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Genotype versus phenotype: Human pigmentation

Gillian Tully *

The Forensic Science Service Ltd., Trident Court, Solihull Parkway, Birmingham B37 7YN, United Kingdom

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Abstract

The natural range of hair and skin colour is a continuous spectrum, controlled by multiple genes in a complex fashion. Many of these genes are as yet unknown, but several key pigmentation genes have been characterised, in particular the melanocortin 1 receptor gene (MC1R). Here, the function and known mutations of MC1R and other human pigmentation genes including *ASIP*, *MATP*, *SLC24A5*, *TYR*, *TYRP1* and *OCA2* are outlined, and a forensic test based on MC1R SNPs presented. The forensic utility of this and potential future genetic tests for phenotypic traits are discussed, in the light of the extensive debate on the ethics of predicting phenotypic traits from crime scene samples.

Keywords: Pigmentation; Phenotype; Genotype; Intelligence; Investigative

1. Variation in human pigmentation

There is a wide range of pigmentation in humans within and between ethnic groups, ranging from the very dark skin, black hair and brown eyes of West African populations, through to the fair skin, blond hair and blue eyes common in Scandinavian populations.

It is chiefly the number, size and distribution of pigment-filled melanosomes, and the ratio of black/brown eumelanin to yellow/red phaeomelanin pigment that gives rise to this variation [1]. The genetics has not been fully elucidated as yet, but there are probably more than 100 genes involved, some of which have major and some minor effects; the effects are quantitative and interactive [2].

2. Outline of melanogenesis

α-Melanocyte stimulating hormone (α-MSH) binds to MC1R, triggering a rise in intracellular cyclic adenosine monophosphate (cAMP) [3] and activation of the microphthalmia transcription factor (MITF) [4]. This activates several enzymes within melanosomes, the first of which is tyrosinase (TYR) [5]; tyrosinase acts on tyrosine to make dopaquinone, and there is then rapid addition of cysteine, as long as it is present. The product of this reaction is then oxidised to give phaeomelanin [6]. If cAMP levels are limited, this form of melanin is favoured and phaeomelanosomes are formed and passed into the surrounding keratinocytes. However, MITF also stimulates tyrosine related protein 1 (TYRP1) and dopachrome tautomerase (DCT) [5], which in the right conditions, produce eumelanin. The proteins Pmel 17, MATP, P and SLC24A5 are all required to give these optimal conditions: Pmel 17 forms the fibrillar matrix on which eumelanin is formed (reviewed in [7]), and MATP, P and SLC24A5 are all involved in cross-membrane transport/trafficking [8–10], favouring eumelanin production and maturation of eumelanosomes. This outline is illustrated in Fig. 1.

3. Known pigmentation genes

In mice, 127 genes have been identified that have an effect on skin, hair or eye colour [11]. In humans, the orthologs of many of these genes have been identified but only around a dozen have been characterised, some of which are associated with disease states but have not been associated with normal pigment variation within or between population groups (reviewed concisely in [2]).

3.1. Melanocortin 1 receptor gene (MC1R)

Probably the best characterised gene involved in normal pigmentation variation in humans is MC1R. It is a 317 amino acid G coupled receptor with seven transmembrane domains,

* Tel.: +44 121 329 5471; fax: +44 121 622 2051.
E-mail addresses: gillian.tully@fss.pnn.police.uk, gill@biltons.plus.com.

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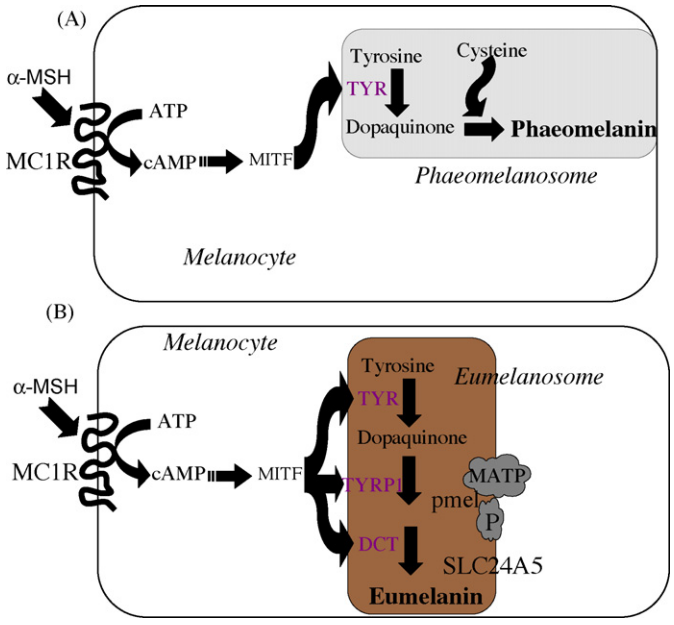

Fig. 1. Outline of melanogenesis. (A) α-Melanocyte stimulating hormone (α-MSH) binds to MC1R, triggering a rise in intracellular cyclic adenosine monophosphate (cAMP) and activation of the microphthalmia transcription factor (MITF). This activates tyrosinase (TYR); tyrosinase acts on tyrosine to make dopaquinone, and there is then rapid addition of cysteine, as long as it is present. The product of this reaction is then oxidised to give phaeomelanin. If cAMP levels are limited, this form of melanin is favoured and phaeomelanosomes are formed and passed into the surrounding keratinocytes. (B) MITF also stimulates tyrosine related protein 1 (TYRP1) and dopachrome tautomerase (DCT), which in the right conditions, produce eumelanin. The proteins Pmel 17, MATP, P and SLC24A5 are all required to give these optimal conditions, favouring eumelanin production and maturation of eumelanosomes.

polymorphism in which was first linked to red hair, fair skin and poor tanning ability in 1995 [12]. This phenotype is known as the RHC phenotype and there have since been a large number of studies on polymorphisms in MC1R, which cause reduced functionality in the receptor to varying degrees (e.g. [13–16]). Table 1 summarises the common polymorphisms in MC1R, their penetrance and functional significance.

MC1R does not appear to have a major role in between ethnic group pigmentation differences [17], although functional MC1R is essential for very dark skin and hair pigmentation. The effects of phenotypic effects of MC1R mutations in Black Jamaicans have been reported [18], with RHC variant genotypes being associated with auburn hair, freckles and ''rust-coloured'' skin.

MC1R variants have also been linked with eye colour [19].

3.2. Agouti signalling protein gene (ASIP)

The role of Agouti signalling protein in human melanogenesis was unclear and somewhat controversial for many years, as in animals it is responsible for hair banding patterns. A polymorphism in the 3′ untranslated region (3′UTR) has been reported [20,21]. It was originally reported as an A to G substitution at position 8818, giving rise to darker skin and hair, although Bonilla et al. [22] showed that G is the ancestral state, with A being a dominant substitution. Agouti signalling protein (ASP) translated from *ASIP* 8818A acts as a strong antagonist to α-MSH, binding to MC1R and thus blocking the cAMP mediated signalling within melanocytes. Phaeomelanin production is therefore favoured, leading to maturation of phaeomelanosomes and lighter colouration. This has been shown to be related to greater levels of mRNA production from the AA relative to the AG genotype, suggesting higher ASP levels and thus more antagonist action at MC1R [23]. Because of the interaction with MC1R, Kanetsky et al. [21] postulated that *ASIP*8818G may explain instances where MC1R typing suggests that the RHC phenotype is likely, but a brown hair phenotype is observed.

ASP polymorphism has also been linked to eye colour variation [19].

3.3. Membrane associated transport protein gene (MATP)

Although the role of MATP in pigmentation is not completely clear, it can cause a form of albinism in humans [24]. Graf et al. [25] reported two SNPs in *MATP* which are not associated with disease states but which are associated with normal variation in pigmentation within and between populations. The 374Leu substitution was present at a significantly higher frequency in Asians (0.887), African Americans (0.586) and Australian Aborigines (0.725) than in Caucasians (0.066). Caucasians with 374Leu tended to have darker pigmentation, the highest frequency of the substitution being seen in

Table 1
Mutations in the MC1R gene, their penetrance and functional significance (where known)

Mutation	Type	Designation	Penetrance (odds ratio)	Functional significance	References (for functional significance and penetrance)
R151C	Mis-sense	R	63.3	Altered cellular location	[16,26]
R160W	Mis-sense	R	63.3	Altered cellular location	[16,26]
D294H	Mis-sense	R	63.3	Impaired G coupling ability	[26,27]
D84E	Mis-sense	R	63.3	Altered cellular location	[16,26]
I155T	Mis-sense	Lack of statistical data—strong familial association		Altered cellular location	[16,26]
V92M	Mis-sense	r	5.1	Reduced α-MSH binding	[26,28,29]
V60L	Mis-sense	r	5.1		[26]
R163Q	Mis-sense	r	5.1	Slightly reduced α-MSH binding	[26,29]
R142H	Mis-sense	Lack of statistical data—strong familial association			[26]

individuals with black hair (odds ratio (OR) 25.6), olive skin (OR 28.6) and dark eyes (OR 3.5). A similar pattern was observed with the Glu272Lys mutation, with odds ratios for black hair, olive skin and dark eyes 43.23, 8.27 and 6.57, respectively. However, the 272Lys substitution may not be a causative mutation, the pigmentation associations reflecting instead linkage disequilibrium with 374Leu [25].

The functional significance of these mutations has not been fully elucidated, but MATP has been implicated in tyrosinase trafficking [30], and Phe374 may alter trafficking. Alternately, it may be involved in proton transport [24], with 374Leu resulting in optimal intramelanosomal pH for eumelanin production [25].

3.4. SLC24A5: golden mutations

The *golden* gene was discovered first in the zebrafish, where it causes a significant lightening of the stripes [10]. The same group identified and characterised the human ortholog, and showed that the substitution alanine to threonine at amino acid 111 had a similar lightening effect on human pigmentation. The effect of this substitution was shown to be partially dominant, and have an effect on skin melanin index of between 7.6 and 11.4 melanin units (95% confidence intervals). This accounts for 25–38% of the European/African difference in skin pigmentation, but it is believed that the lightening effect caused by this gene may be permissive for the effects of other pigmentation genes in Europeans.

Interestingly, the 111thr allele was shown to be virtually fixed in European populations ($f = 0.987$–1.0), whilst the ancestral ala allele had a frequency of 0.93–1.0 in African, Native American and East Asian population samples. This taken together with a marked decrease in heterozygosity in the surrounding 150 kb, points to significant evidence for selective pressure at this locus.

SLC24A5 is believed to code for a potassium-dependent sodium/calcium exchanger spanning the melanosomal membrane, and the calcium may be required for activation of the *silver* gene to produce Pmel 17, which is required to form mature eumelanosomes, and which itself is implicated in eye colour variation [19]; melanosomal pH regulation may also be a role of SLC24A5 protein [10].

3.5. Tyrosinase and tyrosinase related protein 1 genes

Another gene involved in between population pigmentation differences is *TYRP1*. The protein encoded by this gene (TYRP1) was found by Alaluf et al. [31] to be elevated 2.6 times in darkly pigmented African and Indian skin types compared with lightly pigmented Mexican, Chinese and European skin types. Furthermore, Izagirre et al. [32] reported on evidence for adaptive selection operating at this gene in Caucasians.

Although Alaluf et al., found no variation in tyrosinase levels with ethnicity in their study [31], studies of ancestry informative markers by Shriver et al. [17] do point to a role for elevated TYR activity in darkly pigmented skin. A similar study by Frudakis et al. [19] points to a role for TYR, TYRP1 and a third main melanosomal enzyme, dopachrome tautomerase (DCT) in eye colour variation.

3.6. Oculocutaneous ablanism type II gene (OCA2)

The *OCA2* gene encodes the trans-melanosomal membrane protein ‘‘P’’. Although mutations in this gene are responsible for a form of albinism (OCA2), it has also been associated with normal pigmentation variation [9,33,34]. The Arg305Trp polymorphism is associated with between population pigmentation differences; the 305Trp allele is the most common in Caucasians, with a frequency of 0.83, whilst the 305Arg allele is the most common in black-skinned individuals, with a frequency of 0.9 [9]. This and other *OCA2* polymorphisms have also been associated with eye colour variation [19,35].

4. Intelligence use of phenotype prediction

With the increasing volume of information about the genetics of human pigmentation, it is worth considering how prediction of phenotype information from DNA is and could further be used in generating intelligence for the investigative stages of an inquiry.

Generally, the first step in analysis of a crime scene sample is production of a short tandem repeat (STR) profile using a multiplex amplification kit. In the United Kingdom, the SGMplus™ multiplex (Applied Biosystems, Foster City, CA) is used to amplify 10 STR loci plus the XY homologous amelogenin gene. The resultant profile is then compared against the National DNA Database (NDNAD). If the sample matches against a suspect sample on the database, no further intelligence information is required. However, if there is no match against the NDNAD suspect samples, it is worth considering what further intelligence the forensic scientist can add. Initially, any additional intelligence information that can be determined from the STR profile already obtained should be mined. The simplest additional information available is the sex of the individual who left the DNA trace. However, ideally, the investigating officers are looking for very direct intelligence, by preference a name or list of names of potential suspects for further investigation. One recent way of providing further intelligence to assist the police in their investigation is familial searching, whereby if the donor of the DNA sample is not on the NDNAD, a search is conducted to find individuals who share many alleles with the individual who left the DNA sample in question. In this way, a list of potential relatives of the individual of interest can be generated, which can be prioritised according to locality, age and any other known intelligence about the crime [36,37]. Further to this, by exploiting differences between populations in the frequency of STR alleles, an inference regarding the likelihood of obtaining the particular profile if the donor individual came from each of the main ethnic groups can be calculated [38].

If these sources of intelligence are exhausted, the possibility of further DNA analyses can be considered. It is at this stage in the process of intelligence provision that specific phenotype prediction tests would fit. Phenotype prediction clearly involves

an element of uncertainty, due to the interaction of genes and environment, the ability to disguise traits like hair colour by dying and the incomplete nature of the genetic information being utilised for phenotype prediction. Even if our knowledge of, for example, pigmentation genetics were complete, there would in most cases be insufficient DNA present and insufficient resource available to enable the multitude of loci involved to be typed. Given this uncertainty, how then can any intelligence information produced by such tests be employed? It will not lead straight to an offender, but it may be useful particularly in feeding into the process of ordering samples for collection and processing in a mass screen of individuals. Such screens are employed on occasions in serious crimes where no suspects have been identified by other means, but the investigating team have confidence in identifying a pool of potential suspects by, for example, geographic area. These screens are already prioritised by investigators using any available intelligence information, for example, sex, locality, age range, ethnic appearance. Phenotype predictions would feed into this targeting. If a screen is effectively targeted, the offender may be found on the first few batches processed, rather than several thousand samples later. This obviously saves money, but more importantly, reduces the chance of further crimes being committed by the same offender.

On occasion, phenotype prediction may be used in helping to determine the relevance of a piece of physical evidence to the inquiry. One case example which came to the attention of the Forensic Science Service (J.E. Bark, personal communication), involved a shooting in Glasgow. Ballistics information was able to pinpoint the building and indeed the window in the building from which the shot was fired. At this location, a cigarette butt was recovered. An eyewitness had reported a red-haired man running away from the scene; the investigators wanted to know whether or not the cigarette butt was relevant to the inquiry by determining whether or not it had been smoked by a red-haired man. In this instance, the test would have been used in order to decide whether or not to conduct a mass screen to find the individual who had smoked the cigarette.

Critical to successful usage of phenotype prediction is clear, two-way communication between the investigating officers and forensic scientists. DNA typing has become synonymous in the eyes of lay persons with highly discriminating, accurate identification of individuals, and the limitations of any intelligence test must be clearly communicated at every stage.

5. Phenotype prediction tests

For any phenotype prediction test, speed is of the essence. Intelligence becomes of limited value if it cannot be provided quickly to the investigating team. In addition, it must use a minimal amount of sample, as the DNA evidence may be from a contact trace with limited scope for multiple analyses. It should be predictive of trait which is readily observed and difficult to disguise, and should predict the trait as definitively as possible. For example, it would be of little value to predict that a suspect's height may be in the range 5′6″–6′2″, as this range includes the vast majority of the adult male population. As far as possible, the prediction test should not be predictive of disease status or susceptibility.

5.1. MC1R genotyping

In 2001, the first example of a phenotype prediction test for intelligence use in criminal investigations was published [39]. This paper described a multiplex minisequencing protocol for rapid screening of DNA samples for the presence of 12 MC1R variants. In a sample of 197 individuals, 96% of individuals with two ''red hair causing'' mutations had self-described red hair; the remaining 2 individuals had self-described as red-haired in youth. It is noteworthy that Grimes et al. did not classify the V60L, V94M, I155T or R163Q mutations as associated with red hair, although they were typed in the minisequencing assay. The OR for red hair with the V60L, V94M, and R163Q mutations is only 5.1 (see Table 1; [26]). This illustrates a general principle that it is important in a single gene phenotype prediction test for investigative processes to restrict the interpretation of causative mutations to those which have a high penetrance; as a piece of intelligence information, the fact that there is an approximately 5% chance of an individual having red hair is virtually useless.

5.2. Eye colour prediction: Retinome™

A study by Frudakis et al., of 754 SNP loci in 851 individuals [19], identified 61 SNPs associated at some level with iris colour. Around half of these SNPs were independently associated with iris colour, whilst the remainder were associated only if considered as part of a haplotype or diplotype (diploid pair of haplotypes). DNAPrint™ Genomics provide a multiplex SNP based test for prediction of iris colour, based on this work, providing inferences that are reported to be correct ca. 92% of the time (www.dnaprint.com).

6. Ethics

The Human Genetics Commission is the UK Government's independent advisory body on social and ethical issues in human genetics. This body has produced a report which raises public concerns over using genetic information to predict the characteristics of a person [40]. However, as they point out, ''Some genetic information is not considered private because people can see it, for example, your eye colour.'' On this basis, an initial response may be that all traits we would seek to predict are traits that can be observed – otherwise, their value in providing intelligence is limited. Nevertheless, the issue is in reality more complex. Many pigmentation genes are predictive of susceptibility to skin cancers. Clearly, individuals with the RHC phenotype are at higher risk of skin cancer than are dark skinned individuals. It could therefore be argued that this disease susceptibility can be observed based on the individual's phenotype, and so there is no ethical requirement to avoid the prediction. However, taking the example of non-melanoma skin cancer, the MC1R variants most strongly predictive of the RHC phenotype are not the same as those most strongly associated with cancer [41]. If a phenotype prediction test is based on the

most phenotype-informative single nucleotide polymorphisms (SNPs), there would be no need to type the SNPs most informative of disease susceptibility; this is preferable to obtaining unnecessary genetic information by fully sequencing the gene involved. There is, however, often overlap between the two sets of informative SNPs.

The Human Genetics Commission considers instances where an individual may forfeit their right to genetic privacy. They mainly consider instances such as where an individual with an inherited susceptibility to disease will not consent to inform relevant family members who may also be at risk and should be under medical supervision. The Commission writes ''We lead our lives as members of large and small communities and we have certain duties to other members of these communities. Such duties involve not causing harm to others. . .'' Do we forfeit rights when we forfeit responsibilities?

It is certainly incumbent on the forensic science community to avoid as far as possible typing markers which are predictive of disease status or susceptibility, and from an ethical standpoint, restricting genetic typing of coding loci to those which are predictive of an observable trait is advisable.

7. Phenotype prediction: the future

Many groups are working on gene discovery and characterisation, and a large number of SNPs in pigmentation genes have been reported, many of which have been detailed above. Furthermore, by studying ancestry informative markers (AIMs), additional SNPs associated with, if not causative for, pigmentation variation have been discovered (e.g. [17,19]). To date, utilisation of these SNPs for phenotype prediction has not kept pace. As the technology for rapid and multiplexed analyses of ever smaller DNA traces improves, it will be possible to think differently about the process of intelligence prediction. Instead of a sequential process in which the results from one test are incorporated into the investigation prior to deciding whether or not to proceed with the next test, it may be possible to combine many markers and test simultaneously to provide a fuller picture of potential phenotypic characteristics to the investigators in virtually ''real time,'' possibly even at the crime scene.

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