PROCEEDINGS OF THE ROYAL SOCIETY B

rspb.royalsocietypublishing.org

Comment

Cite this article: Jablonski NG, Chaplin G. 2014 Skin cancer was not a potent selective force in the evolution of protective pigmentation in early hominins. *Proc. R. Soc. B* **281**: 20140517.
http://dx.doi.org/10.1098/rspb.2014.0517

Received: 3 March 2014
Accepted: 2 April 2014

Author for correspondence:
Nina G. Jablonski
e-mail: ngj2@psu.edu

The accompanying reply can be viewed at http://dx.doi.org/10.1098/rspb.2014.0940.

Royal Society Publishing

Skin cancer was not a potent selective force in the evolution of protective pigmentation in early hominins

Nina G. Jablonski and George Chaplin

Department of Anthropology, The Pennsylvania State University, 409 Carpenter Building, University Park, PA 16802, USA

Greaves [1] proposed that skin cancer was a potent selective force for the evolution of dark pigmentation in early hominins. Blum [2,3] questioned the role of skin cancer in the evolution of skin pigmentation because it only rarely causes death to individuals of reproductive age. Since Blum's studies, much more data on skin cancer rates has been amassed, and a clearer picture of skin cancer aetiology has emerged. Individuals with lightly pigmented skin, especially those with a tendency to freckle who carry specific polymorphisms of the melanocortin 1 receptor gene (*MC1R*), are most susceptible to skin cancers of all types [4,5]. Other polymorphisms of pigmentation genes also have been associated with elevated risk of skin cancer in people of European descent [6]. Development of the most common skin cancers, namely, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), is associated with chronic sun peak exposure and generally develops in the seventh decade of life. Cutaneous malignant melanoma (CMM) is much rarer, is associated with sunburns, particularly in childhood, and can appear as early as the third or fourth decades of life because of the roughly 20 year lag between damaging exposures and the appearance of disease [4]. This still allows for reproduction and the persistence of familial predisposition to CMM [7].

Greaves' case for skin cancer as a potent agent for natural selection of dark skin pigmentation presupposes that ancestral hominins had skin that was pale or light, and that people in Africa who are entirely lacking eumelanin in their integument owing to *OCA2* albinism are a suitable model for the ancestral state. *OCA2* albinism predisposes individuals to extreme ultraviolet ratiation (UVR)-induced damage to DNA and is associated with severe and often fatal skin cancers (mostly SCC) in the middle of their potential reproductive careers in the third and fourth decades of life [8,9]. Excessively high rates of skin cancer develop in individuals with *OCA2* albinism when compared with other very light-skinned people with *MC1R* variants, probably because of the protective non-pigmentary effects of *MC1R*, specifically the fewer number of p53 clones that develop after UVR exposure [10].

Early hominins never had naked pale skin comparable in function to that of individuals with *OCA2* albinism. All living cattarhine primates have intact pigmentary systems and can develop facultative pigmentation through tanning or have permanently melanized skin [11,12]. Humans evolved from African apes which had the potential to develop protective eumelanin pigmentation through tanning on exposed skin in response to UVR exposure. The skin (and not just the hair follicles) of great apes bears active melanocytes which produce eumelanin upon exposure to strong sunlight [13]. Increased sun exposure on hairless areas results in gradual darkening of the skin, as melanocytes gain competence with increasing age. Based on comparative evolutionary physiology and the principle of parsimony, this must have been the ancestral condition of the last common ancestor of African apes and humans [11,14]. Skin cancers are not among the skin conditions known to afflict living apes [15].

The evolution of functional hairlessness in early hominins was a gradual process, not a sudden one, during which the *MC1R* locus was under increasing selective constraint [16]. Once permanent dark constitutive pigmentation evolved about 1.2 Ma [16], selection eliminated non-synonymous *MC1R* variation in order to maintain a high-eumelanin phenotype [17]. During this

process, the skin of early hominins was never pale-skinned or incapable of tanning, and was never functionally similar to the condition seen in people with *OCA2* albinism. The skin of individuals with albinism is an inappropriate model for the ancestral hominin condition because its pallor is the result of complete and irreversible loss of pigmentary function. Even if this condition were taken as the model for the skin of early hominins, skin cancer still could have been only a weak selective force. Reproduction in ancestral hominins started earlier in life than in modern humans [18], and most reproductive effort would have been completed before skin cancer could have affected reproductive success. It is thus unlikely that skin cancer could have affected maternal fertility significantly. Its effect on child mortality through a grandmaternal effect would have been slighter, given that the effect of grandmaternal survival on child mortality is approximately five times less than that of maternal survival [19].

Factors affecting individuals early in their reproductive career would have had much greater effects on fertility than skin cancer. Considering that skin pigmentation is most highly correlated to autumnal, and not peak, UVR levels, BCC and SCC were unlikely to have been significant selective forces. The most serious skin cancer, CMM, most often is caused by repeated sunburns, which are more common in regions with highly seasonal solar regimes and large changes in the ratio of UVA to UVB throughout the year. Such conditions prevail today in the subtropical and Mediterranean belts, particularly those of the Southern Hemisphere, which experience greater differences between summer and winter UVR levels owing to current orbital parameters [20,21]. CMM risk therefore may have promoted the evolution of tanning ability [22]. Serious sunburns would have been rare, however, before the era of long-distance travel and recreational sun exposure.

In the electronic supplementary material accompanying his article, Greaves criticizes other models for the evolution of dark pigmentation for lack of explanatory power. He focuses special attention on the deficiencies of the folate hypothesis, citing presumed differences in sun exposure between male and female hominins and a lack of experimental evidence for folate sensitivity to UVR. There is no evidence to suggest that female hominins and their offspring experienced any less UVR exposure than males. The evolution of hairlessness and permanent dark pigmentation occurred in the early history of the genus *Homo*, when hominins of both sexes were actively engaged in foraging and hunting in mostly open, sunny environments [23]. In our development of the folate hypothesis, we have gone to lengths to discuss its strengths and evidentiary shortcomings [11,22], and to indicate that effects on folate metabolism were not the only forces acting to promote the evolution of permanent protective eumelanin pigmentation. Evidence for the *in vitro* photolysis of folate and 5-methyltetrahydrofolate (5-MTHF) by UVR [24–26] that we cited in our early studies has been supplemented recently by demonstration of *in vivo* photolysis by UVR in humans [27]. Reduction in the bioavailability of folate and 5-MTHF by UVR would be a significant selective force because it would have almost immediate effects on folate-dependent processes of DNA synthesis and cell division (including early embryogenesis and spermatogenesis) as well as on DNA repair.

Skin cancer is a serious health problem for mobile and long-lived modern humans, and is especially so for individuals suffering from *OCA2* albinism in Africa. What we question here is the validity of applying the model of *OCA2* albinism to human evolution. Loss of skin pigmentation can occur via many genetic pathways, and has evolved many times [28,29]. The deletion mutation at the P locus in individuals with *OCA2* albinism arose in sub-Saharan Africa 2000–3000 years ago, and represents one of the most dramatic examples of loss of pigmentation in the human lineage. Our point is that the absence of pigmentation seen in individuals suffering from *OCA2* albinism is not comparable to the ancestral state seen in early hominins. The transition from an 'ape-like' polymorphic *MC1R* condition—in which individuals were capable of heavy tanning on exposed skin but were not permanently pigmented—to a modern human monomorphic *MC1R* condition with permanent dark pigmentation over a mostly hairless body more than 1 Ma was the key innovation that occurred in the evolution of human skin. Multiple selective pressures were involved, but the most powerful forces were those that affected reproductive success swiftly and with certainty.

References

1. Greaves M. 2014 Was skin cancer a selective force for black pigmentation in early hominin evolution? *Proc. R. Soc. B* **281**, 20132955. (doi:10.1098/rspb.2013.2955)
2. Blum HF. 1961 Does the melanin pigment of human skin have adaptive value? *Q. Rev. Biol.* **36**, 50–63. (doi:10.1086/403275)
3. Blum HF. 1959 *Carcinogenesis by ultraviolet light*, p. 340. Princeton, NJ: Princeton University Press.
4. de Vries E *et al*. 2012 Known and potential new risk factors for skin cancer in European populations: a multicentre case–control study. *Br. J. Dermatol* **167**(Suppl. 2), 1–13. (doi:10.1111/j.1365-2133.2012.11081.x)
5. Rees JL. 2004 The genetics of sun sensitivity in humans. *Am. J. Hum. Genet.* **75**, 739–751. (doi:10.1086/425285)
6. Nan H, Kraft P, Hunter DJ, Han J. 2009 Genetic variants in pigmentation genes, pigmentary phenotypes, and risk of skin cancer in Caucasians. *Int. J. Cancer* **125**, 909–917. (doi:10.1002/ijc.24327)
7. Höiom V *et al*. 2009 MC1R variation and melanoma risk in the Swedish population in relation to clinical and pathological parameters. *Pigment Cell Melanoma Res.* **22**, 196–204. (doi:10.1111/j.1755-148X.2008.00526.x)
8. Hong E, Zeeb H, Repacholi M. 2006 Albinism in Africa as a public health issue. *BMC Public Health* **6**, 212–218. (doi:10.1186/1471-2458-6-212)
9. Mabula J *et al*. 2012 Skin cancers among albinos at a university teaching hospital in northwestern Tanzania: a retrospective review of 64 cases. *BMC Dermatol.* **12**, 1–5. (doi:10.1186/1471-5945-12-5)
10. Robinson S, Dixon S, August S, Diffey B, Wakamatsu K, Ito S, Friedmann PS, Healy E. 2010 Protection against UVR involves MC1R-mediated non-pigmentary and pigmentary mechanisms *in vivo*. *J. Invest. Dermatol.* **130**, 1904–1913. (doi:10.1038/jid.2010.48)
11. Jablonski NG, Chaplin G. 2000 The evolution of human skin coloration. *J. Hum. Evol.* **39**, 57–106. (doi:10.1006/jhev.2000.0403)
12. Jablonski NG. 2004 The evolution of human skin and skin color. *Annu. Rev. Anthropol.* **33**, 585–623. (doi:10.1146/annurev.anthro.33.070203.143955)
13. Montagna W, Yun JS. 1963 The skin of primates. XV. The skin of the chimpanzee (*Pan satyrus*). *Am. J. Phys. Anthropol.* **21**, 189–203. (doi:10.1002/ajpa.1330210211)
14. Rana BK, Didier PJ. 1999 High polymorphism at the human melanocortin 1 receptor locus. *Genetics* **151**, 1547–1557.

15. Bernstein JA, Didier PJ. 2009 Nonhuman primate dermatology: a literature review. *Vet. Dermatol.* **20**, 145–156. (doi:10.1111/j.1365-3164.2009.00742.x)
16. Rogers AR, Iltis D, Wooding S. 2004 Genetic variation at the MC1R locus and the time since loss of human body hair. *Curr. Anthropol.* **45**, 105–124. (doi:10.1086/381006)
17. Harding RM *et al*. 2000 Evidence for variable selective pressures at MC1R. *Am. J. Hum. Genet.* **66**, 1351–1361. (doi:10.1086/302863)
18. Bogin B, Smith BH.1996 Evolution of the human life cycle. *Am. J. Hum. Biol.* **8**, 703–716. (doi:10.1002/(sici)1520-6300(1996)8:6<703::aid-ajhb2>3.0.Co;2-u)
19. Shanley DP, Sear R, Mace R, Kirkwood TBL. 2007 Testing evolutionary theories of menopause. *Proc. R. Soc. B* **274**, 2943–2949. (doi:10.1098/rspb.2007.1028)
20. Relethford JH. 1997 Hemispheric difference in human skin color. *Am. J. Phys. Anthropol.* **104**, 449–457. (doi:10.1002/(SICI)1096-8644(199712)104:4<449::AID-AJPA2>3.0.CO;2-N)
21. Chaplin G, Jablonski NG. 1998 Hemispheric difference in human skin color. *Am. J. Phys. Anthropol.* **107**, 221–224. (doi:10.1002/(SICI)1096-8644(199810)107:2<221::AID-AJPA8>3.0.CO;2-X)
22. Jablonski NG, Chaplin G. 2010 Human skin pigmentation as an adaptation to UV radiation. *Proc. Natl Acad. Sci. USA* **107**(Suppl. 2), 8962–8968. (doi:10.1073/pnas.0914628107)
23. Bobe R, Leakey MG. 2009 Ecology of Plio-Pleistocene mammals in the Omo-Turkana basin and the emergence of *Homo*. In *The first humans: origin and early evolution of the genus* Homo (eds FE Grine, J Fleagle, RE Leakey), pp. 173–184. New York, NY: Springer.
24. Juzeniene A, Thu Tam TT, Iani V, Moan J. 2013 The action spectrum for folic acid photodegradation in aqueous solutions. *J. Photochem. Photobiol. B, Biol.* **126**, 11–16. (doi:10.1016/j.jphotobiol.2013.05.011)
25. Tam TTT, Juzeniene A, Steindal AH, Iani V, Moan J. 2009 Photodegradation of 5-methyltetrahydrofolate in the presence of uroporphyrin. *J. Photochem. Photobiol. B, Biol.* **94**, 201–204. (doi:10.1016/j.jphotobiol.2008.12.003)
26. Branda RF, Eaton JW. 1978 Skin color and nutrient photolysis: an evolutionary hypothesis. *Science* **201**, 625–626. (doi:10.1126/science.675247)
27. Borradale DC, Isenring E, Hacker E, Kimlin MG. 2014 Exposure to solar ultraviolet radiation is associated with a decreased folate status in women of childbearing age. *J. Photochem. Photobiol. B, Biol.* **131**, 90–95. (doi:10.1016/j.jphotobiol.2014.01.002)
28. Manceau M, Domingues VS, Linnen CR, Rosenblum EB, Hoekstra HE. 2010 Convergence in pigmentation at multiple levels: mutations, genes and function. *Phil. Trans. R. Soc. B* **365**, 2439–2450. (doi:10.1098/rstb.2010.0104)
29. Norton HL *et al*. 2007 Genetic evidence for the convergent evolution of light skin in Europeans and East Asians. *Mol. Biol. Evol.* **24**, 710–722. (doi:10.1093/molbev/msl203)