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Skin-deep

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The colour of human skin has been – and still frequently is – at the heart of violent controversy. Political, social and physical. Yet, as the science of human genetics unfolds, we are reminded over and over again that any given human population cannot be defined according to its pigmentation since any skin hue blends gradually into another. However, there is no doubt that there are dark skins, and there are light ones. The darkness – as the lightness – of skin depends on the amount of melanin present in the epidermal cells. And the amount of melanin depends directly – though not solely – on the existence of a protein that has been christened 'solute carrier family 24 member 5' or 'SLC24A5'.

The Immigrants, Sue Jarvis

Scientists have been searching for genes which have a direct influence on skin pigmentation for over a century. Though many involved in various forms of human albinism[1] have been discovered – and over one hundred involved in the coat colours of model organisms such as mice – to date no one had found one gene that had a direct effect on skin colour. The colour of our skin depends on the amount of the pigment melanin present in our epidermal cells. The pigment is found in organelles known as melanosomes, which in turn are found in melanin-producing cells: the melanocytes. Epidermal melanocytes use dendritic protuberances to fire melanosomes into our skin cells, or keratinocytes. And it is the concentration of these skin cell melanosomes which will lend a dark or not so dark hue to the bearer.

Is there a biological advantage in owning a dark skin, or a light skin? Melanin-rich skins – i.e. dark skins – have a greater protection against the sun's harmful ultraviolet rays than melanin-poor skins do. Which is the reason why darker skins are found where the sun hits most. Melanosomes in darker skins actually cap the nucleus of skin cells, thereby protecting the cell's DNA from UV irradiation. On the other hand, a lighter skin – that would be found in the more Northern latitudes – is needed to let sufficient ultraviolet rays through to synthesize vitamin D, which is important for bone growth.

SLC24A5 was discovered in the zebrafish while searching for genes involved in skin cancer. Zebrafish are small freshwater fish found in India and Burma. They have been part of laboratory research since the 1970s because – besides being vertebrates like us – their epidermis and their eggs are transparent, and embryonic development can be observed and tinkered with at every stage. Likewise, even melanocytes and their melanosomes are visible to the naked eye. Whilst dabbling with zebrafish DNA, scientists observed a mutation which turned the zebra-like scale pattern of the fish into a smooth golden one, and the mutation was subsequently named the 'golden gene'. The scientists then turned to humans to see whether

[1] See Spotlight issue August 2004

our genome embraced the same gene. And it does. Moreover, it is so similar that the human version can actually be engineered into the golden zebrafish to give it back its original stripy appearance, proving that SLC24A5 has a direct influence on pigmentation.

Dark skins are loaded with melanin, whilst white skins are not. From an ultrastructural point of view, this means that there are fewer and smaller melanosomes per melanocyte in light skins. What decides on a melanosome's morphology and its melanin content in the first place? SLC24A5 seems to have a pivotal role in melanosome morphogenesis as well as melanin synthesis. The protein is probably an ion exchanger lodged in the melanosome membrane, where it is involved in calcium transport. Calcium is used in the process of melanosome maturation. And if its uptake is lessened, melanosomes present a lower content of melanin, giving skin a paler shade of brown.

So what is the difference observed between a Scotsman and a Nigerian in terms of SLC24A5? One amino acid. Threonine replaces alanine at position 111 in the human sequence. And it is this difference which results in a shift in skin colour. 'White-skin' SLC24A5 probably causes the melanosomes to be not only fewer but also smaller in size, and melanin synthesis is suppressed – all because of a change in calcium transport. The exciting discovery is that the light-skin version of SLC24A5 is found in Europeans, whilst the dark-skin version is found in Africans. What is more, populations that are a mixture of white and black 'blood' – such as the African-American and the African-Caribbean populations – share a mixture of the two versions of SLC24A5. In fact, SLC24A5 accounts for 25 to 38% of the European-African skin melanin index.

Everything seems to fit in very nicely. However, light-skinned East Asians share the same version of SLC24A5 as dark-skinned Africans – which only goes to show that SLC24A5 is part of a far more complex molecular pathway. Like all biological processes. Skin pigmentation cannot be reduced to the doings of one sole protein. Melanin-pigment abnormalities – such as skin cancer or some forms of albinism – should benefit from research on genes such as SLC24A5 which could become a novel target in biotechnology. But one of the most interesting aspects of SLC24A5 is the discovery of a gene that sheds a brighter light upon our past and on how our ancestors sauntered from one continent to another.

Cross-references to Swiss-Prot

Golden protein, *Brachydanio rerio* (Zebrafish) : Q49SH1
Solute carrier family 24 member 5, *Homo sapiens* (Human): Q71RS6

References

1. Lamason R.L., Mohideen M.-A..P.K., Mest J.R., Wong A.C., Norton H.L., Aros M.C., Jurynec M.J., Mao X., Humphreville V.R., Humbert J.E., Sinha S., Moore J.L., Jagadeeswaran P., Zhao W., Ning G., Makalowska I., McKeigue P.M., O'Donnell D., Kittles R., Parra E.J., Mangini N.J., Grunwald D.J., Shriver M.D., Canfield V.A., Cheng K.C.
SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans
Science 310:1782-1786(2005)
PMID: 16357253

2. Sturm R.
A golden age of human pigmentation genetics
Trends Genet. 22:464-468(2006)
PMID: 16857289

3. Müller J., Kelsh R.N.
A golden clue to human skin colour variation
Bioessays 28:578-582(2006)
PMID: 16700060

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