

FINDING NEW LOW PENETRANCE MELANOMA PREDISPOSITION GENES: IS IT ALL ABOUT PIGMENTATION?

Nicholas K. Hayward¹

¹Queensland Institute of Medical Research, Brisbane, QLD 4029, Australia

Family studies have identified three high penetrance melanoma susceptibility genes, and several ongoing studies are attempting to find others. Until very recently, identification of low penetrance genes that contribute to melanoma risk in the general population was limited to candidate gene analyses. Arguably, with a single exception, all of the initial positive associations failed replication in independent samples. The one low penetrance melanoma gene that has been widely replicated across multiple populations is *MC1R*, which encodes the melanocortin 1 receptor. *MC1R* is highly polymorphic and variants have been associated with red hair colour and freckling, known melanoma risk phenotypes. These variants contribute, on average, about a two-fold increased risk of melanoma for each allele carried. Given the well documented association between lighter pigmentation and increased melanoma risk other genes that contribute to natural variation in colouring are logical candidates to test as melanoma predisposition loci. The recent advent of genome-wide association studies (GWASs) using high-density single nucleotide polymorphism (SNP) arrays has enabled unbiased assessment of association between all genes and a trait of interest. Some of the first of such studies were the analysis of genes underlying common pigmentation phenotypes¹⁻³. This has led to the identification of novel as well as many previously known pigmentation genes. Simultaneously, the first GWASs conducted for melanoma uncovered risk alleles at some of the same pigmentation loci^{4,5}. Strikingly, the strongest of these signals is at the *ASIP* locus, which encodes agouti signalling protein, a ligand for MC1R. While other highly ranked SNPs from these studies do not map to pigmentation loci, the obvious question to pose is how much of an individual's melanoma risk is determined by observable colouring phenotypes and the genes that underlie them?

1. Sulem et al, Nat Genet. 2007;39:1443-52.
2. Sulem et al, Nat Genet. 2008;40:835-7.
3. Han et al, PLoS Genet. 2008;4:e1000074.
4. Brown et al, Nat Genet. 2008;40:838-40.
5. Gudbjartsson et al, Nat Genet. 2008;40:886-91.