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Review Article

Forensic DNA Phenotyping: A Review in Korean Perspective

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Forensic DNA phenotyping (FDP) using human externally visible characteristics (EVCs) is an emerging new technique that allows for the prediction of phenotypic traits of a person of interest using relevant sets of genetic markers. This technique predicts not only physical appearances, but also the behavioral characteristics as well as biogeographical information, serving as a powerful supplementary tool to narrow down the investigative pool in various forensic cases. Over the past few years, many countries, Europe and America being at the forefront, have conducted significant research to identify related markers for predicting pigmentation traits such as eye, hair, and skin color. Furthermore, some commercial platforms are now available for practical use in forensic cases. Korea and other Asian countries have also dedicated remarkable research to identify relevant markers to utilize FDP in forensic investigations. However, a slightly different approach is needed because Asians have limited phenotypic variations than Western populations. Thus, medically irrelevant and simple propensity traits such as smoking and alcohol consumption could be used to compensate for the limited phenotypic variations. This article is intended to inform readers about the progress and worldwide trends in EVC research, as well as the whereabouts and future prospects of FDP-related research in Korea. Although various legal and ethical disputes must be resolved beforehand, employing an FDP system can certainly be a powerful complementary tool for providing additional clues in forensic investigations.

Key Words: Forensic DNA phenotyping; Single nucleotide polymorphism; Investigative technique; Phenotype; Pigmentation; Identification

Introduction

Current society understands the importance and capability of forensic DNA phenotyping (FDP), as a promising technique for supplementary investigative tool when the unknown short term repeat (STR) profile from person of interest fails to match anyone from DNA database [1,2]. In cases like these, FDP technique utilizes particular human externally visible characteristics (EVC) to deduce not only the physical appearance but also to estimate biological ages and even certain behavioral characteristics, such as smoking and alcohol consumption behaviors [1-4]. As FDP shows potential for its forensic operability by assuring reliable prediction results, Europe and America have already developed or in the process of developing prediction models, managing FDP as one of the investigative methods.

Though Korea, as other Asian countries, is actively conducting researches regarding human EVCs, there are technological and administrative limitations for implementing such technique in Korea; further assessments and careful considerations are needed regarding the various aspects for introducing EVC

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prediction in criminal investigation. Therefore, this article is intended to inform the readers with the worldwide EVC research progress and the expected prospective advancements of FDP, especially concerning its operability in Korea, by emphasizing its efficacy in various forensic cases.

About Forensic DNA Phenotyping (What Exactly Is Forensic DNA Phenotyping?)

DNA traces left at the crime scenes do not always guarantee definite answers; the critical flaw of conventional STR profile-based personal identification is that we need the source to compare and match with the unknown profile [1,2]. When the evidential DNA fails to find a match, then alternate approach is desperately needed in order to identify the person of interest. This is where we introduce FDP using EVCs. As human eyes are prone to make flaws due to misperceptions or simple memory mistakes [3,5], FDP has been considered as a strong supplementary tool to overcome such drawbacks of human eyewitness reports and aid in police investigation by providing definitive parameters to narrow down the investigative pool [1,2,3,5].

EVCs are human phenotypic traits that can be predicted using specific sets of DNA markers [3,5,6]. The idea of FDP by utilizing EVC was first introduced by Grimes et al. [7] using the *MC1R* gene to predict red hair pigmentation trait [7-10]; because human pigmentation variations were understood as inherited traits [8], EVCs were thought to be promising components to be used to differentiate individuals. Hence, using particular DNA markers that can provide phenotypical information about the unknown possible suspect and such appropriate application of FDP can help narrowing down the investigative pool and can aid in arresting the offender [2,11,12]. Nevertheless, the capacity of FDP technique is not limited to criminal investigation; it can also be used when finding missing persons or for personal identification in mass disaster cases [10].

Ever since the idea of DNA intelligence, a term indicating a novel way of analyzing trace evidence to predict phenotypic aspects of the person of interest, has been introduced in the field of forensics, FDP technique was utilized in various actual criminal cases. For instance, in Louisiana, law enforcements applied FDP to predict the ethnic origin of a serial killer suspect, providing the police and law enforcements with new clues to target the possible suspect [6,13]. After series of its successful function as supplementary investigative tool, FDP began to be marked as promising technique. It allowed to avoid any erroneous convicts by reducing the reliance on human eye witnesses reports through the process of thorough genetic investigation [2,5].

Along with human pigmentation traits, some of the world-wide researches that are being conducted with respect to perceptible information include gender, biogeographical ancestry, facial features, and even certain propensities [2,3,5,9,14]. Recent research trends show that iris color, hair color, and skin color are the most advanced works with operable prediction markers available for forensic applications [10,15]. These are, in fact, the most visible phenotypic traits that involve a relatively small set of markers which can explain a large population variation [2,10]. Other possible phenotypic traits, though still need improvements for practical uses, include: hair shape, such as curly or fizzy hair, facial morphology, skull shape and even some nonsensitive behavioral propensities, such as smoking [1-3].

Development of Forensic DNA Phenotyping: Progress in America/ Europe

Of the numerous countries conducting FDP-related research, Europe and America seem to be taking the most active part in developing phenotypic prediction system; wide variety of EVC researches are published and reliable platforms are readily available for practical forensic caseworks.

As mentioned above, the history of FDP begins with Grimes et al. [7], discovering that *MC1R* is the major gene regulating the expression of red hair, fair skin tone and freckling [3,4]. From that point, large scale of genome-wide association studies have discovered common variants associated with human pigmentations throughout the past several years. Some of those major genes associated with human pigmentation traits include: *MC1R, OCA2, SLC24A5, MATP (SLC45A2), ASIP,*

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and *TYR* [3,8,9,13,14].

As human iris color is known to be almost exclusively determined by the heritable traits [9], several studies have focused their attentions to genetic variations that regulate the eye color variations. The studies have confirmed that *OCA2* gene, as well as other three genes, *HERC2, SLC24A4*, and *SLC24A5*, respectively, were discovered to have significant melanin effects in determining human iris colors by regulating melanin production and expression in the eye [1,3,8,9,12,16]. Moreover, *HERC2* gene was discovered to be strongly associated with blue eye color; further analysis has presented that rs12913832 in *HERC2* was responsible for determining blue and brown eye color variation [3,9,16-18], and also has the highest discrimination power for predicting either light or dark iris color among various population groups [3,12].

In fact, the products utilizing these specific markers for predicting eye colors are already available in the market [4,16-18] and ready for practical uses. The large scale of association studies with over 9,000 samples have found that just six single nucleotide polymorphisms (SNPs) can lead to high categorical prediction values for eye colors [2,17,19]. Recently, using this progress, Walsh et al. [16-18] successfully developed IrisPlex and HIrisPlex model that can predict human eye and hair color with an accuracy rate of over 90% for certain iris and hair colors in European population [3,16-18].

In addition, 36 SNPs from 15 genes have shown their capacities as skin color predicting markers and five-stage skin color prediction model is under development in line with the hair color prediction [19]. For skin color prediction, Stokowski et al. [20] examined predictability of skin color using three genes, *SLC24A5, SLC45A2*, and *TYR*, that showed the strongest association in skin color variation [20,21]. Along with these genes, Maronas et al. [21] has discovered additional 10 SNPs that are the most strongly associated with skin color and these markers can now be used for forensic purposes [20].

The progress continues in Western countries: group of European American scientists are conjoined to develop trait prediction platform that allows simultaneous genotype to infer multiple different phenotypic characteristics. This would allow multiplex genotyping with even low quality/quantity DNA, commonly found in crime scenes, to predict physical traits of the person of interest [5].

Furthermore, along with above mentioned features, prospective fields of FDP related research include, but not limited to, genes that may be associated with stature, hair shape, and facial morphology are also high in interest [2,19] as well as potential markers that may explain certain behavioral characteristics, such as propensity for smoking, alcohol consumptions [4]. Also, more recent studies concentrate on predicting facial morphology; to this point about 50 genes that contribute to facial morphology have been discovered and of those, 24 markers in 20 different genes were distinguished to explain the various patterns in facial shape and morphology [19,22,23]. The continuous research and development will allow these genes to be used as robust prediction markers, providing and differentiating the highly polymorphic and polygenic physical traits as well as biogeographical backgrounds [10,24].

Limitation: More Work Needs to Be Done

Many of the researchers recognize the trait prediction as a promising technique that can aid in searching for unknown person of interest [1,2,3,17,19]. However, despite the prominent progress, any researcher in this related field would agree that there still is much work to be done; additional candidate markers must be discovered and further validation procedures are needed for constructing an accurate population specific prediction system. For instance, because the major population groups for the development and validation process of the majority of markers established for current prediction models are based on European populations, there have been reports that Western population groups tend to show better results compared to other population groups [10,16-18]. Moreover, despite the growing interest and importance for skin color prediction tool in FDP area, there still lacks the consensus methods for categorizing and recording skin color phenotype [21]. Also, current skin color predictors provide better result in exclusion method, meaning they

are better suited for providing the relative skin color prediction result, for instance, differentiating dark skin colored person from the rest of the pool, rather than capable of designating the absolute skin color of the person of the interest [21,25]. Therefore, the consensus, universal guidelines for categorizing skin color variation as well as the improved set of prediction markers would be necessary to manufacture commercialized products for collective uses.

Furthermore, although SNPs associated with freckles, moles, curly hair, skin color, ear lobe shape, and body height are also being considered as candidates for phenotypic predictions, these are of the less common features, and therefore are not ready to provide as promising as the pigmentation traits [2,3,5]. Hence, future research to discover appropriate markers related to these features and repetitive validation steps among various population groups would certainly benefit to interpret multiple traits simultaneously and would strengthen the discrimination power and prediction precisions.

Notwithstanding such advancement in both Europe and America, challenging work still remains: finding the adequate markers that can not only represent the population without violating any ethical and legal perspectives but also have sufficient discrimination power to deduce the person of interest in criminal investigations. This is one of the main reasons why the active usage of FDP is being deferred in practical field and many countries devote to researches of their own to account for population differences [1-3].

In order to operate FDP in practical fields, we must first comprehend the purpose of using FDP and establish strict guidelines and regulations. The question is to what extent should we allow usage of FDP? Albeit it would depend on each country's investigative and legislative systems, certain regulations and conditions must be set forth before employing the system into criminal investigations. For instance, when choosing phenotypic marker sets, principles for selecting relevant SNP markers must be very specific; the objective markers should neither be discriminative nor be against any ethical or legal aspects [1-4]. Moreover, we must understand that one specific marker cannot explain the worldwide population variations. For instance, researcher should be aware that a particular SNP that appeared to be significant in one population group may turn out to be monomorphic in other population groups [22] and thus must be able to find alternate markers to adapt under different circumstances.

The next challenge for implementing FDP would be getting police and law enforcements to attempt to apply such techniques to real forensic cases [18,19]. As law enforcement agencies have tendency to remain conservative standpoint when introducing new technology, Walsh et al. [18] emphasized that full disclosure of detailed research methods for FDP is crucial [19]. Moreover, the origin of samples, sample information, markers used for typing, statistical model version, and other detailed relevant information must all be included in order for FDP to be accepted as trustworthy tool for investigators [19]. This can be particularly important in America as each state government holds different legislative system [1]. Texas, for instance, supports and allows the prediction results from FDP to be used as evidence in criminal investigations, whereas states like Rhode Island and Indiana strictly prohibit any DNA based inferences other than gender [1,4]. As the countries start to revise their legislations and prepare to fully implement EVC as an official investigative tool, EVC related studies will make even more rapid progress and the advanced platforms for highly operable prediction model will soon be ready for use in real forensic cases [2,5].

EVC Research in Korea/East Asia

Despite the fact that countless studies are available regarding FDP and significant EVCs, majority of the present-day studies and prediction system, such as HIrisPlex, are best fit to predict traits for Western populations; population groups with high pigmentation variations and population admixtures [2,3,10,16,17]. Some of the renown researches have already acknowledged that many of these establishments were designed based on researches conducted among Europeans ergo may not ensure the best possible results in elsewhere in the world [26].

For such reasons, current prediction models may not be a suitable model to obtain reliable prediction

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results in East Asian population mainly due to limited phenotypic variations. In order to initiate and maximize the efficacy of FDP in Korea, it is extremely important to find phenotypic markers that can specifically distinguish East Asians, especially Koreans if possible, and to develop an operable prediction model that can target Korean population. Although there are certain SNP markers that are applicable to various different populations regardless of population differences, such as rs12913832 marker for predicting an eye color, these kinds of markers that can be applied to different population groups with low prediction error rate are extremely rare and many of them are yet to be discovered [24].

In fact, when Yun et al. [12], compared the prediction outcomes using two different methods, one being the FROG-kb used in Walsh et al. [16-18]'s IrisPlex system and the other one being Ruiz et al. [27]'s Snipper based on Bayseian form, two systems showed no contradicting predictions among East Asian samples. This finding indicates that while these platforms can be used to rule out East Asians among other population groups, these SNPs would not allow further detailed differentiation within the East Asian groups. The drawback is that these monomorphic traits cannot provide any useful information when finding the investigative leads in Korea, which these platforms would predict every individual as brown eye with dark hair. In other words, alternate approach is required when distinguishing an individual within East Asian populations based on phenotypic traits; additional assessments would be needed to decide which markers to keep and which markers to retract for constructing Korean specific prediction tools [12,20,21].

Furthermore, although Stokowski et al. [20] conducted a phenotypic study in South Asian population, learning about three specific SNP markers, rs1426654 in *SLC24A5*, rs16891982 in *SLC45A2*, and rs1042602 in *TYR*, that determine the skin pigmentations among South Asians, those particular SNPs were confirmed to be monomorphic traits in East Asian as well as African populations [20,21]. In addition, because these markers are predictors for differentiating people into light, intermediate and dark colored skins, such classification is inapplicable in Korean population with very minute skin color variations [20].

However, continuous studies targeting Asian populations have discovered East Asian specific candidate SNPs, rs1545397 (*OCA2*) and rs885479 (*MC1R*), which may explain the pigmentation variations among East Asians [24]. Also, according to Shriver et al. [22], several genes, such as *ADAM17, DCT, ADAMTS20, ATRN, MC1R, LYST, OCA2, EDA, TYRP1, EGFR*, and *DRD2*, may contain SNPs pertinent to skin pigmentation variations in East Asian population [20-22]. Further examination in these genes may lead to discovery of Korean specific pigmentation markers.

Nevertheless, because most of those above mentioned conventional pigmentation markers do not guarantee promising results among Asian populations, the researchers have turned their attentions to other phenotypic traits that are distinctively found in Asian populations hoping to discriminate Asians from other ethnical groups; hair morphology being one of those prominent traits. Human hair morphology, along with skin color and facial features, can be a candidate to differentiate population groups [28]. Previous studies have reported that Asians tend to have hair with larger diameter, higher hair index, and more circular cross-sectioned shaped compared to Caucasians and African Americans [28]. Using such distinctive characteristics, a study revealed that non-synonymous SNP rs3827760 in ectodysplasin A receptor (*EDAR*), a member of the tumor necrosis factor receptor family, is associated with Asian hair thickness and found to be high in allele frequency among East Asian population [28,29]. Moreover, Fujimoto et al. [28,29] found 12 candidate SNPs on 10 hair formation-related genes that can differentiate Asians from other population groups and also noted that rs4752566 in *FGFR2* may also be associated with Asian hair thickness. Further evaluation of these markers can provide means to distinguish hair morphological traits within East Asian population [29].

Furthermore, Lim and Oh [30] presented a study exploring the known SNPs for phenotypic prediction to test whether those SNPs can effectively be used against Korean population. The study provided 20 candidate SNPs, targeting specifically Koreans, to assess the operability and applicability of designed phenotypic prediction markers for visible phenotypic

variants in Korean population [30]. Because there are only limited number of identified markers available for differentiating Koreans based on physical appearances, setting up the appropriate parameters for EVC prediction model is crucial. Therefore, prediction on certain propensities and behavioral characteristics, such as smoking, and alcohol consumption behaviors are may also be beneficial to use for actual forensic applications [30].

In addition, a study was done to explore wide variety of physical traits among Koreans; body mass index, blood pressure, bone density and height were investigated to find unique attributes that can differentiate Koreans from other population groups [31]. Through this research, the candidate markers that may explain parts of height variations in Korean and/or Asians were found; the additional 15 loci that may describe the influential biological functions determining stature were reported [32]. Of those 15 suggestive loci, seven have already been reported to have significant effects among Caucasians [31,32] and, in addition to those, eight new loci (*SUPT3H, EXT1, FREM1, PALM2-AKAP2, NUP37-PMCH, IGF1, KRT20*, and *ANKRD60*) were discovered to have significant associations determining height in Korean population [32,33]. Further studies would allow researchers to trace specific genes and markers responsible for regulating Korean population height and these can provide guidelines for height prediction [31,32].

Although these specific loci may be the potential candidates to height variations specifically in Korean population, we must acknowledge that, as Kayser and colleagues [1-3] has mentioned, human stature is understood to be extremely polygenic and polymorphic trait, and greatly influenced by environmental factors so the prediction range can seriously be fluctuated [1-3]. Height is known to have a high degree of heritability; nevertheless because there are too many genes associated with determining stature and that those genes account only for less than 10% of the variations between individuals [3,34,35], its complexity makes human stature to be one of the less promising features for prediction model as per current knowledge. Thus, the polygenic traits with such complexity will require substantial amount of studies to be used as predictive value and even after so, it is highly possible that these predictive indicators will ever be fully determined for promising outcomes in practical uses [1].

Hence, due to above mentioned reasons and due to the absence of absolute Koran specific predictors, it is appropriate to suggest that Koreans must take rather different approach when applying FDP to forensic cases. Because of such limited phenotypic features, certain traits other than pigmentations must be taken into account in order to compensate for less diverse pigmentation variations [12,31]; that is to concentrate on certain propensity markers to be included to further narrow down the investigative pool. Incorporating the rightful propensity prediction markers could enhance the functionality and the precision rate of the prediction model. Some of the prospect propensity predicting markers may include but not limited to; baldness, smoking, or alcohol consumption patterns. Despite the fact that some of the genetic components responsible for determining certain propensities have already been discovered, or in the process, they still are insufficient for practical uses because there are other conjoining factors, such as environmental, social or nutritional influences, that can affect the manifestation of one's characteristics [1,2,4].

Moreover, even if we successfully find markers for predicting propensities t, we must also find justifiable reasons how those predictors would be meaningful for forensic purposes and consider ways to approach to maximize the efficiency and obtain both genotypically and phenotypically reliable information. Such concerns with respect to constructing Korean specific prediction model lead to future tasks that must be settled for implementing FDP in Korea.

What More Needs to Be Done: Future Remarks

There are multiple aspects, not only scientifically but also ethical or administrative aspects, that need to be deliberated in order to introduce and EVC in Korea for forensic purposes [36]. As one of the countries that currently prohibits the usage of FDP, other than gender inference, in criminal investigation, the current EVC research in Korea holds rather conservative perspective.

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Like many other countries, phenotype inference research explicitly emphasizes that the candidate SNPs must neither be associated with any kinds of diseases, nor include any indicators for potential development of medical conditions [1-4,36]. Any scientific researcher would agree that EVC markers must be chosen with extreme caution and under strict prudence and that only the selective markers those are free from any legal/ethical disputes can be included for further assessments [3,36]. However, progress on current research trends exhibit that it is not only difficult to find unique markers that can differentiate individuals among Asian population but also have very limited genetic studies available targeting only specifically East Asian population, needless to say for targeting only Koreans [10].

As for now, the knowledge we have about human EVC is still limited; it still in unclear how each SNP markers contribute to expression and determination of different phenotypic characteristics [25]. Also, phenotypic traits other than eye, hair and skin color are still in need of more in-depth studies before utilizing those markers in practical applications. As there are only few of known phenotypic and propensities markers available and we have yet to discover other possible candidate markers that may have higher predictability, profound future studies will be necessary to enhance the prediction efficacies. Moreover, in order for the prediction model to be practically operable, a large-scale of international collaborative research will also be extremely beneficial. This will aid in mapping the underlying EVC genes, allowing further progress of EVC studies [2,3]. Additionally, we must acknowledge that these platforms are targeted for practical uses; increasing the number of genetic markers would, indeed, increase the prediction accuracy but also would result in rise of the experimental cost [27]. Therefore, it is necessary to choose the right number and kinds of markers for adequate and efficient experimental results.

Furthermore, with the intention to employ FDP system in Korea, there are several things that not only the scientists but also the law enforcements must consider. Because the purpose of FDP is to serve as supplementary investigative tool in various forensic cases to narrow down search pool, there are many legal and ethical, as well as the management concerns that must be resolved [36]. It is clear that FDP is necessary and beneficial in personal identification; however, despite acknowledging such advantages of FDP, some argue that sensitive confidential matters may provoke unwanted discrimination and inconsiderate dragnets can even point fingers to innocent people if poorly managed [37].

In fact, one of the most prominent disputes for developing and implementing FDP tools in criminal investigations are due to ethical concerns that DNA phenotyping might provoke [3,36]. Like other genetic tests, people fear that FDP may reveal one's unknown or unwanted traits and thus violate one's privacy or right not to know [3,36]. Moreover, if the usage of FDP is allowed in criminal investigation, the phenotyping prediction results may bias the police or law enforcements to falsely target the specific groups of people based on the prediction results [3,36].

Therefore, the basis of DNA phenotyping should be accompanied by solid legislative framework and should thoroughly be managed by establishing strict control over data handling and interpretation to ensure the confidentiality as the genetic profiling from the investigative prediction model would provide confidential personal information [36-38]. It should be designed to apply only to unknown individuals and allow only for predicting features that are as perceptible as to human eyewitnesses by using only the markers that are completely free of any ethical disputes [3,36]. Many scientists would agree that the implementation of FDP and operating prediction model would be about keeping the fine line balance; predicting propensity about smoking shall not be treated as seriously as finding out a propensity about life threatening medical conditions [4,35]. In other words, should the government and scientists can provide respectful guidelines for categorical predictions, immensely useful information can be derived from not only the externally perceptible traits, but also for medically irrelevant propensity analyses.

Given FDP's reliability and capacity, continuous research and development on EVC would advance this system as one of the most powerful supplementary tools for police investigations. One of the ways to

maximize the effects of FDP prediction models would require the collaborative efforts from scientific researchers and law enforcements to agree upon the related laws and legislative agenda, and by doing so, FDP should be a valuable investigative tool for our society that is anticipated to play an important role and contribute to resolve various kinds of forensic cases [1-4,18,38].

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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