Journal of Evolutionary Biology Research Vol. 3(3), pp. 29-32, March 2011
Available online at http://www.academicjournals.org/jebr
ISSN 2141-6583 ©2011 Academic Journals

*Full Length Research Paper*

# Decreasing values, from the North of West Europe to North Africa, of 374F allele frequencies in the skin pigmentation gene SLC45A2: An analysis

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Accepted 10 March 2011

**The 374F mutation in the SLC45A2 gene encoding the membrane associated transporter protein (MATP) has been suggested to be associated with skin color in Caucasians. In this synthesis, we collected the distribution of the 374F allele in 2910 unrelated subjects from 28 European and 4 North African populations. The highest allele frequency was observed in Denmark (0.98) and the lowest frequencies were observed in Tunisia (0.61) and in Algerian Mozabites (0.40). A significant decreasing latitudinal cline in 374F allele frequencies was observed, ranging from the north of West Europe to North Africa ($R^2$ = 0.6781).**

**Key words:** Human skin pigmentation, SLC45A2 gene, 374F mutation, membrane-associated transporter protein (MATP), population study, gradient of allele frequencies, West Europe and North Africa.

## INTRODUCTION

The solute carrier family 45 member 2 (SLC45A2) gene encodes a protein referred to as a membrane-associated transporter protein (MATP), which takes some important part in melanin synthesis in the melanosomes (Fukamachi et al., 2001). It has been established that the SLC45A2 gene plays an important role in human pigmentation (Newton et al., 2001; Inagaki et al., 2004; Rundshagen et al., 2004) more recently, the SLC45A2 has also been identified as a candidate pigmentation gene undergoing recent positive approach (Myles et al., 2007; Lao et al., 2007; Norton et al., 2007). Several polymorphisms in the SLC45A2 gene have been described. Newton et al. (2001) identified initially two polymorphisms, F374L (determined by a G to C transversion C.G11222C in exon 5 of the gene) and T329T in the SLC45A2 gene, and studied their variations in diverse populations form North America, Asia, Europe and Africa. Grad et al. (2005), studying E272K and F374L polymorphisms in 456 Caucasians and in other populations reported that, they were associated with normal human pigmentation variation, that is L374 was significantly associated with dark hair, skin and eye color in Europeans. Soejima et al. (2006) investigating sequence variation in the coding region and exon-flanking sequences surrounding the F374L polymorphism, found low genetic variation in subjects of European descent only; haplotype analysis revealed that one haplotype carrying 374F was over-represented in Europe (suggesting that selection has been recently acting on the corresponding genomic region).

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## MATERIALS AND METHODS

We have studied the *F374L* polymorphism in 1649 subjects from thirteen Eurasian populations and in one African population (Yuasa et al., 2006). The highest allele frequency of the *374F* variant in this study was observed in Germans (0.965), French and Italian showing somewhat lower frequencies, and Turks having a value of 0.615; haplotype analysis confirmed than the haplotype diversity was much lower in Germans than in Japanese, and suggests that the *374F* variant occurred only once in the ancestry of Caucasians. Norton et al. (2007) investigated the distribution of the *374F* variant in 53 populations (including six European and one North African population); they confirmed that the *374F* allele were observed at the highest frequencies in Europeans (and was lacking in African,

**Table 1.** Distribution of *374F* allele frequencies in 32 populations of West Europe and North Africa (N = sample size).

| No. | Country | Region/population | Latitude (°) | N | Frequency of *374f* | References |
|---|---|---|---|---|---|---|
| 1 | Germany | Northrhine-Whestphali | 50.9 | 241 | 0.965 | Yuasa et al. (2006) |
| 2 | | Munich | 48.1 | 93 | 0.962 | " |
| 3 | France | Rheims | 49.2 | 98 | 0.893 | " |
| 4 | Italy | Genoa | 44.5 | 97 | 0.85 | " |
| 5 | Denmark | Copenhagen | 56 | 51 | 0.98 | Lucotte et al. (2010) |
| 6 | England | London | 51.5 | 56 | 0.955 | " |
| 7 | Belgium | Brussels | 50.5 | 53 | 0.934 | " |
| 8 | France | Lille | 50.5 | 64 | 0.945 | " |
| 9 | | Rennes | 48 | 52 | 0.971 | " |
| 10 | | Marseilles | 43.2 | 312 | 0.888 | " |
| 11 | | Perpignan | 43 | 101 | 0.827 | " |
| 12 | | Corsica | 42 | 328 | 0.878 | " |
| 13 | Germany | Mulheim | 50 | 59 | 0.975 | " |
| 14 | Switzerland | Basel | 47.2 | 51 | 0.961 | " |
| 15 | Italy | Roma | 41.9 | 64 | 0.898 | " |
| 16 | | Napoli | 41 | 128 | 0.859 | " |
| 17 | | Sicily | 38 | 39 | 0.833 | " |
| 18 | | Sardinia | 40 | 100 | 0.805 | " |
| 19 | Spain | Barcelona | 41 | 59 | 0.856 | " |
| 20 | | Sevilla | 37.5 | 71 | 0.725 | " |
| 21 | Portugal | North | 42 | 79 | 0.725 | " |
| 22 | | South | 38 | 59 | 0.780 | " |
| 23 | Morocco | Tangier | 35.8 | 123 | 0.691 | " |
| 24 | Algeria | Algier | 36.5 | 141 | 0.709 | " |
| 25 | Tunisia | Tunis | 36.5 | 73 | 0.610 | " |
| 26 | England | Orcades | 59 | 16 | 1 | Norton et al. (2007) |
| 27 | France | | 46 | 29 | 0.91 | " |
| 28 | | Basque | 43 | 24 | 0.94 | " |
| 29 | Italy | Bergamo | 46 | 14 | 0.96 | " |
| 30 | | Tuscan | 43 | 8 | 0.94 | " |
| 31 | | Sardinia | 40 | 28 | 0.68 | " |
| 32 | Algeria | Mozabite | 32 | 30 | 0.40 | " |

East African and Native American populations). We have recently (Lucotte et al., 2010) studied the detailed distribution of the *374F* allele in 2063 unrelated subjects from 18 European and 3 North African populations; the highest allele frequency is observed in Denmark (0.980), and the lowest frequencies are observed in Tunisia (0.610) and in Morocco (0.691). A significant decreasing latitudinal cline in *374F* allele frequencies was established in this study, ranging from the north of West Europe to North Africa.

## RESULTS AND DISCUSSION

The aim of the present investigation is to evaluate the main geographic pattern of the *374F* allele frequencies of the *SLC4512* gene in West Europe and in North Africa. We have colliged results obtained on the subject in the studies of *374F* allele Yuasa et al. (2006), Norton et al. (2007) and our own (Lucotte et al., 2010), concerning a total of 2910 unrelated subjects. Table 1 summarizes data on 32 different populations, 28 of them being West European populations and 4 of North Africa. The *374F* allele frequency is fixed in Orcaidans (Norton et al., 2007). The highest *374F* allele frequency (0.98) was observed in Denmark, and the lowest frequencies were observed in Tunisia (0.61) and in Algerian Mozabites (0.40). The pattern of *374F* allele frequencies reported in the table shows a regular trend of decreasing frequencies with degrees of latitude north. There is a highly significant ($P < 0.001$) correlation ($R^2 = 0.6781$) between *374F* frequencies and latitude (Figure 1). The resulting geographic pattern is that of a regular decreasing cline in

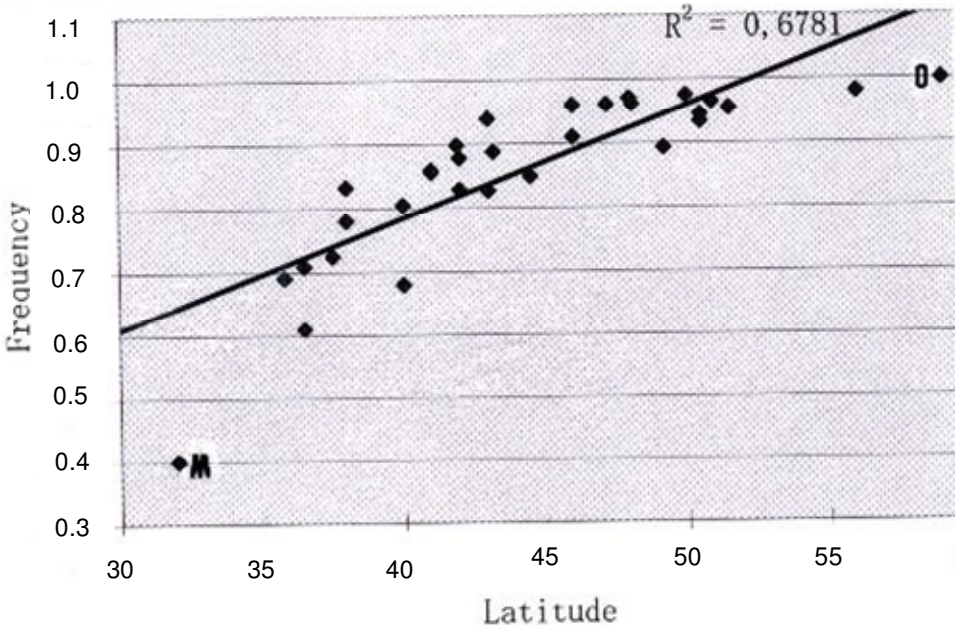


**Figure 1.** Correlation between degrees of latitude North and 374F frequencies in thirty-two populations (Mozabites: M and Orcadians: O are outliners); equation of the regression line: y = 0.8074x – 2.1936.

*374F* frequencies with latitude, from the north of West Europe to North Africa.

The relationship between latitude and skin color has been studied for a long time: several “skin color maps” have been produced since the earliest works of physical anthropology, and all agree on a correlation of darker skin with equatorial proximity (Barsh, 2003). In the literature concerning more than 100 populations (Relethford, 1997), it was shown that skin reflectance is lowest at the equator and then gradually increases for about 8% per 10° of latitude in the northern hemisphere. Although no special measurements of skin color were done in our own studies, the regular decreasing gradient in the *374F* allele with north latitude in our native subjects reflects ultraviolet radiation level and may be associated with skin color variation in these regions.

Graf et al. (2005) proposed that the *374F* allele resulted in a reduction of function of MATP, that altered the intracellular trafficking of melanosomal proteins, so creating a favorable environment for decreased melanin production. Such a functional difference could contribute to lighter skin color, thus allowing increased UV-B absorption for the production of vitamin D3. Therefore, those with the *374F* allele and living at higher latitudes could potentially reduce their risk of developing con-ditions related to vitamin D3 deficiency (Jablonsky and Chaplin, 2000). Results summarized in the present synthesis, concerning large differences in distribution of the *374F* variant together with the decreasing cline in *374F* frequencies from the north of West Europe to North Africa, indicate that *374F* may be an important and perhaps direct factor in various degrees of hypopigmentation in European and North African populations.

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