MELANOCYTES/MELANOGENESIS

The Genetics of Human Pigmentary Disorders

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Interest in the genetics of human and animal pigmentation is longstanding. Variation in human pigmentary form—of skin, hair, and eyes—is one of the most striking polymorphic human traits. Ever since Charles Darwin, biologists have been asking how and why did Nature fashion men so differently across the earth? Moving beyond what we might consider natural physiological variation in skin color to the pathological, human pigmentary disorders such as albinism is often clinically striking. Therefore, some syndromes were described early in modern medical history, and what we would now recognize as modern genetic insights into their nature were present almost as early as the rediscovery of Gregor Mendel's work just over a century ago.

The two decades spanning the start of the twenty-first century have been extraordinarily productive for those interested in human pigment genetics. Of course, the influence and power of what was once called the ''New Genetics'' has been felt across much of modern biomedicine, but to this skin-watcher, at least, few areas of study have seen such progress with apparently so modest an investment in funding. Recounting the story of this advance is necessary not merely to pay homage to those who laid the foundations that later successes were built on, but also as a lesson for those working in other fields of biomedicine where the problems often appear less tractable.

The development of the mouse fancy, and the subsequent institutionalization of this in the twentieth century, provided a fertile resource for those keen to understand mammalian biology (Lamoreux *et al.*, 2010). Interest in this topic, however, was not limited to those, such as skin biologists or dermatologists, whose interests are—professionally speaking—skin deep, but included those far-sighted biologists who recognized that the astonishing diversity of murine coat color mutants offered a way to address the general problem of how genes work. When technological advances in molecular genetics made mammalian gene identification almost routine, the resource of the mouse fancy offered an unrivaled experimental model system both for those interested in human pigmentation and for those whose goals were more general.

PIGMENT GENES: MENDEL FIRST

In 1990, the genetic basis of oculocutaneous albinims 1 (OCA1), a common form of albinism, was shown to be attributable to mutations in the enzyme tyrosinase (Giebel *et al.*, 1990, 1991). Subsequently, many of the other forms of albinism and related disorders were attributed to mutations in a range of other genes: thus mutations at the P locus caused OCA2 (Rinchik *et al.*, 1993); mutations of tyrosinase-related protein (*TRP-1*), OCA3 (Manga *et al.*, 1997); and mutations of a membrane transporter protein (*MATP*), OCA4 (Newton *et al.*, 2001). Genes causing the various types of Hermansky Pudlak syndrome and Griscelli syndromes were discovered, as well as the gene underpinning the Chediak-Higashi syndrome (for reviews see Nordlund *et al.*, 2006). During the same period, the role of the melanocortin 1 receptor (*MC1R*) in causing the quasi-Mendelian trait of red hair, as well as freckling and sun sensitivity, was described (Valverde *et al.*, 1995; Flanagan *et al.*, 2000). Much of this work relied on prior experimental work in the mouse and various degrees of extrapolation to man (Robbins *et al.*, 1993). More recently, other model systems, notably the zebrafish, have provided key insights (Lamason *et al.*, 2005). Finding a gene does not mean that a disorder is understood (let alone cured), but gene identification accelerates future advances by providing a set of tools that facilitate cell biology and physiology. In turn, the clinician benefits from the clinical bootstrapping gene identification allows, with a rationalization of our understanding of the various syndromes and a fresh canvas on which to sketch out relations between genotype and phenotype.

PIGMENT GENES: GETTING MORE COMPLEX

Although often proposed as a research strategy, there is no *a priori* reason why genes involved in highly penetrant and rare disorders should underpin normal physiological variation. In the case of human pigmentation, however, this strategy has been remarkably successful, meaning that many of the genes involved in the highly penetrant disorders such as albinism have proven to be key determinants of physiological variation in skin, hair, and eye color in the general population. There are two practical implications of this. First, such loci contribute to variation in human skin disease, particularly human skin cancer. Hence, whereas red hair approximates to an autosomal recessive trait, variants of the responsible gene (*MC1R*) contribute to susceptibility to sun sensitivity, most notably to skin cancer risk (Smith *et al.*, 1998; Healy *et al.*, 2000). Perhaps the clearest example of this was work showing that particular *MC1R* alleles

were determinants of the age of onset of melanoma in families harboring *p16/CDKN2A* mutations (Box *et al.*, 2001), and other interactions between *MC1R* and *OCA2* on melanoma incidence (Duffy *et al.*, 2004). Whereas the Mendelian disorders allowed us to cleave nature at the joints, facilitating gene identification, what we learned could then be used to study that more subtle variations within the normal population.

Second, the availability of large-scale DNA analysis and genome-wide scans, together with our existing knowledge of the genes involved in pigmentation, has opened up the possibility for robust testing of theories of human evolution. Do we really believe most variation in human pigmentary characteristics is a result of selection, or could neutral change (drift) account for much of it? Is it just skin color that is being selected for, or are other characteristics such as hair color also important? Until the last two decades it was simply not possible to rigorously consider how we could test these theories. Coupling large-scale DNA analysis, knowledge of the many genes contributing to human pigmentation, and examination of diverse world populations through the Human Genome Diversity-CEPH Panel, has moved the study of human evolution from an almost historical science to an experimental one in a way few could have hoped for even in the mid 1980s (Voight *et al.*, 2006; Sabeti *et al.*, 2007; Pickrell *et al.*, 2009; Pritchard *et al.*, 2010; Hancock *et al.*, 2011).

It is of interest to ask why the study of pigmentation genetics has been so fruitful in comparison with the study of other complex traits, such as the inflammatory skin diseases. The importance of the mouse fancy cannot be overstated, allowing the detection of subtle and complex variation in coat color, with our eyes still arguably outperforming our biochemical or cell-based assays. Similarly, and with some pride to any dermatologist, our ability to notice subtle and myriad visual variations in form on human skin and hair easily outperform any machine-based assays. (Imagine a blind observer trying to work out the genetics of freckling based on measures of skin cancer rates.)

Human pigmentary characteristics have a high hereditability, and key physiological components of the system are either visible or easily demonstrable (i.e., erythema). Finally, we have a remarkably good understanding of many aspects of human pigmentary physiology—disorders such as albinism and vitiligo coupled with the historic geographic covariation of skin color and skin cancer afford a coherent view of the importance of pigmentation in the ecological relation between sun and skin color. And we know that this interaction between ourselves and the environment has been consistent over longer periods of time than we can safely say for infectious or inflammatory disease, where changes in our diet and social structures may have confounded the relation between our genetic history and modern phenotypes.

What of the future? It is clear that we have not identified all the genes involved in human pigmentary variation. We also do not have adequate quantitative models of how the known genes interact. Nor can we say with confidence that we really understand the fine details linking crude measures of skin color with sensitivity to the effects of ultraviolet radiation. What seems clear, however, is that ever more mining of our genome and how it relates to our pigmentary diversity across the earth will tell us more and more about the human story.

CONFLICT OF INTEREST

The author states no conflict of interest.

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REFERENCES

Box NF, Duffy DL, Chen W *et al.* (2001) MC1R genotype modifies risk of melanoma in families segregating CDKN2A mutations. *Am J Hum Genet* 69:765–73

Duffy DL, Box NF, Chen W *et al.* (2004) Interactive effects of MC1R and OCA2 on melanoma risk phenotypes. *Hum Mol Genet* 13:447–61

Flanagan N, Healy E, Ray A *et al.* (2000) Pleiotropic effects of the melanocortin 1 receptor (MC1R) gene on human pigmentation. *Hum Mol Genet* 9:2531–7

Giebel LB, Strunk KM, King RA *et al.* (1990) A frequent tyrosinase gene mutation in classic, tyrosinase-negative (type IA) oculocutaneous albinism. *Proc Natl Acad Sci USA* 87:3255–8

Giebel LB, Tripathi RK, Strunk KM *et al.* (1991) Tyrosinase gene mutations associated with type IB ("yellow") oculocutaneous albinism. *Am J Hum Genet* 48:1159–67

Hancock AM, Witonsky DB, Alkorta-Aranburu G *et al.* (2011) Adaptations to climate-mediated selective pressures in humans. *PLoS Genet* 7:e1001375

Healy E, Flannagan N, Ray A *et al.* (2000) Melanocortin-1-receptor gene and sun sensitivity in individuals without red hair. *Lancet* 355:1072–3

Lamason RL, Mohideen MA, Mest JR *et al.* (2005) SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science* 310:1782–6

Lamoreux ML, Delamas V, Larue L *et al.* (2010) *The Colors of Mice. A Model Genetic Network*. Wiley-Blackwell: Chichester, UK

Manga P, Kromberg JG, Box NF *et al.* (1997) Rufous oculocutaneous albinism in southern African Blacks is caused by mutations in the TYRP1 gene. *Am J Hum Genet* 61: 1095–101

Newton JM, Cohen-Barak O, Hagiwara N *et al.* (2001) Mutations in the human orthologue of the mouse underwhite gene (uw) underlie a new form of oculocutaneous albinism, OCA4. *Am J of Hum Genet* 69:981–8

Nordlund JJ, Boissy RE, Hearing VJ *et al.* (eds). (2006) *The Pigmentary System*. Mass, USA: Blackwell Publishing

Pickrell JK, Coop G, Novembre J *et al.* (2009) Signals of recent positive selection in a worldwide sample of human populations. *Genome Res* 19:826–37

Pritchard JK, Pickrell JK, Coop G (2010) The genetics of human adaptation: hard sweeps, soft sweeps, and polygenic adaptation. *Curr Biol* 20:R208–15

Rinchik EM, Bultman SJ, Horsthemke B *et al.* (1993) A gene for the mouse pink-eyed dilution locus and for human type II oculocutaneous albinism. *Nature* 361:72–6

Robbins LS, Nadeau JH, Johnson KR *et al.* (1993) Pigmentation phenotypes of variant extension locus alleles result from point mutations that alter MSH receptor function. *Cell* 72:827–34

Sabeti PC, Varilly P, Fry B *et al.* (2007) Genome-wide detection and characterization of positive selection in human populations. *Nature* 449:913–8

Smith R, Healy E, Siddiqui S *et al.* (1998) Melanocortin 1 receptor variants in an Irish population. *J Invest Dermatol* 111:119

Valverde P, Healy E, Jackson I *et al.* (1995) Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. *Nat Genet* 11:328

Voight BF, Kudaravalli S, Wen X *et al.* (2006) A map of recent positive selection in the human genome. *PLoS Biol* 4:e72