The role of SLC24A5 in skin color

Keith C. Cheng[1,2], MD, PhD and Victor A. Canfield[2], PhD

[1]Jake Gittlen Cancer Research Foundation Department of Pathology and [2]Department of Pharmacology
Penn State College of Medicine
500 University Drive
Hershey, PA 17033
USA

One of the enduring mysteries of biology has been the genetic basis for differences in skin color between human populations. Past efforts to answer this question had focused on the genes responsible for pigmentary diseases of humans, coat-color variants of mice, and the chemistry and biochemistry of pigment formation. Despite huge advances in our understanding of pigmentation, the genes responsible for the most striking variations in skin color remained unknown. Last December, the first paper listed below was published, describing the identification of a new gene involved in vertebrate pigmentation. A mutation in this gene, *SLC24A5*, makes the largest known contribution to skin color differences between humans of African and European ancestry. The light skin color variation may be regarded as a contributor to skin cancer susceptibility. The commented bibliography below includes a sampling of related work on skin color genetics, melanosome biology, model systems for studying pigmentation, cation exchangers, human genomics using the HapMap, one of the possible relationships between *SLC24A5* to other human diseases (age-related macular degeneration), and an historically relevant, uncomfortable but unavoidable topic – race.

It took an unintentional tangent of zebrafish cancer genetics research to discover the first major contributor to the skin color difference between Africans and Europeans (1). This 10-year project demonstrated the critical roles and relevance of model systems and multi-disciplinary approaches in research about human biology. This work began with the positional cloning of the zebrafish *golden* mutation, which causes changes in melanosomal number, size and pigment density that resemble the differences between European and African humans. The human ortholog was able to contribute pigmentary function in *golden* zebrafish. A polymorphic variant of the human ortholog *SLC24A5* that is common in peoples of European ancestry causes an amino acid change (Ala111Thr) at a residue that is otherwise conserved in vertebrate evolution. Admixture mapping suggests that the polymorphism contributes about one-third of the difference in measured skin color in humans. This work is an important example of the relevance of model systems to human biology. We still do not know how *SLC24A5* controls melanosome morphogenesis, what other proteins are involved in the same biochemical pathway, or what its relevance is to other human diseases. The genetic basis of the lighter skin color of East Asians (such as Chinese and Japanese) remains a mystery.

Reviews

These papers (2–7) outline the previous state of knowledge of skin and eye color genetics, the evolution of human skin pigmentation, and adaptation of skin color to sun exposure.

Much has been learned from the study of the chemistry and enzymology of melanins, including the black/brown eumelanin and the red/orange pheomelanin (8).

Melanosomes and skin color

We have known from the first ultrastructural studies of human skin that the determinants of melanosome morphogenesis will be critical to understand the basis of differences in human skin color. These papers (9–14) discuss different aspects of melanosome research. Future work on melanosomes can be expected to integrate knowledge of the role of SLC24A5 in melanosome morphogenesis. Proteomic approaches (15) will add many more pieces to the puzzle of human pigmentation.

Human genes and skin color

These papers (16–18) represent a sampling of the work describing the role of skin color in ancestry, and contributions of various point mutations to human skin color.

Model systems

The mouse represents a primary model system for the study of vertebrate pigmentation (19). Due to the availability of a growing number of pigment mutants, ability to knock out any gene, even during defined times and in defined tissues, it has played, and will continue to play an important role in the understanding of vertebrate pigmentation.

Zebrafish is the newest shining star in vertebrate model system genetics and functional genomics (20–22). The first of these papers describes the adaptation of zebrafish to the color of its environment, a process whose genetic basis remains a mystery. The second is an example of the characterization of a mutation in zebrafish that contributed to new knowledge about vertebrate pigmentation. The third demonstrates the utility of 'knock down' technologies for testing the function of any gene in zebrafish. Knock downs are accomplished using morpholino oligonucleotide-based antisense targeting of RNA to inhibit either translation or RNA splicing. One can inhibit partially to create hypomorphs or totally to create null phenocopies of mutant phenotypes. The effects last for the first several days of development, before dilution eventually decreases the inhibitory effect of the morpholinos.

Cation exchange and pigmentation

Three papers (23–25) describe the family of cation exchange genes of which *SLC24A5* is part, and the beginnings of the definition of their function and functional domains. Two papers (26,27) explore the mechanisms by which organellar pH influences regulation of melanin pigmentation.

Human genomics

The HapMap database of human variation is the beginning of the second phase in the genomic revolution initiated by the sequencing of the human and other genomes. We used a new and simplified approach to the analysis of the HapMap data to help identify the crucial role of SLC24A5 in the evolution of human skin color. The papers from the Kidd laboratory demonstrate some of the power of genotyping multiple populations from around the globe. The others reflect some of the latest analyses of the human genome using the

HapMap. These are the beginnings of a revolution in human genomics (28–31).

Other human diseases

Age-related macular degeneration (ARMD) is the most common form of acquired blindness in humans, and is much more common in lighter-skinned peoples than in darker-skinned peoples (32–34). The relevance of SLC24A5 to ARMD, other human diseases, drug efficacy and toxin susceptibility remains to be determined.

Race and color

Until the last several decades, the study of race has been largely a reflection of a negative side of human nature – what may be regarded as tribalism. Whether purposefully or unwittingly, prominent scientists, philosophers and leaders of Western civilization perpetuated falsehoods that directly contributed to a terrible history. A polymorphism in *SLC24A5* is now linked to the most prominent physical feature linked to race – skin color (35–43). One of our most important contemporary responsibilities as scientists and physicians is to use a uniquely human, positive side of human nature – the ability to work together toward idealistic goals, to learn about the history of race perceptions, to accurately represent our new understanding of these issues to the public, and to lead our evolution toward a more egalitarian future. For the first time, we can more precisely define how trivial changes, such as those contributing to variation in skin color, can make profound and often unjustified social differences in people's lives. In the future, we will be able to genotype ourselves to optimize treatments and toxicities on the basis of other such genetic differences. These papers and books represent a slice of the ongoing discussion that can help us in the important task of demystifying the issue of race.

References

1. Lamason R, Mohideen M, Mest J et al. The zebrafish golden gene: A cation exchanger involved in vertebrate melanin pigmentation. Science 2005: 310: 1782–1786.
2. Harrison G A, Owen J J. Studies on the inheritance of human skin colour. Ann Hum Genet 1964: 28: 27–37.
3. Barsh G S. What controls variation in human skin color? PLoS Biol 2003: 1: 445.
4. Sturm R A, Teasdale R D, Box N F. Human pigmentation genes: identification, structure and consequences of polymorphic variation. Gene 2001: 277: 49–62.
5. Sturm R A, Frudakis T N. Eye colour: portals into pigmentation genes and ancestry. Trends Genet 2004: 20: 327–332.
6. Jablonski N G. The evolution of human skin and skin color. Annu Rev Anthropol 2004: 33: 585–623.
7. Wagner J K, Parra E J, Norton H, Jovel C, Shriver M D. Skin responses to ultraviolet radiation: effects of constitutive pigmentation, sex, and ancestry. Pigment Cell Res 2002: 15: 385–390.
8. Ito S. The IFPCS presidential lecture: a chemist's view of melanogenesis. Pigment Cell Res 2003: 16: 230–236.
9. Szabo G, Gerald A B, Pathak M A, Fitzpatrick T B. Racial differences in the fate of melanosomes in human epidermis. Nature 1969: 222: 1081–1082.
10. Konrad K, Wolff K. Hyperpigmentation, melanosome size, and distribution patterns of melanosomes. Arch Dermatol 1973: 107: 853–860.
11. Boissy R E. The melanocyte. Its structure, function, and subpopulations in skin, eyes, and hair. Dermatol Clin 1988: 6: 161–173.
12. Kushimoto T, Basrur V, Valencia J et al. A model for melanosome biogenesis based on the purification and analysis of early melanosomes. Proc Natl Acad Sci U S A 2001: 98: 10698–10703.
13. Raposo G, Tenza D, Murphy D, Berson J, Marks M. Distinct protein sorting and localization to premelanosomes melanosomes and lysosomes in pigmented melanocytic cells. J Cell Biol 2001: 152: 809–824.
14. Setaluri V. The melanosome: dark pigment granule shines bright light on vesicle biogenesis and more. J Invest Dermatol 2003: 121: 650–660.
15. Basrur V, Yang F, Kushimoto T et al. Proteomic analysis of early melanosomes: identification of novel melanosomal proteins. J Proteome Res 2003: 2: 69–79.
16. Massac A, Cameron N, Baron A et al. Skin pigmentation, biogeographical ancestry and admixture mapping. Hum Genet 2003: 112: 387–399.
17. Graf J, Hodgson R, van Daal A. Single nucleotide polymorphisms in the MATP gene are associated with normal human pigmentation variation. Hum Mutat 2005: 25: 278–284.
18. Bonilla C, Boxill L-A, McDonald S A et al. The g.8818G variant of the Agouti Signaling Protein (ASIP) gene is the ancestral allele and is associated with darker skin color in African Americans. Hum Genet 2005: 116: 402–406.
19. Bennett D C, Lamoreaux M L. The color loci of mice – a genetic century. Pigment Cell Res 2003: 16: 333–344.
20. Sugimoto M, Yuki M, Miyakoshi T, Maruko K. The influence of long-term chromatic adaptation on pigment cells and striped pigment patterns in the skin of zebrafish, *Danio rerio*. J Exp Zool 2005: 303A: 430–440.
21. Schonthaler H B, Lampert J M, von Lintig J, Schwarz H, Geisler R, Neuhauss S C. A mutation in the silver gene leads to defects in melanosome biogenesis and alterations in the visual system in the zebrafish mutant fading vision. Dev Biol 2005: 284: 421–436.
22. Pickart M A, Sivasubbu S, Nielsen A L, Shriram S, King R A, Ekker S C. Functional genomics tools for analysis of zebrafish pigment. Pigment Cell Res 2004: 17: 461–470.
23. Szerencsei R, Winkfield R, Cooper C et al. The Na/Ca-K exchanger gene family. Ann N Y Acad Sci 2002: 976: 382–390.
24. Cai X, Lytton J. The cation/Ca^{2+} exchanger superfamily: phylogenetic analysis and structural implications. Mol Biol Evol 2004: 21: 1692–1703.
25. Kinjo T G, Kang K, Szerencsei R T, Winkfein R J, Schnetkamp P P. Site-directed disulfide mapping of residues contributing to the Ca2+ and K+ binding pocket of the NCKX2 Na+/Ca2+-K+ exchanger. Biochemistry 2005: 44: 7787–7795.
26. Watabe H, Valencia J, Yasumoto K et al. Regulation of tyrosinase processing and trafficking by organellar pH and proteosome activity. J Cell Biol 2004: 279: 7971–7981.
27. Smith D R, Spaulding D T, Glenn H M, Fuller B B. The relationship between Na(+)/H(+) exchanger expression and tyrosinase activity in human melanocytes. Exp Cell Res 2004: 298: 521–534.
28. Voight B F, Kudaravalli S, Wen X, Pritchard J K. A map of recent positive selection in the human genome. PLoS Biol 2006: 4: 0446–0458.
29. Kim J J, Verdu P, Pakstis A J, Speed W C, Kidd J R, Kidd K K. Use of autosomal loci for clustering individuals and populations of East Asian origin. Hum Genet 2005: 117: 511–519.
30. Kidd K K, Pakstis A J, Speed W C et al. Developing a SNP panel for forensic identification of individuals. Forensic Sci Int 2005: [Epub ahead of print].
31. Sabeti P C, Schaffner S F, Fry B et al. Positive natural selection in the human lineage. Science 2006: 312: 1614–1620.
32. Yates J R, Moore A T. Genetic susceptibility to age related macular degeneration. J Med Genet 2000: 37: 83–87.
33. Ambati J, Ambati B K, Yoo S H, Ianchulev S, Adamis A P. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol 2003: 48: 257–293.
34. Friedman D S, O'Colmain B J, Munoz B et al. Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004: 122: 564–572.

35. Gould S J. The Mismeasure of Man. New York: W W Norton & Co, 1981.
36. Marks J. Human Biodiversity: Genes, Race and History. New York: De Gruyter, 1995.
37. Edward A W. Human genetic diversity: Lewontin's fallacy. BioEssays 2003: 25: 798–801.
38. Collins F S. What we do and don't know about 'race', 'ethnicity', genetics and health at the dawn of the genome era. Nat Genet 2004: 36 (11 Suppl.): S13–S15.
39. Jorde L B, Wooding S P. Genetic variation, classification and 'race'. Nat Genet 2004: 36 (11 Suppl.): S28–S33.
40. Kahn J. Misreading race and genomics after BiDil. Nat Genet 2005: 37: 655–656.
41. Parra E J, Kittles R A, Shriver M D. Implications of correlations between skin color and genetic ancestry for biomedical research. Nat Genet 2004: 36 (11 Suppl.): S54–S60.
42. Race, Ethnicity, and Genetics Working Group. The use of racial, ethnic, and ancestral categories in human genetics research. Am J Hum Genet 2005: 77: 519–532.
43. Leroi A M. A family tree in every gene. J Genet 2005: 84: 3–6.