doi.org/10.56121/2181-2926-2022-1-23-29

Article

COMBINED GENETIC DISORDERS IN PATIENTS WITH COAGULOPATHYEЙ

Makhmudova A.D.[1], Berger I.V.[2], Madasheva O.G.[3], Ulugova Sh.T.[4]

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1. Doctor of Medical Sciences, Deputy Director for the Scientific Department of the RSNPMC of Hematology.
2. Doctor of Philosophy (PhD) of Medical Sciences, Deputy Chief Physician at the Republican Scientific and Practical Medical Center for Hematology (RNPMCH) of the Ministry of Health of the Republic of Uzbekistan. **ORCID**.
3. Doctoral student at the Republican Scientific and Practical Medical Center for Hematology (RNPMCH) of the Ministry of Health of the Republic of Uzbekistan.
4. Doctor of the higher category. doctoral student at the Republican Scientific and Practical Medical Center for Hematology (RNPMCH) of the Ministry of Health of the Republic of Uzbekistan, **ORCID**

Abstract. The article presents the available literature data on combined pathologies with hereditary coagulopathy and includes our own statistical calculations and 4 clinical cases of a combination of Hemophilia A, von Willebrand disease with hard palate defects, the genetic locus of which is located in the immediate vicinity of the F8 gene. Mutations and changes in the protein structure of the F8 gene can lead to the development of both sporadic forms of hemophilia and occur in patients with a hereditary predisposition. Research methods: coagulological, examination and questionnaire data. Conclusion: it is necessary to widely introduce methods of molecular genetic research and prenatal diagnostics in Uzbekistan.

Key words: F8 gene, Hemophilia A, von Willebrand disease, hereditary pathologies, chromosomal disorders, cleft palate, color blindness.

Academic Editor: Arzikulov A. Professor, Andijan State Medical Institute

Received: 20 may 2022
Accepted: 27 May 2022
Published: 31 May 2022

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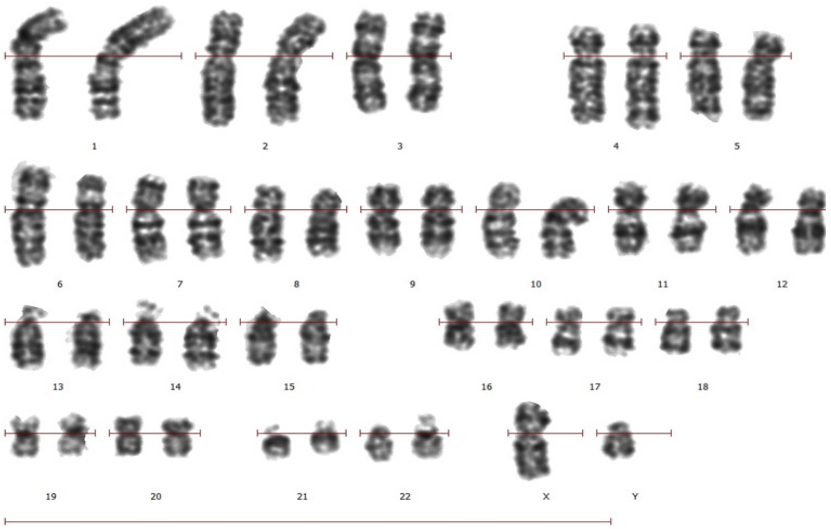
Introduction. The X chromosome contains 867 identified genes; most of these genes are responsible for the development of tissues such as bones, nerves, blood, liver, kidneys, retina, ears, ear, heart, skin, and teeth. There are at least 533 disorders due to the involvement of genes on the X chromosome. A «trait» or «disorder» defined by a gene on the X chromosome demonstrates X-linked inheritance [1].

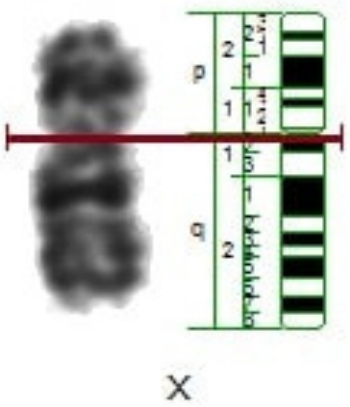
The normal human karyotype includes 22 autosomes and 2 sex chromosomes (XX for women and XY for men). Figure 1 shows a photo of a male karyotype obtained in the laboratory of molecular genetics and cytogenetics on a direct light fluorescent microscope Axio Scope.A1 (Zeiss, Germany) at the RSNPMC of Hematology of the Ministry of Health of the Republic of Uzbekistan.

It is known that the F8 and F9 genes located on the X chromosome at the Xq28 and Xq27 loci are responsible for the formation of blood coagulation factors VIII and IX [2,8,9]. Changing genes in these locations leads to the development of such pathologies as Hemophilia A, Hemophilia B and von Willebrand disease.

Figure 2 shows a map of the X chromosome and loci responsible for the development of sex-related hereditary diseases, in particular hemophilia A, hemophilia B, and von Willebrand disease. In these regions of the gene, many different mutations can occur, which also lead to the development of such diseases as hemolytic anemia, adrenoleukodystrophy, blinding with bright colors, etc. [1].



Rice. 1 Chromosome set of a healthy person, male karyotype, normal (46, XY). The photo was taken in the Laboratory of Molecular Cytogenetics of the Republican Scientific and Practical Center for Hematology of the Ministry of Health of the Republic of Uzbekistan. Ph.D. Assesorova Yu.Yu.



Rice. 2 X-chromosome with an ideogram. Location of the F8 and F genes 9. The arrows mark the Xq28 and Xq2 loci responsible for the development of hemophilia A and B. P is the short arm, q is the long arm. Dark and light stripes are segments conditionally taken as a gene. Photo taken by Ph.D. Assesorova Yu.Yu. in the laboratory of molecular cytogenetics of the SRCPM of Hematology of the Ministry of Health of the Republic of Uzbekistan.

27 exons contains the F8 gene and encodes two alternative transcripts. The first option contains instructions for making the large glycoprotein isoform A, the ß-globulin (antihemophilic globulin) protein, which is called coagulation factor VIII. The second transcript encodes a small protein (isoform B), which mainly consists of the phospholipid-binding domain of factor VIIIa and is required for coagulant activity [1,8].

The F8 gene can be called by its content as a “gene within a gene”, since an RNA gene (MIR1184-1) and two pseudogenes (EEF1A1P31, LOC100419792) are nested in its structure, and 2 protein-coding genes (F8A1) are located on the opposite positive strand , H2AB1) and 2 recombination regions (LOC106146150, LOC106146143). Coagulation factor VIII is composed of multiple Cu-oxidase (CuRO) and FA58C domains. This protein circulates in the blood in an inactive form, which is associated with another molecule, von Willebrand factor [7].

Changes in these genes of factors VIII and IX, leading to the

development of pathology, can be represented by single nucleotide substitutions that change the reading frames, deletions of chromosome fragments containing these loci, inversions, and other genetic rearrangements [12]. Until recently, the genetic diagnosis of hemophilia, taking into account the subtype of the disease, was difficult due to the fact that the construction of this gene is extremely complex and rather voluminous, and also due to the wide range of potential mutations. An effective study of the genetic determinant of the disease has become possible due to the development of DNA sequencing techniques and the improvement of molecular cytogenetic equipment.

M.J. McGinniss et all. (USA, 1993) it was shown that 40% of patients with severe hemophilia A, who previously failed to identify any mutation during screening or sequencing, have inversions of the F8 gene. Patients have one of two major inversions—with a breakpoint in intron 22 or with a breakpoint in either of the two copies of the F8 gene (Inversion with a breakpoint in the distal portion of the F8 gene is the more common variant) [7]. These inversions explain why deletions and point mutations have not yet been found in such patients and why transcription of intron 22 and exon 23 is impossible [11].

Quite a few cases of a combination of congenital FVIII deficiency and color blindness are known in the world [12], since the segments responsible for color perception and hemophilia gene loci are quite close to each other. The OPN1LW, OPN1MW, and OPN1SW genes code for red, green, and blue-sensitive receptors. Mutations in the OPN1LW and OPN1MW genes lead to the development of red-green color blindness, and in the OPN1SW gene, blue-yellow color blindness. If a mutation simultaneously affects two genes, OPN1LW and OPN1MW, monochromasia develops [2].

Back in 1991, when working with data from the decoding of the human genome, a gene was found that is also located on the X chromosome and is responsible for the development of the “cleft palate” - an altered TBX22 gene [1].

Cleft palate is one of the most common congenital malformations and, according to different authors, occurs in 1 born baby per 1000, which is 0.1%, most of which are boys [6]. In some European regions (Denmark, Czech Republic) and the Russian Federation, these figures are an order of magnitude higher, and 1 child out of 600–700 babies is born with this defect, and half of them also have a defect in the form of a cleft lip [3]. Most often, the cleft palate is registered in infants born in Asia and North America, and is almost never found among the inhabitants of Africa [4].

The results of whole genome sequencing conducted in 2004 in Scandinavia from 574 families from 13 populations showed the relationship of different loci of chromosomes 1, 2, 4, 6, 14, 17 and 19 (IRF6, TGF-α, MSX1, T-βr1, FOXFE1, RTCH, ROR2, TGF-β3, RARA, PVRL1) with the risk of developing non-syndromic congenital cleft lip with/without palate [5]. Some of the candidate genes in the development of facial cleft belong to the growth factor genes (TGF-α, TGF-β3) and transcription factor genes (MSX1, IRF6, TBX22), some to the genes that control the synthesis of enzymes involved in the metabolism of xenobiotics (CYP1A1, GSTM1, NAT2) or folic acid (MTHFR), some of the genes regulate the body’s immune responses (PVRL1, IRF6) [10]. Studies of IRF6 gene polymorphisms have also revealed associations with congenital cleft palate in many populations

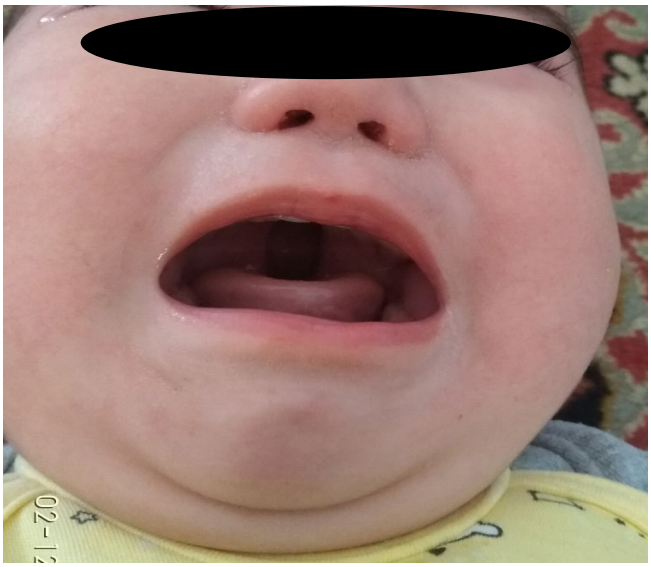
[5].

Own data. In 2010, our research group created and is still maintaining an electronic national register of patients with hemophilia and other coagulopathies covering all regions of the Republic of Uzbekistan.

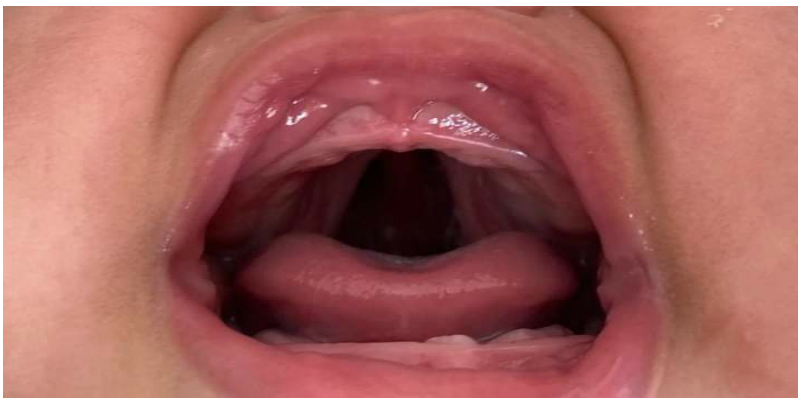
Research methods: coagulological, examination and questionnaire data.

According to our registry, by the end of 2021, 1987 patients with hereditary coagulopathy are registered. Analysis of the data showed that among all patients - 30% are sporadic cases of the onset of diseases. Since hemophilia is not always registered at the birth of a child, moderate and mild forms of the disease can be detected at the age of 3, we provide statistical data for 2019. According to the State Statistics Committee, 815.9 thousand newborns were born in the Republic of Uzbekistan in 2019. The number of registered patients born in 2019 was 16 patients with Hemophilia A, 5 patients with Hemophilia B and 29 children with von Willebrand disease. Thus, there are 6 children suffering from hemophilia per 100,000 newborns in Uzbekistan, while according to world statistics, this figure is 10:100,000 newborns. 50% of all cases reported each year are severe (i.e. less than 1% of clotting factors).

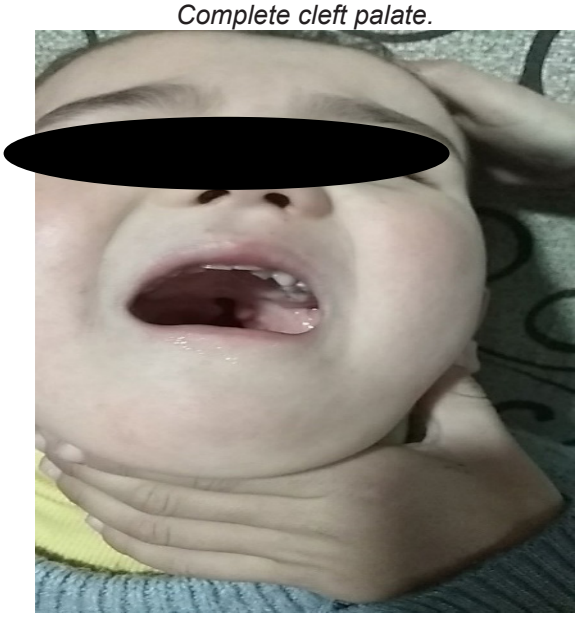
Among the patients of the Republic, children with Hemophilia A and von Willebrand disease with combined pathology in the form of a cleft palate (cleft palate) were identified. 2 patients diagnosed with hemophilia A and 2 patients with von Willebrand disease. Patients with hereditary coagulopathy and color blindness were not registered in the Republic of Uzbekistan.



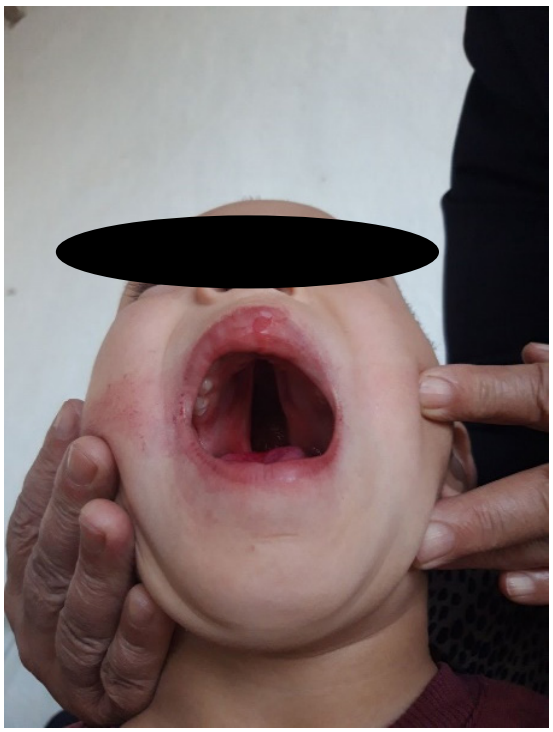
Child, 11 months (2020). von Willebrand disease, factor VIIIa level of 3%, and complete cleft palate. Heredity is favored through the maternal line. Also in the family there are 2 more children with a mild severity of the disease, without pathology of the hard palate.



Child, 2021 Hemophilia A severe (factor VIII level - 1%), heredity is not traced. Complete cleft palate.



Child, 4 years old (2018). von Willebrand disease, factor VIIIa 7%, and partial cleft palate. Heredity is burdened, there are cases of the disease in male relatives on the maternal side.



Child, born in 2016 Hemophilia A factor VIII level - 3%, and complete cleft palate.

Heredity is burdened. The child underwent a successful operation and restoration of the defect. The operation was carried out under constant monitoring of hemostasis parameters and the corresponding administration of blood coagulation factor preparations.

The only treatment for such patients with congenital pathology of the palate is surgery with suturing the defect or installing an implant. For patients with a deficiency of blood coagulation factors, these operations should be carried out exclusively with the replacement of an adequate amount of blood coagulation drugs, at the rate of 50-60 mg / kg - at least 3 times a day. It is recommended to maintain the missing clotting factor at least 50% for a minimum of 14 days. Otherwise, the operation may be complicated by profuse bleeding, failure of the sutures and the development of other complications associated with the failure of the coagulation link of hemostasis.

With timely surgical intervention and defect plasty, this anomaly does not pose a danger to life. If the defect is not corrected in time, then numerous complications and inflammatory diseases of the nasopharynx develop.

Conclusion: The solution to this problem is the possibility of determining X-linked diseases before the birth of a child. For all regions of Uzbekistan and neighboring countries of the CIS, it is necessary to introduce mandatory molecular genetic testing for chromosomal pathologies for all couples entering into marriage and persons with a predisposition to hereditary diseases, as well as to actively introduce prenatal diagnostics. Prenatal diagnosis will allow, long before the moment of birth, to find out whether everything is in order with the health of the child or whether he has inherited any pathological abnormalities in the genetic material.

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