

BIOLOGICAL RESEARCH

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PROBLEMS OF COLLECTING GENETIC HISTORY, INTERPRETATION OF PEDIGREES WITH COMMON AND RARE DERMATOLOGICAL, SKELETAL, DENTAL AND OTHER PECULIARITIES THAT AFFECT THE APPEARANCE AND HEALTH OF A HUMAN**Olga Filiptsova, Olga Naboka, Oleg Kryskiv, Andriy Zakhariiev, Tetiana Martyniuk, Natalia Khokhlenkova, Olha Kaliuzhnaia, Svitlana Bobro, Liudmyla Petrovska, Yuliia Osypenko**

The aim of the study was to analyze the problem of constructing and interpreting human pedigrees, which include some signs that are easily detected during a clinical examination and the collection of primary history.

Materials and methods. 2 pedigrees from own sources and 2 pedigrees of famous people from literary sources are presented. They serve as the examples of using the provided data for further medical and genealogical analysis.

Results and discussion. The results indicate that pedigree analysis is a primary and informationally important tool for the further algorithm of diagnosis and treatment of subjects. The effect of the quantity, quality and testing level of the presented genealogical information for a full pedigree analysis and the use of its possibilities is demonstrated. Pedigree analysis demonstrated that the number of absolute units of quantitative information presented (total number of generations and members of the pedigree) and absolute units of qualitative information (traits/medical conditions listed and their level of detail) may not be associated with the value of genetic conclusions. It has been shown that the largest number of members in a generation is usually represented for the generation of the propositus. Thus, smaller pedigrees, where more units of information are represented per member, can be of greater value for genetic conclusions. An analysis of one's own pedigrees showed that, on average, less than one trait can be represented per person in the pedigree. Additionally, small pedigrees with available molecular genetic data may be of greatest value, even retrospectively.

Conclusions. It is shown that pedigrees can represent valuable primary information for clinicians regarding the further algorithm of the subject dealing and serve as a tool for the scientific thinking development in the educational process

Keywords: Pedigree, pedigree analysis, human appearance, molecular genetic analysis, retrospective genetic analysis, propositus

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1. Introduction

Pedigrees allow a deeper understanding of human genetic disorders. They are used to help establish inheritance patterns and identify individuals at risk for a disease. Pedigree analysis can be useful for identifying genetic disorders that exhibit mechanisms, such as autosomal dominant or recessive inheritance, X-linked inheritance, and anticipation [1]. Pedigree analysis is an ancient and powerful approach to understanding the underlying genetic determinants of human health, but identifying, recruiting, and genotyping families can be difficult, time-consuming, and expensive [2]. Family history, which has been used for years to determine disease risk, captures important information, such as cultural, genetic, behavioral, and environmental factors that family members tend to share. The presence of one or more relatives of the first or second degree of relationship with a certain disease is usually considered a positive family history. At the same time, for many complex traits and diseases, the use of only family history and pedigree construct-

ing is insufficient and additional research is needed [3], but it is still the initial stage of human genetic analysis.

The aim of the study was to analyze the problem of constructing and interpreting human pedigrees, which include some signs that are easily detected during a clinical examination and the collection of primary history.

2. Materials and methods

The study was conducted at the National University of Pharmacy in 2020–2023.

The research used a genealogical method, which involved the initial consideration of 4 pedigrees constructed according to classical rules.

Pedigree No. 1 was presented by a Moroccan female who was temporarily studying in Ukraine. At the time of presentation, the age of the respondent was 20 years. Pedigree No. 2 was presented by a female resident of Ukraine, whose age at the time of compilation was 47 years. Both pedigrees are anonymous and can be consid-

ered as models when working with similar pedigrees for any medical and biological purposes.

Pedigree No. 3 was compiled on the basis of literary sources and constructed as a pedigree fragment of the American actress Angelina Jolie family [4]. Pedigree No. 4 is taken as a fragment of Tutankhamun's pedigree from the literary source [5].

The collection of information was carried out taking into account the ethical requirements when dealing with humans in accordance with the Declaration of Helsinki (World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects). All participants in the experiment gave written consent to the study.

3. Results

Fig. 1–4 present typical pedigrees, which are constructed according to the general rules for presenting pedigrees.

Fig. 1 presents the largest of the pedigrees available in our research, which shows 5 consecutive generations, the total number of individuals in the pedigree is 249. Of them, there are 8 individuals in the first (I) generation (4 males and 4 females), in the second (II) generation there are 39 people (20 males and 19 females), in the third (III) generation there are 60 people (30 males and 30 females), in the fourth (IV) generation there are 87 people (46 males and 41 females) and in the fifth (V) generation there are 45 people (27 males and 18 females).

It is obvious that the largest number of represented individuals is observed in the fourth generation, to which the propositus belongs (by number 23, if the calculation was carried out starting from the first member of the generation from left to right). Among her own characteristics, which the propositus considers to have a genetic basis, she has indicated short stature, "cleft tongue" and "Roman foot."

In other members of the pedigree, in addition to those indicated by the propositus, traits or diseases are indicated that are easy to track visually or by simple and common symptoms. These include hypertension/tension/high blood pressure, vision loss/blindness, diabetes, eczema/foot eczema, heart disease, stature (tall or short), hair loss, fever, intestine disease, high cholesterol, allergy (without specifying allergen, what causes it), stomach disease, Alzheimer's disease, early death (cause specified, fever), cancer (unspecified location and type), gallbladder disease, smoking, vaginal bleeding, hemorrhoids, breast cancer, lung cancer, language problems, albinism, hyperthyroidism, breathing problems, leg infections, physical resemblance to father, French ethnicity, stomach cancer, death at age 100, heart failure, virus/viral disease, 0(+) group by ABO blood type and Resus, amnesia, bladder stones, prostate cancer, paralysis, and sweet taste preferences.

It should be noted that when specifying different conditions and diseases, the propositus uses similar phrases, for example, hypertension/tension/high

blood pressure or virus/virus disease. But whether this indicates the use of completely synonymous constructions (virus/virus disease) or still similar but not the same conditions (hypertension/tension/high blood pressure), it is not possible to establish from the primary data and requires further discussing with the propositus and making clarifications. Since English, in which the pedigree of the propositus from Morocco was presented, is not her native language, a certain probability of possible nuances of not quite correct translation of information should be assumed. So, for example, in one of the studies it was shown that the role of interpreters during medical interviews is usually performed by relatives of patients who are not professional interpreters and are prone to potentially dangerous translation errors. In this study, conducted to assess these errors in the emergency department, 20 interviews with Azeri patients were recorded. They did not speak Persian, so the translation was carried out by relatives as interpreters from the Persian language. It was shown that the total number of omission and addition errors, observed in Azeri-Persian translation, was significantly higher than in Persian-Azeri translation, while mistranslation errors were almost the same. Relatives with a higher level of education made fewer errors. It was generally concluded that non-professional interpreters cannot effectively facilitate patient-physician communication, and errors can have important clinical consequences [6].

It is also clear from the analysis of the pedigree that the propositus does not always have accurate information about specific diseases, for example, in several cases only the general location of the disease is indicated (heart disease, stomach disease, intestinal disease, gallbladder disease) or no location is indicated at all (cancer). In some cases, it is unclear whether the condition is congenital or acquired. For example, it is logical to assume that vision loss is an acquired condition, while blindness is a congenital condition. Thus, further discussing with the propositus is needed to clarify such information, if possible, and it can still be provided.

Still, the fairly large number (47) of traits, medical conditions, ethnic origin, habits, life expectancy, etc. presented is commendable. Thus, a simple calculation shows that the average number of traits per person (taking into account their uniqueness) is $47/249 = 0.19$ traits.

Among the traits that are directly or indirectly related to appearance, we should point out albinism, which is inherited mainly as an autosomal recessive trait [7], eczema, in the pathogenesis of which both genetic factors and environmental factors play a role [8], human growth, which is characterized by a complex type of inheritance and a high heritability coefficient [9], and hair loss, a trait that is also characterized by a complex type of inheritance and can be presented both individually and as part of different syndromes [10].

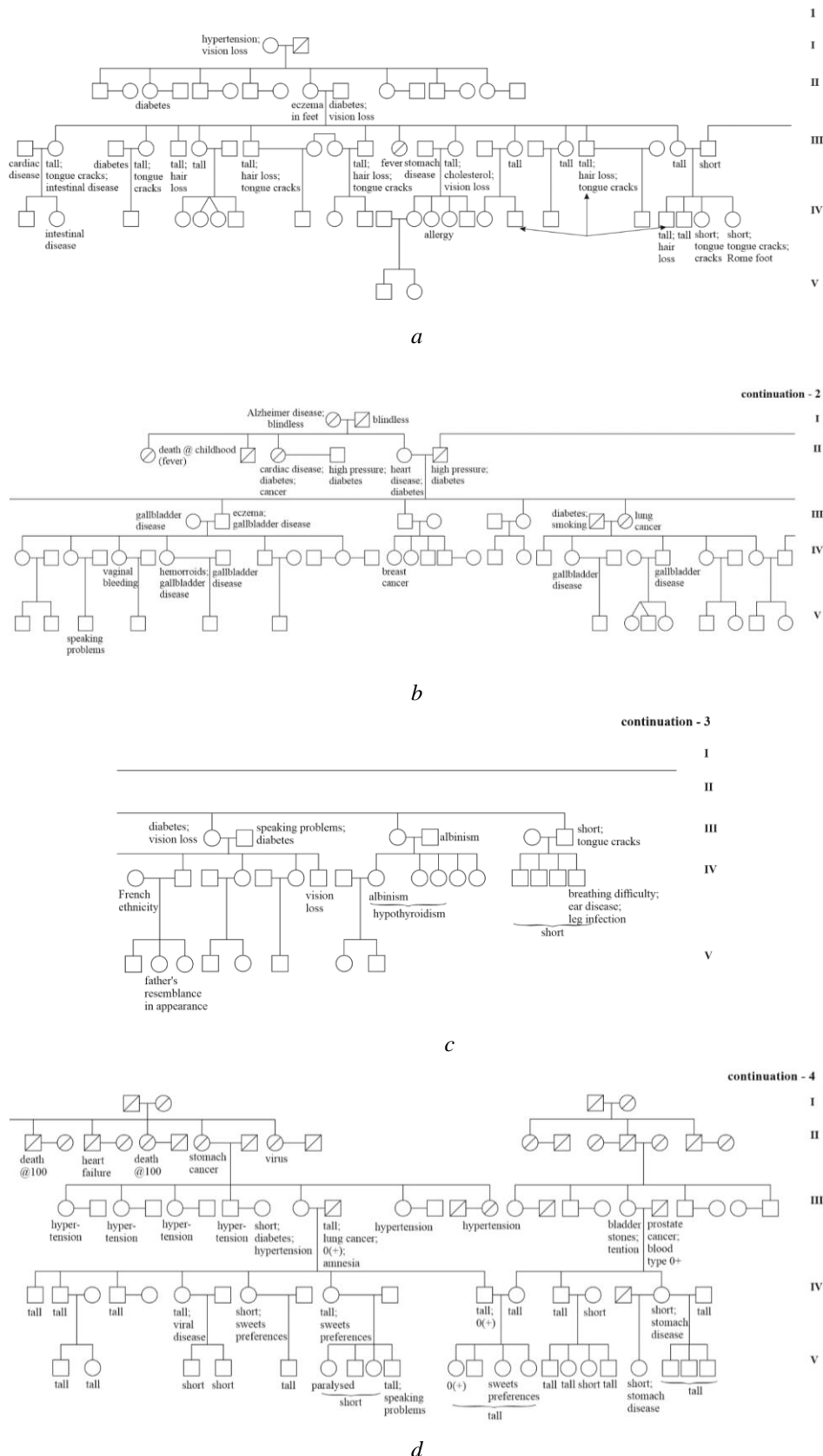


Fig. 1. Illustrative pedigree No. 1 (a Moroccan female, own data): *a* – page 1 of the pedigree; *b* – page 2 of the pedigree; *c* – page 3 of the pedigree; *d* – page 4 of the pedigree.

Among the rare traits, such a trait as "tongue cracks" deserves attention. During the clinical examination of the propositus (for ethical reasons, the picture is not provided), it was noticed that the propositus has changes in

the topography of the mucous membrane of the dorsal surface of the anterior part of the tongue, which are manifested in the following way: on the entire dorsal surface of the tongue from its tip to the level of the palato-lingual arches,

there is an increase in the size of the filiform papillae of the tongue (*papillae filiformes*). The increase in the height of the papillae is quite uniform, on the dorsal surface of the tongue they reach up to 6-8 mm. The color of the papillae is whitish gray, with a slightly yellowish tint on the back of the tongue. There is no pronounced pigmentation of the papillae on the back of the tongue. Conical papillae of the tongue (*papillae conicae*) as a separate type of papillae among hypertrophied filiform papillae are not visualized. At the same time, taste mushroom-like papillae (*papillae fungiformes*) are visible only on the edges of the tongue, it was not possible to visualize them on the dorsal surface due to the increase in the size of thread-like papillae. Leaf-shaped papillae (*papillae foliatae*) also could not be identified on the lateral surfaces of the tongue near the palatolinguinal arches due to the increase in the size of filiform papillae. Eight grooved taste papillae (*papillae vallatae*) are visible on the dorsal surface of the tongue between the terminal furrow and the zone of the tongue mucosa, which is covered with enlarged filiform papillae.

The mucous membrane of the posterior part of the tongue is of the usual appearance: moist, intact, has a slightly bumpy surface, which is most likely associated with the placement of intramucosal solitary lymphoid follicles. The mucous membrane of the lower surface of the tongue, the lateral surfaces of the tongue, as well as the mucous membrane of the hard and soft palate are intact, moist, and of the normal appearance. According to the above-mentioned clinical signs, a diagnosis can be suggested: "hypertrophy of the filiform papillae of the tongue." According to the analysis of the literature, similar morphological changes of the tongue are presented as a separate nosology in ICD-10: K.14.3 ("hypertrophy of the papillae of the tongue"). Histologically, the pathology is described as an abnormality of the histoarchitectonics of the epithelial plate of the tongue mucosa in the form of a pronounced elongation of thread-like papillae with hair-like spiers of keratinocytes [11]. This pathology still does not have a precisely established etiology, according to modern ideas, possible causes of its development are: tobacco smoking, use of electronic cigarettes, wipers, xerostomia, the presence of oxidants in the composition of hygienic mouthwashes, hyposalivation, the local effect of ionizing radiation, and in general, electromagnetic radiation. Also, hypertrophy of the papillae of the tongue mucosa is associated with old age, general weakness, taking medications, lack of coarse food in the diet, and poor oral hygiene [11]. There are also data that hypertrophy of tongue papillae is accompanied by long-term use of drugs: drugs containing bismuth salts, as well as oral forms of penicillin, chlorpromazine, ranitidine, tetracycline, olanzapine; use of interferons and prednisolone [12, 13]. One of the morphological characteristics of hypertrophy of tongue papillae is dark (brown, black) pigmentation of mucosal areas with enlarged tongue papil-

lae, which is associated with the vital activity of oral mucosal microflora [11]. Changes in the composition of the microbiome of the oral cavity, with the colonization of the mucous membrane by pigment-forming microflora can be a sign of suppression of the body's natural resistance factors or immunodeficiency. This is indicated by data on cases of hypertrophy of tongue papillae with pigmentation during long-term use of corticosteroids, which are immunosuppressants [12], as well as cases of this pathology, associated with colonization of the oral mucosa by fungi of the *Candida* family.

In the studied case, there is no hyperpigmentation of the mucous membrane of the tongue, accordingly, an abnormality of the microbiome of the oral mucosa, as a cause of the pathology, may not be considered.

Fig. 2 presents the second largest pedigree available in our study, which also describes 5 consecutive generations, the total number of people in the pedigree is 25. Of them, there are 2 people in the first (I) generation (1 male and 1 female), in the second (II) generation there are 5 people (3 males and 2 females), in the third (III) generation there are 6 people (3 males and 3 females), in the fourth (IV) generation there are 8 people (4 males and 4 females) and in the fifth (V) generation there are 4 people (3 males and 1 female).

The propositus in the fourth generation is indicated by an arrow (female, resident of Ukraine, age at the time of compilation of the pedigree 47 years old). According to the propositus, all representatives of the pedigree are of Slavic ethnic origin.

From the traits, presented by the propositus, it is possible to trace those that are both directly and indirectly related to appearance, or not associated with appearance at all. Such traits include diastema, myopia, "Greek foot", B(+) blood group according to the ABO system and Resus, and alcoholism. So, for example, it is known that diastema (gap mainly between anterior incisors) is a fairly common feature in human populations and is a clinical feature that has many underlying etiological factors that may be interdependent or independent [14].

It should be noted that for each of the 8 deceased individuals, the cause of death is indicated on the pedigree, namely, death by natural causes (at the age of 93, 96 and 99), an accident, medical error, cancer diseases (breast cancer, colon cancer, bladder cancer) and bleeding due to stomach ulcer.

A total of 10 traits are given in this pedigree (taking into account the diseases that caused the death of some individuals), that is, the average number of traits per person (taking into account their uniqueness) is $10/25=0.4$ traits. Thus, despite the much smaller number of mentioned members of the pedigree, more detailed genealogical information is obviously provided, which is quite important for in-depth genetic analysis and calculation of genetic risks and prognoses.

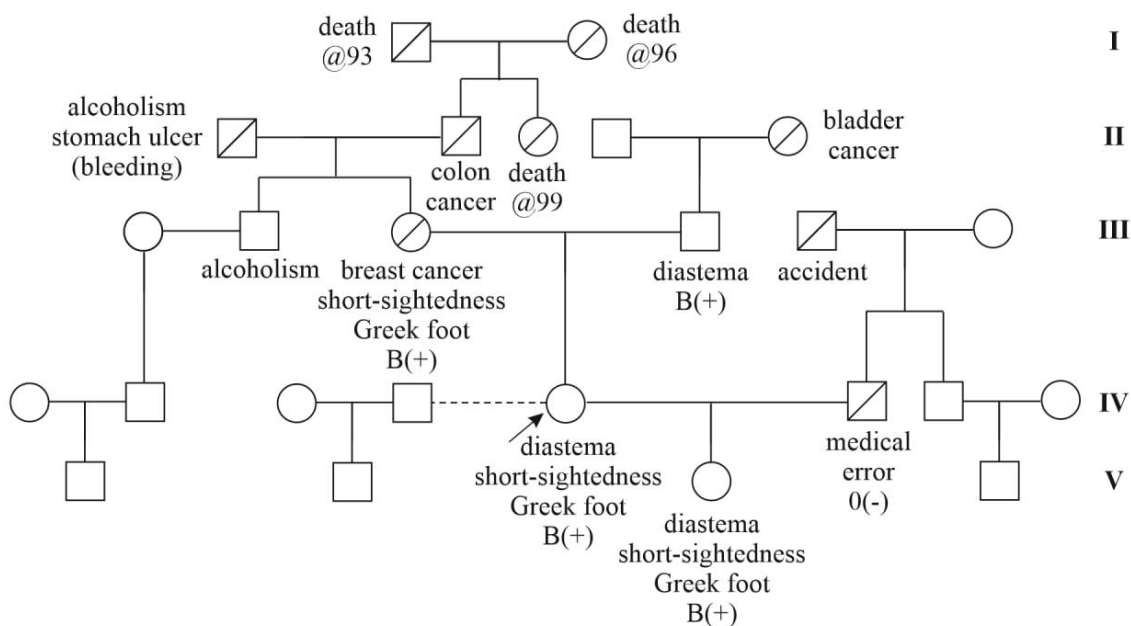


Fig. 2. Illustrative pedigree No. 2 (anUkrainian female, own data)

It is worth noting, that for a rather small number of individuals, represented in the pedigree, 3 have cancer diseases that became the cause of death. At first glance, such data can be considered as those that can cover the genetic history of the proband. But, taking into account the high prevalence of cancer in contemporary human populations, different locations of cancer in the mentioned relatives and a rather low coefficient of heritability of cancer, it is possible to come to a more optimistic conclusion. Thus, the proband's mother had breast cancer, her maternal grandmother had intestinal cancer, and her paternal grandmother had bladder cancer, that is, obviously different forms of the disease, the trigger of which could be various factors. These factors may not be characteristic of the lifestyle of the proband and, thus, do not increase the risk of such a pathology. Thus, scientific evidence indicates that ordinary people have an extremely incorrect understanding of the causes of cancer and the need for appropriate testing and determination of genetic prognosis. In one study, only about 5 % of respondents were knowledgeable about cancer genetics [15].

Another interesting, quite common and easily visualized sign is the "Greek foot", or Morton's toe (a condition, in which the second toe is longer than the first). In the presented second pedigree, the proband, her mother and daughter have such a trait, which may indicate an autosomal dominant type of inheritance. But, according to the latest data, there is no clear answer regarding the mechanism of inheritance of the "Greek foot" [16].

It is also noteworthy, that there are three long-livers in the pedigree, that is, people who lived to be 90 years old or more. In relation to the proband, all these persons are relatives of the 3rd degree of relationship on the maternal line. As well documented in many studies, the heritability coefficient of life span is quite small and, according to various data, is no more than 30 % [17].

Fig. 3 presents the third pedigree, which is the pedigree of the American actress Angelina Jolie family (the proband is shown with an arrow, the pedigree is constructed according to literary sources). Her family has

become a fairly frequent illustrative example in human genetics, in particular, in cancer genetics. The pedigree contains 4 consecutive generations, the total number of persons in this pedigree is 12. Of them, there is 1 person (1 female) in the first (I) generation, 3 persons (1 male and 2 females) are in the second (II) generation, in the third (III) generations there are 2 people (1 male and 1 female), the fourth (IV) generation contains 6 people (3 males and 3 females, namely the children of the proband, three of whom are adopted, which is indicated by the dotted "line of children").

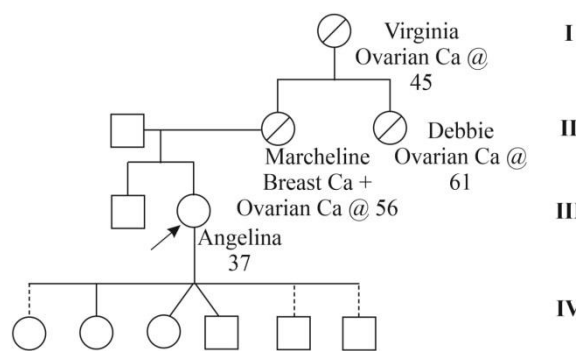


Fig. 3. Illustrative pedigree No. 3 (Angelina Jolie family fragment, from the literature source).

The actress's family attracted a lot of attention from the scientific community in connection with her publication of the results of genetic analysis, according to which she has a mutation in the *BRCA1* gene, received from her mother. After this discovery, numerous changes in health care practices were registered, the so-called "Jolie effect". These included increased referrals for females with a family history of breast cancer, increased rates of contralateral mastectomies, which the actress herself ran for, and health insurance reimbursement for *BRCA1* testing. Jolie later also credited her experience with salpin-

go-oophorectomy for reducing the risk of developing both breast and ovarian cancer [18].

The study of such pedigrees of famous people is not only socially significant for the general public, because in this case, famous people, regardless of the profession and the presented medical condition, are a kind of opinion leaders. Similar examples are also important for illustrating educational material for students of relevant specialties.

Fig. 4 presents the fourth pedigree (according to literary sources). It contains 5 consecutive generations, the total number of individuals in this pedigree is 10. In each generation, 2 individuals are represented. The pedigree is constructed retrospectively, and the propositus is Tutankhamun, the pharaoh of Ancient Egypt. The peculiarity of this pedigree is the presence of the consanguineous marriage (inbreeding effect), whose descendant, according to historical data, was Tutankhamun.

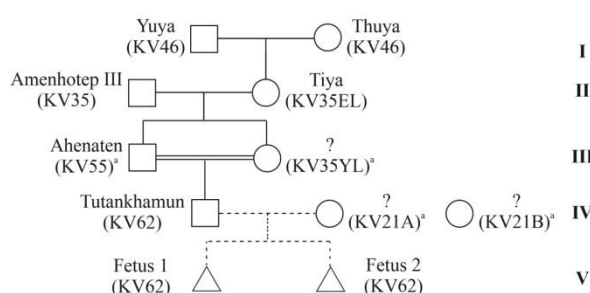


Fig. 4. Illustrative pedigree No. 4 (Tutankhamun family fragment, from the literature source).

As it is well known, for a long time the identification of several royal Egyptian mummies, the exact relationships between some members of the royal family, and the possible diseases and causes of death have been the subject of debate. Recently, the royal mummies have undergone detailed anthropological, radiological and genetic studies. Genetic fingerprints made it possible to build a pedigree of 5 generations of Tutankhamun's direct ancestry. Mummy KV55 and KV35YL have been identified as Tutankhamun's parents. No signs of gynecomastia and craniosynostosis or Marfan syndrome were found, but an accumulation of malformations in Tutankhamun's family was evident. Several pathologies have been diagnosed in Tutankhamun, and genetic testing for *Plasmodium falciparum*-specific genes revealed evidence of tropical malaria in 4 mummies, including Tutankhamun's mummy. These findings suggest avascular bone necrosis combined with malaria infection as the most likely cause of Tutankhamun's death. Tutankhamun's walking disorder and malaria are confirmed by the discovery of a cane and an afterlife pharmacy in his tomb. Thus, the expediency of collecting data on the kinship and diseases of the pharaohs while retrospectively establishing the possible causes of death was shown [5].

Limitations of the study. The study contains only 4 pedigrees and cannot be the base for generalized conclusions.

Prospects for further research. In our future research, we plan to analyze more pedigrees and determine associations between genealogical data collecting and some population sample characteristics.

4. Conclusions

In the study 4 illustrative pedigrees highlight the challenge of collecting genealogical history, analyzing easily visualized traits, and predicting their inheritance for various members of pedigrees, including dermatological, dental, skeletal, and other visible peculiarities of human appearance. It is shown that the initial results of the analysis of pedigrees can encourage further research and clarification, reveal individual errors in the interpretation of signs, and also be appropriate for influencing a wide range of the population for the prevention and early diagnosis of some diseases.

The pedigree analysis demonstrated that the number of absolute units of quantitative information presented (total number of generations and members of the pedigree) and absolute units of qualitative information (traits/medical conditions listed and their level of detail) may not be associated with the value of genetic conclusions. Thus, smaller pedigrees, where more units of information are represented per member, can be of greater value for genetic conclusions. Additionally, small pedigrees with available molecular genetic data may be of greatest value, even retrospectively.

The results of the conducted work indicate that pedigree analysis is a primary and informatively important tool for the further algorithm of diagnosis and treatment of patients and the use of such information in the educational process.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results, presented in this article.

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Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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