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Genetic Study of X-Linked Recessive Ichthyosis in Eastern Ukraine

O. M. Fedota[a], L. V. Roshcheniuk[b, c], I. O. Sadovnychenko[a, c, *], J. V. Gontar[d], I. M. Merenkova[c, e], V. M. Vorontsov[b], and P. P. Ryzhko[b]

[a] *V.N. Karazin Kharkiv National University, Kharkiv, 61022 Ukraine*
[b] *Regional Clinical Dispensary for Skin and Venereal Diseases no. 1, Kharkiv, 61052 Ukraine*
[c] *Kharkiv National Medical University, Kharkiv, 61022 Ukraine*
[d] *LLC Medical Center IGR, Kyiv, 03115 Ukraine*
[e] *Kharkiv Municipal Maternity Hospital no. 1, Kharkiv, 61045 Ukraine*
**e-mail: sadovnychenko@gmail.com*

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Abstract—X-linked recessive ichthyosis (OMIM 308100) is a form of ichthyosis caused by abnormal keratinization and can result in disability, social maladaptation, and decreased quality of life for patients and their families. In most cases the disease is caused by a complete or partial deletion of the steroid sulfatase (*STS*) gene. This study estimated the prevalence of X-linked recessive ichthyosis, the inbreeding coefficient (or fixation index) F_{ST}, and the selection coefficient in individuals of eastern Ukraine (namely, Kharkiv oblast). The genealogical method was used to assess the genetic structure of families with a history of this disease. Fluorescent in situ hybridization (FISH) was carried out to detect the deletion of the *STS* gene in patients and their relatives. The prevalence of the disease in eastern Ukraine was 1.5×10^{-4} males, it ranged from 4.9×10^{-5} to 4.9×10^{-4} males in the districts, and from 2.2×10^{-4} males in the town of Krasnograd to 3.7×10^{-3} males in a village of Balakliia district. The burden of X-linked recessive ichthyosis was found to be positively correlated with the inbreeding coefficient F_{ST} in all the studied districts ($r = 0.976$). Over the past 10 years, the inbreeding coefficient F_{ST} increased 1.8 times and the prevalence of X-linked recessive ichthyosis increased 1.4–4.3 times in most districts of the region. The clinical genealogical analysis of nine large families revealed no females with X-linked recessive ichthyosis among relatives of probands, while 21.4% ($n = 14$) of the first-degree male relatives and 12.0% ($n = 25$) of the second-degree male relatives had ichthyosis. In most patients and their mothers from eastern Ukraine, FISH detected an interstitial deletion of the *STS* gene, ish del(X)(p22.31p22.31)(STS-), but no *KAL1* gene deletions. In men with X-linked recessive ichthyosis, the average number of children per person was 2.5 times lower than in healthy relatives, and their offspring was characterized by the prevalence of females over males in a 3 : 1 ratio. In obligate heterozygous females, the average number of children per person was 2.2, and the sex ratio in the offspring approached 1 : 1.

Keywords: X-linked recessive ichthyosis, prevalence, inbreeding, deletion, *STS* gene
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INTRODUCTION

Ichthyosis includes a group of monogenic dermatoses that are associated with keratinization disorders and can lead to disability, social maladaptation, and adversely affect patient's quality of life (Mazereeuw-Hautieri et al., 2019). The second most common form of ichthyosis, X-linked recessive ichthyosis (OMIM 308100), is caused by deletions or point mutations in the steroid sulfatase gene *STS* (OMIM 300747) located at locus Xp22.3 (Toral-López et al., 2015). This gene encodes the steroid sulfatase enzyme (EC 3.1.6.2), which cleaves sulfated precursors of steroid hormones and cholesterol (Hackl et al., 2012; Mueller et al., 2015). *STS* gene expression was observed in keratinocytes, fibroblasts, leukocytes, bones, kidneys, liver, endocrine glands, brain, and in some tissues responsible for the reproductive function, including the endometrium, ovaries, testes, prostate, mammary gland, prostate, and breast, while its highest expression was shown for placenta (Mueller et al., 2015; Toral-López et al., 2015). The clinical picture of X-linked ichthyosis is manifested at birth or in the first weeks of life and may include lesions of most of the skin with dark brown polygonal scales (Elias et al., 2010; Toral-López et al., 2015).

Deletions of the Xp22.3 locus, in addition to the *STS* gene, often include genes *HDHD1A*, *PNPLA4*, *ASS*, *NLGN4X*, *VCX*, and *KAL1* (Diociaiuti et al., 2019). Patients with X-linked ichthyosis may have comorbidities, such as skeletal abnormalities, dysfunc-

tion of the endocrine, nervous and sensory systems, hypogonadotropic hypogonadism, oncopathology, autism, attention deficit hyperactivity disorder, mental retardation, aggression, etc.; however, they are not specific only for this disease (Fernandes et al., 2010; Elias et al., 2014; Toral-López et al., 2015; Dmytruk et al., 2016; Panchenko et al., 2019).

The prevalence of this disease among men is 1 : 6000–1 : 1500, its cases in women are rare (Murtaza et al., 2014; Diociaiuti et al., 2019). Genetic polymorphism and the pleiotropic effect of mutations in the Xp22.3 locus were described in patients with X-linked ichthyosis from different countries and ethnic groups, but such information is still not available in Ukrainian sources.

The purpose of this study is to determine the genetic features of X-linked ichthyosis in eastern Ukraine on the example of Kharkiv oblast.

MATERIALS AND METHODS

Primary information was collected by individual registration of probands at Regional Clinical Dermatological and Venereological Dispensary no. 1 and dermatological and venereological dispensaries of Kharkiv oblast. Data encompassing 82 patients and 1435 their first- to third-degree relatives were analyzed. The sample for genealogical analysis included nine randomly selected families from different districts of the oblast. Extended ascending pedigrees consisted of up to 31 first to third-degree relatives, a total of 169 people.

Point prevalence of ichthyosis in the districts of Kharkiv oblast was calculated as a the number of patients divided by the population of a certain area using data from the Main Department of Statistics in Kharkiv oblast and other state and local authorities. The genetic structure of urban and rural populations was estimated using the inbreeding coefficient F_{ST} (Cavalli-Sforza and Bodmer, 1971; Altukhov, 2003). The selection coefficient was determined by the genotype relative fitness value (Relethford, 2012).

Molecular cytogenetic analysis of the *STS* gene using the method of fluorescent in situ hybridization (FISH) was carried out on venous blood samples of eight probands and three of their mothers from nine families.

Deletions of *STS* gene were localized on metaphase chromosomes as follows. Peripheral blood cells were first cultured: 0.5 mL of whole blood was added to tubes containing 4.5 mL of PBmax medium (Gibco, United States). Cultivation was carried out at the temperature of +37°C for 72 h. Colchicine, 50 μL per volume of medium, was administered to accumulate lymphocytes in the metaphase stage. At the end of the cultivation, the blood cells were precipitated by centrifugation, the resulting precipitate was treated with a hypotonic solution of 0.075 M potassium chloride for 20 min at the temperature of +37°C. Lymphocytes were fixed with a 3 : 1 mixture of ethanol and acetic acid cooled to +4°C prepared *ex tempore*. After final centrifugation, the cell suspension was distributed on cooled wet glass and air-dried (Vorsanova et al., 1999; Zerova-Lyubimova and Gorovenko, 2003).

A mixture of probes for Kallmann syndrome (KAL1) and steroid sulfatase (STS) (Cytocell, UK) was applied to the area of the preparation with metaphase plates. Marked in green in the figures, the STS probe was 282 kB in size and covered the *STS* gene and most of the *HDHD1A/STS* genes. Marked in red in the figures, the KAL1 probe had a size of 334 kb and covered the entire *KAL1* gene and markers DXS278 and DXS7053. We used it to control the correctness of hybridization of fluorescent samples, because genes *STS* and *KAL1* are located next to each other and the fluorescent labels have different colors. The probe mixture, in addition to the above, also contained a control probe for the X-chromosome centromere (DXZ1), marked in green. Hybridization lasted from 4 to 12 h. To remove sample residues, preparations were washed in SSC saline solutions and ethyl alcohol solutions. Fluorescent signals were detected according to the standard protocol. Microscopic analysis was carried out using a fluorescence microscope equipped with an appropriate set of filters and the automatic image processing software ISIS (MetaSystems, Germany) (Lichter and Ried, 1994).

The data were checked for normal distribution by the methods of Shapiro–Wilk and Kolmogorov–Smirnov, and statistical hypotheses were tested according to Mann–Whitney, Student, and Wilcoxon. The relationship between traits was studied using Pearson correlation analysis. Distribution series were estimated using the χ^2 test (Armitage et al., 2013).

RESULTS AND DISCUSSION

The prevalence of X-linked recessive ichthyosis among the population of the studied oblast is 1.5×10^{-4} men, which corresponds to this indicator in Western Europe, 3.3×10^{-4}–5.0×10^{-4}; however, it is an order of magnitude higher than in Eastern European countries, 1.1–6.4×10^{-5} (Sukalo et al., 2013; Amelina et al., 2014; Oji, 2017). In the districts of Kharkiv oblast, the prevalence of this form of ichthyosis varies between 4.9×10^{-5}–4.9×10^{-4} men. In the last 10 years, in most of the studied areas, this indicator has statistically significantly increased by 1.4–4.3 times ($p < 0.001$). X-linked ichthyosis was most commonly found in one of the villages of Balakliia district, 3.7×10^{-3}, and the lowest rate was observed in Krasnograd, 2.2×10^{-4} men. The difference in the prevalence of the disease in districts, cities, and villages may be due to specifics of migration processes, marital structure, advancement of their transport infrastructure, etc. (Craig et al., 2010; Barrett, 2016).

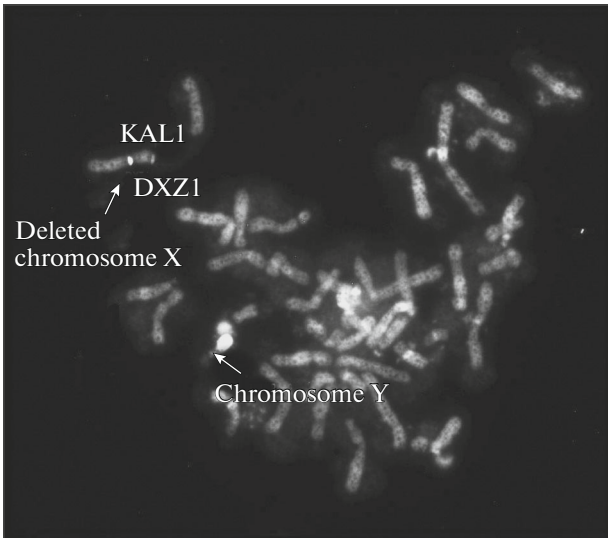

Fig. 1. Male karyotype with detected X-chromosomal deletion ish del(X)(p22.31p22.31)(STS-), magnification 10 × 100 (original).

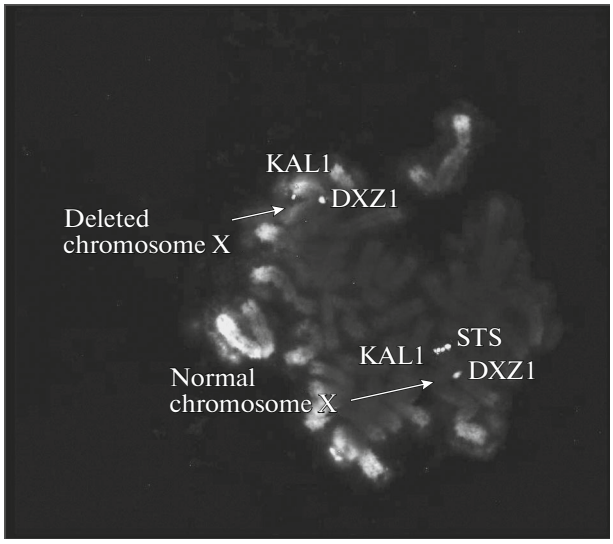

Fig. 2. Female karyotype with detected X-chromosomal deletion ish del(X)(p22.31p22.31)(STS-), magnification 10 × 100 (original).

It was found that the prevalence of X-linked recessive ichthyosis in the settlements of the studied areas is positively correlated with the inbreeding coefficients F_{ST} ($r = 0.976$, $p < 0.001$). Analysis of the dynamics of random inbreeding in cities and villages of these areas since 2008 showed an increase of 1.8 times ($p = 0.012$), which may be a prerequisite for the birth of homozygous women.

Clinical and genealogical analysis of families with X-linked ichthyosis did not reveal women with corresponding clinical signs. A study of hereditary burden in families showed that, in probands 21.4% ($n = 14$), individuals had ichthyosis among first-degree male relatives of mothers and 12.0% ($n = 25$) among second-degree male relatives of mothers. There were also 15 affected relatives of the third-, fourth-, and fifth-degree. The results of clinical and genealogical analysis are an important step in identifying the type of inheritance and differential diagnosis of the disease, but it is required to carry out molecular analysis to finally confirm the form of pathology.

Molecular cytogenetic analysis showed that the signal from the KAL1 locus was visualized in all samples, so Kallman's syndrome was not considered in the studied families further on. An interstitial deletion of the *STS* gene, ish del(X)(p22.31p22.31)(STS-), was found in seven probands and two mothers from eight families with a typical clinical picture of X-linked ichthyosis (Figs. 1, 2). In a family of four patients with diagnostic traits similar to X-linked ichthyosis, no deletion of the *STS* gene was confirmed, and no presence of mutations R501X and 2282del4 in the filaggrin gene (*FLG*) was detected earlier; the karyotype of the mother of two probands was mos45,X[20]/46,XX[80]. Thus, X-linked recessive ichthyosis is caused by deletion of the *STS* gene in 87.5% of patients, while, according to the literature, 85–90% of cases of pathology are caused by deletions and the rest by point mutations (Diociaiuti et al., 2019).

The Xp22.3 locus is known to be homologous to the pseudogenic locus Yq11; it avoids inactivation and has increased recombination capacity (Canueto et al., 2010). Deletions of the *STS* gene are thought to be due to the presence of several flanking copies of the G1.3 and CRI-S232 repetitive sequence families, resulting in unequal homologous recombination in women and intrachromosomal rearrangement in the X chromosome in men (Toral-López et al., 2008; Diociaiuti et al., 2019). Intensification of recombination processes and higher frequency of chromosomal aberrations may be facilitated by the increase in the degree of homozygosity of the population due to the increase in inbreeding rates (Fedota et al., 2017).

The frequency of crossing over between X and Y chromosomes in spermatogenesis can also affect the reproductive function, in particular, due to changes in the number of male gametes (Faisal and Kauppi, 2016).

Analysis of the structure of families with confirmed X-linked ichthyosis showed that the average number of children in male patients is lower than in healthy relatives, 0.9 compared with 2.3 ($p = 0.014$) (Table 1). It was 1.7 in healthy men, 2.3 in obligate heterozygous females, and 2.7 in women with undetermined genotypes.

There was a shift in the ratio of male and female sexes among children of male patients towards females, 4 : 12 or 1 : 3 ($p = 0.045$), while healthy relatives were observed to have no deviation from a 1 : 1 ratio (Table 1).

Table 1. Structure of families with X-linked ichthyosis

Sex offspring	Sex of parents			
	men		women	
	affected, $n = 17$	healthy, $n = 3$	obligate heterozygotes, $n = 18$	with undetermined genotype, $n = 3$
Men				
affected, $n = 20$	0	0	20	0
healthy, $n = 18$	4	3	6	5
Women				
obligate heterozygotes, $n = 17$	12	0	5	0
with undetermined genotype, $n = 15$	0	2	10	3
Average number of children per person	0.9	1.7	2.3	2.7

Wives of male patients did not show reproductive losses in the early stages of pregnancy up to 7 weeks, so gametic selection is likely if the viability of sperm carrying the corresponding Y chromosome is reduced as a result of crossing over. The relative fitness in patients with X-linked recessive ichthyosis was 0.56, and the coefficient of selection against the hemizygous genotype was 0.44. At the same time, the literature shows that sexual development and fertility in male patients hardly deviate from the age norm, which is probably due to the presence of an alternative metabolic pathway responsible for androgen activation (Fernandes et al., 2010; Idkowiak et al., 2016; Sánchez-Guijo et al., 2016). According to other authors, genetic polymorphism of ichthyosis serves as an additional argument in favor of investigating this disease in every country, region, and ethnic group (Craig et al., 2010; Diociaiuti et al., 2019).

It is known that steroid sulfatase deficiency in the placenta of women heterozygous for mutations in the *STS* gene causes failure of labor (Elias et al., 2014), which is known to be associated with high maternal and fetal complications as well as perinatal losses (Tatarchuk, 2015). In our study, in obligate heterozygotes, the average number of children per woman was 2.2 ± 0.2, while the regional average was 1.4 ± 0.1 ($p = 0.011$)[1], so we can conclude that their level of fertility is not reduced.

This may be due to the phenomenon described in the literature, the heterozygote advantage (Hedrick, 2012). It is known that steroid sulfatase deficiency reduces the likelihood of developing hormonal tumors (Rizner, 2016), including uterine leiomyomas, ovarian cysts, breast cancer, etc. (Radzinskij and Totchiev, 2014), which, in turn, extends the reproductive period in women and healthy life expectancy. It is likely that the increased adaptability of women in the social structure of the family may be an argument in favor of the "grandmothering effect" (Kachel et al., 2011), which consists in the ability of their daughters to have their first child at an earlier age and reduce the interval between the birth of children up to 1 year.

[1] According to the data of the National Statistics Service of Ukraine.

CONCLUSIONS

The prevalence of X-linked recessive ichthyosis among the population of eastern Ukraine is 1.5×10^{-4} men, and it increased 1.4–4.3 times over the past 10 years. A positive association was found between the population rates of X-linked recessive ichthyosis and the inbreeding coefficients F_{ST} in the settlements of the studied areas ($r = 0.976$). An interstitial deletion of the STS gene, ish del(X)(p22.31p22.31)(STS-), was detected in patients with X-linked ichthyosis and their relatives. It is shown that females prevailed over males in a 3 : 1 ratio in the offspring of male patients.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. The study was carried out in accordance with the basic bioethical norms of the Helsinki Declaration of the World Medical Association on the Ethical Principles of Medical Research (2000, as amended in 2008), the Universal Declaration on Bioethics and Human Rights (1997), and the Convention on Human Rights and Biomedicine of the Council of Europe (1997). Informed consent was obtained from all individual participants involved in the study.

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