pawelek shared with me words of his son, Unitarian Universalist minister, Joshua Pawelek (Pawelek 2006), "...the denial of race will not work, for it leads to a denial of racism—and you can't address a problem if you don't think it exists." These ideas supported my decision to stand behind the notion that informed discussion about the genetics of human skin color could clarify our thinking about race, and diminish racism among our youth. These discussions laid the foundation for using the *golden* story to demystify skin color and race during my travels to present our work.

Among the more challenging questions were, "Is *SLC24A5* the 'race' gene?" and "Is this the 'white' gene?" My answer was that *SLC24A5* is neither the "race" nor "white" gene because it is only one factor in both race and skin color. One of my scientific colleagues has pointed out that "Skin color does not equal race" (Schneider *et al*. 2002). *As traditionally used, race is a sociological concept with both genetic and non-genetic components*. The inclusion of these two different components contributes greatly to making the term so controversial. The obvious physical (and therefore most commonly genetic) features of race include skin color, facial features, hair and eye color; the sociological aspects of race, or tribe, include nationality, language culture, and social advantage/disadvantage—and are not genetically determined. It is also simplistic to call *SLC24A5* gene the "white" gene since the *SLC24A5* protein is present and active in the pigment cells of all races. The European variant is simply less active. Since the different type of mutation in *golden* zebrafish is most likely to result in lack of any function, and the fish still develop some pigment, it is most likely that *SLC24A5* acts by modifying the degree, rather than determining the presence or absence, of pigmentation.

Demystifying Skin Color and Race

In discussions with the Race, Ethnicity and Genetics Working Group of the National Human Genome Research Institute and with Institute Director Francis Collins on the day of release of the *Science* magazine story on 16 December 2005 (Lamason et al. 2005), I suggested, on the basis of the above arguments, the possibility that the most responsible thing for us to do, as scientists, would be to face the challenge of the relationship between race and skin color, rather than to avoid it. After discussion, we all agreed that we could use this type of molecular understanding to begin, as Dr. Collins put it, to "demystify" skin color for the lay public. This viewpoint began to be conveyed that very

afternoon during interviews that appeared in the next 24 hours on the television programs, ABC's *World News Tonight* and *Good Morning America*, and in radio and newspaper coverage. Theodore Shaw, President of the NAACP Legal Defense and Educational Fund, said in the *Good Morning America* segment that the average person would not care about the finding, or fundamentally change his behavior even if he did learn about it (Shaw 2005). While this is likely true of adults, *our children, before they learn tribal attitudes, are more likely to be receptive to learning that skin color is determined by just a few letters out of the instruction book of life*. While this hypothesis remains to be proven, there is reason to believe that teaching our youth to recognize tribalism, and to distinguish between genetic and environmental impacts on human outcomes, will diminish the systematic injustices of racism perpetrated on the basis of skin color. In the face of a vast potential benefit of pursuing this course of action and no significant negative consequences, such a course of action, as long as it responsibly managed and polished along the way, would seem wise to follow.

Skin Pigmentation, Science, and Race

At this point in human and scientific history, it is clear that human pigmentation is determined by a finite number of genes that affect one or more aspects of how melanin pigments are formed, the morphology of the organelles containing that pigment, and the transport of those organelles to the bulk of our skin cells (*keratinocytes*), resulting in the color of our hair and eyes. The evidence suggests that the most extreme natural differences in pigmentation may be due to biological advantages of dark skin in habitats with extreme sun exposure, and the advantages of diminished pigmentation in habitats of limited sun exposure. Skin color may be one of just a small number of specific human traits that differ between traditional racial groups, and are associated with clear genetic mechanisms and genomic evidence of selection.

In contrast to the selective forces apparent for skin color, most—perhaps all—other physical and biochemical traits characteristic of each group exist solely on the basis of random genetic variation within large populations, followed by population bottlenecks—that is, the small number of individuals (the "founder population") who gave rise to each group outside of Africa. Within human tribes that have historically been limited to specific regions, distinguishing physical characteristics of each population are stronger, not because of selection but rather because of the limited range of genetic variation that is associated with small founder populations. Other traits for which there are both biological mechanisms for and genomic signatures of selection, such as the sickle cell trait based on resistance to malaria, are common within individual populations (Tishkoff & Williams 2002) but far from universal within those groups. No matter how many variations are eventually found to determine

physical traits, such as pigmentation, we already know that there will be but a small minority of traits that exist by evolutionary chance within each major human population.

Education

There are at least three reasons as to why education serves as an antidote to racism. First, by educating our youth about the biological basis of skin color and the genetic components of race, and the environmental determination of values, cultures and habits of mind, it becomes obvious that social advantages associated with light skin are based on biologically false assumptions that are grounded in tribal emotions. Students can become aware of the complex but well-documented history of social prejudice-driven pseudo-science (Gould 1996) that underlies our heritage of discrimination, and learn to recognize the associated fallacies.

The second major reason is that education is now necessary for success in our new information-based society. Less educated populations are marginalized in modern society. No matter what importance we may place on more traditional forms of social or cultural education, functioning in modern society requires a minimum set of knowledge and habits of mind that are facilitated by education in problem-solving fields such as science, mathematics, and engineering, together with the acquisition of self-management and people management skills required for handling of today's volumes of data and personnel—these skills are required for smoothly functioning modern societies to be built and maintained. Societies, from the national level to local communities to the family, must work together to fulfill the compelling responsibility for educating the currently underprivileged. It is of equal importance that the leaders of the underprivileged stir up an unwavering commitment to education—an education that plays an important role in the acquisition of knowledge and skills that increases the likelihood of success. It is important to note a key responsibility that only the underprivileged can control, and that must be fulfilled in every location where educational solutions are developed. This responsibility is to inculcate positive attitudes toward education. The motivation for consistency in such an attitude is especially great, since academic success is the single best way to put to rest claims that lack of achievement is due to genetically determined intellectual ability.

The third reason education is so important is something that is obvious to any musician: the so-called "intelligence" that matters—the ability to solve problems—is created by opportunity, a commitment to solving those problems, learning functional habits of mind, and making a commitment to disciplined practicing of learned and creative ways to solve those problems. The biological basis of this view is our knowledge that learning creates new neural circuits (Gase & Schlaug 2003) and may even increase neuronal volume (Schneider *et al.*

2002). Lack of education deprives people of knowledge needed for the best jobs and impedes development of the ability to solve problems; therefore, depriving people of education is an effective manipulation to keep people down. Even with the highest possible motivation, a potential Einstein cannot make contributions without proper education and academic opportunity. Thus, anyone not blinded by competitive tribalism can see that a sweeping range of abilities is present in all populations, and that discussion about the genetics of intelligence has been a poor excuse for not taking responsibility for providing opportunity for subjugated peoples. It is heartening to see that there is significant motion today toward making education possible for everyone. Our very survival may depend upon our ability, across the globe, to choose modes of education that are dedicated to universal, not tribal, interests.

Conclusions

The term *race* derives from a natural human interest in categorizing the components of our world. From the beginning, the concept of race has been contaminated by scientifically incorrect assumptions that seem to have been motivated by our tribal tendencies to justify how "us" is better than "them." As used today, race refers to both physical features that are genetically determined and other features that are environmentally determined. Racism is now deeply and insidiously embedded within our societies. It seems reasonable to act on the possibility that resolving the societal problems of racism will benefit from a direct and open acknowledgement of our natural tendency toward tribal motivations and the irrational justifications that follow. Scientists can help discredit racism by teaching about the depth of fundamental biological similarities between all humans, breaking down the construct of race into components that are more precise and less burdened by tribalism, such as "ancestry," "genetics," and "environment." To further the equal treatment of humans regardless of ancestry, scientists can persistently remind society that genetics and race are invalid excuses for not attending to the social inequalities stemming from racism. Education can play a central role in work toward a society free of racism if it includes a firm grounding in the method and practice of the sciences and is freed of misanthropic expressions of tribalism. For this approach to succeed, we must work hard toward ensuring that education is accorded the importance it deserves, and that non-tribal, evidence-based education becomes the ideal sought by all. Furthermore, education can and should cultivate habits of mind that improve the capacity to exploit opportunity and achieve self-fulfillment, while promoting greater harmony in the societies of the future. There is reason for optimism: when in the last 1000 years might we have imagined a discussion of such a touchy topic as race, put together by scholars of globally diverse ancestry, dedicated to the common good?

Acknowledgments I thank my colleagues around the world for valuable discussions about skin color and race, my family and lab for tolerating this obsession for the past two years. Many colleagues generously shared their time, knowledge, and perspectives. I am particularly indebted to Stephen Oppenheimer, Robert Jones, Scott Thompson, Jonathan Weker, and Philip Wilson. Lindsay Rush and Shou Ling Leong made valuable suggestions across multiple drafts, as did Anthony Cheng, who also helped by researching tribalism and the evolution of scientific perceptions of human variation. I thank Ken Kidd for generously generating data, Victor Canfield and Jason Mest for producing Fig. 1.2, and Sarah Frey for editorial assistance.

References

Ajose, F. O. A. (2005). Consequences of skin bleaching in Nigerian men and women. *International Journal of Dermatology*, 44, 41–43.

Bamshad, M., Wooding, S., Salisbury, B. A., & Stephens. J. C. (2004). Deconstructing the relationship between genetics and race. *Nature Reviews Genetics*, 5, 598–609.

Barsh, G. S. (2003). What controls variation in human skin color? *PLoS Biology*, 1, 019–022.

Blumenbach, J. F. (1865) The anthropological treatises of Johann Friedrich Blumenbach and the inaugural dissertation of John Hunter, M.D. on the varieties of man, translated by T. Bendyshe. London: Longman, Green, Longman, Roberts, & Green.

Bolognia, J. L., & Orlow, S. J. (2003). Chapter 65: Melanocyte biology. In Bolognia, J. L., Jorizzo, J. L., & Rapini, R. P. (Eds.). *Dermatology* (p. 935). London (UK): Mosby.

Butts, H. (2003). Skin color perception and self-esteem. *The Journal of Negro Education*, 32, 122–128.

Cheng, K. C., & Canfield, V. A. (2006). The role of SLC24A5 in skin color. *Investigative Dermatology*, 16, 836–838.

Chi, A., Valencia, J. C., Hu, Z.-Z., Watabe, H., Yamaguchi, H., Mangini, N. J., Huang, H., Canfield, V. A., Cheng, K. C., Yang, F., Abe, R., Yamagishi, S., Shabanowitz, J., Hearing, V. J., Wu, C., Appella, E., & Hunt, D. F. (2006). Proteomic and bioinformatic characterization of the biogenesis and function of melanosomes. *Journal of Proteome Research*, 5, 3135–3144.

Collins, F. S. (2004). What we do and don't know about 'race', 'ethnicity', genetics, and health at the dawn of the genome era. *Nature Genetics*, 36, S13–S15.

Fukamachi, S., Shimada, A., & Shima, A. (2001). Mutations in the gene encoding B, a novel transporter protein, reduce melanin content in medaka. *Nature Genetics*, 28, 381–385.

Gase, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *The Journal of Neuroscience*, 23, 9240–9245.

Gould, S. J. (1996). *The mismeasure of man*. New York: Norton.

Gould, S. J., & Lewontin, R. C. (1979). The spandrels of San Marco and the Panglossian paradigm: A critique of the adaptationist programme. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, 205 (No. 1161, *The Evolution of Adaptation by Natural Selection*), 581–598.

Hall, R. (1995). The bleaching syndrome: African Americans' response to culture domination vis-à-vis skin color. *Journal of Black Studies*, 26, 172–184.

[HapMap] (2007). The International HapMap Project, a database of human genetic variation. Available at http://www.hapmap.org/.

Jablonski, N. G. (2004). The evolution of human skin and skin color. *Annual Review of Anthropology*, 33, 585–623.

———. (2006). *Skin: A natural history*. Berkeley, CA: University of California Press.

James, C., Thomas, M., Lillie-Blanton, M., & Garfield, R. (2007). Key facts: Race, ethnicity and medical care, 2007 update. Menlo Park, CA: J. Kaiser Family Foundation. Available at http://www.kff.org/minorityhealth/6069.cfm.

Kahn, J. (2005). Misreading race and genomics after BiDil. *Nature Genetics*, 37, 655–656.

Lamason, R. L., Mohideen, M.-A. P. K., Mest, J. R., Wong, A. C., Norton, H. L., Aros, M. C., Jurynec, M. J., Mao, X., Humphreville, V. R., Humbert, J. E., Sinha, S., Moore, J. L., Jagadeeswaran, P., Zhao, W., Ning, G., Makalowska, I., McKeigue, P. M., O'Donnell, D., Kittles, R., Parra, E. J., Mangini, N. J., Grunwald, D. J., Shriver, M. D., Canfield, V. A., & Cheng, K. C. (2005). SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science*, Dec. 16, 310, (5755)1782–1786.

Lieschke, G. J., & Currie, P. D. (2007). Animal models of human disease: Zebrafish swim into view. *Nature Reviews Genetics*, 8, 353–367.

Linné, C. (1767). Systema naturae (13th Ed.) Vindobonae [Vienna]: Ioannis Thomae.

Lorenz, K. (1966). On aggression. M. K. Wilson (Trans.). New York: Harcourt, Brace & World.

Mahé, A., Ly, F., Aymard, G., & Dangou, J. M. (2003). Skin diseases associated with the cosmetic use of bleaching products in women from Dakar, Senegal. *British Journal of Dermatology*, 148, 493–500.

Marks, J. (1995). *Human biodiversity: Genes, race, and History*. New York: Walter de Gruyter.

Moore, J. L., Rush, L. M., Breneman, C., Mohideen, M.-A. P., & Cheng, K. C. (2006). Zebrafish genomic instability mutants and cancer susceptibility. *Genetics*, 174, 585–600.

Mountain, J. L., & Risch, N. (2004). Assessing genetic contributions to phenotypic differences among "racial" and "ethnic" groups. *Nature Genetics*, 36, S48–S53.

Newton, J. M., Cohen-Barak, O., Hagiwara, N., Gardner, J. M., Davisson, M. T., King, R. A., & Brilliant, M. H. (2001). Mutations in the human orthologue of the mouse *underwhite* gene (*uw*) underlie a new form of oculocutaneous albinism, OCA4. *American Journal of Human Genetics*, 69, 981–988.

Norton, H. L., Kittles, R. A., Parra, E., McKeigue, P., Mao, X., Cheng, K. C., Canfield, V. A., Bradley, D. G., McEvoy, B., Shriver, M. D. (2007). Genetic evidence for the convergent evolution of light skin in Europeans and East Asians. *Molecular Biology and Evolution*, 24, 710–722.

Ntambwe, M. (2004). Mirror mirror on the wall, who is the FAIREST of them all? *Science in Africa*, www.scienceinafrica.co.za/2004/march/skinlightening.htm.

Ofili, A. N., Eze, E. U., Onunu, A. N. (2006). Prevalence of use of skin lightening agents amongst University of Benin undergraduates in Benin City, Nigeria, *Nigerian Medical Practitioner*, 49, 24–27.

Oppenheimer, S. (2004). *Out of eden*. London (UK): Constable & Robinson.

Pawelek, J. M. (2006). *Racism and spiritual death in the United States of America,* Sermon, 15 January 2006, the Unitarian Universalist Society: East, Manchester, CT. Available at http://www.uuse.org/html/past_services/2006/01/15_racism_spiritual_death.htm.

Race, Ethnicity, and Genetics Working Group. (2005). The use of racial, ethnic, and ancestral categories in human genetics research. *The American Journal of Human Genetics*, 77, 519–532.

Rangel, M. A. (2007). Is parental love colorblind? Allocation of resources within mixed families. *Harris School Working Paper Series,* 07.14.

Sankar, P., & Cho, M. K. (2002). Toward a new vocabulary of human genetic variation. *Science*, 298, 1337–1338.

Schneider, P., Scherg, M., Dosch, H. G., Spect, H. J., Gutschalk, A., & Rupp, A. (2002). Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. *Nature Neuroscience*, 5, 688–694.

Schwartz, R. S. (2001). Editorial: Racial profiling in medical research. *New England Journal of Medicine*, 344, 1392–1393.

[SEER] Surveillance Epidemiology and End Results. National Cancer Institute website, providing information on cancer. Available at http://seer.cancer.gov/csr/1975_2004 sections.html.

Shaw, T. (2005). Theodore Shaw interview, on ABC Television program, *Good Morning America*, 17 December 2005.

Soejima, M., & Koda, Y. (2007). Population differences of two coding SNPs in pigmentation-related genes *SLC24A5* and *SLC45A2*. *International Journal of Legal Medicine*, 121, 36–39.

Sternberg, R. J., Grigorenko, E. L., & Kidd, K. K. (2005). Intelligence, race, and genetics. *American Psychologist*, 60, 46–59.

Stokowski, R. P., Krishna Pant, P. V., Dadd, T., Fereday, A., Hinds, D. A., Jarman, C., Filsell, W., Ginger, R.S., Green, M. R., van der Ouderaa, F. J., & Cox, D. R. (2007). A genomewide association study of skin pigmentation in a South Asian population. *American Journal of Human Genetics*, 81, 1119–1132.

Streisinger, G. (1984). Attainment of miminal biological variability and measurements of genotoxicity: Production of homozygous diploid zebrafish. *National Cancer Institute Monograph*, 65, 53–58.

Sturm, R. A. (2006). A golden age for human pigmentation genetics. *Trends in Genetics*, 22, 464–468.

Sulem, P., Gudbjartsson, D. F., Stacey, S. N., Helgason, A., Rafnar, T., Magnusson, K. P., Manolescu, A., Karason, A., Palsson, A., Thorleifsson, G., Jakobsdottir, M., Steinberg, S., Pálsson, S., Jonasson, F., Sigurgeirsson, B., Thorisdottir, K., Ragnarsson, R., Benediktsdottir, K. R., Aben, K. K., Kiemeney, L. A., Olafsson, J. H., Gulcher, J., Kong, A., Thorsteinsdottir, U., & Stefansson, K. (2007). Genetic determinants of hair, eye, and skin pigmentation in Europeans. *Nature Genetics*, 39, 1443–1452 (2007).

Terando, A. M., Faries, M. B., Morton, D. L. (2007). Vaccine therapy for melanoma: Current status and future directions. *Vaccine*, 25S, B4–B16.

Tishkoff, S. A., & Williams, S. M. (2002). Genetic analysis of African populations: Human evolution and complex disease. *Nature Review Genetics*, 3, 611–621.

Yates J. R., & Moore, A. T. (2000). Genetic susceptibility to age related macular degeneration. *Journal of Medical Genetics*, 37, 83–87.