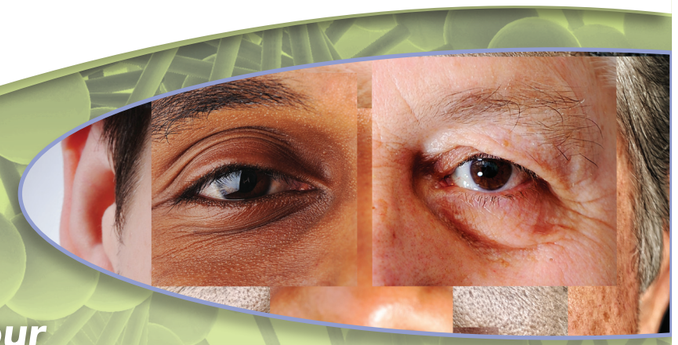
PUBLIC UNDERSTANDING OF BIOTECHNOLOGY



Genetics of Skin Colour

Background

Skin colour is one of the most noticeable of all human physical characteristics. Because the variation between people is so striking, it is not surprising that it has caused much interest and controversy. The colour of human skin is influenced by both internal and external factors but is primarily due to pigments, the most important of which is melanin, produced in the body. The colour of our skin, hair and eyes is controlled by inherited genes.

What causes differences in skin colour?

The skin is made up of cells which have the basic structure of a nucleus, which contains the genes, surrounded by cytoplasm, which has a different composition depending on the cell type. The top layers of the skin are called the epidermis and stratum corneum (or "horny layer"). The epidermis is made up of several layers of living cells (keratinocytes). These cells grow from the bottom layer and flatten, becoming specialised as they move to the surface. They eventually become packages of keratin held together by intervening layers of lipid in the stratum corneum from where they are continuously shed as scale. On this journey, which takes an individual cell about 28 days, it loses its nucleus which stores its genetic material or DNA.

The skin pigment, melanin, is made in cells called melanocytes that remain at the base of the epidermis. Melanin is made and packaged into tiny bundles called melanosomes, which are transferred to keratinocytes, via the melanocyte's arm-like projections (Fig 1). These melanosome particles give protection to the DNA against ultraviolet (UV) rays from the sun. It is this melanin inside the keratinocytes which is mainly responsible for the colour of an individual's skin. When epidermal cells travel towards the skin's surface, they carry their melanin with them, and it remains even after the nucleus is lost.

Amazingly, the palette of human skin colour, famously described in South Africa as the Rainbow Nation, is the result of variations in the packaging and type of melanin produced. People generally have the same number of melanocytes irrespective of their skin colour; but those with black/brown skin have melanosomes that are large, contain more concentrated melanin and are arranged individually, compared to paler skinned people who have smaller melanosomes, with less melanin, which are grouped together in a membrane structure.

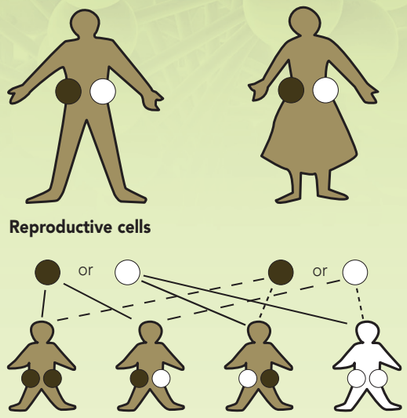
Melanocytes are factories for melanin production, which is a complex process involving many different stages. Two types of melanin are produced, namely eumelanin which is a dark brown/black pigment and pheomelanin which is a lighter reddish/yellow pigment. Changes in the amount of each pigment produced is under genetic control and the ratio of eu- to pheo-melanin is responsible for variations in both skin and hair colour. Thus the melanocytes of pale-skinned redheads produce lots of pheomelanin, whilst those of people with a range of skin colours from "beige" to "black" and with hair from blonde to brown to black produce more eumelanin than pheomelanin.

A striking variation in skin colour is seen in people with albinism; here small genetic changes that cause an interruption in any one of the many steps that control melanin production result in failure to produce the pigment and the person has extremely pale skin.

What does melanin do?

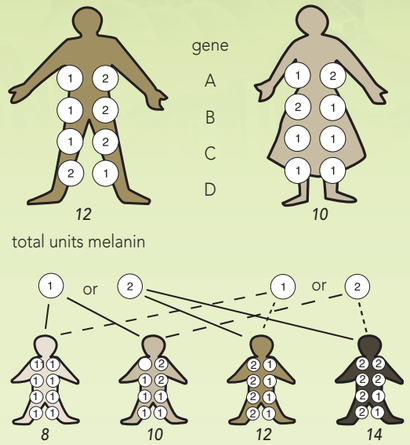
Melanin is found in the skin, hair, eyes, lining of the brain, inner ear, and brain stem. In the skin, melanin acts as a sunscreen to protect the skin from the harmful effects of sunlight. The harmful rays of invisible light, UV light, can be divided into UVA, B and C. As little UVC reaches the earth surface, it is UVA and UVB that cause damage to the skin. It is not only the sun's rays that damage the skin, any UV light exposure, including that of sun beds used for salon and home tanning, is just as damaging. Melanin protects the skin from this damage by scattering and absorbing some of the UV energy. In the absence of melanin, UV energy penetrates the skin where it can cause damage to the DNA in the nucleus of the still living epidermal cells. This damage can be spontaneously fixed by the cell's repair machinery. Un-repaired, accumulated damage can cause cells to multiply uncontrollably, resulting in skin cancers. The amount of UV exposure over a life time, as well the shade of skin colour, influence the chance of developing skin cancers. People with skin in which there is little or no eumelanin, or

Fig 3a
Monogenic Inheritance - Albinism one gene



Albinism is a monogenic trait, it follows a Mendelian pattern of recessive inheritance under the control of a single primary gene. The parents (albinism carriers) both carry a gene variant that prevents melanin production; as they each also have a melanin-producing variant, they have pigmented skin. Depending on which variant their children inherit from each parent, they will be non-carriers, carriers or have no skin pigment (albino).

Fig 3 b
Polygenic Inheritance - Normal skin colour variation -many genes



Normal skin colour is a polygenic trait, following a multi-factorial pattern of inheritance under the control of an interacting set of genes and environmental influences, eg,skin darkening (tanning) induced by sunlight. In this representation, variant 2 of each gene results in more pigment, so the more 2s a person has, the darker their skin shade (represented by total melanin units under each person). Consequently, children may have a lighter or darker skin shade than either of their parents (as was the case with Sandra Laing). Note: only four sets of genes, with apportioning and recombining of gene variants at only one of these, are shown. It is believed that more than 20 genes affect skin colour in humans.

additively conferred more melanin units to her skin than her parents' own combinations and she was classified as "coloured". These gene variants were passed down by her parents even though they were not apparent in them.

Predicting complex human traits from genetic studies of an individual's DNA underlies the widely advocated concept of targeted or personalised medicine. Predicting externally visible characteristics, including skin, hair and eye colour from DNA has important forensic implications. This information can be used, backed-up by legislation, to provide identifiable characteristics of perpetrators from DNA recovered from a crime scene. Such technology will also permit investigation on archeological material allowing for better understanding of the history of skin colour selection pressures and when and where they occurred. Skin colour prediction is currently difficult but eye colour prediction is already approved for forensic use in the Netherlands.

In conclusion, human skin colour is controlled by the complex interplay of many different genetic variants, many of which control production and cellular arrangement of melanin; which have been molded by the environment and selection pressures in different regions of the world over thousands of years. Thus skin colour does indeed have a biologic or genetic basis. The notion of race is a discriminatory socio-political concept which cannot be scientifically assigned based on skin colour. The Sarah Laing story should serve as a tragic reminder of the futility of racial classification and prevent the use of DNA profiling from straying into discriminatory practices.

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which predominantly contains pheomelanin, are at increased risk of developing skin cancers. Thus people with albinism or very pale skin generally suffer sunburn easily, even without tanning, when exposed to the sun and are at greatest risk.

However the presence of melanin is not sufficient protection against sun-induced skin damage. Patients born with normal melanin containing skin but carrying mutations in the genes that are responsible for the cellular DNA repair mechanisms develop aggressive, disfiguring skin cancers at a very early age. This occurs in people with all skin types including those with normal dark skin. This is in sharp contrast to people with albinism who lack melanin yet only develop their cancers much later in life (Fig 2)..

Why different skin colours in different parts of the world?

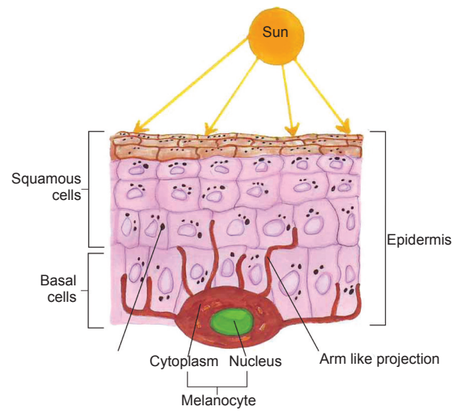
The prevailing scientific view of the origin of modern man is the "Out of Africa" theory, which proposes that the rest of the world has been populated by the descendents of independent waves of small clans of humans who migrated from Africa within the last 100 000 years. It is postulated that the ancestral skin colour of these early humans was dark brown. Thus changes in skin colour with selection for paler skin types occurred following the dispersion out of Africa of early populations into different latitudes globally, giving rise to the many shades of skin colour present today.

It is known that in pale skinned people, UV light can cause sunburn and damage the genetic material in skin cells and induce skin cancer. Because most sun induced skin cancers develop well past the reproductive age in people older than 50 years, skin cancer and protection from sunburn are unlikely to have been significant evolutionary factors for the natural selection of ancestral skin colour.

Nina Jablonski and George Chaplin noted that in areas where UV radiation was highest, people's skins were darkest and vice versa. They and others have suggested that UV exposure does not only induce skin cancer but has other consequences which may have contributed to the development of skin colour variation over long periods of time. Two plausible hypotheses have been explored. Firstly, UV rays are also known to break down folate (vitamin B6) in the blood vessels just beneath the skin. Folate is essential for dividing cells and therefore the developing foetus is most vulnerable to the effects of low folate levels. A shortage of folate can result in abnormalities of the spine and brain of the baby which is why pregnant women are advised to take folate supplements. It is thought that melanin offers protection from UV-induced folate damage in the same way that it lessens DNA damage. Thus individuals with a paler skin living in areas of high UV radiation, for example within the tropics, would be less likely to reproduce successfully and would have fewer descendents over a long period of time. Secondly, sunlight UV radiation is needed to form vitamin D in the skin. This vitamin is essential for processing calcium, needed for making strong bones and for healthy pregnancies. Shortage of calcium, especially early in life, causes children to develop weak bones (a disease called rickets); and can reduce survival and hence the number of descendents who will contribute to future generation. So dark

Fig 1

The brick wall-like structure of epidermal cells and their relationship to a melanocyte which has arm-like projections that transfer melanosomes (containing melanin) to adjacent cells. More melanin is deposited on the side of the cell closest to the rays of the sun (thus, protect the nucleus like an umbrella). Note that as cells move toward the surface they flatten eventually losing their nucleus before being shed.



eumelanin-enriched skin reduces UV penetration and thus limits the ability of the skin to make vitamin D. In countries at higher latitudes with reduced amounts of UV light, vitamin D production is likely to be less efficient in individuals with dark skin.

Thus, it is reasoned that, originally, it was advantageous for people living in regions with high UV radiation to have dark skins, which protected them from folate damage, while still allowing formation of enough vitamin D. This is known as natural "selection pressure", a phenomenon that occurs over many generations and in this case refers to the preferential survival of dark skinned descendants resulting in a predominantly dark skinned population in areas of high UV radiation. But, as these ancestral people moved into regions with lower UV radiation, the high melanin content in their skin reduced UV-mediated vitamin D synthesis and strong bone formation. A situation therefore arose where the selection pressure was in favour of reducing the amount of melanin, resulting in the preferential survival of pale skinned descendants. The outcome of these selective pressures is that as people moved and settled in regions of the world with different amounts of UV radiation, the colour of their skin would

Fig 2

Two children of equal age from Africa, one with albinism and the other with xeroderma pigmentosa.The former has no melanin and no skin cancer; the latter has eumelanin but already has skin cancer.

have to adapt and strike a balance between being dark enough to limit sun destruction of folate and light enough to allow vitamin D production and calcium absorption. Voluntary or forced migrations in recent years have seen people move to areas where there is a solar and hence UV light mismatch relative to their skin colours. This poses a potential health risk for future generations because of the consequent imbalances in vitamin D and folate metabolism.

In contrast to this fitness selection advantage proposed for skin colour, it is more difficult to explain eye and hair colour variations by the same genetic adaptation. There is currently no direct evidence on when colour variations of skin, hair and eye arose from the ancestral type..

What about skin colour genes?

Melanin is made in melanocytes in a complex multi-step "assembly line", which is under the control of many different genes. Genes are the units of inheritance that carry the code that determines the body's components and are responsible for giving us our recognisable characteristics. Genes are made of DNA and are carried on paired chromosomes in the cell's nucleus, one member of each pair contributed from our mother's egg and the other from our father's sperm. One couple can therefore have children who have many different combinations of genes, depending on how these are apportioned in the sperm and egg cells and paired at conception. Small differences, called variants, in individual genes of each pair can give rise to different outcomes, for example, skin colour.

The inheritance of genetic variation is easier to follow when only one pair of genes affects a characteristic, for example in albinism (monogenic inheritance), and one can predict the likely outcome (Fig 3A). However, when scores of genes are involved in producing the final products, for example eu- and pheo-melanin2 which account for shades of skin colour (polygenic inheritance), it is much harder to predict what the outcome will be (Fig 3B). Thus, depending on the combinations and underlying genetic variation in the gene pairs following conception, a spectrum of skin colours may be seen between parents and their individual children.

While molecular and genetic studies have shown a variety of changes in many genes associated with skin colour variations, it is important to prove that they function to produce that particular variation. Currently, research suggests that functional variants in more than twenty known genes determine human skin colour. Their products are nearly all involved in stages of melanin production, some variants specified by a particular gene encourage the production of more melanin, others switch the ratio of eu- to pheo-melanin or alter packaging of melanin into melanosomes. Multiple genes determine skin colour but it is an unusual form of polygenic inheritance compared to traits such as body height because it follows a semi-monogenic inheritance pattern where a major gene effect predominates. For example, a variant of the human equivalent of the zebra fish gene accounts for up to 30% of the difference in melanin-determined skin colour between Europeans and Africans.

Particular variants in the many genes determining skin colour are found more commonly in certain populations, reflecting past selection pressures; for example, almost 100% of pale skinned Europeans have the same variant of the SLC24A5 gene, thought to have become prevalent in this population group about 6 000 years ago, while this variant is virtually absent in African and Asian populations. Such underlying genetic homogeneity explains why children generally have a similar skin tone as their parents. In contrast, if there is underlying genetic heterogeneity, for example, resulting from recent admixture of population groups, children may inherit different combinations of particular variants from their two parents. This explains why skin colour in children of one set of parents, each with visibly different amounts of melanin ("black" or "white"), can range from very pale to very dark.

Thus, masked variants of genes in very pale skinned parents can be rearranged and combined to produce a much darker skinned child, as was the case in the tragic story of Sandra Laing who was born to "white" parents in apartheid South Africa. She inherited a set of skin colour-determining gene variants that