HOMO - Journal of Comparative Human Biology 68 (2017) 134–144

Contents lists available at ScienceDirect

HOMO - Journal of Comparative Human Biology

journal homepage: www.elsevier.com/locate/jchb

Association of five SNPs with human hair colour in the Polish population

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ARTICLE INFO

Article history:
Received 7 September 2015
Accepted 12 November 2016

Keywords:
Hair pigmentation
SNP
MC1R
OCA2
HERC2
SLC24A5
SLC45A2
TPCN2
TYR
TYRP1

ABSTRACT

Twenty-two variants (single nucleotide polymorphisms – SNPs) of the genes involved in hair pigmentation (OCA2, HERC2, MC1R, SLC24A5, SLC45A2, TPCN2, TYR, TYRP1) were genotyped in a group of 186 Polish participants, representing a range of hair colours (45 red, 64 blond, 77 dark). A genotype-phenotype association analysis was performed.

Using *z*-statistics we identified three variants highly associated with different hair colour categories (rs12913832:A>G in HERC2, rs1805007:T>C and rs1805008:C>T in MC1R). Two variants: rs1800401:C>T in OCA2 and rs16891982:C>G in SLC45A2 showed a high probability of a relation with hair colour, although that probability did not exceed the threshold of statistical significance after applying the Bonferroni correction. We created and validated mathematical logistic regression models in order to test the usefulness of the sets of polymorphisms for hair colour prediction in the Polish population. We subjected four models to stratified cross-validation. The first model consisted of three polymorphisms that proved to be important in the associative analysis. The second model included, apart from the mentioned polymorphisms, additionally rs16891982:C>G in SLC45A. The third model included, apart from the variants relevant in the associating analysis, rs1800401:C>T in OCA. The fourth model consisted of the set of polymorphisms from the first model supplemented with rs16891982:C>G in SLC45A and rs1800401:C>T in OCA. The validation of our models has shown that the inclusion of rs16891982:C>G in SLC45A and rs1800401:C>T in OCA increases the prediction of red hair in comparison with the algorithm including only rs12913832:A>G in HERC2, rs1805007:T>C and rs1805008:C>T in MC1R. The model consisting of all the five above-mentioned genetic variants has shown good prediction accuracies, expressed by the area under the curve (AUC) of the receiver operating characteristics: 0.84 for the red-haired, 0.82 for the dark-haired and 0.71 for the blond-haired.

A genotype-phenotype association analysis brought results similar to those in other studies and confirmed the role of rs16891982:C>G, rs12913832:A>G, rs1805007:T>C and rs1805008:C>T in hair colour determination in the Polish population. Our study demonstrated for the first time the possibility of a share of the rs1800401:C>T SNP in the OCA2 gene in hair colour determination. Including this single nucleotide polymorphism in the actual hair colour predicting models would improve their predictive accuracy.

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http://dx.doi.org/10.1016/j.jchb.2017.02.002
0018-442X/

Introduction

Natural pigmentation is a variable human trait that functions mainly as a protection system against the damaging effects of ultraviolet radiation (UVR) (Jablonski and Chaplin, 2000). The pigmentary phenotype is distinctive of geographical ancestry and varies between populations (Shriver et al., 2003). In Europeans, hair colour is highly variable and ranges from light blond to black with an additional variety of red hair shades. Hair colour is a polygenic trait determined by a large subset of genes. These genes encode proteins that either regulate melanin synthesis or act at different stages of it. Melanin is a polymeric pigment produced in the melanosomes, responsible for the colour of the skin, iris and hair (Barsh, 1996; Ortonne and Prota, 1993; Sturm et al., 2003). The presence of different hair colour phenotypes among humans is due to polymorphic substitutions in the pigmentary genes. These single nucleotide polymorphisms (SNPs) lead to subtle changes in the expression or the function of the coded proteins, which in turn affect the production and distribution of melanin subtypes, i.e. eumelanin and pheomelanin. The observed colour is the result of the overall amount of pigment and of the ratio of eumelanin to pheomelanin, which depends on the activity of the rate-limiting enzyme tyrosinase, and on the availability of its main substrates: tyrosine and cysteine. The whole pathway is regulated by the melanocortin hormone (αMSH) which acts via its receptor – melanocortin 1 receptor (MC1R) localised in the melanocyte plasma membrane (Ortonne and Prota, 1993; Valverde et al., 1995). It is well known that certain variants of the MC1R gene cause diminished signal transduction, which can result in red hair colour (Beaumont et al., 2007; Schiöth et al., 1999). Although the MC1R and TYR genes seem to play a major role in pigment production, there are other proteins whose function in this process is not fully explained, but their genetic association with phenotype is undeniable (Barsh, 1996). The SLC45A2, TPCN2, SLC24A5 and OCA2 genes encode, for the most part, transporter proteins that are speculated to supply substrates and cofactors for the melanin synthesis and regulate the pH and the ionic composition of the melanosomal lumen (Brilliant, 2001; Cook et al., 2009; Graf et al., 2005; Lamason et al., 2005; Sulem et al., 2008; Valenzuela et al., 2010). Their allelic variants seem to act as a switch between dark and light hair colour (Cook et al., 2009; Mengel-From et al., 2009). Although large progress has been made in the field of genetics of human pigmentation and a few genotype-based hair colour determination models for Europeans have been published (Branicki et al., 2011; Kastelic and Drobnič, 2012; Sulem et al., 2007; Valenzuela et al., 2010; Walsh et al., 2013), this topic is still being studied extensively. Many questions regarding the interactions of the genes involved in the process of melanogenesis and the patterns of phenotype inheritance remain to be answered. One must also remember that hair pigmentation is additionally influenced by environmental factors such as sun exposure (Hessefort et al., 2008), diet (Finner, 2013), hormonal metabolism (Slominski et al., 2004; Tobin, 2008; van Beek et al., 2008), and also by an individual's age (Sitek et al., 2012; Sitek et al., 2013). It is still necessary to continue research in this field, since populations from different geographical regions and of mixed ancestry might differ in the SNP pool that correlates with a given hair colour.

The main goal of this study was to investigate the relations of SNPs within the selected candidate pigmentary genes with hair colour in the Polish population and to determine their effect on hair colour prediction.

Materials and methods

Participants

All participants were adult volunteers aged over 18 years and living in Poland, who donated saliva samples to the Biobank Lab at the Department of Molecular Biophysics of the University of Lodz – POPULOUS collection. Sample collection and anthropological data acquisition through a questionnaire were performed as previously described (Koszarska et al., 2014; Strapagiel et al., 2016). For this study, 186 individuals were randomly chosen and categorised into three distinct groups according to their declared, self-assessed natural hair colour. The mean age of the participants at the time of taking samples of biological material and of the examination was 39.97 years, sd = 14.24 years. Their age ranged from 18 to 74 years. We established groups representing three major hair colour categories according to the Fischer-Saller's scale, i.e., red, blond and dark (Table 1). The proportions of the individuals in each hair colour category were evened out by enlarging the red-haired group in order to increase the ability to reveal associations between the categories and genetic variants. Thus, it should be noted that the frequencies of the studied hair colours do not reflect their real proportions in the Polish population. The frequency of red-haired individuals in the Polish population is about 0.7% (0.9% when including red blond), as calculated from data gathered by the Biobank Lab at the University of Lodz (Table 1a). The established red-haired group consisted of 45 individuals representing shades of red from blond-red to copper-red. The dark-haired group included 77 individuals whose hair colour ranged from light brown through chestnut to black. Sixty-four individuals represented the blond-haired group with shades ranging from platinum blond through blond to dark/honey blond.

Table 1
Hair colour classification into three distinct categories.

Hair colour category	Declared hair colour	*N* (%) in the 186 participants group
Dark	Black, dark brown, brown, chestnut	77 (41.4)
Blond	Dark blond, blond, light blond	64 (34.4)
Red	Red, red-blond	45 (24.2)