Human Adaptation

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ABSTRACT

Following the success of the Human Genome Project, the subject of human variation and the adaptation of human populations to their environments has continued to attract substantial research interest. However, there also is ongoing controversy as to whether or not improved biological fitness via genetic selection should be regarded as the essential component of adaptation/adaptability, or equivalent weights should be given to physiological and cultural attributes. The profile and inheritance of skin colour-determining genes such as *ASIP* and *OCA2* in different human populations illustrate contrasting aspects of this issue. The implications and outcomes of adaptation under differing environmental settings are assessed in biological and cultural terms, with particular focus on four skin pigment-associated pathologies: skin cancers and melanoma, nutritional rickets in childhood, age-related osteomalacia, and oculocutaneous albinism.

1. INTRODUCTION

The study of human adaptability/adaptation has a long and distinguished tradition in the disciplines of Physical and Biological Anthropology and Human Biology, and formed a core topic of the International Biological Programme (IBP) which ran from 1964 to 1974. Within the 53 sub-themes of the IBP Human Adaptability programme, an estimated 800 expeditions and field visits were conducted on some 1.25 million individuals, with the theme 'Genetic Constitution' accounting for 23% of all investigations [1].

While these initial studies into human adaptation were largely influenced by the concept of Darwinian selection of specific gene variants, such as sickle cell trait [2], the development of Sociobiology during the 1970s and 1980s led to the roles of physiological or developmental adaptation and cultural adaptation being increasingly emphasized [3,4]. This change in emphasis resulted in the proposal that 'An adaptation can be considered as any characteristic of an organism that increases its fitness' [3].

Skin pigmentation studies provide a good framework for this inter-disciplinary approach to human adaptation, and as part of the IBP skin colour measurements were conducted in a wide range of populations from the Andes to the Arctic and the tropical Solomon Islands. However, in the wake of the Human Genome Project, most recent studies into skin colour variation have once again concentrated on the underlying role of genes, and to date 24 human pigmentation genes have been identified, dispersed across the human genome on chromosomes 2,3,5,6,9,11,12,13,15,20,22 [5].

2. THE PRIMARY BIOLOGICAL ROLE OF HUMAN SKIN PIGMENTATION

2.1 Skin colour and latitude

Anthropological studies have indicated that among indigenous populations, skin reflectance and hence dark skin colour is lowest at the Equator. In the Northern hemisphere an increase in skin reflectance of approximately 8.2% for every 10 degrees of altitude is observed for males and 8.1% for females. Comparable data for the Southern hemisphere are 3.3% for males and 4.7% for females, therefore suggesting higher UV radiation and darker skin colours at equivalent latitudes south of the Equator [6].

2.2 The nature and biological role of skin pigmentation

Skin colour is determined by the pigment melanin, which protects against potential mutational damage caused by ultra-violet (UV) radiation. Activation of the melanocortin-1 receptor (MC1R) promotes melanin production in the melanosomes in the dermis, with MATP and P proteins additionally contributing to pigment synthesis [7]. Melanosome size differs in individuals with dark, intermediate or light skins, and the melanosomes of dark skin also are more widely dispersed [7].

The level of UV protection afforded to an individual is proportional to the concentration of melanin in the dermis. In general, less melanin is required in the skin of individuals living at higher latitudes because of the lower levels of UV radiation they encounter in everyday life. However, exceptions do occur, for example, among peoples living in mountainous regions with consequent greater UV exposure.

3. SELECTION AGAINST SKIN PIGMENTATION

3.1 Recent negative selection pressures on human pigmentation genes

Single nucleotide polymorphism (SNP) studies on DNA samples from volunteers of sub-Saharan African, East Asian and European ancestry have identified recent positive selection at human pigmentation gene loci. In one such study based on ~800,000 SNPs, European skin colour was identified as subject to ongoing adaptive evolution, along with genes involved in fertility and reproduction, skeletal development, brain development and function, MHC-mediated immunity, and components of the electron transport chain [8]. By comparison, a similarly organized study using ~1.2 million SNPs identified 101 regions of the human genome, among them genes encoding pigmentation pathways, where a recent selective sweep had taken place and the genes had attained a frequency of ~100%, i.e., fixation of these mutations had occurred [9]. The question that arises is why such selection should have arisen, and specifically with respect to pigmentation genes, the nature of the advantages and disadvantages that have accrued?

3.2 Sunlight and Vitamin D synthesis

Although skin pigmentation is needed for protection against UV radiation in regions with high background UV levels, vitamin D synthesis is dependent on adequate exposure of 7-dehydrocholesterol in the skin to the UV component of sunlight. Where dietary vitamin D levels are marginal, melanin can prevent UV penetration and impede the activation of vitamin D, which is required for normal skeletal development and maintenance. Under these circumstances, it would be expected that mutations resulting in lighter skin colouration would be subject to positive mutation [10,11].

3.3 Inter-ethnic differences in skin colour gene profiles

The Out of Africa movement of humans predominantly involved migration to regions north of the Equator where, as previously indicated, UV radiation effects are lower than at equivalent southern latitudes [6]. As illustrated in Table 1, some genes appear to influence skin pigmentation in all human populations, whereas ancestry-specific genes have been described in African, European, South Asian and East Asian populations [12-15].

Table 1: The geographical distribution of skin pigmentation genes [5,12-15]

Genes	Populations
ASIP, OCA2, TYR	World-wide
ADTB3A	Africans
ASIP, SLC24A4, SLC24A5, IRF4, MATP	Europeans
SLC24A5, SLC45A2	South Asians
DCT	East Asians

The evidence to date suggests that the lightening of skin colour observed in Europeans and East Asians has resulted not from the expression of the same genes but via convergent evolution, enabling more efficient vitamin D mobilization from the diet in both ancestry groups [12].

4. SKIN PIGMENTATION DISORDERS

Four major skin pigment-associated pathologies affecting human populations can be identified:

4.1 Skin cancers and melanoma

There are three major types of human skin cancers: i) basal cell carcinoma, which is the most common form of human skin neoplasm and mainly affects people over 40 years of age; ii) squamous cell carcinoma in which cells in the surface epithelium develop into a malignant tumour; and iii) melanoma, which most frequently is associated with episodic sunburn and has a high risk of metastasis.

Within populations of European ancestry the incidence of cutaneous (malignant) melanoma has been doubling approximately every 10 years, with ~10% of cases familial. In part this reflects the changed lifestyle of many European and North American populations, with vacations taken in Mediterranean countries and tropical climates in which UV radiation levels are high. However, in Australia where a large majority of the non-indigenous population originated in north-west Europe, everyday exposure to high UV radiation is the major cause for the high rates of non-melanoma skin cancers [16-18].

Some 380,000 skin cancer cases are treated in Australia each year, representing 1.8% of the national population, and skin cancers are responsible for >80% of all new cancers. Melanoma is now the third most common cancer in men (after prostate cancer and bowel cancer) and in women (after breast cancer and bowel cancer), with >1,600 deaths per year [16-18].

Susceptibility to malignant melanoma is associated with a variety of genes located on different chromosomes, including the pigmentation genes *MC1R* (melanocortin 1 receptor), *OCA2* (oculocutaneous albinism 2), *ASIP* (agouti

signalling protein) and *TYR* (tyrosinase) [19,20]. Two additional highly penetrant melanoma-predisposing genes recently have been described, *CDKN2A* and *CDK4*, and a genome-wide study has indicated a melanoma risk locus on chromosome 20q11.22 in early-onset cases of the disease [21].

4.2 Nutritional rickets in childhood

As noted in section 3.2, vitamin D is mainly synthesized via the action of sunlight. Childhood rickets, which was common in urban Europe and North America in the 19th and early 20th centuries, is caused by hypovitaminosis D, which in turn results from inadequate diet and the poor environmental living conditions that prevailed in countries undergoing industrialization [22,23].

Nutritional rickets was reported in U.K. South Asian children in the 1970s, with the most severe cases observed among Hindu children on a strict vegetarian diet, including a high intake of *chappatti* (unleavened bread) [24]. Subsequent research has indicated that this problem has persisted in the U.K. [25-27], and even in Australia with a high level of intense sunlight, immigrant Asian and African children are at increased risk of rickets [28].

In the U.K. an estimated 94% of otherwise healthy adult Pakistani females were found to be vitamin D-deficient, and similar low vitamin D levels have been described in Pakistani women resident in Norway [29,30]. Pakistani mothers with low 25-hydroxy vitamin D3 levels had smaller babies, indicating poorer fetal growth because of lower serum calcium and phosphate, and secondary hypothyroidism due to elevated serum parathyroid hormone (PTH) levels [30].

It appears that this problem is much more widespread than previously suspected. For example, low vitamin D levels have been observed among Muslim Bedouin and Ultra-Orthodox Jewish mothers in Israel. As both of these communities prescribe very modest clothing for females, whose lives are largely conducted indoors, the underlying cause of the problem would appear to be inadequate exposure to sunlight, leading to reduced vitamin D synthesis [31].

4.3 Age-related osteomalacia

Over 30% of people >65 years of age in the U.K. are estimated to have vitamin D insufficiency [32]. In older people with osteomalacia there is a loss of skeletal mass caused by inadequate mineralisation of the normal osteoid tissue. However, among elderly stroke patients in Japan it was found that their decreased levels of bone mineral density and resultant osteoporosis could be successfully treated by simple exposure to sunlight [33].

In Australia, highly publicized and successful media campaigns are in place to ensure that people are aware of the risks of skin cancer from over-exposure to UV radiation. Unfortunately, over-avoidance of sunlight by older people has led to increasing levels of osteomalacia, since many persons in the >65 year age group spend much of their lives indoors and so fail to synthesize adequate levels of vitamin D [34].

4.4 Oculocutaneous albinism (OCA)

Two main types of oculocutaneous albinism have been defined: i) OCA1, in which affected individuals have mutations in the gene for the enzyme tyrosinase which catalyzes the first two steps of melanin biosynthesis, resulting in little or no pigment production in their skin; ii) OCA2, where individuals have some residual tyrosinase production, leading to fair to sandy coloured hair and light brown or occasionally light blue irises.

The overall prevalence of OCA2 in Sub-Saharan Africa has been estimated as 1/3,900 to 1/15,000 [35,36], but it can be much higher in certain tribes and clans, e.g., ~1/800 in the *Vhatavhatsindi* clan in Zimbabwe [37]. A 2.7 kilobase deletion is the common OCA2 mutation in Sub-Saharan African populations (and therefore also among African-Americans), but a range of other more rare mutations also have been described [35,38]. By comparison, the prevalence of OCA2 in the Native American Navaho tribe is due to a 122.5 kilobase deletion in the skin pigmentation P gene, with 1/1,500-1/2,000 persons affected [39].

In Sub-Saharan Africa there is strong physiological selection against persons with OCA2 due to their lack of protective melanin and heightened UV sensitivity, with consequent ocular problems and high rates of skin cancer [36]. The high rates of this disadvantageous mutation may therefore be due to genetic drift, and/or to positive cultural selection, as has been described in the *Vhatavhatsindi* and the Navaho.

Conversely, reports indicate that in East Africa negative cultural influences also apply, with active discrimination against people with OCA2. This discrimination recently has resulted in albinos ranging in age from babies to adults being murdered, with their hair, blood, skin and various body parts utilized by witchdoctors for the preparation of potions to bring financial success [40,41].

5. DISCUSSION AND CONCLUSIONS

Skin colour variation in human populations can be used both to inform discussion on the drivers of human adaptation and to pose questions relating

to adaptive evolution in the future. In terms of the inter-relationships between genetic, physiological and cultural determinants of human adaptation it would appear that all three factors are significant. This conclusion also can be drawn from the disruptional influence of long-distance migration and modern lifestyles on the previous balance between the advantageous and disadvantageous health outcomes of skin pigmentation, attained after many generations of selection. Thus in Australia there are high rates of skin cancer among European migrants and their descendants, whereas in South Asian children resident in the U.K. are more likely to suffer from nutritional rickets.

From a Physiological Anthropology perspective what remains to be established is whether in systems and pathways in which genetic variation still exists, e.g., with respect to skin colour in Europeans [8], evolutionary pressures may reverse or at least lessen in future generations. But what of systems which have attained genetic fixation, as also has been suggested for human pigmentation pathways [9]? With global warming and increasing UV levels, can cutaneous tissue adaptively increase the numbers of melanosomes through generational time? Or will future generations be dependent on the routine application of UV-blocking agents to minimize skin cancer, but at the potential cost of vitamin D insufficiency in women, rickets in their children, and osteomalacia in the elderly?

6. REFERENCES

[1] Collins, K.J. & Weiner, J.S. (1977). Human Adaptability, London: Taylor and Francis, pp. 1-23.

[2] Gould, S.J. & Lewontin RC. (1979). The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptionist programme. Proceedings of the Royal Society of London, series B, 205, 581-598.

[3] Barash, D.P. (1982). Sociobiology and Behavior. New York: Elsevier, 2nd ed., p. 24.

[4] Durham, W.H. (1991) Coevolution. Stanford: Stanford University Press, pp. 14-15.

[5] Myles, S., Somel, M., Tang, K., Kelso, J. & Stoneking, M. (2007) Identifying genes underlying skin pigmentation differences among human populations. Human Genetics 120, 613-621.

[6] Relethford, J.H. (1997), Hemispheric difference in human skin color. American Journal of Physical Anthropology 104, 449-457.

[7] Barsh, G.S. (2003). What controls variation in human skin color? PLoS Biology 1, 019-022.

[8] Voight, B.F., Kudaravalli, S., Wen, X. & Pritchard, J.K. (2006). A map of recent positive selection in the human genome. PLoS Biology 4, e72.

[9] Williamson, S.H., Hubisz, M.J., Clark, A.G., Payseur, B.A., Bustamente, C.D. & Nielsen, R. (2007). Localizing recent adaptive evolution in the human genome. PLoS Genetics 3, e90.

[10] Rana, B., Hewett-Emmett, D., Jin, L., Chang, B.H., Sambuughin, N., Lim, M. et al. (1999). High polymorphism at the human melanocortin 1 receptor locus. Genetics 151, 607-613.

[11] Jablonski, N.G. & Chaplin, G. (2000). The evolution of human skin coloration. Journal of Human Evolution 39, 57-106.

[12] Norton, H., Kittles, R.A., Parra, E., McKeigue, P., Mao, X., Cheng K. et al. (2006). Genetic evidence for the convergent evolution of light skin in Europeans and East Asians. Molecular Biology and Evolution 24, 71-722.

[13] Stokowski, R.P., Krishna Pant, P.V., Dadd, T., Fereday, A., Hinds, D.A., Jarman, C. et al. (2007). A genomewide association study of skin pigmentation in a South Asian population. American Journal of Human Genetics 81, 1119-1132.

[14] Sulem, P., Gudbjartsson, D.F., Stacey, S.N., Helgason, A., Rafnar, T., Magnusson, K.P. et al. (2007). Genetic determinants of hair, eye and skin pigmentation in Europeans. Nature Genetics 39, 1443-1452.

[15] Sulem, P., Gudbjartsson, D.F., Stacey, S.N., Helgason, A., Rafnar, T., Jakobsdottir, M. et al. (2008). Two newly identified genetic determinants of pigmentation in Europeans. Nature Genetics 40, 835-837.

[16] Australian Institute of Health and Welfare (AIHW) (2005). States and territories GRIM (General Record of Incidence of Mortality) Books. Canberra: AIHW.

[17] Australian Institute of Health and Welfare (AIHW) and Australasian Association of Cancer Registries (2007). Cancer in Australia: and overview, 2006. Cancer Series Number 37. Canberra: AIHW.

[18]Sunsmart (2008) Skin cancer overview. Retrieved 29.07.08 from http://www.sunsmart.com.au/browse.asp

[19] Jannot, A.-S., Meziani, R., Bertrand, G., Gérard, B., Descamps, V., Archimbaud, A. et al. (2005). Allele variations in the OCA2 gene (pink-eyed-dilution locus) are associated with genetic susceptibility to melanoma. European Journal of Human Genetics 13, 913-920.

[20] Gudbjartsson, D.F., Sulem, P., Stacey, S.N., Goldstein, A.M., Rafnar, T., Sigurgeirsson, B. et al. (2008). ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nature Genetics 40, 886-891.

[21] Brown, K.M., MacGregor, S., Montgomery, G.W., Craig, D.W., Zhao, Z.Z., Iyadurai, K. et al. (2008), Common sequence variants on 20q11.22 confer melanoma susceptibility. Nature Genetics 40, 838-840.

[22] Allgrove, J. (2004). Is nutritional rickets returning? Archives of Disease in Childhood 89, 699-701.

[23] Rajakumar, K. & Thomas, S.B. (2005). Reemerging nutritional rickets: a historical perspective. Archives of Pediatric and Adolescent Medicine 159, 335-341.

[24] Dunnigan, M.G., Glekin, B.M., Henderson, J.B., McIntosh, W.B., Sumner, D. & Sutherland, G.R. (1985). Prevention

of rickets in Asian children: assessment of the Glasgow campaign. British Medical Journal 291, 239-242.

[25] Iqbal, S.J., Kaddam, I., Wassif, W., Nichol, F. & Walls, J. (1994). Continuing clinically severe vitamin D deficiency of Asians in the UK (Leicester). Postgraduate Medical Journal 70, 708-714.

[26] Shaw, N.J. & Pal, B.R. (2002). Vitamin D deficiency in UK Asian families: activating a new concern. Archives of Disease in Childhood 86, 147-149.

[27] Ladhani, S., Srinivasan, L., Buchanan, C. & Allgrove, J. (2004). Presentation of vitamin deficiency. Archives of Diseases in Childhood 89, 781-784.

[28] Robinson, P.D., Högler, W., Craig, M.E., Verge, C.F., Walker, J.L., Piper, A.C. et al. (2006). The re-emerging burden of rickets: a decade of experience from Sydney. Archives of Disease in Childhood 91, 564-568.

[29] Roy, D.K., Berry, J.L., Pye, S.R., Adams, J.E., Swarbrick, C.M., King, Y. et al. (2007). Vitamin D status and bone mass in UK South Asian women. Bone 40, 200-204.

[30] Brunvand, L., Quigstad, E., Urdal, P. & Haug, E. (1996). Vitamin deficiency and fetal growth. Early Human Development 45, 27-33.

[31] Weisman, Y. (2003). Vitamin D deficient rickets and osteomalacia in Israel. Israel Medical Association Journal 5, 289-290.

[32] Patient UK (2008). Vitamin D deficiency. Retrieved 29.07.08 from patient.co.uk/ showdoc/40001117

[33] Sato, Y., Metoki, N., Iwamoto, J. and Satoh, K. (2003). Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients. Neurology 61, 338-342.

[34] Working Group of the Australian and New Zealand Bone and Mineral Society (2005). Vitamin D and adult bone health in Australia and New Zealand: a position statement. Medical Journal of Australia 182, 282-285.

[35] Stevens, G., van Beukering, J., Jenkins, T. & Ramsay, M. (1995). An intragenic deletion of the P gene is the common mutation causing tyrosinase-positive oculocutaneous albinism in southern African Negroids. American Journal of Human Genetics 56, 586-591.

[36] Hong, E.S., Zeeb, H. & Repacholi, M.H. (2006). Albinism in Africa as a public health issue. BMC Public Health 6, 212.

[37] Lund, P.M. (2005). Oculocutaneous albinism in southern Africa: population structure, health and genetic care. Annals of Human Biology 32, 168-173.

[38] Stevens, G., Ramsay, M & Jenkins, T. (1997). Oculocutaneous albinism (OCA2) in sub-Saharan Africa: distribution of the common 2.7 kb P gene deletion mutation. Human Genetics 99, 523-527.

[39] Yi, Z., Garrison, N., Cohen-Barak, O., Karafet, T.M., King, R.A., Erickson, R.P. et al. (2003). A 122.5-kilobase deletion of the P gene underlies the high prevalence of oculocutaneous albinism type 2 in the Navajo population. American Journal of Human Genetics 72, 62-72.

[40] Albinos, long shunned, face threat in Tanzania – The New York Times, 08.06.08. Retrieved 29.07.08 from www.nytimes.com/2008/06/08/world/africa/08albino/html.

[41] Living in fear: Tanzania's albinos. BBC, 21.07.08. Retrieved from news.bbc.co.uk/ 2/hi/Africa/7527729.stm