of disruption to HH signalling, thus modulating the extent of biological response, which is reflected in the malignant phenotype.

It is also clear that the genetic background in which the HH signalling pathway is perturbed will influence tumour development. Thus there will be genes that will effect susceptibility or modify the severity of the phenotype. This is highlighted in studies where $PTCH^{-/+}$ mice crossed with a carcinogenesis-resistant strain developed significantly fewer BCC than those crossed with a carcinogenesis-sensitive strain.[13] Accumulating studies demonstrate that polymorphism within genes associated with handling the results of exposure to UV, such as reactive oxygen species (GST, CYP450) or DNA repair (XPD), are significantly associated with risk of BCC development.[8]

Therefore, it is possible that the extent of disruption to HH signalling and the genetic background in which this disruption occurs may influence subsequent genetic events that lead to tumour progression in BCC. The challenge for the future lies in identifying those other loci involved in BCC development. For example, the tumour suppressor gene p53 has long been implicated in BCC development but its involvement in relation to hedgehog signalling and the phenotypic diversity observed in BCC has not been adequately studied.[8] The advance of methodologies for studying global genomic events such as the use of SNP microarrays described by the Teh et al and the development of high throughput sequencing and genotyping technologies should aid in this search. Further, the establish-

ment of national blood/tumour banks such as the Biobank project (http://www.ukbiobank.ac.uk/) should help in the study of correlating genetic events with the diversity of patient phenotype often observed. Collectively these data might help to rationalise the use of mechanism-based therapies in this and other heterogeneous diseases ■

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Pigmentary Diversity

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Identifying the genes causing human diversity

Ian J Jackson

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The genetic basis of variation in skin pigmentation between people of African, Asian and European origins has only recently come under study, and is far from being fully understood. Recent work indicates that variation in a gene of the solute channel family, *SLC24A5*, may be one of the major causes of skin colour differences between European and non-European populations.[1] The conservation of linked variants around the locus in Europeans indicates

that this variant swept rapidly, under selection, though the population.

Casual observation of individuals in admixed populations, or of multiethnic parentage, would suggest that the genetics of normal skin pigmentation is not simple. It is clearly multigenic and the genes appear additive, rather than dominant, in their effects. The difference between dark and light skin is not simply one of amount of melanin pigment, but also of ultrastructure of the melanosomes, which are the melanocyte organelles within which melanin is synthesised and exported to neighbouring keratinocytes.

Why do different populations have different skin colour? It is assumed that there has been selection for colour, but what was the selective agent? There is a broad correlation between skin lightness and latitude; the further north, the paler the skin. This correlates reasonably well with UV incidence, which is lower at higher latitudes. At high-UV locations, nearer to the equator, the most likely selection pressure is sunburn and skin cancer. Melanin acts as an effective sunscreen, protecting dark-skinned individuals from burning (which probably was a powerful selection in itself in hunter-gatherer society) which consequently protects against skin cancer. However, the nature of selection that acted to produce lighter skin as early humans migrated from Africa, and even lighter skin as they moved into Europe, is controversial. The vitamin D hypothesis, first put forward 70 + years ago, is well known, and cites rickets as the selective agent.[2] Vitamin D is synthesised in skin through the action of UV, and there is much data showing variation of circulating vitamin D according to sun exposure. There are also certain groups, such as Asians in Northern Europe, who have in the past suffered the vitamin D-deficient bone disease, rickets, apparently because of inadequate UV. Some have made strong arguments against the vitamin D hypothesis[3] but there is no convincing alternative at the moment.

Evidence for selection acting to maintain dark skin in African populations came from the *MC1R* gene. Variants of this gene are very common in Europeans, where in some populations, the majority of alleles are functionally impaired variants. Two variant alleles normally results in red hair and skin that has a greater susceptibility to UV burning. Even a single variant allele results in skin that is at greater risk from UV.[4] By contrast, in Africans the gene is highly invariant, quite unlike most other genes in the African population, which usually show greater diversity than in Europe. This is clear evidence of selection to maintain function.[5] It is less clear whether there has been selection for functional variants in Europe; much of the data are consistent with neutrality, allowing the sequence to drift, rather than positive selection.

The *SLC24A5* gene, on the other hand, shows strong evidence of powerful selection in Europe. This gene was isolated from zebrafish as the gene affected by the *golden* series of mutations. Fish homozygous for *golden* have reduced pigmentation and smaller, irregular melanosomes. Genetic crosses followed by transgenic rescue and sequence analysis identified *slc24a5* as the mutant gene.[1] This encodes a member of the large family of solute carrier proteins, which transport a wide range of molecules across cell membranes, and many of which are mutated in human diseases. The SLC24 subfamily are potassium-dependent sodium/calcium exchange proteins.

SLC24A5 has a striking pattern of variation in human populations. A coding variant in the gene has previously been described as one of a set of ancestry-informative markers. The ancestral form encodes alanine at residue 111, whereas a derived allele encodes threonine. Alanine is present at this position in all known members of the SLC24 subfamily of proteins, suggesting the change to threonine has functional consequences. The derived variant is universally present on all European chromosomes analysed, while chromosomes of African and Asian origin almost invariably carry the ancestral form. The population difference puts this variant in the top 0.01% of all variants studied. Furthermore, analysis of the HapMap Consortium data[6] found that *SLC24A5* was within a chromosomal region that has a striking reduction of heterozygosity of SNPs in the European population. In fact, at 150 kb it is the longest such segment identified in the genome.[1] Such a long conserved homozygous haplotype indicates that there has been strong selection on a gene or genes, which has swept this segment across the population, and selection for homozygosity eliminated recombination between SNPs, which maintained a long haplotype.

Excellent evidence that the genetic variant really does affect pigmentation comes from examining admixed populations such as African-American and African-Caribbean populations in which there has been a historic introduction of European alleles into a largely African gene pool. These populations have previously been studied and some of the variation in skin pigmentation is associated with variation in two known pigmentation genes *TYR* and *OCA2*.[7] The impact of the European, Thr111, variant in the admixed population is considerable. Homozygosity for this variant appears to contribute between a quarter to one-third of the pigmentation difference between European and African skin type.[1] However, it should be borne in mind that the numbers of individuals in the admixed population who are homozygous for Thr111 is relatively small (about 7%) and there is, of course, considerable overlap in the distributions.

Another solute channel gene *SLC45A2*, or *MATP*, which is affected in human, mouse and fish pigmentary mutants, also shows strong association with ethnic ancestry. More than 90% of European chromosomes have a derived allele which is rare or absent in Africans. The small number of people of European descent with the ancestral form of the gene appear to have significantly more pigmented skin[8] and there is clear evidence for a selective sweep of the chromosomal segment around the *SLC45A2* in the European population.[9]

In summary, combining good phenotyping with genetic analysis of large, multiethnic populations is beginning to shed light on how evolution has shaped the diversity of the human race. Coupled with genetics of model organisms and human diseases we are now able to identify individual genes that contribute to human diversity ∎

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