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Forensic DNA phenotyping: A promising tool to predict human appearance for forensic purposes

Pushpesh Kushwaha *, Umema Ahmed and Manisha Rana

Department of Forensic Science, Vivekananda Global University, Jaipur, Rajasthan, India- 303012.

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Abstract

Forensic DNA phenotyping (FDP) based on Next Generation Sequencing (NGS) is an emerging technique that is generally based on the idea that each individual is genetically unique, except monozygotic twins. This technique portrays an individual's externally visible characteristics (EVCs) from DNA obtained from biological samples. Various studies seeking to link the relationship between polymorphisms and phenotypic characteristics are increasing and have shown promising results in helping forensic sciences and are becoming one of the most useful additional tools for helping investigating agencies in different types of criminal cases and individual's identification. Eye, hair and skin color can now be predicted reliably and accuracy. Although, FDP has not yet been implemented routinely in the forensic science field due to the lack of complete genetic knowledge of phenotypes. Also, in some countries its application has given rise to a number of ethical, social and legal issues, which is being the most restrictive barrier to the implementation of FDP.

Keywords: Forensic Science; Forensic DNA phenotyping; DNA; Externally visible characteristics; Forensic genetics

1. Introduction

Since the use of various DNA technologies to enhance the activities in Forensic casework worldwide, there has been a tremendous growth in the potential ways they can be used. The identification of individual via the process of Short Tandem Repeats (STR) has been considered the golden standard in forensic genetics (1–3). But, a major limitation of this comparative approach of DNA analysis is that it generally fails to identify persons where we don't have any suspect or control sample. Sometimes, cold cases may take longer periods of time before the evidence STR profile is matched with a known person after a long-long investigation or after a mass screening. In cases of mass screening, larger number of persons (from hundreds to thousands), from the same geographic region where the crime occurred, voluntarily provide biological sample for DNA profiling. But, the actual perpetrator may not participate voluntarily, due to awareness of the provided sample, leading to identification. This may waste time as well as resources. In this condition, forensic DNA phenotyping (FDP) can be useful tool. This review addresses the emerging technology in the field of forensic genetics i.e. forensic DNA phenotyping. FDP is a set of techniques that depicts the lineage and externally visible characteristics of individuals on the basis of a biological sample (4,5).

The use of this technology started very late in the early 2000s and progressed very slowly due to little knowledge about the science of most human Externally Visible Characters (EVCs). The basic reason for this little genetic knowledge is that the research funding strategies generally focuses more on disease-related variations than on normal human variations (6).

Various studies are there which have portrayed the existence of polymorphisms associated with skin, hair, eye color, facial features, stature, and baldness using various markers respective of the character. The genetic analysis of these genetic markers can contribute significantly to increase the accurate information on the physical characteristics of an

* Corresponding author: Pushpesh Kushwaha

individual. Of all the EVCs, those that involve pigmentation i.e., variation in the coloration of the human iris, head hair and skin are the best examples of practical FDP. So, pigmentation traits genetics is advanced than other EVCs

Although, irrespective of the advancements, this tool also has lots of limitations and this is the reason why it has yet to be used in the field of criminal justice system in countries like India. Also, its application has led to various debates in the society about ethical, social and legal situations which must be resolved in order to use FDP as a routine tool in forensic science (7,8).

1.1. Phenotype prediction from DNA markers

1.2. Eye color

Human traits which have most color variations, Eye color varies from light shades of blue to dark shades of brown or black, also intermediate colors such as gray, hazel, yellow and green. The color difference has a common pattern related to the pigmentation of the skin and hair, which generally depends on the amount and number of melanin and melanosomes respectively. In some studies, gender of the individual has also been seen as an influencing factor in prediction of eye pigmentation. Women have been observed to have darker eyes than men. However, this has not been proved genetically that X-chromosomal gene contribute to human eye color variation (6,9–12).

The initial studies based on prediction of DNA-based iris color prediction were published in the year 2007 (3,13) and the first comprehensive DNA prediction study on eye color was published in 2009 by Liu et al (14,15). The first developed phenotyping tool was Irisplex System which consists of 6 SNPs (*HERC2*, *OCA2*, *SLC24A4*, *SLC45A2*, *TYR*, and *IRF4*). The IrisPlex assay is highly sensitive, delivering complete 6-SNP profiles down to about 30 pg input DNA This tool basically differentiates brown and blue eyes accurately. The IrisPlex assay was tested by the European DNA Profiling Group (EDNAP) in a multi-center exercise comprising around 20 laboratories, and was found to be easy to implement and highly reliable. However, the accuracy rate in Asian population was less, suggesting further research to be done in this population. Further research also needs to be done to identify new genetic variants and increase the accuracy of the current variants (5,16–18).

1.2.1. Hair color

Hair color is among the most noticeable EVCs with a variety of phenotypes. Initial studies on hair color were focused to red hair only. The basic differences in hair color are due to melanin type's i.e. brown/black eumelanin and red/yellow pheomelanin. Grimes et al. predicted the hair color for the very first time. Hair color in FDP has already been researched by many researchers like Branicki et al., Sulem et al., and Valenzuela et al (8,19–22).

MC1R SNP was the first to be used to demonstrate red hair and later on, other genes, such as *SLC45A2*, *SLC24A5,* and *HERC2* were used which were based on 22 SNPs which increased the accuracy rate for hair color differentiation (5).

In 2013, a new advanced system was developed by adding 18 new hair color markers to the 6 already existing Irisplex SNPs. This test system is known as HIrisPlex system and is known to have a single multiplex genotyping assay for SNPs associated with eye and hair color and comprises of markers *MC1R* SNPs *(*indel*, Y152OCH, N29insA, rs1805006, rs11547464, rs1805007, rs1805008, rs1805009, rs1805005, rs2228479, rs1110400,* and *rs885479), SLC45A2 (rs28777* & *rs16891982), KITLG (rs12821256), EXOC2 (rs4959270), IRF4 (rs12203592), TYR (rs1042602 and rs1393350), OCA2 (rs1800407), SLC24A4 (rs2402130 & rs12896399), HERC2 (rs12913832), ASIP/PIGU (rs2378249),* and *TYRP1 (rs683)* (3,9,12,17,23).

One challenge faced by current hair prediction models is that the prediction is only accurate on adult populations. So, the accurate hair prediction is challenging in the individuals who had hair color changes throughout life. In future, quantitative hair color prediction should be focused as research on this aspect is very less (12,20,24,25).

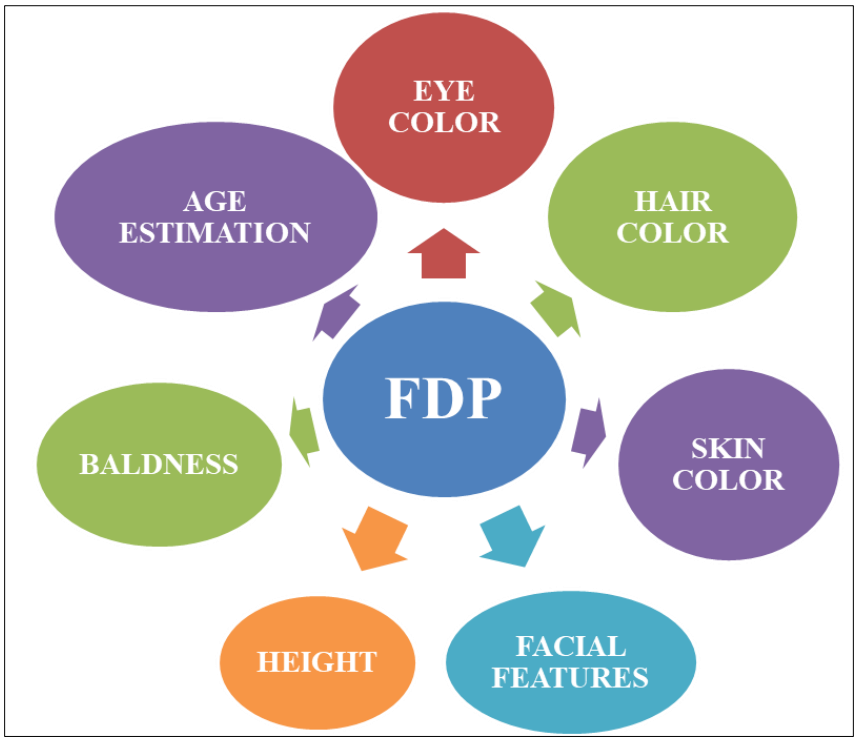

Figure 1 Various characters employed for Forensic DNA Phenotyping

1.2.2. Skin color

This EVC is one of the most complex and less studied variation of pigmentation. This could be because of the heterogeneous distribution of pigmentation variation. The skin pigmentation is thought to be emerged as the response against ultraviolet radiation. The regions nearer to Equator line would portray dark skin tone and regions in distance to Equator line would portray lighter skin tone and the shade will get lighter from darker depending on the distance. And this becomes difficult in FDP studies due to variation due to specific area (7,9,15,21,26).

A prediction model was given which was based on 36 markers where skin tones were taken in to account- three (light, dark, dark–black) or five (very pale, pale, intermediate, dark, dark–black) and predicting 83%-97% and 72%-97% respectively for both. The compiled results were used from IrisPlex, HIrisPlex, and HIrisPlex-S systems to portray eye, hair, and skin color from biological samples (27,28).

As only a very few studies have been done yet, it becomes important to add more data through research in order to predict skin color accurately. As demonstrated earlier for eye and hair pigmentation for future, skin pigment prediction should also be done in accordance with quantitative prediction (21,29).

1.2.3. Facial features

Identification through facial features is the easiest of all. One can easily predict facial features using FDP by studying the facial landmarks like width of lips, nostrils, face height, nostril width etc. Some markers are used in facial feature prediction, which were initially found in facial deformities studies as they are related to craniofacial development linking to the normal facial variation. Some genes which are used in this prediction are *PRDM16* and *TP63*. First step towards facial feature prediction refers to (8,30) where, ancestral and gender information was used to predict the face. Other studies are also there but very less in number. The approach to predict facial features needs to be taken more serious as this will set a landmark in forensic casework analysis, if developed completely. The knowledge about facial variation is very scarce yet, this aspect needs to be researched more as this can be a gold standard technique in the field of FDP (6,7,31–34).

1.2.4. Stature

Until 2008, only a few genes have been described as associated with human height. Aulchenko et al. (2009) did the very first systematic study on body height in 2009 (3,8,35). Although, body stature has very vast data availability if we talk about anthropological aspect. A large number of studies are there related to stature identification but for FDP, the area

has been researched very less. The genes which are used in FDP are associated with growth such as fibroblast growth factor and growth plate. However, many of them are not directly helping in human growth. For prediction of stature, there are no significant values of height related variants. Initially, 65% accuracy rate was obtained which still could not surpass 75% rate. This means a lot of SNPs are yet to be discovered. So, a lot of research still needs to be done as the current information is very less (7,36–38).

Table 1 Indicates the EVCs and their associated genetic markers

Externally Visible Characters (EVCs)	**Markers**
Eye color	HERC2, IRF4, LOC105370627, OCA2, SLC45A2, TYR, SLC24A4
Hair color	EXOC2, HERC2, IRF4, KITLG, MC1R, OCA2, SLC24A4, SLC45A2, TYR, PIGU
Baldness	AR/EDA2R, EBF1, HDAC9, TARDBP, 20 p11, TCHH, PTK6, HOXC13, RPTL, TRAF2, FLG-AS1, FRAS1, S100A11, GATA3, PX14, LIPH, KRTAP2-3
Facial features	ADAMTS2, ASPH, C5orf50, COL11A1, COL17A1, CTNND2, DNMT3B, EVC2, FBN1, FGFR1, FGFR2, GDF5, LRP6, PAX3, POLR1D, PRDM16, RAI1, RELN, ROR2, SATB2, SEMA3E, SLC35D1, TP63, UFD1L
Height	ACAN, DNM3, EFEMP1, FBXW11, GH region, GHSR, GPR126, HHIP, HMGA1, HMGA1, IHH, LCORL, MICA, NOG, NPR3, PML, PPIF, SDR16C5, SOCS2
Skin color	ANKRD11, ASIP, BNC2, DEF8, HERC2, IRF4, KITLG, MC1R, OCA2, PIGU, RALY, SLC24A4, SLC45A2, TYR, TYRP1, SLC24A5

1.2.5. Baldness

As per the current studies over the feature of baldness, 12 genomic regions have been identified so far which are related to the initial onset of androgenic alopecia (AGA). AGA is associated to male baldness which is a strong hereditary factor, displaying a heritability of around 80% and genes related to it are AR/EDA2R, TARDBP, HDAC9, AUTS2, SETBP1, PAX1/FOXA2, WNT10A, 17q21.31, 3q25, 5q33.3, and 12p12.1 (8,15,39–41).

The trait of hair loss needs to be studied more as all the studies are done on initial onset patterns. So, studies related to late onset baldness needs to be done as they may predict FDP in a better way (5,6).

1.2.6. Age estimation

If age can be predicted then EVCs such as baldness, wrinkles etc. would strongly get benefitted. Age itself is an EVC as it is visible to a certain extent. Predicting the age of an unknown person can strongly help in the investigation process and can provide further leads as the number of suspects can be reduced. Several studies are there for prediction of genes responsible for age and established the relation of T-cell numbers with age. They decrease with ageing and this was used by Zubakov et al. in 2010 for estimating age by quantifying the sjTREC (3,8,42,43).

The field of epigenetics has been advanced in recent years and DNA methylation detection technologies have been useful to the age estimation of an individual as age is dependent on methylation. The level of methylation is more in childhood and it decreases after reaching adult stage. Also, CpG candidate markers are highly promising. This variation can be used to estimate the age of individual using biological samples accurately (5,9,44,45).

2. Case studies

In 2010, a female was sexually assaulted in daytime in Florida (USA). On DNA analysis from samples collected from crime scene, DNA database did not found any matches. After 7 years, a private DNA phenotype company on contract basis, predicted a facial composite of a male subject, having a light brown skin, brown-hazel eyes, and black hair. This lead to the re-investigation of the case and police found a suspect with similar matching characteristics. The DNA analysis of the biological samples from the suspect showed that semen sample found on the victim shared the same STR profile and match was done using FDP.

Another case was of a 19 year old girl whose body was found near road in November 2009. Skin tissue in deceased fingernail was found on investigation. And the sample was sent for DNA analysis. Also, at the same time, police was

hunting down another lead, a number she dialed before she was killed. This lead them to a group of unregistered Mexican workers. Swabs were taken from them and DNA analysis was done but none of them matched with the profile obtained from crime scene sample. Neither, it matched with the FBI database and the case went cold. In 2015, due to FDP, re-investigation was done. The sample from crime scene showed a man of northern European descent with characteristic's having pale skin, freckles, brown hair, and light eyes. The portrait led to the arrest of the accused and the DNA profile from his samples matched with the questioned sample at the crime scene and case was solved.

There are a number of cases where no record was found in the database and the case went to cold. Such cases Have been re-investigated using FDP technology and the predicted picture of the culprit was portrayed which resumed the investigation. It proves that FDP technology is highly valuable in forensic casework (3,5,6,23).

3. Legal and Ethical Perspective of FDP

The predicted scope of FDP technologies and their potential application in forensic work may be significantly adapted for seeking additional information in any criminal investigations. However, its tendency to reveal crucial information which might be categorized as private or personal appears to bring up various ethical and social issues especially regarding discrimination (46). A number of researchers including Kayser and Schneider 2009; MacLean 2013; Silva de Cerqueira et al. 2016 favor the fact that the phenotypic character carried by an individual is not only known to him but is also visible to everyone who has seen the person before, thereby such visible characters do not remain private to a specific individual. However, legal procedure faced by innocents falling under the group of individual bearing a questioned EVC might cause negative impact on individuals' life as well as discomfort in their social life. Various social and ethical researchers critic the implementation of FDP stating that the information so revealed by such analysis may results in racial and ethnical discrimination majorly towards minorities (49). Some of the researchers also come-up with the point that the scientific approach towards FDP will not be understandable to the persons within police and criminal justice system without any scientific background, and therefore, they may over-interpret the data from FDP and there is a possibility of taking false direction in the casework and ultimately resulting in wastage of resources. However, in response to this issue raised, application of FDP must be implemented only after establishment of standard protocols and regulation of a balanced weightage given to FDP data. Also, FDP data must not be blindly selected for finding leads, but must be accomplished with certain corroborative evidences (7,50) .

Data protection is another point debated over implementation of FDPs. Steps must be taken toward protection and vigilance of data related to phenotyping. All such data must be erased after case disposals. All the data depositories and laboratories engaged in analysis and storage of such data must be regulated by guidelines regarding the time period for storage of such data in case of disposed cases as well as for cases that are not yet solved (51). Certain regulatory measures must be taken for establishing and maintaining the confidentiality of EVC data for appropriate application within forensic caseworks (5,6,46).

4. Conclusion

Forensic DNA Phenotyping is an emerging technology for human identification purpose and many researches are being carried out for advancement and development of this technique. FDP techniques are focused towards identification of unknown individuals by determination of their age, gender, stature and other EVCs. Inspite of being a powerful technology in the field of forensic science, criticisms regarding privacy infringement and data storage and surveillance have slowed down its growth and development. Forensic researchers need to work further for developing FDP markers and analytical techniques to ameliorate forensic caseworks replacing the traditionally employed protocols. Employment of standardized regulation and utility of FDP data coupled with other corroborative evidences will enhance the applicability of FDP in forensic caseworks and will help in solving crime which will lead to a crime free society.

Compliance with ethical standards

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Disclosure of conflict of interest

The author(s) report no conflicts of interests in this work.

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