CANCER GENETICS

Pigmentation and skin-cancer risk

Pigmentation traits, including fair skin, red or blonde hair, blue or green eyes, and freckles, are known risk factors for skin cancer, owing in part to the ability of darker pigmentation to protect skin from the sun's damaging effects. Now, three studies in *Nature Genetics* provide fresh insights into the genetic factors underlying these effects, reporting that a subset of common variants associated with human pigmentation traits confer risk of cutaneous melanoma, basal cell carcinoma or both.

Building on their discovery last year of common variants associated with hair, eye and skin pigmentation traits in Europeans, Sulem *et al.* performed an expanded genome-wide association study for pigmentation-associated variants in 5,130 Icelanders, with replication in additional Icelandic and Dutch samples. They found robust evidence for association at two new loci: a haplotype near *ASIP* (agouti signalling protein) on chromosome 20q11.22 that is associated with red hair colour, freckling and skin sensitivity to sun; and two coding variants in *TPCN2* (two pore segment channel 2) that are associated with blond versus brown hair.

Gudbjartsson *et al.* then tested these and published pigmentation variants for association with cutaneous melanoma and basal cell carcinoma. Variants at two loci were found to be associated with risk of both forms of skin cancer: the *ASIP* haplotype described above, and a coding variant in *TYR* (tyrosinase) that was previously shown to be associated with eye colour variation and tanning response.

Independently, Brown *et al.* used a pooling strategy to perform a genome-wide scan for variants associated with melanoma susceptibility in samples from Australia. They discovered multiple variants on chromosome 20q11.22 that were associated with melanoma risk, refined the signal by genotyping 33 SNPs in a combined sample of 2,019 cases and 2,105 controls, and showed that the risk variants were preferentially associated with early-onset cases.

Notably, the 20q11.22 region highlighted in all three studies lies in the vicinity of *ASIP*, the product of which has a well-established role in pigmentation. However, as Brown *et al.* note, the peak of association resides several hundred kilobases away from *ASIP*, and the causal variants could, in principle, be mediating their effects through any of a number of genes in the region. Given the strong biological evidence implicating ASIP in the regulation of pigmentation, and the fact that variants in another component of the agouti pathway, *MC1R* (melanocortin 1 receptor), are associated with a similar range of traits, it is reasonable to hypothesize that the causal variants at chromosome 20q11.22 influence *ASIP* expression. Indeed, a precedent for such long-range effects is established for another pigmentation locus, *OCA2* (oculocutaneous albinism 2), in which variants located 200 kb away from the *OCA2* transcriptional start site regulate *OCA2* expression.

Although additional fine-mapping and expression studies will be needed to resolve the basis for the association at chromosome 20q11.22, the parallels between this locus and *MC1R* suggest that the smoking gun, once it is found, will incriminate *ASIP* as the culprit.

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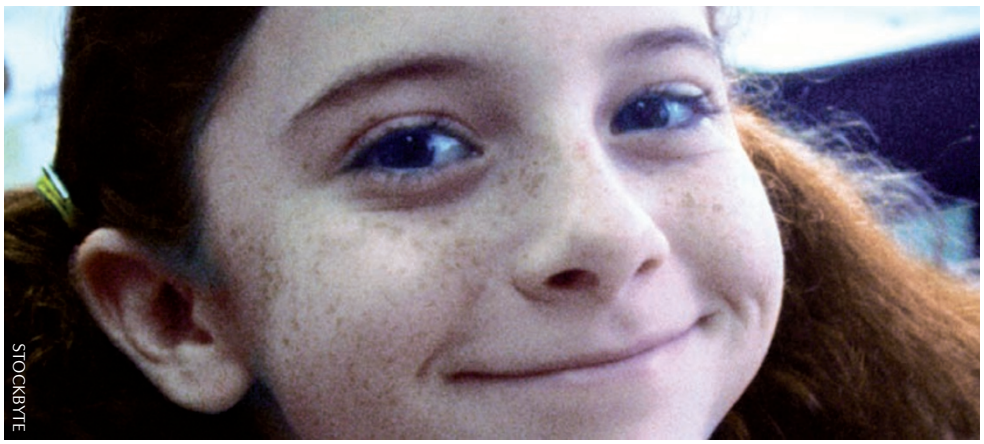

STOCKBYTE

ORIGINAL RESEARCH PAPERS Sulem, P. *et al.* Two newly identified genetic determinants of pigmentation in Europeans. *Nature Genet.* 18 May 2008 (doi:10.1038/ng.160) | Gudbjartsson, D. F. *et al.* *ASIP* and *TYR* pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. *Nature Genet.* 18 May 2008 (doi:10.1038/ng.161) | Brown, K. M. *et al.* Common sequence variants on 20q11.22 confer melanoma susceptibility. *Nature Genet.* 18 May 2008 (doi:10.1038/ng.163)

FURTHER READING Sulem, P. *et al.* Genetic determinants of hair, eye and skin pigmentation in Europeans. *Nature Genet.* **39**, 1443–1452 (2007)