Chapter

Forensic DNA Phenotyping

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Abstract

The basis for DNA analysis used in forensic research is the concept that everyone, excluding monozygotic twins, shares a genetic makeup. By directly comparing the genetic profile of short tandem repeats obtained from biological samples of unknown origin to a reference sample profile, DNA collected from biological samples can individually identify this material. The requirement for a reference sample for comparison is one of the main drawbacks of this method. Studies looking at the connection between specific polymorphisms and specific phenotypic traits are multiplying, and the results are encouraging for forensic sciences. Externally visible characteristics (EVCs), such as skin color, eye color, hair color, height, facial features, and male baldness pattern, can be inferred from biological samples for forensic purposes. This technique is called "forensic DNA phenotyping" (FDP). Therefore, without the necessity for a reference sample for comparative analysis, FDP offers additional information about the subject to which a specific biological sample belongs. So that this new technology does not encourage segregation or ethnic persecution of certain population groups, several ethical and legal considerations need to be made. Despite this, using these techniques to guide investigations and identify both suspects and victims has helped in a number of actual incidents.

Keywords: deoxyribonucleic acid, skin color, eye color, polymorphism, biological samples

1. Introduction

The basic goal of forensic DNA analysis is to create DNA profiles for identification using biological evidence. The ultimate objective is to identify the source of that biological stuff, which is the individual. Short tandem repeats (STRs), which make up most conventional DNA profiles, can fail to match suspects or entries in DNA databases when created from crime scene samples. In these situations, the donor of the crime scene sample is still unknown, and the evidence cannot be used to support the case any further. The prediction of outwardly visible characteristics (EVCs) from DNA is known as forensic DNA phenotyping [1].

Forensic DNA phenotype (FDP) looks at certain regions of the genome that are connected either directly or indirectly for normal variance in physical appearance between individuals, circumventing the limits of DNA databases and ancestry testing alone. In order to forecast head hair pigmentation, skin pigmentation, eye pigmentation, and other phenotypic features, researchers have created systems like IrisPlex and

Snipper 2.5 that leverage single nucleotide polymorphism (SNP) multiplexing [2, 3]. Additional traits may be predicted through further research.

SNPs, which are single base alterations, or INDELS, which are insertions or deletions that take place at a particular region in the genome, are used in these experiments. These variants not only provide novel leads but also enable the generation of phenotypic profiles from DNA materials as little as 60 pg./l, which is a significant reduction from the published ranges required for a conventional STR profile [3, 4].

2. Advancements in forensic DNA typing

Molecular biology techniques are always improving, opening up new ways to effectively genotype difficult forensic materials and extract genetic material. These have mainly concentrated on the study of genetic marker types that are different from those used in traditional STR typing to help identify humans [5–7]. SNP typing provides an alternate tool for investigations in circumstances where STR typing is unsuccessful. Due to the smaller amplicon size, SNPs can be useful in genotyping highly degraded DNA [8–10].

2.1 Identity informative SNPs

Comparative to conventional testing, which is still difficult, the identification of informative SNPs could be a substantial tool for the identification of individuals [11]. These SNPs will have minimal heterogeneity within particular groups but strong heterozygosity across populations. Consequently, to research the heterozygosity and heterogeneity of various human groups, population-specific informative SNPs are needed [12].

2.2 SNPs for intelligence gathering

SNPs examined for forensic purposes do not directly establish identity, but they can give information that helps detectives focus their search for a positive match. When STR profiling cannot reliably identify an individual, this is advantageous (either from no matches to a database or where no profile can be obtained from degraded remains). Due to the uniqueness of these alleles for particular groups [9, 13–16] or due to their relationship with variations in hair and eye color [2, 16], certain SNP markers found on nuclear and mitochondrial DNA have been employed in forensic investigations of genetic ancestry.

2.3 Phenotype-informative SNPs

Genes implicated in complex traits like EVCs have been identified by genome-wide association studies (GWAS) [17, 18]. The combined effects of several genes that regulate the synthesis or localization of melanin determine the human pigmentation in skin, hair, and eye color [17]. Differential skin, hair, and eye color have been found to be substantially correlated with a number of SNPs [18]. The discovery of genetic markers that infer height, hair and shaft shape [17], facial features [19], and male pattern baldness [20, 21] is a further area of potential SNP typing for externally apparent attributes.

3. DNA phenotyping

3.1 Eye color

Eye color is one the most valuable colors among the phenotypic characteristics, which ranges from dark shades to a light blue shade through intermediate (such as hazel, gray, green, and yellow) colors. These differences follow a similar pattern to the color of hair and skin due to the number of melanosomes and the amount of melanin present in the outer layer of the iris; brown eye color has high melanin amount than blue eye color [22]. This phenomenon was conformed through phenotyping tools (Irisplex) developed and validated. The Irisplex system consisted of six SNPs present among different genes (IRF4, TYR, OCA2, SLC24A4, SLC45A2, and HERC2). The accuracy (>90%), was checked both on admixed and on homogeneous population throughout the world [23–27]. Along with these results, some Asian population did not demonstrate the same results [28]. When the accuracy of intermediate eye color was matched with blue and brown, it showed very lower accuracy [4, 29, 30]. A study by Popiech et al. [31] revealed gene–gene interaction among the three primary pigment genes (OCA2, TYRP1, and HERC2) related with green eye color, despite the difficulty in predicting these intermediate colors, encouraging the development of future prediction models. Gender is another topic that has been considered in relation to the manipulation of eye pigmentation. It has been noted that men tend to have lighter eyes than women do in various European countries [25, 31, 32]. More research will be required to assess this link because no genetic element has yet been identified to account for this variation.

3.2 Hair color

One of the most noticeable EVCs with a wide range of phenotypes is hair color, along with skin and eye colors. Red/yellow pheomelanin and brown/black eumelanin are two distinct types of proteins that are primarily responsible for defending hair color [32]. People with red hair have more pheomelanin than eumelanin, whereas people with dark hair have more eumelanin than those with red hair, and people with blond hair have less of each form of melanin overall [33]. These changes in hair color increased in Europe, which changed from ancestral hair color due the human mating preferences [32]. In the process of melanogenesis control by numerous genes, MC1R was one of the first to determine a strong perceptive rule for red hair, freckles, and fair skin. Later, successive associations of other genes were also found such as HERC2, SLC24A5, and SLC45A2, and based on 22 SNP, a predictive model was developed, which showed 81–93% accuracy for each hair color category [34]. In 2013, modification was made in the Irisplex system by adding 18 hair color markers, and the name was changed to HIrisplex System. This system consisted of markers such as SLC45A2, MC1R, OCA2, HERC2, TYRP1, IRF4, TYR, ASIP, SLC24A4, and EXOC2 genes, and some genes were added from the model previously created by Branicki et al. [35]. It can reach similar accuracy values (75–92%) [36]. Despite good result of HIrisplex System, there were some difficulties in the prediction of hair color, which changes with age (mainly in childhood). Majority of the studies avoid younger population for sampling reason because they have different phenotypes in the early stage of life. So prediction model used for phenotyping showed accurate results for adult samples as compared to childhood; the markers of age-dependent phenotypes partially predict that the blond hair color and accuracy for hair color is lower (80% for black, 78% for red, and 69% for brown) through HIrisplex. In a study carried out on young population aged 6 to 13, the

result explained that hair color darkening occurred at stage of life above then 13 year of age. Hirisplex incorrectly predicted blond hair color of the younger population aged 6 to 13. So additional new SNP sets are needed to overcome this error rate [3].

3.3 Skin color

One of the most diversely researched pigmentation phenotypes is skin color. The development of skin pigmentation is thought to have resulted from an evolutionary reaction to the concentration of ultraviolet light between various planet zones. Contrarily, in locations distant from the Equator, where UV light intensity is lower and lighter skin is permitted, areas adjacent to the Equator would have higher UV intensity and a higher frequency of dark hair color [37].

The evolutionary factor makes the phenotype/genotype linkage research difficult; besides, this phenomenon also creates difficulties in the correlation studies that are only applicable to a single specific population. However, the linkage found in admixed populations did not have the same bias as in more homogeneous populations, such as Europeans [38]. Beside these research studies, other studies were performed on same populations, which were not able to distinguish skin color among different groups of African, Native Americans, and Asian [39]. Based on these evolutionary differences, a skin prediction model was created consisting of 36 SNPs from 16 pigmentation genes [4]. The developed prediction model has the ability to predict skin color; colors were categories of scale, three category scale (dark, light, and dark-black) to five category scale (dark-black, pale, dark, intermediate, and very pale). The prediction accuracies for the three-category scales have 72%–97%, while that for five-category scales have 83%–97. Some of the previous studies have been found associated with admixed population for genes such as HERC2 [40], SLC24A5 [39, 41], and SLC45A2 [42, 43]. These studies can be used for future applications. HIrisplex-s, HIrisplex, and Irisplex were grouped into a single tool, which is openly available for hair, skin, and eye color prediction using genotypes date from DNA (from https://hirisplex.erasmusmc.nl/); different eye, hair, and skin colors are predicted on the basis of probability values obtained from the prediction model having 41 markers.

3.4 Height

Until 2008, various investigations were conducted and found a few genes to be associated with human height. The results of various association studies revealed that 54 loci had a direct correlation with height variance. The number of genetic markers rose over time, reaching 180 in 2010 and 700 in 2014 [40, 43–46]. The discovered genes played a major role in the growth signaling pathway as well as the expression of genes in crucial tissues including fibroblast growth factor [40]. Despite the enormous number of height-related variants, they have little scientific significance. While the initial studies obtained accuracy values of ~65%, the most current studies failed to increase this value >75%, demonstrating the large number of SNPs still to be discovered and how complex this trait may be [47]. Moreover, human height may have a different etiology other than genetic aspects, such as gestational (placental features and maternal health aspects such as nutrition, pathologies, and drugs), hormonal, and environmental factors (nutrition and lifestyle) mainly during childhood [48]. Among all EVCs, the facial shape prediction is one of the major objectives when studying phenotyping, glimpsing the final "DNA facial composite". The face morphology is studied from the distances between facial landmarks, as nostril width, lip width, distance between eyes, and face height. Some of the genetic markers associated with

facial features are initially found in syndromes and facial deformity disease studies (such as cleft palate, cleft lip, and other craniofacial dysplasia). Some of these markers are then correlated to craniofacial development and consequently linked to the normal variation of facial shape [19]. For example, PAX3 gene encodes a transcription factor present in neural crest cells, which was also related to Waardenburg syndrome and was later associated with the nasion position [49]. Other candidate genes have been identified following patterns similar to PAX3, such as PRDM16 and TP63. However, similar to height determination, each of these genetic markers seems to have a small contribution toward the total face morphology [19]. The approach used by Claes et al. [50] based primarily on data obtained from admixed populations employs a first step in which the sample ancestry and gender are used to create a base face, in which data from 24 SNPs will subsequently be used, to convey nose, lips, face roundness, jaw, chin, and supraorbital crest information to this primary face. Other studies also found significant associations with facial width, eyebrow width, distance between eyes, columella inclination, nose bridge width, nostril width, and mouth shape [51, 52].

3.5 Baldness

According to research, the genetic basis of male pattern baldness, also known as androgenic alopecia, is significant and accounts for roughly 80% of its heritability. The X chromosomes q12 region, which contains the genes AR and EDA2R, which are, respectively, directly linked to the synthesis of androgen receptor and ectodysplasin A2 receptor, the 20p11 region, and the genes EBF1, TARDBP, and HDAC9, which have the potential for prediction, are among the many loci that may be implicated. These five SNPs exhibit the highest association values as yet, with a total accuracy of 76.2%. The accuracy rises to 86.4% with the inclusion of 10 markers (rs1050286, rs1160312, rs4679955, rs962458, rs6625150, rs12007229, rs913063, rs6945541, rs1041668, and rs966881), showing that when paired with stronger markers, even SNPs with low prediction accuracy can have high accuracy [20, 52, 53].

3.6 Age estimation

It has been shown that age estimation of an individual benefits from epigenetic study using DNA methylation detection methods, which take a different approach from those previously shown here (SNP typing mostly). Because it completes the data gathered by the EVCs outlined here, age estimation is essential in the forensic context. By establishing the age range of the sample source, one may reduce the number of potential suspects while simultaneously improving the final face composite [54]. DNA methylation changes during the course of an individual's life; levels increase during childhood and then decrease once they reach adulthood [55]. These changes can be detected and used to determine an individual's age from biological samples with as few as seven markers and a variety of origins (tissues and bodily fluids) and in a variety of contexts (either from human remains or from a crime scene) with high accuracy (deviation of 3.15 years relative to the real chronological age) [56].

3.7 Ancestry

Certain DNA markers can disclose an individual's ancestry, allowing for a thorough investigation of their biogeographic contributions (Africa, Europe, Asia, and Amerindian). As a result, ancestry informative markers (AIMs) can be utilized to

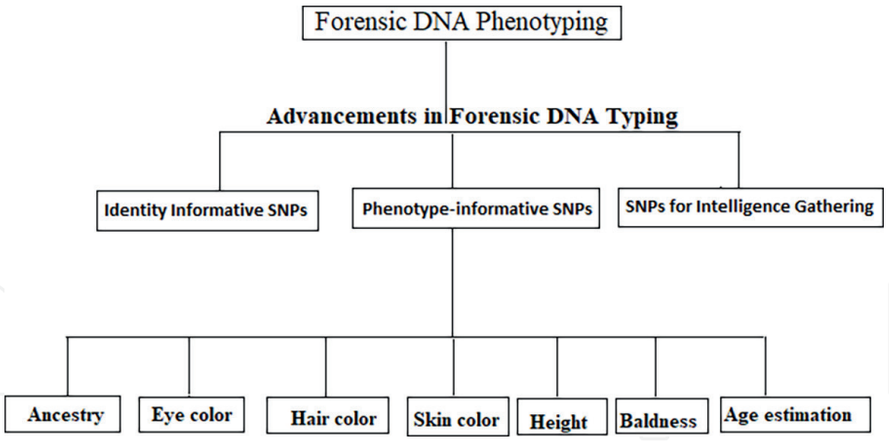

Figure 1.
Flowchart showing the search results and screening process.

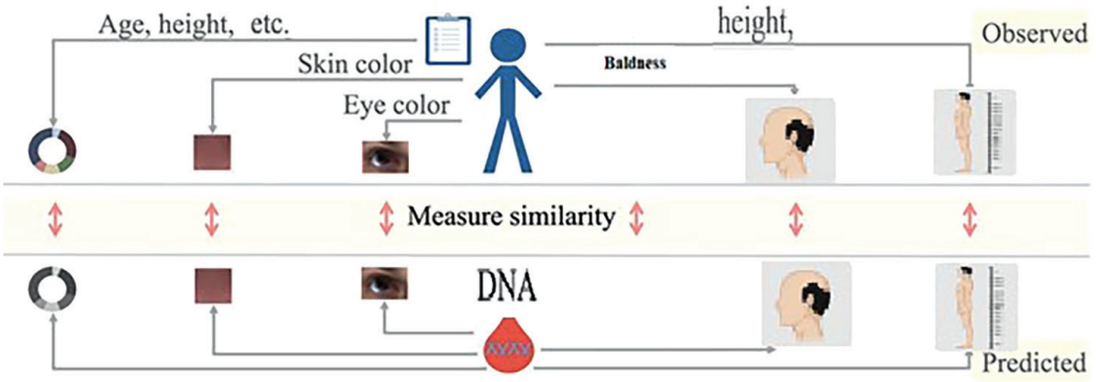

Figure 2.
Current and emerging trends in human identification.

infer someone's ancestry, providing evidence to support potential witnesses or even providing fresh information regarding forensic evidence [54]. But when evaluating someone's appearance, ancestry knowledge cannot be the only thing taken into account. One must understand the difference between ancestry and the false notion of race: a person's percentage of ancestry will not always match how they appear on the outside. When AIMs demonstrate that there is no correlation between exterior traits (ethnic background) and evolutionary biogeographic origin, this is especially clear in samples of admixed populations (**Figures 1** and **2**) [54] .

4. Conclusion

A complete "DNA facial composite" is already a spectacle for forensic prediction, according to the research presented here on genetic phenotyping. A set of genetic markers were found to be used to precisely predict the majority of human extremely visible characteristics for forensic use faster than ever. To confirm data from the global population and to examine the relationship between genetic markers and ancestry or other populations, additional diverse population studies are needed. These techniques are still utilized in forensic investigations with excellent accuracy, despite some ethical and legal challenges.

Conflict of interest

The authors declare no conflict of interest.

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