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Plenty New Under the Sun

Jonathan Rees[1]

Variation at the melanocortin 1 receptor (*MC1R*) is very common in most non-African world populations. A range of variants predispose to skin cancer, including melanoma. What remains unclear are the mechanisms linking gene variation with sun sensitivity or tumor risk. In particular, it remains unclear whether pigmentary effects of the *MC1R* can account for all of the increase in cancer risk.

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The modern study of the genetics of normal human pigmentary variation is just over ten years old (Rees, 2003). The field may not yet be mature, but there is a clear feeling that the first few chapters of this particular story can now be written: in broad outline we now know which genes account for most variation in human skin and hair color. The paper by Stratigos and colleagues (2006, this issue), in which melanocortin 1 receptor (*MC1R*) variants have been studied in relation to pigmentary phenotype and melanoma, is a welcome addition to the literature — welcome, because most previous studies of pigmentary genetics have concentrated on northern rather than southern European populations, and because the paper highlights some of the uncertainties in our understanding of the mechanisms by which *MC1R* variation affects phenotype.

The first modern study of the genetics of red hair was carried out almost a century ago by the Davenports at what was then the Carnegie Institute and is now famous worldwide as Cold Spring Harbor Laboratory (reviewed by Rees, 2003). The Davenports studied kindreds with red hair and suggested that the red-hair trait approximated to an autosomal recessive. They were right, although not all subsequent work came to the same conclusion. The next seminal advance, following a few unsuccessful attempts at mapping the red-hair trait in humans, came from the marriage of mouse and molecular genetics. The genes underlying a range of murine coat-color mutations were cloned, and within years the genetic bases for some rare mendelian pigmentary syndromes in humans were identified. One gene, the melanocortin 1 receptor, the subject of the study by Stratigos *et al.* (2006), was cloned in mice by Roger Cone's group in 1993 (Robbins *et al.*, 1993). Work in mice showed that signaling through this pathway led to an increase in the ratio of eumelanin to pheomelanin in hair (Robbins *et al.*, 1993). Conversely, the absence of, or a reduction in, signaling, whether due to mutation at the *mc1r* or absence of the ligand α-melanocyte-stimulating hormone, resulted in a relative overproduction of pheomelanin, leading to a yellow coat.

Shortly after Cone and colleagues' work in mice, it was reported that most red-haired persons harbored homozygous diminished-function alleles at the *MC1R* (Valverde *et al.*, 1995). The human *MC1R* codes for a 317-amino acid G-coupled receptor, and many non-African human populations show a striking degree of variation at this locus (Wong and Rees, 2005). Over 75 different *MC1R* alleles in humans have been identified (Wong and Rees, 2005), and Stratigos *et al.* (2006) show that even in a southern European population 38% of the control population shows *MC1R* variants. A striking feature of the *MC1R* is that a large number of the alleles appear to be quantitatively different in terms of function; that is, rather than all the alleles associated with red hair being complete loss-of-function alleles, they show varying degrees of signaling activity (Ringholm *et al.*, 2004). Given that there is evidence for a clear additive (or dosage) effect among 0, 1, and 2 variant alleles, a range of physiological activity can arise from a single locus. *MC1R* heterozygotes are intermediate for hair eumelanin and pheomelanin ratios, and those with different shades of red hair appear to differ at the *MC1R* (Naysmith *et al.*, 2004). Thus, although red hair approximates to an autosomal recessive trait, the more closely one studies the phenotype, the more subtle the relation between particular alleles and

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phenotype becomes. So if we ignore for one moment complex genetics (in which by definition the phenotype depends on many different loci), in the case of hair and skin color, nature can even fashion a graded series of responses from only one locus. That there are indeed many loci just adds to the richness of the system.

> The risk of melanoma could not be solely accounted for in terms of pigmentation.

Stratigos and colleagues (2006) examined the relation between *MC1R* and melanoma. Previous studies predominantly in northern European populations have shown that *MC1R* alleles are risk factors for most forms of skin cancer, including melanoma (Palmer *et al.*, 2000). An unresolved issue, however, is whether the mechanism of elevation of melanoma risk in those persons who harbor *MC1R* variants is solely accounted for in terms of pigmentation or whether alternative non-pigmentary pathways are involved. Indeed, in the study by Stratigos *et al.* (2006) the risk of melanoma could not be solely accounted for in terms of pigmentation. In other words, when pigmentation measures were factored into the regression equation, *MC1R* sequence was still a key explanatory variable. How can this be explained? First, α-melanocyte-stimulating hormone has a myriad of biological activities, and *MC1R* is expressed on a number of cell types other than melanoma. For instance, recent work has highlighted that the *MC1R* may be a key determinant of nociception (Mogil *et al.*, 2003). One popular view is that the association between *MC1R* and skin cancers is a result of inflammatory or immune mechanisms influencing tumorigenesis. It is suggested that such pathways are in addition to (or even instead of) the effects of *MC1R* on skin melanins. However, even the relation between *MC1R* and sun sensitivity is also far from clear. It has long been taught that persons with red hair, hair that is characterized by a relative increase in pheomelanin over eumelanin, show analogous changes in their skin. Work by Tony Thody in the 1990s challenged this view, and a recent larger study has suggested that pigment switching between eumelanin and pheomelanin may be less important than the total amounts of melanins (Hennessy *et al.*, 2005, and Thody, references therein). The mouse, and in particular follicular melanogenesis, may not therefore be a good guide to what is happening in the interfollicular skin. More studies in humans and better assays for melanin are needed.

Even though we may be uncertain as to the nature of the pathways linking *MC1R* with cancer risk, surprising though it may seem, it is still possible to assess the relative quantitative contributions of such alternative pathways. In a critical study, Dwyer and colleagues studied a group of patients with melanoma and control subjects, and, besides carrying out *MC1R* sequencing, they also assayed the pigmentary phenotype by measuring skin reflectance on the upper inner arm (Dwyer *et al.*, 2004). They then used a now fairly standard receiver operating characteristic (ROC) curve analysis to estimate how much information sequencing provided over and above that provided by skin color. They found that the additional information provided by *MC1R* was greater for basal-cell carcinoma than for melanoma, but even for basal-cell carcinoma the amount of information provided was modest. So, if age and sex could predict 42 of the 640 cases of basal-cell carcinoma expected in a cohort of 10,000 over 10 years, skin reflectance allowed prediction of a further 14 cases (56 in total), and adding in *MC1R* sequence would only add another two cases (58 in total). Why is this important to our interpretation of the data presented by Stratigos *et al.* (2006)? First, it suggests that any putative pathways linking *MC1R* variation and cancer risk (beyond skin color) are numerically small. Second, and of much greater importance, it serves to remind us that although we may identify and report modest odds ratios between genes and a disease state, in many instances we are perhaps an order of magnitude out in our ability to provide predictions of a future disease state that are meaningful for individual patients. So whereas our accumulating knowledge might gradually allow screening for melanoma to be considered, one has the feeling that there is a whole chunk of pigmentary biology that is still invisible to us. It seems, therefore, that some chapters of this particular story remain to be written.

CONFLICT OF INTEREST

The author states no conflict of interest.

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