LARGE FAMILY GENETIC ANALYSIS: EFFECTS OF VARIEGATED PORPHYRIA AND HEMOPHILIA B ON REPRODUCTIVE TRAITS

Dorofieieva V. B., C., D., Fedota O. A., E., F.

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Introduction. The relevance of the study of genetic pathologies is due to the growing prevalence in most countries, disability and mortality of persons, high costs of support and treatment. The modern classifications include various forms of porphyria and hemophilia. The study of pathologies in historical persons, when it is possible to collect information from different sources regarding members of a large family over a long period of time, is of interest for understanding the mechanisms of the development of the disease at the present time.

Aim is to analyze the genetic characteristics of variegated porphyria and hemophilia B in a large family.

Materials and methods. Data from current guidelines and clinical protocols, scientific literature and genetic databases (OMIM) on various forms of porphyria and hemophilia are analyzed. Information about 1362 people from the British royal family in 18–20th centuries was collected from open sources and scientific literature. A pedigree of 10 generations, 27 nuclear families with persons with variegated porphyria and hemophilia B has been compiled. Genealogical, segregation, linkage, statistical analysis was performed. The results were used to study reproductive traits.

Results. Genealogical analysis showed a family accumulation of porphyria – its prevalence among relatives in a large family was 1.8 %, which is three orders of magnitude higher than among the population of different countries. It was established that there is no statistically significant difference in the sex ratio among patients with the specified pathologies. Data from genealogical and segregation analysis and a penetration rate of 92 % suggest an autosomal dominant type inheritance with incomplete penetrance of disease which is consistent with the literature. The independent nature of inheritance of variegated porphyria and hemophilia B was established. It was found that in persons with porphyria reproductive traits are 3.3–4.1 times differ than the reproductive traits of persons with porphyria and hemophilia at the same time. A statistically significant difference was established between the analyzed traits of patients with porphyria, who at the same time are carriers of the mutation that causes hemophilia, and the indicators of healthy individuals.

KEY WORDS: variegated porphyria, hemophilia B, large family tree, genealogical analysis, reproductive traits

INFORMATION ABOUT AUTHORS
Valeria Dorofieieva, Student of School of Medicine V. N. Karazin Kharkiv National University, 6, Svobody Sq., Kharkiv, Ukraine, 61022; e-mail: valeriadorofieieva@gmail.com, ORCID ID: 0000-0003-3463-7352
Olena Fedota, Doctor of Biology, Full Professor, Department of Obstetrics and Gynecology of School of Medicine V. N. Karazin Kharkiv National University, 6, Svobody Sq., Kharkiv, Ukraine, 61022; e-mail: omfedota@karazin.ua, ORCID ID: 0000-0001-9659-383X

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INTRODUCTION

Research on genetic pathologies is especially relevant, as their prevalence is increasing in many countries, they lead to disability, mortality, require high costs for maintenance and treatment [1, 2, 3]. There are currently more than 250 monogenic nosological units in Ukraine that require almost constant care and significant material and moral resources. For example, the State Budget of Ukraine for 2022 provides UAH 300 million for the treatment of children with spinal muscular atrophy which is enough for 5 patients, but there are more than 200 of them in Ukraine [4, 5]. As a rule, in most
monogenic pathologies, pleiotropic effects of genes are noted with affects the cardiovascular, respiratory, endocrine, reproductive and other systems. Therefore, the research of these pathologies is especially relevant for primary prevention and formation of risk groups. It is expected that the number of patients with monogenic pathologies will increase over time. Among the groups of these diseases, among monogenic pathologies, modern classifications include various forms of porphyria and hemophilia [6, 7].

Porphyria belongs to a group of genetic diseases associated with impaired heme biosynthesis and the accumulation of its toxic metabolites. As a result of a defect in the activity of one of the enzymes of the cycle there is a partial blockage of a certain stage of heme synthesis, which is accompanied by accumulation in toxic concentrations of porphyrin metabolism metabolites, leading to damage to all nervous systems and anemia. The incidence in the world is 1:10,000 population. Asymptomatic carrier of the mutation – 1:1000 people. More common in Northern Europe [8–12].

The pathogenesis of clinical manifestations in acute hepatic porphyria is due to the involvement of the autonomic nervous system. Damage to the skin in porphyria is associated with increased sensitivity to sunlight due to the accumulation of porphyrins in the skin. There are a number of risk factors that can transport latent porphyria to the clinical stage: starvation; infections; alcohol; some drugs; cyclic changes in the hormonal profile in women; insolation [13, 14, 15].

Modern classification of porphyrrias include 8 forms [16]. The clinic of porphyria is clear and polymorphic. According to the clinical course of porphyria can be divided into 2 groups: 1. With a predominance of neurological disorders: porphyria due to deficiency of δ-aminolevulinic acid dehydratase (ALAD gene, AR-type of inheritance (TI)), acute intermittent porphyria (HMBS gene, AD-TI), hereditary coproporphyria (CPOX gene, AD-TI), variegated porphyria (HFE, PPOX genes, AD-TI); 2. With predominant skin lesions: congenital erythropoietic porphyria (UROS gene, AR-TI), erythropoietic protoporphyria (FECH gene, AD-TI), late cutaneous porphyria (UROD, HFE genes, AD-TI) [17–21]. Diagnosis of porphyria consists of history taking, analysis of the clinical picture with 3–4 main symptoms, biochemical diagnosis and DNA testing [22, 23]. To date, there are no treatments that successfully, effectively and sustainably correct impaired porphin metabolism. Therefore, in most cases, pathogenetic therapy is used. Modern treatment includes: excretion of toxic complexes with heavy metal ions; excretion of excess porphyrin from the person’s body; restoration of functional capacity of the erythropoietic system and liver; protection of the skin from the sun to eliminate the photodynamic effect [24, 25].

Variegated porphyria (porphyria variegate) belongs to the group of hepatic or acute porphyria. This pathology can be manifested by violations of the integrity of the skin, increased photosensitivity with blistering, increased trauma to the skin with subsequent scarring and hyperpigmentation. The incidence in the world is about 1,3:100,000 population [26]. It has been known in Great Britain since the time of Mary Stuart and James I. The most famous historical figure with this disease is George III, King of Great Britain and Ireland [11].

Hemophilia is a genetic disease of the hemostasis system characterized by decreased or impaired synthesis of coagulation factors VIII (hemophilia A), IX (hemophilia B), XI (hemophilia C). Hemophilia is inherited by a recessive trait linked to the sex X chromosome, the same type of hemophilia and the same severity of the disease are inherited. In the general population of patients with hemophilia 30–40 % of cases are sporadic hemophilia caused by pathological gene mutations [27]. Hemophilia A is more common occurring in 1:5000 male births, where as hemophilia B occurs in 1:30000 male births. Hemophilia is found in all ethnic groups; there is no geographic or racial predilection [28]. 2569 patients with hemophilia and Willebrand’s disease were registered in Ukraine, 667 of them (27 %) were children [29].

Diagnosis of hemophilia is based on the use of screening tests; confirmation of the diagnosis by determining the level of blood coagulation factors and genetic analysis [30]. The most characteristic and specific symptom of hemophilia is hemorrhage to large joints –
hemarthrosis [31]. Different types of hemostatic agents and coagulation drugs are available for the treatment of hemophilia. Coagulation factor concentrates (CFC) are the best treatment for patients with hemophilia [30].

The study of pathologies in historical persons, when it is possible to collect information from different sources regarding members of a large family over a long period of time, is of interest for understanding the mechanisms of the development of the disease at the present time.

**OBJECTIVE**

The aim of the study is to analyze the genetic characteristics of variegated porphyria and hemophilia B in a large family.

**MATERIALS AND METHODS**

**Characteristics of sources on porphyria and hemophilia**

Information from scientific literature sources and the OMIM genetic database on genes and mutations associated with variegated porphyria (OMIM 176200) [32] and hemophilia B (OMIM 306900) [33] and other traits was studied. The data of modern recommendations and clinical protocols, scientific literature on various forms of porphyria and hemophilia are analyzed [20, 34].

**Characteristics of the individuals**

Much historical and medical literature on members of the British royal family in 18th–20th centuries has been studied [11, OMIM]. Information about the members of the large family was obtained from open sources and scientific literature. Data about 1362 persons of a large family, the British royal family, was collected. A pedigree consisting of 10 generations, 27 nuclear families with persons with hemophilia B and variegated porphyria was compiled and analyzed. Information on quantitative and qualitative characteristics of persons were collected: sex, years and life expectancy, data on children, diseases, gynecological history, reproductive traits.

Ethics statements. Patient consent for publication – not applicable. Ethics approval – not applicable.

**Genealogical analysis**

A large genealogical tree of the ruling dynasties of Great Britain was built, starting with George III and Charlotte Mecklenburg-Strelitzka (18th century). The prevalence of variegated porphyria in the studied family was assessed and the family accumulation of the disease was monitored. Data on the prevalence of variegated porphyria in European countries were obtained from the OMIM database.

**Segregation analysis**

Weinberg’s formula was used to calculate the segregation frequency (SF) and its standard error (SSF):

\[
SF = \frac{(A - N)}{(T - N)},
\]

\[
SSF = \sqrt{\frac{SF(1 - SF)}{(T - N)}},
\]

where \(A\) – the total number of persons in the sample;

\(N\) – number of families;

\(T\) – the total number of children in the sample.

Penetration index was estimated as the ratio of the number of persons in whom the phenotypic manifestations of the analyzed allele were observed to the total number of persons in whom the analyzed allele is present in the required number of copies for the phenotypic manifestation [35].

**Linkage analysis**

The analysis of linkage of variegated porphyria and hemophilia was performed by study the compliance of the distribution of these traits in the analyzed pedigree with Mendelian patterns of independent inheritance of traits [35].

**Statistical analysis and Software**

Statistical analysis to verify the compliance of the nature of the distribution of traits with the Mendelian model of inheritance was performed using the criteria Fisher’s \(\varphi\)-transformation and criteria \(\chi^2\). Calculations were performed and databases were created using Microsoft Excel software of Windows 10 Pro operating system, AMD Ryzen 3 3200U with Radeon Vega Mobile Gfx 2.60 GHz processor, conductor code: 00330-50000-00000-AAOEM.

Connection with scientific topics

The work was carried out as part of the research project «Genetic prerequisites for the development and correction of genetic pathology at various stages of human and animal ontogenesis» (state registration number 0119U102493, 2019–2022) of the
School of Medicine of V. N. Karazin Kharkiv National University.

RESULTS AND DISCUSSION

Variegated porphyria in the British royal family. Porphyria has been known in Britain since the time of Mary Stuart and James I, but the most famous case in the history of the country is George III – King of Great Britain and Ireland [11]. On the example of King George III (04.06.1738–29.01.1820) the literature presents typical manifestations of variegated porphyria. The King showed the following signs of illness: hypersensitivity to sunlight, sounds and touch, abdominal pain and colic, nausea, constipation, rheumatism, lameness, profuse sweating, frequent pulse, skin rash, red, orange, brown or purple urine, blindness, deafness, sleep problems, dementia. Attacks of the king’s illness were noted at least 4 times: in 50, 62, 65, 72 years. He died at the age of 81 [11, 36, 37].

Hemophilia B in the British royal family. Hemophilia is also called the royal disease because of the most famous carrier of the mutation that causes hemophilia, Queen Victoria. She had 9 children and because of her offsprings, hemophilia spread to other royal houses [38]. A number of cases of increased trauma and subsequent fatalities associated with hemophilia in males among members of the British royal family have been reported. For example, Friedrich of Hesse-Darmstadt, the grandson of Queen Victoria, died of internal bleeding after falling out of a window due to hemophilia at 2 years old [39].

Genealogical analysis of variegated porphyria in a large pedigree. A large genealogical family of Great Britain was built, starting with George III and his wife, Charlotte Mecklenburg-Strelitz. A genealogical analysis of a large pedigree with porphyria, from 1362 people, 10 generations. Particular attention was paid to persons and probably persons with variegated porphyria, persons with hemophilia B and carriers of mutations that cause this disease. Fig. 1 and fig. 2 demonstrate examples inheritance in families a large pedigree with persons with variegated porphyria, persons with hemophilia B and carriers of mutations that cause this disease.

![Fig. 1. Example of a fragment of a large pedigree 1](image1)

![Fig. 2. Example of a fragment of a large pedigree 2](image2)
It was found that the prevalence of variegated porphyria in the studied family is 1.8 %, which is 3 orders of magnitude less than in different countries, where it is 0.0013 %, [40] thus in the analyzed family there is a familial accumulation of the disease. Analysis of a sex ratio among persons in a large family is demonstrated in table 1.

Analysis of a sample of persons or probably persons (n = 25) for variable porphyria revealed individuals of both sexes in a large pedigree and showed that the ratio of women to men with porphyria was 3.1%:2.9 %, or 1:1, p > 0.05, which is probably in favor of the autosomal model of inheritance.

It was established that also there is no statistically significant difference in the sex ratio among patients with the specified pathologies.

### Table 1

<table>
<thead>
<tr>
<th>Relatives</th>
<th>Women, n (%)</th>
<th>Men, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>387 (46)</td>
<td>453 (54)</td>
<td>840 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Of them, porphyria is sick, or probably sick

<table>
<thead>
<tr>
<th></th>
<th>12 (3.1)</th>
<th>13 (2.9)</th>
<th>25 (3.0)</th>
</tr>
</thead>
</table>
| Of them, porphyria is sick
| 4 (1.0)             | 10 (2.2) | 14 (1.7) |

Among them, persons with porphyria and are carriers of the mutation that causes hemophilia at the same time

<table>
<thead>
<tr>
<th></th>
<th>4 (1.0)</th>
<th>0 (0)</th>
<th>4 (0.5)</th>
</tr>
</thead>
</table>
| Among them are carriers of the mutation that causes hemophilia
| 4 (1.0)             | 0 (0)   | 4 (0.5) |

Among them are persons with hemophilia

|                     | 0 (0) | 12 (2.7) | 12 (1.4) |

### Segregation analysis

The results of segregation analysis demonstrated in the table 2 showed that for variegated porphyria it is possible to accept the hypothesis of multiple, both dominant and recessive types of inheritance. According to our results of segregation and genealogical analysis, variegated porphyria has a type of inheritance – autosomal dominant with incomplete penetrance.

### Table 2

<table>
<thead>
<tr>
<th>Phenotype of parents</th>
<th>Number of families</th>
<th>Number of children</th>
<th>Number of affected children</th>
<th>SF</th>
<th>mSF</th>
<th>SFD</th>
<th>SFr</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N*N</td>
<td>2</td>
<td>10</td>
<td>4</td>
<td>0.25</td>
<td>0.15</td>
<td>0</td>
<td>0.25</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>N*A</td>
<td>9</td>
<td>45</td>
<td>18</td>
<td>0.25</td>
<td>0.15</td>
<td>0.5</td>
<td>0.5</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Notes: N - one parent is healthy, A - one parent is affected, SF - empirical segregation frequency, mSF - its standard error, SFD, SFr - theoretically expected segregation frequencies, p - significance level.

According to OMIM, variegated porphyria may be an autosomal dominant trait found in approximately half of the offspring of adult persons and caused by mutations in the PPOX gene (Protoporphyrinogen oxidase, OMIM 600923), [26, 41] which is localized in 1q23.3. Fig. 3 demonstrates the manifestation of porphyria in a nuclear family from a large pedigree.
Fig. 3. The fragment shows the manifestation of porphyria in a nuclear family from a large pedigree

**Determination of the penetrance of the mutation that causes variegated porphyria**

According to the analysis of a large pedigree, the penetrance of the mutation was 92%. Fig. 4 demonstrates a fragment of a large pedigree with an obligate heterozygote without clinical symptoms of porphyria in a nuclear family from a large pedigree.

In addition to the *PPOX* gene, other genes that may affect the development of porphyria, such as the *HFE* gene (*Homeostatic iron regulator*, OMIM 613609), have been described [42, 43]. Its effect may explain incomplete penetrance. The *HFE* gene, located in 6p22.2, affects the following phenotypes: Alzheimer disease, susceptibility to; microvascular complications of diabetes 7; porphyria cutanea tarda, susceptibility to; porphyria variegata, susceptibility to; transferrin serum level QTL2; hemochromatosis.

Fig. 4. A fragment of a large pedigree demonstrates the presence of an obligate heterozygote without clinical symptoms of porphyria

**Estimating of linkage of variegated porphyria and hemophilia B in a large family**

The results of the analysis of the association of porphyria and hemophilia B in nuclear families with 6–9 off springs from a large pedigree allowed to reject the hypothesis of their possible linkage, \( p = 0.918 \times 0.608 \). Fig. 5 demonstrates examples nuclear families and persons with porphyria and carriers of a mutation that causes hemophilia at the same time. But the independent distribution of pathological signs does not exclude the possibility of influencing the interaction of non-allelic genes on the nature of the manifestation and degree of manifestation of clinical signs of disease, which was studied by analyzing the reproductive parameters of persons with porphyria and hemophilia.
Analysis of reproductive traits of persons with variegated porphyria and hemophilia B

The analysis of reproductive traits of 4 groups of persons from a large family with different pathologies is demonstrated in table 3.

Table 3
Reproductive traits of persons with porphyria, hemophilia, porphyria and hemophilia at the same time

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Reproductive traits of persons with different pathologies</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Persons, n</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Average life expectancy, years, $\bar{X} \pm S_{\bar{X}}$ **</td>
<td>60,4±5,7</td>
<td>69,3±5,3</td>
</tr>
<tr>
<td>Pregnancies, in spouses, n</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Pregnancies per person, in spouses, n, $\bar{X} \pm S_{\bar{X}}$ **</td>
<td>3,2±1,5</td>
<td>1,8±1,1</td>
</tr>
<tr>
<td>Reproductive losses, in spouses, n *</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive losses per person, in spouses, n, $\bar{X} \pm S_{\bar{X}}$ **</td>
<td>0,3±0,2</td>
<td>0</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–18 years, n</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>0–18 years per person, n, $\bar{X} \pm S_{\bar{X}}$ **</td>
<td>3,0±1,5</td>
<td>1,8±1,1</td>
</tr>
<tr>
<td>18+ years, n</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>18+ years per person, n, $\bar{X} \pm S_{\bar{X}}$ **</td>
<td>2,4±1,3</td>
<td>1,8±1,1</td>
</tr>
</tbody>
</table>

Notes: *Reproductive losses include: miscarriage, spontaneous loss of a pregnancy, stillbirth. **$\bar{X} \pm S_{\bar{X}}$ – mean value ± standard error.
The analysis of reproductive traits of 14 persons with porphyria from a large family showed that with an average life expectancy of 64.8 ± 1.7 years of persons, the average number of pregnancies per person was 2.5 ± 0.7, reproductive losses – 0.2 ± 0.2. Number of children born – 37, children over 18 – 31, the average number of children born per person – 2.6 ± 1.1, children over 18 – 2.2 ± 0.9.

The analysis of reproductive traits of 4 persons with porphyria and carriers of a mutation that causes hemophilia at the same time showed that with an average life expectancy of 55.5 ± 9.9 years of persons, the average number of pregnancies per person was 7.3 ± 0.9, reproductive losses – 0. Number of children born – 29, children over 18–24, the average number of children born per person – 7.3 ± 0.9, children over 18 – 6.0 ± 1.6.

The analysis of reproductive traits of 4 persons carriers of a mutation that causes hemophilia showed that with an average life expectancy of 88.0 ± 3.3 years of persons, the average number of pregnancies per person was 4.5 ± 1.0, reproductive losses – 0.5 ± 0.3. Number of children born – 16, children over 18 – 14, the average number of children born per person – 4.0 ± 0.7, children over 18 – 3.5 ± 1.0.

The analysis of reproductive traits of 4 persons with hemophilia showed that with an average life expectancy of 22.1 ± 4.3 years of persons, the average number of pregnancies per person was 0.25 ± 0.2, reproductive losses – 0. Number of children born – 3, children over 18 – 3, the average number of children born per person – 0.25 ± 0.2, children over 18 – 0.25 ± 0.2.

The analysis of reproductive traits of 12 healthy persons from a large family showed that with an average life expectancy of 69.0 ± 3.1 years of persons, the average number of pregnancies per person was 3.8 ± 0.7, reproductive losses – 0.4 ± 0.2. Number of children born – 41, children over 18–38, the average number of children born per person – 3.4 ± 0.7, children over 18 – 3.2 ± 0.7.

Due to the analysis of reproductive traits of persons with porphyria, hemophilia, porphyria and hemophilia simultaneously, it was found that in persons with porphyria reproductive traits are statistically significantly differ by 3.3–4.1 times than the reproductive traits of persons with porphyria and hemophilia at the same time, \( p = 0.0021 \).

A statistically significant difference was established between the analyzed traits of patients with porphyria, who at the same time are carriers of the mutation that causes hemophilia, and the indicators of healthy individuals, \( p = 0.022 \).

We can assume that porphyria, as a pathology of metabolism, and hemophilia, as a pathology of hemostasis, have mutually compensatory mechanisms of influence on the organism, which allows individuals with a combination of these pathologies to more successfully realize their reproductive potential, compared to individuals suffering from porphyria or who are mutation carriers, which causes hemophilia. We would like to emphasize the special role of sex hormones in triggering attacks of acute porphyria in women, since it is the change in their level in the organism that is the most frequent cause of attacks [44]. According to Daphne Vassiliou and Eliane Sardh [45] the results of a 20-year study of 44 pregnant women with acute hepatic porphyria who gave birth to 44 children showed that only 9% (4) of women suffered an attack of porphyria during pregnancy. Authors concluded that pregnancy in patients with porphyria often proceeds without complications. Cyclical changes in the hormonal profile, such as the menstrual cycle, are significant triggering factors capable of realizing asymptomatic mutation carriers and turning the latent course of porphyria into the clinical stage.

Therefore, in historical times, in the absence of effective treatment methods, multiple pregnancy throughout the entire fertile age became an available relief approach.

Currently, it is actual to do genetic testing before puberty to reduce the risk appearance of acute symptoms of porphyria, the cumulative risk of which among asymptomatic patients at the time of diagnosis is 26.7–58.3% [46].

**CONCLUSIONS**

According to the results of genealogical analysis, prevalence of variegated porphyria in the studied family was 1.8%, which is three orders of magnitude higher than among the population of different countries. It was
established that there is no statistically significant difference in the sex ratio among patients with the specified pathologies. An autosomal dominant type of inherited variegated porphyria with incomplete penetrance 92% has been estimated. The independent nature of the inheritance of variegated porphyria and hemophilia B has been established confirmed. It was found that in persons with porphyria reproductive traits are 3.3–4.1 times differ than the reproductive traits of persons with porphyria and hemophilia at the same time. A statistically significant difference was established between the analyzed traits of patients with porphyria, who at the same time are carriers of the mutation that causes hemophilia, and the indicators of healthy individuals.

GRATITUDE

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42. OMIM 613609. [Internet]. [cited 2022 Oct 26]. Available from: omim.org/entry/613609?search=613609&highlight=613609


Вступ. Актуальність дослідження генетичних патологій обумовлена зростанням їхньої поширеності у більшості країн, інвалідизації та летальність хворих, великих витратами на супровідування. Сучасна класифікація генетичних хвороб включає, зокрема, різні форми порфірії та гемофілії. Вивчення патології в історичних осіб, коли є можливість зібрати інформацію з різних джерел про членів великої родини за тривалий період часу, представляє інтерес для розуміння механізмів розвитку захворювання.

Мета роботи – аналіз генетичних особливостей варієгатної порфірії та гемофілії В у великої родині.

Матеріали та методи. Проаналізовано дані сучасних рекомендацій та клінічних протоколів, наукової літератури та генетичних баз даних (OMIM) щодо різних форм порфірії та гемофілії. З відкритих джерел та наукової літератури зібрано відомості про 1362 особи з Британії, а також дані генеалогічного та сегрегаційного аналізу, що стосуються 27 ядерних сімей з хворими на варієгатну порфірію та гемофілію В. Проведено генеалогічний, сегрегаційний, статистичний аналіз та аналіз з членів великої родини.

Результати. Генеалогічний аналіз показав сімейне накопичення порфірії – її поширеність серед родичів у великий родини складає 1,8 %, що на три порядки вище, ніж серед населення різних країн. Встановлено, що статистично значущої різниці у співвідношенні статей серед осіб із зазначеними патологіями немає. Дані генеалогічного та сегрегаційного аналізу, та показник пенетрантності 92 %, свідчать про аутосомно-домінантний тип успадкування з неповною пенетрантністю, що згідно з даними літератури, відповідає присутній у варієгатній порфірії та гемофілії В. Доведено, що у хворих на порфірію репродуктивні ознаки в 3,3–4,1 рази відрізняються від репродуктивних ознак у хворих на порфірію та гемофілію В однаково. Встановлено значущу різницю між проаналізованими ознаками хворих на порфірію, які водночас є носіями мутації, що обумовлює гемофілію, та показниками здорових осіб.

КЛЮЧОВІ СЛОВА: варієгатна порфірія, гемофілія В, великий родовід, генеалогічний аналіз, репродуктивні ознаки

ІНФОРМАЦІЯ ПРО АВТОРІВ

Дорофєєва Валерія Романівна, студентка медичного факультету Харківського національного університету імені В. Н. Каразіна, пл. Свободи, 6, Харків, Україна. 61022; e-mail: valeriadorofieieva@gmail.com, ORCID ID: 0000-0003-3463-7352

Федота Оlena Михайлівна, д. біол. н., професор кафедри акушерства та гінекології, медичний факультет, Харківський національний університет імені В. Н. Каразіна, пл. Свободи, 6, Харків, Україна, 61022; e-mail: omfedota@karazin.ua, ORCID ID: 0000-0001-9659-383X

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